Supporting Information

Structure-Based Design of Novel Human Toll-like Receptor 8 Agonists

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Supporting Information

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Experimental Section

Protein expression, purification and crystallization: The extracellular domain of human Toll-like receptor 8 (hTLR8, residues 27–827) was prepared as described previously,[1] and was concentrated to 16 mg/mL in 10 mM MES (pH 5.5), 50 mM NaCl. The protein solutions for the crystallization of hTLR8/ Compound **3** complex contained hTLR8 (8.5 mg/mL) and Compound **3** (protein: chemical ligand molar ratio of 1: 10) in a crystallization buffer containing 7 mM MES (pH 5.5), 35 mM NaCl. Crystallization experiments were performed with sitting-drop vapor-diffusion methods at 293 K. Crystals of hTLR8/**3** complex were obtained with reservoir solutions containing 9-12% (w/v) PEG3350, 0.3 M potassium formate, and 0.1 M sodium citrate (pH 4.4).

Data collection and structure determination: Diffraction dataset was collected on beamlines PF-AR NE3A (Ibaraki, Japan) under cryogenic condition at 100 K. Crystals of hTLR8/Compound **3** complex were soaked into a cryoprotectant solution containing 15% (w/v) PEG3350, 0.23 M potassium formate, 75 mM sodium citrate pH 4.4, 7.5 mM MES pH 5.5, 38 mM NaCl, and 25% glycerol. The dataset was processed using the HKL2000 package.[2] hTLR8/**3** structure was determined by the molecular replacement method using the Molrep program[3] with the hTLR8/CL097 structure (PDB ID: 3W3J) as a search model. The model was further refined with stepwise cycles of manual model building using the COOT program[4] and restrained refinement using REFMAC[5] until the R factor was converged. Compound **3** molecule, *N*-glycans, and water molecules were modeled into the electron density maps at the latter cycles of the refinement. The quality of the final structure was evaluated with PROCHECK. The statistics of the data collection and refinement are also summarized in Table 1. The coordinates have been deposited in the Protein Database (PDB ID: 3WN4).

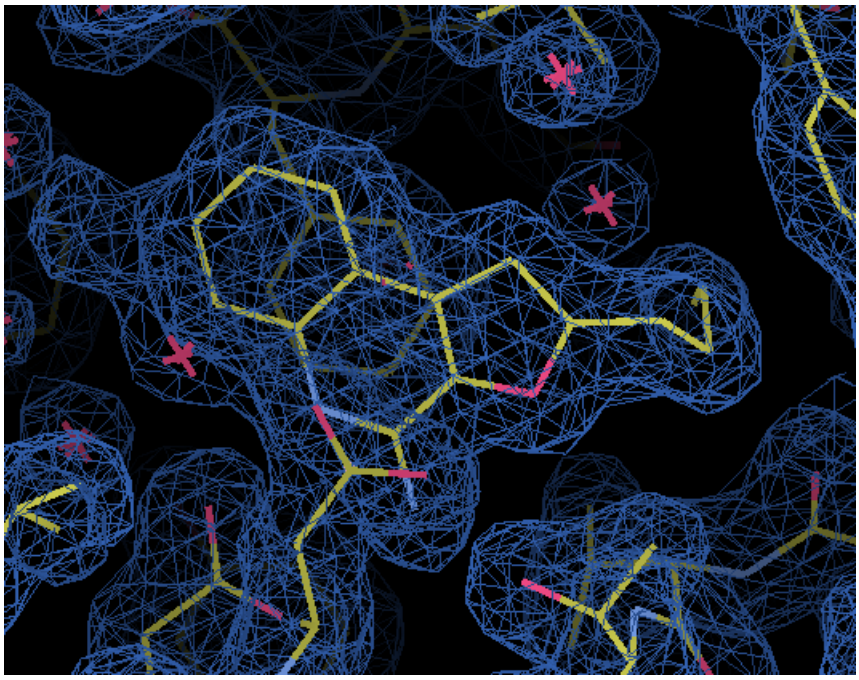


Fig. S1. Representative 2Fo-Fc electron density map of **3** in the binding pocket of TLR8 in the refined model. Densities are contoured at 1.0-σ level. Color codes: yellow, C; pink, O; blue, N.

Table 1. Data collection and refinement statistics[a]

	hTLR8/Compound **3**
Data Collection	
X-ray source	PF-AR NE3A
Wavelength	1.0000
Space group	*C*2
Unit cell	
a (Å)	138.4
b (Å)	103.5
c (Å)	70.7
β (°)	106.7
Resolution (Å)	1.8
Completeness (%)	97.0 (96.0)
Redundancy	3.4 (3.1)
R_{merge} (*I*)[b]	0.123 (0.778)
Average *I/σ(I)*	23.4 (1.7)
Refinement	
Resolution	27.2-1.8
No. of reflections	80153
Model	1×TLR8
Average *B*-factor	29.2
R (%)[c]	16.8
R_{free} (%)[d]	20.8
Rms deviations	
Bond length (Å)	0.019
Bond angles (°)	2.0

[a] Values in parentheses are for the shell with the highest resolution.
[b] $R_{merge}(I) = \Sigma|I - \langle I \rangle|/\Sigma I$, where *I* is the diffraction intensity.
[c] $R = \Sigma|F_o - F_c|/\Sigma F_o$, where F_o and F_c are the observed and calculated structure amplitudes, respectively.
[d] R_{free} is an *R* value for a 5% subset of all reflections, but was not used in the refinement.

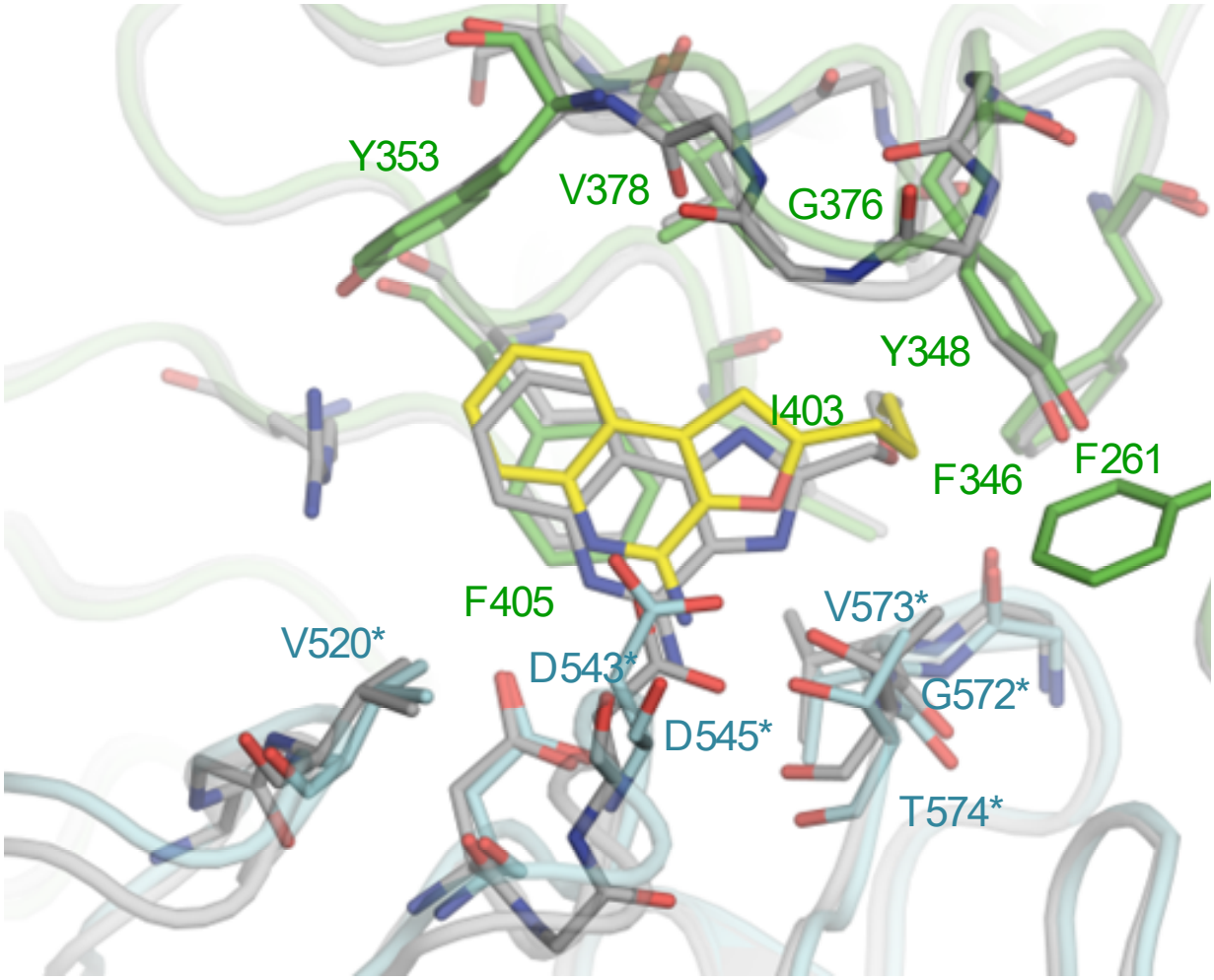


***Fig. S2*.** Superposition of TLR8/Compound **2** and TLR8/Compound **3** complexes. Compound **3** is depicted in yellow. The two protomers of TLR8 in the TLR8/Compound **3** complex are shown in green and cyan, respectively. All molecules in TLR8/Compound **2** complex are shown in gray.

Human TLR2/-3/-4/-5/-7/-8/-9 Reporter Gene assays (NF-κB induction): The induction of NF-κB was quantified using human TLR2/-3/-4/-5/-7/-8/-9-specific HEK-Blue™ reporter gene assays as previously described by us. HEK293 cells stably co-transfected with the appropriate hTLR, MD2, and secreted alkaline phosphatase (sAP), were maintained in HEK-Blue™ Selection medium containing zeocin and normocin. Stable expression of secreted alkaline phosphatase (sAP) under control of NF-κB/AP-1 promoters is inducible by appropriate TLR agonists, and extracellular sAP in the supernatant is proportional to NF-κB induction. HEK-Blue™ cells were incubated at a density of ~10^5 cells/ml in a volume of 80 µl/well, in 384-well, flat-bottomed, cell culture-treated microtiter plates until confluency was achieved, and subsequently stimulated with graded concentrations of stimuli. sAP was assayed spectrophotometrically using an alkaline phosphatase-specific chromogen (present in HEK-detection medium as supplied by the vendor) at 620 nm.

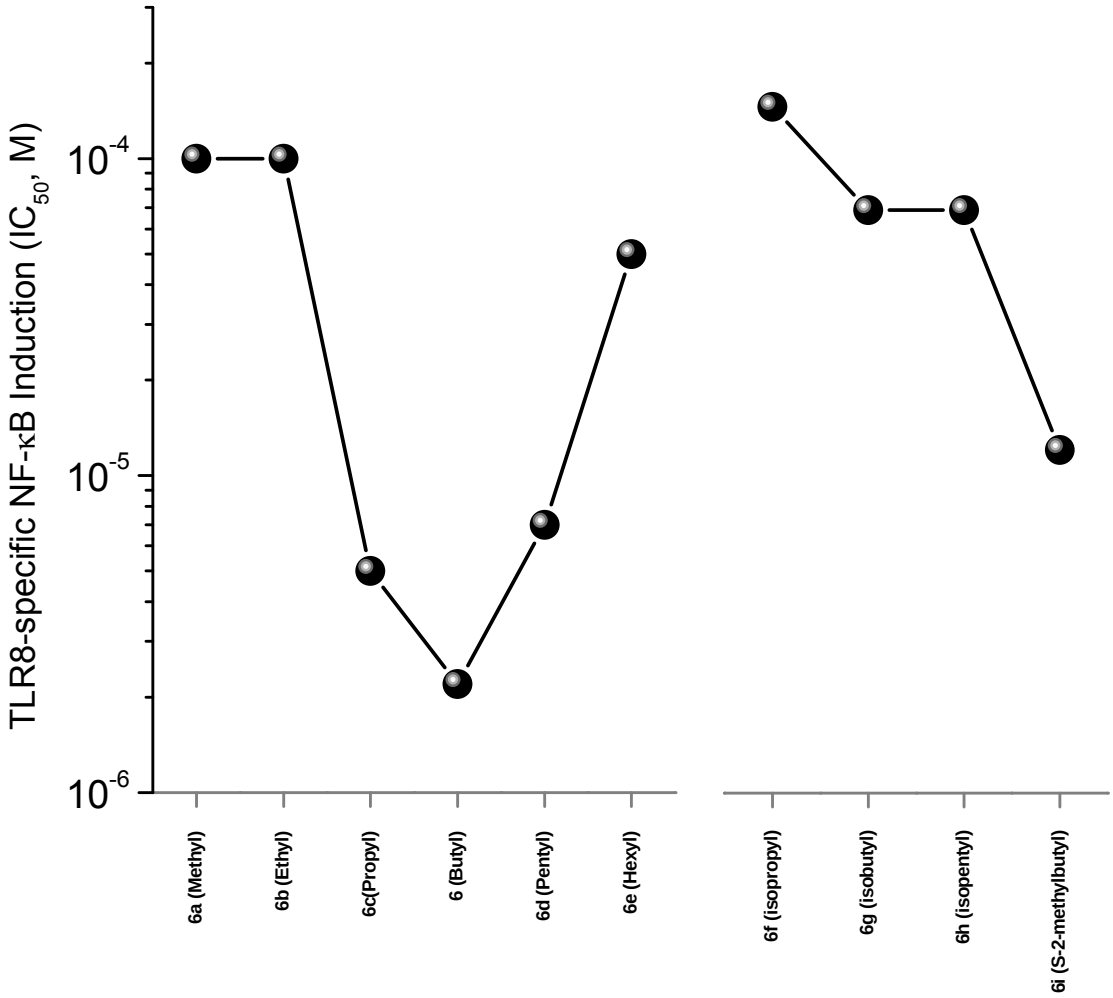


***Fig. S3*.** Human TLR8-agonistic potency (EC_{50} values) of a homologous series of 3-alkyl analogues (**6a-6e**), showing maximal activity with a C3-butyl chain. Branched chain analogues (**6f-6i**) are less potent.

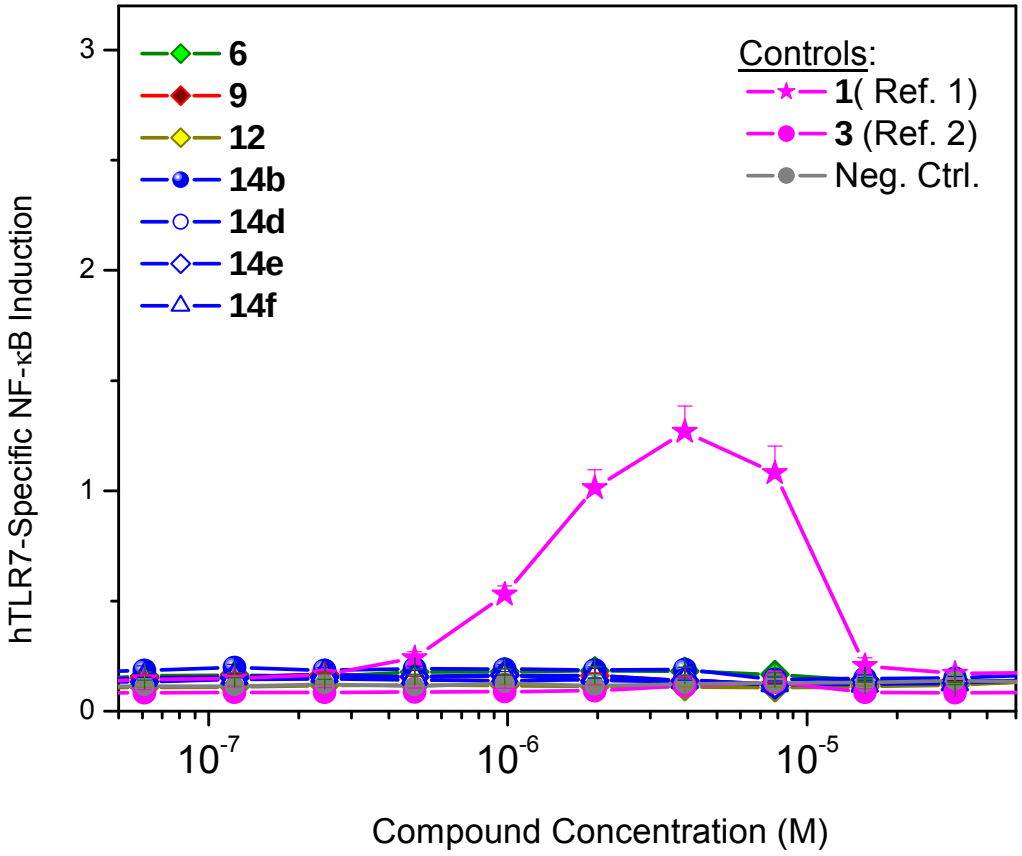
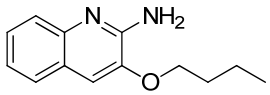
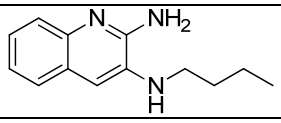
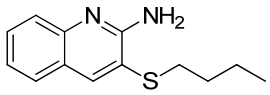
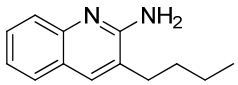
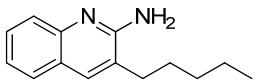
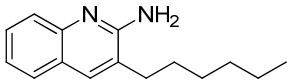
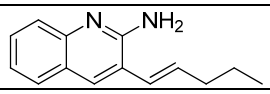
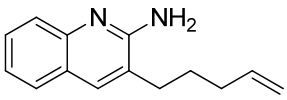
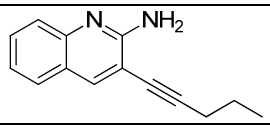
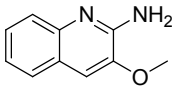
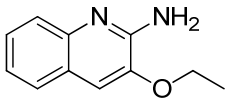
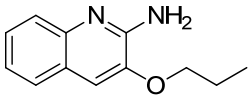
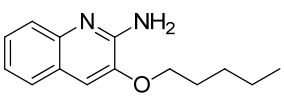
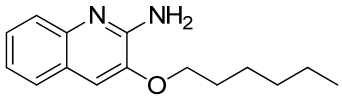
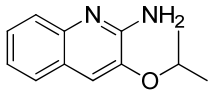
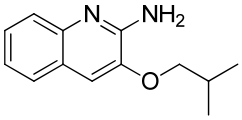
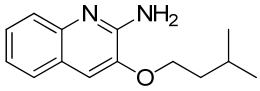
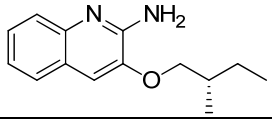
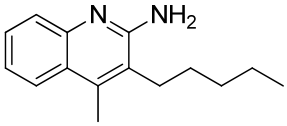
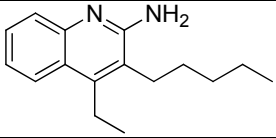
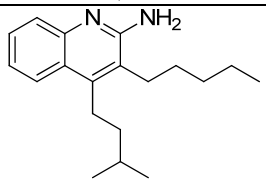
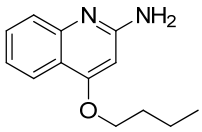
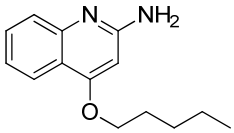
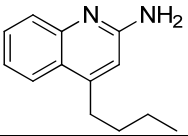
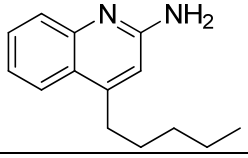


Fig. S4. Counter-screens in human TLR7 reporter cell line of the 3-substituted 2-aminoquinolines confirm pure TLR8-agonistic activity. No activity was observed in TLR2, TLR3, TLR4, TLR5, TLR7, TLR9, TLR10, Nod1 and Nod2 reporter cells (data not shown).

Table 2.

EC_{50} values of compounds in human TLR8-specific reporter gene assays

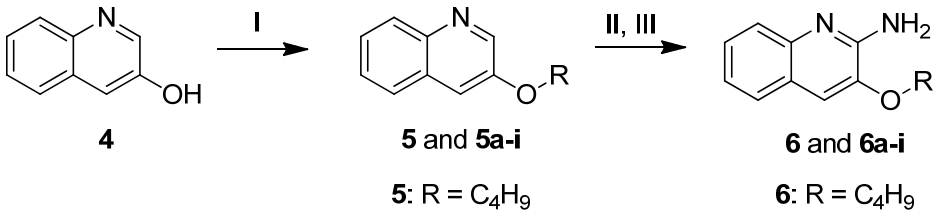
Compound Number	Structure	Agonistic Activity EC_{50} (μM)
		TLR8
6		2.18
9		4.28
12		4.16
14a		0.41
14b		0.2
14c		Inactive
14d		2.67
14e		0.49
14f		12.96
6a		100
6b		100
6c		5
6d		7

6e		50
6f		100
6g		50
6h		50
6i		10
21a		Inactive[a]
21b		Inactive
21c		Inactive
24a		Inactive
24b		Inactive
27a		Inactive
27a		Inactive

a: EC_{50} values >500 μM

Immunoassays for cytokines: Fresh human peripheral blood mononuclear cells (hPBMC) were isolated from human blood obtained by venipuncture with informed consent and as per institutional guidelines on Ficoll-Hypaque gradients. Aliquots of PBMCs (10^5 cells in 100 μL/well) were stimulated for 12 h with graded concentrations of test compounds. Supernatants were isolated by centrifugation, and were assayed in triplicates using analyte-specific multiplexed cytokine/chemokine bead array assays. PBMC supernatants were also analyzed for 41 chemokines and cytokines (EGF, Eotaxin, FGF-2, Flt-3 ligand, Fractalkine, G-CSF, GM-CSF, GRO, IFN-α2, IFN-γ, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17, IL-1ra, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IP-10, MCP-1, MCP-3, MDC (CCL22), MIP-1α, MIP-1β, PDGF-AA, PDGF-AB/BB, RANTES, TGFα, TNF-α, TNF-β, VEGF, sCD40L) using a magnetic bead-based multiplexed assay kit (Milliplex MAP Human Cytokine/Chemokine kit). Data were acquired and processed on a MAGPIX instrument (EMD Millipore, Billerica, MA) with an intra-assay coefficients of variation ranging from 4-8% for the 41 analytes.

General. All of the solvents and reagents used were obtained commercially and used as such unless noted otherwise. Moisture- or air-sensitive reactions were conducted under nitrogen atmosphere in oven-dried (120 ºC) glass apparatus. The solvents were removed under reduced pressure using standard rotary evaporators. Flash column chromatography was carried out using RediSep Rf 'Gold' high performance silica columns on CombiFlash Rf instrument unless otherwise mentioned, while thin-layer chromatography was carried out on silica gel (200 µm) CCM pre-coated aluminum sheets. Purity for all final compounds was confirmed to be greater than 97% by LC-MS using a Zorbax Eclipse Plus 4.6 mm x 150 mm, 5 µm analytical reverse phase C18 column with H_2O-isopropanol or H_2O-CH_3CN gradients (10-90% nonpolar phase, over 15 min) and an Agilent ESI-QTOF mass spectrometer (mass accuracy of 3 ppm) operating in the positive ion (or negative ion, as appropriate) acquisition mode. Chemical shifts are expressed in ppm (δ) and TMS was used as reference (δ = 0 ppm).



4 **5** and **5a-i** **6** and **6a-i**

5: R = C_4H_9 **6**: R = C_4H_9

a: R = CH_3, b: R = C_2H_5, c: R = C_3H_7, d: R = C_5H_{11}, e: R = C_6H_{13}, f: R = $CH(CH_3)_2$

g: R = $CH_2CH(CH_3)_2$, h: R = $C_2H_4CH(CH_3)_2$, **i**: R =

Scheme S1. Syntheses of 3-alkoxyquinolin-2-amine analogues. Reagents: (i) RI, NaH, DMSO; (ii) *m*-CPBA, $CHCl_3$; (iii) (a) benzoyl isocyanate, CH_2Cl_2, (b) NaOMe, MeOH.

General procedure for the synthesis of 3-(Butyloxy)quinoline (5): To a stirred solution of quinolin-3-ol **4** (299 mg, 2.06 mmol) in DMSO were added K_2CO_3 (569 mg, 4.12 mmol) and butyl iodide (352 µL, 3.10 mmol). The resulting reaction mixture was stirred at 80 ^oC for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with diethyl ether (3 x 15 mL). The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and the crude material was purified by flash chromatography to obtain **5** as colorless liquid (250 mg, 60%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.9 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 4.08 (t, *J* = 6.5 Hz, 2H), 1.89 – 1.81 (m, 2H), 1.60 – 1.50 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.72, 145.10, 143.5, 129.3, 129.0, 127.1, 126.8, 126.6, 112.9, 68.2, 31.2, 19.3, 14.0. MS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{15}NO$: 202.1226, found: 202.1238.

Compounds **5a-5i** were synthesized according to the general procedure for the synthesis of **5.**

3-(Ethyloxy)quinoline (5b). Colorless liquid (282 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.9 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.50 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.36 (d, *J* = 2.8 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 1.51 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 145.0, 143.6, 129.3, 129.0, 127.1, 126.8, 126.7, 113.0, 64.0, 14.8. MS (ESI) m/z $[M+H]^+$ calcd for $C_{11}H_{11}NO$: 174.0913, found: 174.0947.

3-(Propyloxy)quinoline (5c). Colorless liquid (277 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.9 Hz, 1H), 8.06 – 8.01 (m, 1H), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 4.03 (t, *J* = 6.5 Hz, 2H), 1.93 – 1.85 (m, 2H), 1.09 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 145.0, 143.5, 129.3, 129.0, 127.1, 126.7, 126.6, 112.9, 69.9, 22.5, 10.6. MS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{13}NO$: 188.1070, found: 188.0989.

3-(Pentyloxy)quinoline (5d). Colorless liquid **(**310 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.9 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.55 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.36 (d, *J* = 2.8 Hz, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 1.92 – 1.84 (m, 2H), 1.54 – 1.47 (m, 2H), 1.45 – 1.38 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 145.0, 143.6, 129.3, 129.0, 127.1, 126.8, 126.7, 113.0, 68.5, 28.9, 28.3, 22.6, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{17}NO$: 216.1383, found: 216.1295.

3-(Hexyloxy)quinoline (5e). White solid (381 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.9 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.36 (d, *J* = 2.8 Hz, 1H), 4.08 (t, *J* = 6.5 Hz, 2H), 1.90 – 1.83 (m, 2H), 1.55 – 1.48 (m, 2H), 1.42 – 1.32 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 145.0, 143.5, 129.3, 129.0, 127.1, 126.8, 126.6, 113.0, 68.5, 31.7, 29.2, 25.8, 22.7, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{19}NO$: 230.1539, found: 230.1733.

3-(Isopropyloxy)quinoline (5f). Colorless liquid (320 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 2.9 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.37 (d, *J* = 2.8 Hz, 1H), 4.69 (hept, *J* = 6.1 Hz, 1H), 1.43 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.4, 145.8, 143.5, 129.3, 129.0, 127.1, 126.8, 126.7, 114.5, 70.7, 21.9. MS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{13}NO$: 188.1070, found: 188.1058.

3-(Isobutyloxy)quinoline (5g). White solid (200 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.9 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 3.85 (d, *J* = 6.5 Hz, 2H), 2.18 (dp, *J* = 13.3, 6.7 Hz, 1H), 1.09 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 145.1, 143.5, 129.3, 129.0, 127.1, 126.8, 126.6, 113.0, 74.8, 28.3, 19.4. MS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{15}NO$: 202.1226, found: 202.1210.

3-(Isopentyloxy)quinoline (5h). White solid (384 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.9 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.71 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.36 (d, *J* = 2.8 Hz, 1H), 4.11

(t, *J* = 6.6 Hz, 2H), 1.94 – 1.85 (m, 1H), 1.76 (q, *J* = 6.7 Hz, 2H), 1.00 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 145.0, 143.5, 129.3, 129.0, 127.1, 126.8, 126.6, 112.9, 66.8, 37.9, 25.2, 22.7. MS (ESI) m/z [*M*+H]$^+$ calcd for $C_{14}H_{17}NO$: 216 .1383, found: 216.1401.

(*S*)-3-(2-Methylbutyloxy)quinoline (5i). White solid (300 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 2.9 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.9, 1.6 Hz, 1H), 7.49 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.36 (d, *J* = 2.8 Hz, 1H), 3.94 (dd, *J* = 8.9, 6.0 Hz, 1H), 3.86 (dd, *J* = 8.9, 6.5 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.68 – 1.58 (m, 1H), 1.38 – 1.28 (m, 1H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 145.1, 143.5, 129.3, 129.0, 127.1, 126.8, 126.6, 112.9, 73.3, 34.7, 26.3, 16.7, 11.5. MS (ESI) m/z [*M*+H]$^+$ calcd for $C_{14}H_{17}NO$: 216.1383, found: 216.1305.

General procedure for the synthesis of 3-(Butyloxy)quinolin-2-amine (6). To a stirred solution of substrate **5** (200 mg, 0.1 mmol) in $CHCl_3$ was added *m*-CPBA (667 mg, 3.86 mmol), the resulting reaction mixture was stirred at r.t. for 4 h. After completion of reaction (by TLC), the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, crude material was purified over SiO_2 using CH_2Cl_2:MeOH as an eluent. To a stirred solution of *N*-oxide of **5** (150 mg, 0.691 mmol) in CH_2Cl_2 was added benzoylisocyanate (304 mg, 2.07 mmol). The resulting reaction mixture was stirred at 55 ^{o}C for 1 h. After completion of reaction (monitored by TLC), the solvent was evaporated. The residue was re-dissolved in MeOH (5 mL), NaOMe (186 mg, 3.45 mmol) was added and refluxed for 2 h. The solvent was evaporated and the crude material was purified by flash chromatography to furnish **6** as a white solid (125 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.60 (m, 1H), 7.54 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.24 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.12 (s, 1H), 5.12 (s, 2H), 4.12 (t, *J* = 6.5 Hz, 2H), 1.90 – 1.84 (m, 2H), 1.59 – 1.50 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.9, 142.7, 142.3, 126.9, 126.3, 125.5, 125.1, 122.9, 111.3, 68.2, 31.2, 19.5, 14.0. MS (ESI) m/z [*M*+H]$^+$ calcd for $C_{13}H_{16}N_2O$: 217.1335, found: 217.1392.

Compounds **6a-6i** were synthesized according to the general procedure for the synthesis of **6.**

3-(Methyloxy)quinolin-2-amine (6a). White solid (100 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 1H), 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.43 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.13 (s, 1H), 5.13 (s, 2H), 3.96 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 143.3, 142.5, 127.0, 126.3, 125.5, 125.0, 123.0, 110.8, 55.6. MS (ESI) m/z [*M*+H]$^+$ calcd for $C_{10}H_{10}N_2O$: 175.0866, found: 175.0908.

3-(Ethyloxy)quinolin-2-amine (6b). White solid (195 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.24 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.11 (s, 1H), 5.15 (s, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 1.51 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.9, 142.6, 142.4, 126.9, 126.3, 125.5, 125.1, 122.9, 111.3, 64.1, 14.8. MS (ESI) m/z [*M*+H]$^+$ calcd for $C_{11}H_{12}N_2O$: 189.1022, found: 189.1074.

3-(Propyloxy)quinolin-2-amine (6c). White solid (160 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.24 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.11 (s, 1H), 5.14 (s, 2H), 4.07 (t, *J* = 6.5 Hz, 2H), 1.96 – 1.87 (m, 2H), 1.10 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.9, 142.7, 142.3, 126.9, 126.3, 125.5, 125.1, 122.9, 111.4, 70.0, 22.5, 10.8. MS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{14}N_2O$: 203.1179, found: 203.1233.

3-(Pentyloxy)quinolin-2-amine (6d). White solid (70 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, 1H), 7.54 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.23 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.11 (s, 1H), 5.14 (s, 2H), 4.10 (t, *J* = 6.5 Hz, 2H), 1.92 – 1.85 (m, 2H), 1.53 – 1.45 (m, 2H), 1.45 – 1.37 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.9, 142.7, 142.3, 126.9, 126.3, 125.5, 125.1, 122.9, 111.3, 68.5, 28.8, 28.4, 22.6, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2O$: 231.1492, found: 231.1554.

3-(Hexyloxy)quinolin-2-amine (6e). White solid (180 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.42 (ddd, *J* = 8.3, 7.1, 1.4 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.11 (s, 1H), 5.18 (s, 2H), 4.10 (t, *J* = 6.5 Hz, 2H), 1.91 – 1.83 (m, 2H), 1.55 – 1.46 (m, 2H), 1.41 – 1.32 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.9, 142.7, 142.3, 126.8, 126.3, 125.4, 125.1, 122.9, 111.3, 68.5, 31.7, 29.1, 25.9, 22.7, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{20}N_2O$: 245.1648, found: 245.1721.

3-(Isopropyloxy)quinolin-2-amine (6f). White solid (100 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.41 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.23 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.10 (s, 1H), 5.26 (s, 2H), 4.70 (dt, *J* = 12.1, 6.1 Hz, 1H), 1.43 (d, *J* = 6.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.6, 141.2, 132.1, 128.7, 126.8, 126.2, 125.3, 122.8, 112.3, 70.7, 21.9. MS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{14}N_2O$: 203.1179, found: 203.1106.

3-(Isobutyloxy)quinolin-2-amine (6g). White solid (100 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.09 (s, 1H), 5.34 (s, 2H), 3.85 (d, *J* = 6.5 Hz, 2H), 2.18 (dp, *J* = 13.3, 6.7 Hz, 1H), 1.08 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.1, 142.7, 142.3, 126.8, 126.3, 125.3, 125.0, 122.8, 111.3, 74.7, 28.2, 19.4. MS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{16}N_2O$: 217.1335, found: 217.1394.

3-(Isopentyloxy)quinolin-2-amine (6h). White solid (115 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.23 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 7.10 (s, 1H), 5.28 (s, 2H), 4.12 (t, *J* = 6.6 Hz, 2H), 1.91 – 1.82 (m, 1H), 1.76 (q, *J* = 6.7 Hz, 2H), 1.00 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0, 142.7, 142.3, 126.8, 126.3, 125.4, 125.0, 122.8, 111.2, 66.9, 37.8, 25.3, 22.7. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2O$: 231.1492, found: 231.1407.

(*S*)-3-(2-Methylbutyloxy)quinolin-2-amine (6i). White solid (124 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.42 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 7.24 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.12 (s, 1H), 5.12 (s, 2H), 3.97 (dd, *J*

= 9.0, 6.0 Hz, 1H), 3.90 (dd, *J* = 9.0, 6.5 Hz, 1H), 2.03 – 1.92 (m, 1H), 1.66 – 1.56 (m, 1H), 1.39 – 1.29 (m, 1H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.9, 142.8, 142.3, 126.9, 126.3, 125.5, 125.1, 122.9, 111.3, 73.2, 34.7, 26.4, 16.8, 11.5. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2O$: 231.1492, found: 231.1549.

Synthesis of 3-Azido-2-chloroquinoline (7).[6] To a stirred solution of (2-chloroquinolin-3-yl)boronic acid (200 mg, 0.966 mmol) in MeOH were added $CuSO_4.5H_2O$ (25 mg, 0.096 mmol) and sodium azide (75 mg, 1.159 mmol). The resulting reaction mixture was stirred at r.t. for 4 h. After completion of reaction (monitored by TLC), the solid was filtered and washed with methanol to give **7** as a brown solid (170 mg, 86%), which was used for next step without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.70 (dd, *J* = 11.2, 4.0 Hz, 1H), 7.59 (dd, *J* = 11.2, 3.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.0, 143.4, 132.2, 129.9, 128.6, 128.2, 127.7, 126.5, 125.1. MS (ESI) m/z $[M+H]^+$ calcd for $C_9H_5ClN_4$: 205.0276, found: 205.0330.

Synthesis of 2-Chloroquinolin-3-amine (8). To a stirred solution of compound **7** (200 mg, 0.490 mmol) in EtOH (2 mL), was added Pt/C (125 mg) under nitrogen atmosphere. The reaction mixture was then stitted under H_2 (50 psi) for 1 h. The catalyst was removed by filtration, solvent was evaporated under reduced pressure, and the crude residue purified by flash chromatography using CH_2Cl_2:MeOH as an eluent to obtain compound **8** as a white solid (156 mg, 86 %). ^{1}H NMR (500 MHz, MeOD) δ 7.75 – 7.72 (m, 1H), 7.65 – 7.62 (m, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.44 – 7.41 (m, 2H). ^{13}C NMR (126 MHz, MeOD) δ 142.2, 142.0, 140.4, 130.9, 128.2, 128.1, 127.0, 126.7, 117.4. MS (ESI) m/z $[M+H]^+$ calcd for $C_9H_7ClN_2$: 179.0371, found: 179.0457.

Synthesis of N^3-Butylquinoline-2,3-diamine (9). To a solution of **8** (130 mg, 0.730 mmol) in DMF was added butyl iodide (99 µL, 0.876 mmol) under the nitrogen, the resulting mixture was stirred at 60 °C for 12 h. The solvent was evaporated under reduced pressure, diluted with water and extracted with ethyl acetate to obtain *N*-butyl-2-chloroquinolin-3-amine (50 mg, 0.213 mmol). The alkylated compound was dissolved in 1M ammonia solution (in methanol 2 mL). The reaction mixture was then heated to 100 °C for 24 h. The solvent was evaporated under reduced pressure, and the crude residue purified by flash chromatography using CH_2Cl_2:MeOH as an eluent to obtain compound **9** as a white solid (15 mg, 33%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 7.6 Hz, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.06 (t, *J* = 7.2 Hz, 1H), 7.98 (t, *J* = 7.3 Hz, 1H), 7.75 (s, 1H), 6.33 (s, 1H), 3.96 (dd, *J* = 11.9, 6.9 Hz, 2H), 2.51 – 2.42 (m, 2H), 2.32 – 2.22 (m, 2H), 1.76 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 141.5, 134.8, 134.7, 134.3, 134.0, 132.2, 132.2, 117.6, 52.4, 39.6, 29.5, 23.3. MS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{17}N_3$: 216.1495, found: 216.1484.

Synthesis of 3-Bromoquinoline 1-oxide (11). To a stirred solution of substrate **10** (400 mg, 1.92 mmol) in $CHCl_3$ was added *m*-CPBA (1288 mg, 5.76 mmol). The resulting reaction mixture was stirred at r.t. for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and the crude material was purified by flash chromatography to get **11** as white solid (360 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.8 Hz, 1H), 8.62 (d, *J* = 1.6 Hz, 1H),

7.89 (s, 1H), 7.81 – 7.73 (m, 2H), 7.66 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 137.3, 130.7, 130.4, 130.0, 127.8, 127.5, 120.0, 114.5. MS (ESI) m/z $[M+H]^+$ calcd for C_9H_6BrNO: 223.9706, found: 223.9662.

Synthesis of 3-(Butylthio)quinolin-2-amine (12). To a stirred solution of *N*-oxide of **11** (89 mg, 0.381 mmol) in CH_2Cl_2 was added benzoylisocyanate (168 mg, 1.145 mmol). The resulting reaction mixture was stirred at 55 ^oC for 1 h. After completion of reaction (monitored by TLC), the solvent was evaporated. The residue was re-dissolved in MeOH (5 mL), NaOMe (102 mg, 1.90 mmol) was added and refluxed for 2 h. The solvent was evaporated and the crude material was purified by flash chromatography to furnish **12** as a white solid (75 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.25 (ddd, *J* = 8.0, 4.5, 1.2 Hz, 1H), 5.49 (s, 2H), 2.87 (t, 2H), 1.64 – 1.57 (m, 2H), 1.48 – 1.39 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 147.3, 141.9, 130.1, 127.1, 125.8, 124.5, 123.0, 117.9, 34.5, 31.5, 21.9, 13.8. MS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{16}N_2S$: 233.1107, found: 233.1059.

General procedure for the synthesis of 3-Butylquinoline 1-oxide (13a). To a stirred solution of substrate **11** (100 mg, 0.446 mmol) in 1,4-dioxane was added butylboronic acid (91 mg, 0.892 mmol), $Pd(PPh_3)_4$ (25 mg, 0.0228 mmol) and K_2CO_3 (184 mg, 1.33 mmol). The resulting reaction mixture was stirred at 90 ^oC under nitrogen atmosphere for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, crude material was purified by flash chromatography using CH_2Cl_2:MeOH as an eluent to obtain **13a** as a white solid (72 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.7 Hz, 1H), 8.45 (d, *J* = 1.3 Hz, 1H), 7.79 (dd, 1H), 7.69 (ddd, *J* = 8.6, 6.9, 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.53 (s, 1H), 2.72 (t, 2H), 1.72 – 1.65 (m, 2H), 1.44 – 1.35 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 137.0, 136.3, 130.4, 129.6, 128.9, 127.7, 125.2, 119.8, 33.0, 32.8, 22.2, 14.0. MS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{15}NO$: 202.1226, found: 202.1152.

Compounds **13b-13f** were synthesized according to the general procedure for the synthesis of **13a.**

3-Pentylquinoline 1-oxide (13b). White solid **(**80 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.7 Hz, 1H), 8.45 (d, *J* = 1.2 Hz, 1H), 7.82 – 7.77 (m, 1H), 7.69 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.53 (s, 1H), 2.70 (t, 2H), 1.75 – 1.66 (m, 2H), 1.38 – 1.30 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 137.0, 136.4, 130.4, 129.6, 128.9, 127.8, 125.2, 119.8, 33.3, 31.9, 30.4, 22.6, 14.1. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{17}NO$: 216.1383, found: 216.1380.

3-Hexylquinoline 1-oxide (13c). White solid (80 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 8.7 Hz, 1H), 8.45 (d, *J* = 1.0 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.69 (ddd, *J* = 8.5, 6.9, 1.2 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.53 (s, 1H), 2.71 (t, *J* = 7.7 Hz, 2H), 1.72 – 1.64 (m, 2H), 1.40 – 1.27 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0,

137.0, 136.4, 130.4, 129.6, 128.9, 127.8, 125.1, 119.8, 33.3, 31.7, 30.7, 28.8, 22.7, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{19}NO$: 230.1539, found: 230.1425.

(*E*)-3-(Pent-1-en-1-yl)quinoline 1-oxide (13d). White solid (72 mg, 75%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.7 Hz, 1H), 8.64 (d, *J* = 1.3 Hz, 1H), 7.79 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.67 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.57 (s, 1H), 6.42 – 6.34 (m, 2H), 2.25 (td, *J* = 7.3, 5.6 Hz, 2H), 1.58 – 1.48 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.3, 135.5, 134.1, 132.0, 130.4, 129.8, 129.1, 128.1, 125.3, 122.7, 119.9, 35.3, 22.3, 13.8. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{15}NO$: 214.1226, found: 214.1071.

3-(Pent-4-en-1-yl)quinoline 1-oxide (13e). White solid (70 mg, 73%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 8.7 Hz, 1H), 8.44 (d, *J* = 0.9 Hz, 1H), 7.79 (d, 1H), 7.69 (ddd, *J* = 8.5, 6.9, 1.2 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.53 (s, 1H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.07 – 4.98 (m, 2H), 2.72 (t, 2H), 2.13 (dd, *J* = 14.3, 7.1 Hz, 2H), 1.85 – 1.75 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.1, 137.8, 136.9, 135.9, 130.4, 129.7, 128.9, 127.8, 125.2, 119.8, 115.7, 33.0, 32.5, 29.8. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{15}NO$: 214.1226, found: 214.1069.

3-(Pent-1-yn-1-yl)quinoline 1-oxide (13f). White solid (68 mg, 72%). ^1H NMR (500 MHz, CDCl3) δ 8.68 (d, J = 8.7 Hz, 1H), 8.50 (d, J = 1.0 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.74 (s, 1H), 7.73 – 7.68 (m, 1H), 7.64 – 7.58 (m, 1H), 2.43 (t, J = 7.0 Hz, 2H), 1.70 – 1.61 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 137.6, 130.6, 130.0, 129.3, 128.5, 128.0, 119.9, 118.7, 95.2, 76.2, 22.0, 21.5, 13.8. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{13}NO$: 212.1070, found: 212.0947.

General procedure for the synthesis of 3-Butylquinolin-2-amine (14a). To a stirred solution of *N*-oxide of **13a** (50 mg, 0.248 mmol) in CH_2Cl_2 was added benzoylisocyanate (109 mg, 0.741 mmol). The resulting reaction mixture was stirred at 55 ^oC for 1 h. After completion of reaction (monitored by TLC), the solvent was evaporated. The residue was re-dissolved in MeOH (5 mL), NaOMe (67 mg, 1.24 mmol) was added and refluxed for 2 h. The solvent was evaporated and the crude material was purified by flash chromatography using CH_2Cl_2:MeOH as an eluent to furnish **14a** as a white solid (40 mg, 81%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.51 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.27 – 7.22 (m, 1H), 4.81 (s, 2H), 2.59 (t, 2H), 1.78 – 1.65 (m, 2H), 1.52 – 1.41 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 146.5, 135.6, 128.9, 127.1, 125.7, 124.7, 123.8, 122.7, 31.1, 30.2, 22.7, 14.1. MS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{16}N_2$: 201.1386, found: 201.1327.

Compounds **14b-14f** were synthesized according to the general procedure for the synthesis of **14a.**

3-Pentylquinolin-2-amine (14b). White solid (125 mg, 83%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.51 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.26 – 7.22 (m, 1H), 4.83 (s, 2H), 2.58 (t, 2H), 1.78 – 1.68 (m, 2H), 1.46 – 1.34 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 146.6, 135.5, 128.9,

127.1, 125.7, 124.7, 123.8, 122.7, 31.8, 31.3, 27.7, 22.7, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2$: 215.1543, found: 215.1407.

3-Hexylquinolin-2-amine (14c). White solid (82 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.60 (dd, 1H), 7.51 (ddd, 1H), 7.26 – 7.21 (m, 1H), 4.83 (s, 2H), 2.58 (t, 2H), 1.78 – 1.68 (m, 2H), 1.49 – 1.39 (m, 2H), 1.38 – 1.28 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 146.5, 135.5, 128.9, 127.1, 125.7, 124.7, 123.8, 122.7, 31.8, 31.4, 29.3, 28.0, 22.8, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{20}N_2$: 229.1699, found: 229.1574.

(*E*)-3-(Pent-1-en-1-yl)quinolin-2-amine (14d). White solid (37 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 8.3, 7.0 Hz, 1H), 7.23 (t, *J* = 7.7, 7.2 Hz, 1H), 6.38 (d, *J* = 15.5 Hz, 1H), 6.28 – 6.19 (m, 1H), 5.05 (d, *J* = 12.5 Hz, 2H), 2.24 (td, *J* = 9.8, 6.0 Hz, 2H), 1.58 – 1.48 (m, 2H), 0.98 (td, *J* = 7.3, 1.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 147.0, 136.5, 134.1, 129.2, 127.4, 125.7, 124.6, 124.4, 122.8, 122.1, 35.5, 22.5, 13.9. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{16}N_2$: 213.1386, found: 213.1228.

3-(Pent-4-en-1-yl)quinolin-2-amine (14e). White solid (38 mg, 76%)**.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.60 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.52 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.25 (ddd, *J* = 8.0, 4.9, 1.1 Hz, 1H), 5.86 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.12 – 5.06 (m, 1H), 5.06 – 5.02 (m, 1H), 4.86 (s, 2H), 2.63 – 2.56 (m, 2H), 2.20 (dd, *J* = 14.1, 7.1 Hz, 2H), 1.88 – 1.79 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 146.5, 138.1, 135.8, 129.0, 127.1, 125.6, 124.6, 123.4, 122.8, 115.7, 33.4, 30.5, 27.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{16}N_2$: 213.1386, found: 213.1225.

3-(Pent-1-yn-1-yl)quinolin-2-amine (14f). White solid (35 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.26 – 7.21 (m, 1H), 5.26 (s, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 1.72 – 1.65 (m, 2H), 1.09 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.6, 146.8, 140.0, 130.2, 127.3, 125.9, 123.4, 123.0, 107.4, 97.1, 76.2, 22.3, 21.8, 13.8. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{14}N_2$: 211.1230, found: 211.1234.

Synthesis of 4-Chloro-3-iodoquinoline (16). Substrate 3-iodoquinolin-4-ol **15** (1000 mg, 3.69 mmol) was dissolved in 25 mL of $POCl_3$.The resulting reaction mixture was stirred at 100 ^{o}C for 2 h. After completion of reaction (monitored by TLC), the solvent was evaporated under reduced pressure and added ice cold water. The solid was filtered and dried under the vacuum to get **16** as a white solid (900 mg, 85%). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 9.15 (s, 1H), 8.21 (dd, *J* = 8.4, 0.8 Hz, 1H), 8.09 – 8.04 (m, 1H), 7.88 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.75 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H). ^{13}C NMR (126 MHz, DMSO) δ 156.6, 146.8, 144.9, 131.0, 129.4, 129.1, 126.6, 124.4, 96.9. MS (ESI) m/z $[M+H]^+$ calcd for C_9H_5ClIN: 289.9228, found: 289.9264.

Synthesis of 4-Chloro-3-(pent-1-yn-1-yl)quinoline (17). To a stirred solution of 4-chloro-3-iodoquinoline **16** (500 mg, 1.730 mmol) in acetonitrile:triethylamine (3:1) were added the pent-1-yne (341 µL, 3.46 mmol), $Pd(PPh_3)_4$ (92.4 mg, 0.08 mmol) and CuI (13.14 mg, 0.069 mmol). The resulting reaction mixture was stirred at 70 ^{o}C under nitrogen

atmosphere for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with ethylacetate (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, crude material was purified by flash chromatography using CH_2Cl_2:MeOH as an eluent to obtain **17** as a white solid (325 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.23 (ddd, *J* = 8.4, 1.4, 0.5 Hz, 1H), 8.08 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.73 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.64 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 2.54 (t, *J* = 7.0 Hz, 2H), 1.77 – 1.68 (m, 2H), 1.12 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 147.2, 143.2, 130.3, 129.9, 128.1, 126.1, 124.4, 118.3, 99.9, 76.1, 22.1, 21.9, 13.7. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{12}ClN$: 230.0731, found: 230.0823.

General procedure for the synthesis of 4-Methyl-3-(pent-1-yn-1-yl)quinoline (18a). To a stirred solution of substrate **17** (150 mg, 0.655 mmol) in 1,4-dioxane were added the methylboronic acid (78 mg, 1.31 mmol), $Pd(PPh_3)_4$ (37 mg, 0.032 mmol) and K_2CO_3 (271 mg, 1.965 mmol). The resulting reaction mixture was stirred at 90 ^oC under nitrogen atmosphere for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, crude material was purified by flash chromatography using CH_2Cl_2:MeOH as an eluent to obtain **18a** as a colorless liquid (100 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.05 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.99 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.67 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.56 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 2.80 (s, 3H), 2.51 (t, *J* = 7.0 Hz, 2H), 1.71 (dt, *J* = 14.4, 7.3 Hz, 2H), 1.11 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 146.5, 145.8, 130.1, 129.2, 127.5, 126.9, 124.1, 118.1, 97.4, 77.8, 22.4, 21.8, 16.5, 13.8. MS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{15}N$: 210.1277, found: 210.1214.

Compounds **18b-18c** were synthesized according to the general procedure for the synthesis of **18a.**

General procedure for the synthesis of 4-Methyl-3-pentylquinoline (19a). To a stirred solution of compound **18a** (125 mg, 0.586 mmol) in EtOH (2 mL), was added Pt/C (125 mg) under nitrogen atmosphere. The reaction mixture was then stirred under H_2 (50 psi) for 1 h. The catalyst was removed by filtration, solvent was evaporated under reduced pressure, and the crude residue purified by flash chromatography using CH_2Cl_2:MeOH as an eluent to obtain compound **19a** as a white solid (86 mg, 68 %).

Compounds **19b-19c** were synthesized according to the general procedure for the synthesis of **19a.**

General procedure for the synthesis of 4-Methyl-3-pentylquinoline 1-oxide (20a). To a stirred solution of substrate **19a** (100 mg, 0.469 mmol) in $CHCl_3$ was added *m*-CPBA (243 mg, 1.408 mmol). The resulting reaction mixture was stirred at r.t. for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and the crude material was purified by flash

chromatography using CH_2Cl_2:MeOH as an eluent to obtain **20a** as white solid (91 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 8.5 Hz, 1H), 8.41 (s, 1H), 8.00 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.70 (ddd, *J* = 8.5, 6.9, 1.2 Hz, 1H), 7.64 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 2.72 (t, 2H), 2.59 (s, 3H), 1.68 – 1.57 (m, 2H), 1.43 – 1.30 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 137.0, 134.0, 132.0, 130.3, 129.2, 128.6, 124.5, 120.2, 31.6, 31.5, 30.2, 22.6, 14.1, 13.8. MS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{19}NO$: 230.1539, found: 230.1426.

Compounds **20b-20c** were synthesized according to the general procedure for the synthesis of **20a.**

4-Ethyl-3-pentylquinoline 1-oxide (20b). White solid (140 mg, 78%) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 8.6, 0.9 Hz, 1H), 8.42 (s, 1H), 8.05 – 7.98 (m, 1H), 7.74 – 7.67 (m, 1H), 7.64 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 3.05 (q, *J* = 7.6 Hz, 2H), 2.71 (t, 2H), 1.70 – 1.61 (m, 2H), 1.42 – 1.35 (m, 4H), 1.29 (t, *J* = 7.6 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.9, 138.0, 137.0, 133.4, 129.4, 129.1, 128.6, 124.4, 120.4, 31.8, 30.9, 30.8, 22.6, 20.9, 15.2, 14.1. MS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{21}NO$: 244.1696, found: 244.1690.

4-Isopentyl-3-pentylquinoline 1-oxide (20c). White solid (60 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.42 (s, 1H), 7.98 (d, 1H), 7.70 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.64 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 3.03 – 2.94 (m, 2H), 2.75 – 2.64 (m, 2H), 1.80 (dt, *J* = 13.2, 6.6 Hz, 1H), 1.69 – 1.59 (m, 2H), 1.49 (ddd, *J* = 15.4, 6.7, 5.0 Hz, 2H), 1.42 – 1.34 (m, 4H), 1.05 (d, *J* = 6.6 Hz, 6H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.9, 137.0, 133.5, 129.6, 129.1, 128.6, 125.1, 124.4, 120.4, 39.9, 31.8, 30.9, 30.7, 29.0, 25.8, 22.7, 22.6, 14.1. MS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{27}NO$: 286.2165, found: 286.2300.

General procedure for the synthesis of 4-Methyl-3-pentylquinolin-2-amine (21a). To a stirred solution of *N*-oxide of **20a** (50 mg, 0.218 mmol) in CH_2Cl_2 was added benzoylisocyanate (96 mg, 0.653 mmol). The resulting reaction mixture was stirred at 55 ^oC for 1 h. After completion of reaction (monitored by TLC), the solvent was evaporated. The residue was re-dissolved in MeOH (5 mL), NaOMe (105 mg, 1.94 mmol) was added and refluxed for 2 h. The solvent was evaporated and the crude material was purified by flash chromatography using CH_2Cl_2:MeOH as an eluent to furnish **21a** as a white solid (35 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.29 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.86 (s, 2H), 2.70 – 2.64 (m, 2H), 2.58 (s, 3H), 1.62 – 1.56 (m, 2H), 1.46 – 1.35 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 145.8, 141.8, 128.7, 126.3, 124.7, 123.9, 122.6, 121.8, 32.2, 28.3, 28.3, 22.7, 14.4, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{20}N_2$: 229.1699, found: 229.1612.

Compounds **21b-21c** were synthesized according to the general procedure for the synthesis of **21a.**

4-Ethyl-3-pentylquinolin-2-amine (21b). White solid (36 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.48 (dd, *J* = 11.1, 4.0 Hz, 1H),

7.29 – 7.23 (m, 1H), 4.83 (s, 2H), 3.02 (q, *J* = 7.6 Hz, 2H), 2.66 – 2.59 (m, 2H), 1.59 (dt, *J* = 11.8, 7.6 Hz, 2H), 1.49 – 1.34 (m, 4H), 1.27 (t, *J* = 7.6 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.3, 147.4, 146.5, 128.5, 126.6, 123.8, 123.5, 122.6, 121.0, 32.4, 28.7, 27.9, 22.7, 21.4, 15.0, 14.2. MS (ESI) m/z [*M*+H]$^+$ calcd for $C_{16}H_{22}N_2$: 243.1856, found: 243.1877.

4-Isopentyl-3-pentylquinolin-2-amine (21c). White solid (19 mg, 77%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.30 – 7.24 (m, 1H), 4.83 (s, 2H), 3.00 – 2.92 (m, 2H), 2.65 – 2.58 (m, 2H), 1.85 – 1.75 (m, 1H), 1.61 (dt, *J* = 11.9, 7.6 Hz, 2H), 1.53 – 1.35 (m, 6H), 1.04 (d, *J* = 6.6 Hz, 6H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2, 146.5, 128.5, 126.5, 123.8, 123.7, 122.6, 121.1, 39.7, 32.4, 29.1, 28.6, 28.0, 26.3, 22.6, 22.6, 14.2. MS (ESI) m/z [*M*+H]$^+$ calcd for $C_{19}H_{28}N_2$: 285.2325, found: 285.2429.

General procedure for the synthesis of 4-(Butyloxy)quinoline (23a). To a stirred solution of quinolin-4-ol **22** (472 mg, 3.25 mmol) in DMSO were added K_2CO_3 (898 mg, 6.50 mmol) and butyliodide (555 µL, 4.87 mmol). The resulting reaction mixture was stirred at 80 ^{o}C for 4 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with diethyl ether (3 x 15 mL). The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and the crude material was purified by flash chromatography to obtain **23a** as white solid (350 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.2 Hz, 1H), 8.23 (dd, *J* = 8.3, 1.0 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 6.72 (d, *J* = 5.2 Hz, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 1.97 – 1.90 (m, 2H), 1.65 – 1.56 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9, 151.6, 149.4, 129.8, 129.0, 125.6, 122.0, 121.7, 100.8, 68.3, 31.1, 19.5, 14.0. MS (ESI) m/z [*M*+H]$^+$ calcd for $C_{13}H_{15}NO$: 202.1226, found: 202.1221.

Compound **23b** was synthesized according to the general procedure for the synthesis of **23a.**

4-(Pentyloxy)quinoline (23b). White solid (365 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.2 Hz, 1H), 8.22 (dd, *J* = 8.3, 1.0 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 6.71 (d, *J* = 5.2 Hz, 1H), 4.18 (t, *J* = 6.4 Hz, 2H), 1.95 (dt, *J* = 14.4, 6.5 Hz, 2H), 1.54 (ddd, *J* = 12.0, 8.5, 6.3 Hz, 2H), 1.44 (dq, *J* = 14.4, 7.1 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 151.6, 149.3, 129.8, 129.0, 125.6, 122.0, 121.7, 100.8, 68.6, 28.7, 28.4, 22.6, 14.2. MS (ESI) m/z [*M*+H]$^+$ calcd for $C_{14}H_{17}NO$: 216.1383, found: 216.1507.

General procedure for the synthesis of 4-(Butyloxy)quinolin-2-amine (24a). To a stirred solution of substrate **23a** (238 mg, 1.18 mmol) in $CHCl_3$ was added *m*-CPBA (612 mg, 3.55 mmol), the resulting reaction mixture was stirred at r.t. for 4 h. After completion of reaction (by TLC), the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, crude material was purified over SiO_2 using CH_2Cl_2:MeOH as an eluent. To a stirred solution of *N*-oxide of **23a** (151 mg, 0.697 mmol) in CH_2Cl_2 was added benzoylisocyanate (304 mg, 2.07 mmol). The resulting reaction mixture was stirred at 55

^{o}C for 1 h. After completion of reaction (monitored by TLC), the solvent was evaporated. The residue was re-dissolved in MeOH (5 mL), NaOMe (186 mg, 3.45 mmol) was added and refluxed for 2 h. The solvent was evaporated and the crude material was purified by flash chromatography to furnish **24a** as a white solid (78 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.59 (ddd, *J* = 8.4, 1.1, 0.5 Hz, 1H), 7.53 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.22 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 6.02 (s, 1H), 4.70 (s, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 1.93 – 1.85 (m, 2H), 1.63 – 1.52 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0, 158.4, 148.7, 130.2, 125.7, 122.0, 121.9, 118.1, 90.0, 68.1, 31.1, 19.5, 14.0. MS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{16}N_2O$: 217.1335, found: 217.1347.

Compound **24b** was synthesized according to the procedure for the synthesis of **24a.**

4-(Pentyloxy)quinolin-2-amine (24b). White solid (60 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.60 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.22 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.01 (s, 1H), 4.96 (s, 2H), 4.08 (t, *J* = 6.4 Hz, 2H), 1.95 – 1.87 (m, 2H), 1.56 – 1.48 (m, 2H), 1.47 – 1.38 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 158.4, 148.1, 130.4, 125.2, 122.1, 122.0, 117.9, 90.0, 68.5, 28.7, 28.4, 22.6, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2O$: 231.1492, found: 231.1529.

General procedure for the synthesis of 4-Butylquinoline (26a). To a stirred solution of substrate **25** (187 mg, 1.14 mmol) in 1,4-dioxane were added the butylboronic acid (234 mg, 2.28 mmol), $Pd(PPh_3)_4$ (37 mg, 0.032 mmol) and K_2CO_3 (472 mg, 3.42 mmol). The resulting reaction mixture was stirred at 90 ^{o}C under nitrogen atmosphere for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, crude material was purified by flash chromatography using CH_2Cl_2:MeOH as an eluent to obtain **26a** as a colorless liquid (100 mg, 73%).Colorless liquid (170 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.4 Hz, 1H), 8.11 (dd, *J* = 8.4, 0.7 Hz, 1H), 8.04 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.69 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.23 (d, *J* = 4.4 Hz, 1H), 3.09 – 3.04 (m, 2H), 1.78 – 1.71 (m, 2H), 1.51 – 1.42 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3, 148.9, 148.5, 130.3, 129.1, 127.7, 126.3, 123.7, 120.9, 32.3, 32.0, 22.9, 14.0. MS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{15}N$: 186.1277, found: 186.1444.

Compound **26b** was synthesized according to the procedure for the synthesis of **26a.**

4-Pentylquinoline (26b). Colorless liquid (190 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.4 Hz, 1H), 8.11 (dd, *J* = 8.4, 0.7 Hz, 1H), 8.04 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.70 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.56 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.23 (d, *J* = 4.4 Hz, 1H), 3.09 – 3.04 (m, 2H), 1.81 – 1.75 (m, 2H), 1.46 – 1.36 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 148.9, 148.5, 130.4, 129.1, 127.8, 126.3, 123.8, 120.9, 32.3, 32.0, 29.9, 22.7, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{17}N$: 200.1434, found: 200.1579.

General procedure for the synthesis of 4-Butylquinolin-2-amine (27a). To a stirred solution of substrate **26a** (173 mg, 0.935 mmol) in $CHCl_3$ was added *m*-CPBA (483 mg,

2.80 mmol), the resulting reaction mixture was stirred at r.t. for 4 h. After completion of reaction (by TLC), the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, crude material was purified over SiO_2 using CH_2Cl_2:MeOH as an eluent. To a stirred solution of *N*-oxide of **26a** (125 mg, 0.621 mmol) in CH_2Cl_2 was added benzoylisocyanate (273 mg, 1.86 mmol). The resulting reaction mixture was stirred at 55 ^oC for 1 h. After completion of reaction (monitored by TLC), the solvent was evaporated. The residue was re-dissolved in MeOH (5 mL), NaOMe (168 mg, 3.10 mmol) was added and refluxed for 2 h. The solvent was evaporated and the crude material was purified by flash chromatography to furnish **27a** as a white solid (100 mg, 80%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.68 – 7.65 (m, 1H), 7.53 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.27 (ddd, *J* = 8.2, 5.6, 1.3 Hz, 1H), 6.57 (s, 1H), 4.75 (s, 2H), 2.97 – 2.89 (m, 2H), 1.76 – 1.66 (m, 2H), 1.45 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.9, 150.5, 148.1, 129.5, 126.8, 123.6, 123.4, 122.5, 110.9, 32.0, 31.9, 22.9, 14.1. MS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{16}N_2$: 201.1386, found: 201.1423.

Compound **27b** was synthesized according to the procedure for the synthesis of **27a.**

4-Pentylquinolin-2-amine (27b). White solid (120 mg, 79%).^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.67 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.54 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H), 7.27 (ddd, *J* = 6.9, 5.1, 1.2 Hz, 1H), 6.57 (s, 1H), 4.72 (s, 2H), 2.93 (t, 2H), 1.77 – 1.69 (m, 2H), 1.45 – 1.33 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.9, 150.6, 148.1, 129.5, 126.8, 123.6, 123.4, 122.6, 110.9, 32.3, 32.0, 29.5, 22.7, 14.2. MS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{18}N_2$: 215.1543, found: 215.1575.

