Supporting Information

Copper-Catalyzed Intermolecular Carboesterification of Unactivated Aliphatic Alkenes with α-Carbonyl Alkyl Bromides via a SET Process: Efficient Synthesis of γ-Lactones

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1. General Information

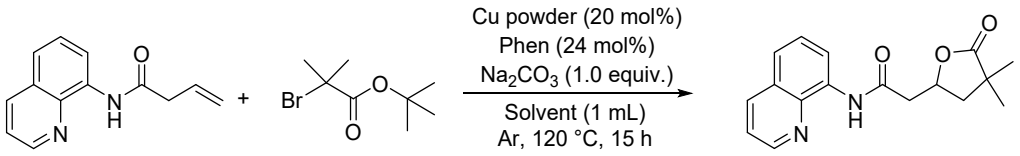
Unless otherwise noted, all manipulations were carried out under an argon atmosphere, and all reagents were purchased from commercial suppliers without further purification. Dry MeCN was distilled over sodium hydride. Dry THF was distilled over sodium-benzophenone. All glassware and stirring bars were dried in an oven at 110 °C overnight unless otherwise stated.

Reactions were monitored by Thin Layer Chromatography (TLC) on plates (GF254) visualized by UV or stained with diazotization reagent and bromocresol green. The products were purified by column chromatography over silica gel (200-300 size).

NMR spectra were recorded on Bruker DPX-400 spectrometer (^{1}H: 400 MHz; ^{13}C: 100 MHz; ^{19}F: 376 MHz) and TMS was used as internal standard. ^{1}H, ^{13}C and ^{19}F multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplet s, td = triplet of dublets, m = multiplet, br = broad. Melting points were measured using a WC-1 microscopic apparatus and are uncorrected. High resolution mass spectra were ensured on an Agilent Technologies 1290-6540 UHPLC/Accurate-Mass Quadrupole Time-of-Flight LC/MS.

2. Optimization of Reaction Conditions

Table S1. Optimization of Solvent[a]

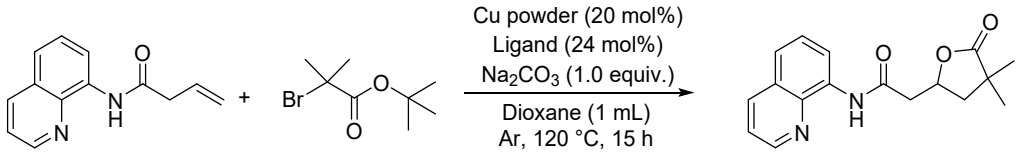


1a **2a** **3aa**

Entry	Solvent	Yield (%)[b]
1	DCE	40
2	1,4-Dioxane	66
3	THF	61
4	t-AmylOH	44
5	Toluene	48
6	DMA	<5%
7	1,4-Dioxane:THF (9:1)	62
8[c]	MeCN	48

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), Cu powder (20 mol%), Phen (24 mol%), Na_2CO_3 (1.0 equiv.) in Solvent (1.0 mL) at 120 °C under the argon atmosphere for 15 h. [b]Isolated yield. [c]MeCN (0.2 mL).

Table S2. Optimization of Ligand[a]



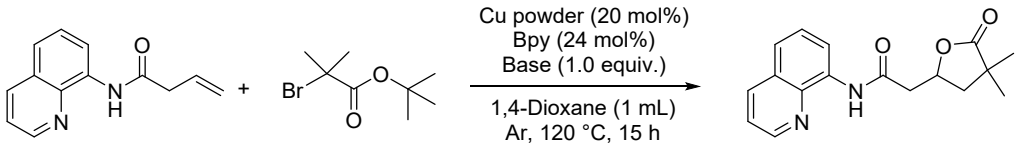
1a **2a** **3aa**

Entry	Ligand	Yield (%)[b]
1	2,9-dimethyl-1,10-	<5%

	phenanthroline	
2	Phen	66
3	Dtbpy	78
4	Bpy	82
5	PPh_3	71
6	DPPE	<5%

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), Cu powder (20 mol%), Ligand (24 mol%), Na_2CO_3 (1.0 equiv.) in 1,4-Dioxane (1.0 mL) at 120 °C under the argon atmosphere for 15 h. [b]Isolated yield.

Table S3. Optimization of Base[a]

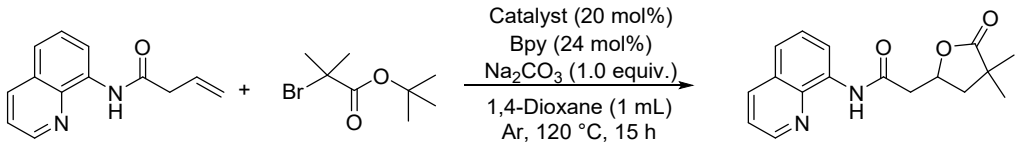


1a **2a** **3aa**

Entry	Base	Yield (%)[b]
1	Na_2CO_3	82
2	K_2CO_3	19
3	Cs_2CO_3	<5%
4	NaOAc	39
5	^{t}BuONa	<5%
6	K_3PO_4	53
7	K_2HPO_4	46

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), Cu powder (20 mol%), Bpy (24 mol%), Base (1.0 equiv.) in 1,4-Dioxane (1.0 mL) at 120 °C under the argon atmosphere for 15 h. [b]Isolated yield.

Table S4. Optimization of Catalyst[a]



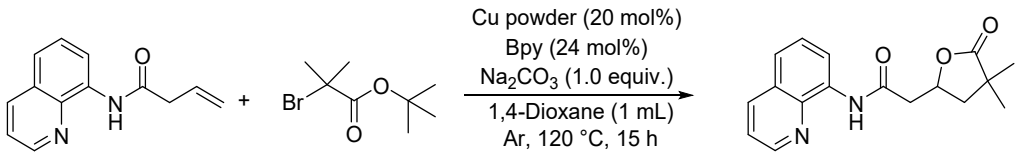
1a **2a** **3aa**

Entry	Catalyst	Yield (%)[b]
1	$Cu(OTf)_2$	73
2	$CuF_2{\cdot}2H_2O$	67
3	$CuBr_2$	78
4	CuI	76
5	CuCl	69
6	CuSCN	76
7	CuOAc	74
8	CuBr	79
9	Cu powder	82
10[c]	Cu powder	77

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), Catalyst (20 mol%), Bpy (24 mol%), Na_2CO_3 (1.0 equiv.)

in 1,4-Dioxane (1.0 mL) at 120 °C under the argon atmosphere for 15 h. [b]Isolated yield. [c]Cu powder (20 mol%), Bpy (20 mol%).

Table S5. Control Experiment[a]

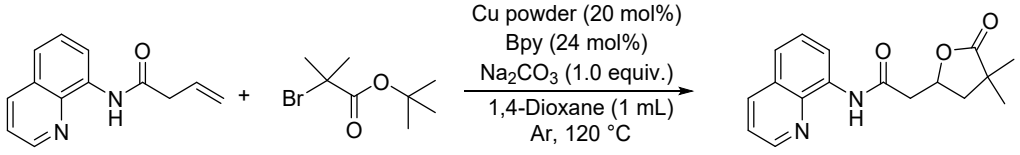


1a **2a** **3aa**

Entry		Yield (%)[b]
1	standard	82
2	Without Cu powder	<5
3	Without Bpy	66
4	Without Na_2CO_3	<5
5	With 0.1 mL H_2O	37
6	In air instead of Ar	50
7	In O_2 instead of Ar	52

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), Cu powder (20 mol%), Bpy (24 mol%), Na_2CO_3 (1.0 equiv.) in 1,4-Dioxane (1.0 mL) at 120 °C under the argon atmosphere for 15 h. [b]Isolated yield.

Table S6. Optimization of Time[a]

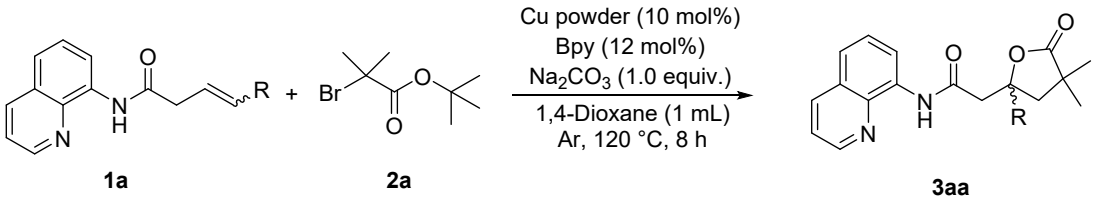


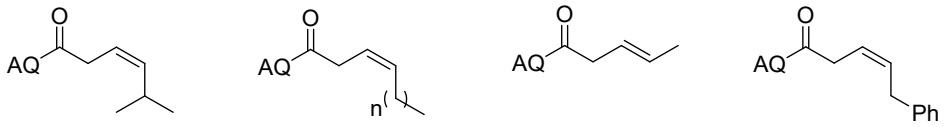
1a **2a** **3aa**

Entry	Time/h	Yield (%)[b]
1	4	74
2	5	74
3	8	80
4	12	81
5[c]	**8**	**81**

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), Cu powder (20 mol%), Bpy (24 mol%), Na_2CO_3 (1.0 equiv.) in 1,4-Dioxane (1.0 mL) at 120 °C under the argon atmosphere for 15 h. NR = no reaction. [b]Isolated yield. [c]Cu powder (10 mol%), Bpy (12 mol%).

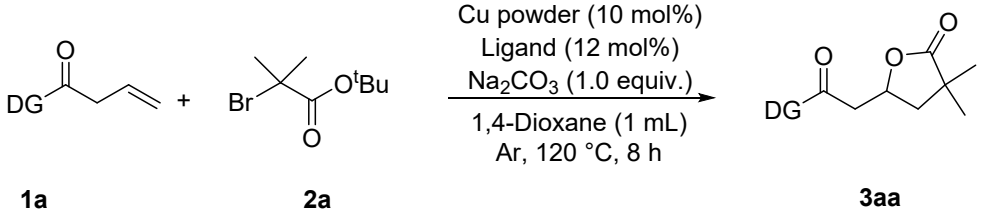
Table S7. Unsuccessful Examples of Unactivated Alkenes[a,b]

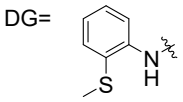
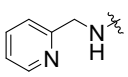




[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), Cu powder (10 mol %), Bpy (12 mol%), Na_2CO_3 (1.0 equiv.) in 1,4-Dioxane (1.0 mL) at 120 °C under the argon atmosphere for 8 h. [b]Isolated yield.

Table S8. Screen of Directing Group[a]

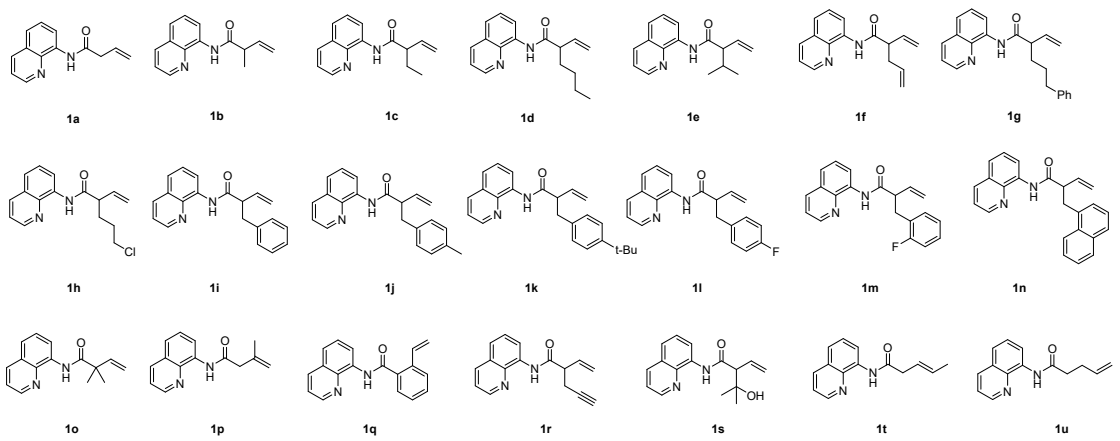


Entry	Ligand	Yield (%)[b]
1	8-Aminoquinoline	
	DG=  **A** 20%	 **B** 26%

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), Cu powder (10 mol%), 8-Aminoquinoline (12 mol%), Na_2CO_3 (1.0 equiv.) in 1,4-Dioxane (1.0 mL) at 120 °C under the argon atmosphere for 8 h. [b]Isolated yield.

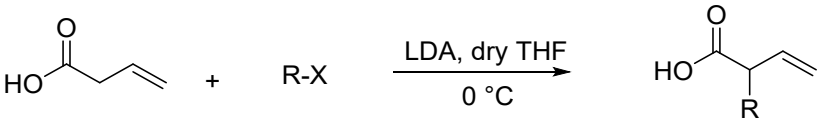
3. Experimental Procedure

3.1 General Procedure for Synthesis of Alkene Substrates 1



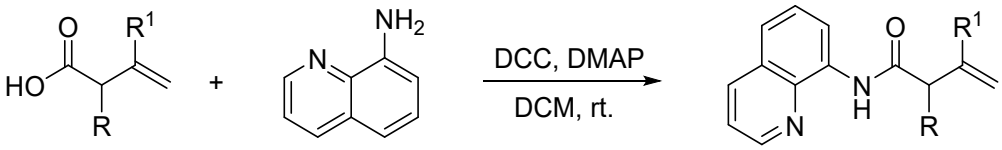
Alkene substrates **1a**[1], **1b**[2], **1c**-**1n**[3], **1o**[1], **1p**[4], **1q**[5], **1r**[3], **1s**[6], **1t**[7], **1u**[1] were prepared according to the reported procedures.

3.1.1 General Procedure for α-Substituted Vinyl Acetic Acids



A solution of LDA (6.6 ml, 13.2 mmol, 2.0 M in THF, 2.2 equiv.) in dry THF (8 mL) was added to a solution of vinyl acetic acid (6 mmol, 1.0 equiv.) in dry THF (3 mL) dropwise at 0 °C, and the resulting solution was stirred for 45 min. Then an alkylating agent (1.14 mL, 10 mmol, 1.0 equiv.) was added slowly at 0 °C and then the mixture was stirred for 30 min. After that, the resulting mixture was stirred for 3 h at room temperature, and water was added to the mixture. The mixture was acidified with 1M hydrochloric acid until pH = 2~3. The milky solution was then extracted with EtOAc (3 × 40 mL). The combined organic layers were dried by anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Analysis of the crude ^1H NMR spectrum revealed the amount of the desired acid. The combined organic layers were carried forward to the next step without further purification.

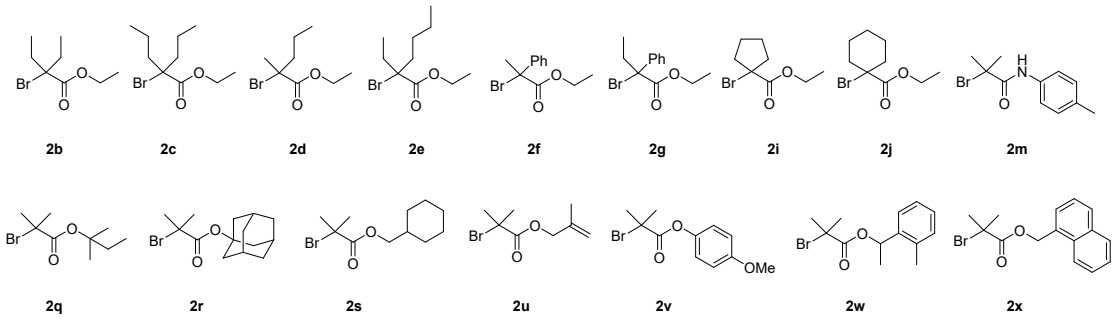
3.1.2 General Procedure for Substrates 1



A 100 mL two-necked round-bottom flask was equipped with a magnetic stir bar and charged with corresponding vinyl acetic acid (1.12 mL, 13 mmol), 8-aminoquinoline (1.44 g, 10 mmol), DMAP (0.1 equiv., 1.3 mmol) in 30 mL anhydrous CH_2Cl_2 at 0 ℃. After DCC (1.1 equiv., 13 mmol) in CH_2Cl_2 (20 mL) was added dropwise to the solution, the reaction was then warmed to room temperature and stirred for 16 h. The deep brown solution was diluted with EtOAc (80 mL),

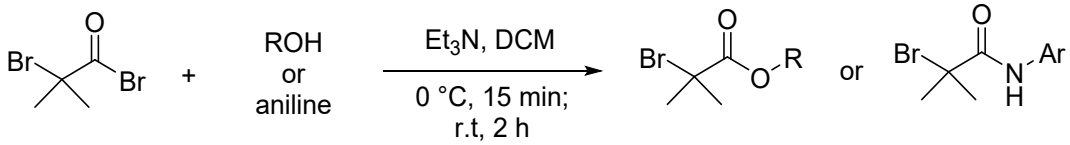
and washed with sat. $NaHCO_3$ (2 × 70 mL) and brine (1 × 70 mL). The combined organic solvent was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane/ethyl acetate = 15:1) (V/V) to afford the target product.

3.2 General Procedure for the Synthesis of α-Carbonyl Alkyl Bromides 2



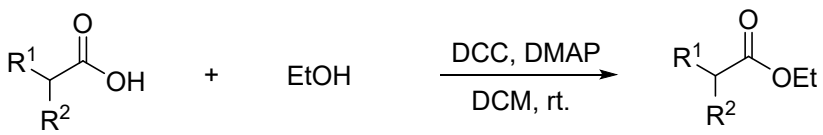
Substrates **2b**-**2j**[8], **2m**-**2x**[9] were prepared according to the corresponding literature methods.

3.2.1 General Procedure for 2-Bromoisobutyl Esters



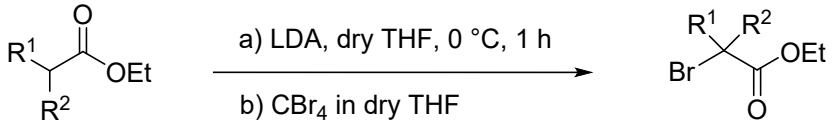
A 50 mL two-necked round-bottom flask was equipped with a magnetic stir bar and charged with corresponding alcohol or aniline (10 mmol, 1.0 equiv.) and triethylamine (10 mmol, 1.0 equiv.) in 15 mL anhydrous CH_2Cl_2 at 0 ℃ for 5-10 min. Subsequently, 2-bromoisobutyryl bromide (10 mmol, 1.0 equiv.) was added dropwise over 15 min to a stirred cooled solution. Upon completion, the reaction was stirred at 0 °C for 30 min, followed by stirring at room temperature for an additional 2 h. The reaction mixture was then transferred into a separatory funnel and washed with 0.1 M HCl (2 × 50 mL), saturated $NaHCO_3$ (1 × 50 mL), and brine (1 × 50 mL), and the combined organic solvent was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane/ethyl acetate = 30:1) (V/V) to afford the target product.

3.2.2 General Procedure for α-Carbonyl Alkyl Bromides



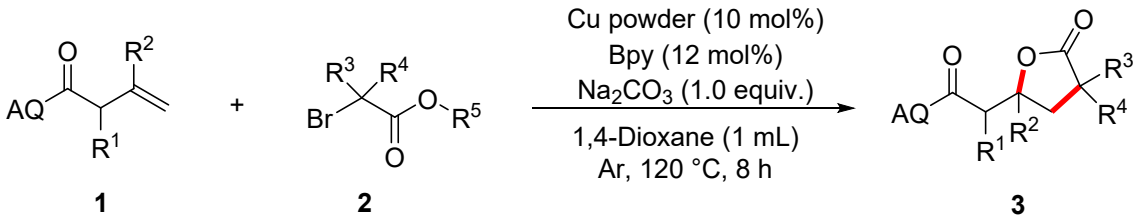
A 100 mL two-necked round-bottom flask was equipped with a magnetic stir bar and charged with carboxylic acid (15 mmol, 1.0 equiv.), ethanol (25.5 mmol, 1.7 equiv.), DMAP (0.45mmol, 0.03 equiv.) dissolved in 30 mL anhydrous DCM at 0 °C. After DCC (19.5 mmol, 1.3 equiv.) in DCM (20 mL) was added dropwise to the solution, the reaction was then warmed to room temperature, and stirred overnight. After the removal of solvent (DCM) by evaporation, the resulting

mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (hexane/ethyl acetate = 30/1) (V/V) to give the ester product.



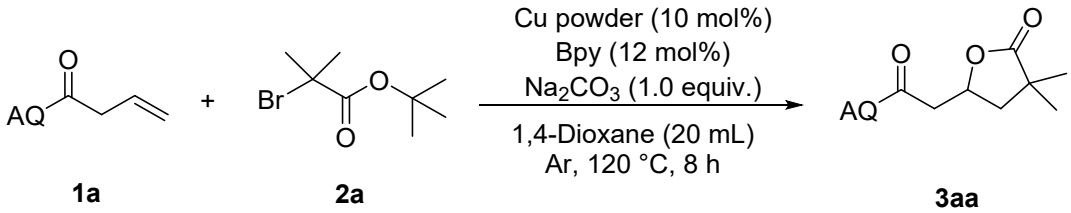
Under argon atmosphere, a 25 mL two-necked round-bottom flask was equipped with a magnetic stir bar and a rubber septum, and charged with LDA (5.5 ml, 5.5 mmol, 1.1 equiv.) in dry THF (8 mL) at 0 °C. The corresponding ester starting material (5 mmol, 1.0 equiv.) was added dropwise to the reaction and the reaction was further stirred for 1 h. Then a solution of CBr_4 (1.0 equiv.) in THF (3 mL) was added to the reaction slowly. Until the ester starting material was consumed, the reaction mixture was quenched with aq. NH_4Cl solution (10 mL) and extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by column chromatography (hexane/ethyl acetate = 15/1) (V/V) on silica gel to afford the desired α-bromocarboxylate product.

3.3 General Procedure for Products 3



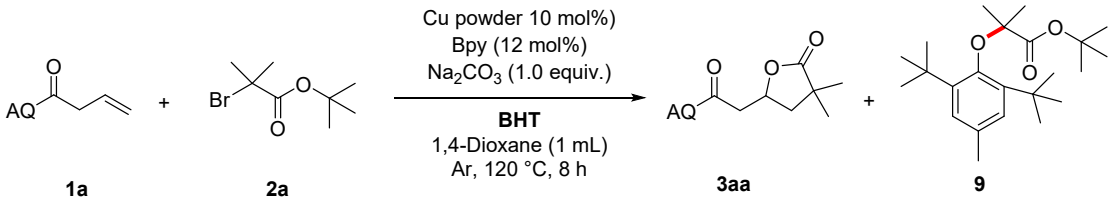
A Schlenk tube was equipped with a magnetic stir bar and charged with an alkene **1** (0.1 mmol, 1.0 equiv.), Cu powder (0.01 mmol, 0.1 equiv.), Bpy (0.012 mmol, 0.12 equiv.), Na_2CO_3 (0.1 mmol, 1.0 equiv.) in 1,4-Dioxane (1.0 mL). Under argon atmosphere, an alkyl bromide **2** (0.2 mmol, 2.0 equiv.) was added quickly, and the resulting mixture was degassed three times and heated at 120 ℃ for 8 h. Upon completion, the reaction mixture was cooled to room temperature, and DCM (20 mL) was added. The resulting mixture was filtered through a pad of Celite, concentrated in vacuum. The residue was purified by column chromatography on silica gel (100-200 mesh) to afford a corresponding product **3**.

3.4 Gram-scale Experiment



An oven-dried 50 mL Schlenk three-necked flask was equipped with a magnetic stirrer bar and charged with N-(8-quinolinyl)-3-butenamide **1a** (5 mmol, 1.0 equiv.), Cu powder (0.5 mmol, 0.1 equiv.), Bpy (0.6 mmol, 0.12 equiv.), Na_2CO_3 (5 mmol, 1.0 equiv.) in 1,4-Dioxane (20 mL). Under the argon atmosphere, *tert*-butyl α-bromoisobutyrate **2a** (10 mmol, 2.0 equiv.) was added quickly, and the resulting mixture was degassed three times and heated at 120 ℃ for 8 h. Upon completion, the reaction mixture was cooled to room temperature, and DCM (20 mL) was added. The resulting mixture was filtered through a pad of Celite, and concentrated in vacuum. The residue was purified by column chromatography (hexane/ethyl acetate = 5/1) (V/V) to afford **3aa** (1.014 g) as a light yellow solid in 68% yield.

3.5 The Experiment of Trapping the Radicals

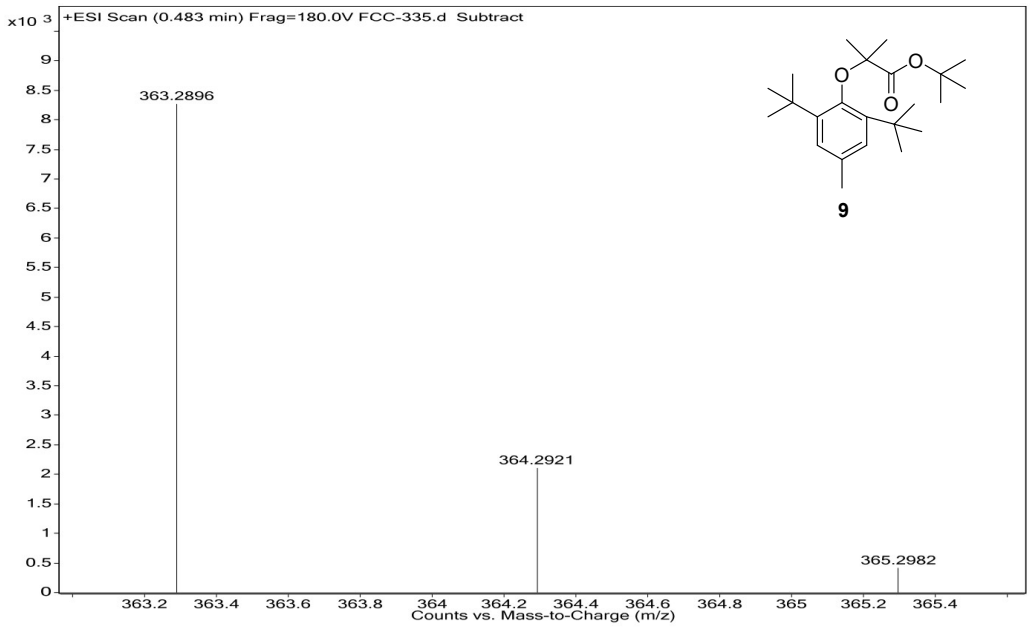


1a **2a** **3aa** **9**

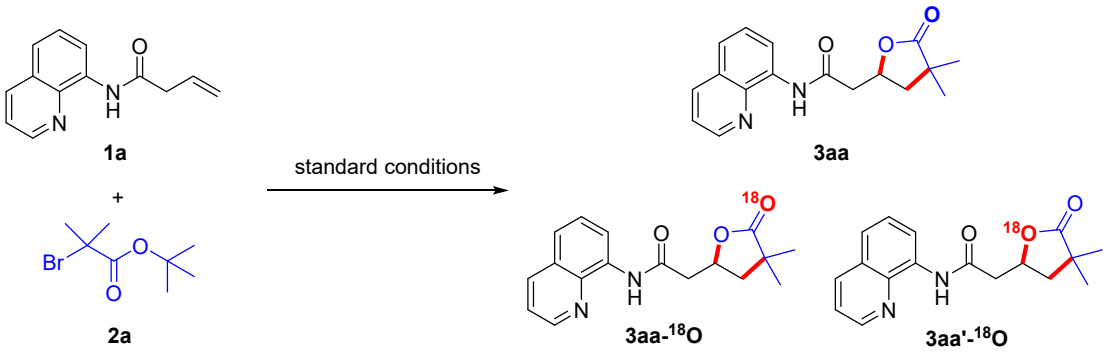
Radical scavenger	**3aa** Yield (%)	**9**
BHT (2.0 equiv.)	trace	89%
BHT (4.0 equiv.)	trace	94%

A Schlenk tube was equipped with a magnetic stir bar and charged with N-(8-quinolinyl)-3-butenamide **1a** (0.1 mmol, 1.0 equiv.), Cu powder (0.01 mmol, 0.1 equiv.), Bpy (0.012 mmol, 0.12 equiv.), Na_2CO_3 (0.1 mmol, 1.0 equiv.), BHT (2.0 or 4.0 equiv.) in 1,4-Dioxane (1.0 mL). Under argon atmosphere, *tert*-butyl α-bromoisobutyrate **2a** (0.2 mmol, 2.0 equiv.) was added quickly, and the resulting mixture was degassed three times and heated at 120 ℃ for 8 h. Upon completion, the reaction mixture was cooled to room temperature, and DCM (20 mL) was added to the reaction system. The resulting mixture was filtered through a pad of Celite, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (100-200 mesh) using hexane-ethyl acetate as an eluent (50/1) (V/V) to afford an adduct of BHT and α-carbonyl alkyl bromide as the product **9**.

9: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 2H), 1.48 (s, 9H), 1.24 (s, 21H), 1.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 174.7, 146.8, 143.9, 80.9, 49.1, 43.0, 34.9, 29.5, 28.1, 22.0, 21.8; HRMS (ESI) calcd for $C_{23}H_{39}O_3^+$ ([M + H]$^+$) : 363.2894, found: 363.2896.

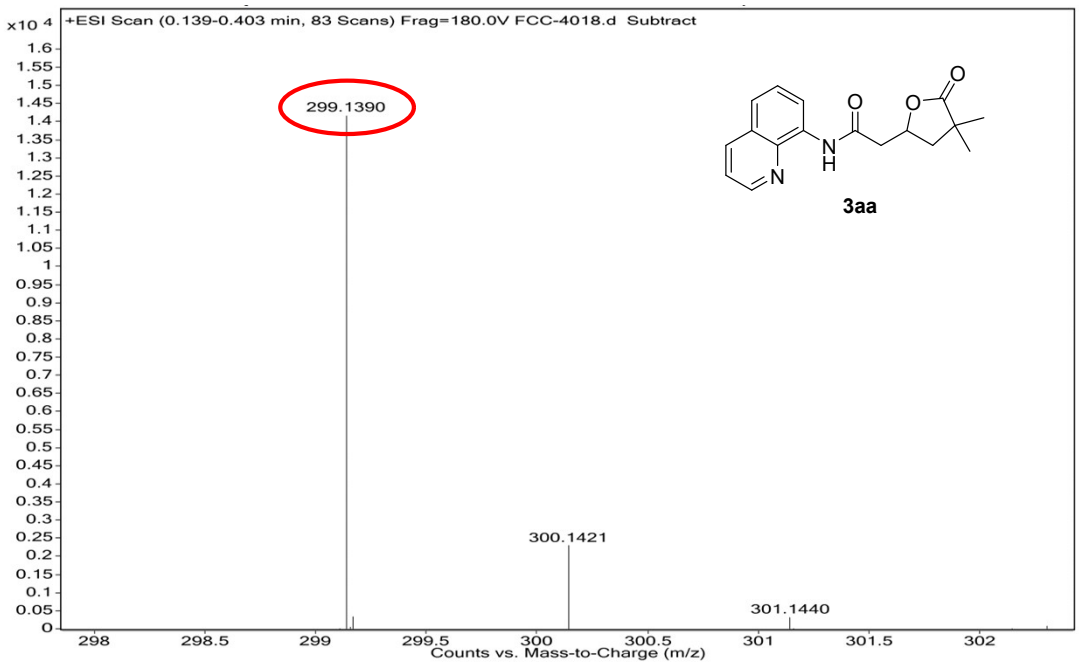


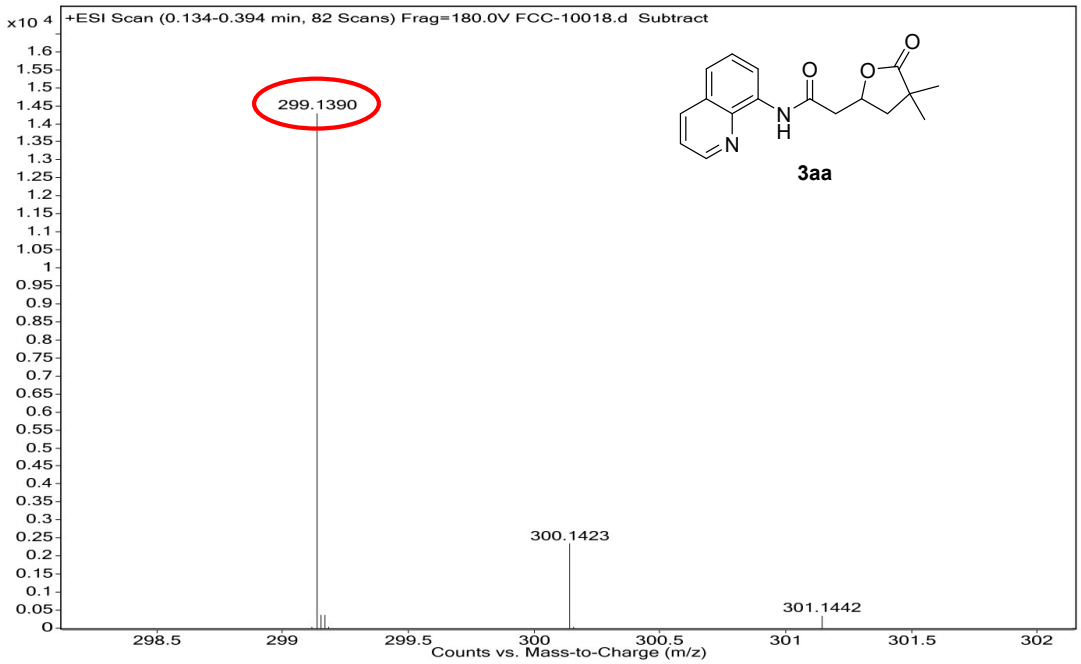
3.6 Isotopic Labelling Experiments



$H_2{}^{18}O$ (x equiv.)	Yield (%)
$H_2{}^{18}O$ (4.0 equiv.)	**3aa** (65%), **3aa/3aa'-^{18}O** (0%)
$H_2{}^{18}O$ (10.0 equiv.)	**3aa** (54%), **3aa/3aa'-^{18}O** (0%)

A Schlenk tube was equipped with a magnetic stir bar and charged with N-(8-quinolinyl)-3-butenamide **1a** (0.1 mmol, 1.0 equiv.), Cu powder (0.01 mmol, 0.1 equiv.), Bpy (0.012 mmol, 0.12 equiv.), Na_2CO_3 (0.1 mmol, 1.0 equiv.), $H_2{}^{18}O$ (4.0 or 10.0 equiv.) in 1,4-Dioxane (1.0 mL). Under argon atmosphere, *tert*-butyl α-bromoisobutyrate **2a** (0.2 mmol, 2.0 equiv.) was added quickly, and the resulting mixture was degassed three times and heated at 120 ℃ for 8 h. Upon completion, the reaction mixture was cooled to room temperature, and DCM (20 mL) was added. The resulting mixture was filtered, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (100-200 mesh).





4. Computational details

All geometry optimizations and transition state searches were performed with the program Gaussian 09 using the nonlocal method B3LYP.[10, 11] The LANL2DZ (Hay and Wadt's double-zeta effective core potential) basis set was used for Cu atom, and the 6-31G(d,p) basis set was used for C, H, O, N and Br atoms.[12] Solvation energies were obtained with the Truhlar's SMD solvation model, using acetonitrile as the model solvent.[13] The D3 version of Grimme's dispersion (GD3) was incorporated into the geometry optimizations. Throughout, we have employed harmonic vibrational

frequency calculations to confirm that the structures have been properly optimized. Intrinsic reaction coordination (IRC) calculations were performed to verify the connections between the transition state and the corresponding reactant and the product.[14] Single-point energy calculations were conducted with the 6-311G(2d,p)/LanL2TZ(f) basis set and the B3LYP functional.[12] The last number account for 1 atom/1M standard state change at 343.15K. All the relative energies throughout the paper are in kcal/mol and refer to Gibbs free energies with inclusion of the thermal contribution to the Gibbs free energy and the free energy of solvation.

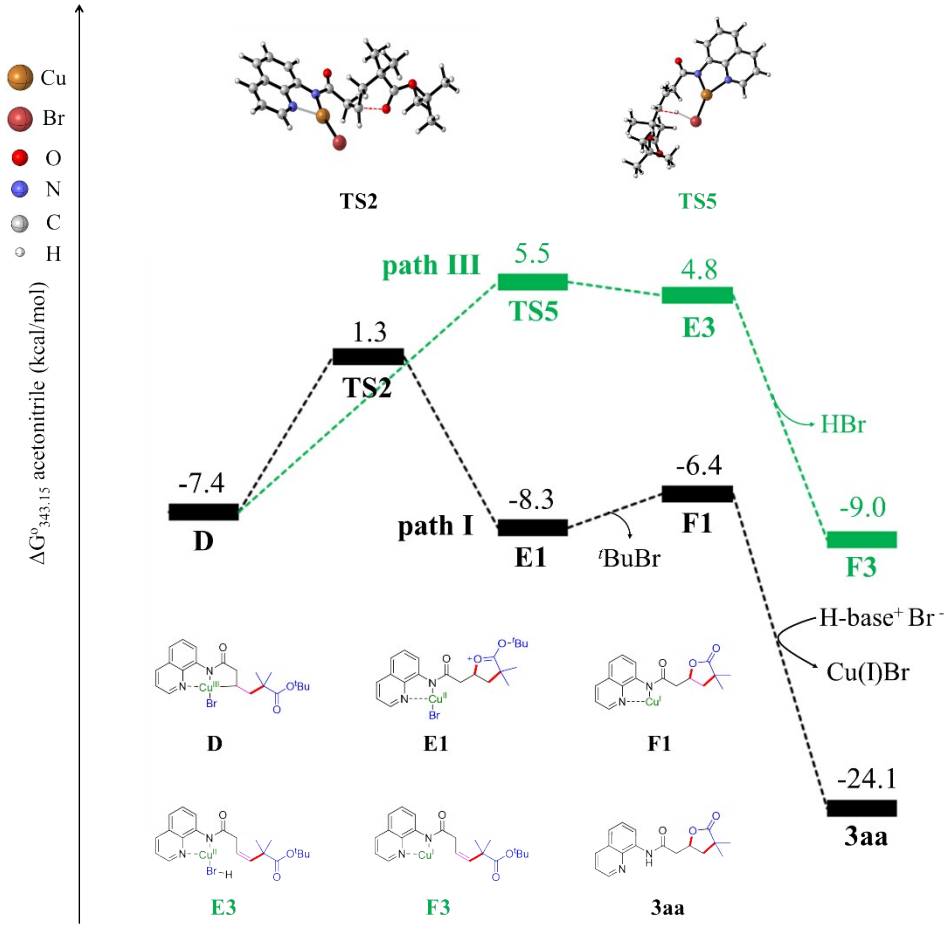


Figure S1 The energy profiles of intramolecular cyclization and concerted H-Br elimination.

Another is to cleave the Cu-C bond starting from the **D** by *β*-H transferring to the Br atom bound to the Cu center, with a $\Delta G^{\circ\ddagger}$ value of 12.9 kcal/mol and a negative Gibbs free energy change (ΔG°) value of 12.2 kcal/mol (path III). Then, the elimination of HBr gives the complex **F3**, with exoergicity of 1.6 kcal/mol. Therefore, our calculation showed that the *β*-H elimination is not a promising alternative route for production of the **3aa**, because this step lies 12.9 kcal/mol above **D** on the free energy profile. The highest transition state along path I is at 8.7 kcal/mol as well. Therefore, path I is more preferred than path III in terms of activation barriers and reaction energies.

