Supporting Information

Vinyl Sulfone-Based Inhibitors of Non-Structural Protein 2 Block the Replication of Venezuelan Equine Encephalitis Virus

Huaisheng Zhang,[‡] Moeshia Harmon,[‡] Sheli R. Radoshitzky,[ϕ] Veronica Soloveva,[ψ,†] Christopher D. Kane,[σ] Allen J. Duplantier,[ψ] Ifedayo Victor Ogungbe[‡*]

[‡]Department of Chemistry, Physics, and Atmospheric Sciences, Jackson State University, Jackson, MS, 39217-0095

[ϕ]The Geneva Foundation, Countermeasure Development Division, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Frederick, MD 21702-5011

[ψ]Cherokee Nation Assurance, Countermeasure Development Division, US Army Medical Research Institute of Infectious Diseases (USAMRIID), Frederick, MD 21702-5011

[σ]Research Program Office, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), Frederick, MD 21702-5011

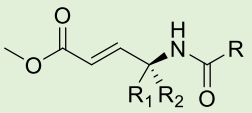
[†]Merck Research Laboratories, Cambridge, MA, USA

*Corresponding Author: ifedayo.v.ogungbe@jsums.edu

Content

1. Supplementary Data

Table S1. Anti-VEEV activity of compound 17-43. BE(2)-M17 and Neuro-2a cells were treated with the indicated compounds and 2 h later inoculated with VEEV TC83. After 7 h, cells were fixed, and stained with antibodies against E2. High-content quantitative image-based analysis was used to measure relative infection rates.

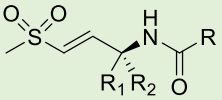


17-23: R_1 and R_2 = H

24, 25: R_1 = CH_3 and R_2 = H

26, 27: R_1 and R_2 = CH_3

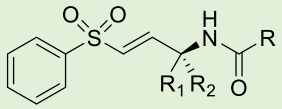
28-30: R_1 = Benzyl and R_2 = H



31-35: R_1 = CH_3 and R_2 = H

36, 37: R_1 = Benzyl and R_2 = H

38, 39: R_1 and R_2 = CH_3



40-43: R_1 = Benzyl and R_2 = H

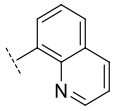
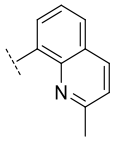
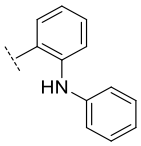
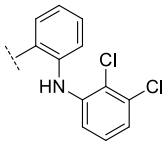
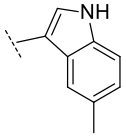
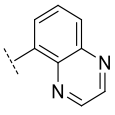
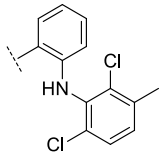
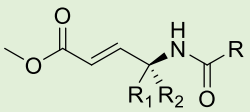
Entry	R	Human BE(2)-M17 (TC83)			Mouse Neuro-2a (TC83)		
		EC_{50} (µM)	CC_{50} (µM)	SI	EC_{50} (µM)	CC_{50} (µM)	SI
17		>25	>25	-	>25	>25	-
18		>25	>25	-	>25	>25	-
19		>25	>25	-	>25	>25	-
20		>25	>25	-	>25	1.50	<0.02
21		>25	>25	-	>25	>25	-
22		>25	>25	-	>25	>25	-
23		>25	>25	-	>25	24	<1

Table S1 (Continued)

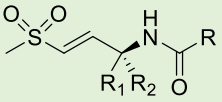


17-23: R_1 and R_2 = H

24, 25: R_1 = CH_3 and R_2 = H

26, 27: R_1 and R_2 = CH_3

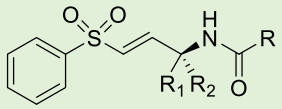
28-30: R_1 = Benzyl and R_2 = H



31-35: R_1 = CH_3 and R_2 = H

36, 37: R_1 = Benzyl and R_2 = H

38, 39: R_1 and R_2 = CH_3



40-43: R_1 = Benzyl and R_2 = H

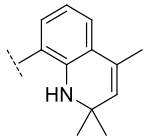
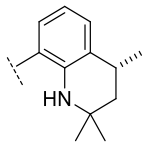
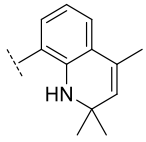
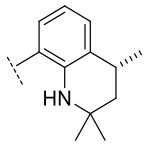
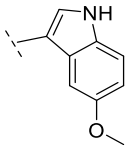
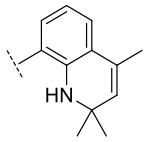
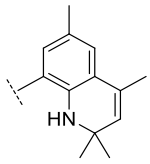
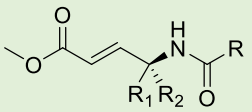
Entry	R	Human BE(2)-M17 (TC83)			Mouse Neuro-2a (TC83)		
		EC_{50} (µM)	CC_{50} (µM)	SI	EC_{50} (µM)	CC_{50} (µM)	SI
24		>25	>25	-	>25	>25	-
		>25	>25	-	>25	>25	-
25		>25	>25	-	>25	>25	-
26		>25	>25	-	>25	>25	-
27		>25	>25	-	>25	>25	-
28		>50	>50	-	>50	>50	-
29		>50	>50	-	>50	>50	-
30		>50	>50	-	>50	>50	-

Table S1 (Continued)

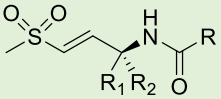


17-23: R_1 and R_2 = H

24, 25: R_1 = CH_3 and R_2 = H

26, 27: R_1 and R_2 = CH_3

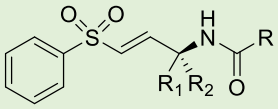
28-30: R_1 = Benzyl and R_2 = H



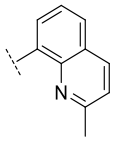
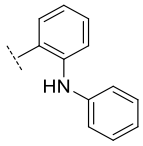
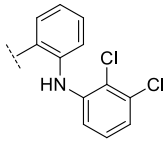
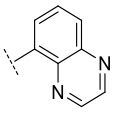
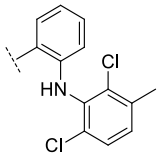
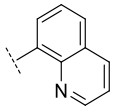
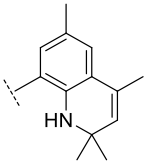
31-35: R_1 = CH_3 and R_2 = H

36, 37: R_1 = Benzyl and R_2 = H

38, 39: R_1 and R_2 = CH_3



40-43: R_1 = Benzyl and R_2 = H

Entry	R	Human BE(2)-M17 (TC83)			Mouse Neuro-2a (TC83)		
		EC_{50} (µM)	CC_{50} (µM)	SI	EC_{50} (µM)	CC_{50} (µM)	SI
31		>25	>25	-	>25	>25	-
32		>25	27	-	>25	>25	-
33		>25	6	<0.2	>25	15.5	<1
34		>25	>25	-	>25	>25	-
35		18 ± 1	15	<1	>25	>25	-
36		>25	>25	-	>25	>25	-
37		32 ± 17	>50	>1.5	>50	>50	-

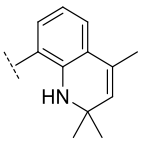
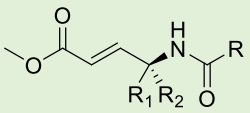
38		>25	>25	-	>25	>25	-

Table S1 (Continued)

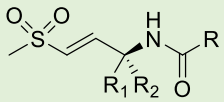


17-23: R_1 and R_2 = H

24, 25: R_1 = CH_3 and R_2 = H

26, 27: R_1 and R_2 = CH_3

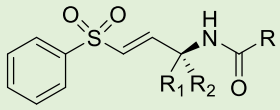
28-30: R_1 = Benzyl and R_2 = H



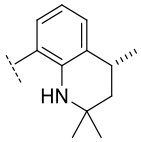
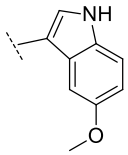
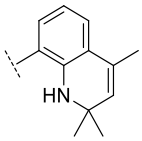
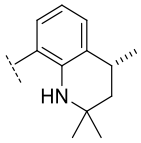
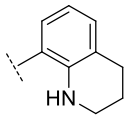
31-35: R_1 = CH_3 and R_2 = H

36, 37: R_1 = Benzyl and R_2 = H

38, 39: R_1 and R_2 = CH_3



40-43: R_1 = Benzyl and R_2 = H

Entry	R	Human BE(2)-M17 (TC83)			Mouse Neuro-2a N2A (TC83)		
		EC_{50} (µM)	CC_{50} (µM)	SI	EC_{50} (µM)	CC_{50} (µM)	SI
39		>25	>25	-	>25	>25	-
40		24 ± 5	>50	>2	>25	>50	-
41		>50	>50	-	>50	>50	-
42		>50	>50	-	>50	>50	-
43		8 ± 2	50	>6	>50	>50	-
ML336	Ref. **1**	0.01 ± 0.00	>2.5	>250	0.02 ± 0.01	>2.5	>125

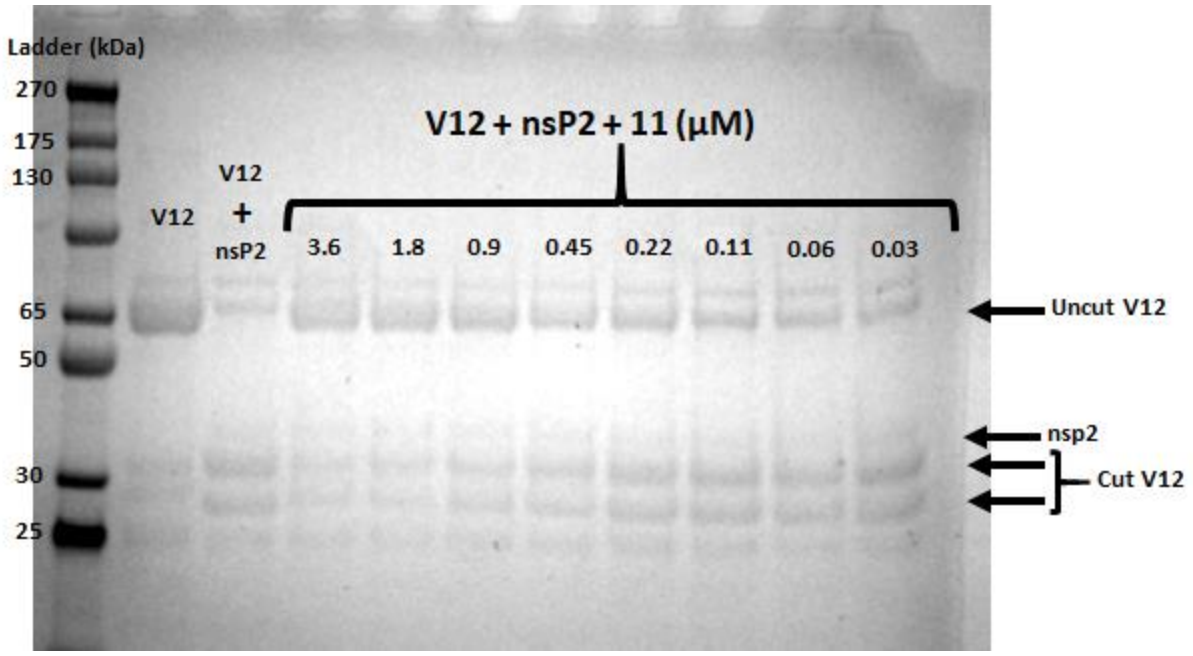


Figure S1. Inhibition of VEEV nsP2 protease by compound **11** in a gel discontinuous assay. V12: CFP-YFP FRET substrate; nsP2: tag-free non-structural protease 2. Lane 1 is V12 alone, Lane 2 is V12 + nsP2, Lanes 3-10 are V12 + nsP2 + **11** at 3.6, 1.8, 0.9, 0.45, 0.22, 0.11, 0.06 and 0.03 μM, respectively. The molecular weight (MW) of uncut V12, the two V12 fragments (cut v12) and tag-free nsP2 are 58.3, 30.9, 27.4, and 38.29 kDa, respectively. The reactions were carried out in 50 mM HEPES buffer pH 7.4 for 24 h at room temperature. The concentrations of VEEV nsP2 and V12 were 1 μM and 10 μM, respectively.

2. Bioassays

a. Antiviral assay:

Primary screen: HeLa cells were plated 24 h before compound treatment at 2,000 cells/well in 35 μL of culture media/well in imaging 384 well assay plates (Aurora 384, IQ-EB, 384 IQ-EB/NB, 200mclear, #1052-11130). Two hundred compounds were screened in 2 replicates at 4 final concentrations (0.24, 1.2, 6, and 30 μM) using 100x compound stocks in 100% DMSO stored on 384 well source plates. Compounds were diluted in media to generate a 10x intermediate concentration using the Perkin Elmer Janus Modular Dispense Technology platform with 384–tip head and 5 μL of diluted compound were transferred immediately into the assay plates containing HeLa cells. RIID reference control E (ChemDiv, Inc., San Diego, CA) was used as control compound. The control's starting concentrations was 2.5 μM and it was tested in 8 doses at 2-fold dilution. DMSO concentration in all wells was normalized to 1%. Two h post compound treatment, assay plates were transferred to BSL-3 suites for VEEV (IC-SH3) infection (MOI = 0.2, 10 μL of virus mix/well). Cells were fixed in 10% formalin 24 h post virus inoculation.

Dose Responses: For EC_{50} and CC_{50} determination, the HP-D300 digital dispenser was used to generate 8- point dose response with a 3-fold step dilution. Each dose was dispensed in triplicate. For each 384 well plate, one or two control compounds were used for quality control. DMSO concentration in all wells was normalized to 0.5-1%. VeroE6 (4,000 cells/well), HeLa (5,000 cells/well), human BE(2)-M17 (6,000 cells/well) and mouse Neuro-2a cells (6,000 cells/well) were

seeded similarly to the primary screen, one day prior to virus inoculation. Cells were infected with VEEV IC-SH3 at MOI=0.01 (VeroE6) or 0.1 (HeLa). BE(2)-M17 and Neuro-2a cells were infected with VEEV-TC83 at MOI of 1.2 and 3.5, respectively. Vero and HeLa cells were infected with VEEV-Trinidad at MOI of 0.1 and 0.01, respectively. Cells were fixed in 10% formalin 20 h (VEEV ICSH3 and Trinidad) or 7 h (VEEV TC83) post virus inoculation. In some dose responses, Neuro-2a cells were infected with VEEV-TC83 at a MOI of 0.005 and fixed in 10% formalin 20 h post virus inoculation. ML366, 2-[(*E*)-(1,4-dimethyl-2-piperazinylidene)amino]-5-nitro-N-phenylbenzamide, purchased from Aurora Fine Chemicals LLC (ID Number: A35.434.430) was used as positive control . For dose response studies with primary mouse cortical neurons (Lonza, #M-CX-300), cells were seeded in 96-well plates (Sigma, #M0562-32EA; 70,000 cells/well) according to the manufacturer's instructions. Dose response studies were performed as described above with the exception that only 5 doses were tested per compound and that each dose was tested in duplicate. Cells were inoculated with VEEV TC83 at MOI=0.04 and fixed in 10% formalin 20 h later.

Immunostaining: Detection and quantification of viral infection in assay plates was performed using a high-content imaging (HCI) assay to measure viral antigen production after immunofluorescent labelling. To detect viral infection, inactivated plates were transferred into BSL-2 lab for immunostaining. Assay wells were incubated with permeabilization/blocking buffer containing 3% BSA/0.1% Triton/PBS for 1 h. Assay wells were then stained for 1 h with a primary antibody against VEEV E2 (mm 1A4A) diluted 1,000-fold in blocking buffer. Following incubation, the primary antibody was removed, and the cells washed 3 times with 1xPBS. Cells were subsequently incubated for 1 h with DyLight-488-conjugated goat anti-mouse IgG (Thermo Fisher, #35502B), diluted 1,000-fold in blocking buffer. Cells were also stained with Hoechst3332 (Thermo Fisher) for nuclei detection and CellMask Deep Red (Thermo Fisher, #C10046) for optimal detection of cytoplasm for at least 30 min before image acquisition.

Image and data analysis: Images were acquired on the Opera confocal imaging instrument (Perkin Elmer) using 10x Air objective (five fields were acquired per each well). Signal from virus staining was detected by CCD cameras at 488nm emission wavelength, nuclei staining at 400 nm and cytoplasm staining at 640nm. Image analysis was performed simultaneously with image acquisition using PE Acapella algorithms. The assay quality of each plate was assessed using the Z′ (Z prime factor). Assay results were considered acceptable if $Z' > 0.5$. Additionally, the % infection rate, consistency of cell counts per well and results for internal positive control compounds were also used as quality control criteria for each plate. Dose response curve analysis (to determine EC_{50} values) was performed using GeneData Screener software applying Levenberg-Marquardt algorithm (LMA) for curve-fitting strategy. Most of the curve-fittings were done using 2-, 3- or 4- parameter non-linear regression. Fitting strategy was considered acceptable if a conversion produced $R^2 > 0.8$.

b. Recombinant Expression and Assay of VEEV nsP2 and V12 Substrate

I. Expression and Purification: VEEV nsP2 and V12 were expressed in *E. coli* (BL-21(DE3)) as reported by Hu and co-workers with some modifications.[2] Fresh 4 x 800 µL cultures of *E. coli* (BL-21(DE3)), from 1 mL transformation/expression culture screens, were used to inoculate 4 x 500 mL of LB media containing 50 µg/mL ampicillin and 0.25 µg/mL

chloramphenicol. The cultures were grown to an OD600 of approximately 0.8 (about 6 h) and induced with 0.5 mM isopropyl β-D-1-thiogalactopyranoside (IPTG) overnight at 17˚C. The cells were pelleted and stored at -20˚C or lysed for immediate purification. Cell lysis was carried out using 50 mM Tris, pH 7.6, 500 mM NaCl, 5 % glycerol, 2 mM BME, bugbuster reagent, and lysonase. The lysates were sonicated 6 times for 30 second intervals. Lysates were clarified by centrifugation at 4,600 rpm for 30 minutes. The lysates were loaded onto Ni-NTA columns equilibrated with 50 mM Tris, pH 7.6, 500 mM NaCl, 2 mM BME, 5 % glycerol, 15 mM imidazole. The column was then washed with 20 column volumes of the equilibration buffer, followed by with the same buffer containing 30 mM imidazole. The proteins were eluted using the same buffer containing 300 mM imidazole. VEEV nsP2 was dialyzed overnight at 4˚C against 50 mM Tris pH 7.6, 250 mM NaCl, 5 mM dithiothreitol (DTT), 10 % glycerol. The partially purified VEEV nsP2 was then incubated with thrombin sepharose beads (Biovision) at 12˚C for 42 h to remove the thioredoxin tag. The thrombin sepharose beads were sedimented at 2000 rpm for 3 minutes, and the supernatant was loaded onto Ni-NTA column equilibrated with 50 mM Tris, pH 7.6, 500 mM NaCl, 2 mM BME, 5 % glycerol, 15 mM imidazole. The column was washed successively with the equilibration buffer containing 15 mM (2 X 10 mL), 30 mM (2 X 10 mL), and 300 mM (2 X 10 mL), as described above. The tag-free VEEV nsP2 protease was found in the flow through and in fractions eluted with 15 mM imidazole. The fractions were pooled, dialyzed against 50 mM Tris pH 7.6, containing 250 mM NaCl, 5 mM dithiothreitol (DTT), and 10 % glycerol, flash frozen, and stored at -80˚C. The V12 substrate was dialyzed against 50 mM Tris (pH 7.6) and 150 mM NaCl overnight at 4˚C and further purified on a Q-sepharose column. The sepharose column was equilibrated and washed with 50 mM Tris (pH 7.6) buffer containing 150 mM NaCl. The V12 substrate was in the flow through. The substrate fractions were pooled, flash frozen and stored at -80˚C.

II. Discontinuous Gel Assay: VEEV nsP2 and V12 were buffer exchanged into 50 mM HEPES buffer pH 7.4, and the protein concentrations were adjusted to 1 μM and 10 μM, respectively. The inhibitors, **11-13** (30 mM in DMSO) were serially diluted with HEPES buffer to prepare stock solutions: 100 μM, 50 μM, 25 μM, 12.5 μM, 6.25 μM, 3.13 μM, 1.56 μM, and 0.78 μM. The assay mixtures were prepared using 44 μL of 10 μM V12 substrate, 10 μL of 1 μM VEEV nsP2, and 2 μL of inhibitors at different concentrations, in a half area 96-well plate. The plate was sealed, and the mixtures were incubated for 24 h at room temperature. Subsequently, 20 μL of SDS sample buffer was mixed with 20 μL of each reaction mixture, heated for 10 minutes at 70˚C, and allowed to cool on ice. The protein samples were resolved on 4-12% SDS-PAGE gels (SurePAGE, Bis-Tris, GenScript) using Tris-MOPS SDS Running buffer. The gels were imaged on a Bio-Rad Gel Dock Imager and the bands were quantified using NIH Image J.[3]

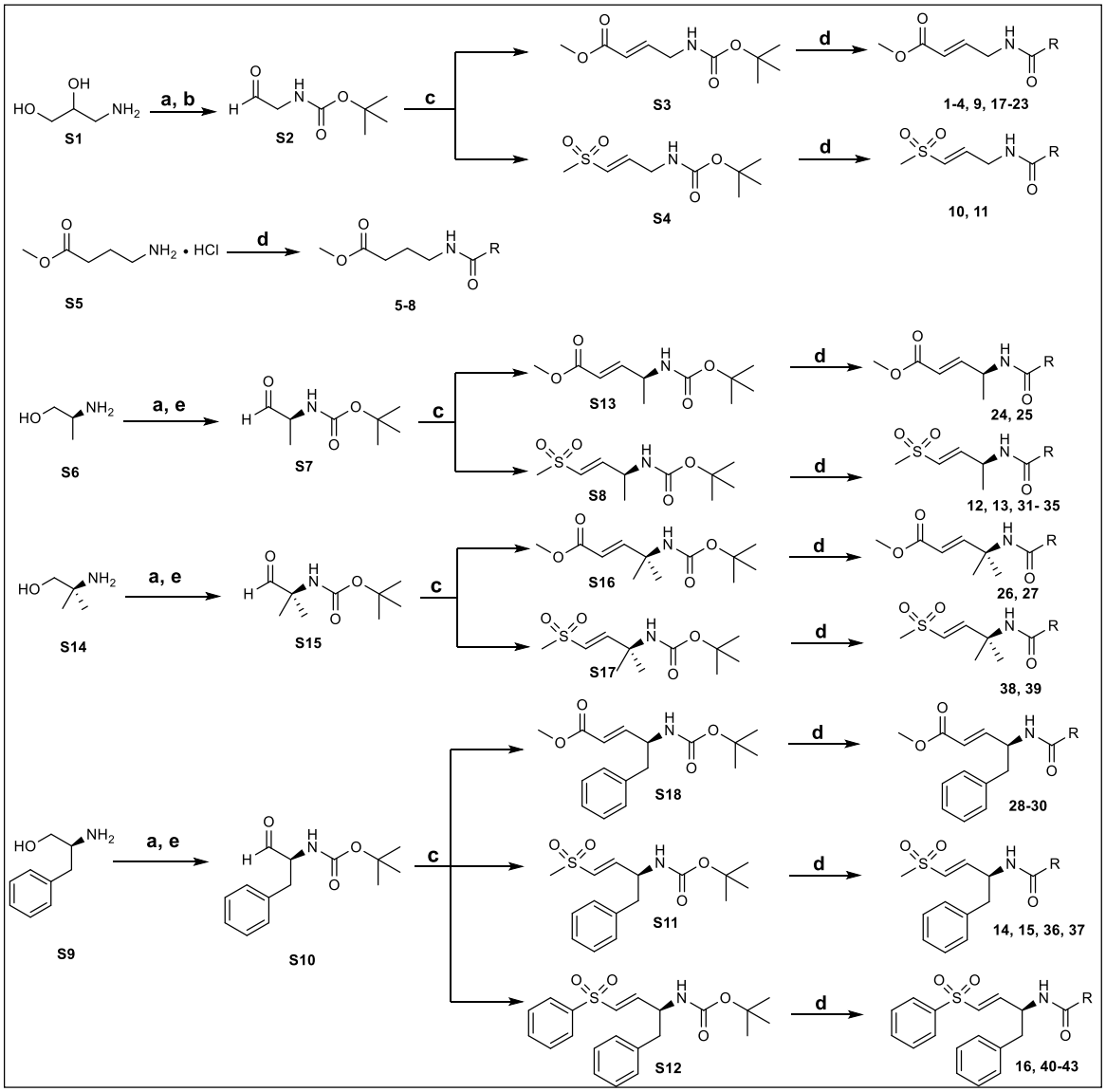
3. Covalent Docking

Ligand structures were built with MOE '18 for Windows and their geometries were optimized using the AMBER 10:EHT force field. The docking simulations were carried out using the covalent docking option in MOE '18. Michael acceptor/vinyl sulfone and 1,4-addition/Michael addition were selected as functional group and reaction class, respectively. Both rigid receptor and induced fit refinements were used. The force constant for refinements was set to 100 with radius offset of 0.4, gradient of 0.01, and 500 iterations. The number of pose placements was set to 30 while 5 poses were retained. The complexes were visually

inspected and analyzed with MOE and Molegro Virtual Docker. The 2D & 3D representation of protein-ligand complex was prepared using MOE '18.[4,5]

4. Synthesis and Product Characterization Data

The compounds were synthesized as shown in **Scheme SI** below. Reagents were purchased from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on Varian 500 MHz



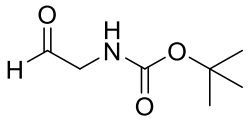
Scheme SI. Synthesis of target compounds **1-43**. Reagents and conditions: (a) CH_2Cl_2:CH_3OH, Et_3N, Boc_2O, 23 °C, 2 h; (b) H_2O, $NaIO_4$, RT, 1 h, >90%; (c) NaH, THF, methyl diethylphosphonoacetate, diethyl((methylsulfonyl)methyl) phosphonate or diethyl((phenylsulfonyl)methyl) phosphonate, 0 °C, 25 min, 40-70%; (d) 33% TFA in DCM, 0 °C, 1.5 h. Then ACN, R-COOH, Et_3N, HBTU, RT, 16 h, 30-40%; (e) DMP, H_2O-DCM, 23 °C, 1 h, 40-60%.

(Agilent, Santa Clara, CA, USA) and Bruker Ultrashield Avance 400 (Bruker, Billerica, MA, USA) spectrometers. Thin layer chromatography (TLC) and NMR were used to monitor reactions, and purification conditions. Compounds were purified by column chromatography on silica gel or on pre-coated preparative TLC plates. Accurate mass information was obtained on Synapt G2 HDMS instrument operated in positive or negative ESI mode. HPLC-UV analysis was carried out on a Shimadzu Prominence HPLC-UV system using isocratic elution with 90% MeOH, 5% ACN, and 5% H_2O (Pinnacle II C18 5μM, 200 x 4.6 mm column; flowrate = 0.5 mL/min).

Synthesis of S2

(±)-3-amino-1,2-propanediol (**S1**, 11.29 g, 124 mmol) was dissolved in CH_2Cl_2:CH_3OH (1:5; 1 M) and triethylamine (2 mL, 14.7 mmol) was added. Di-*tert*-butyl dicarbonate (32.5 g, 149 mmol) was dissolved in dichloromethane (0.8 M, 186 mL) and added slowly to the reaction mixture. The resulting reaction was stirred at 23˚C for 2 h followed by TLC analysis that showed full consumption of the starting material. The reaction mixture was evaporated under reduced pressure, and the residue was purified by column chromatography with EtOAc:hexanes 1:4, then dried on high vacuum to yield the Boc-protected amino diol as a white solid (21.82 g, 92% yield). The Boc-protected amino diol (21.82 g, 113mmol) was suspended in H_2O (0.6M, 190 mL) and the flask was covered in foil (to protect $NaIO_4$ from light). $NaIO_4$ (29.2 g, 137 mmol) was then added and the reaction was stirred for 1 h. A white precipitate had formed after 1h, and TLC analysis showed full consumption of the starting material. The precipitate was filtered, and the aqueous layer was extracted with $CHCl_3$ (8×50 mL). The organic layer was dried with $MgSO_4$, filtered, and evaporated to yield **S2** as a light-yellow oil, which was used without further purification (12.65 g, 64% yield).

***tert*-Butyl (2-oxoethyl)carbamate (S2)**



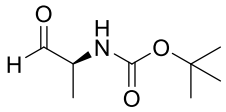
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (s, 1H), 5.26 (s, 1H), 4.04 (d, J = 6.5 Hz, 2H), 1.43 (s, 9H).

General method for synthesis of S7, S10, and S15

S6, **S9** and **S14** were Boc-protected and extracted as described above. Dess-Martin periodinane (5.25 mmol) was added to a solution of the Boc-protected amino alcohols (2.5 mmol) in water-saturated dichloromethane (20 mL). The resulting suspension was stirred at 23˚C, and the progress of the reaction was monitored by TLC. Additional 10 mL portions of water-saturated dichloromethane were added (three portions over 15 min) once the rate of conversion has slowed considerably. After 25 min, no remaining starting materials were detected by TLC, and the reaction mixtures were diluted with diethyl ether (40 mL) followed by the addition a solution of sodium thiosulfate (11 mol eq) in 80% saturated aqueous sodium bicarbonate

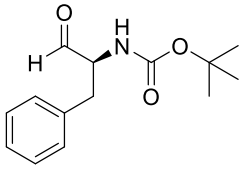
solution (40 mL). The mixtures were stirred rapidly for 10 min until both phases were clear. Once the layers were separated, the aqueous layer was extracted 2 more times with diethyl ether. The organic layers were evaporated under reduced pressure. The residue was purified by column chromatography and dried to yield **S7, S10, and S15** (40-60% yield).

***tert*-Butyl (S)-(1-oxopropan-2-yl)carbamate (S7)**



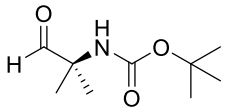
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H), 5.11 (s, 1H), 4.23 (s, 1H), 1.45 (s, 9H), 1.33 (d, J = 7.5 Hz, 3H).

***tert*-Butyl (S)-(1-oxo-3-phenylpropan-2-yl)carbamate (S10)**



^{1}H NMR (500 MHz, $CDCl_3$) 9.63 (s, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.17 (d, J = 7.5 Hz, 2H), 5.05 (s, 1H), 4.44 (m, 1H), 3.11 (d, J = 6.5 Hz, 2H), 1.43 (s, 9H).

***tert*-Butyl (2-methyl-1-oxopropan-2-yl)carbamate (S15)**



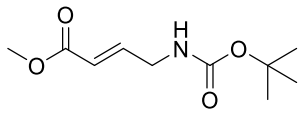
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 4.99 (s, 1H), 1.43 (s, 9H), 1.32 (s, 6H).

General method for the synthesis of S3, S4, S8, S11-13, S16-S18

Sodium hydride (1.5 eq)-tetrahydrofuran (THF) solutions were cooled to 0°C, methyl diethylphosphonoacetate (i), diethyl ((methylsulfonyl)methyl) phosphonate (ii) or diethyl((phenylsulfonyl)methyl) phosphonate (iii), in THF was added dropwise (1.0 eq). The reactions were stirred at 0°C for 20 min. Thereafter, compounds **S2, S7, S10, and S15** (1.0 eq) in THF were added. After stirring for 5 minutes, the reactions were quenched with saturated aqueous solution of sodium bicarbonate.

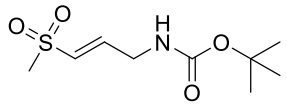
The mixtures were diluted with ethyl acetate and water. The layers were separated, and the aqueous layers were extracted with ethyl acetate (3 times). The organic layers were dried over $MgSO_4$, filtered, and evaporated. The mixtures were purified by flash column chromatography to obtain compounds **S3, S4, S8, S11-13, S16-S18** (40-70% yield).

Methyl (E)-4-((*tert*-butoxycarbonyl)amino)but-2-enoate (S3)



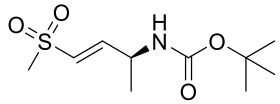
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dt, J = 15.5 Hz, J =5.0 Hz, 1H), 5.94 (dt, J = 15.5 Hz, J = 1.5 Hz, 1H), 4.73 (s, 1H), 3.92 (s, 2H), 3.73 (s, 3H), 1.44 (s, 9H).

***tert*-Butyl (E)-(3-(methylsulfonyl)allyl)carbamate (S4)**



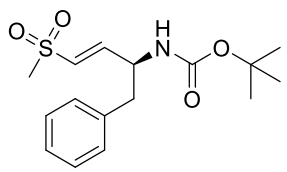
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (dt, J = 19.0 Hz, J = 5.5 Hz, 1H), 6.44 (d, J = 18.5 Hz, 1H), 5.25 (t, J = 7.5 Hz, 1H), 3.90 (s, 2H), 2.87 (s, 3H), 1.37 (s, 9H).

***tert*-Butyl (*S*,*E*)-(4-(methylsulfonyl)but-3-en-2-yl)carbamate (S8)**



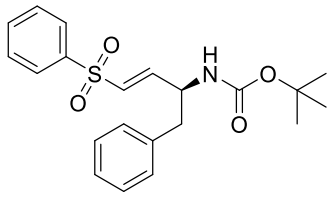
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (dd, J = 15.0 Hz, J = 5.0 Hz, 1H), 6.55 (dd, J = 15.0 Hz, J = 1.5 Hz, 1H), 4.65 (d, J = 7.0 Hz, 1H), 4.45 (s, 1H), 2.93 (s, 3H), 1.43 (s, 9H), 1.29 (d, J = 7.0 Hz, 3H).

***tert*-Butyl (*S*,*E*)-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)carbamate (S11)**



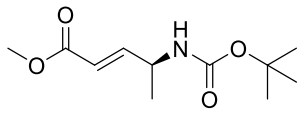
^{1}H NMR (500 MHz, $CDCl_3$) 7.29 (t, J = 7.5 HZ, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 7.5 Hz, 2H), 6.91 (dd, J = 15.5 Hz, J = 5.0 Hz, 1H), 5.85 (d, J = 16.0 Hz, 1H), 4.64 (t, J = 7.5 Hz, 1H), 4.60 (s, 1H), 3.70 (s, 3H), 2.87 (d, J = 5.5 Hz, 2H), 1.38 (s, 9H).

***tert*-Butyl (*S,E*)-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)carbamate (S12)**



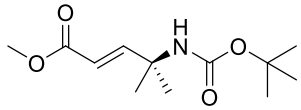
^{1}H NMR (500 MHz, $CDCl_3$) 7.81 (d, J = 7.5 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.28-7.21 (m, 3H), 7.11 (d, J = 7.0 Hz, 2H), 6.93 (dd, J = 15.0 Hz, J = 5.0 Hz, 1H), 6.32 (dd, J = 15.0 Hz, J = 1.5 Hz, 1H), 4.66 (s, 1H), 4.52 (s, 1H), 2.87 (d, J = 6.0 Hz, 2H), 1.35 (s, 9H).

Methyl (*S,E*)-4-((*tert*-butoxycarbonyl)amino)pent-2-enoate (S13)



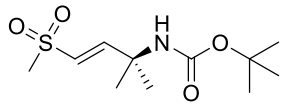
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (dd, J = 15.5 Hz, J = 4.5 Hz, 1H), 5.88 (dd, J = 15.5 Hz, J = 1.5 Hz, 1H), 4.58 (s, 1H), 4.38 (s, 1H), 3.71 (s, 3H), 1.42 (s, 9H), 1.24 (d, J = 7.0 Hz, 3H).

Methyl (*E*)-4-((*tert*-butoxycarbonyl)amino)-4-methylpent-2-enoate (S16)



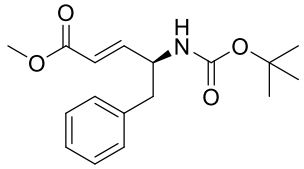
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, J = 16.0 Hz, 1H), 5.82 (d, J = 15.5 Hz, 1H), 4.69 (s, 1H), 3.70 (s, 3H), 1.39 (s, 9H), 1.37 (s, 6H).

***tert*-Butyl (*E*)-(2-methyl-4-(methylsulfonyl)but-3-en-2-yl)carbamate (S17)**



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (d, J = 15.0 Hz, 1H), 6.38 (d, J = 15.0 Hz, 1H), 4.73 (s, 1H), 2.94 (s, 3H), 1.42 (s, 15H).

Methyl (*S,E*)-4-((*tert*-butoxycarbonyl)amino)-5-phenylpent-2-enoate (S18)



^{1}H NMR (500 MHz, $CDCl_3$) 7.28 (t, J = 7.5 HZ, 2H), 7.21 (t, J = 7.0 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 6.90 (dd, J = 16.0 Hz, J = 5.0 Hz, 1H), 5.85 (d, J = 15.5 Hz, 1H), 4.69 (d, J = 9.0 Hz, 1H), 4.60 (s, 1H), 3.69 (s, 3H), 2.87 (d, J = 6.0 Hz, 2H), 1.37 (s, 9H).

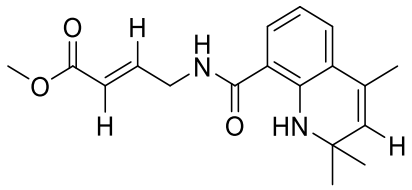
General method for the synthesis of 1-4, 9-43

Compounds **S3, S4, S8, S11-13, S16-S18** (0.1 mmol) were dissolved in 33% TFA-dichloromethane solution (1.5 mL) and allowed to stir at 0 °C for 1.5 h. The solutions were concentrated and washed twice with 5 mL toluene to remove any remaining TFA. The deprotected amines were re-dissolved in 2 mL of anhydrous acetonitrile and the corresponding acids (0.10 mmol), Et_3N (31 µL, 0.218 mmol) and HBTU (41.7 mg, 0.11 mmol) were added. The solutions were allowed to stir overnight. The reactions were quenched with brine (5 mL). The aqueous layers were extracted three times with 10 mL of ethyl acetate. The extracts were concentrated, and the amides were purified on prep-TLC plates using EtOAc:hexanes 2:1 (30-40% yield).

General method for synthesis of 5-8

Methyl-4-aminobutyrate hydrochloride (**S5,** 0.23 mmol) was dissolved in 4 x 2 mL of anhydrous acetonitrile and corresponding acids (0.23 mmol), Et_3N (65 µL, 0.457 mmol) and HBTU (41.7 mg, 0.23 mmol) were added. The solutions were allowed to stir overnight. The mixtures were concentrated and purified on prep-TLC plates using EtOAc:hexanes 2:1 to obtain the amides (30-40 % yield).

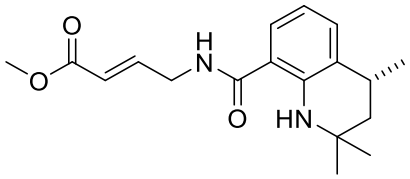
Methyl (*E*)-4-(2,2,4-trimethyl-1,2-dihydroquinoline-8-carboxamido)but-2-enoate (1)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 7.00 (dt, J = 15.5 Hz, J = 5.0 Hz, 1H), 6.47 (t, J = 8.0 Hz, 1H), 6.22 (s, 1H), 5.99 (dt, J = 15.5 Hz, J = 1.5 Hz, 1H), 5.35 (s, 1H), 4.19 (m, 2H), 3.73 (s, 3H), 1.97 (d, J = 1.0 Hz, 3H), 1.32 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 166.6, 146.2, 144.6, 129.1, 127.5, 127.0, 126.2, 122.9,

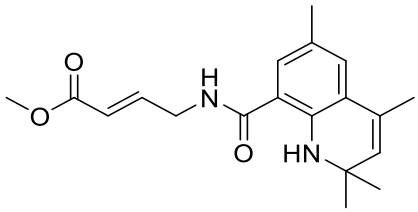
121.5, 114.1, 111.5, 51.8, 51.7, 40.3, 32.2, 19.2. HRMS $[M-H]^+$ calculated for $C_{18}H_{23}N_2O_3$: 315.1709; found: 315.1705. HPLC-UV: 97.8%.

Methyl (*E*)-4-(2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-8-carboxamido)but-2-enoate (2)



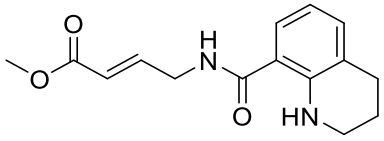
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.00 (dt, J = 15.5 Hz, J = 5.0 Hz, 1H), 6.50 (t, J = 7.5 Hz, 1H), 6.24 (s, 1H), 5.99 (dt, J = 15.5 Hz, J = 2.0 Hz, 1H), 4.18 (m, 2H), 3.73 (s, 3H), 2.91 (m, 1H), 1.73 (dd, J = 12.5 Hz, J = 5.0 Hz, 1H), 1.40 (t, J = 12.5 Hz, 1H), 1.34 (d, J = 6.5 Hz, 3H), 1.29 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 166.6, 146.3, 144.7, 130.1, 127.4, 125.2, 121.4, 113.7, 112.3, 51.8, 49.0, 43.4, 40.3, 31.6, 29.0, 27.8, 20.3. HRMS $[M-H]^+$ calculated for $C_{18}H_{25}N_2O_3$: 317.1865; found: 317.1869. HPLC-UV: 95.5%.

Methyl (*E*)-4-(2,2,4,6-tetramethyl-1,2-dihydroquinoline-8-carboxamido)but-2-enoate (3)



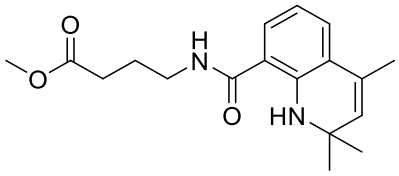
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.00 (dt, J = 19.5 Hz, J = 6.5 Hz, 1H), 6.98 (s, 1H), 6.94 (s, 1H), 6.25 (t, J = 7.0 Hz, 1H), 5.98 (dt, J = 19.5 Hz, J = 2.5 Hz, 1H), 5.36 (s, 1H), 4.18 (m, 2H), 3.73 (s, 3H), 2.20 (s, 3H), 1.96 (d, J = 1.5 Hz, 3H), 1.29 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 166.4, 144.5, 129.5, 128.0, 127.5, 126.1, 121.3, 51.66, 40.2, 31.4, 20.6, 19.0. HRMS $[M-H]^+$ calculated for $C_{19}H_{25}N_2O_3$: 329.1865; found: 329.1866. HPLC-UV: 98.4%.

Methyl (*E*)-4-(1,2,3,4-tetrahydroquinoline-8-carboxamido)but-2-enoate (4)



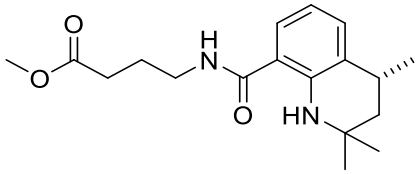
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.99 (m, 2H), 6.44 (t, J = 7.5 Hz, 1H), 6.23 (s, 1H), 5.98 (dt, J = 16.0 Hz, J = 1.5 Hz, 1H), 4.17 (m, 2H), 3.73 (s, 3H), 3.37 (t, J = 6.0 Hz, 2H), 2.77 (t, J = 6.0 Hz, 2H), 1.89 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 166.6, 147.1, 144.8, 132.6, 125.1, 122.9, 121.4, 113.8, 112.5, 51.8, 41.2, 40.3, 27.9, 20.9. HRMS $[M-H]^+$ calculated for $C_{15}H_{19}N_2O_3$: 275.1396; found: 275.1396. HPLC-UV: 98.1%.

Methyl 4-(2,2,4-trimethyl-1,2-dihydroquinoline-8-carboxamido)butanoate (5)



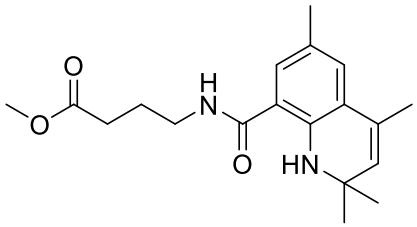
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.14 (dd, J = 8.0 Hz, J = 0.5 Hz, 1H), 7.08 (dd, J = 7.0 Hz, J = 1.0 Hz, 1H), 6.46 (t, J = 7.5 Hz, 1H), 6.36 (s, 1H), 5.34 (d, J = 1.0 Hz, 1H), 3.67 (s, 3H), 3.43 (q, J1 = 7.0 Hz, J2 = 12.5 Hz, 2H), 2.43 (t, J = 7.5 Hz, 2H), 1.96 (s, 3H), 1.96 (m, 2H), 1.31 (1, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 169.8, 145.9, 129.0, 127.65, 126.6, 126.3, 122.7, 114.1, 112.4, 51.9, 51.6, 39.3, 32.1, 31.8, 24.6, 19.2. HRMS $[M-H]^+$ calculated for $C_{18}H_{25}N_2O_3$: 317.1865; found: 317.1859. HPLC-UV: 96.0%.

Methyl 4-(2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-8-carboxamido)butanoate (6)



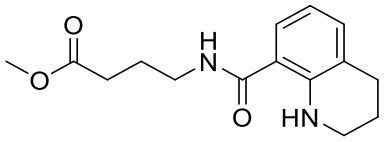
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 6.49 (t, J = 8.0 Hz, 1H), 6.32 (s, 1H), 3.67 (s, 3H), 3.43 (q, J1 = 6.5 Hz, J2 = 13.0 Hz, 2H), 2.90 (m, 1H), 2.42 (t, J = 7.0 Hz, 2H), 1.93 (m, 2H), 1.71 (dd, J = 13.0 Hz, J = 5.5 Hz, 1H), 1.39 (t, J = 15.5 Hz, 1H), 1.33 (d, J = 6.5 Hz, 3H), 1.29 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (125MHz, $CDCl_3$) δ 174.2, 170.3, 146.1, 129.7, 127.1, 125.2, 113.6, 113.2, 51.8, 48.9, 43.5, 39.2, 31.7, 28.9, 27.8, 24.7, 20.3. HRMS $[M-H]^+$ calculated for $C_{18}H_{27}N_2O_3$: 319.2022; found: 319.2018. HPLC-UV: 96.7%.

Methyl 4-(2,2,4,6-tetramethyl-1,2-dihydroquinoline-8-carboxamido)butanoate (7)



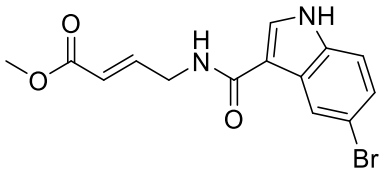
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.92 (s,1H), 6.36 (s, 1H), 5.35 (s, 1H), 3.67 (s, 3H), 3.42 (q, J1 = 7.0 Hz, J2 = 13.0 Hz, 2H), 2.42 (t, J = 7.0 Hz, 2H), 2.20 (s, 3H), 1.95 (s, 3H), 1.94 (m, 2H), 1.29 (s, 6H). ^{13}C NMR (125MHz, $CDCl_3$) δ 174.2, 169.8, 130.7, 129.4, 128.9, 12.7, 127.6, 126.2, 123.0, 112.6, 51.8, 51.5, 39.2, 31.7, 24.6, 20.7, 19.2. HRMS $[M-H]^+$ calculated for $C_{19}H_{27}N_2O_3$: 331.2022; found: 331.2020. HPLC-UV: 98.7%.

Methyl 4-(1,2,3,4-tetrahydroquinoline-8-carboxamido)butanoate (8)



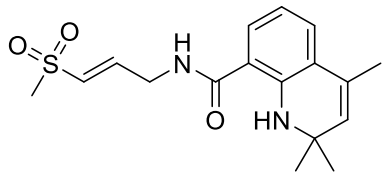
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 7.0 Hz, 1H), 6.43 (t, J = 7.5 Hz, 1H), 6.30 (s, 1H), 3.66 (s, 3H), 3.42 (q, J = 6.0 Hz, 2H), 3.36 (t, J = 5.5 Hz, 2H), 2.75 (t, J = 6.5 Hz, 2H), 2.42 (t, J = 7.5 Hz, 2H), 1.92 (m 2H), 1.87 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 170.1, 146.8, 132.2, 125.1, 122.7, 113.7, 113.4, 51.8, 41.2, 39.2, 31.7, 27.9, 24.7, 20.9. HRMS $[M-H]^+$ calculated for $C_{15}H_{21}N_2O_3$: 277.1552; found: 277.1555. HPLC-UV: 98.1%.

Methyl (*E*)-4-(5-bromo-1H-indole-3-carboxamido)but-2-enoate (9)



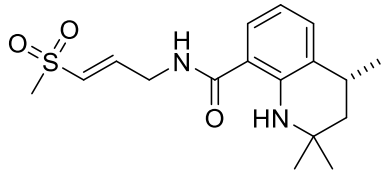
^{1}H NMR (500 MHz, Acetone-d_6) δ 10.88 (s, 1H), 8.45 (m, 1H), 8.10 (d, J = 3.0 Hz, 1H), 7.63 (s, 1H), 7.44 (dd, J = 8.5 Hz, J = 0.5 Hz, 1H), 7.28 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H), 6.99 (dt, J = 16.0 Hz, J = 5.0 Hz, 1H), 5.98 (dt, J = 16.0 Hz, J = 1.5 Hz, 1H), 4.19-4.17 (m, 2H), 3.65 (s, 3H). ^{13}C NMR (125 MHz, Acetone-d_6) δ 166.8, 165.0, 147.0, 136.1, 129.3, 129.1, 125.8, 124.6, 121.2, 114.6, 114.4, 114.3, 111.7, 51.5, 40.3. HRMS $[M]^-$ calculated for $C_{14}H_{13}BrN_2O_3$: 335.0031; found: 335.0043. HPLC-UV: 99.9%.

(*E*)-2,2,4-trimethyl-*N*-(3-(methylsulfonyl)allyl)-1,2-dihydroquinoline-8-carboxamide (10)



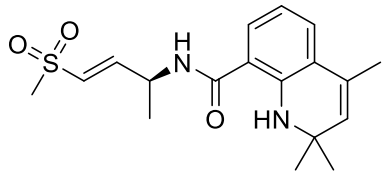
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 7.01 (dt, J = 15.0 Hz, J = 4.0 Hz, 1H), 6.53 (d, J = 15.0 Hz, 1H), 6.49 (t, J = 8.0 Hz, 1H), 6.31 (t, J = 5.0 Hz, 1H), 5.36 (s, 1H), 4.27 (m, 2H), 2.95 (s, 3H), 1.97 (s, 3H), 1.32 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 145.1, 144.6, 129.7, 129.0, 127.4, 127.1, 126.1, 122.8, 114.1, 110.8, 51.6, 42.8, 39.4, 32.1, 19.0. HRMS $[M-H]^+$ calculated for $C_{17}H_{23}N_2O_3S$: 335.1429; found: 335.1429. HPLC-UV: 97.2%.

(*E*)-2,2,4-trimethyl-*N*-(3-(methylsulfonyl)allyl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (11)



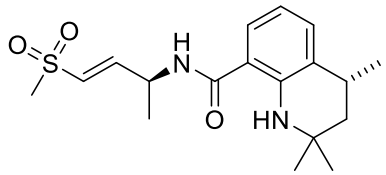
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.00 (dt, J = 15.0 Hz, J = 4.25 Hz, 1H), 6.52 (d, J = 15.0 Hz, 1H), 6.52 (t, J = 7.5 Hz, 1H), 6.35 (t, J = 4.75 Hz, 1H), 4.25 (m, 2H), 2.93 (s, 3H), 1.75 (dd, J = 13 Hz, J = 5.0 Hz, 1H), 1.51 (s, 1H), 1.40 (t, J = 13 Hz, 1H), 1.35 (d, J = 6.5 Hz, 3H), 1.29 (s, 3H), 1.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 146.2, 144.7, 130.2, 129.7, 127.5, 126.1, 125.1, 113.8, 43.2, 42.7, 39.50, 31.4, 28.9, 27.7, 20.2. HRMS $[M-H]^+$ calculated for $C_{17}H_{25}N_2O_3S$: 337.1586; found: 337.1579. HPLC-UV: 99.9%.

(*S, E*)-2,2,4-trimethyl-*N*-(4-(methylsulfonyl)but-3-en-2-yl)-1,2-dihydroquinoline-8-carboxamide (12)



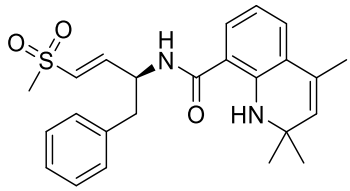
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 7.0 Hz, 1H), 6.95 (dd, J = 15.0 Hz, J = 4.5 Hz, 1H), 6.50 (d, J = 15.5 Hz, 1H), 6.47 (t, J = 8.0 Hz, 1H), 6.05 (d, J = 7.5 Hz, 1H), 5.35 (s, 1H), 4.93 (m, 1H), 2.94 (s, 3H), 1.97 (s, 3H), 1.42 (d, J = 7.5 Hz, 3H), 1.32 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 148.8, 146.3, 129.1, 129.0, 127.5, 127.1, 126.2, 122.8, 114.1, 111.1, 51.7, 45.4, 42.9, 32.2, 32.2, 19.9, 19.1. HRMS $[M-H]^+$ calculated for $C_{18}H_{25}N_2O_3S$: 349.1586; found: 349.1584. HPLC-UV: 99.1%.

(*S,E*)-2,2,4-trimethyl-*N*-(4-(methylsulfonyl)but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (13)



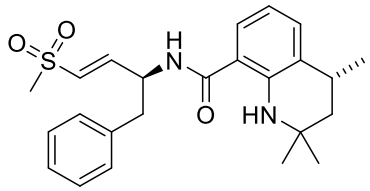
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.20 (dd, J = 7.5 Hz, J = 3.0 Hz, 1H), 6.94 (dt, J = 15.0 Hz, J = 5.0 Hz, 1H), 6.52-6.48 (m, 2H), 6.08 (t, J = 7.0 Hz, 1H), 4.93 (m, 1H), 2.94 (d, J = 5.5 Hz, 3H), 1.74 (dd, J = 12.5 Hz, J = 5.0 Hz, 1H), 1.41 (m, 3H), 1.34 (dd, J = 7.0 Hz, J = 2.0 Hz, 3H), 1.22 (d, J = 5.5, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 148.8, 148.8, 130.3, 129.0, 129.0, 127.5, 125.2, 113.7, 111.9, 49.0, 45.4, 43.4, 42.9, 31.1, 29.0, 27.8, 20.3, 19.8. HRMS $[M-H]^+$ calculated for $C_{18}H_{27}N_2O_3S$: 351.1742; found: 351.1735. HPLC-UV: 97.0%.

(*S,E*)-2,2,4-trimethyl-*N*-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)-1,2-dihydroquinoline-8-carboxamide (14)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.0 Hz, 2H), 7.10 (dd, J = 7.5 Hz, J = 1.0 Hz, 1H), 7.02-6.97 (m, 2H), 6.44 (t, J = 8.0 Hz, 1H), 6.39 (dd, J = 15.0 Hz, J = 1.5 Hz, 1H), 6.07 (d, J = 7.5 Hz, 1H), 5.14 (m, 1H), 3.05 (d, J = 7.0 Hz, 2H), 2.88 (s, 3H), 1.95 (d, J = 15.0 Hz, 3H), 1.30 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 147.0, 146.1, 135.5, 129.8, 129.3, 129.0, 128.9, 127.4, 127.4, 127.0, 125.9, 122.7, 114.0, 110.9, 51.6, 50.2, 42.8, 40.0, 32.1, 32.1, 19.0. HRMS $[M-Cl]^-$ calculated for $C_{24}H_{28}ClN_2O_3S$: 459.1509; found: 459.1517. HPLC-UV: 97.8%.