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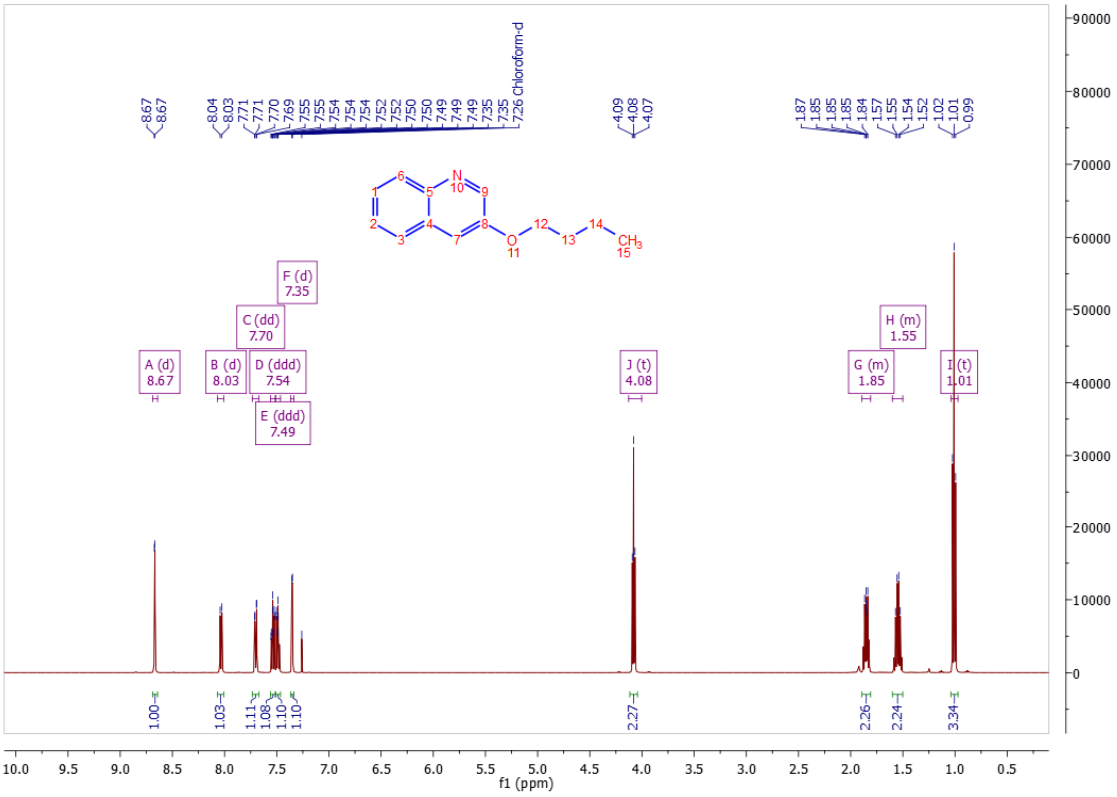
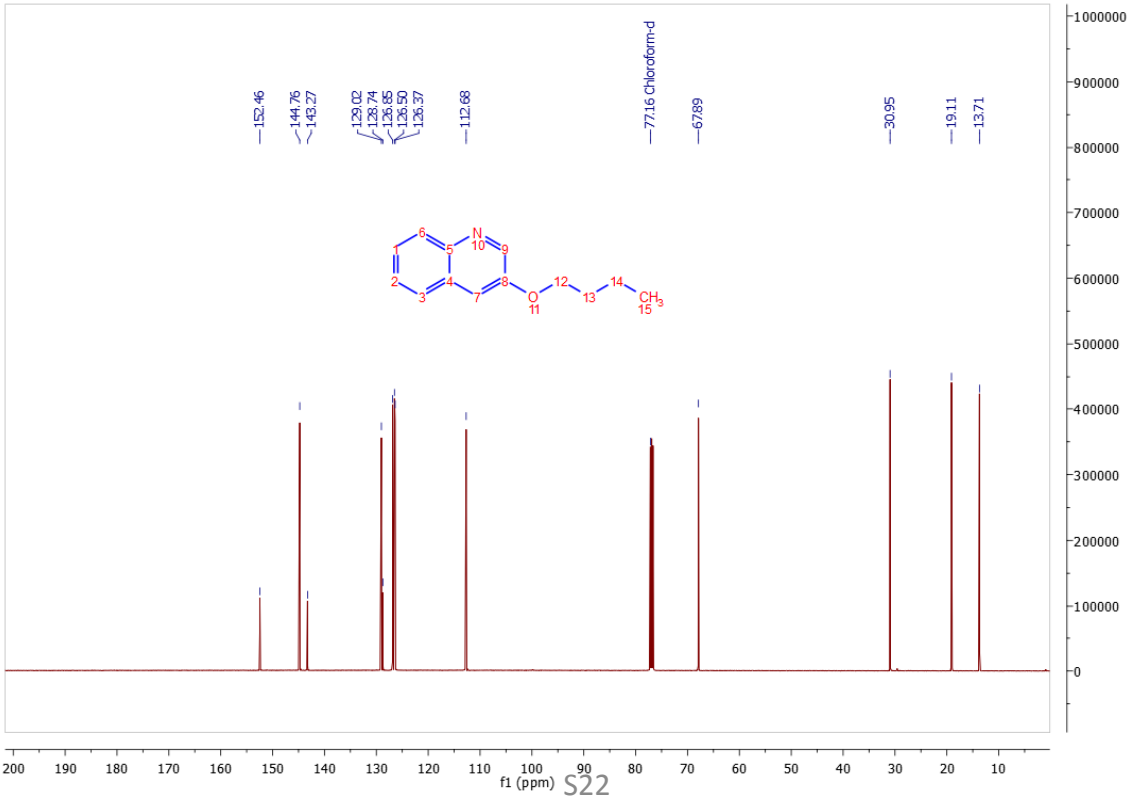
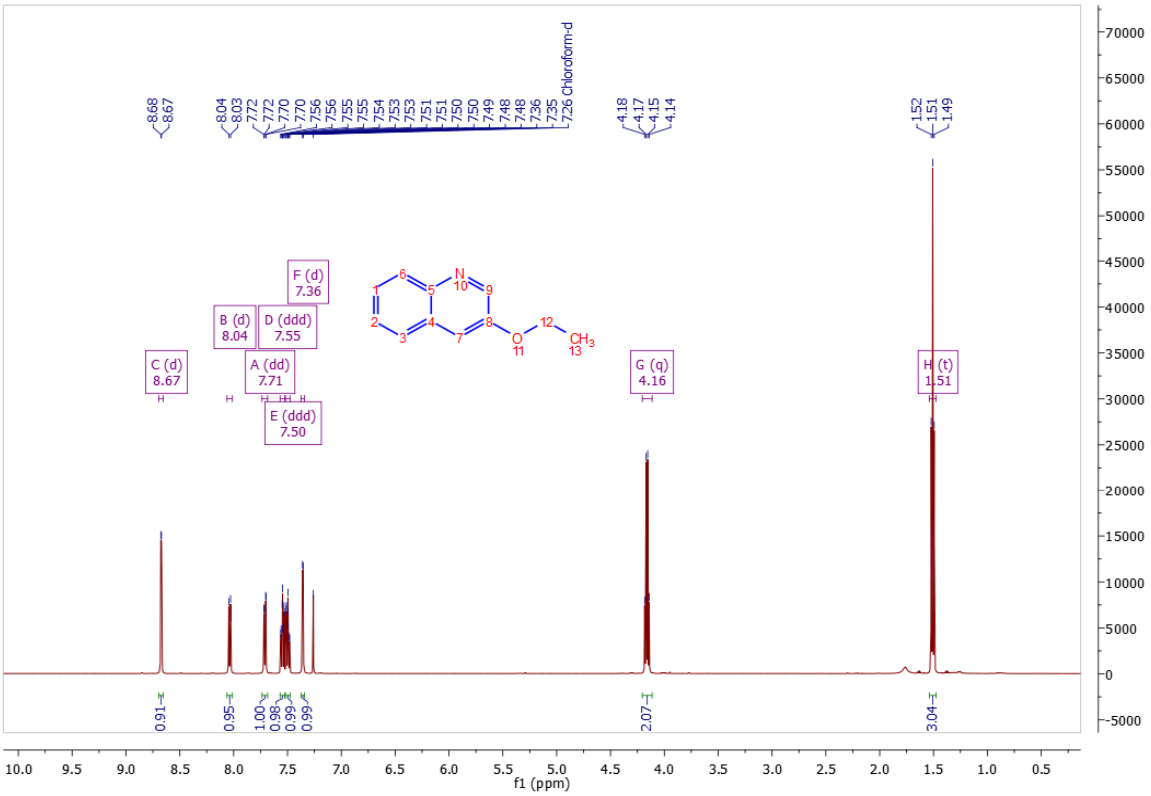
^{1}H,^{13}C Spectra and LC-MS Characterization of Compounds

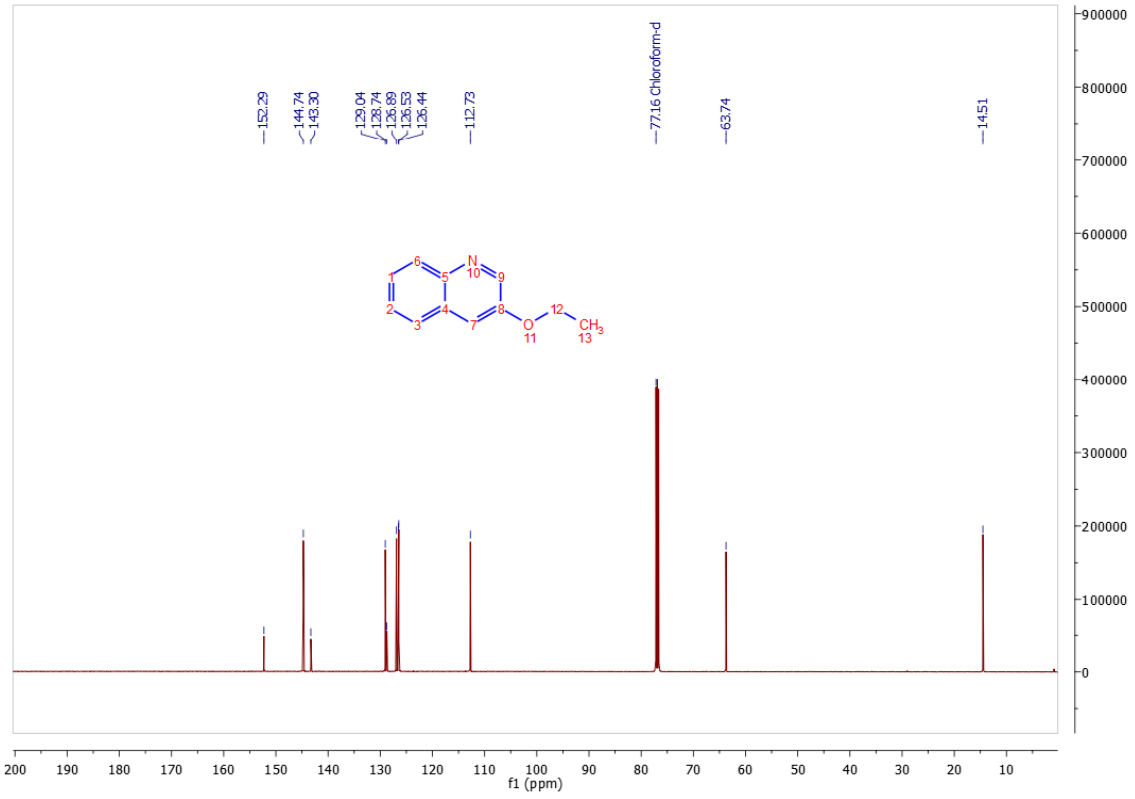
Compound **5:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



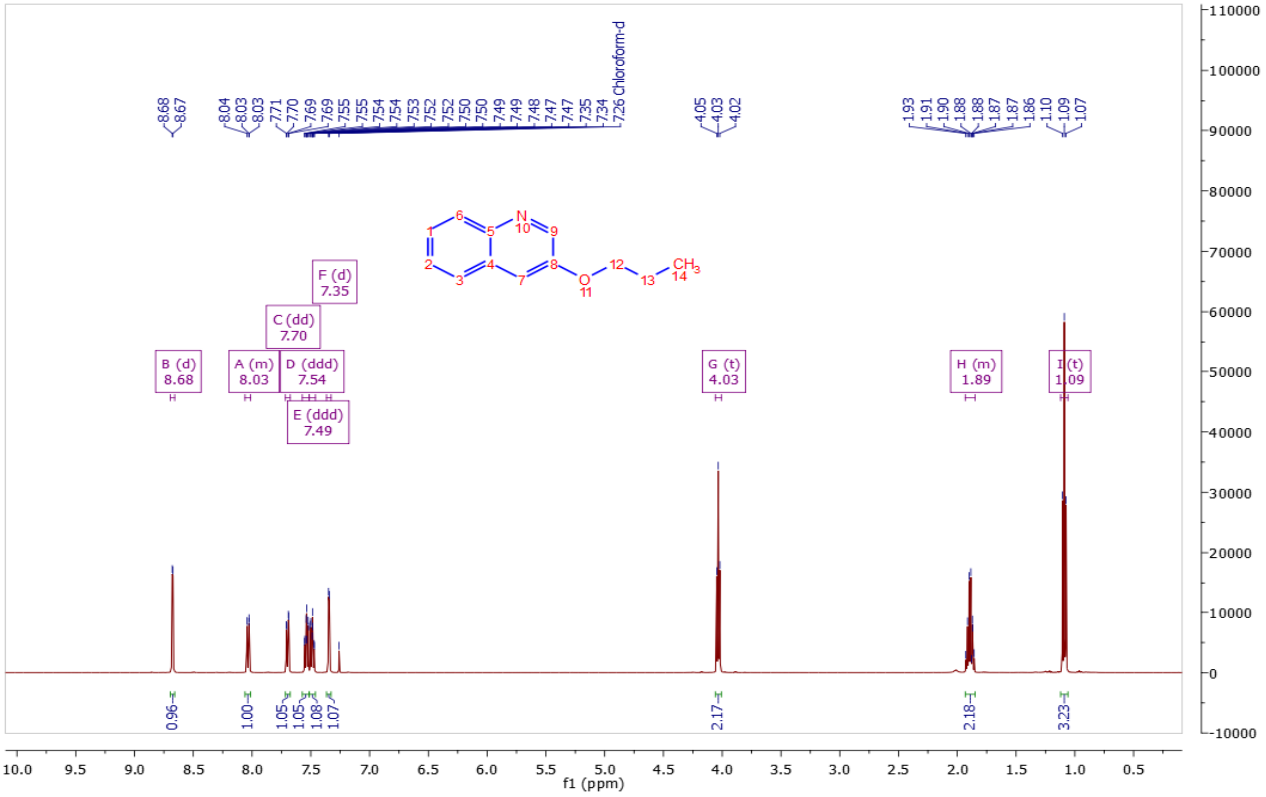


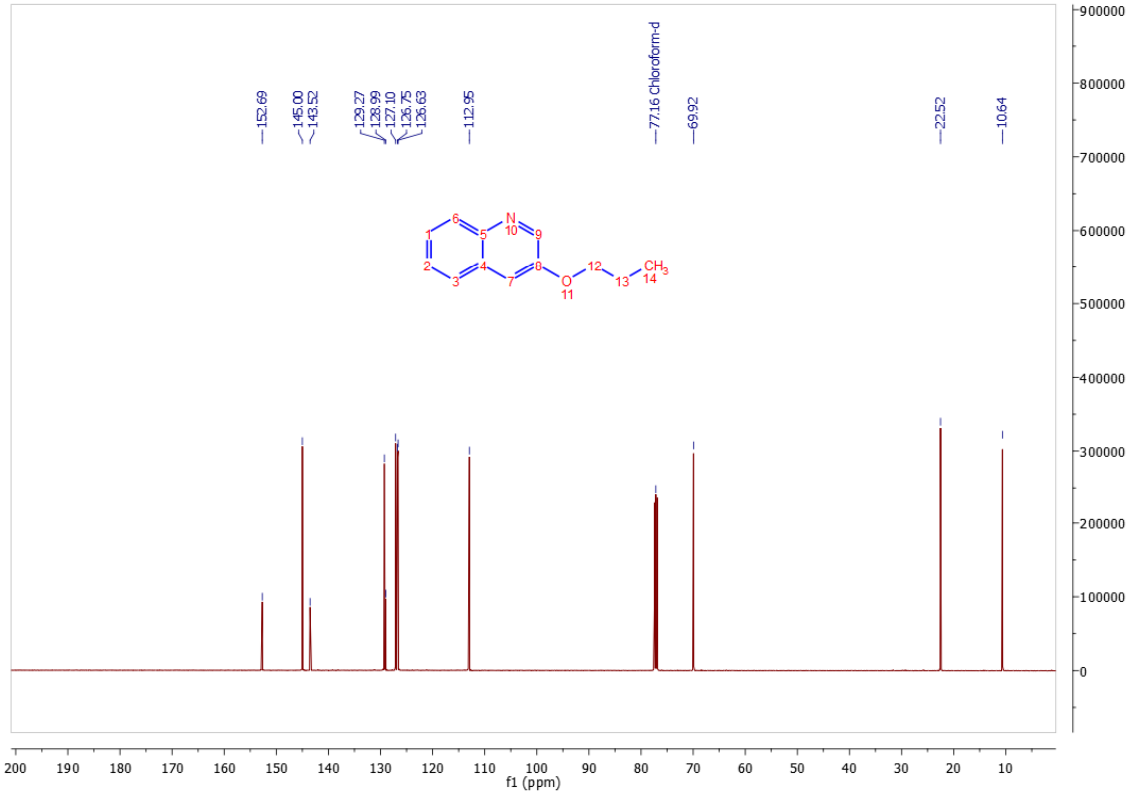
Compound **5b:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



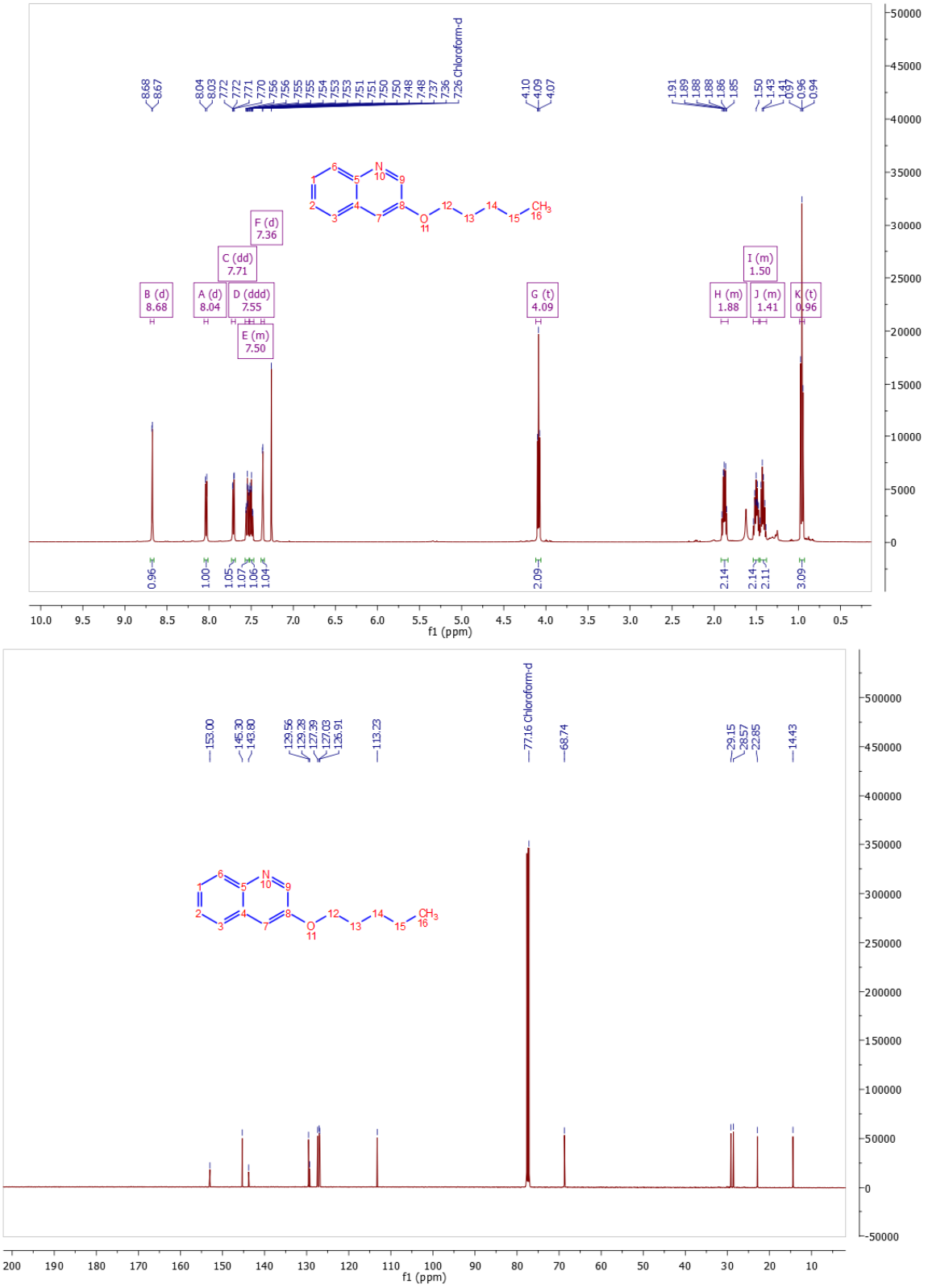


Compound **5c:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)

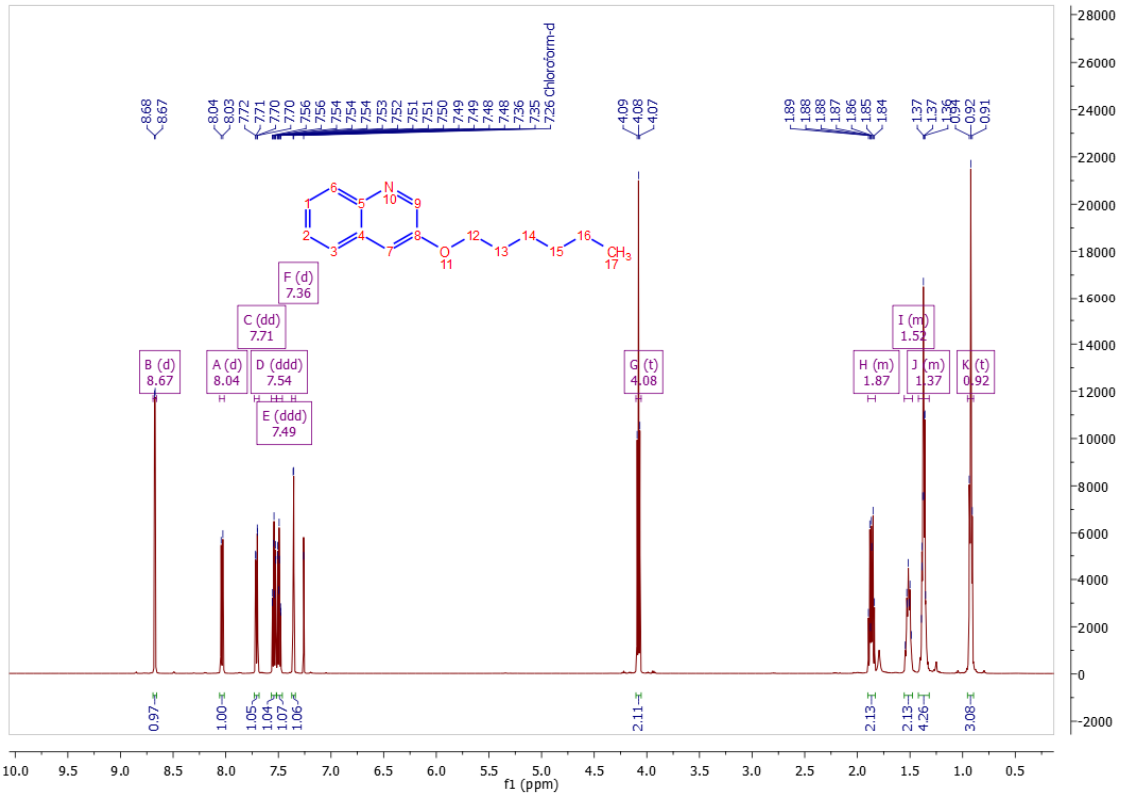


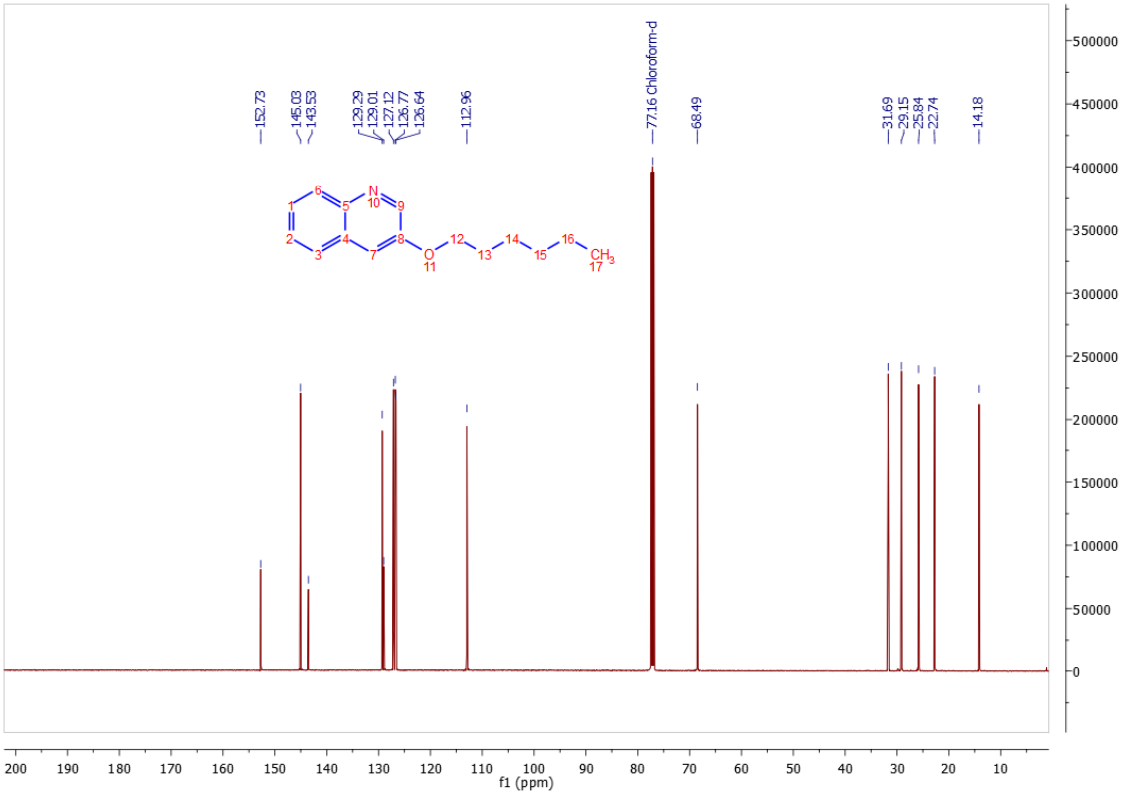


Compound **5d:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)

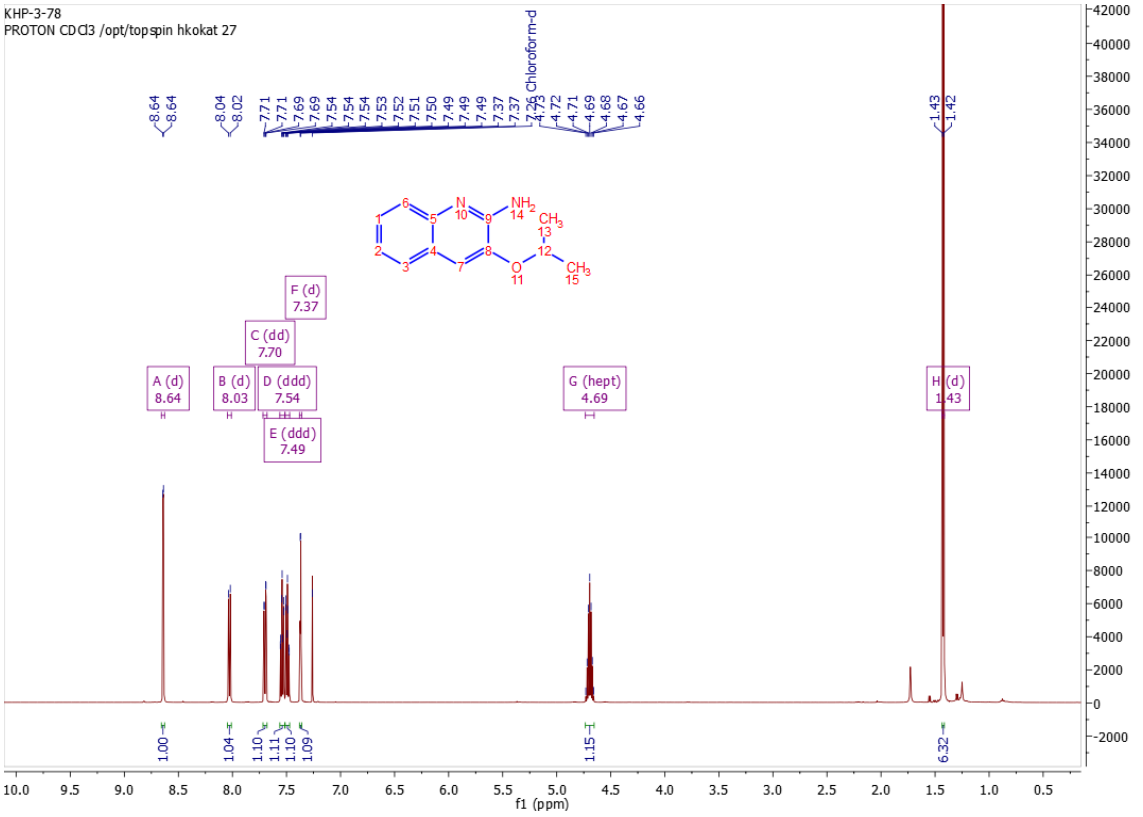


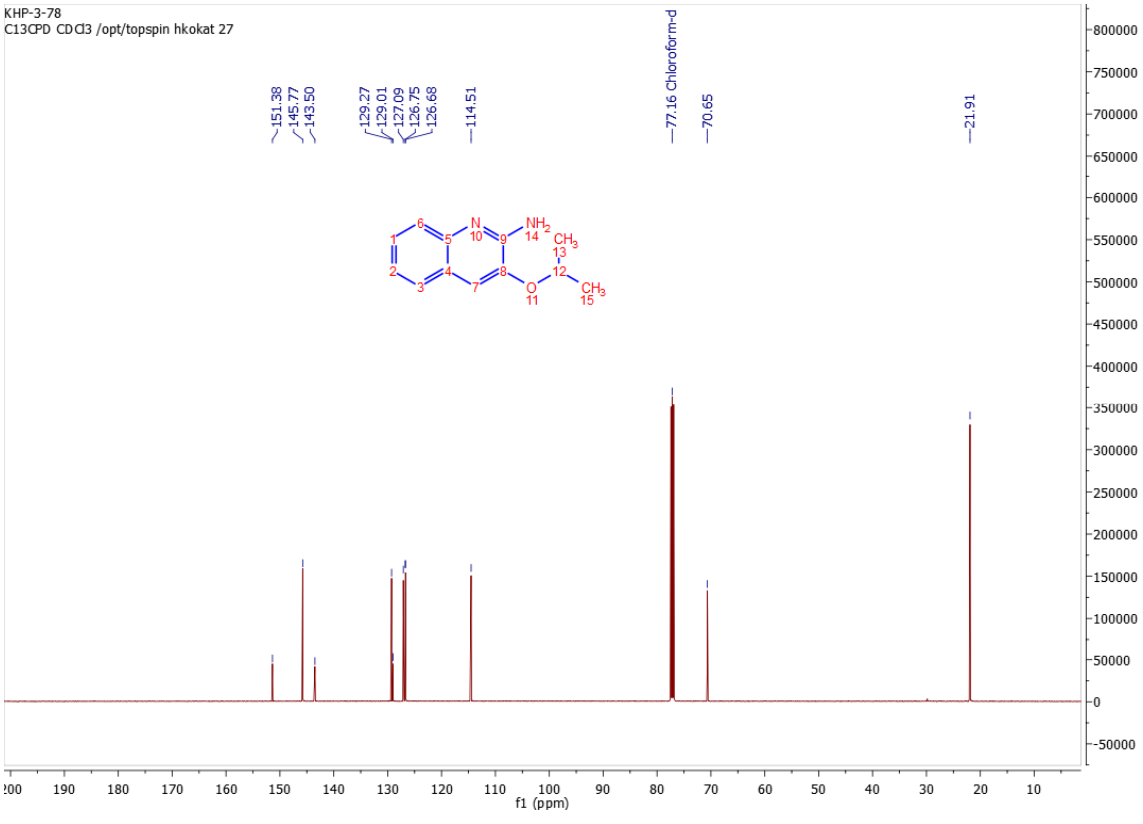
Compound **5e:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



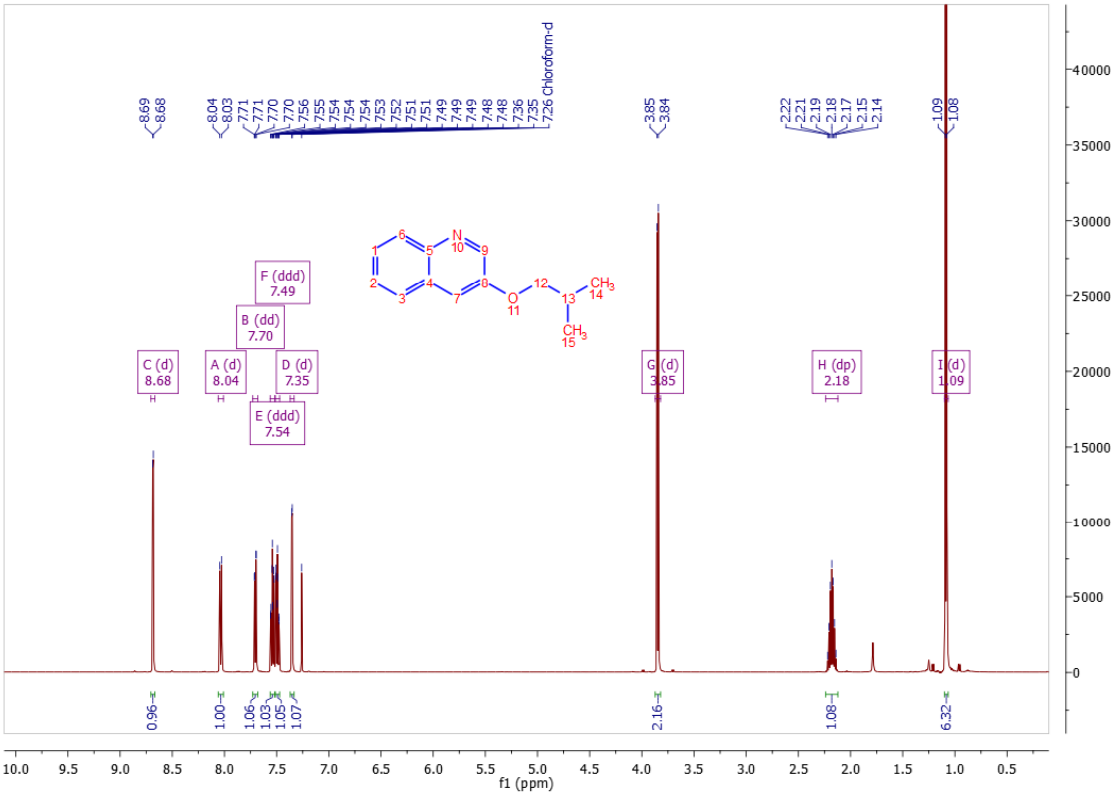


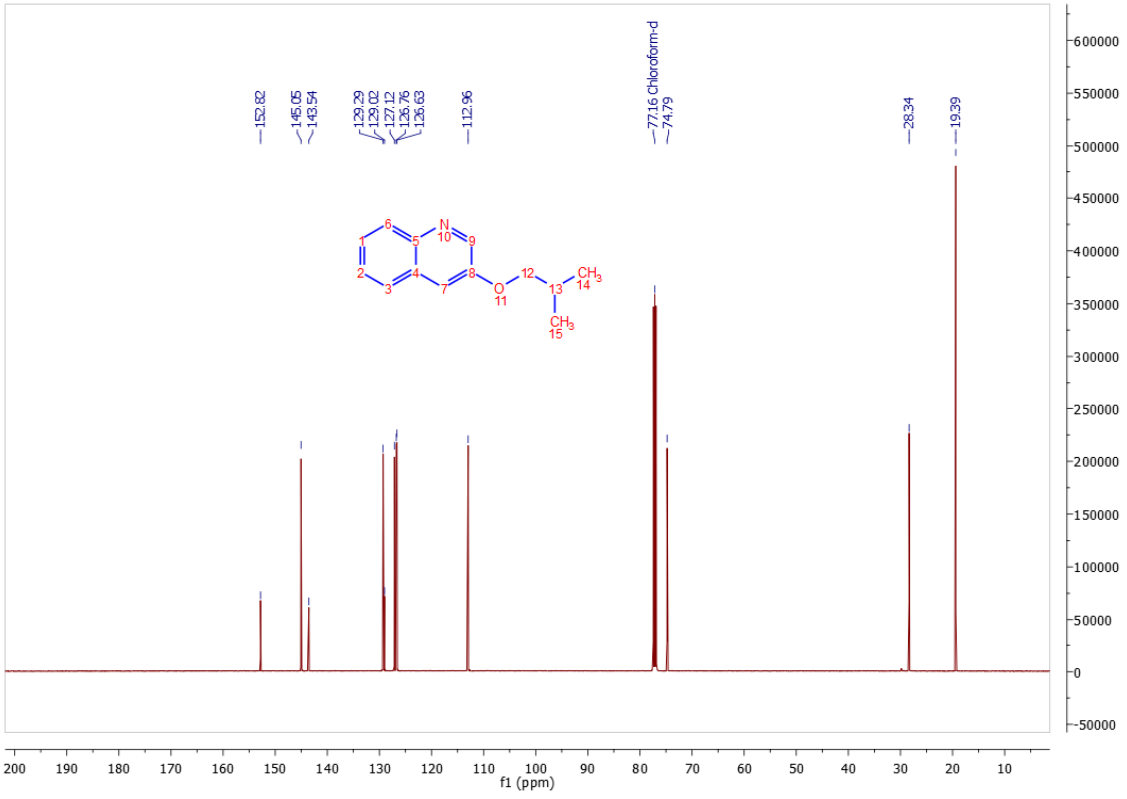
Compound **5f:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



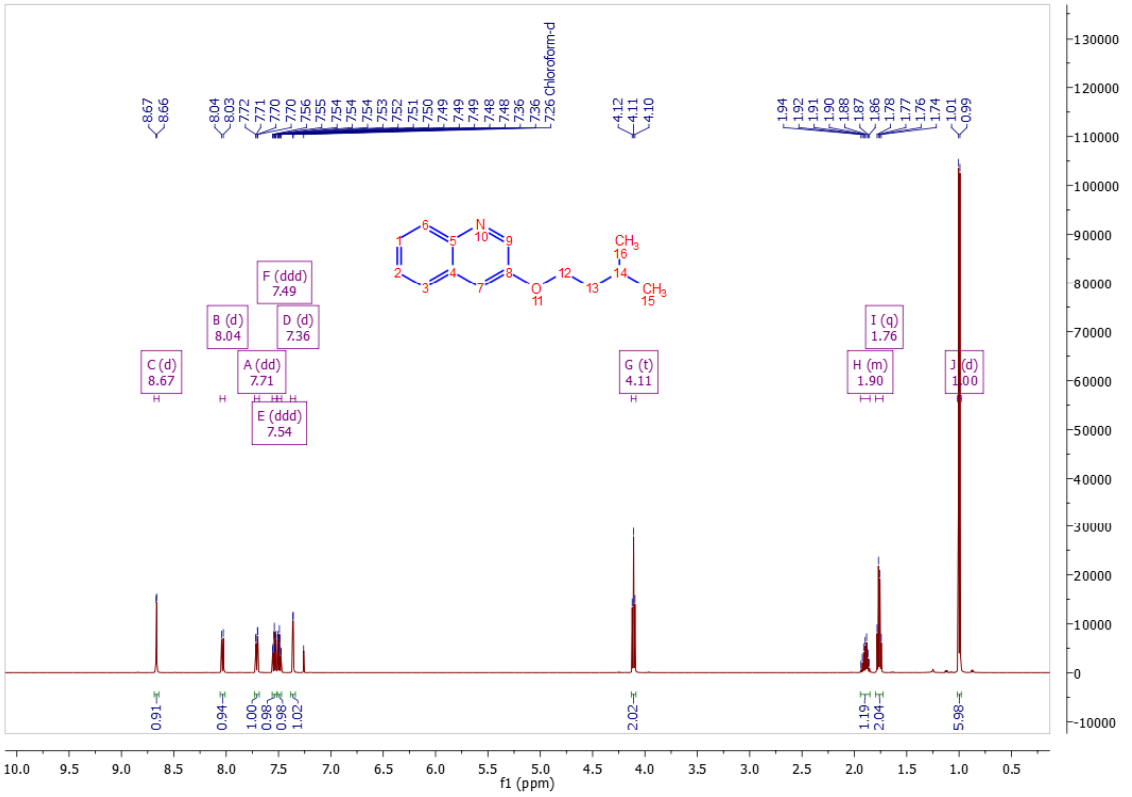


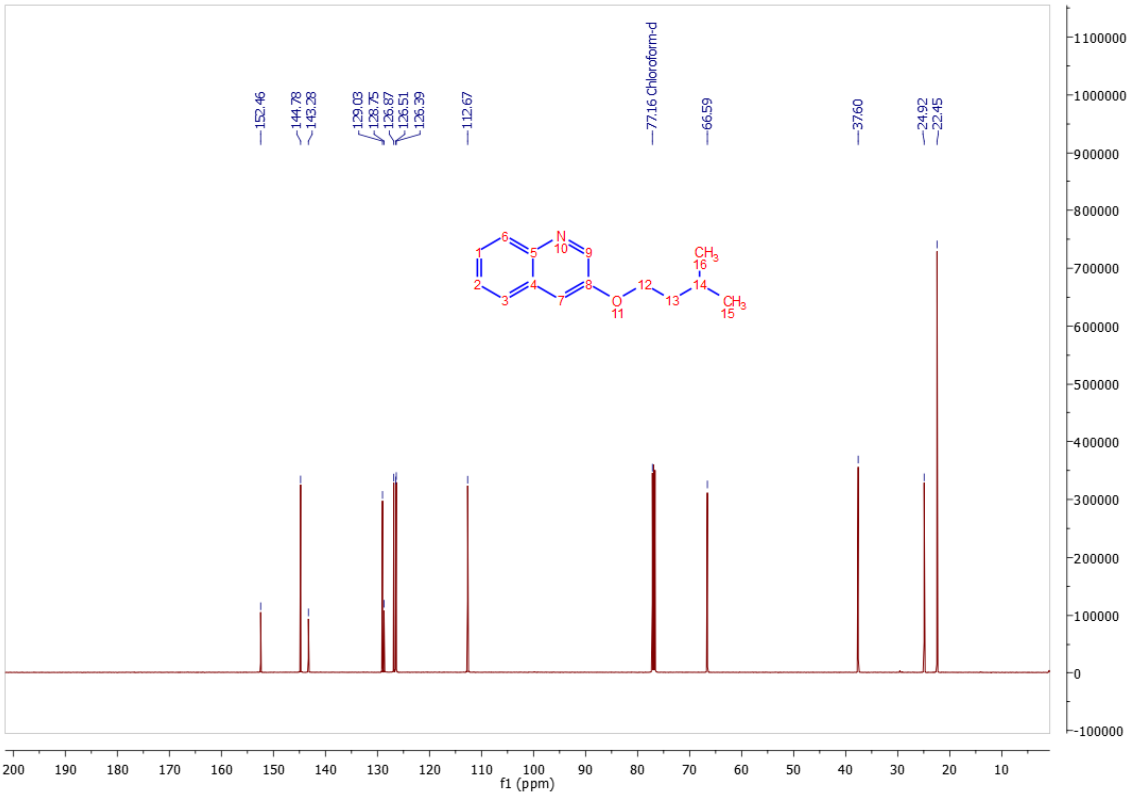
Compound **5g:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



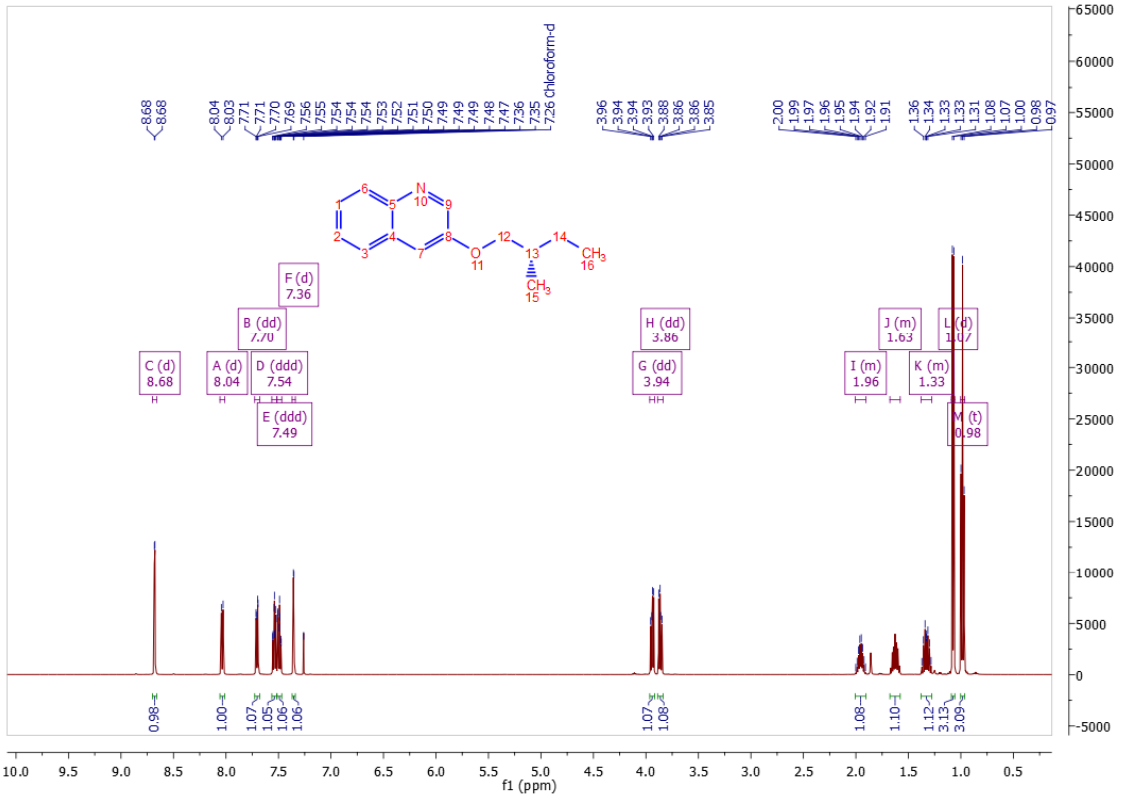


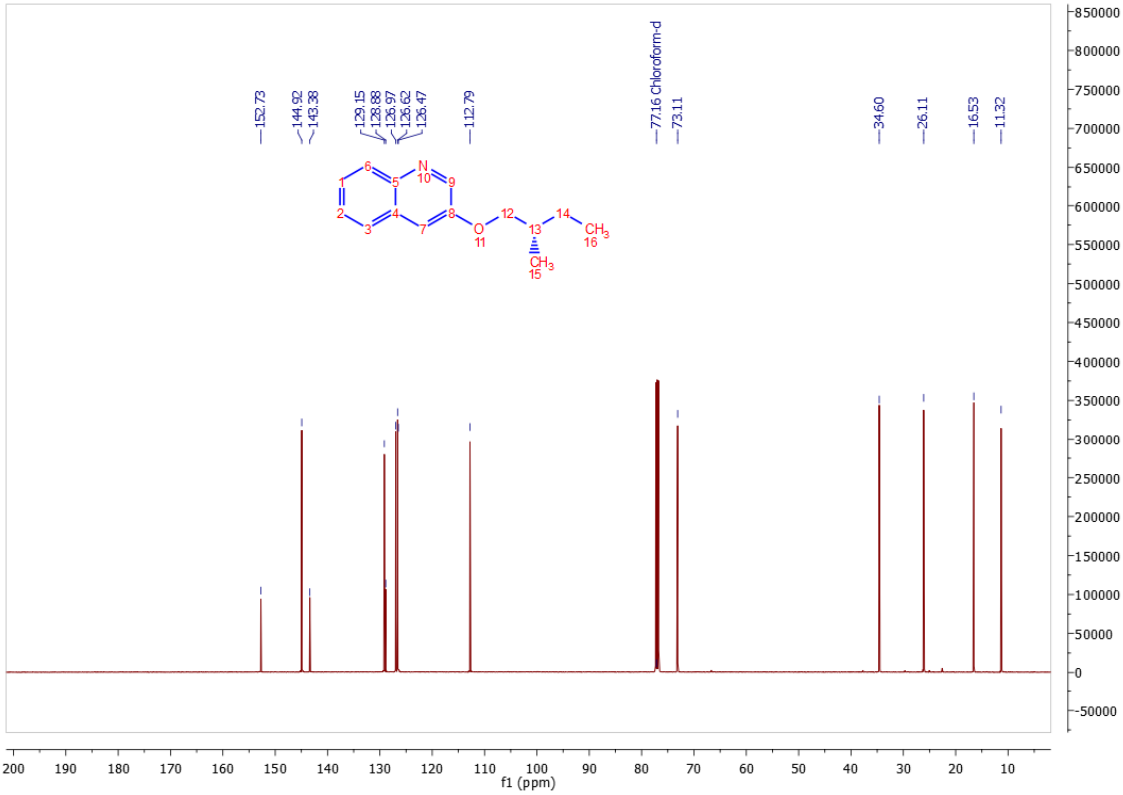
Compound **5h:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



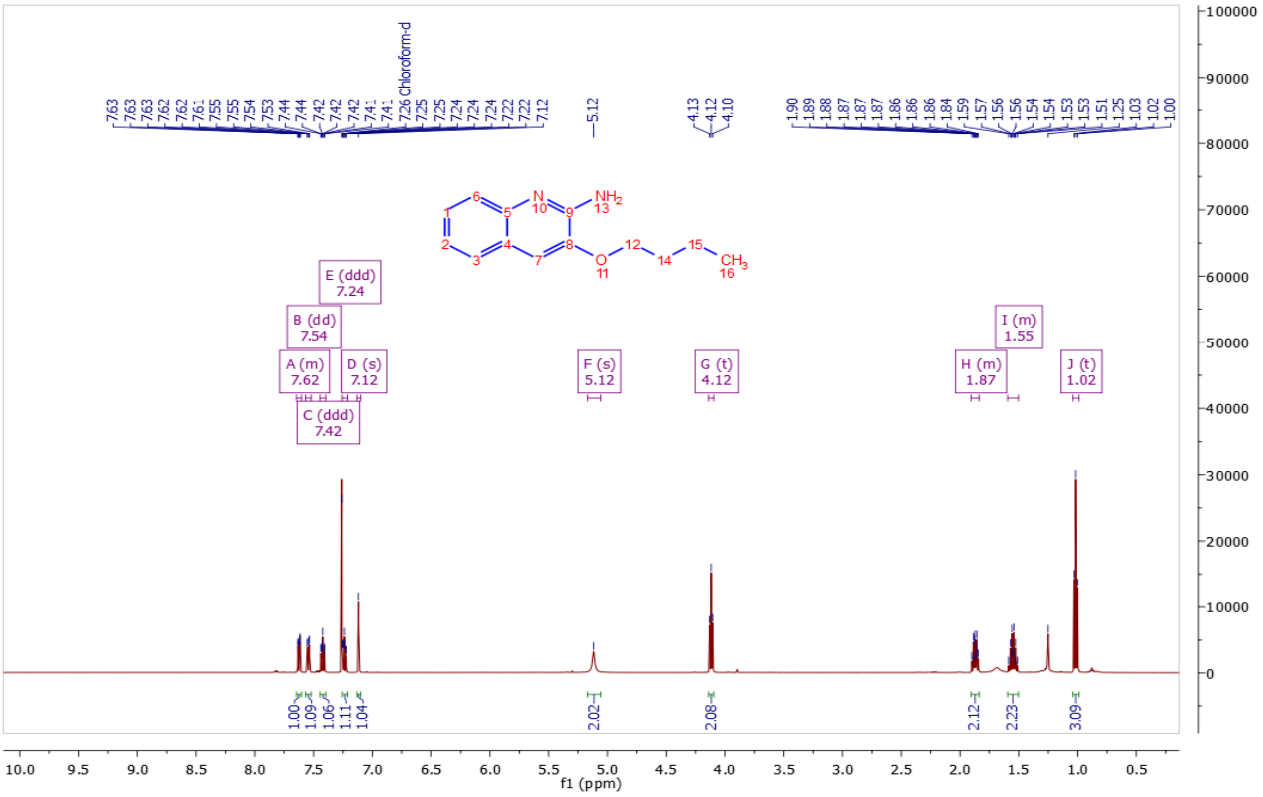


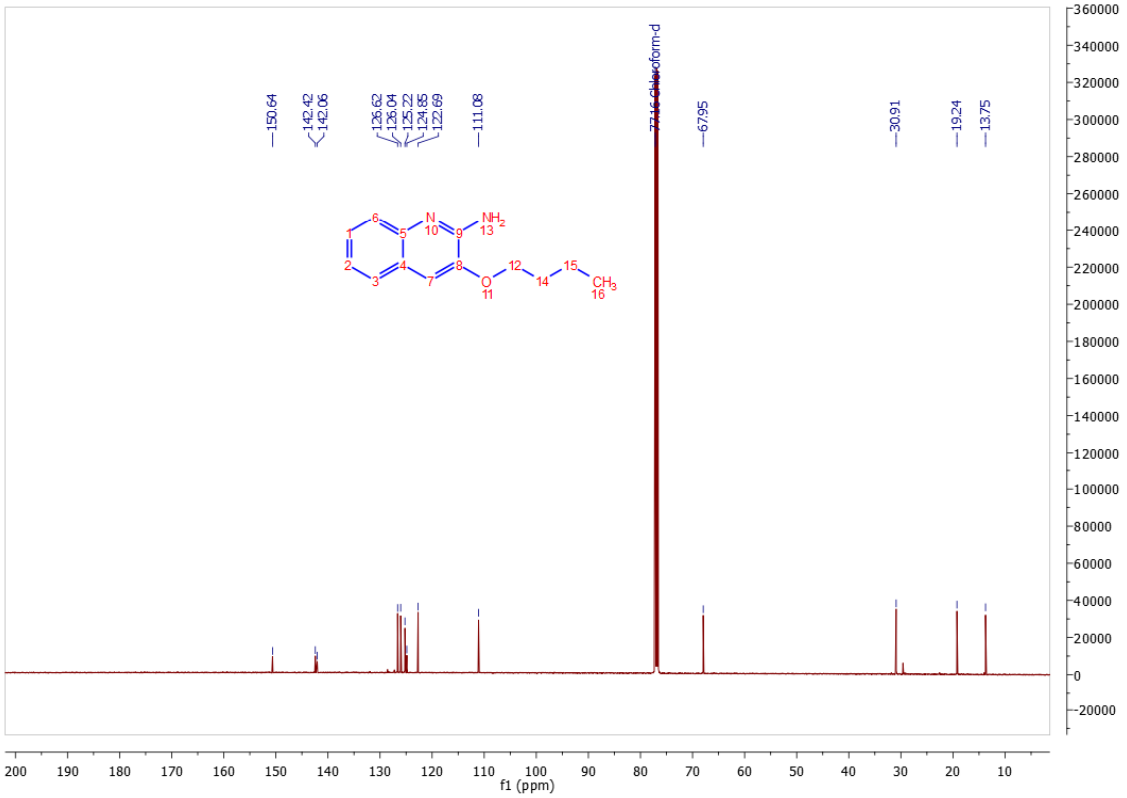
Compound **5i:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



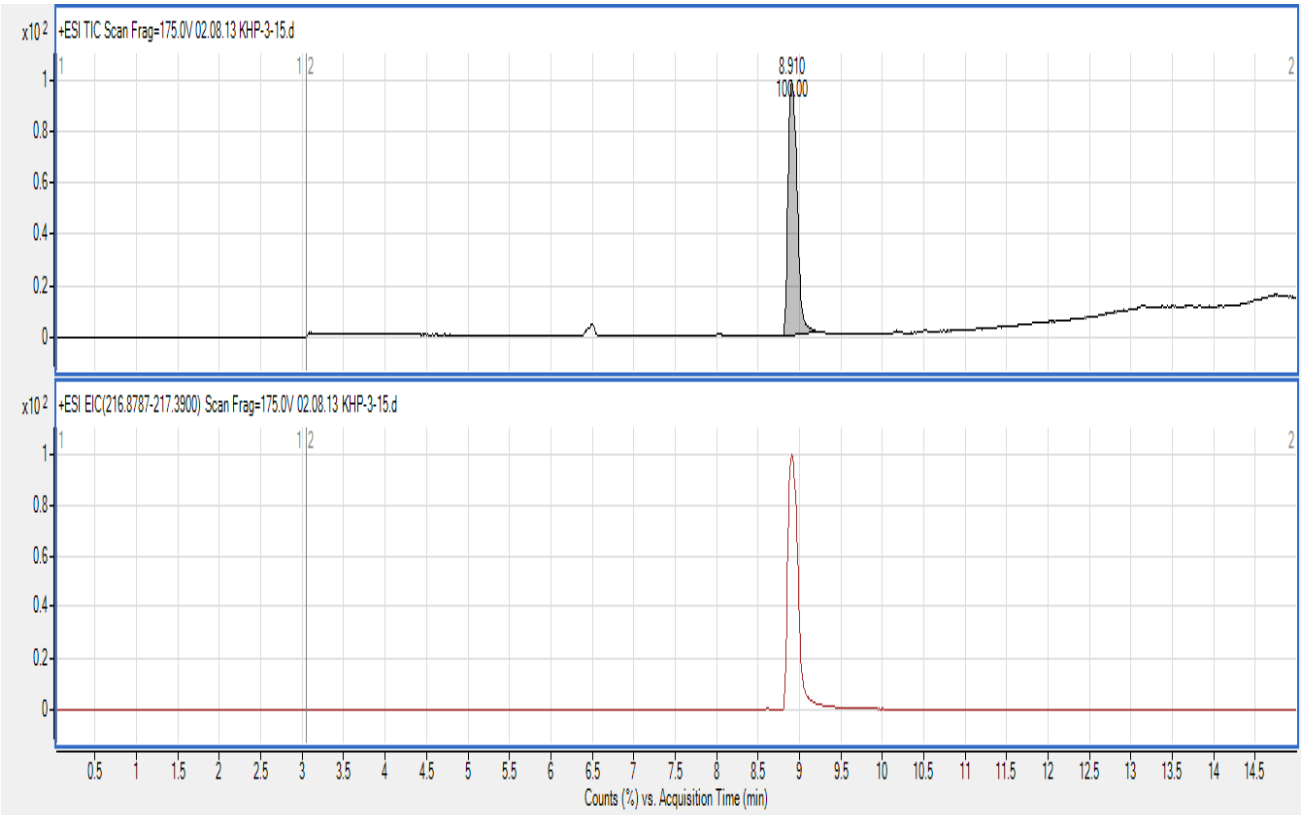


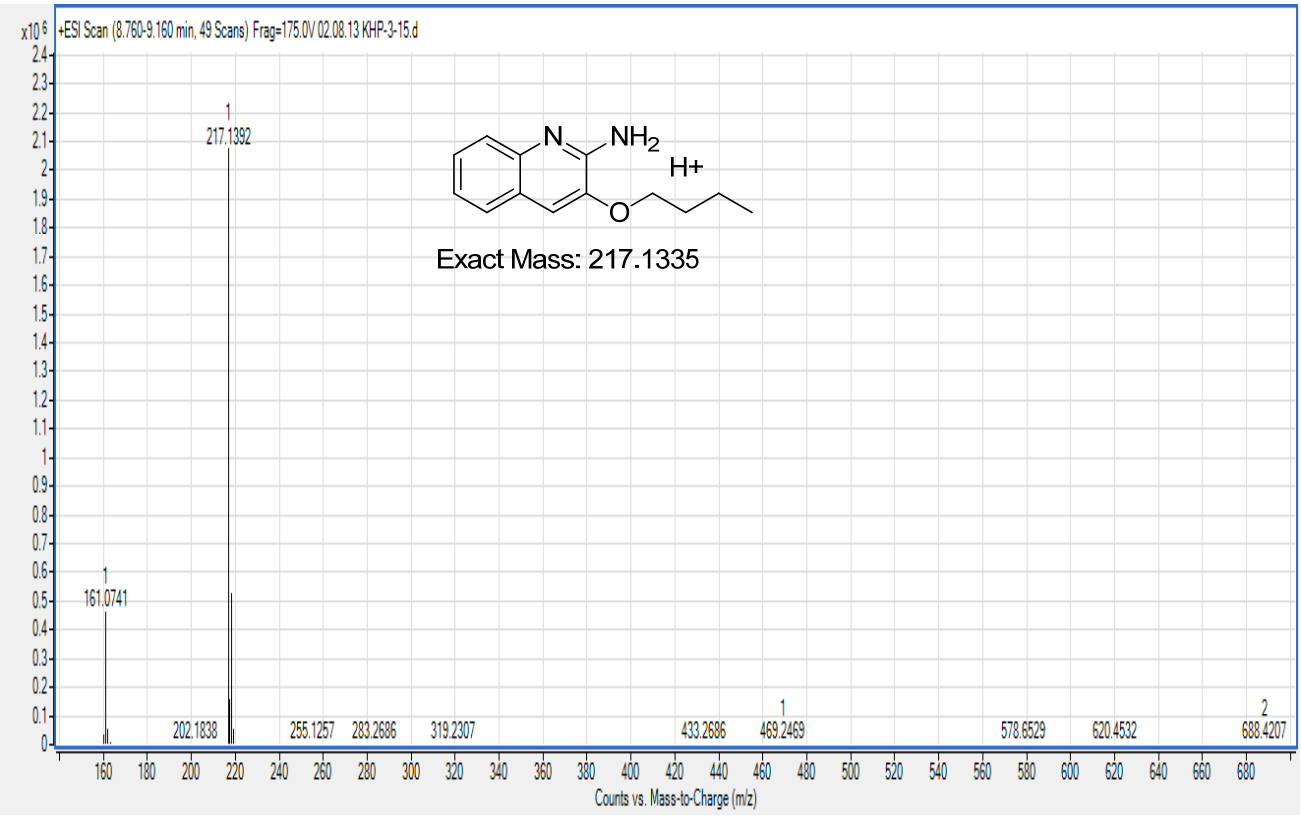
Compound **6:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)