Cartesian Coordinates of Optimized Structures

2a

Geometry with 26 atoms:
Total energy: -3038.528675950

O	0.481256	1.228098	-1.406897
C	0.211814	0.732382	-0.328905
O	1.049681	0.067874	0.465191
C	2.447059	-0.230759	0.065809
C	-1.193295	0.817913	0.292180
C	3.222380	1.075199	-0.107525
H	2.852138	1.646366	-0.959649
H	3.138600	1.688577	0.795288
H	4.280272	0.846068	-0.270054
C	2.439509	-1.088828	-1.199065
H	3.457568	-1.432607	-1.406711
H	1.801063	-1.966153	-1.055409
H	2.078182	-0.525761	-2.060685
C	2.967157	-1.022882	1.263469
H	2.374886	-1.930959	1.411561
H	4.008929	-1.309895	1.093544
H	2.916536	-0.420271	2.175559
C	-1.183233	0.964053	1.806907
H	-2.205643	0.979684	2.192191
H	-0.627520	0.159609	2.288113
H	-0.703396	1.917587	2.059536
C	-2.035621	1.874418	-0.402240
H	-1.603225	2.859119	-0.189233
H	-2.045539	1.731160	-1.483088
H	-3.059155	1.855293	-0.021568
Br	-2.004738	-1.005559	-0.153701

3aa

Geometry with 40 atoms:
Total energy: -993.827457764

C	3.915552	2.823394	-0.279675
C	4.678007	1.750494	0.123610
C	4.086818	0.463302	0.214285
C	2.705369	0.359780	-0.128064
C	2.552210	2.611422	-0.595713
H	5.847718	-0.610866	0.882623
H	4.337259	3.819974	-0.359026
H	5.728410	1.870607	0.375136
C	4.796472	-0.696711	0.623222
C	2.051574	-0.918697	-0.055796
H	1.934154	3.448175	-0.916149
C	2.772234	-2.031243	0.347494

C	4.142145	-1.907018	0.684068
H	2.280107	-2.991524	0.402717
H	4.679361	-2.798149	0.995944
N	1.962254	1.431031	-0.525873
C	-0.206041	-1.933191	-0.393729
O	0.072865	-3.078599	-0.045699
C	-2.023127	-0.123877	-0.915125
H	-1.400426	0.414529	-1.635677
C	-2.081354	0.602843	0.447712
H	-1.674394	1.611960	0.342974
H	-1.490276	0.083171	1.205304
O	-3.374462	-0.058881	-1.453770
C	-4.265220	0.364034	-0.525232
O	-5.444692	0.462684	-0.782807
C	-3.580077	0.656783	0.809235
C	-1.619492	-1.597518	-0.861138
H	-2.296695	-2.142828	-0.198080
H	-1.734354	-2.034864	-1.860138
N	0.699185	-0.905934	-0.416904
H	0.402006	0.020311	-0.710227
C	-3.993441	-0.445138	1.806390
H	-3.510269	-0.265430	2.772215
H	-5.077963	-0.440259	1.953553
H	-3.699590	-1.439945	1.457891
C	-4.026786	2.030793	1.326612
H	-3.535407	2.249811	2.280223
H	-3.768750	2.824133	0.617283
H	-5.109713	2.047184	1.482158

A

Geometry with 25 atoms:

Total energy: -464.307951896

O	0.567945	-1.655409	-0.004230
C	0.735638	-0.433738	-0.003307
O	-0.266827	0.479663	0.001081
C	-1.683508	0.085020	0.000903
C	2.041683	0.209366	-0.006798
C	2.161451	1.698935	-0.003021
H	3.205694	2.012156	-0.086104
H	1.591003	2.147631	-0.825658
H	1.746128	2.126501	0.920359
C	3.266568	-0.638421	0.005901
H	3.021544	-1.701833	0.014256
H	3.894104	-0.423458	-0.871267

H	3.886383	-0.408048	0.884821
C	-2.405676	1.432792	0.004479
H	-3.488856	1.278161	0.005408
H	-2.136067	2.011661	0.893481
H	-2.138171	2.015301	-0.882793
C	-2.008080	-0.705455	1.271004
H	-3.087854	-0.877273	1.327538
H	-1.496975	-1.668848	1.276466
H	-1.703753	-0.138311	2.156826
C	-2.009460	-0.699454	-1.272547
H	-3.089322	-0.870803	-1.328815
H	-1.705887	-0.128199	-2.155981
H	-1.498605	-1.662939	-1.283035

B

Geometry with 28 atoms:

Total energy: -882.894266410

C	3.028625	-2.287096	0.053776
C	3.625218	-1.046299	0.026934
C	2.826387	0.125993	-0.000399
C	1.407920	-0.038829	-0.000944
C	1.620405	-2.362440	0.053197
H	4.461293	1.549432	-0.028078
H	3.614785	-3.199523	0.076355
H	4.707532	-0.947364	0.027308
C	3.381500	1.433045	-0.025848
C	0.534506	1.120790	-0.024896
H	1.118076	-3.324763	0.076226
C	1.134506	2.382569	-0.046461
C	2.539702	2.525627	-0.047479
H	0.492267	3.253484	-0.059648
H	2.960234	3.528005	-0.066748
N	0.838638	-1.290128	0.026580
N	-0.807868	0.824795	-0.016662
C	-1.837636	1.698441	0.063041
O	-1.805137	2.937965	0.088593
C	-3.188086	0.945327	0.202899
H	-3.390927	0.843356	1.276706
H	-3.977665	1.574302	-0.222503
C	-3.203205	-0.416760	-0.455211
H	-3.188448	-0.400962	-1.547104
C	-3.393740	-1.624248	0.167323
H	-3.565482	-2.528457	-0.410604
H	-3.560723	-1.681808	1.241766

Cu -1.251788 -1.160304 -0.032326

Br-

Geometry with 1 atoms:
Total energy: -2574.247273620
Br 0.000000 0.000000 0.000000

CuBr

Geometry with 2 atoms:
Total energy: -2770.364963710
Cu 0.000000 0.000000 -1.255933
Br 0.000000 0.000000 1.040630

C(closed-shell)

Geometry with 54 atoms:
Total energy: -3921.821222820
C -0.248791 -3.817891 -0.259164
C -1.586675 -4.004352 -0.532843
C -2.479204 -2.903026 -0.503281
C -1.935837 -1.618512 -0.199464
C 0.200734 -2.517986 0.045011
H -4.274415 -3.996794 -1.033382
H 0.456191 -4.641763 -0.268826
H -1.974660 -4.991142 -0.770263
C -3.864390 -3.022350 -0.785928
C -2.771126 -0.441889 -0.155551
H 1.245455 -2.340195 0.288139
C -4.128100 -0.618839 -0.452754
C -4.654017 -1.892453 -0.759474
H -4.780685 0.240396 -0.423451
H -5.714960 -1.971572 -0.980891
N -0.602460 -1.467044 0.052940
N -2.126936 0.738166 0.189488
C -2.789011 1.914522 0.430095
O -4.019307 2.060787 0.453483
C -1.889014 3.104024 0.754478
H -1.077044 3.166548 0.019087
H -2.495882 4.008923 0.629615
C -1.299675 3.106649 2.144642
H -0.680811 3.977009 2.365571
C -1.475235 2.182839 3.092938
H -2.075915 1.291620 2.928789
H -1.017454 2.289881 4.072738
Cu -0.139912 0.600899 -0.009578

Br	0.220779	1.853233	-2.113212
O	1.725256	0.726959	0.573607
C	2.474674	-0.144739	1.096228
O	3.615976	-0.558149	0.538108
C	4.015465	-0.202967	-0.847005
C	2.181027	-0.726584	2.376993
C	4.111116	1.314207	-1.018111
H	3.123758	1.774379	-1.065994
H	4.683249	1.753535	-0.194295
H	4.641851	1.527315	-1.951892
C	3.017236	-0.839575	-1.813916
H	3.379233	-0.706558	-2.838515
H	2.926517	-1.912529	-1.617952
H	2.036747	-0.366093	-1.740822
C	5.391241	-0.857373	-0.955842
H	5.322550	-1.933485	-0.769230
H	5.794129	-0.703062	-1.960711
H	6.085203	-0.419998	-0.231332
C	3.133599	-1.621708	3.068795
H	2.617279	-2.547031	3.363108
H	4.014838	-1.859128	2.475526
H	3.447117	-1.152398	4.014283
C	0.871904	-0.446393	2.994591
H	0.888067	-0.615788	4.073715
H	0.512819	0.560857	2.758110
H	0.121855	-1.130402	2.557856

C(open-shell)

Geometry with 54 atoms:

Total energy: -3921.850005100

C	1.823207	3.408646	-1.420609
C	3.175285	3.174568	-1.285085
C	3.636089	1.962778	-0.708397
C	2.649492	1.024243	-0.287180
C	0.914654	2.427699	-0.973115
H	5.764571	2.349551	-0.863955
H	1.447585	4.326400	-1.859676
H	3.902779	3.909738	-1.618203
C	5.007682	1.640981	-0.541490
C	3.010689	-0.237093	0.301716
H	-0.159555	2.565342	-1.045827
C	4.373319	-0.508872	0.438723
C	5.346798	0.428228	0.019725
H	4.677383	-1.446595	0.879359

H	6.394665	0.170753	0.149383
N	1.319577	1.289437	-0.433084
N	1.938943	-1.040526	0.679179
C	2.054292	-2.250813	1.293666
O	3.114864	-2.791445	1.633434
C	0.731781	-2.991542	1.519549
H	0.563471	-3.599496	0.623926
H	0.887941	-3.682372	2.355527
C	-0.500511	-2.156141	1.764399
H	-1.428155	-2.542744	1.350260
C	-0.549294	-1.022914	2.489996
H	0.336761	-0.591309	2.947639
H	-1.492442	-0.514251	2.661029
Cu	0.172578	-0.360392	0.111090
Br	-0.234470	-1.974373	-1.785727
O	-1.567288	0.643444	-0.125510
C	-2.479991	1.175886	0.546834
O	-3.766868	0.981426	0.269536
C	-4.235437	-0.020129	-0.726247
C	-2.271329	2.078634	1.659002
C	-3.806483	-1.412150	-0.263597
H	-2.730272	-1.549240	-0.374521
H	-4.099586	-1.573673	0.778949
H	-4.310425	-2.162520	-0.881393
C	-3.703045	0.320122	-2.119397
H	-4.245430	-0.279762	-2.857637
H	-3.877777	1.377060	-2.346172
H	-2.638808	0.096482	-2.203053
C	-5.751065	0.151027	-0.654723
H	-6.039839	1.167212	-0.940697
H	-6.233368	-0.553348	-1.338260
H	-6.114039	-0.043110	0.359294
C	-3.449045	2.679087	2.352587
H	-3.134006	3.421667	3.089352
H	-4.136214	3.149019	1.639490
H	-4.030245	1.902558	2.869516
C	-0.897458	2.409356	2.123307
H	-0.826094	2.269624	3.209864
H	-0.125317	1.815288	1.637338
H	-0.684966	3.472753	1.936959

D

Geometry with 54 atoms:

Total energy: -3921.470713640

C	4.568217	1.786164	1.675353
C	5.152058	0.548168	1.838504
C	4.579132	-0.594349	1.223362
C	3.401866	-0.394935	0.448374
C	3.399866	1.894545	0.893573
H	6.003341	-2.065487	1.937231
H	4.986222	2.674569	2.135762
H	6.051376	0.430853	2.436833
C	5.107817	-1.905754	1.344550
C	2.750049	-1.485745	-0.213614
H	2.901095	2.846209	0.739661
C	3.299266	-2.756861	-0.063426
C	4.468538	-2.949307	0.710966
H	2.827825	-3.596964	-0.551639
H	4.864083	-3.957267	0.799955
N	2.842165	0.846067	0.307273
N	1.616072	-1.127309	-0.950909
C	0.869736	-1.984510	-1.718305
O	1.074656	-3.187636	-1.864180
C	-0.252728	-1.237193	-2.427676
H	0.087755	-1.062326	-3.454655
H	-1.132109	-1.886245	-2.478484
C	-0.597030	0.082799	-1.772595
H	-0.607991	0.915373	-2.474453
C	-1.780626	0.180736	-0.835015
H	-2.636275	-0.079123	-1.479728
H	-1.899491	1.233260	-0.564697
Cu	1.106820	0.709066	-0.782675
Br	0.425435	2.974377	-0.727273
O	-3.418431	0.264279	2.158340
C	-3.278112	-0.263488	1.070042
O	-4.277395	-0.579971	0.232891
C	-5.696595	-0.301515	0.546639
C	-1.915299	-0.666854	0.468135
C	-5.903847	1.205099	0.706400
H	-6.974003	1.414653	0.801675
H	-5.391553	1.583421	1.591650
H	-5.527502	1.734318	-0.175059
C	-6.417582	-0.822861	-0.695243
H	-6.220613	-1.890220	-0.835782
H	-7.496659	-0.679204	-0.587020
H	-6.082865	-0.286696	-1.588796
C	-6.111187	-1.088833	1.790291
H	-7.190905	-0.988016	1.939236

H	-5.879959	-2.150983	1.660021
H	-5.598288	-0.722078	2.680224
C	-0.822144	-0.331775	1.491797
H	0.131106	-0.757390	1.169378
H	-0.700908	0.749292	1.608259
H	-1.070163	-0.753944	2.468943
C	-1.952493	-2.189071	0.213702
H	-2.684976	-2.448839	-0.554206
H	-0.973055	-2.559831	-0.093687
H	-2.225220	-2.714882	1.135672

E1

Geometry with 54 atoms:

Total energy: -3921.464696490

C	5.639791	1.842143	0.951092
C	6.177078	0.591033	0.747048
C	5.354469	-0.471463	0.290889
C	3.971938	-0.188467	0.056559
C	4.266723	2.034973	0.695105
H	6.905744	-1.985822	0.246627
H	6.245133	2.672226	1.299765
H	7.230933	0.398680	0.930982
C	5.854660	-1.779654	0.066430
C	3.068591	-1.224179	-0.407739
H	3.805103	3.007425	0.843082
C	3.621841	-2.495130	-0.606718
C	4.989846	-2.757669	-0.373877
H	2.971985	-3.288469	-0.944793
H	5.359389	-3.765064	-0.549577
N	3.468628	1.065955	0.267442
N	1.750891	-0.835542	-0.623303
C	0.777955	-1.723117	-0.943906
O	0.859943	-2.961379	-1.063000
C	-1.243819	-0.896047	0.252082
H	-0.652155	-0.211689	0.858483
C	-1.670854	-2.172106	0.995103
H	-1.407582	-2.095720	2.052242
H	-1.165888	-3.042416	0.571724
Cu	1.435532	1.192687	-0.187054
O	-2.531200	-0.143447	0.049563
C	-3.537306	-0.869594	0.372565
O	-4.733690	-0.448082	0.284387
C	-5.128045	0.954300	-0.242444
C	-3.212388	-2.265562	0.834663

C	-0.609039	-1.079238	-1.115243
H	-1.226817	-1.742305	-1.725725
H	-0.531336	-0.097213	-1.588509
Br	-0.358088	2.698237	-0.115377
C	-4.462772	2.007179	0.634302
H	-3.387509	2.080896	0.457898
H	-4.916688	2.972885	0.391160
H	-4.650256	1.801614	1.692326
C	-4.716066	1.020694	-1.705447
H	-3.631075	1.028700	-1.822079
H	-5.139162	0.182564	-2.266157
H	-5.111232	1.950678	-2.125046
C	-6.636792	0.915570	-0.061456
H	-6.899894	0.797092	0.993377
H	-7.057952	1.858155	-0.421377
H	-7.077083	0.095327	-0.635013
C	-3.639872	-3.240594	-0.287598
H	-3.364469	-4.254660	0.014903
H	-4.721417	-3.201424	-0.444930
H	-3.136774	-3.012390	-1.231351
C	-3.944698	-2.590341	2.145472
H	-3.639568	-3.584592	2.483561
H	-3.695269	-1.865930	2.926499
H	-5.028012	-2.590776	1.996839

E2

Geometry with 54 atoms:

Total energy: -3921.427698590

C	5.160943	1.716873	-2.213479
C	5.464533	2.054858	-0.914571
C	4.732721	1.488830	0.161686
C	3.684520	0.565095	-0.152444
C	4.111757	0.803814	-2.441004
H	5.809502	2.516400	1.736943
H	5.703434	2.135836	-3.054227
H	6.263664	2.757155	-0.692440
C	5.011345	1.814857	1.512706
C	2.900142	-0.053671	0.904780
H	3.836982	0.514527	-3.451168
C	3.230311	0.309385	2.216879
C	4.260388	1.228686	2.507208
H	2.676861	-0.142821	3.026023
H	4.459595	1.468812	3.548641
N	3.407966	0.254924	-1.459520

N	1.859646	-0.901686	0.523049
C	1.178979	-1.658300	1.421068
O	1.447442	-1.836430	2.622455
C	-0.051474	-2.422056	0.884326
H	0.302401	-3.395979	0.526418
H	-0.684630	-2.619166	1.750647
C	-1.373693	-0.336661	-0.072810
H	-2.014257	-0.137085	-0.935023
H	-0.477183	0.284991	-0.197869
Cu	1.817837	-1.036271	-1.515781
O	-2.300910	2.596236	1.279124
C	-2.690870	1.533656	0.829368
O	-3.674087	1.398059	-0.074495
C	-4.374511	2.555433	-0.669026
C	-2.105231	0.157629	1.214254
C	-0.864655	-1.771712	-0.228265
H	-0.314250	-1.805622	-1.171636
Br	-2.387236	-3.050606	-0.696769
C	-1.139676	0.374986	2.390298
H	-0.747168	-0.571103	2.762548
H	-0.294256	1.004847	2.100212
H	-1.659086	0.874449	3.213777
C	-3.265259	-0.756616	1.657746
H	-3.970573	-0.937177	0.846103
H	-2.882170	-1.721310	1.998503
H	-3.804818	-0.293408	2.491877
C	-5.107741	3.336782	0.422437
H	-4.406589	3.825929	1.099497
H	-5.739925	4.100115	-0.042226
H	-5.749539	2.664924	1.001467
C	-3.375427	3.419099	-1.440830
H	-2.834133	2.810158	-2.172374
H	-3.914615	4.204108	-1.980531
H	-2.655084	3.887416	-0.768863
C	-5.366514	1.887700	-1.620112
H	-6.049919	1.234974	-1.068039
H	-5.955603	2.649113	-2.139971
H	-4.839019	1.285375	-2.366397

F1

Geometry with 40 atoms:

Total energy: -1189.399499000

C	-3.920981	-2.627873	0.119665
C	-4.617817	-1.471931	0.388712

C	-3.965507	-0.213036	0.325557
C	-2.578711	-0.195389	-0.028717
C	-2.555478	-2.526485	-0.214421
H	-5.694078	0.975704	0.871364
H	-4.395202	-3.602671	0.160693
H	-5.671572	-1.504263	0.652967
C	-4.642170	1.002157	0.602253
C	-1.852519	1.062437	-0.118108
H	-1.969209	-3.415224	-0.429384
C	-2.576444	2.224642	0.178214
C	-3.943262	2.187201	0.527228
H	-2.057240	3.171037	0.137904
H	-4.448444	3.126128	0.740545
N	-1.914193	-1.367124	-0.285823
N	-0.524526	0.994184	-0.520703
C	0.320547	2.059362	-0.471932
O	0.094556	3.202269	-0.032606
C	2.739983	1.589306	0.138367
H	2.891726	2.553529	0.628169
C	4.061409	0.917487	-0.281139
H	4.893242	1.354561	0.278583
H	4.262408	1.053052	-1.346699
Cu	0.045159	-0.961099	-0.769774
O	2.194007	0.713829	1.175968
C	2.766587	-0.507453	1.147423
O	2.392040	-1.405301	1.873370
C	3.888025	-0.567421	0.109766
C	1.724904	1.750745	-0.997112
H	2.062064	2.593665	-1.610327
H	1.715921	0.855710	-1.623833
C	5.147668	-1.172510	0.744889
H	4.949166	-2.190075	1.094872
H	5.957443	-1.210209	0.008871
H	5.486758	-0.575592	1.597960
C	3.410765	-1.463740	-1.052677
H	4.182597	-1.511195	-1.827641
H	3.216801	-2.478581	-0.692010
H	2.492219	-1.084486	-1.514592

F2

Geometry with 54 atoms:

Total energy: -3725.864038240

C	3.822170	-1.184116	-2.611168
C	4.467993	-0.991153	-1.410884

C	3.764566	-1.193041	-0.195014
C	2.398120	-1.593986	-0.295196
C	2.464005	-1.583111	-2.598791
H	5.385726	-0.690529	1.152958
H	4.330328	-1.034672	-3.558086
H	5.509097	-0.681815	-1.375984
C	4.346483	-0.998816	1.085471
C	1.630724	-1.788140	0.903720
H	1.937036	-1.738620	-3.538402
C	2.228864	-1.594714	2.137182
C	3.586443	-1.199066	2.216207
H	1.649333	-1.734731	3.038438
H	4.025793	-1.051709	3.198468
N	1.770568	-1.780827	-1.491051
C	-0.769566	-1.843966	1.531745
O	-0.635374	-1.521716	2.709252
C	-2.153700	-1.923085	0.882403
H	-2.388877	-2.973832	0.679742
H	-2.855640	-1.570359	1.635045
C	-1.573084	0.214993	-0.565565
H	-1.597733	0.491892	-1.622662
H	-0.525083	-0.020527	-0.366480
O	-0.566265	2.973062	1.584538
C	-0.702609	2.289690	0.585300
O	0.199458	2.185936	-0.401506
C	1.559149	2.760881	-0.305168
C	-1.972415	1.467605	0.277725
C	-2.280592	-1.135411	-0.437774
H	-1.901331	-1.752718	-1.253302
Br	-4.241618	-1.032676	-0.910128
N	0.286382	-2.140557	0.705494
H	0.087937	-2.338209	-0.272276
C	-2.886421	2.399591	-0.556377
H	-2.392013	2.705334	-1.484225
H	-3.812170	1.879618	-0.815660
H	-3.141057	3.300271	0.012014
C	-2.658535	1.149414	1.615802
H	-3.603247	0.629371	1.441169
H	-2.026405	0.533070	2.259337
H	-2.872375	2.078567	2.148867
C	1.471068	4.286267	-0.289461
H	0.982345	4.639745	0.619527
H	2.479224	4.710417	-0.337160
H	0.906917	4.643010	-1.157295

C	2.269031	2.194868	0.926083
H	2.201642	1.103760	0.930595
H	3.327171	2.472333	0.893024
H	1.833998	2.578021	1.849888
C	2.218246	2.253957	-1.587093
H	1.675987	2.612411	-2.467643
H	3.250339	2.612162	-1.643823
H	2.228836	1.160860	-1.605844

G

Geometry with 53 atoms:

Total energy: -1151.447792600

C	5.868521	2.647388	0.476088
C	6.412058	1.382817	0.476739
C	5.581397	0.261723	0.216588
C	4.200785	0.522359	-0.035041
C	4.485290	2.795108	0.214289
H	7.109842	-1.265746	0.390201
H	6.475800	3.525028	0.671645
H	7.469122	1.225001	0.673388
C	6.057861	-1.075715	0.197940
C	3.313124	-0.575656	-0.303174
H	4.038905	3.787881	0.209986
C	3.809206	-1.869115	-0.314985
C	5.182210	-2.106027	-0.062811
H	3.141747	-2.694211	-0.518285
H	5.540415	-3.131243	-0.079251
N	3.675822	1.779985	-0.032012
C	0.907870	-1.019174	-0.793309
O	0.960409	-2.244918	-0.886528
C	-1.153763	-0.299150	0.418882
H	-0.593815	0.245442	1.179241
C	-1.665392	-1.663802	0.903973
H	-1.540274	-1.740320	1.985784
H	-1.110978	-2.473915	0.428931
O	-2.405526	0.515387	0.236976
C	-3.445767	-0.245386	0.290210
O	-4.623433	0.193423	0.126180
C	-5.005503	1.661219	-0.201536
C	-3.172074	-1.704282	0.537937
C	-0.419294	-0.272234	-0.919646
H	-1.014387	-0.785010	-1.677944
H	-0.270160	0.767515	-1.223754
N	1.978985	-0.215420	-0.533648

H	1.829434	0.789491	-0.482209
C	-4.543287	2.533801	0.955106
H	-3.456074	2.608943	1.006895
H	-4.947688	3.538004	0.797160
H	-4.929425	2.154308	1.905198
C	-4.373536	2.009339	-1.540139
H	-3.285649	2.067192	-1.478800
H	-4.657868	1.279975	-2.303583
H	-4.750822	2.990259	-1.844116
C	-6.519056	1.554046	-0.281259
H	-6.936737	1.222800	0.673331
H	-6.926532	2.540974	-0.516740
H	-6.819230	0.855779	-1.067144
C	-3.460231	-2.472366	-0.774688
H	-3.211179	-3.524933	-0.615659
H	-4.518489	-2.396631	-1.039232
H	-2.860844	-2.096403	-1.608302
C	-4.059074	-2.235426	1.675336
H	-3.791423	-3.277369	1.871190
H	-3.911717	-1.659182	2.593458
H	-5.115303	-2.193526	1.396210

HBr

Geometry with 2 atoms:

Total energy: -2574.774155870

Br	0.000000	0.000000	0.039572
H	0.000000	0.000000	-1.385030

TS1(closed-shell)

Geometry with 54 atoms:

Total energy: -3921.375927400

C	2.745173	-3.602945	-0.445718
C	3.873028	-2.947548	-0.887440
C	3.951567	-1.533842	-0.800491
C	2.830322	-0.837809	-0.251418
C	1.690532	-2.837815	0.092981
H	5.938772	-1.343475	-1.646206
H	2.655982	-4.682755	-0.499677
H	4.712331	-3.496958	-1.305456
C	5.090052	-0.805948	-1.233396
C	2.835909	0.609236	-0.149962
H	0.786303	-3.317512	0.458418
C	3.990071	1.269970	-0.587997
C	5.094048	0.566713	-1.116443

H	4.024248	2.347041	-0.521685
H	5.962356	1.134491	-1.440226
N	1.731349	-1.516596	0.188266
N	1.681416	1.189620	0.371333
C	1.552475	2.545475	0.502417
O	2.296709	3.434834	0.072030
C	-1.963395	2.414460	0.197361
H	-2.813066	2.737280	-0.392299
H	-2.107350	1.582820	0.884057
Cu	0.225578	-0.235170	0.947346
Br	-1.117450	-0.324619	2.904751
O	-1.162862	-0.702017	-0.794656
C	-1.939325	0.069850	-1.362987
O	-3.254206	-0.073963	-1.469889
C	-3.980137	-1.271463	-0.956140
C	-1.446186	1.290019	-2.061889
C	0.262982	2.964200	1.255052
H	0.495867	3.914791	1.746545
H	-0.014950	2.215477	1.999487
C	-0.848320	3.181505	0.282484
H	-0.730331	4.020085	-0.403557
C	-2.359898	2.137022	-2.860606
H	-2.000748	3.169163	-2.899210
H	-2.307365	1.751345	-3.893299
H	-3.397485	2.092098	-2.535095
C	-0.000432	1.354630	-2.300426
H	0.564624	1.204173	-1.370238
H	0.274133	0.493296	-2.930504
H	0.297476	2.278759	-2.796326
C	-3.390421	-2.538378	-1.575603
H	-4.041722	-3.383304	-1.332071
H	-3.343478	-2.444743	-2.665222
H	-2.391108	-2.747019	-1.192115
C	-5.400844	-1.024502	-1.455831
H	-5.428723	-0.992200	-2.549332
H	-6.053849	-1.832725	-1.114329
H	-5.787015	-0.077486	-1.066865
C	-3.909984	-1.270323	0.566900
H	-4.334078	-0.345276	0.969220
H	-4.497082	-2.111724	0.949705
H	-2.884534	-1.361129	0.924826

TS1(open-shell)

Geometry with 54 atoms:

Total energy: -3921.370278370

C	2.360989	-3.705446	-0.305518
C	3.639630	-3.233161	-0.517341
C	3.904850	-1.841313	-0.454376
C	2.808395	-0.979534	-0.159924
C	1.334594	-2.782399	-0.020791
H	6.031320	-1.929563	-0.869376
H	2.132129	-4.764377	-0.353673
H	4.455282	-3.916286	-0.737773
C	5.190395	-1.276155	-0.657637
C	2.972541	0.449546	-0.100384
H	0.309904	-3.103581	0.141571
C	4.260304	0.952855	-0.296459
C	5.346460	0.091818	-0.570883
H	4.419832	2.020934	-0.259502
H	6.328874	0.531616	-0.718800
N	1.561577	-1.480011	0.063255
N	1.815540	1.182278	0.144739
C	1.717549	2.512591	-0.124197
O	2.534175	3.200606	-0.749548
C	-1.822946	2.475145	-0.652932
H	-2.670684	2.832875	-1.226648
H	-2.061153	1.941639	0.265666
Cu	0.249426	-0.001655	0.661319
Br	-0.764047	0.583289	2.756156
O	-1.342541	-0.851619	-0.392360
C	-2.141256	-0.220684	-1.119039
O	-3.456618	-0.414013	-1.088160
C	-4.123396	-1.385686	-0.182744
C	-1.737122	0.807609	-2.088383
C	0.406778	3.172477	0.363302
H	0.684697	4.205208	0.605648
H	0.039582	2.679291	1.264141
C	-0.647685	3.200654	-0.694686
H	-0.451352	3.832462	-1.559380
C	-2.758174	1.251042	-3.105936
H	-2.423823	2.165827	-3.603937
H	-2.859161	0.473013	-3.876022
H	-3.744375	1.416987	-2.670947
C	-0.328562	0.738784	-2.613688
H	0.411261	0.500939	-1.852812
H	-0.281409	-0.039294	-3.388945
H	-0.049824	1.687413	-3.079425
C	-3.574126	-2.792678	-0.422272

H	-4.213464	-3.514750	0.095144
H	-3.586907	-3.028825	-1.491154
H	-2.555228	-2.896051	-0.048427
C	-5.581325	-1.289177	-0.627993
H	-5.688776	-1.594965	-1.673330
H	-6.199670	-1.944454	-0.007776
H	-5.948410	-0.263672	-0.524193
C	-3.950132	-0.919859	1.259699
H	-4.359891	0.087359	1.386376
H	-4.496315	-1.597988	1.923680
H	-2.900682	-0.903123	1.553834

TS2

Geometry with 54 atoms:

Total energy: -3921.448141950

C	5.616918	1.038971	0.996937
C	5.929627	-0.298621	0.890750
C	4.962596	-1.222725	0.415366
C	3.678156	-0.707049	0.062833
C	4.324147	1.461590	0.620628
H	6.196609	-3.001634	0.551645
H	6.338332	1.763616	1.359501
H	6.914504	-0.664768	1.168639
C	5.218960	-2.611706	0.283807
C	2.631338	-1.578529	-0.422645
H	4.028367	2.506143	0.682249
C	2.939252	-2.936877	-0.529521
C	4.216319	-3.434161	-0.180759
H	2.179892	-3.614185	-0.890425
H	4.399197	-4.500343	-0.287025
N	3.401759	0.624874	0.175424
N	1.419000	-0.959674	-0.743550
C	0.335270	-1.644206	-1.203412
O	0.224012	-2.861798	-1.389641
C	-1.116448	0.347044	-0.509313
H	-1.126690	1.377909	-0.834555
C	-1.166616	0.083903	0.973940
H	-1.134174	1.046014	1.489415
H	-0.295789	-0.496580	1.286682
Cu	1.375341	0.985993	-0.410263
O	-3.167623	0.371180	-0.630498
C	-3.507427	-0.238537	0.398058
O	-4.734592	-0.563872	0.703781
C	-5.917088	-0.254108	-0.174806

C	-2.450877	-0.693068	1.391082
C	-0.852289	-0.719568	-1.535723
H	-1.735519	-1.351589	-1.648849
H	-0.662800	-0.242637	-2.502712
Br	0.876588	3.273001	-0.270102
C	-7.065433	-0.869711	0.616817
H	-7.144712	-0.409515	1.606085
H	-8.003963	-0.706450	0.079924
H	-6.916382	-1.946525	0.739862
C	-5.732139	-0.945450	-1.522606
H	-4.919684	-0.499353	-2.097758
H	-5.528523	-2.011195	-1.380883
H	-6.658808	-0.845425	-2.095722
C	-6.059300	1.260644	-0.288320
H	-6.097582	1.716242	0.705764
H	-5.235227	1.701078	-0.852057
H	-6.995194	1.488223	-0.807506
C	-2.283406	-2.224651	1.266125
H	-1.557085	-2.561287	2.011954
H	-3.235847	-2.726751	1.457665
H	-1.920332	-2.529041	0.281675
C	-2.855611	-0.332688	2.829023
H	-3.065556	0.737019	2.926553
H	-3.745455	-0.892086	3.129335
H	-2.038412	-0.589151	3.509928

TS3

Geometry with 54 atoms:

Total energy: -3921.425532160

C	-4.745633	0.322516	-2.635498
C	-5.152716	-0.891353	-2.128878
C	-4.512741	-1.435871	-0.985476
C	-3.452625	-0.680425	-0.395665
C	-3.688936	1.001287	-1.994007
H	-5.687690	-3.254478	-0.879291
H	-5.215729	0.761325	-3.509068
H	-5.962228	-1.447796	-2.593830
C	-4.881545	-2.685985	-0.424899
C	-2.750814	-1.177888	0.770049
H	-3.337770	1.959985	-2.365474
C	-3.152108	-2.417798	1.273579
C	-4.203863	-3.151724	0.680437
H	-2.635621	-2.814101	2.135557
H	-4.476350	-4.109286	1.116788

N	-3.069950	0.523835	-0.923359
N	-1.745209	-0.353872	1.266093
C	-0.889053	-0.733873	2.235401
O	-0.835801	-1.809279	2.856278
C	0.092538	0.387415	2.637578
H	-0.460468	1.153289	3.190653
H	0.810491	-0.043800	3.362447
C	1.022488	1.066833	1.708192
H	1.360008	2.018125	2.104137
C	2.013070	0.531392	0.750065
H	2.856116	0.381416	1.457830
H	2.341760	1.375049	0.135940
Cu	-1.485985	1.345874	0.177121
Br	-0.093588	3.205328	0.240750
O	3.264655	-0.869712	-2.155149
C	3.210862	-0.791546	-0.942416
O	4.270037	-0.762618	-0.121124
C	5.665889	-0.811144	-0.616028
C	1.894926	-0.740902	-0.129892
C	0.721212	-0.665661	-1.112218
H	0.812724	-1.450784	-1.866606
H	-0.219378	-0.803229	-0.579923
H	0.691922	0.299280	-1.627491
C	1.840327	-2.044422	0.696982
H	2.679536	-2.100626	1.395441
H	0.911829	-2.119998	1.263299
H	1.896045	-2.909216	0.026701
C	6.475864	-0.738756	0.676917
H	7.545079	-0.769161	0.447795
H	6.261610	0.189916	1.215128
H	6.235274	-1.583440	1.329830
C	5.938440	0.404612	-1.502180
H	7.005678	0.444090	-1.742045
H	5.371686	0.353479	-2.432674
H	5.670880	1.325300	-0.973618
C	5.905304	-2.135880	-1.340397
H	5.632022	-2.975926	-0.693841
H	5.323645	-2.193490	-2.261194
H	6.967727	-2.224576	-1.588330

TS4

Geometry with 54 atoms:

Total energy: -3725.782638380

C	-5.401640	0.319342	2.419270

C	-5.728153	0.968017	1.249786
C	-4.984044	0.704142	0.070211
C	-3.921164	-0.241585	0.174055
C	-4.326286	-0.601168	2.412714
H	-6.057350	2.047466	-1.249232
H	-5.948931	0.499947	3.338546
H	-6.546499	1.681980	1.212319
C	-5.244963	1.330107	-1.177382
C	-3.128490	-0.536969	-0.986154
H	-4.053967	-1.122885	3.328252
C	-3.407301	0.087117	-2.189319
C	-4.469028	1.020211	-2.272271
H	-2.810600	-0.137680	-3.062290
H	-4.665107	1.496150	-3.228490
N	-3.609470	-0.878175	1.337581
C	-1.129891	-1.862906	-1.634589
O	-1.029074	-1.547277	-2.807666
C	-0.077196	-2.813162	-0.951742
H	-0.541387	-3.396846	-0.154486
H	0.289733	-3.454310	-1.758372
C	1.314469	-1.713850	0.915911
H	2.438502	-1.934617	0.873557
H	0.771845	-2.375830	1.593619
O	0.905975	0.615848	-0.746745
C	1.503225	0.733857	0.318812
O	2.332878	1.712530	0.631539
C	2.754007	2.743220	-0.357322
C	1.251336	-0.237125	1.480504
C	0.982933	-1.934029	-0.458937
H	1.636096	-1.491031	-1.204068
Br	4.483142	-1.463450	0.004063
N	-2.092410	-1.456395	-0.768245
H	-2.070473	-1.806060	0.187374
C	2.229882	-0.082848	2.645309
H	3.256779	-0.242556	2.309501
H	2.147549	0.917060	3.078735
H	1.988991	-0.815208	3.423202
C	-0.193736	0.036236	1.949789
H	-0.901113	-0.059768	1.125569
H	-0.473230	-0.666206	2.740696
H	-0.266851	1.052575	2.352251
C	3.799709	3.531154	0.428174
H	4.641986	2.887531	0.699522
H	4.174179	4.357688	-0.182595

H	3.365571	3.944024	1.344021
C	3.381995	2.057927	-1.571454
H	4.080709	1.282049	-1.241702
H	2.624633	1.593369	-2.204291
H	3.921670	2.805589	-2.161547
C	1.551430	3.614706	-0.713954
H	0.788920	3.035907	-1.237687
H	1.110983	4.049684	0.188960
H	1.879763	4.431556	-1.364399

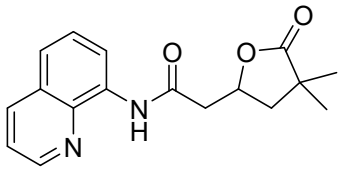
^{t}BuBr

Geometry with 14 atoms:

Total energy: -2732.027900020

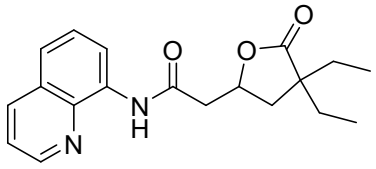
Br	-1.187267	-0.000026	-0.000142
C	0.871075	-0.000005	0.000078
C	1.304124	-0.103389	-1.456848
H	0.944439	0.746074	-2.043505
H	2.401091	-0.105884	-1.493152
H	0.944675	-1.027270	-1.917650
C	1.303245	1.313674	0.639088
H	0.942540	1.397003	1.667644
H	2.400147	1.346632	0.656186
H	0.943803	2.174337	0.068883
C	1.303343	-1.210198	0.818226
H	2.400253	-1.240045	0.840096
H	0.942316	-1.147557	1.848151
H	0.944370	-2.142866	0.375058

5. Characterization Data of Products 3



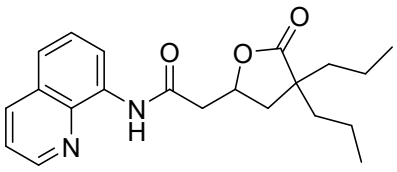
3aa

2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl) acetamide (**3aa**): light yellow solid (hexane/EtOAc = 2/1, yield: 81%), mp 170-175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.81 (dd, J = 4.24 Hz, 1.64 Hz, 1H), 8.75-8.70 (m, 1H), 8.16 (dd, J = 8.28 Hz, 1.64 Hz, 1H), 7.55-7.51 (m, 2H), 7.47-7.44 (m, 1H), 5.07-5.00 (m, 1H), 3.05 (dd, J = 15.08 Hz, 7.00 Hz, 1H), 2.86 (dd, J = 15.06 Hz, 5.73 Hz, 1H), 2.39 (dd, J = 12.81 Hz, 5.89 Hz, 1H), 1.95 (dd, J = 12.80 Hz, 10.20 Hz, 1H), 1.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 167.2, 148.3, 138.2, 136.4, 134.0, 127.9, 127.2, 122.0, 121.7, 116.7, 73.4, 43.7, 43.2, 40.4, 24.9, 24.3; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_3^+$ ([M + H]$^+$) : 299.1390, found: 299.1387.



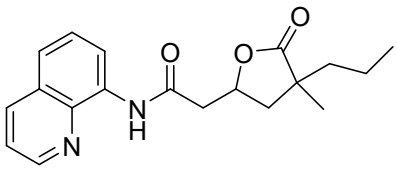
3ab

2-(4,4-diethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl) acetamide (**3ab**): light yellow solid (hexane/EtOAc = 3/1, yield: 45%), mp 107-109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.82 (dd, J = 4.16 Hz, 1.56 Hz, 1H), 8.75-8.71 (m, 1H), 8.16 (dd, J = 8.27 Hz, 1.56 Hz, 1H), 7.56-7.51 (m, 2H), 7.48-7.46 (m, 1H), 5.03-4.96 (m, 1H), 3.05 (dd, J = 15.06 Hz, 6.72 Hz, 1H), 2.85 (dd, J = 15.04 Hz, 6.04 Hz, 1H), 2.35 (dd, J = 13.26 Hz, 6.72 Hz, 1H), 2.01 (dd, J = 13.20 Hz, 9.56 Hz, 1H), 1.71-1.62 (m, 4H), 0.98 (t, J = 7.45 Hz, 3H), 0.91 (t, J = 7.40 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 167.3, 148.3, 138.2, 136.3, 134.0, 127.9, 127.2, 121.9, 121.7, 116.6, 73.6, 48.6, 44.2, 37.6, 29.0, 28.2, 8.7, 8.6; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_3^+$ ([M + H]$^+$) : 327.1703, found: 327.1703.



3ac

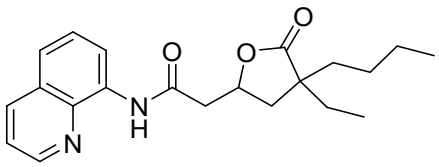
2-(5-oxo-4,4-dipropyltetrahydrofuran-2-yl)-N-(quinolin-8-yl) acetamide (**3ac**): light yellow solid (hexane/EtOAc = 5/1, yield: 42%), mp 85-89 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.81 (dd, J = 4.24 Hz, 1.60 Hz, 1H), 8.75-8.71 (m, 1H), 8.16 (dd, J = 8.28 Hz, 1.60 Hz, 1H), 7.56-7.51 (m, 2H), 7.48-7.45 (m, 1H), 5.03-4.95 (m, 1H), 3.04 (dd, J = 15.05 Hz, 6.66 Hz, 1H), 2.84 (dd, J = 15.00 Hz, 6.00 Hz, 1H), 2.37 (dd, J = 13.26 Hz, 6.70 Hz, 1H), 2.01 (dd, J = 13.21 Hz, 9.60 Hz, 1H), 1.65-1.53 (m, 4H), 1.47-1.30 (m, 3H), 1.25-1.13 (m, 1H), 0.94-0.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 167.3, 148.3, 138.2, 136.3, 134.0, 127.9, 127.2, 121.9, 121.7, 116.7, 73.7, 48.0, 44.1, 39.0, 38.5, 38.3, 17.6, 14.4, 14.3; HRMS (ESI) calcd for $C_{21}H_{27}N_2O_3^+$ ([M + H]$^+$) : 355.2016, found: 355.2016.



3ad

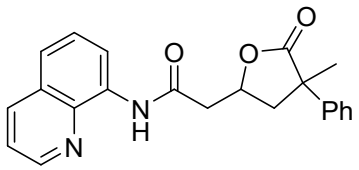
2-(4-methyl-5-oxo-4-propyltetrahydrofuran-2-yl)-N-(quinolin-8-yl) acetamide (**3ad**): brown yellow oil (hexane/EtOAc = 3/1, yield: 40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.82-8.81 (m, 1H), 8.75-8.71 (m, 1H), 8.16 (dd, J = 8.24 Hz, 1.16 Hz, 1H), 7.56-7.52 (m, 2H), 7.48-7.45 (m, 1H), 5.06-4.97 (m, 1H), 3.08-3.02 (m, 1H), 2.88-2.82 (m, 1H), 2.54-2.24 (m, 1H), 2.04-1.86 (m, 1H), 1.62-1.33 (m, 4H), 1.28-1.27 (m, 3H), 0.95-0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

181.0, 180.9, 167.3, 167.2, 148.3, 138.2, 136.3, 134.0, 127.9, 127.2, 121.9, 121.7, 116.7, 73.6, 73.5, 44.1, 44.1, 44.0, 43.7, 41.3, 40.3, 39.8, 39.7, 23.4, 22.5, 17.7, 17.7, 14.3, 14.3; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_3^+$ ([M + H]$^+$) : 327.1703, found: 327.1703.



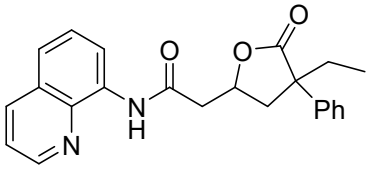
3ae

2-(4-butyl-4-methyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)acetamide (**3ae**): yellow oil (hexane/EtOAc = 5/1, yield: 38%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.82-8.81 (m, 1H), 8.75-8.71 (m, 1H), 8.16 (dd, J = 8.28 Hz, 1.60 Hz, 1H), 7.56-7.51 (m, 2H), 7.48-7.45 (m, 1H), 5.04-4.95 (m, 1H), 3.07-3.01 (m, 1H), 2.89-2.82 (m, 1H), 2.36 (dd, J = 13.24 Hz, 6.72 Hz, 1H), 2.05-1.98 (m, 1H), 1.72-1.50 (m, 4H), 1.34-1.25 (m, 4H), 1.00-0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 180.3, 167.3, 148.3, 138.2, 136.3, 134.0, 127.9, 127.2, 121.9, 121.7, 116.7, 73.6, 48.3, 48.2, 44.1, 38.1, 37.9, 36.2, 35.2, 29.4, 28.8, 26.5, 26.4, 23.0, 23.0, 13.9, 8.7, 8.7; HRMS (ESI) calcd for $C_{21}H_{27}N_2O_3^+$ ([M + H]$^+$) : 355.2016, found: 355.2016.



3af

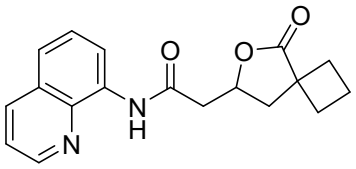
2-(4-methyl-5-oxo-4-phenyltetrahydrofuran-2-yl)-N-(quinolin-8-yl)acetamide (**3af**): light yellow solid (hexane/EtOAc = 2/1, yield: 43%, *dr* = 2:1.1), mp 173-175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 0.55H), 9.90 (s, 1H), 8.82-8.79 (m, 1.55H), 8.75-8.68 (m, 1.55H), 8.17 (dd, J = 8.24 Hz, 1.52 Hz, 1.55H), 7.54-7.45 (m, 6.48H), 7.42-7.39 (m, 1.10H), 7.38-7.34 (m, 3.10H), 7.30-7.28 (m, 1.55H), 5.21-5.14 (m, 1H), 4.85-4.78 (m, 0.55H), 3.10-3.00 (m, 2.10H), 2.89 (dd, J = 15.09 Hz, 5.84 Hz, 0.55H), 2.80 (dd, J = 15.06 Hz, 6.45 Hz, 1H), 2.74 (dd, J = 13.04 Hz, 6.32 Hz, 1H), 2.57 (dd, J = 12.99 Hz, 8.60 Hz, 1H), 2.25-2.19 (m, 0.55H), 1.69 (s, 3H), 1.69 (s, 1.65H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 167.1, 148.3, 142.3, 140.3, 138.2, 136.4, 134.0, 129.0, 128.7, 127.9, 127.2, 126.0, 125.7, 122.0, 121.7, 116.7, 73.6, 48.0, 43.6, 43.3, 25.5; HRMS (ESI) calcd for $C_{22}H_{21}N_2O_3^+$ ([M + H]$^+$) : 361.1547, found: 361.1547.



3ag

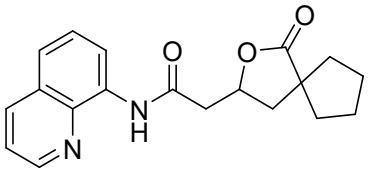
2-(4-ethyl-5-oxo-4-phenyltetrahydrofuran-2-yl)-N-(quinolin-8-yl)acetamide (**3ag**): light yellow oil (hexane/EtOAc = 4/1, yield: 51%, *dr* = 5:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 0.60H), 9.86 (s,

1H), 8.82-8.78 (m, J = 4.20 Hz, 1.52 Hz, 0.60H), 8.79 (dd, J = 4.20 Hz, 1.56 Hz, 1H), 8.75-8.69 (m, 1.6H), 8.17-8.15 (m, 1.6H), 7.56-7.44 (m, 8H), 7.38-7.34 (m, 3.20H), 7.30-7.27 (m, 1.60H), 5.17-5.10 (m, 1H), 4.87-4.80 (m, 0.60 H), 3.11-2.98 (m, 2.20H), 2.93-2.81(m, 1.60H), 2.74 (dd, J = 15.00 Hz, 6.77 Hz, 1H), 2.56 (dd, J = 13.21 Hz, 7.89 Hz, 1H), 2.21 (dd, J = 13.02 Hz, 10.97 Hz, 0.60H), 2.10-1.87 (m, 3.20H), 0.88-0.81 (m, 4.80H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 167.2, 148.3, 140.7, 138.2, 136.3, 134.0, 128.9, 128.5, 127.9, 127.2, 127.1, 126.5, 126.4, 122.0, 121.7, 116.7, 73.6, 51.8, 43.6, 40.0, 32.5, 9.0; HRMS (ESI) calcd for $C_{23}H_{23}N_2O_3^+$ ([M + H]$^+$) : 375.1703, found: 375.1703.