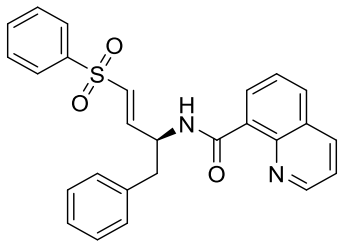
(*S,E*)-2,2,4-trimethyl-*N*-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (15)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d J = 30.0 Hz, 1H), 7.33 (m, 2H), 7.28 (m 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.21 (m, 2H), 7.05 (dd, J = 15.5 Hz, J = 3.0 Hz, 1H), 6.98 (dd, J = 15.0 Hz, J = 4.5 Hz, 1H), 6.48 (td, J = 7.5 Hz, J = 1.5 Hz, 1H), 6.39 (m, 1H), 6.12 (t, J = 7.5 Hz, 1H), 5.14 (m, 1H), 3.05 (m, 2H), 2.89 (m, 1H), 2.87 (d, J = 2.5 Hz, 3H), 1.73 (dd, J = 12.5 Hz, J = 5.0 Hz, 1H), 1.38 (t, J = 12.5 Hz, 1H), 1.34 (dd, J = 7.0 Hz, J = 2.5 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H), 1.20 (s, 3H). ^{13}C NMR (125

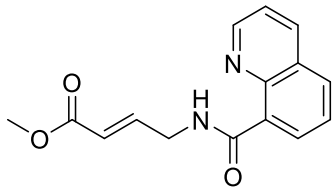
MHz, $CDCl_3$) δ. 169.4, 147.2, 146.5, 135.6, 130.2, 129.9, 129.4, 129.0, 127.5, 125.1, 113.7, 111.7, 50.4, 49.0, 43.3, 42.9, 40.1, 31.6, 29.0, 27.8, 20.3. HRMS $[M\text{-}Cl]^-$ calculated for $C_{24}H_{30}ClN_2O_3S$: 461.1666; found: 461.1668. HPLC-UV: 98.0%.

(*S*,*E*)-*N*-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)quinoline-8-carboxamide (16)



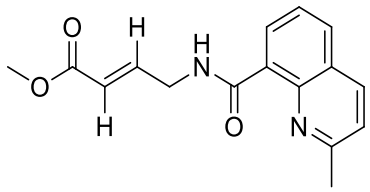
^1H NMR (500 MHz, $CDCl_3$) δ 11.67(d, J = 8.5 Hz, 1H), 8.78 (dd, J = 7.0 Hz, J = 1.5 Hz, 1H), 8.73 (dd, J = 4.0 Hz, J = 2.0 Hz, 1H), 8.29 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H), 7.98 (dd, J = 8.5 Hz, J = 1.5 Hz, 1H), 7.81 (m, 2H), 7.66 (t, J = 7.75 Hz, 1H), 7.59 (t, J = 7.0 Hz, 1H), 7.51-7.48 (m, 3H), 7.27-7.23 (m, 5H), 7.18 (dd, J = 15.0 Hz, J = 5.0 Hz, 1H), 6.44 (dd, J = 15.0 Hz, J = 1.5 Hz, 1H), 5.45 (m, 1H), 3.22-3.11 (m, 2H). ^{13}C NMR (125MHz, $CDCl_3$) δ 165.2, 149.2, 146.5, 145.4, 140.2, 137.8, 136.2, 134.0, 13.3, 132.3, 130.5, 129.7, 129.2, 128.4, 128.4, 127.8, 127.6, 126.9, 126.5, 121.0, 51.2, 40.5. HRMS $[M\text{-}Cl]^-$ calculated for $C_{26}H_{22}ClN_2O_3S$: 477.1040; found: 477.1039. HPLC-UV: 97.6%.

Methyl (*E*)-4-(quinoline-8-carboxamido)but-2-enoate (17)



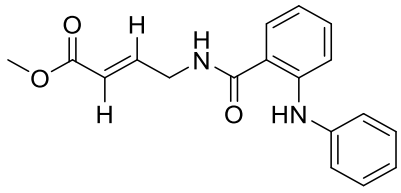
^1H NMR (500 MHz, $CDCl_3$) δ 11.61 (s, 1H), 8.94 (dd, J = 4.5 Hz, J = 1.5 Hz, 1H), 8.87 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 8.30 (dd, J = 8.5 Hz, J = 1.5 Hz, 1H), 7.99 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.51 (dd, J = 8.5 Hz, J = 4.5 Hz, 1H), 7.15 (dt, J = 15.5 Hz, J = 4.5 Hz, 1H), 6.10 (dt, J = 16.0 Hz, J = 2.0 Hz, 1H), 4.43 (m, 2H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 166.1, 149.5, 145.7, 145.4, 138.0, 134.2, 132.3, 128.6, 128.3, 126.7, 121.1, 120.9, 51.7, 40.6. HRMS $[M\text{-}H]^+$ calculated for $C_{15}H_{15}N_2O_3$: 271.1083; found: 271.1081. HPLC-UV: 98.7%.

Methyl (*E*)-4-(2-methylquinoline-8-carboxamido)but-2-enoate (18)



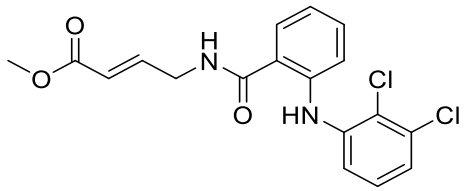
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.88 (s, 1H), 8.82 (d, J = 7.0 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.18 (dt, J = 15.5 Hz, J = 4.5 Hz, 1H), 6.18 (d, J = 16.0 Hz, 1H), 4.45 (m, 2H), 3.73 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 164.8, 145.3, 145.1, 137.8, 133.89, 131.9, 125.6, 121.8, 120.5, 118.0, 51.6, 40.4, 29.7. HRMS $[M-H]^+$ calculated for $C_{16}H_{17}N_2O_3$: 285.1239; found: 285.1244. HPLC-UV: 99.8%.

Methyl (*E*)-4-(2-(phenylamino)benzamido)but-2-enoate (19)



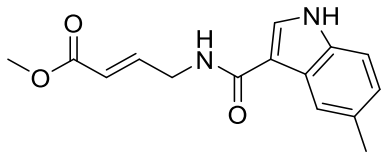
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.46 (dd, J = 7.5 Hz, J = 1.0 Hz, 1H), 7.34 (t, J = 7.5, 1H), 7.29 (m, 2H), 7.28 (m, 1H), 7.19 (d, J = 7.5 Hz, 2H), 7.02 (t, J = 7.0 Hz, 1H), 6.99 (dt, J = 16.0 Hz, J = 5.0 Hz, 1H), 6.77 (t, J = 7.5 Hz, 1H), 6.42 (s, 1H), 6.00 (dt, J = 15.5 Hz, J = 1.5 Hz, 1H), 4.21 (m, 2H), 3.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 166.5, 145.9, 144.2, 141.4, 132.7, 129.4, 127.5, 122.7, 121.7, 121.1, 118.0, 117.4, 115.6, 51.8, 40.5. HRMS $[M-H]^+$ calculated for $C_{18}H_{19}N_2O_3$: 311.1396; found: 311.1398. HPLC-UV: 99.3%.

Methyl (*E*)-4-(2-((2,3-dichlorophenyl)amino)benzamido)but-2-enoate (20)



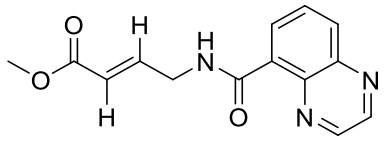
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 8.5 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 8.5 Hz, 2H), 7.03 (t, J = 7.5 Hz, 1H), 6.99 (dt, J = 15.0 Hz, J = 4.5 Hz, 1H), 6.80 (t, J = 7.5 Hz, 1H), 6.70 (s, 1H), 6.51 (d, J = 15.0 Hz, 1H), 4.29 (m, 2H), 2.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 145.9, 144.54, 141.4, 133.0, 130.0, 129.5, 127.7, 122.9, 121.1, 118.3, 117.1, 115.9, 42.9, 39.7. HRMS $[M-H]^+$ calculated for $C_{18}H_{17}C_{l2}N_2O_3$: 379.0616; found: 379.0609. HPLC-UV: 95.5%.

Methyl (*E*)-4-(5-methyl-1H-indole-3-carboxamido)but-2-enoate (21)



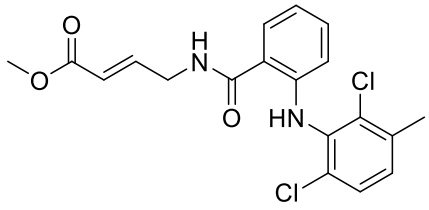
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.74 (d, J = 9.5 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.5 Hz, 1H), 7.05 (dt, J = 15.5 Hz, J = 5.0 Hz, 1H), 6.21 (s, 1H), 6.03 (dd, J = 15.5 Hz, J = 2.0 Hz, 1H), 4.30 (m, 2H), 3.72 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 165.5, 145.1, 134.7, 131.4, 128.3, 124.9, 124.8, 121.4, 119.7, 111.7, 111.4, 51.8, 40.3, 21.7. HRMS $[M-H]^+$ calculated for $C_{15}H_{17}N_2O_3$: 273.1239; found: 273.1245. HPLC-UV: 99.9%.

Methyl (*E*)-4-(quinoxaline-5-carboxamido)but-2-enoate (22)



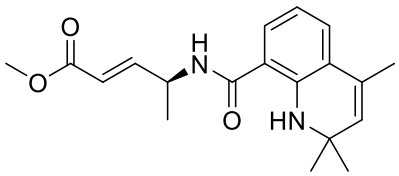
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.99 (d, J = 1.5 Hz, 1H), 8.91 (dd, J = 7.5 Hz, J = 1.5 Hz, 1H), 8.88 (d, J = 1.5 Hz, 1H), 8.30 (dd, J = 8.5 Hz, J = 1.5 Hz, 1H), 7.93 (t, J = 8.0 Hz, 1H), 7.12 (dt, J = 15.5 Hz, J = 4.75 Hz, 1H), 6.07 (dt, J = 16.0 Hz, J = 1.75 Hz, 1H), 4.44-4.41 (m, 2H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 164.9, 145.0, 144.0, 143.0, 143.2, 140.8, 134.6, 134.1, 130.4, 128.7, 121.3, 51.8, 40.3. HRMS $[M-H]^+$ calculated for $C_{14}H_{14}N_3O_3$: 272.1035; found: 272.1044. HPLC-UV: 99.8%.

Methyl (*E*)-4-(2-((2,6-dichloro-3-methylphenyl)amino)benzamido)but-2-enoate (23)



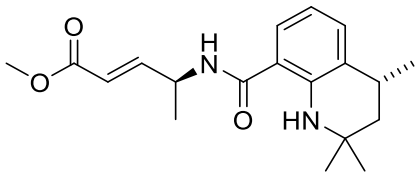
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.49 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 7.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.02 (dt, J = 15.5 Hz, J = 5.0 Hz, 1H), 6.77 (t, J = 7.0 Hz, 1H), 6.54 (s, 1H), 6.38 (d, J = 8.0 Hz, 1H), 6.03 (dt, J = 15.5 Hz, J = 1.5 Hz, 1H), 4.25 (m, 2H), 3.73 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 166.8, 145.9, 144.4, 136.0, 135.2, 133.8, 132.0, 130.7, 127.0, 127.3, 127.4, 121.9, 118.0, 116.7, 115.0, 51.8, 40.4, 20.7. HRMS $[M-H]^+$ calculated for $C_{19}H_{19}Cl_2N_2O_3$: 393.0773; found: 393.0773. HPLC-UV: 97.0%.

Methyl (*S*,*E*)-4-(2,2,4-trimethyl-1,2-dihydroquinoline-8-carboxamido)pent-2-enoate (24)



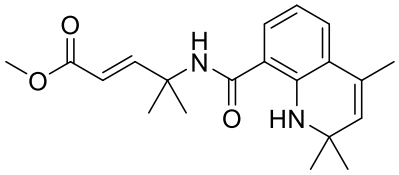
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.0 Hz, 1H), 6.98 (dd, J = 15.5 Hz, J = 5.0 Hz, 1H), 6.46 (t, J = 7.5 Hz, 1H), 5.97 (s, 1H), 5.96 (dd, J = 15.5 Hz, J = 1.5 Hz, 1H), 5.35 (s, 1H), 4.87 (m, 1H), 3.73 (s, 3H), 1.96 (s, 3H), 1.38 (d, J = 7.0 Hz, 3H), 1.32 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 166.8, 149.3, 146.2, 129.1, 127.5, 126.9, 126.2, 122.8, 120.2, 114.0, 111.7, 51.8, 51.7, 45.7, 32.2, 32.1, 20.2, 19.2. HRMS $[M-H]^+$ calculated for $C_{19}H_{25}N_2O_3$: 329.1865; found: 329.1861. HPLC-UV: 95.3%.

Methyl (*S*,*E*)-4-(2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-8-carboxamido)pent-2-enoate (25)



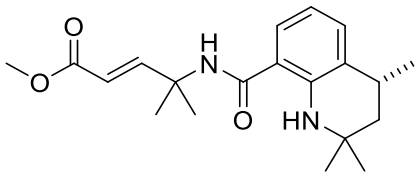
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.18 (dd, J = 7.5 Hz, J = 4.5 Hz, 1H), 6.97 (dd, J = 16.0 Hz, J = 4.5 Hz, 1H), 6.50 (m, 1H), 5.95 (m, 2H), 4.86 (m, 2H), 3.73 (s, 3H), 2.91 (m, 1H), 1.72 (dd, J = 12.5 Hz, J = 4.5 Hz, 1H), 1.37 (m, 4H), 1.33 (dd, J = 7.0 Hz, J = 1.5 Hz, 3H), 1.28 (d, J = 4.0 Hz, 3H), 1.21 (d, J = 4.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 166.8, 149.3, 146.3, 130.0, 127.3, 125.1, 120.1, 113.6, 112.3, 51.81, 49.0, 45.7, 43.4, 31.6, 29.1, 27.8, 20.3, 20.1. HRMS $[M-H]^+$ calculated for $C_{19}H_{27}N_2O_3$: 331.2022; found: 331.2016. HPLC-UV: 99.1%.

Methyl (*E*)-4-methyl-4-(2,2,4-trimethyl-1,2-dihydroquinoline-8-carboxamido)pent-2-enoate (26)



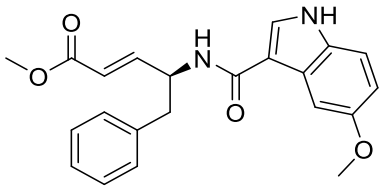
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.15 (d, J = 15.5 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 7.0 Hz, 1H), 6.45 (t, J = 7.5 Hz, 1H), 5.99 (s, 1H), 5.90 (d, J = 16.0 Hz, 1H), 5.33 (s, 1H), 3.73 (s, 3H), 1.96 (s, 3H), 1.54 (s, 6H), 1.30 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 167.2, 153.8, 145.9, 129.2, 127.5, 126.7, 126.3, 122.8, 118.3, 114.0, 112.8, 53.9, 51.7, 51.7, 32.1, 27.6, 19.2. HRMS $[M-H]^+$ calculated for $C_{20}H_{27}N_2O_3$: 343.2022; found: 343.2026. HPLC-UV: 99.8%.

Methyl-(*E*)-4-methyl-4-(2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-8-carboxamido)pent-2-enoate (27)



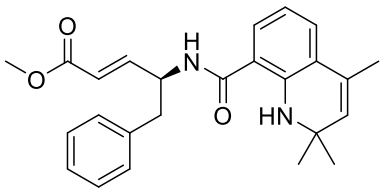
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 16.5 Hz, 1H), 6.49 (t, J = 7.75 Hz, 1H), 5.99 (s, 1H), 5.91 (d, J = 16.0 Hz, 1H), 3.72 (s, 3H), 2.94-2.86 (m, 1H), 1.72 (dd, J = 12.5 Hz, J = 4.5 Hz, 1H), 1.54 (s, 3H), 1.53 (s, 3H), 1.38 (t, J = 12.75 Hz, 1H), 1.33 (d, J = 6.5 Hz, 3H), 1.27 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 167.2, 153.8, 146.0, 129.8, 127.3, 125.3, 118.3, 113.8, 113.6, 53.9, 51.7, 49.0, 43.6, 31.6, 28.9, 27.8, 27.7, 27.5, 20.4. HRMS $[M-H]^+$ calculated for $C_{20}H_{29}N_2O_3$: 345.2178; found: 345.2175. HPLC-UV: 97.1%.

Methyl (*S*,*E*)-4-(5-methoxy-1H-indole-3-carboxamido)-5-phenylpent-2-enoate (28)



^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.52 (d, J = 2.5 Hz, 1H), 7.38 (s, 1H), 7.28 (t, J = 7.0 Hz, 1H), 7.22 (t, J = 7.5 Hz, 3H), 7.05 (dd, J = 15.5 Hz, J = 5.0 Hz, 1H), 6.85 (dd, J = 9.0 Hz, 1H), 6.08 (d, J = 8.0 Hz, 1H), 5.93 (d, J = 15.5 Hz, 1H), 5.20 (m, 1H), 3.78 (s, 3H), 3.05 (d, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 165.3, 155.6, 148.2, 136.4, 131.3, 129.4, 128.8, 127.8, 127.1, 125.8, 121.0, 113.5, 112.8, 111.1, 102.0, 55.9, 51.8, 50.8, 40.4. HRMS $[M]^-$ calculated for $C_{21}H_{19}ClN_2O_3$: 379.1658; found: 379.1656. HPLC-UV: 99.9%.

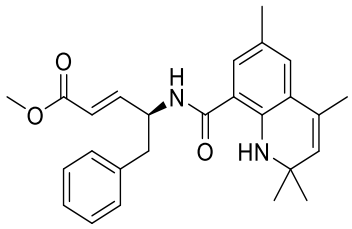
Methyl (*S*,*E*)-5-phenyl-4-(2,2,4-trimethyl-1,2-dihydroquinoline-8-carboxamido)pent-2-enoate (29)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.32 (t, J = 7.0 Hz, 2H), 7.26 (t, J = 3.75 Hz, 1H), 7.21 (d, J = 7.0 Hz, 2H), 7.08 (d, J = 7.0 Hz, 1H), 7.02 (dd, J = 15.5 Hz, J = 5.0 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H), 6.42 (t, J = 8.0 Hz, 1H), 5.95 (d, J = 8.0 Hz, 1H), 5.89 (dd, J = 15.5 Hz, J = 1.5 Hz, 1H), 5.34 (s, 1H), 5.09 (m, 1H), 3.72 (s, 3H), 3.07-2.98 (m, 2H), 1.95 (d, J = 1.5 Hz, 3H), 1.30 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 166.6, 147.6, 146.0, 136.2, 129.4, 129.1, 128.8, 127.5, 127.2, 126.9,

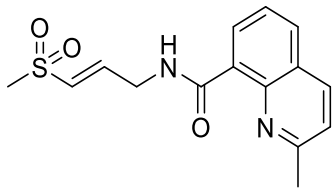
126.0, 122.8, 121.1, 114.1, 111.8, 51.8, 51.7, 50.7, 40.5, 32.1, 29.8, 19.1. HRMS $[M]^-$ calculated for $C_{25}H_{28}N_2O_3$: 403.2022; found: 403.2022. HPLC-UV: 95.0%.

Methyl-(*S*,*E*)-5-phenyl-4-(2,2,4,6-tetramethyl-1,2-dihydroquinoline-8-carboxamido)pent-2-enoate (30)



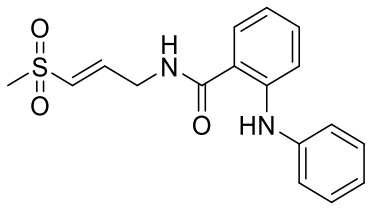
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 7.5 Hz, 2H), 7.26 (t, J = 7.25 Hz, 1H), 7.21 (d, J = 7.0 Hz, 2H), 7.02 (dd, J = 15.5 Hz, J = 5.0 Hz, 1H), 6.92 (s, 1H), 6.77 (s, 1H), 5.93 (d, J = 8.0 Hz, 1H), 5.89 (dd, J = 15.5 Hz, J = 1.5 Hz, 1H), 5.35 (s, 1H), 5.09 (m, 1H), 3.72 (s, 3H), 3.07-2.99 (m, 2H), 2.18 (s, 3H), 1.95 (d, J = 0.5 Hz, 3H), 1.28 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 166.6, 147.6, 136.2, 129.6, 129.5, 128.8, 128.1, 127.6, 127.2, 126.0, 121.1, 51.8, 50.8, 40.5, 32.2, 31.6, 29.8, 20.7, 19.2. HRMS $[M]^-$ calculated for $C_{26}H_{30}N_2O_3$: 417.2178; found: 417.2181. HPLC-UV: 96.8%.

(*E*)-2-methyl-*N*-(3-(methylsulfonyl)allyl)quinoline-8-carboxamide (31)



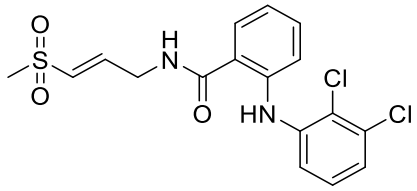
^{1}H NMR (500 MHz, $CDCl_3$) δ 11.95 (s, 1H), 8.81 (d, J = 7.0 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.15 (dt, J = 15.5 Hz, J = 4.0 Hz, 1H), 6.68 (dt, J = 15.5 Hz, J = 1.5 Hz, 1H), 4.52 (m, 2H), 2.94 (s, 3H), 2.80 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 159.0, 145.5, 140.1, 138.2, 134.1, 132.3, 129.6, 126.9, 125.8, 122.1, 43.0, 39.9, 25.7. HRMS $[M\text{-}H]^+$ calculated for $C_{15}H_{17}N_2O_3S$: 305.0960; found: 305.0960. HPLC-UV: 95.0%.

(*E*)-*N*-(3-(methylsulfonyl)allyl)-2-(phenylamino)benzamide (32)



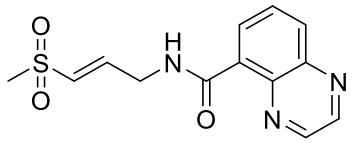
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.36 (m, 2H), 7.32 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 7.05 (dd, J = 8.0 Hz, J = 1.0 Hz, 1H), 6.97 (dt, J = 15.5 Hz, J = 5.0 Hz, 1H), 6.91 (m, 1H), 6.49 (s, 1H), 5.98 (d, J = 16.0 Hz, 1H). 4.23 (m, 2H), 3.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 166.4, 143.9, 143.4, 140.7, 133.8, 132.5, 127.8, 127.1, 123.3, 122.9, 121.8, 120.1, 117.3, 116.4, 51.8, 40.5. HRMS $[M-H]^+$ calculated for $C_{17}H_{19}N_2O_3S$: 331.1116; found: 331.1123. HPLC-UV: 95.6%.

(*E*)-2-((2,3-dichlorophenyl)amino)-*N*-(3-(methylsulfonyl)allyl)benzamide (33)



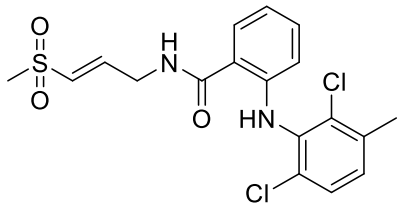
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 3.5 Hz, 2H), 7.32 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 7.10 (t, J = 8.0 Hz, 1H), 7.07 (dt, J = 8.0 Hz, J = 1.5 Hz, 1H), 6.98 (dt, J = 15.0 Hz, J = 4.0 Hz, 1H), 6.94 (m, 1H), 6.75 (t, J = 5.5 Hz, 1H), 6.51 (dt, J = 15.5 Hz, J = 1.5 Hz, 1H), 4.31 (m, 2H), 2.92 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 144.4, 143.5, 140.6, 133.9, 132.8, 130.0, 127.9, 127.2, 123.2, 123.0, 120.3, 119.7, 117.5, 116.4, 42.9, 39.7. HRMS $[M-H]^+$ calculated for $C_{17}H_{17}Cl_2N_2O_3S$: 399.0337; found: 399.0336. HPLC-UV: 99.9%.

(*E*)-*N*-(3-(methylsulfonyl)allyl)quinoxaline-5-carboxamide (34)



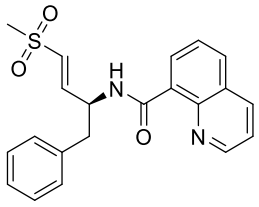
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.80 (s, 1H), 9.00 (d, J = 1.5 Hz, 1H), 8.89 (d, J = 2.0 Hz, 1H), 8.87 (dd, J = 7.0 Hz, J = 1.5 Hz, 1H), 8.32 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 7.94 (t, J = 8.0 Hz, 1H), 7.10 (dt, J = 15.0 Hz, J = 4.5 Hz, 1H), 6.59 (dt, J = 15.0 Hz, J = 2.0 Hz, 1H), 4.49 (m, 2H), 2.93 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 145.1, 144.9, 143.6, 143.3, 140.2, 134.7, 134.2, 130.2, 129.8, 128.4, 42.9, 39.9. HRMS $[M-H]^+$ calculated for $C_{13}H_{14}N_3O_3S$: 292.0756; found: 292.0755. HPLC-UV: 99.9%.

(*E*)-2-((2,6-dichloro-3-methylphenyl)amino)-*N*-(3-(methylsulfonyl)allyl)benzamide (35)



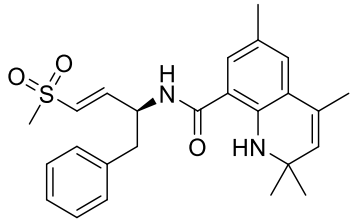
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.25 (t, J = 8.5 Hz, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.01 (dt, J = 15.5 Hz, J = 4.5 Hz, 1H), 6.81 (t, J = 7.5 Hz, 1H), 6.71 (t, J = 5.5 Hz, 1H), 6.57 (d, J = 15.0 Hz, 1H), 6.39 (d, J = 8.5 Hz, 1H), 4.33 (s, 2H), 2.94 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 145.8, 144.7, 136.5, 135.5, 133.4, 132.7, 130.3, 129.8, 128.0, 127.8, 127.5, 118.1, 116.2, 115.0, 42.9, 39.7, 20.7. HRMS $[M-H]^+$ calculated for $C_{18}H_{19}Cl_2N_2O_3S$: 413.0493; found: 413.0500. HPLC-UV: 99.2%.

(*S*,*E*)-*N*-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)quinoline-8-carboxamide (36)



^{1}H NMR (500 MHz, $CDCl_3$) δ 11.73 (d, J = 8.0 Hz, 1H), 8.80 (m, 2H), 8.30 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H), 7.99 (dd, J = 8.0 Hz, J = 1.0 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.51 (dd, J = 8.0 Hz, J = 4.0 Hz, 1H), 7.31 (m, 3H), 7.26 (m, 1H), 7.12 (dd, J = 15.0 Hz, J = 4.5 Hz, 1H), 6.46 (dd, J = 15.0 Hz, J = 1.5 Hz, 1H), 5.43 (m, 1H), 3.22-3.13 (m, 2H), 2.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 149.4, 148.0, 145.6, 138.0, 136.3, 134.2, 132.5, 129.8, 127.7, 128.6, 128.6, 127.2, 126.7, 121.2, 51.5, 43.0, 40.4. HRMS $[M-Cl]^-$ calculated for $C_{21}H_{20}ClN_2O_3S$: 415.0883; found: 415.0879. HPLC-UV: 99.1%.

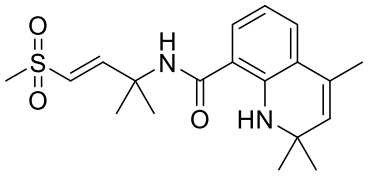
(*S*,*E*)-2,2,4,6-tetramethyl-*N*-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)-1,2-dihydroquinoline-8-carboxamide (37)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.34 (t, J= 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 7.0 Hz, 2H), 6.99 (dd, J = 15.5 Hz, J = 5.0 Hz, 1H), 6.94 (s, 1H), 6.80 (s, 1H), 6.40 (dd, J = 15.5 Hz, J = 1.5 Hz, 1H), 6.06 (d, J = 8.0 Hz, 1H), 5.36 (s, 1H), 5.14 (m,1H), 3.05 (d, J = 6.0 Hz, 2H), 2.88 (s, 3H), 2.19 (s, 3H), 1.95 (d, J = 1.0 Hz, 3H), 1.28 (s, 6H). ^{13}C NMR

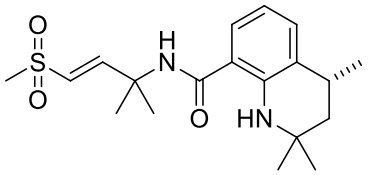
(125 MHz, $CDCl_3$) δ 168.9, 147.2, 135.6, 129.9, 129.5, 129.4, 129.0, 128.3, 127.5, 125.9, 123.1, 111.2, 51.6, 50.3, 42.9, 40.2, 31.8, 20.7, 19.2. HRMS [M-Cl]$^-$ calculated for $C_{25}H_{30}ClN_2O_3S$: 473.1666; found: 473.1668. HPLC-UV: 98.4%.

(*E*)-2,2,4-trimethyl-*N*-(2-methyl-4-(methylsulfonyl)but-3-en-2-yl)-1,2-dihydroquinoline-8-carboxamide (38)



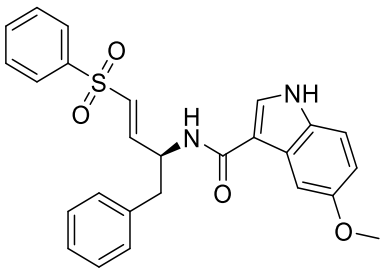
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.05 (d, J = 15.5 Hz, 1H), 6.47 (t, J = 7.5 Hz, 1H), 6.42 (d, J = 15.5 Hz, 1H), 6.04 (s, 1H), 5.34 (s, 1H), 2.97 (s, 3H), 1.96 (s, 3H), 1.56 (s, 6H), 1.30 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 152.8, 146.0, 129.1, 127.5, 127.3, 127.0, 126.3, 122.8, 114.1, 112.1, 53.6, 51.7, 43.1, 32.2, 27.4, 19.1. HRMS [M-H]$^+$ calculated for $C_{19}H_{27}N_2O_3S$: 363.1742; found: 363.1742. HPLC-UV: 96.7%.

(*E*)-2,2,4-trimethyl-*N*-(2-methyl-4-(methylsulfonyl)but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (39)



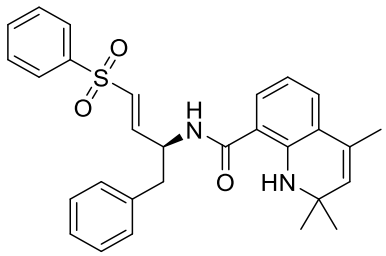
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.24 (d, J = 7.0 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.04 (d, J = 15.5 Hz, 1H), 6.51 (t, J = 7.5 Hz, 1H), 6.43 (d, J = 15.0 Hz, 1H), 6.03 (s, 1H), 2.98 (s, 3H), 2.90 (m, 1H), 1.73 (dd, J = 12.5 Hz, J = 5.0 Hz, 1H), 1.56 (s, 3H), 1.55 (s, 3H), 1.40 (m, 2H), 1.33 (d, J = 7.0 Hz, 3H), 1.27 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 152.8, 146.1, 130.1, 127.4, 127.4, 125.2, 113.8, 113.2, 53.6, 49.0, 43.4, 43.2, 31.6, 29.0, 27.8, 27.5, 27.3, 20.3. HRMS [M-H]$^+$ calculated for $C_{19}H_{29}N_2O_3S$: 365.1899; found: 365.1897. HPLC-UV: 99.9%.

(*S,E*)-5-methoxy-*N*-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)-1H-indole-3-carboxamide (40)



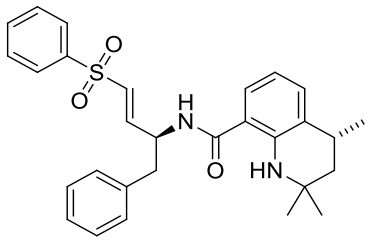
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.78 (d, J = 7.5 Hz, 2H), 7.59 (m, 2H), 7.48 (t, J = 8.0 Hz, 2H), 7.38 (d, J = 2.0 Hz, 1H), 7.27-7.21 (m, 4H), 7.17 (m, 2H), 7.09 (dd, J = 15.0 Hz, J = 5.0 Hz, 1H), 6.87 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H), 6.40 (dd, J = 15.0, J = 2.0 Hz, 1H), 6.07 (d, J = 8.0 Hz, 1H), 5.28 (m, 1H), 3.77 (s,3H), 3.12-3.02 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 155.5, 146.3, 139.7, 135.8, 133.5, 131.1, 130.7, 129.3, 129.3, .128.7, 127.6, 127.5, 127.1, 125.6, 113.6, 112.6, 110.8, 101.9, 55.7, 50.1, 40.1, 29.7. HRMS $[M]^-$ calculated for $C_{26}H_{24}N_2O_4S$: 459.1378; found: 459.1380. HPLC-UV: 96.9%.

(*S*,*E*)-2,2,4-trimethyl-*N*-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)-1,2-dihydroquinoline-8-carboxamide (41)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.24 (m, 1H), 7.17 (m, 2H), 7.07 (m, 2H), 6.98 (d, J = 7.5 Hz, 1H), 6.41 (t, J = 8.0 Hz, 1H), 6.33 (dd, J = 15.0 Hz, J = 2.0 Hz, 1H), 6.01 (d, J = 8.0 Hz, 1H), 5.32 (s, 1H), 5.14 (m, 1H), 3.02-3.00 (m, 2H), 1.94 (d, J = 1.0 Hz, 3H), 1.28 (s, 3H), 1.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 146.2, 145.7, 140.0, 135.6, 133.6, 130.9, 129.4, 129.4, 129.1, 129.0, 127.8, 127.5, 127.4, 127.1, 126.0, 122.8, 114.0, 111.2, 51.7, 50.2, 40.2, 32.2, 32.1, 29.8, 19.1. HRMS $[M]^-$ calculated for $C_{29}H_{30}N_2O_3S$: 485.1899; found: 485.1895. HPLC-UV: 95.8%.

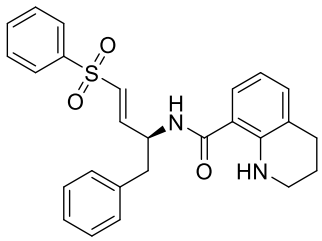
(*S*,*E*)-2,2,4-trimethyl-*N*-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (42)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 2H),7.63-7.59 (m, 2H), 7.53-7.49 (m, 2H), 7.30-7.26 (m, 2H), 7.25-7.20 (m, 2H), 7.16 (t, J = 7.0 Hz, 2H), 7.06-02 (m, 1H), 6.99 (dd, J = 13.0 Hz, J = 8.0 Hz, 1H), 6.44 (td, J = 7.5 Hz, J = 2.5 Hz, 1H), 6.33 (dt, J = 15.5 Hz, J = 2.0 Hz, 1H), 5.96 (t, J = 9.0 Hz, 1H), 5.14 (m, 1H), 3.05-3.01 (m, 2H), 2.91-2.83 (m, 1H), 1.70 (dt, J = 12.5 Hz, J = 4.5 Hz, 1H), 1.36 (m, 1H), 1.32 (q, J = 10.5 Hz, 3H), 1.25 (s, 3H), 1.17 (d, J = 12.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 146.3, 145.8, 140.1, 135.6, 133.5, 130.8, 130.1, 129.4, 129.4, 128.9, 127.8, 127.4, 125.0, 113.6, 111.7,

50.2, 49.0, 43.3, 40.2, 31.6, 29.8, 29.0, 27.7, 20.2. HRMS $[M]^-$ calculated for $C_{29}H_{32}N_2O_3S$: 487.2055; found: 487.2058. HPLC-UV: 99.9%.

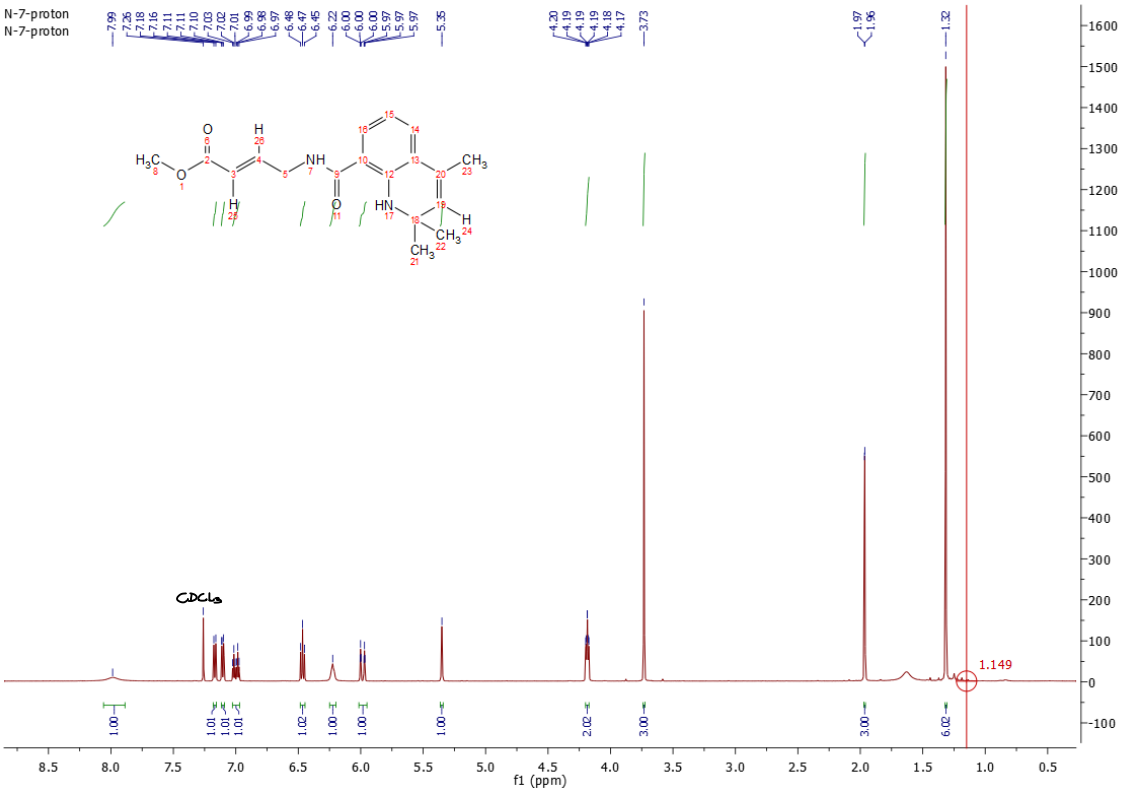
(*S*,*E*)-*N*-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (43)

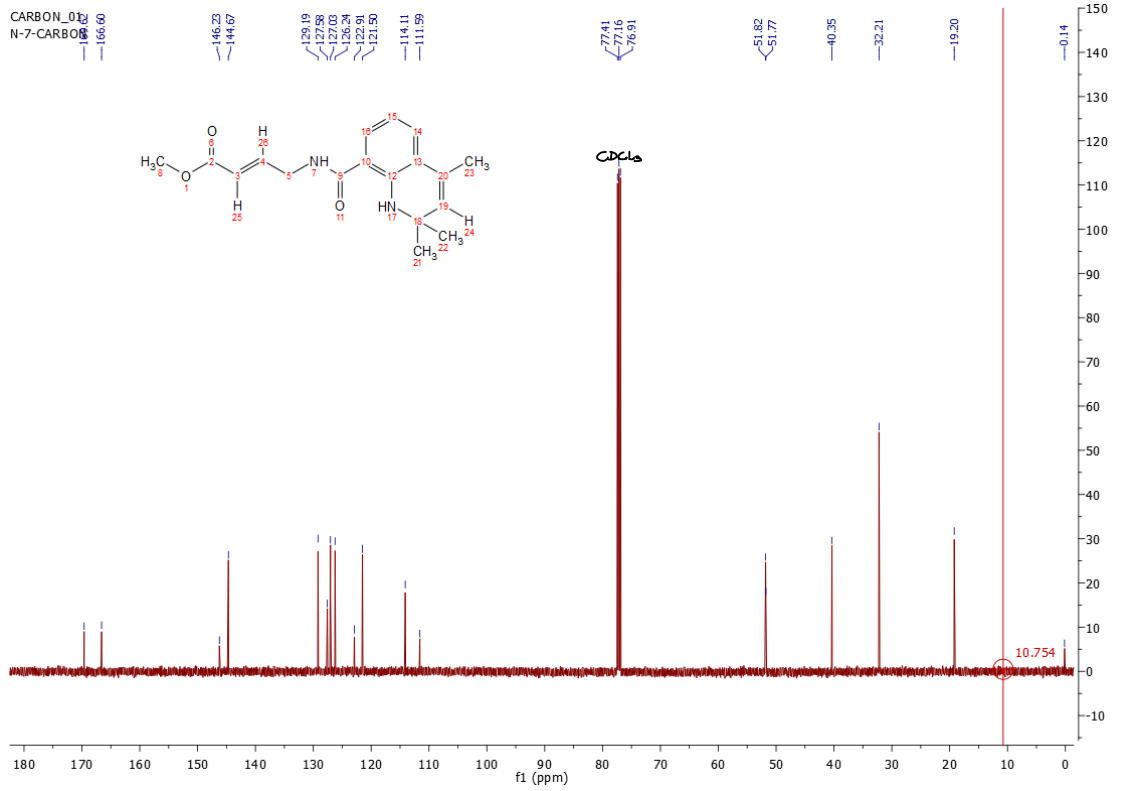


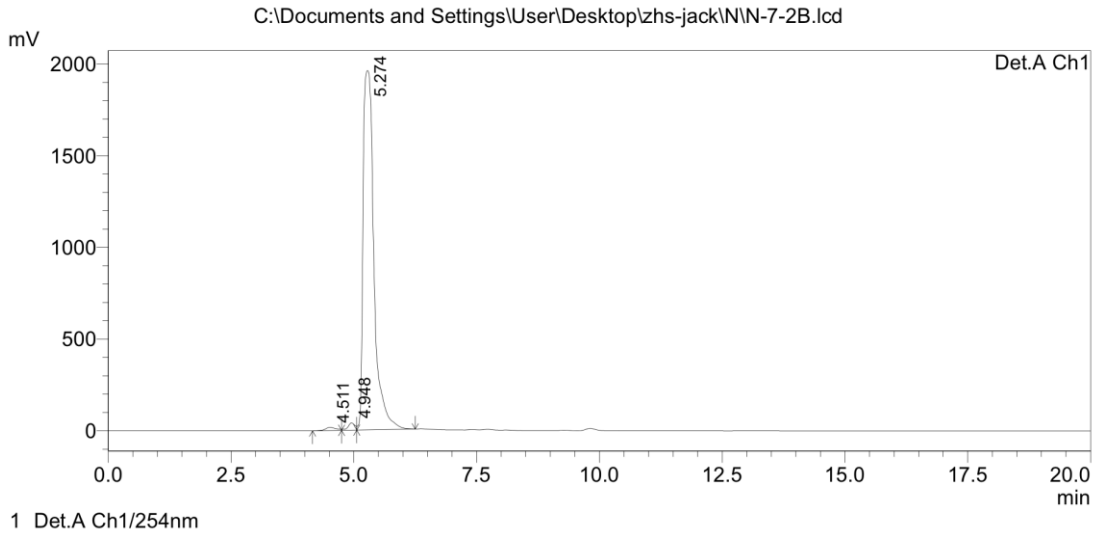
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 2H), 7.46 (s, 1H), 7.29 (t, J = 7.5, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 6.5 Hz, 2H), 7.04 (dd, J = 15.0 Hz, J = 5.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 2H), 6.38 (t, J = 8.0 Hz, 1H), 6.34 (dd, J = 15.0 Hz, J = 1.5 Hz, 1H), 6.02 (d, J = 8.0 Hz, 1H), 5.14 (m, 1H), 3.35-3.28 (m, 2H), 3.02 (d, J = 7.0 Hz, 2H), 2.73 (t, J = 6.5 Hz, 2H), 1.86 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 146.9, 145.7, 139.9, 135.6, 133.4, 132.6, 130.7, 129.3, 129.2, 128.8, 127.6, 127.2, 124.9, 122.8, 113.7, 112.1, 50.1, 41.0, 40.1, 27.8, 20.6. HRMS $[M]^-$ calculated for $C_{26}H_{26}N_2O_3S$: 445.1586; found: 445.1578. HPLC-UV: 95.0%.

5. ^{1}H, ^{13}C NMR and HPLC-UV Data

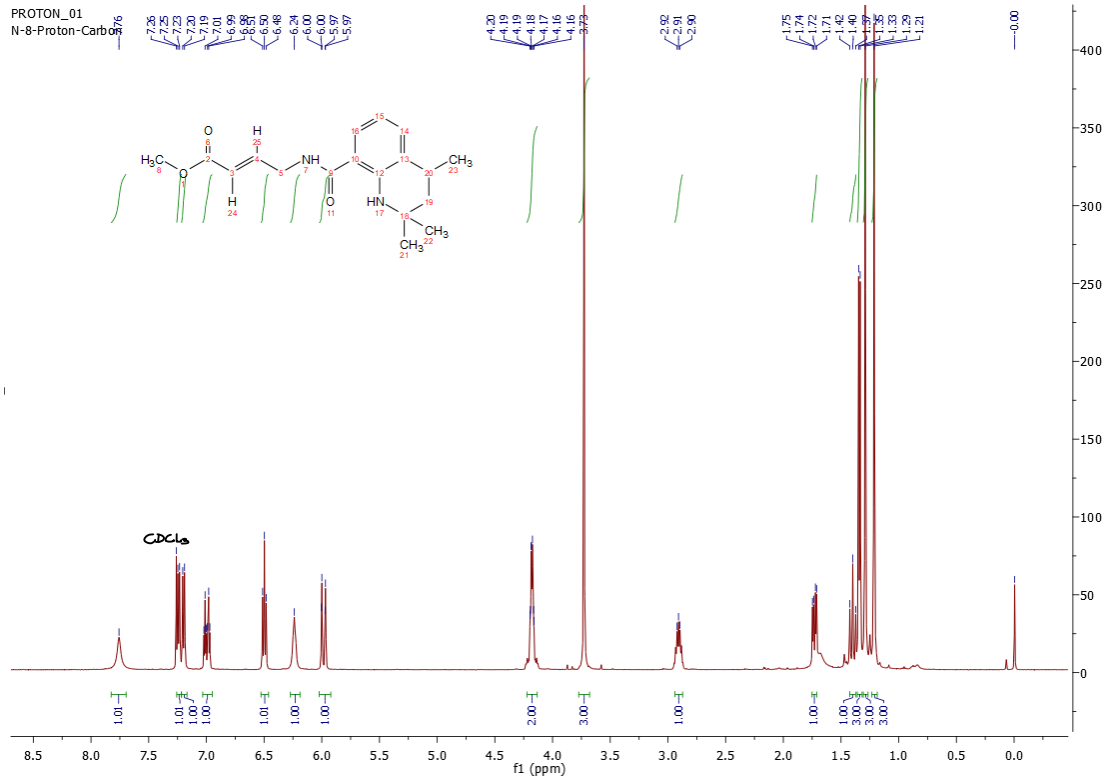
Methyl (*E*)-4-(2,2,4-trimethyl-1,2-dihydroquinoline-8-carboxamido)but-2-enoate (1)

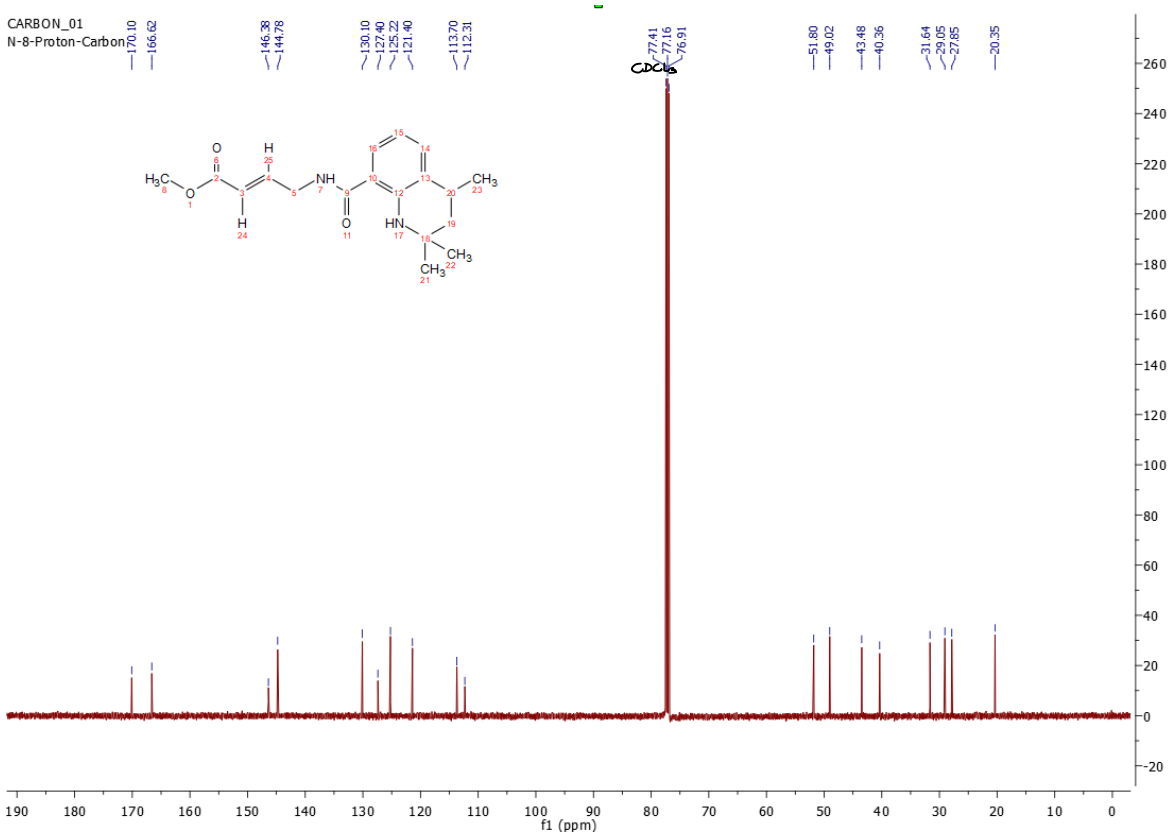

N-7-proton
N-7-proton
CDCl3
1.149
f1 (ppm)

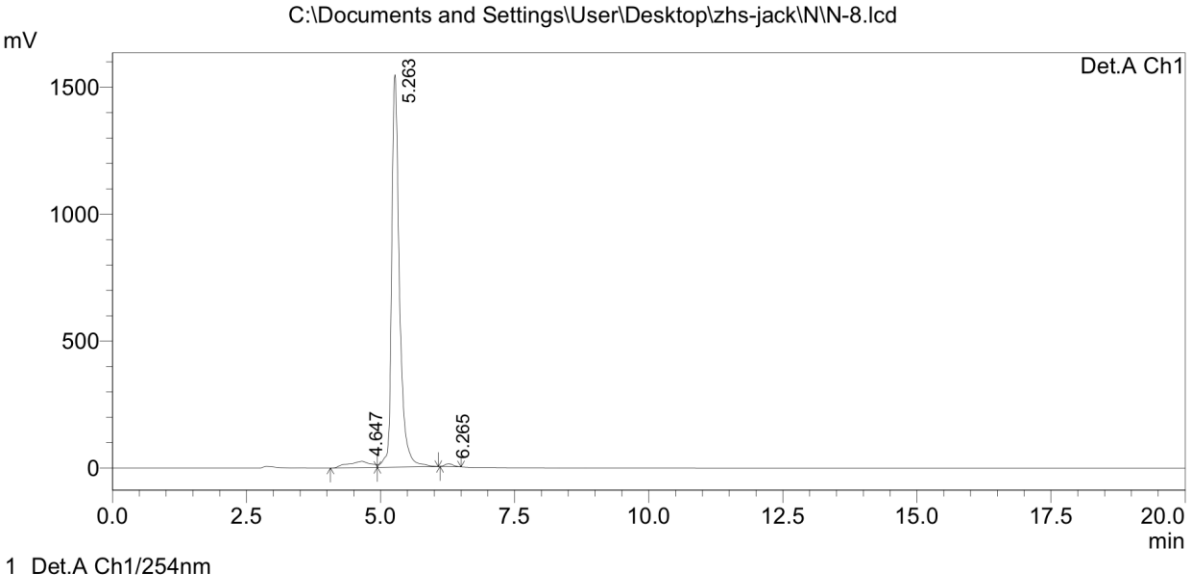

CARBON_01
N-7-CARBON
CDCl3
10.754
f1 (ppm)



Methyl (*E*)-4-(2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-8-carboxamido)but-2-enoate (2)