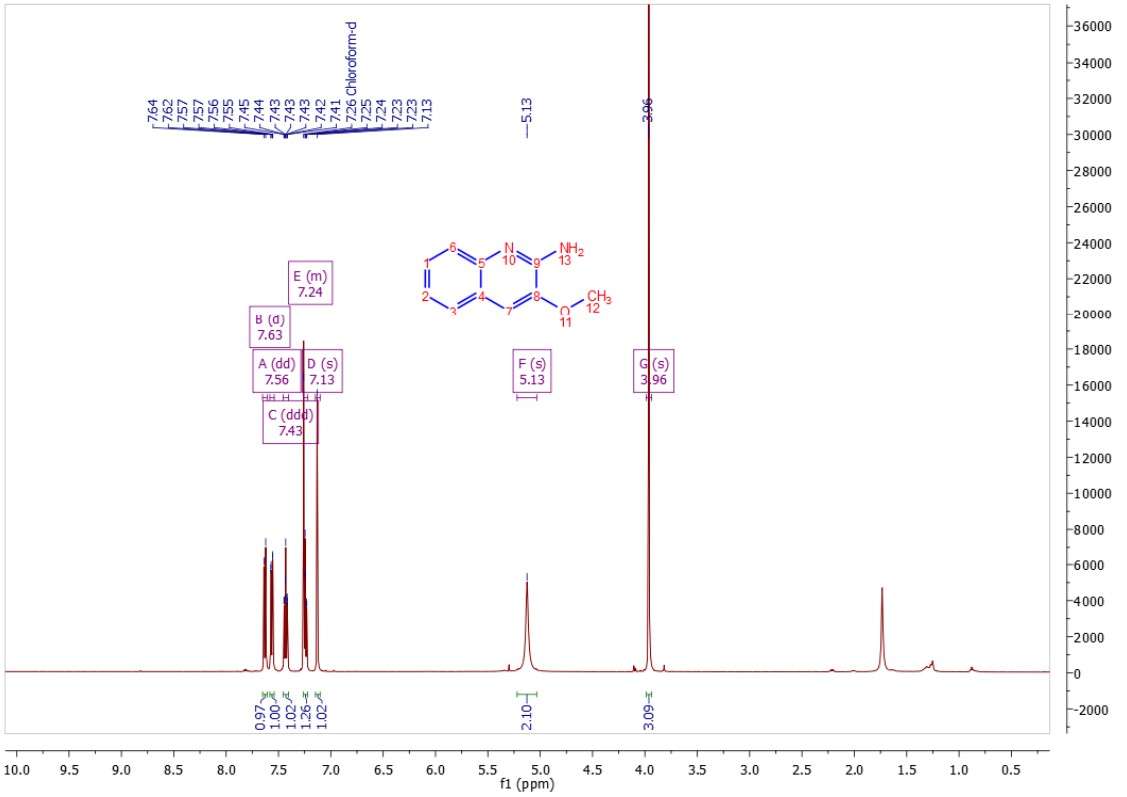
Compound **6:** LC-MS

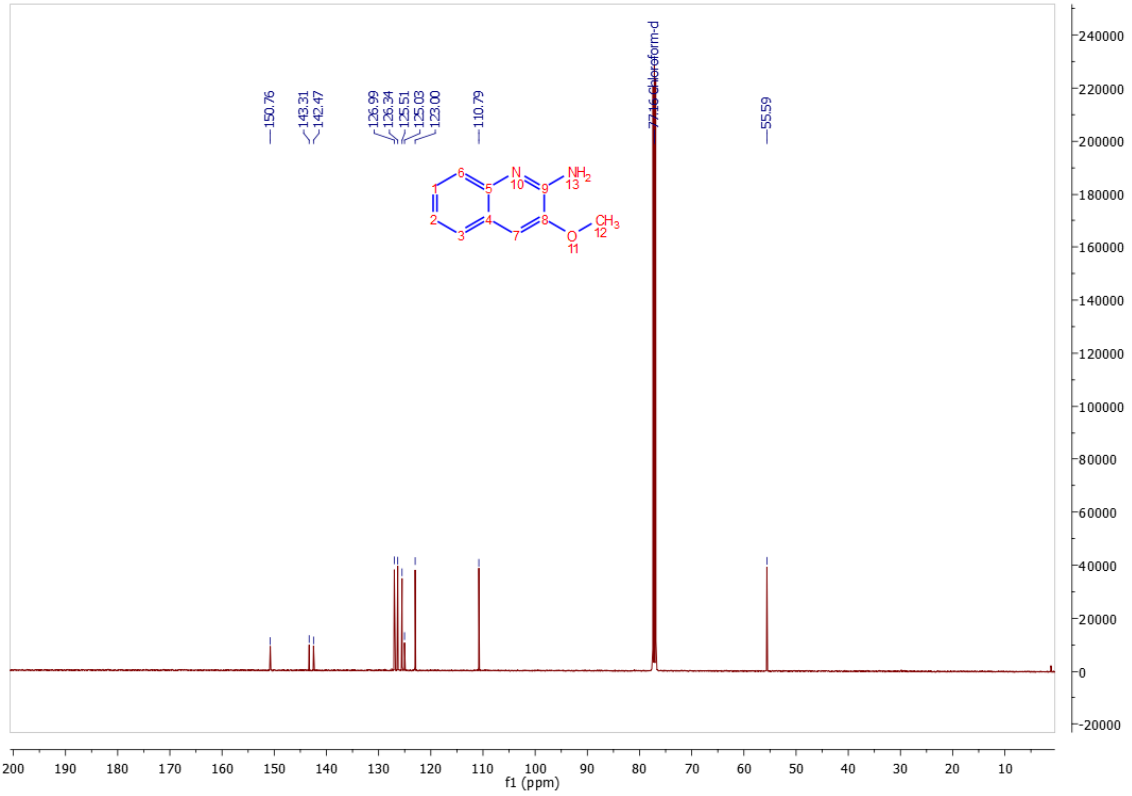




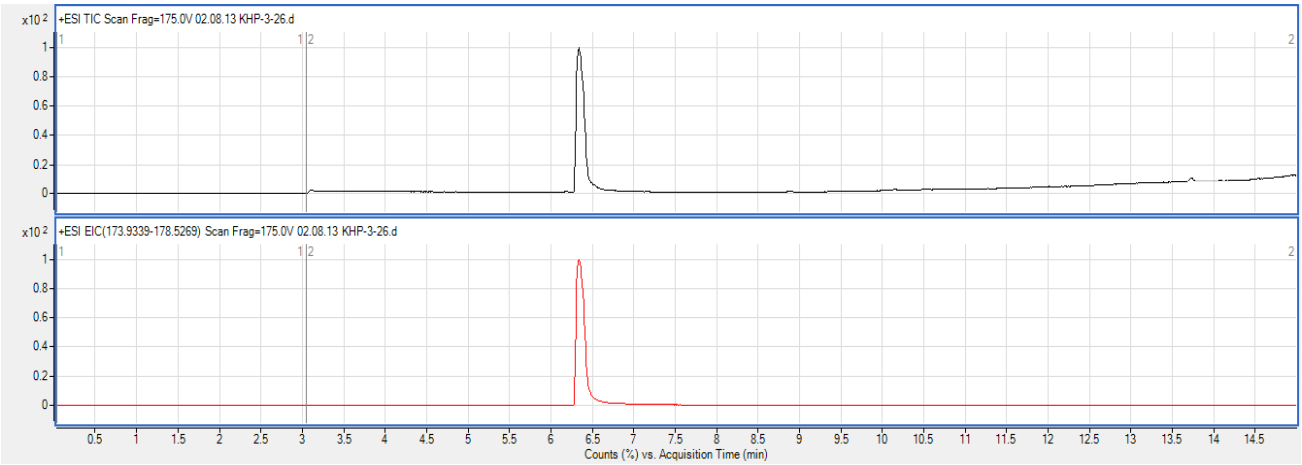
Exact Mass: 217.1335

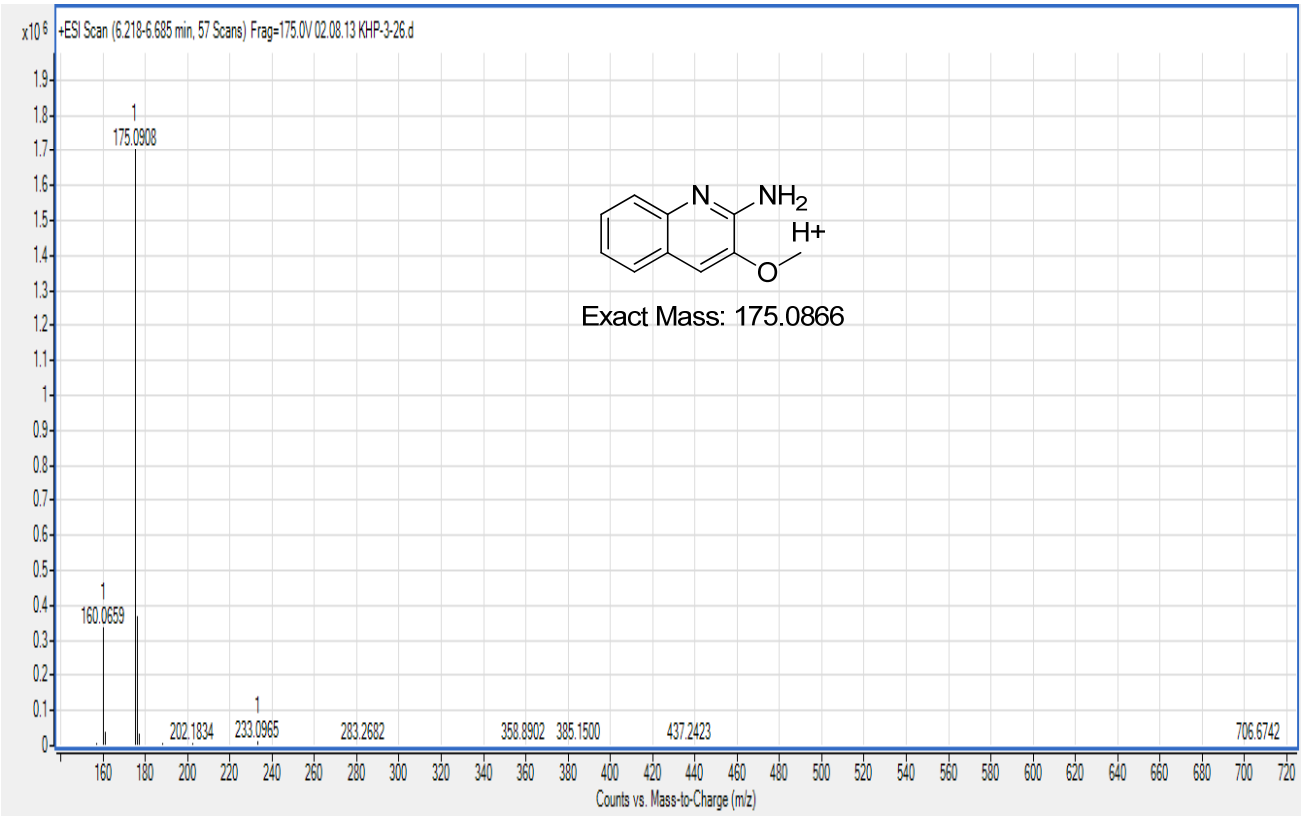
Compound **6a:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



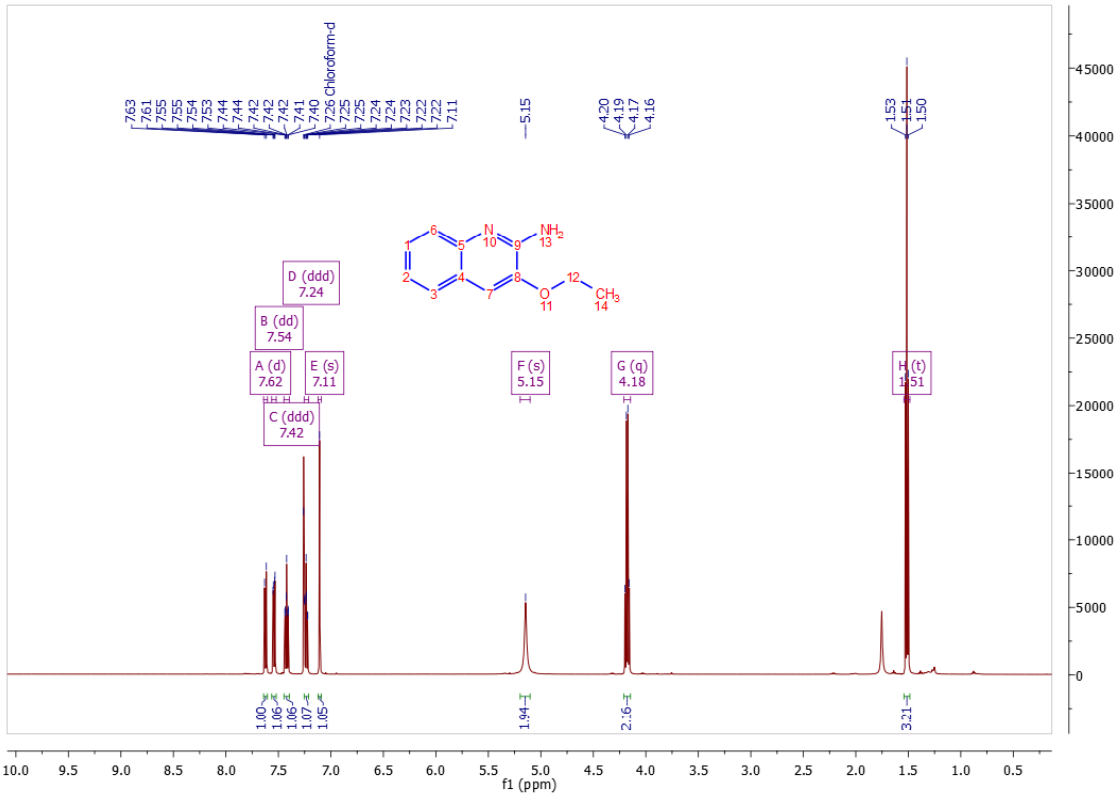


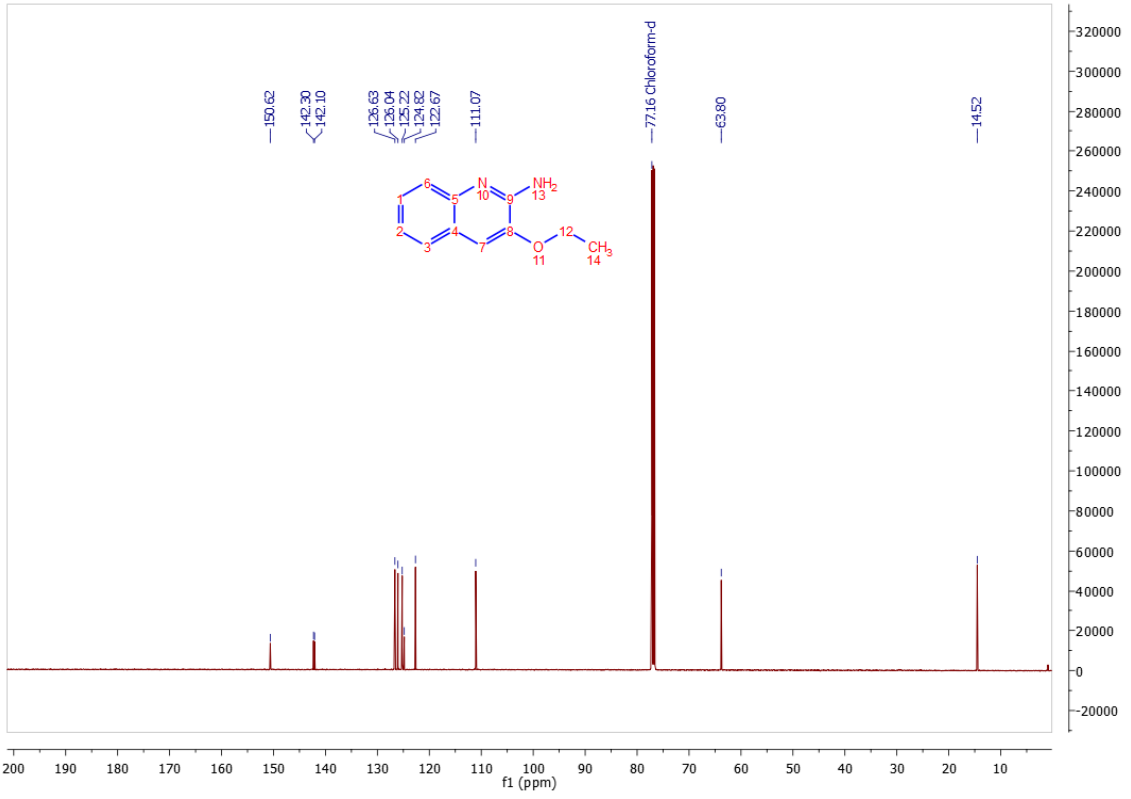
Compound **6a:** LC-MS



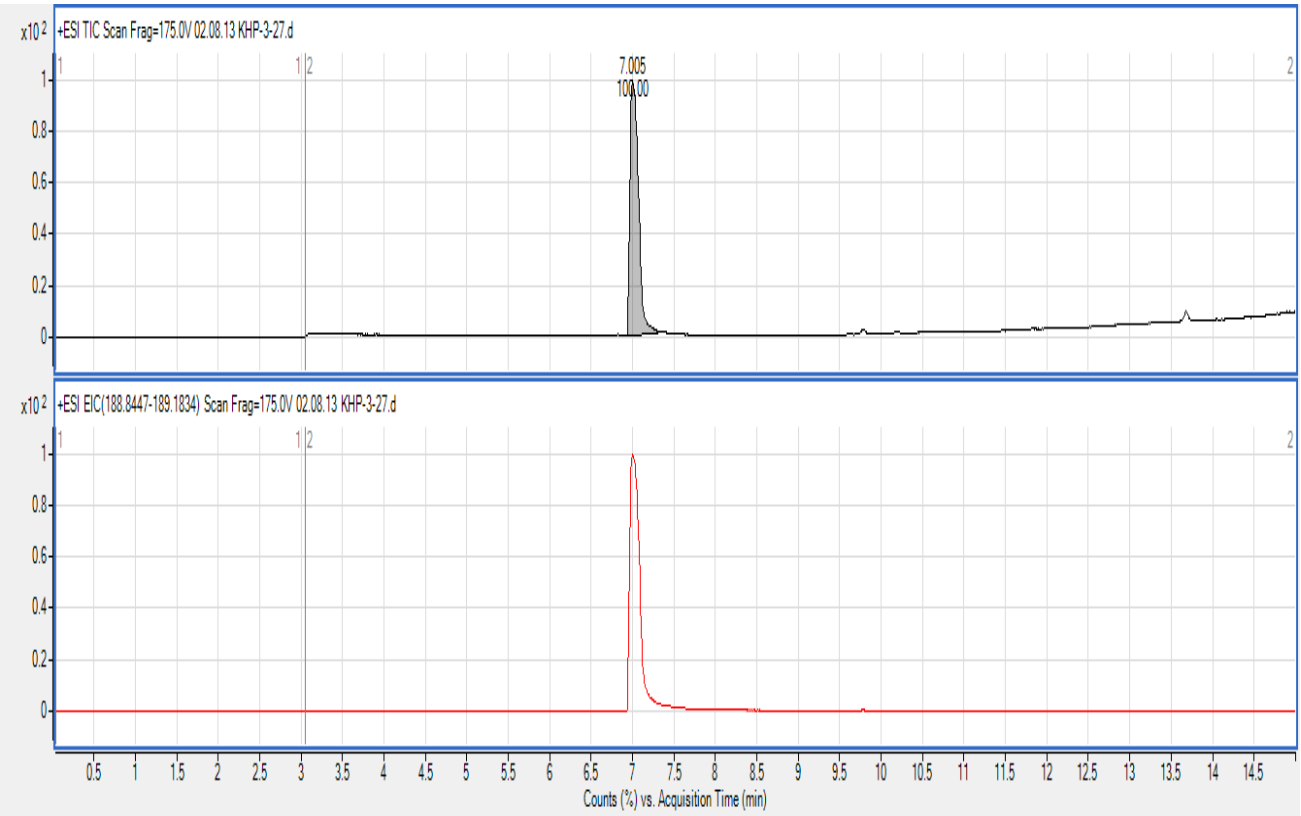


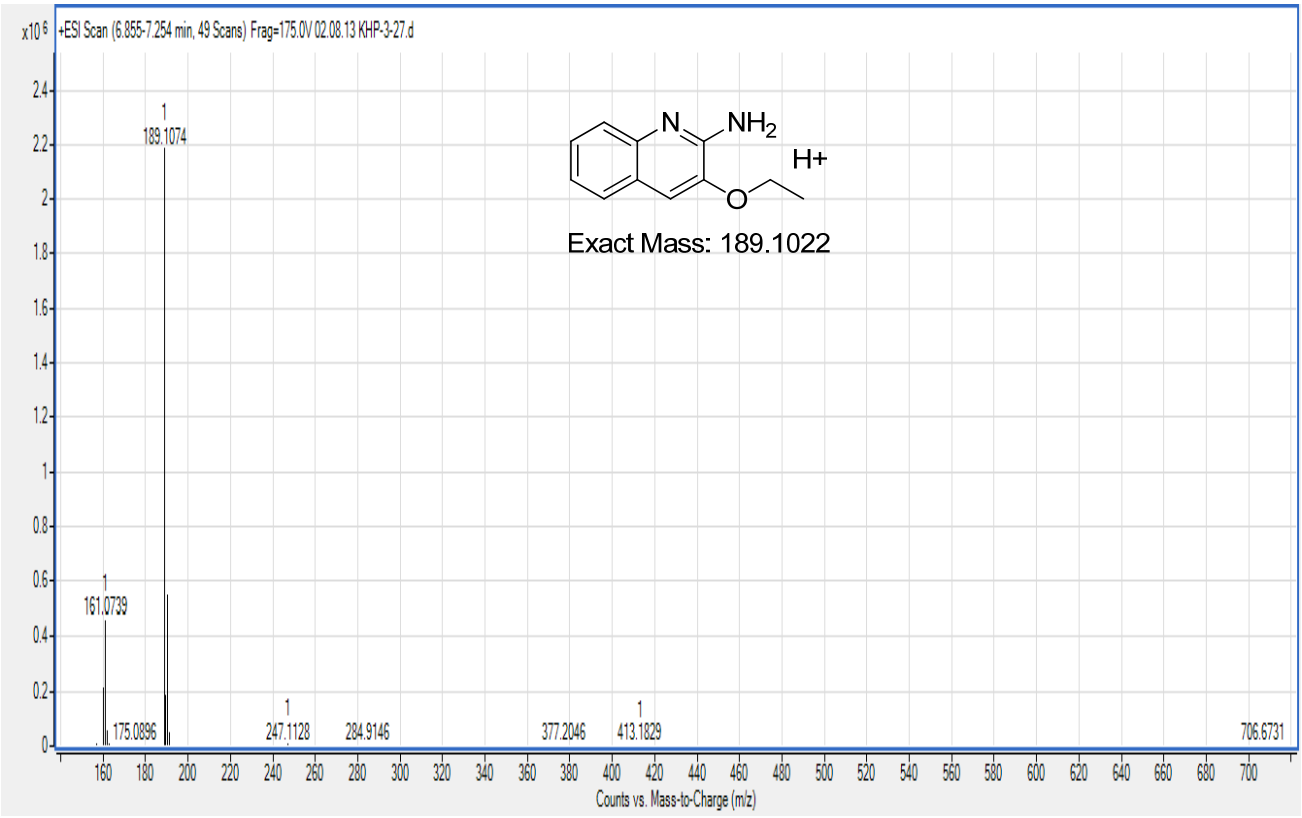
Compound **6b:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



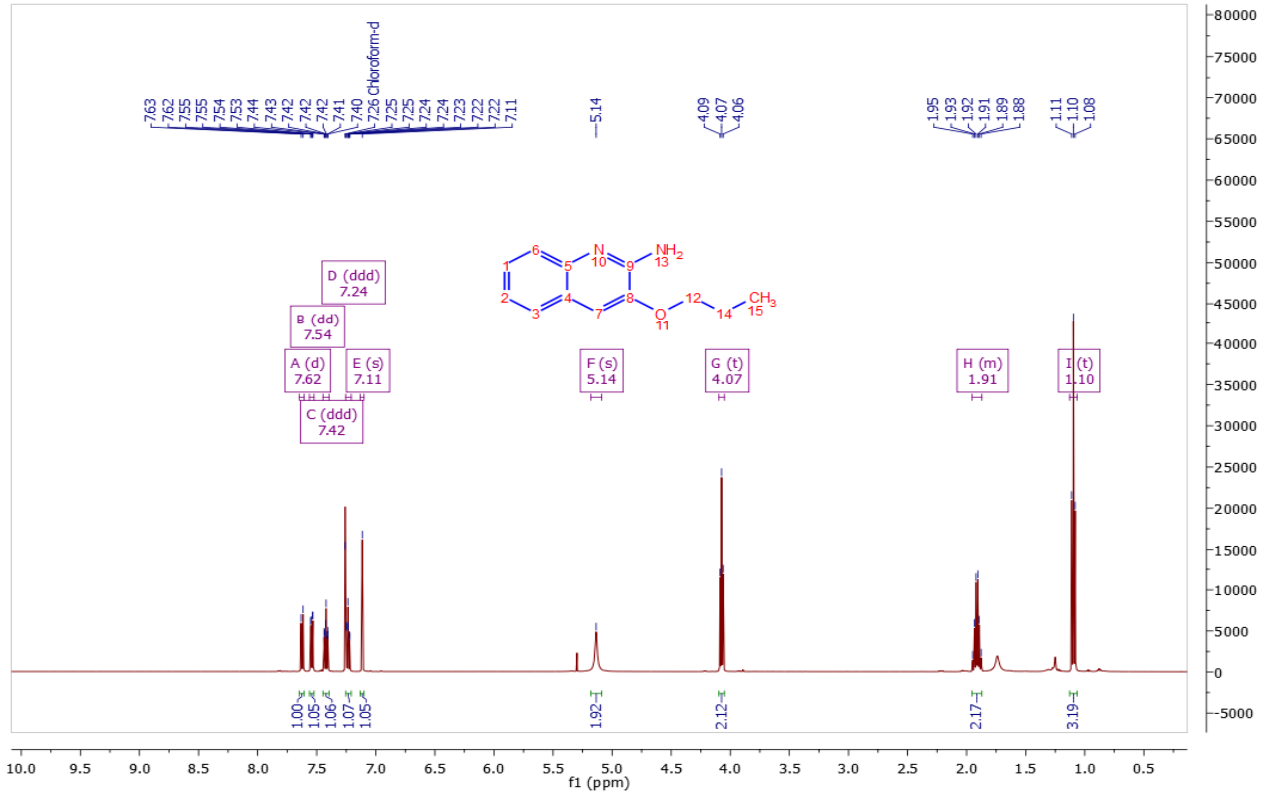


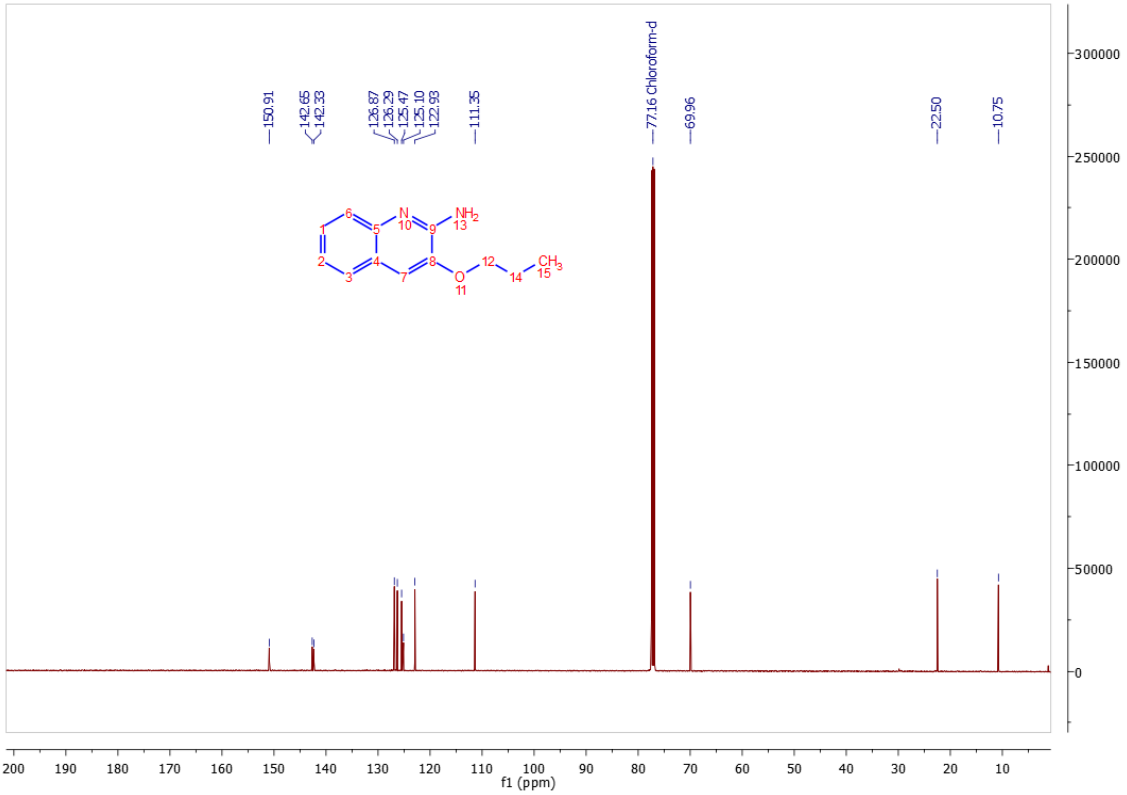
Compound 6b: LC-MS



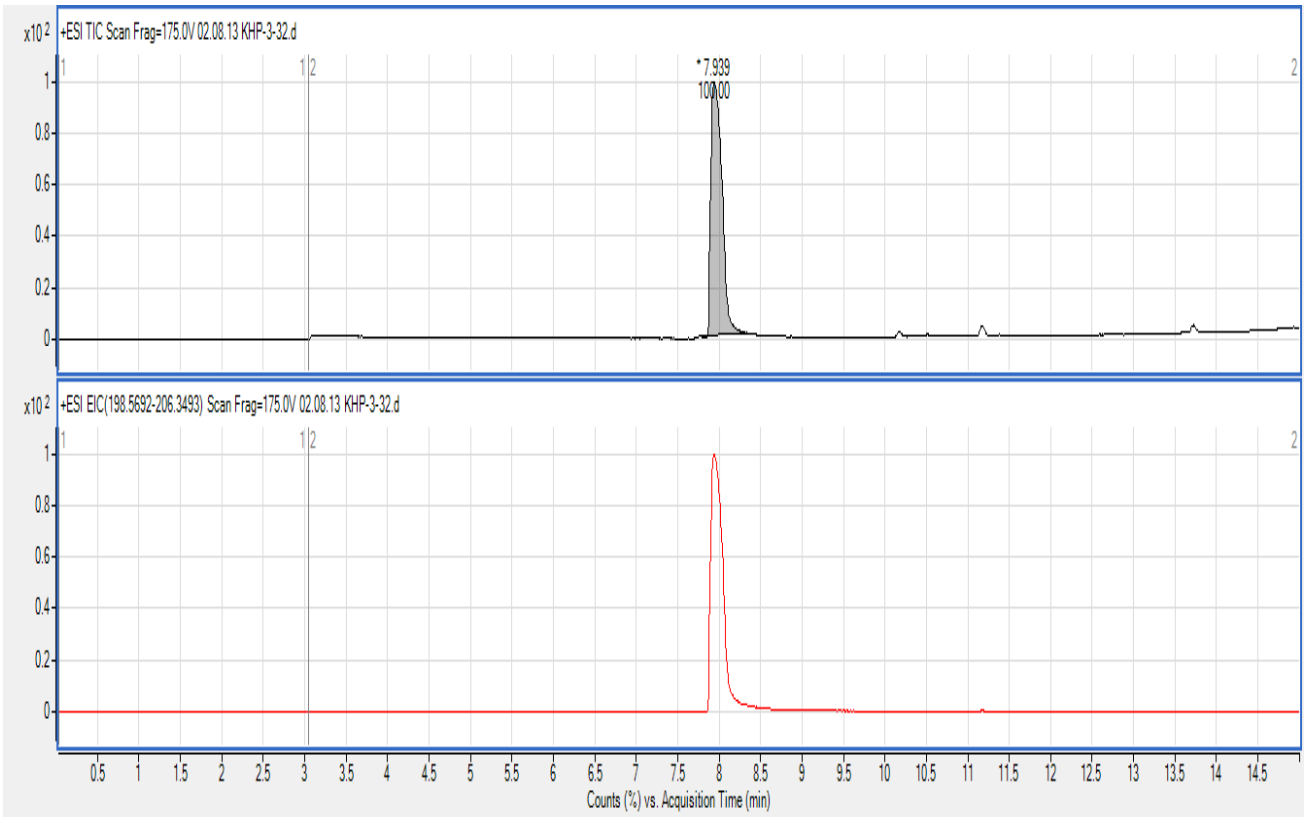


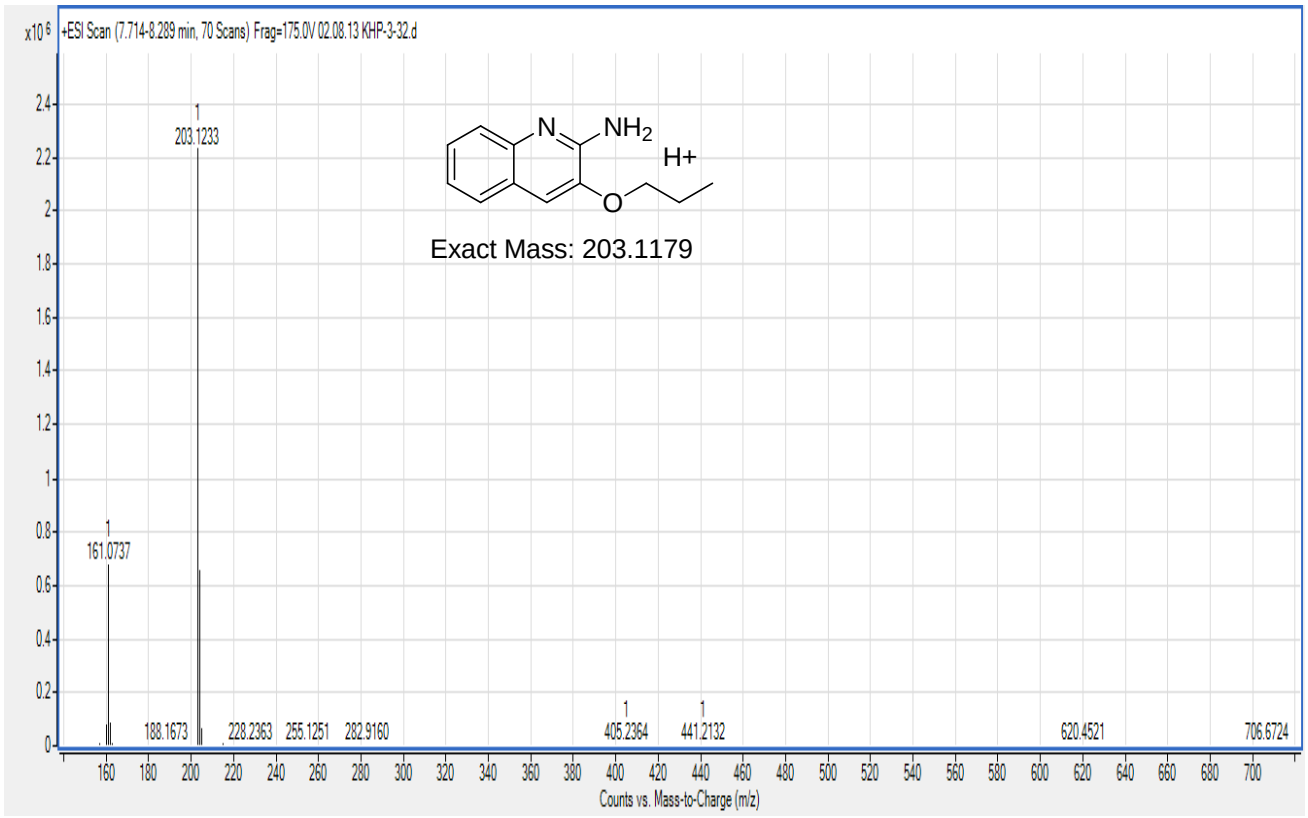
Compound **6c:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



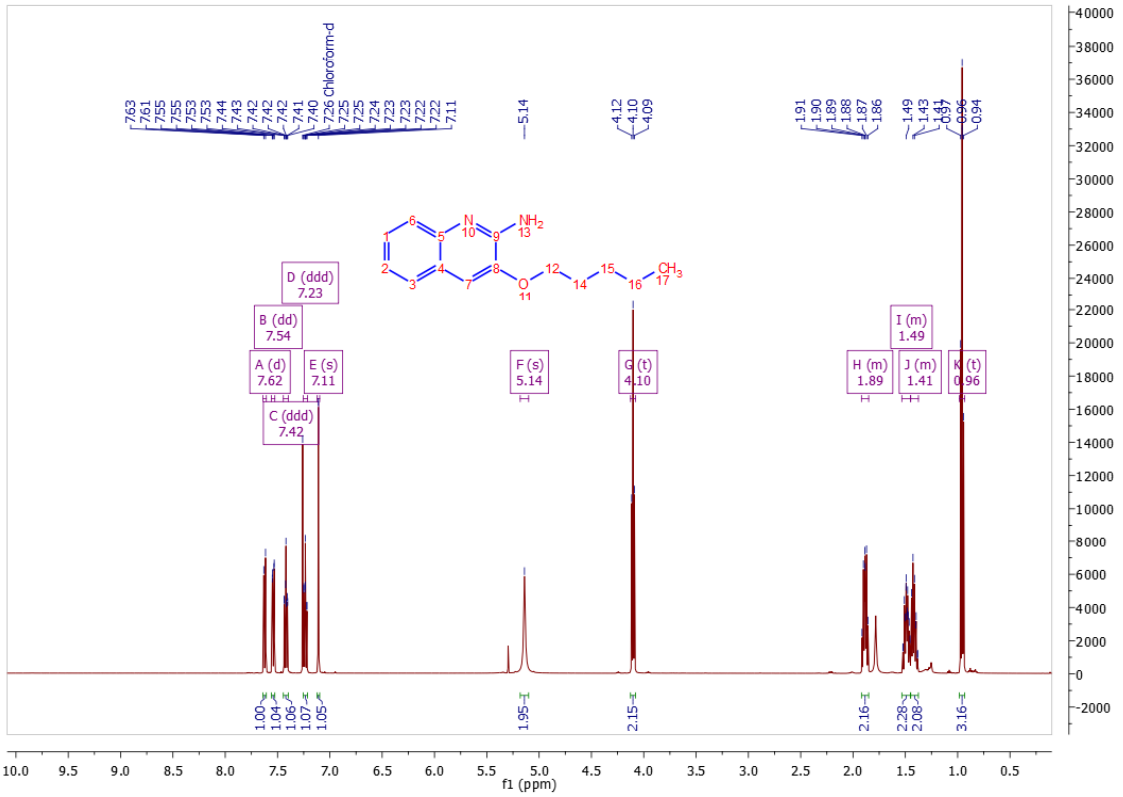


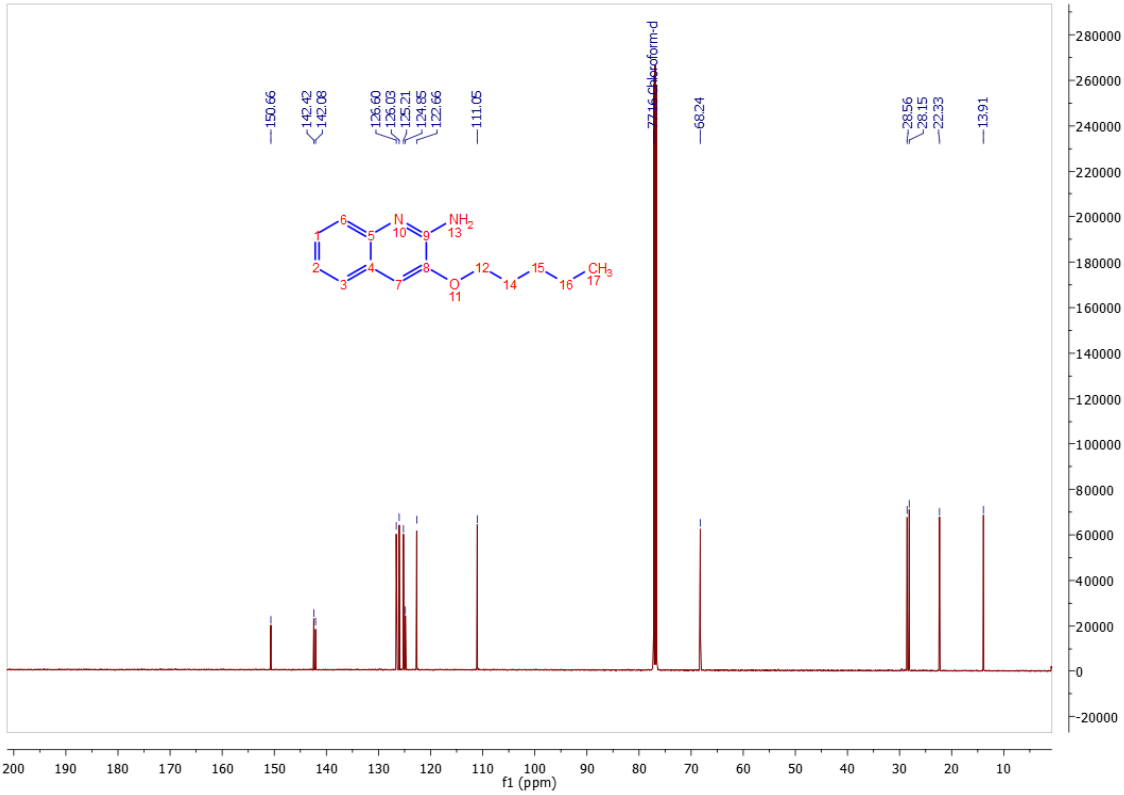
Compound **6c:** LC-MS



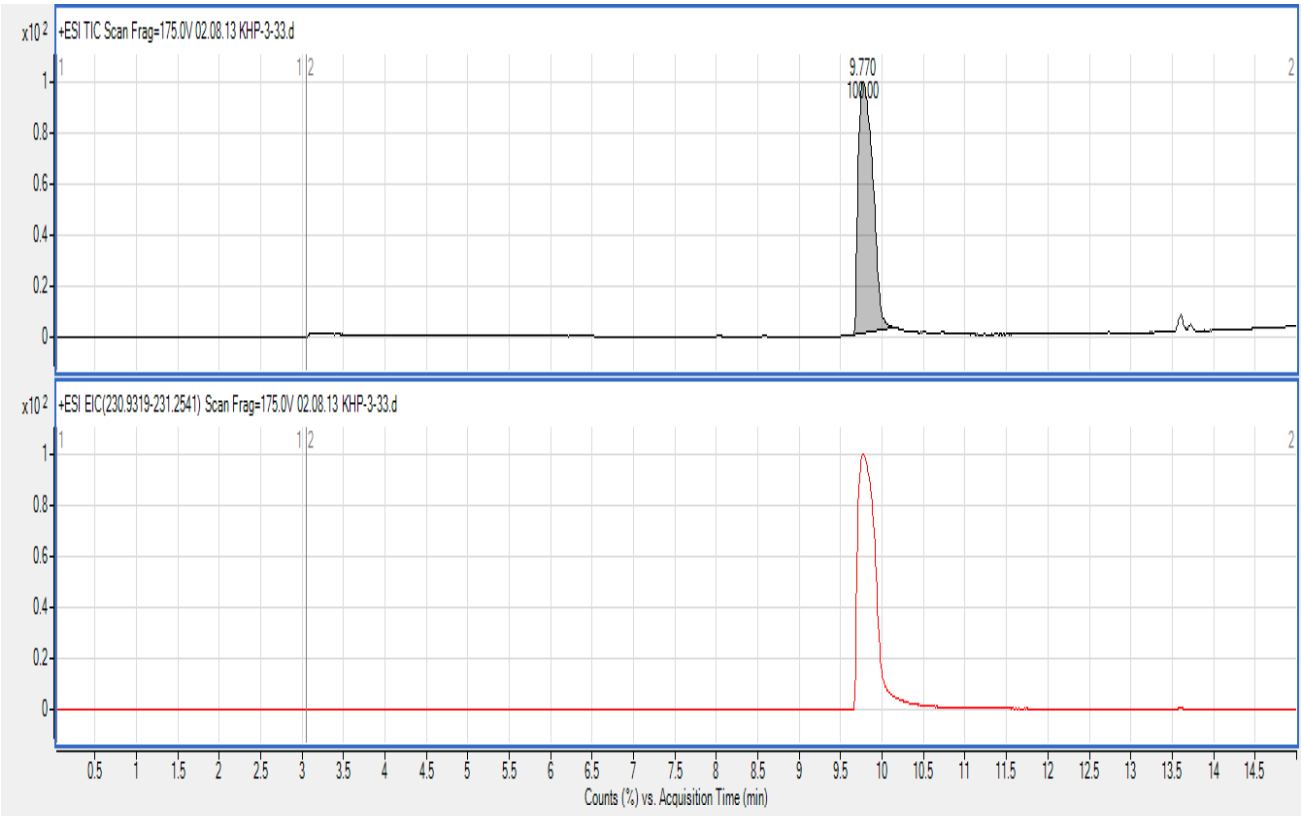


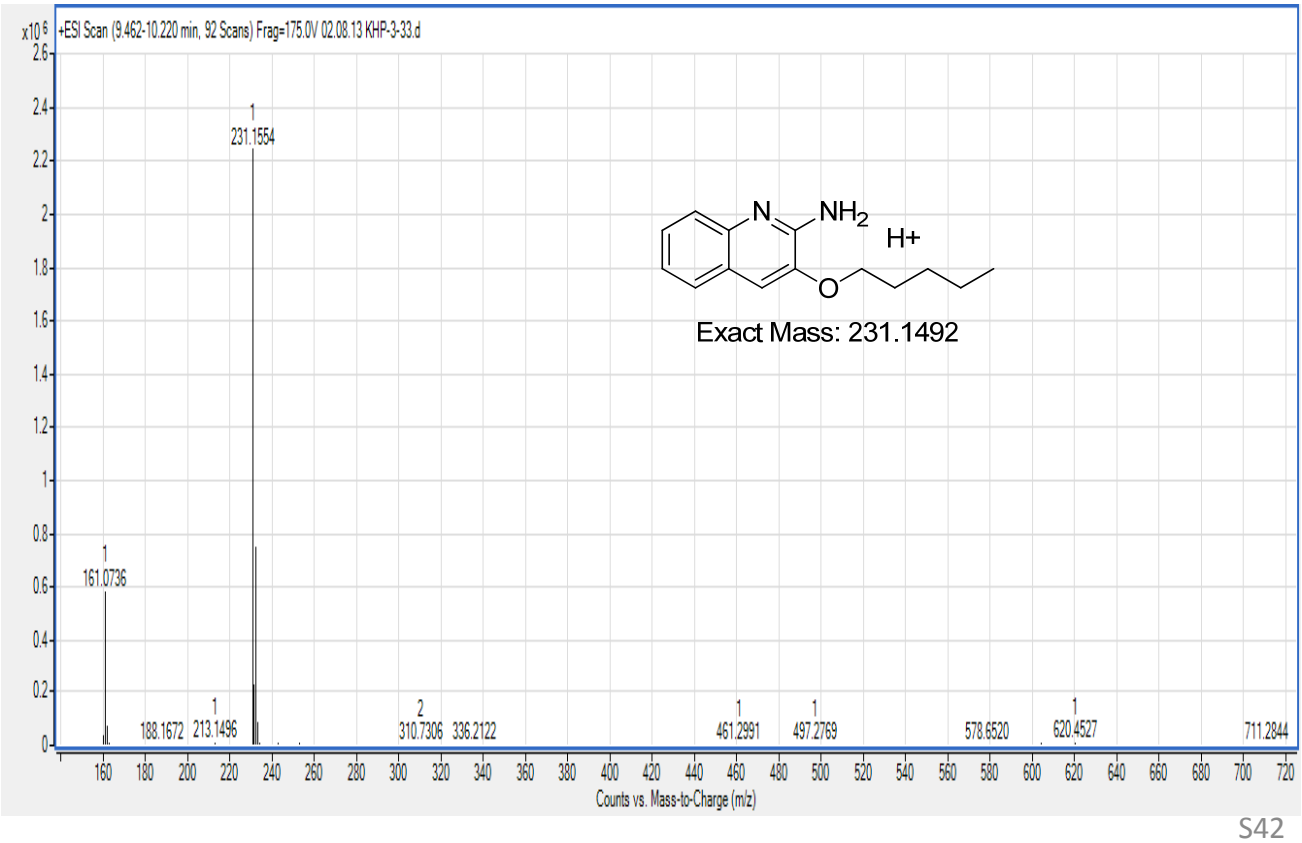
Compound **6d:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



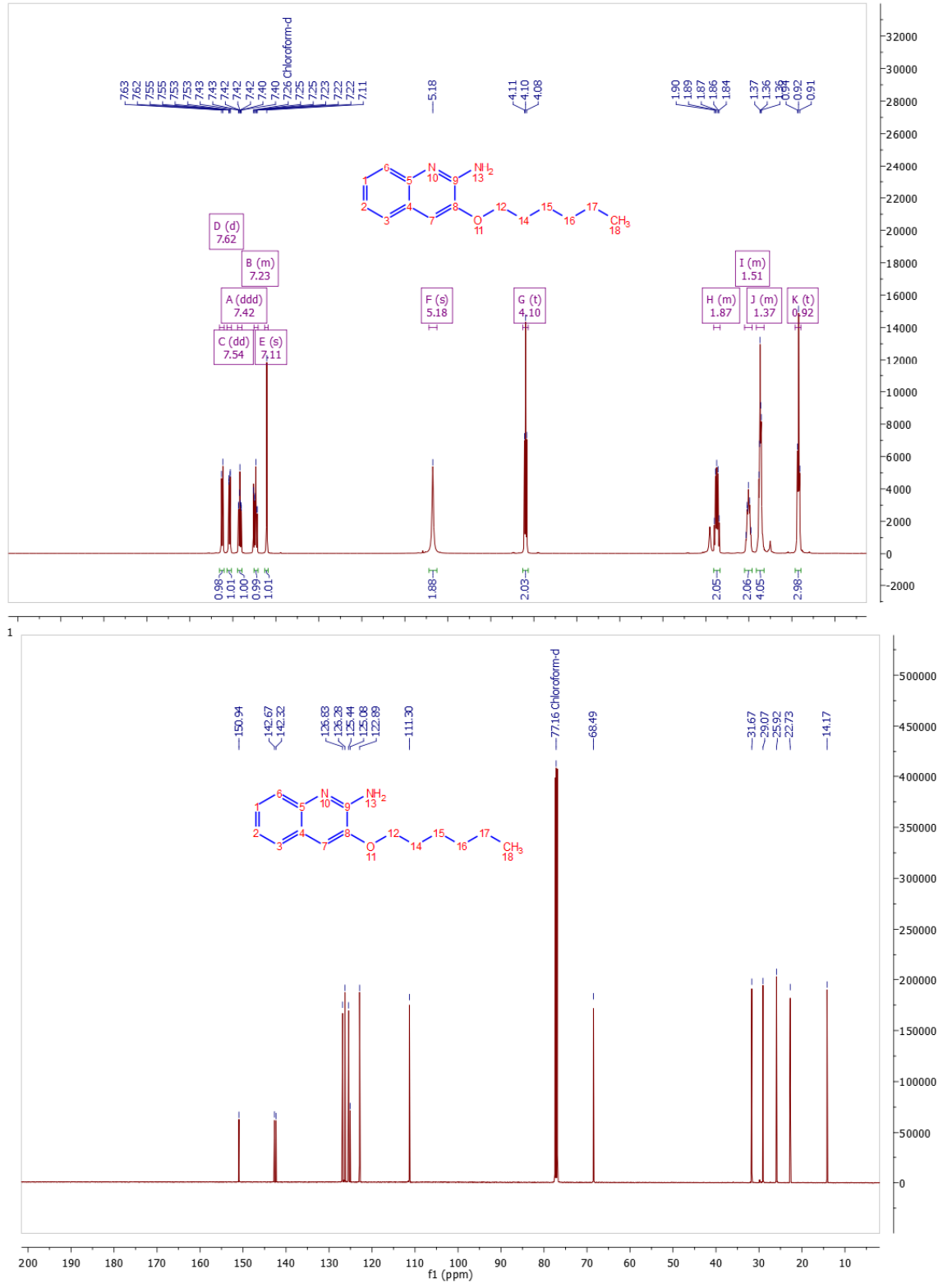


Compound **6d:** LC-MS

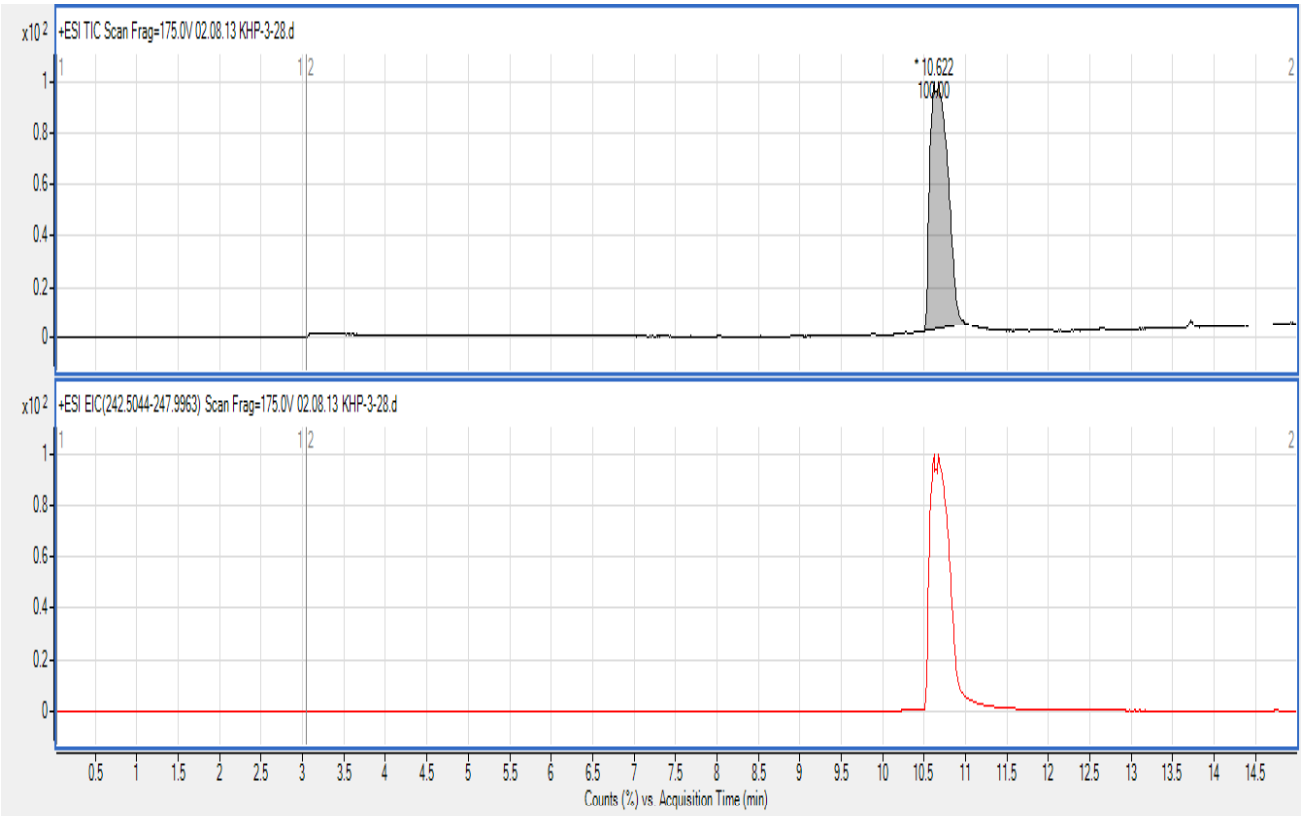


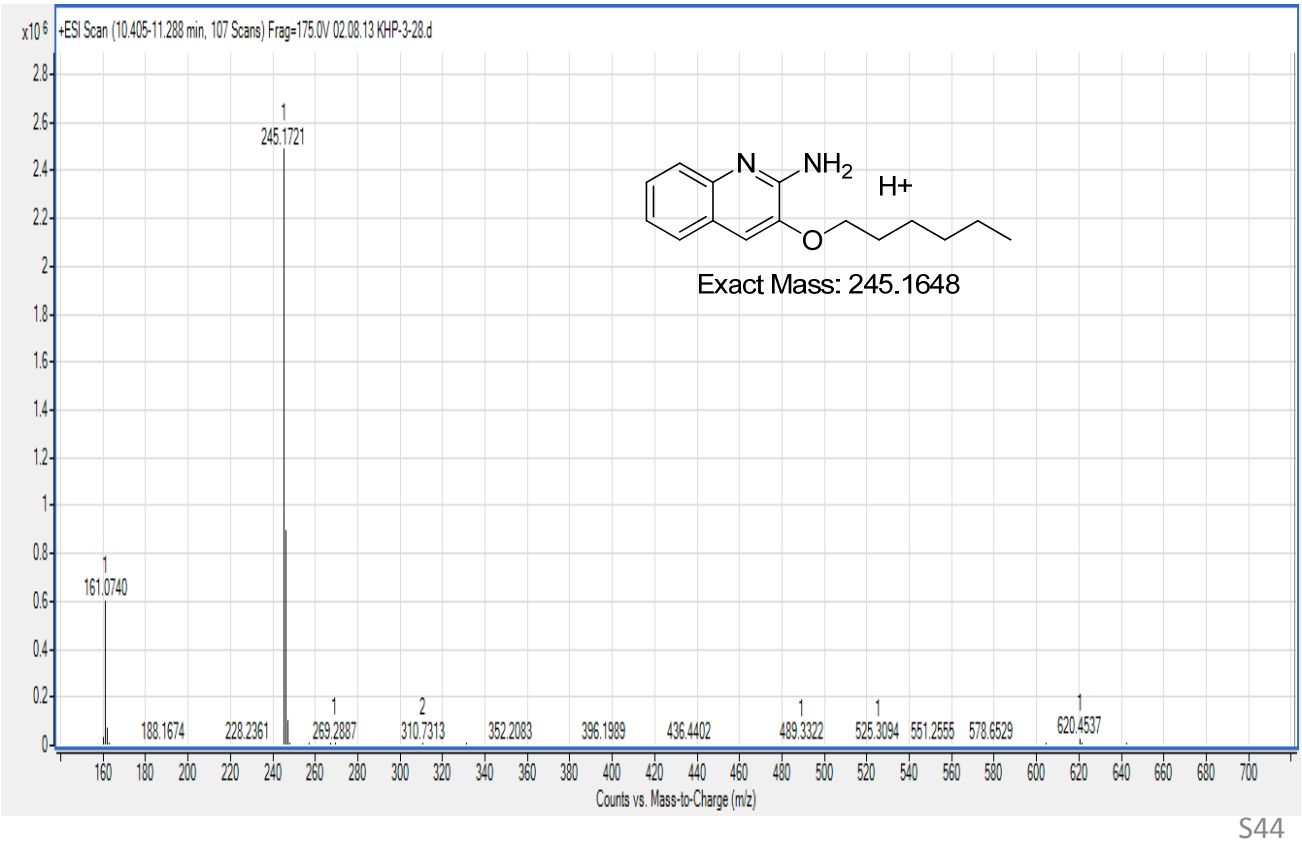


Compound **6e:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)

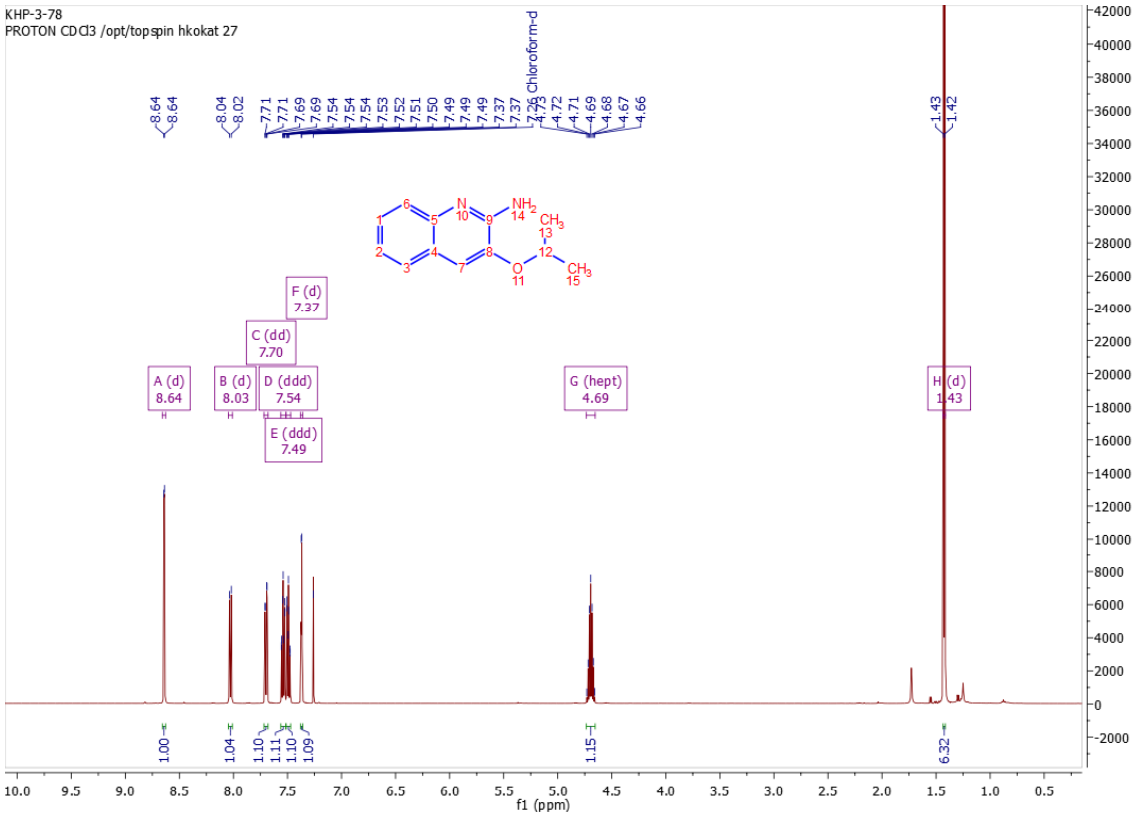


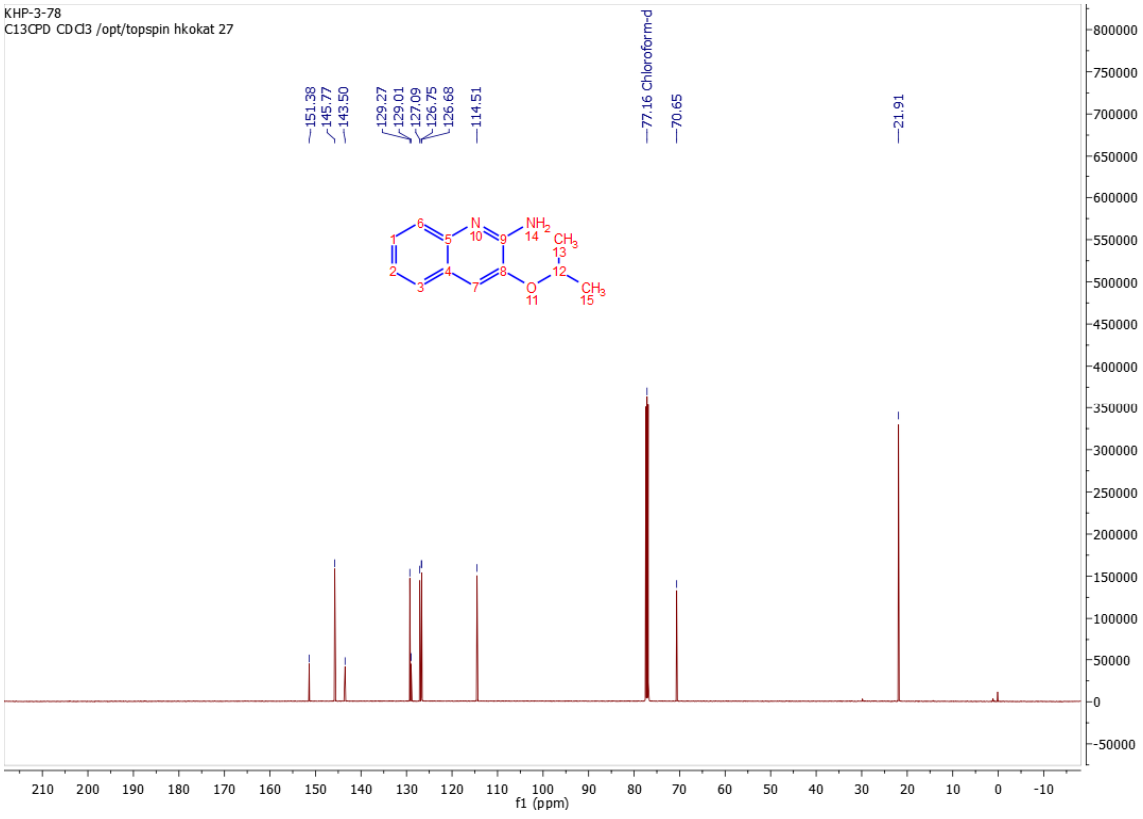
Compound **6e:** LC-MS



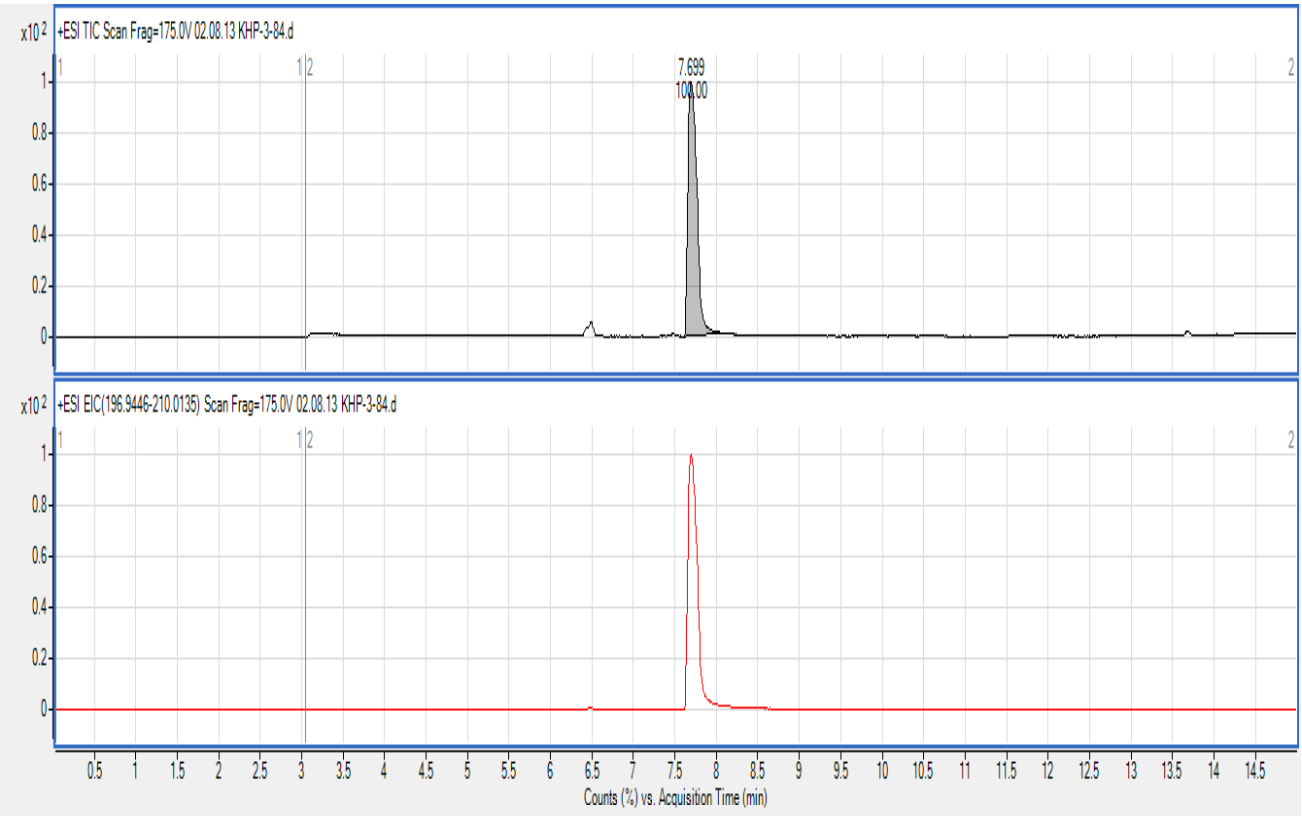


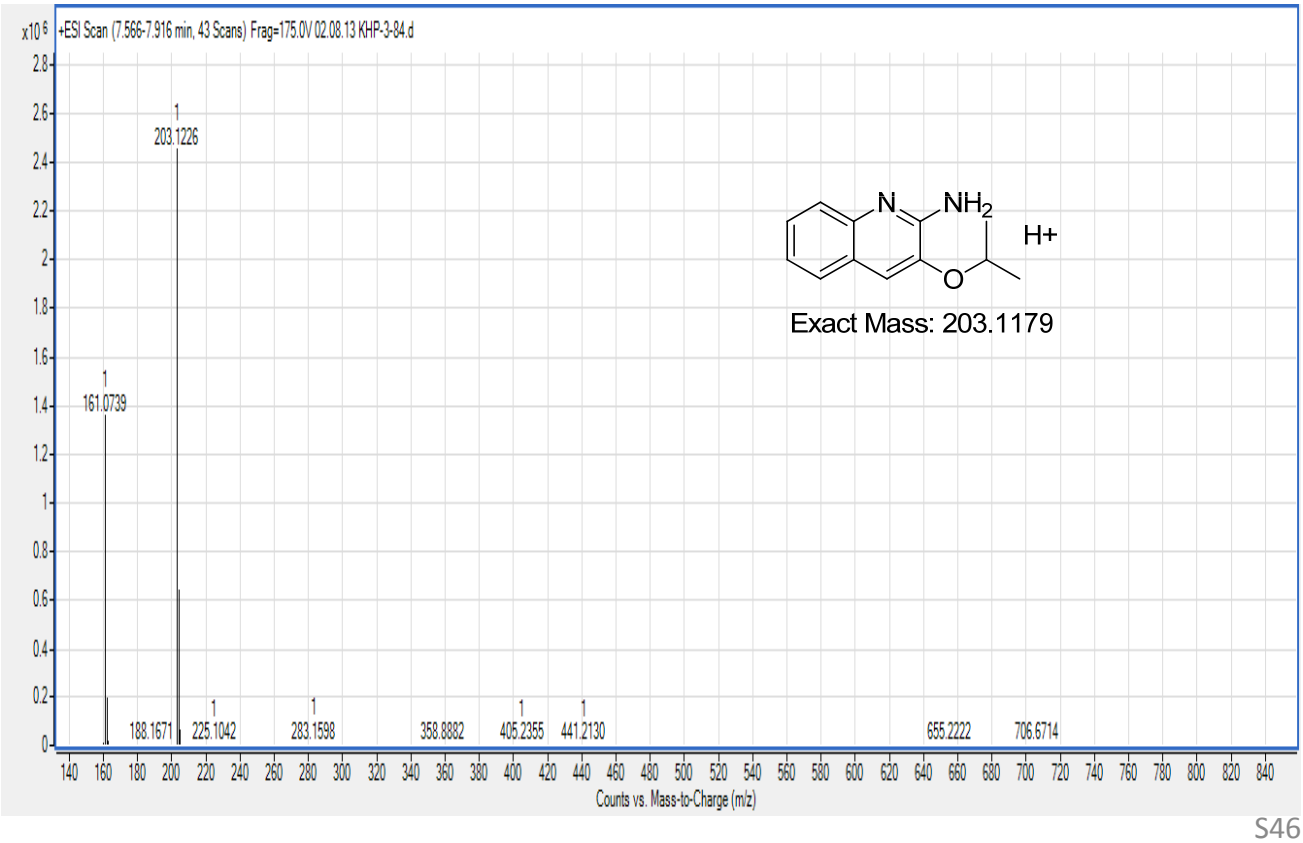
Compound **6f:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)