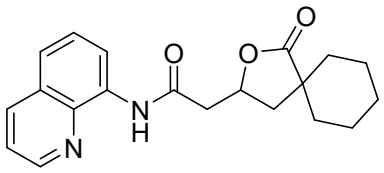
3ah

2-(5-oxo-6-oxaspiro[3.4]octan-7-yl)-N-(quinolin-8-yl)acetamide (**3ah**): yellow solid (hexane/EtOAc = 2/1, yield: 57%), mp 168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.80 (dd, J = 4.20 Hz, 1.60 Hz, 1H), 8.75-8.70 (m, 1H), 8.16 (dd, J = 8.29 Hz, 1.64 Hz, 1H), 7.55-7.51 (m, 2H), 7.47-7.44 (m, 1H), 4.96-4.90 (m, 1H), 3.02 (dd, J = 15.07 Hz, 6.81 Hz, 1H), 2.82 (dd, J = 15.04 Hz, 6.11 Hz, 1H), 2.69 (dd, J = 13.00 Hz, 6.04 Hz, 1H), 2.63-2.55 (m, 1H), 2.51-2.43 (m, 1H), 2.18-2.10 (m, 3H), 2.08-1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 167.2, 148.3, 138.2, 136.3, 134.0, 127.9, 127.2, 121.9, 121.7, 116.6, 73.8, 44.3, 43.4, 41.7, 31.7, 29.2, 16.5; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_3^+$ ([M + H]$^+$) : 311.1390, found: 311.1390.



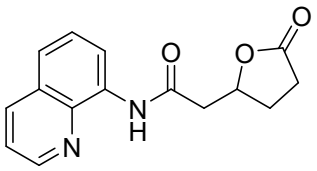
3ai

2-(1-oxo-2-oxaspiro[4.4]nonan-3-yl)-N-(quinolin-8-yl)acetamide (**3ai**): yellow oil (hexane/EtOAc = 3/1, yield: 37%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.81 (dd, J = 4.08 Hz, 1.32 Hz, 1H), 8.74-8.72 (m, 1H), 8.17 (dd, J = 8.27 Hz, 1.28 Hz, 1H), 7.56-7.52 (m, 2H), 7.48-7.45 (m, 1H), 5.02-4.95 (m, 1H), 3.08 (dd, J = 15.06 Hz, 6.88 Hz, 1H), 2.86 (dd, J = 15.02 Hz, 5.92 Hz, 1H), 2.45 (dd, J = 12.73 Hz, 5.81 Hz, 1H), 2.22-2.17 (m, 1H), 2.00-1.79 (m, 5H), 1.70-1.61 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 167.3, 148.3, 138.2, 136.4, 134.0, 127.9, 127.2, 121.9, 121.7, 116.7, 74.1, 50.1, 43.5, 43.0, 37.3, 36.7, 25.5, 25.4; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_3^+$ ([M + H]$^+$) : 325.1547, found: 325.1547.



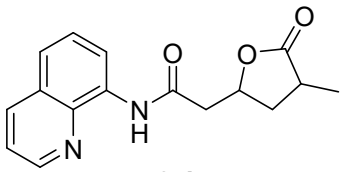
3aj

2-(1-oxo-2-oxaspiro[4.5]decan-3-yl)-N-(quinolin-8-yl)acetamide (**3aj**): light yellow solid (hexane/EtOAc = 3/1, yield: 45%), mp 181-184 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.81 (dd, J = 4.16 Hz, 1.52 Hz, 1H), 8.75-8.71 (m, 1H), 8.16 (dd, J = 8.28 Hz, 1.52 Hz, 1H), 7.55-7.51 (m, 2H), 7.47-7.44 (m, 1H), 5.03-4.96 (m, 1H), 3.06 (dd, J = 15.09 Hz, 6.72 Hz, 1H), 2.86 (dd, J = 15.06 Hz, 5.99 Hz, 1H), 2.61 (dd, J = 13.01 Hz, 6.20 Hz, 1H), 1.89-1.57 (m, 7H), 1.54-1.50 (m, 1H), 1.47-1.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 167.3, 148.3, 138.2, 136.3, 134.0, 127.9, 127.2, 121.9, 121.7, 116.7, 73.7, 44.9, 43.9, 39.4, 34.3, 31.4, 25.2, 22.1, 22.0; HRMS (ESI) calcd for $C_{20}H_{23}N_2O_3^+$ ([M + H]$^+$) : 339.1703, found: 339.1703.



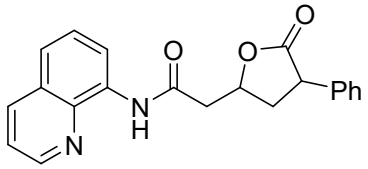
3ak

2-(5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl) acetamide (**3ak**): white solid (hexane/EtOAc = 1/1, yield: 24%), mp 115-120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.81 (dd, J = 4.24 Hz, 1.64 Hz, 1H), 8.75-8.70 (m, 1H), 8.17 (dd, J = 8.28 Hz, 1.60 Hz, 1H), 7.56-7.52 (m, 2H), 7.48-7.45 (m, 1H), 5.13-5.06 (m, 1H), 3.07 (dd, J = 15.14 Hz, 6.59 Hz, 1H), 2.90 (dd, J = 15.16 Hz, 6.11 Hz, 1H), 2.64-2.51 (m, 3H), 2.16-2.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 167.1, 148.3, 138.2, 136.4, 134.0, 127.9, 127.3, 122.0, 121.7, 116.7, 43.4, 28.6, 27.8; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_3^+$ ([M + H]$^+$) : 271.1077, found: 271.1076.



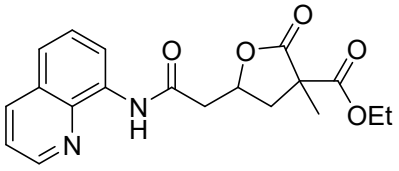
3al

2-(4-methyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)acetamide (**3al**): white solid (hexane/EtOAc = 2/1, yield: 34%), mp 153-155 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96-9.93 (m, 1H), 8.81-8.80 (m, 1H), 8.73-8.71 (m, 1H), 8.18-8.15 (m, 1H), 7.56-7.51 (m, 2H), 7.48-7.45 (m, 1H), 5.16-4.91 (m, 1H), 3.08-3.00 (m, 1H), 2.91-2.69 (m, 2.4H), 2.42-2.35 (m, 0.6H), 2.24-2.17 (m, 0.6H), 1.79-1.68 (m, 0.6H), 1.35-1.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 178.8, 167.1, 148.3, 138.29, 138.26, 136.4, 136.3, 134.07, 134.01, 127.9, 127.2, 122.0, 121.9, 121.7, 116.7, 74.8, 74.7, 43.5, 43.2, 37.1, 35.8, 35.2, 33.9, 15.8, 15.0; HRMS (ESI) calcd for $C_{16}H_{17}N_2O_3^+$ ([M + H]$^+$) : 285.1234, found: 285.1233.



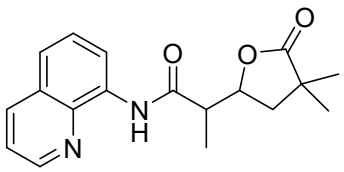
3am

2-(5-oxo-4-phenyltetrahydrofuran-2-yl)-N-(quinolin-8-yl)acetamide (**3am**): light yellow oil (hexane/EtOAc = 1/1, yield: 33%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99-9.97 (m, 1H), 8.81-8.72 (m, 2H), 8.16-8.14 (m, 1H), 7.55-7.52 (m, 2H), 7.47-7.43 (m, 1H), 7.37-7.27 (m, 5H), 5.27-5.06 (m, 1H), 4.02-3.92 (m, 1H), 3.16-3.07 (m, 1H), 3.01-2.91 (m, 1.5H), 2.74-2.61 (m, 1H), 2.32-2.26 (m, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 176.1, 167.09, 167.03, 148.3, 138.27, 136.7, 136.42, 136.40, 136.1, 134.05, 134.0, 129.0, 128.8, 128.1, 127.9, 127.7, 127.6, 127.5, 127.2, 122.08, 122.05, 121.7, 116.7, 75.3, 74.8, 46.9, 45.4, 43.2, 43.1, 37.6, 36.0; HRMS (ESI) calcd for $C_{21}H_{19}N_2O_3^+$ ([M + H]$^+$) : 347.1390, found: 347.1403.



3an

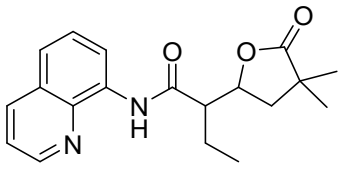
ethyl 3-methyl-2-oxo-5-(2-oxo-2-(quinolin-8-ylamino)ethyl)tetrahydrofuran-3-carboxylate (**3al**): light yellow solid (hexane/EtOAc = 2/1, yield: 53%), mp 101-103 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.82 (dd, J = 4.20 Hz, 1.64 Hz, 1H), 8.75-8.70 (m, 1H), 8.18 (dd, J = 8.28 Hz, 1.64 Hz, 1H), 7.55-7.52 (m, 2H), 7.49-7.46 (m, 1H), 5.18-5.11 (m, 1H), 4.25 (q, J = 7.12 Hz, 2H), 3.17 (dd, J = 15.21 Hz, 6.85 Hz, 1H), 2.96 (dd, J = 15.16 Hz, 6.32 Hz, 1H), 2.70 (dd, J = 13.21 Hz, 8.34 Hz, 1H), 2.48 (dd, J = 13.24 Hz, 6.80 Hz, 1H), 1.58 (s, 3H), 1.29 (t, J = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 170.5, 166.9, 148.3, 138.2, 136.4, 133.9, 127.9, 127.2, 122.0, 121.7, 116.6, 74.4, 62.3, 51.1, 43.3, 39.9, 20.0, 13.9; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_5^+$ ([M + H]$^+$) : 357.1445, found: 357.1445.



3ba

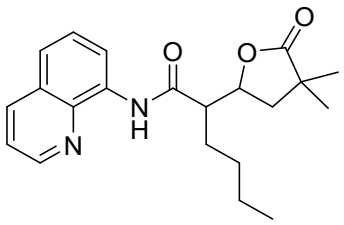
2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)propenamide (**3ba**): light yellow solid (hexane/EtOAc = 4/1, yield: 71%), mp 83-87 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (s, 1H), 8.82 (dd, J = 4.20 Hz, 1.60 Hz, 1H), 8.74-8.70 (m, 1H), 8.17 (dd, J = 8.24 Hz, 1.56 Hz, 1H), 7.56-7.51 (m, 2H), 7.49-7.45 (m, 1H), 4.72-4.66 (m, 1H), 2.90-2.83 (m, 1H), 2.30 (dd, J = 12.84 Hz, 5.89 Hz, 1H), 1.99 (dd, J = 12.81 Hz, 10.18 Hz, 1H), 1.52 (d, J = 6.88 Hz, 3H), 1.28 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 171.0, 148.4, 138.3, 136.4, 134.0, 127.9, 127.2, 122.0, 121.7, 116.7, 78.2, 47.8, 41.4, 40.4, 24.9, 24.4, 15.1; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_3^+$ ([M +

H]$^+$) : 313.1547, found: 313.1547.



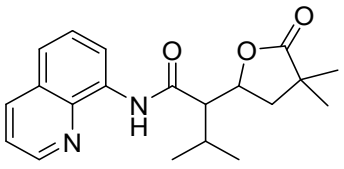
3ca

2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl) butanamide (**3ca**): light yellow solid (hexane/EtOAc = 3/1, yield: 70%), mp 76-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.83 (dd, J = 4.24 Hz, 1.64 Hz, 1H), 8.77-8.73 (m, 1H), 8.18 (dd, J = 8.24 Hz, 1.64 Hz, 1H), 7.55-7.53 (m, 2H), 7.49-7.46 (m, 1H), 4.72-4.66 (m, 1H), 2.67 (td, J = 8.74 Hz, 4.94 Hz, 1H), 2.27 (dd, J = 12.79 Hz, 5.79 Hz, 1H), 2.00-1.95 (m, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.07 (t, J = 7.45 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 170.2, 148.6, 138.3, 136.4, 133.9, 127.9, 127.2, 122.0, 121.8, 116.6, 55.7, 41.6, 40.3, 24.9, 24.3, 23.4, 11.6; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_3^+$ ([M + H]$^+$) : 327.1703, found: 327.1701.



3da

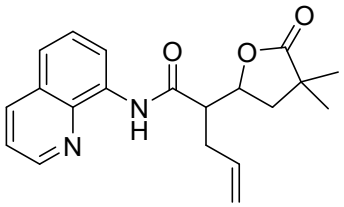
2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl) hexanamide (**3da**): light yellow oil (hexane/EtOAc = 4/1, yield: 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.83 (dd, J = 4.20 Hz, 1.64 Hz, 1H), 8.77-8.72 (m, 1H), 8.18 (dd, J = 8.28 Hz, 1.64 Hz, 1H), 7.56-7.53 (m, 2H), 7.49-7.46 (m, 1H), 4.71-4.65 (m, 1H), 2.75-2.69 (m, 1H), 2.26 (dd, J = 12.79 Hz, 5.81 Hz, 1H), 2.07-1.91 (m, 3H), 1.47-1.34 (m, 4H), 1.26 (s, 3H), 1.25 (s, 3H), 0.88 (t, J = 6.96 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 170.4, 148.4, 138.3, 136.4, 133.9, 127.9, 127.2, 122.0, 121.8, 116.6, 54.2, 41.5, 40.3, 29.9, 29.3, 24.9, 24.3, 22.7, 13.8; HRMS (ESI) calcd for $C_{21}H_{27}N_2O_3^+$ ([M + H]$^+$) : 355.2016, found: 355.2020.



3ea

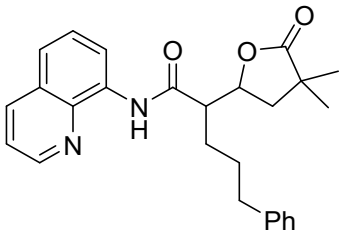
2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-3-methyl-N-(quinolin-8-yl) butanamide (**3ea**): light yellow solid (hexane/EtOAc = 4/1, yield: 70%), mp 129-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.82 (dd, J = 4.24 Hz, 1.64 Hz, 1H), 8.76-8.71 (m, 1H), 8.17 (dd, J = 8.28 Hz, 1.64 Hz, 1H), 7.56-7.50 (m, 2H), 7.48-7.45 (m, 1H), 4.88-4.82 (m, 1H), 2.63 (dd, J = 8.56 Hz, 6.07 Hz, 1H), 2.42-2.35 (m, 1H), 2.30 (dd, J = 12.77 Hz, 5.81 Hz, 1H), 2.09 (dd, J = 12.75 Hz, 10.21 Hz,

1H), 1.28 (s, 3H), 1.25 (s, 3H), 1.18 (d, J = 6.97 Hz, 3H), 1.11 (d, J = 6.80 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 169.5, 148.4, 138.3, 136.3, 133.9, 127.9, 127.2, 121.9, 121.7, 116.5, 75.9, 59.7, 41.5, 40.0, 28.7, 24.9, 24.4, 21.3, 19.1; HRMS (ESI) calcd for $C_{20}H_{25}N_2O_3^+$ ([M + H]$^+$) : 341.1860, found: 341.1864.



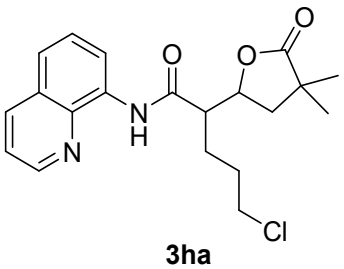
3fa

2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)pent-4-enamide (**3fa**): light yellow oil (hexane/EtOAc = 4/1, yield: 55%), mp 107-109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 8.82 (dd, J = 4.20 Hz, 1.60 Hz, 1H), 8.73-8.71 (m, 1H), 8.17 (dd, J = 8.28 Hz, 1.59 Hz, 1H), 7.54-7.53 (m, 2H), 7.49-7.46 (m, 1H), 5.93-5.83 (m, 1H), 5.21-5.17 (m, 1H), 5.08-5.06 (m, 1H), 4.74-4.68 (m, 1H), 2.85-2.81 (m, 1H), 2.72-2.68 (m, 2H), 2.28 (dd, J = 12.81 Hz, 5.86 Hz, 1H), 2.02 (dd, J = 12.76 Hz, 10.21 Hz, 1H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 169.5, 148.4, 138.3, 136.3, 134.0, 133.8, 127.9, 127.2, 122.0, 121.7, 118.2, 116.7, 53.7, 41.4, 40.3, 34.2, 24.9, 24.4; HRMS (ESI) calcd for $C_{20}H_{23}N_2O_3^+$ ([M + H]$^+$) : 339.1703, found: 339.1712.



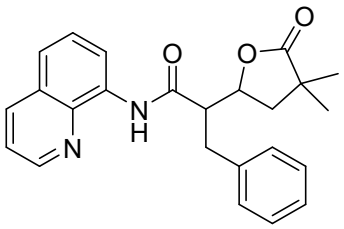
3ga

2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-5-phenyl-N-(quinolin-8-yl)pentanamide (**3ga**): light yellow oil (hexane/EtOAc = 5/1, yield: 74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.81 (dd, J = 4.21 Hz, 1.60 Hz, 1H), 8.75-8.71 (m, 1H), 8.17 (dd, J = 8.37 Hz, 1.61 Hz, 1H), 7.55-7.51 (m, 2H), 7.48-7.45 (m, 1H), 7.23-7.19 (m, 2H), 7.14-7.11 (m, 3H), 4.69-4.63 (m, 1H), 2.75-2.70 (m, 1H), 2.67 (t, J = 7.71 Hz, 2H), 2.24 (dd, J = 12.81 Hz, 5.80 Hz, 1H), 2.05-1.94 (m, 3H), 1.88-1.79 (m, 1H), 1.77-1.70 (m, 1H), 1.25 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 170.1, 148.4, 141.7, 138.3, 136.3, 133.8, 128.4, 128.3, 127.9, 127.2, 125.8, 122.1, 121.8, 116.7, 54.1, 41.5, 40.3, 35.9, 29.9, 29.1, 24.9, 24.3; HRMS (ESI) calcd for $C_{26}H_{29}N_2O_3^+$ ([M + H]$^+$) : 417.2173, found: 417.2176.



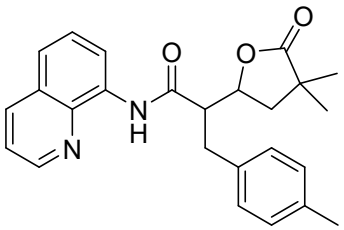
3ha

5-chloro-2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)pentanamide (**3ha**): light yellow oil (hexane/EtOAc = 3/1, yield: 38%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.83 (dd, J = 4.24 Hz, 1.60 Hz, 1H), 8.75-8.70 (m, 1H), 8.18 (dd, J = 8.28 Hz, 1.56 Hz, 1H), 7.57-7.52 (m, 2H), 7.50-7.47 (m, 1H), 4.71-4.65 (m, 1H), 3.62-3.52 (m, 2H), 2.82-2.77 (m, 1H), 2.26 (dd, J = 12.82 Hz, 5.82 Hz, 1H), 2.12-1.88 (m, 5H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 169.6, 148.5, 138.3, 136.4, 133.7, 127.9, 127.2, 122.2, 121.8, 116.8, 53.4, 44.5, 41.4, 40.3, 30.1, 27.6, 24.8, 24.3; HRMS (ESI) calcd for $C_{20}H_{24}ClN_2O_3^+$ ([M + H]$^+$) : 375.1470, found: 375.1471.



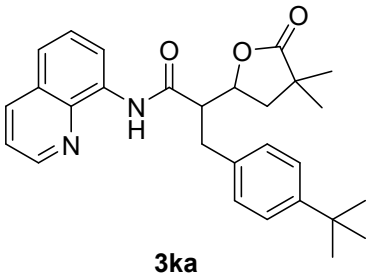
3ia

2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-3-phenyl-N-(quinolin-8-yl)propenamide (**3ia**): colorless oil (hexane/EtOAc = 3/1, yield: 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.69-8.65 (m, 2H), 8.11 (dd, J = 8.24 Hz, 1.56 Hz, 1H), 7.50-7.48 (m, 2H), 7.43-7.39 (m, 1H), 7.26-7.23 (m, 2H), 7.18 (t, J = 7.29 Hz, 2H), 7.10-7.07 (m, 1H), 4.77-4.71 (m, 1H), 3.30 (dd, J = 13.63 Hz, 4.46 Hz, 1H), 3.20 (dd, J = 13.57 Hz, 9.97 Hz, 1H), 3.03-2.98 (m, 1H), 2.30 (dd, J = 12.84 Hz, 5.88 Hz, 1H), 2.03 (dd, J = 12.75 Hz, 10.21 Hz, 1H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 169.4, 148.2, 138.2, 138.2, 136.1, 133.7, 128.9, 128.6, 127.8, 127.1, 126.6, 122.0, 121.6, 116.6, 56.1, 41.4, 40.4, 36.2, 24.9, 24.4; HRMS (ESI) calcd for $C_{24}H_{25}N_2O_3^+$ ([M + H]$^+$) : 389.1860, found: 389.1863.



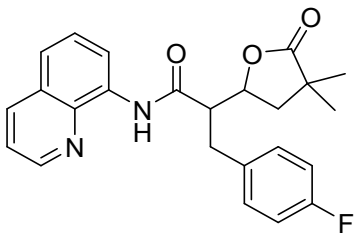
3ja

2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)-3-(*p*-tolyl)propenamide (**3ja**): light yellow solid (hexane/EtOAc = 5/1, yield: 74%), mp 107-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.70-8.65 (m, 2H), 8.12 (dd, J = 8.23 Hz, 1.59 Hz, 1H), 7.52-7.48 (m, 2H), 7.43-7.39 (m, 1H), 7.12 (d, J = 7.96 Hz, 2H), 6.98 (d, J = 7.79 Hz, 2H), 4.76-4.69 (m, 1H), 3.25 (dd, J = 13.65 Hz, 4.55 Hz, 1H), 3.16 (dd, J = 13.57 Hz, 9.60 Hz, 1H), 3.01-2.96 (m, 1H), 2.30 (dd, J = 12.81 Hz, 5.85 Hz, 1H), 2.17 (s, 3H), 2.03 (dd, J = 12.82 Hz, 10.24 Hz, 1H), 1.27 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 169.5, 148.1, 138.2, 136.2, 136.1, 135.0, 133.8, 129.3, 128.8, 127.8, 127.1, 121.9, 121.6, 116.6, 56.1, 41.4, 40.4, 35.8, 24.9, 24.4, 20.9; HRMS (ESI) calcd for $C_{25}H_{27}N_2O_3^+$ ([M + H]$^+$) : 403.2016, found: 403.2019.



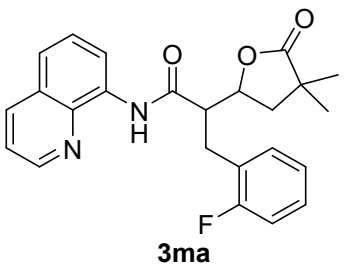
3ka

3-(4-(*tert*-butyl)phenyl)-2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)propenamide (**3ka**): white solid (hexane/EtOAc = 4/1, yield: 65%), mp 130-133 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.68-8.66 (m, 2H), 8.11 (dd, J = 8.24 Hz, 1.48 Hz, 1H), 7.53-7.48 (m, 2H), 7.42-7.38 (m, 1H), 7.19-7.14 (m, 4H), 4.78-4.72 (m, 1H), 3.27 (dd, J = 13.65 Hz, 4.53 Hz, 1H), 3.16 (dd, J = 13.60 Hz, 9.80 Hz, 1H), 3.01-2.95 (m, 1H), 2.31 (dd, J = 12.84 Hz, 5.88 Hz, 1H), 2.02 (dd, J = 12.74 Hz, 10.24 Hz, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 169.6, 149.3, 148.1, 138.2, 136.2, 135.1, 133.8, 128.5, 127.8, 127.2, 125.4, 121.9, 121.6, 116.5, 56.1, 41.4, 40.4, 35.8, 34.2, 31.1, 24.9, 24.4; HRMS (ESI) calcd for $C_{28}H_{33}N_2O_3^+$ ([M + H]$^+$) : 445.2486, found: 445.2489.



3la

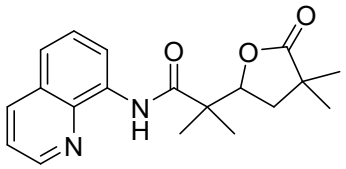
2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-3-(4-fluorophenyl)-N-(quinolin-8-yl) propanamide (**3la**): light yellow solid (hexane/EtOAc = 5/1, yield: 67%), mp 151-153 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.69-8.64 (m, 2H), 8.12 (dd, J = 8.28 Hz, 1.52 Hz, 1H), 7.51-7.48 (m, 2H), 7.44-7.40 (m, 1H), 7.21-7.18 (m, 2H), 6.87-6.83 (m, 2H), 4.76-4.70 (m, 1H), 3.30 (dd, J = 13.73 Hz, 4.01 Hz, 1H), 3.16 (dd, J = 13.55 Hz, 10.20 Hz, 1H), 2.96-2.90 (m, 1H), 2.32 (dd, J = 12.82 Hz, 5.81 Hz, 1H), 2.00 (dd, J = 12.72 Hz, 10.20 Hz, 1H), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 169.2, 161.7 (d, J = 244.7 Hz), 148.2, 138.1, 136.2, 133.8 (d, J = 3.2 Hz), 133.5, 130.4 (d, J = 8.0 Hz), 127.8, 127.1, 122.1, 121.7, 116.5, 115.4 (d, J = 21.2 Hz), 56.6, 41.6, 40.4, 35.6, 24.9, 24.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.44 (s, 1F); HRMS (ESI) calcd for $C_{24}H_{24}FN_2O_3^+$ ([M + H]$^+$) : 407.1765, found: 407.1765.



3ma

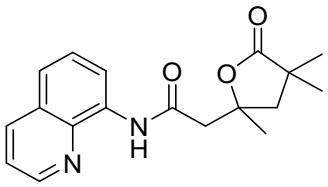
2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-3-(2-fluorophenyl)-N-(quinolin-8-yl)propanamide (**3ma**): light yellow solid (hexane/EtOAc = 4/1, yield: 72%), mp 132-138 ℃; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 9.69 (s, 1H), 8.71 (dd, J = 4.20 Hz, 1.60 Hz, 1H), 8.67-8.62 (m, 1H), 8.11 (dd, J = 8.28 Hz, 1.63 Hz, 1H), 7.52-7.46 (m, 2H), 7.43-7.40 (m, 1H), 7.27-7.23 (m, 1H), 7.11-7.05 (m, 1H), 6.97-6.91 (m, 2H), 4.78-4.72 (m, 1H), 3.38 (dd, J = 12.93 Hz, 3.86 Hz, 1H), 3.20-3.08 (m, 2H), 2.31 (dd, J = 12.85 Hz, 5.89 Hz, 1H), 2.05 (dd, J = 12.80 Hz, 10.19 Hz, 1H), 1.28 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 169.1, 161.1 (d, J = 245.40 Hz), 148.2, 138.2, 136.1, 133.7, 131.4 (d, J = 4.42 Hz), 128.5 (d, J = 8.13 Hz), 127.7, 127.1, 125.0 (d, J = 15.85 Hz), 124.1 (d, J = 3.56 Hz), 122.0, 121.6, 116.6, 115.4 (d, J = 21.91 Hz), 54.0, 41.1, 40.3, 29.6, 29.6, 24.9, 24.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.40 (s, 1F); HRMS (ESI) calcd for $C_{24}H_{24}FN_2O_3^+$ ([M + H]$^+$) : 407.1765, found: 407.1767.



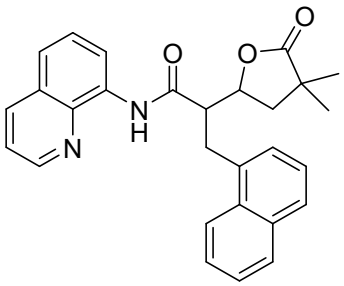
3na

2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-2-methyl-N-(quinolin-8-yl)propenamide (**3na**): white solid (hexane/EtOAc = 2/1, yield: 25%), mp 117-122 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.83 (dd, J = 4.24 Hz, 1.68 Hz, 1H), 8.74-8.69 (m, 1H), 8.15 (dd, J = 8.29 Hz, 1.65 Hz, 1H), 7.55-7.50 (m, 2H), 7.47-7.44 (m, 1H), 4.74 (dd, J = 10.77 Hz, 6.13 Hz, 1H), 2.15 (dd, J = 12.92 Hz, 6.13 Hz, 1H), 1.99 (dd, J = 12.89 Hz, 10.81 Hz, 1H), 1.47 (s, 6H), 1.30 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 173.1, 148.5, 138.8, 136.2, 134.2, 127.9, 127.2, 121.8, 121.7, 116.6, 81.1, 46.3, 40.5, 38.7, 24.8, 24.6, 21.7, 21.1; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_3^+$ ([M + H]$^+$) : 327.1703, found: 327.1704.



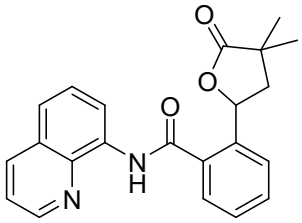
3oa

N-(quinolin-8-yl)-2-(2,4,4-trimethyl-5-oxotetrahydrofuran-2-yl), acetamide (**3oa**): light yellow solid (hexane/EtOAc = 4/1, yield: 52%), mp 106-108 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.83 (dd, J = 4.20 Hz, 1.60 Hz, 1H), 8.73-8.69 (m, 1H), 8.15 (dd, J = 8.24 Hz, 1.56 Hz, 1H), 7.54-7.49 (m, 2H), 7.47-7.44 (m, 1H), 2.98 (d, J = 14.70 Hz, 1H), 2.92 (d, J = 14.70 Hz, 1H), 2.61 (d, J = 13.60 Hz, 1H), 2.13 (d, J = 13.61 Hz, 1H), 1.64 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 167.2, 148.4, 138.3, 136.3, 134.1, 127.9, 127.2, 121.9, 121.7, 116.6, 80.7, 49.8, 46.8, 40.7, 28.7, 27.8, 27.2; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_3^+$ ([M + H]$^+$) : 313.1547, found: 313.1547.



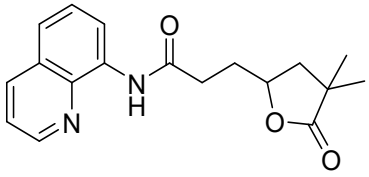
3pa

2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-3-(naphthalen-1-yl)-N-(quinolin-8-yl)propenamide (**3pa**): light yellow solid (hexane/EtOAc = 4/1, yield: 35%), mp 127-132 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.60 (dd, J = 6.72 Hz, 2.20 Hz, 1H), 8.42 (dd, J = 4.20 Hz, 1.52 Hz, 1H), 8.17-8.15 (m, 1H), 8.04 (dd, J = 8.24 Hz, 1.48 Hz, 1H), 7.77-7.75 (m, 1H), 7.56-7.51 (m, 2H), 7.49-7.42 (m, 3H), 7.34-7.31 (m, 2H), 7.15-7.11 (m, 1H), 4.91-4.85 (m, 1H), 3.95 (dd, J = 13.84 Hz, 3.68 Hz, 1H), 3.52 (dd, J = 13.84 Hz, 10.61 Hz, 1H), 3.15-3.10 (m, 1H), 2.37 (dd, J = 12.80 Hz, 5.76 Hz, 1H), 1.99 (dd, J = 12.76 Hz, 10.26 Hz, 1H), 1.32 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 169.6, 147.9, 137.9, 136.0, 134.3, 134.0, 133.5, 131.5, 128.7, 127.6, 127.4, 127.4, 127.0, 126.3, 125.5, 125.3, 123.6, 121.9, 121.5, 116.5, 55.6, 41.7, 40.5, 33.7, 24.9, 24.4; HRMS (ESI) calcd for $C_{28}H_{27}N_2O_3^+$ ([M + H]$^+$) : 439.2016, found: 439.2015.



3qa

2-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl)benzamide (**3qa**): light yellow solid (hexane/EtOAc = 5/1, yield: 69%), mp 117-120 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.86 (dd, J = 6.69 Hz, 2.12 Hz, 1H), 8.80 (dd, J = 4.20 Hz, 1.60 Hz, 1H), 8.19 (dd, J = 8.28 Hz, 1.60 Hz, 1H), 7.81-7.79 (m, 1H), 7.69-7.67 (m, 1H), 7.62-7.57 (m, 3H), 7.50-7.46 (m, 2H), 6.09 (dd, J = 9.44 Hz, 6.48 Hz, 1H), 2.88 (dd, J = 13.00 Hz, 6.45 Hz, 1H), 2.05 (dd, J = 12.99 Hz, 9.48 Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.2, 166.7, 148.4, 140.3, 138.6, 136.4, 134.4, 134.1, 131.4, 128.2, 128.0, 127.3, 127.1, 125.9, 122.2, 121.8, 116.5, 75.8, 46.9, 40.7, 25.1, 24.5; HRMS (ESI) calcd for $C_{22}H_{21}N_2O_3^+$ ([M + H]$^+$) : 361.1547, found: 361.1547.



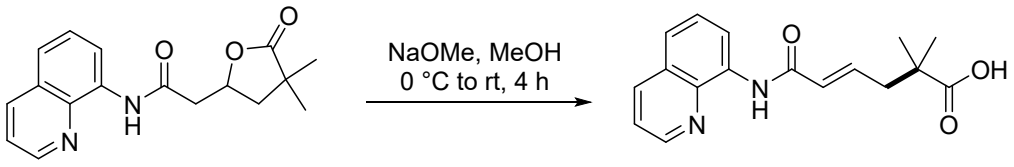
3ua

3-(4,4-dimethyl-5-oxotetrahydrofuran-2-yl)-N-(quinolin-8-yl) propenamide (**3ua**): brown solid (hexane/EtOAc = 2/1, yield: 55%), mp 84-90 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.81 (dd, J = 4.21 Hz, 1.48 Hz, 1H), 8.77-8.71 (m, 1H), 8.16 (dd, J = 8.29 Hz, 1.48 Hz, 1H), 7.56-7.50

(m, 2H), 7.48-7.45 (m, 1H), 4.62-4.55 (m, 1H), 2.86-2.73 (m, 2H), 2.35-2.22 (m, 2H), 2.07-1.98 (m, 1H), 1.81 (dd, J = 12.73 Hz, 9.97 Hz, 1H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 170.3, 148.2, 138.2, 136.3, 134.2, 127.9, 127.3, 121.7, 121.6, 116.4, 76.1, 43.4, 40.5, 33.7, 31.3, 25.0, 24.4; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_3^+$ ([M + H]$^+$) : 313.1547, found: 313.1549.

6. Removal of Directing Group & Derivative Reaction of 3aa

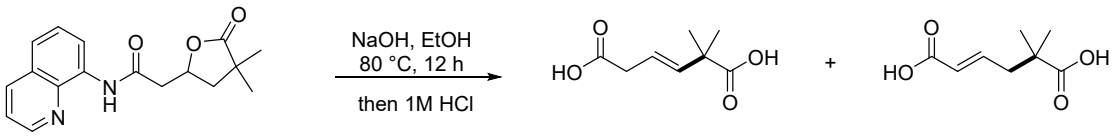
The procedure for the synthesis of compound 4[15]



3aa **4** (95 %)

To a solution of **3aa** (0.2 mmol, 1.0 equiv.) in MeOH (2.05 mL) was added sodium methoxide (0.8 mmol, 4.0 equiv.) at 0 ℃, and the mixture was allowed to warm to room temperature. After being stirred at same temperature for 4 h, the mixture was diluted with saturated NH_4Cl (1 mL) at 0 ℃ and extracted with EtOAc (20 mL × 3). The combined organic extracts were washed with brine (20 mL × 2), dried and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc = 1:1) to afford **4** in 95% yield as light yellow solid. mp 121-132 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 9.84 (s, 1H), 8.83 (dd, J = 7.40 Hz, 1.36 Hz, 1H), 8.79 (dd, J = 4.24 Hz, 1.64 Hz, 1H), 8.14 (dd, J = 8.24 Hz, 1.56 Hz, 1H), 7.55-7.47 (m, 2H), 7.45-7.42 (m, 1H), 7.09-7.01 (m, 1H), 6.24 (d, J = 15.12 Hz, 1H), 2.55 (dd, J = 7.68 Hz, 0.76 Hz, 2H), 1.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 163.9, 148.1, 141.6, 138.4, 136.5, 134.4, 127.9, 127.5, 127.4, 121.7, 121.6, 117.1, 42.3, 42.2, 24.9; HRMS (ESI) calcd for $C_{17}H_{19}N_2O_3^+$ ([M + H]$^+$) : 299.1390, found: 299.1390.

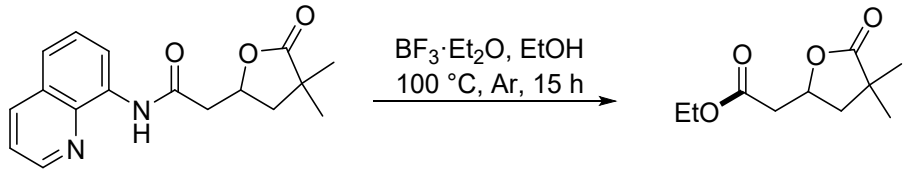
The procedure for the synthesis of compound 5 and 5'



3aa 63 % **5** (2: 1.3) **5'**

A mixture of **3aa** (0.2 mmol, 1.0 equiv.) and NaOH (2 mmol, 20 equiv.) was heated in ethanol (3.0 mL) for 12 h at 80 ℃. After the mixture was cooled to room temperature and diluted with water (3.0 mL), the solution of 1M hydrochloric acid was added until the pH value was about 2-3. The mixture was then extracted with CH_2Cl_2 (20 ml × 3). The combined organic extracts were washed with brine (20 mL × 2) and dried over anhydrous Na_2SO_4. After the organic material was concentrated in vacuum, the product was purified by column chromatography on silica gel (100-200 mesh) to afford a mixture of **5** and **5'** as a mixture (*dr* = 2.7:1) in 63 % overall yield as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 3.30H), 7.06-6.98 (m, 0.65H), 5.89-5.80 (m, 1.65 H), 5.70-5.63 (m, 1H), 3.12 (dd, J = 6.88 Hz, 1.12 Hz, 2H), 2.47 (dd, J = 7.73 Hz, 0.92 Hz, 1.30H), 1.33 (s, 6H), 1.24 (s, 3.90H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 178.0, 138.1, 120.4, 44.1, 42.1, 24.6; HRMS (ESI) calcd for $C_8H_{11}O_4^-$ ([M - H]$^-$) : 171.0663, found: 177.0651.

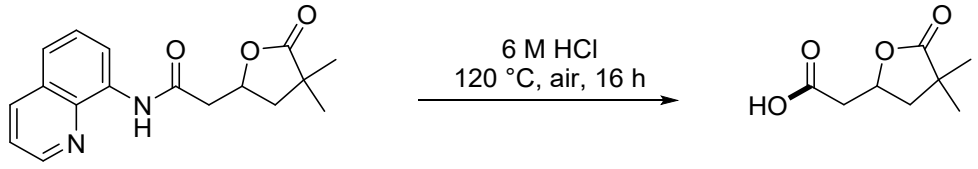
The procedure for the synthesis of compound 6 [3]



3aa **6** (96 %)

To a dry tube was added **3aa** (0.20 mmol, 1.0 equiv.), anhydrous EtOH (2.0 mL), followed by the addition of $BF_3 \cdot Et_2O$ (1.2 mmol, 6.0 equiv.) at ambient temperature. The mixture was degassed three times with argon, and then allowed to stir at 100 ℃. After 15 h, the reaction was cooled to ambient temperature. The mixture was diluted with dichloromethane and then quenched by Et_3N (2.0 mmol, 10 equiv.). Rotary evaporation of the organic solvent and further purification by flash column chromatography (hexane/EtOAc = 8:1) afforded the desired products **6** in 96% as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87-4.80 (m, 1H), 4.20-4.15 (m, 2H), 2.81 (dd, J = 16.17 Hz, 6.91 Hz, 1H), 2.60 (dd, J = 16.16 Hz, 6.17 Hz, 1H), 2.30 (dd, J = 12.76 Hz, 6.05 Hz, 1H), 1.83 (dd, J = 12.71 Hz, 10.01 Hz, 1H), 1.29-1.26 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 169.6, 72.7, 61.0, 43.0, 40.3, 40.2, 24.9, 24.4, 14.1; HRMS (ESI) calcd for $C_{10}H_{17}O_4^+$ ([M + H]$^+$) : 201.1121, found: 201.1119.

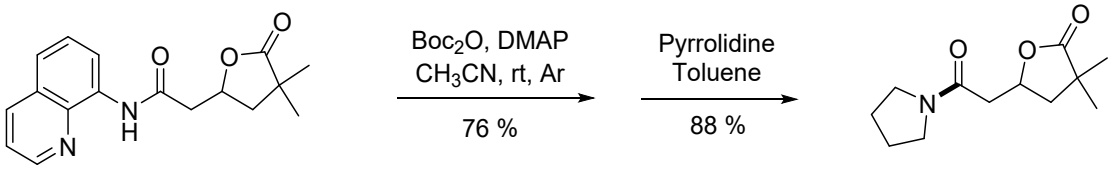
The procedure for the synthesis of compound 7 [16]



3aa **7** (97 %)

To a dry Schlenk tube equipped with a magnetic stir bar were added **3aa** (0.2 mmol, 1.0 equiv.) and 6 M HCl (1.5 mL). The tube was sealed and heated at 120 ℃ for 16 h. The mixture was then diluted with water, then extracted with EtOAc (20 ml × 3). The organic layers were combined, dried, and concentrated under vacuum. The residue was further purification by flash column chromatography (hexane/EtOAc = 1:1) afforded the desired free acid **7** in 97% as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 4.87-4.80 (m, 1H), 2.86 (dd, J = 16.60 Hz, 7.16 Hz, 1H), 2.69 (dd, J = 16.60 Hz, 5.90 Hz, 1H), 2.32 (dd, J = 12.80 Hz, 6.04 Hz, 1H), 1.85 (dd, J = 12.80 Hz, 10.00 Hz, 1H), 1.29 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 175.0, 72.4, 42.9, 40.3, 39.9, 24.8, 24.3; HRMS (ESI) calcd for $C_8H_{12}NaO_4^+$ ([M + Na]$^+$) : 195.0628, found: 195.0627.

The procedure for the synthesis of compound 8 [17]

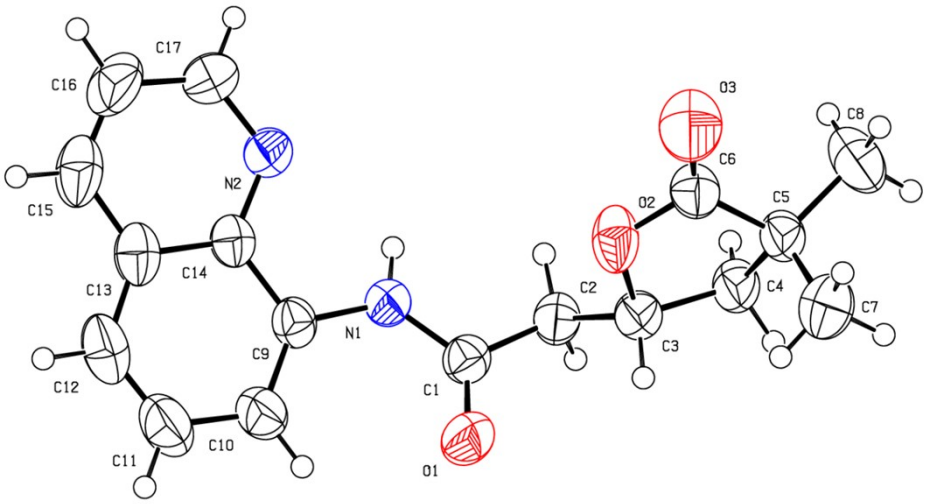


3aa **8**

To a dry Schlenk tube containing a magnetic stir bar, were added **3aa** (0.2 mmol, 1.0 equiv.), DMAP (0.3 mmol, 1.5 equiv.), and Boc anhydride (0.8 mmol, 4.0 equiv.). The reaction tube was evacuated and backfilled with Ar (× 3), followed by addition of anhydrous MeCN (3 mL). The reaction mixture was stirred at rt for 2 h. After completion, the reaction was concentrated under vacuum and purified by column chromatography (hexane/EtOAc = 1:2) to afford the Boc-protected amide. The Boc amide was then dissolved in toluene (0.5 M), followed by addition of pyrrolidine (1.5 equiv.). The reaction mixture was heated under N_2 atmosphere at 60 ℃ overnight. Upon completion, the organic mixture was concentrated under vacuum and purified by column chromatography (PE/EA = 1:1) to afford product **8** as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98-4.91 (m, 1H), 3.52-3.38 (m, 4H), 2.86 (dd, J = 15.60 Hz, 6.24 Hz, 1H), 2.50 (dd, J = 15.64 Hz, 6.64 Hz, 1H), 2.41 (dd, J = 12.86 Hz, 5.90 Hz, 1H), 2.02-1.92 (m, 2H), 1.90-1.79 (m, 3H), 1.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 167.4, 73.9, 46.8, 45.7, 43.7, 40.5, 40.3, 26.0, 24.9, 24.3, 24.3; HRMS (ESI) calcd for $C_{12}H_{20}NO_3^+$ ([M + H]$^+$) : 226.1438, found: 226.1438.