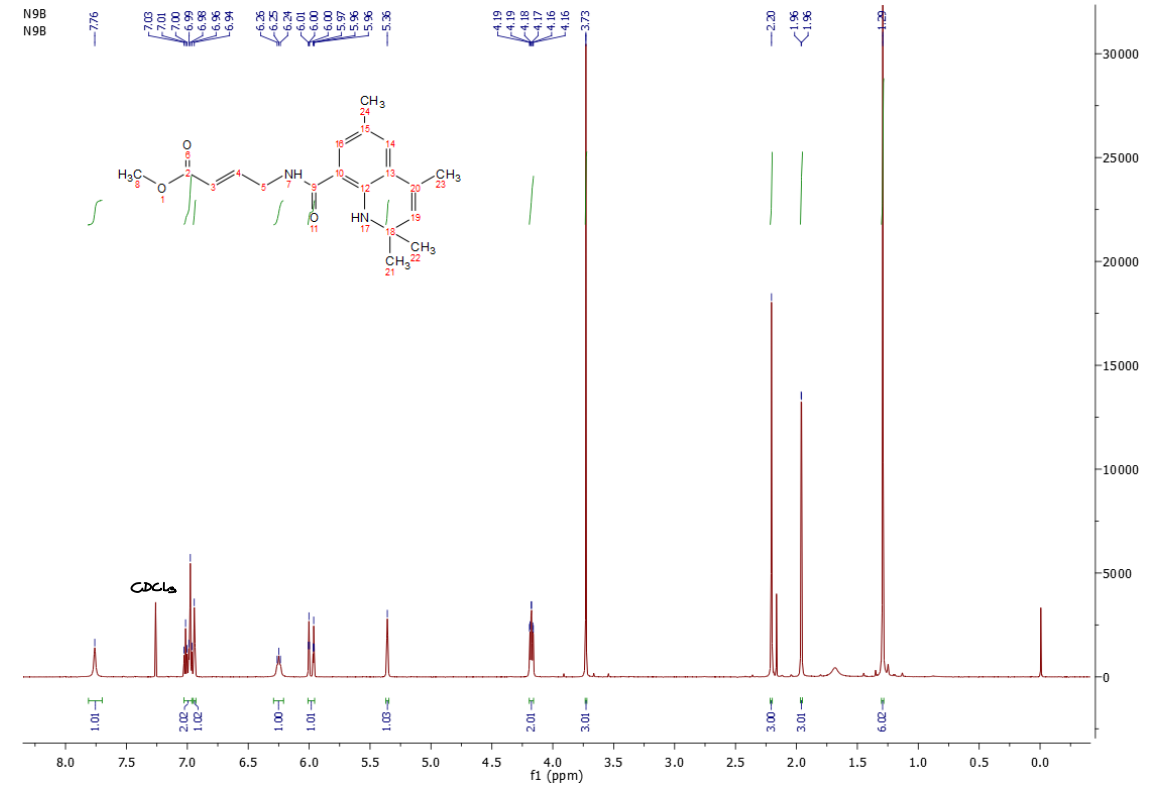


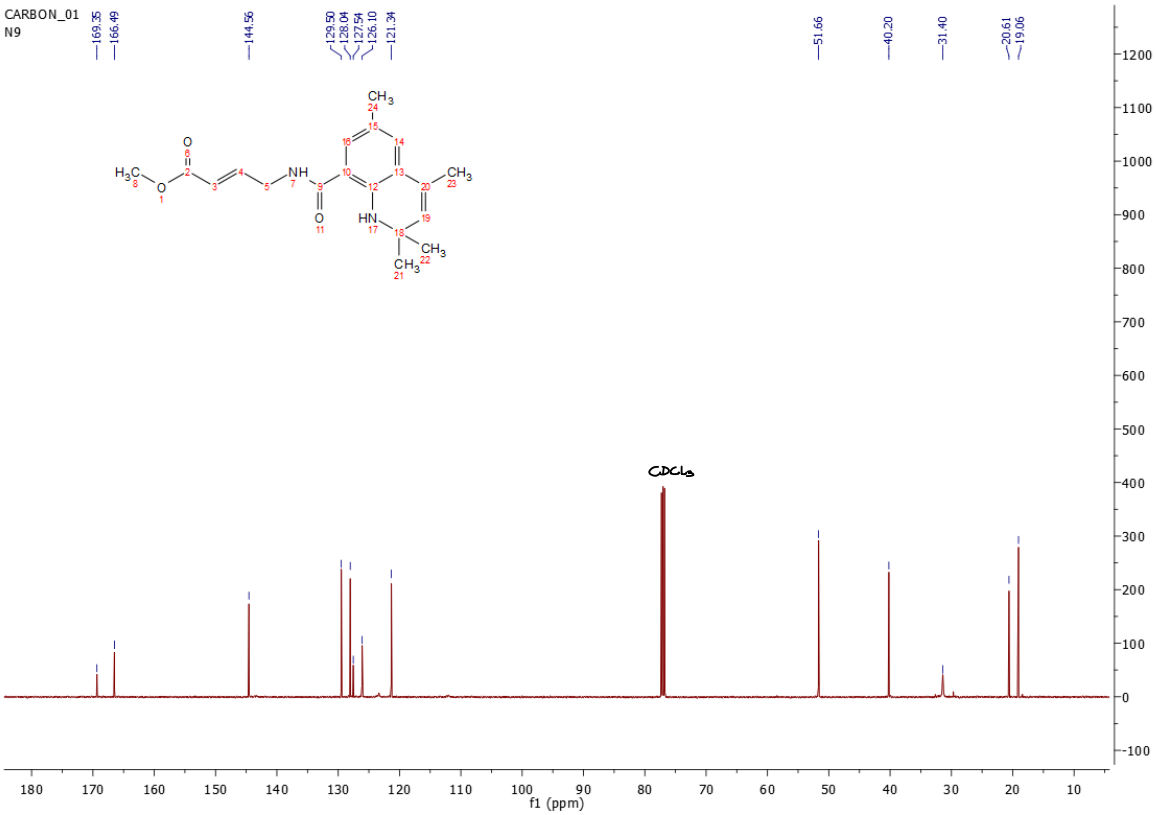


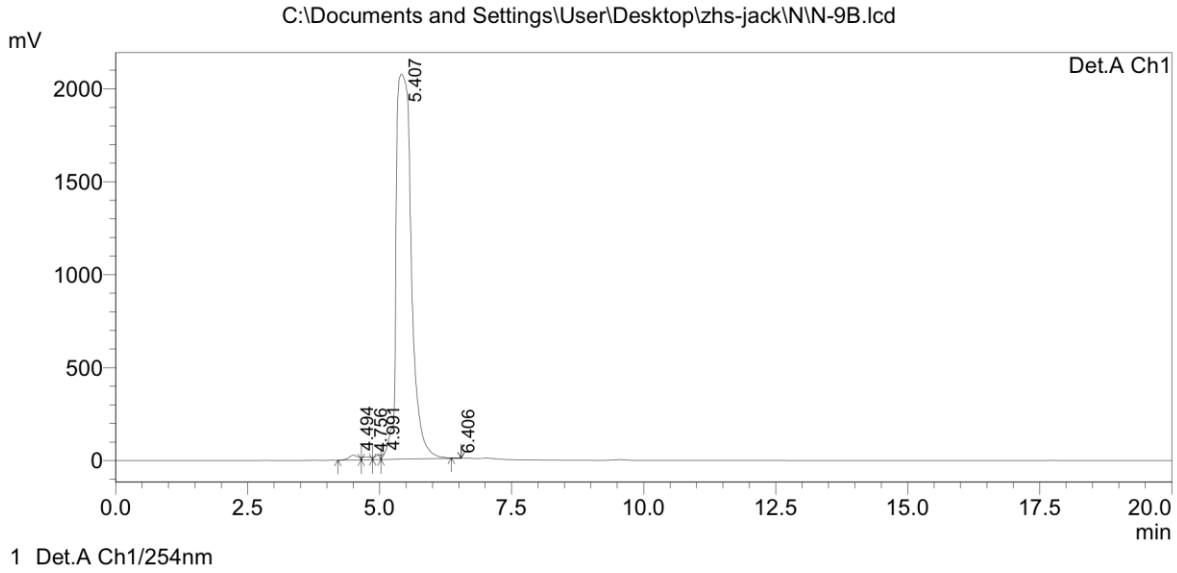


1 Det.A Ch1/254nm

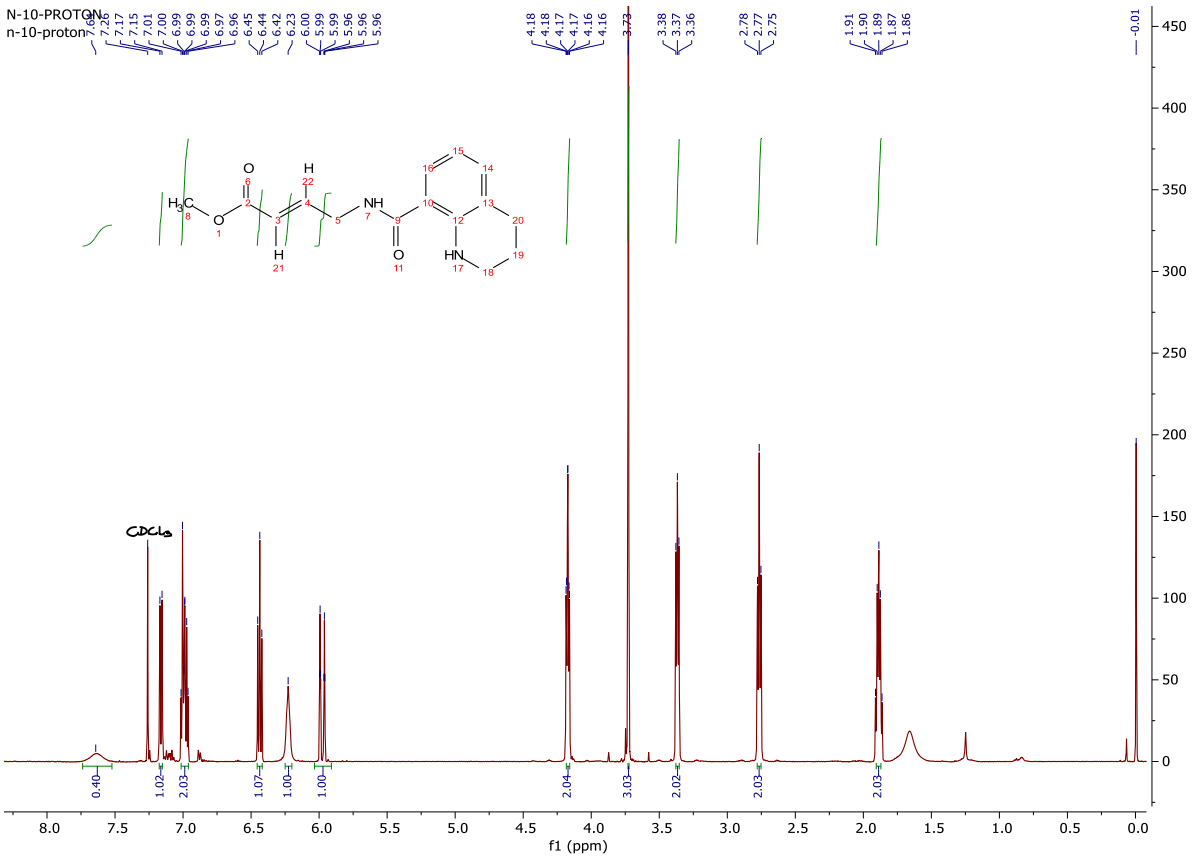
Methyl (*E*)-4-(2,2,4,6-tetramethyl-1,2-dihydroquinoline-8-carboxamido)but-2-enoate (3)

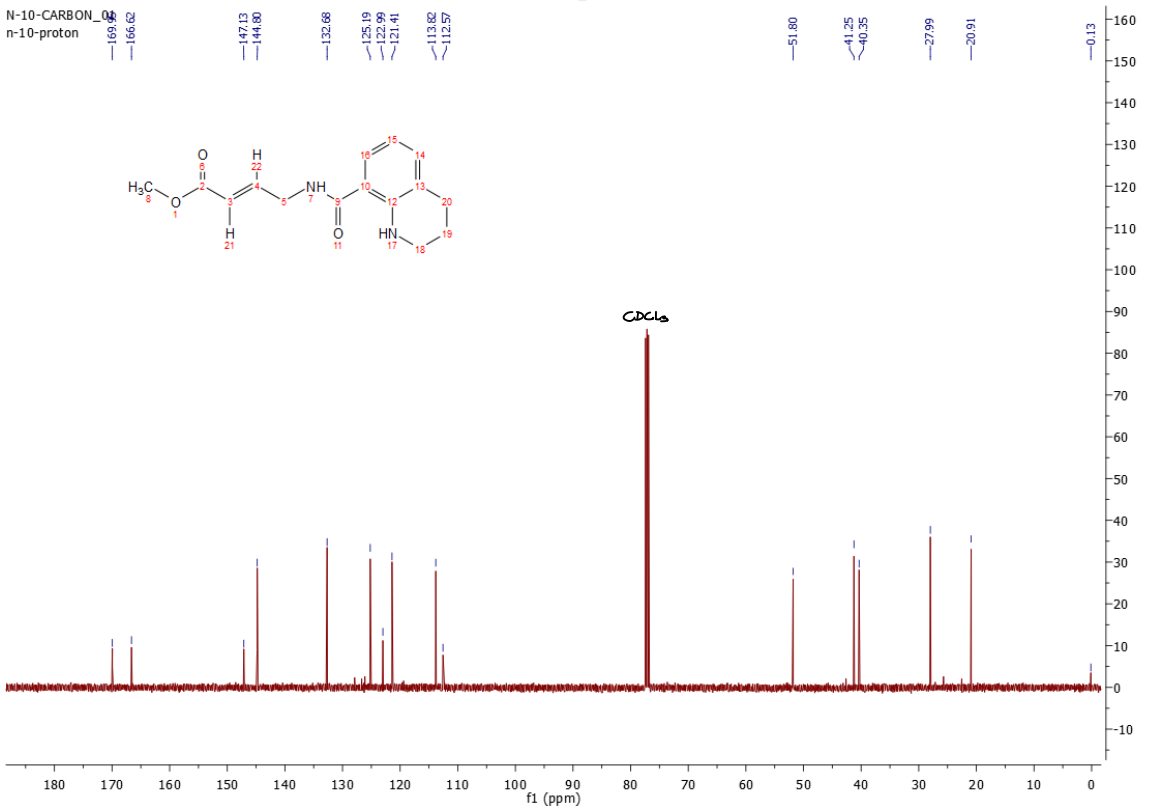


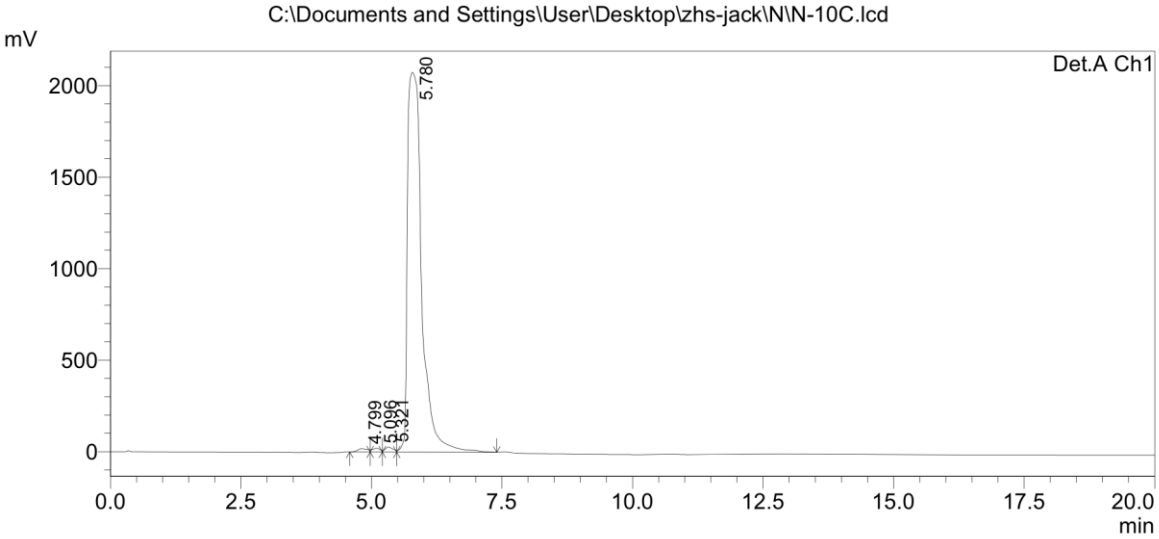




Methyl (*E*)-4-(1,2,3,4-tetrahydroquinoline-8-carboxamido)but-2-enoate (4)

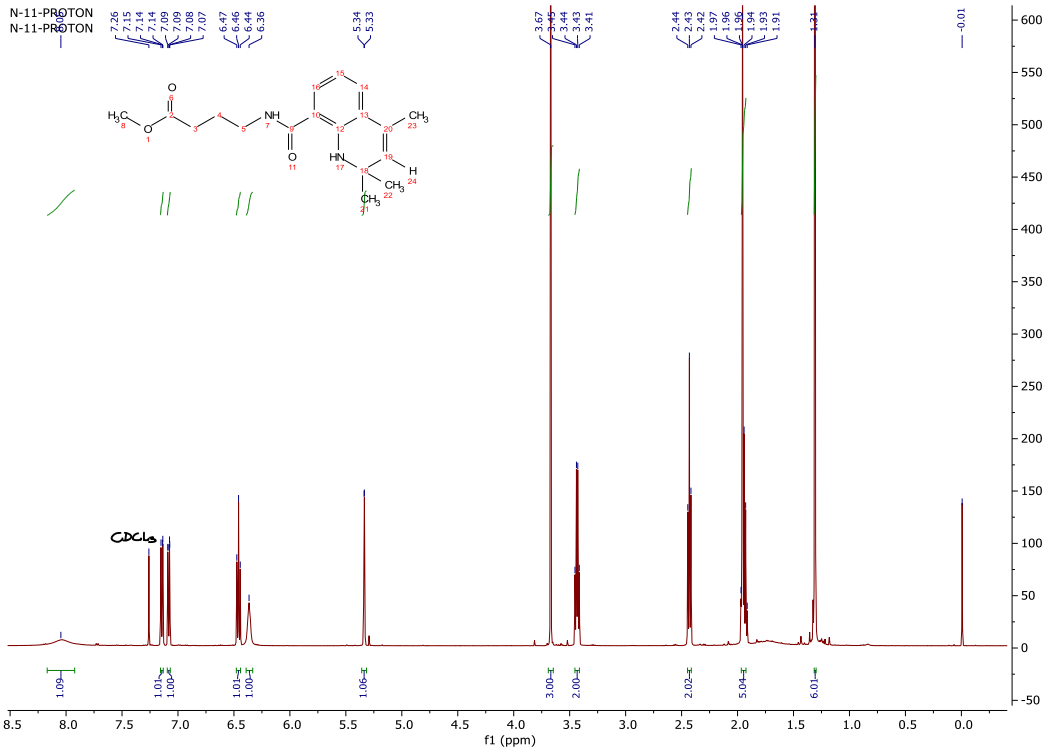


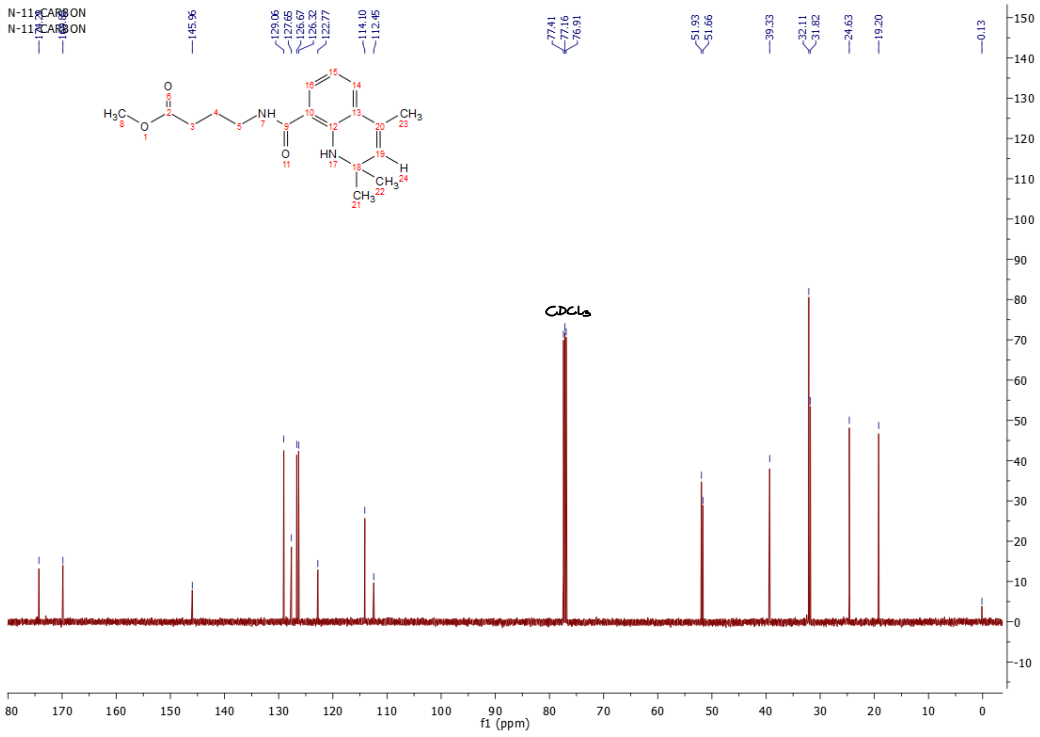


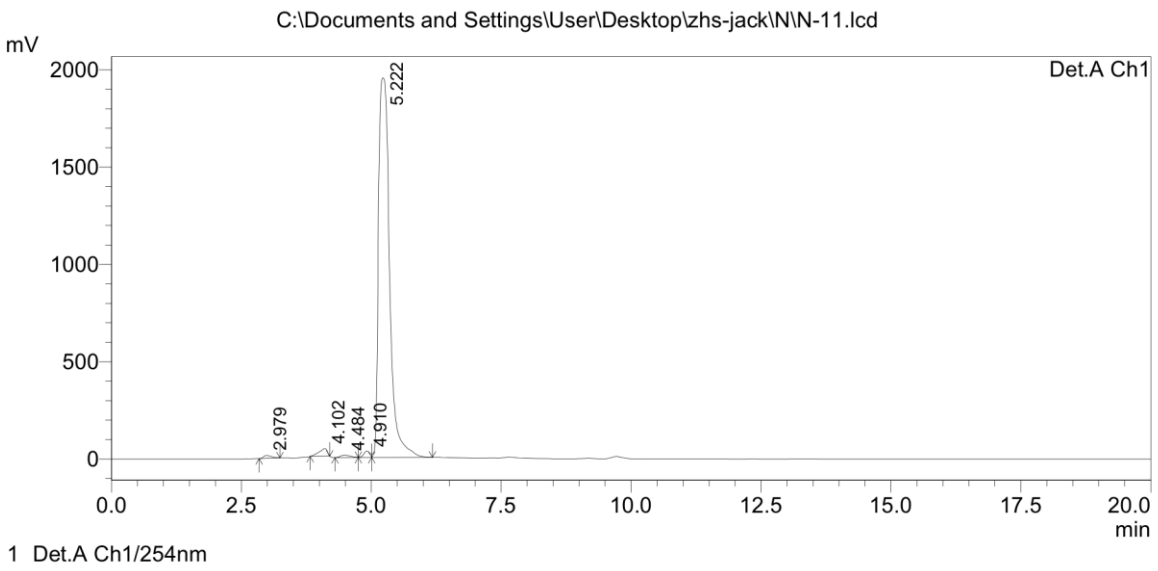


1 Det.A Ch1/254nm

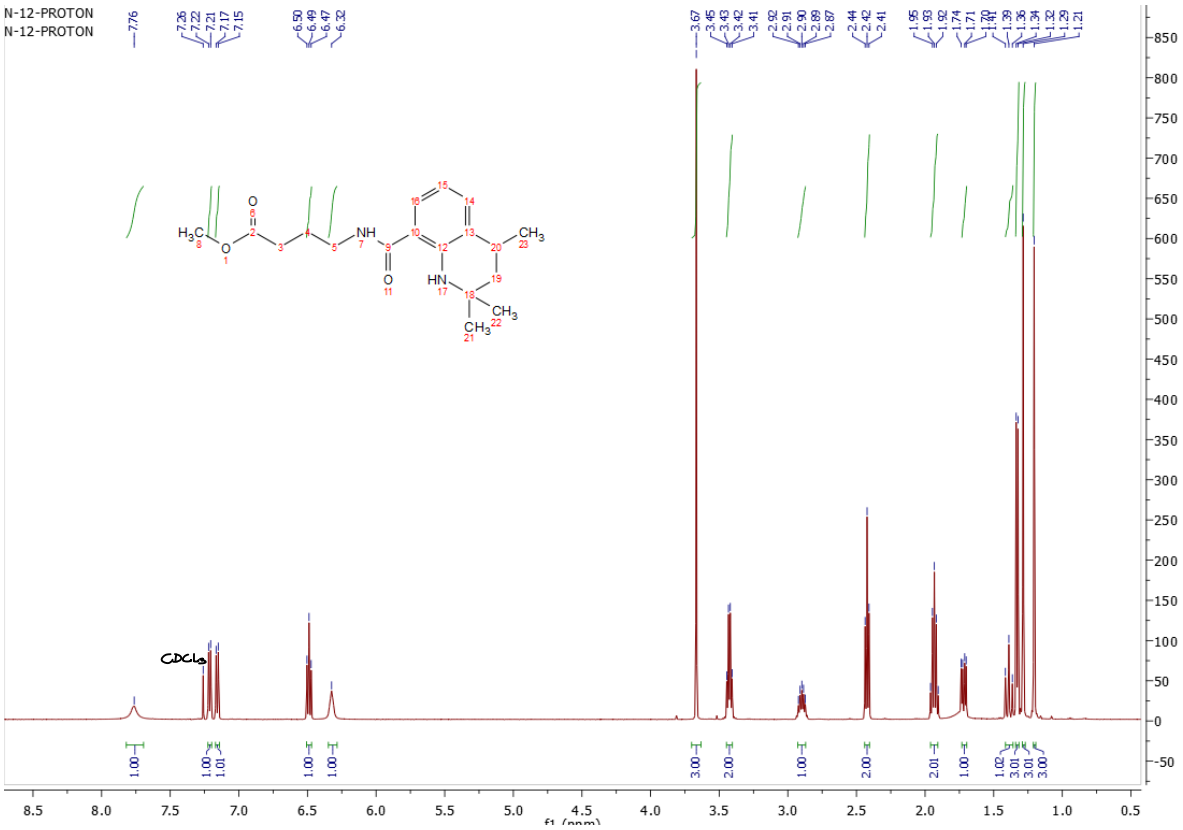
Methyl 4-(2,2,4-trimethyl-1,2-dihydroquinoline-8-carboxamido)butanoate (5)

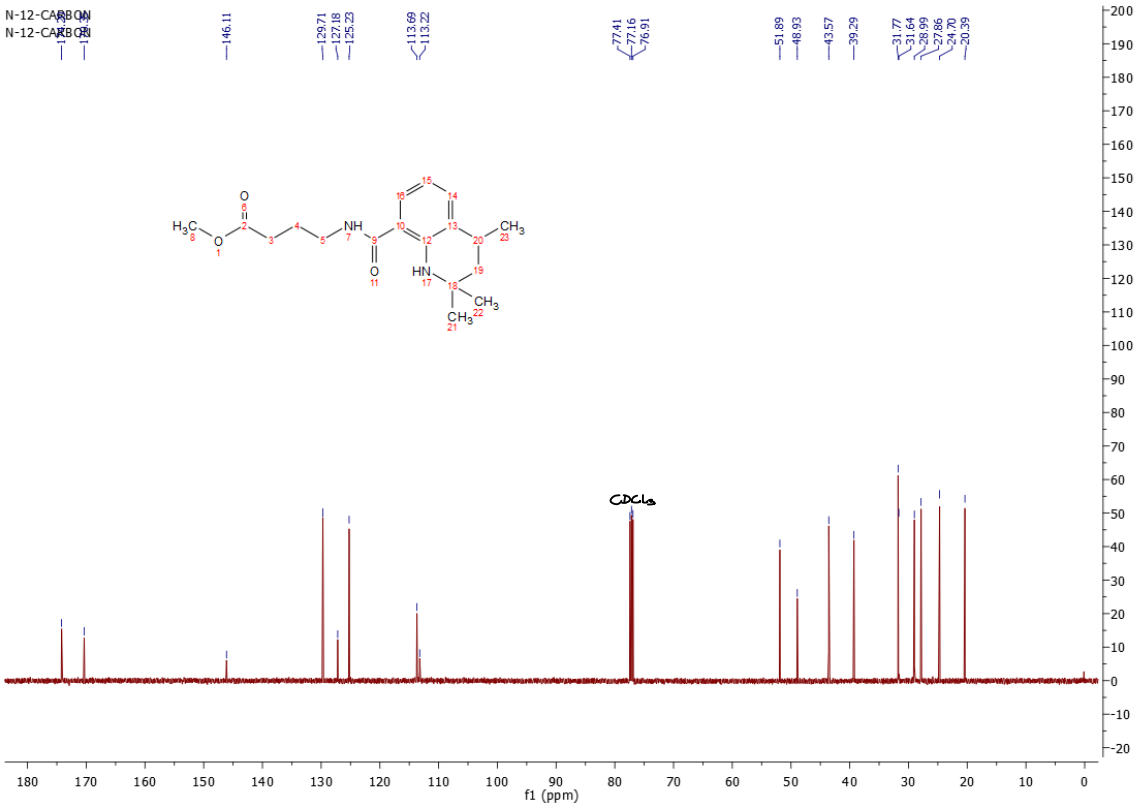


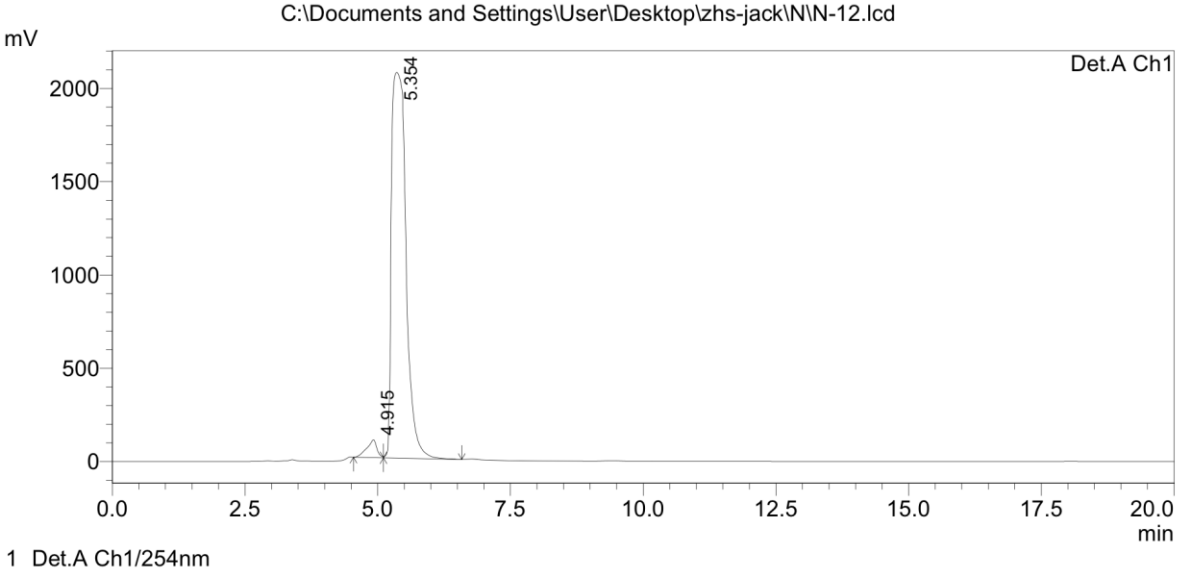




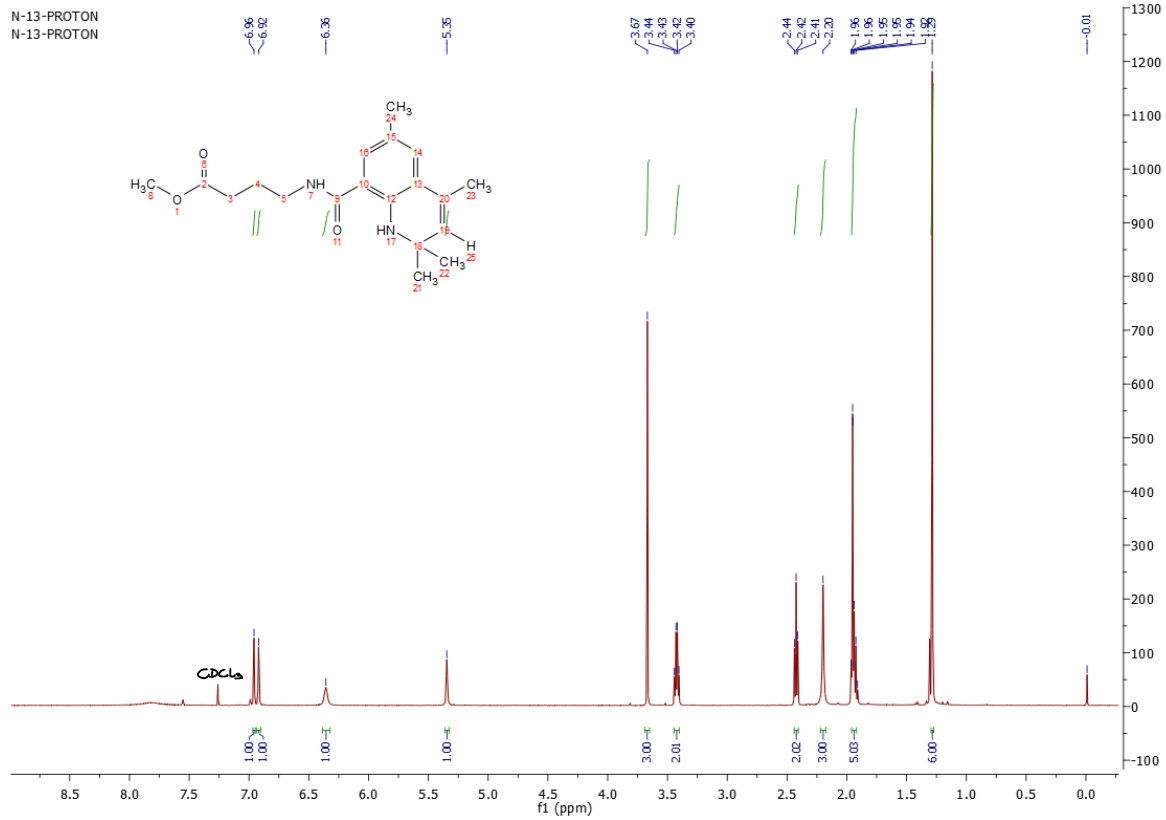
Methyl 4-(2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-8-carboxamido)butanoate (6)

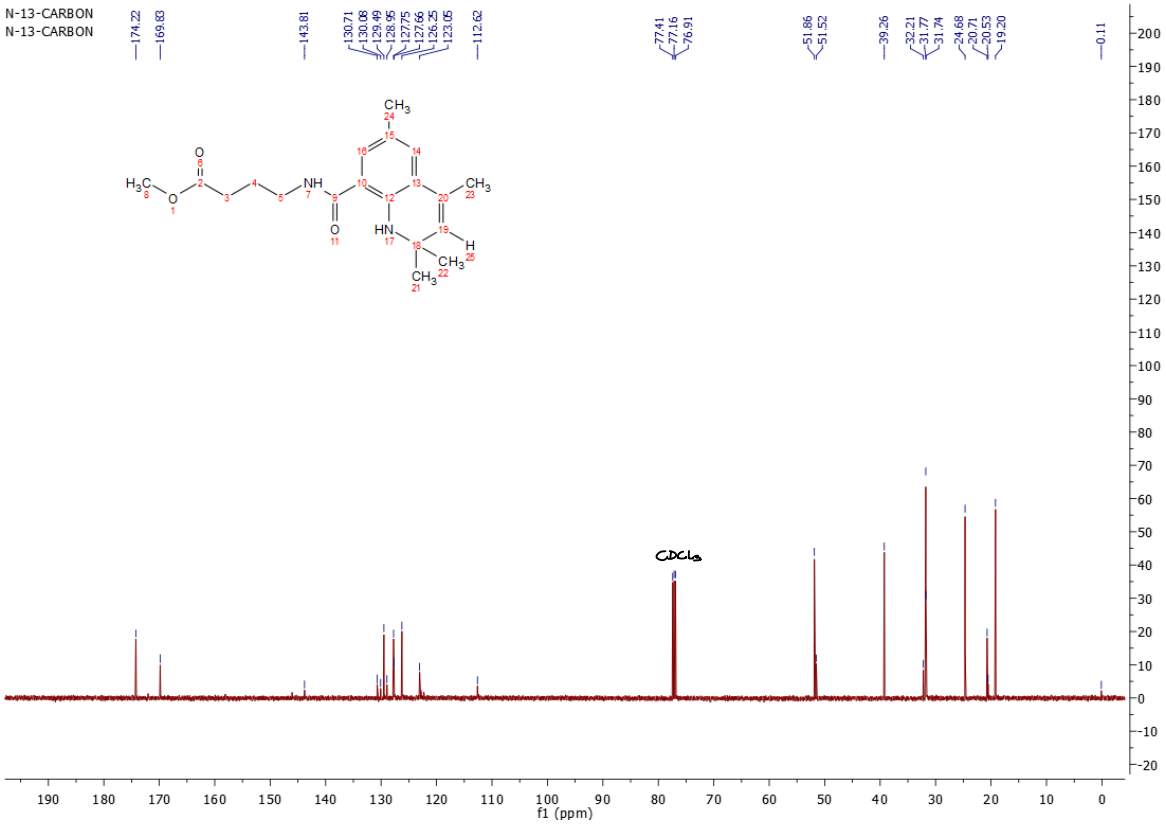


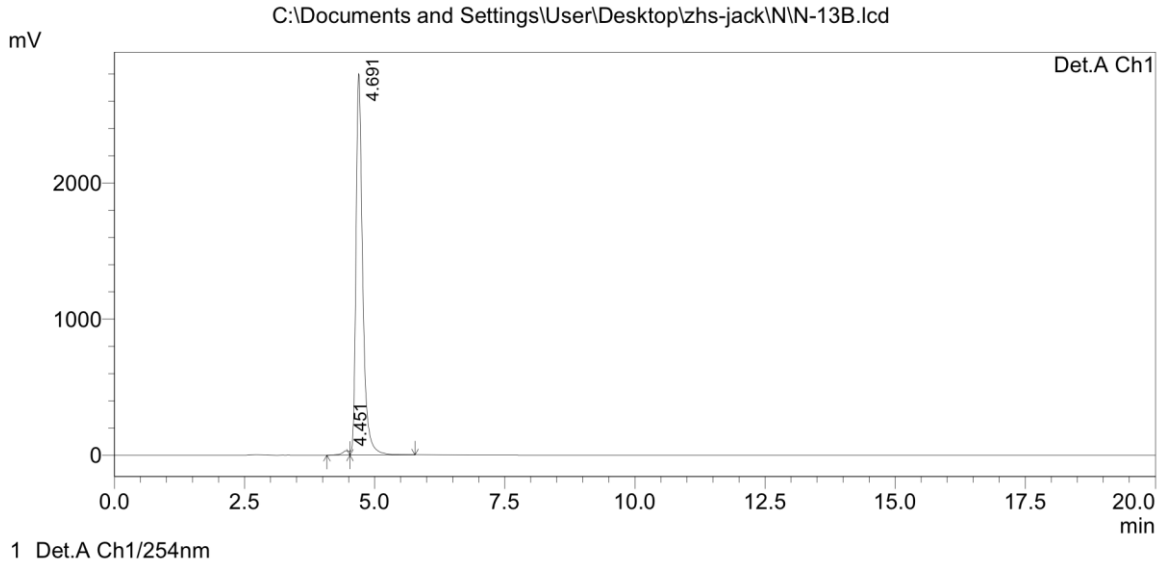

N-12-CARBON
146.11
129.71
127.18
125.23
113.69
113.22
77.41
77.16
76.91
51.89
48.93
43.57
39.29
31.77
31.64
28.99
27.86
24.70
20.39
CDCl3
f1 (ppm)


C:\Documents and Settings\User\Desktop\zhs-jack\N\N-12.lcd
mV
Det.A Ch1
5.354
4.915
min
1 Det.A Ch1/254nm

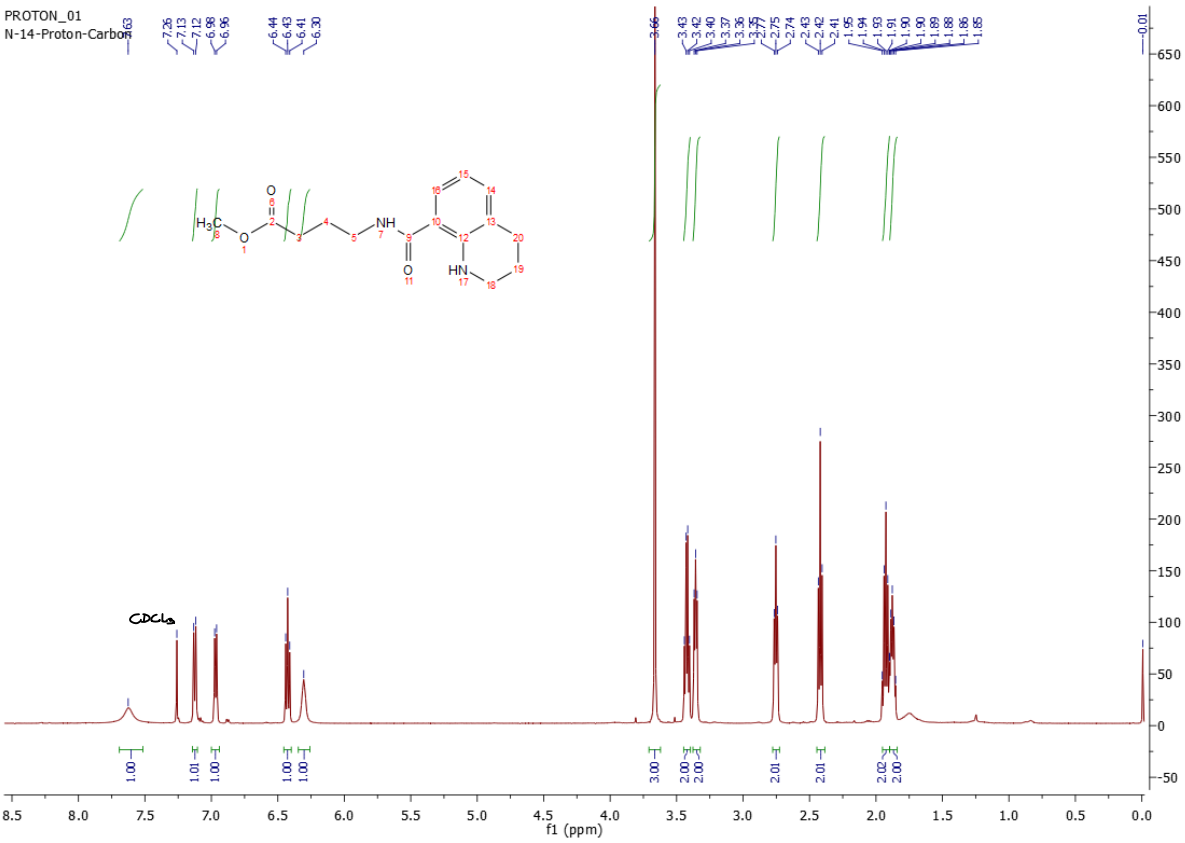
Methyl 4-(2,2,4,6-tetramethyl-1,2-dihydroquinoline-8-carboxamido)butanoate (7)

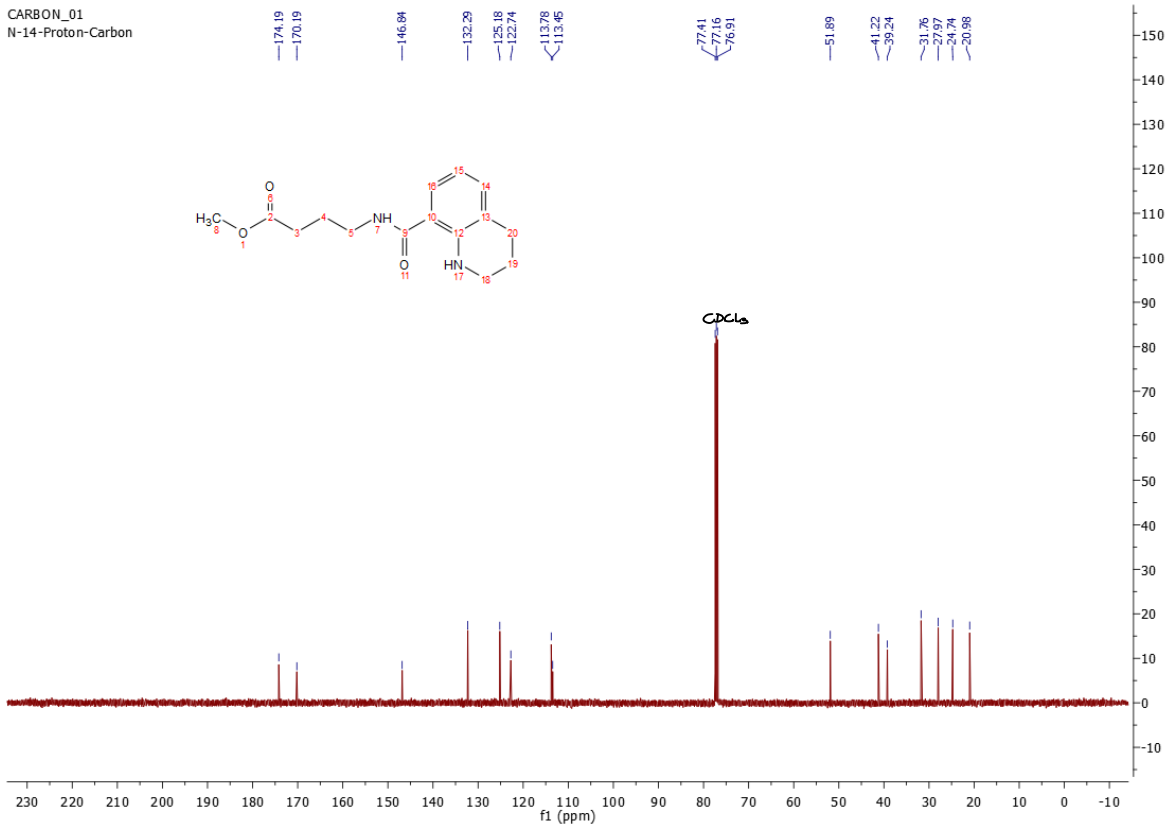


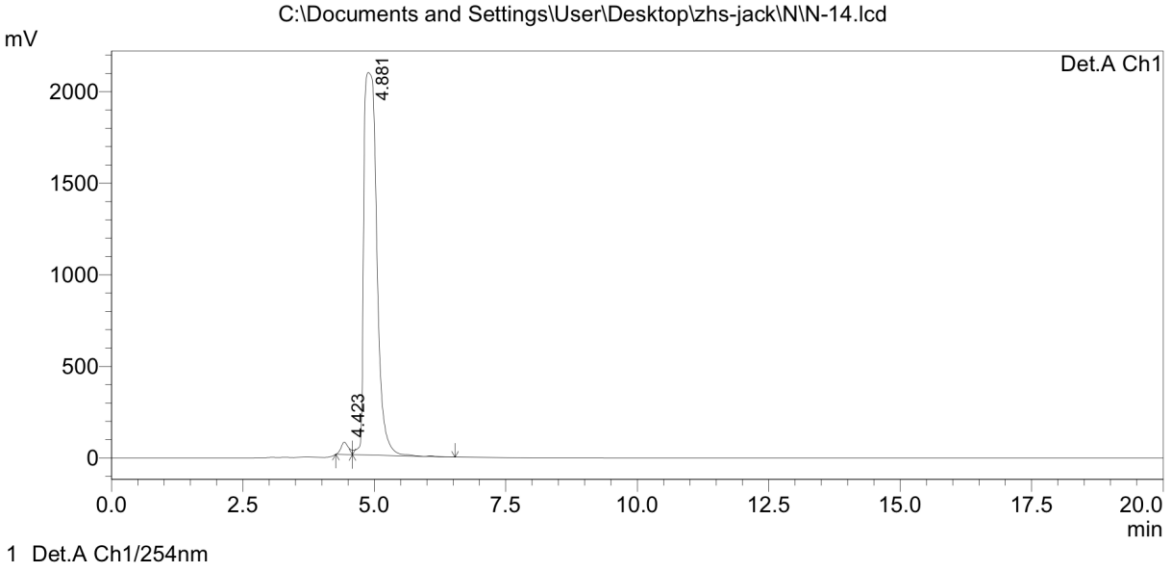




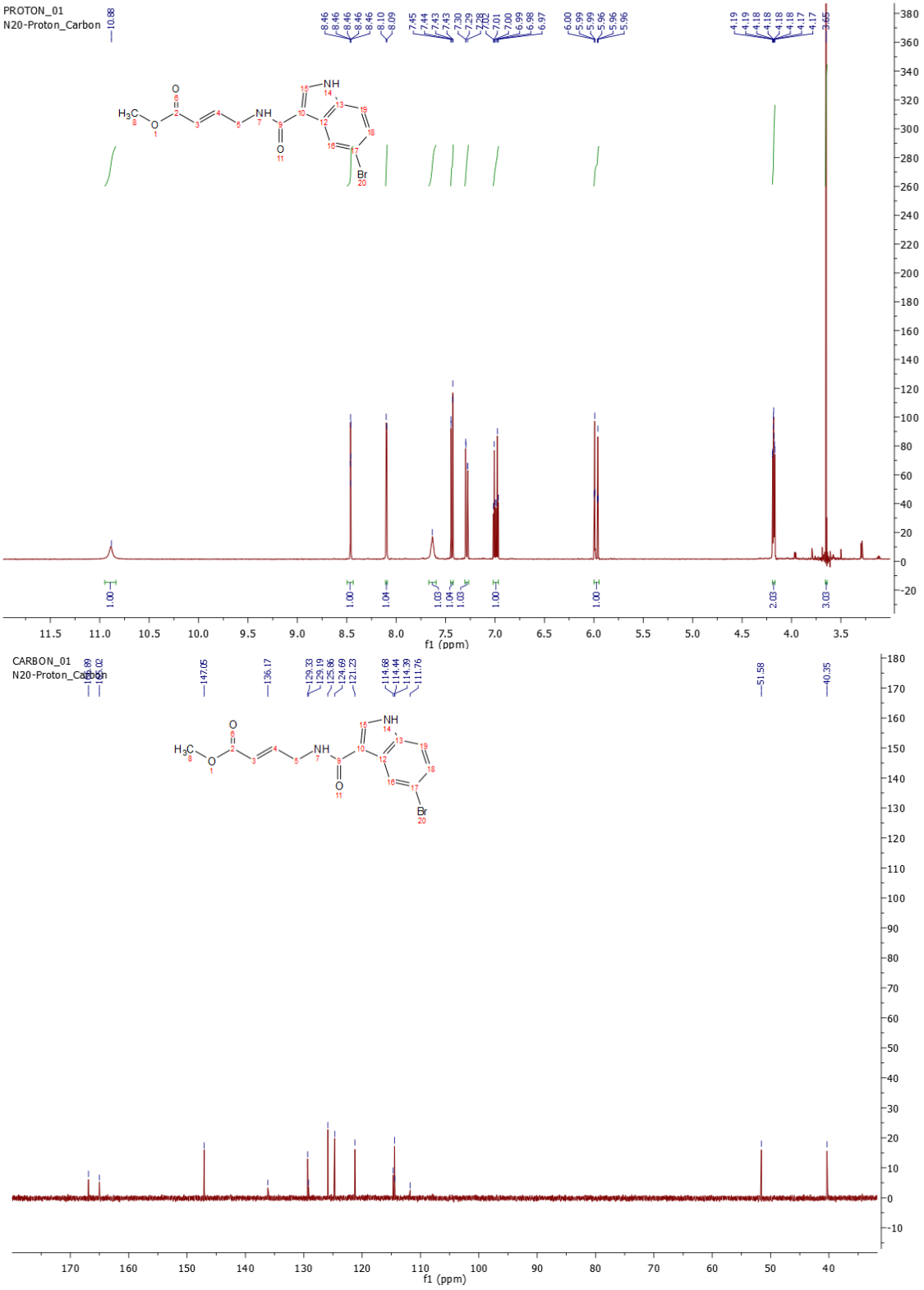
Methyl 4-(1,2,3,4-tetrahydroquinoline-8-carboxamido)butanoate (8)

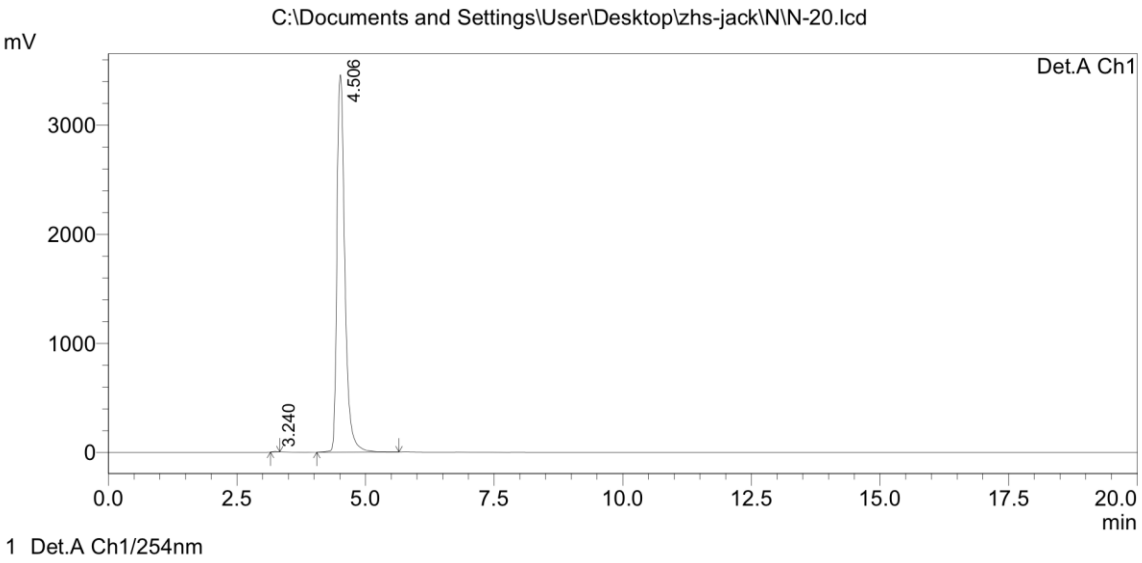



CARBON_01
N-14-Proton-Carbon
174.19
170.19
146.84
132.29
125.18
122.74
113.78
113.45
77.41
77.16
76.91
51.89
41.22
39.24
31.76
27.97
24.74
20.98
CDCl3
f1 (ppm)

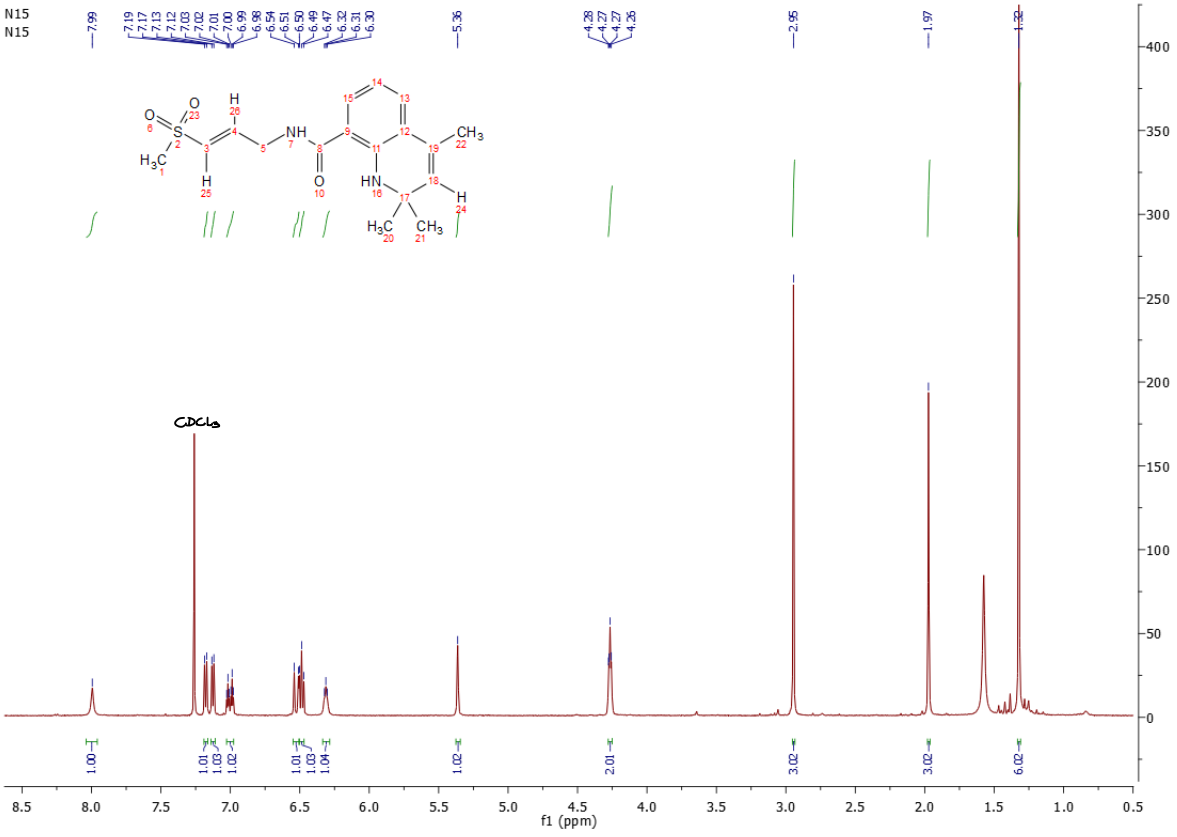

C:\Documents and Settings\User\Desktop\zhs-jack\N\N-14.lcd
mV
Det.A Ch1
4.881
4.423
min
1 Det.A Ch1/254nm