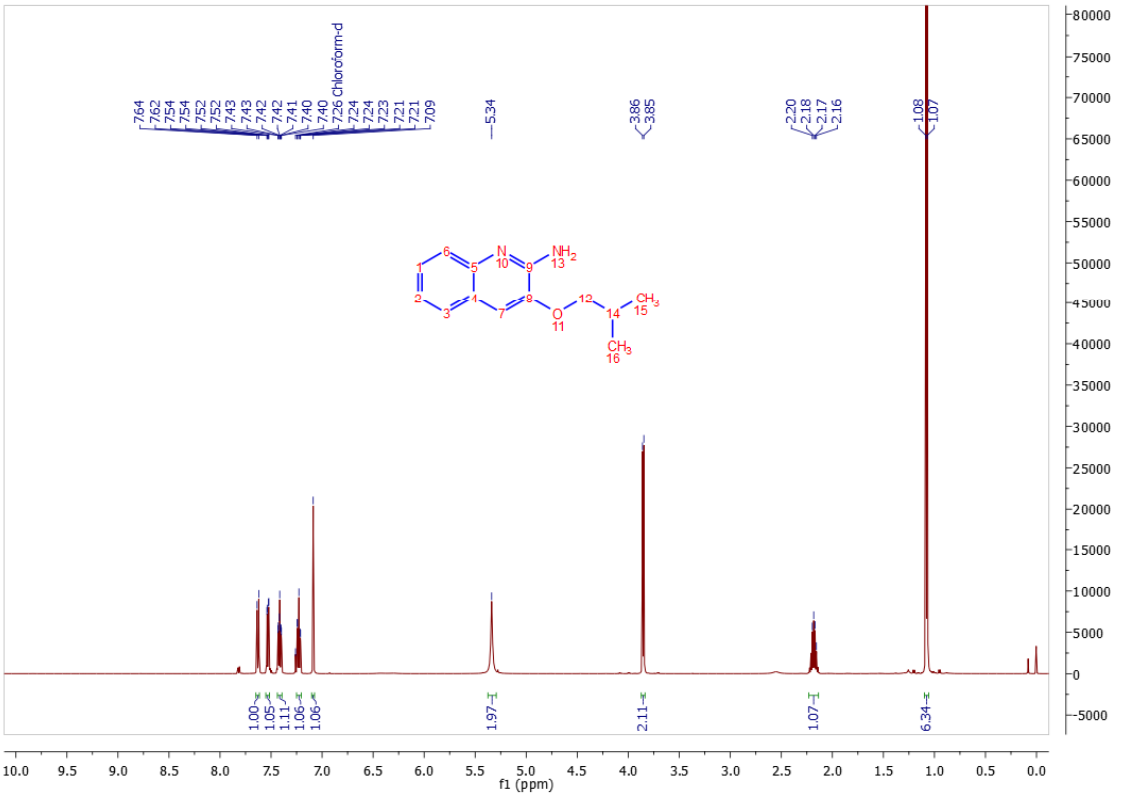
Compound **6f:** LC-MS

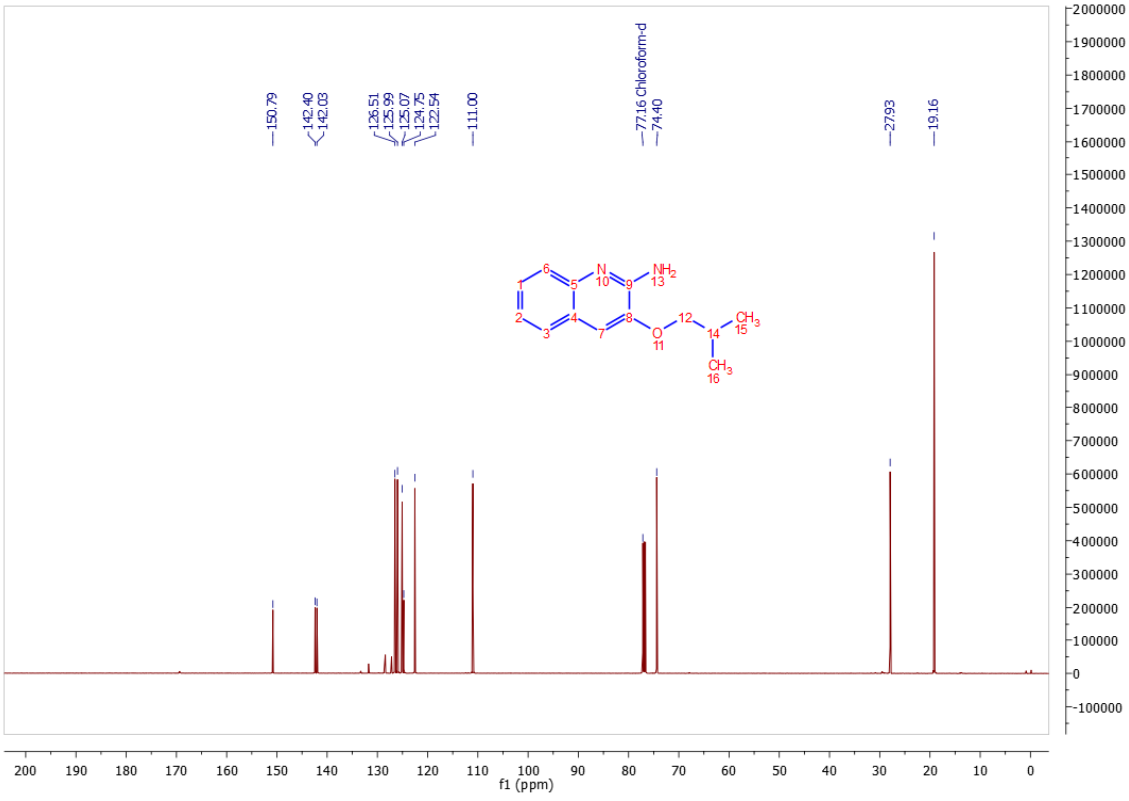




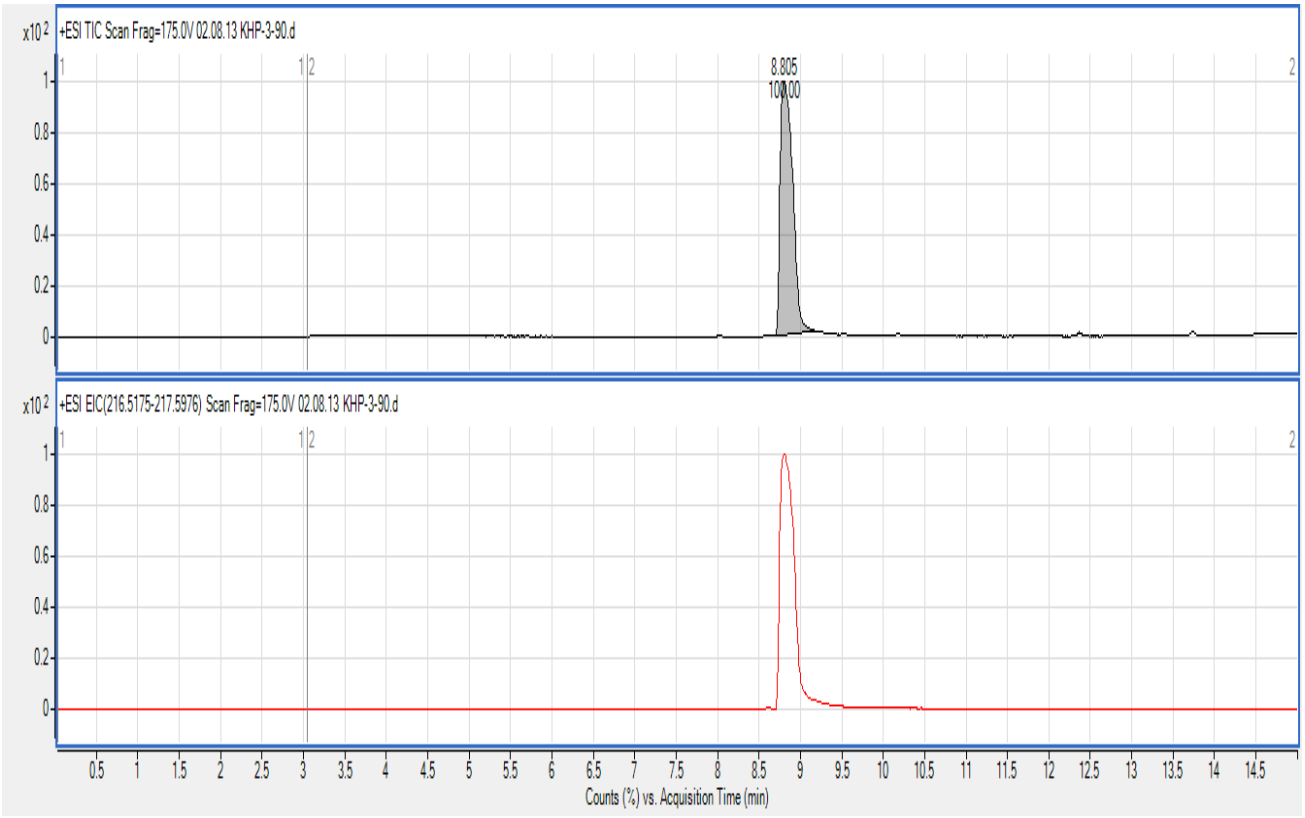
Exact Mass: 203.1179

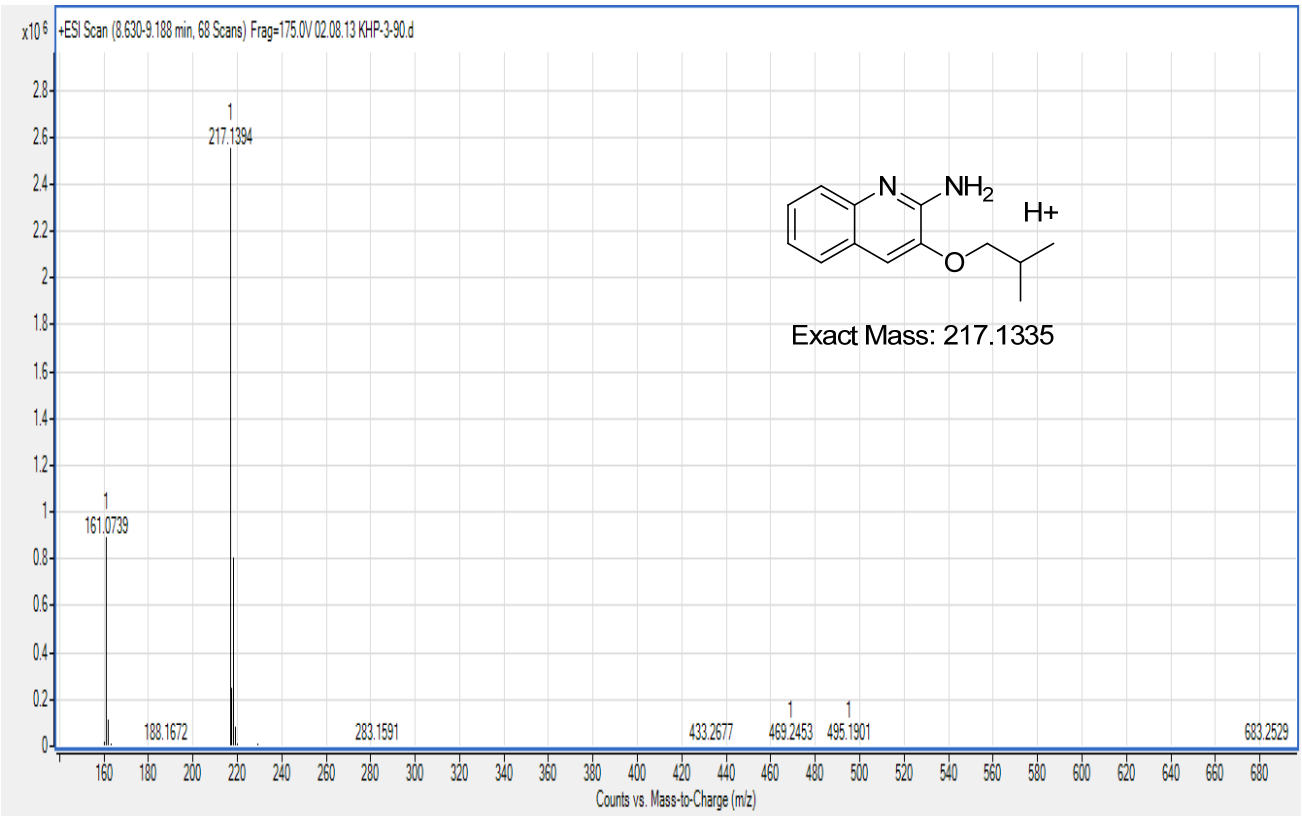
Compound **6g:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



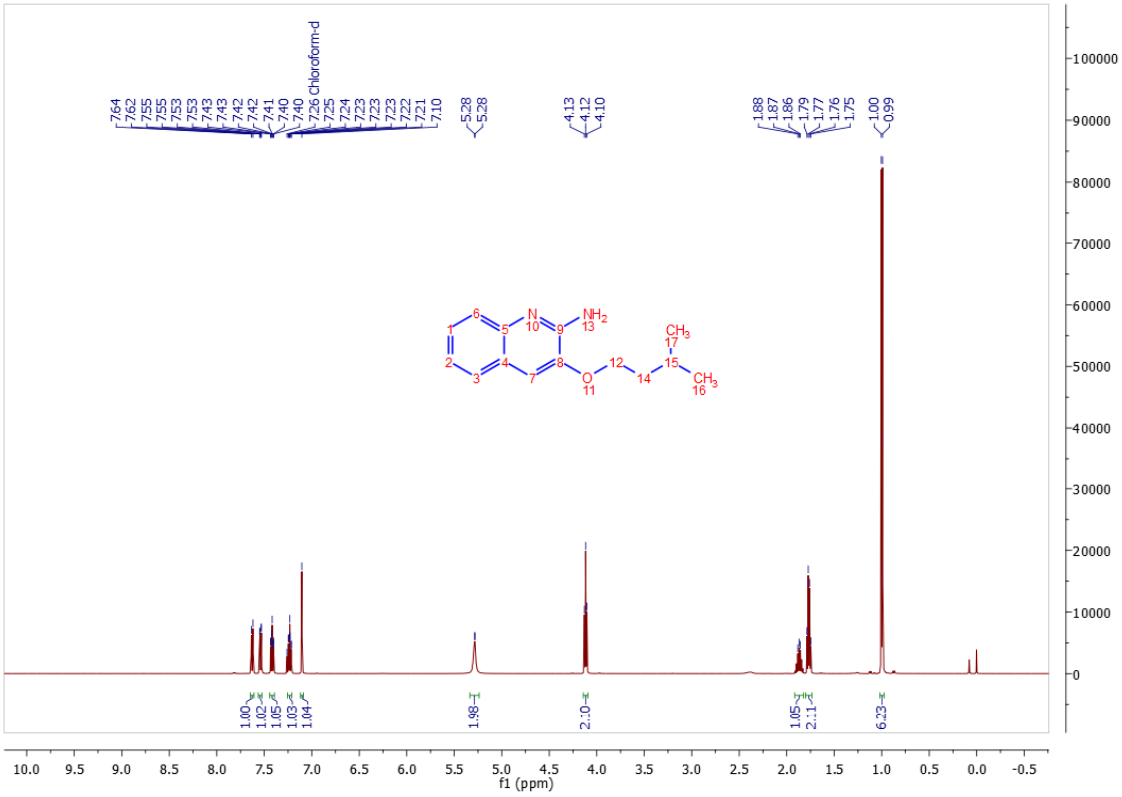


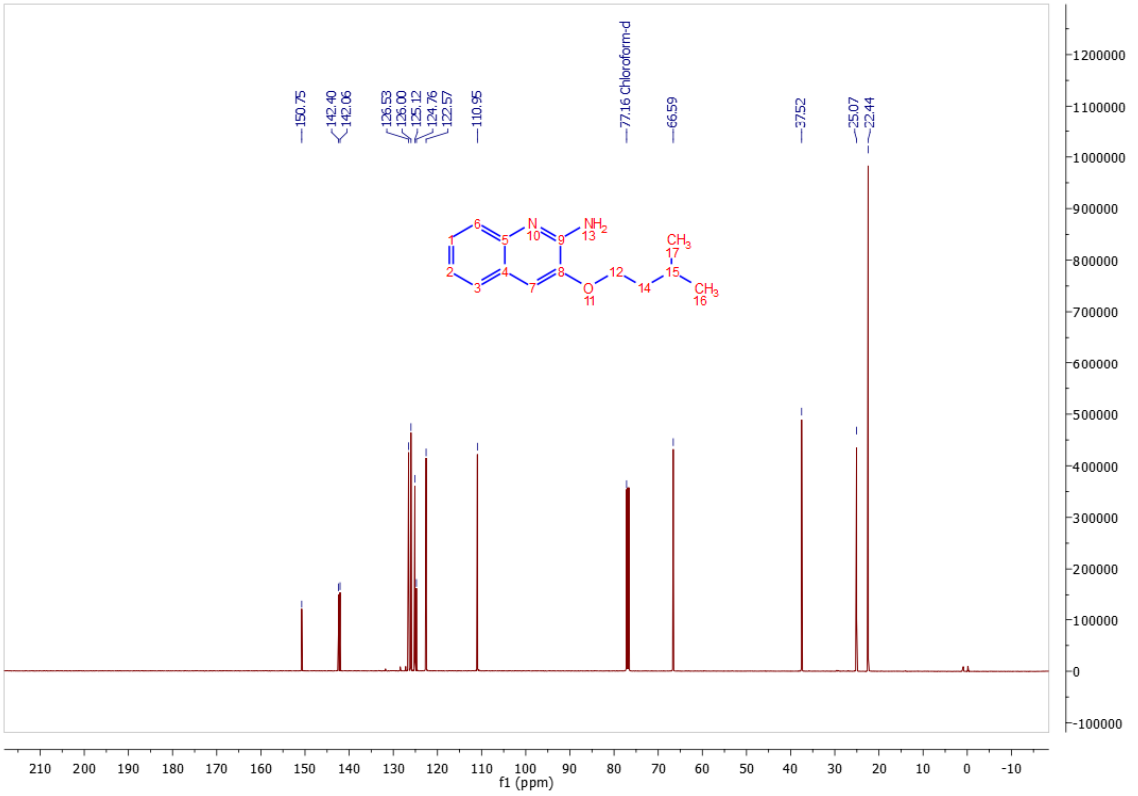
Compound **6g:** LC-MS



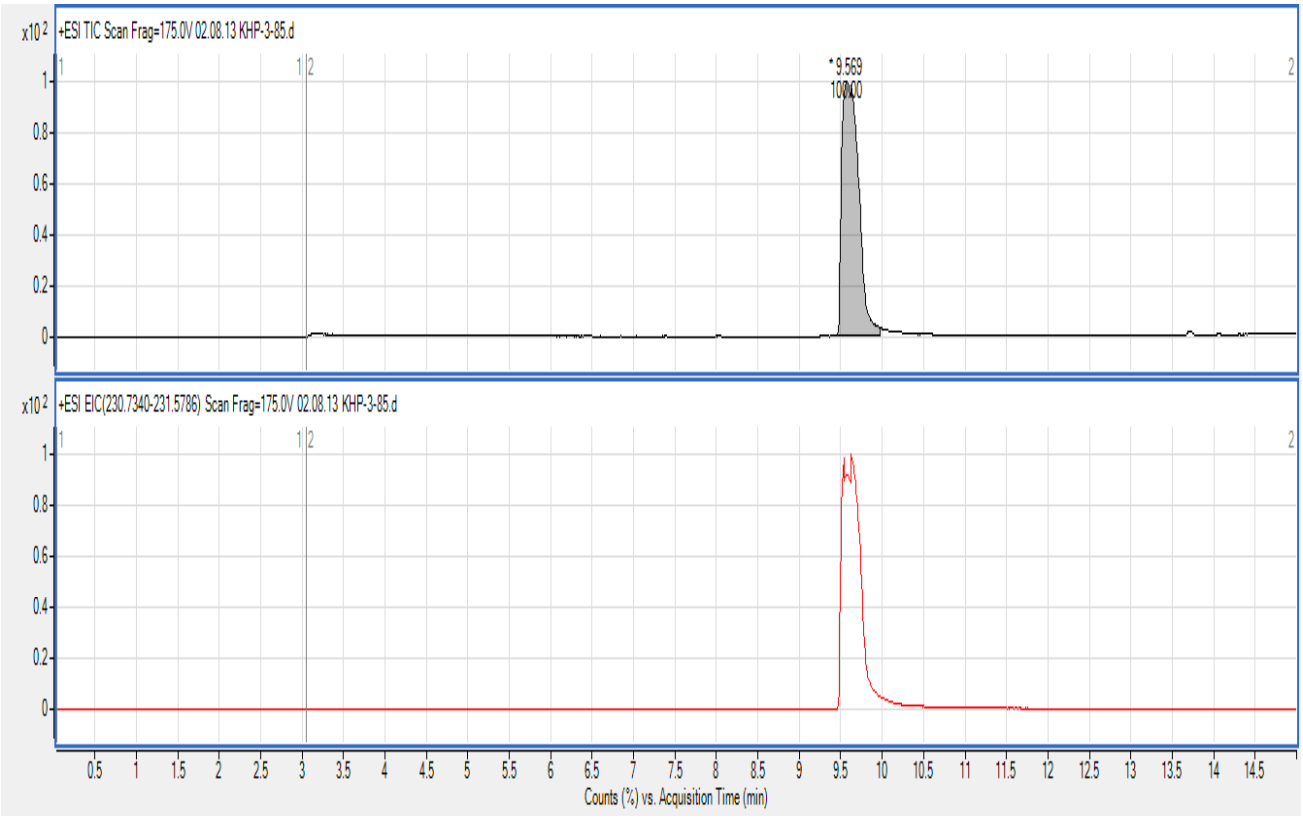


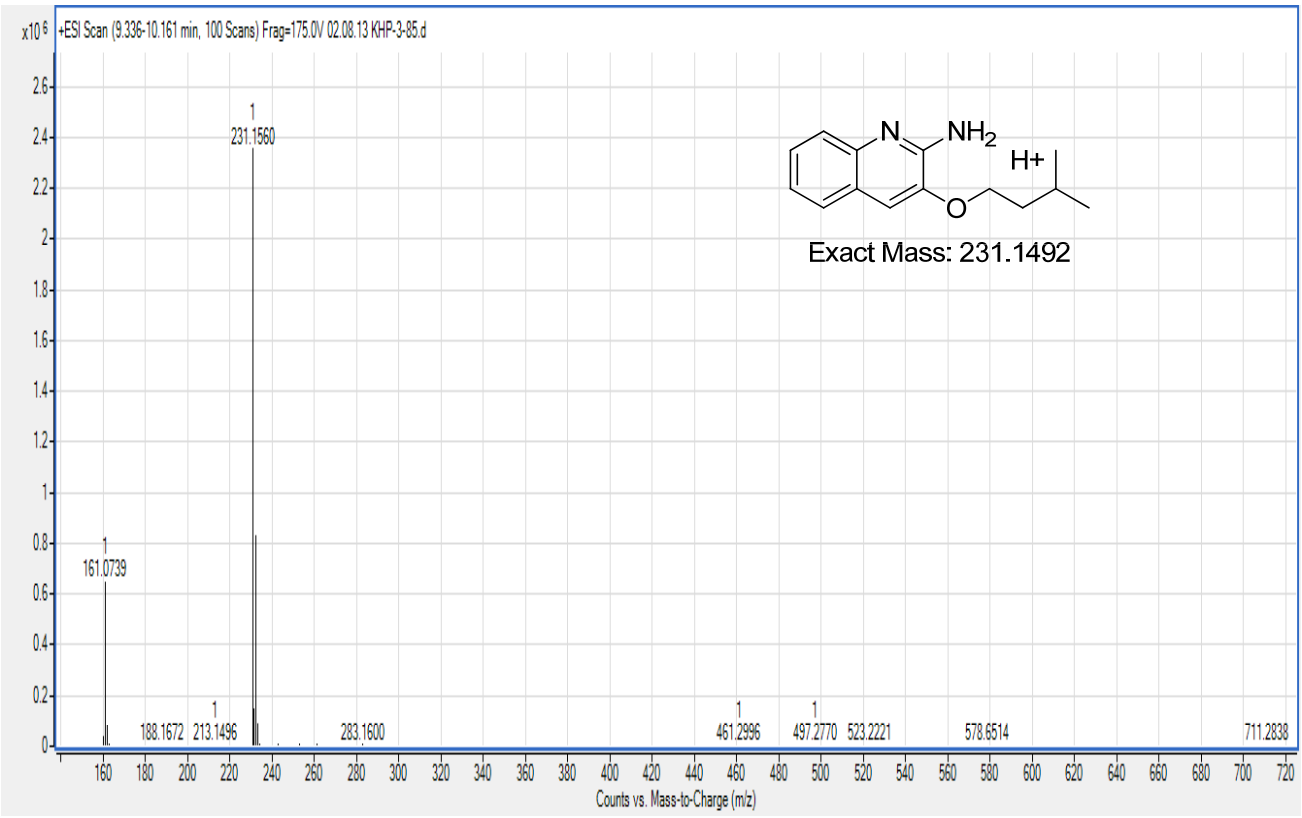
Compound **6h:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



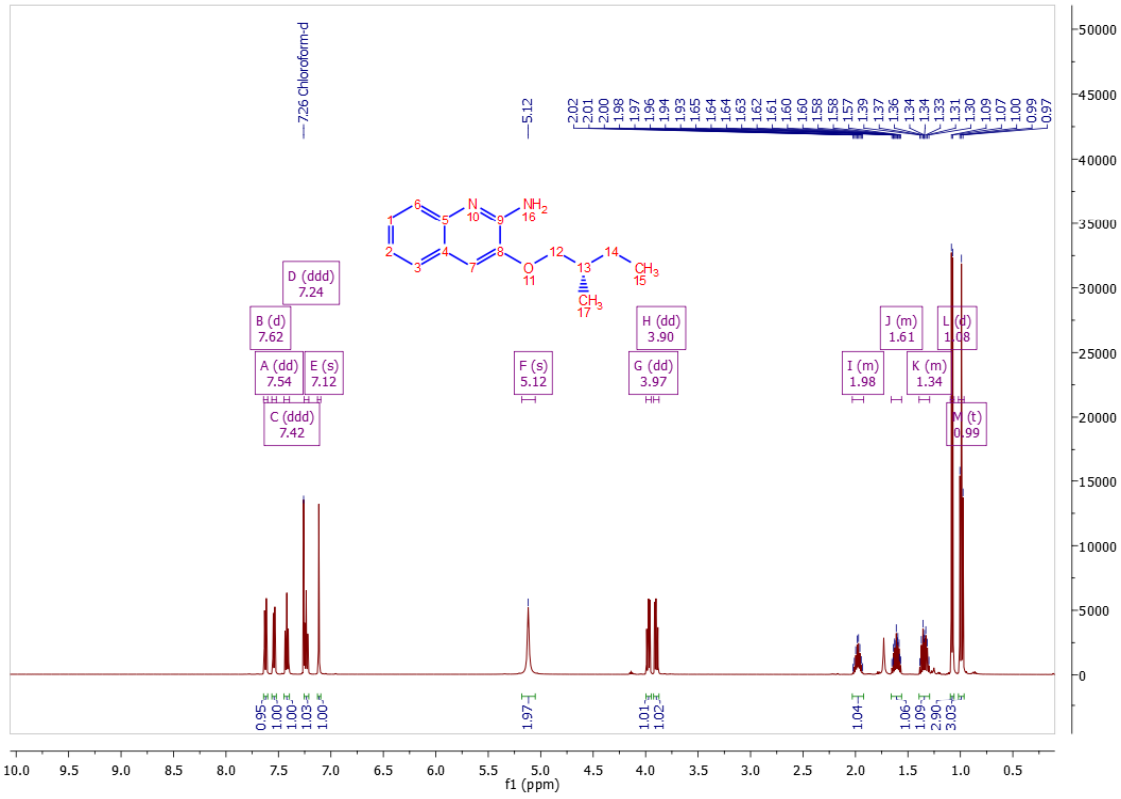


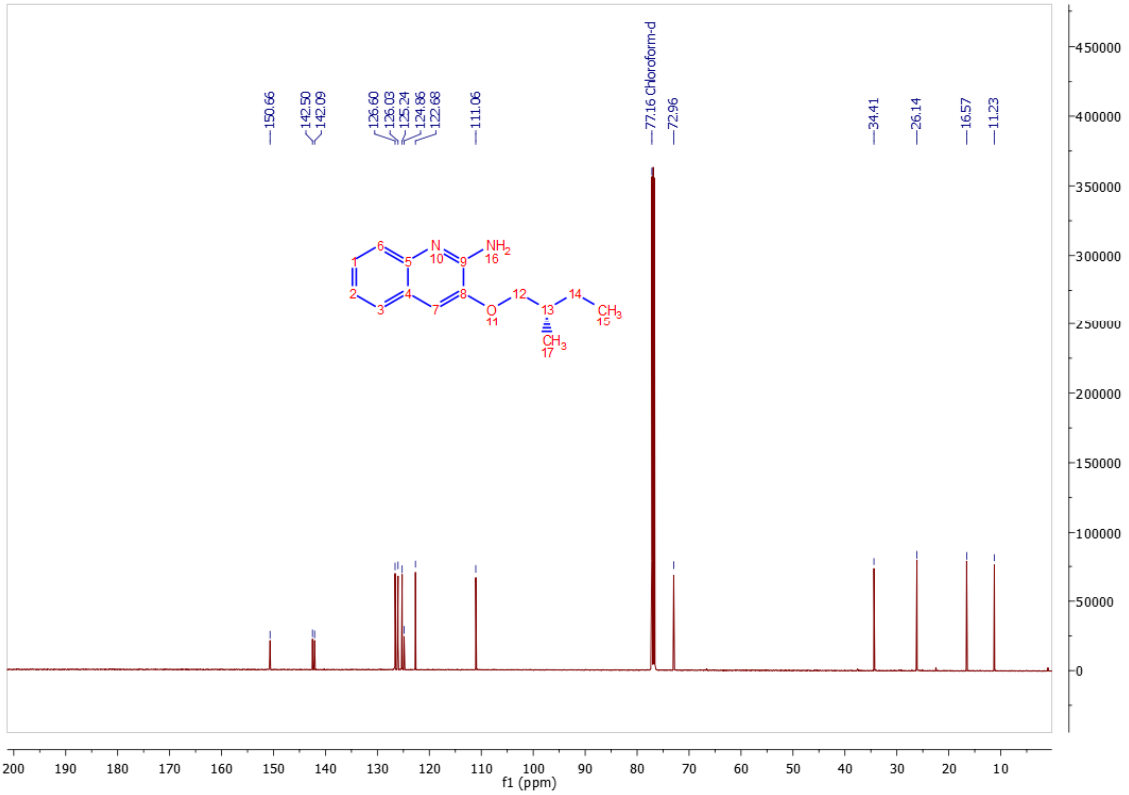
Compound **6h:** LC-MS



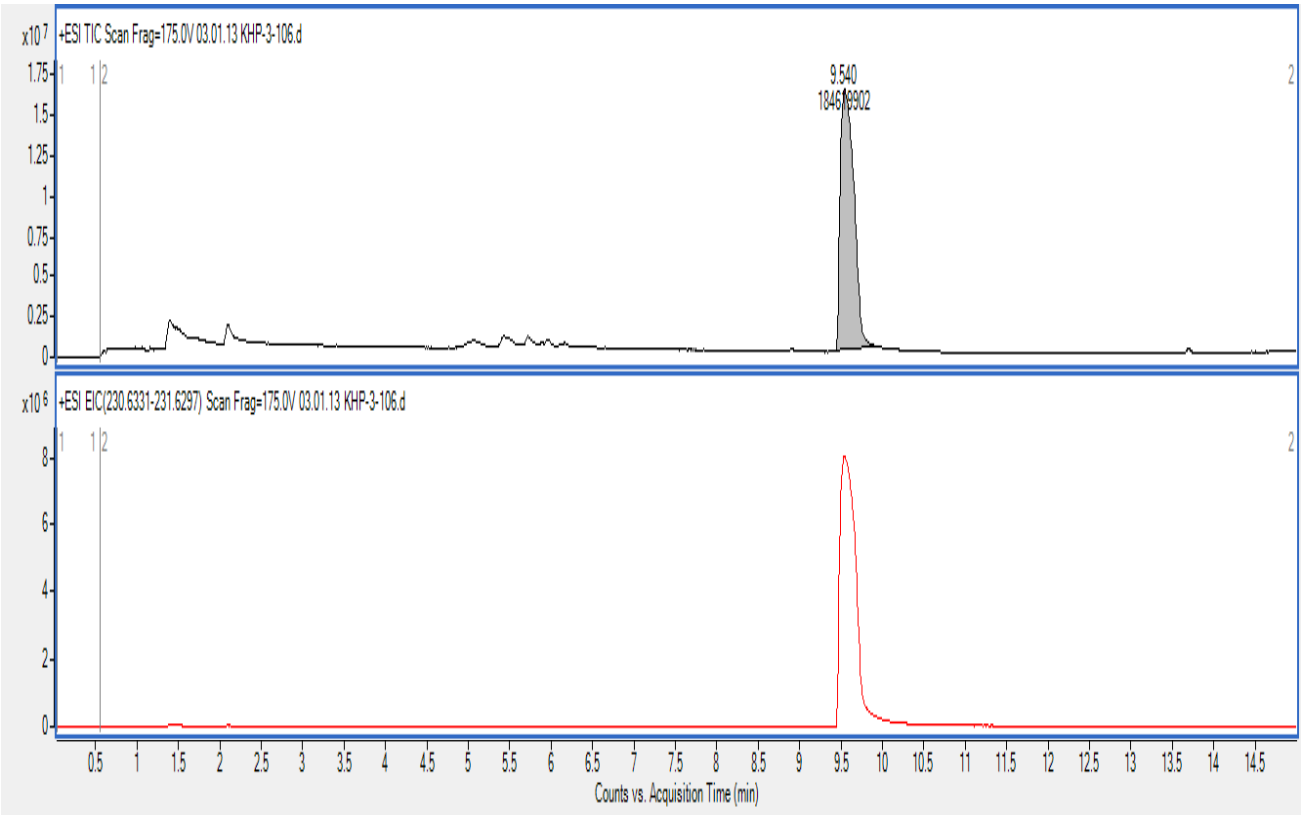


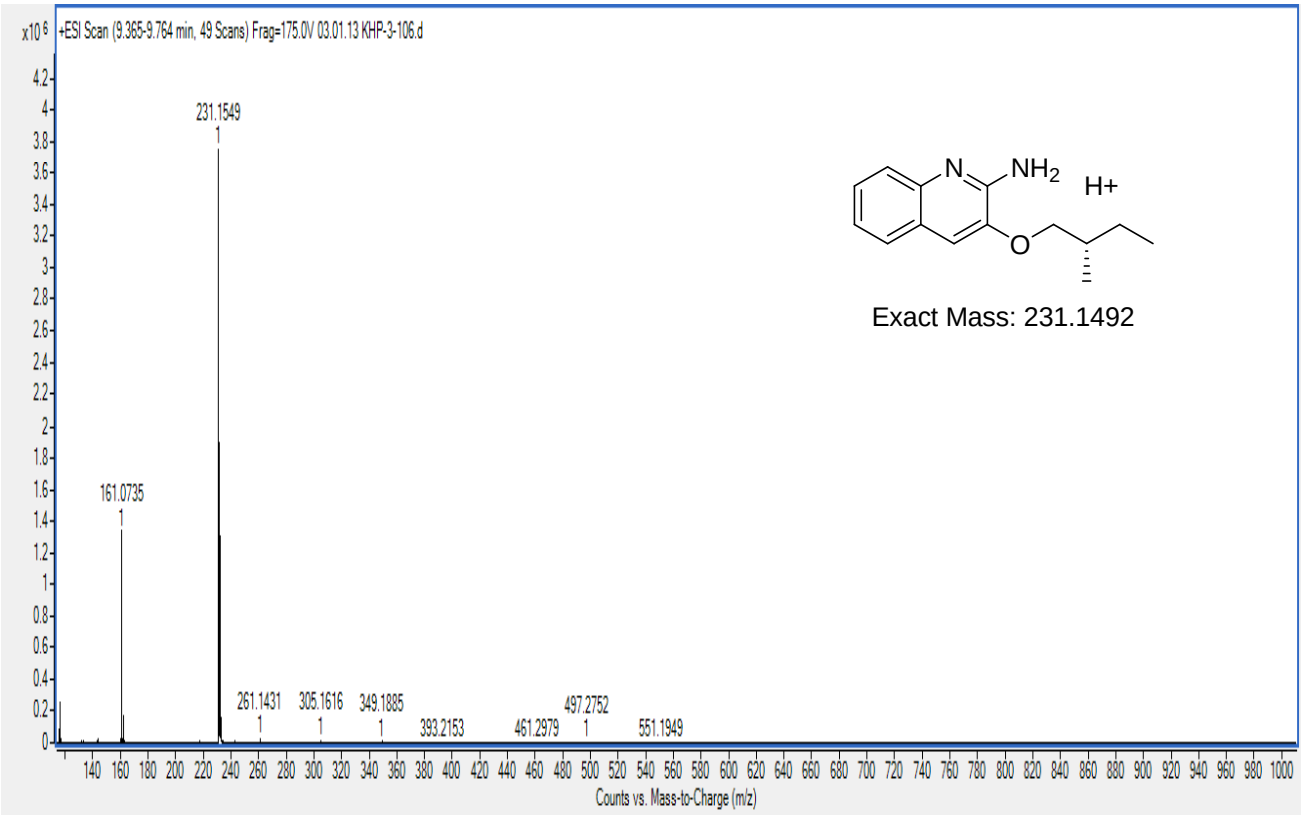
Compound **6i:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)





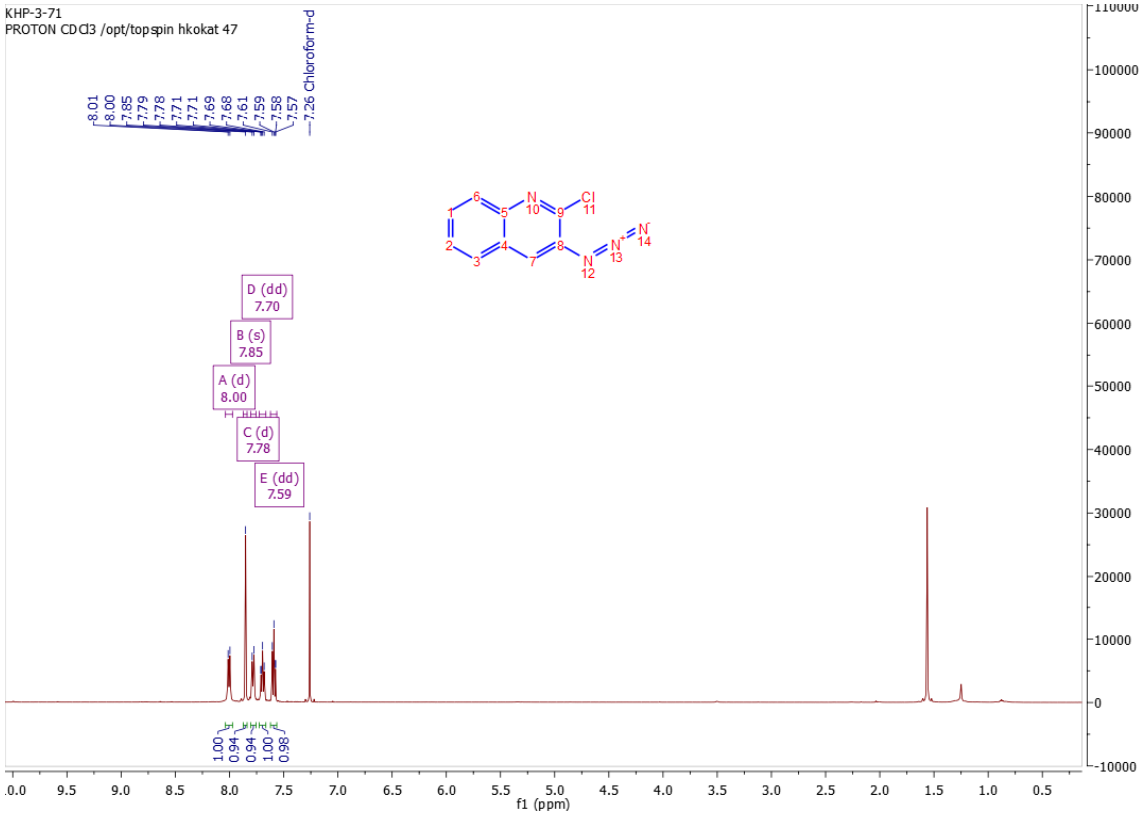
Compound **6i:** LC-MS

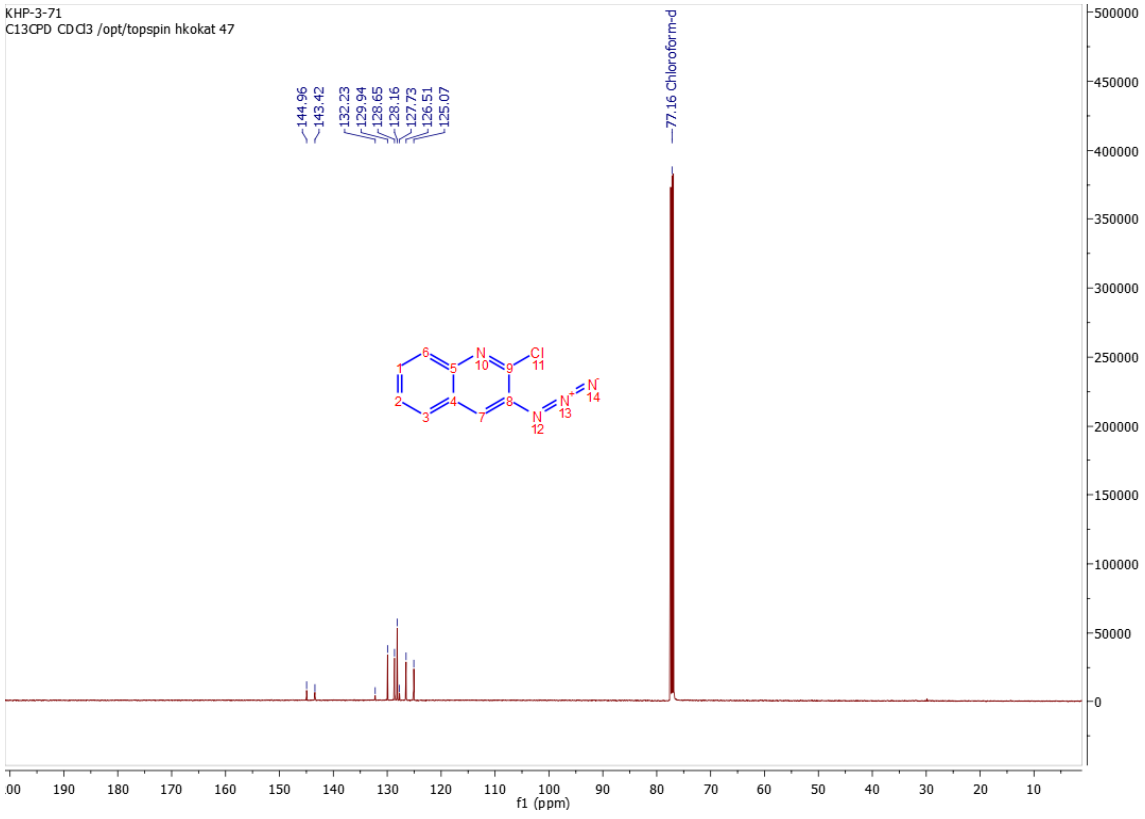




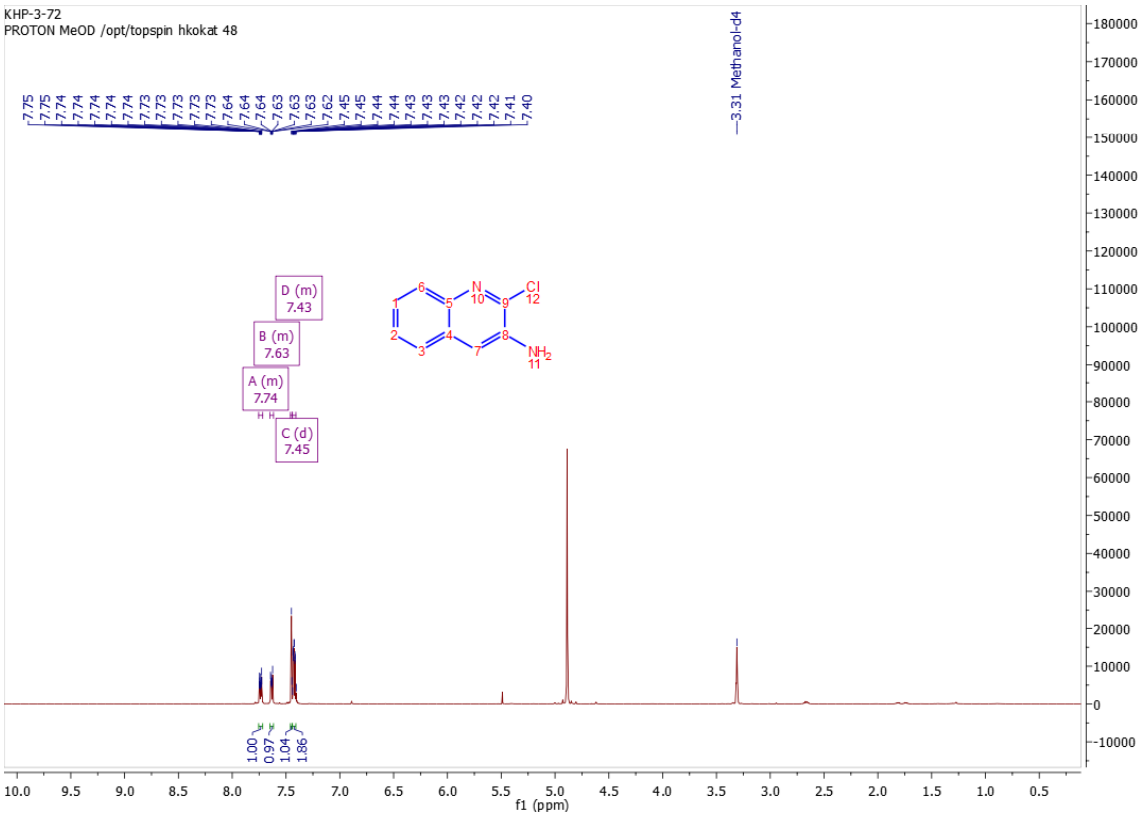
Exact Mass: 231.1492

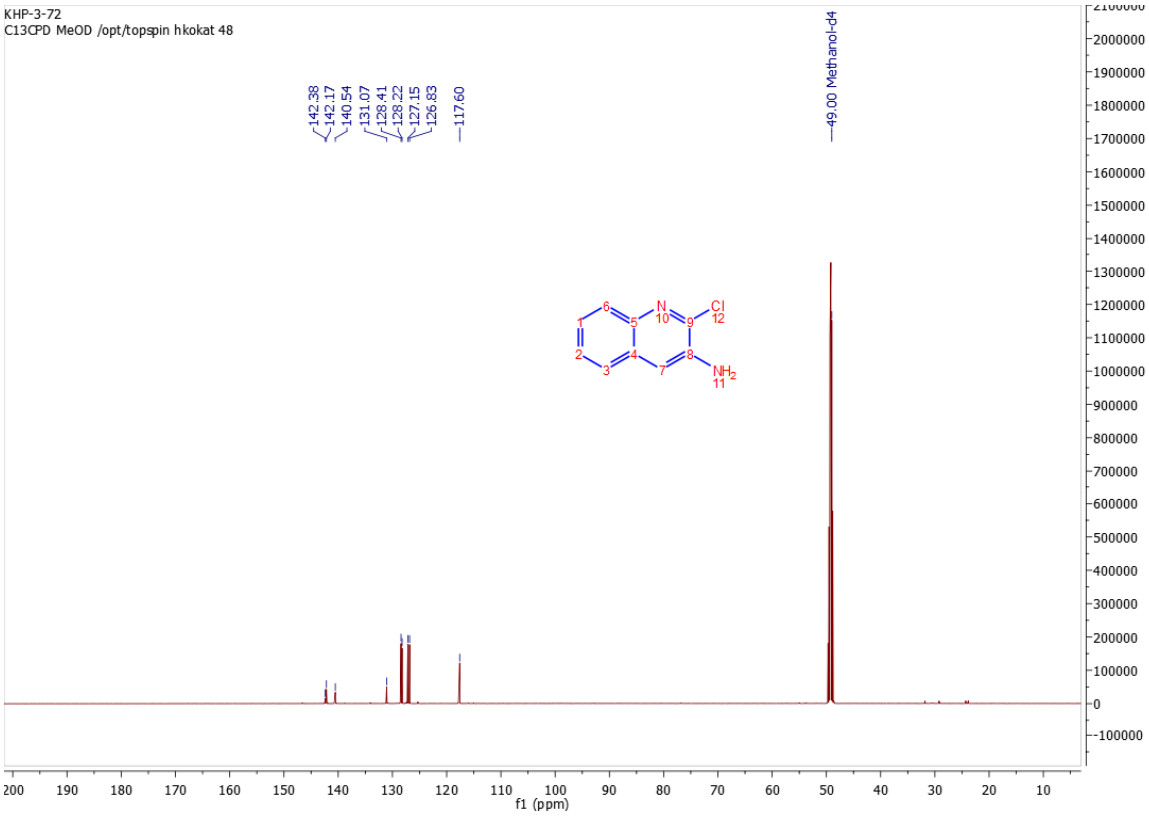
Compound **7:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



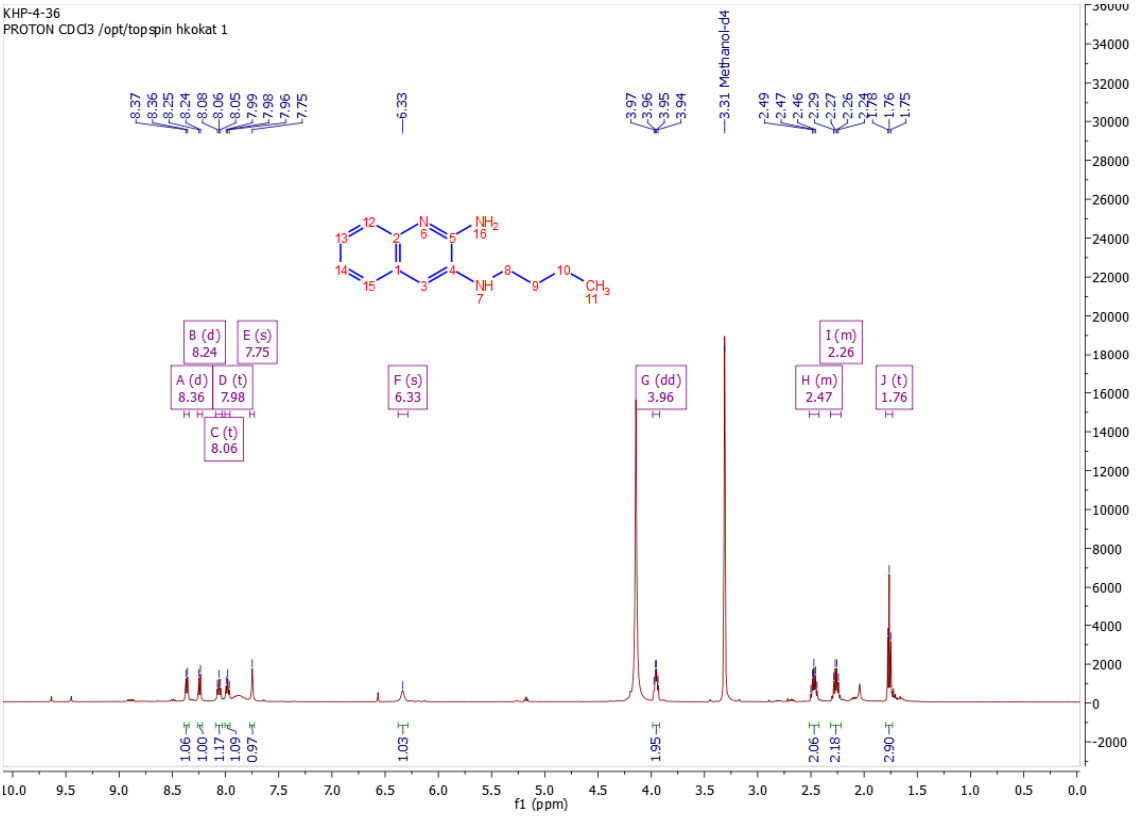


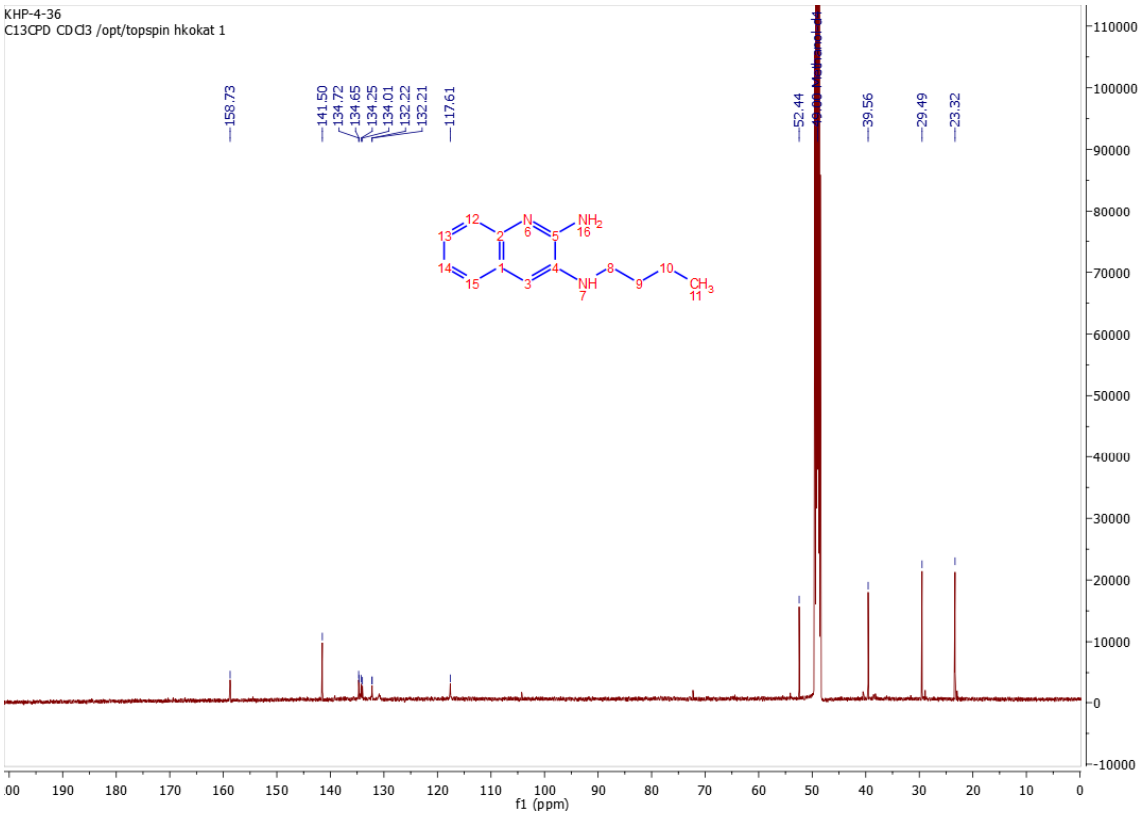
Compound **8:** ^{1}H and ^{13}C NMR Spectrum (MeOD)



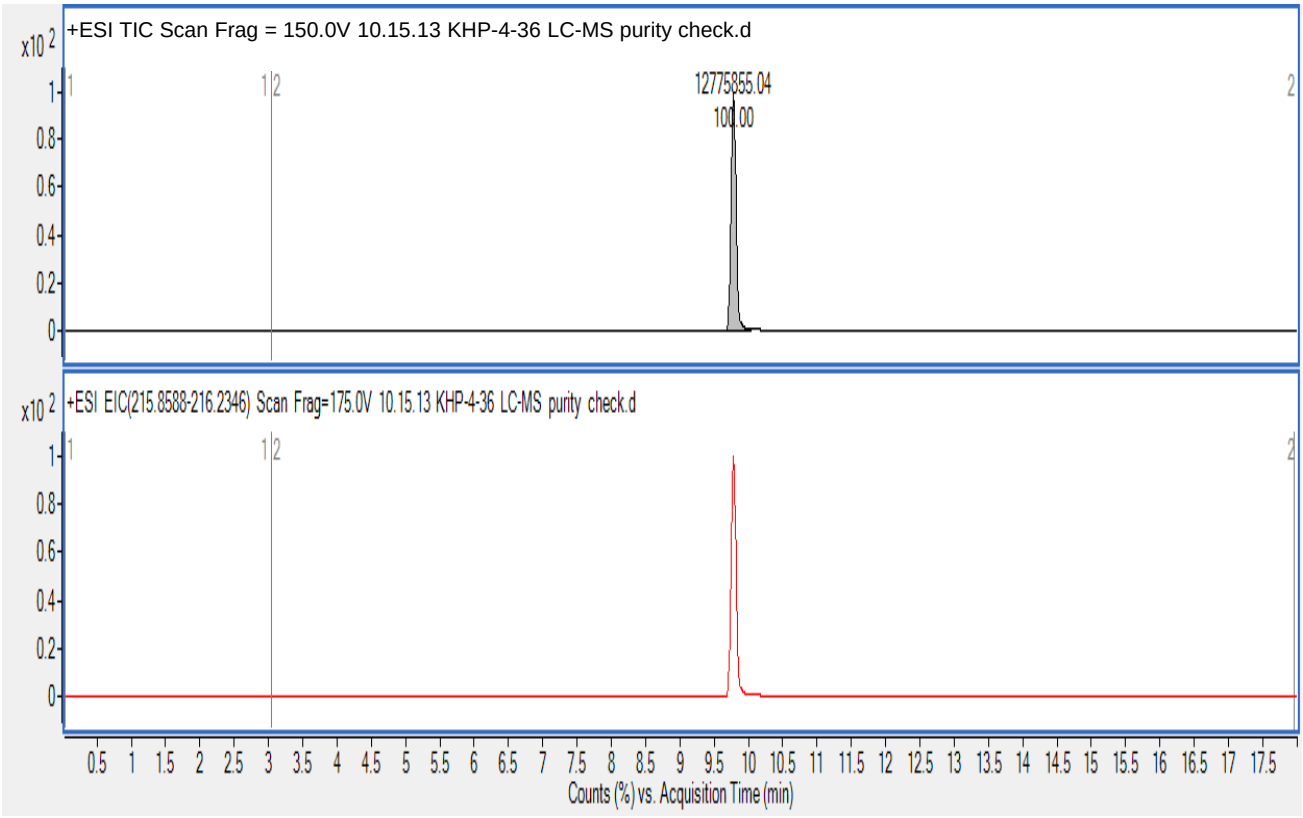


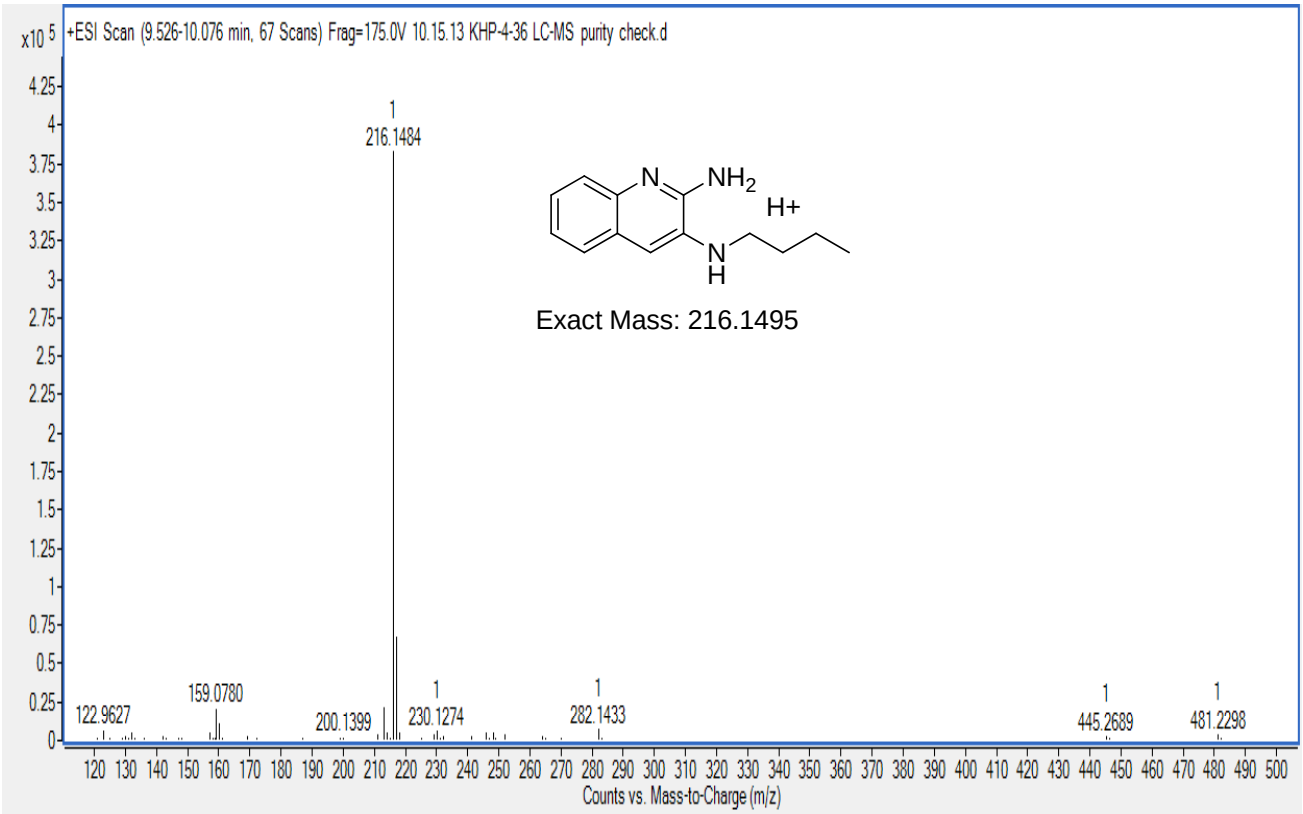
Compound **9:** ^{1}H and ^{13}C NMR Spectrum (MeOD)