7. The Single Crystal X-ray Diffraction Study

The Single Crystal X-ray Diffraction Study of **3aa**



CCDC: 2088153 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table S7 Crystal data and structure refinement for CCDC: 2088153 (3aa) (displacement ellipsoids are drawn at the 30% probability level).

Identification code	202009192_tw
Empirical formula	$C_{17}H_{18}N_2O_3$
Formula weight	298.33
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	12.8383(5)

b/Å	13.0290(5)
c/Å	9.3932(4)
α/°	90
β/°	104.569(4)
γ/°	90
Volume/Å^3	1520.69(11)
Z	4
ρ_{calc}g/cm^3	1.303
μ/mm^{-1}	0.736
F(000)	632.0
Crystal size/mm^3	0.2 × 0.14 × 0.07
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.114 to 134.158
Index ranges	-15 ≤ h ≤ 14, -15 ≤ k ≤ 15, -3 ≤ l ≤ 11
Reflections collected	2716
Independent reflections	2716 [R_{int} = ?, R_{sigma} = 0.0229]
Data/restraints/parameters	2716/1/206
Goodness-of-fit on F^2	1.099
Final R indexes [I>=2σ (I)]	R_1 = 0.0738, wR_2 = 0.2262
Final R indexes [all data]	R_1 = 0.0813, wR_2 = 0.2327
Largest diff. peak/hole / e Å^{-3}	0.45/-0.23

8. References

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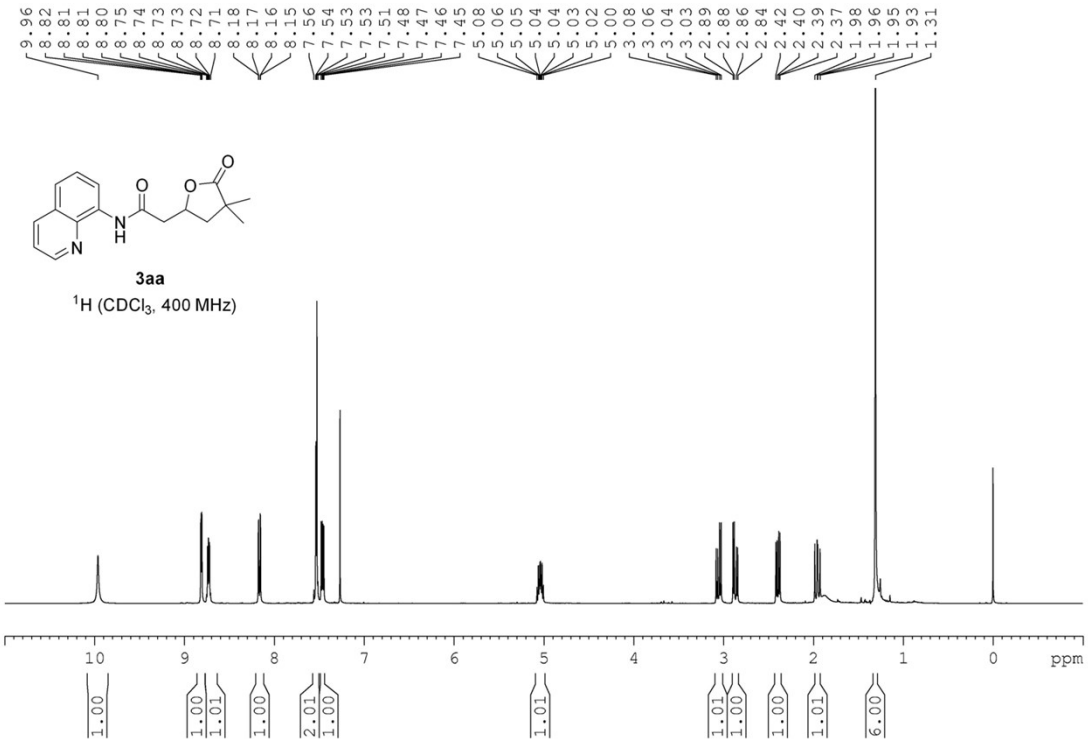
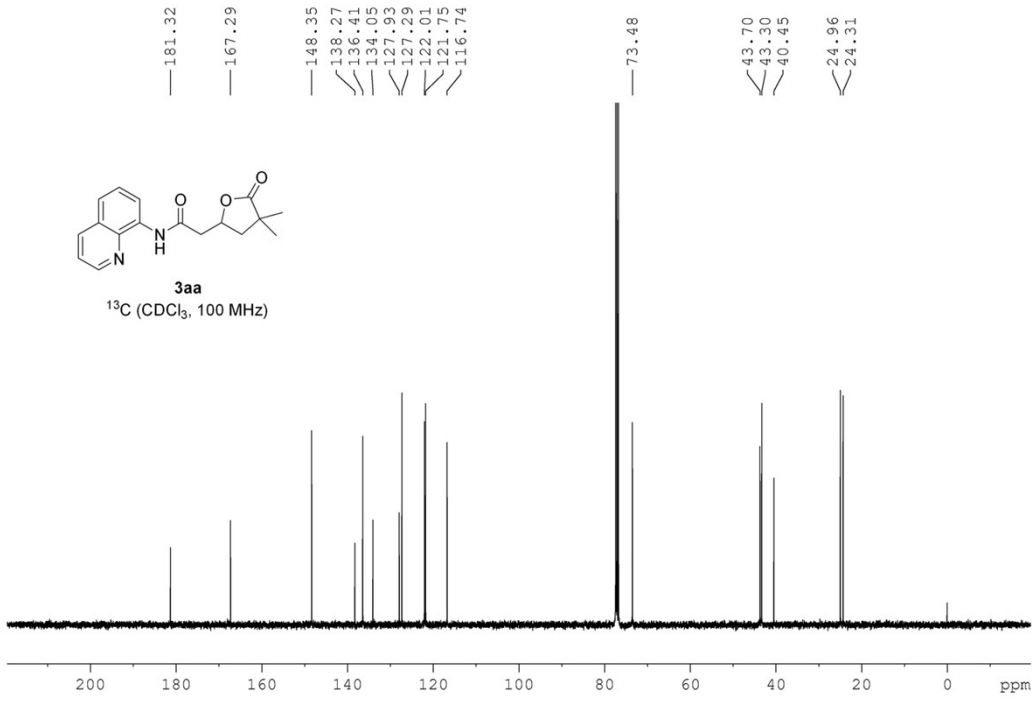
9. NMR and HRMS Spectra

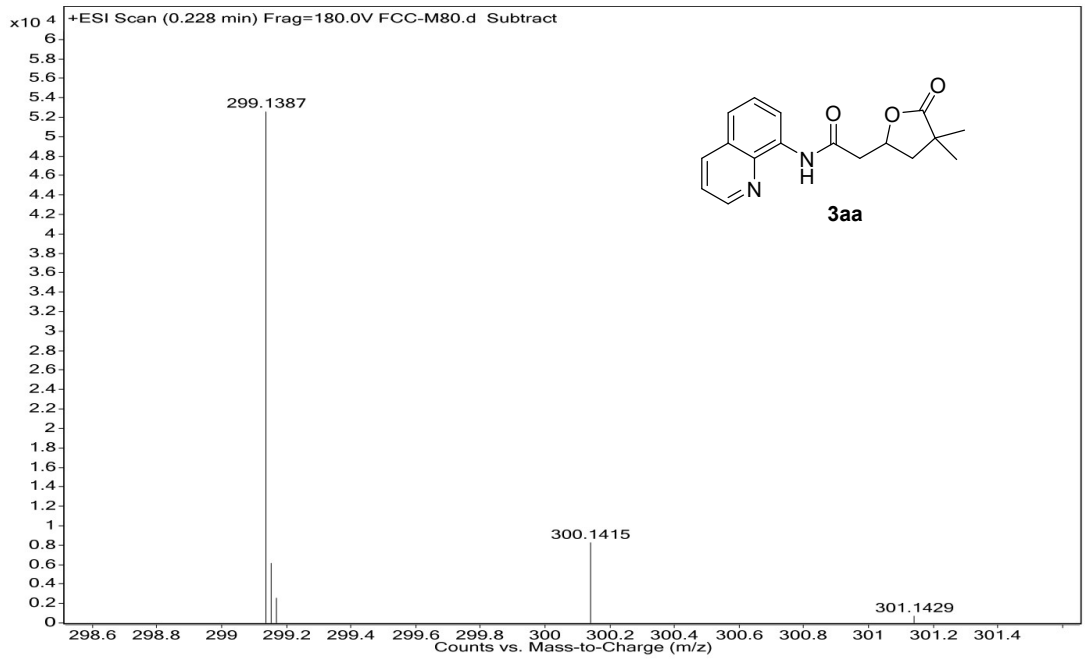
^{1}H NMR Spectra of **3aa**



^{13}C NMR Spectra of **3aa**



HRMS Spectra of **3aa**



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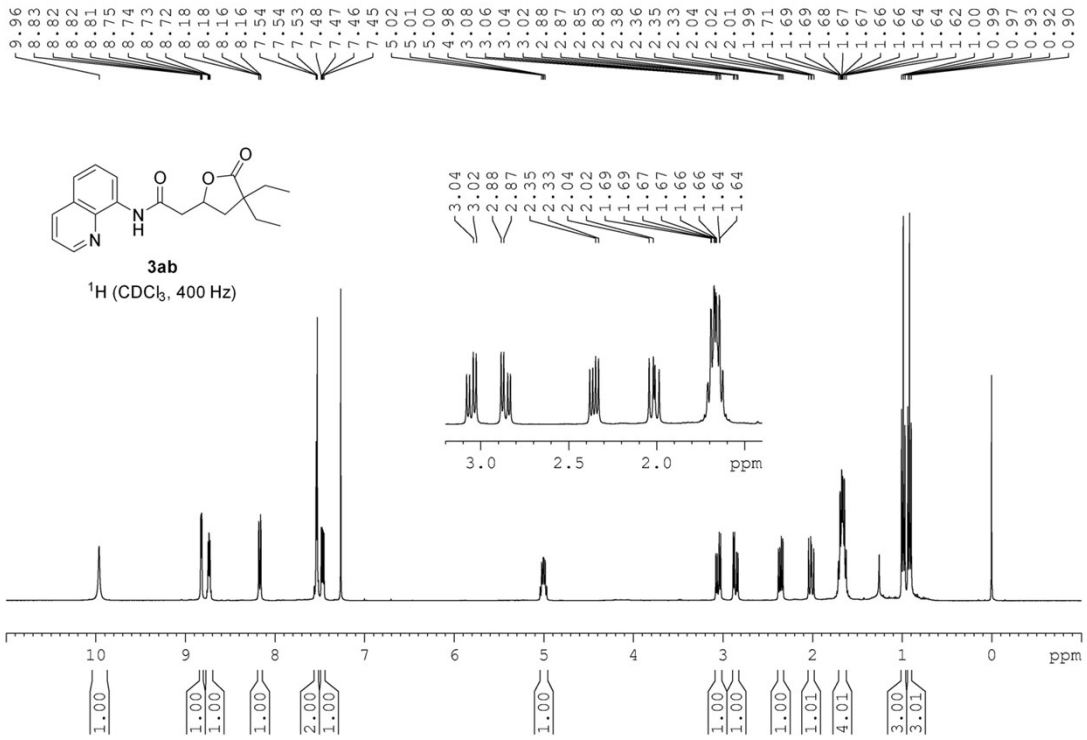

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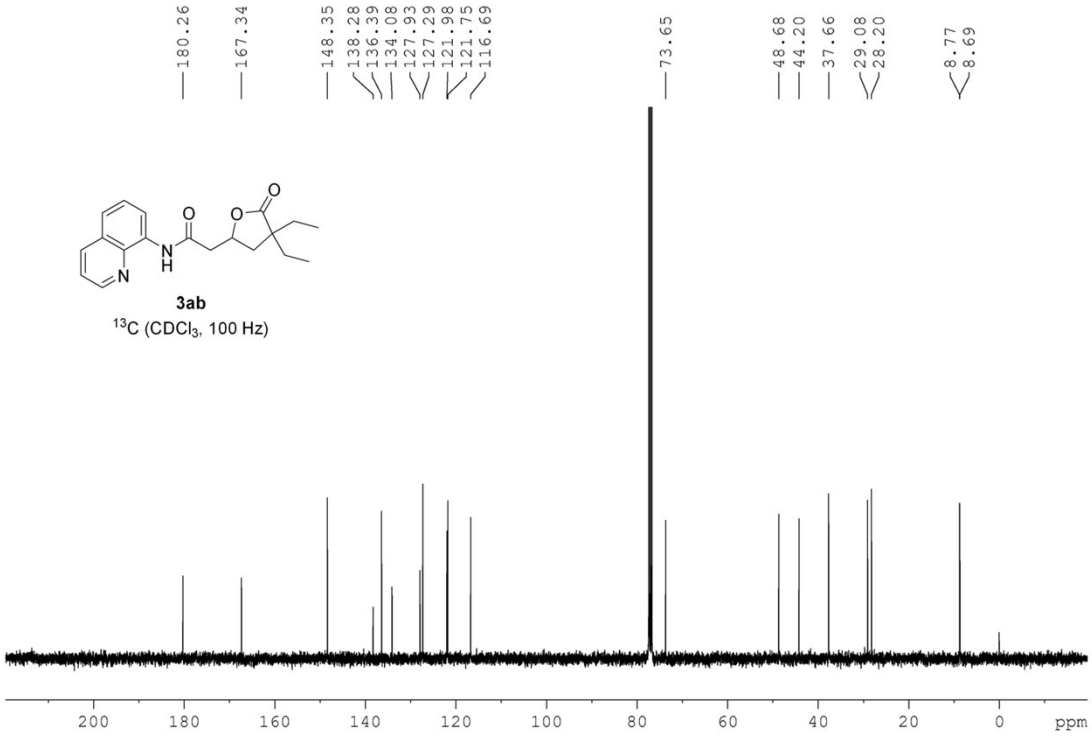

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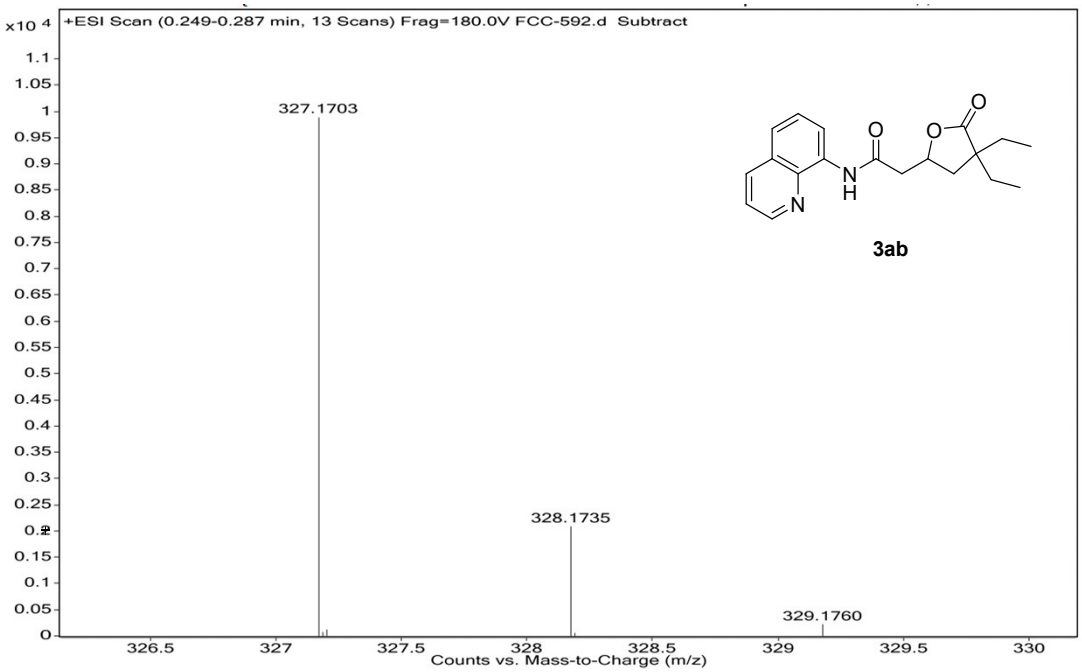

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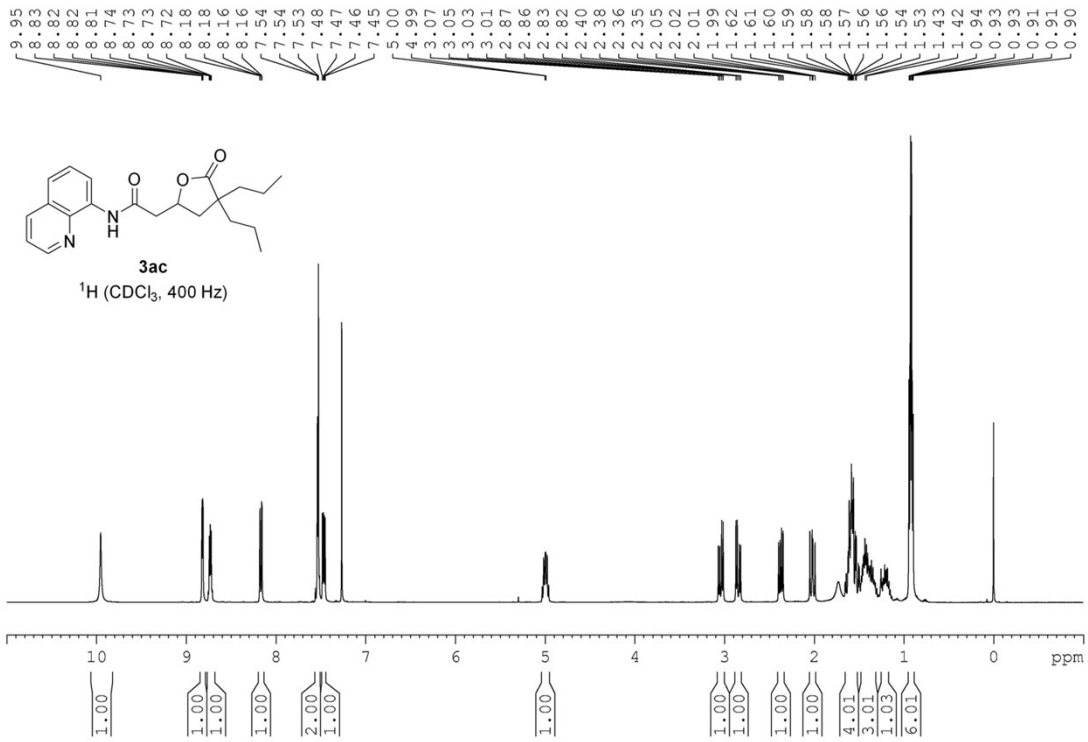

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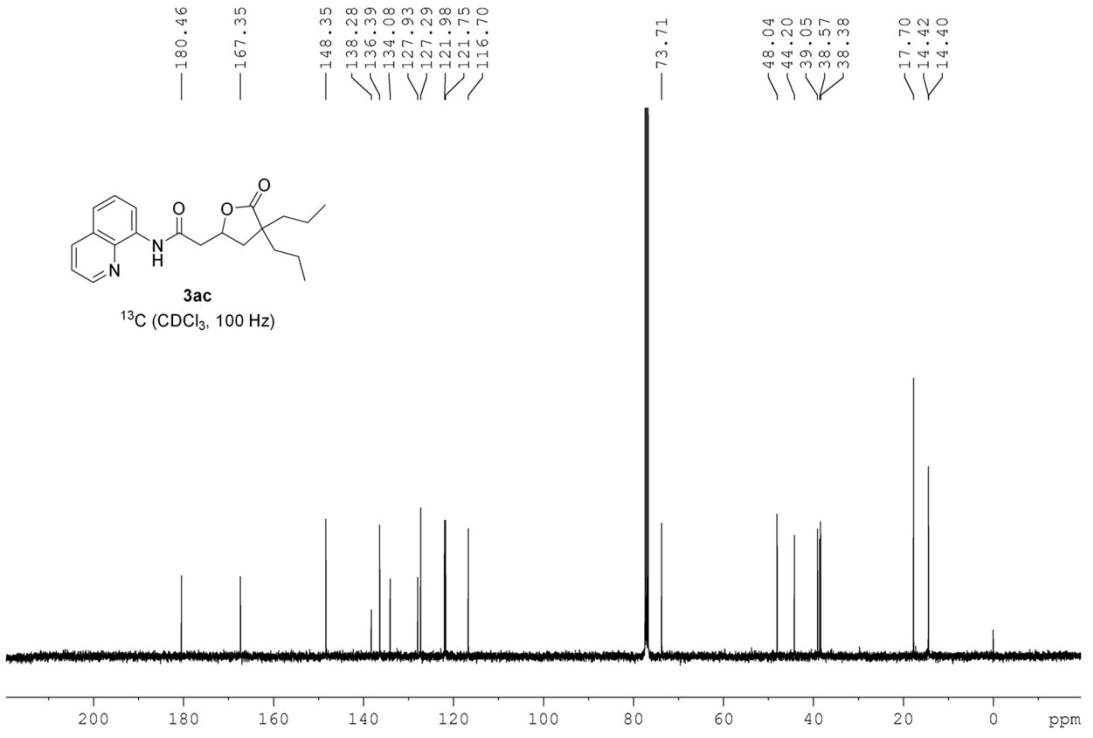

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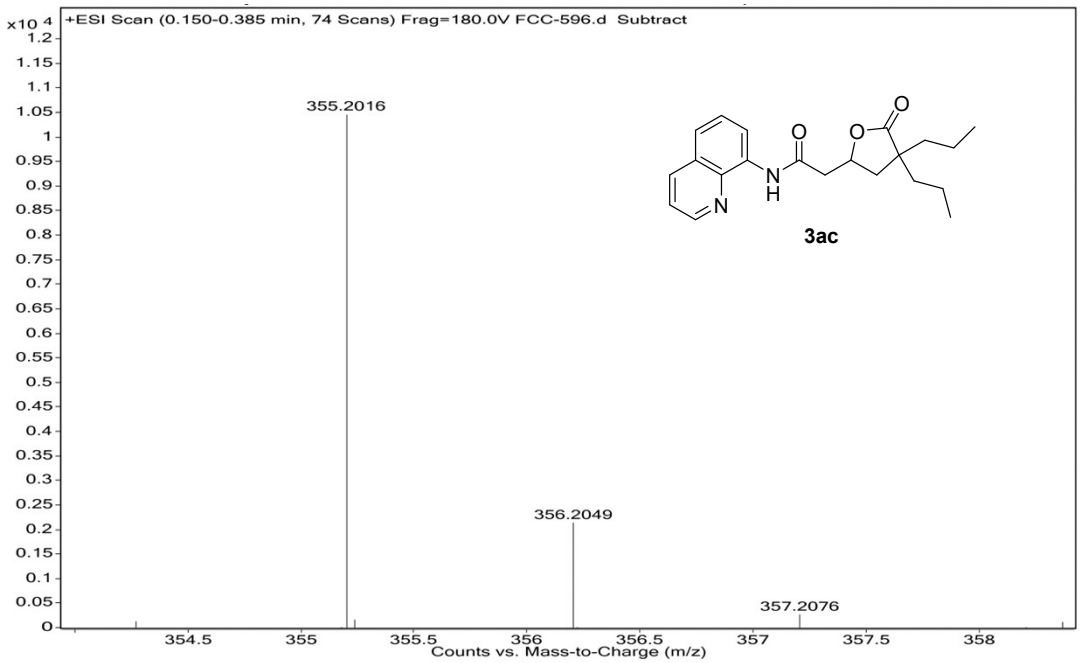

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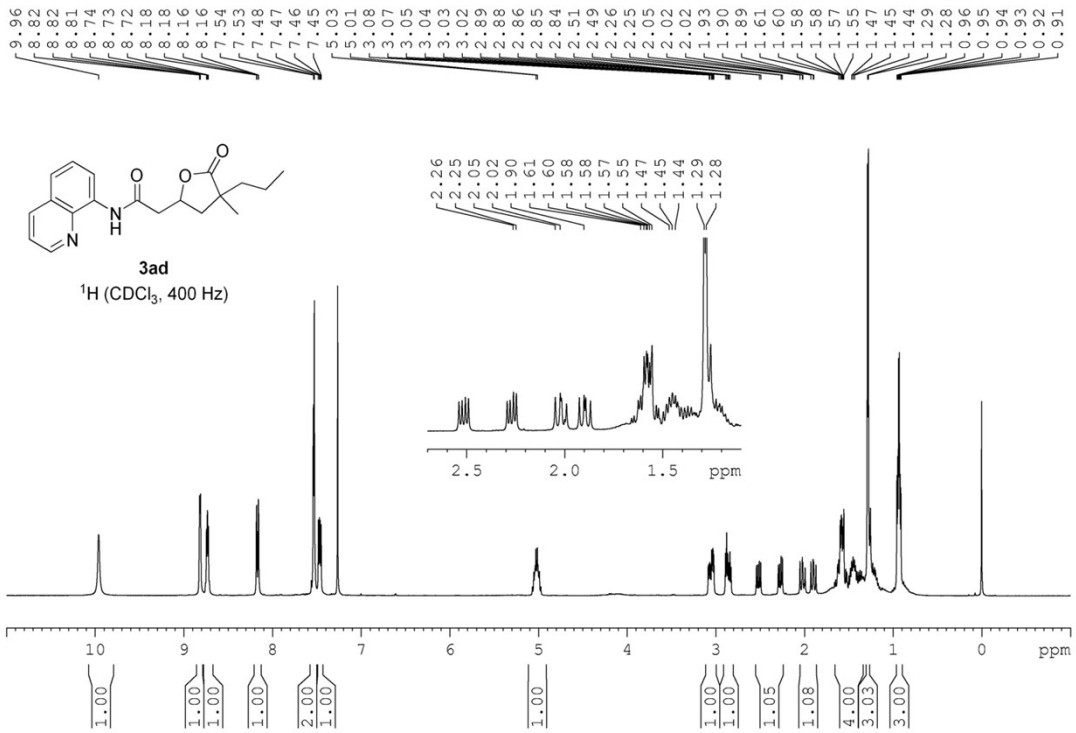

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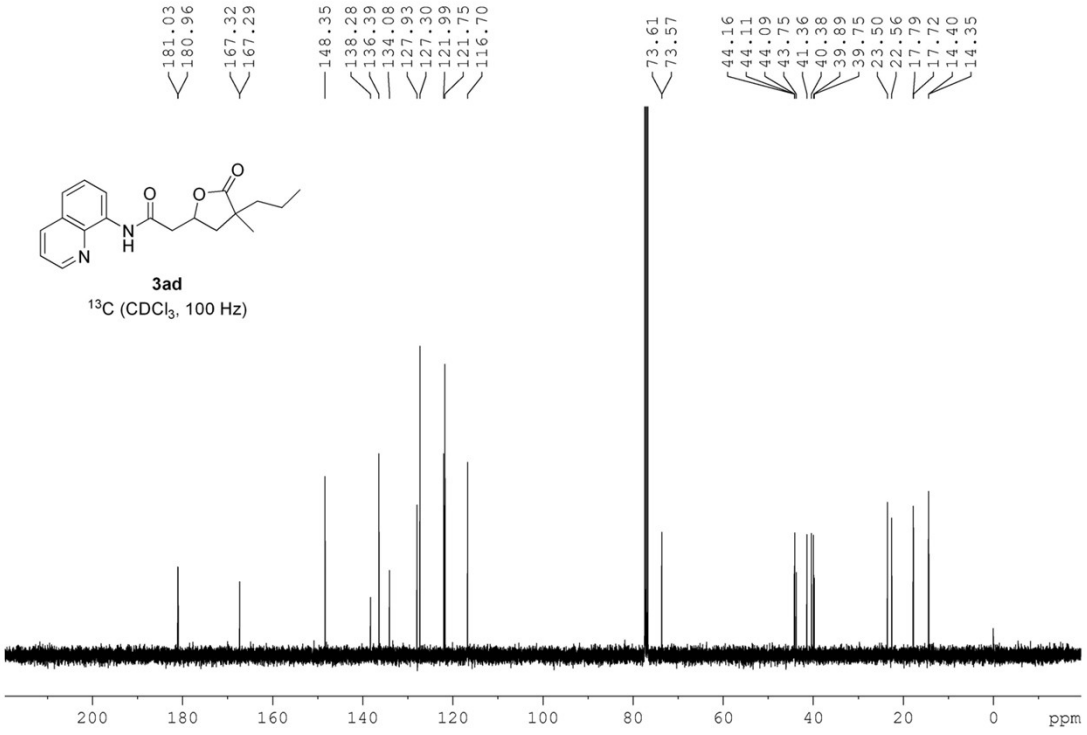

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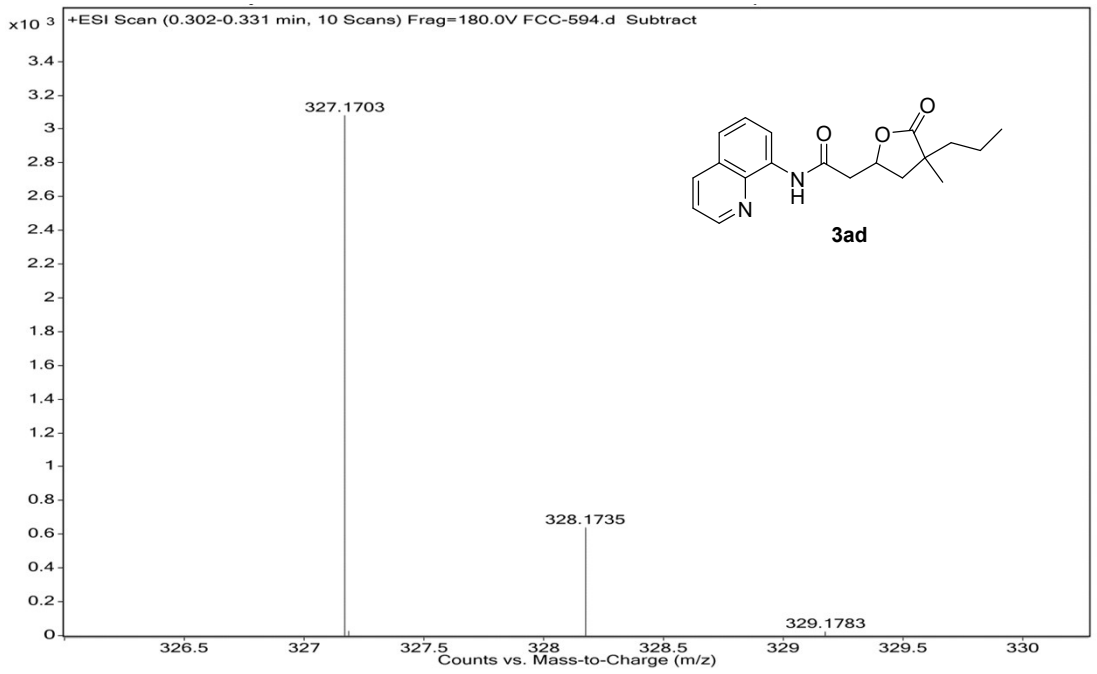

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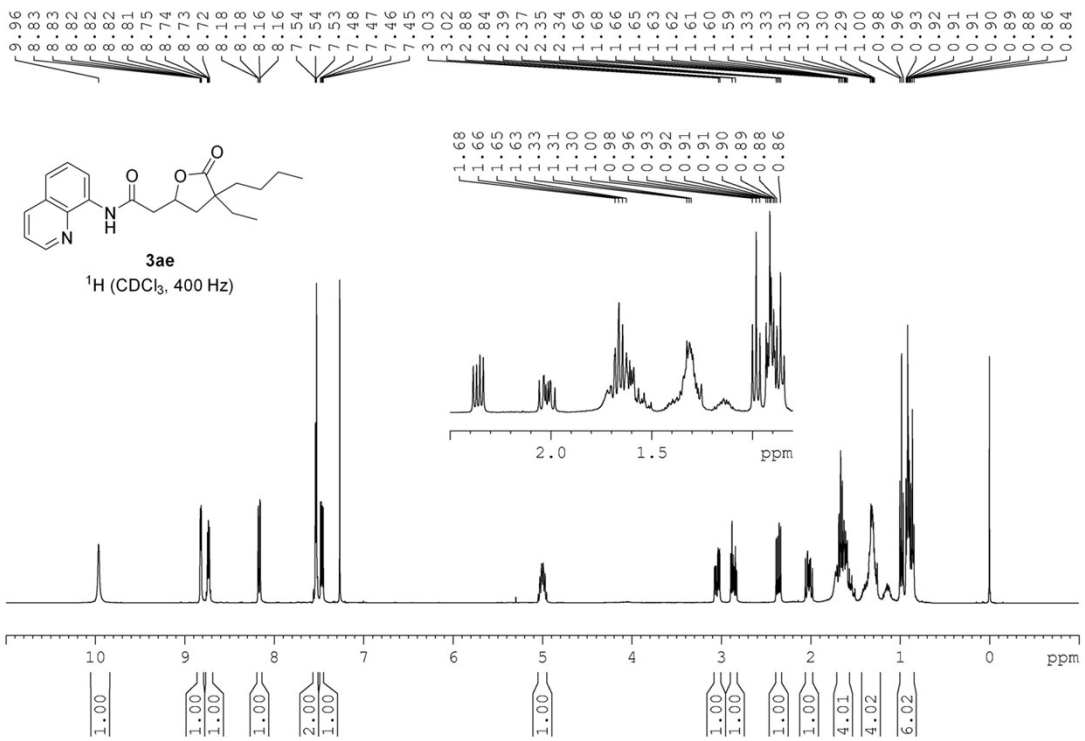

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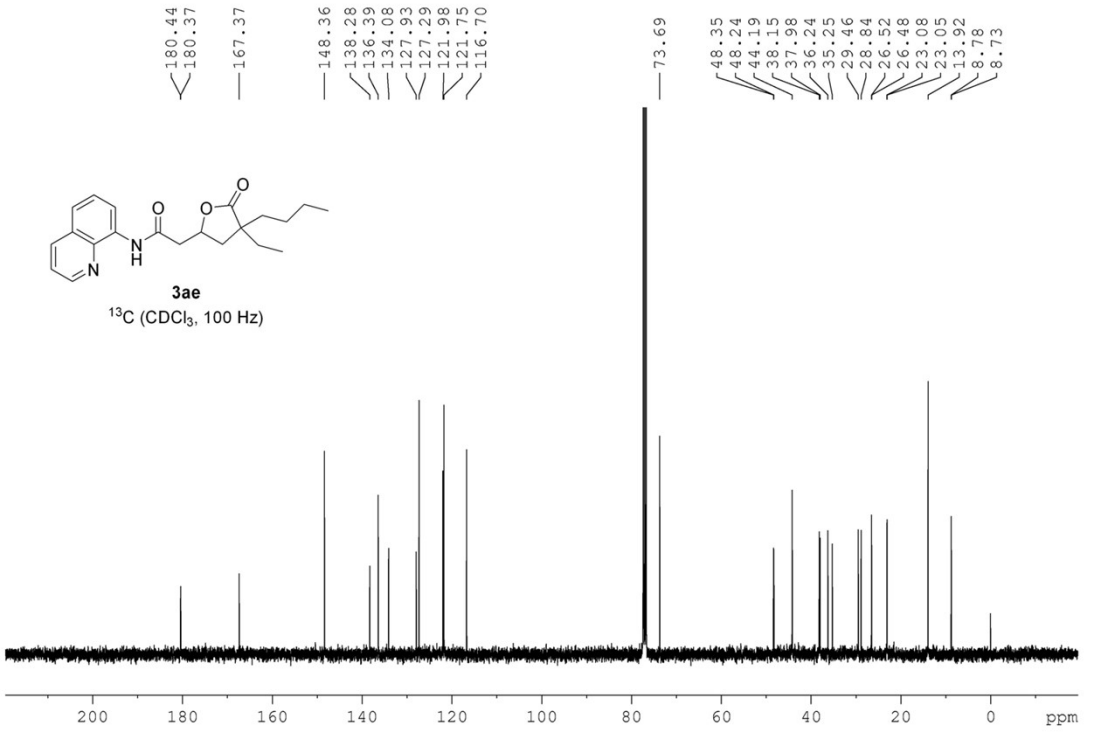

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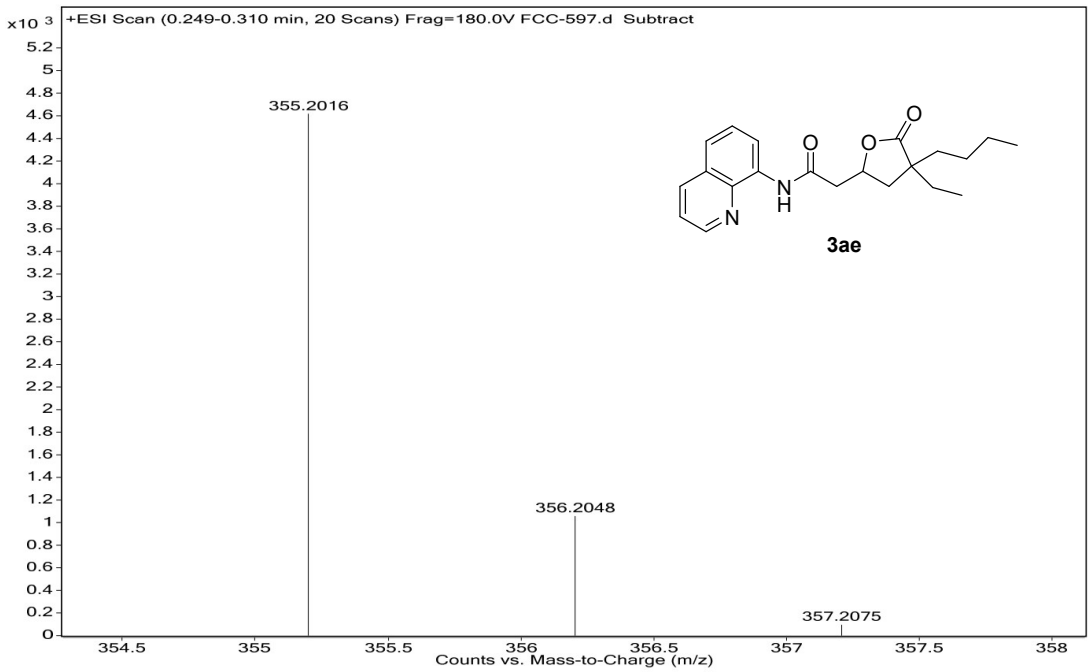

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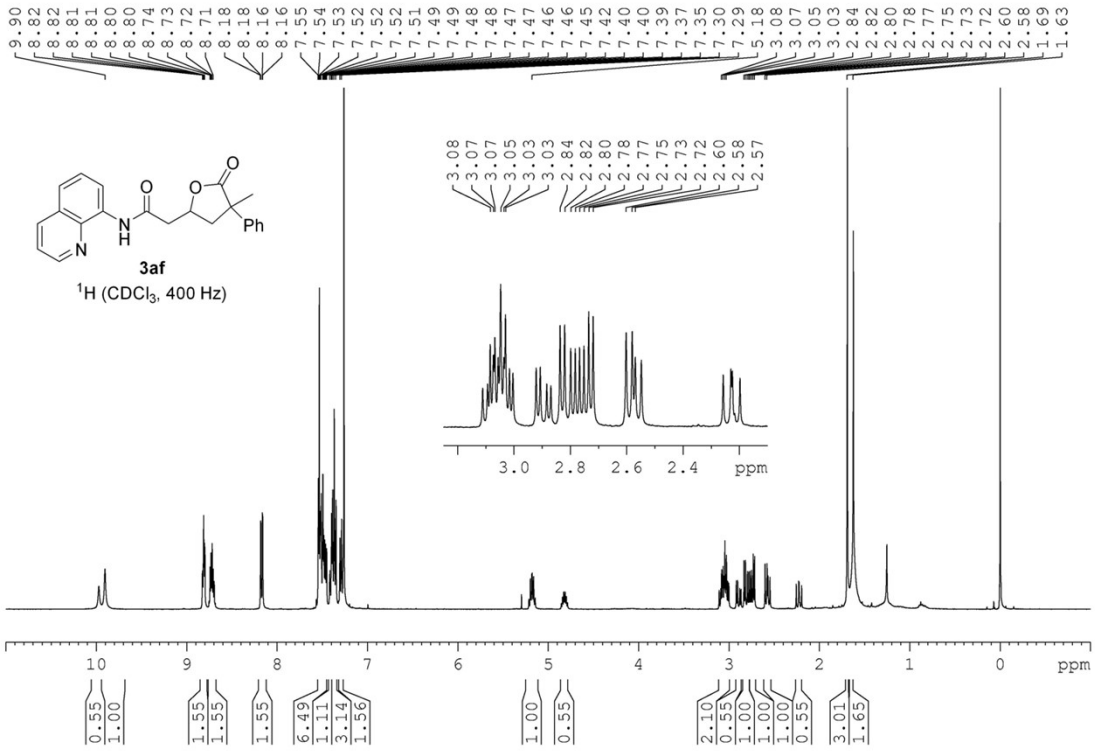

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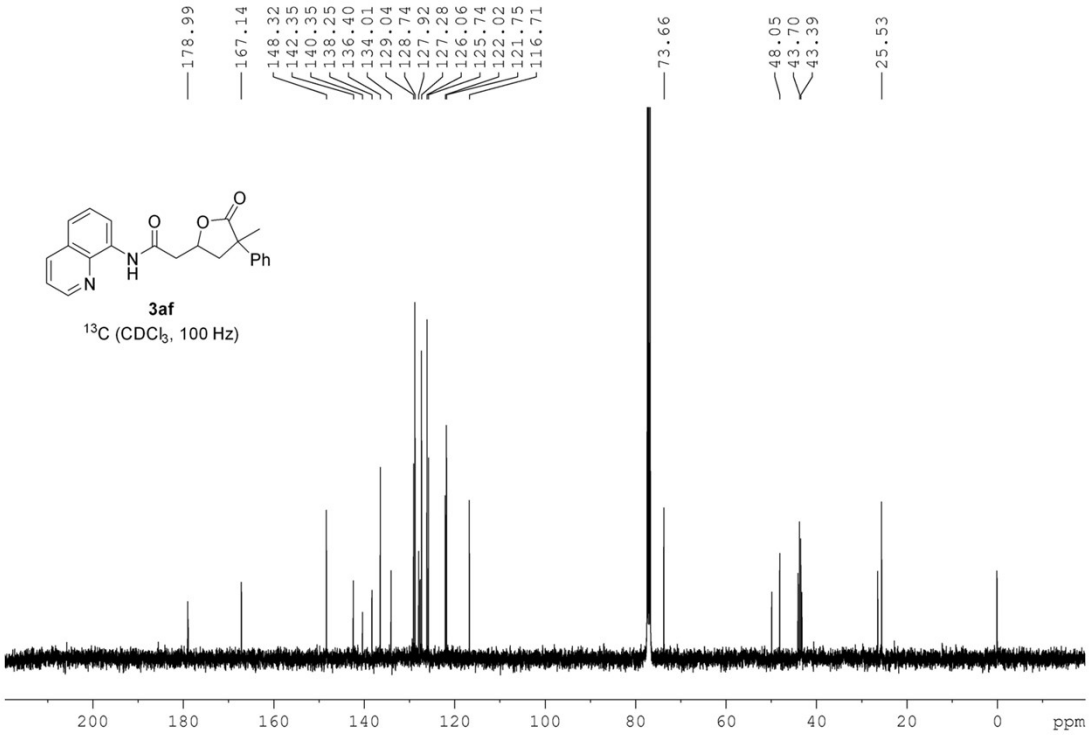