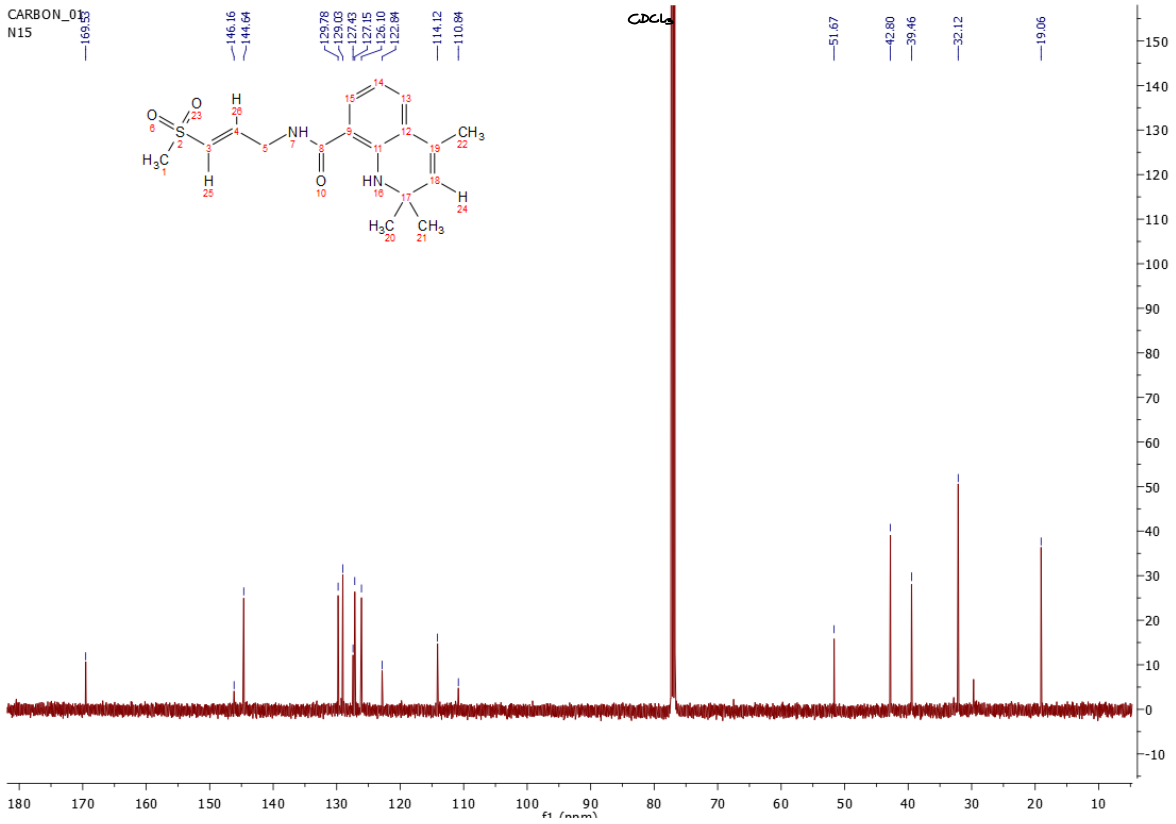
Methyl (*E*)-4-(5-bromo-1H-indole-3-carboxamido)but-2-enoate (9)



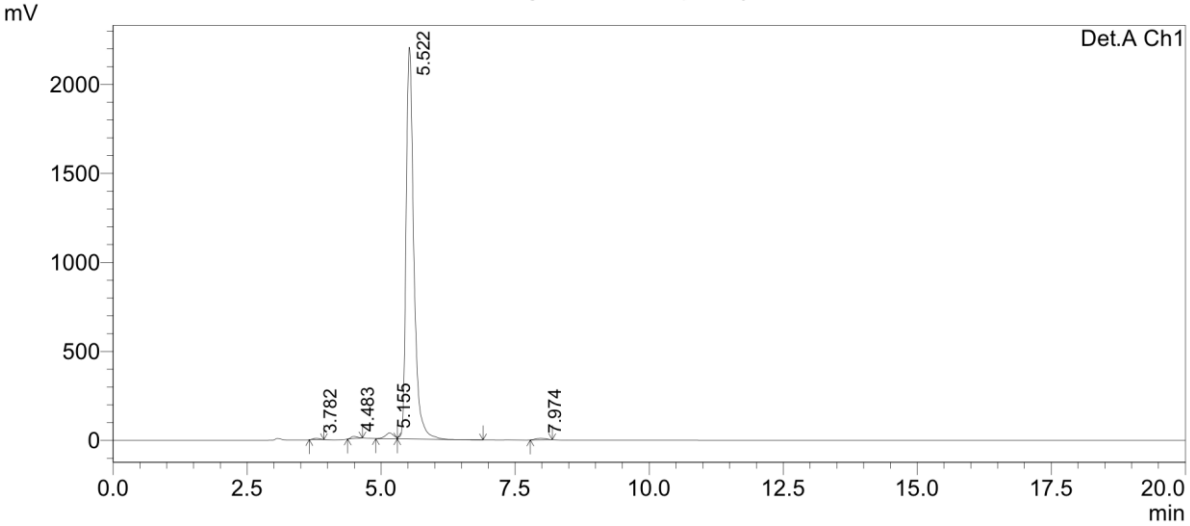


(*E*)-2,2,4-trimethyl-*N*-(3-(methylsulfonyl)allyl)-1,2-dihydroquinoline-8-carboxamide (10)



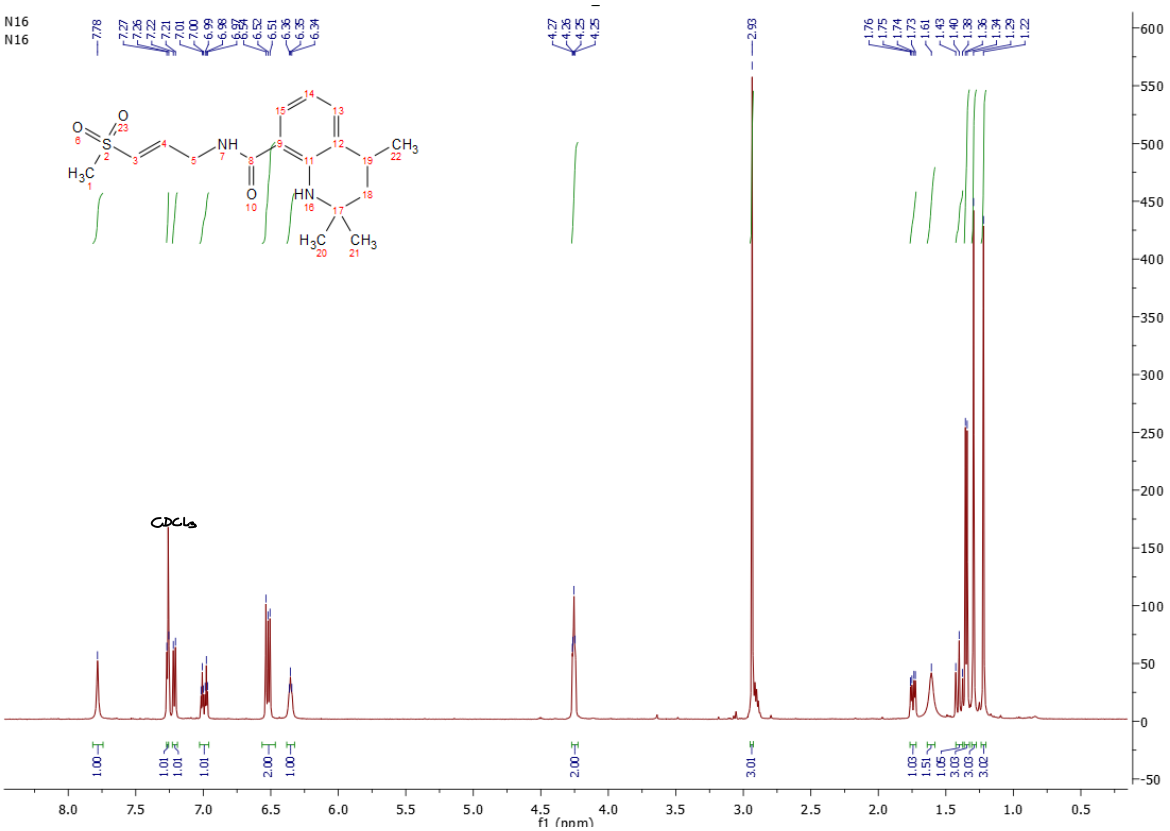


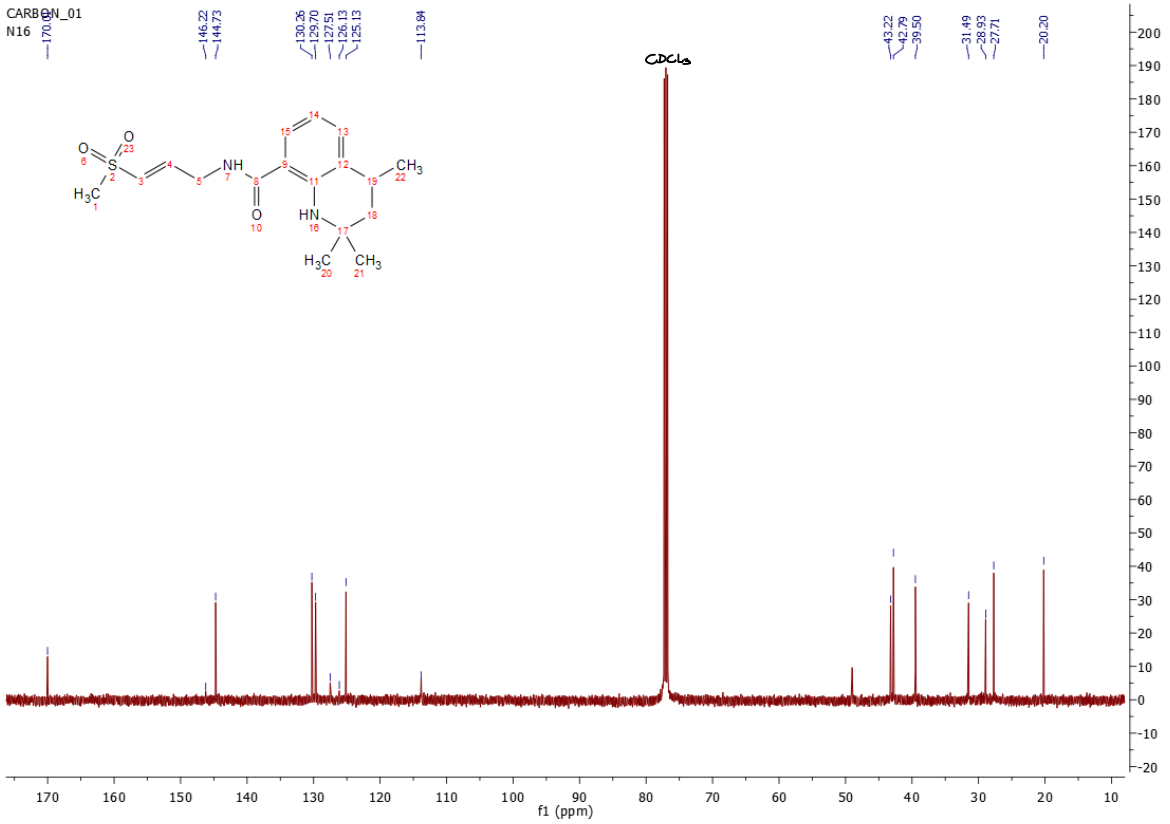
C:\Documents and Settings\User\Desktop\zhs-jack\N\N-15B.lcd

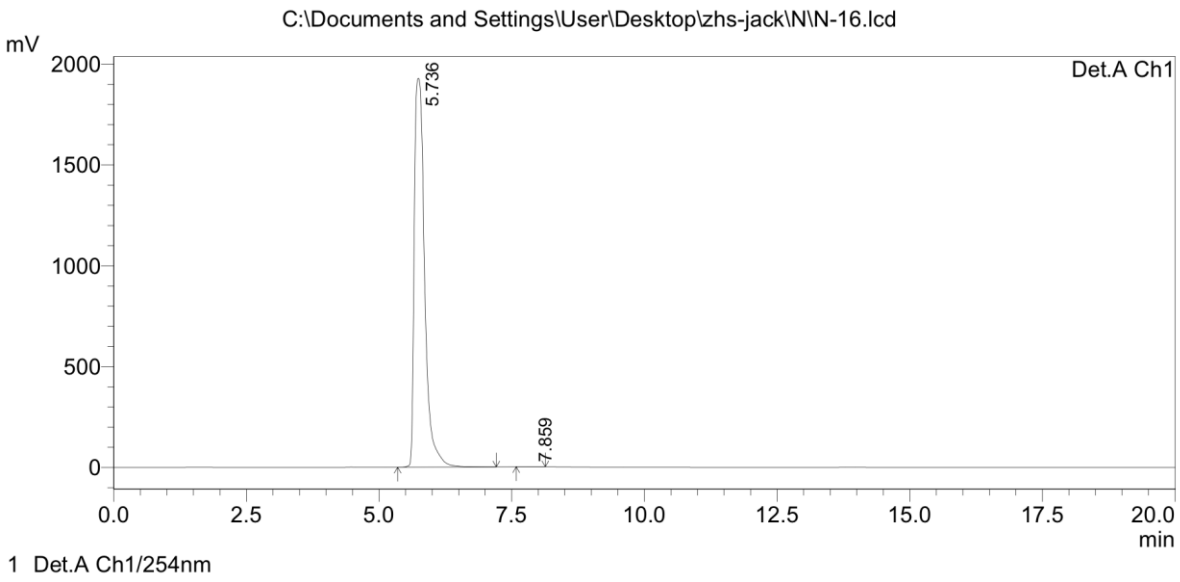


1 Det.A Ch1/254nm

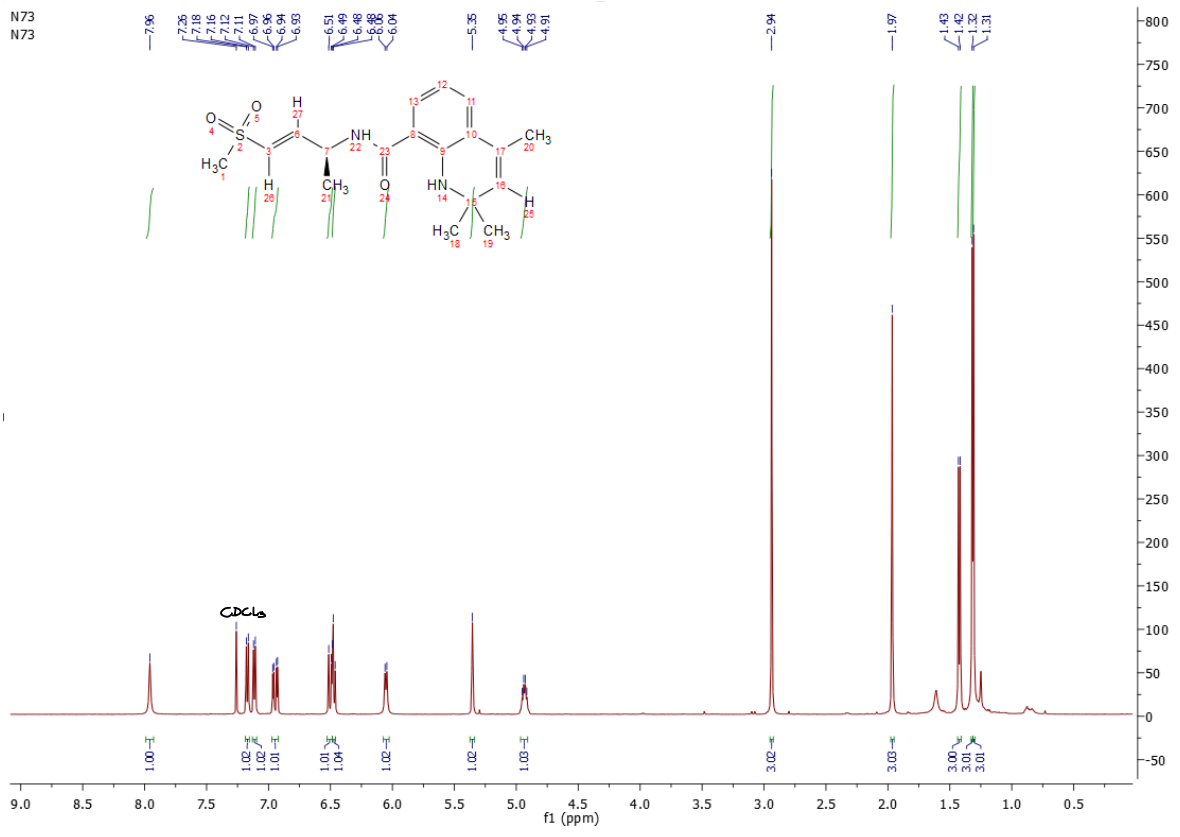
(*E*)-2,2,4-trimethyl-*N*-(3-(methylsulfonyl)allyl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (11)

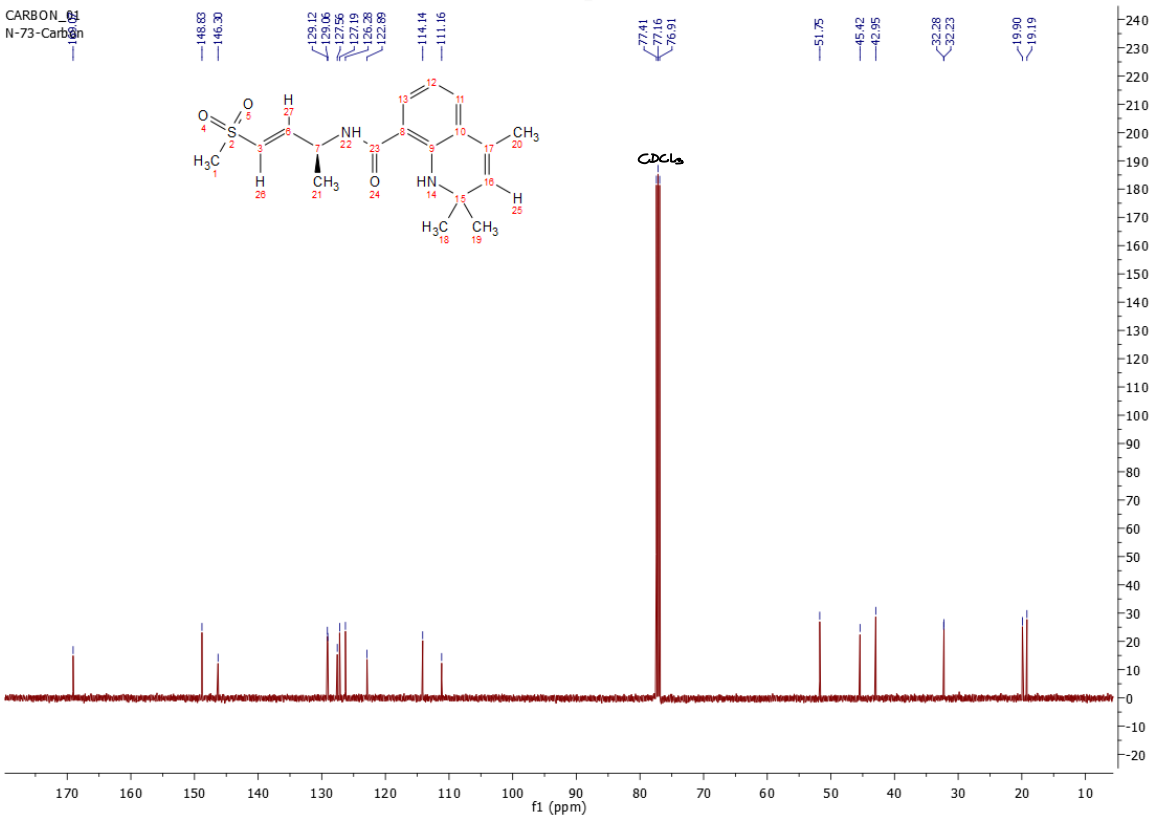




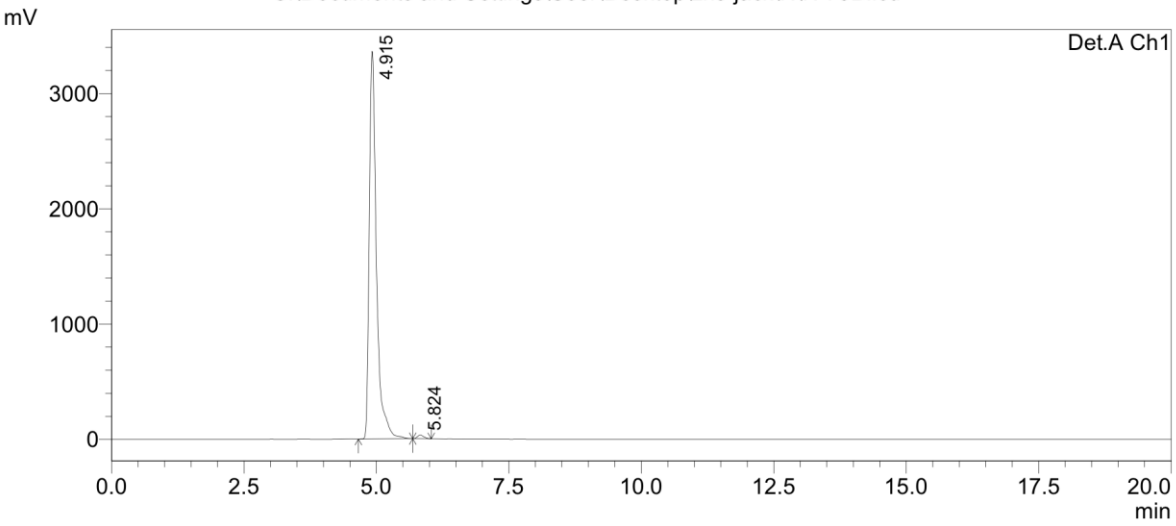


(*S*, *E*)-2,2,4-trimethyl-*N*-(4-(methylsulfonyl)but-3-en-2-yl)-1,2-dihydroquinoline-8-carboxamide (12)



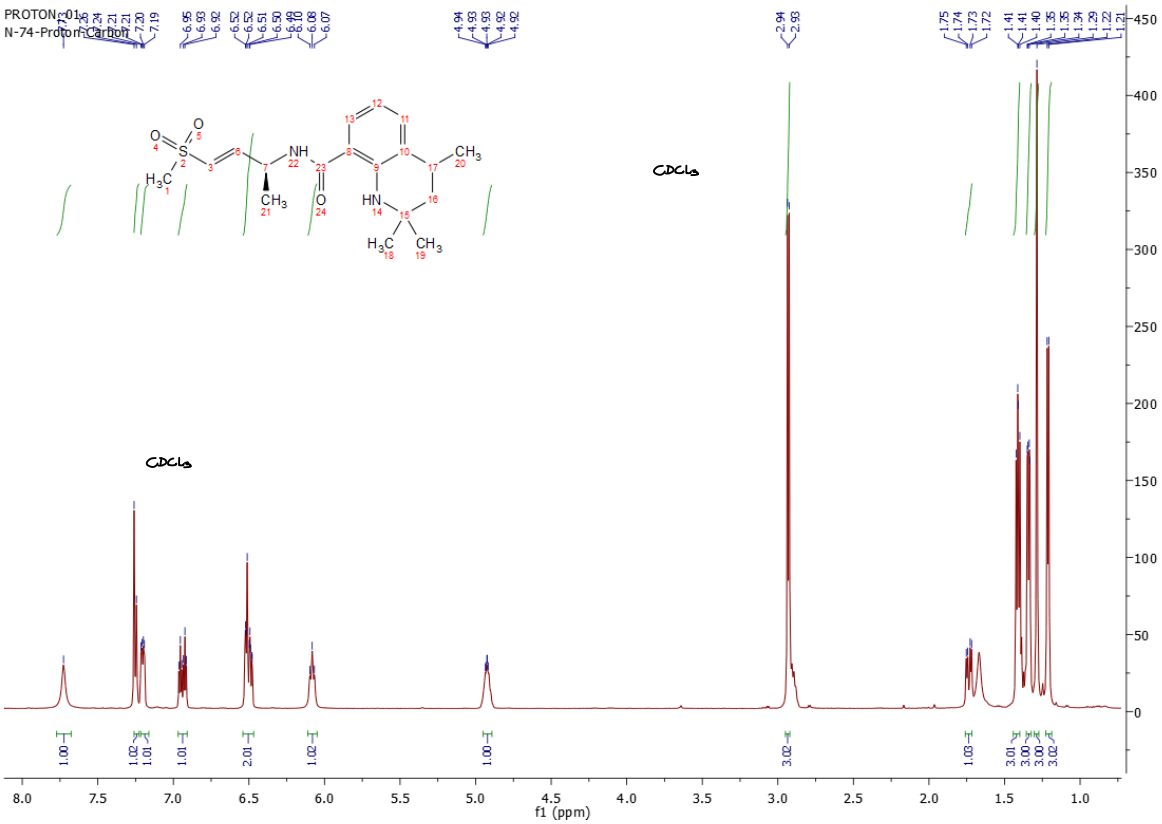


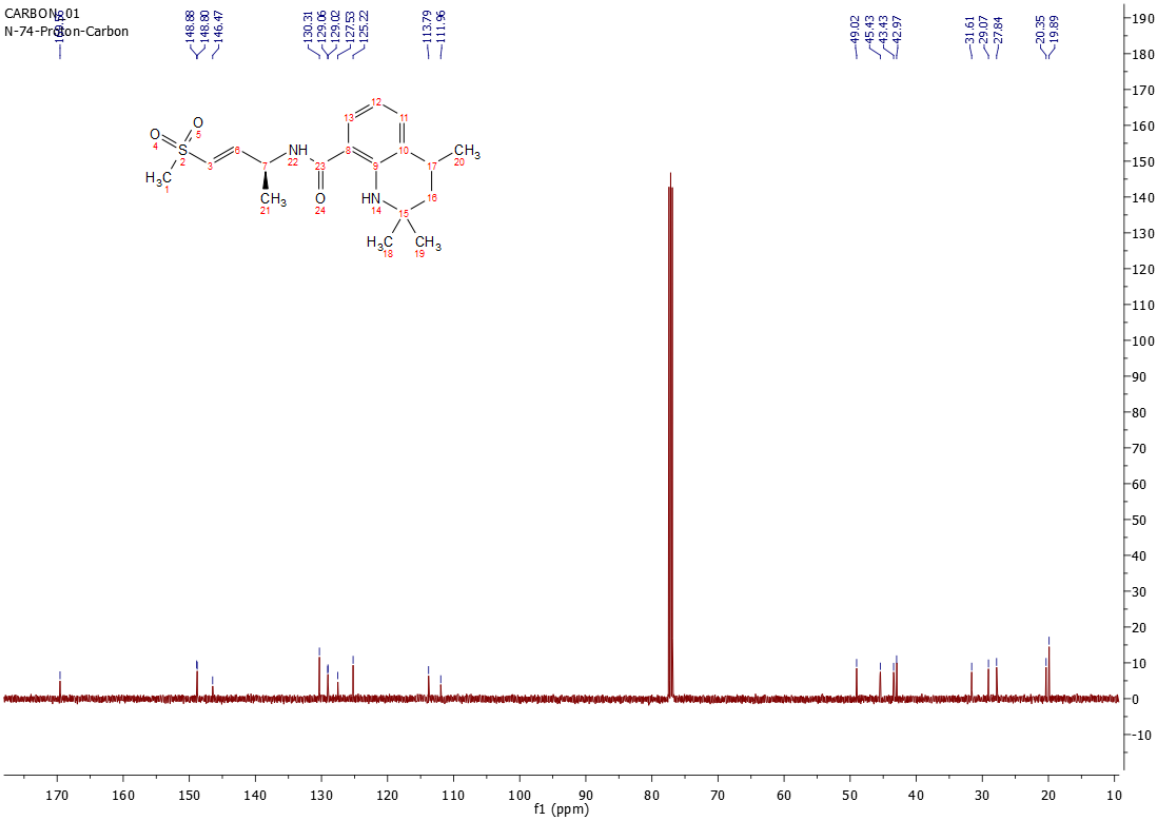
C:\Documents and Settings\User\Desktop\zhs-jack\N\N-73B.lcd

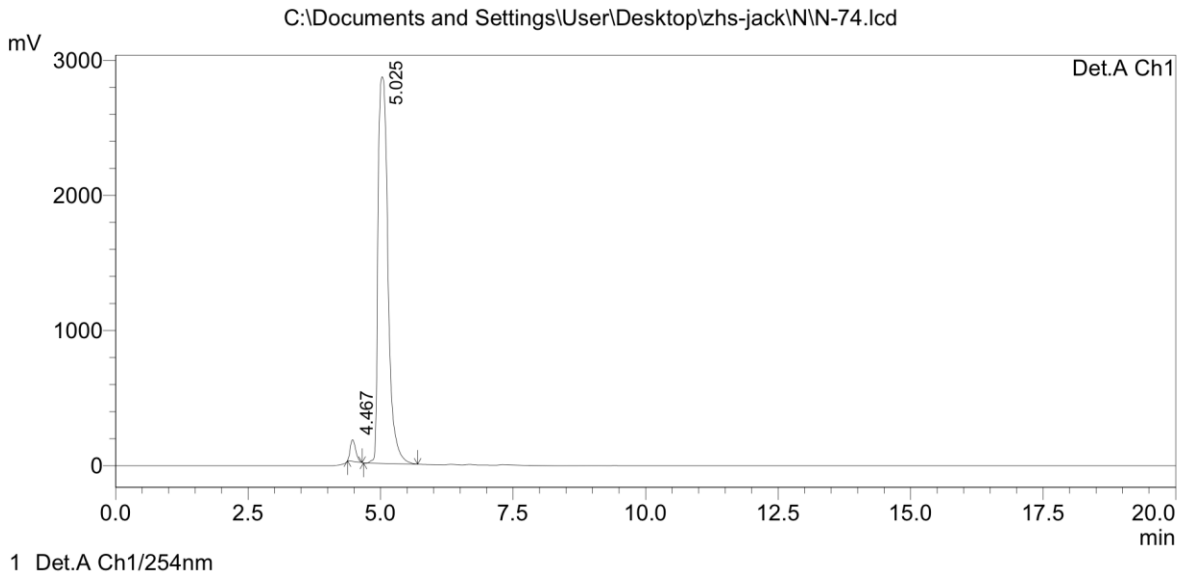


1 Det.A Ch1/254nm

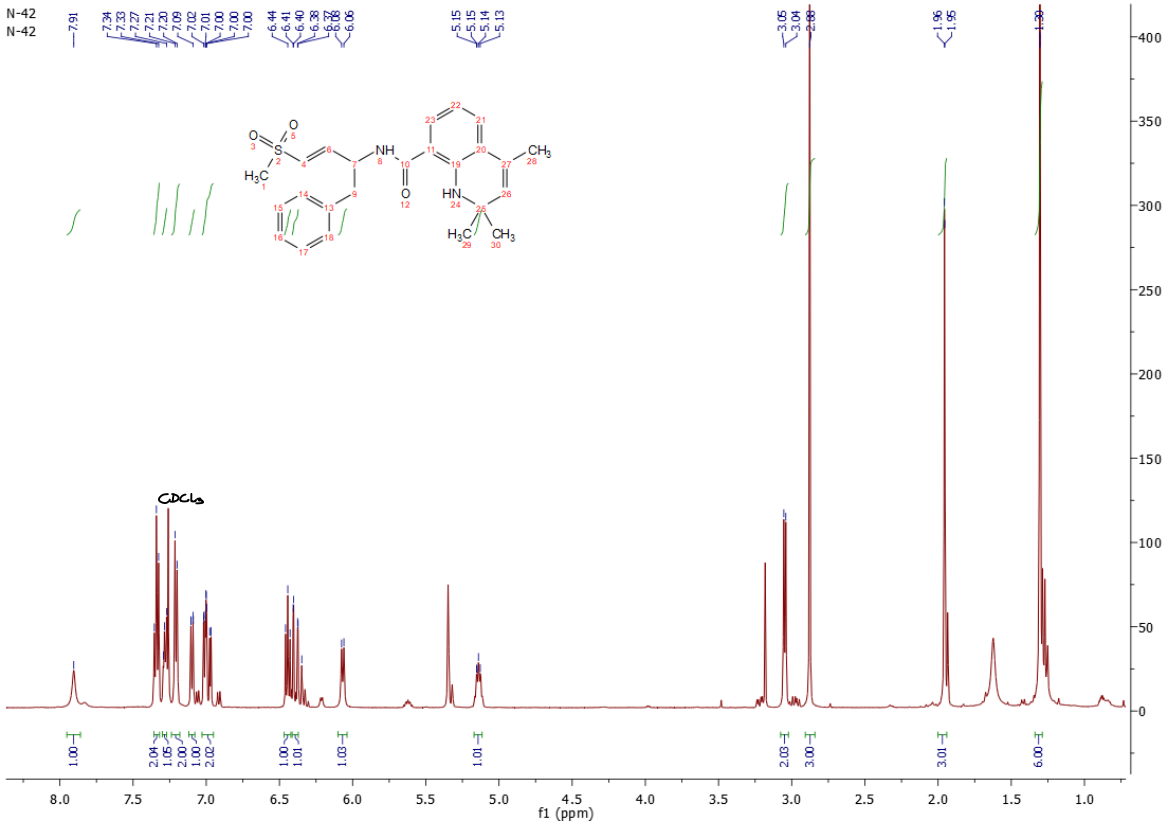
(*S*,*E*)-2,2,4-trimethyl-*N*-(4-(methylsulfonyl)but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (13)

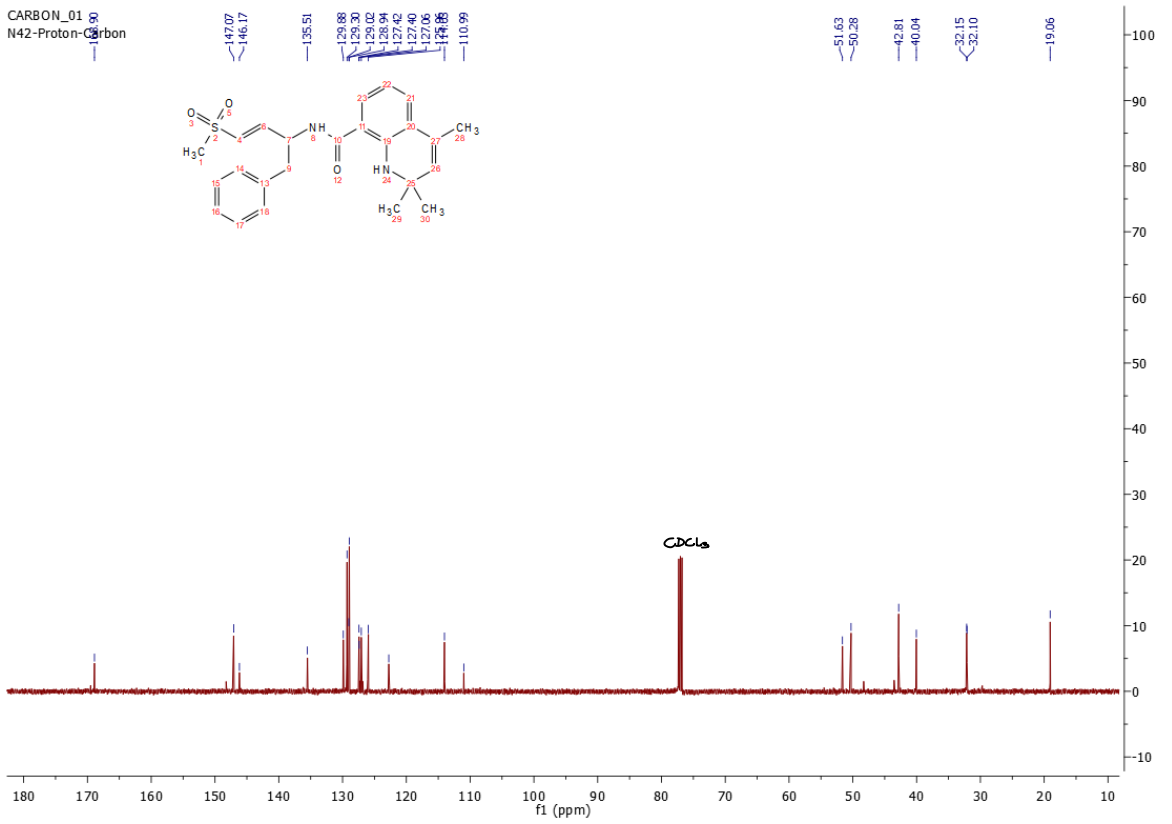


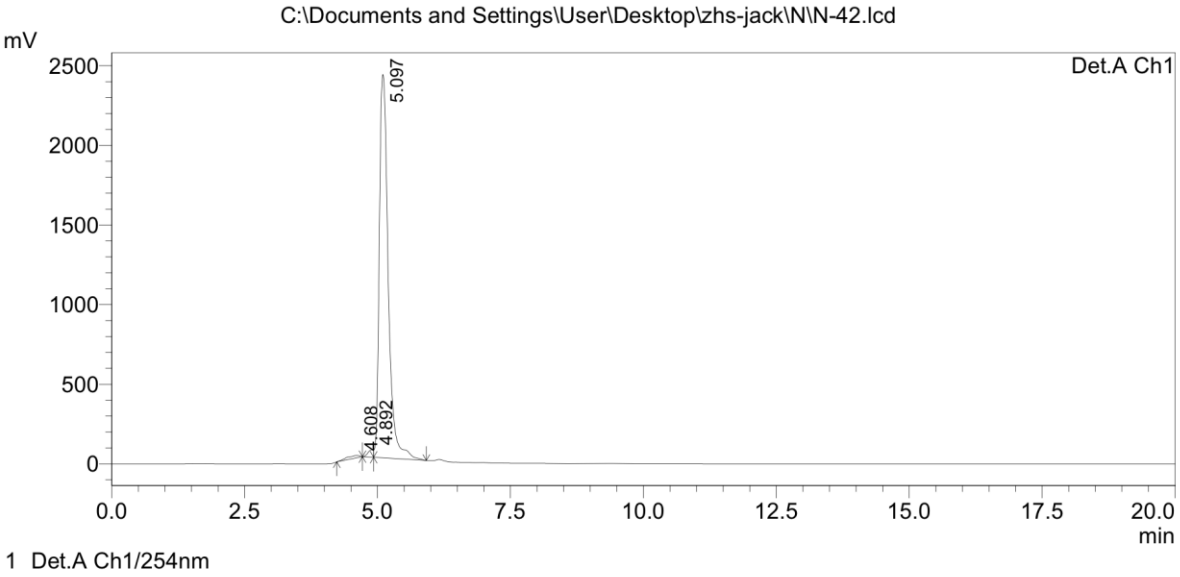




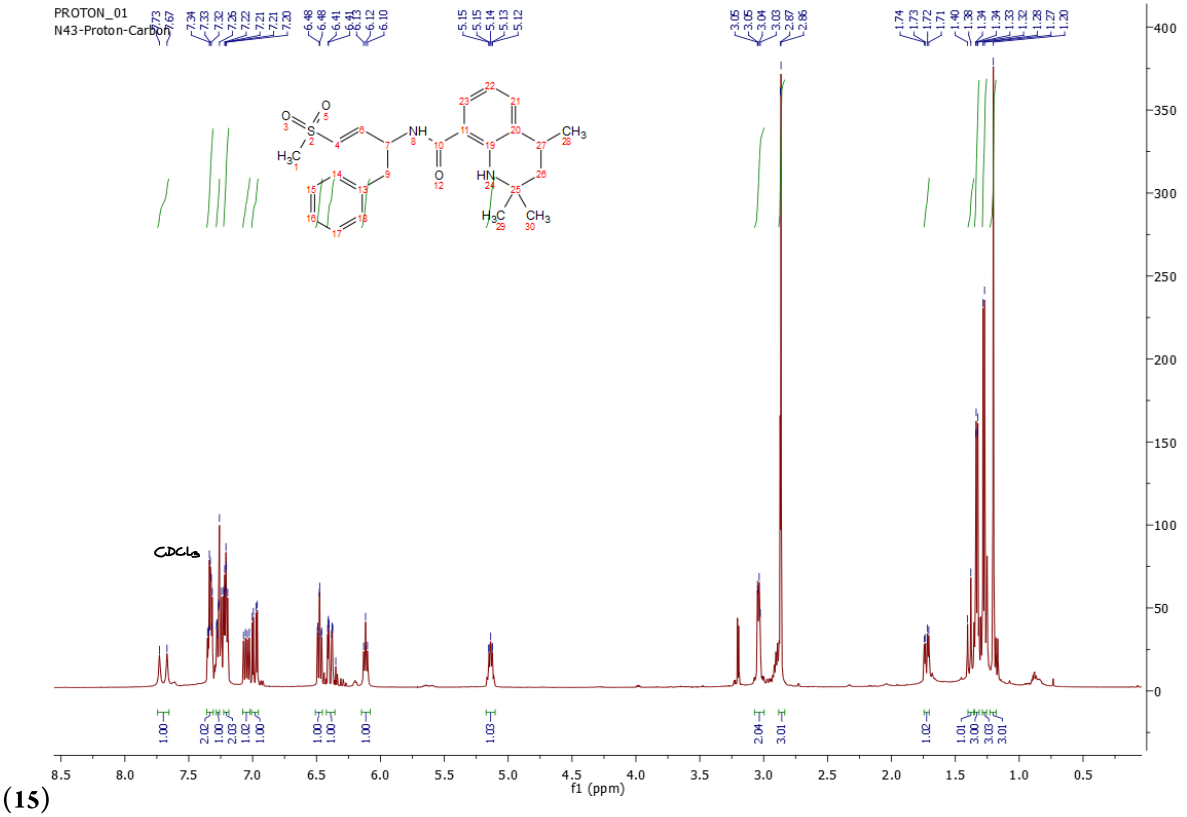
(*S*,*E*)-2,2,4-trimethyl-*N*-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)-1,2-dihydroquinoline-8-carboxamide (14)



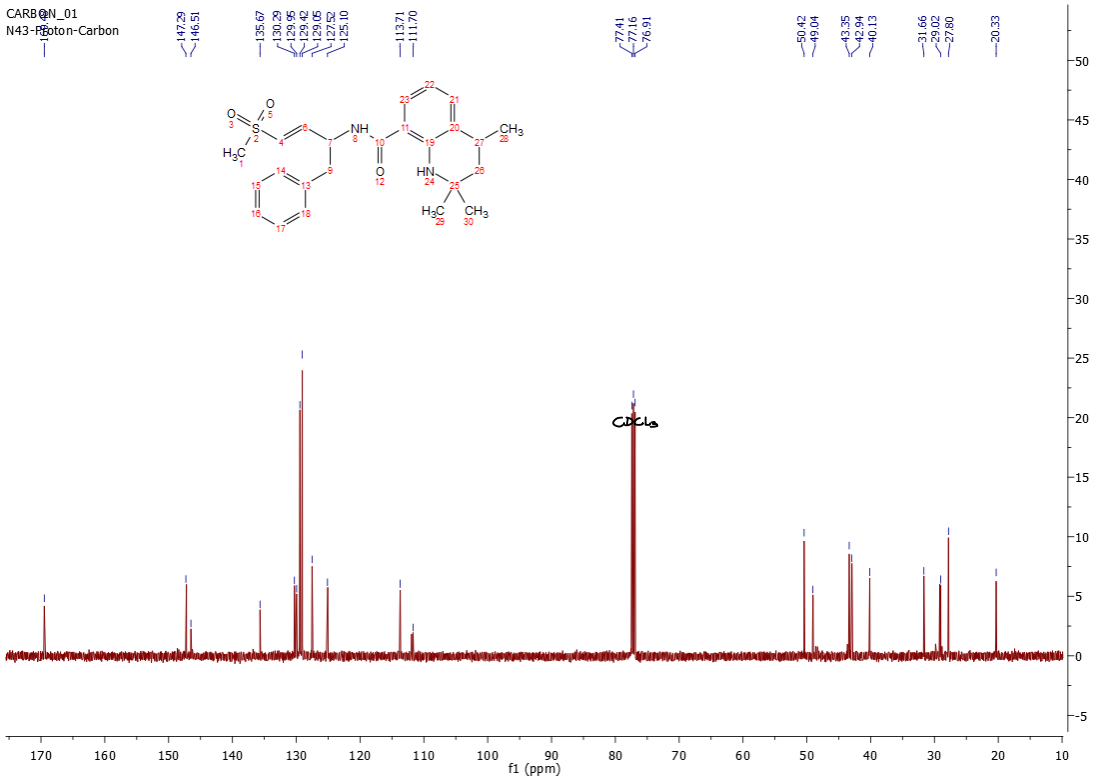

CARBON_01
N42-Proton-Carbon
171.80
147.07
146.17
135.51
129.88
129.30
129.02
126.94
127.42
127.40
127.06
110.99
51.63
50.28
42.81
40.04
32.15
32.10
19.06
CDCl3
f1 (ppm)

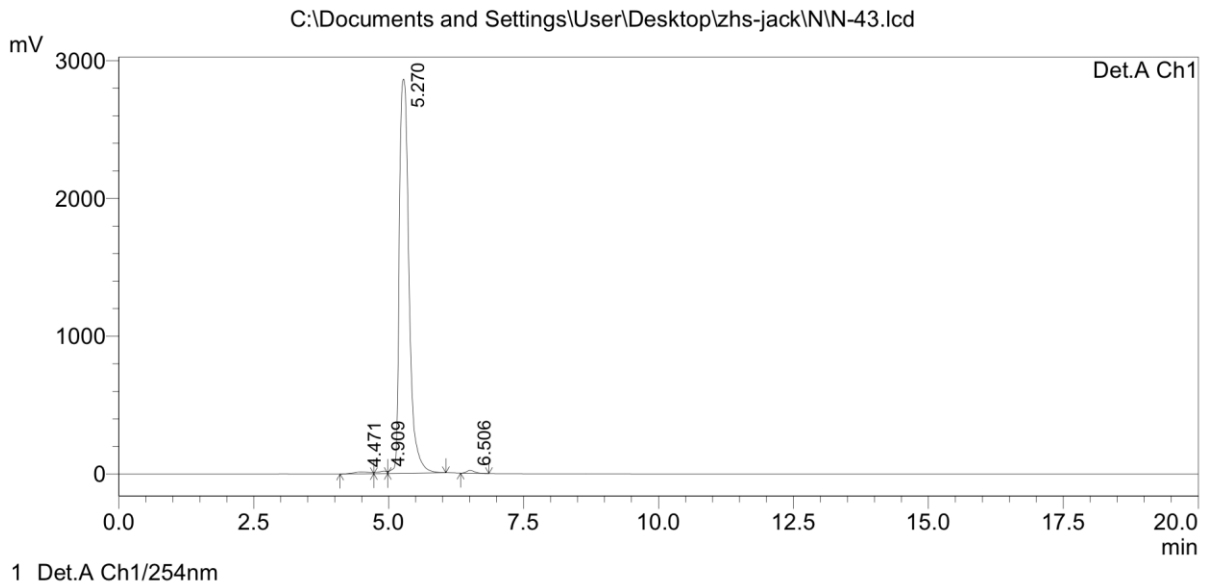

C:\Documents and Settings\User\Desktop\zhs-jack\N\N-42.lcd
mV
Det.A Ch1
5.097
4.608
4.892
min
1 Det.A Ch1/254nm

(*S*,*E*)-2,2,4-trimethyl-*N*-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)-1,2,3,4-tetrahydroquinoline-8-carboxamide

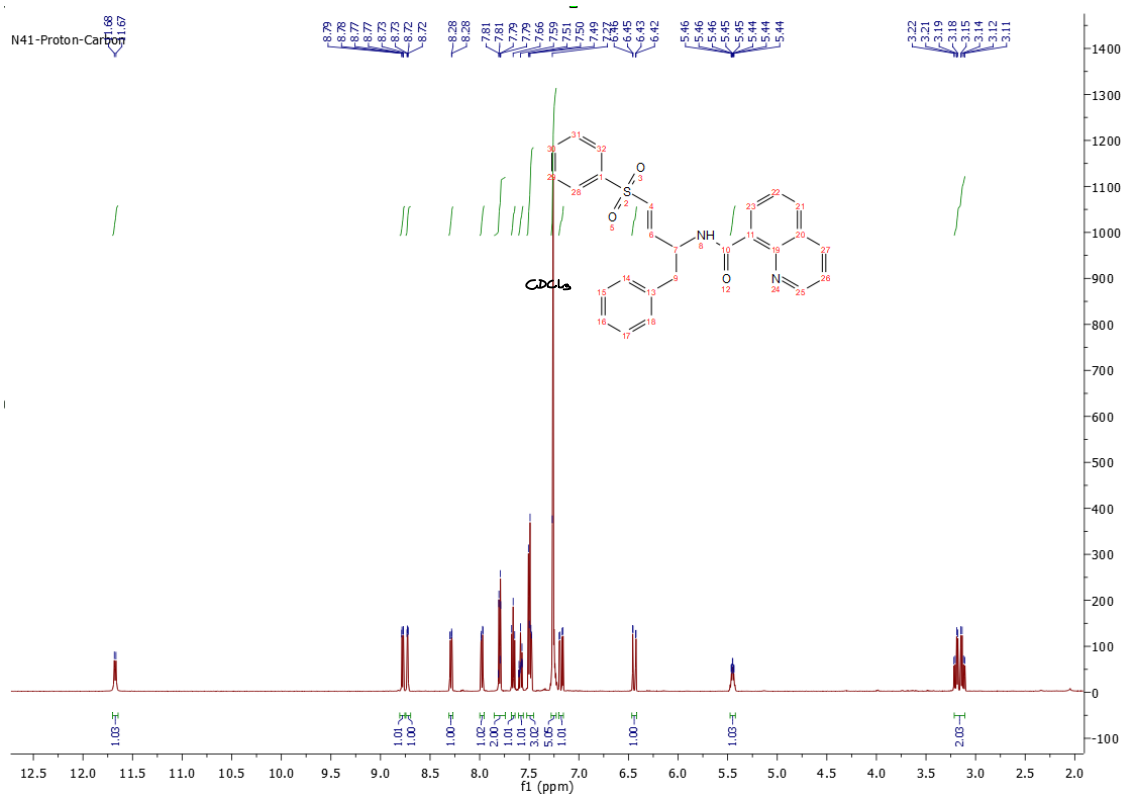


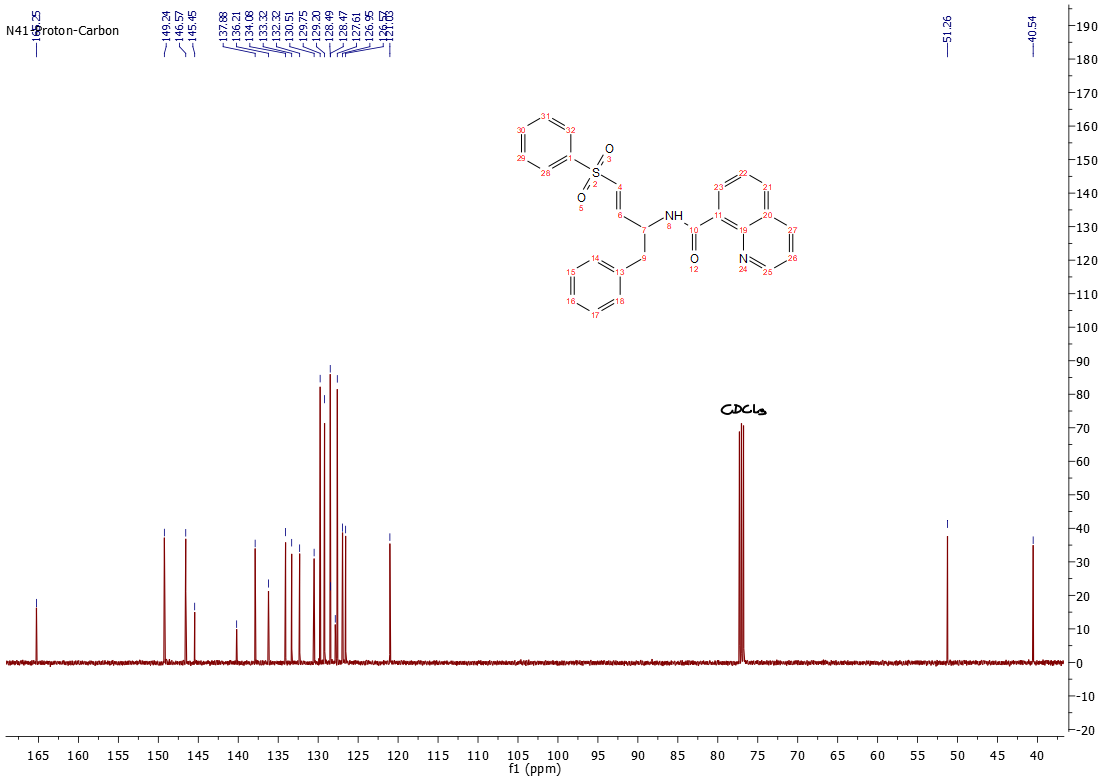
(15)

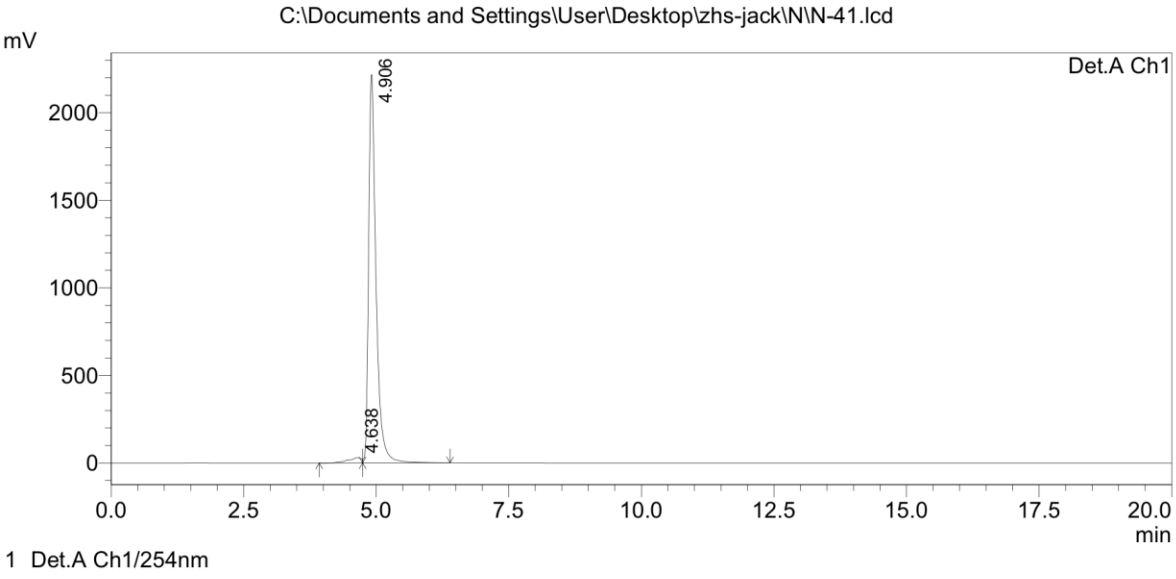




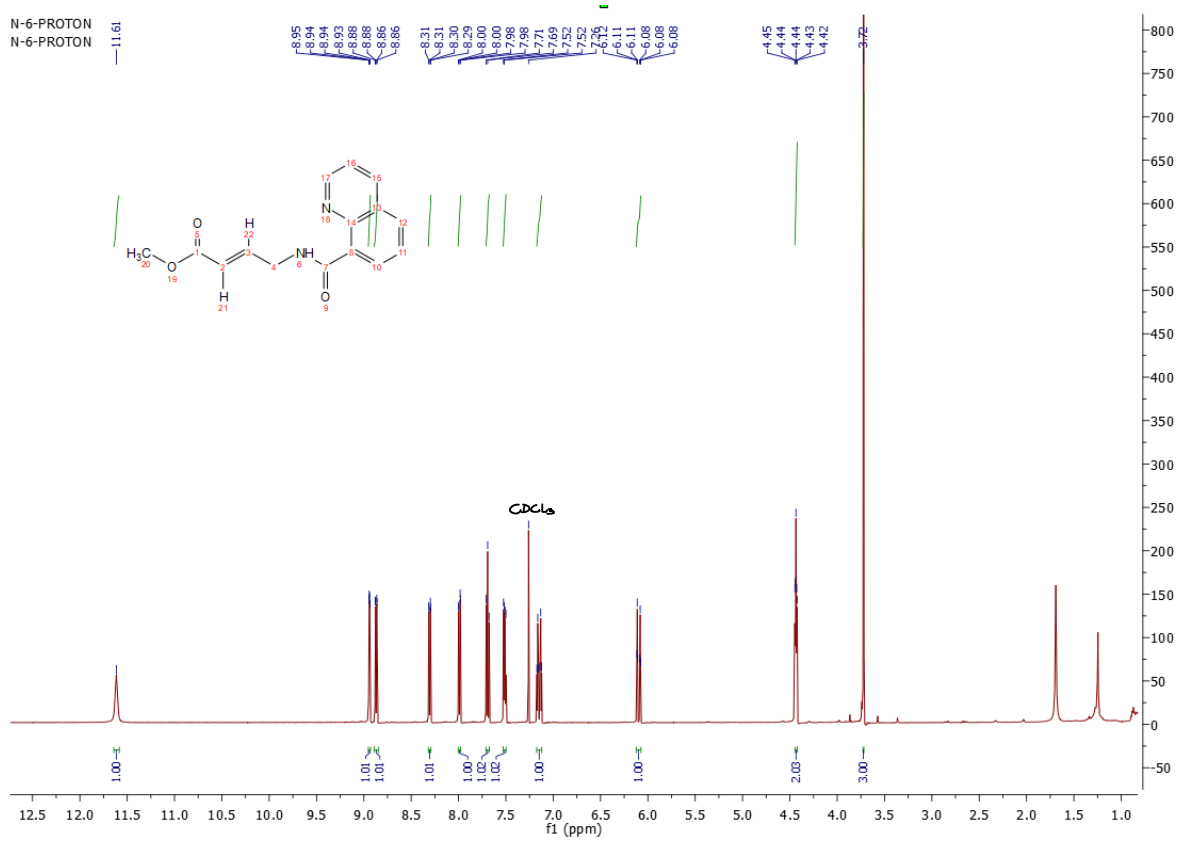
(*S*,*E*)-*N*-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)quinoline-8-carboxamide (16)