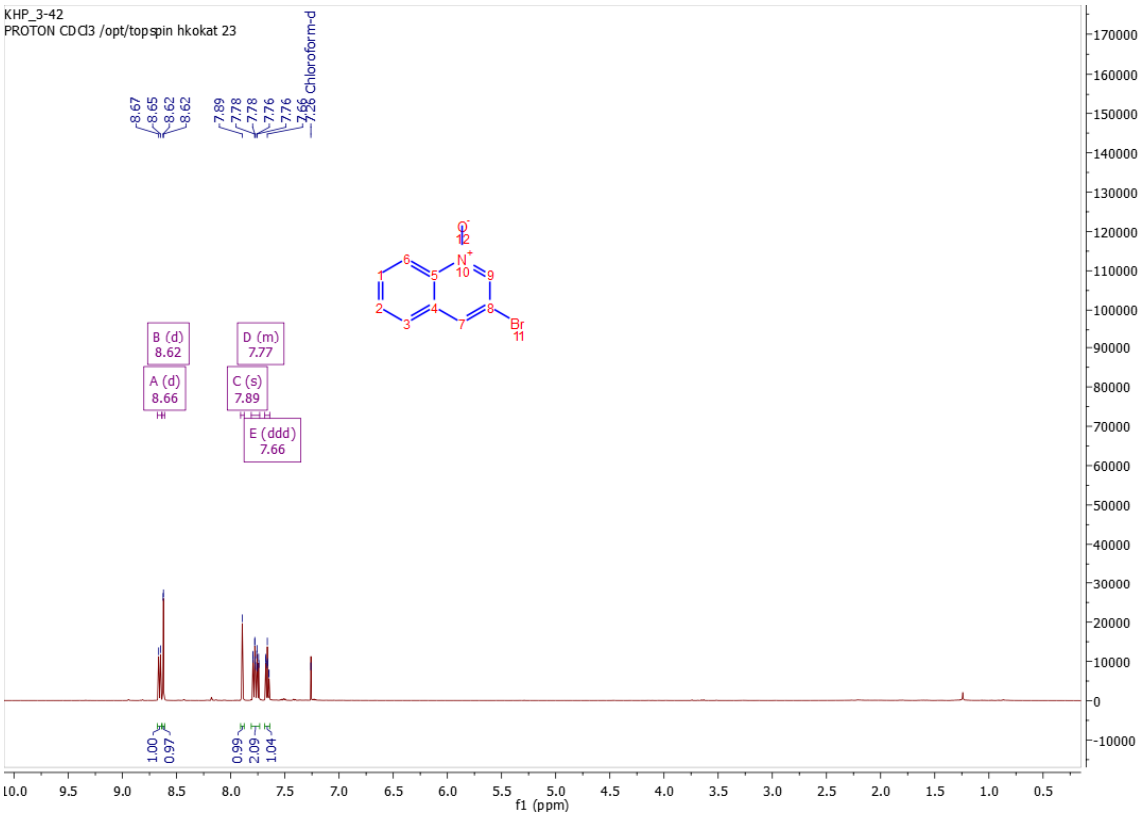
Compound **9:** LC-MS

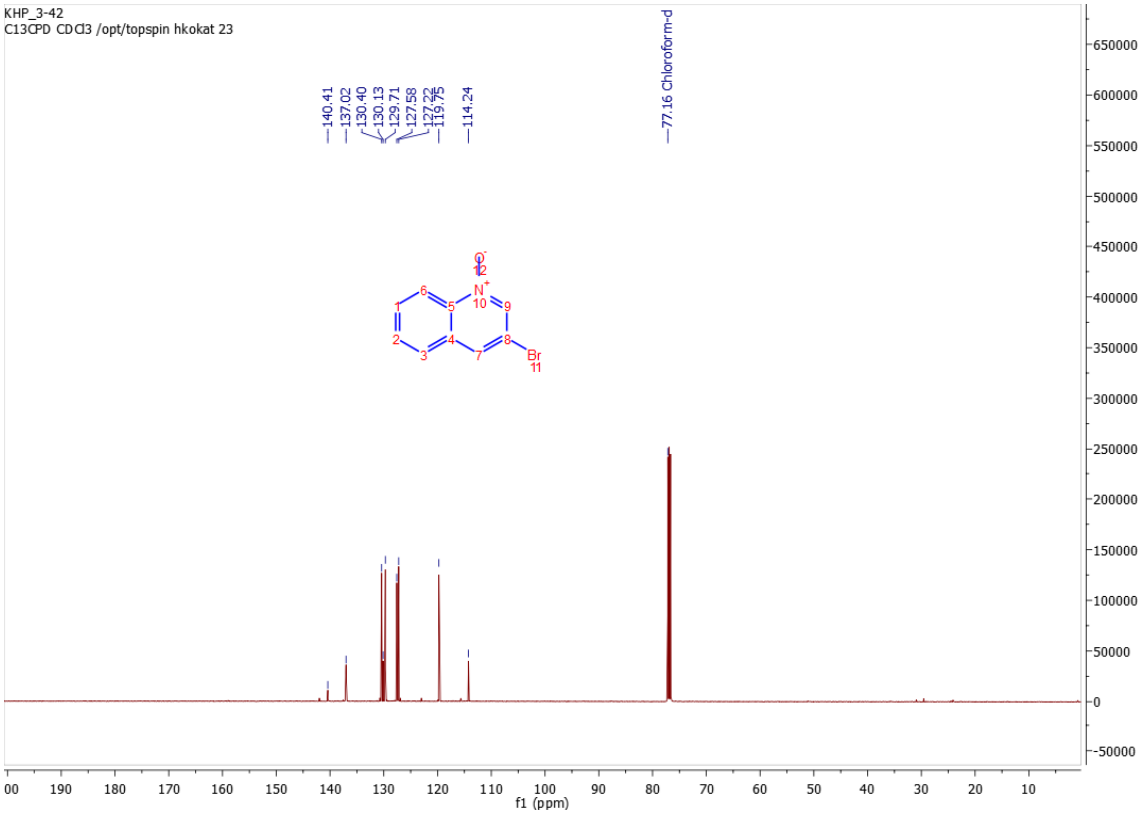




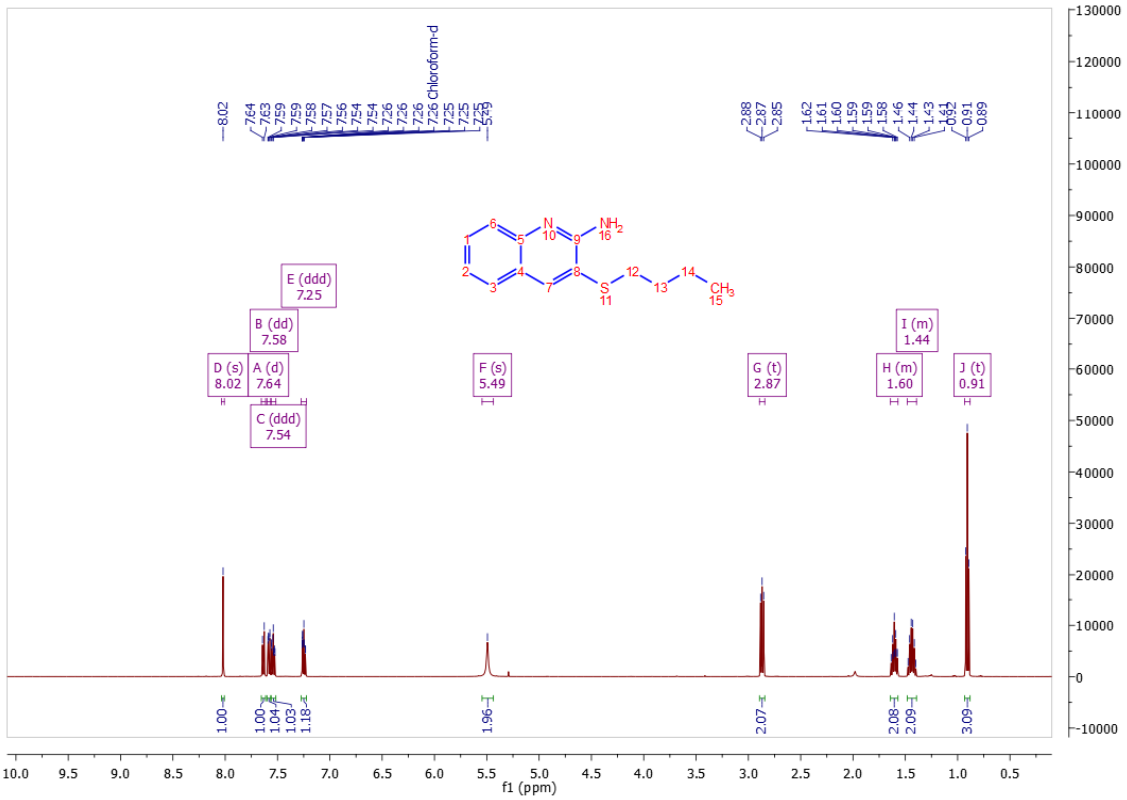
Exact Mass: 216.1495

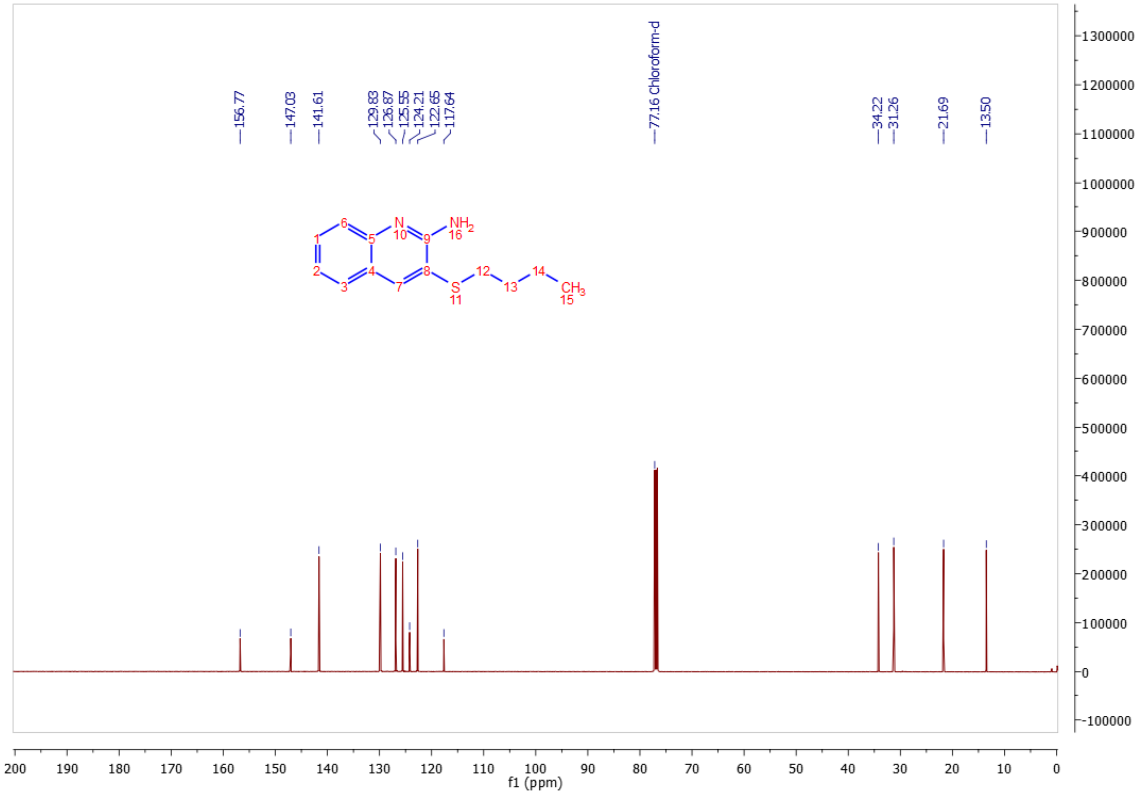
Compound **11:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



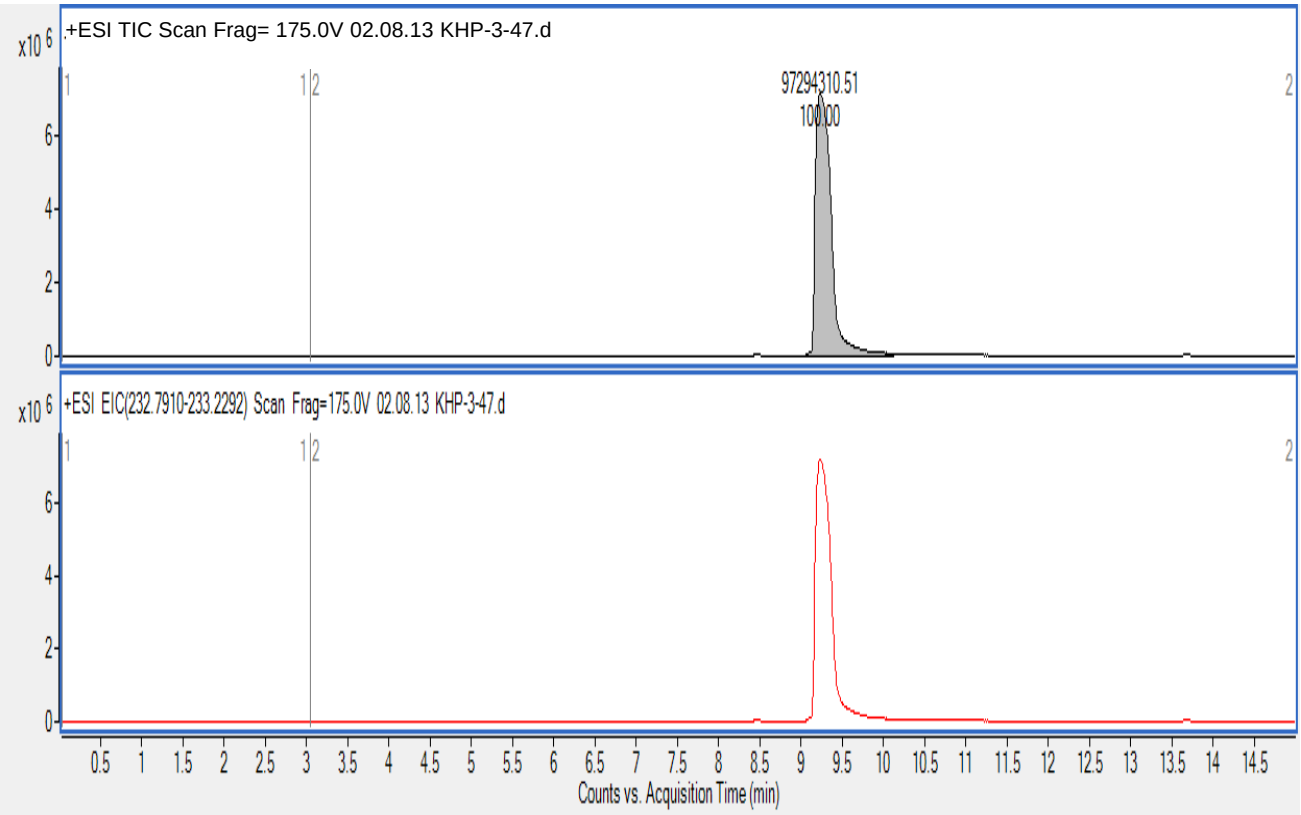


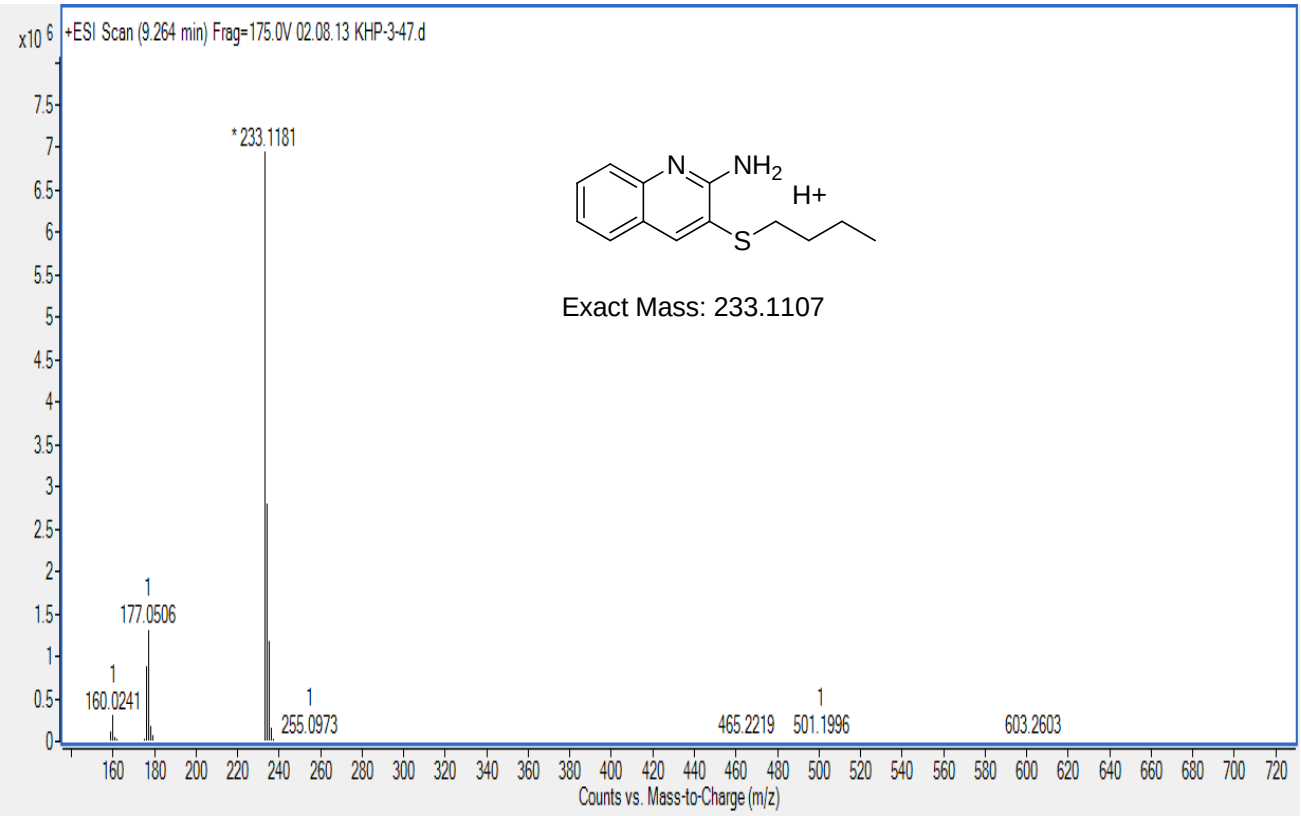
Compound **12:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)





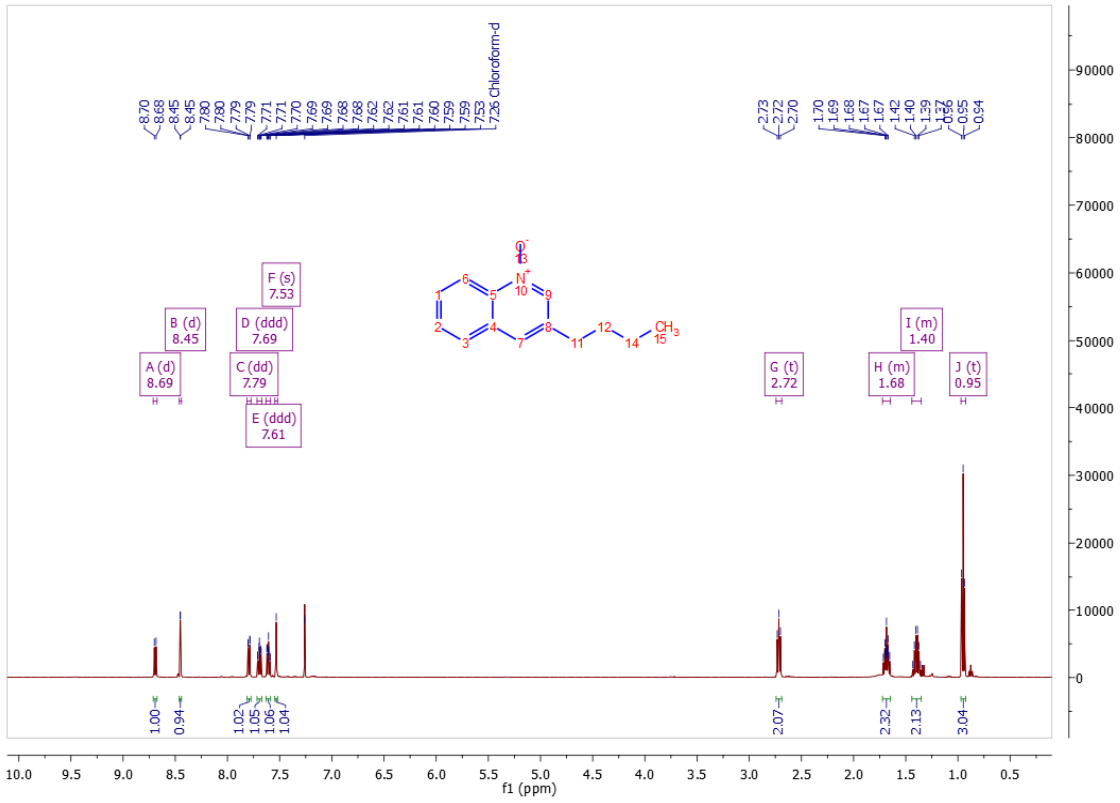
Compound **12:** LC-MS

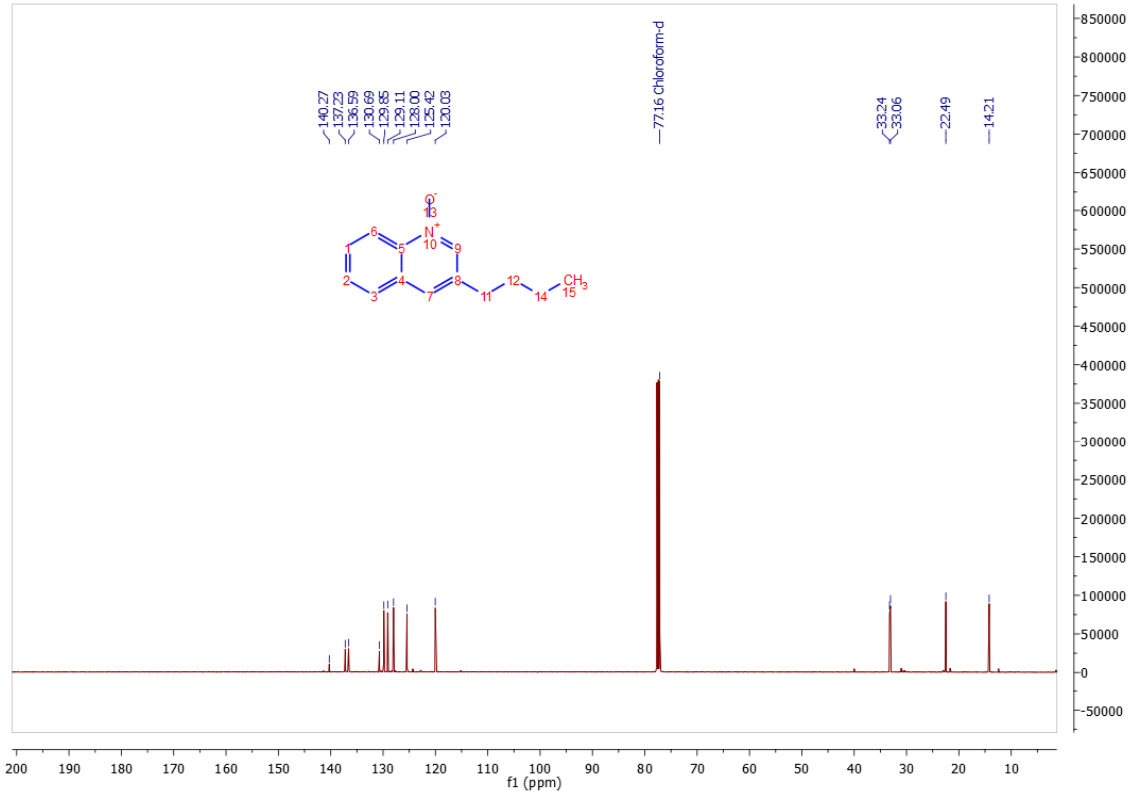




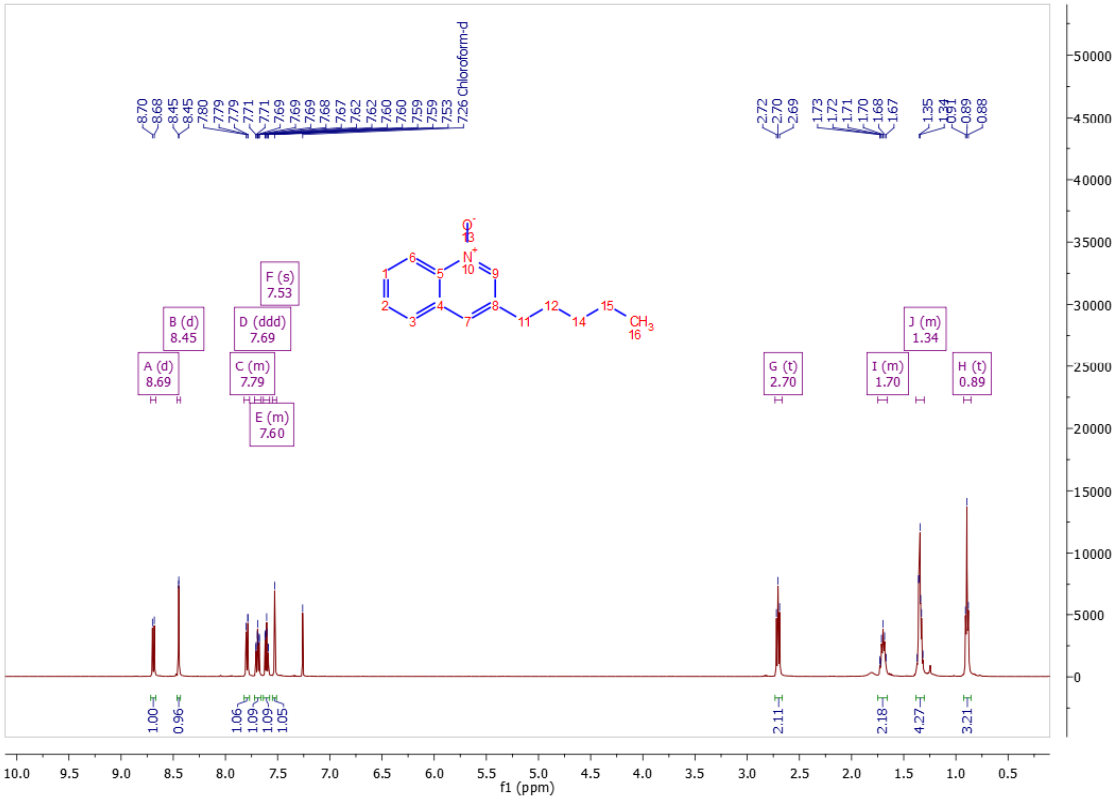
Exact Mass: 233.1107

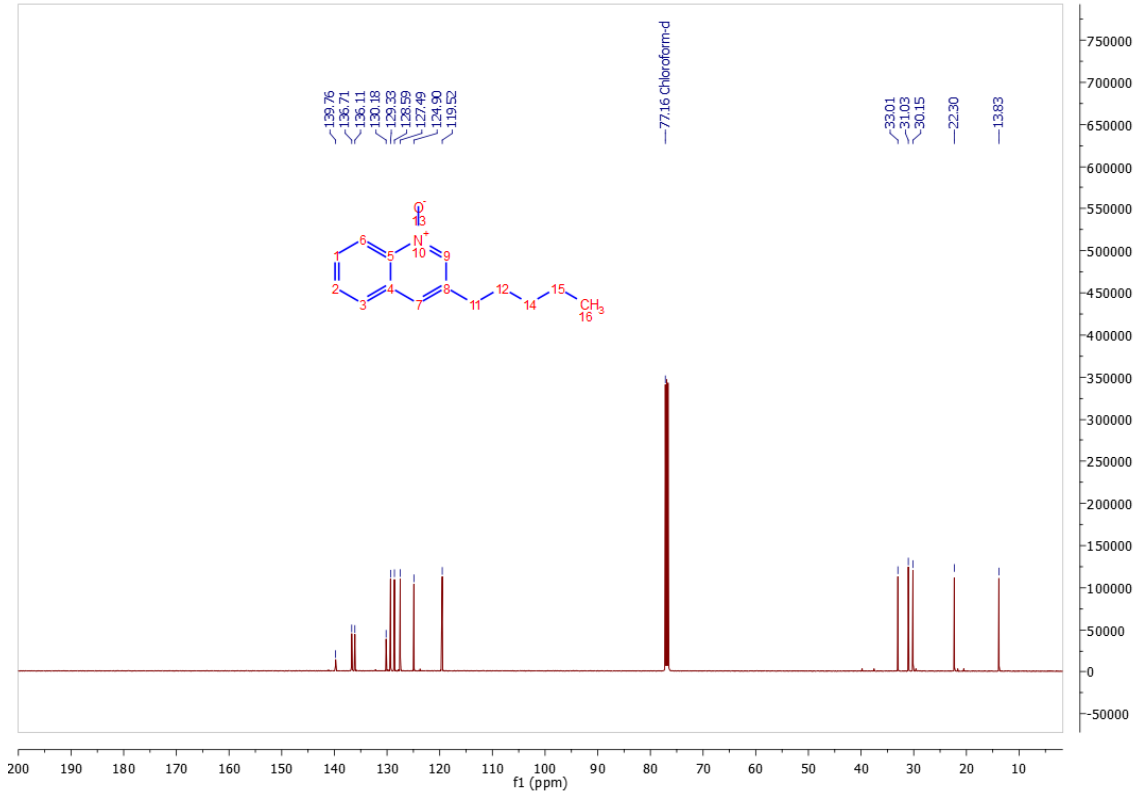
Compound **13a:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



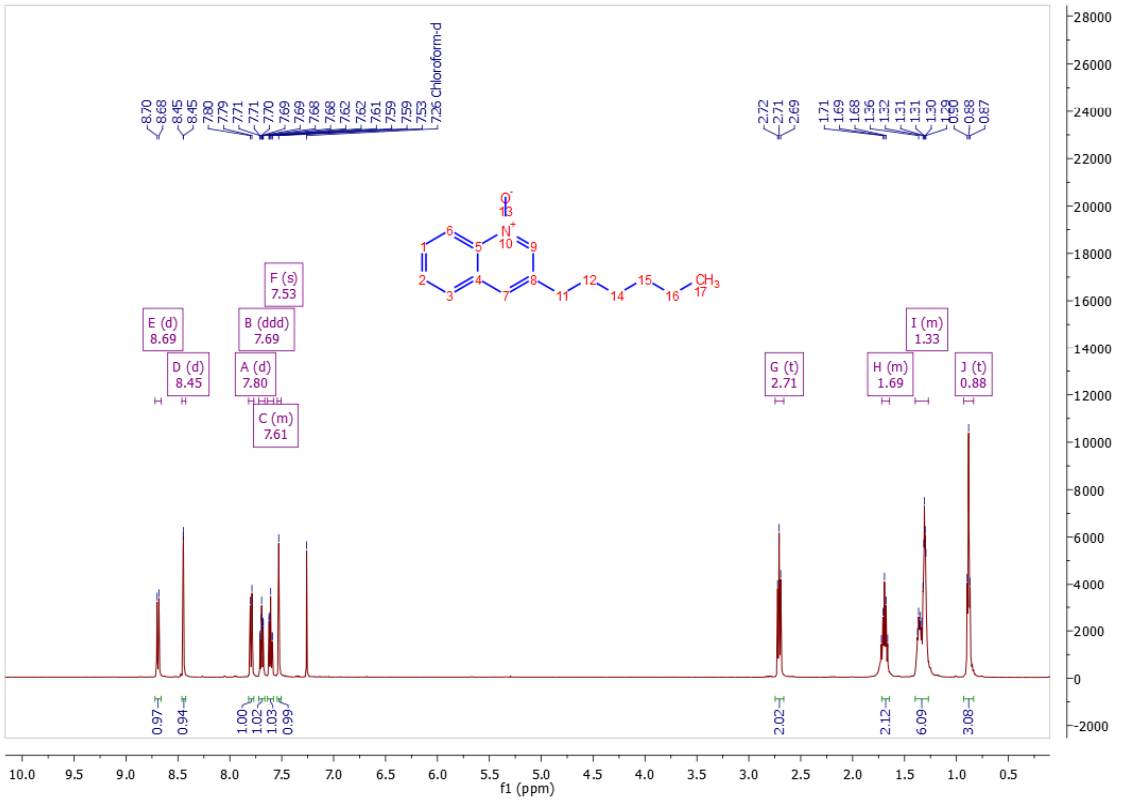


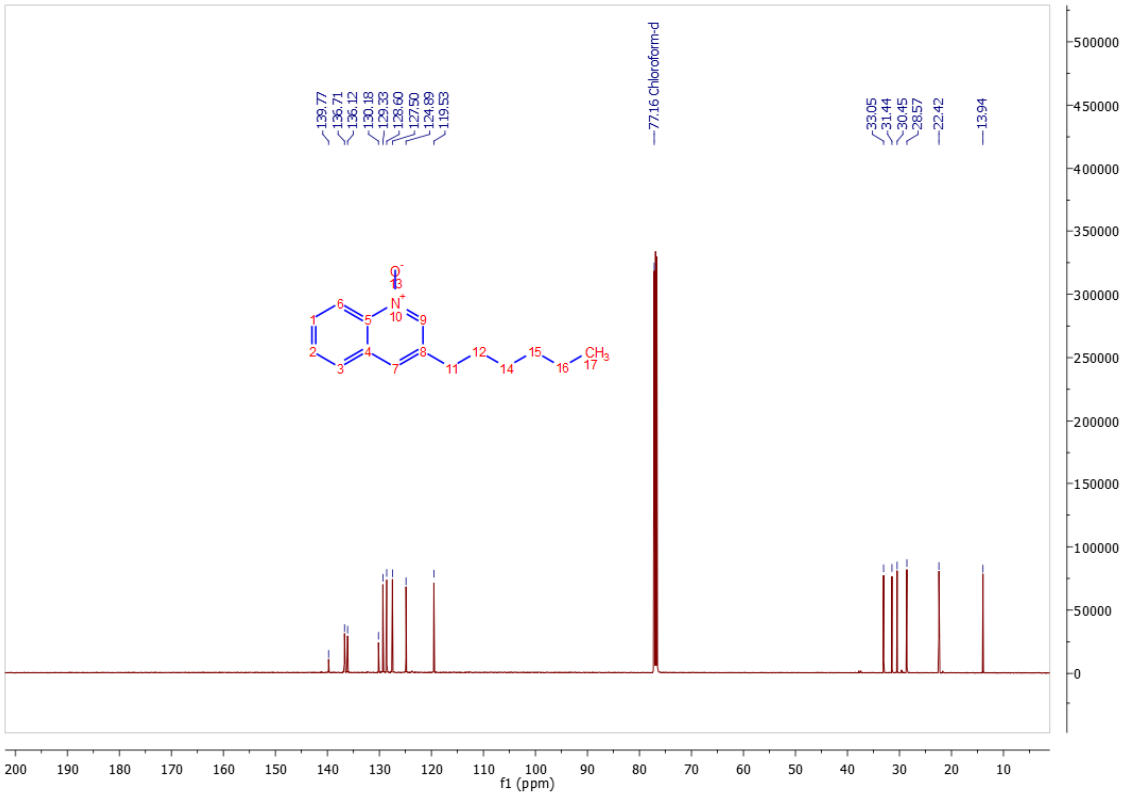
Compound **13b:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



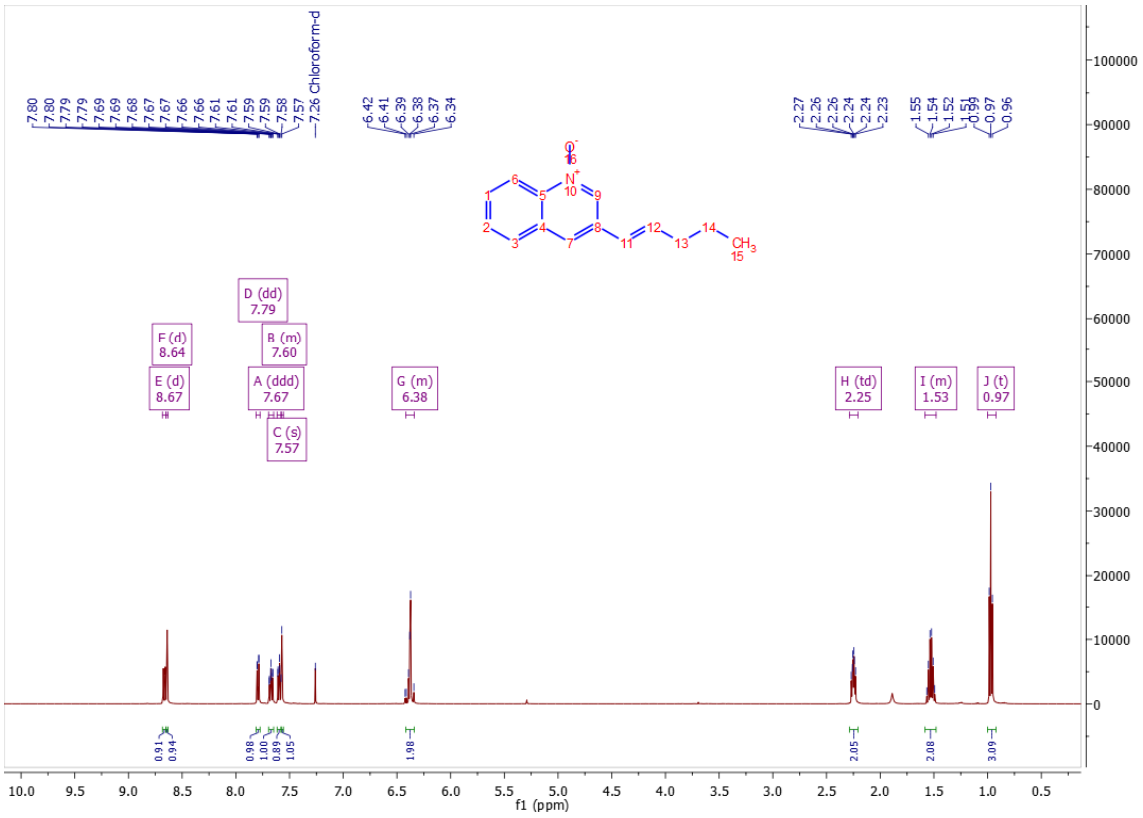


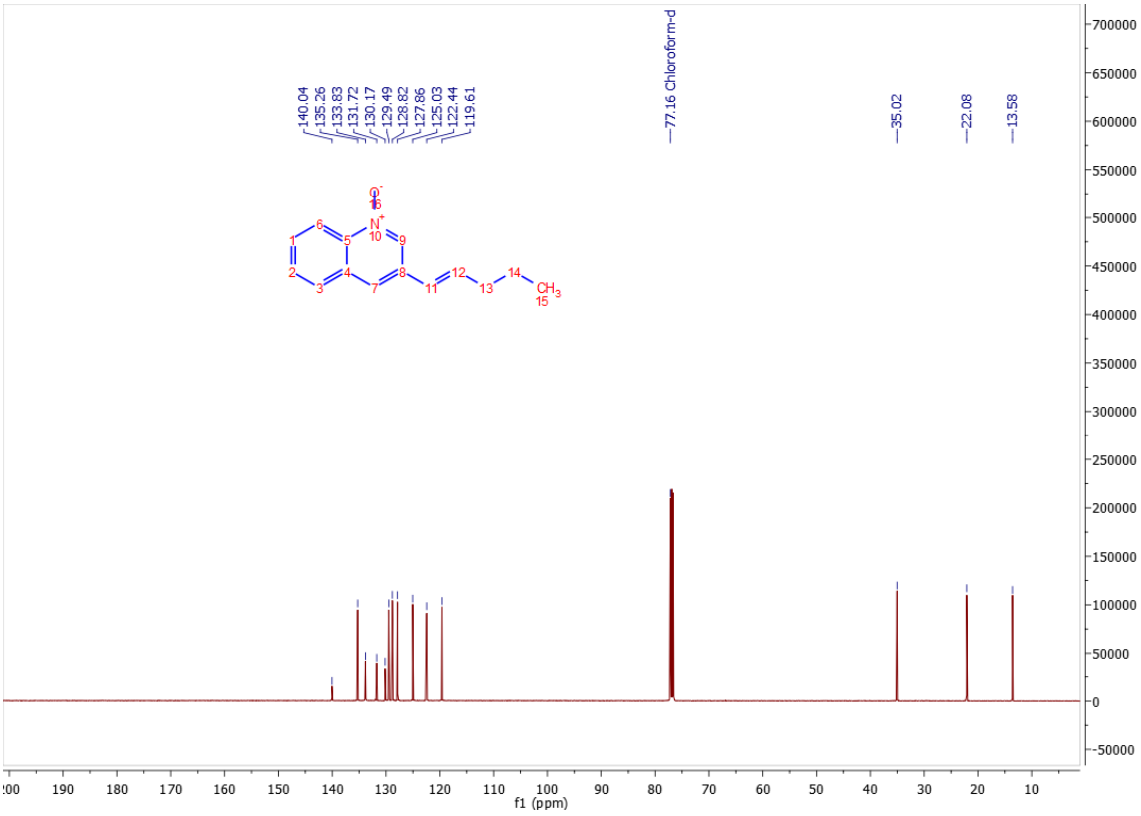
Compound **13c:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



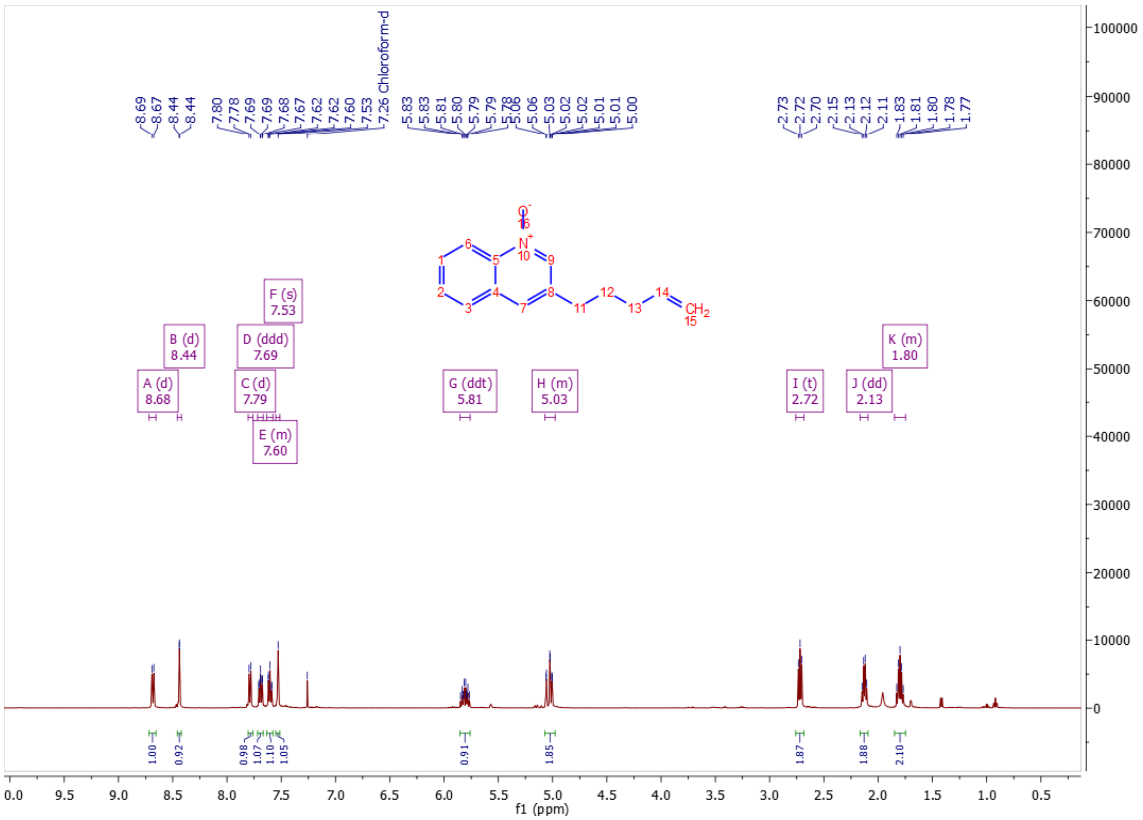


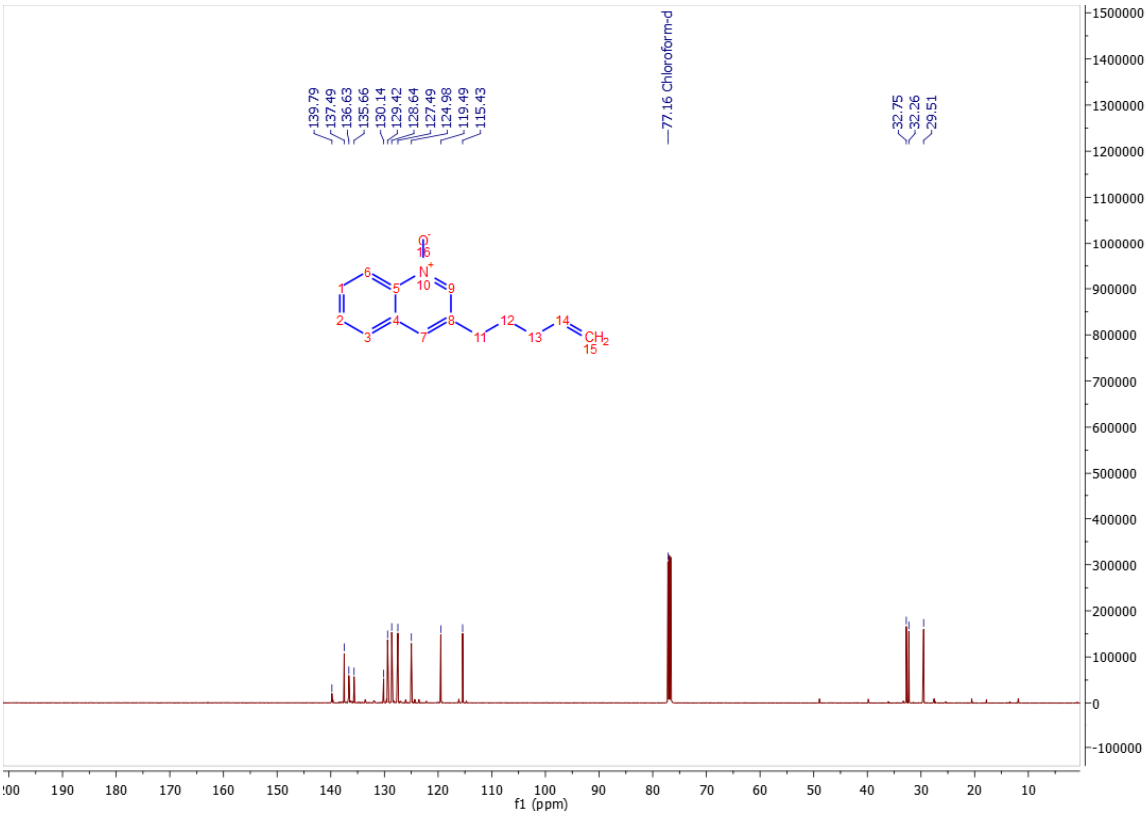
Compound **13d:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



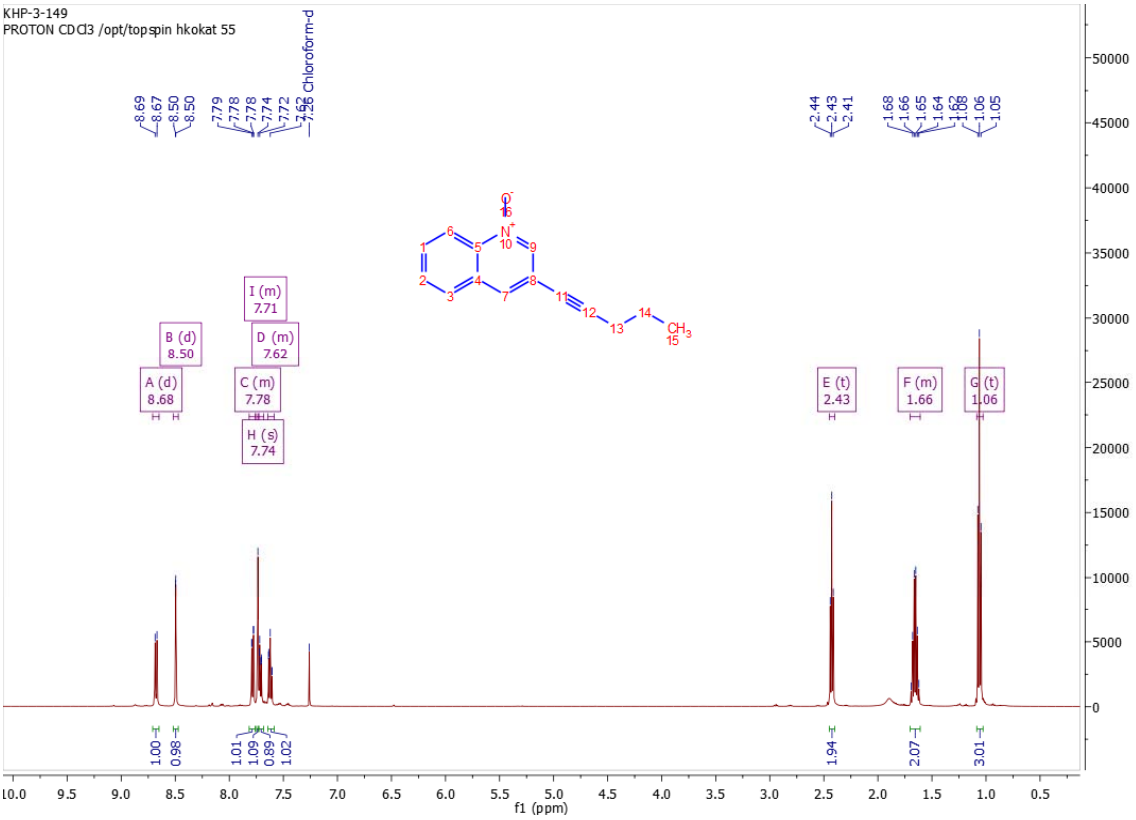


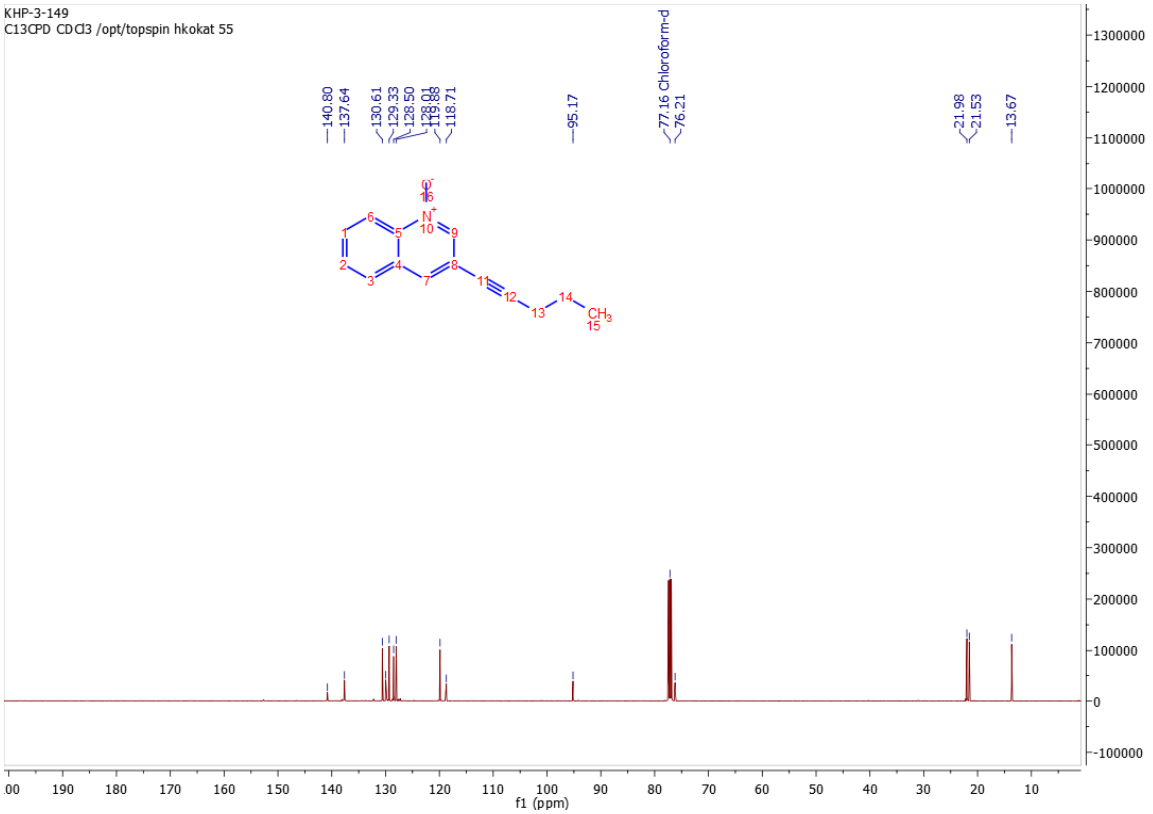
Compound **13e:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



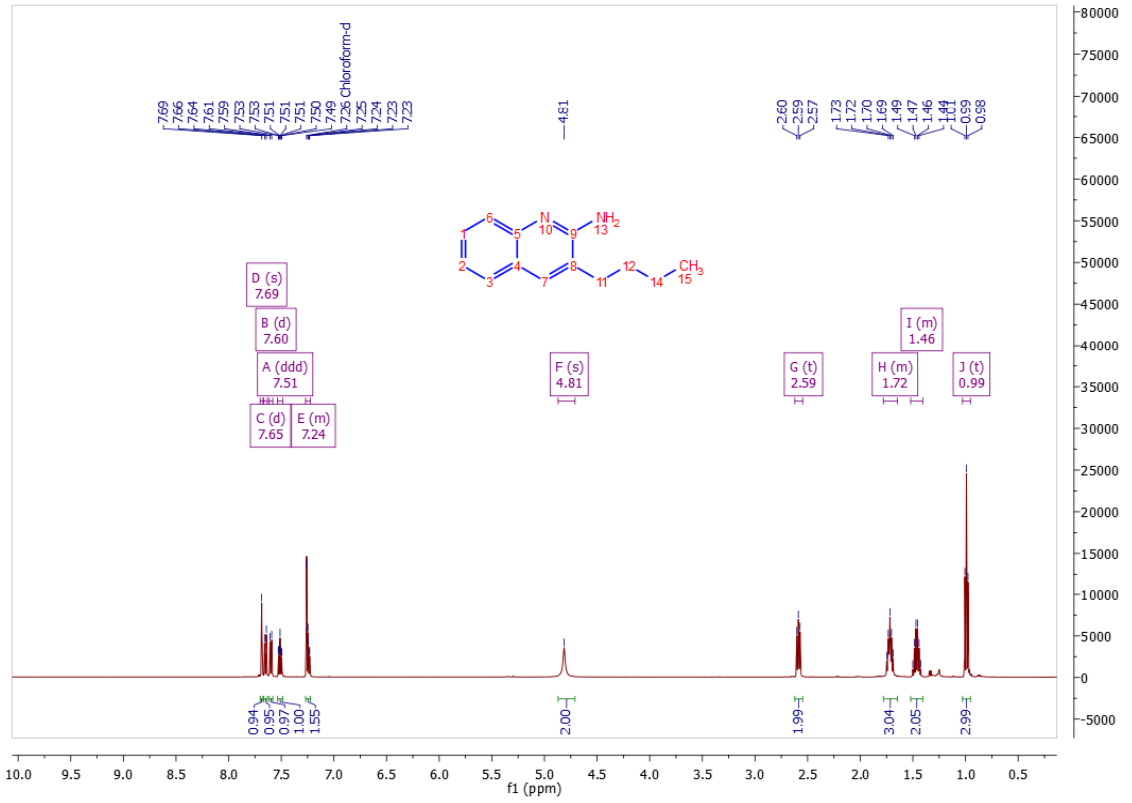


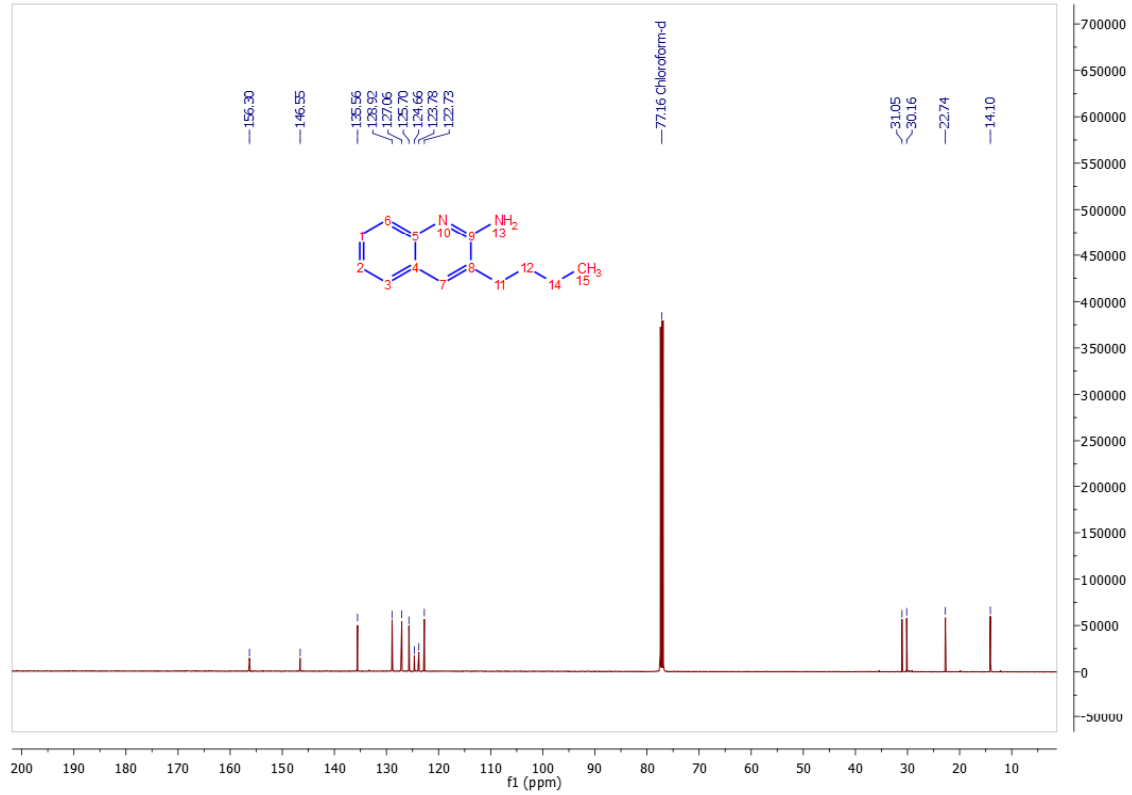
Compound **13f:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



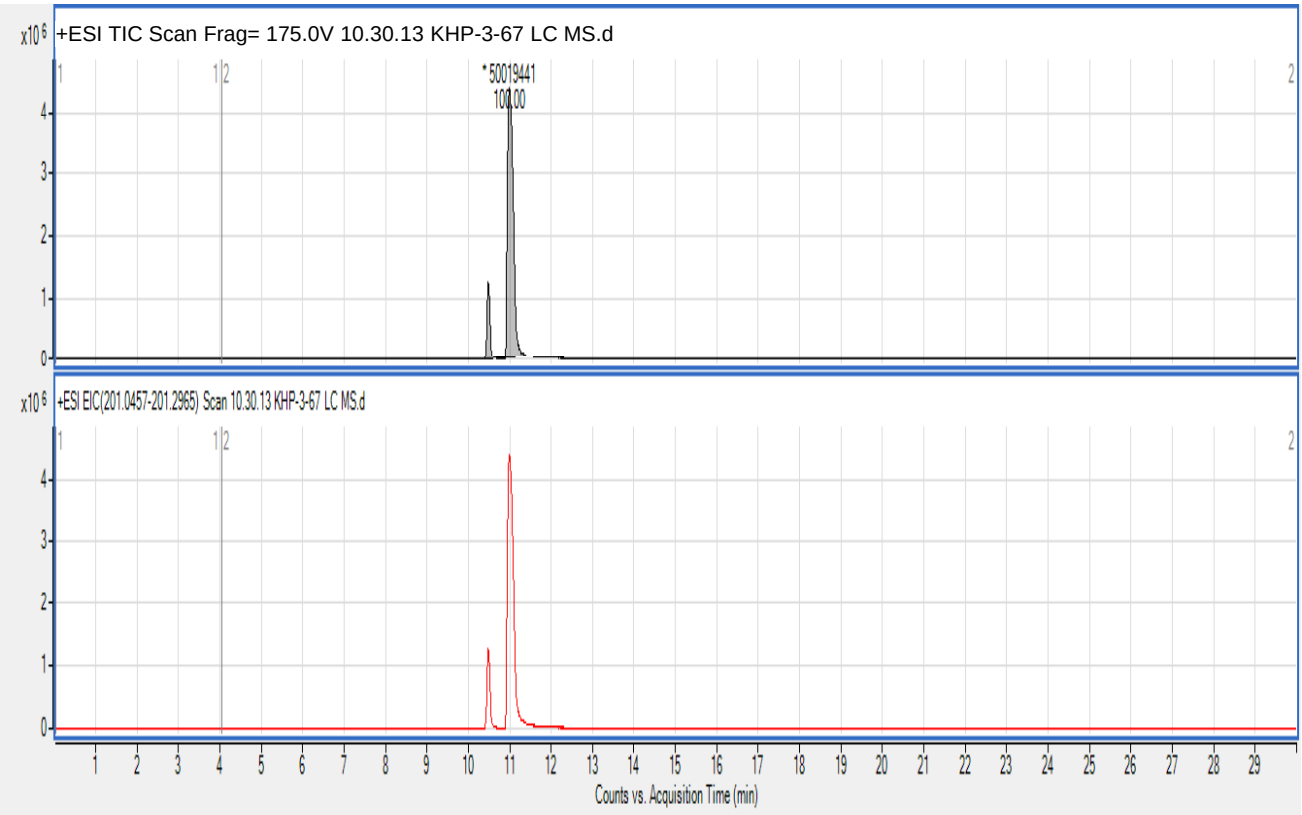


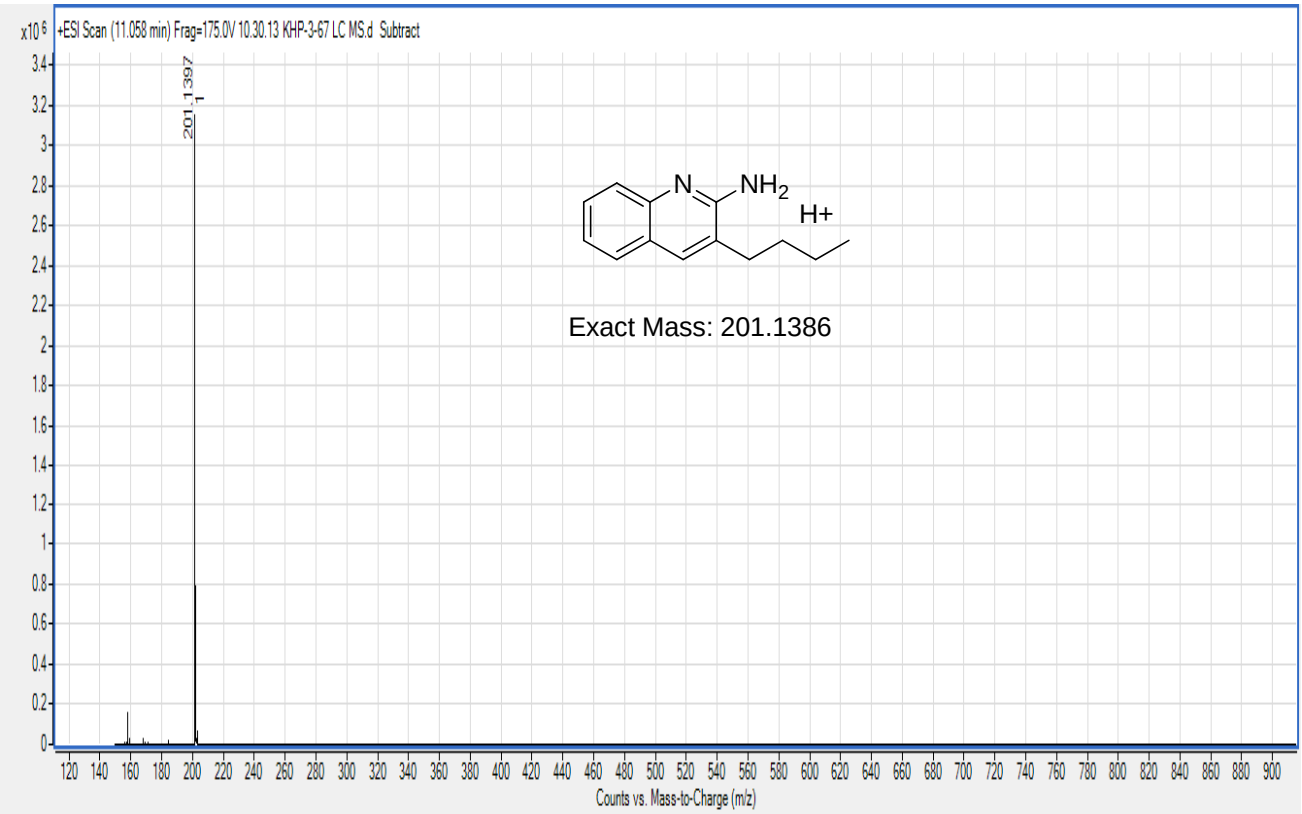
Compound **14a:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)