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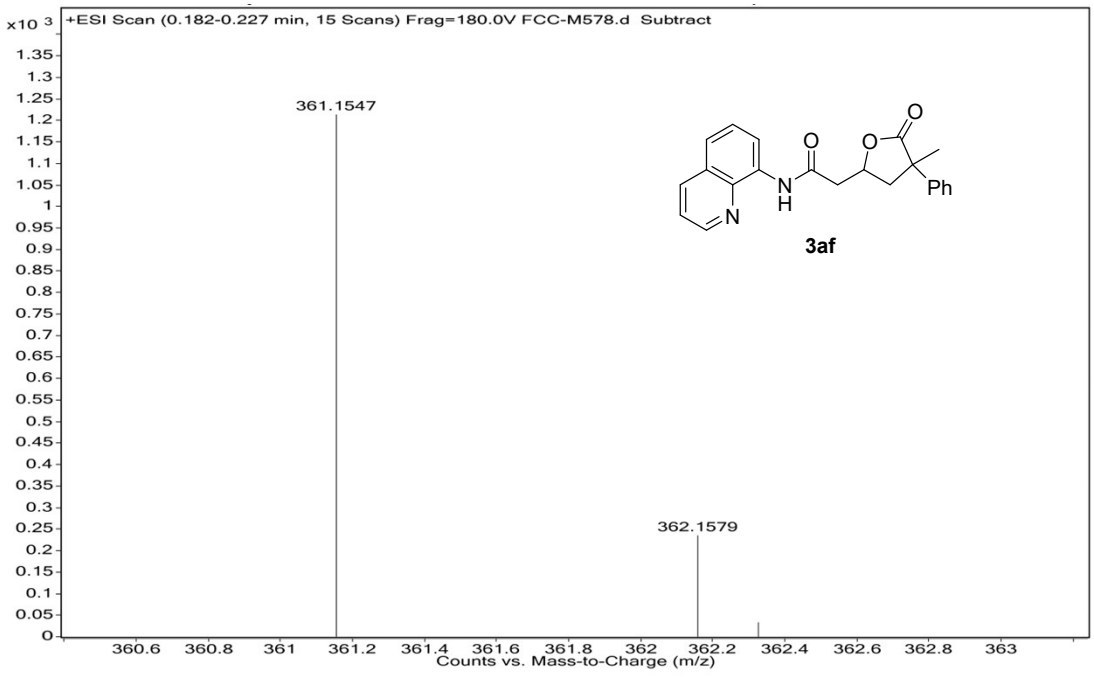

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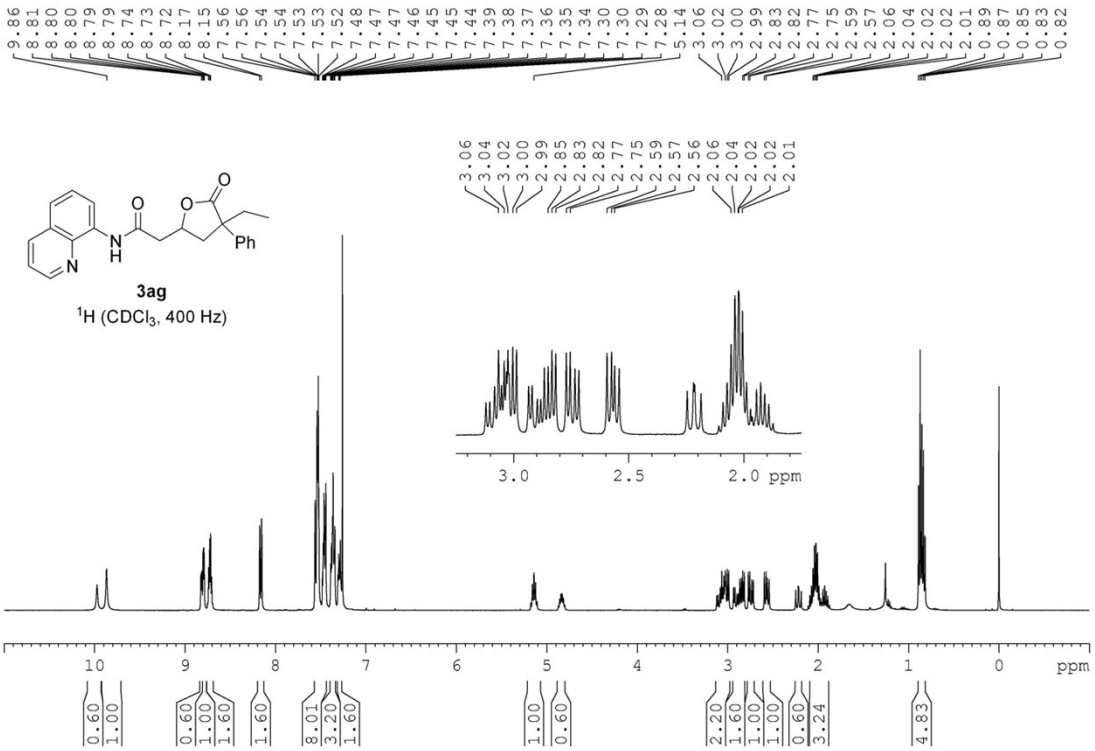

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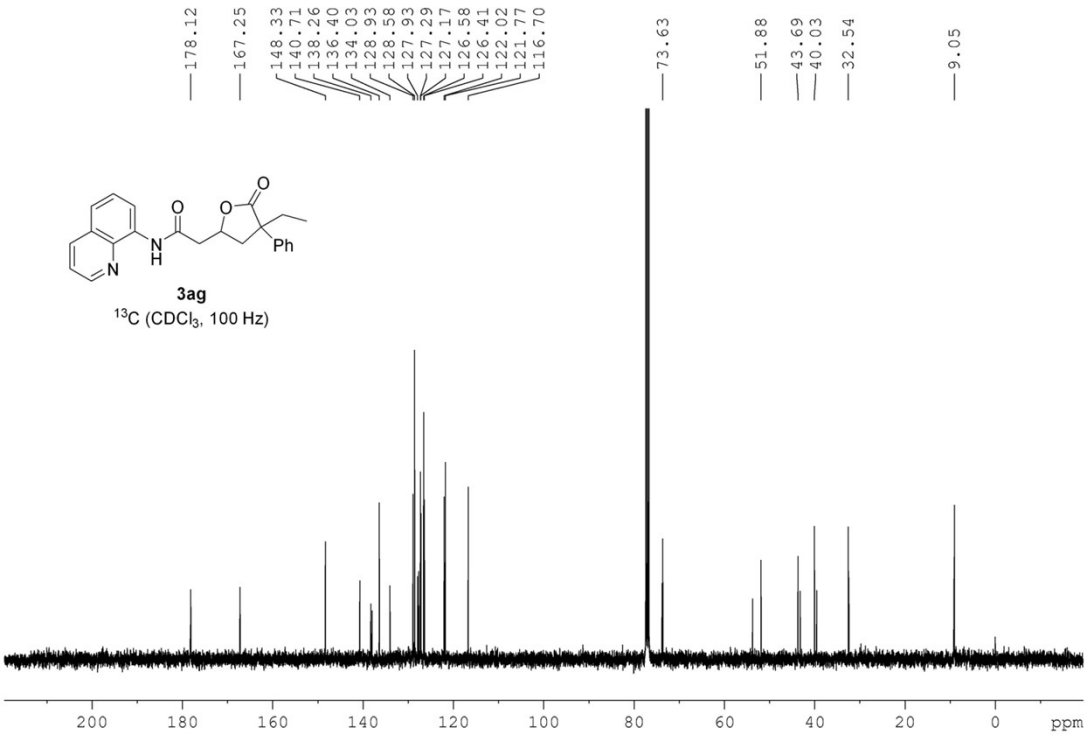

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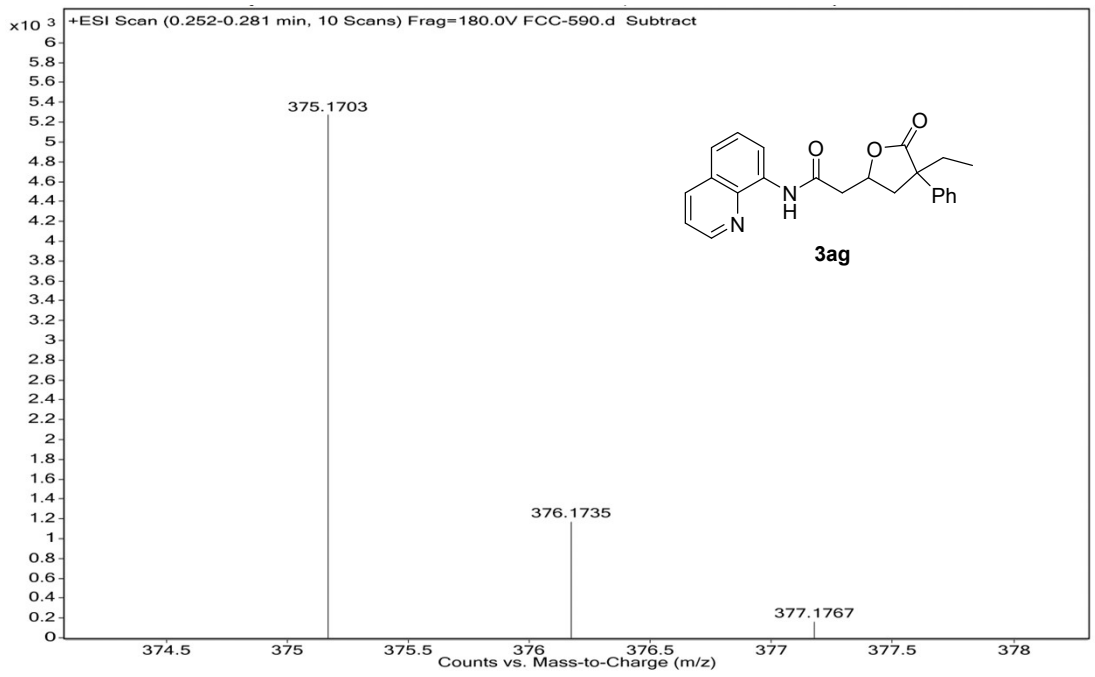

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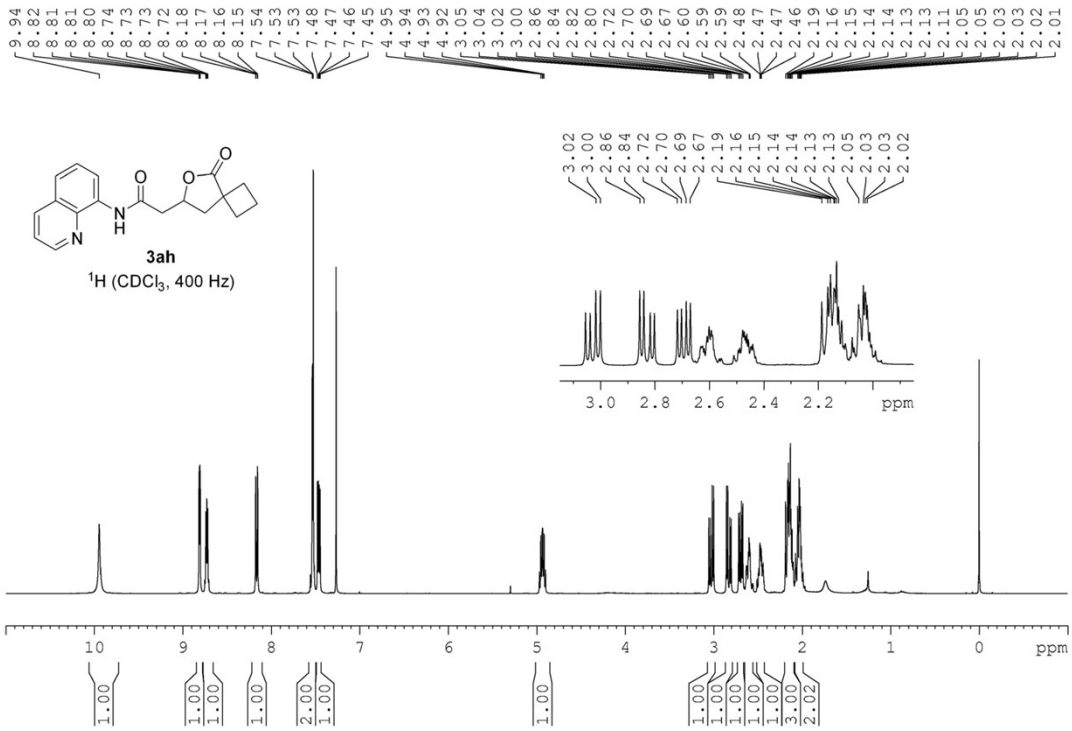

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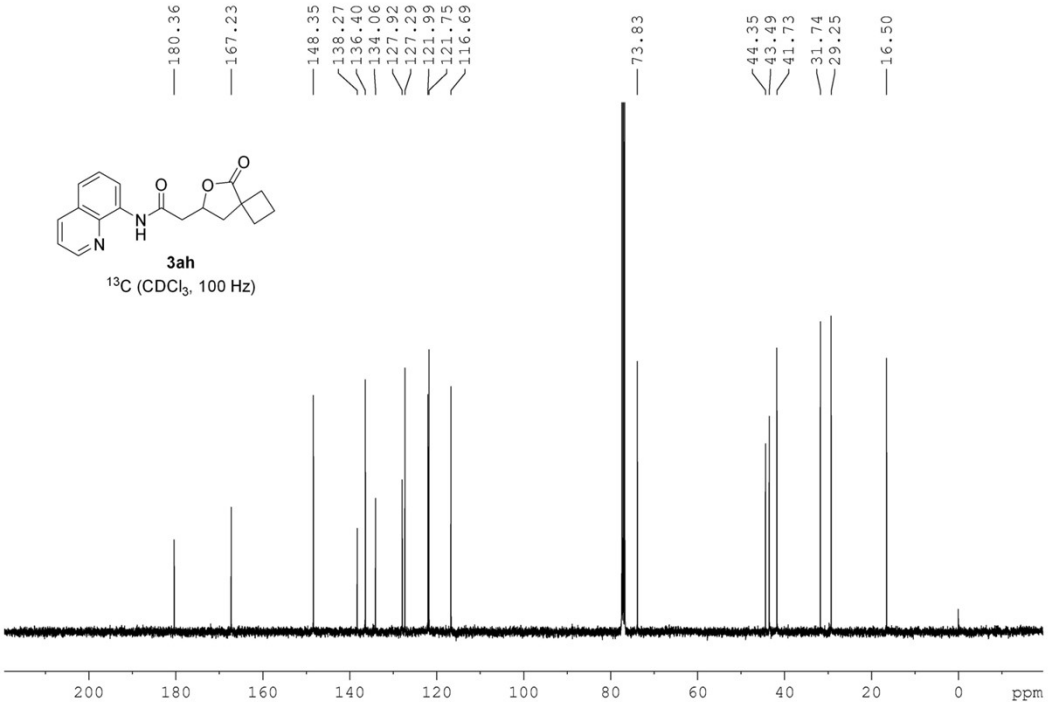

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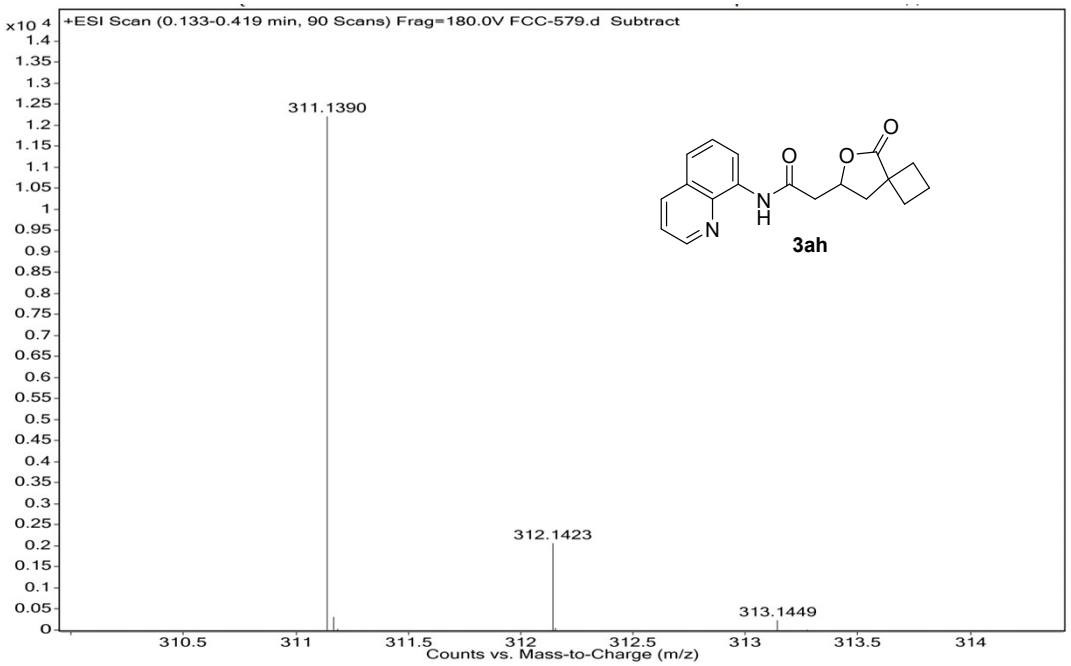

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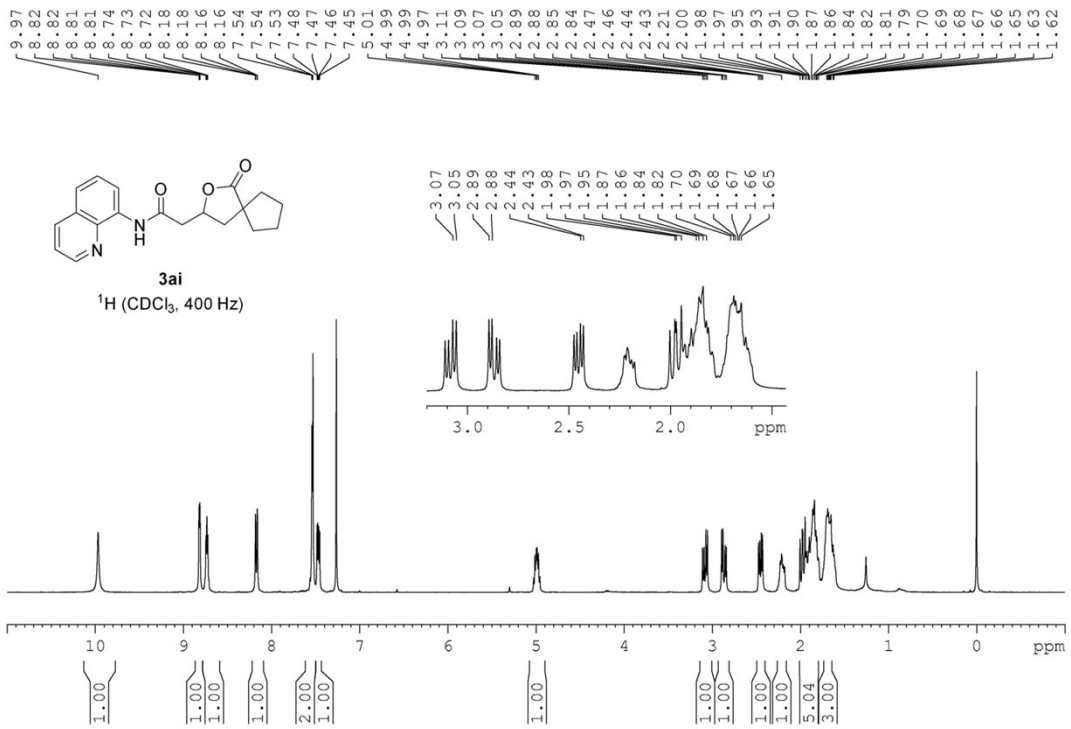

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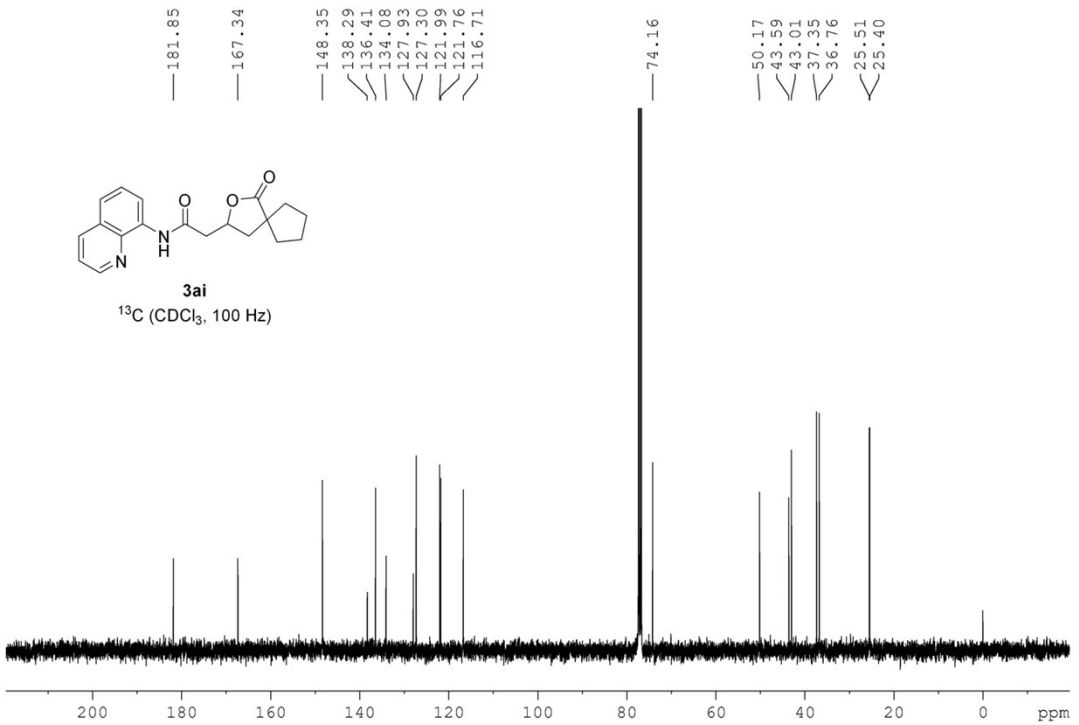

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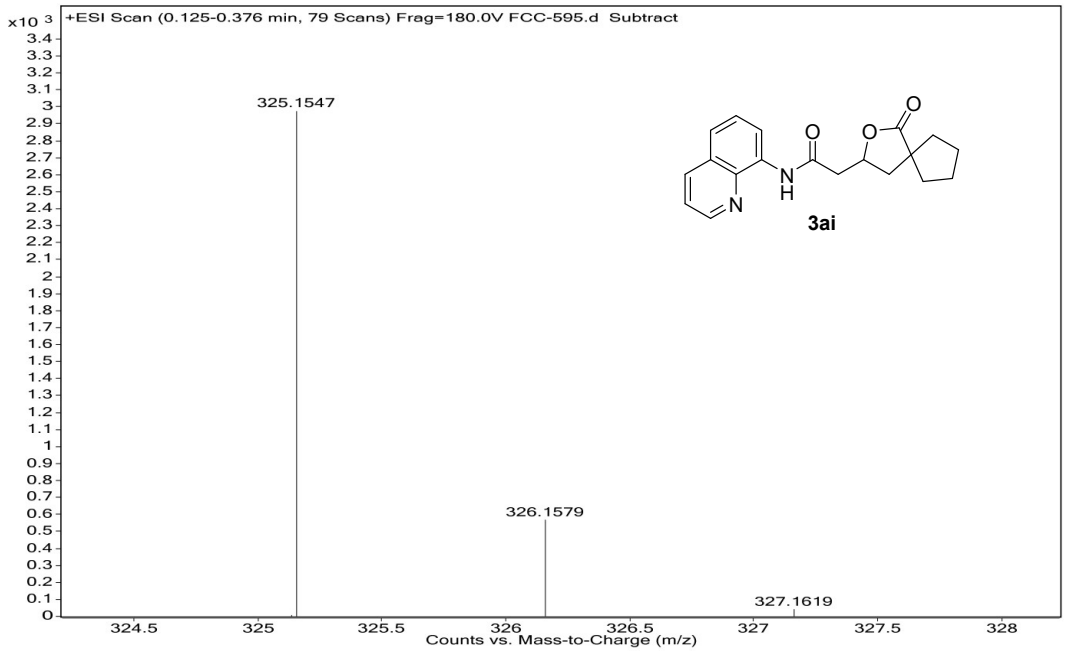

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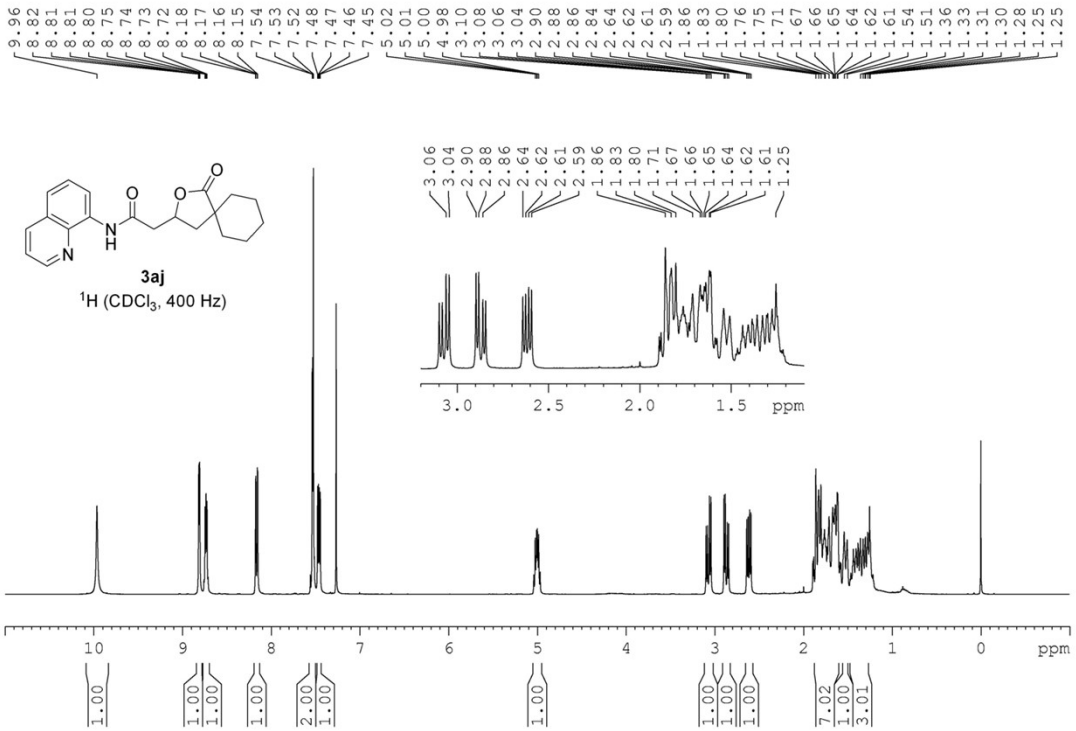

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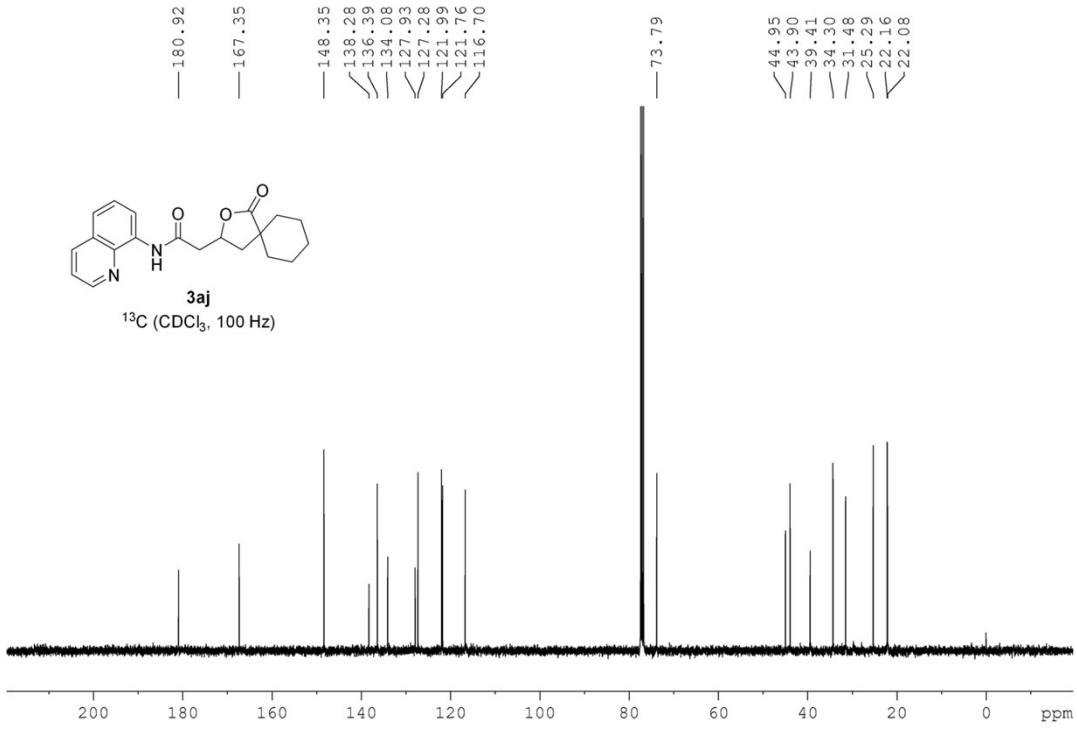

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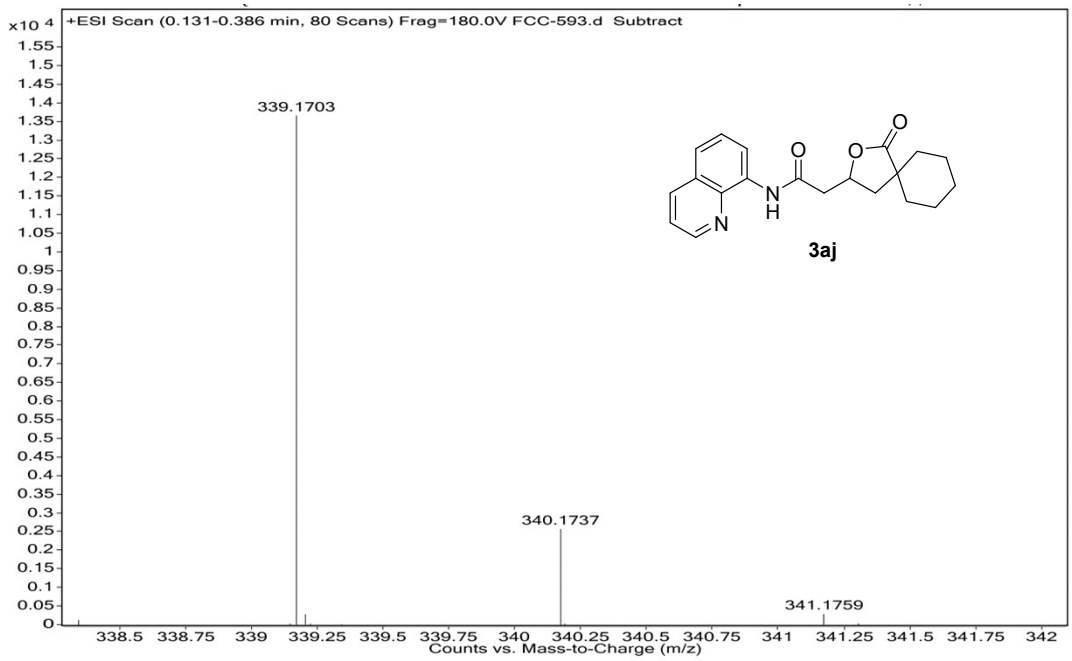

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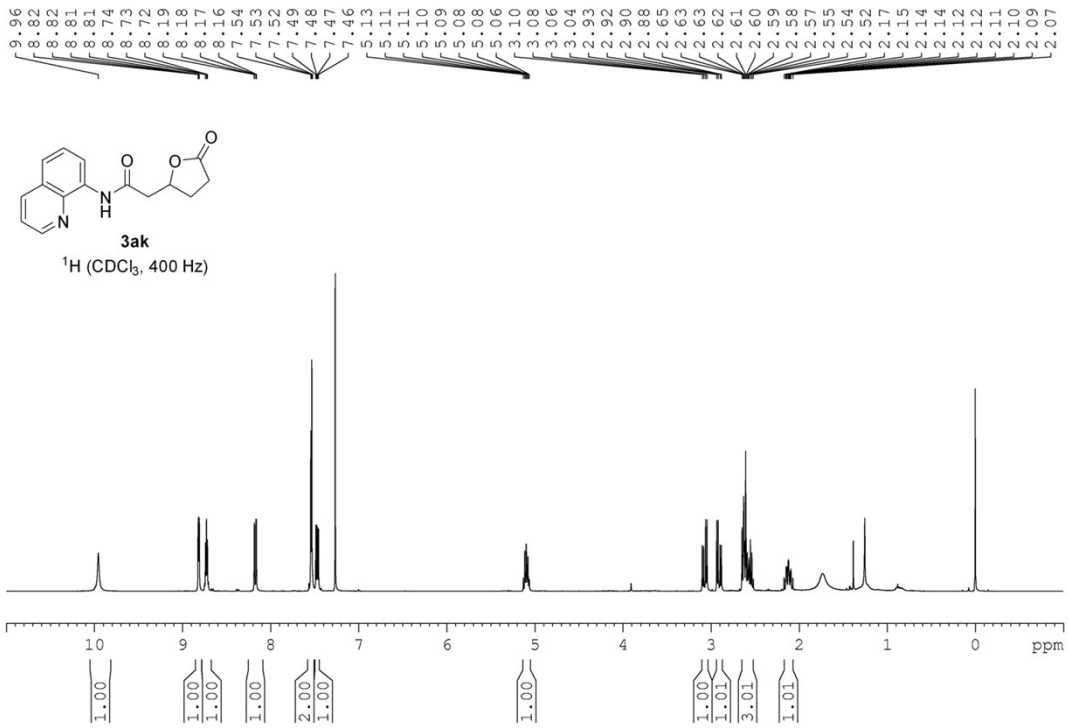

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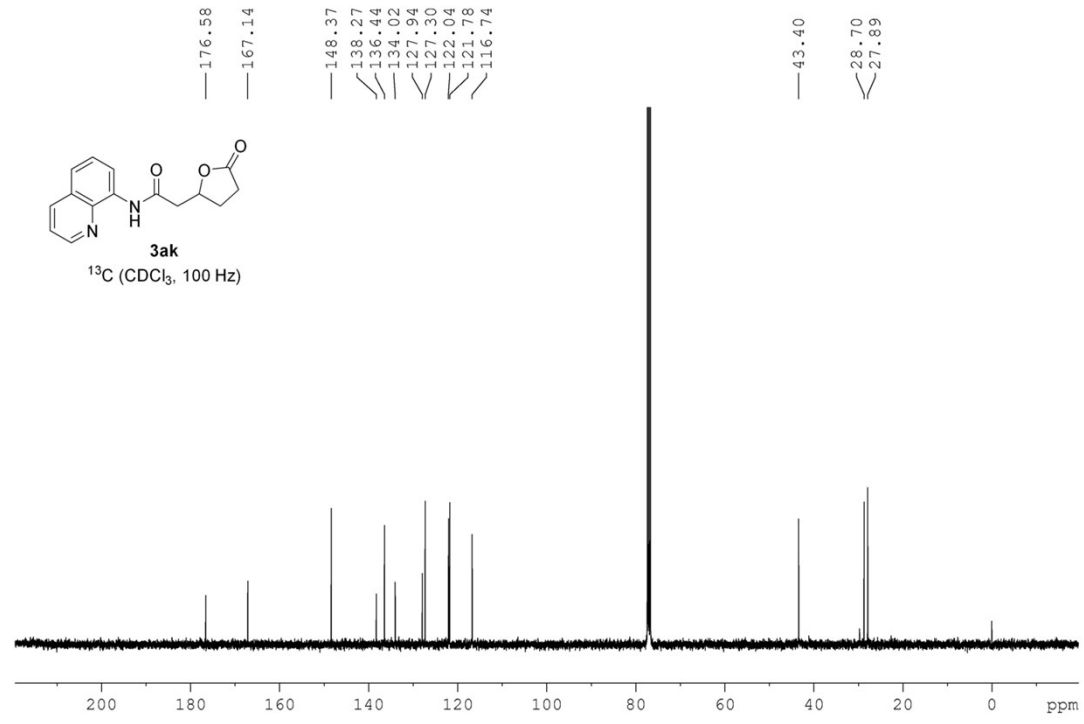

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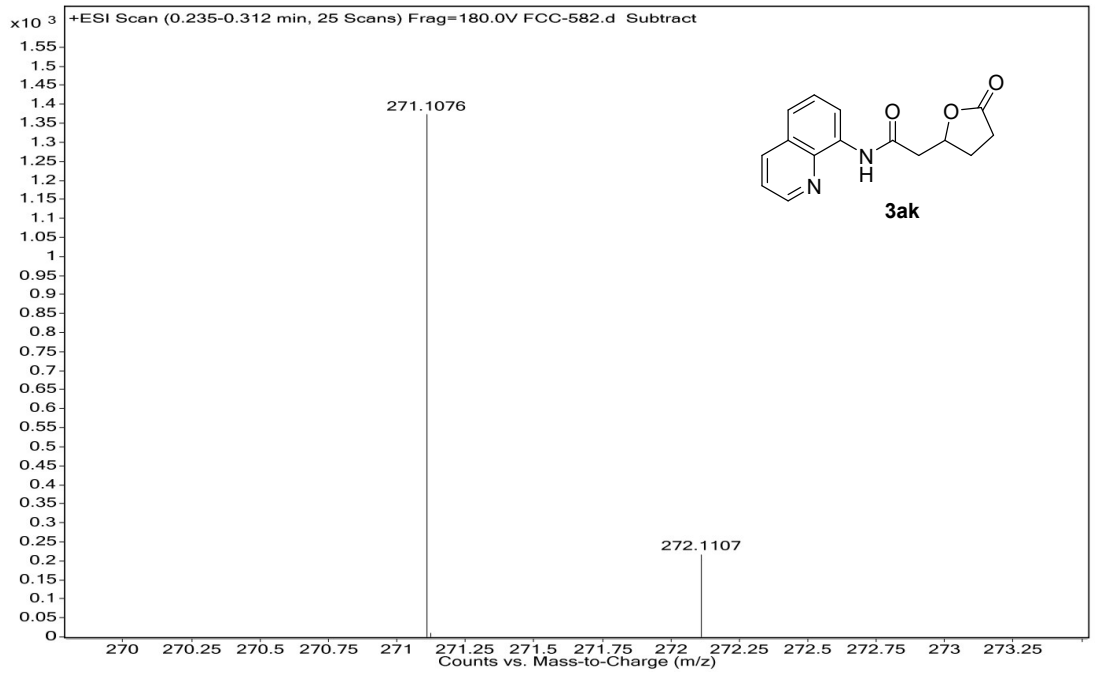

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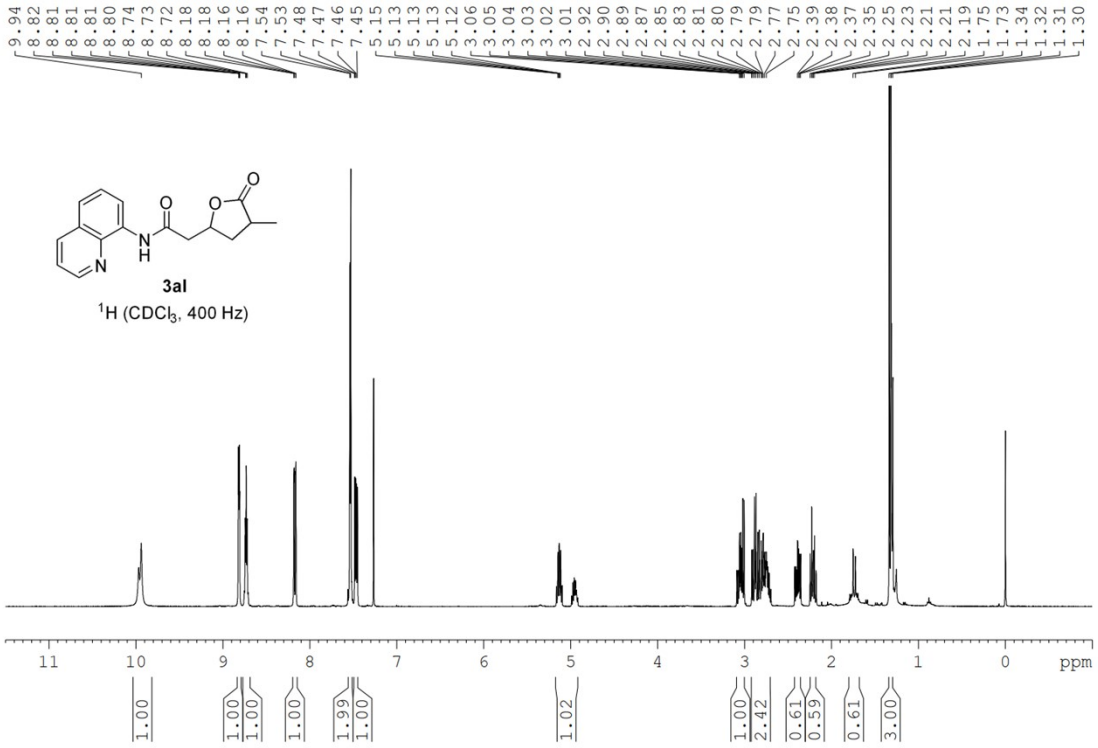

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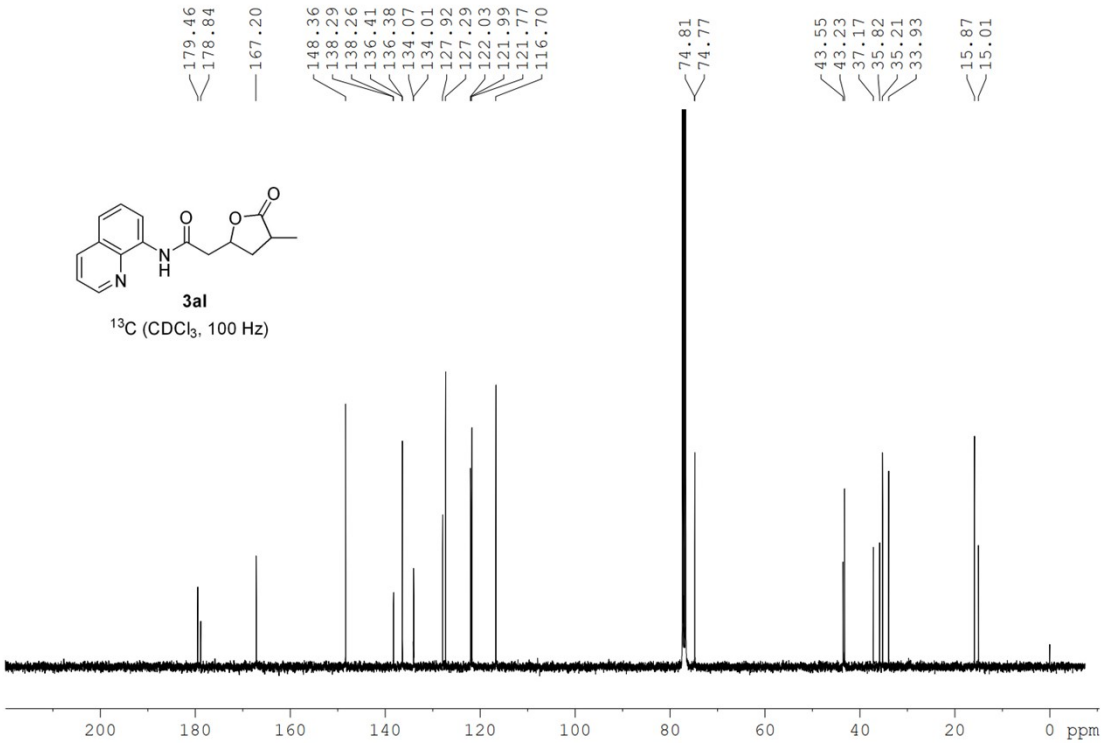