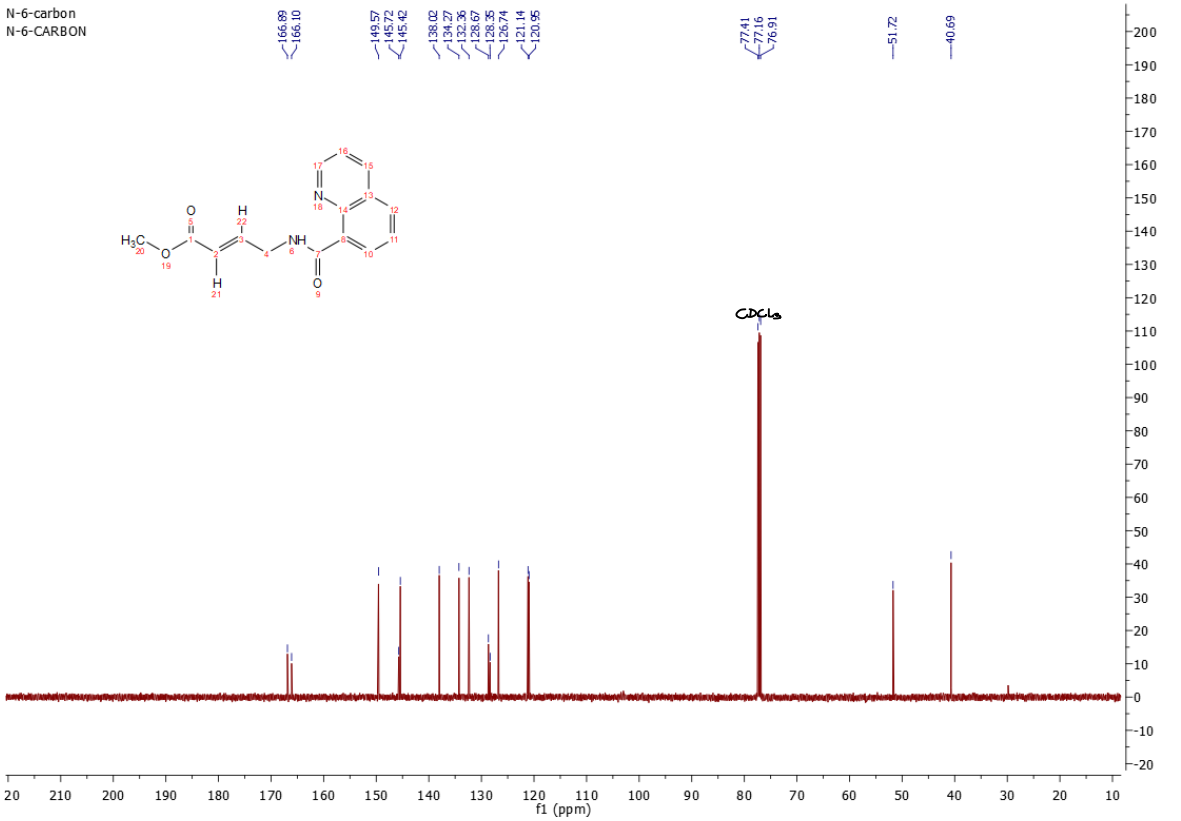


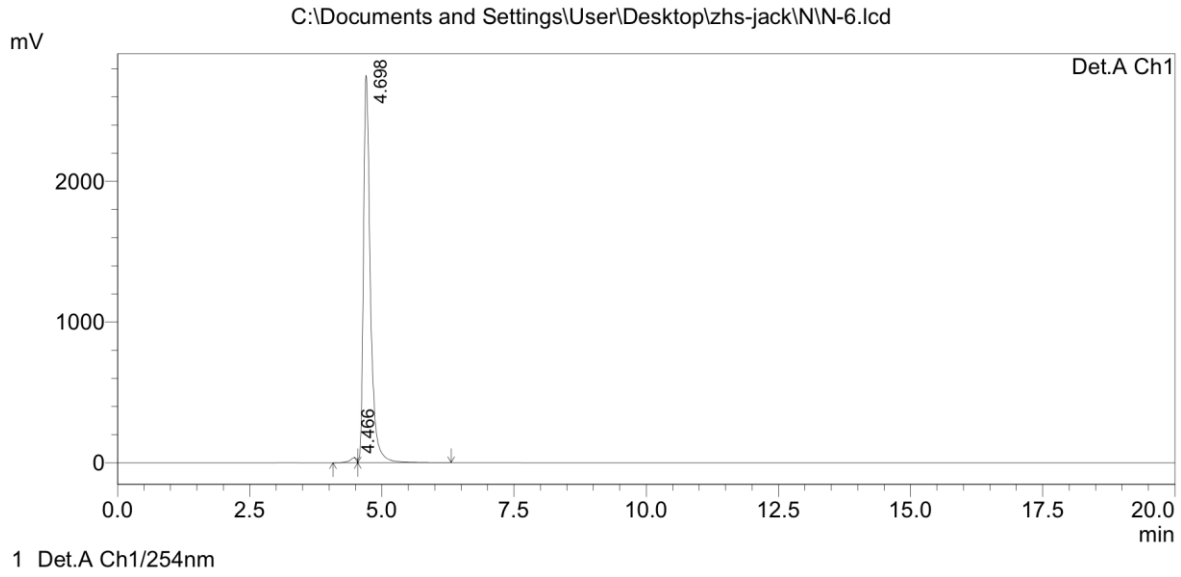

N41-Proton-Carbon
CDCl3
f1 (ppm)


C:\Documents and Settings\User\Desktop\zhs-jack\N\N-41.lcd
mV
Det.A Ch1
4.906
4.638
min
1 Det.A Ch1/254nm

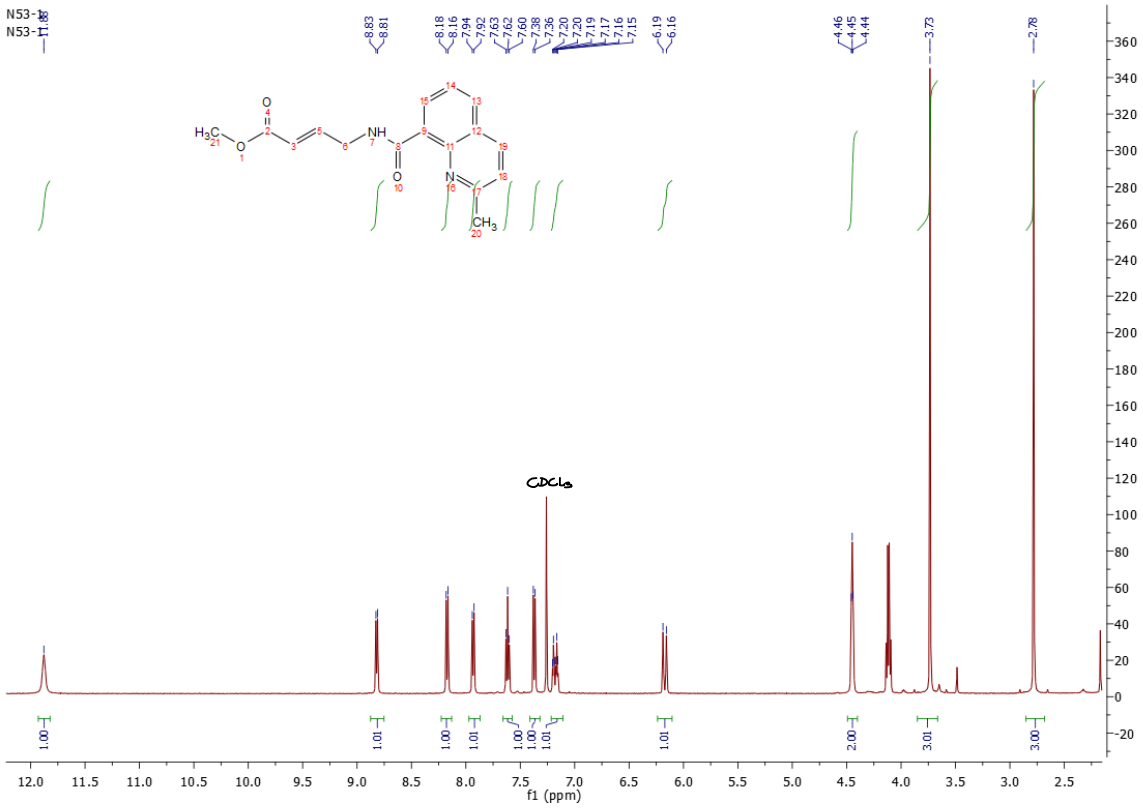
Methyl (*E*)-4-(quinoline-8-carboxamido)but-2-enoate (17)

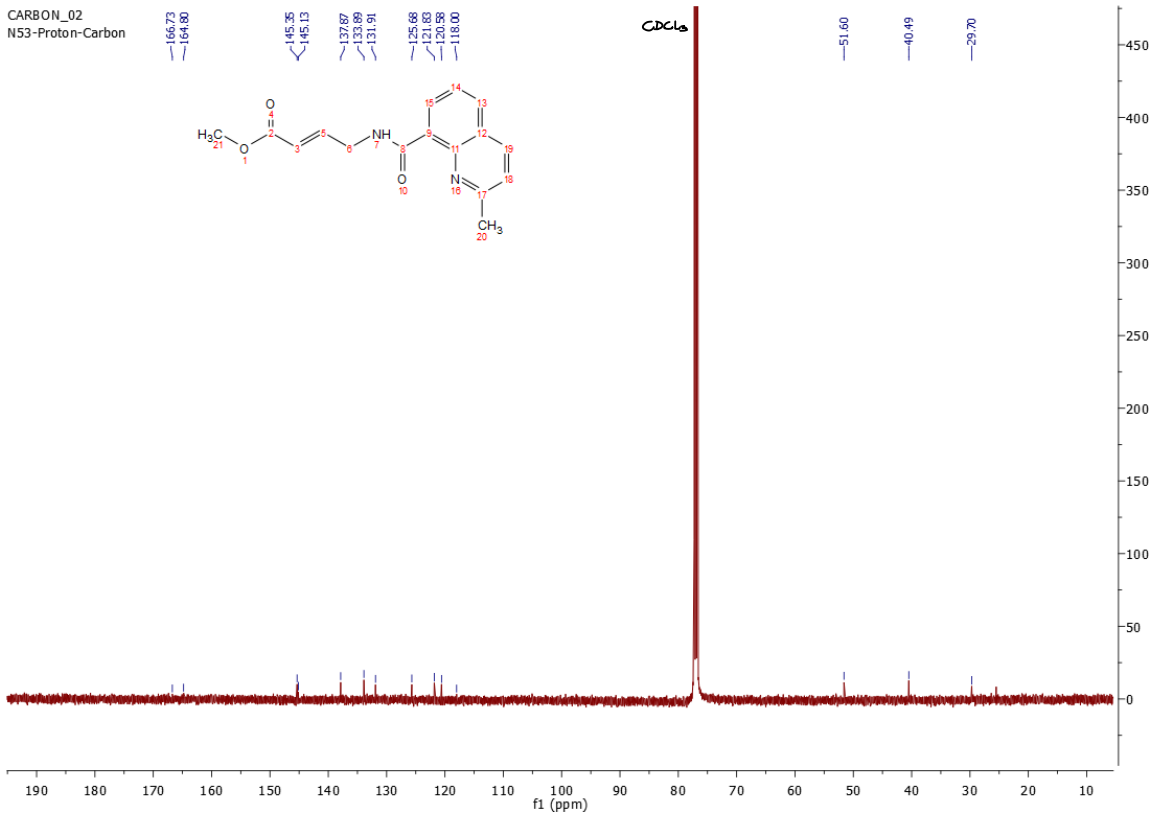


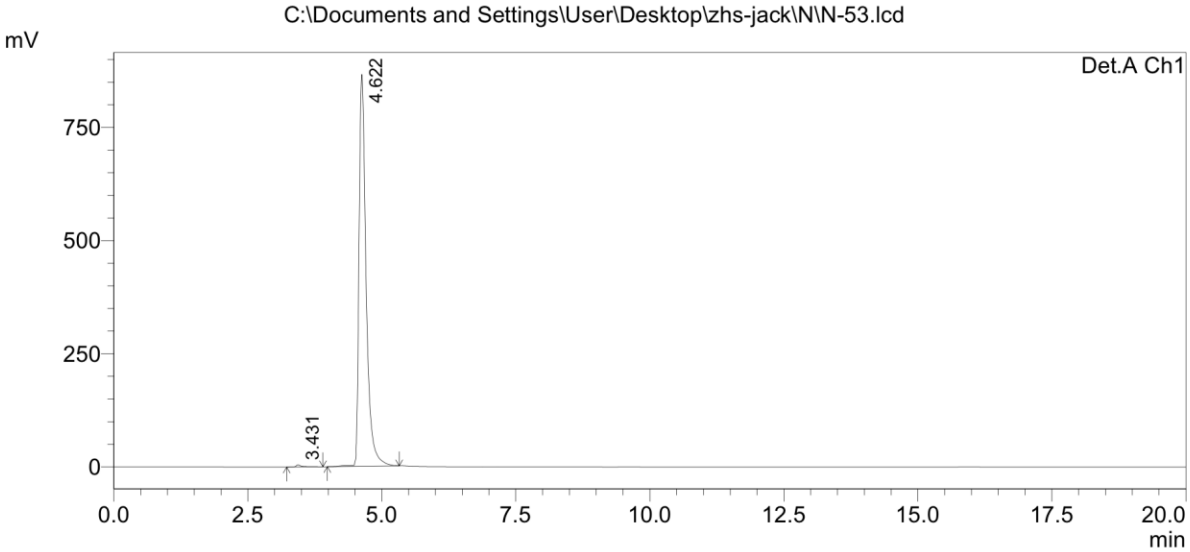




Methyl (*E*)-4-(2-methylquinoline-8-carboxamido)but-2-enoate (18)

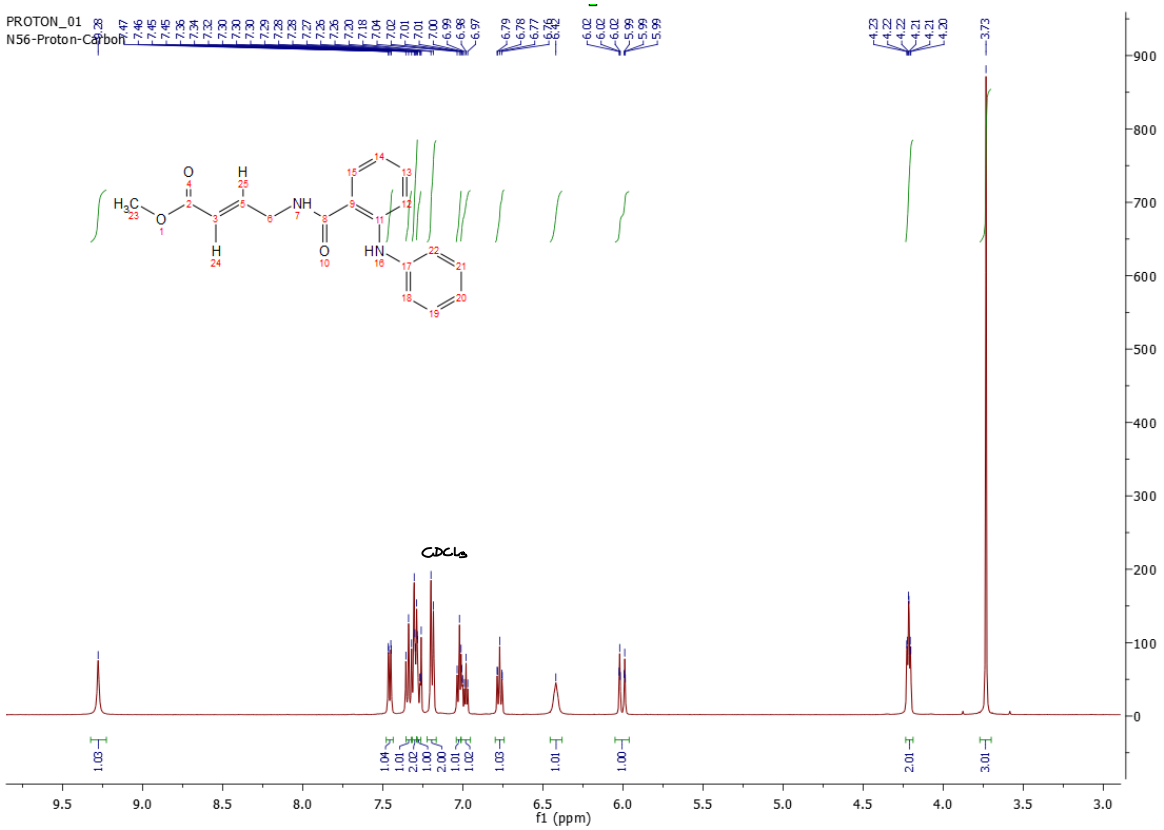


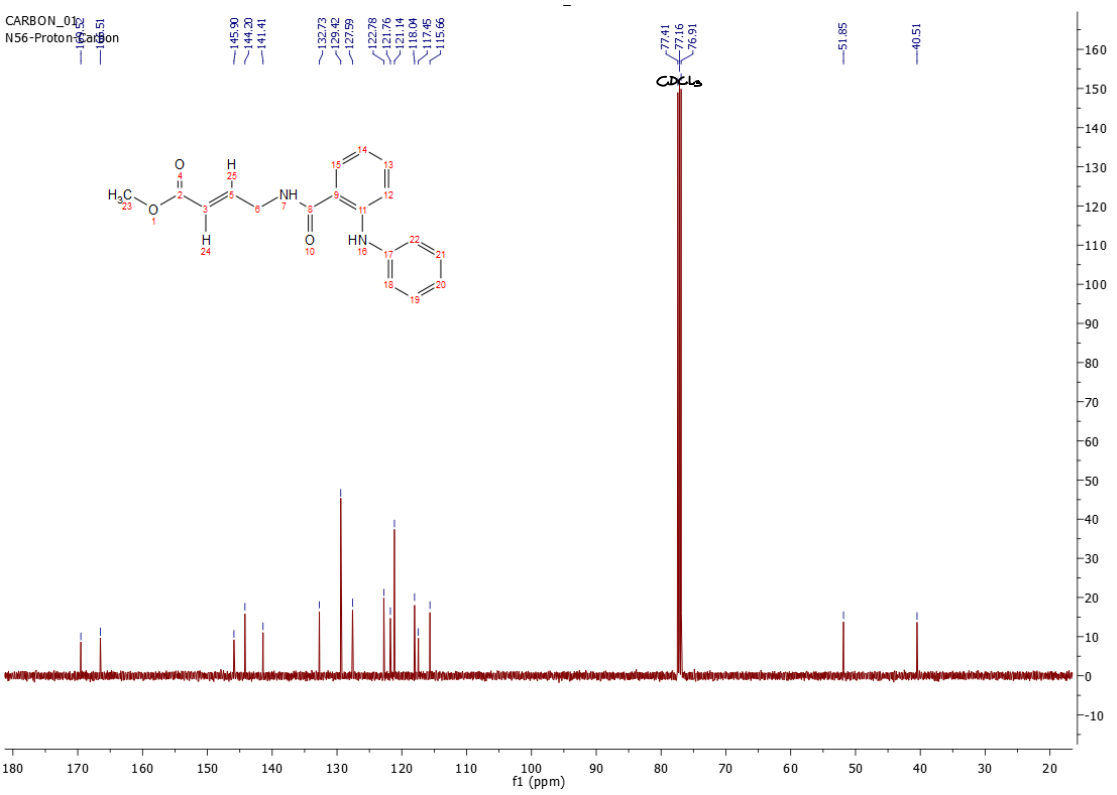


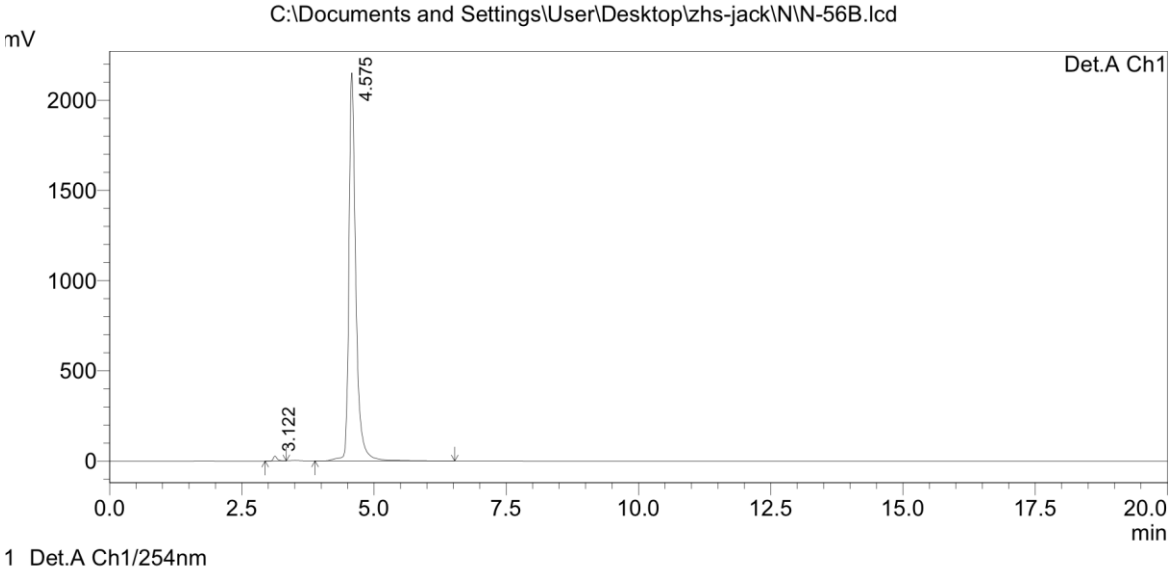


1 Det.A Ch1/254nm

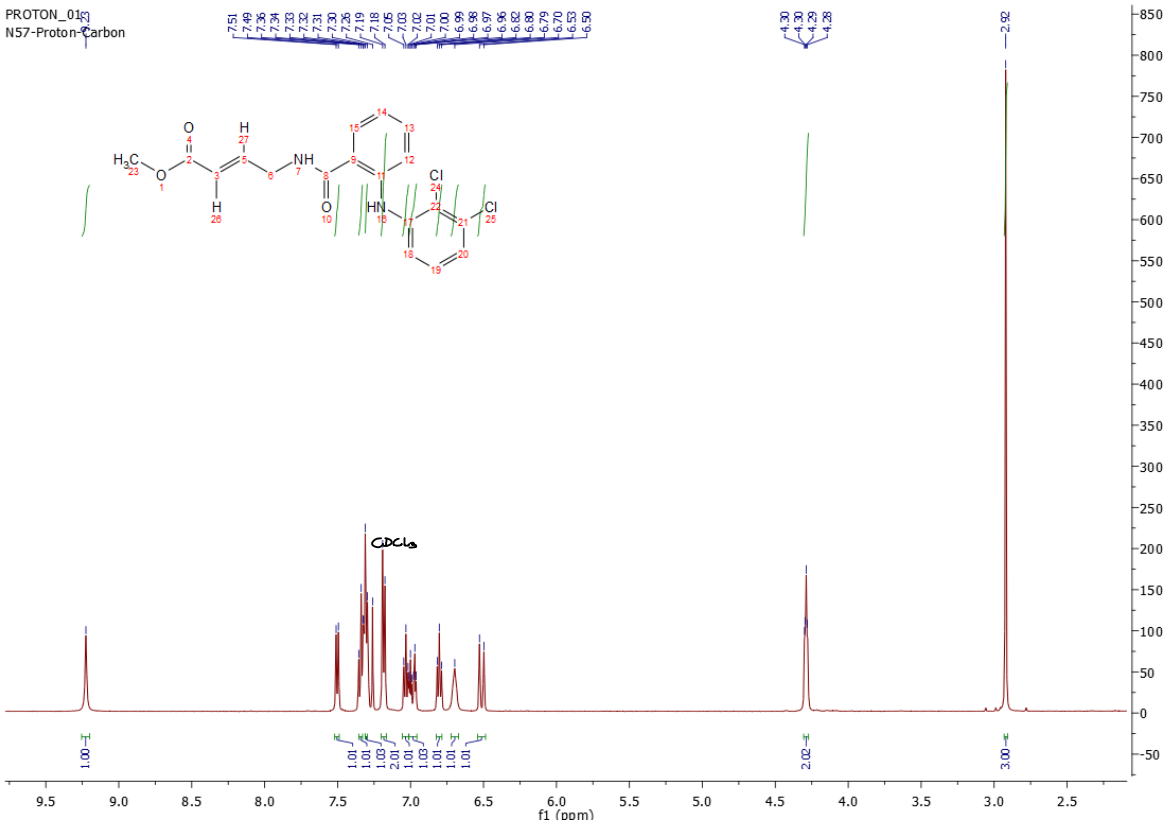
Methyl (*E*)-4-(2-(phenylamino)benzamido)but-2-enoate (19)

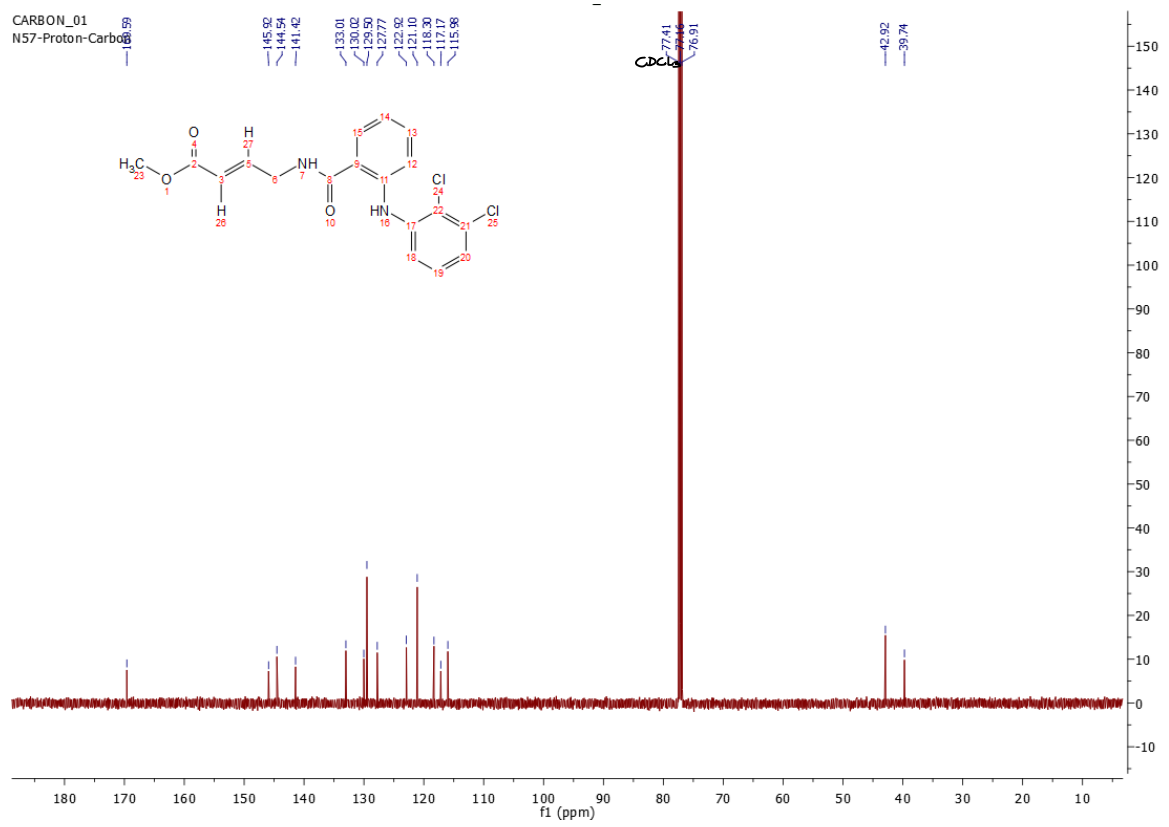


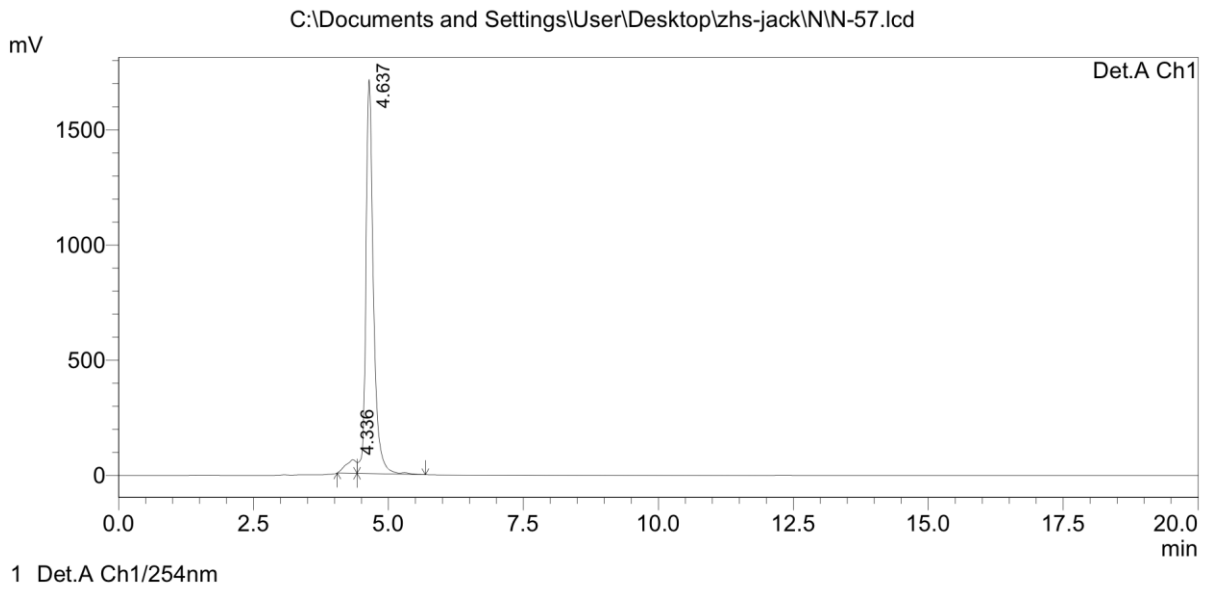




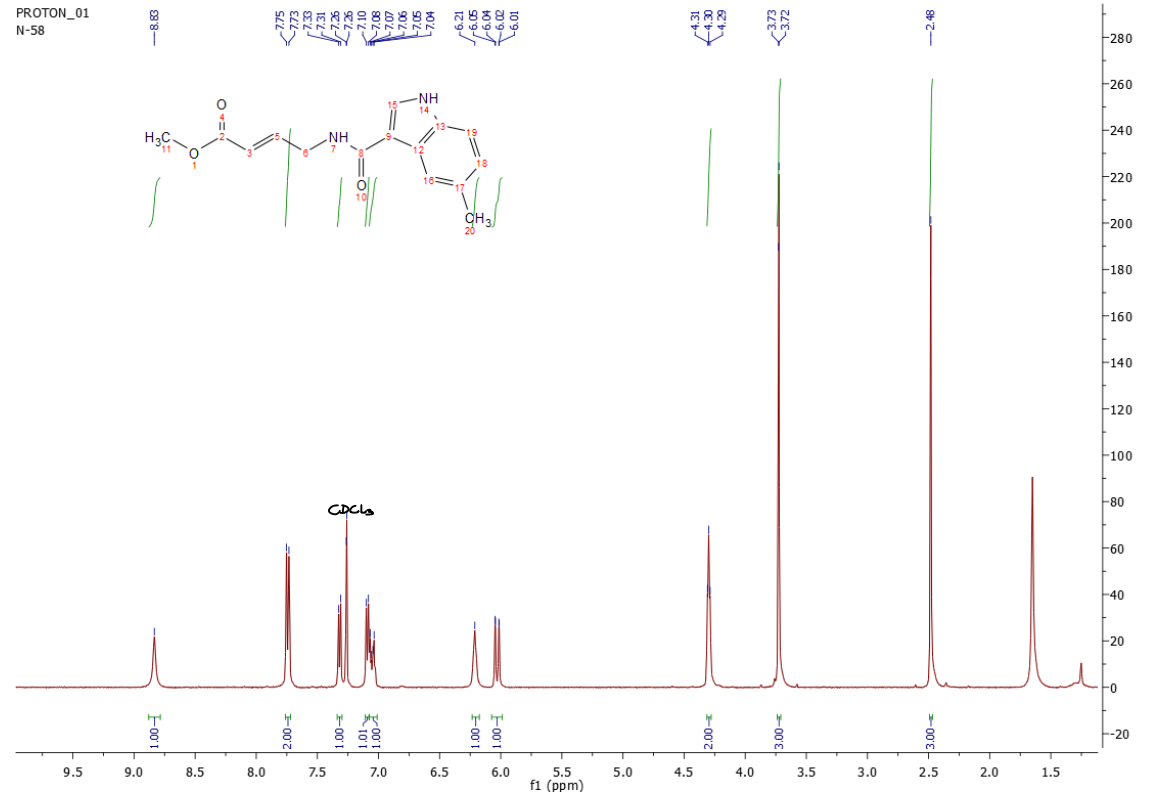
Methyl (*E*)-4-(2-((2,3-dichlorophenyl)amino)benzamido)but-2-enoate (20)

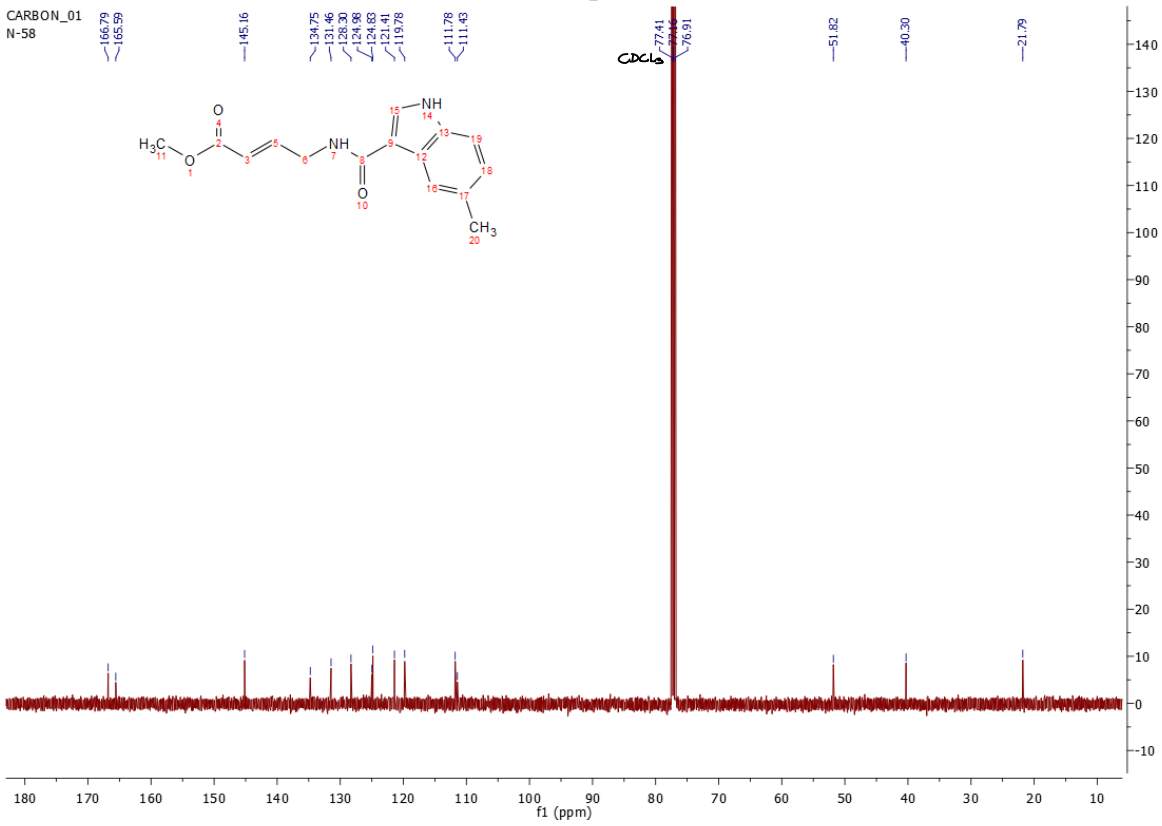

PROTON_01
N57-Proton-Carbon
7.51
7.49
7.36
7.34
7.33
7.32
7.31
7.30
7.25
7.19
7.18
7.05
7.03
7.02
7.01
7.00
6.99
6.98
6.97
6.96
6.82
6.80
6.79
6.70
6.53
6.50
4.30
4.30
4.29
4.28
2.92
CDCl3
1.00
1.01
1.01
1.03
2.01
1.01
1.03
1.01
1.01
1.01
2.02
3.00
f1 (ppm)

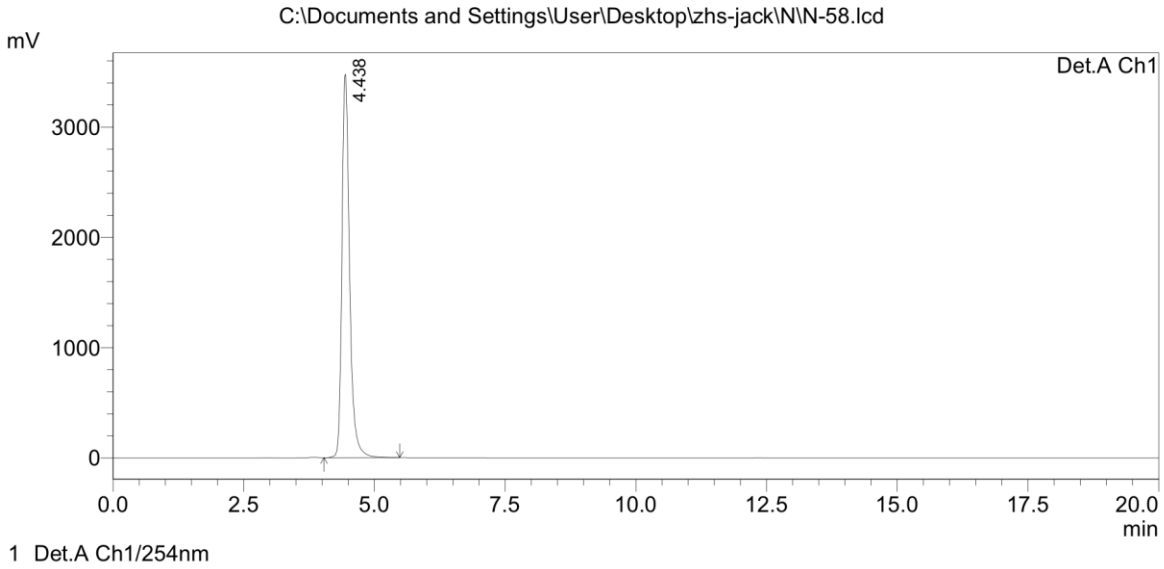

CARBON_01
N57-Proton-Carbon
166.59
145.92
144.54
141.42
133.01
130.02
129.50
127.77
122.92
121.10
118.30
117.17
115.98
77.41
77.16
76.91
CDCl3
42.92
39.74
f1 (ppm)



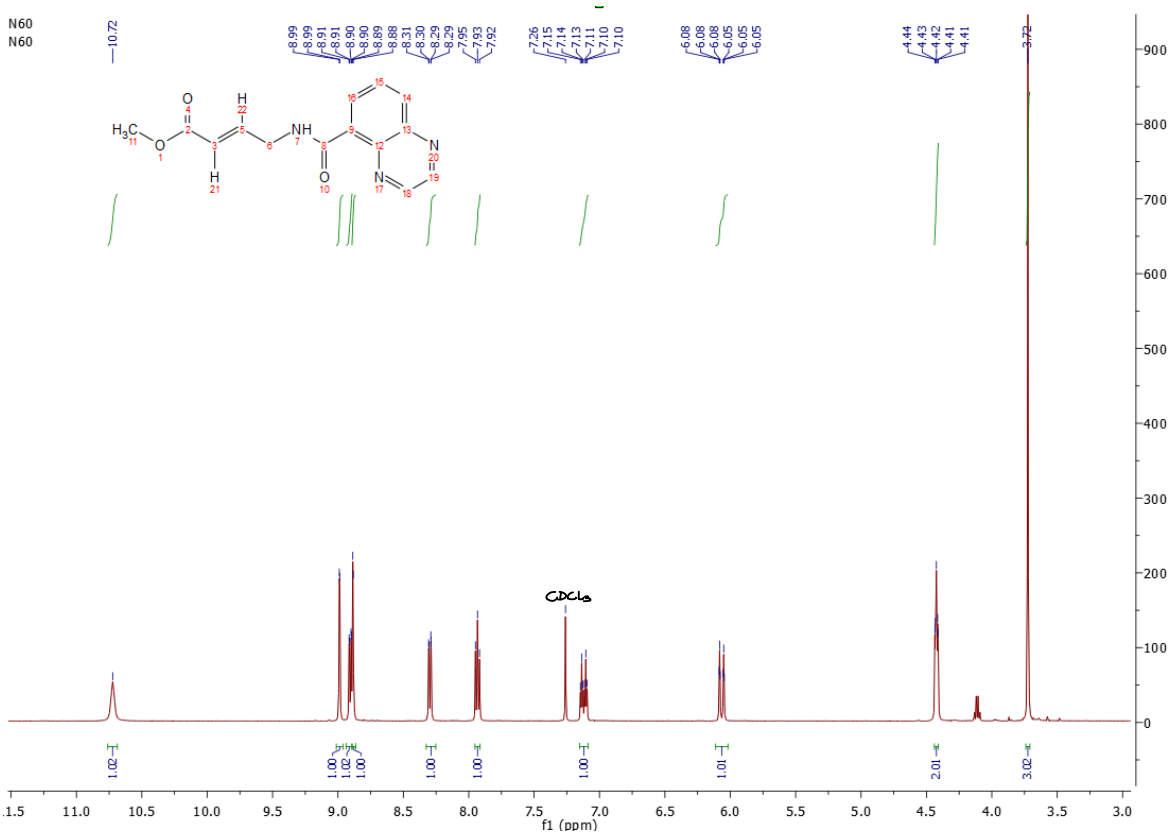
Methyl (*E*)-4-(5-methyl-1H-indole-3-carboxamido)but-2-enoate (21)

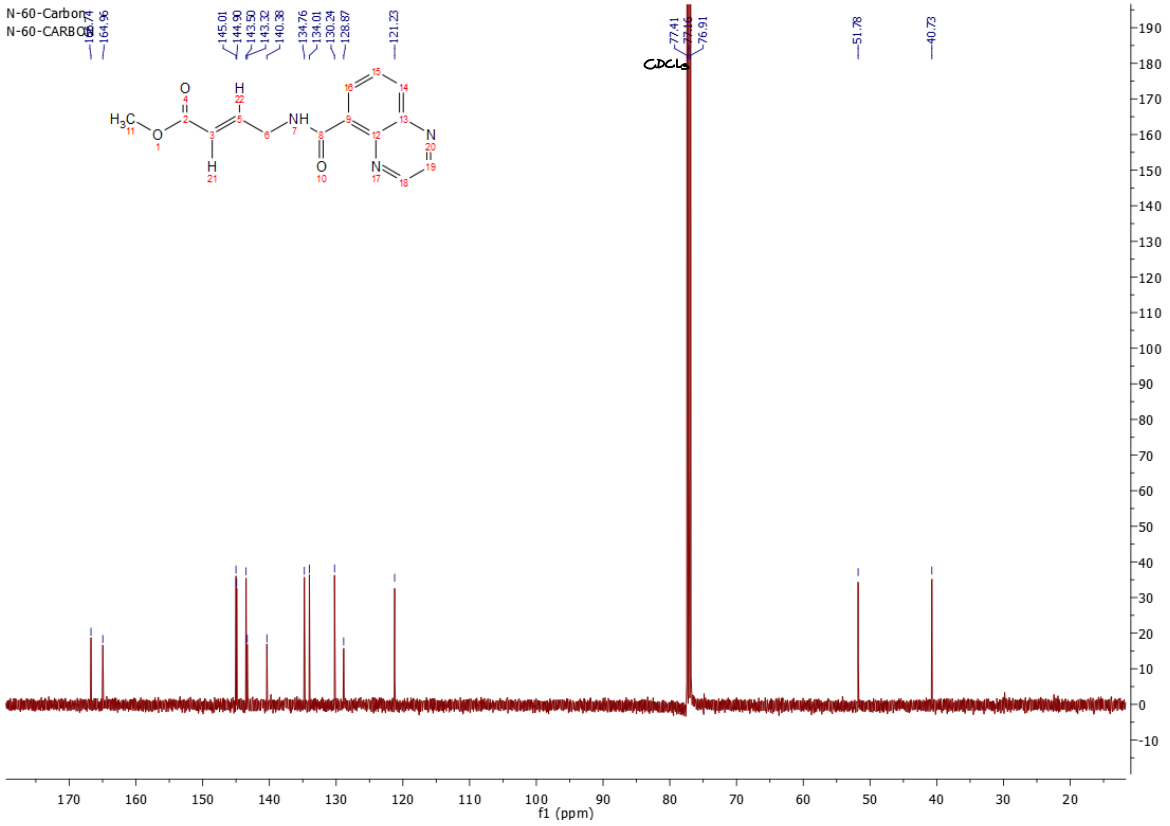

PROTON_01
N-58
8.83
7.75
7.73
7.33
7.31
7.26
7.26
7.10
7.08
7.07
7.06
7.05
7.04
6.21
6.05
6.04
6.02
6.01
4.31
4.30
4.29
3.73
3.72
2.48
CDCl3
f1 (ppm)

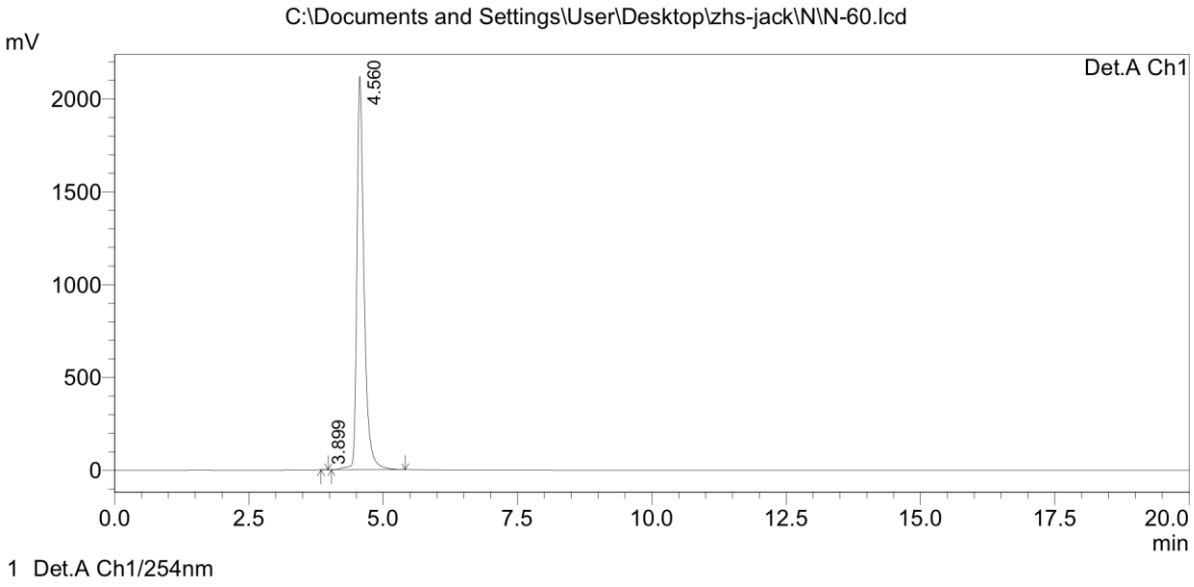

CARBON_01
N-58
166.79
165.59
145.16
134.75
131.46
128.30
124.98
124.83
121.41
119.78
111.78
111.43
77.41
77.16
76.91
CDCl3
51.82
40.30
21.79
f1 (ppm)



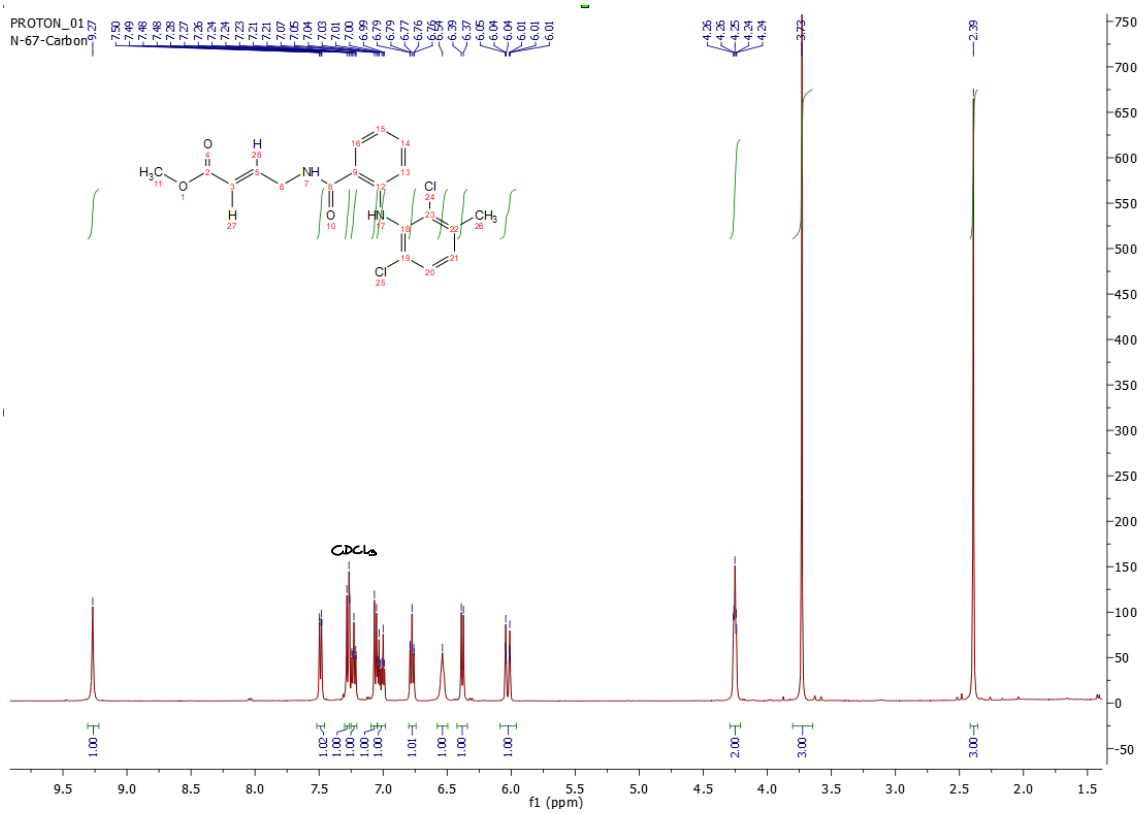
Methyl (*E*)-4-(quinoxaline-5-carboxamido)but-2-enoate (22)

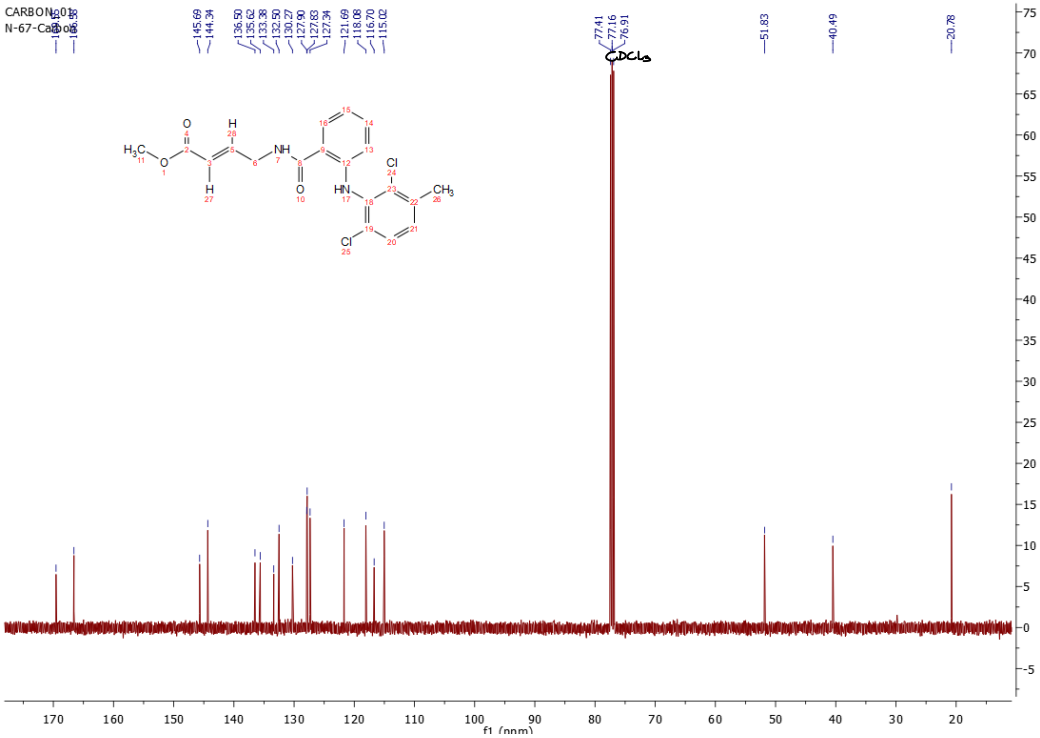


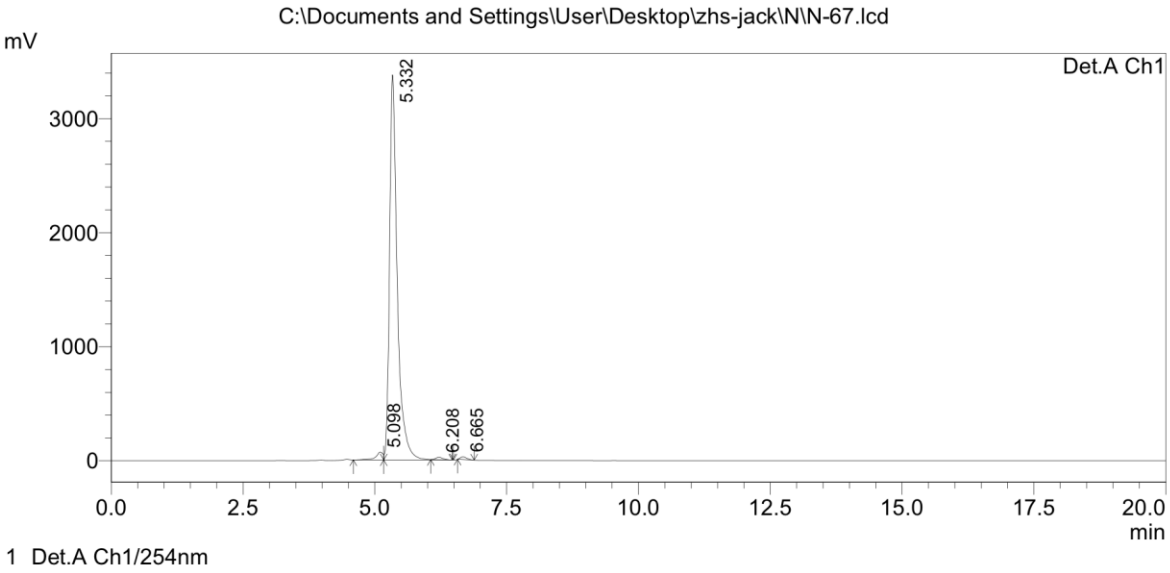

N-60-Carbon
N-60-CARBON
164.96
145.01
144.90
143.50
143.32
140.38
134.76
134.01
130.24
128.87
121.23
77.41
77.16
76.91
CDCl3
51.78
40.73
f1 (ppm)