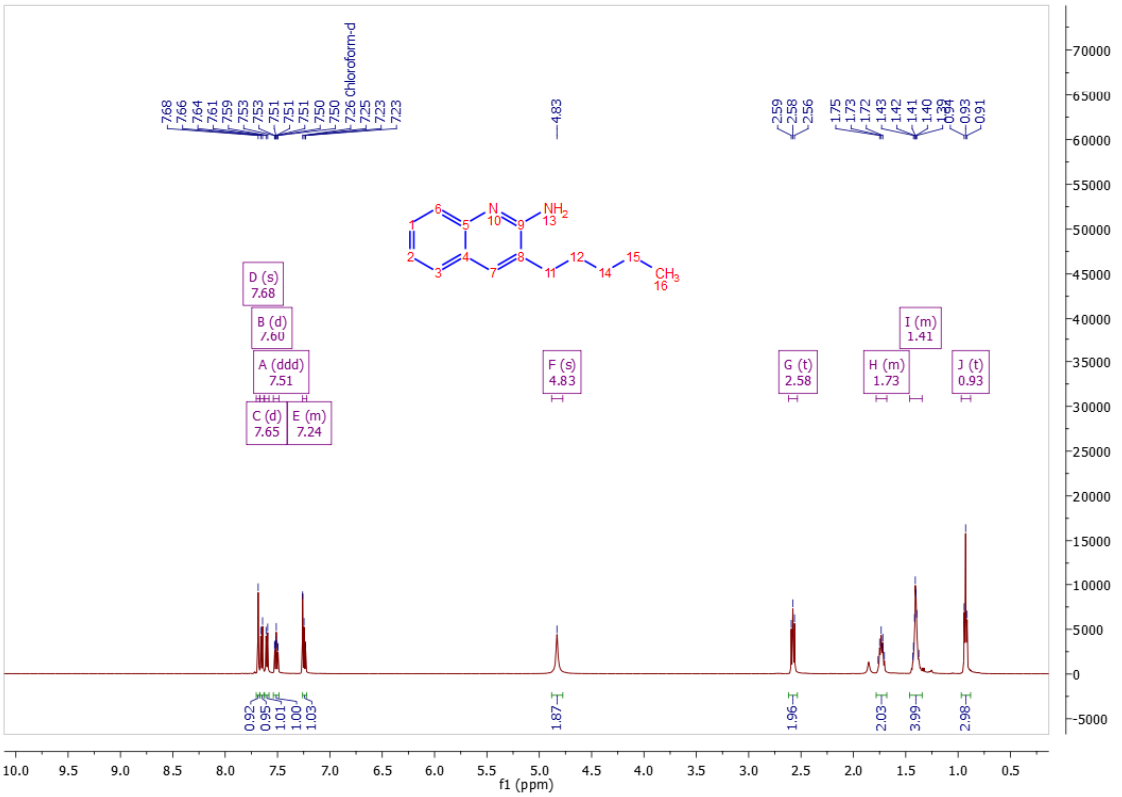
Compound **14a:** LC-MS

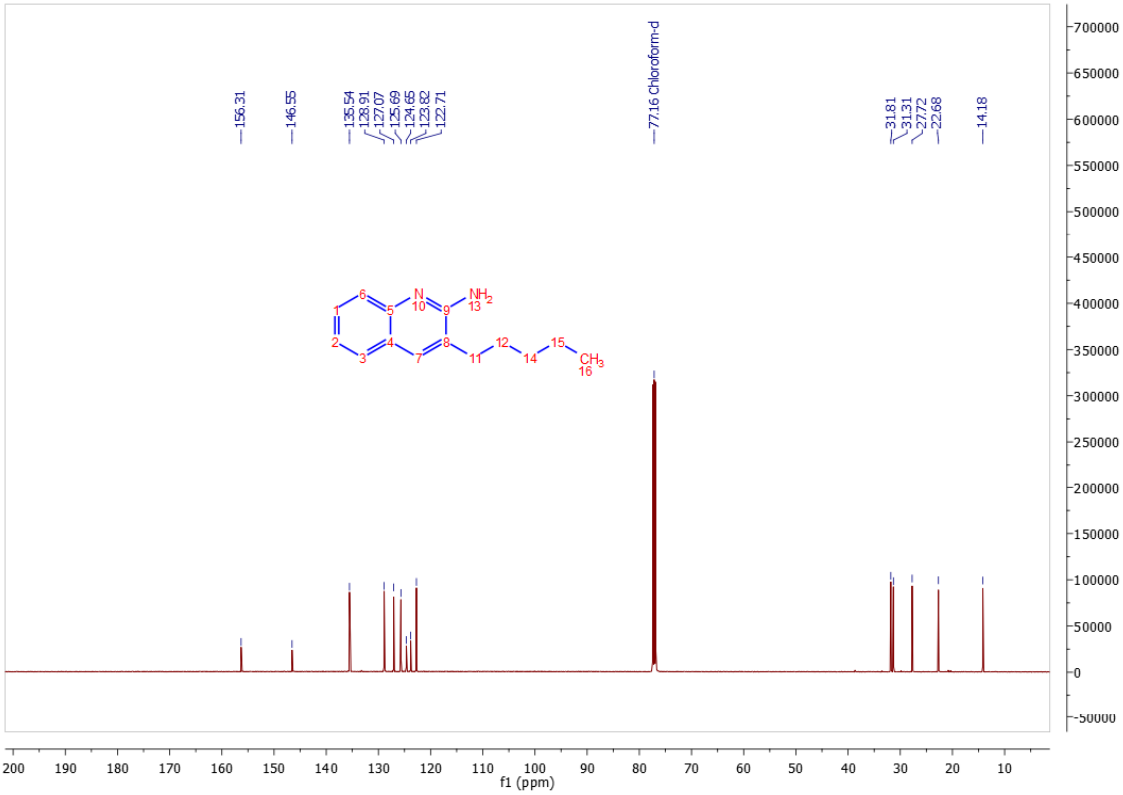




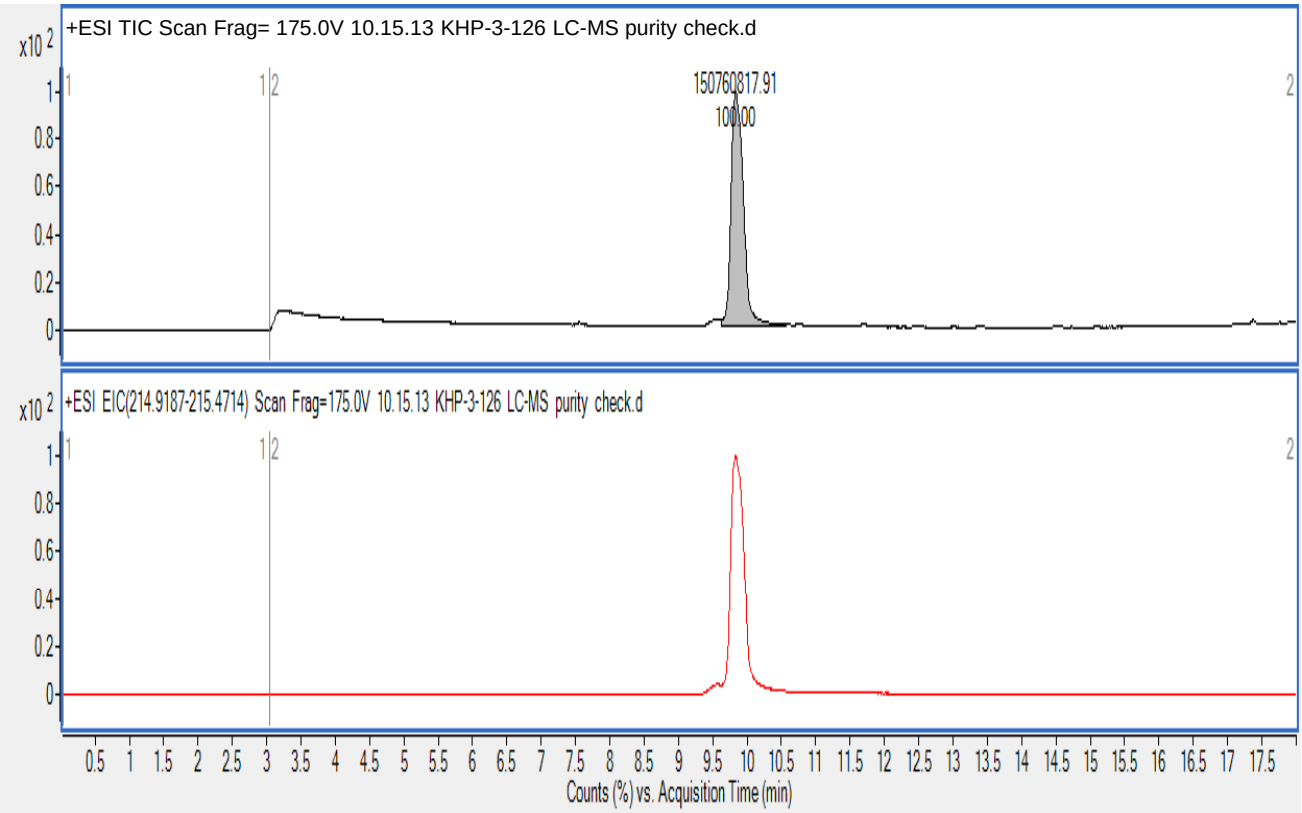
Exact Mass: 201.1386

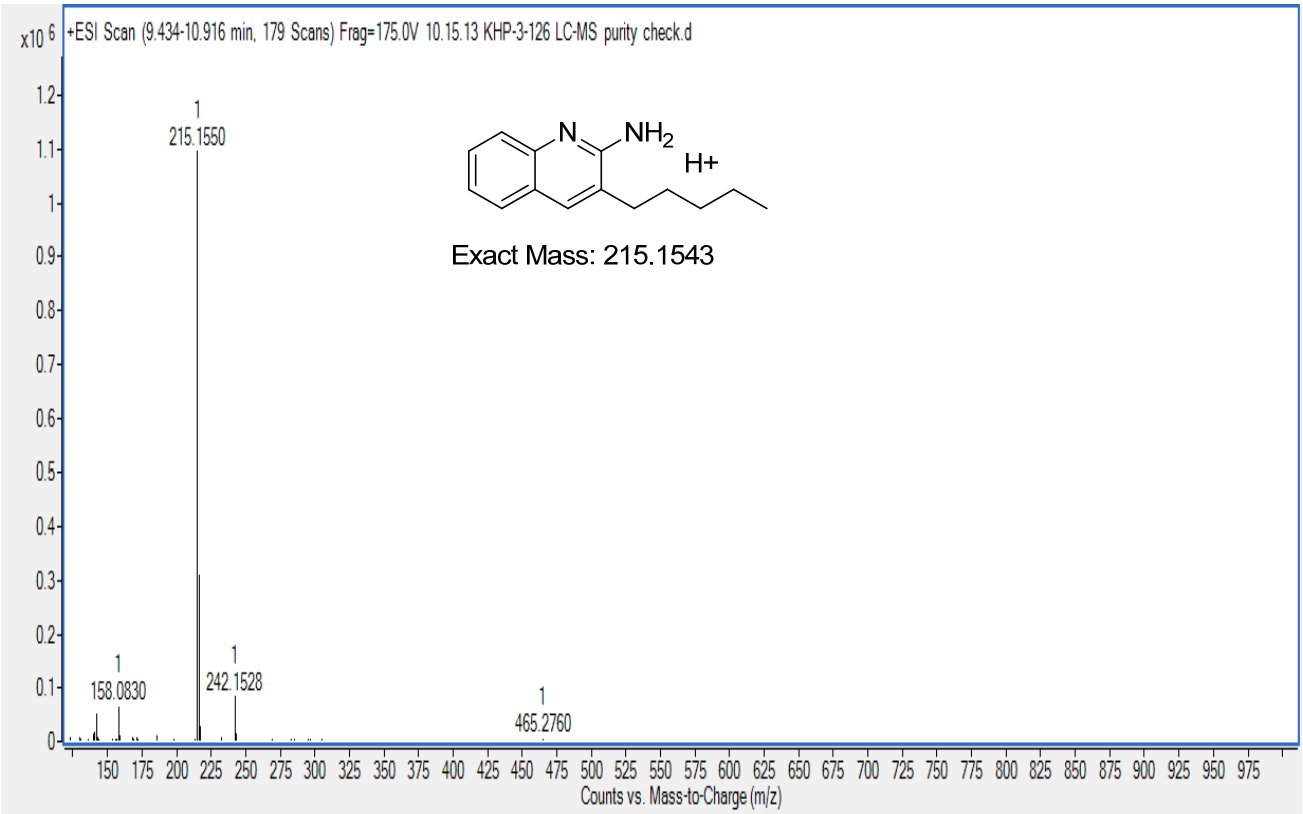
Compound **14b:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



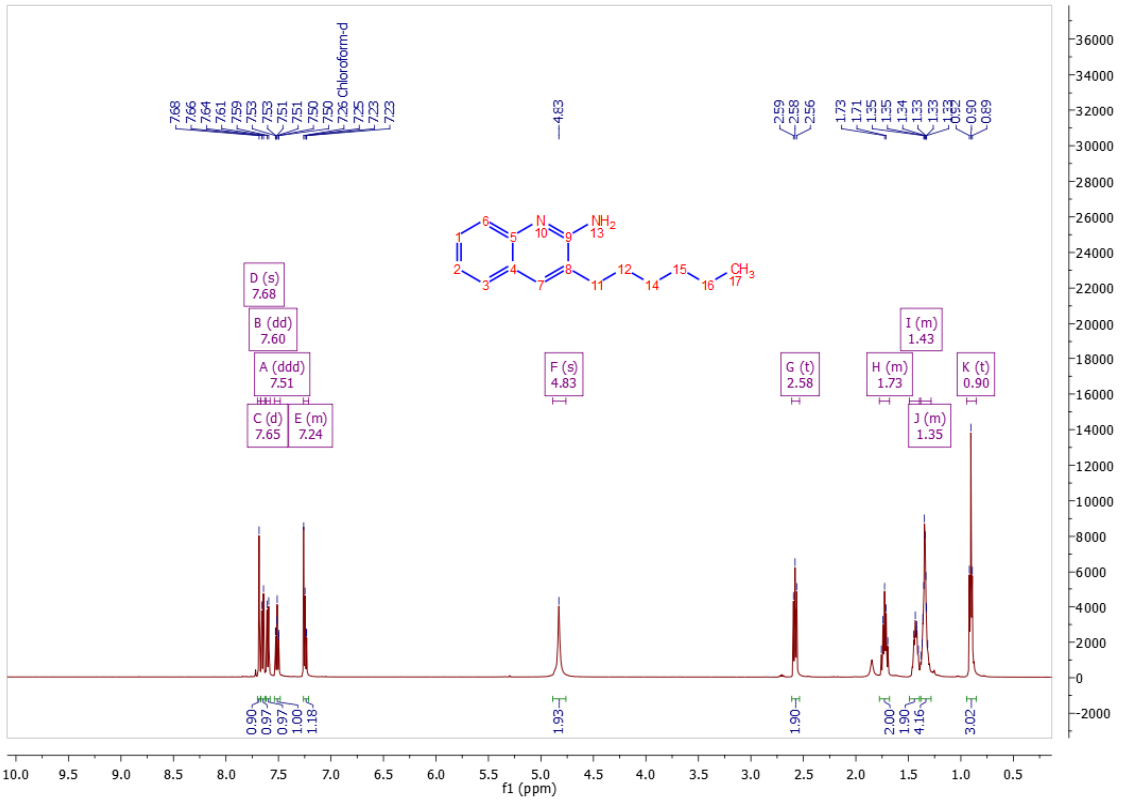


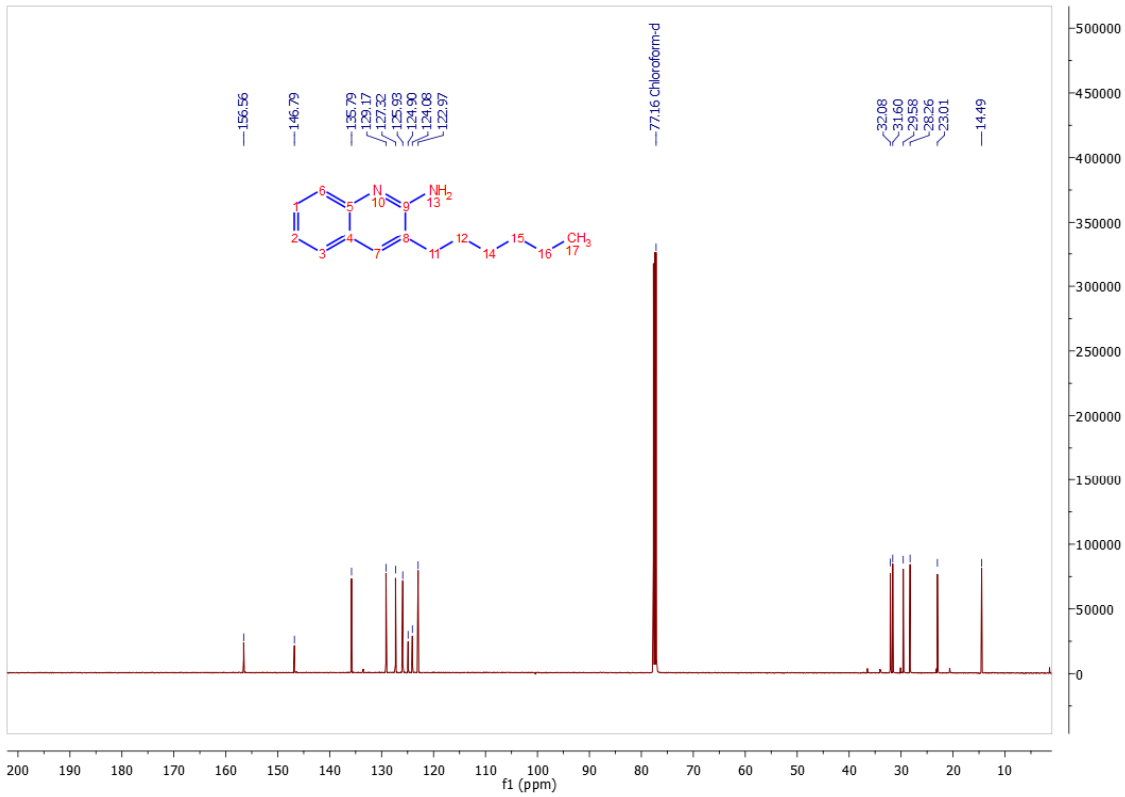
Compound **14b:** LC-MS



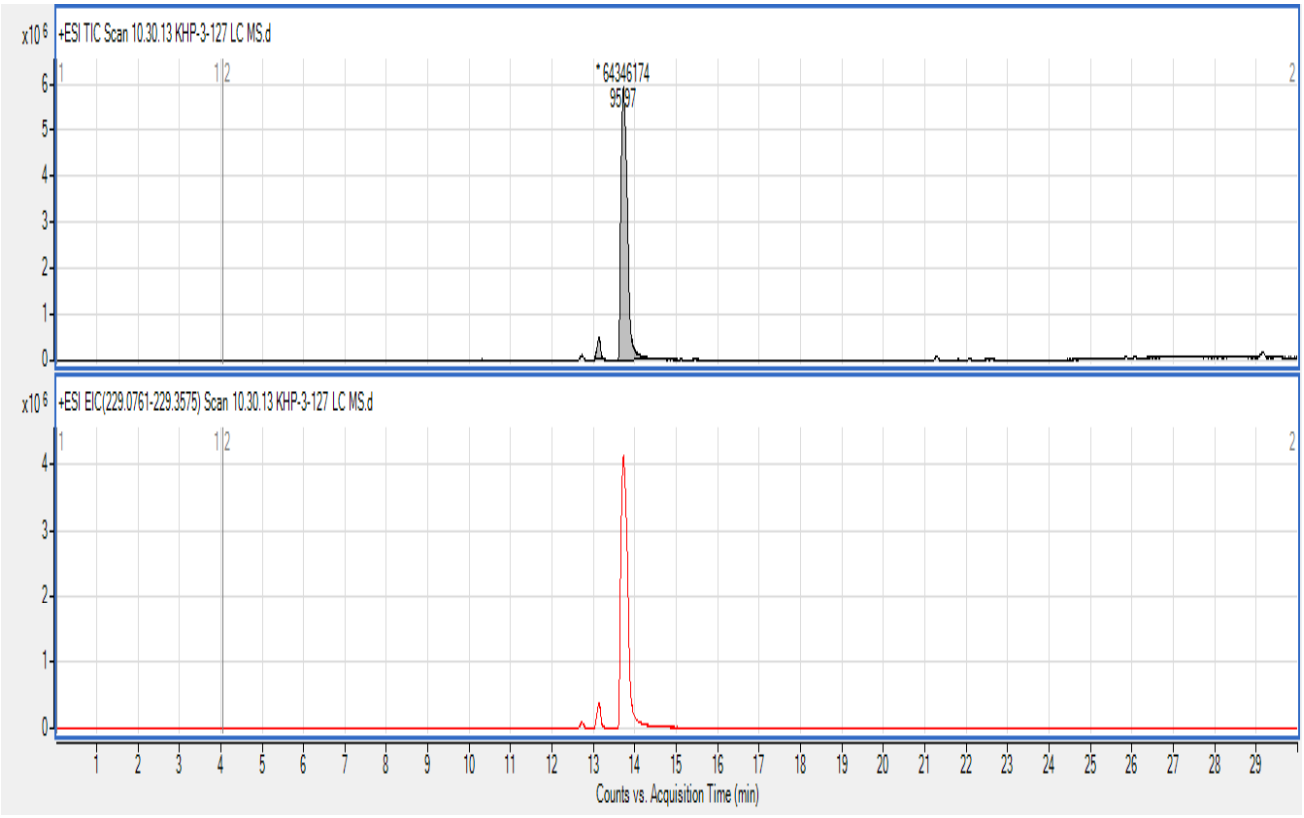


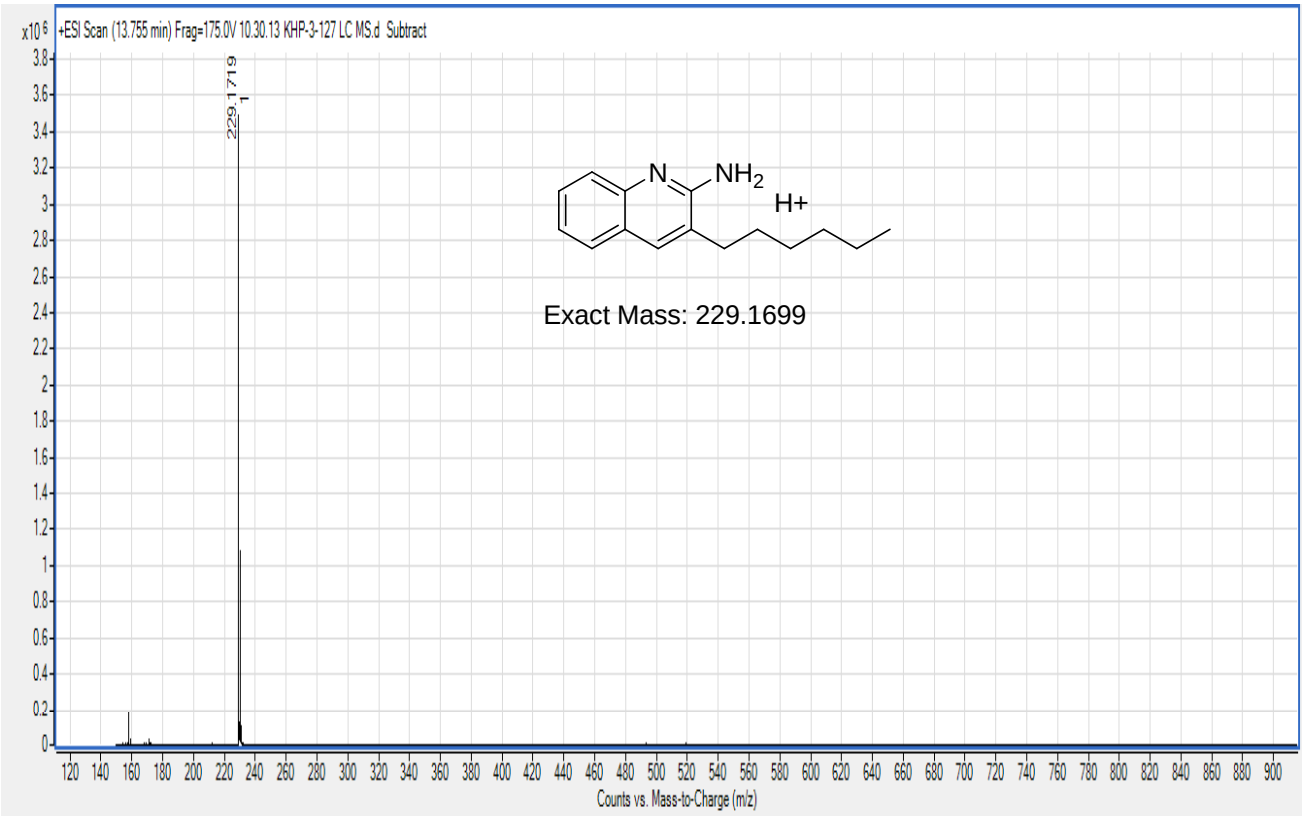
Compound **14c:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



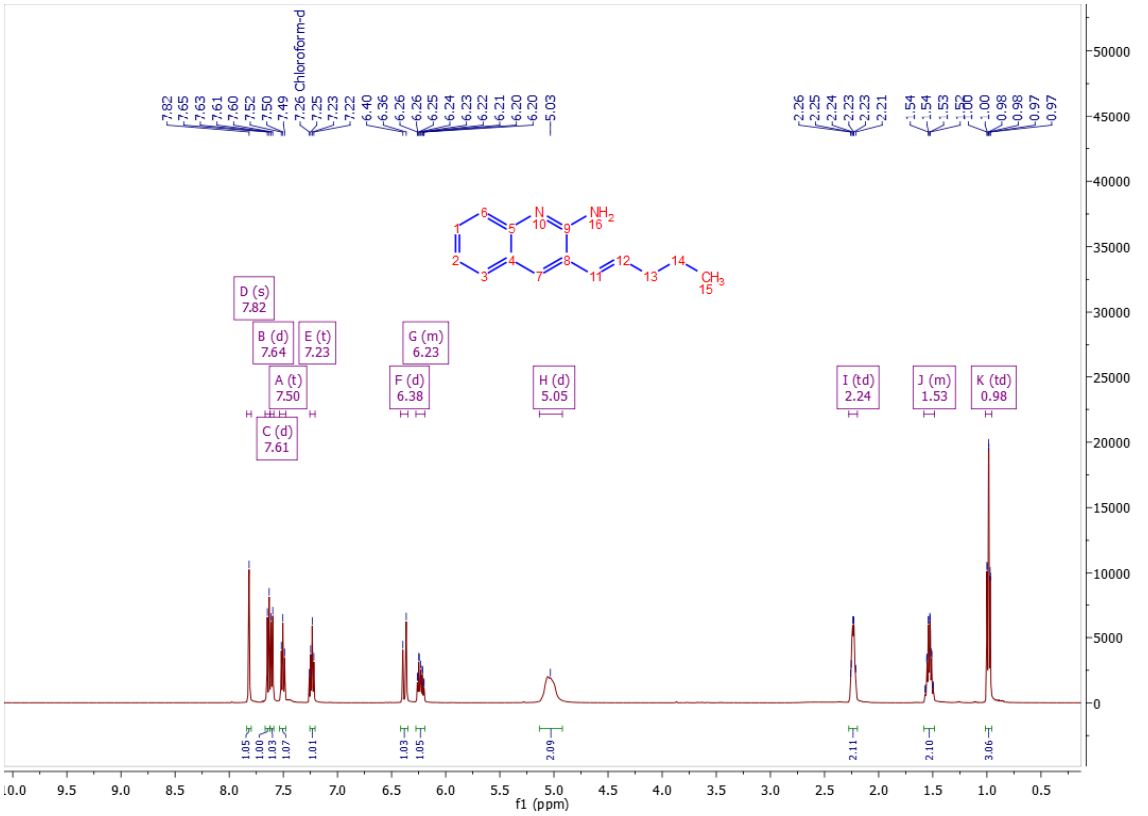


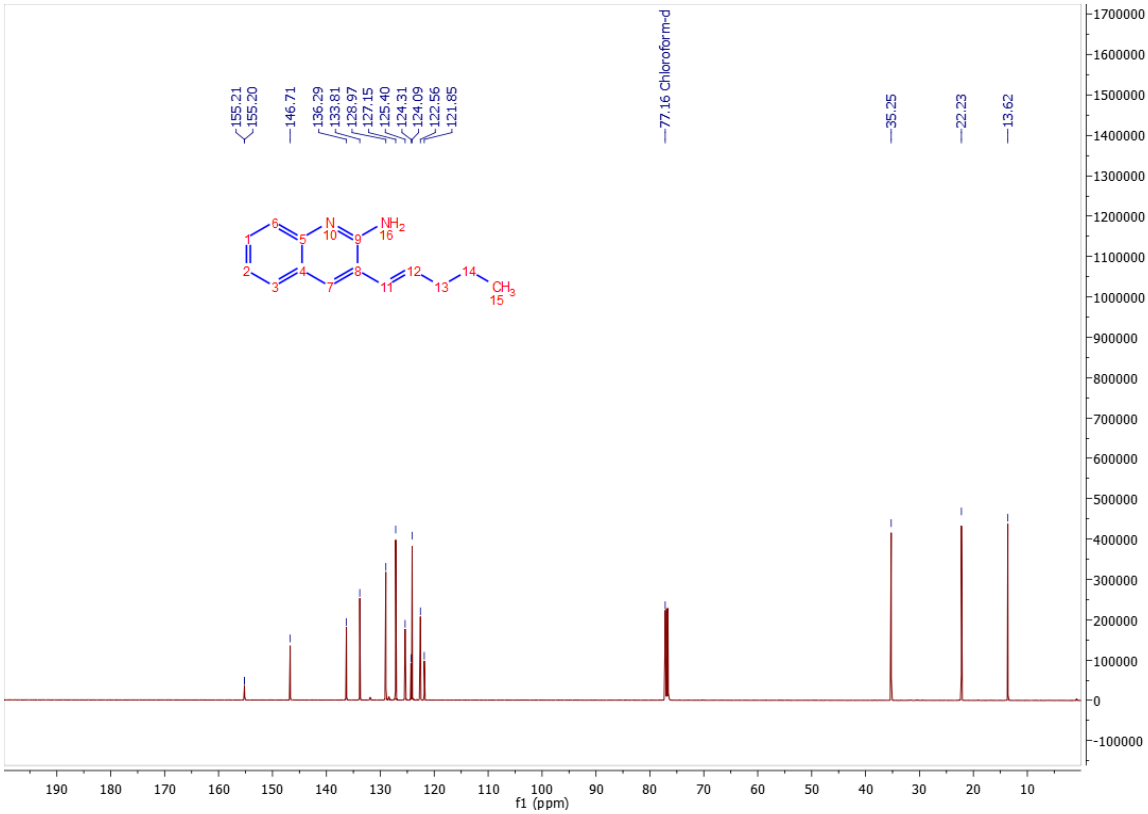
Compound **14c:** LC-MS



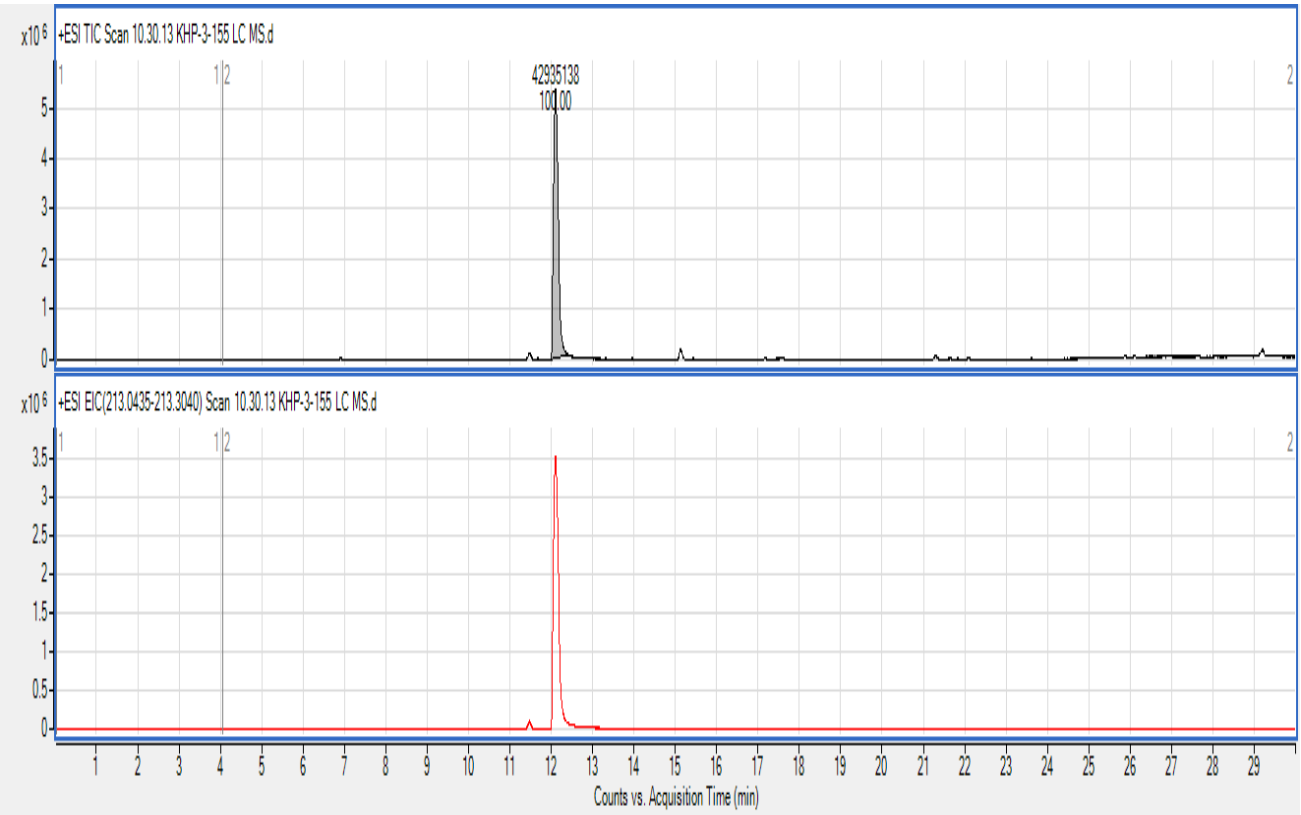


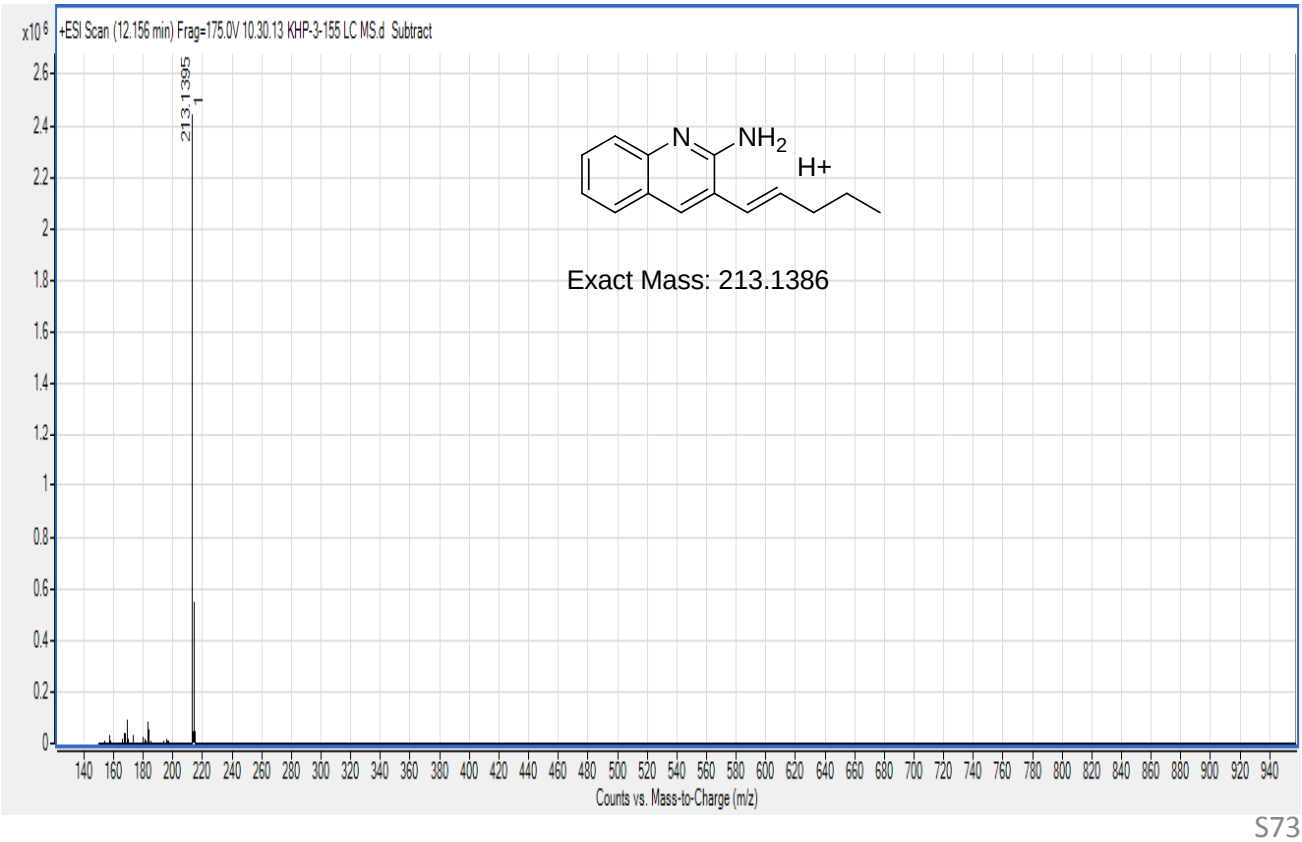
Compound **14d:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



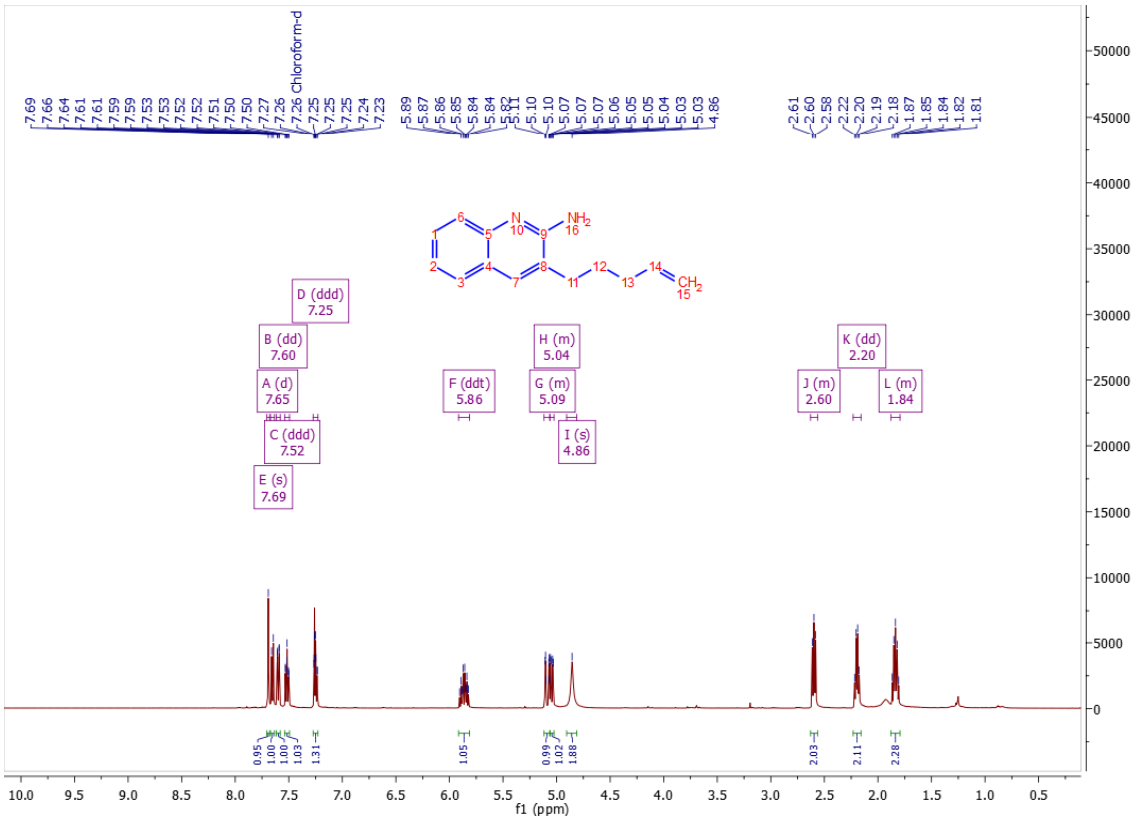


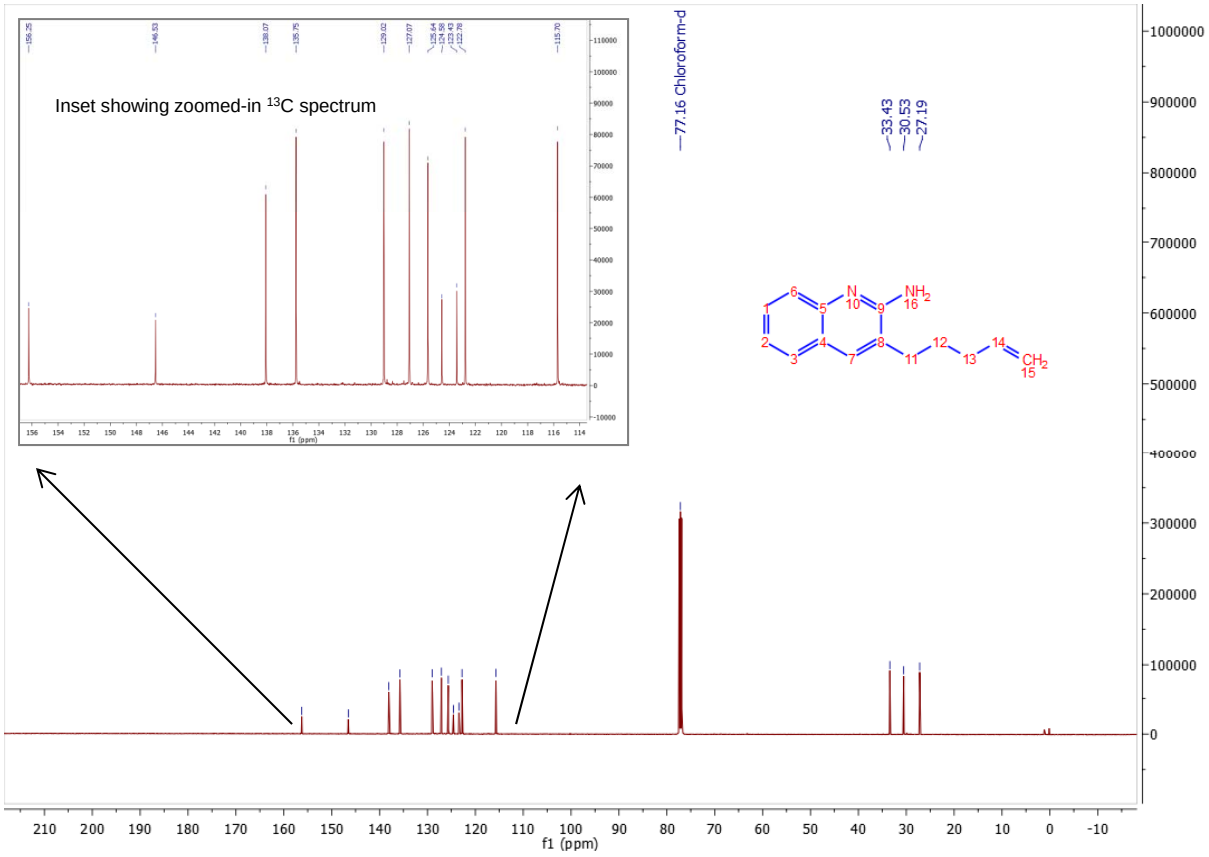
Compound **14d:** LC-MS



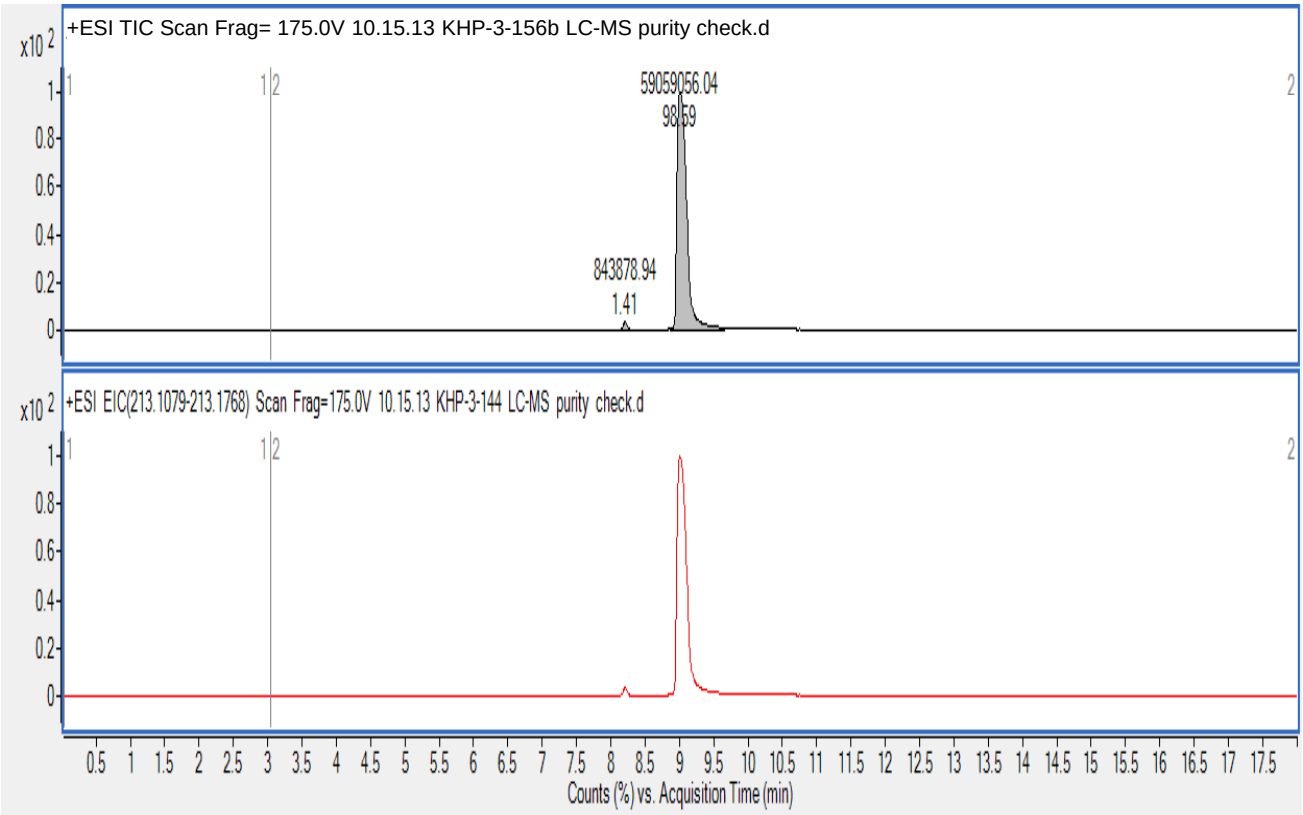


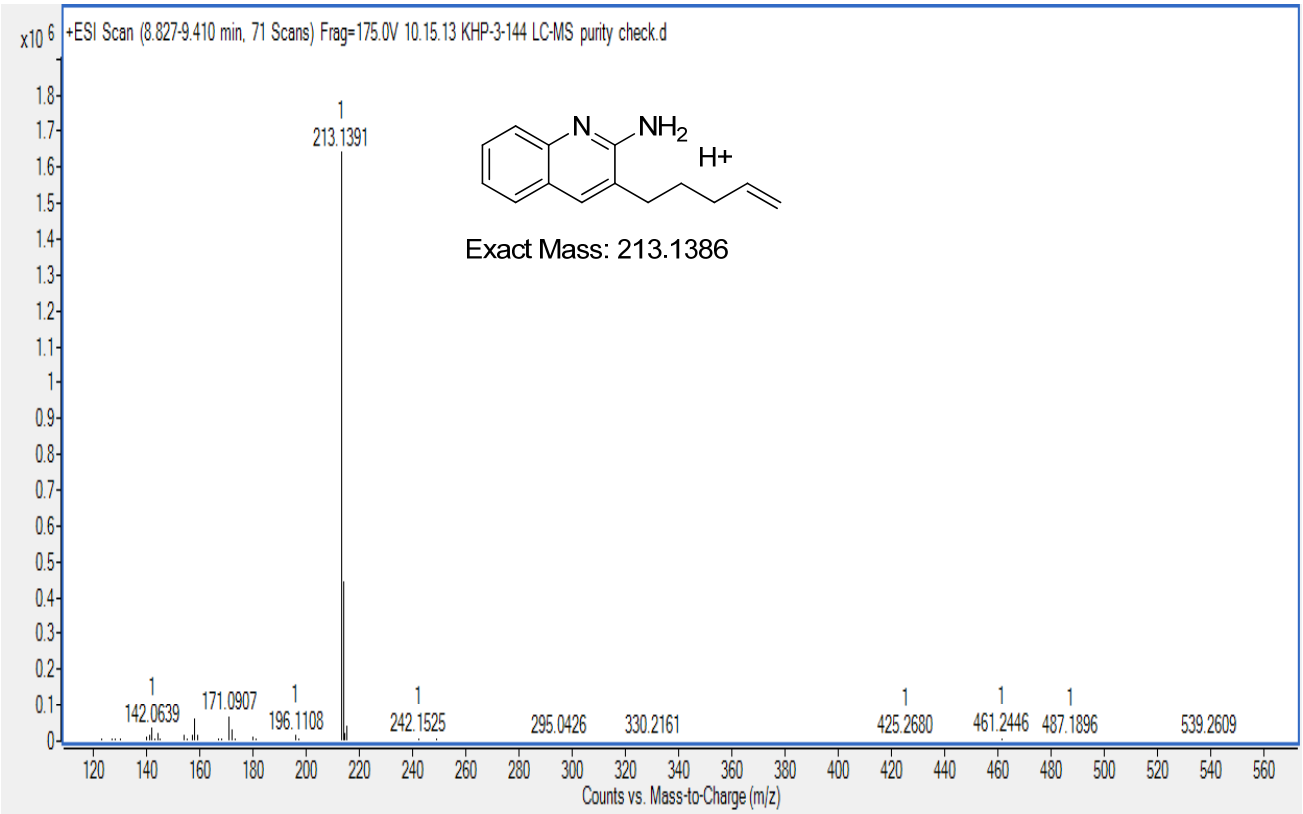
Compound **14e:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



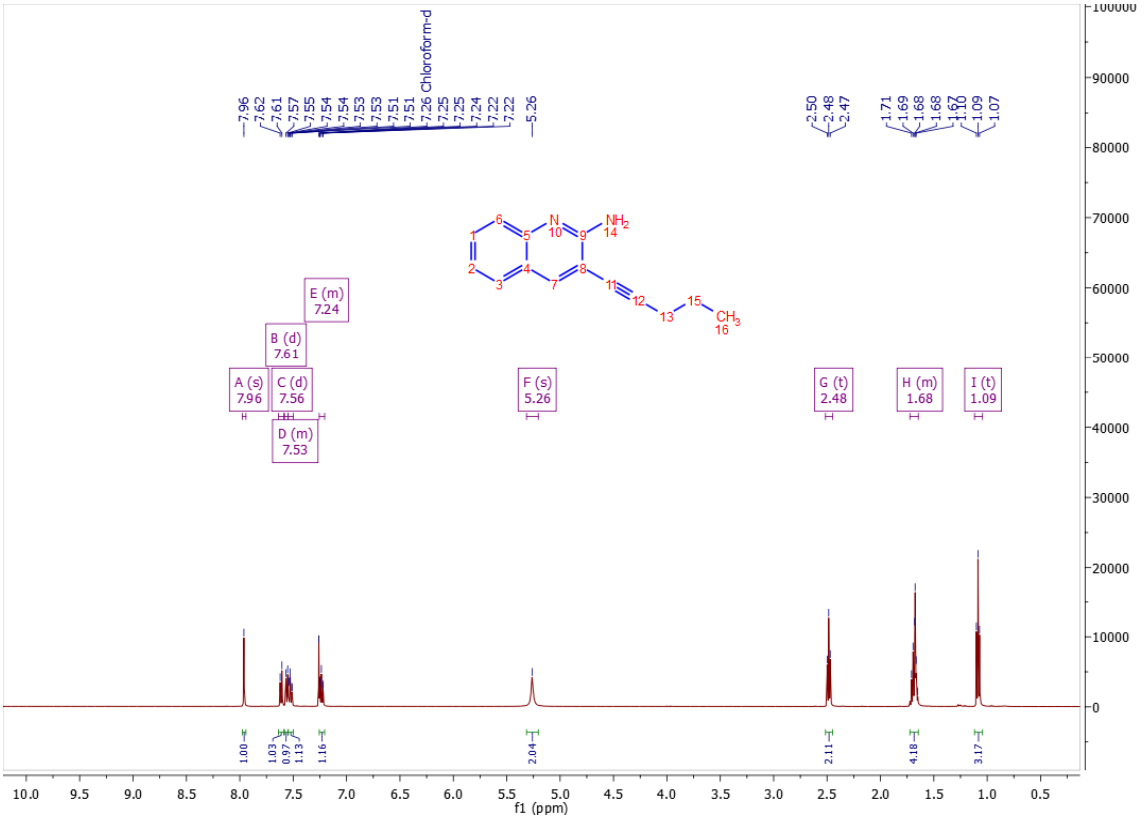


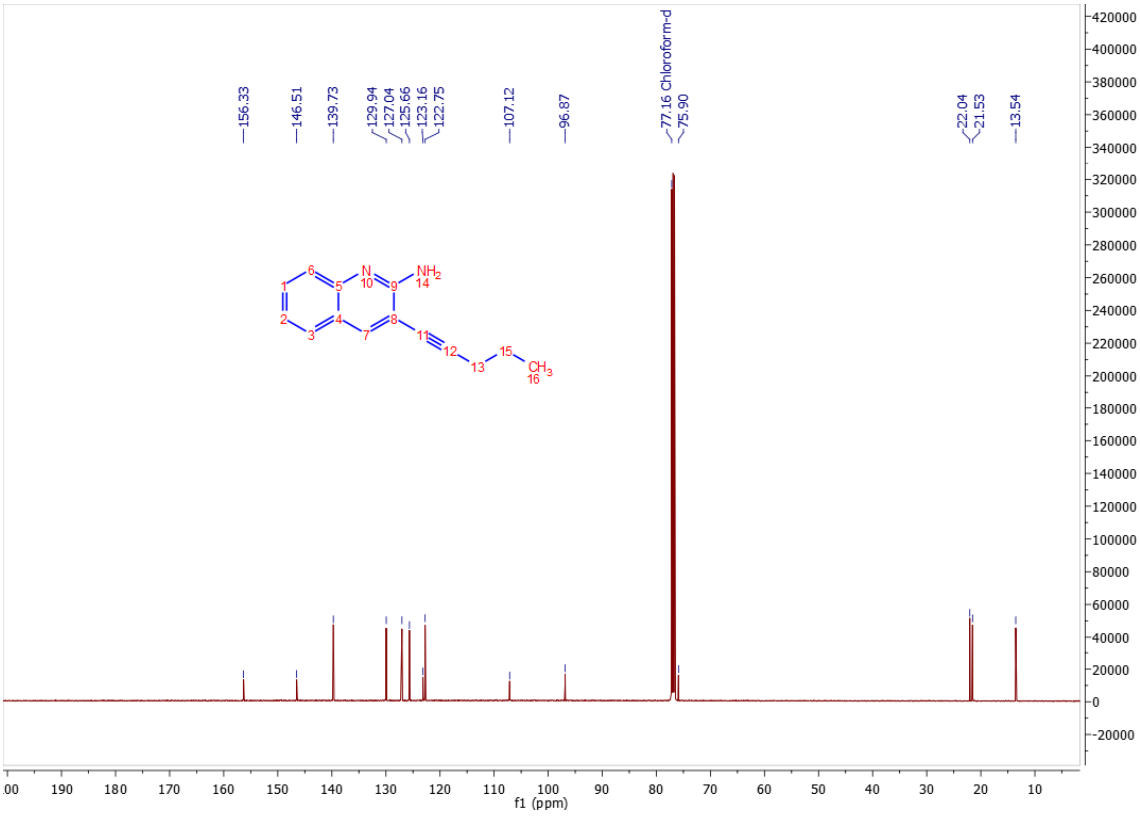
Compound **14e:** LC-MS



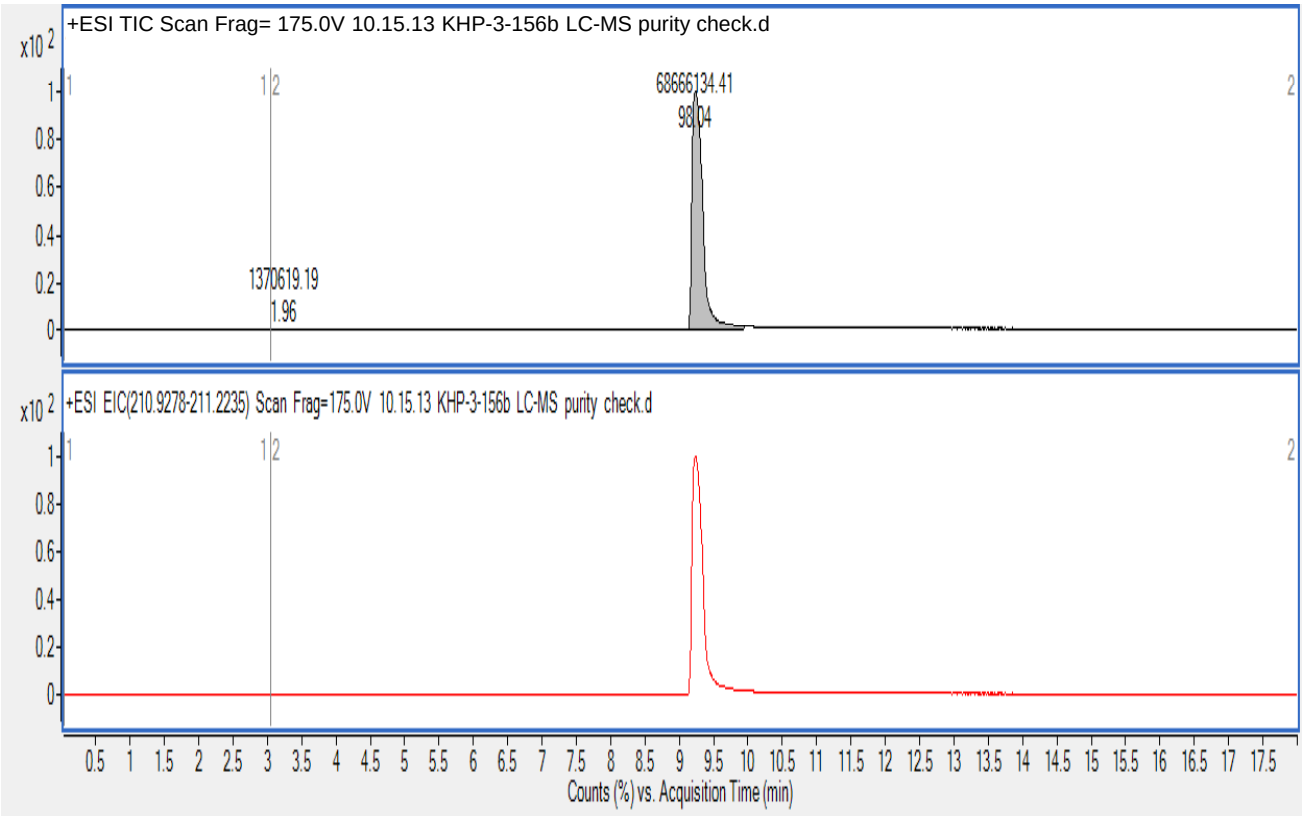


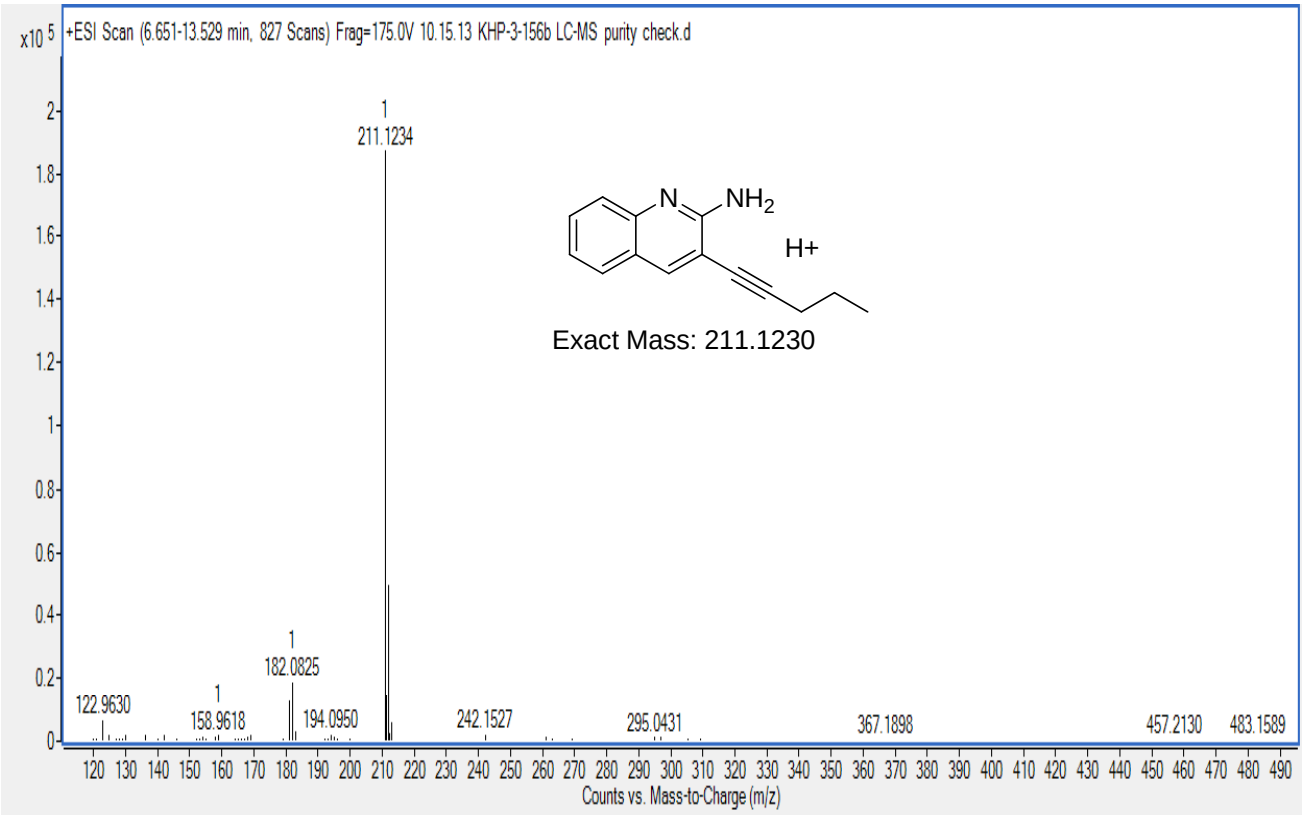
Compound **14f:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)





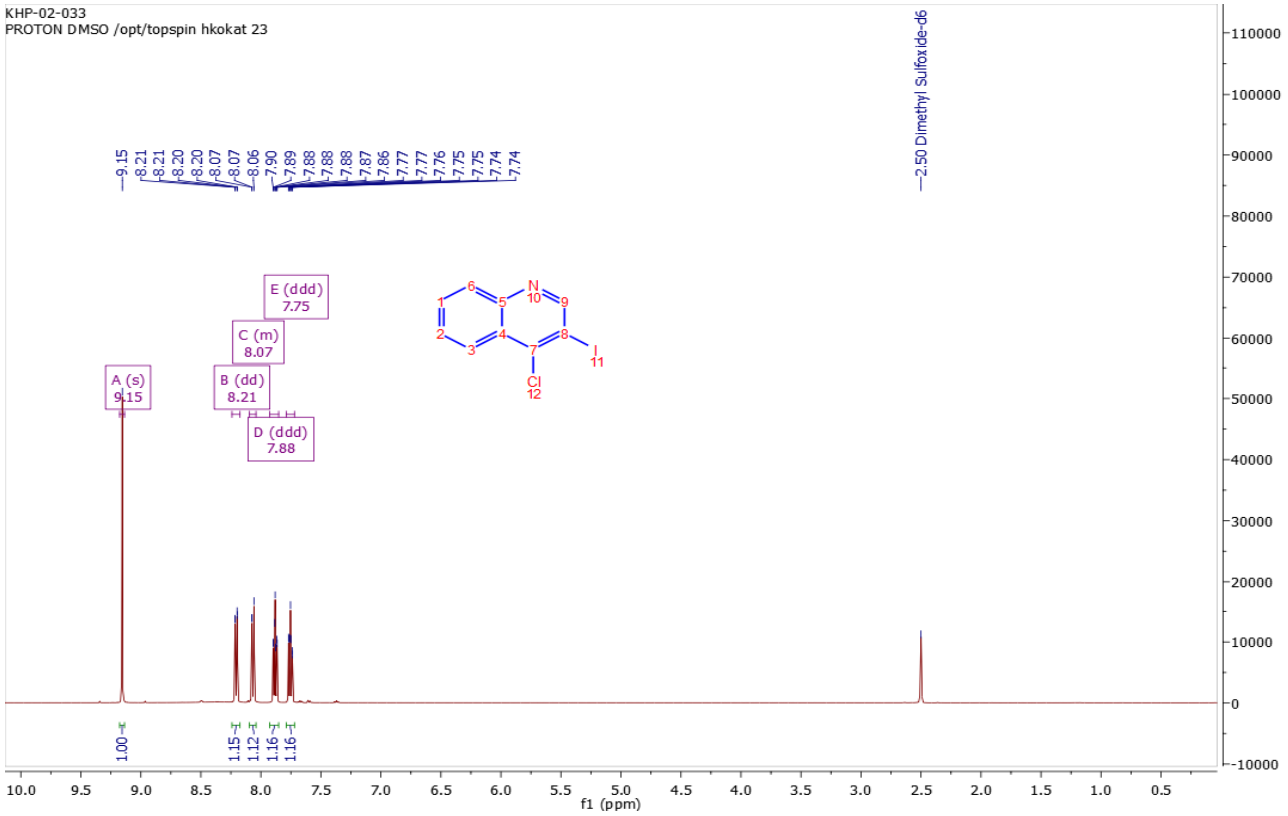
Compound **14f:** LC-MS

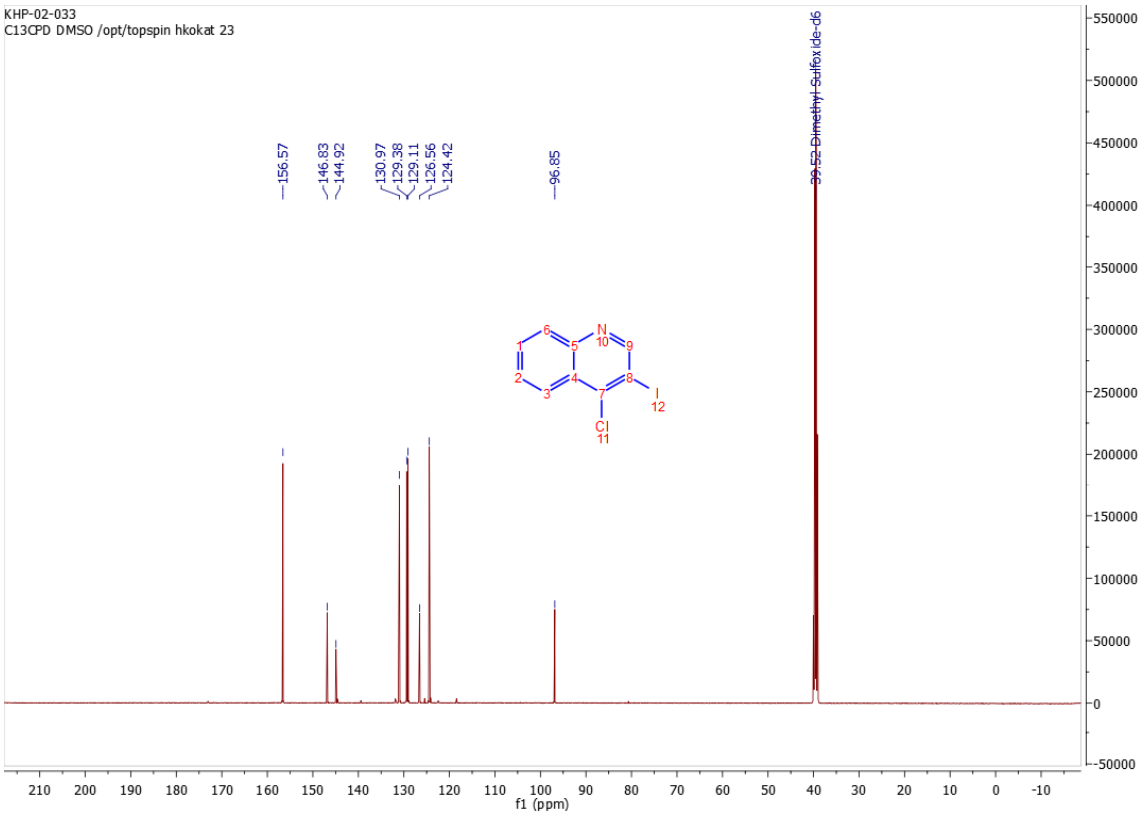




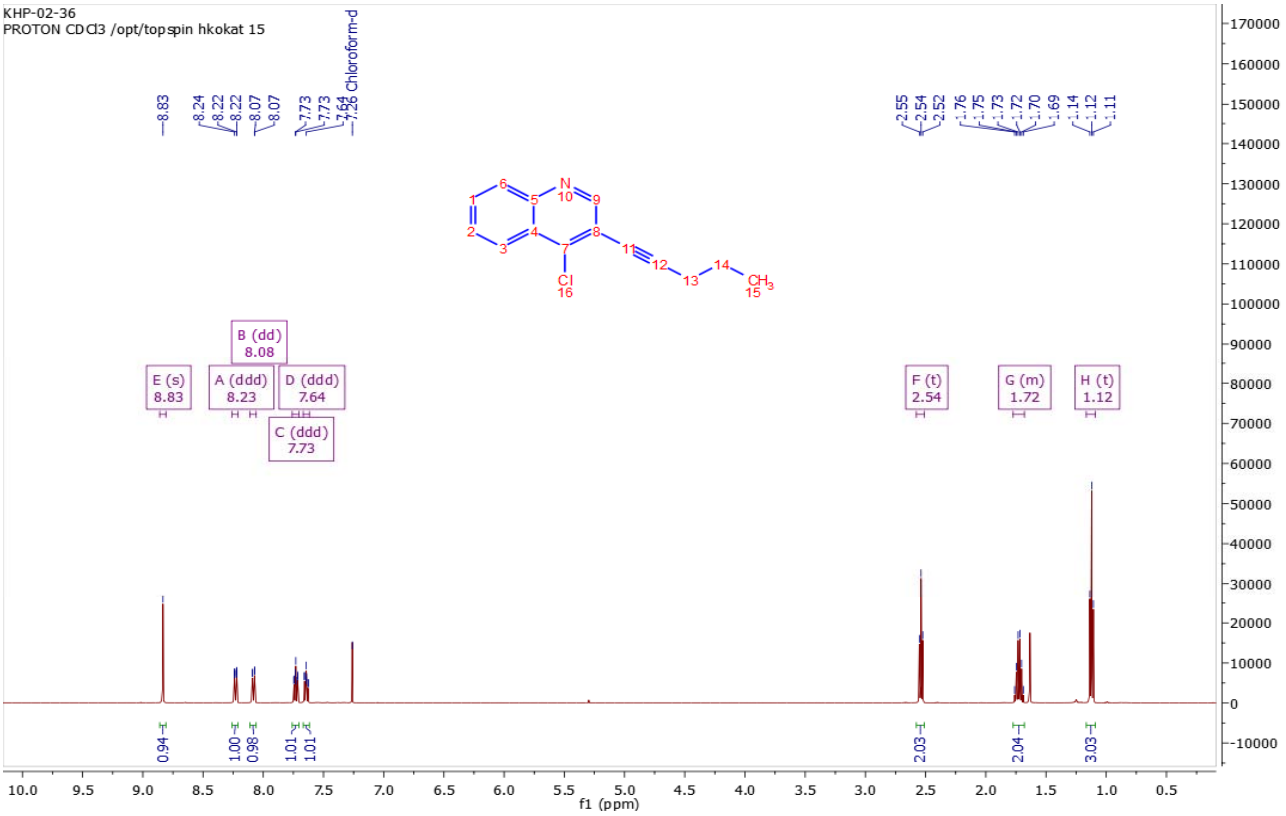
Exact Mass: 211.1230

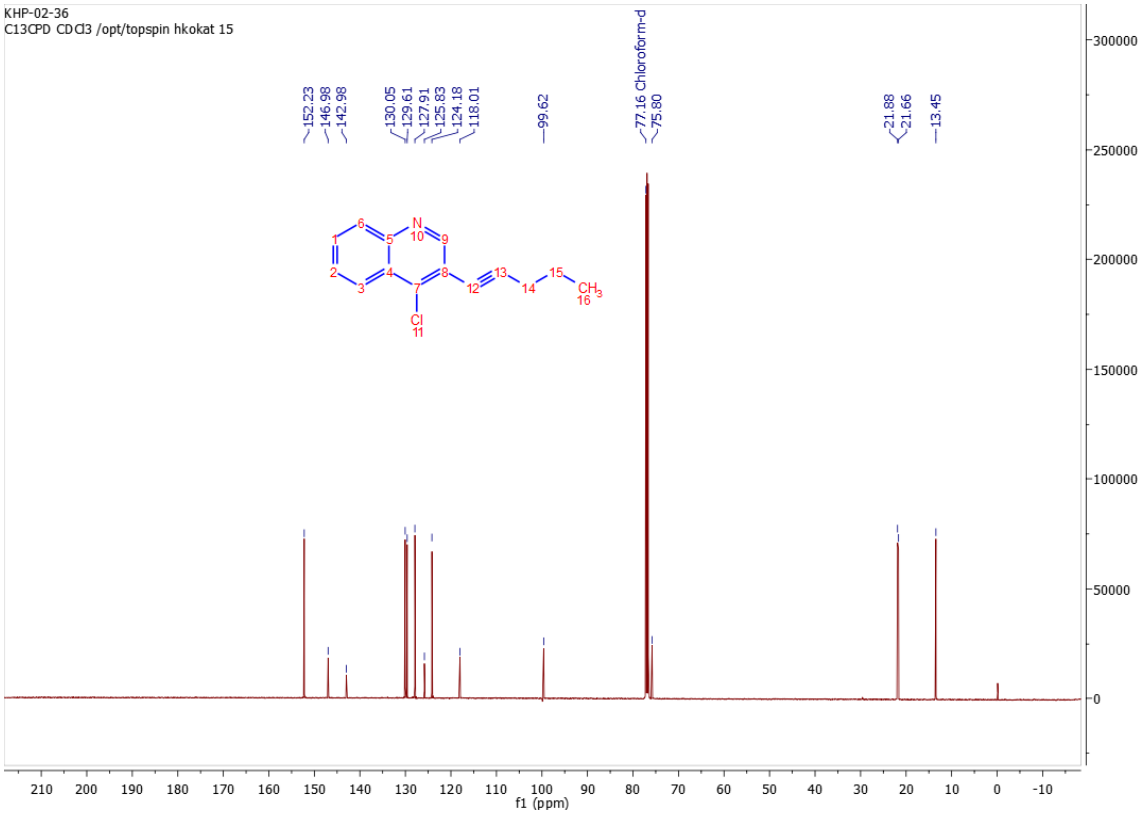
Compound **16:** ^{1}H and ^{13}C NMR Spectrum ($DMSO\text{-}d_6$)