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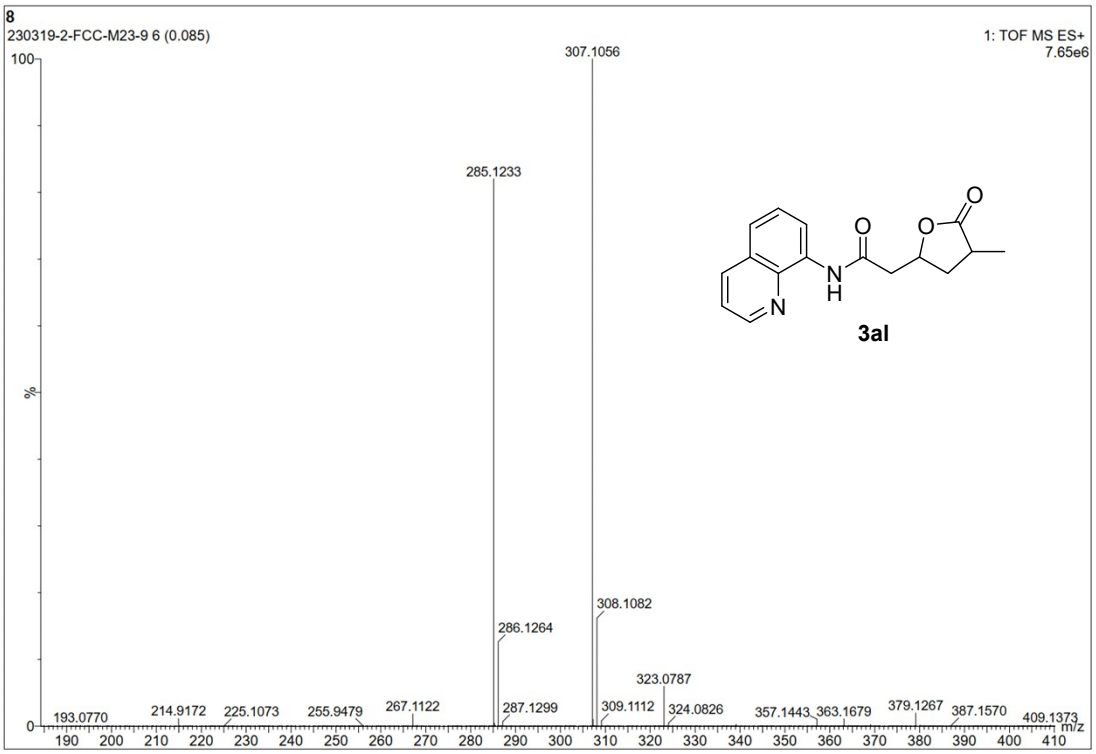

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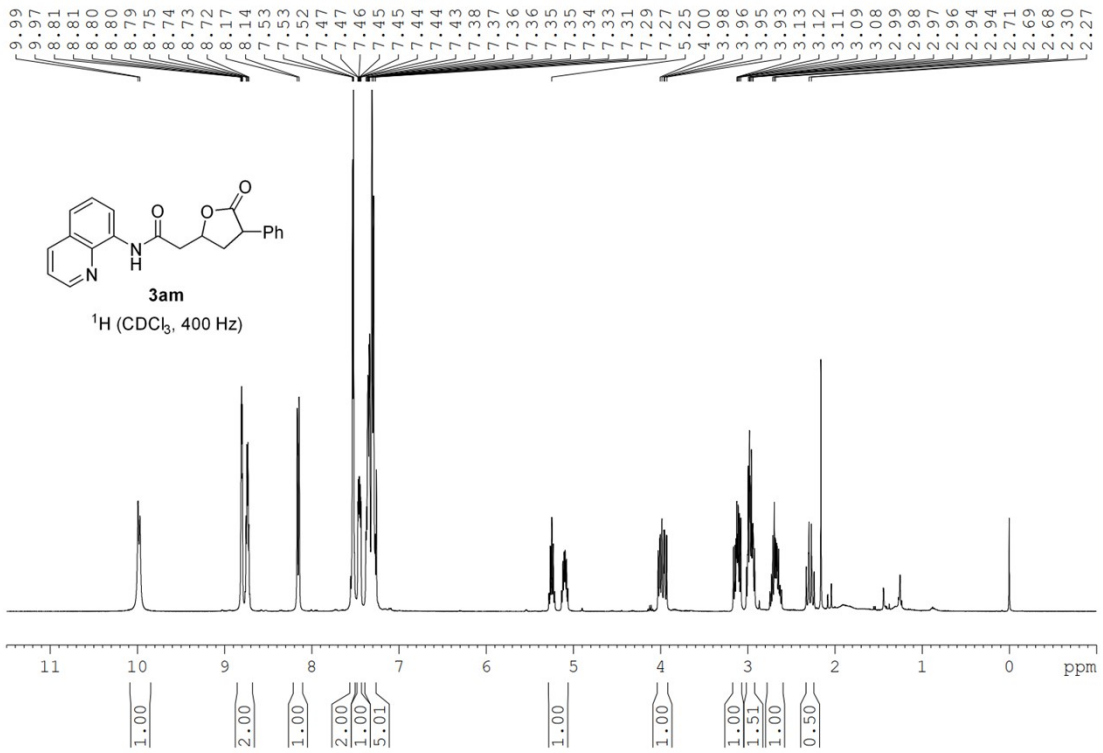

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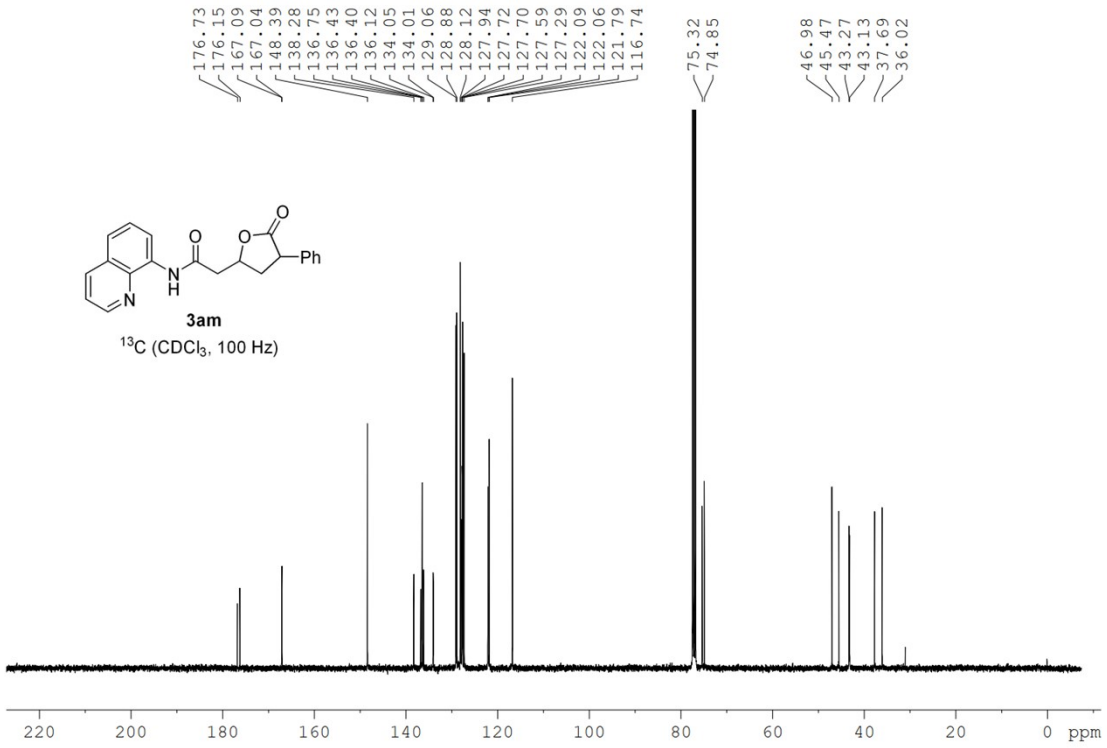

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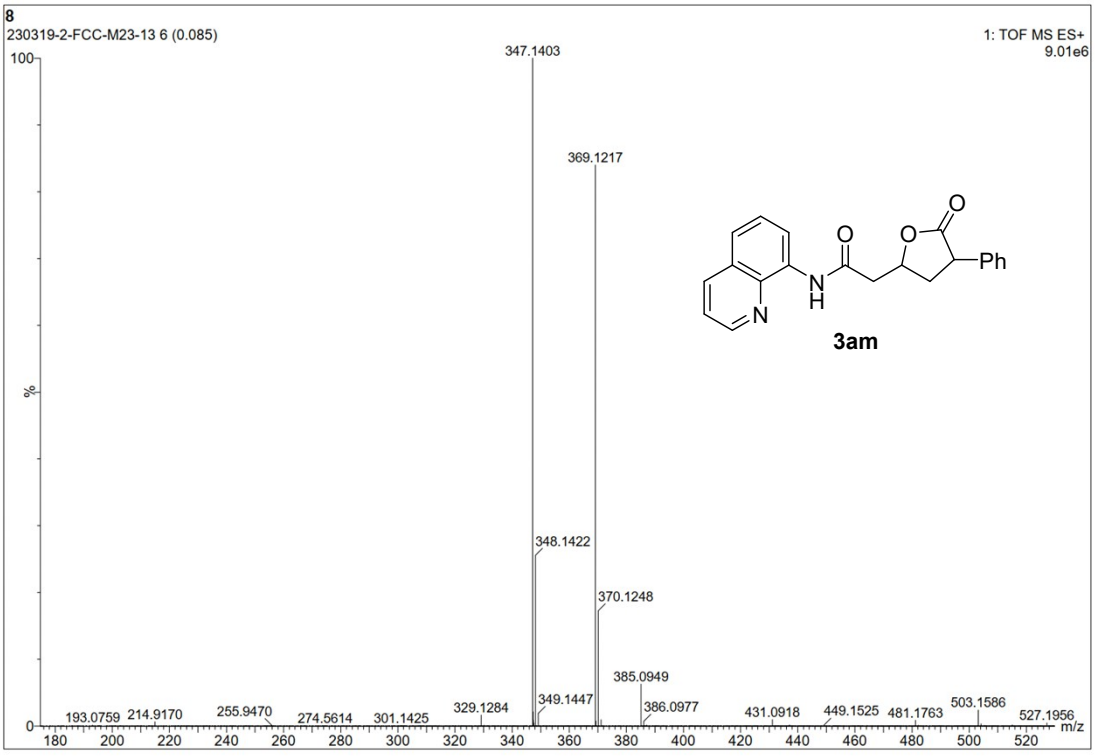
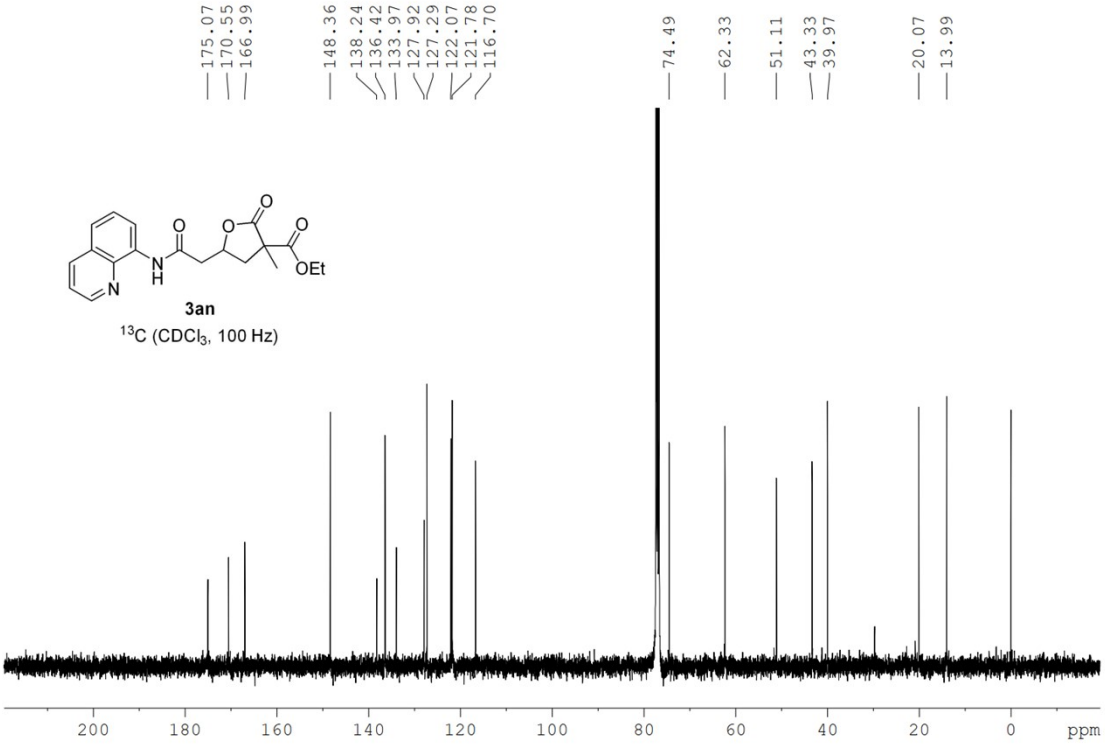


^{1}H NMR Spectra of **3an**

^{13}C NMR Spectra of **3an**



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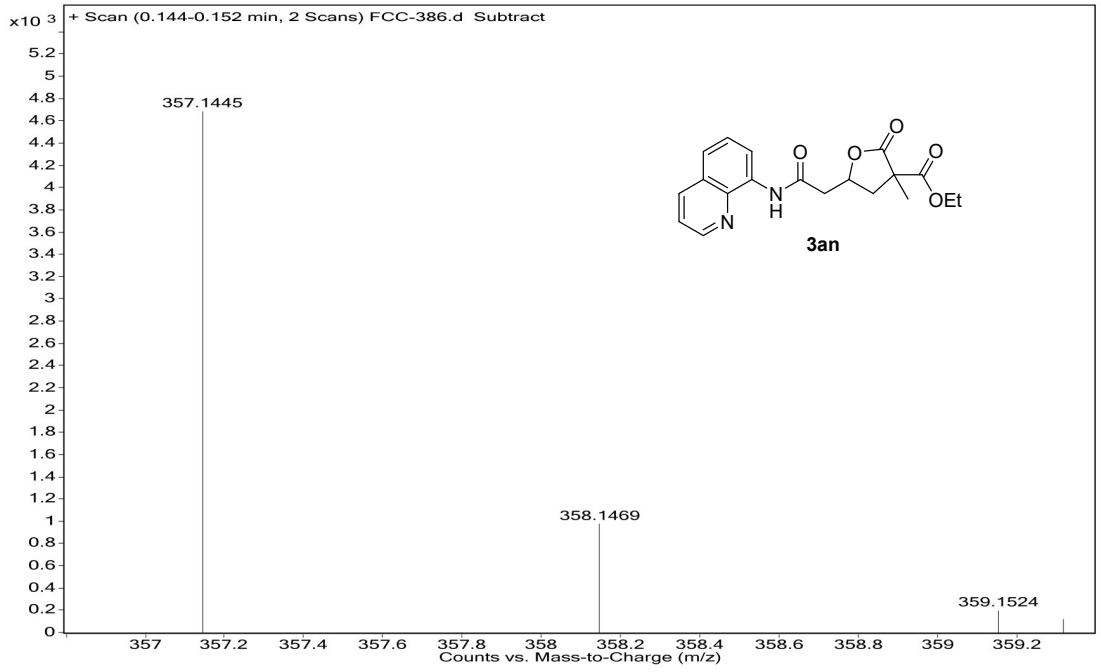

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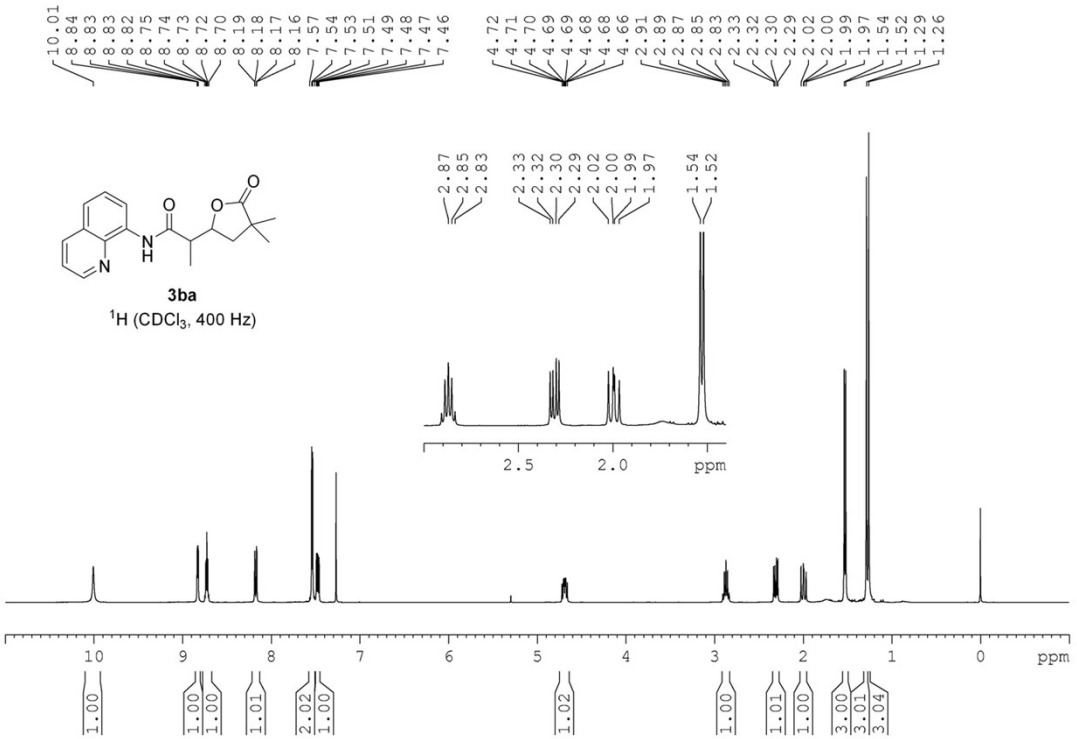

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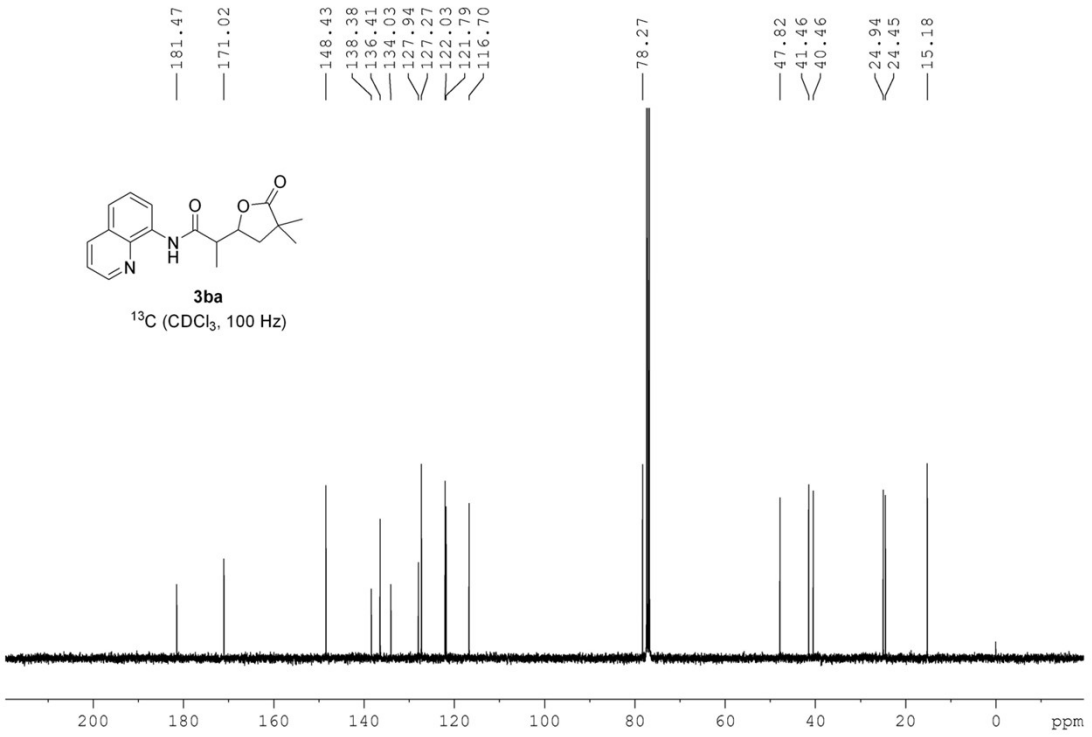

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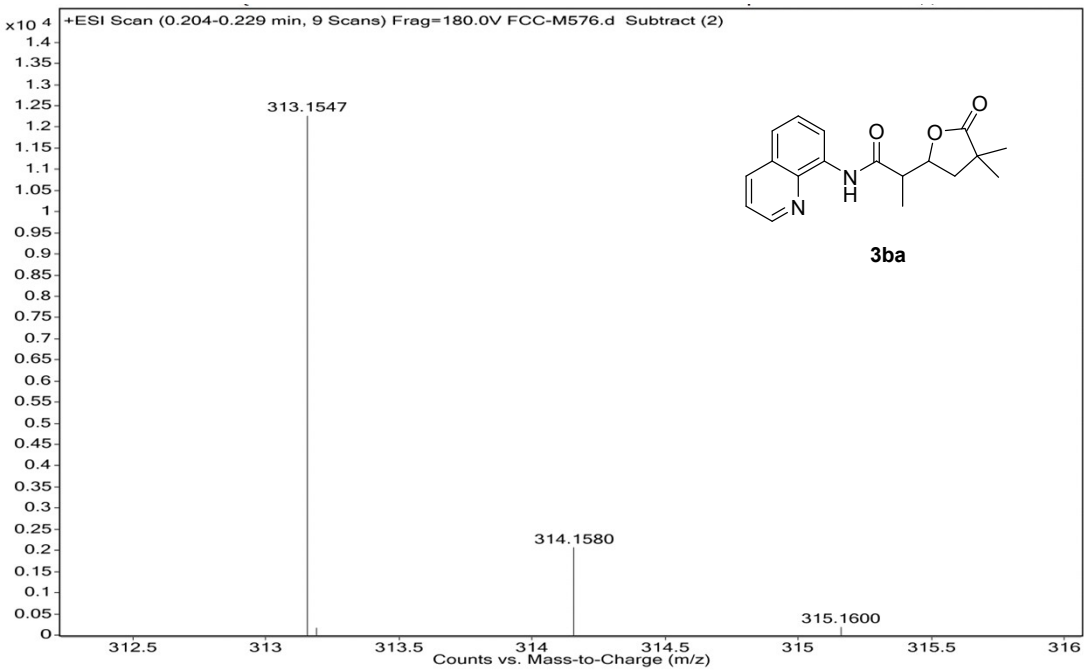
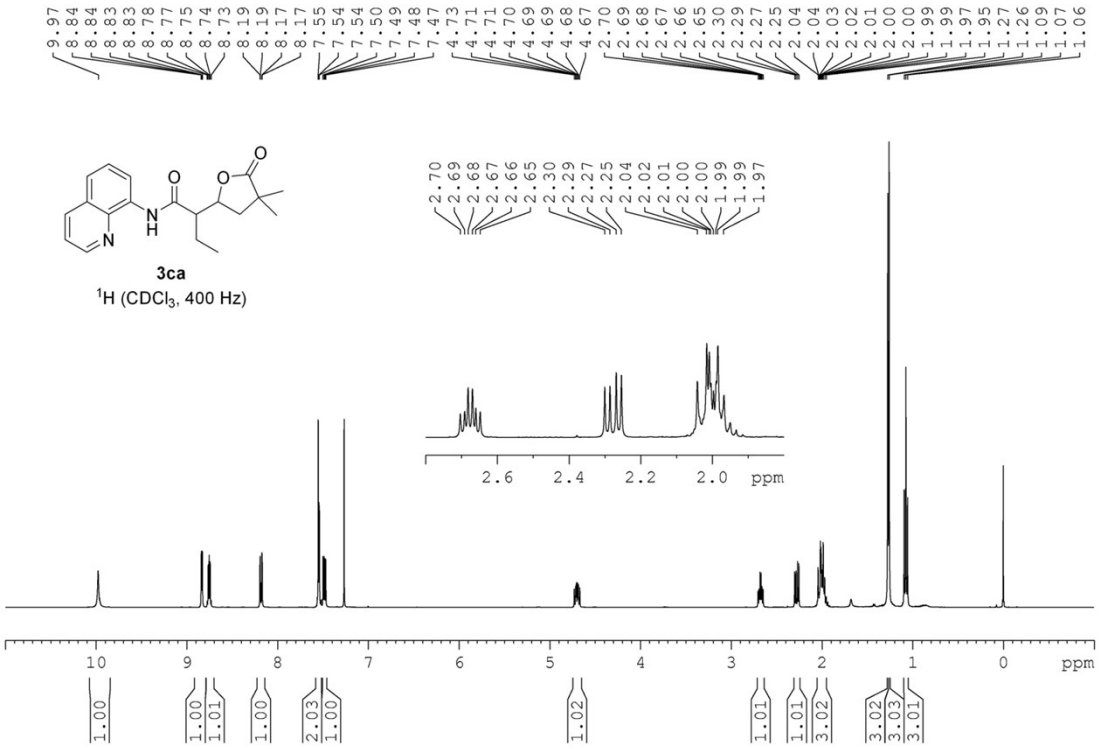
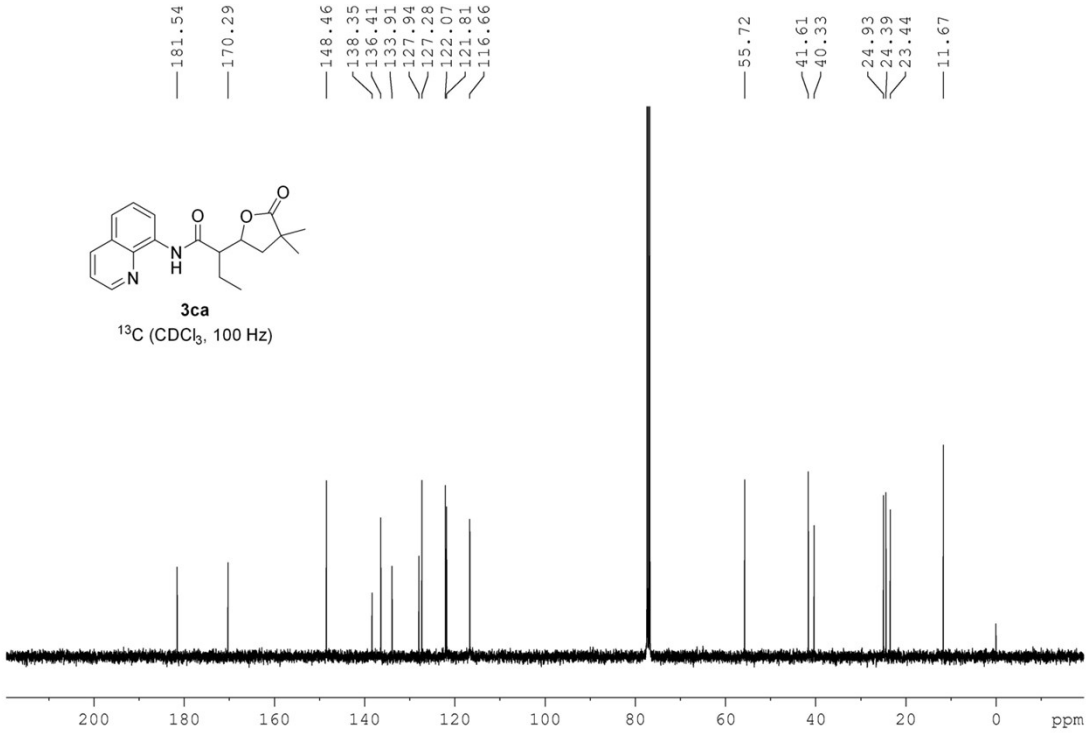