C:\Documents and Settings\User\Desktop\zhs-jack\N\N-60.lcd
mV
Det.A Ch1
4.560
3.899
min
1 Det.A Ch1/254nm

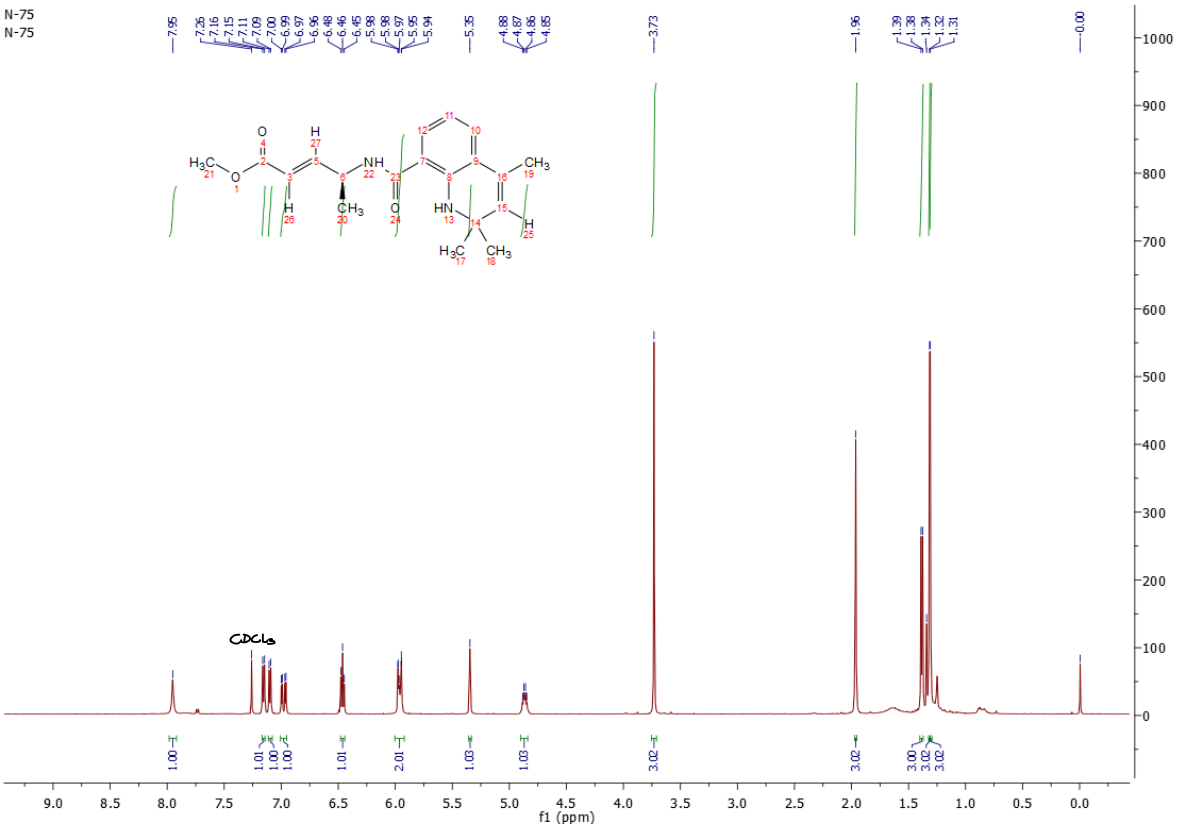
Methyl (*E*)-4-(2-((2,6-dichloro-3-methylphenyl)amino)benzamido)but-2-enoate (23)

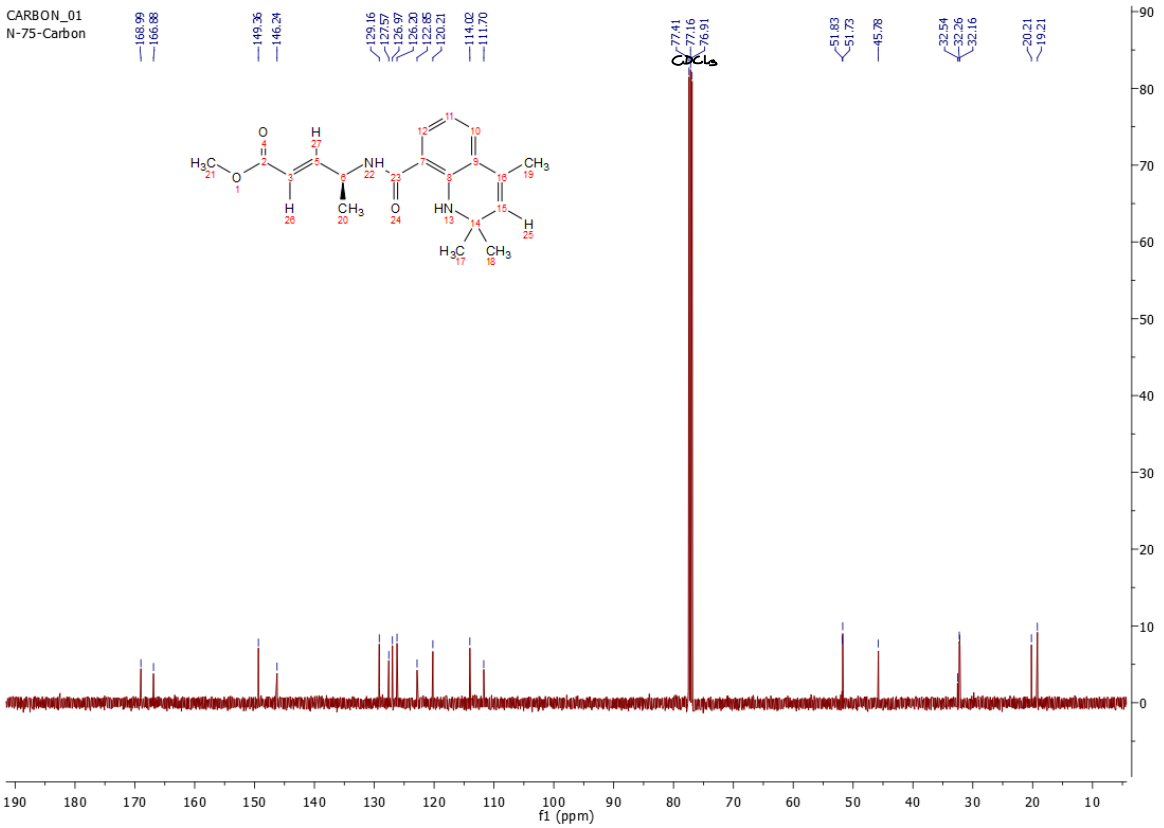


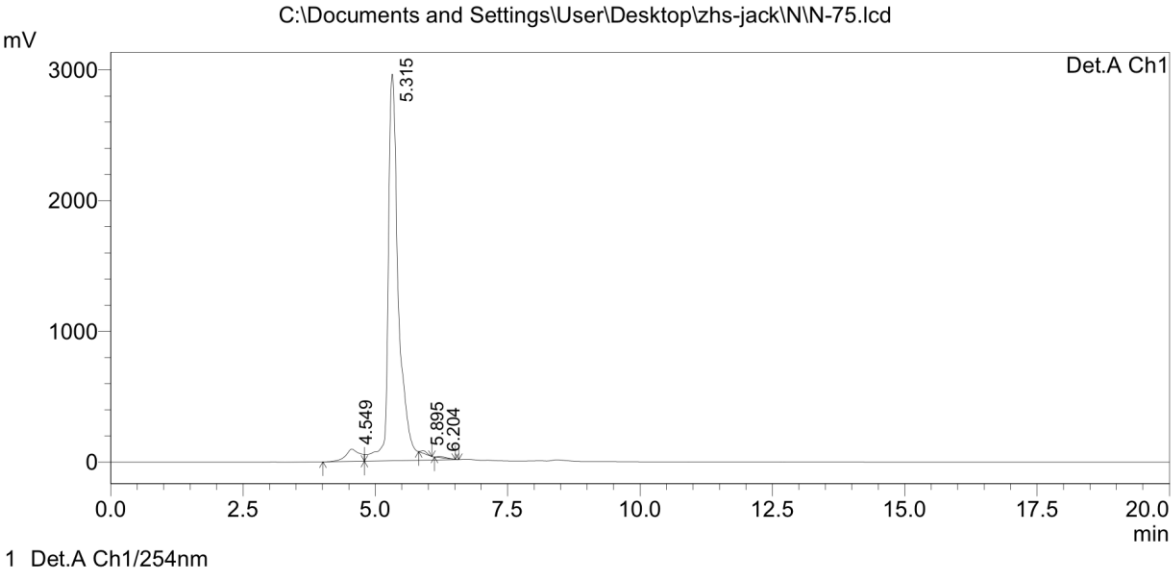




Methyl (*S*,*E*)-4-(2,2,4-trimethyl-1,2-dihydroquinoline-8-carboxamido)pent-2-enoate (24)

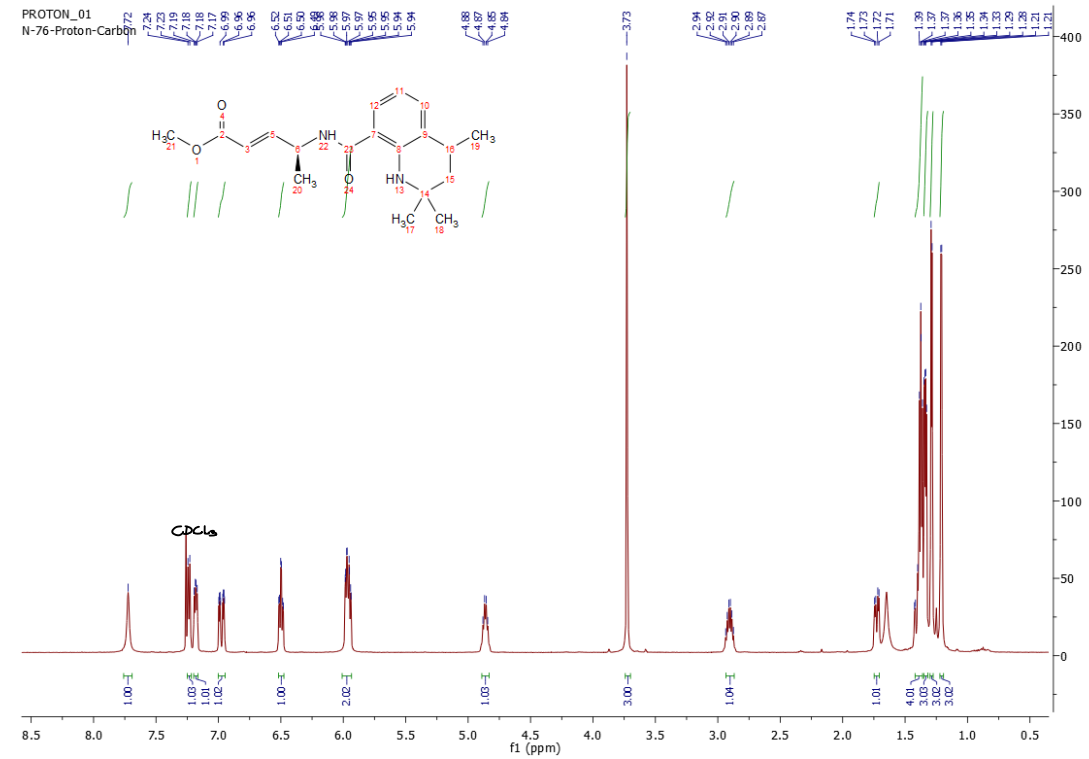


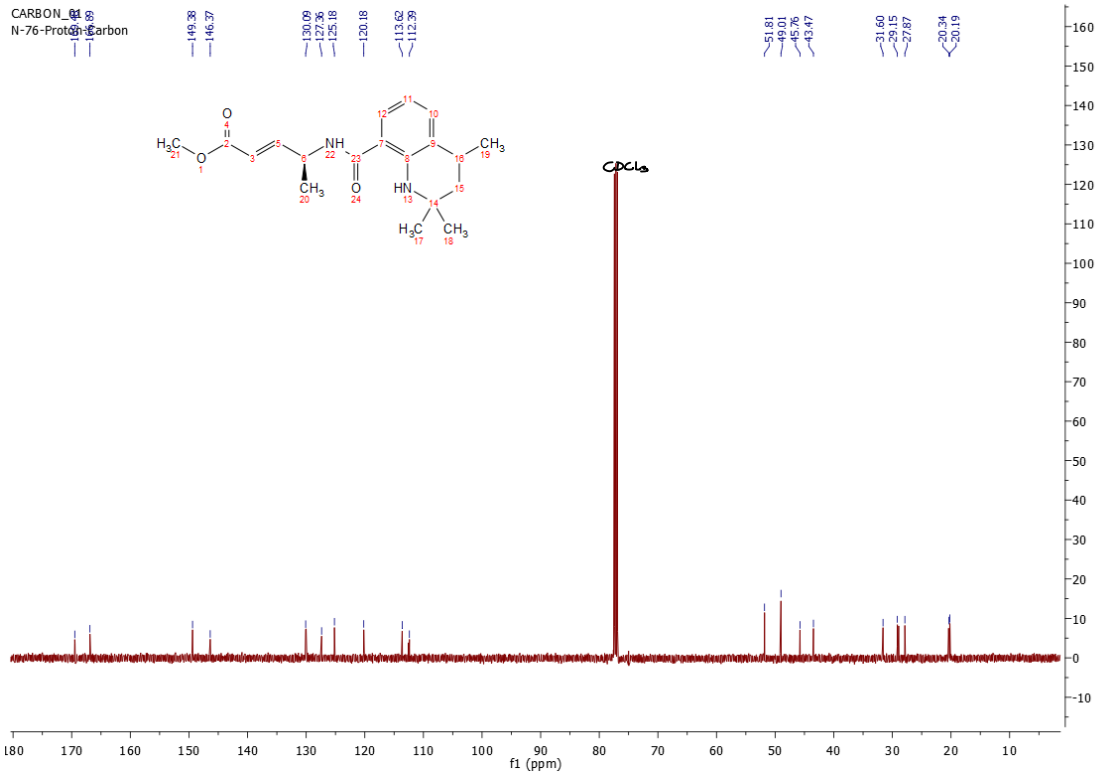


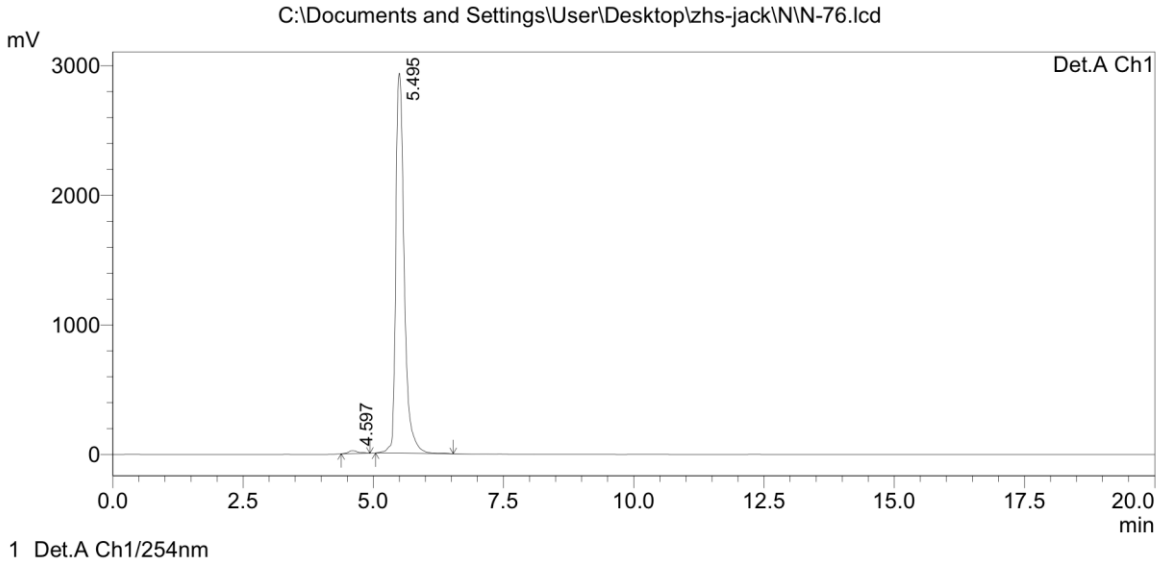


1 Det.A Ch1/254nm

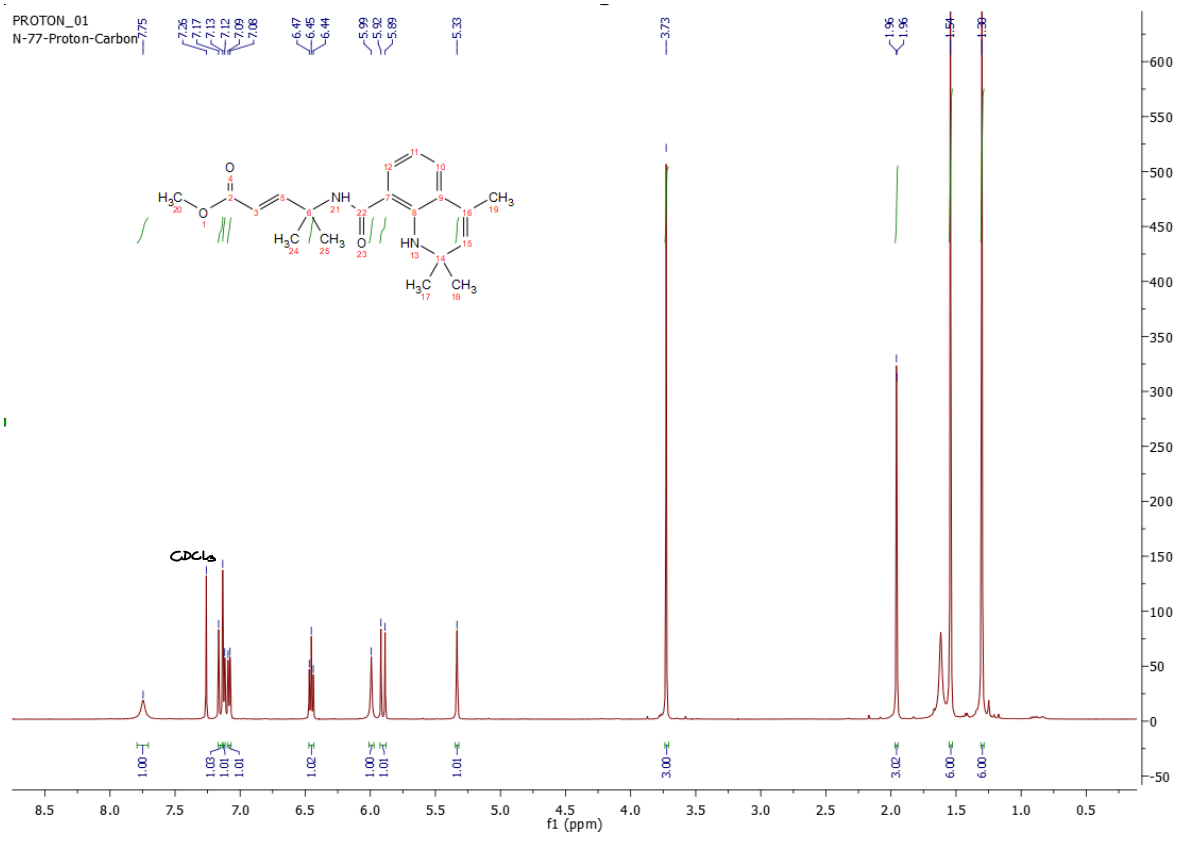
Methyl (*S*,*E*)-4-(2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-8-carboxamido)pent-2-enoate (25)

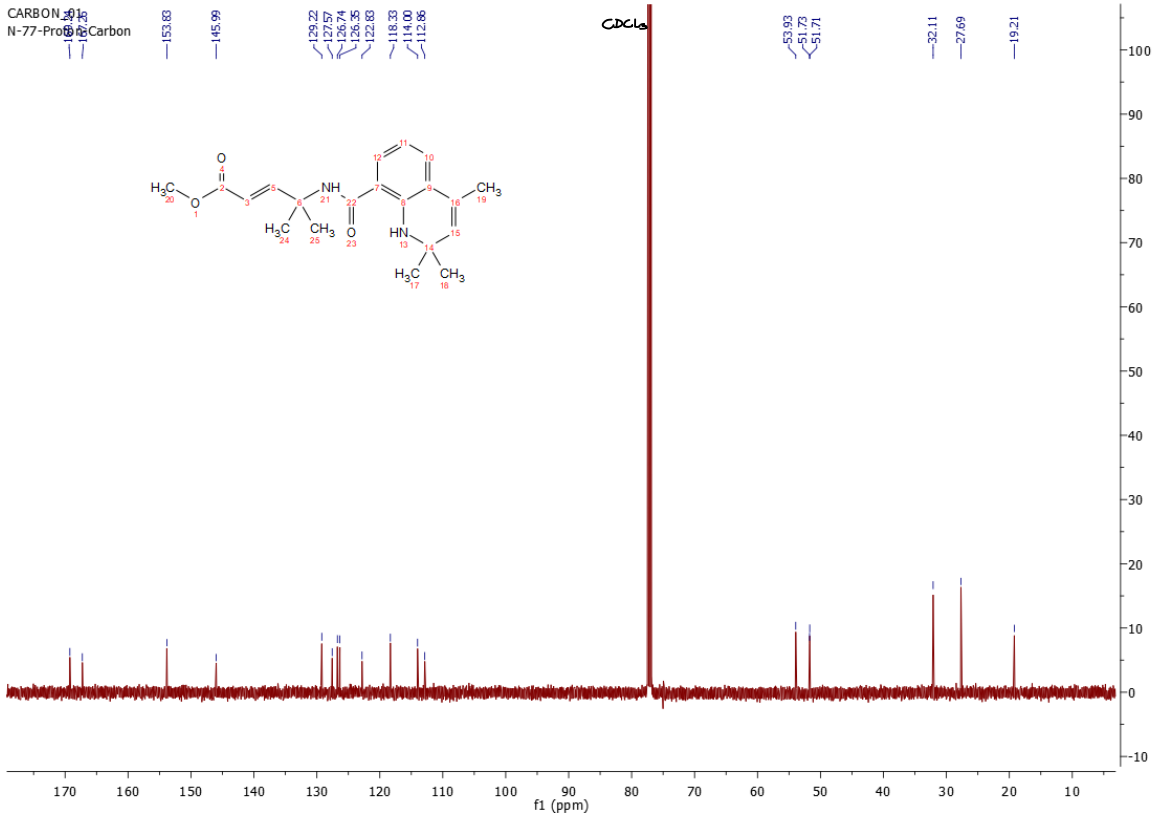


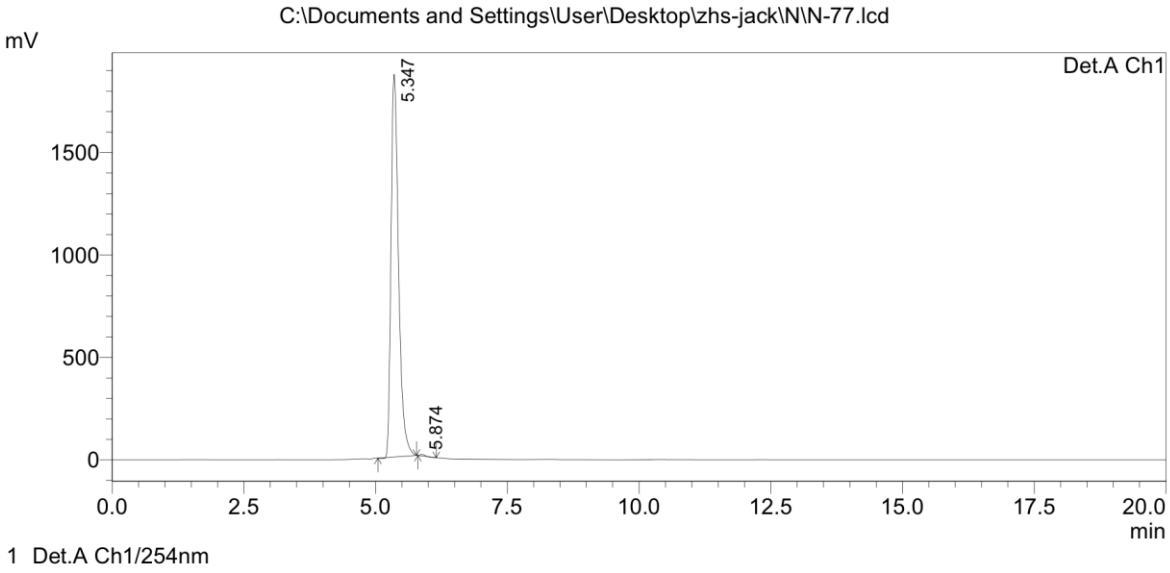




Methyl (*E*)-4-methyl-4-(2,2,4-trimethyl-1,2-dihydroquinoline-8-carboxamido)pent-2-enoate (26)

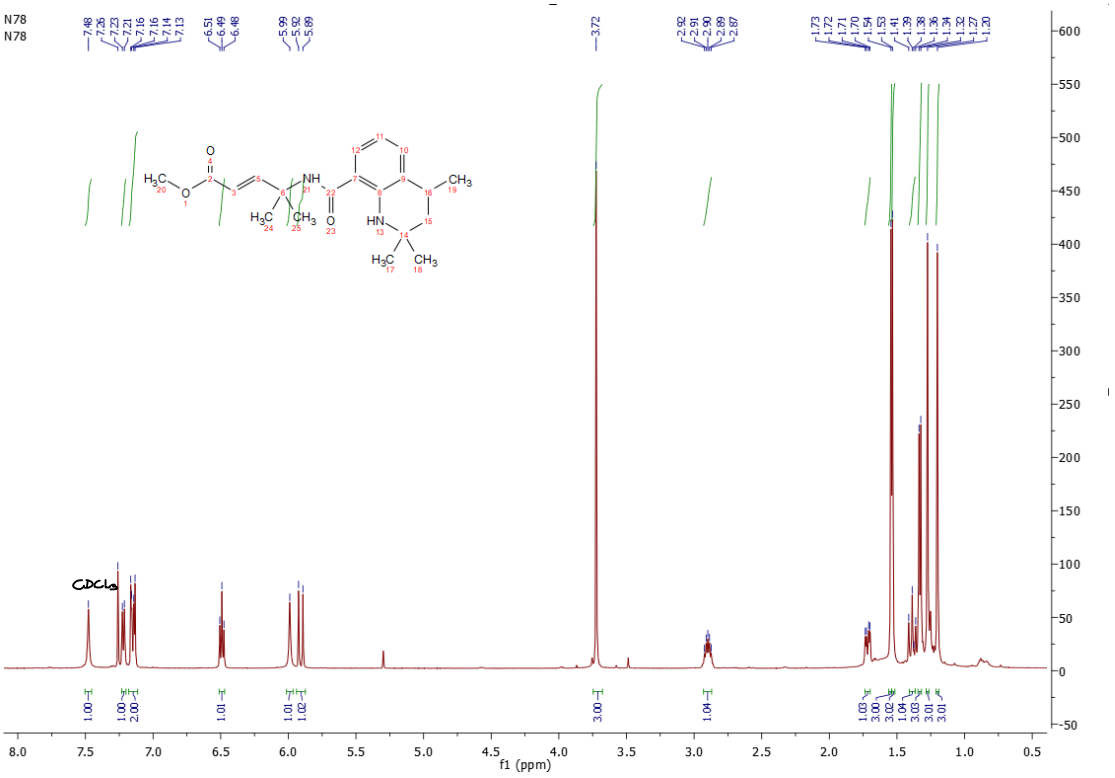


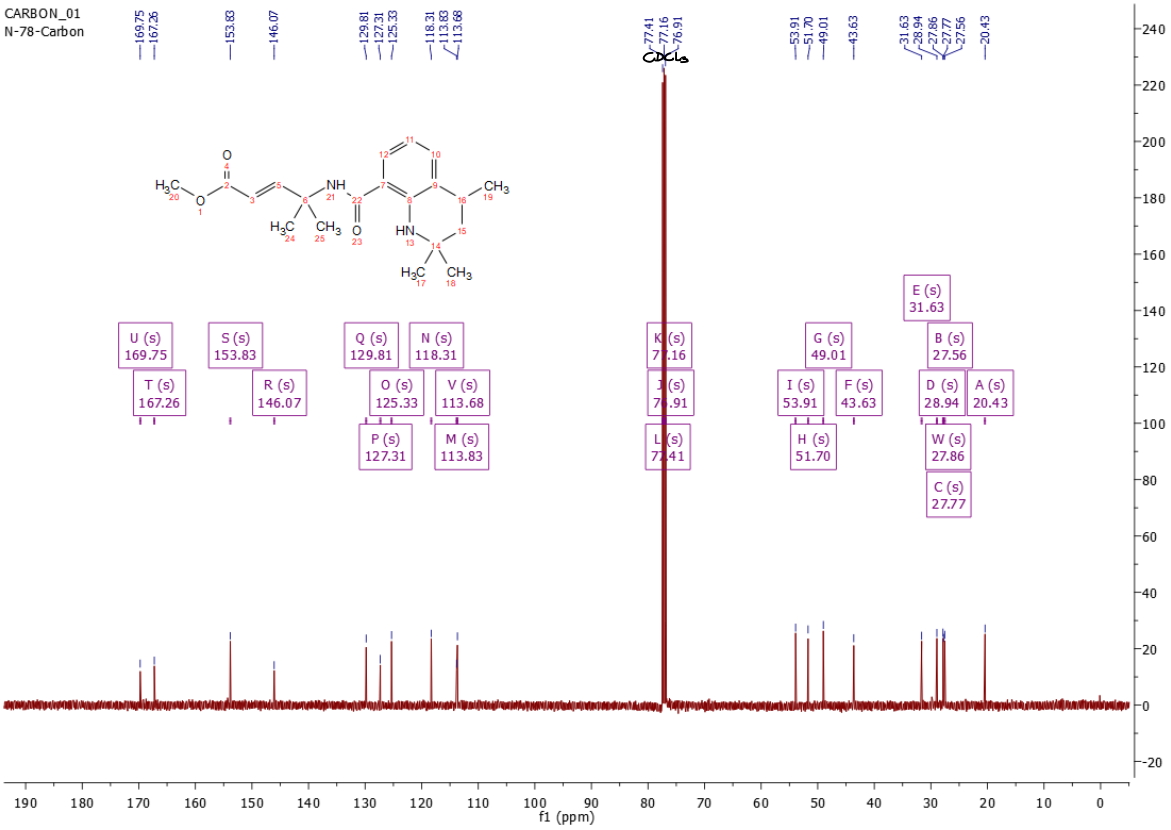


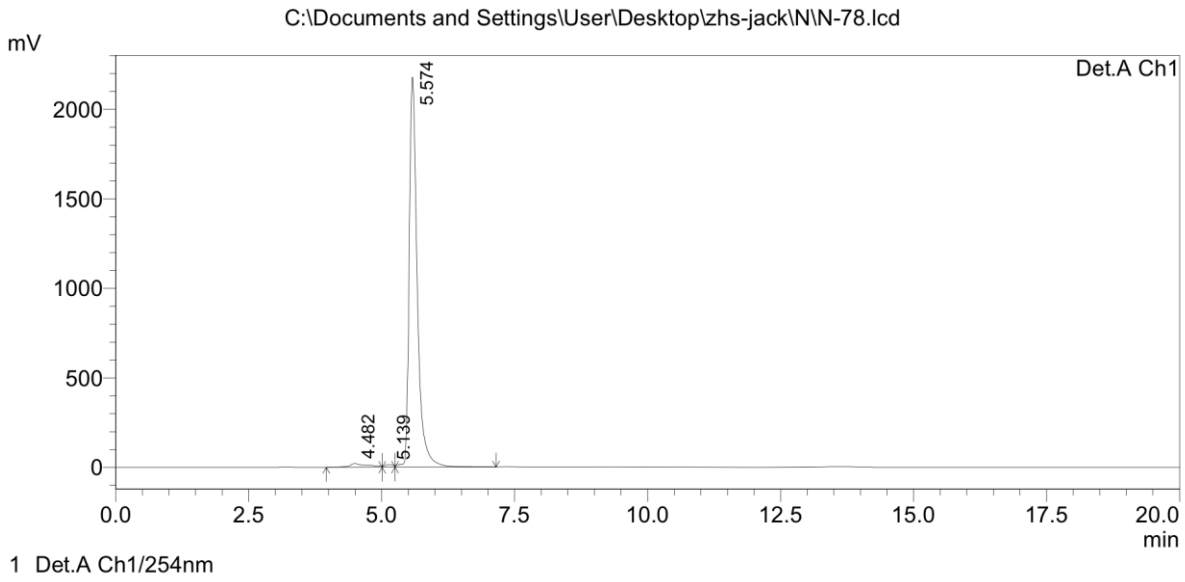


1 Det.A Ch1/254nm

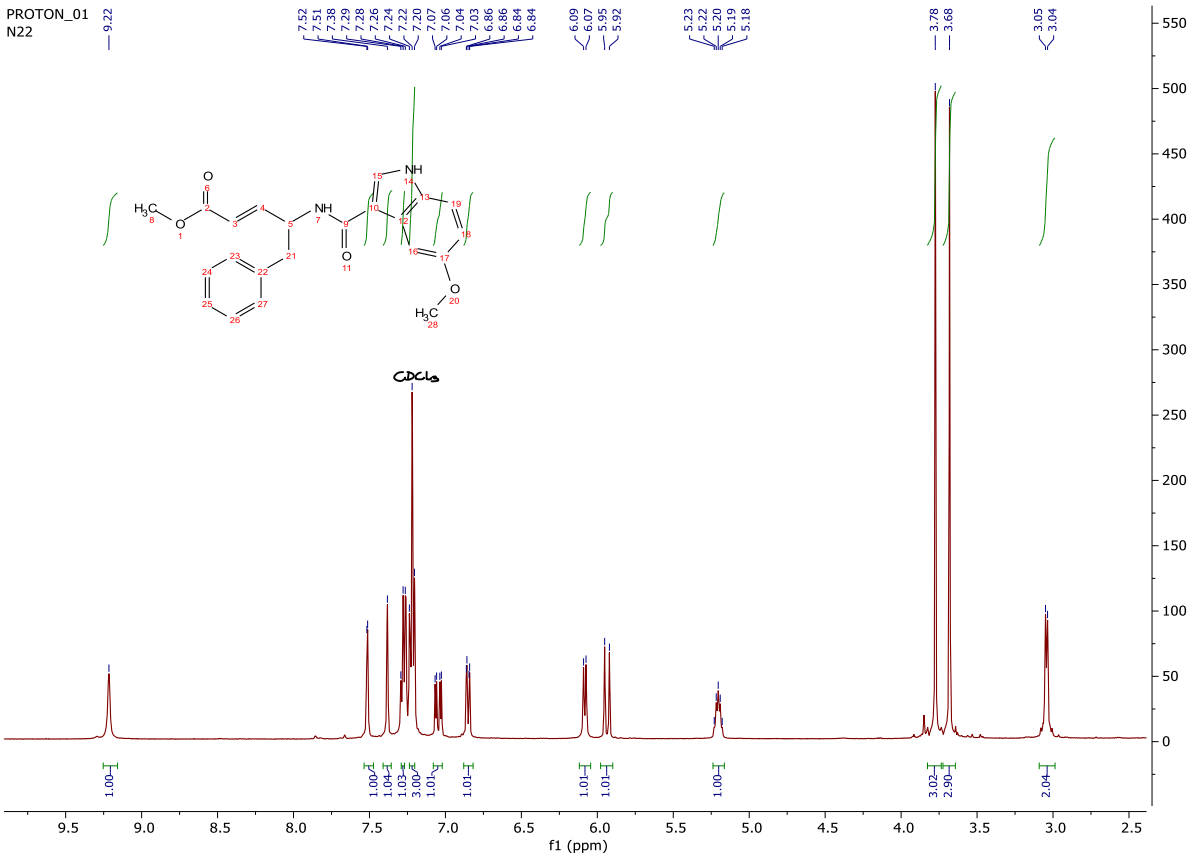
Methyl-(*E*)-4-methyl-4-(2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline-8-carboxamido)pent-2-enoate (27)

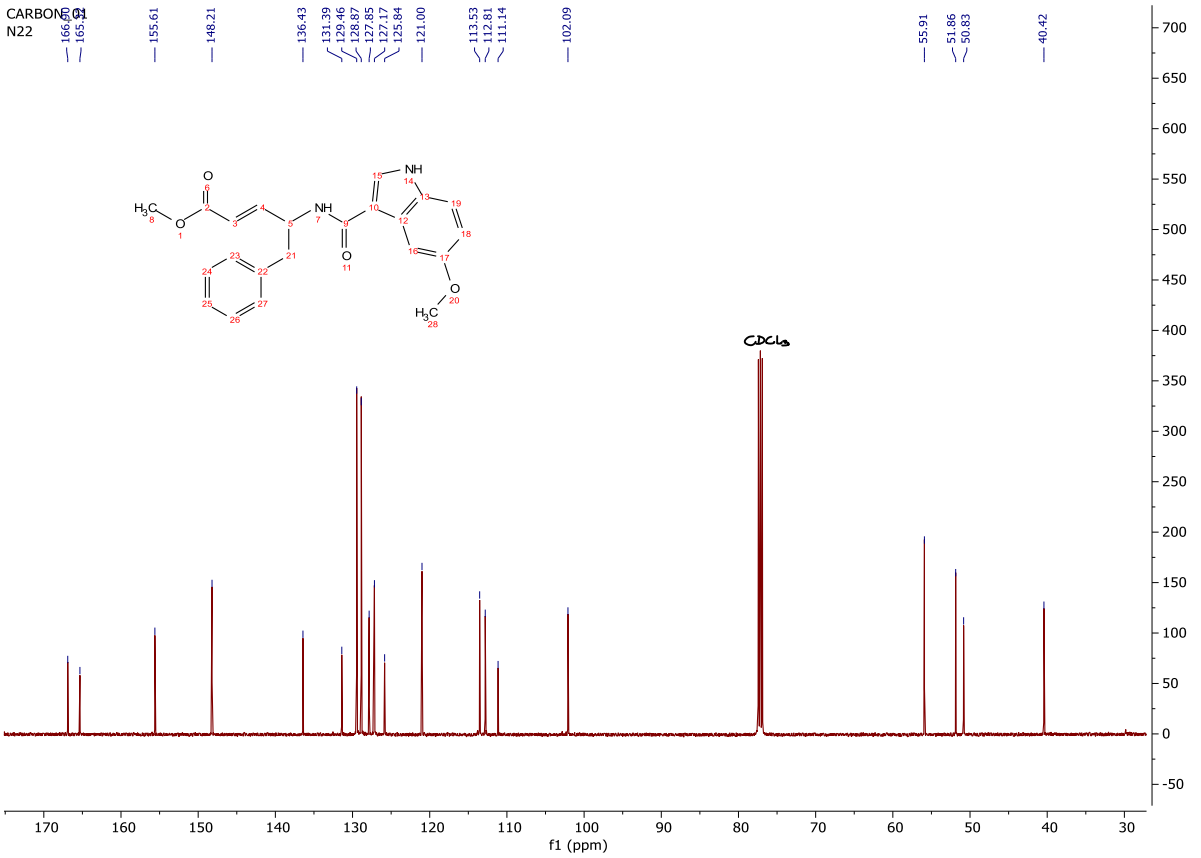


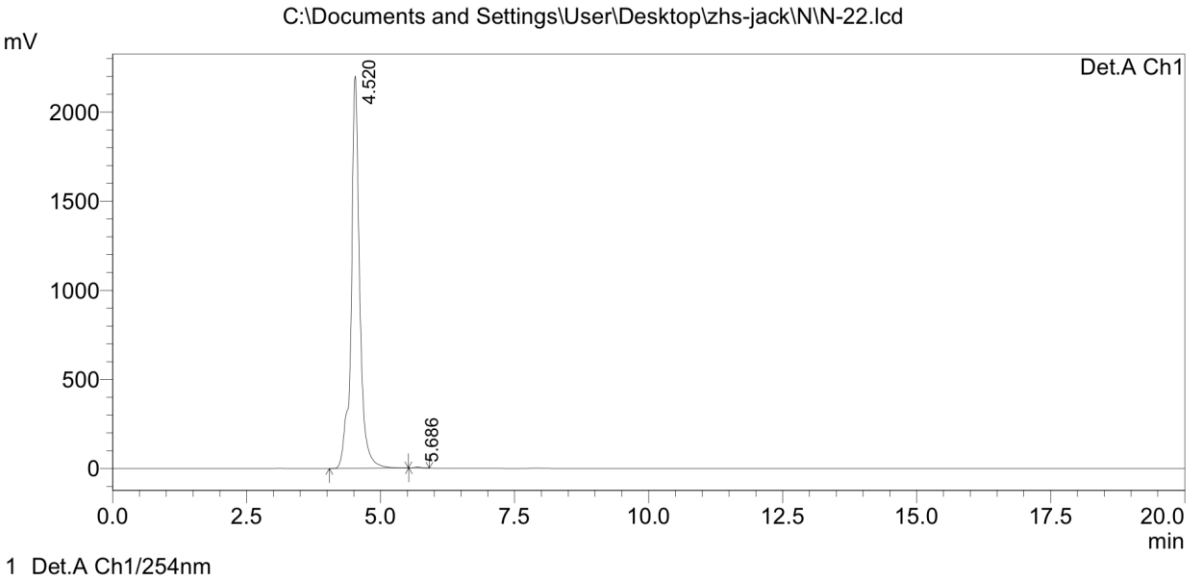




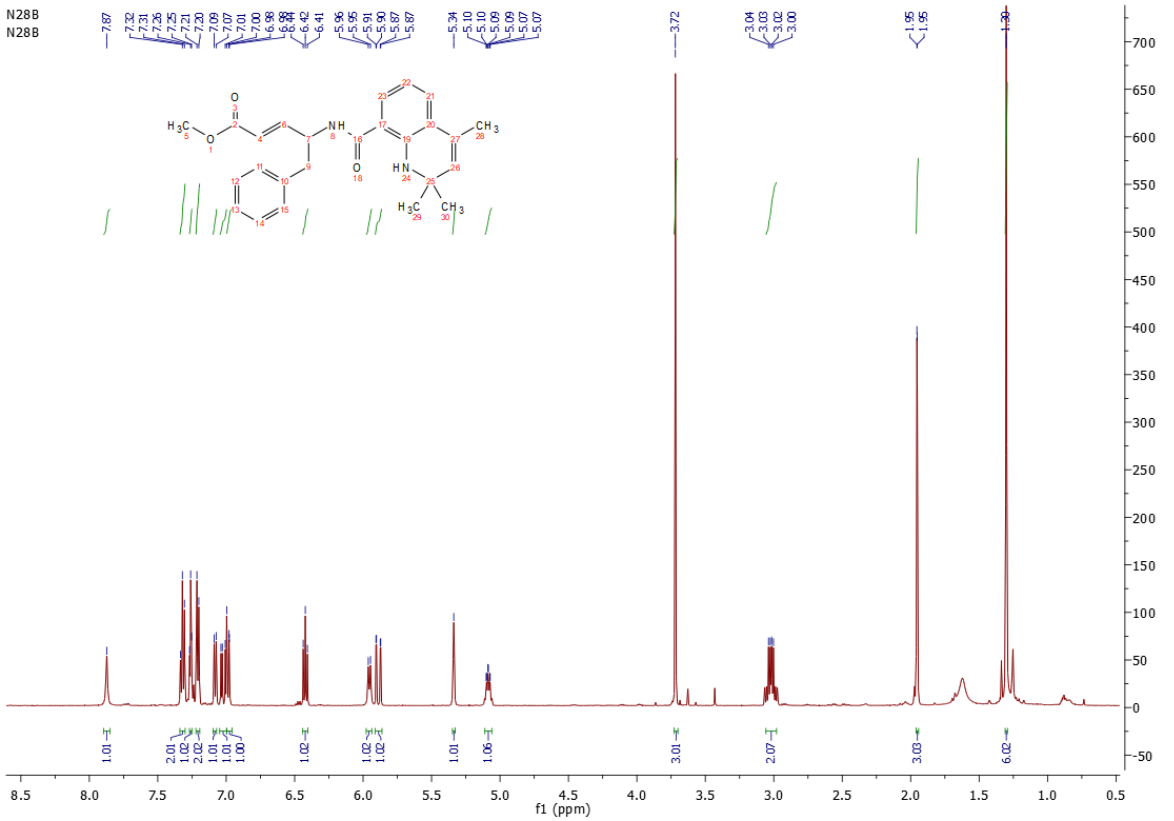
Methyl (*S*,*E*)-4-(5-methoxy-1H-indole-3-carboxamido)-5-phenylpent-2-enoate (28)

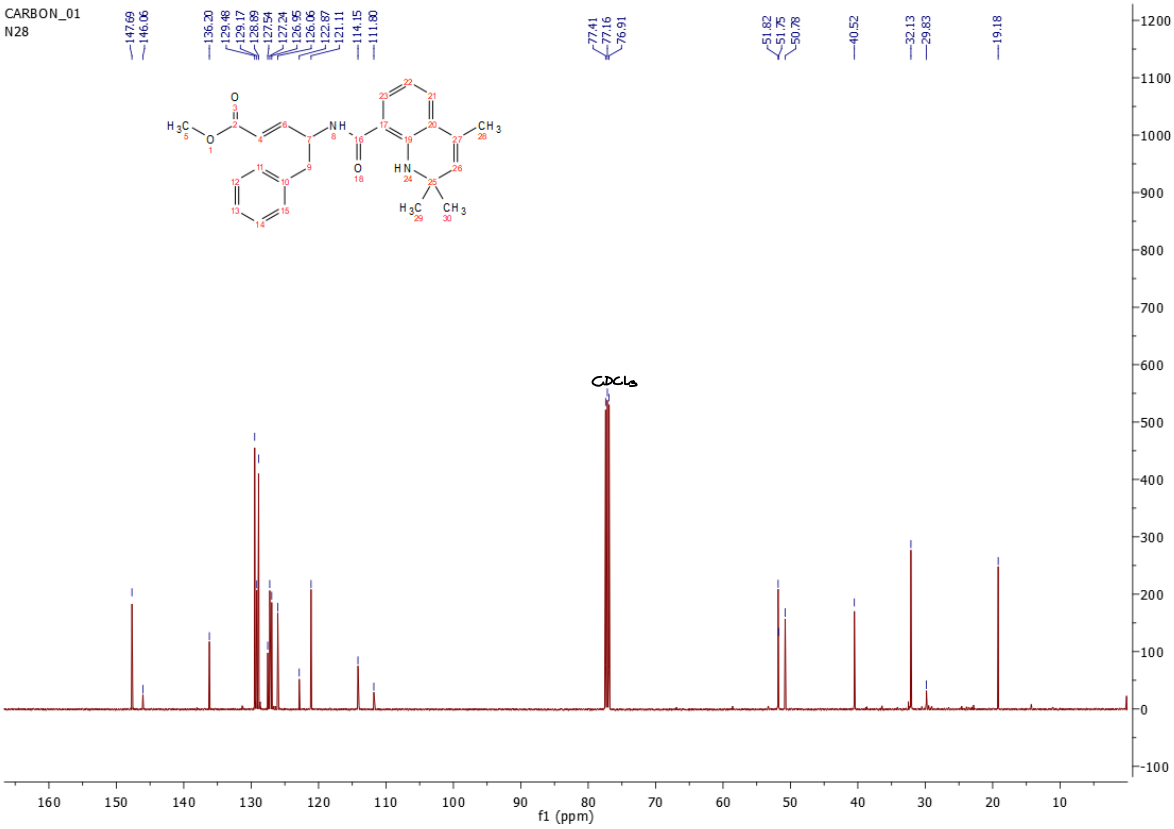


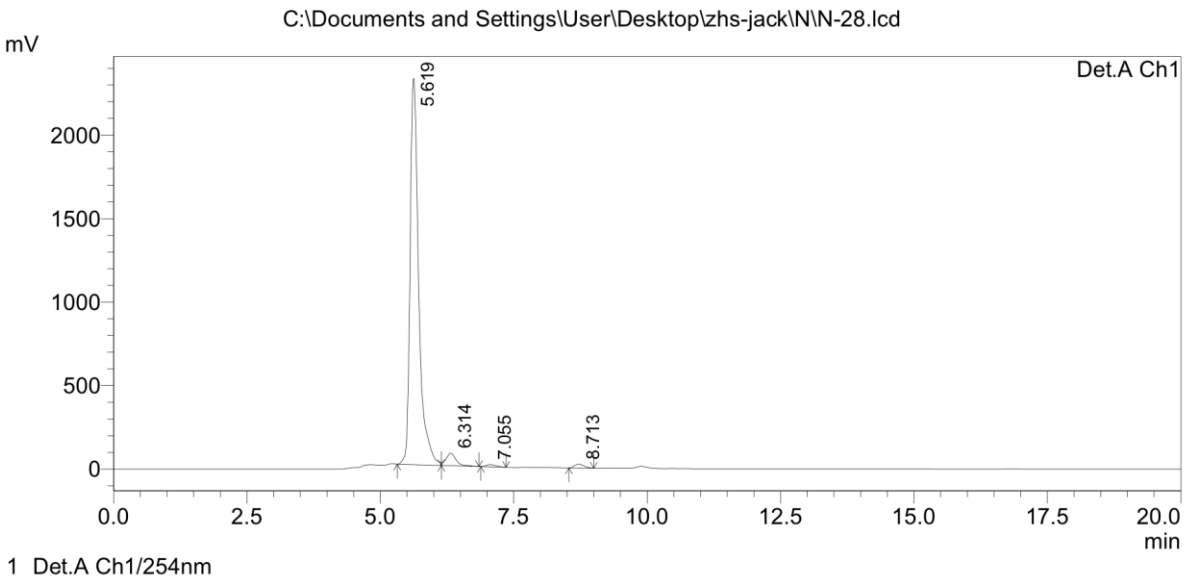

CARBON-01
N22
166.64
165.41
155.61
148.21
136.43
131.39
129.46
128.87
127.85
127.17
125.84
121.00
113.53
112.81
111.14
102.09
55.91
51.86
50.83
40.42
CDCl3
f1 (ppm)


C:\Documents and Settings\User\Desktop\zhs-jack\N\N-22.lcd
mV
Det.A Ch1
4.520
5.686
min
1 Det.A Ch1/254nm

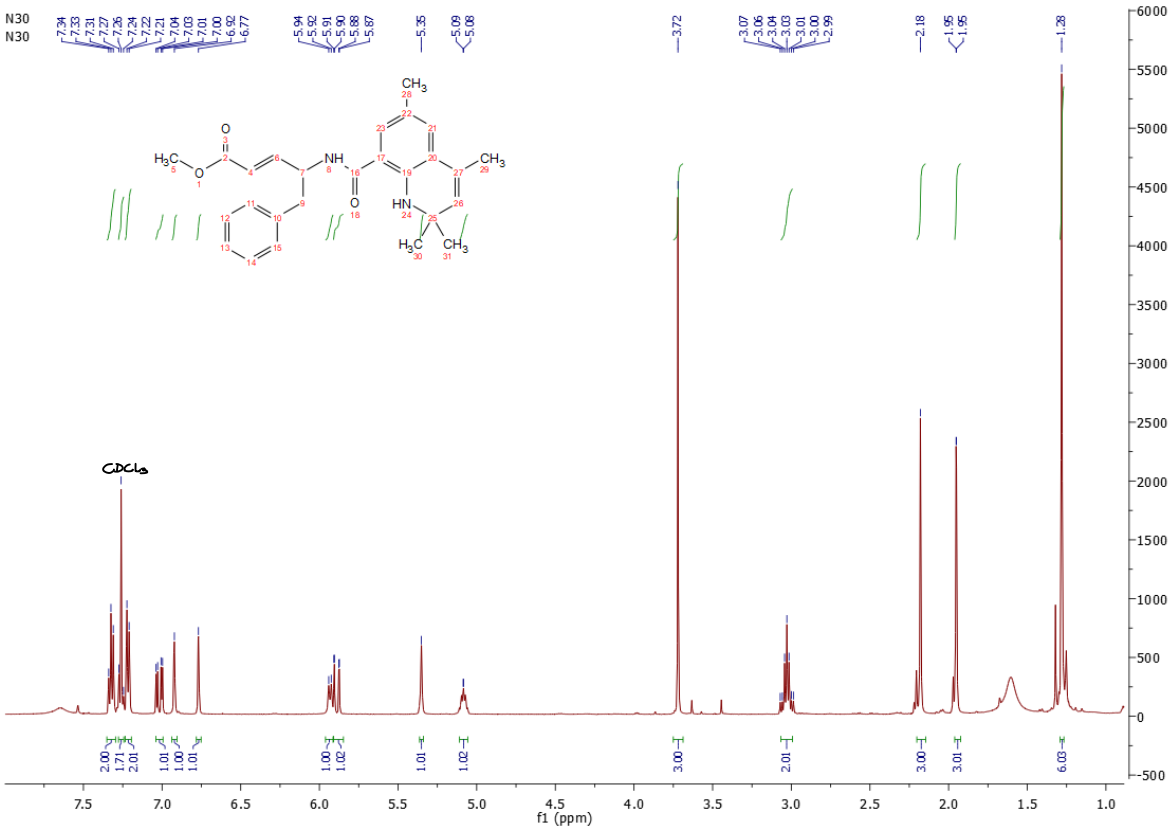
Methyl (*S*,*E*)-5-phenyl-4-(2,2,4-trimethyl-1,2-dihydroquinoline-8-carboxamido)pent-2-enoate (29)