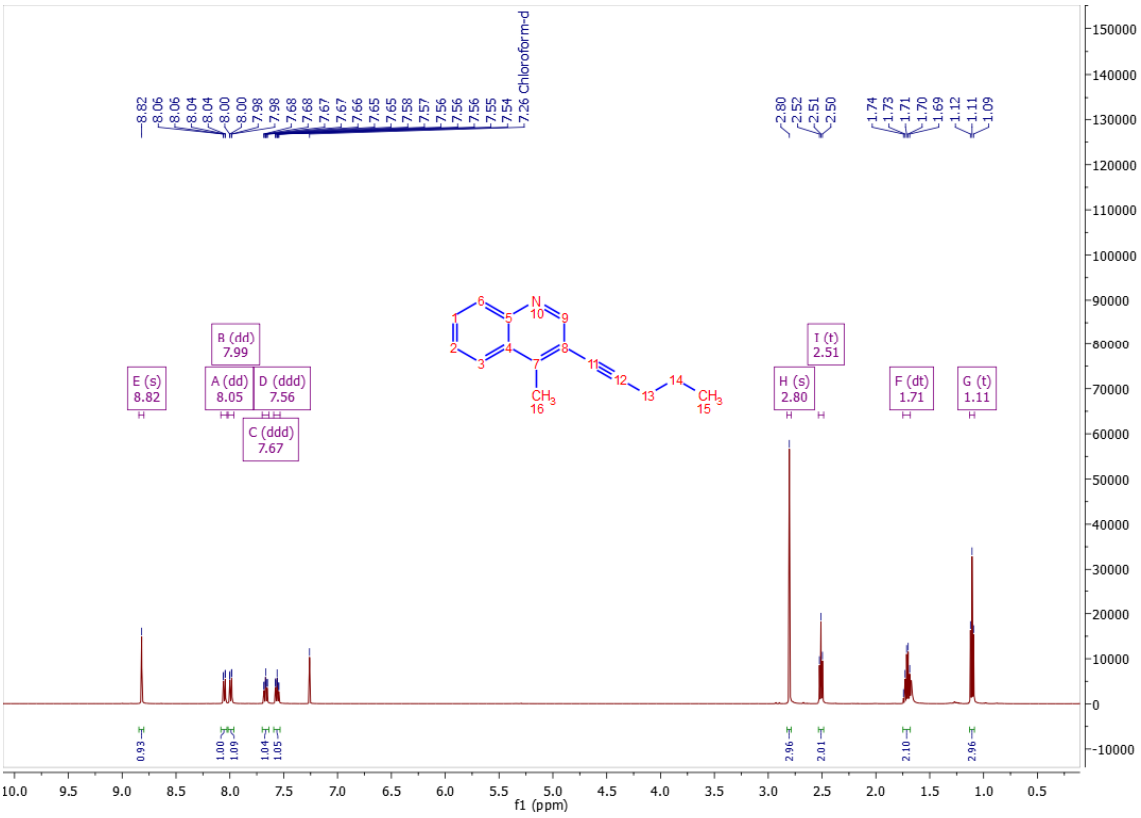


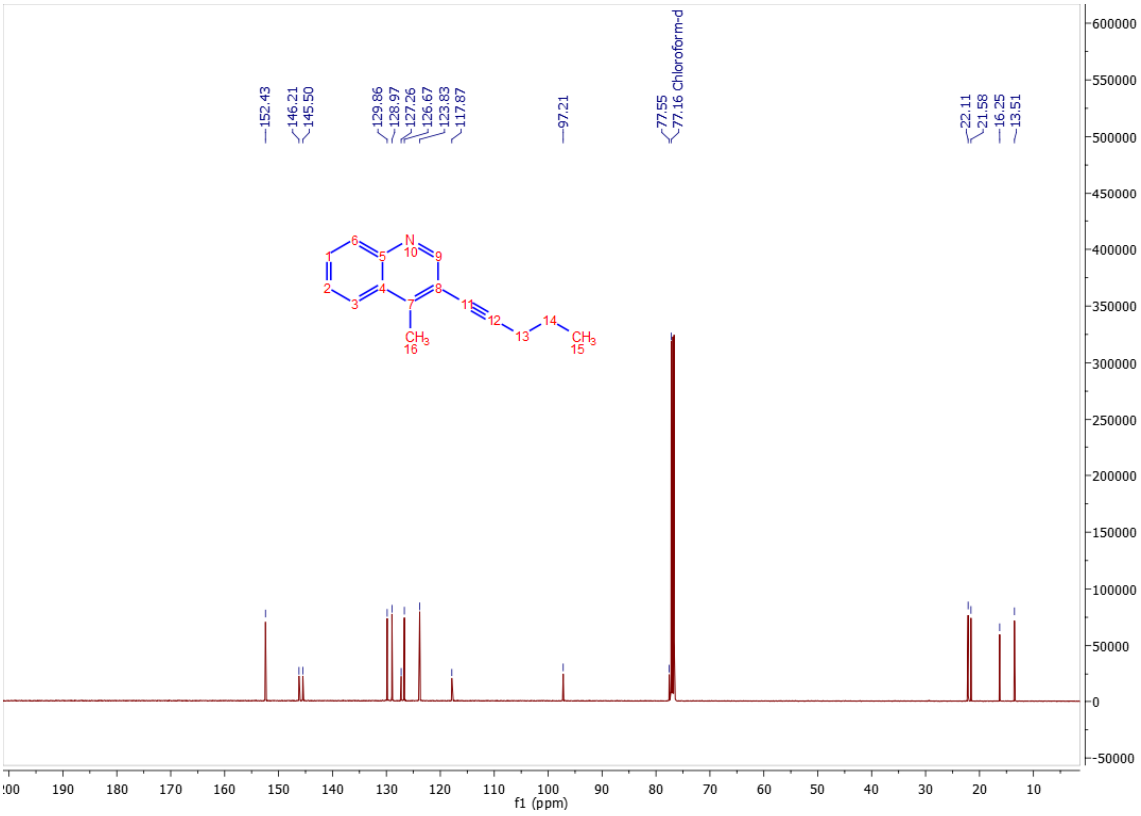
Compound **17:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



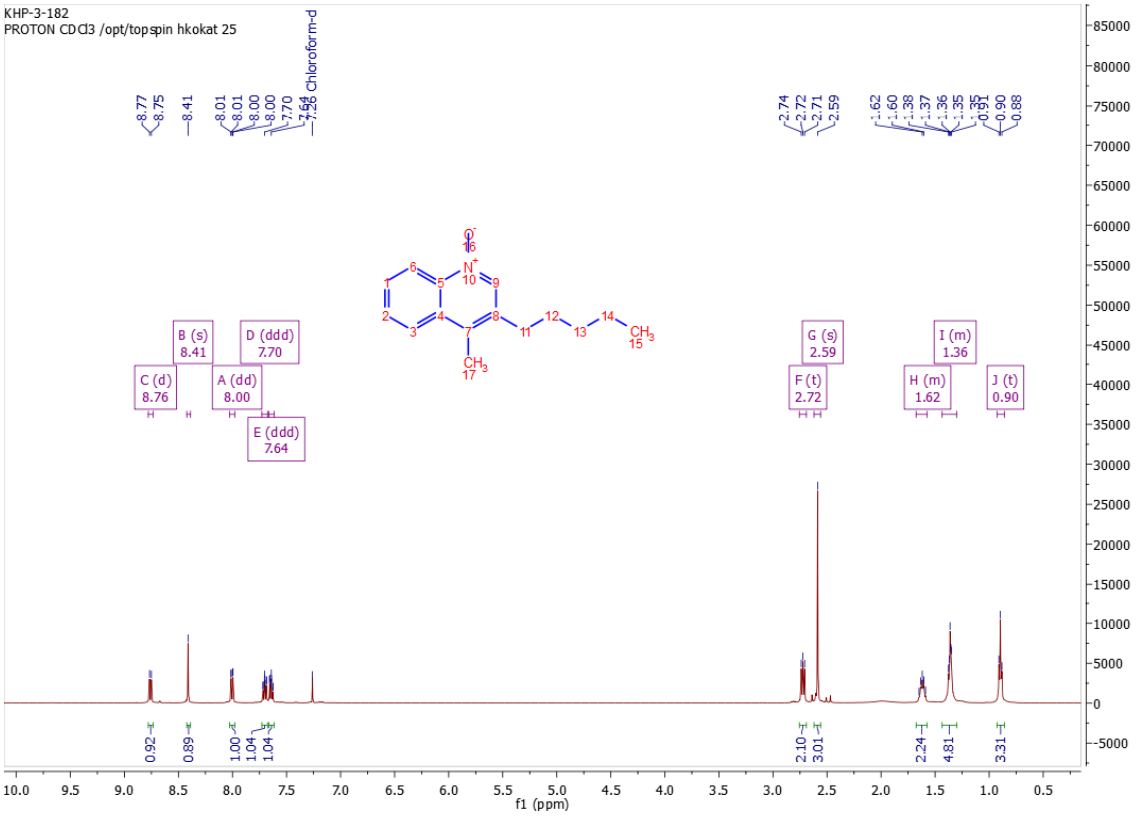


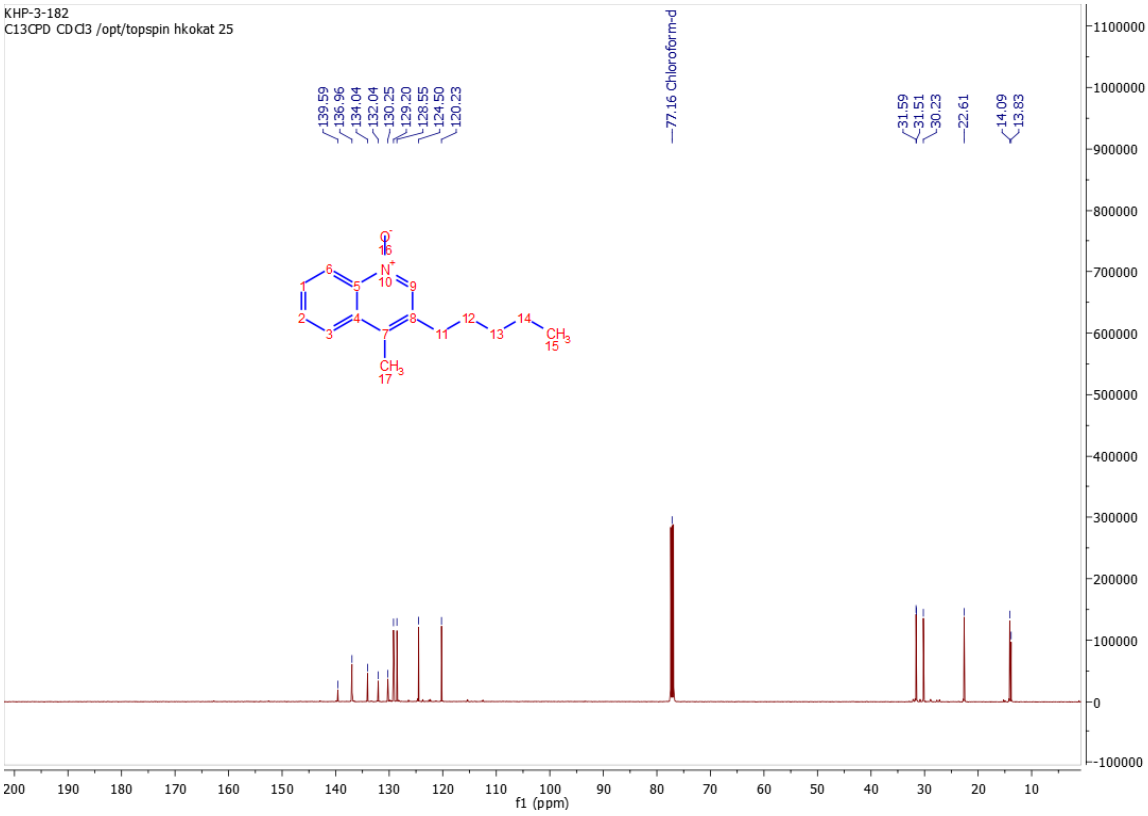
Compound **18a:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



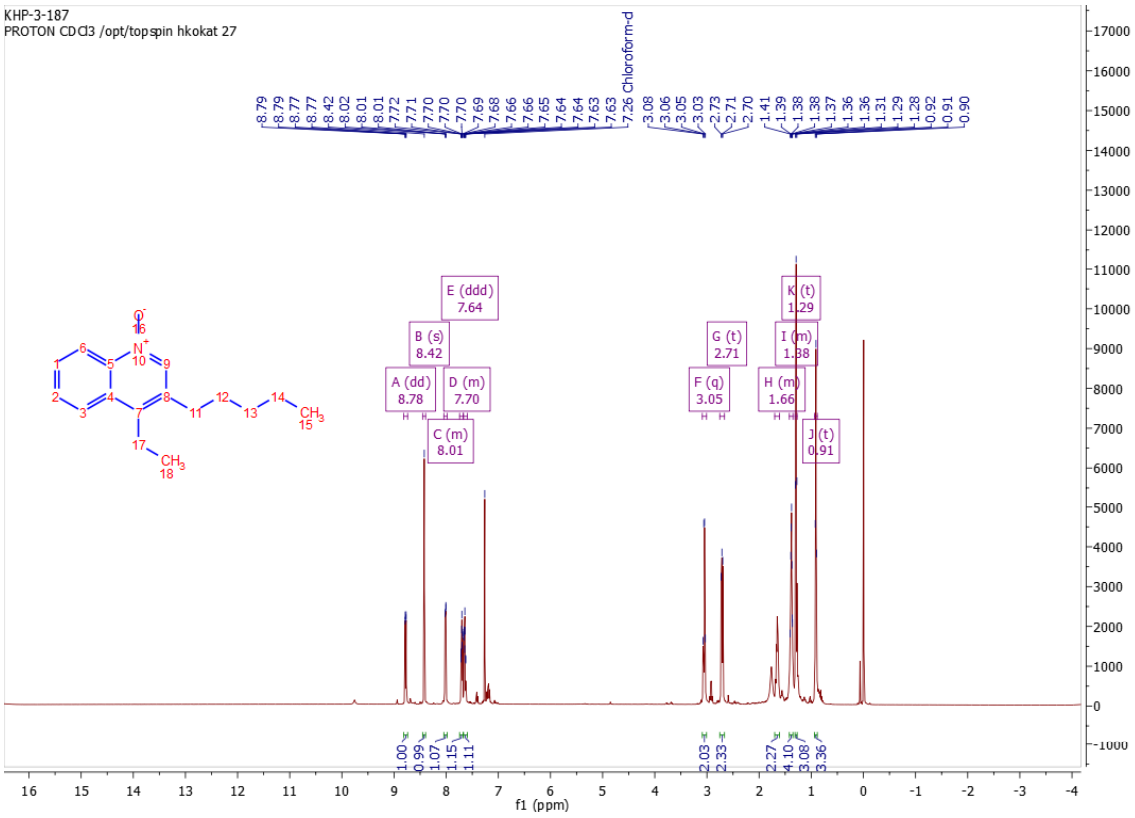


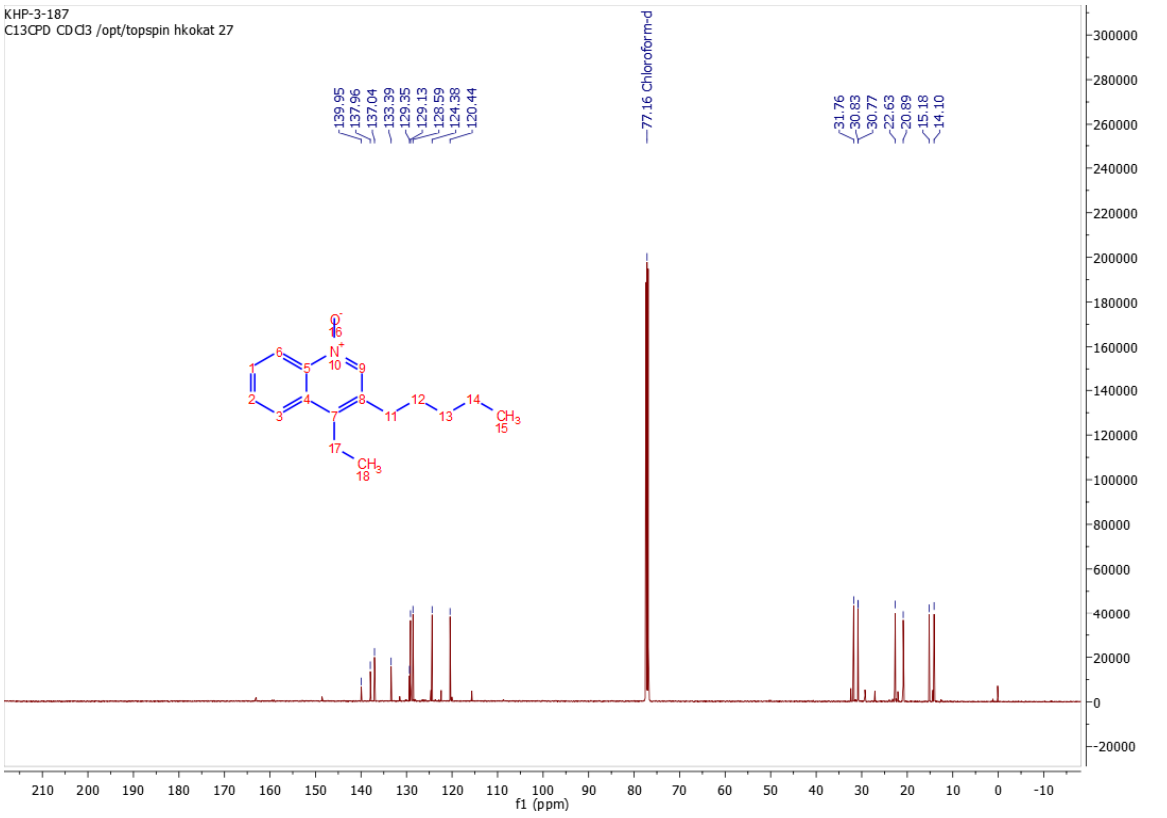
Compound **20a:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



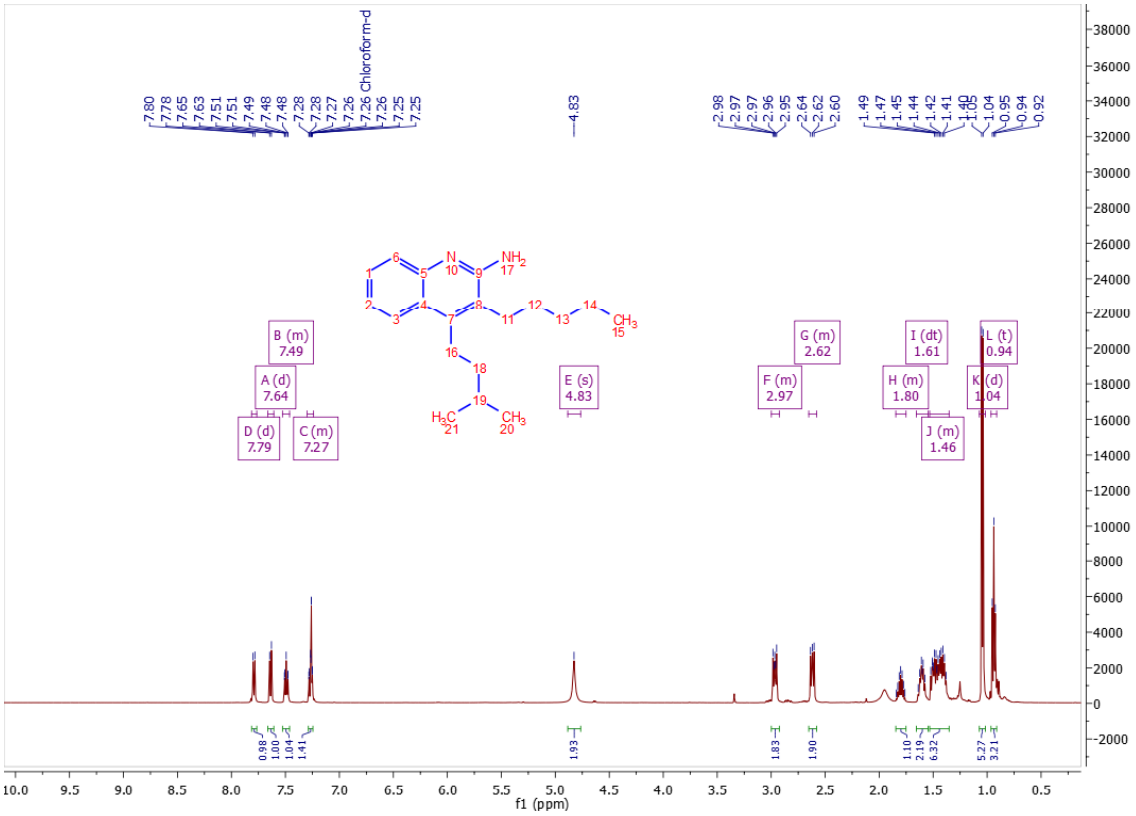


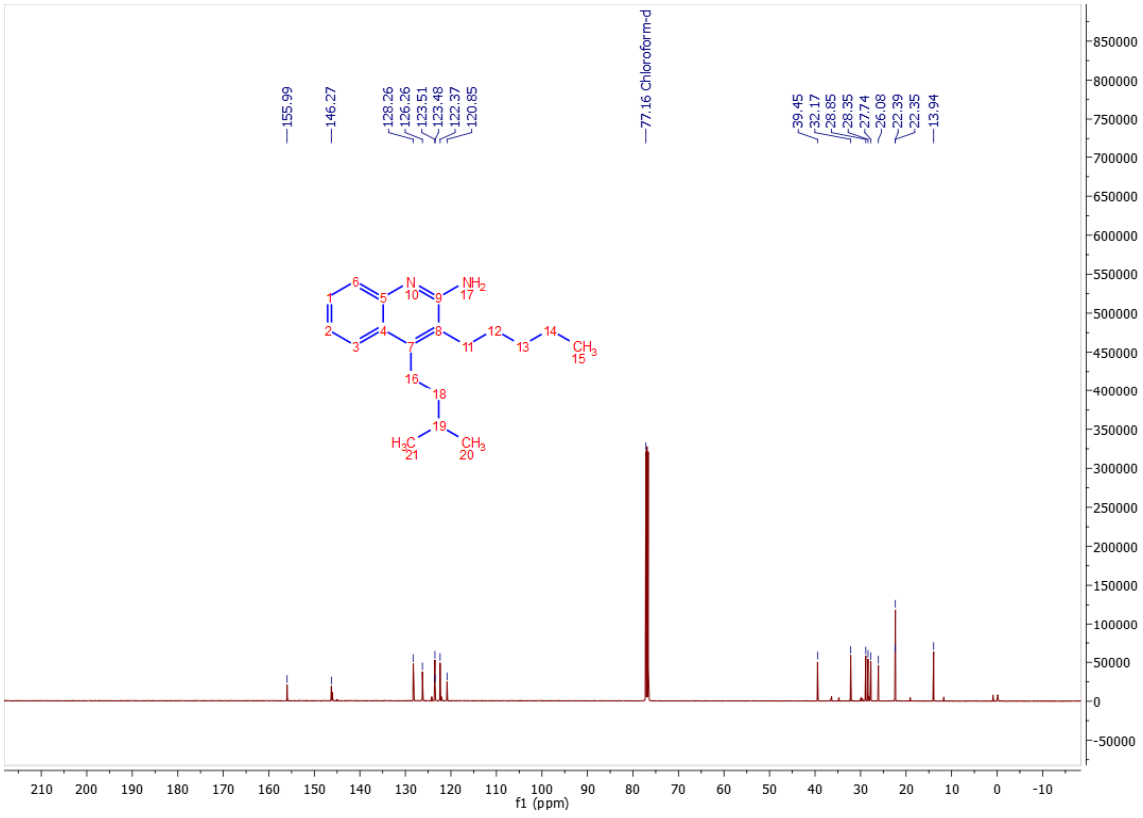
Compound **20b:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



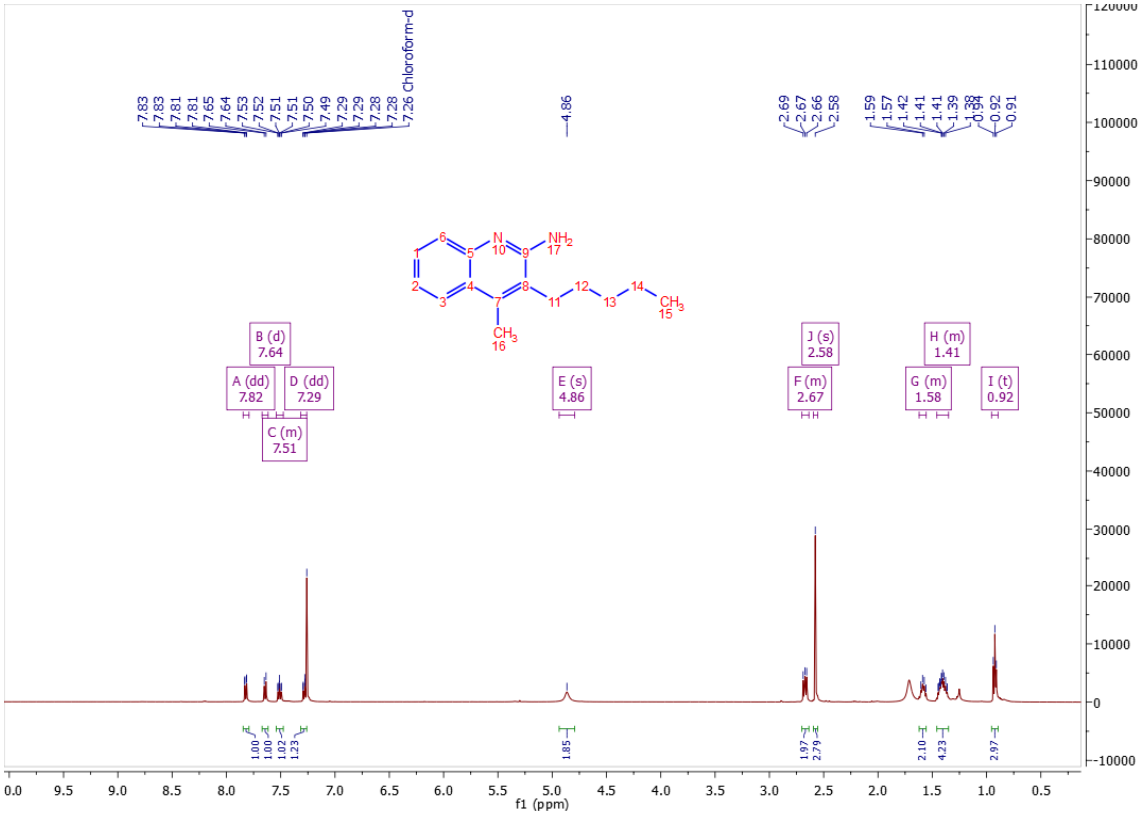


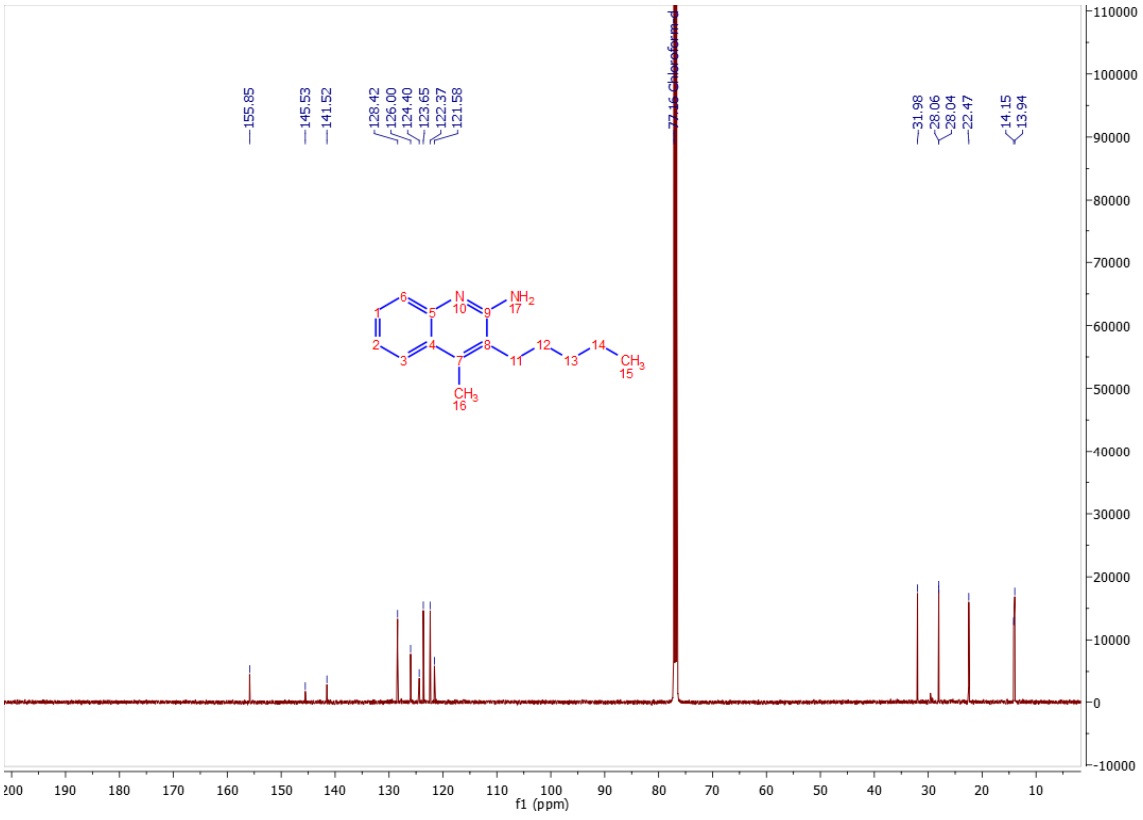
Compound **20c:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



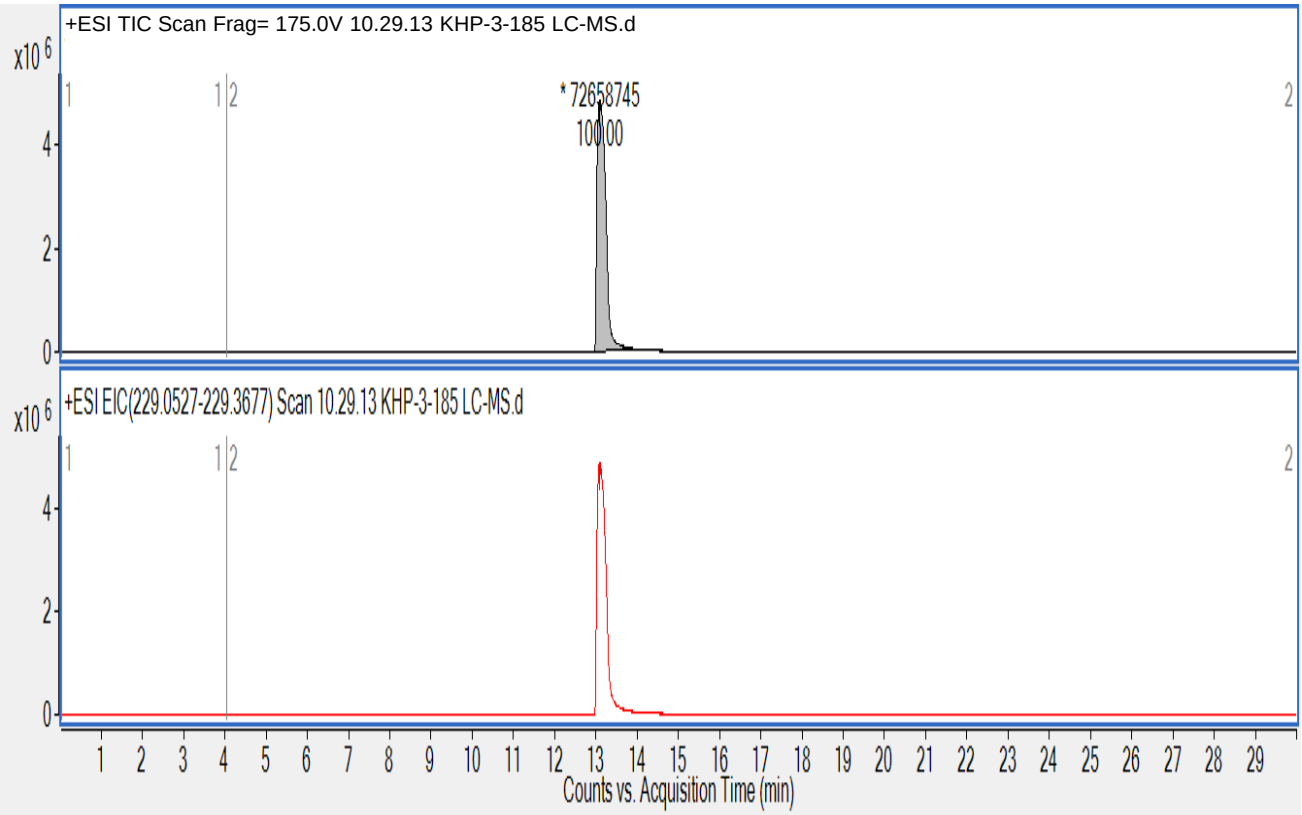


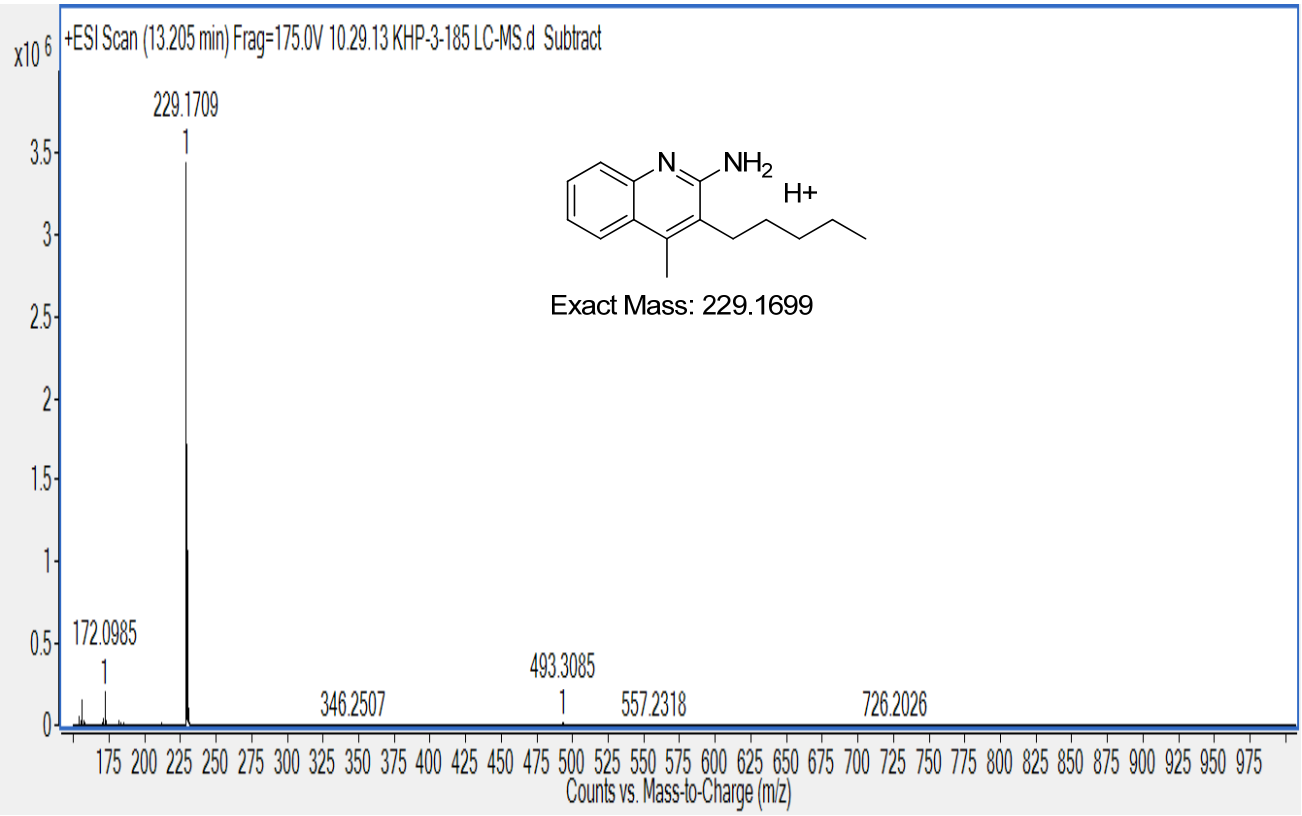
Compound **21a:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



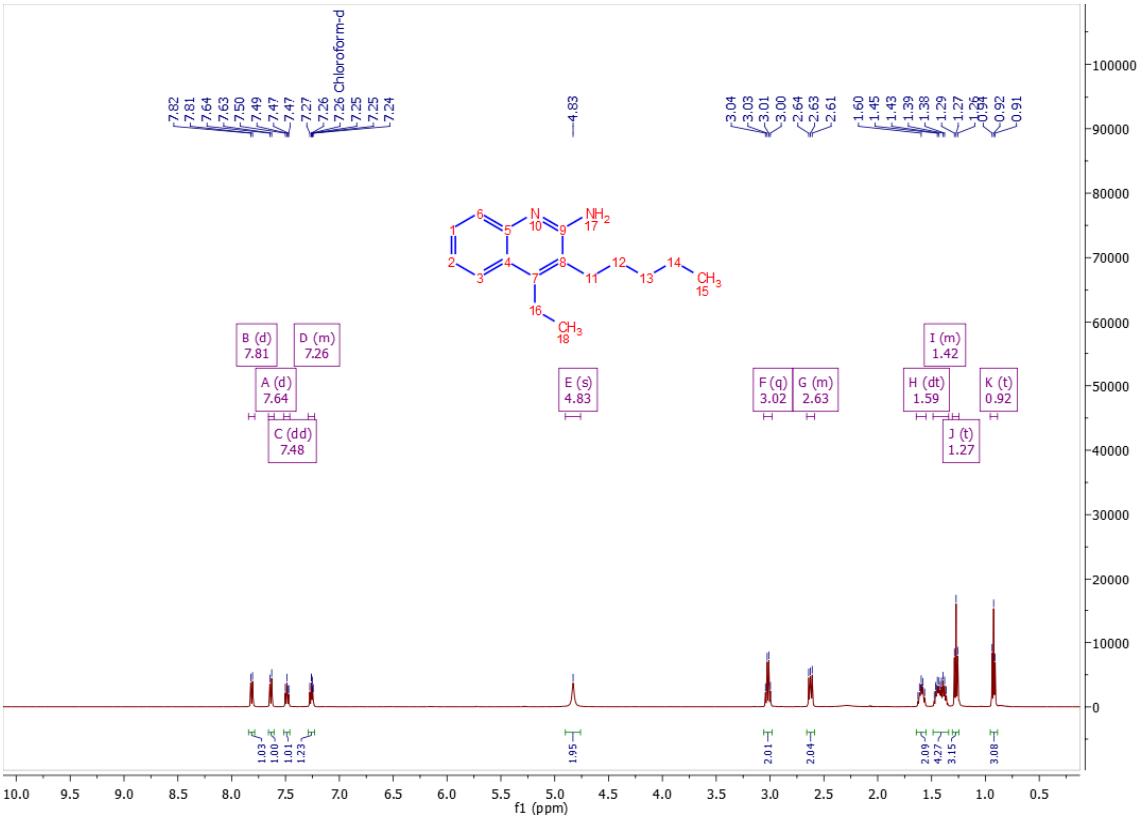


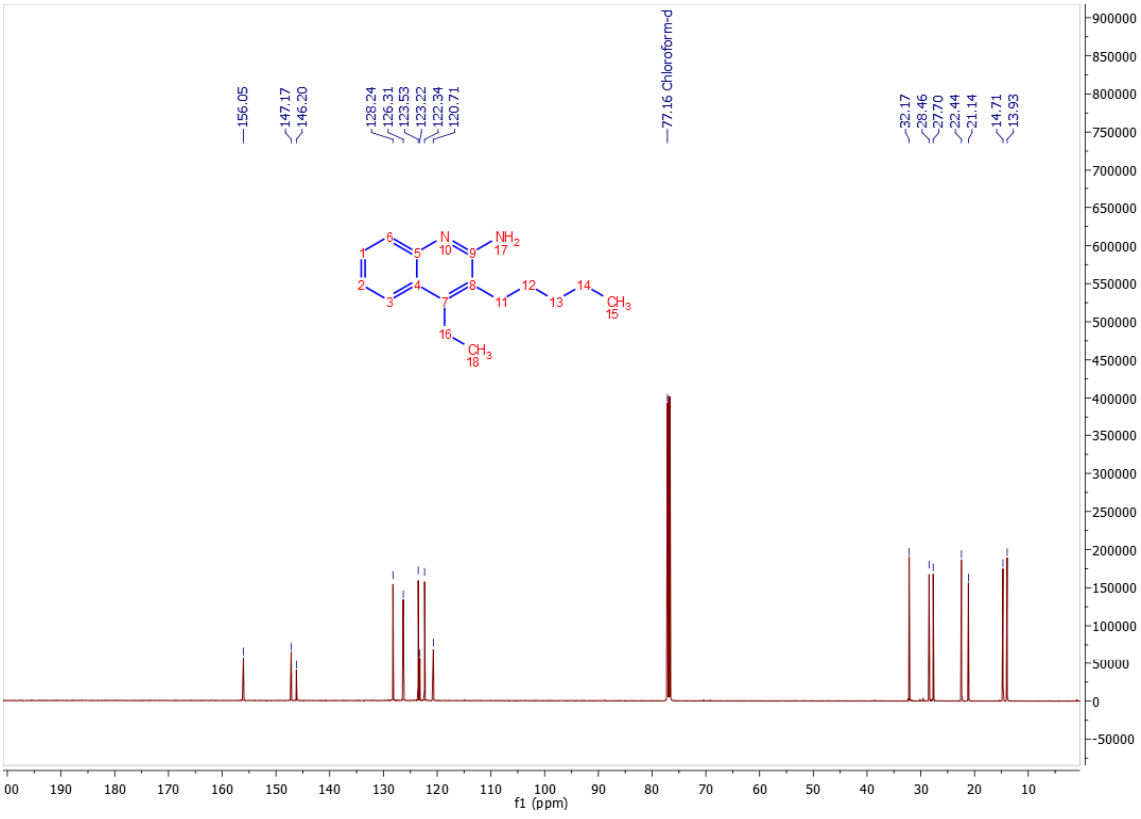
Compound **21a:** LC-MS



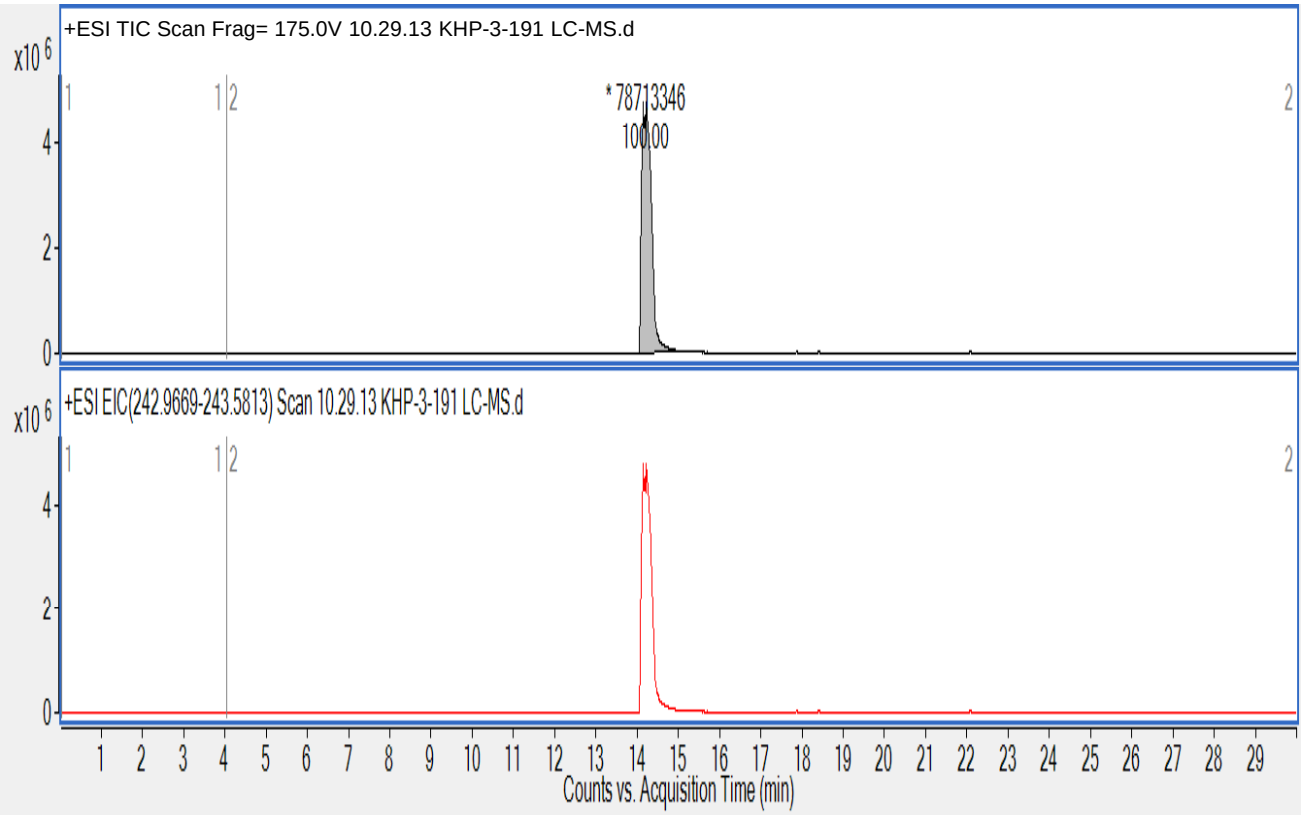


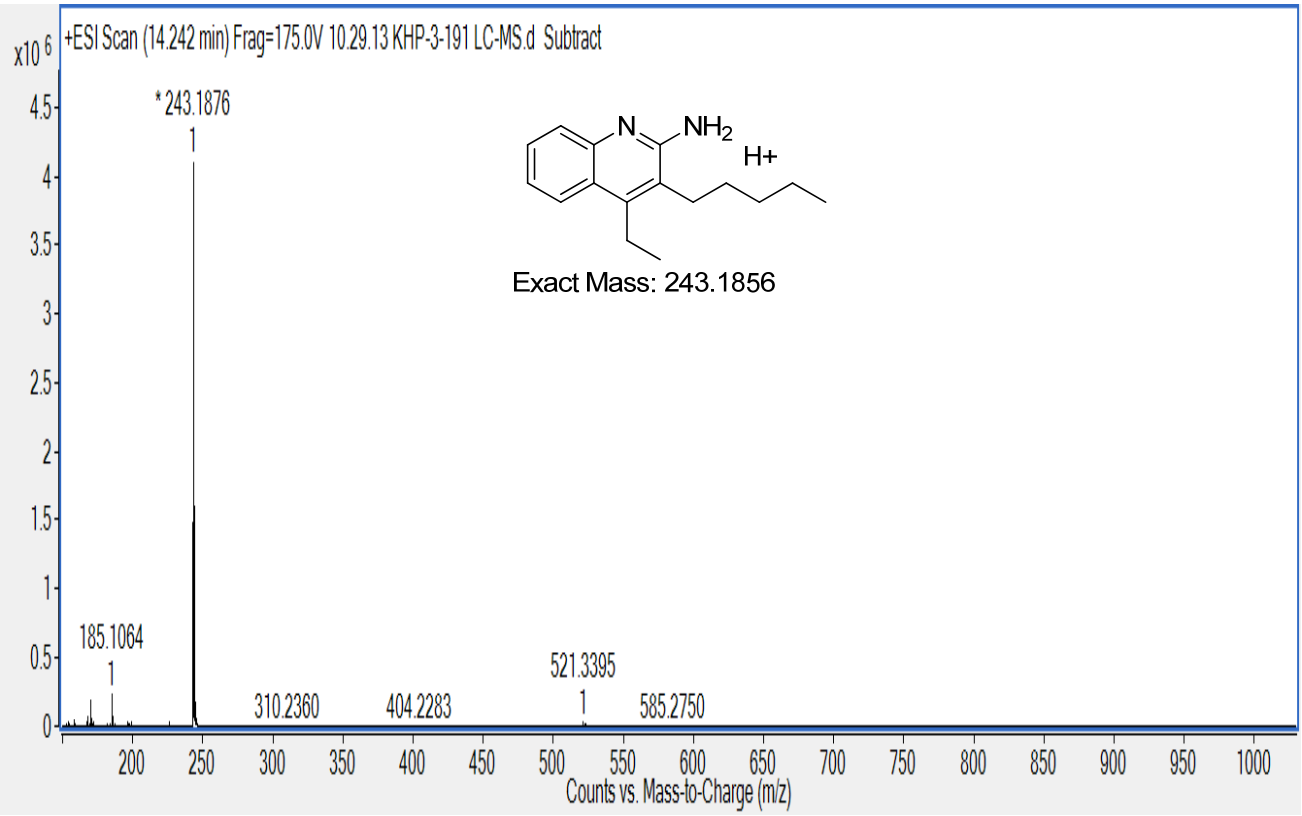
Compound **21b:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



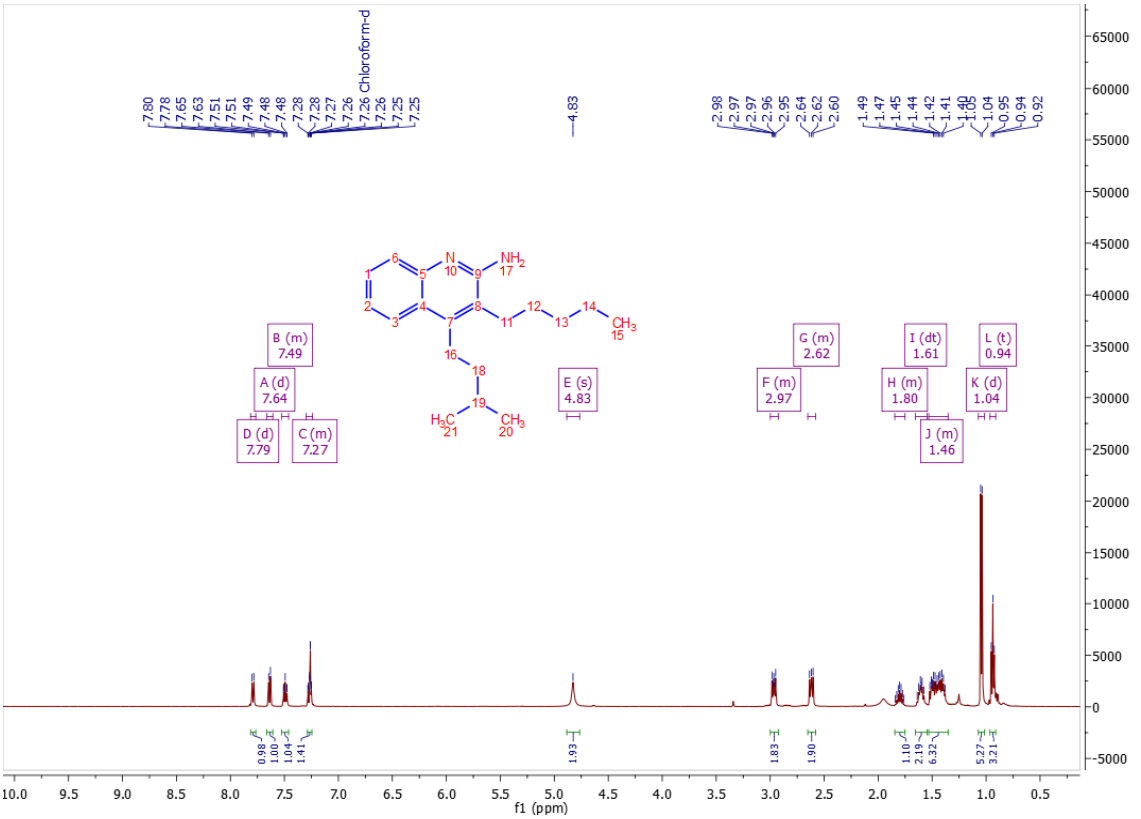


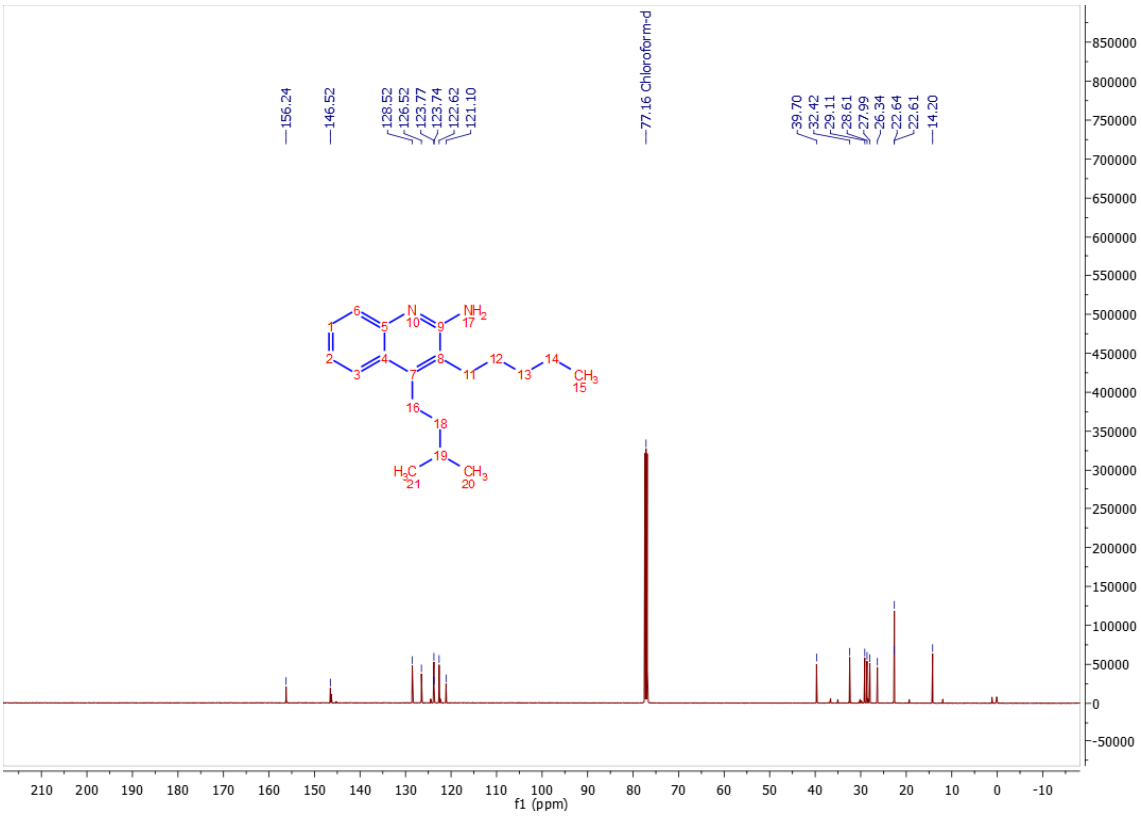
Compound **21b:** LC-MS



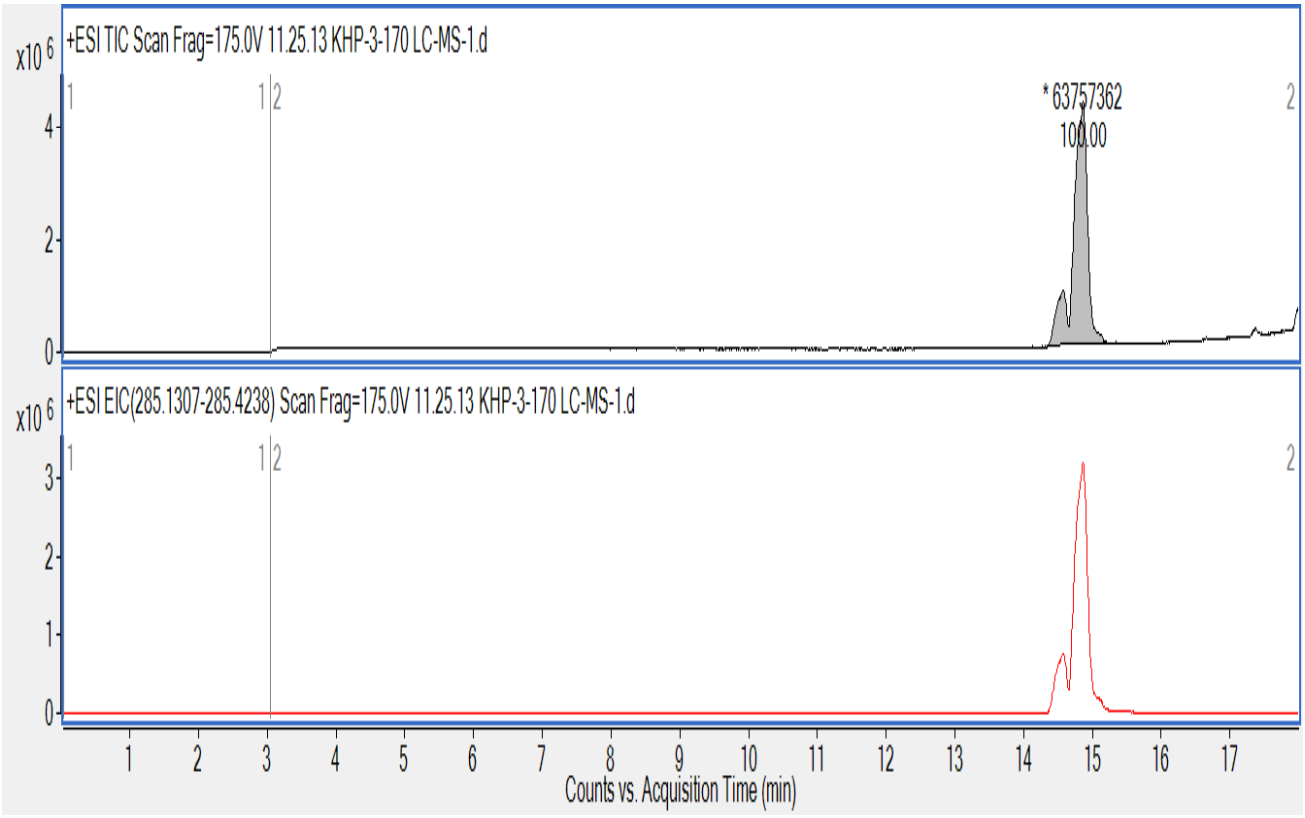


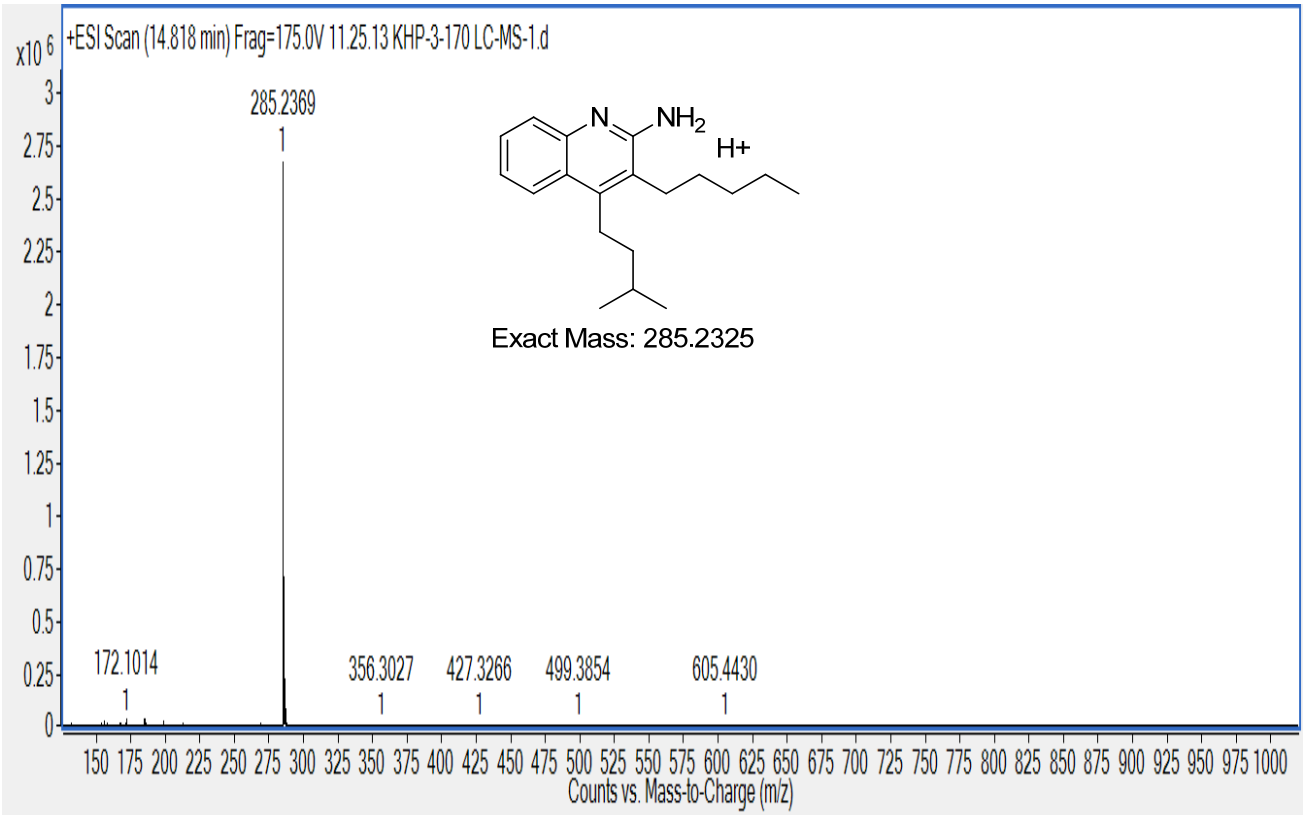
Compound **21c:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