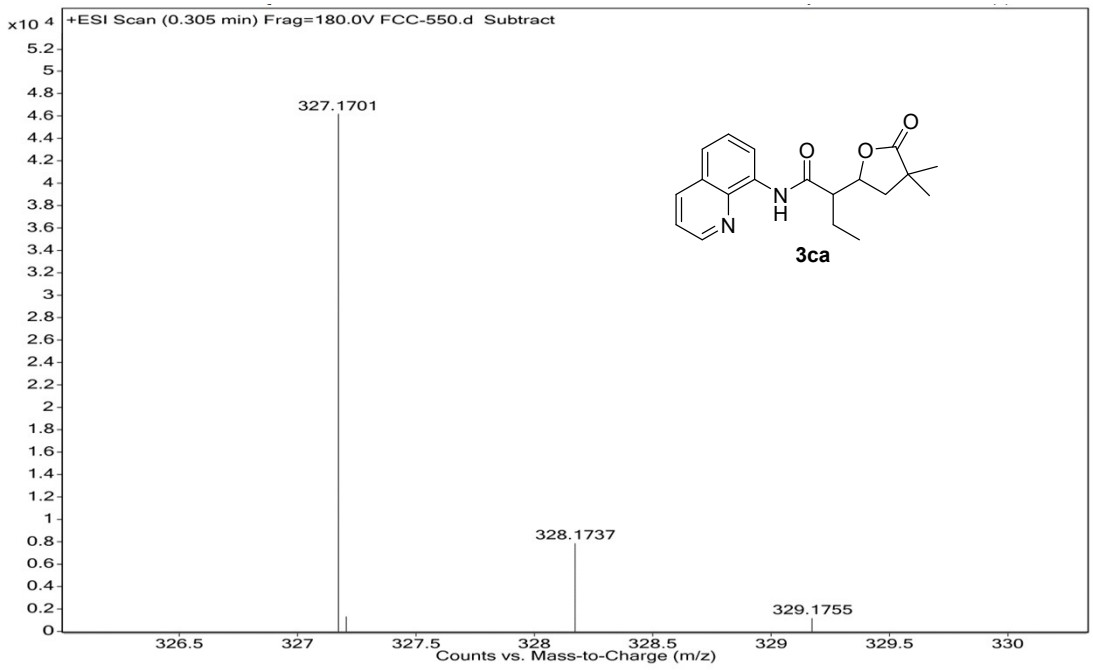
^{1}H NMR Spectra of **3ca**



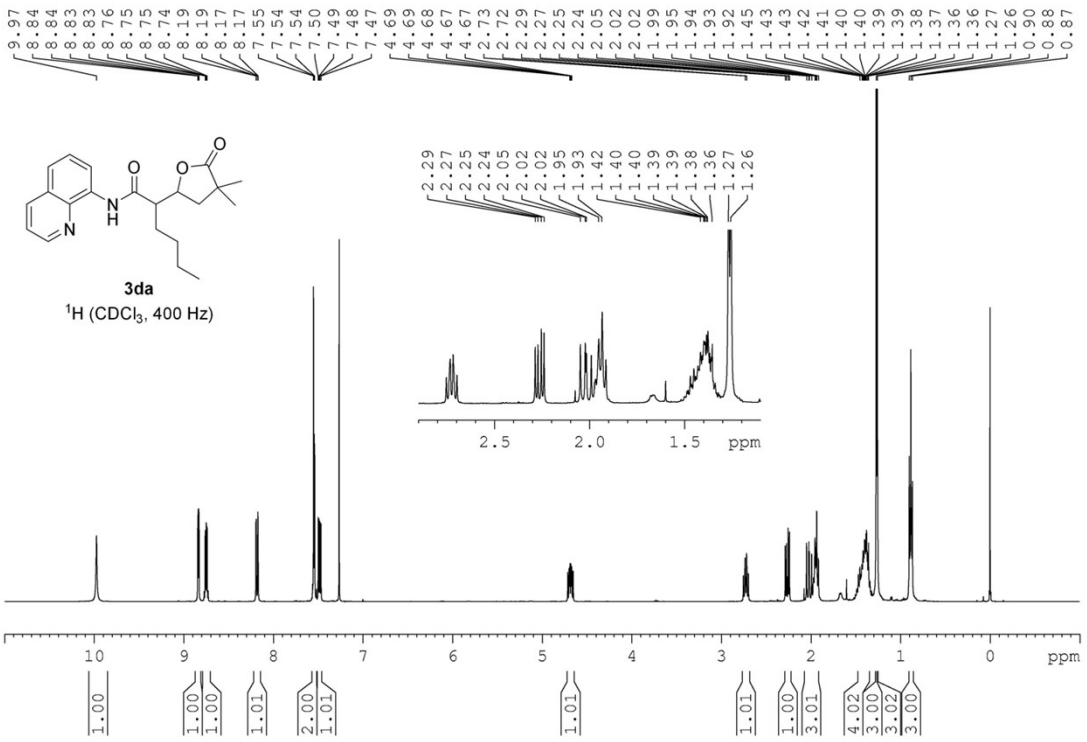
^{13}C NMR Spectra of **3ca**



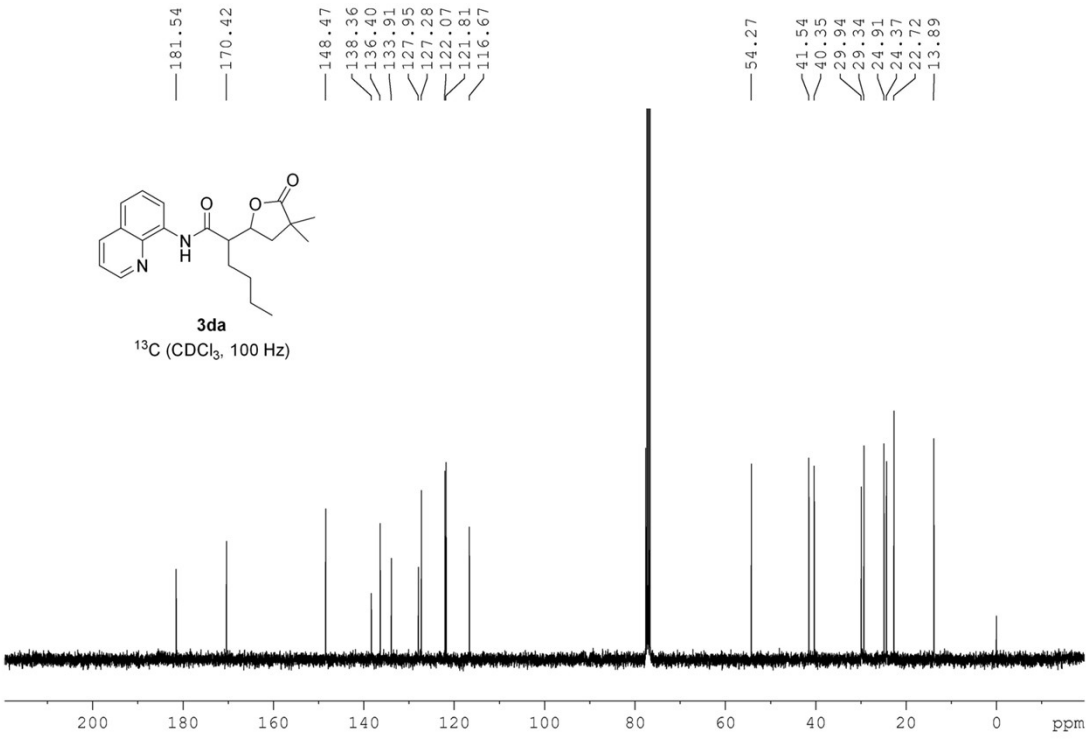
HRMS Spectra of **3ca**



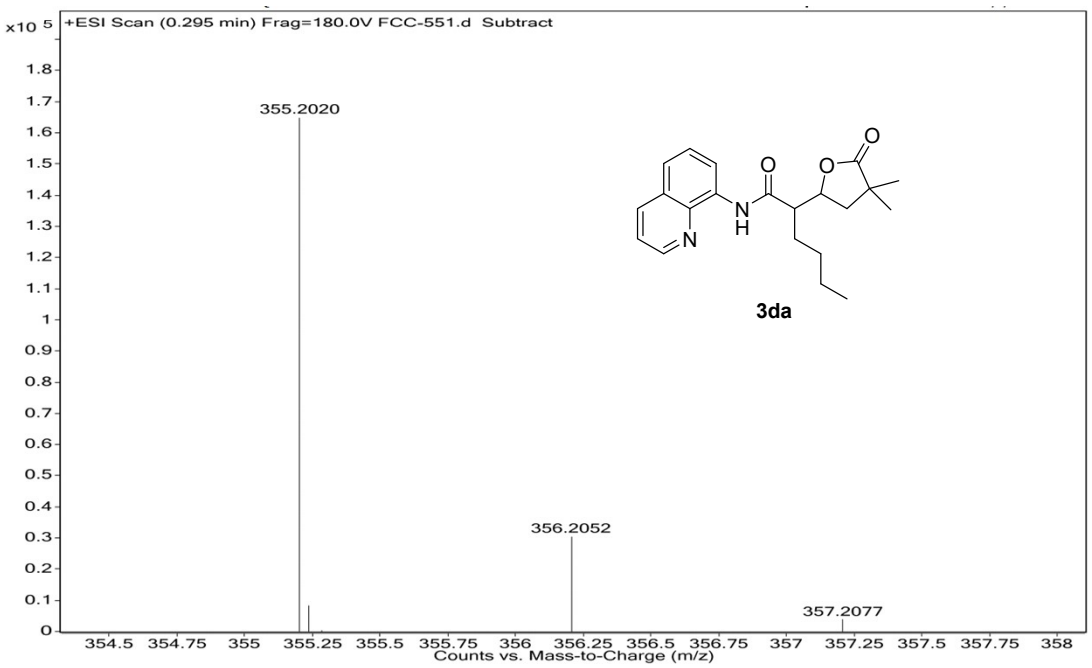
^{1}H NMR Spectra of **3da**



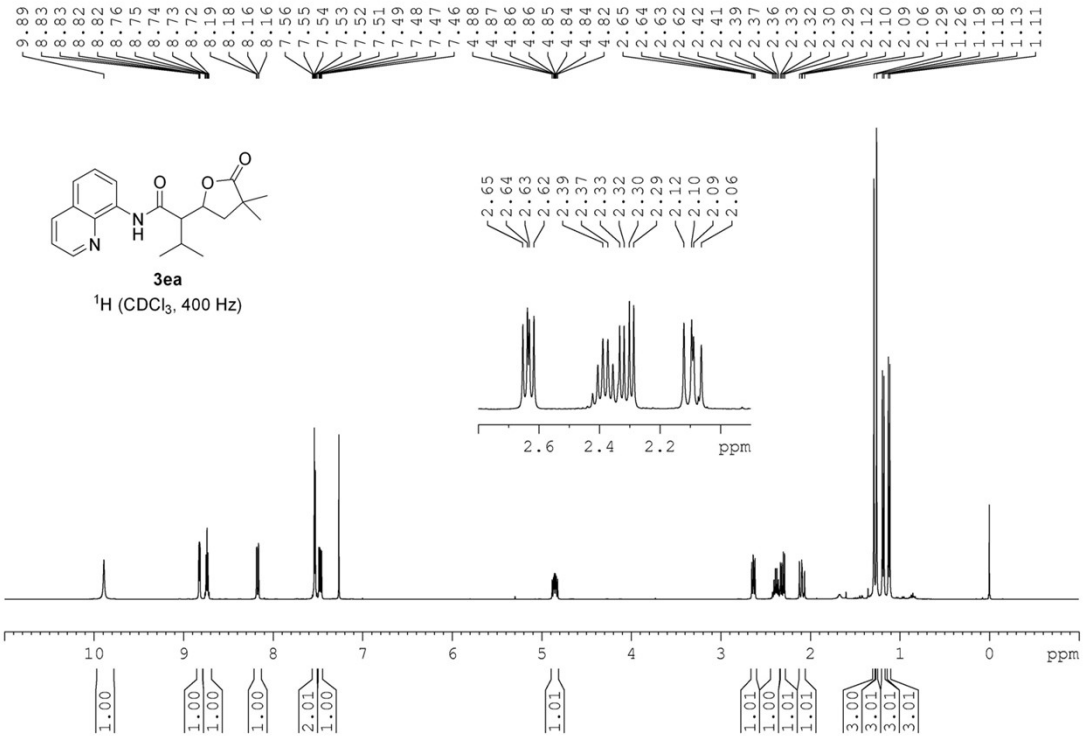
^{13}C NMR Spectra of **3da**



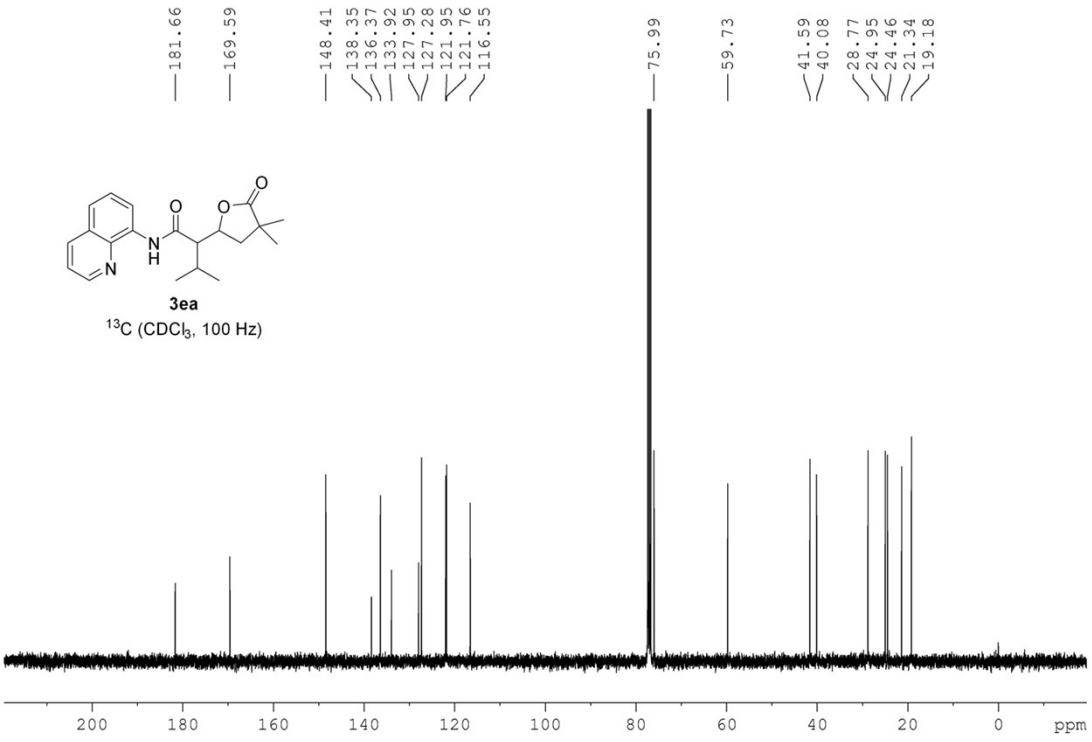
HRMS Spectra of **3da**



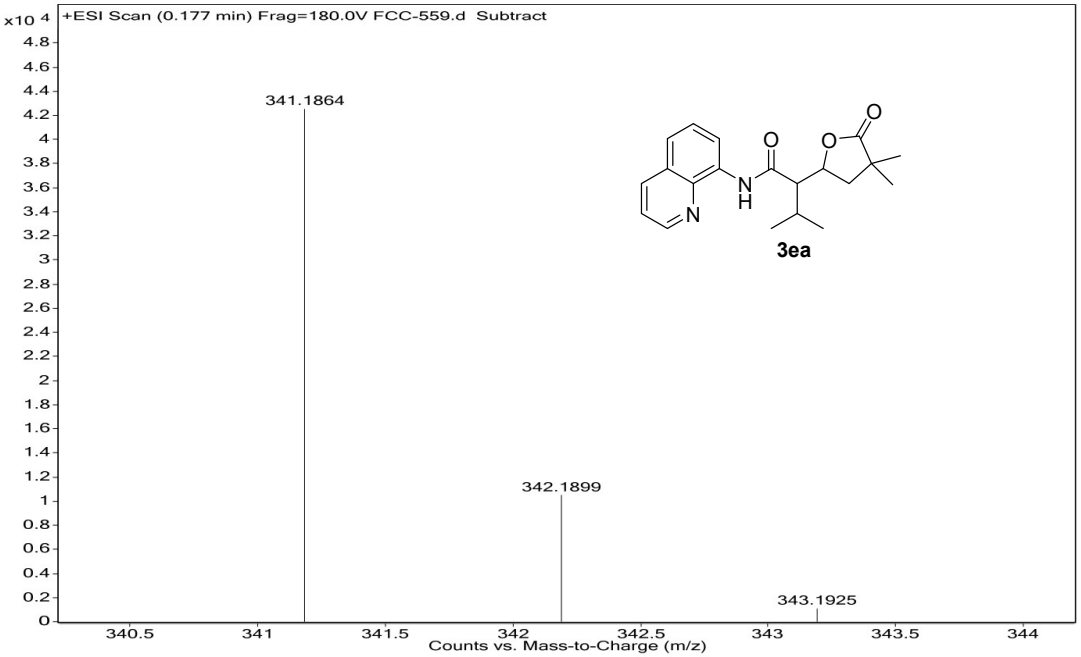
^{1}H NMR Spectra of **3ea**



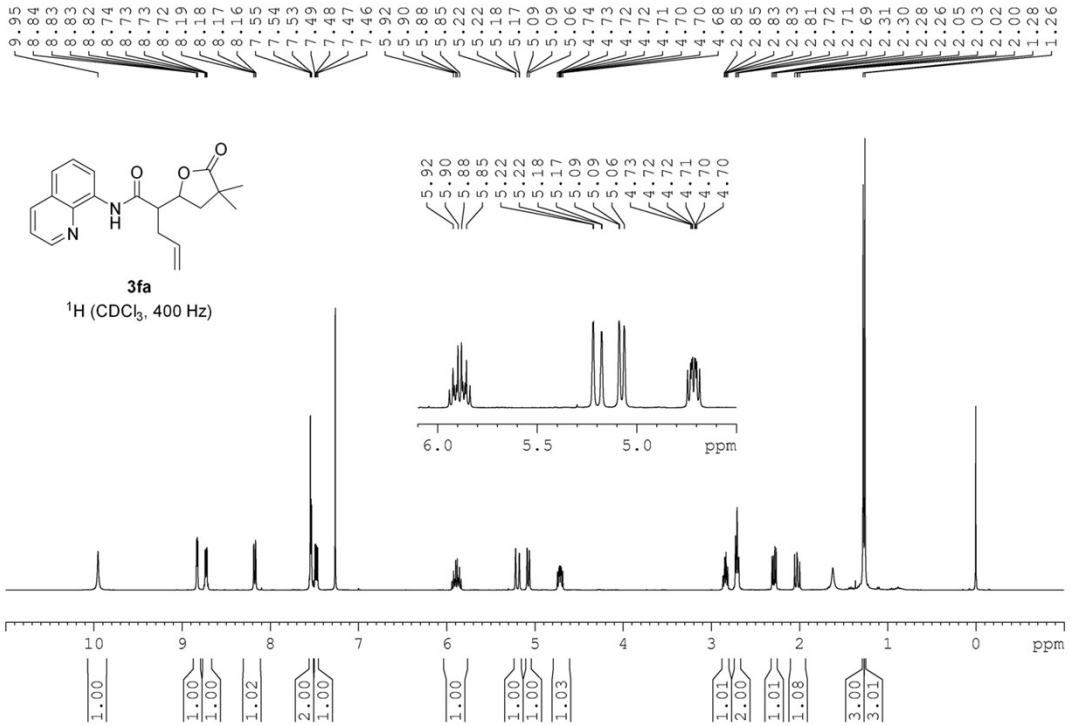
^{13}C NMR Spectra of **3ea**



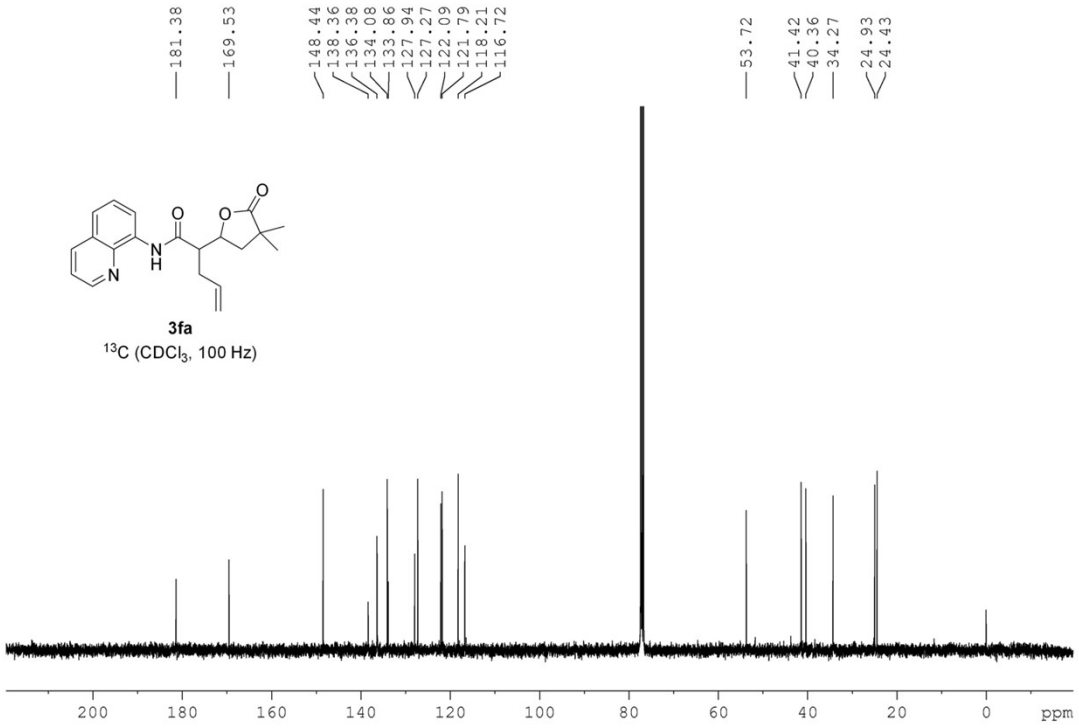
HRMS Spectra of **3ea**



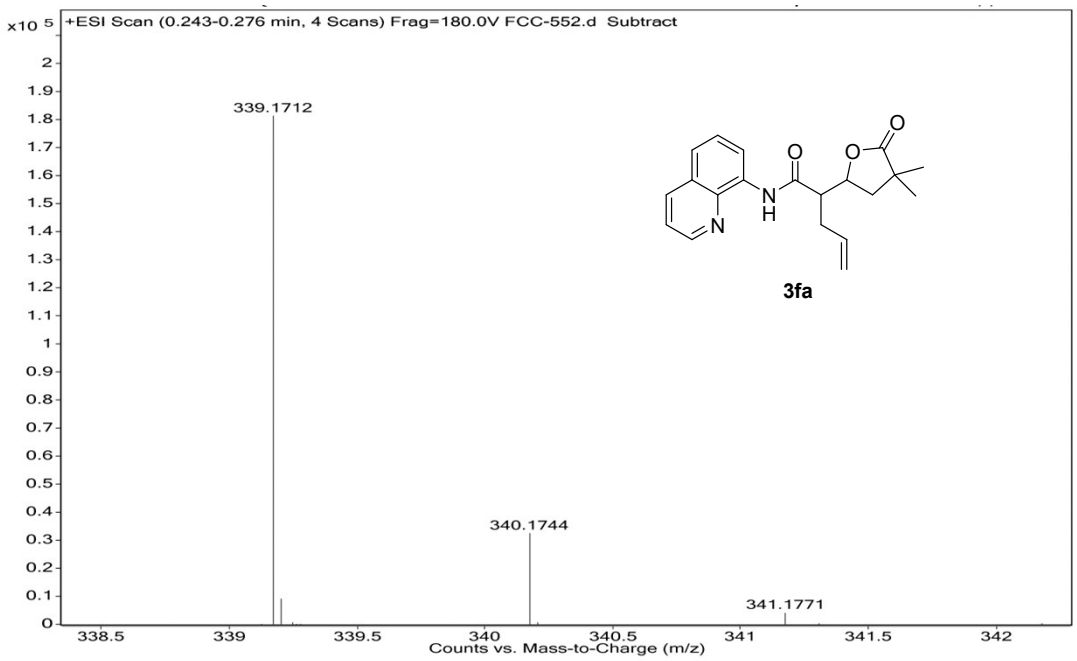
^{1}H NMR Spectra of **3fa**



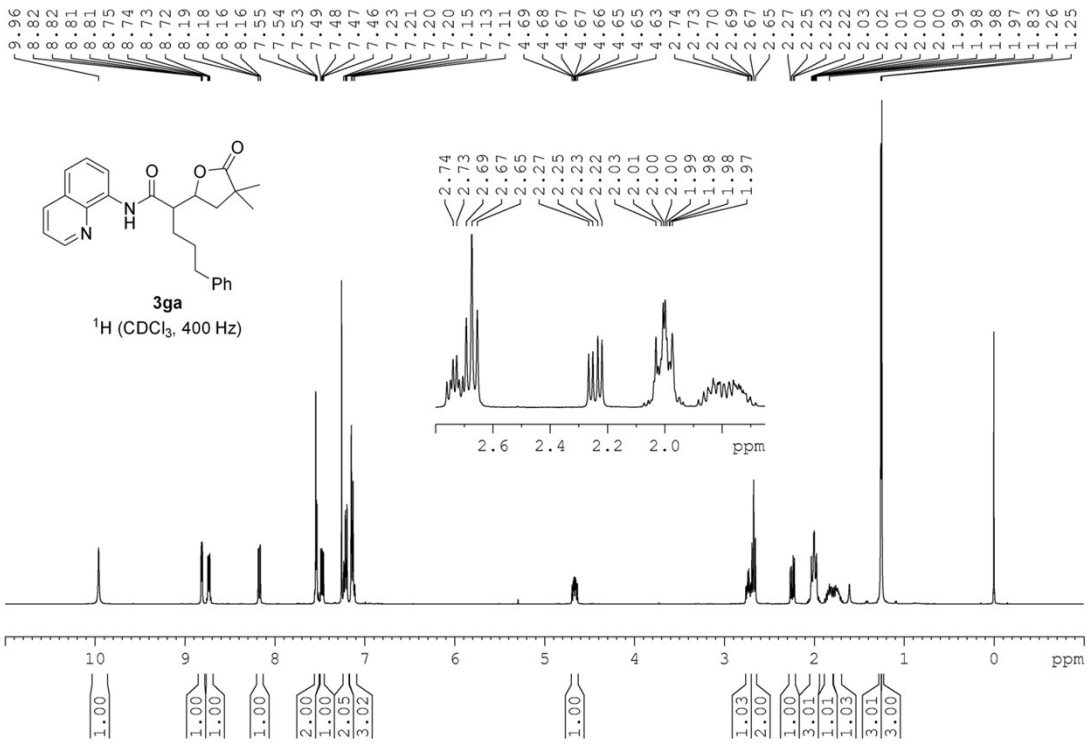
^{13}C NMR Spectra of **3fa**



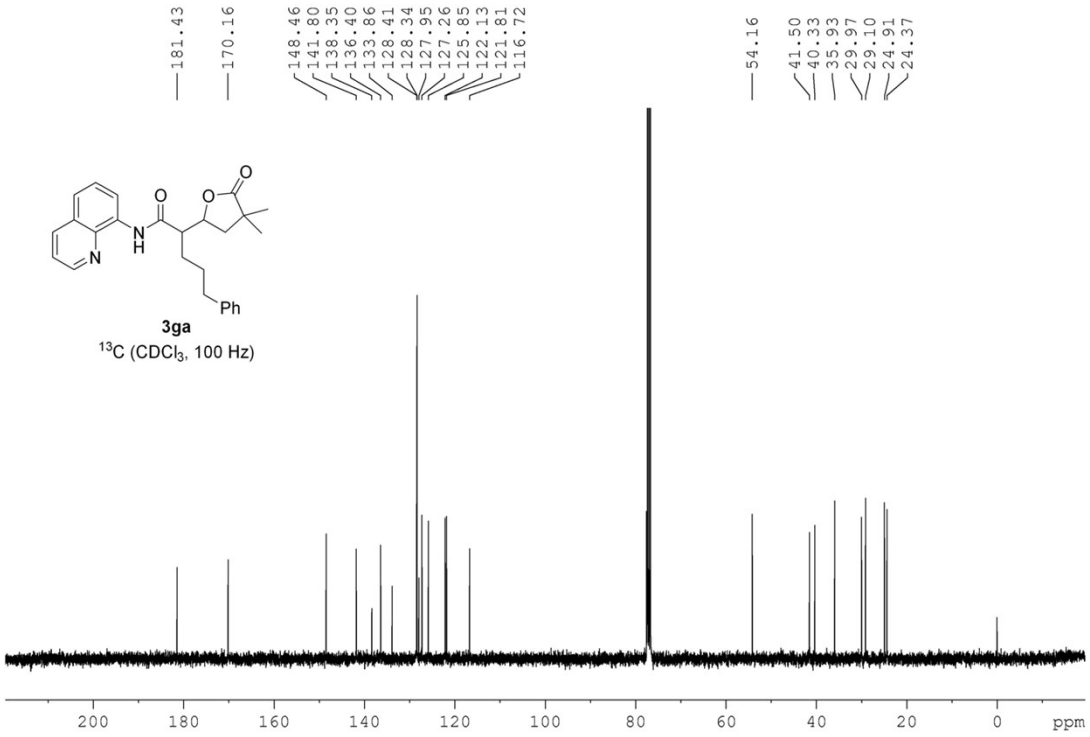
HRMS Spectra of **3fa**



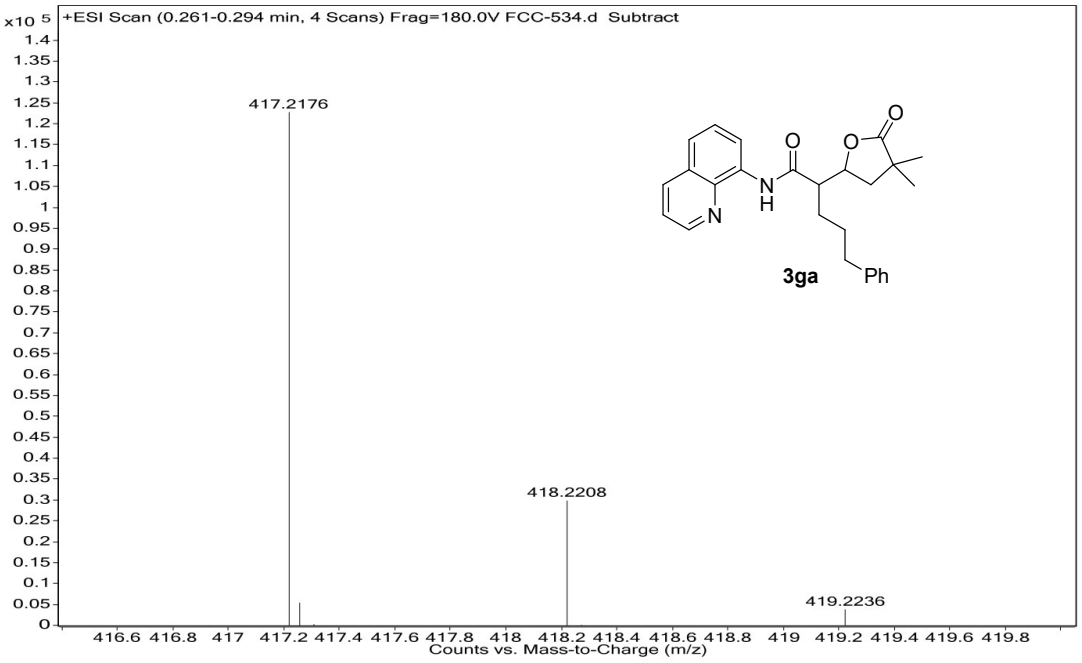
^{1}H NMR Spectra of **3ga**



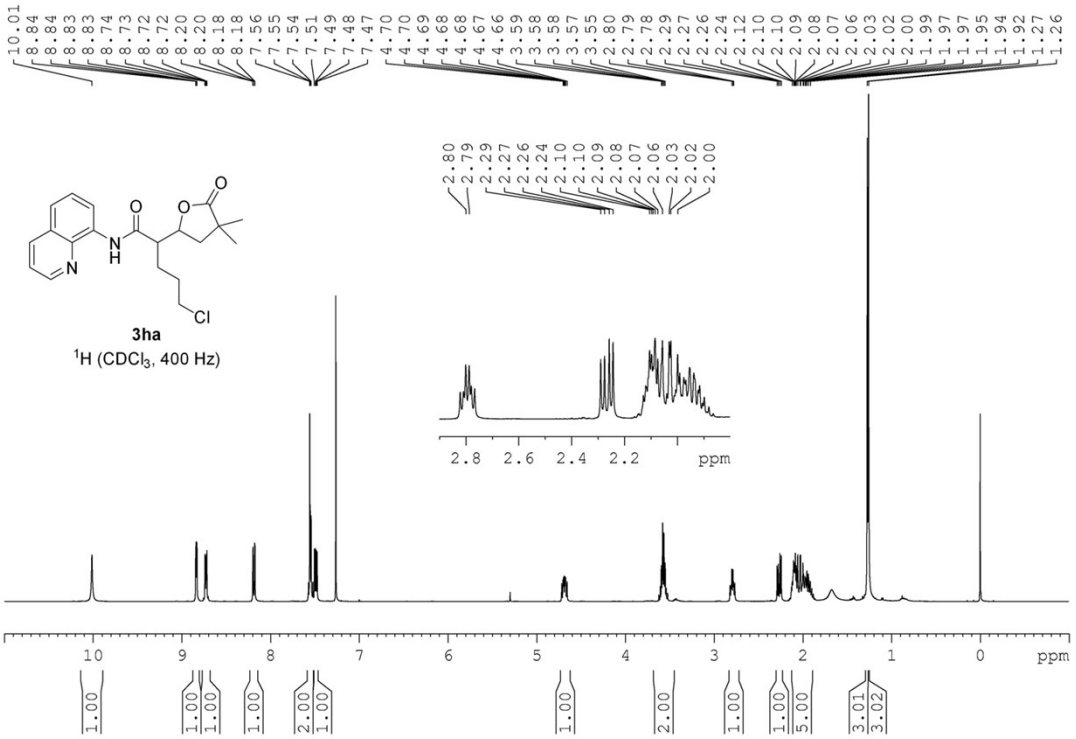
^{13}C NMR Spectra of **3ga**



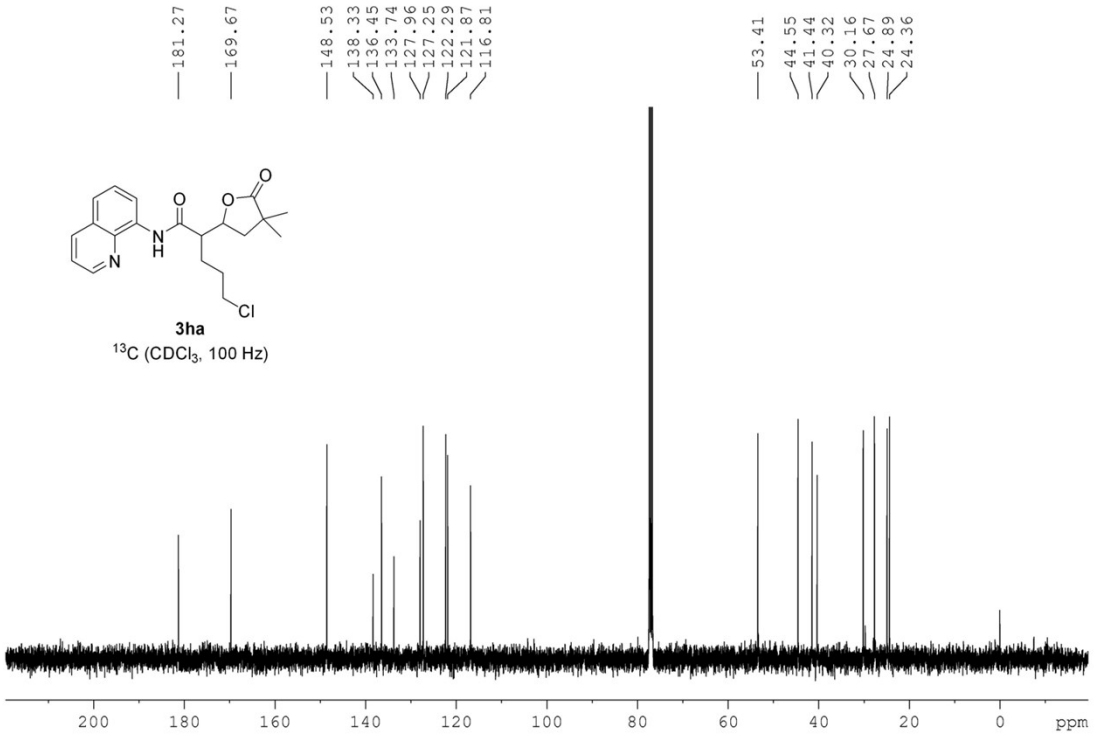
HRMS Spectra of **3ga**



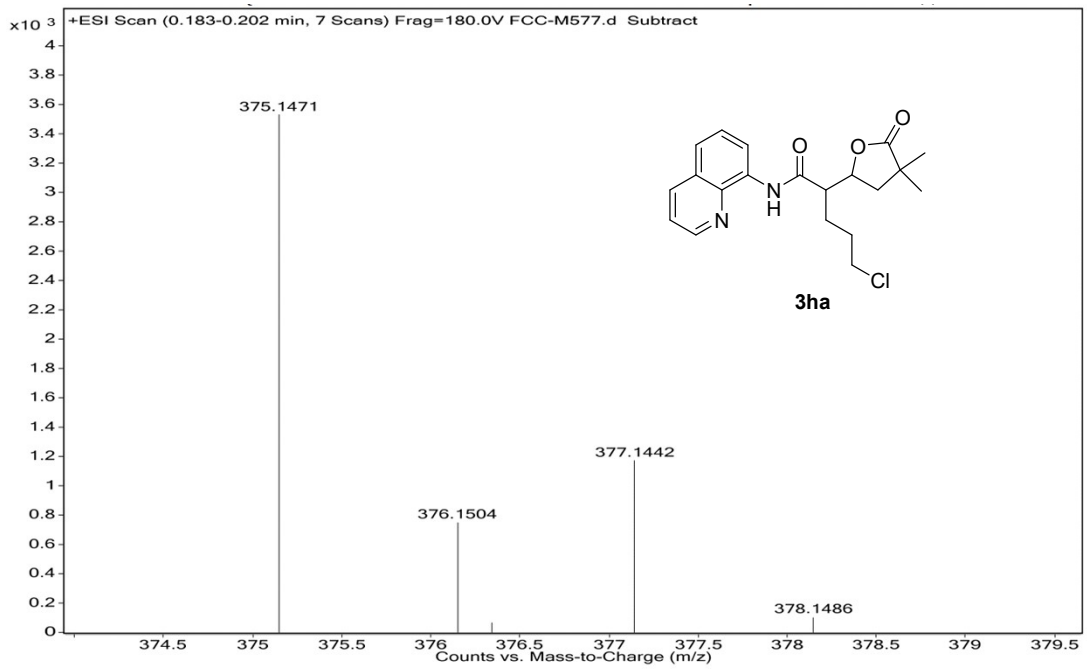
^{1}H NMR Spectra of **3ha**



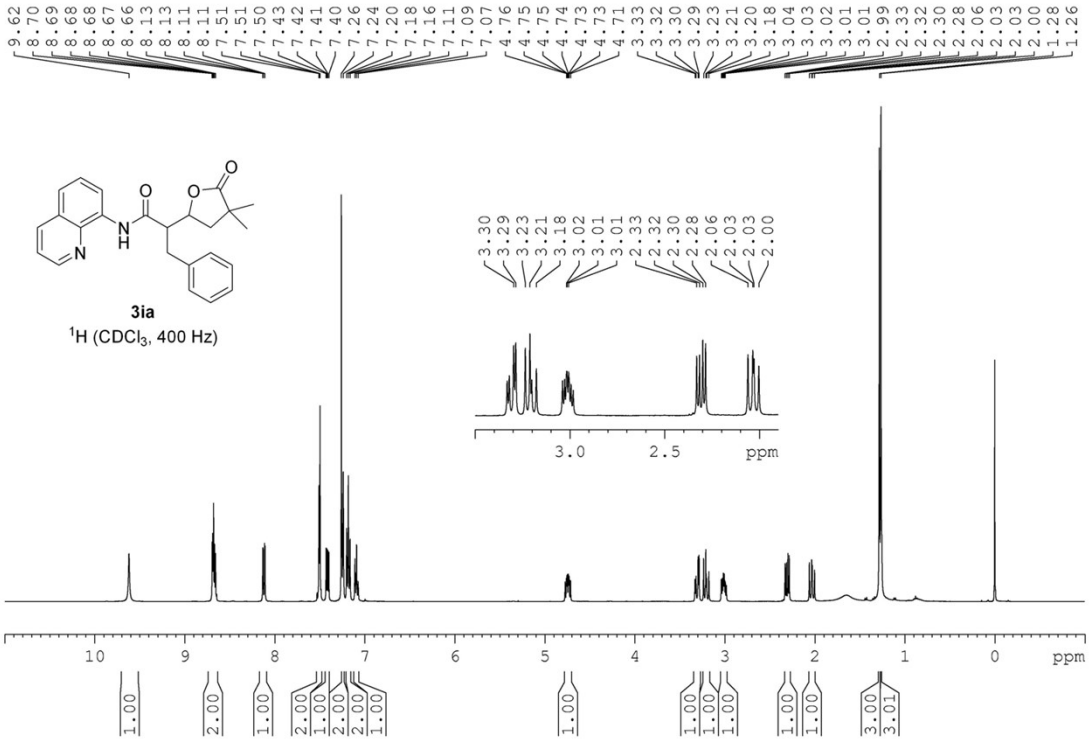
^{13}C NMR Spectra of **3ha**



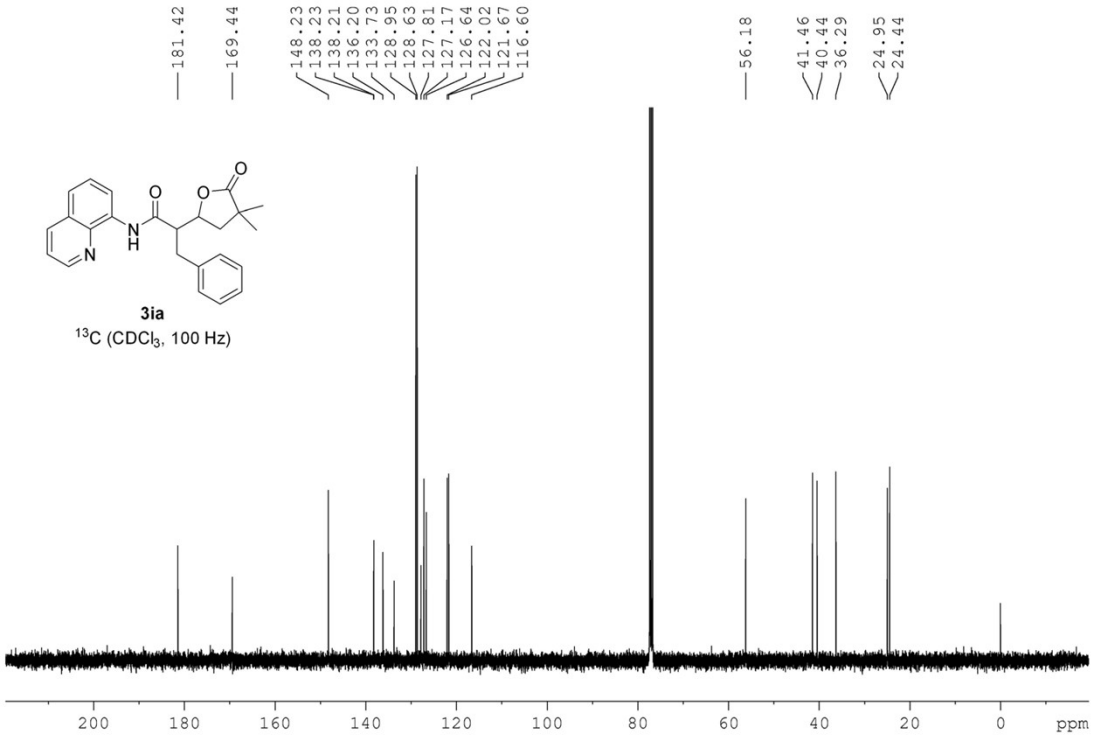
HRMS Spectra of **3ha**



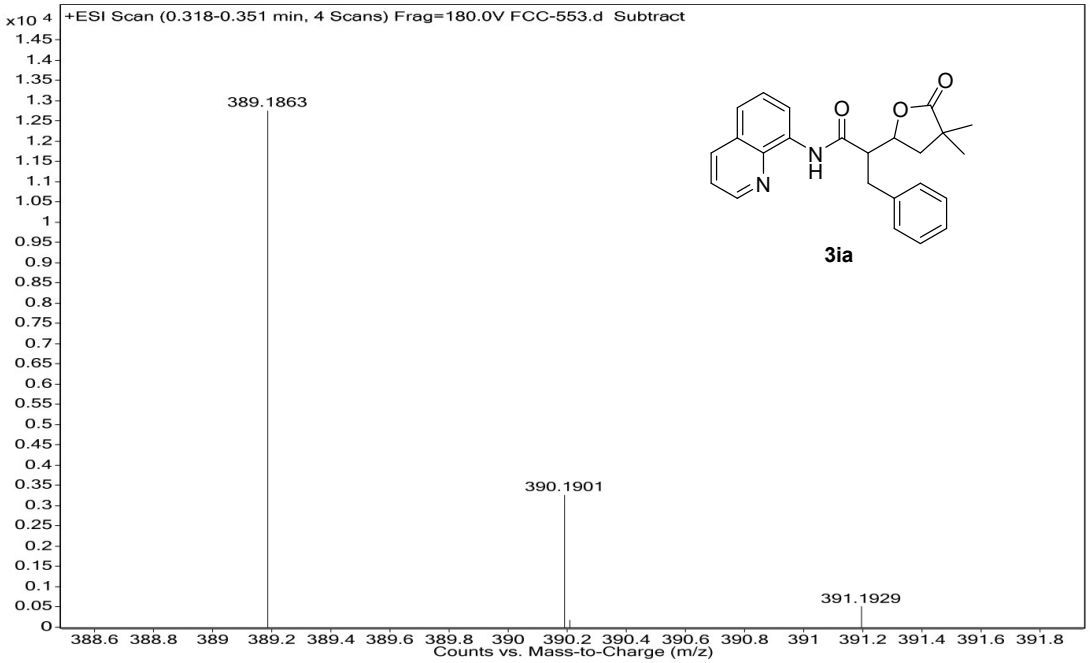
^{1}H NMR Spectra of **3ia**



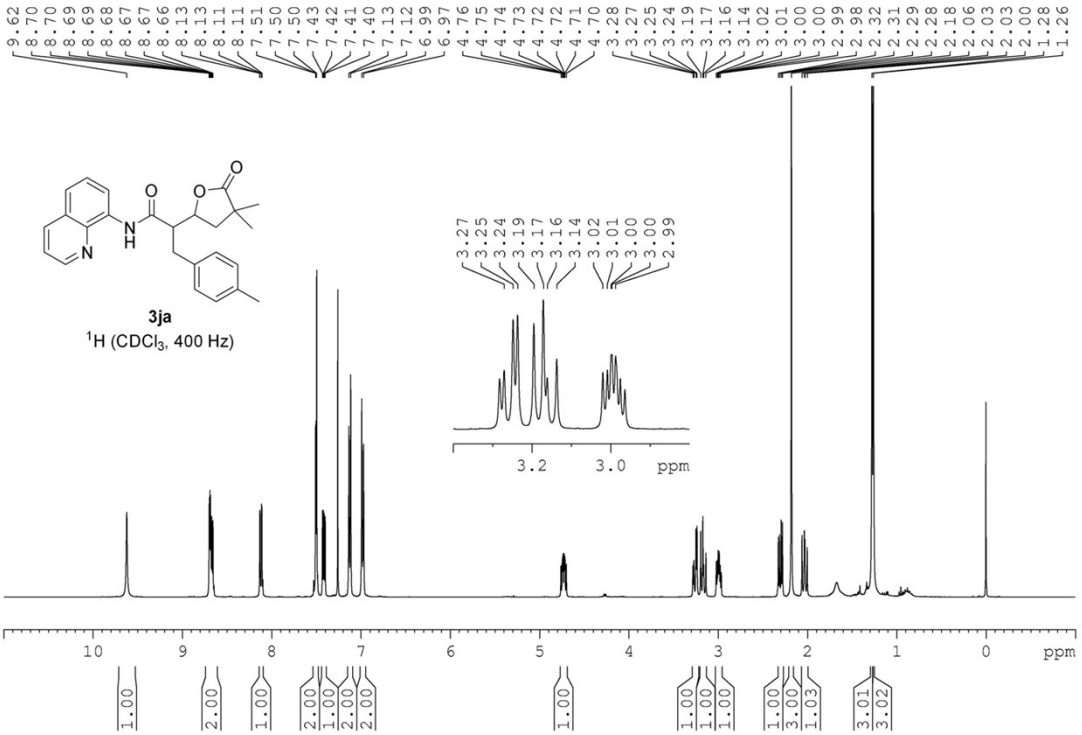
^{13}C NMR Spectra of **3ia**



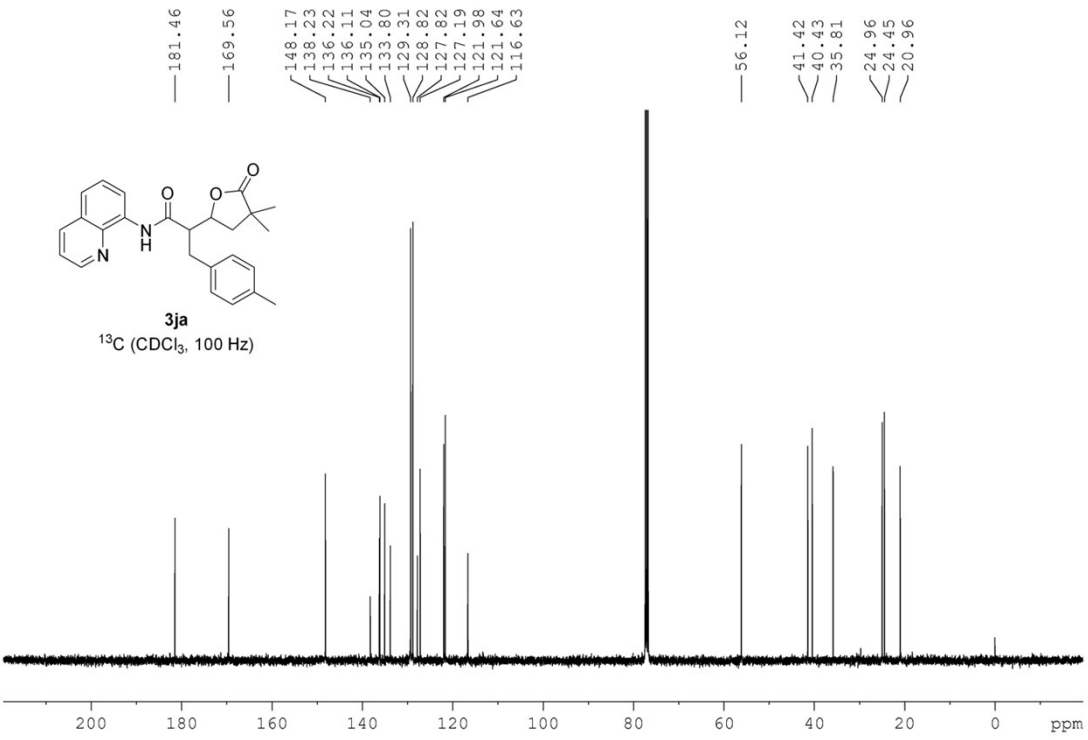
HRMS Spectra of **3ia**



^{1}H NMR Spectra of **3ja**



^{13}C NMR Spectra of **3ja**



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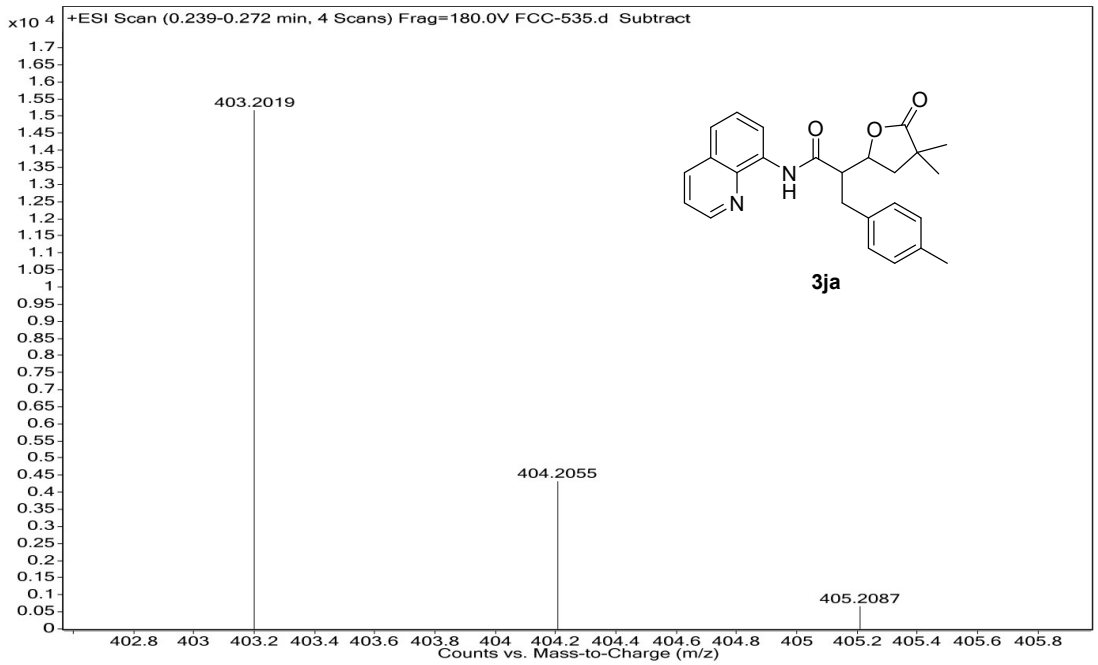
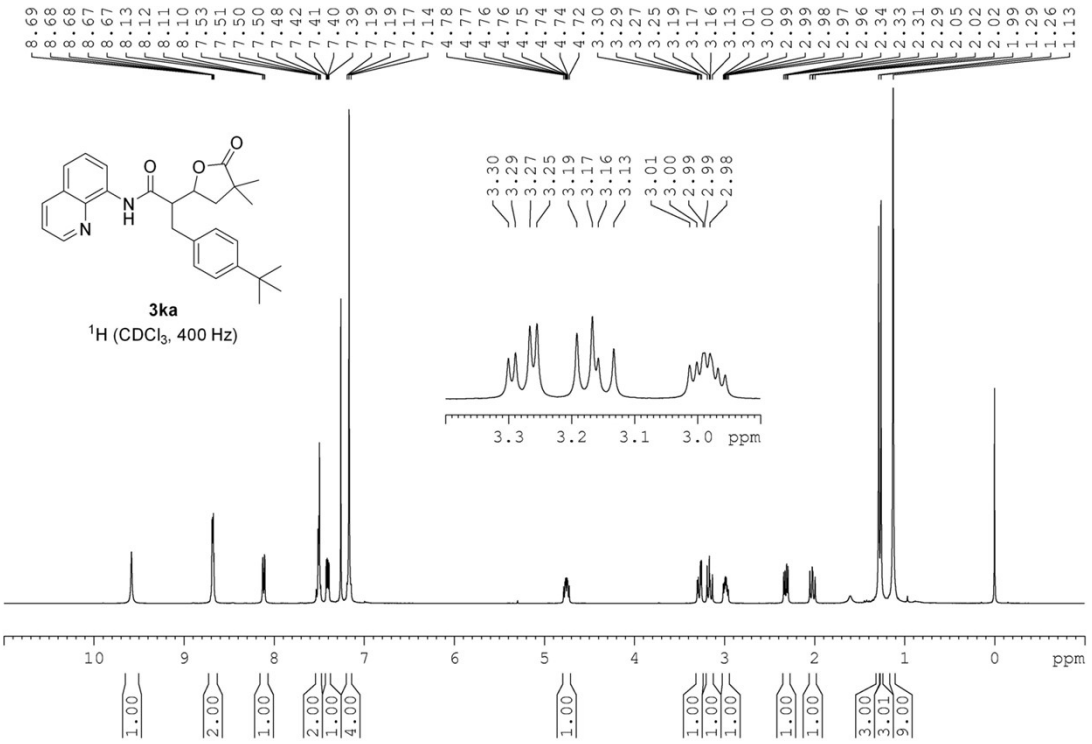
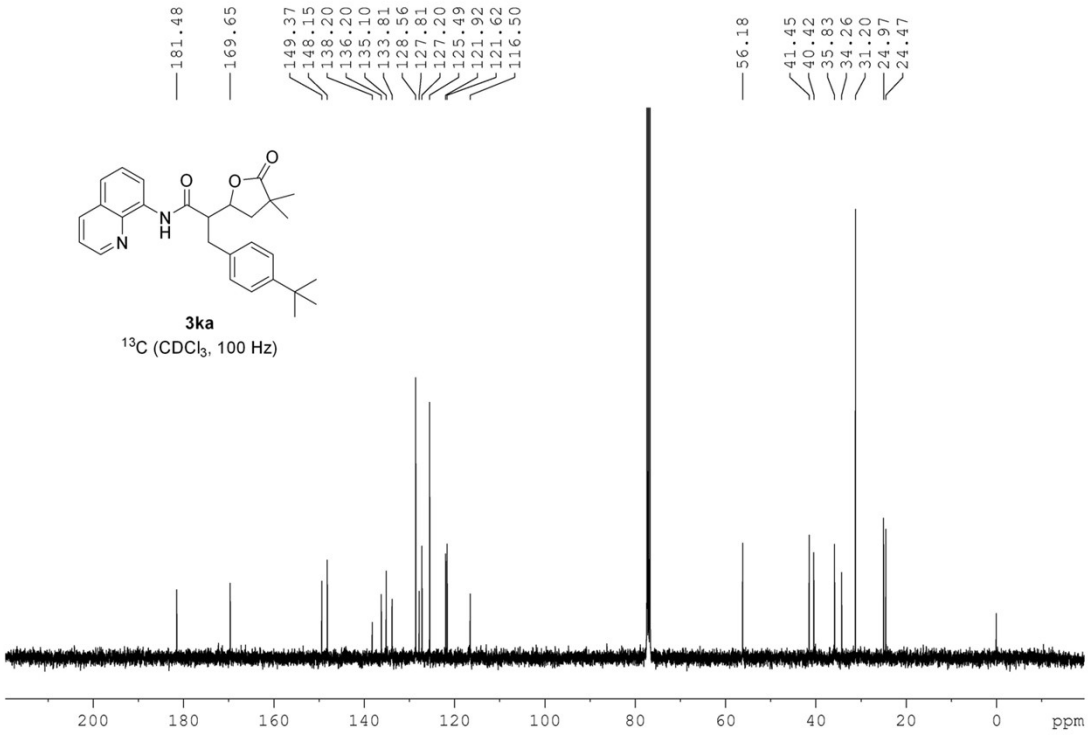