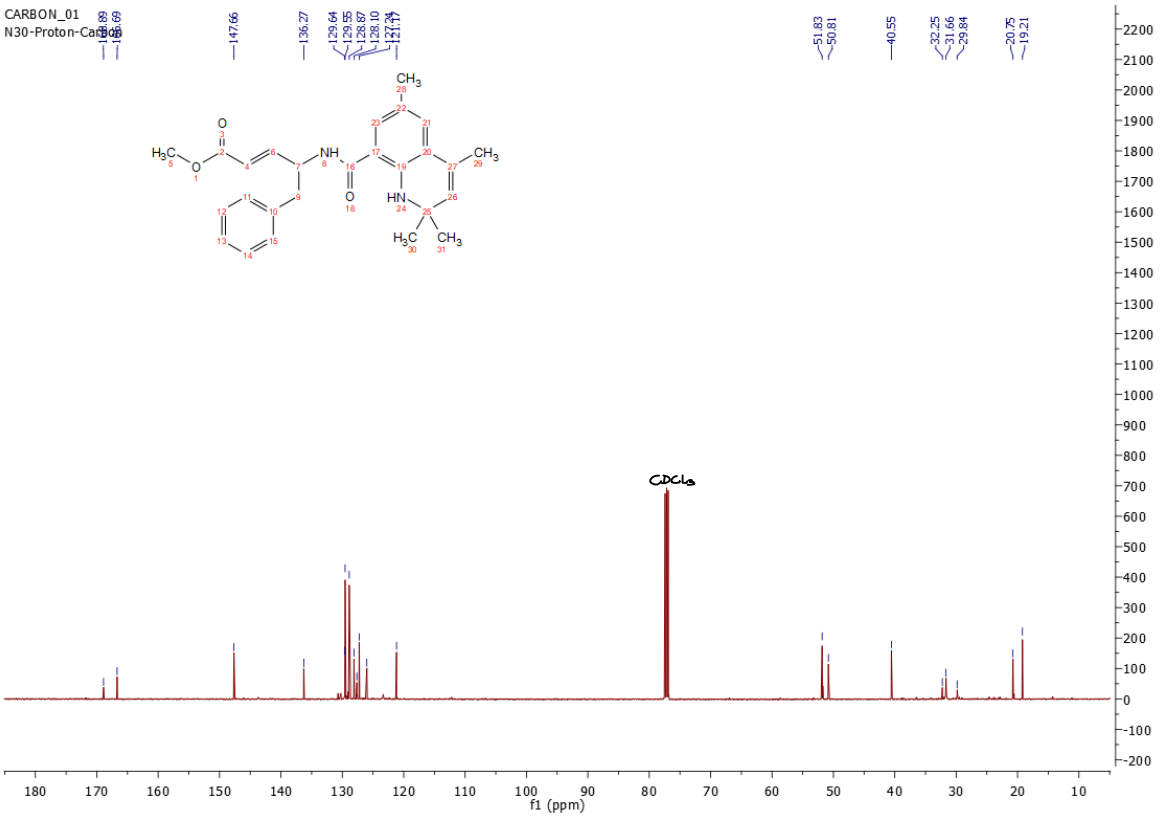


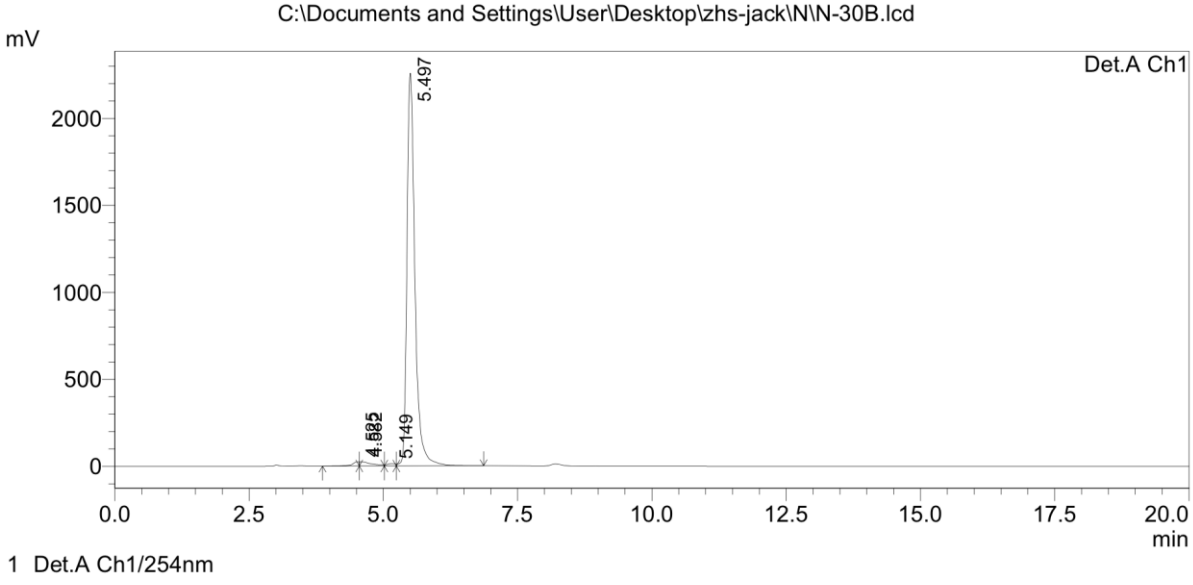




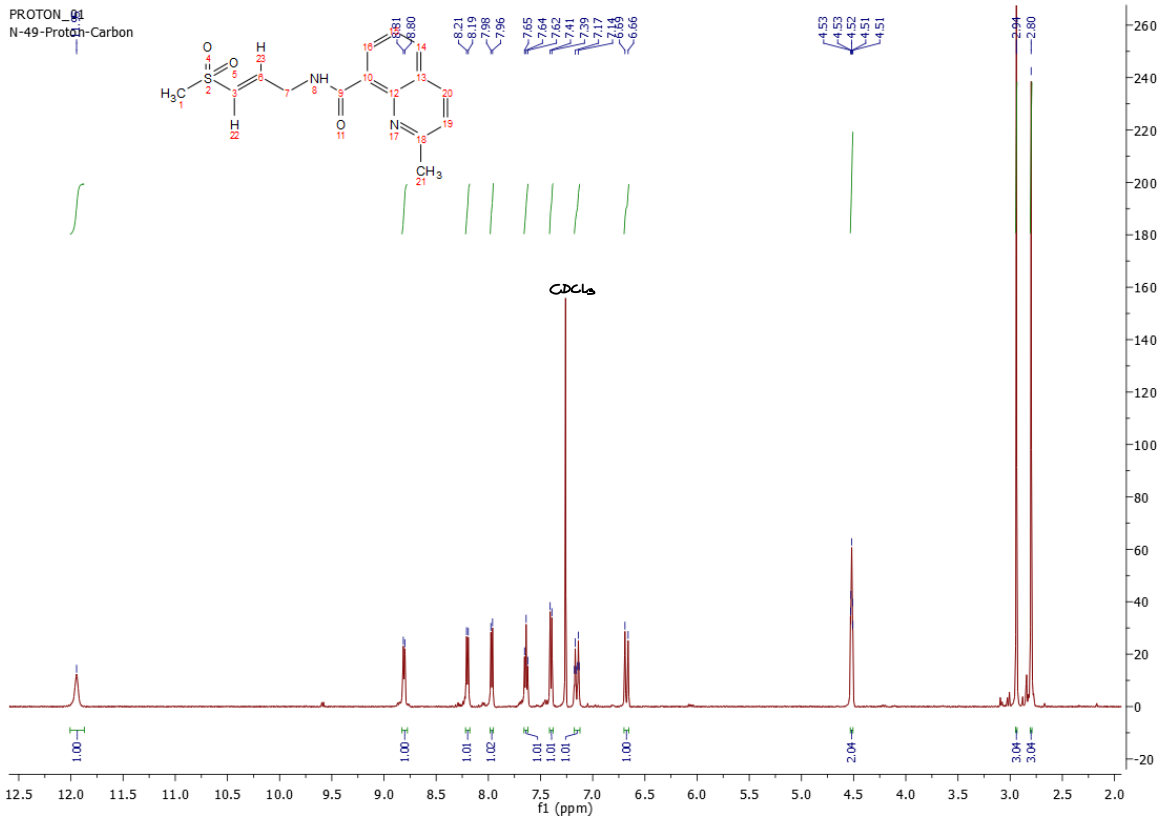
Methyl-(*S*,*E*)-5-phenyl-4-(2,2,4,6-tetramethyl-1,2-dihydroquinoline-8-carboxamido)pent-2-enoate (30)

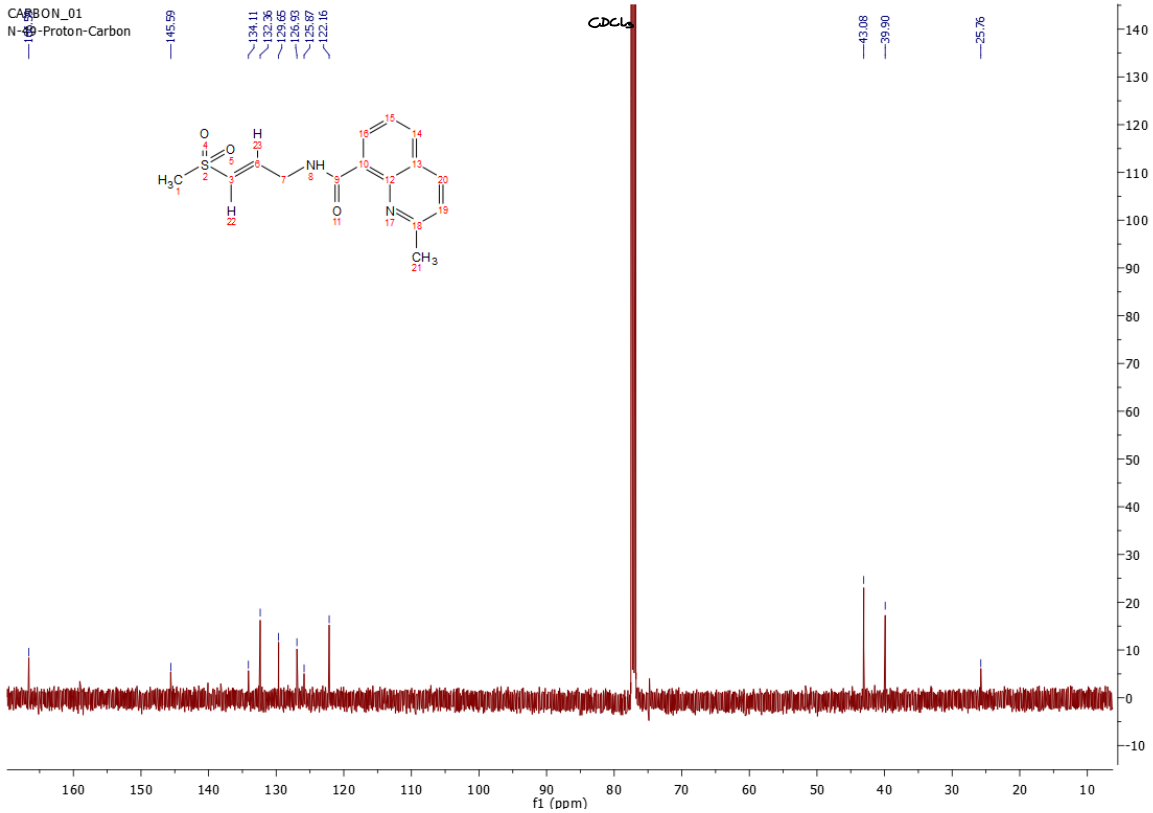


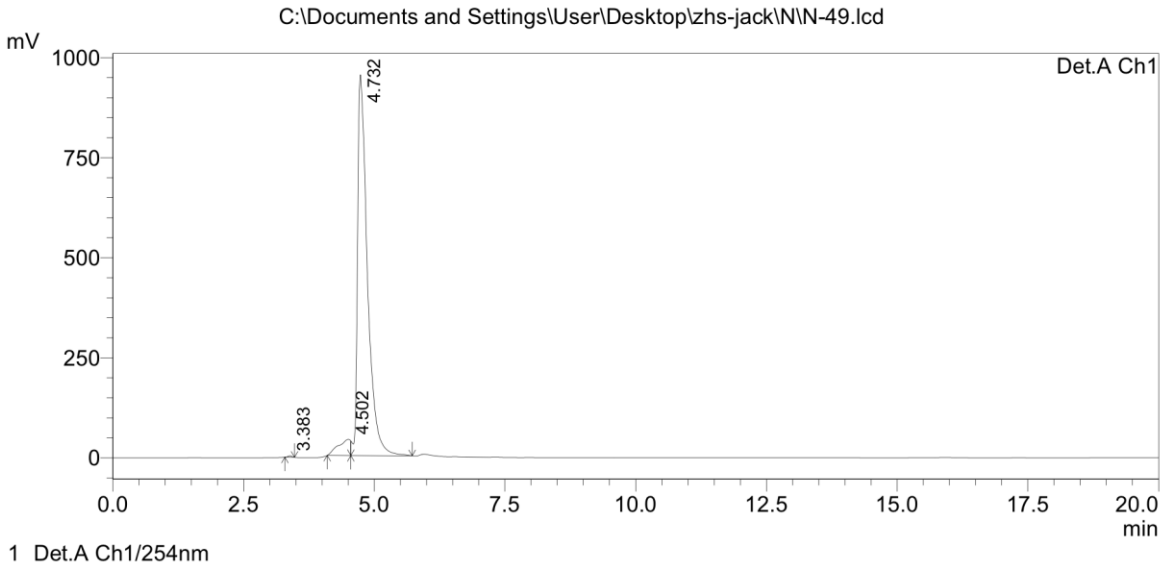

CARBON_01
N30-Proton-Carbon
147.66
136.27
129.64
129.55
128.87
128.10
127.24
121.17
51.83
50.81
40.55
32.25
31.66
29.84
20.75
19.21
CDCl3
f1 (ppm)


C:\Documents and Settings\User\Desktop\zhs-jack\N\N-30B.lcd
mV
Det.A Ch1
5.497
5.149
min
1 Det.A Ch1/254nm

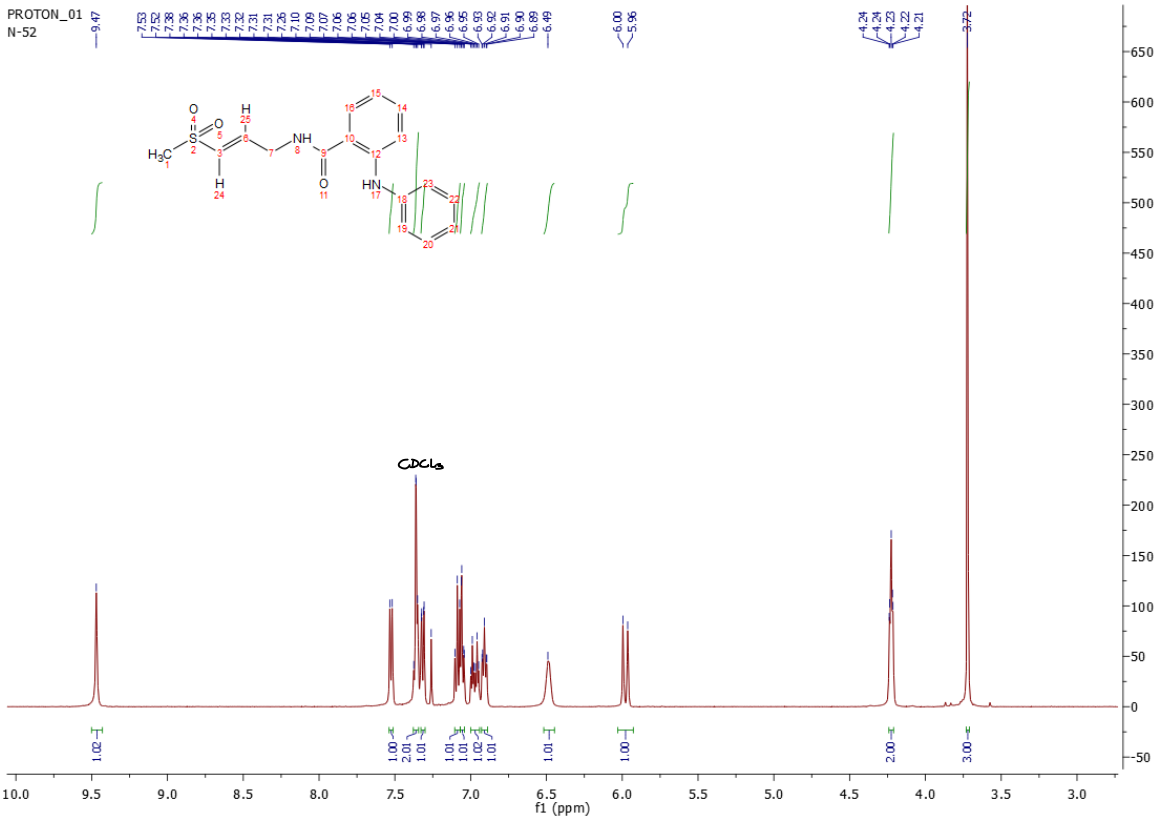
(*E*)-2-methyl-*N*-(3-(methylsulfonyl)allyl)quinoline-8-carboxamide (31)

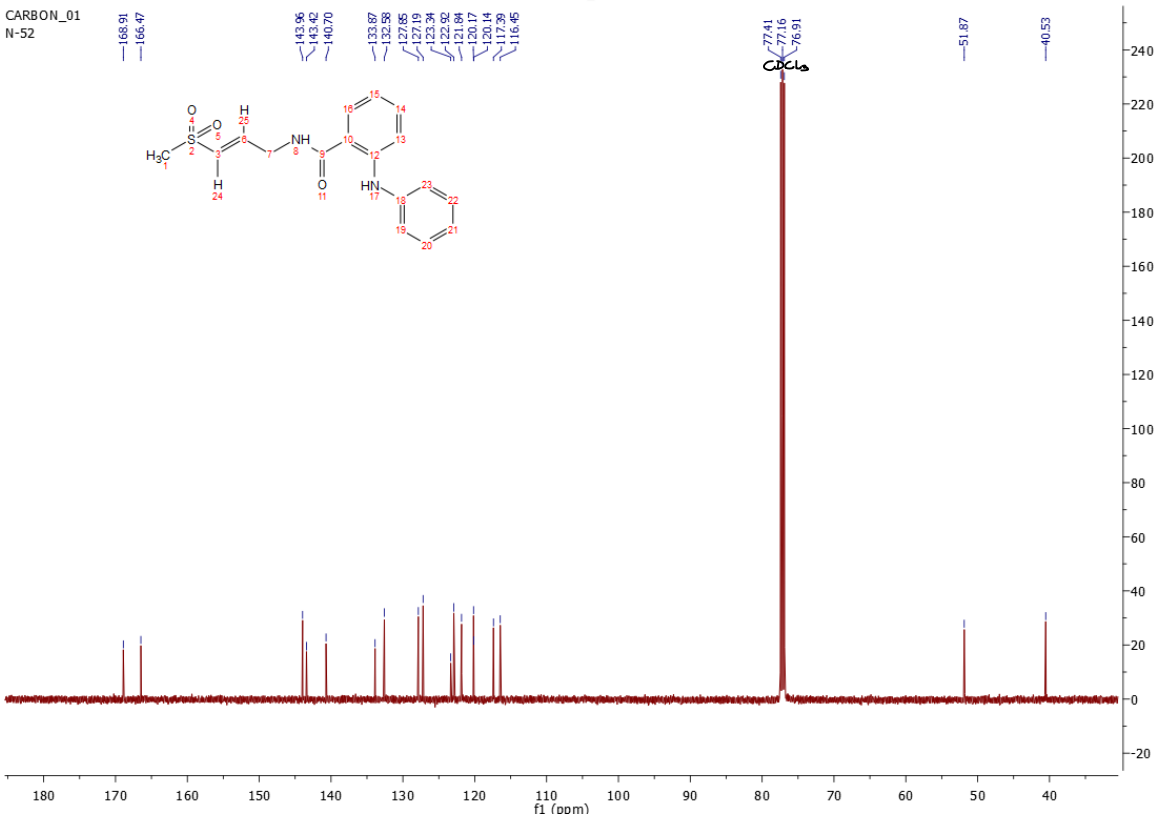


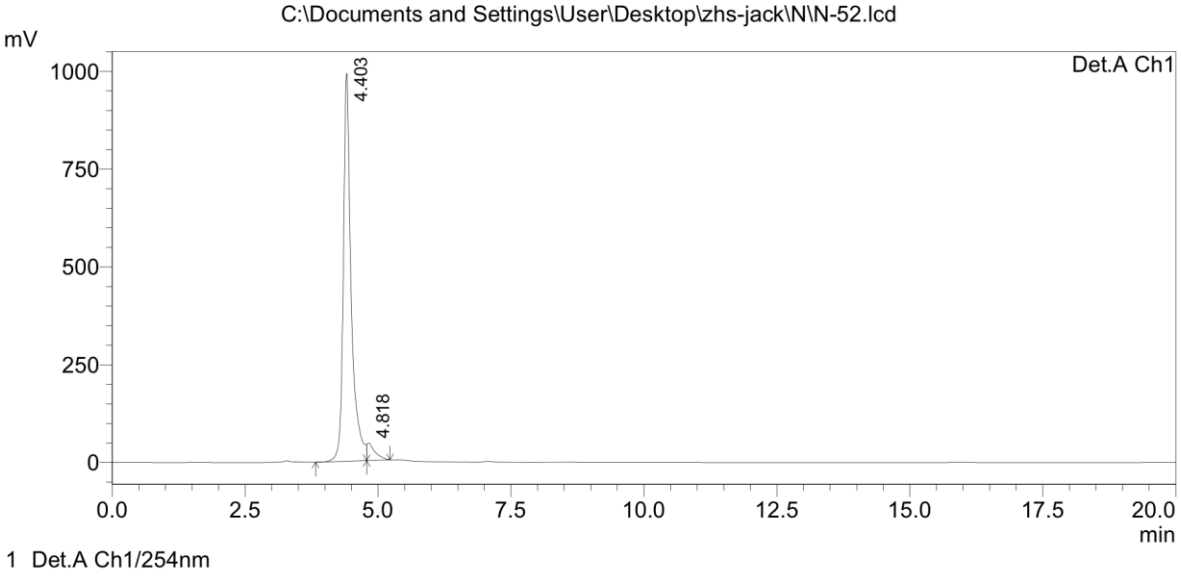




(*E*)-*N*-(3-(methylsulfonyl)allyl)-2-(phenylamino)benzamide (32)

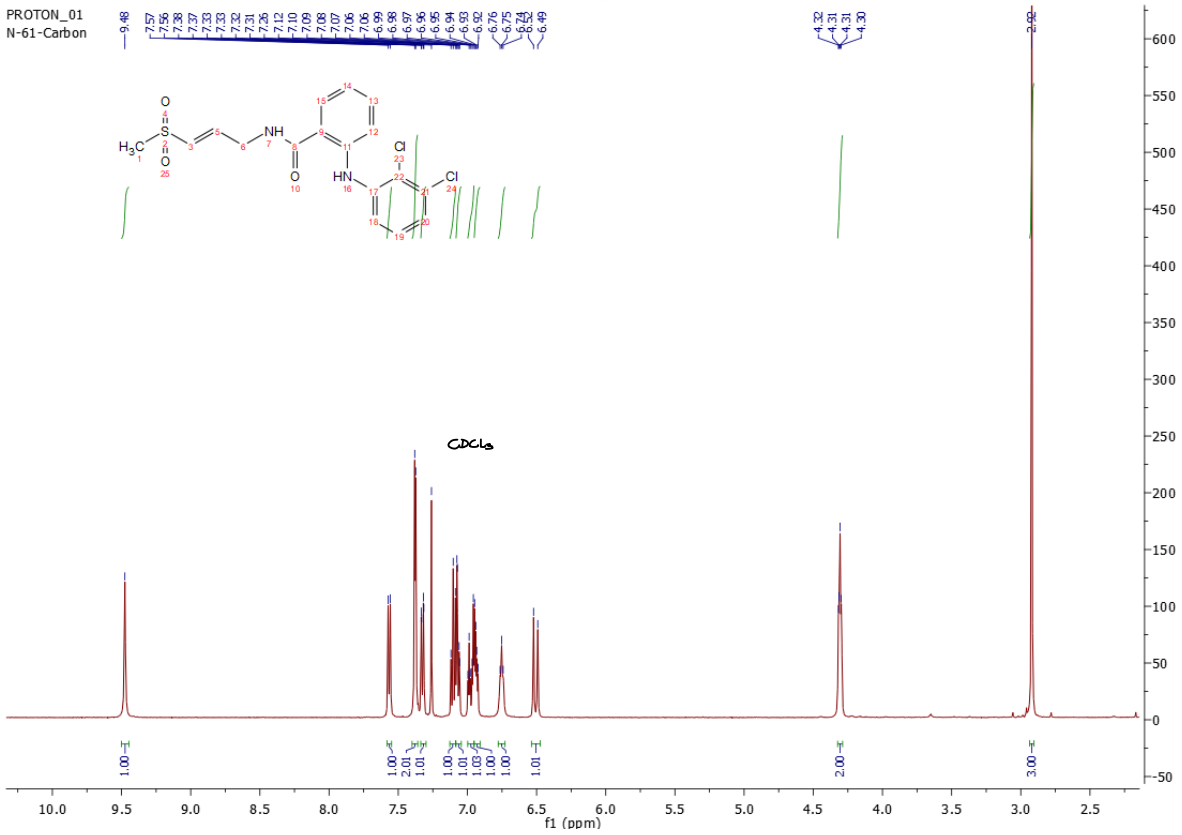


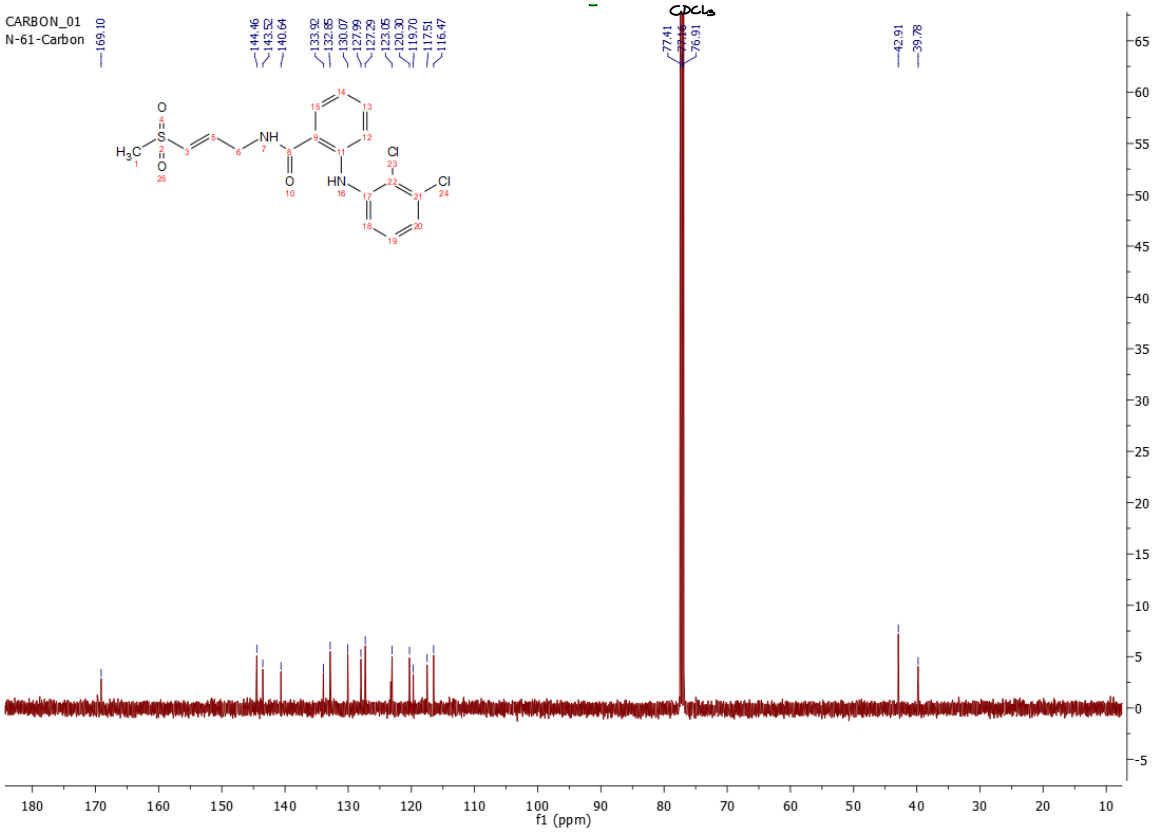


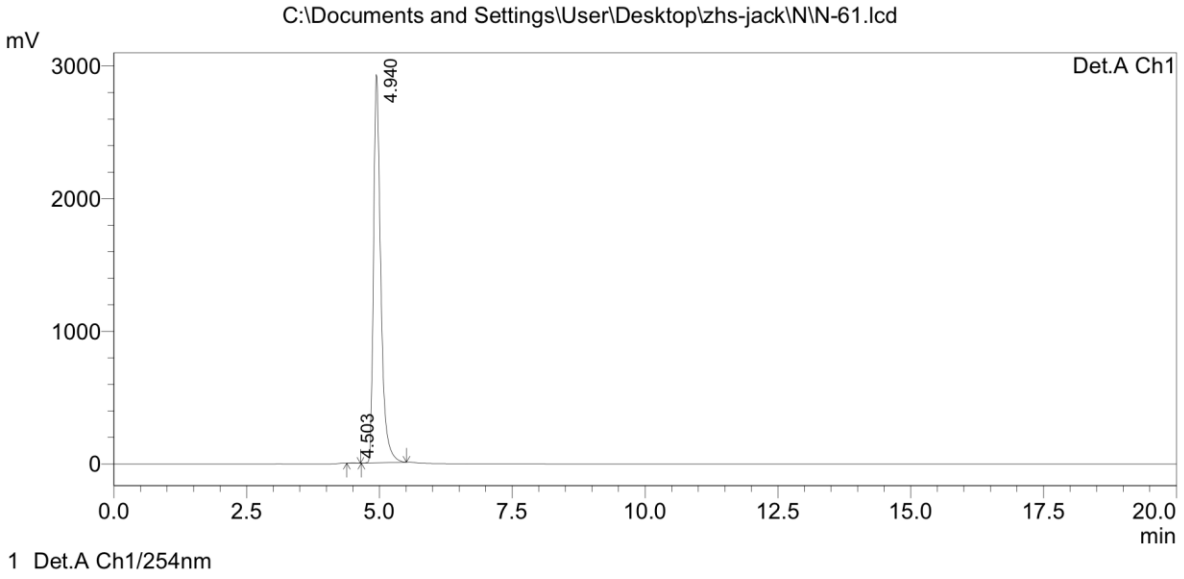


1 Det.A Ch1/254nm

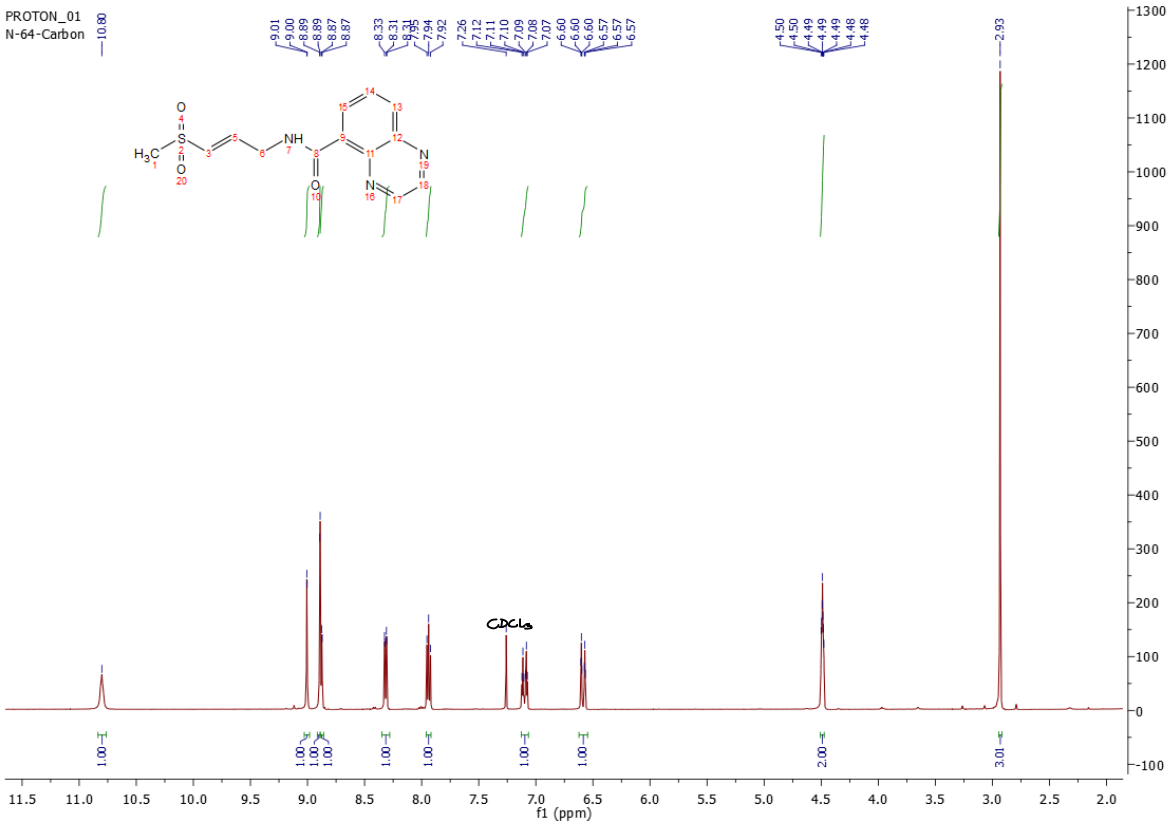
(*E*)-2-((2,3-dichlorophenyl)amino)-*N*-(3-(methylsulfonyl)allyl)benzamide (33)

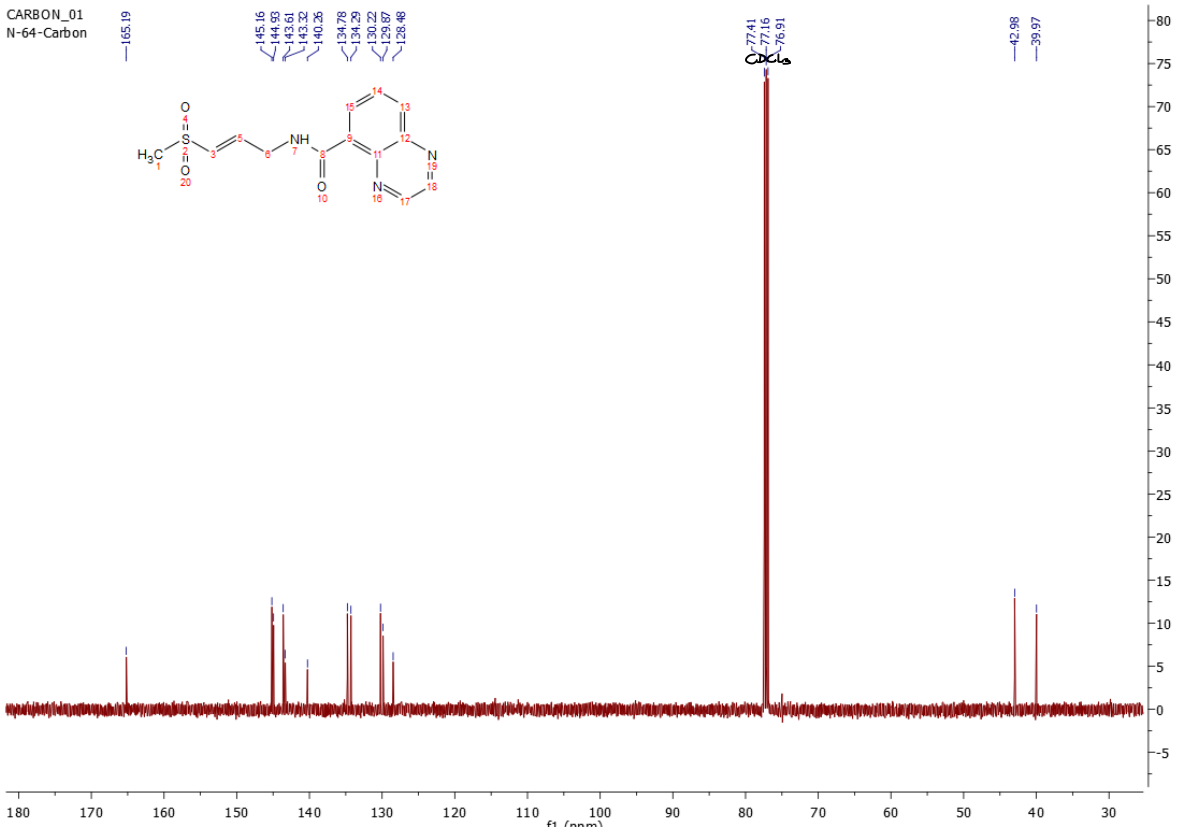


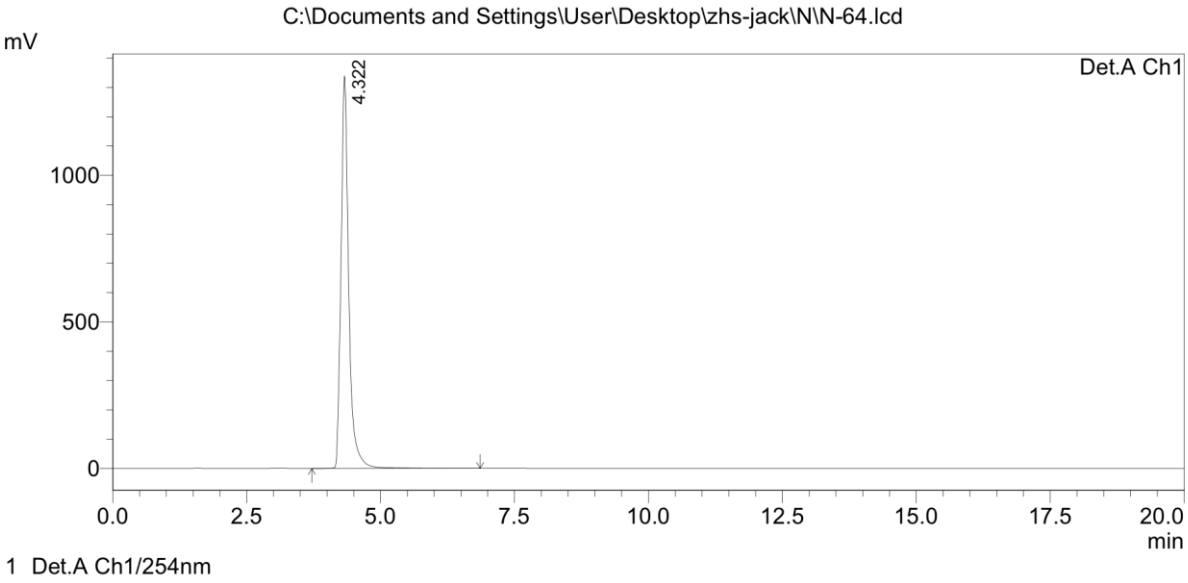




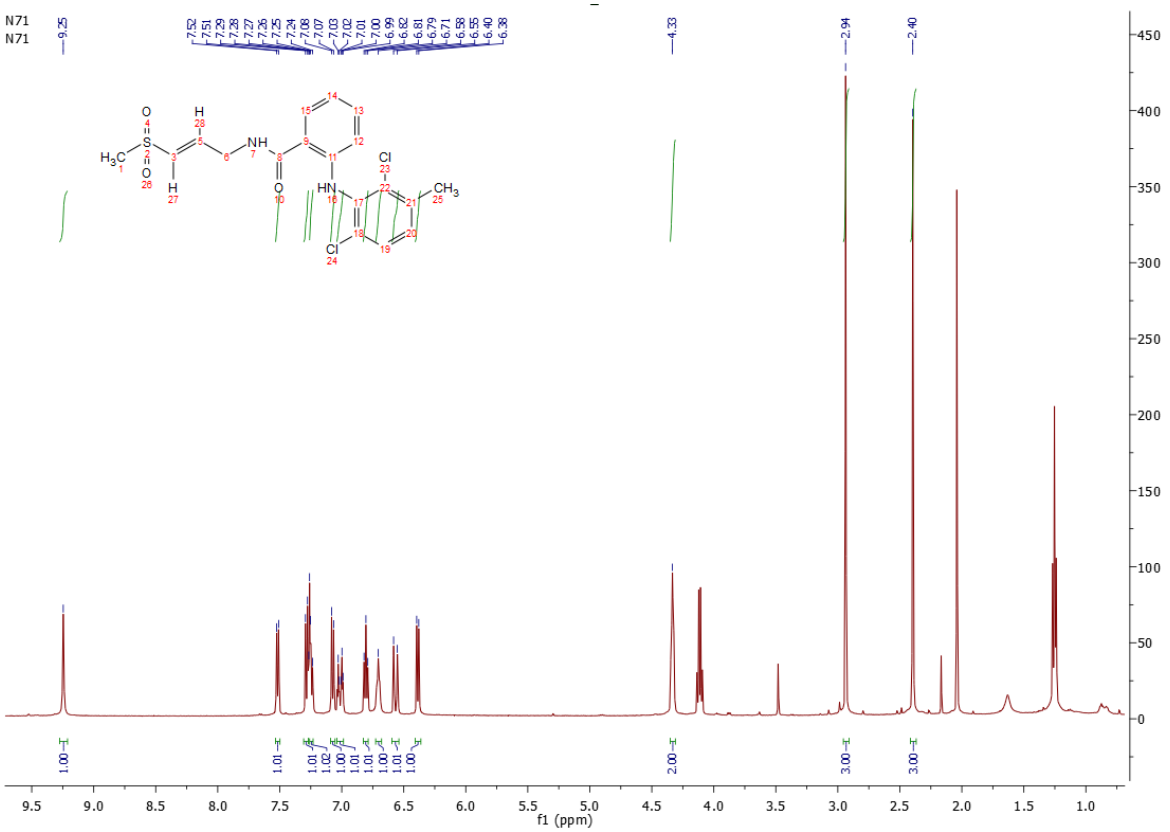
(*E*)-*N*-(3-(methylsulfonyl)allyl)quinoxaline-5-carboxamide (34)

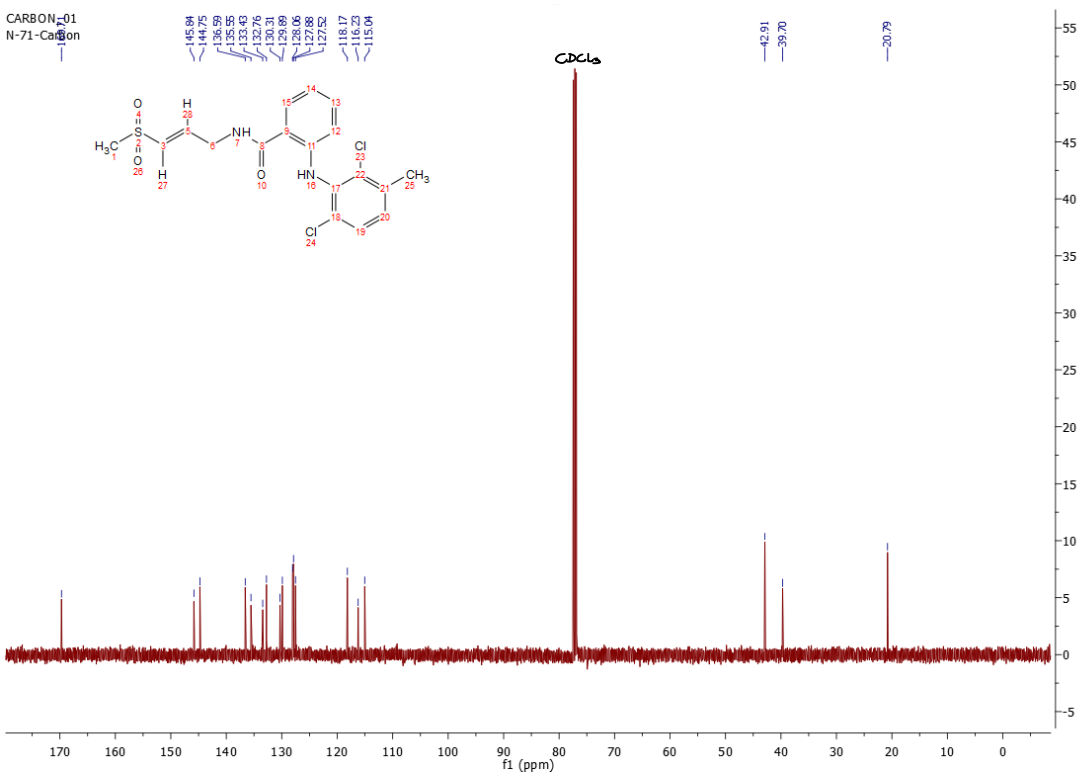


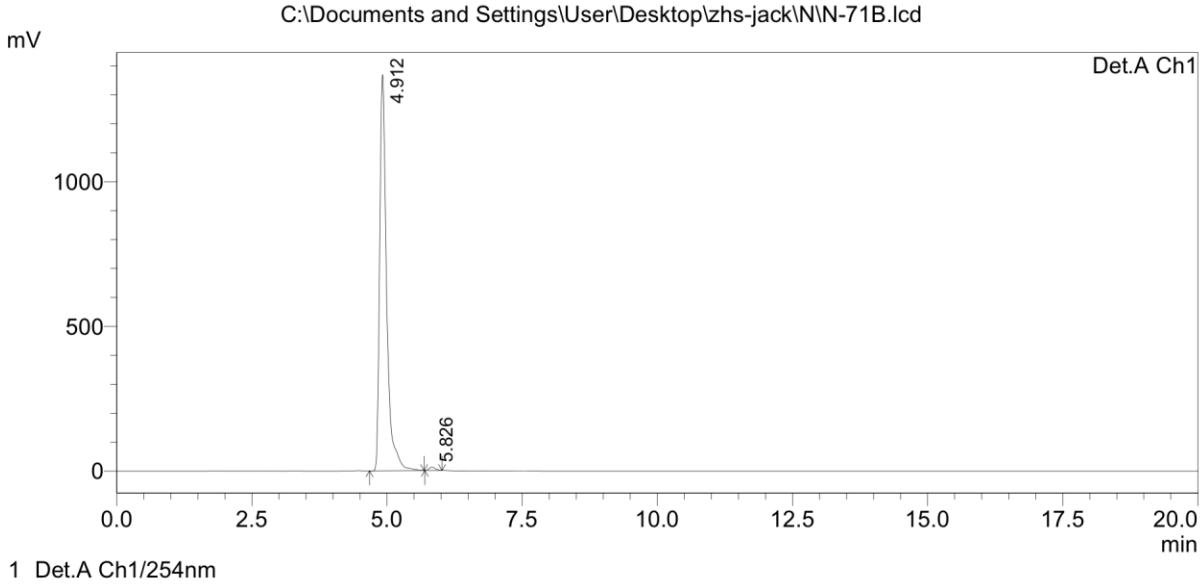

CARBON_01
N-64-Carbon
165.19
145.16
144.93
143.61
143.32
140.26
134.78
134.29
130.22
129.87
128.48
77.41
77.16
76.91
42.98
39.97
CDCl3
f1 (ppm)


C:\Documents and Settings\User\Desktop\zhs-jack\N\N-64.lcd
mV
Det.A Ch1
4.322
1000
500
0
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0
min
1 Det.A Ch1/254nm

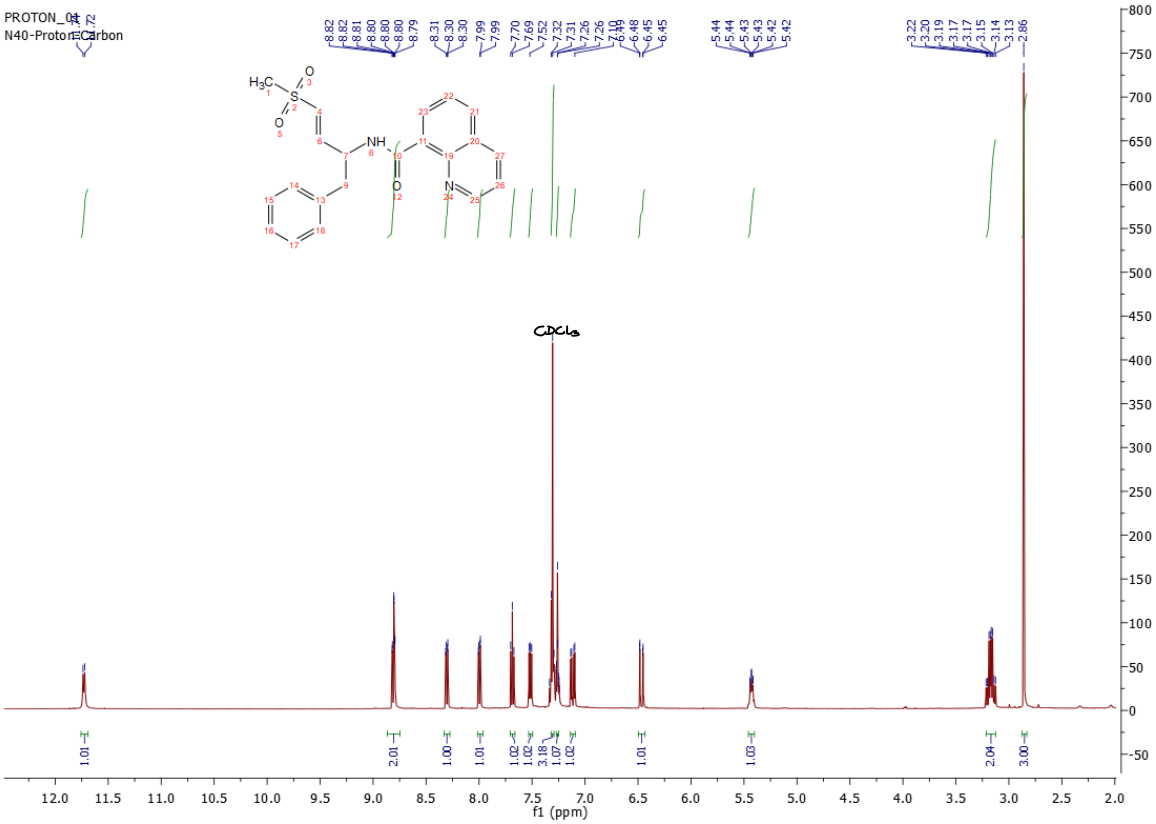
(*E*)-2-((2,6-dichloro-3-methylphenyl)amino)-*N*-(3-(methylsulfonyl)allyl)benzamide (35)

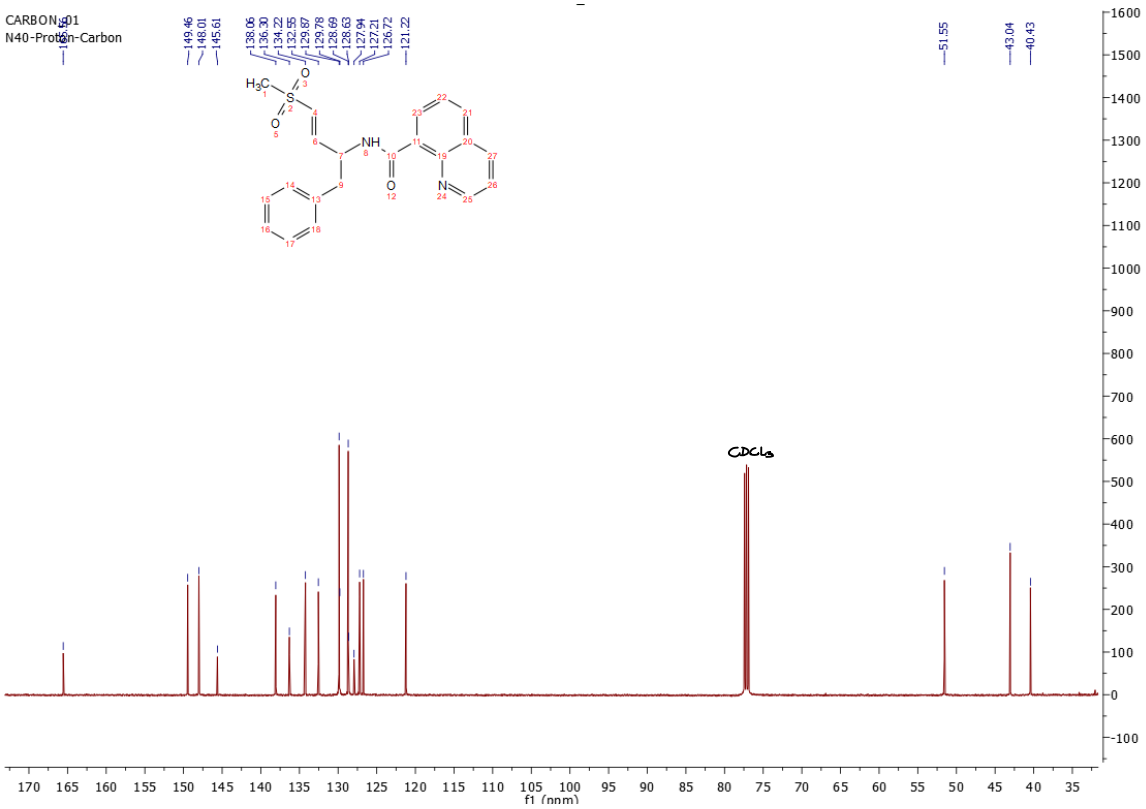


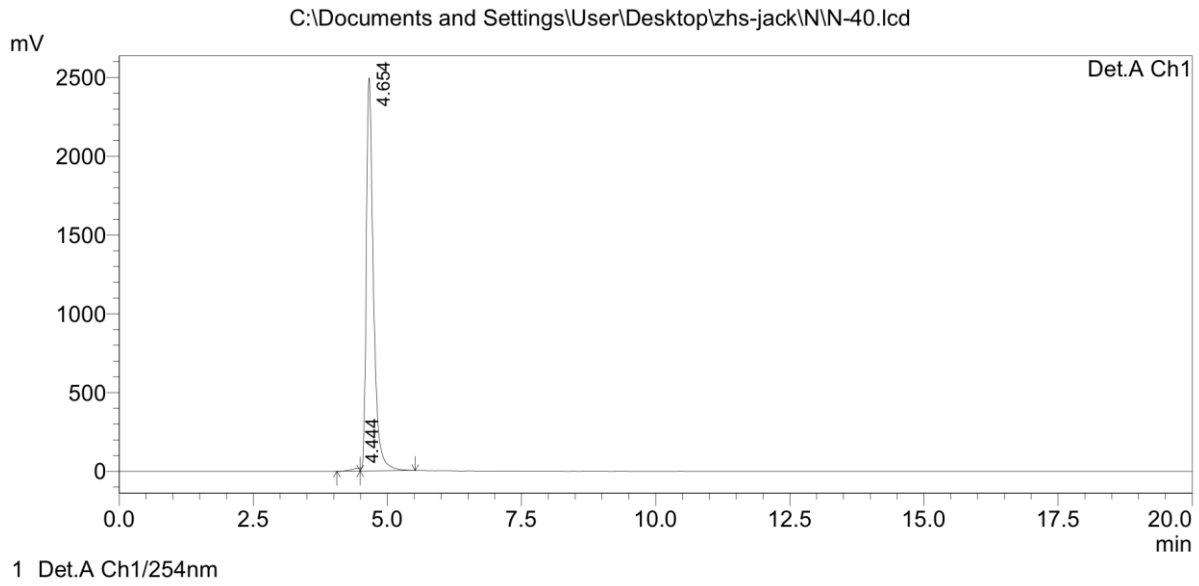




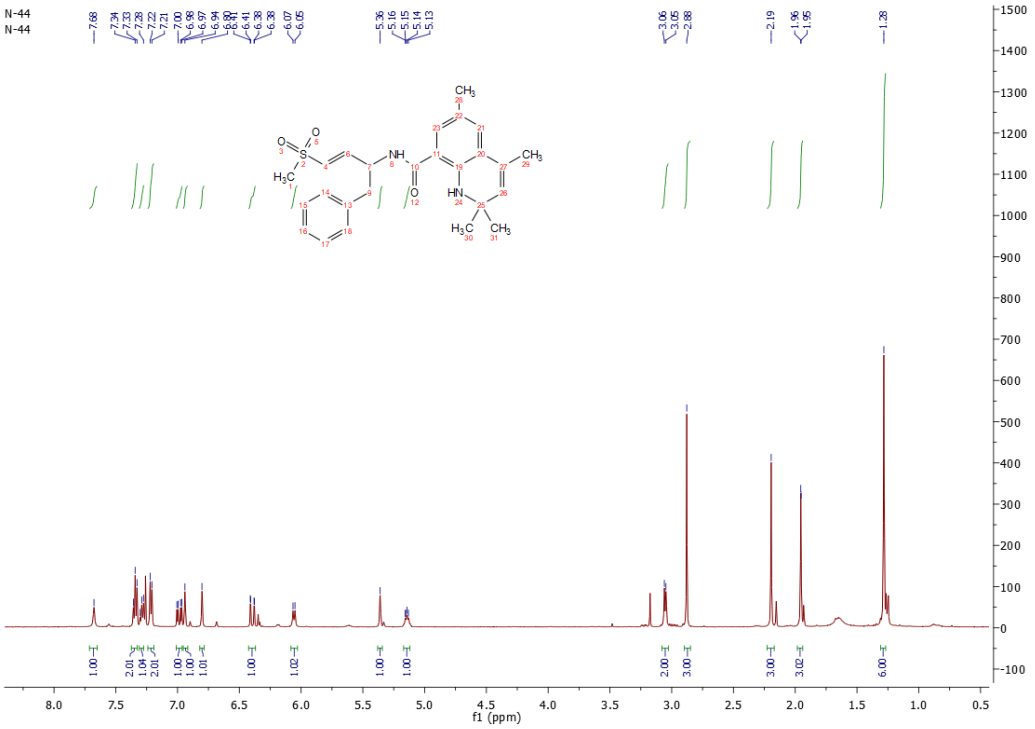
(*S*,*E*)-*N*-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)quinoline-8-carboxamide (36)