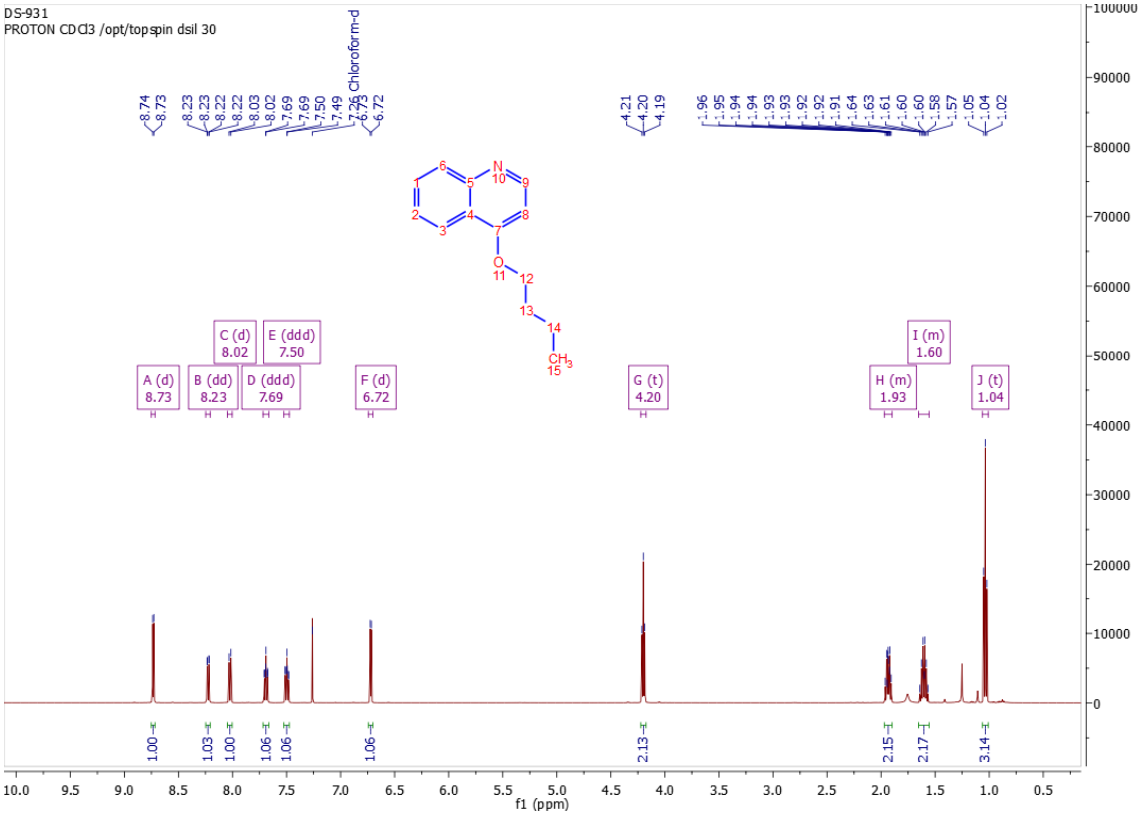


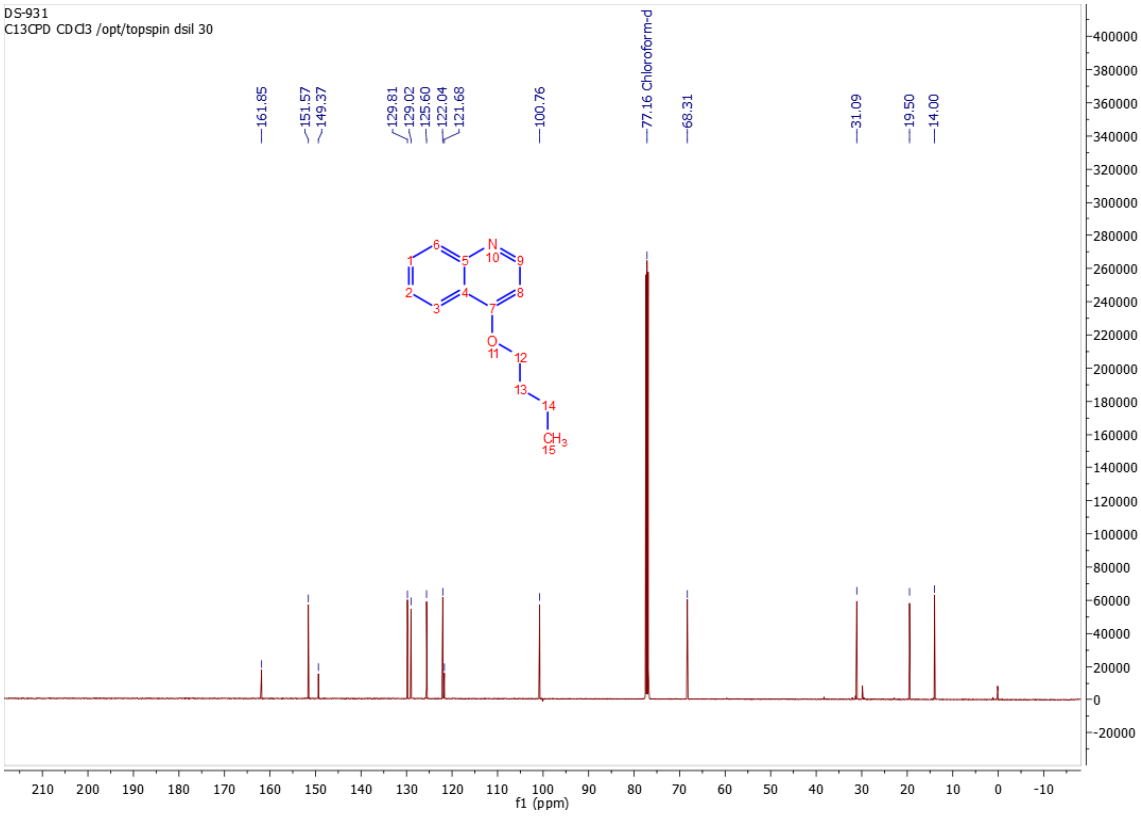
Compound **21c:** LC-MS



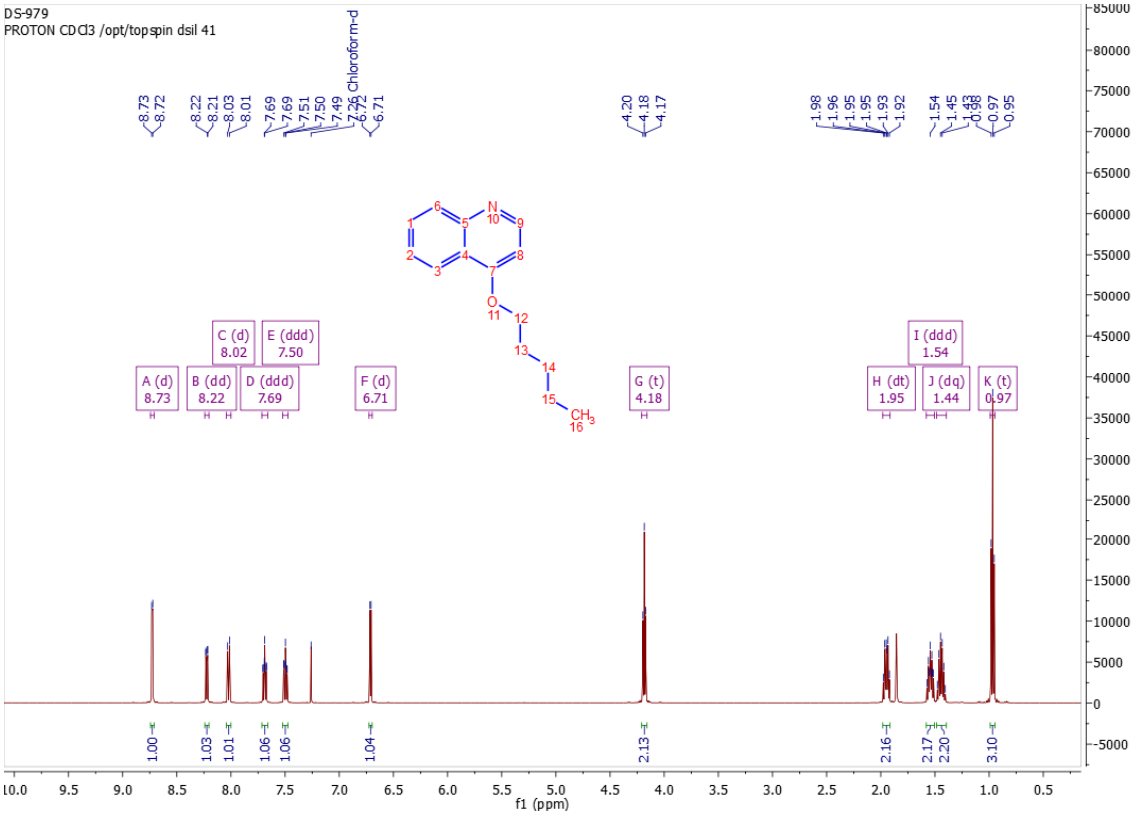


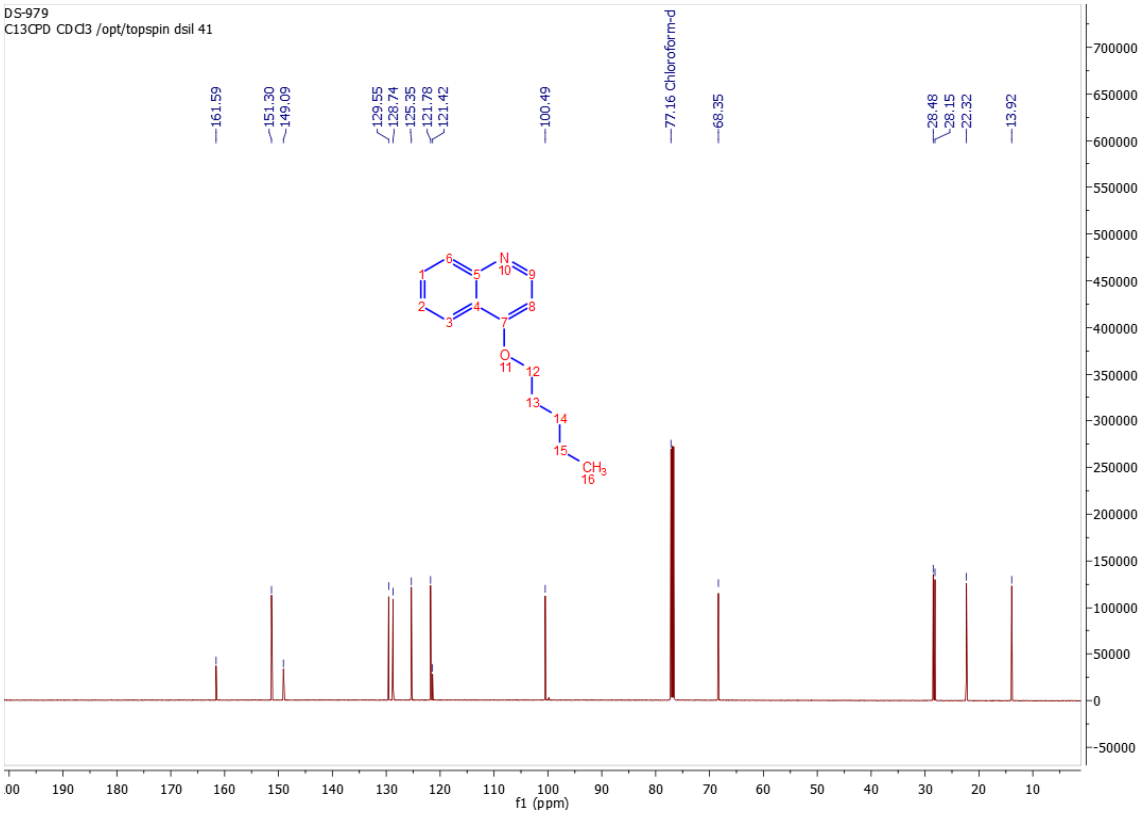
Compound **23a:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



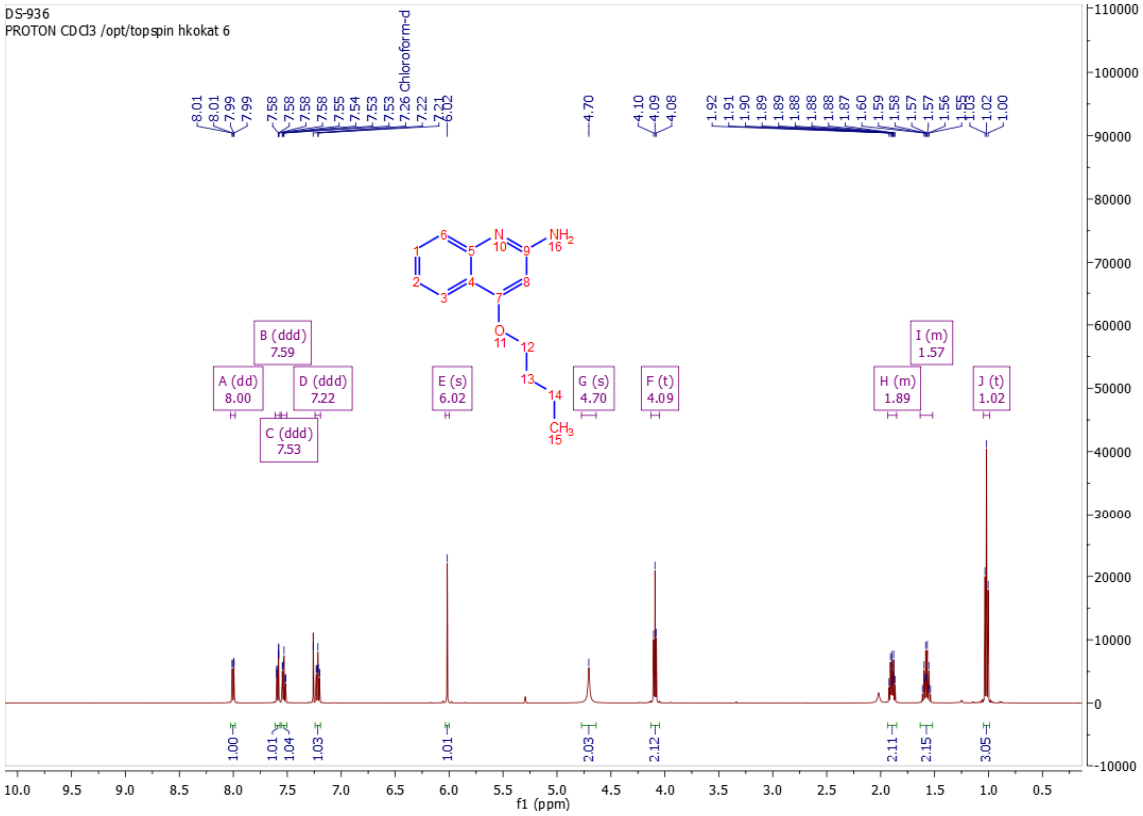


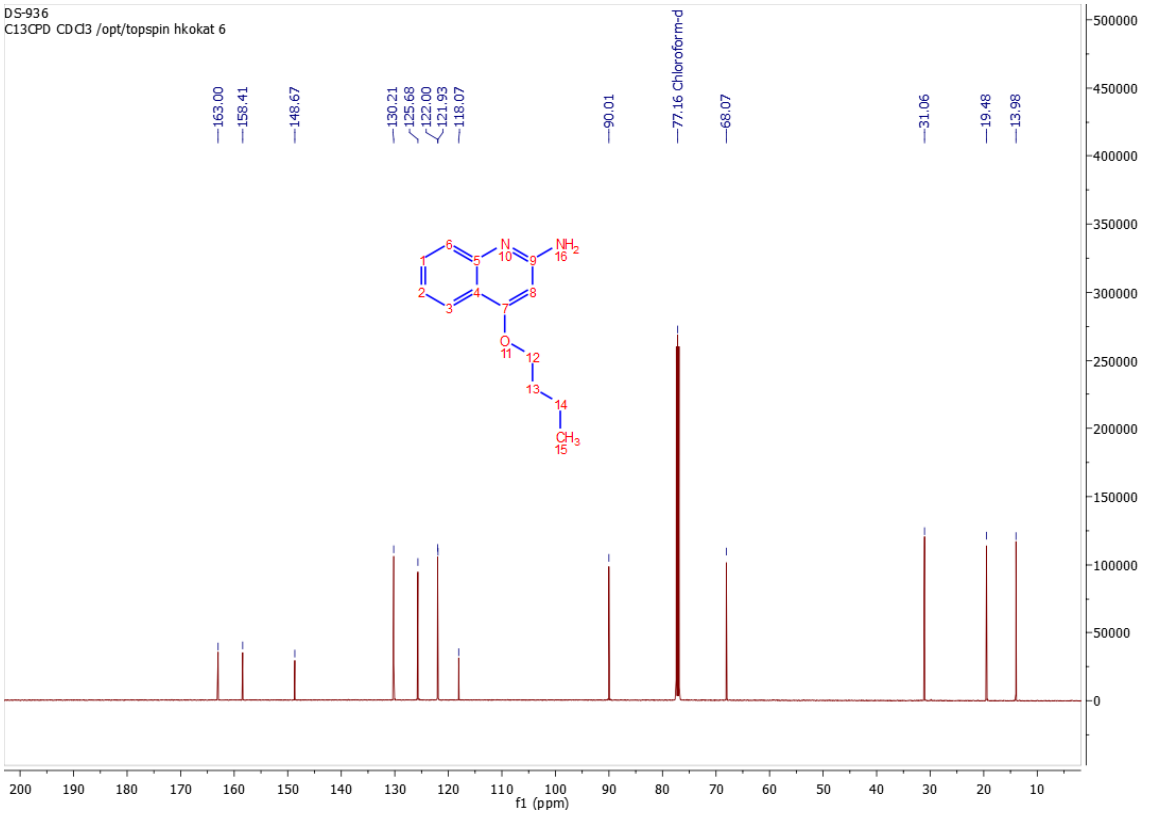
Compound **23b:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



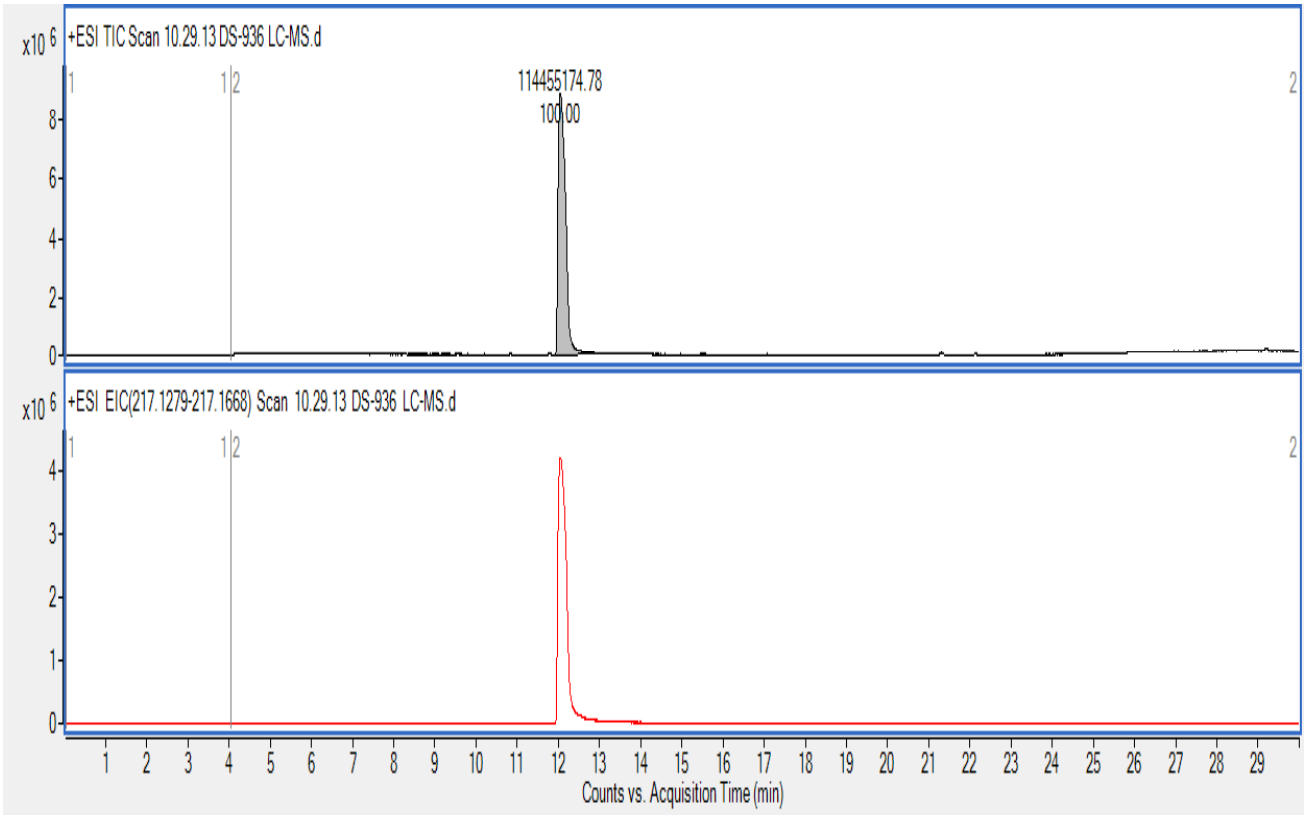


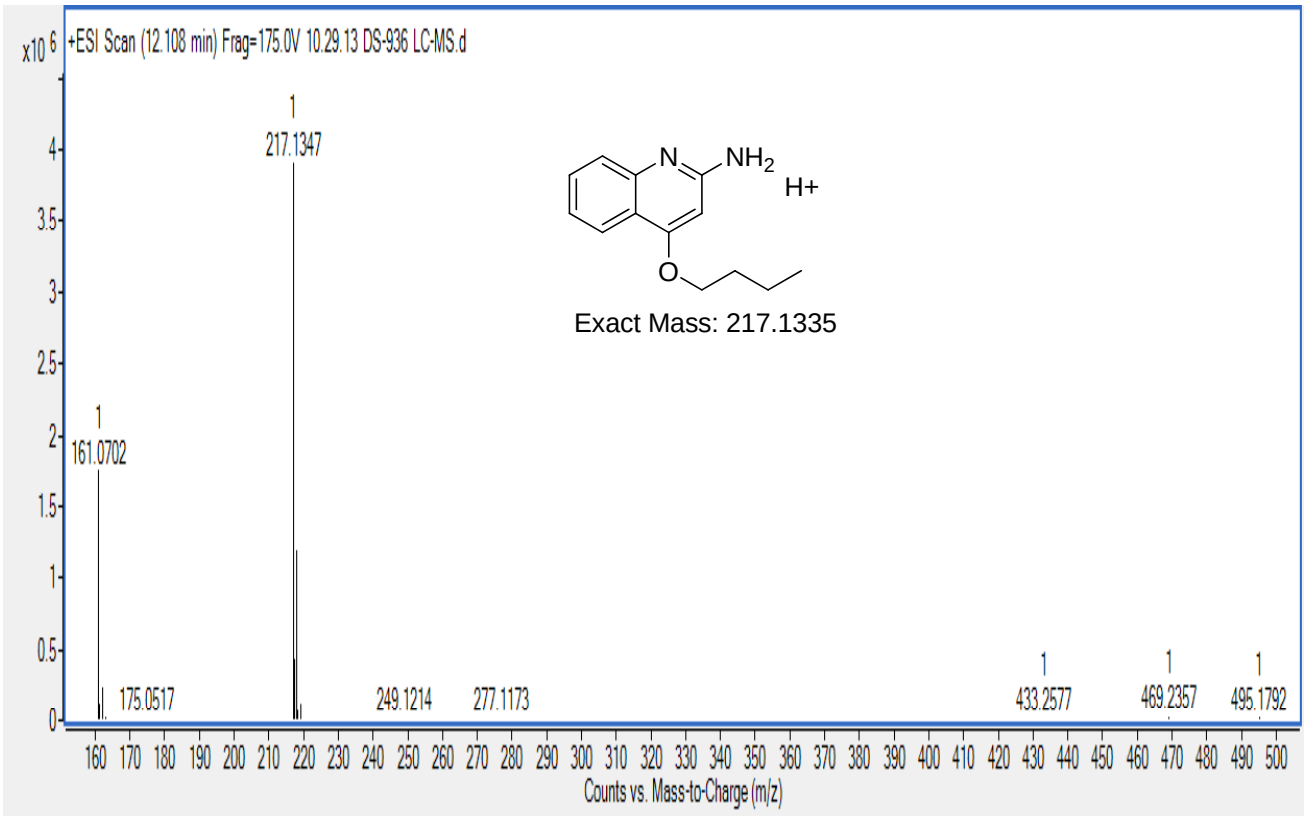
Compound **24a:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)





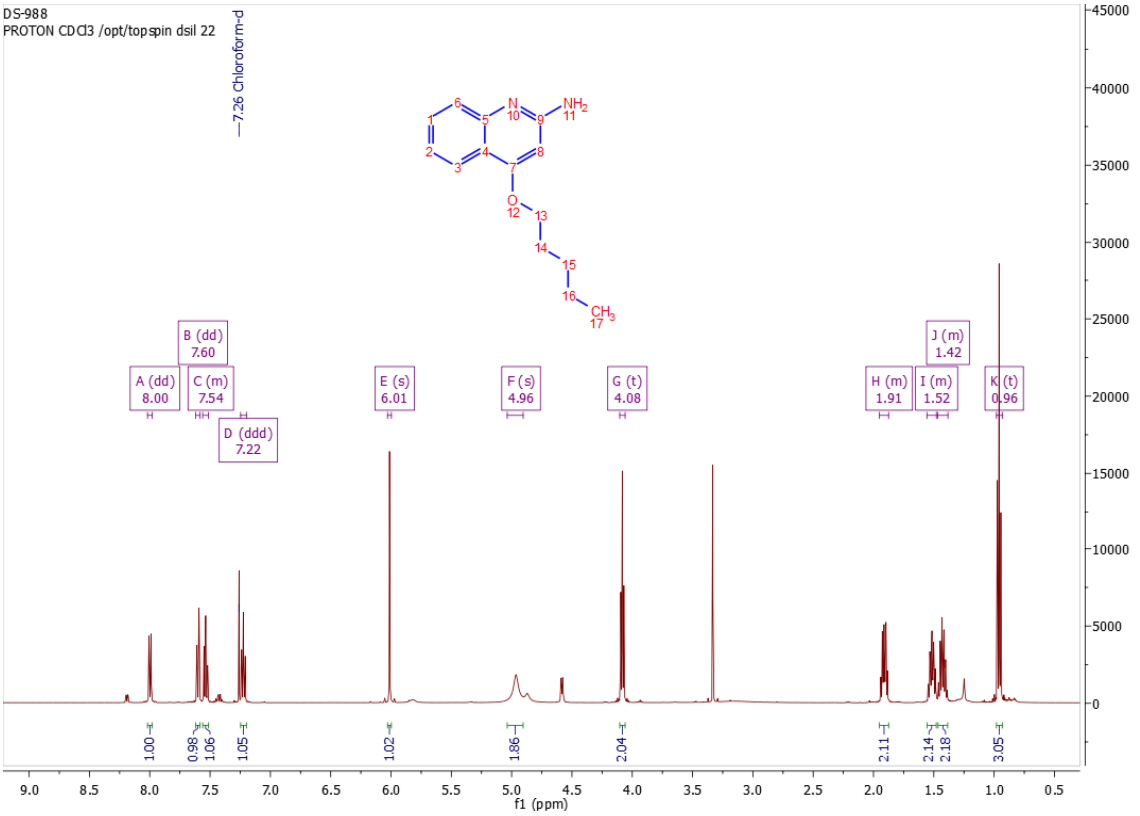
Compound **24a:** LC-MS

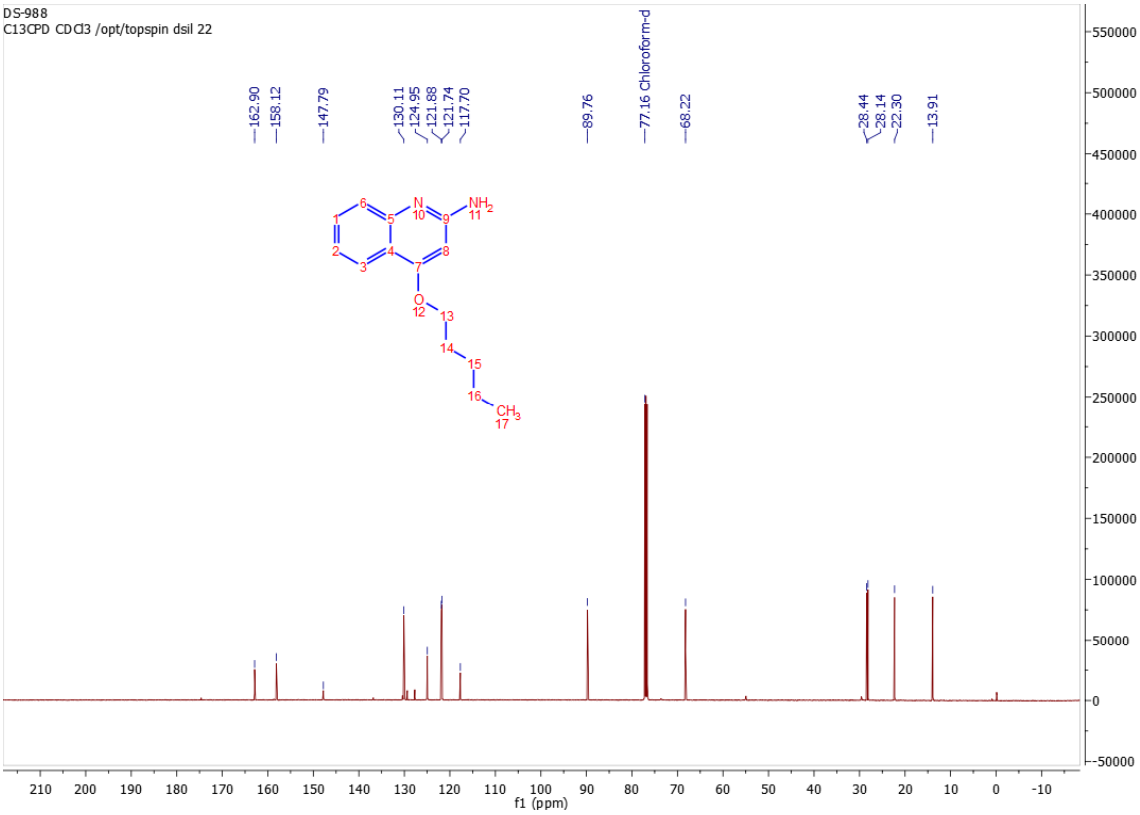




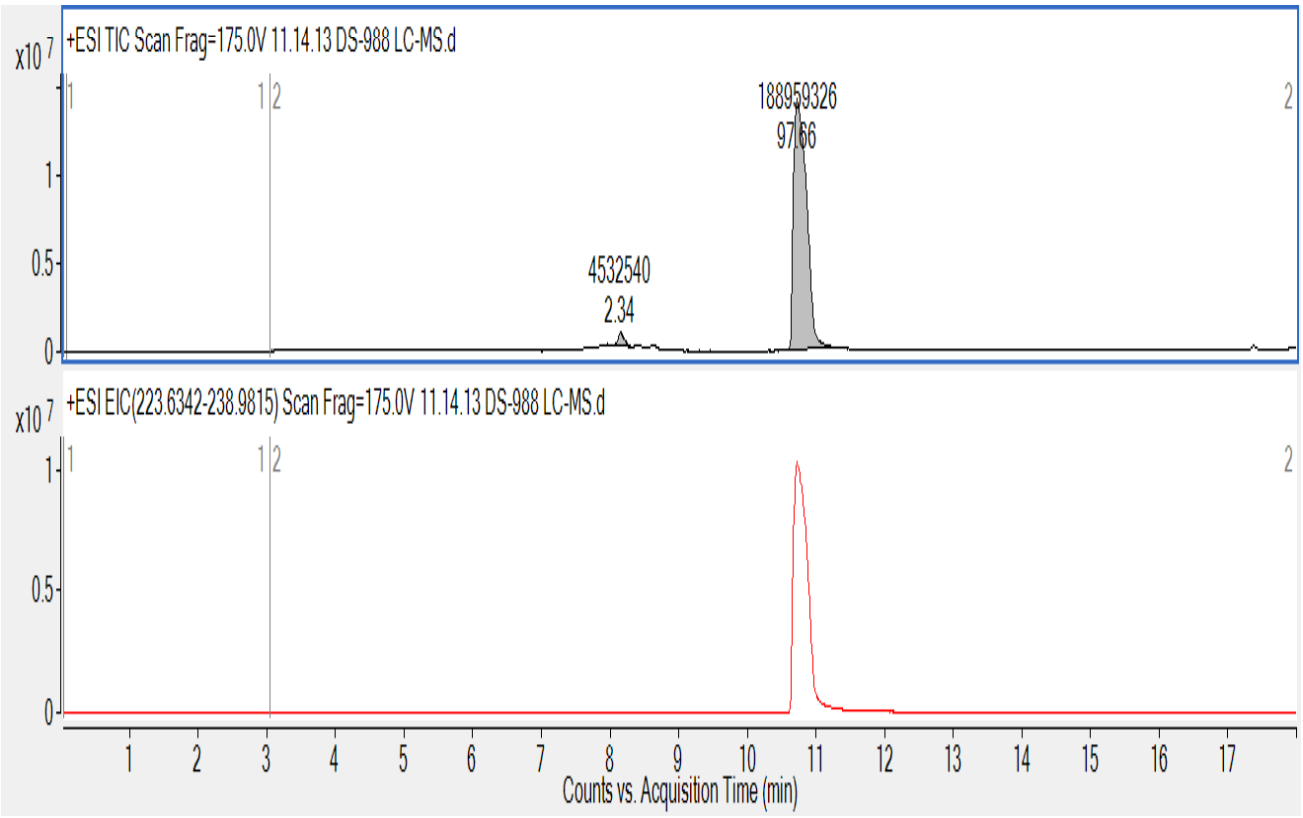
Exact Mass: 217.1335

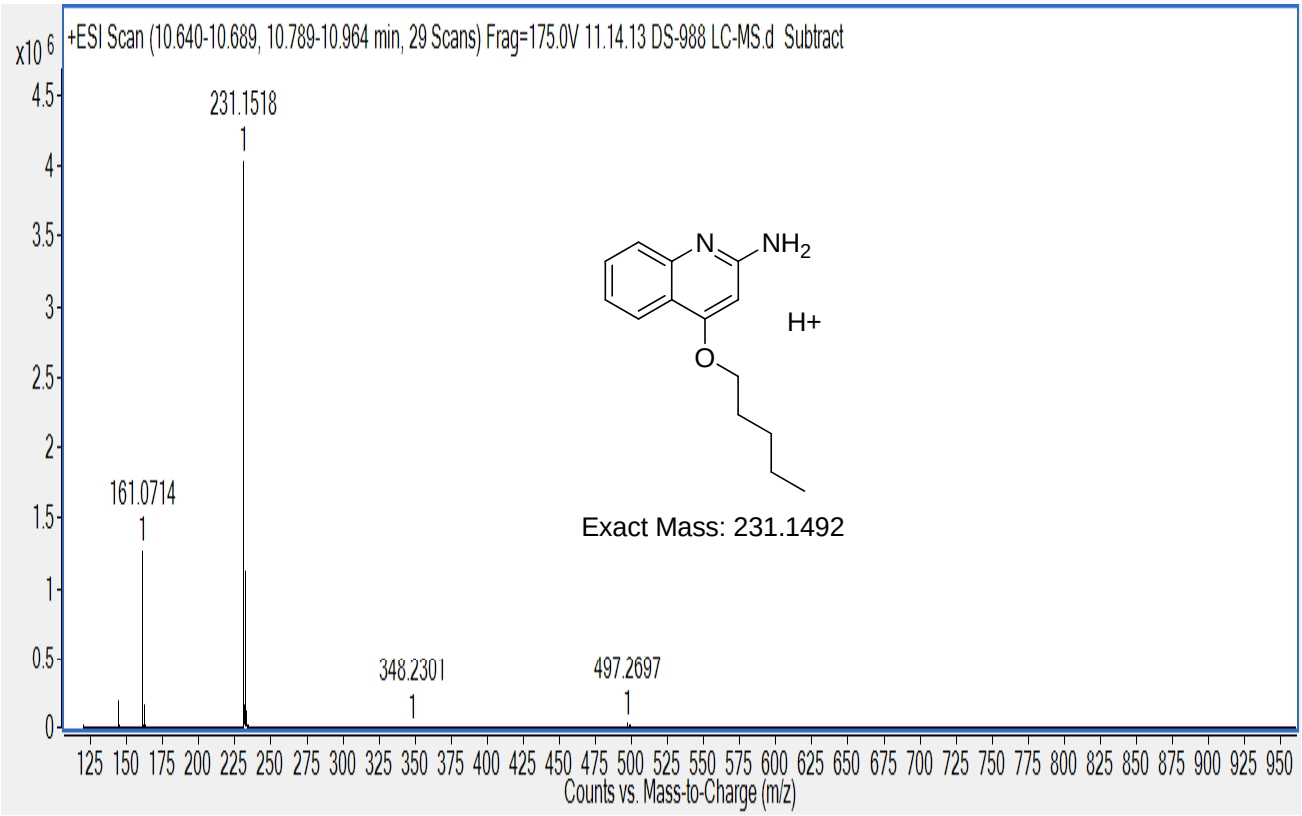
Compound **24b:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



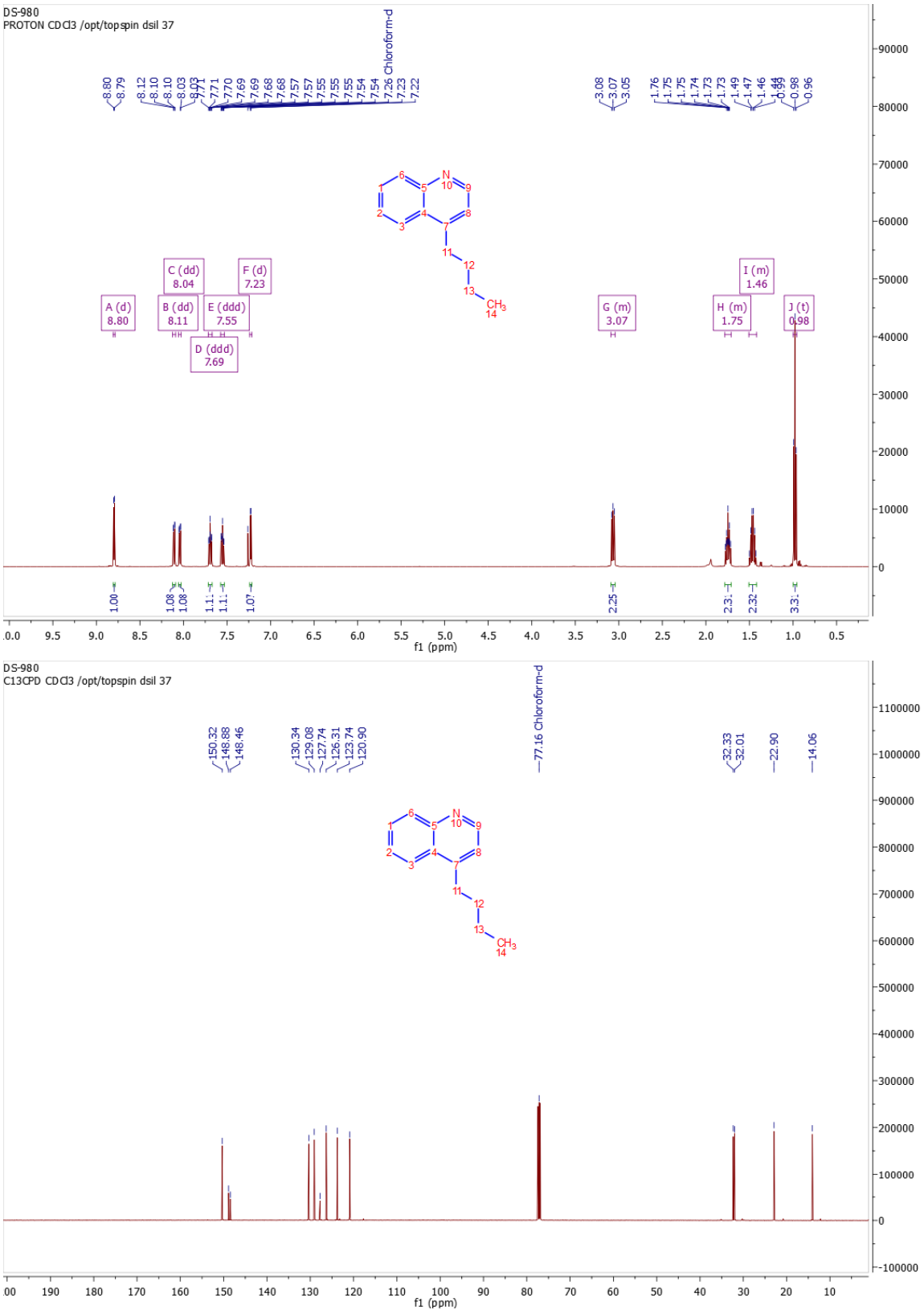


Compound **24b:** LC-MS

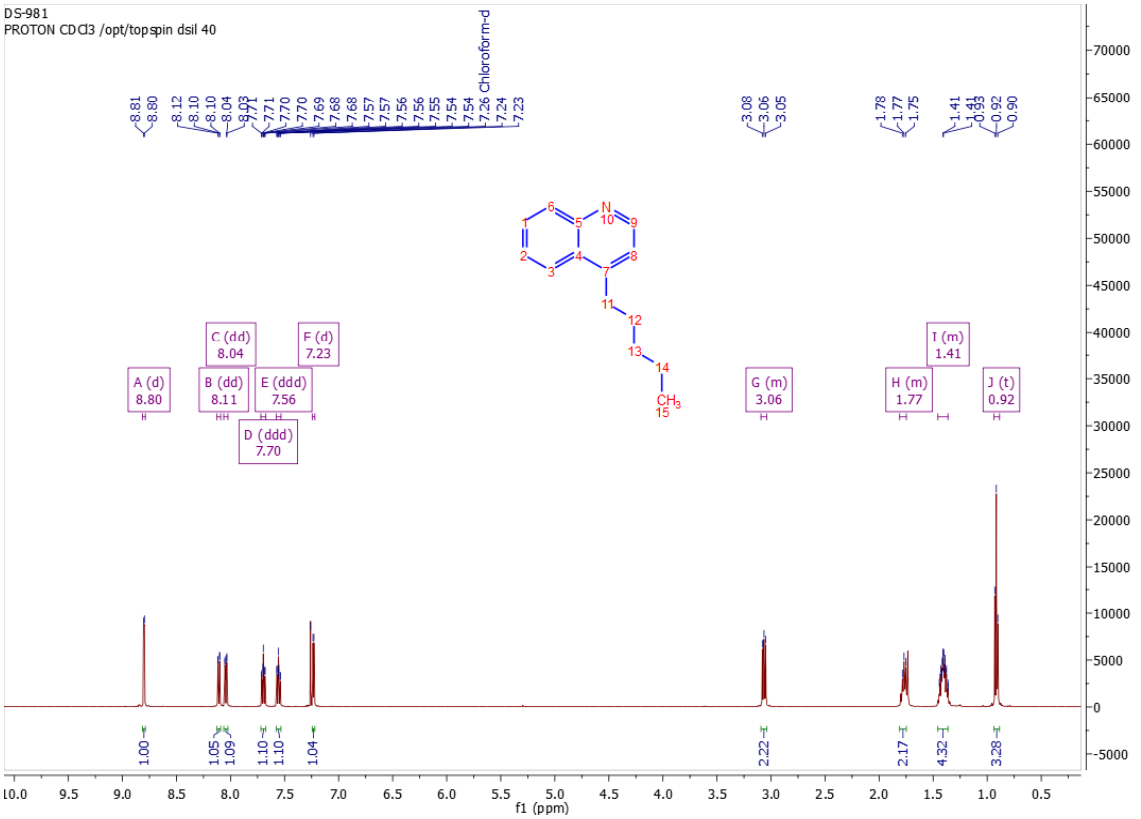


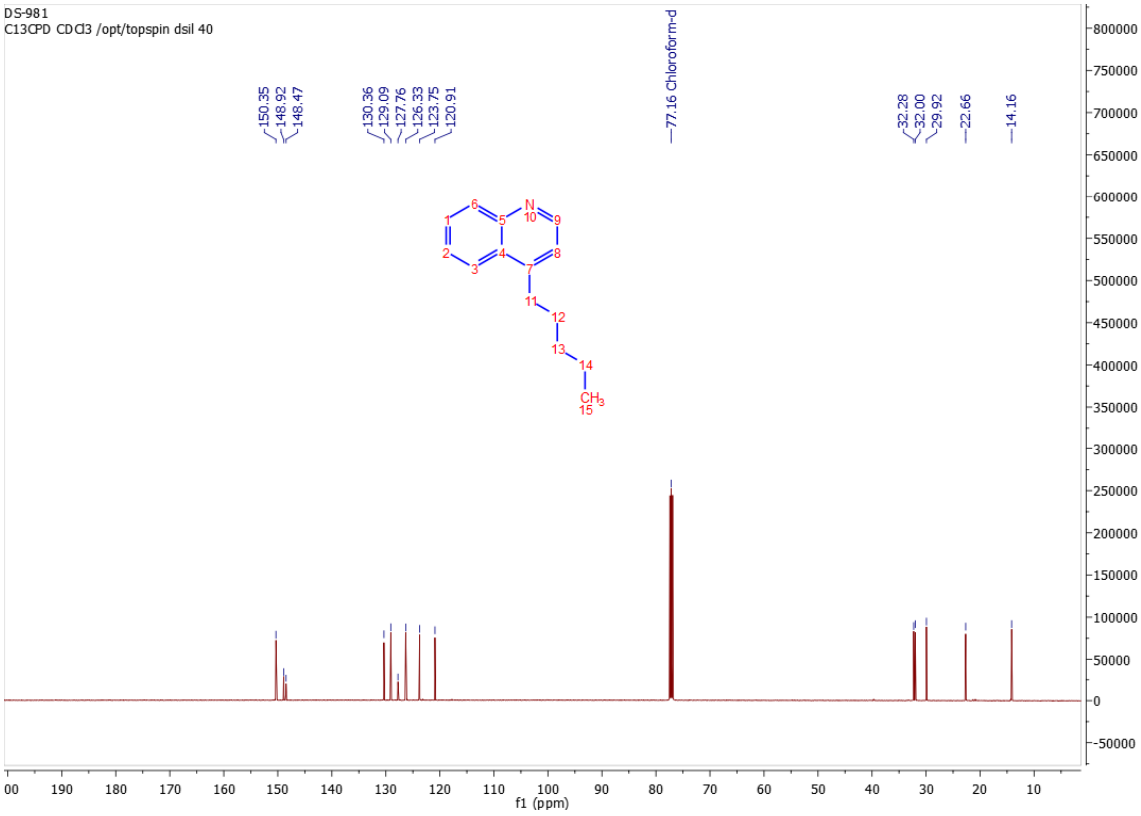


Compound **26a:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)

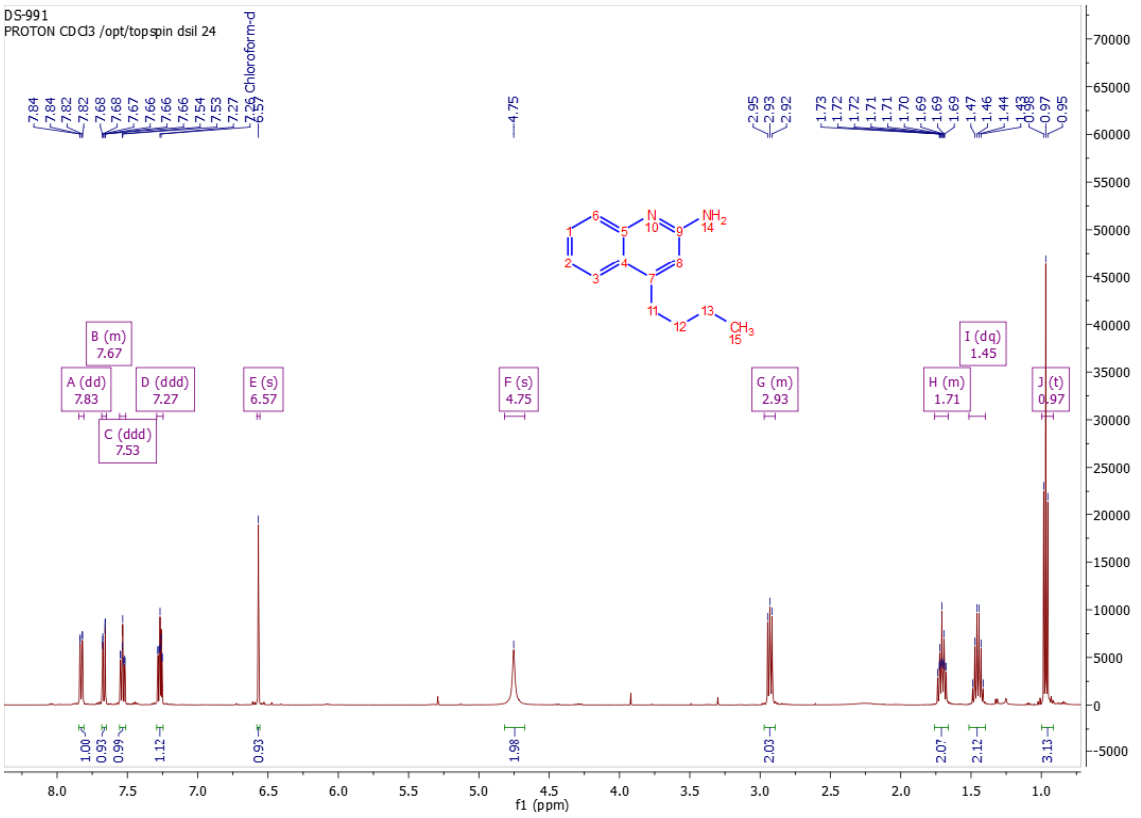


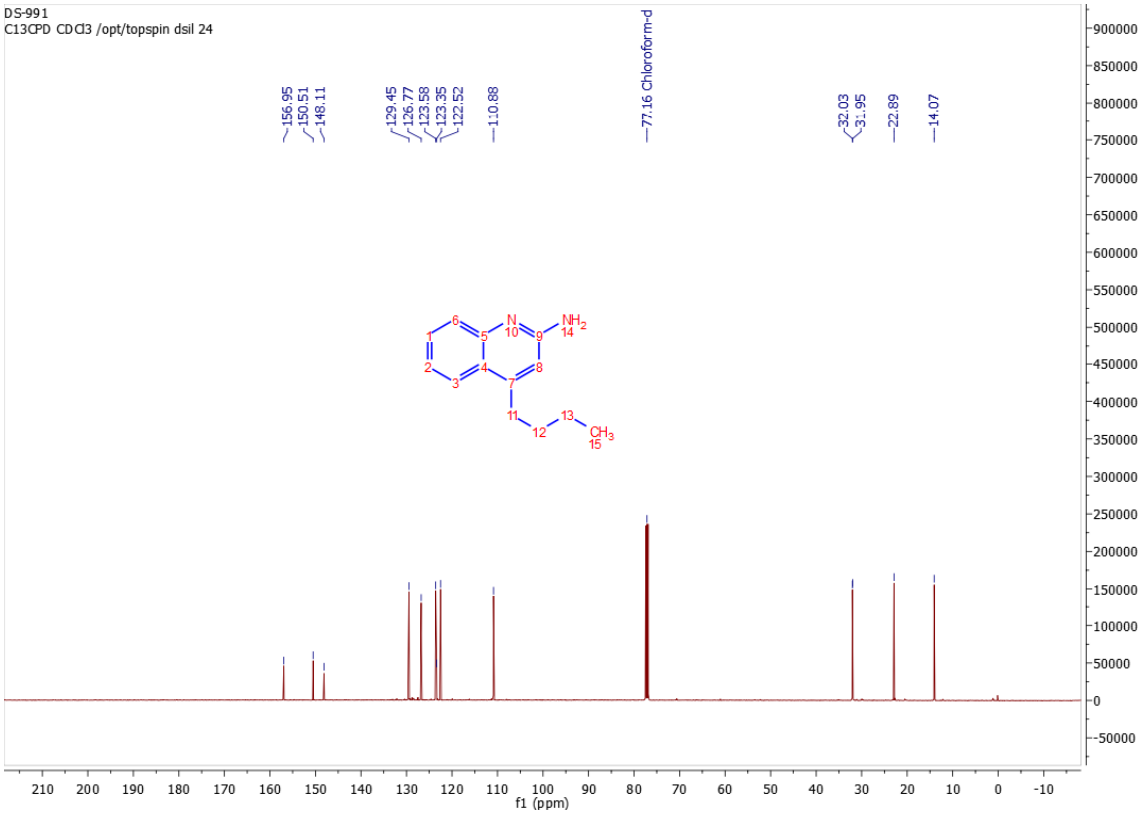
Compound **26b:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



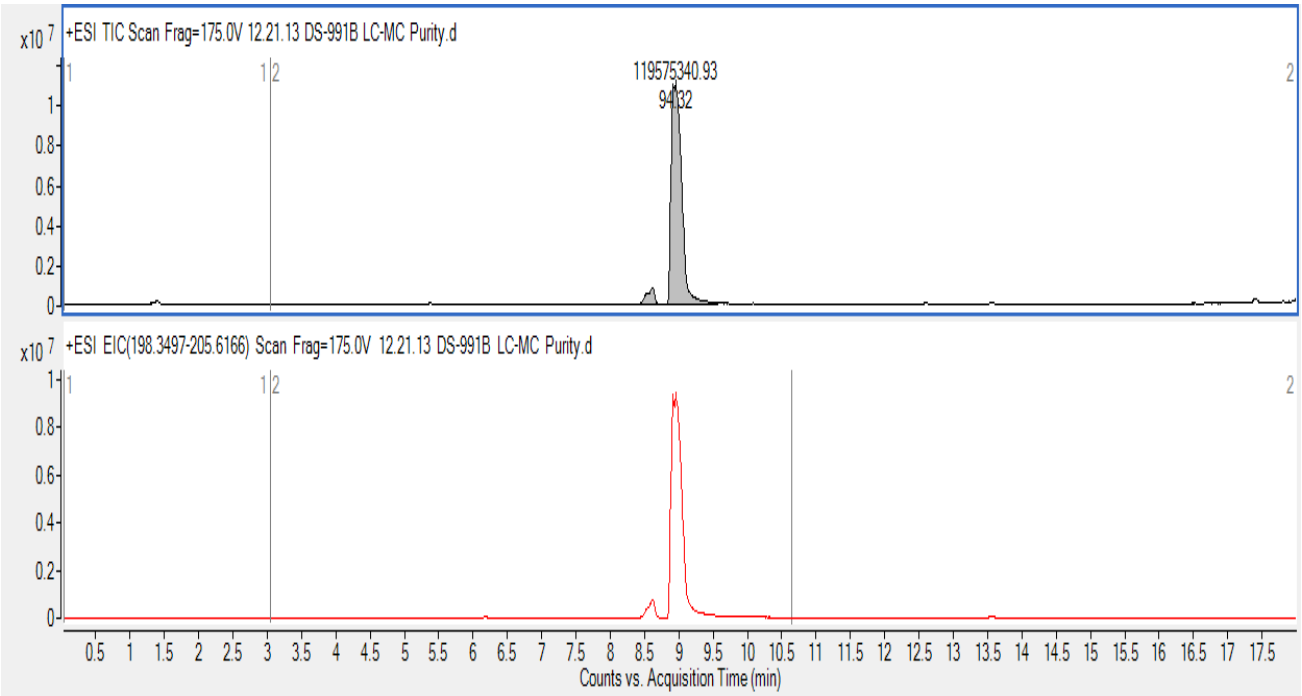


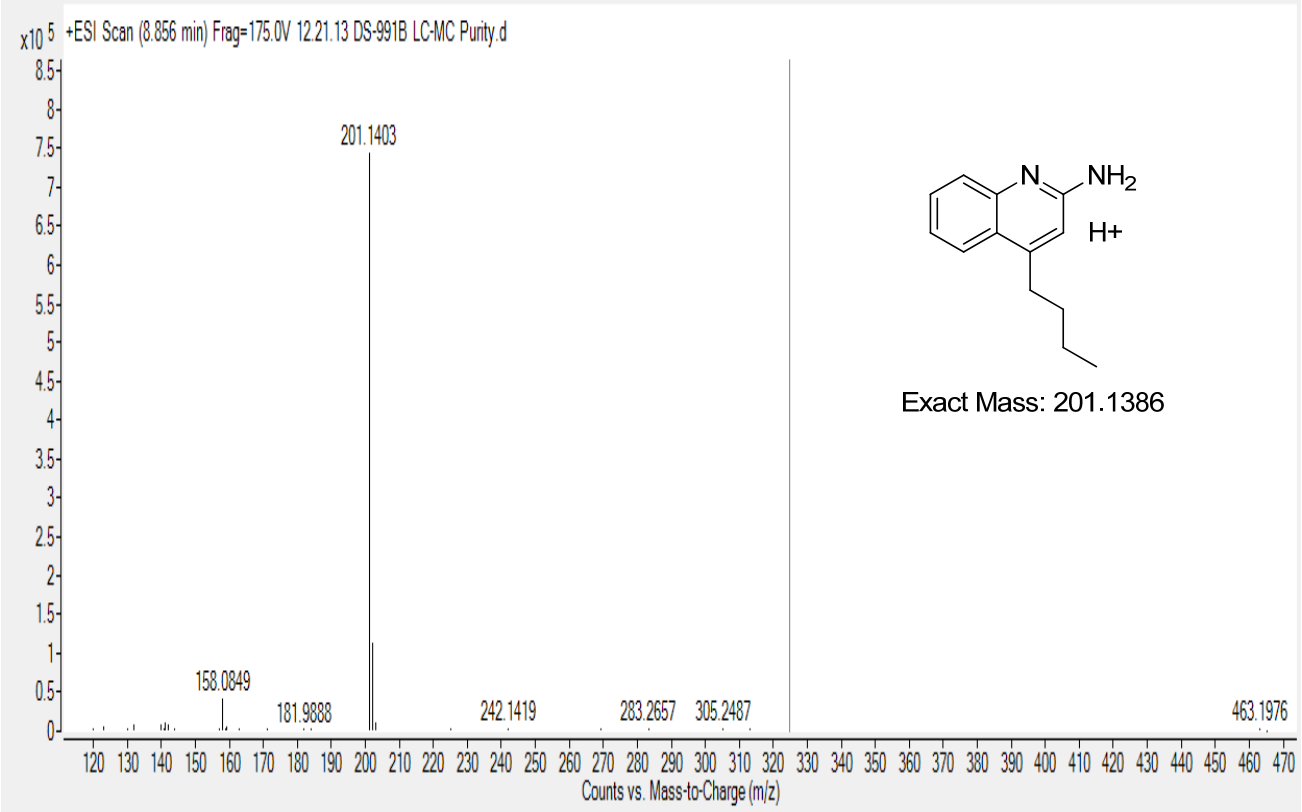
Compound **27a:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)



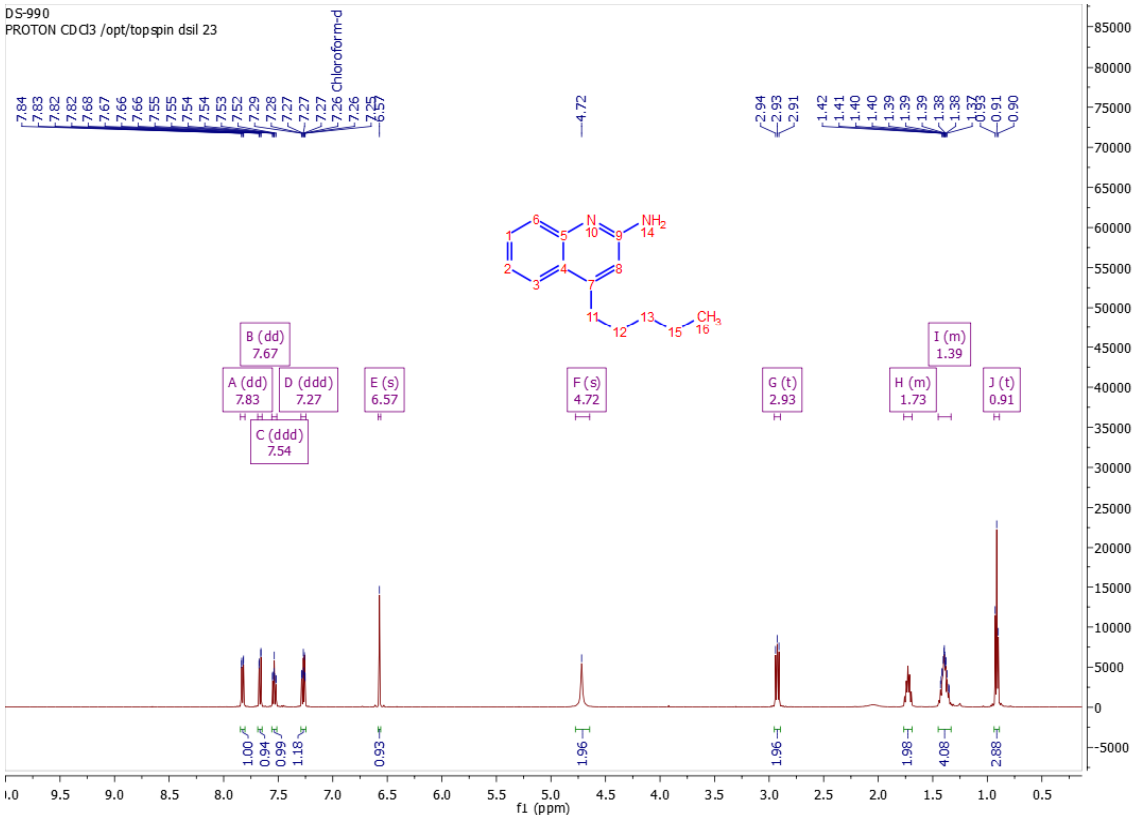


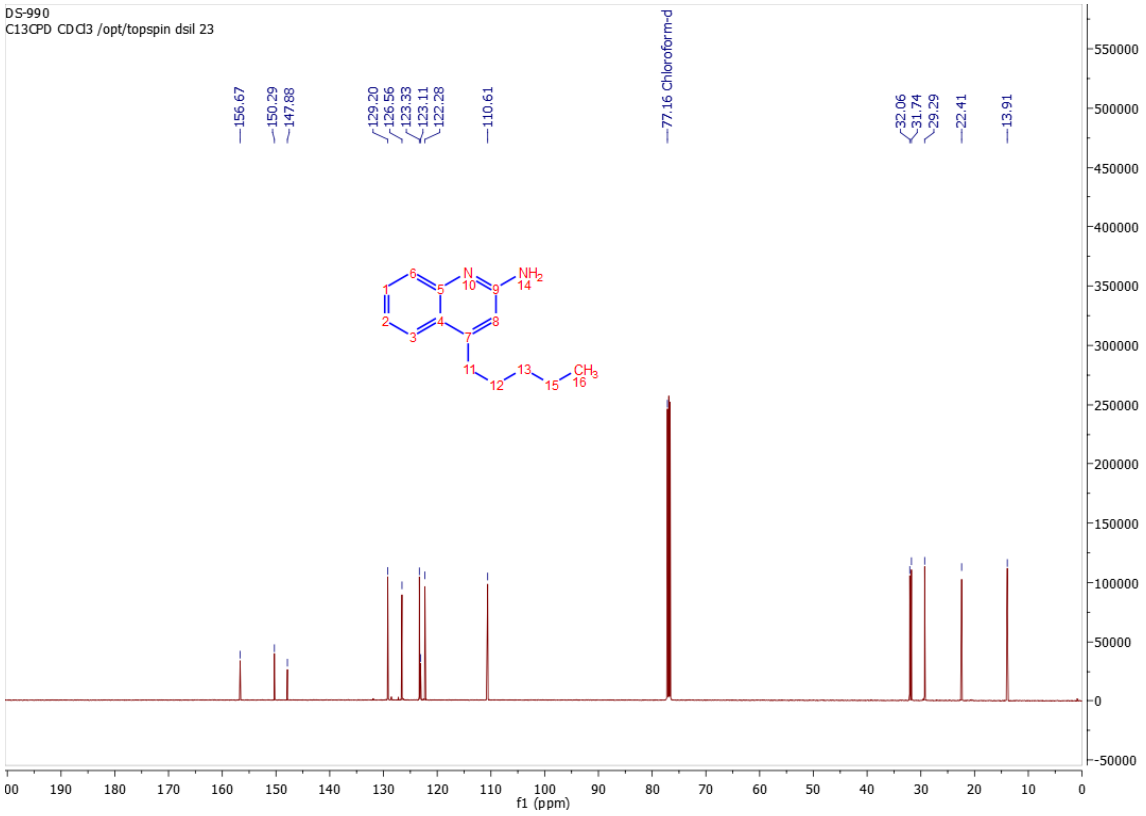
Compound **27a:** LC-MS





Compound **27b:** ^{1}H and ^{13}C NMR Spectrum ($CDCl_3$)





Compound **27b:** LC-MS