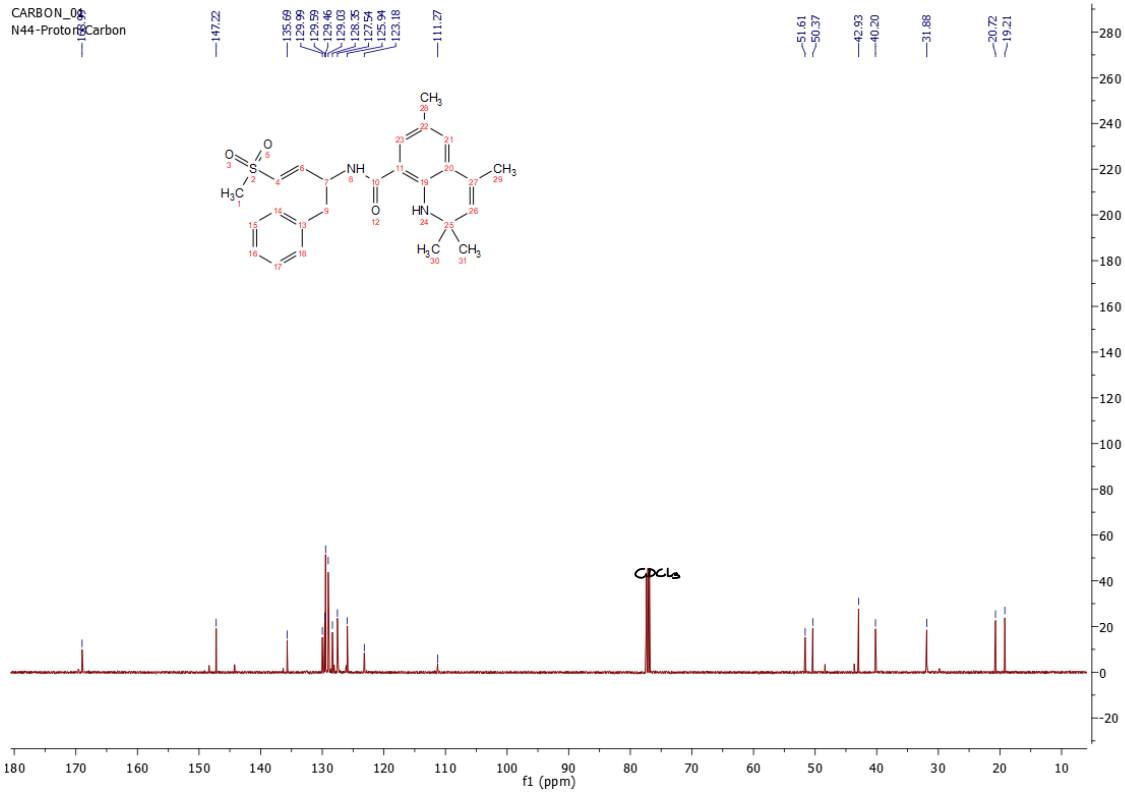

PROTON_01
N40-Proton-Carbon
CDCl3
f1 (ppm)

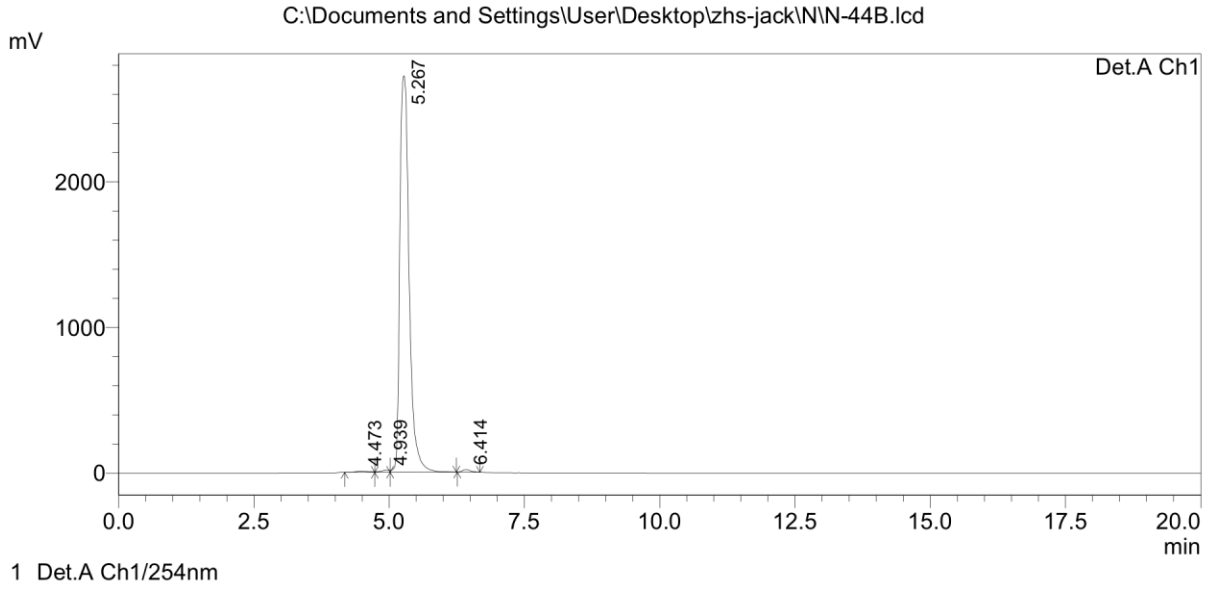

CARBON_01
N40-Proton-Carbon
CDCl3
f1 (ppm)



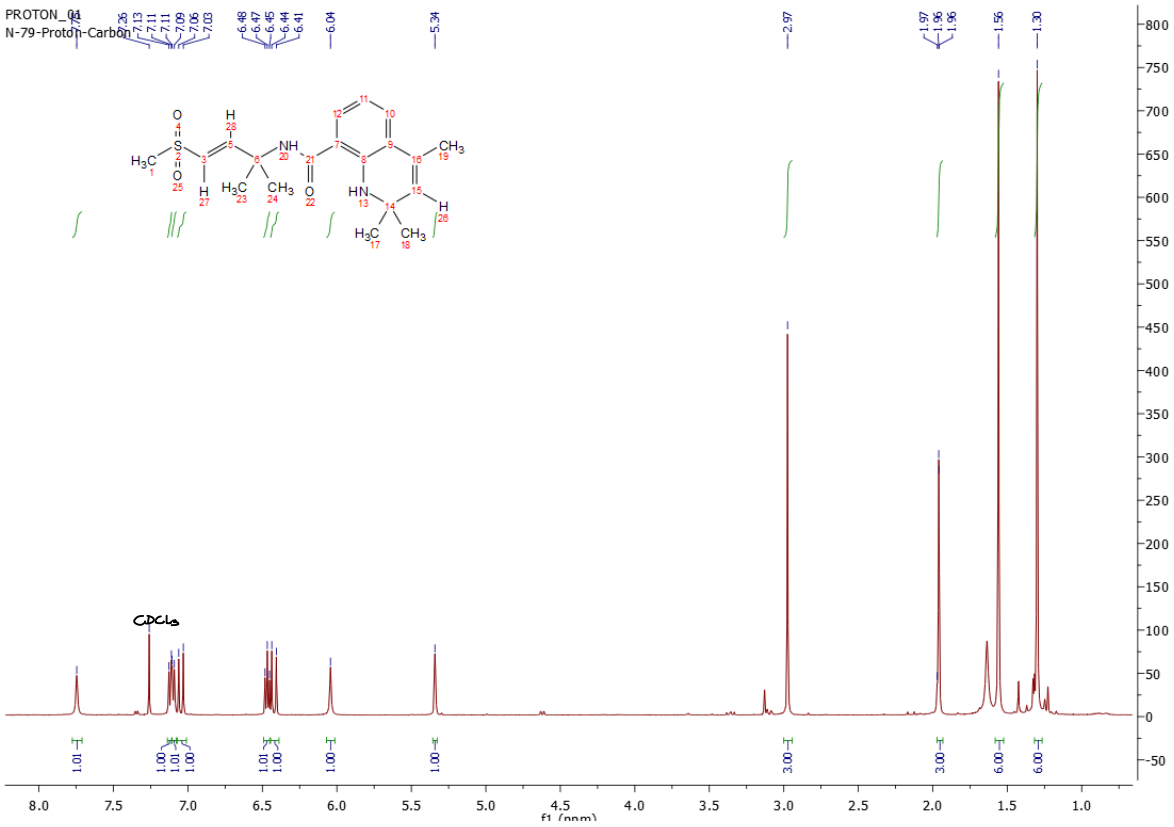
(*S*,*E*)-2,2,4,6-tetramethyl-*N*-(4-(methylsulfonyl)-1-phenylbut-3-en-2-yl)-1,2-dihydroquinoline-8-carboxamide (37)

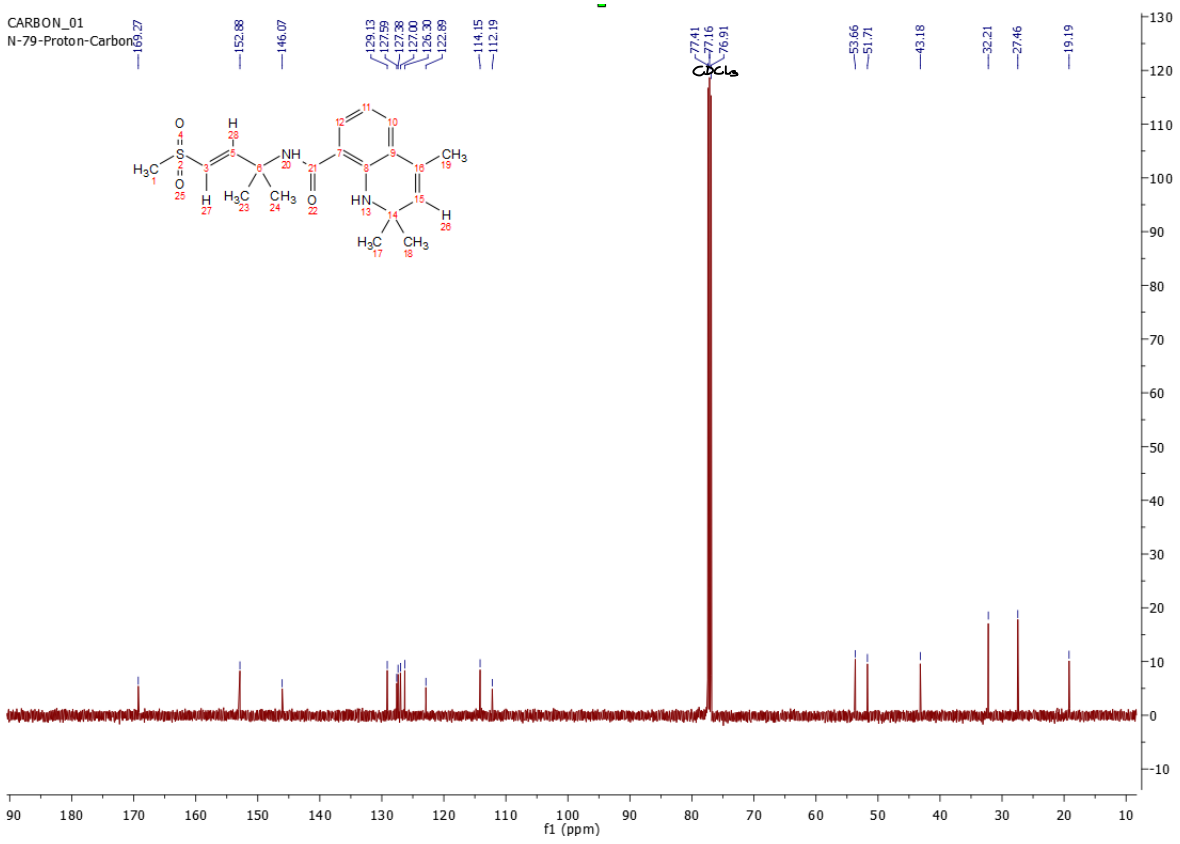

N-44
N-44
f1 (ppm)

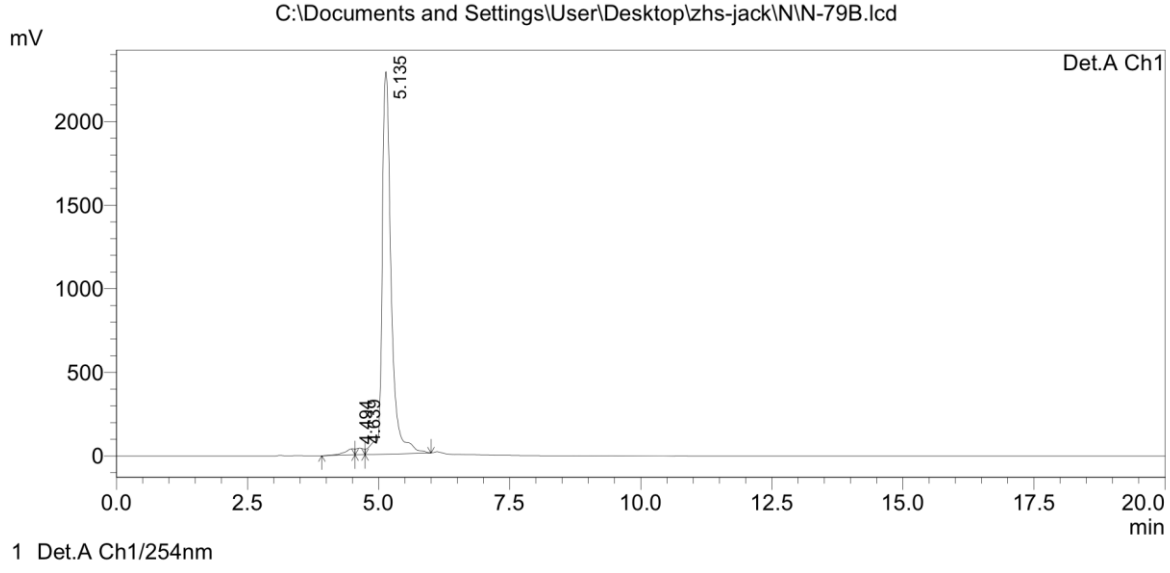

CARBON_04
N44-Proton&Carbon
CDCl3
f1 (ppm)



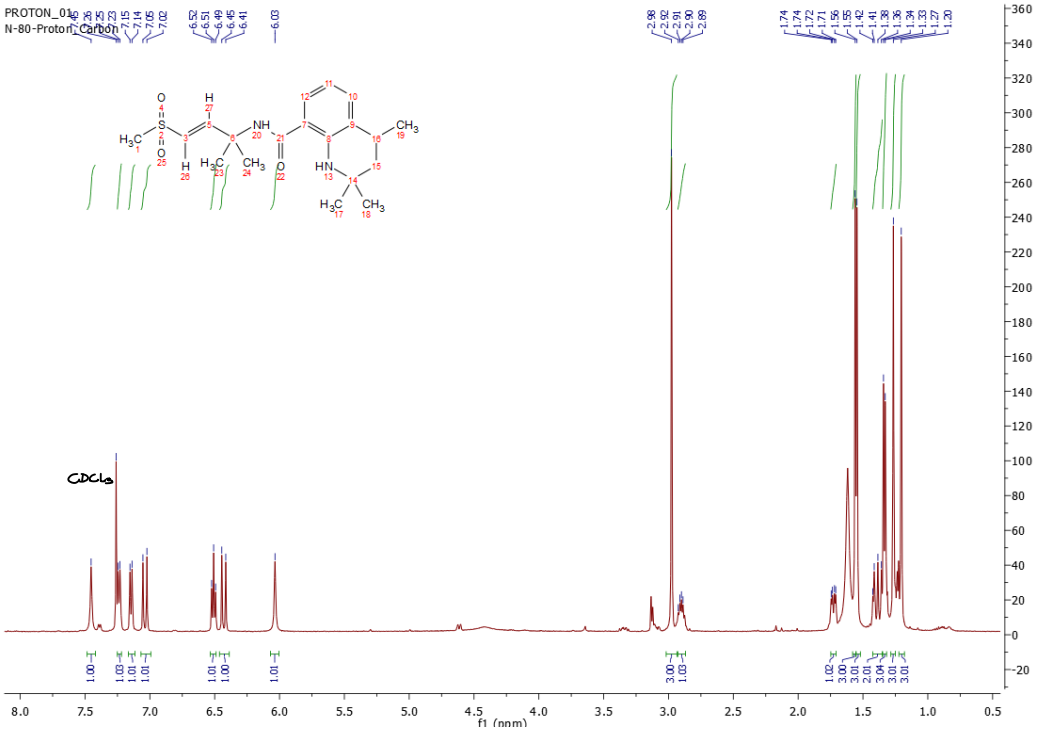
(*E*)-2,2,4-trimethyl-*N*-(2-methyl-4-(methylsulfonyl)but-3-en-2-yl)-1,2-dihydroquinoline-8-carboxamide (38)

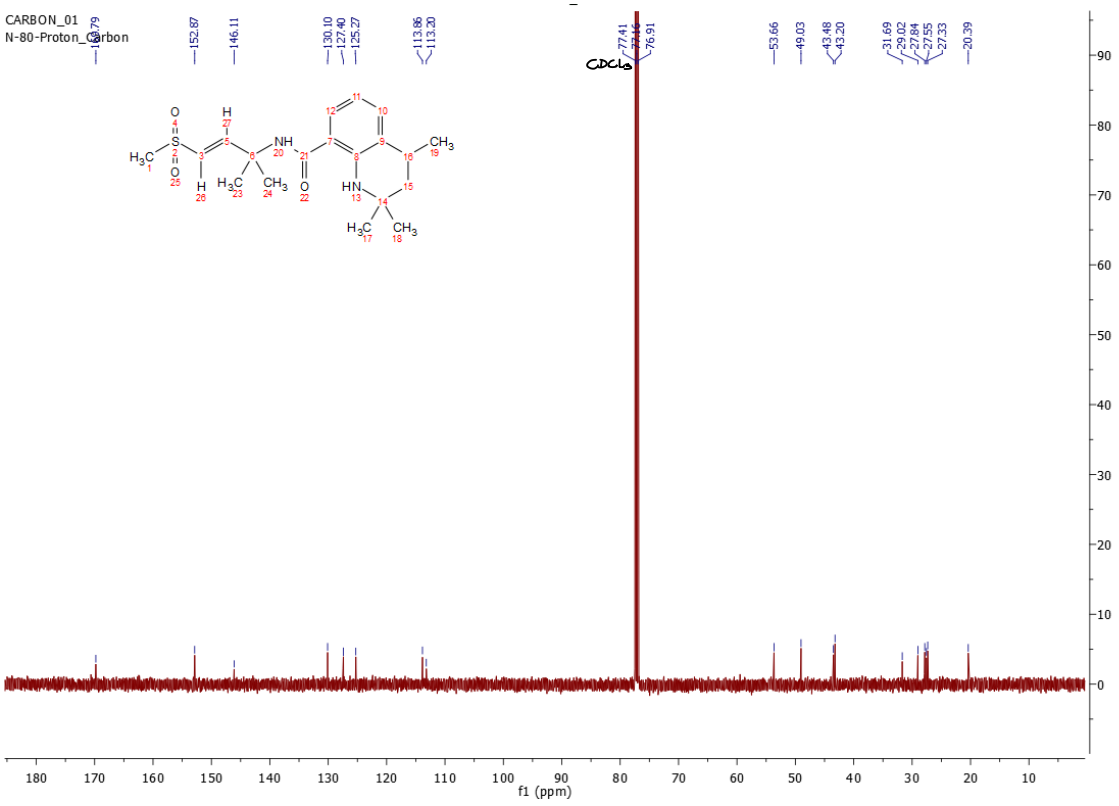


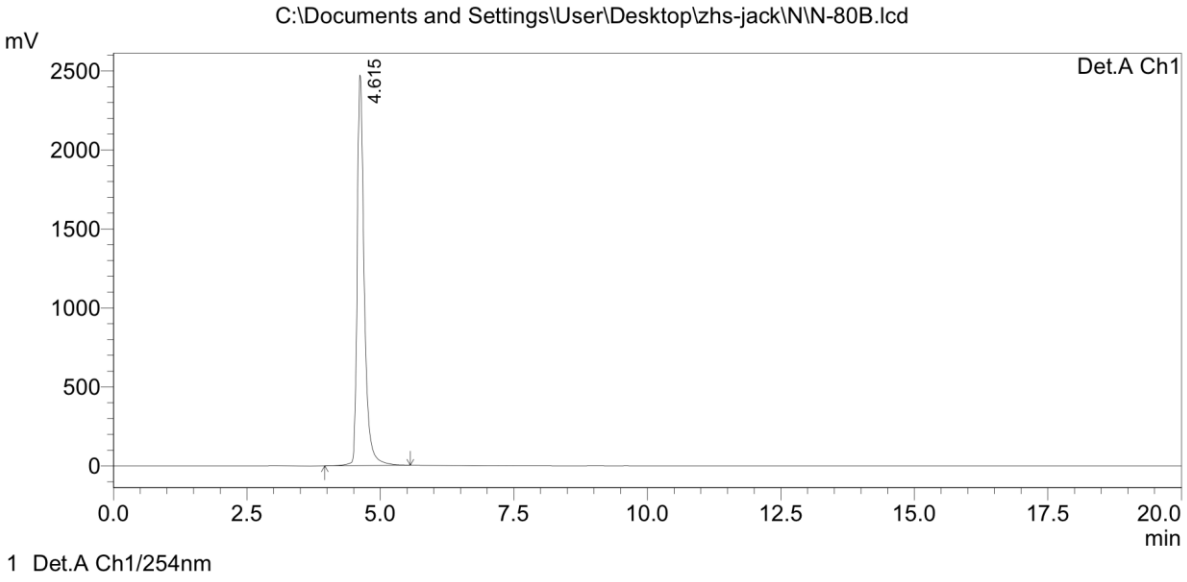

CARBON_01
N-79-Proton-Carbon
169.27
152.88
146.07
129.13
127.99
127.38
127.00
126.30
122.89
114.15
112.19
77.41
77.16
76.91
CDCl3
53.66
51.71
43.18
32.21
27.46
19.19
f1 (ppm)


C:\Documents and Settings\User\Desktop\zhs-jack\N\N-79B.lcd
mV
Det.A Ch1
5.135
4.494
4.839
min
1 Det.A Ch1/254nm

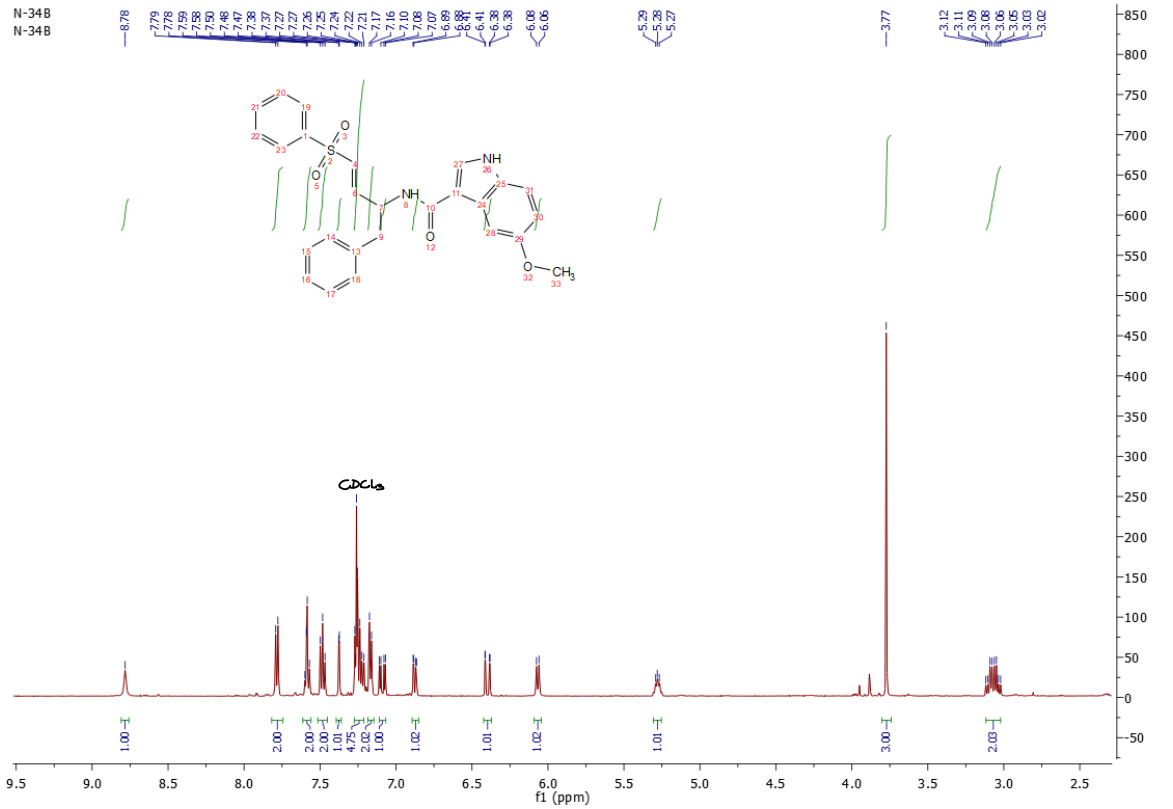
(*E*)-2,2,4-trimethyl-*N*-(2-methyl-4-(methylsulfonyl)but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (39)

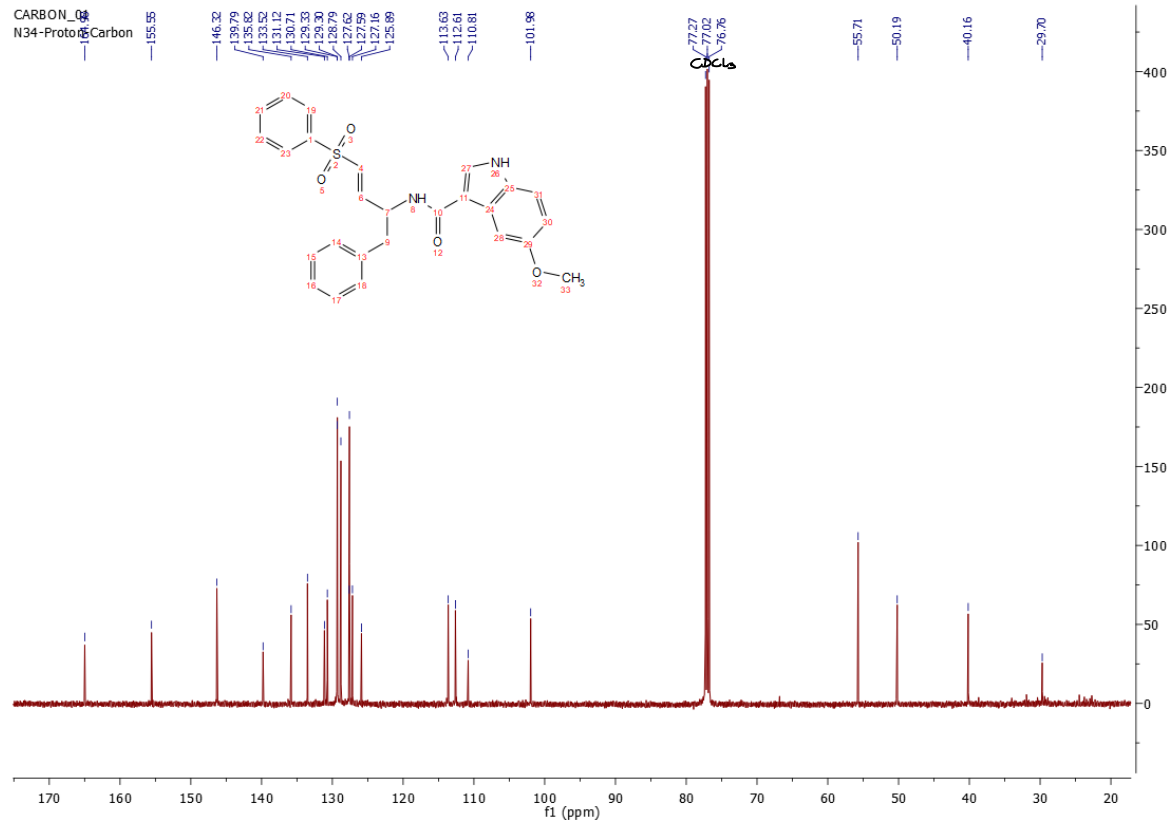


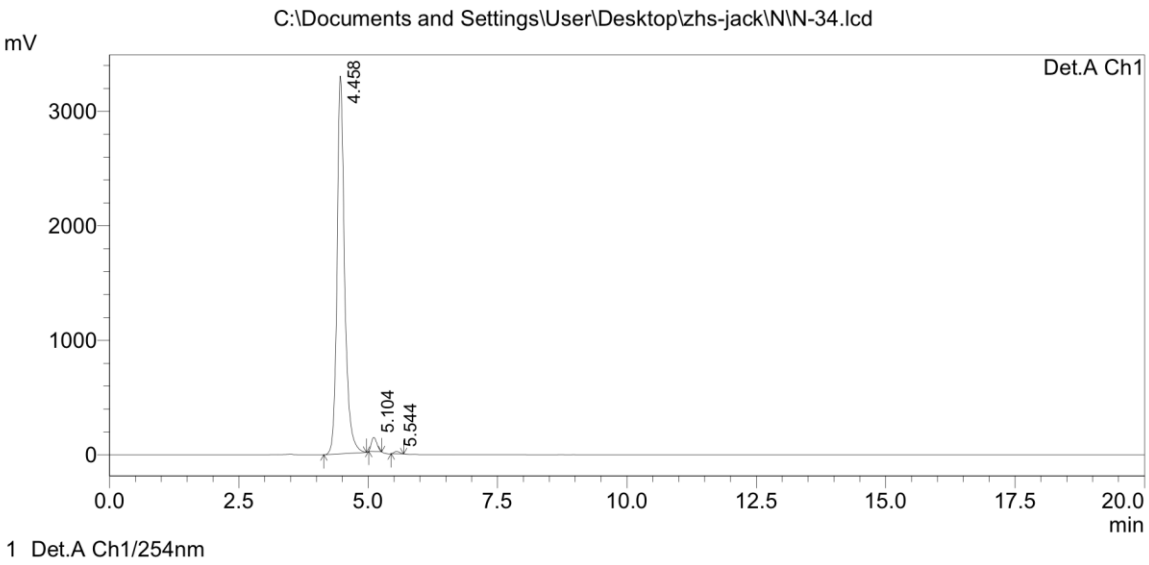




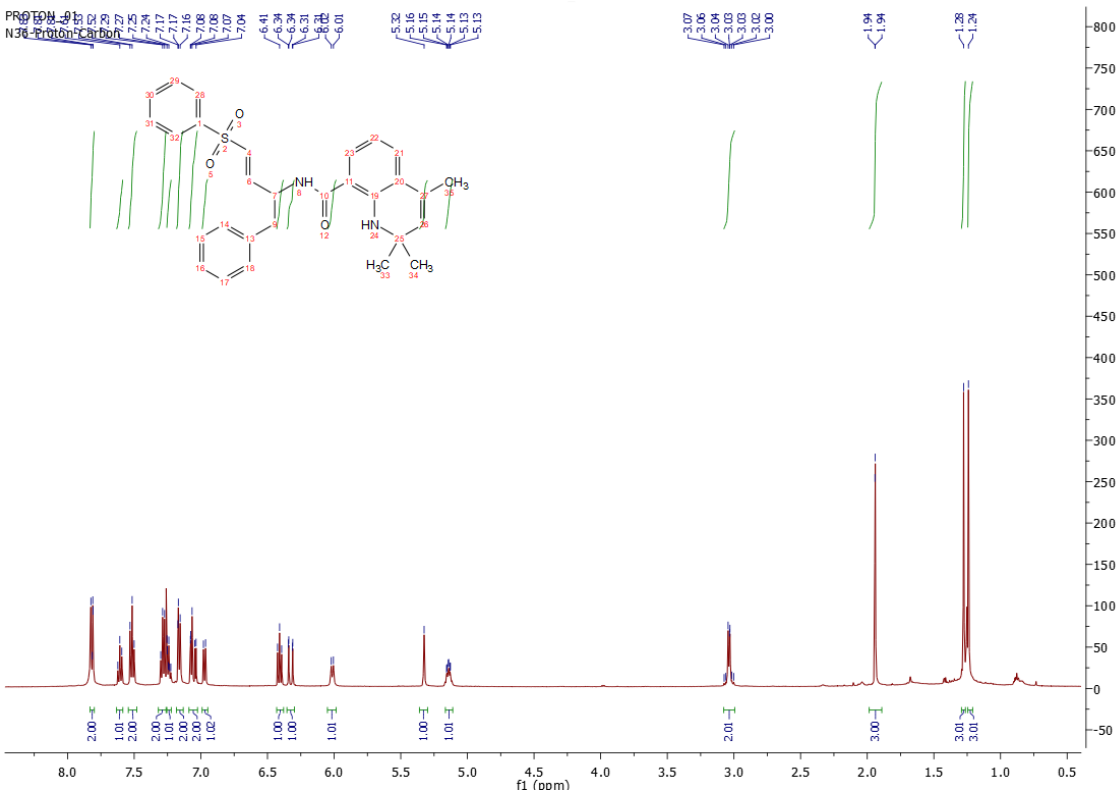
(*S*,*E*)-5-methoxy-*N*-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)-1H-indole-3-carboxamide (40)

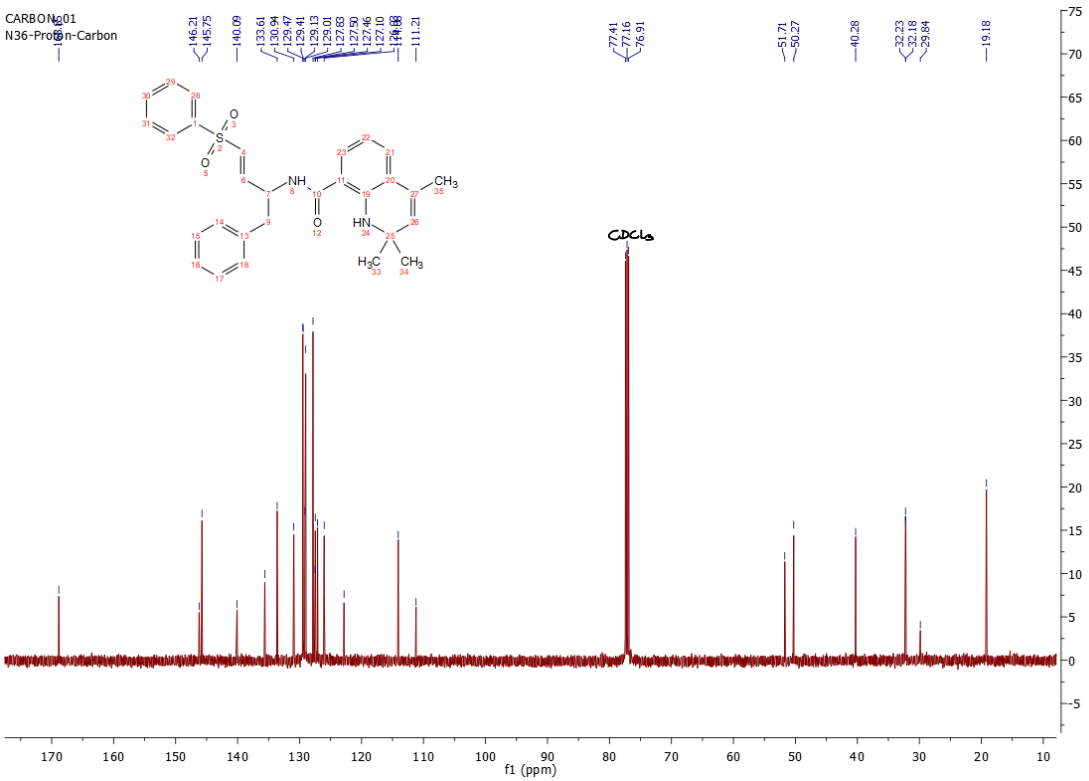

N-34B
N-34B
CDCl3
f1 (ppm)

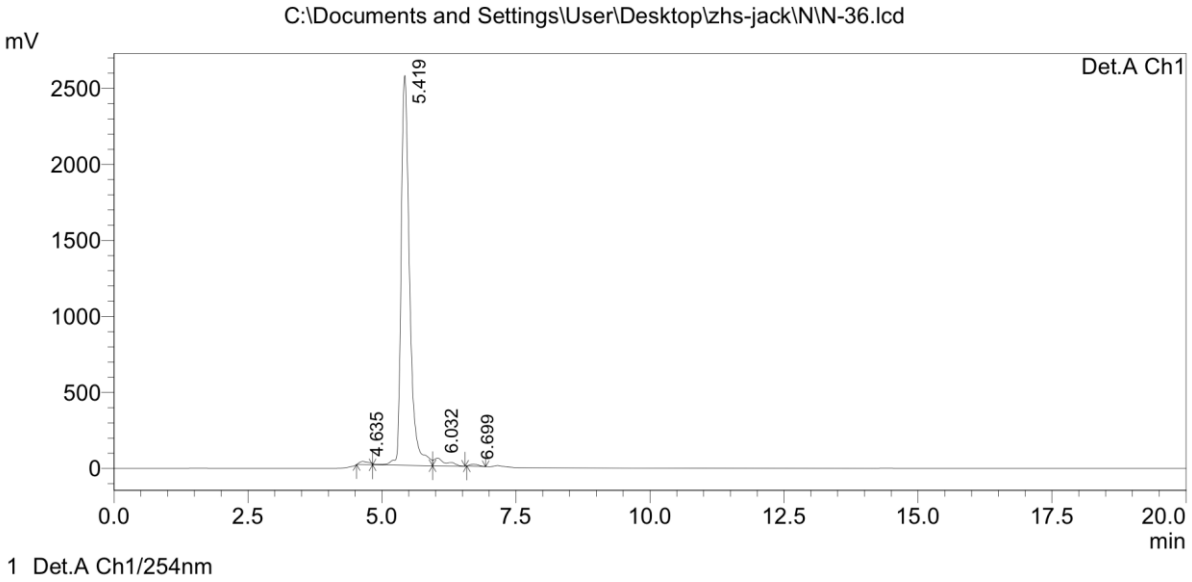

CARBON_01
N34-Proton&Carbon
CDCl3
f1 (ppm)



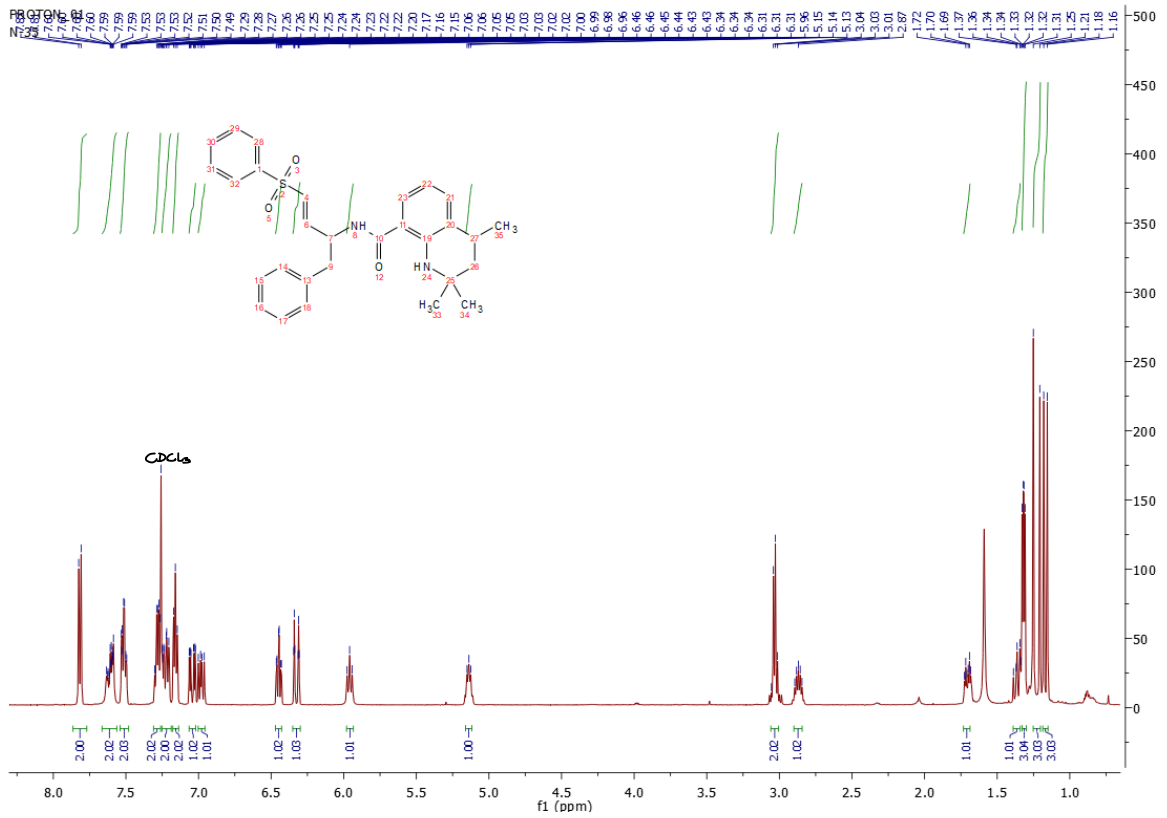
(*S*,*E*)-2,2,4-trimethyl-*N*-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)-1,2-dihydroquinoline-8-carboxamide (41)

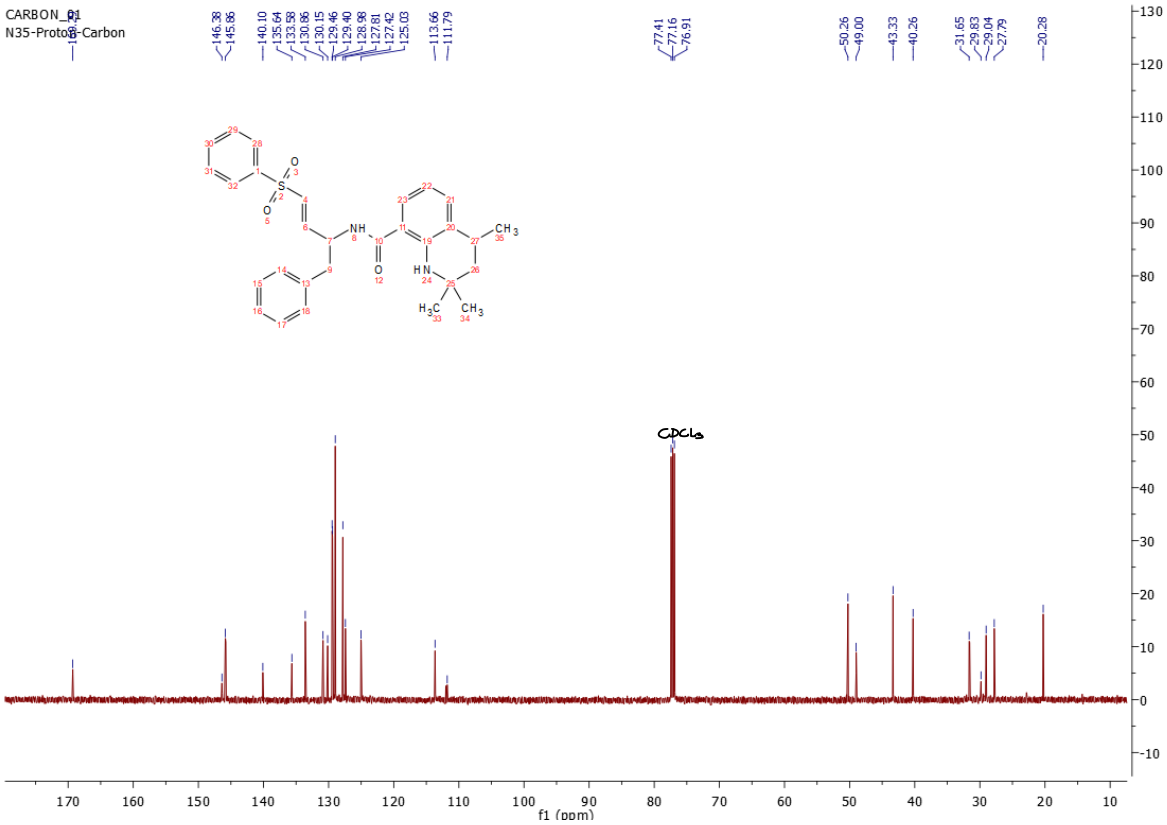


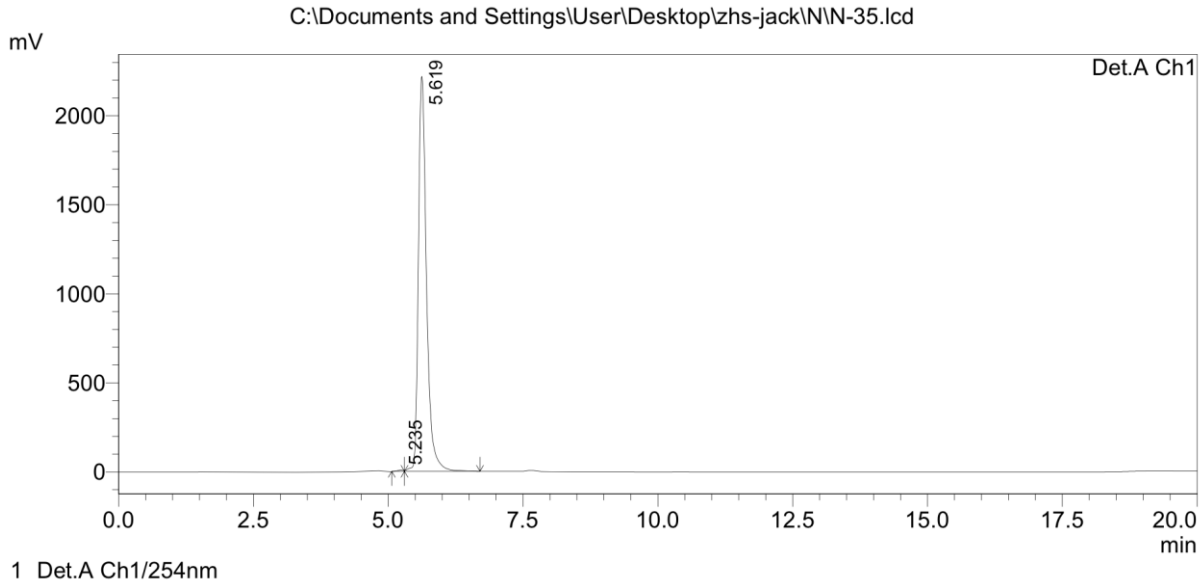




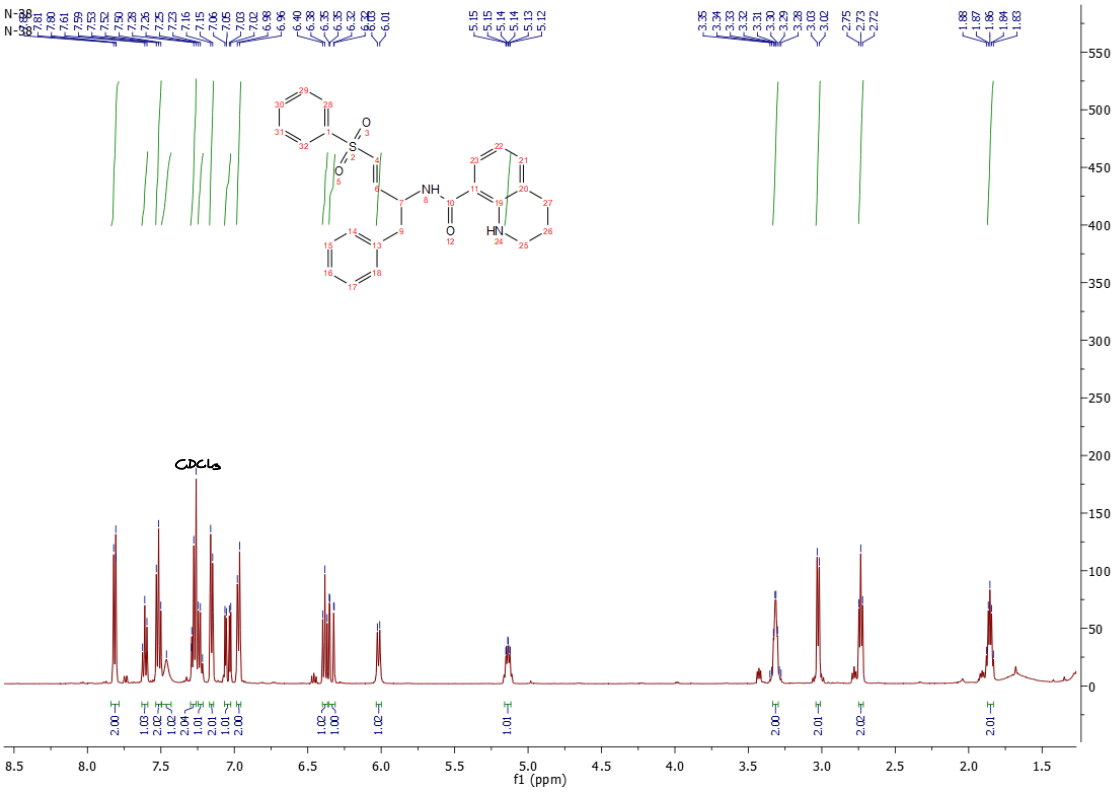
(*S*,*E*)-2,2,4-trimethyl-*N*-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (42)

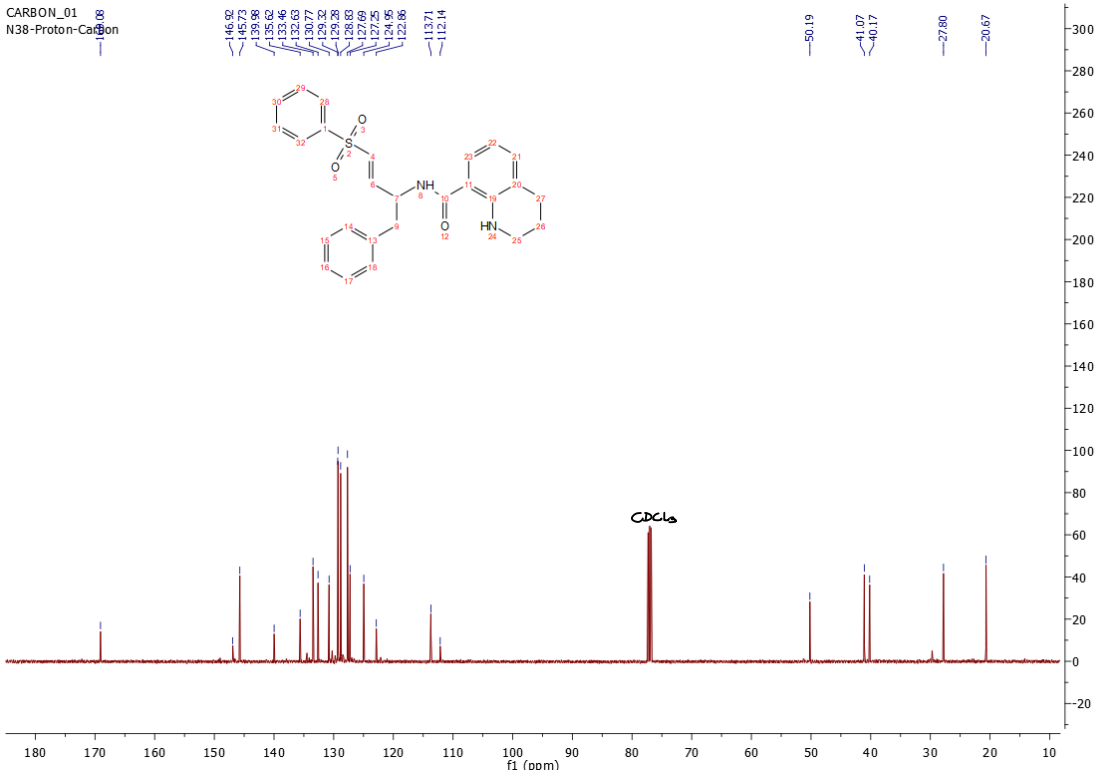

CDCl3
f1 (ppm)

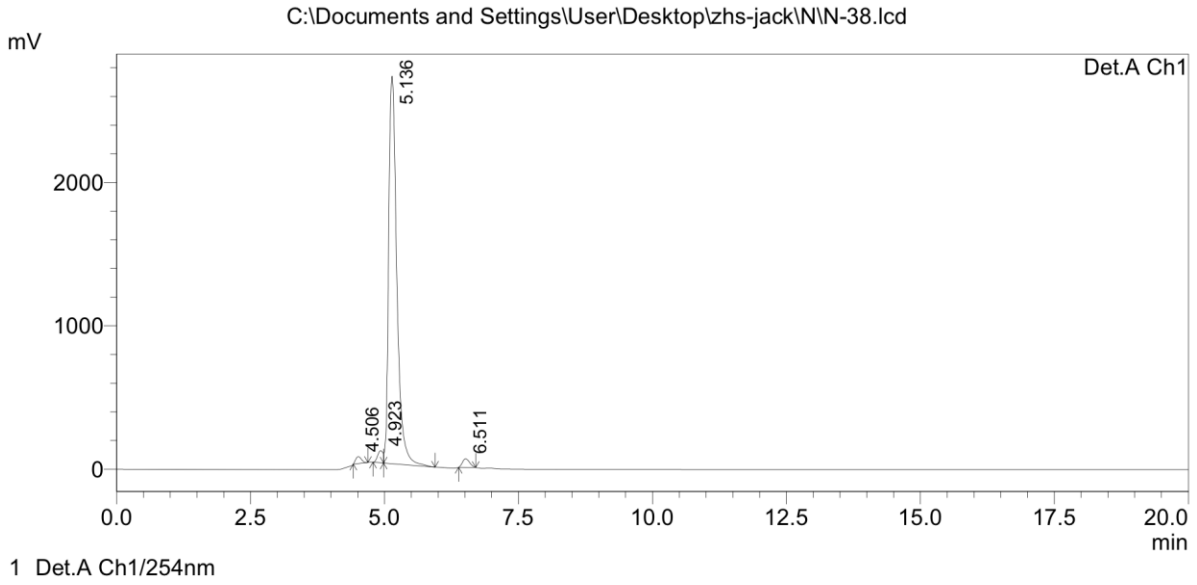

CARBON_01
N35-Proton-Carbon
CDCl3
f1 (ppm)



(*S*,*E*)-*N*-(1-phenyl-4-(phenylsulfonyl)but-3-en-2-yl)-1,2,3,4-tetrahydroquinoline-8-carboxamide (43)


N-38
CDCl3
f1 (ppm)


CARBON_01
N38-Proton-Carbon
CDCl3
f1 (ppm)



References

1. Skidmore, A.M.; Adcock, R.S.; Jonsson, C.B.; Golden, J.E.; Chung, D.H. Benzamidine ML336 inhibits plus and minus strand RNA synthesis of Venezuelan equine encephalitis virus without affecting host RNA production. Antiviral Research 2020, 174, 104674.
2. Hu, X.; Compton, J.R.; Leary, D.H.; Olson, M.A.; Lee, M.S.; Cheung, J.; Ye, W.; Ferrer, M.; Southall, N.; Jadhav, A.; Morazzani, E.M. Kinetic, Mutational, and Structural Studies of the Venezuelan Equine Encephalitis Virus Nonstructural Protein 2 Cysteine Protease. Biochemistry 2016, 55, 3007-3019.
3. Rasband, W.S.; ImageJ, U. S. National Institutes of Health, Bethesda, Maryland, USA, https://imagej.nih.gov/ij/, 1997-2018.
4. Thomsen, R.; Christensen, M.H. MolDock: a new technique for high-accuracy molecular docking. J Med Chem. 2006, 49, 3315–3321.
5. Molecular Operating Environment (MOE), 2018.01; Chemical Computing Group ULC, 1010 Sherbrooke St. est, Suite #910, Montreal, QC, Canada, H3A 2R7, 2018.