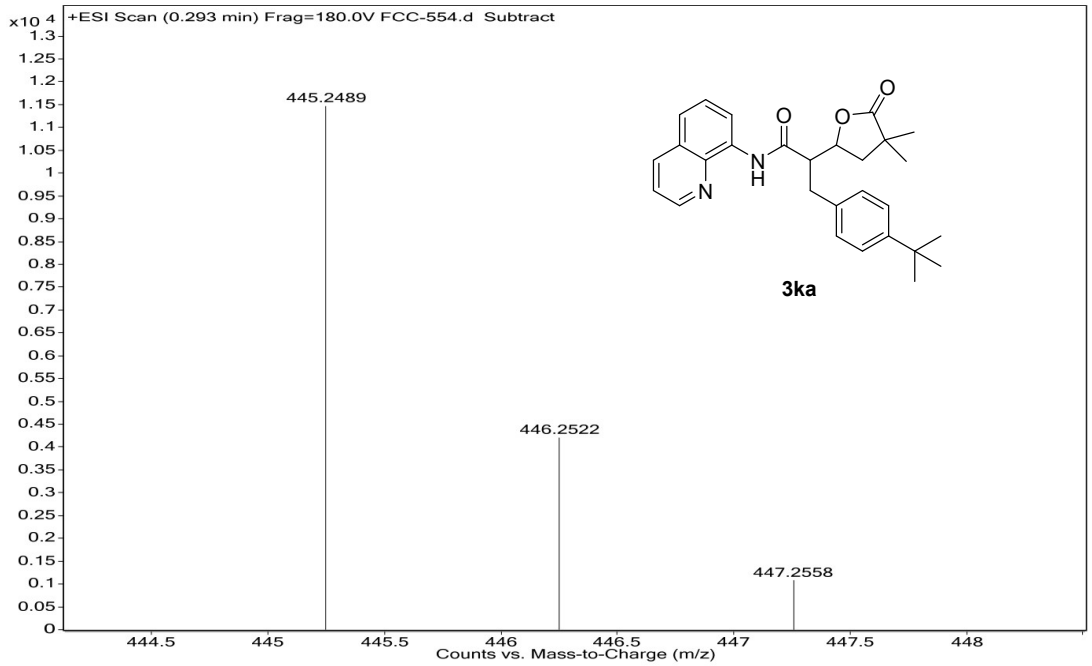
^{1}H NMR Spectra of **3ka**



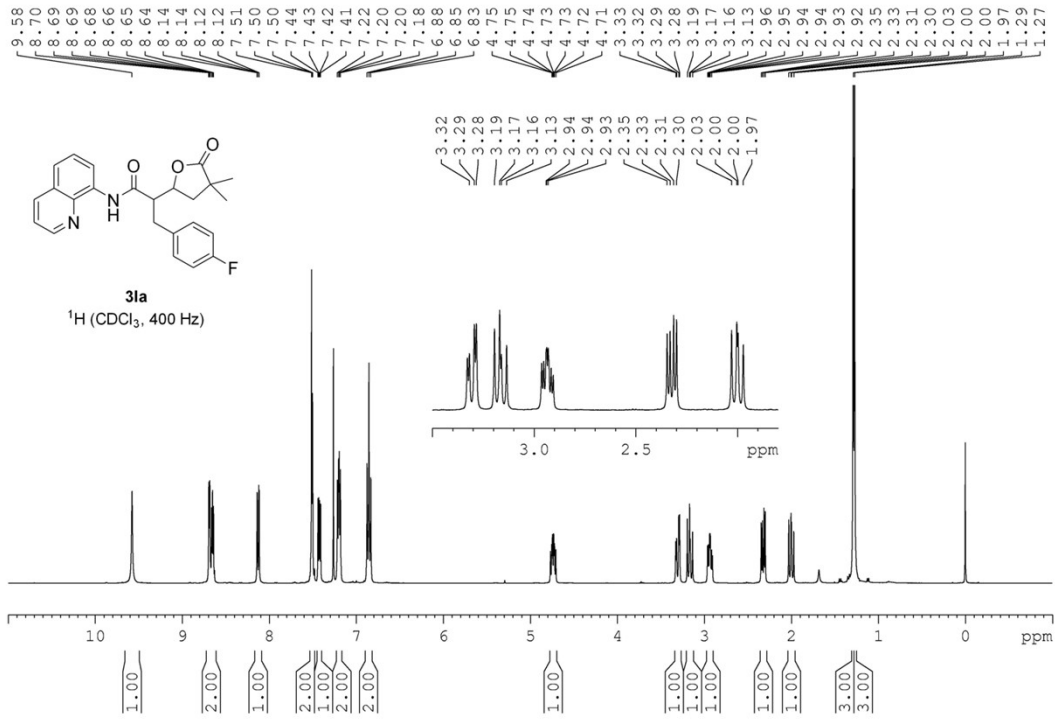
^{13}C NMR Spectra of **3ka**



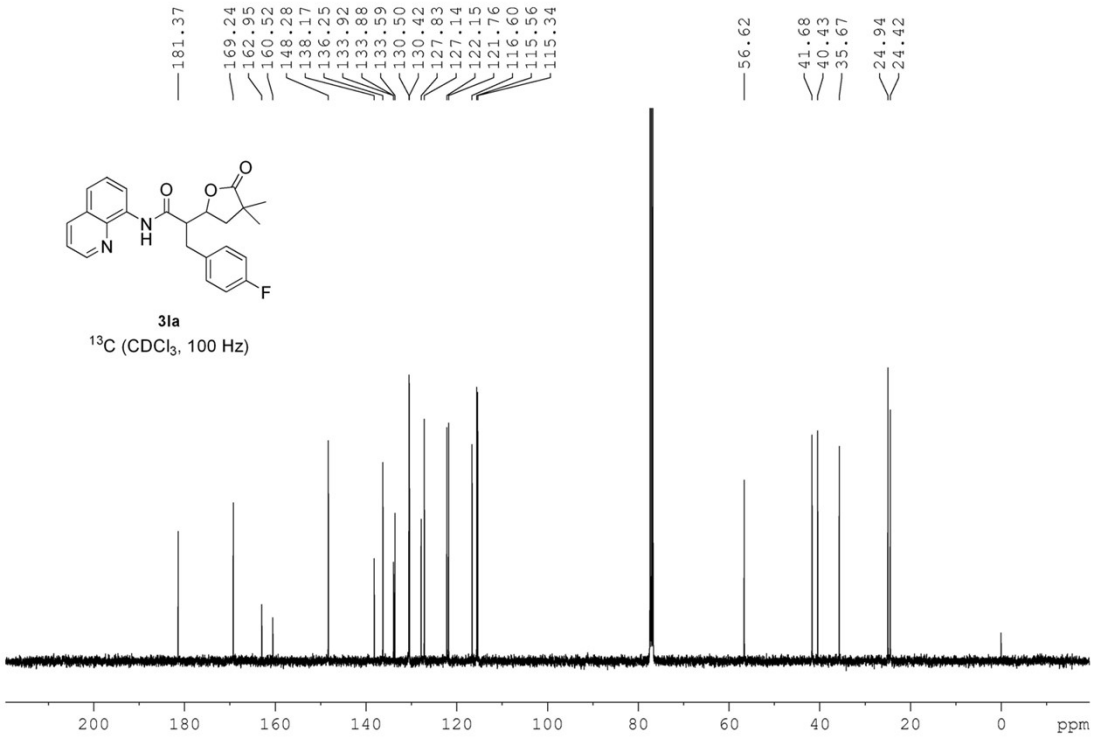
HRMS Spectra of **3ka**



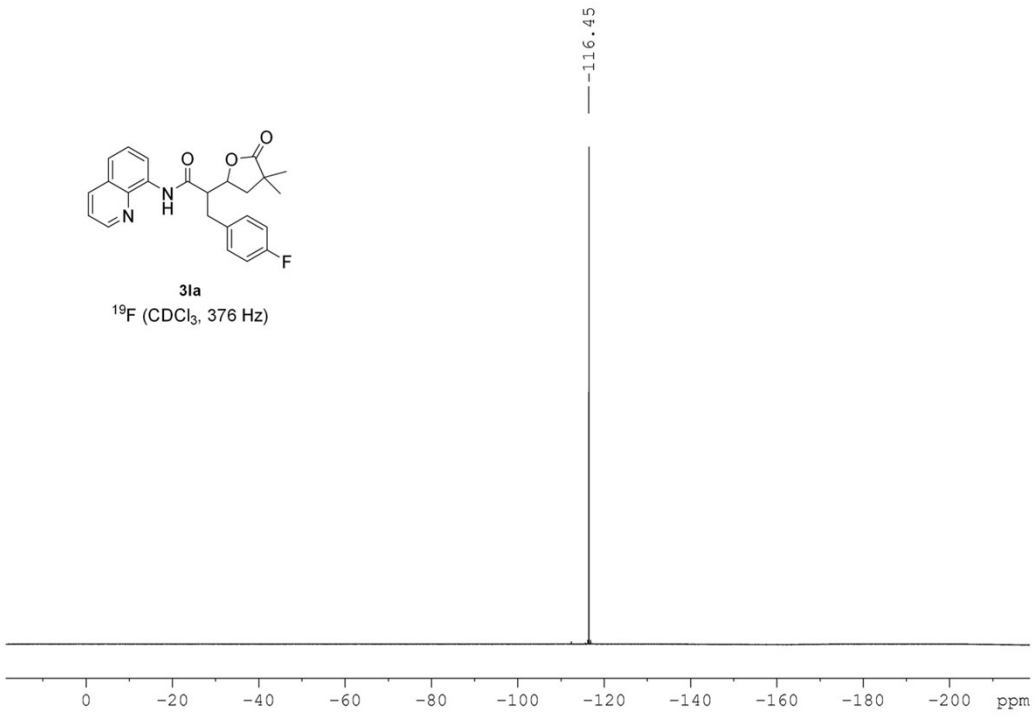
^{1}H NMR Spectra of **3la**



^{13}C NMR Spectra of **3la**



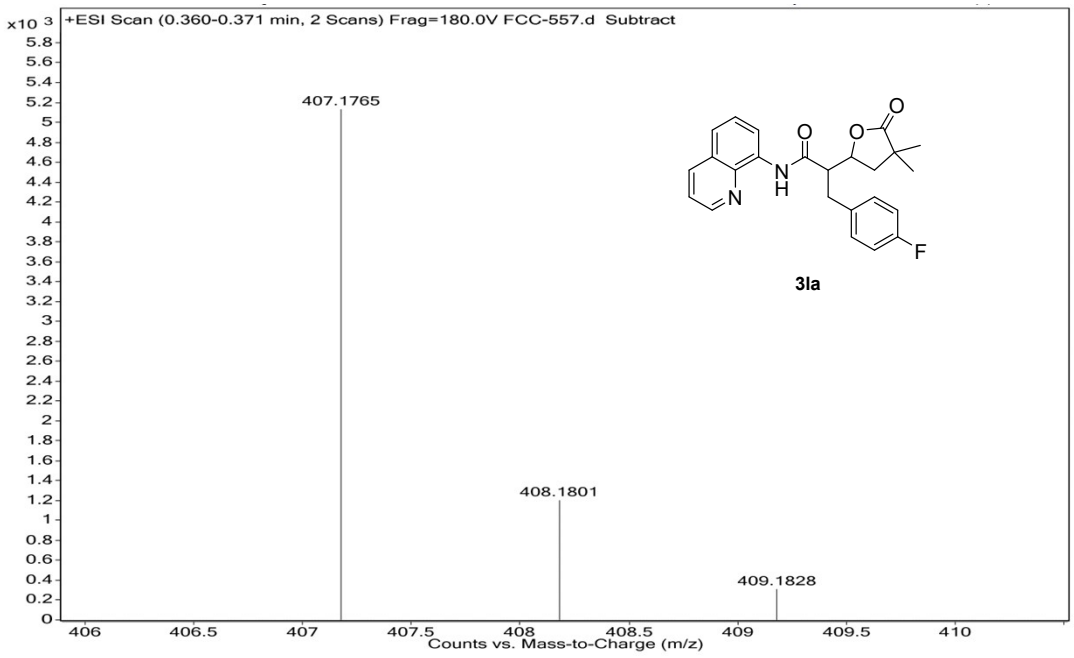
^{19}F NMR Spectra of **3la**



3la

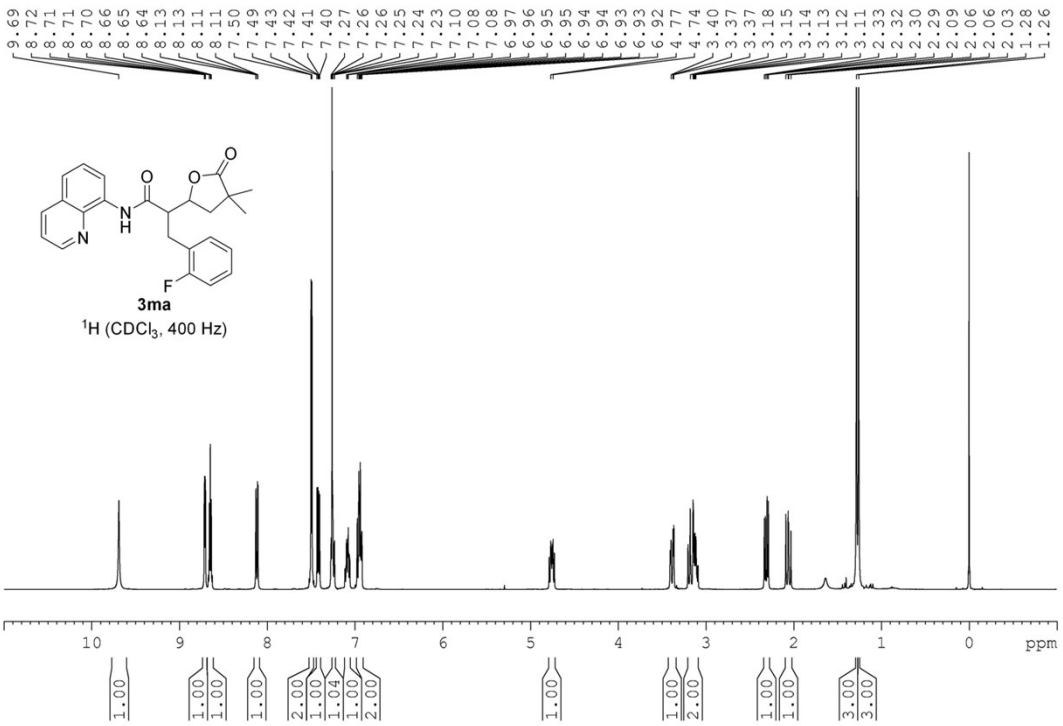
^{19}F ($CDCl_3$, 376 Hz)

HRMS Spectra of **3la**

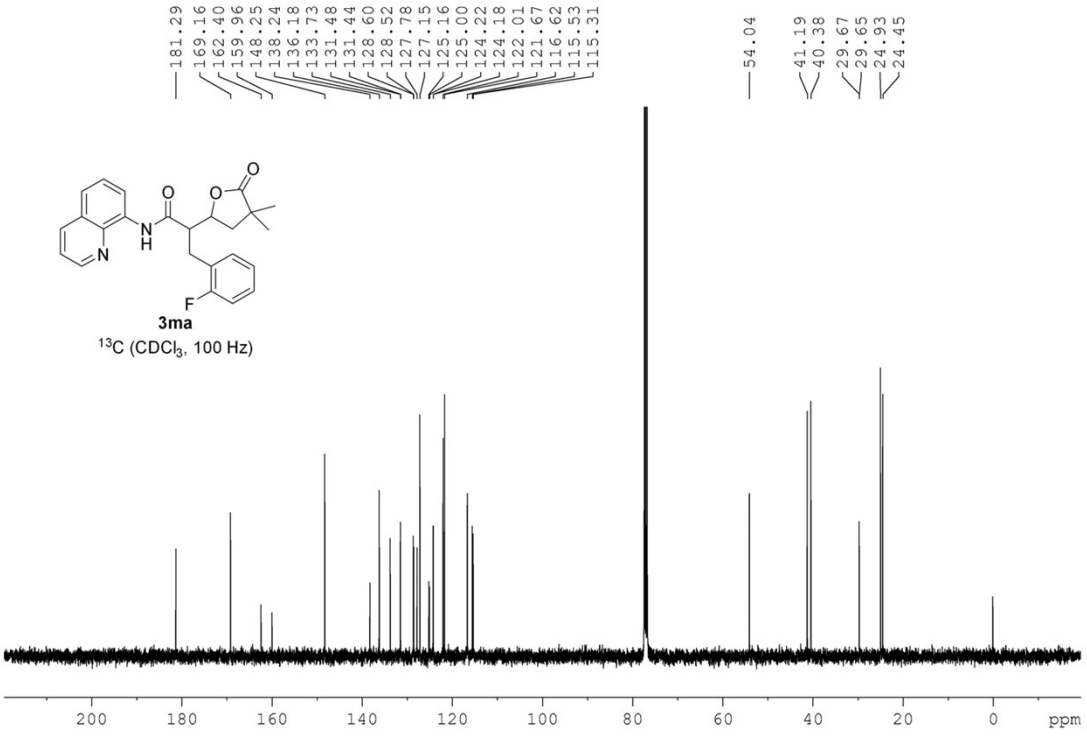


3la

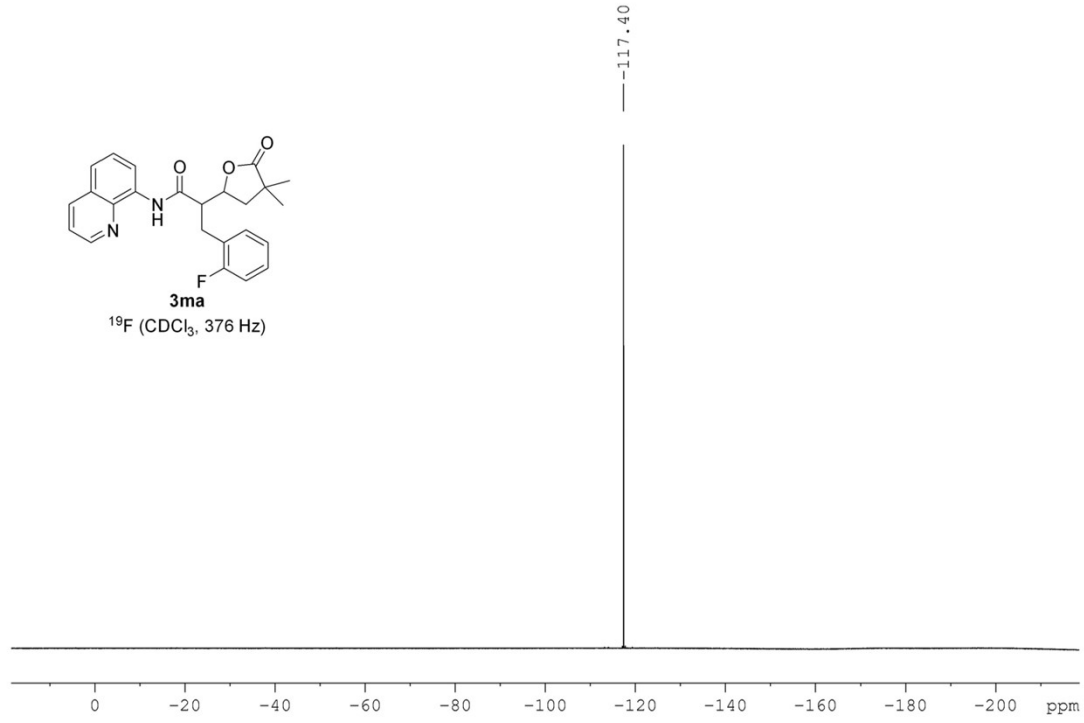
^{1}H NMR Spectra of **3ma**



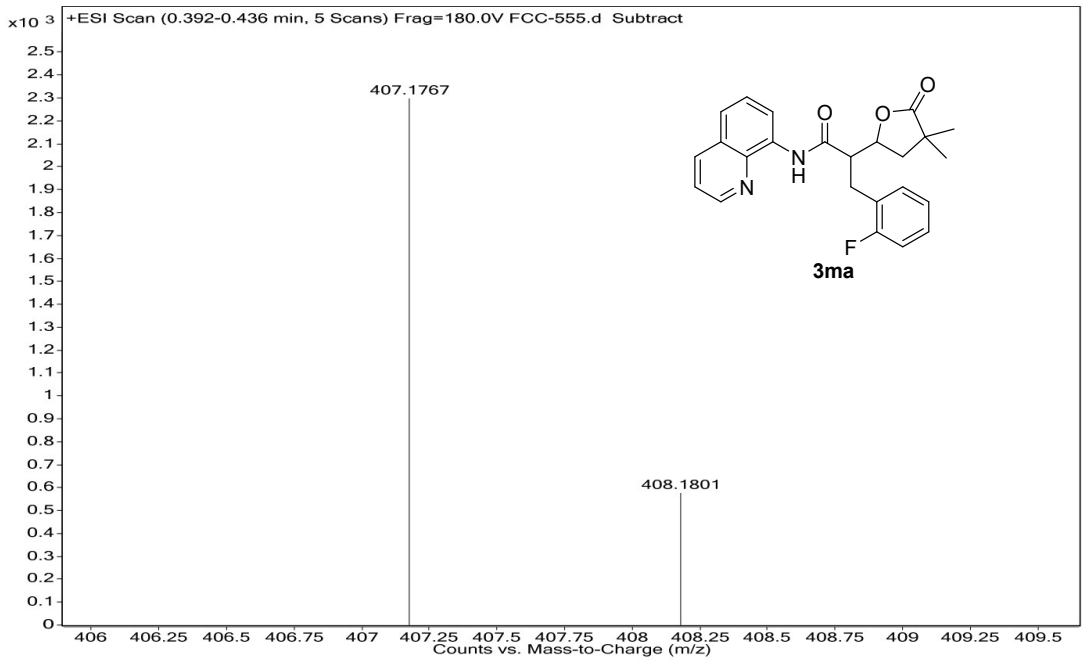
^{13}C NMR Spectra of **3ma**



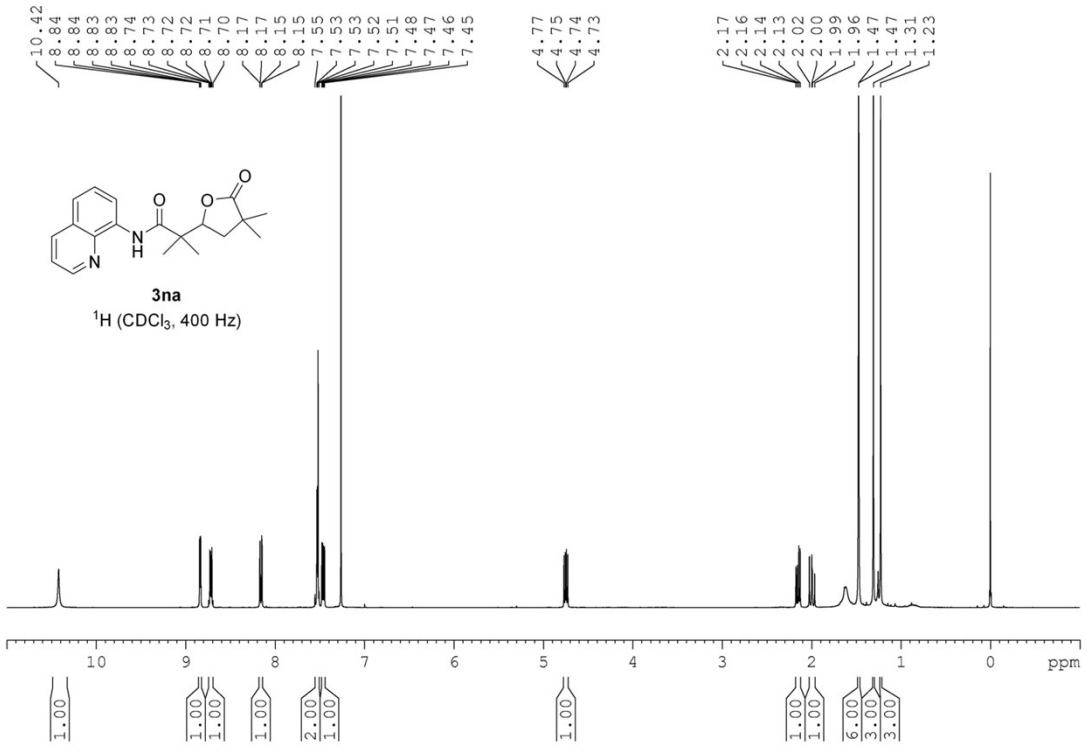
^{19}F NMR Spectra of **3ma**



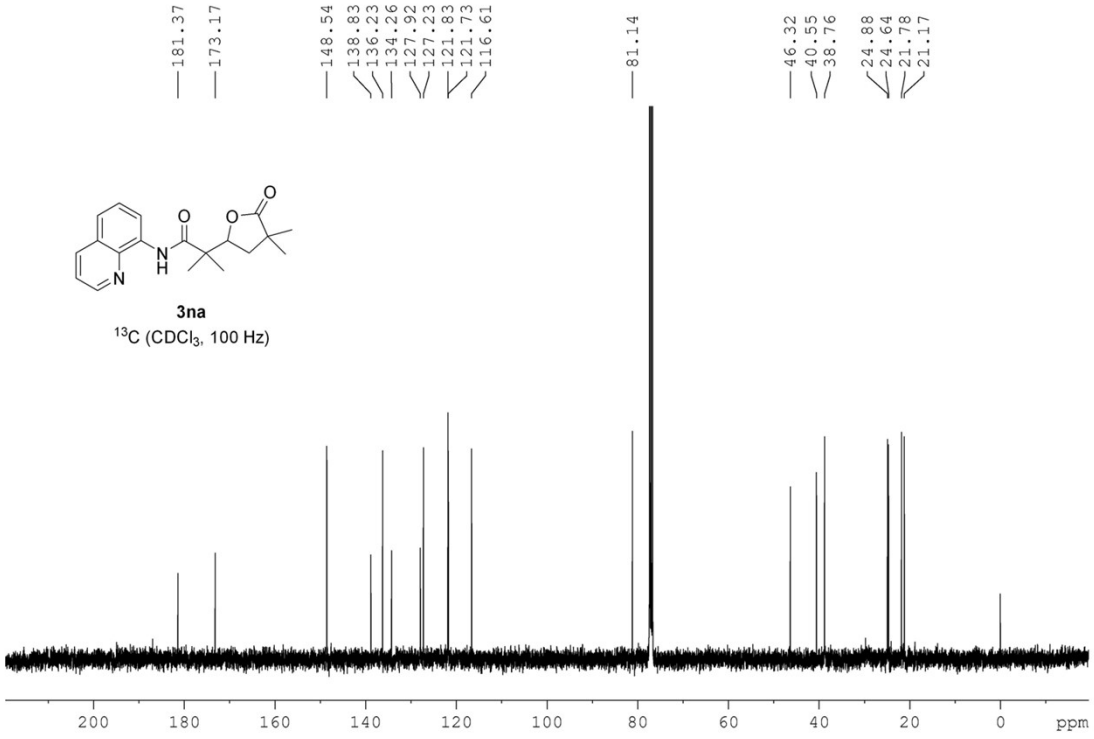
HRMS Spectra of **3ma**



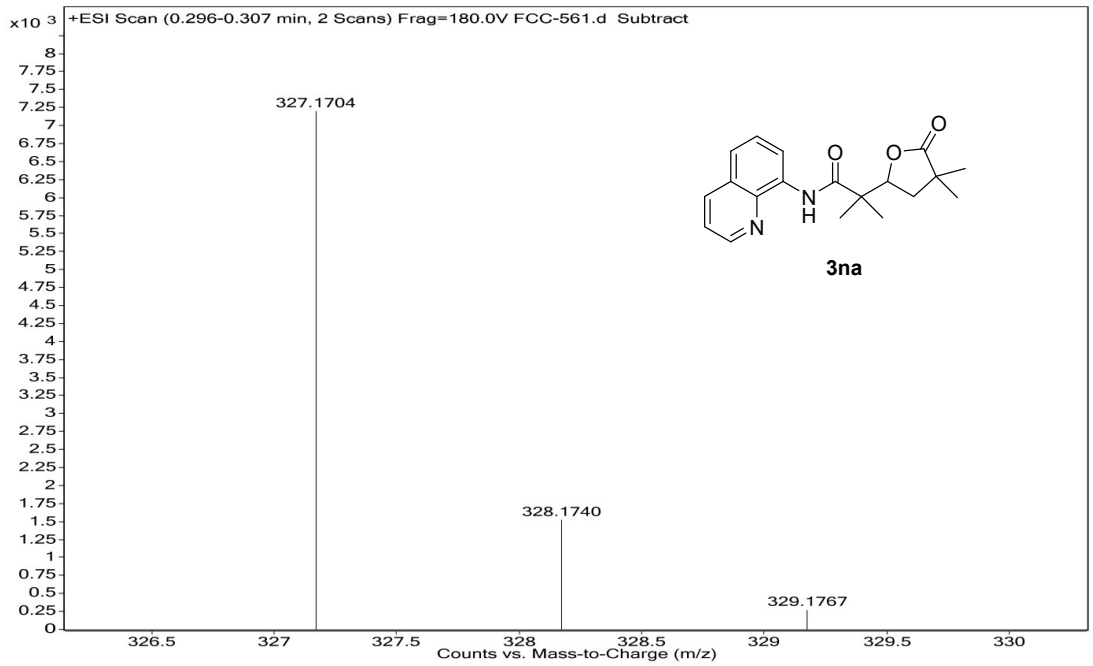
^{1}H NMR Spectra of **3na**



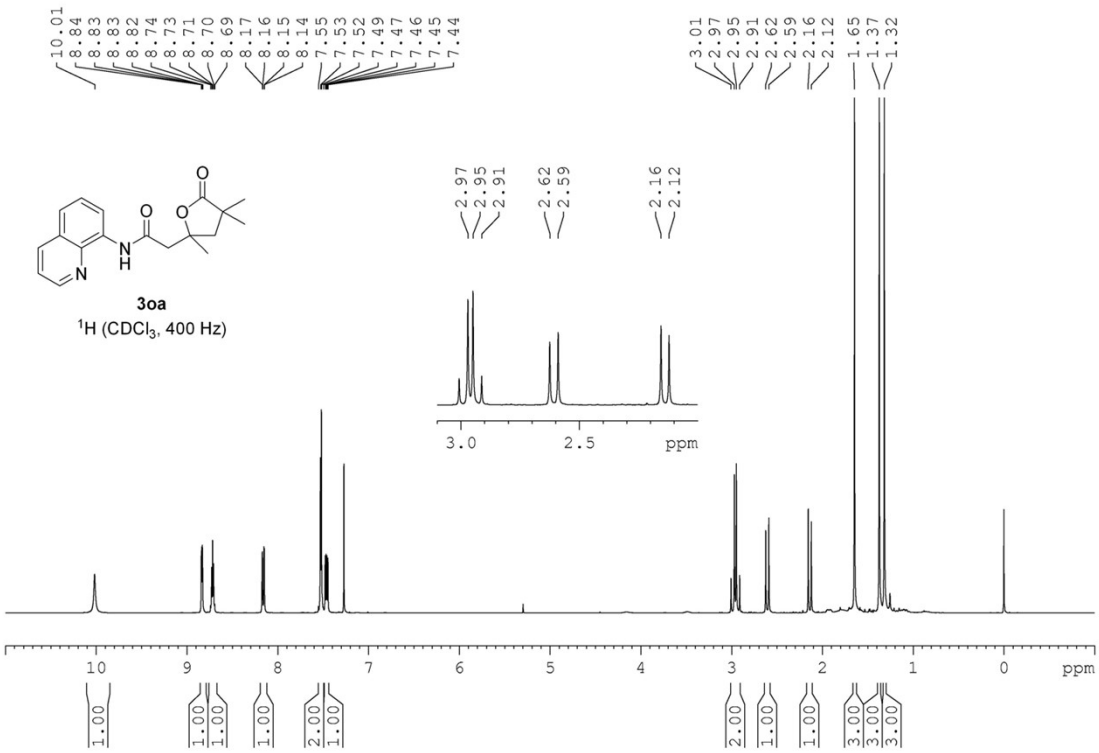
^{13}C NMR Spectra of **3na**



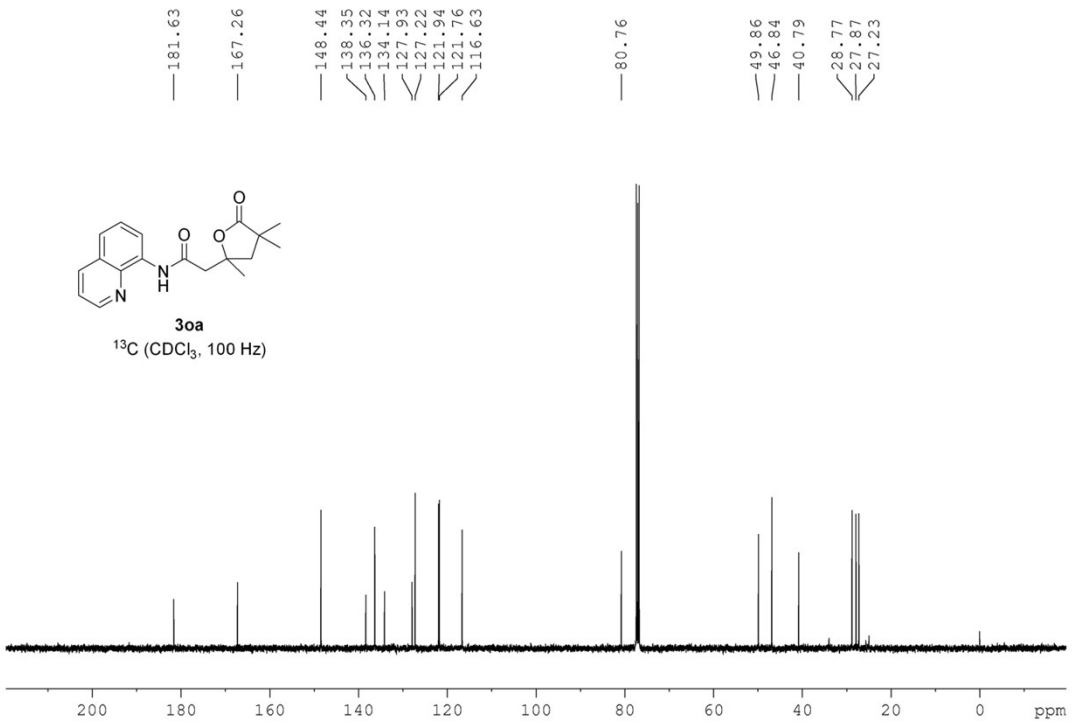
HRMS Spectra of **3na**



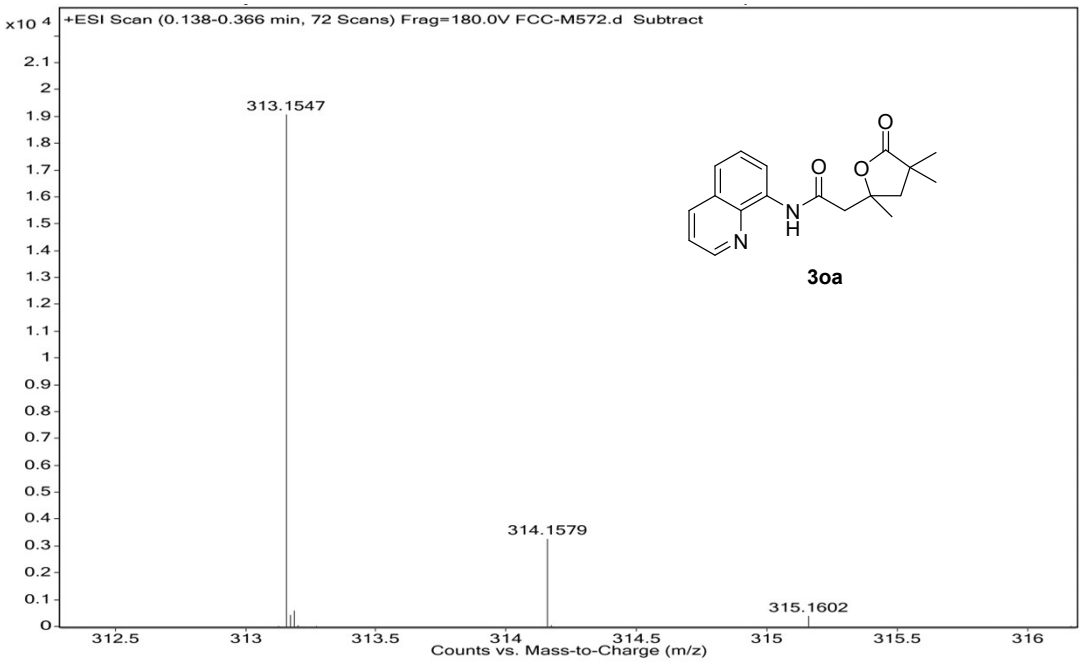
^{1}H NMR Spectra of **3oa**



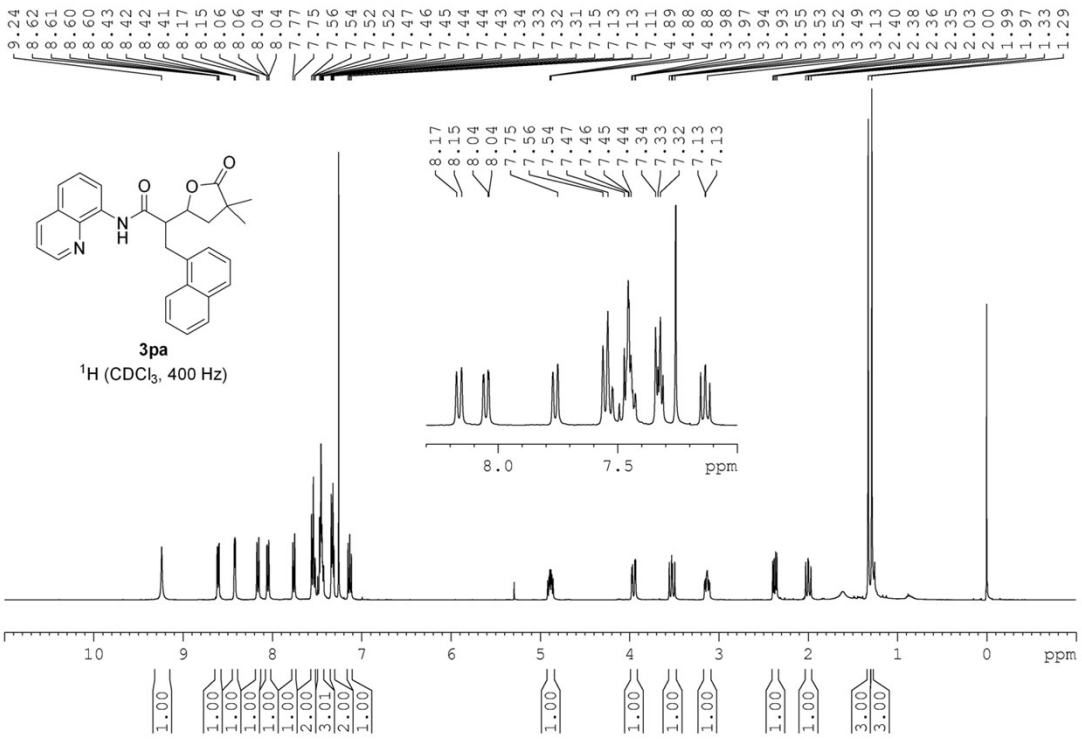
^{13}C NMR Spectra of **3oa**



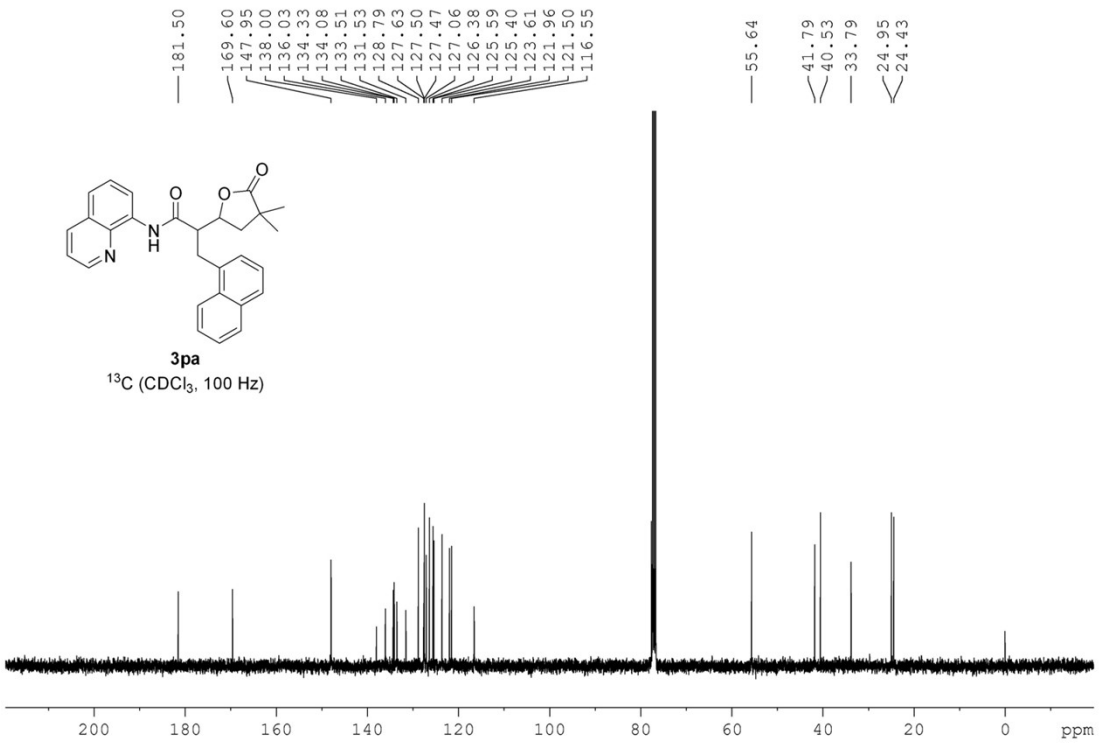
HRMS Spectra of **3oa**



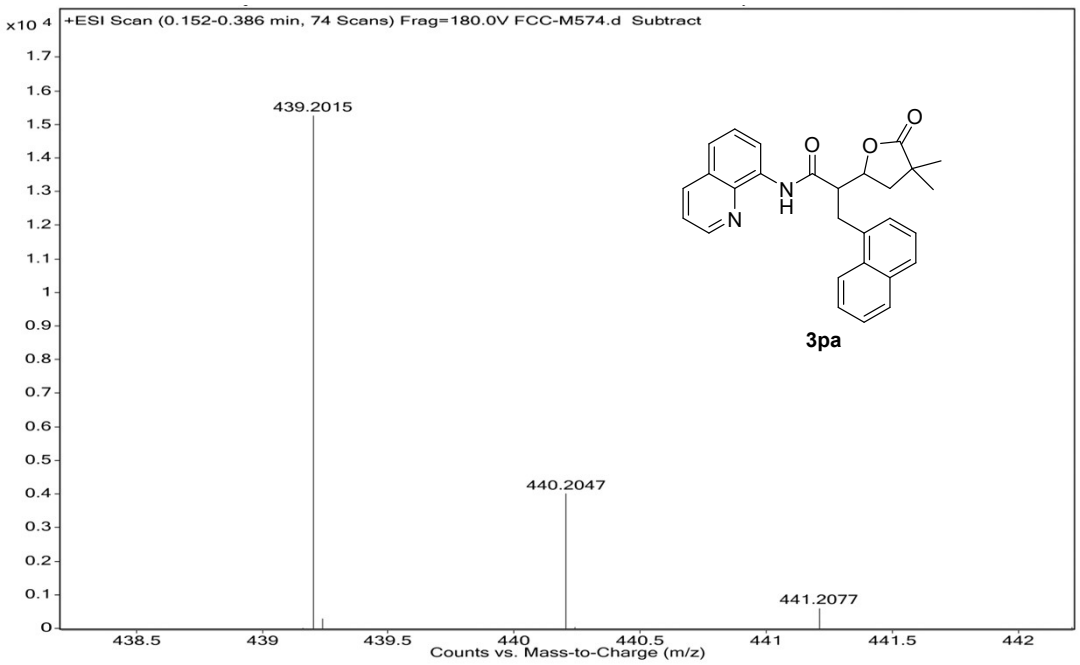
^{1}H NMR Spectra of **3pa**



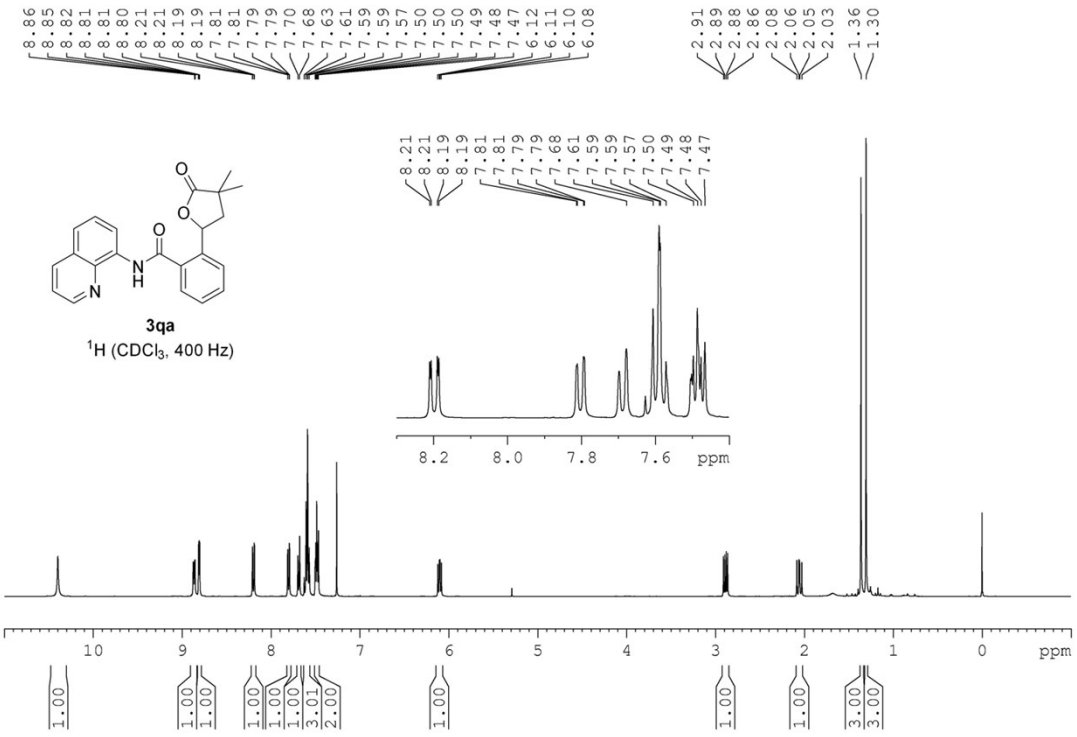
^{13}C NMR Spectra of **3pa**



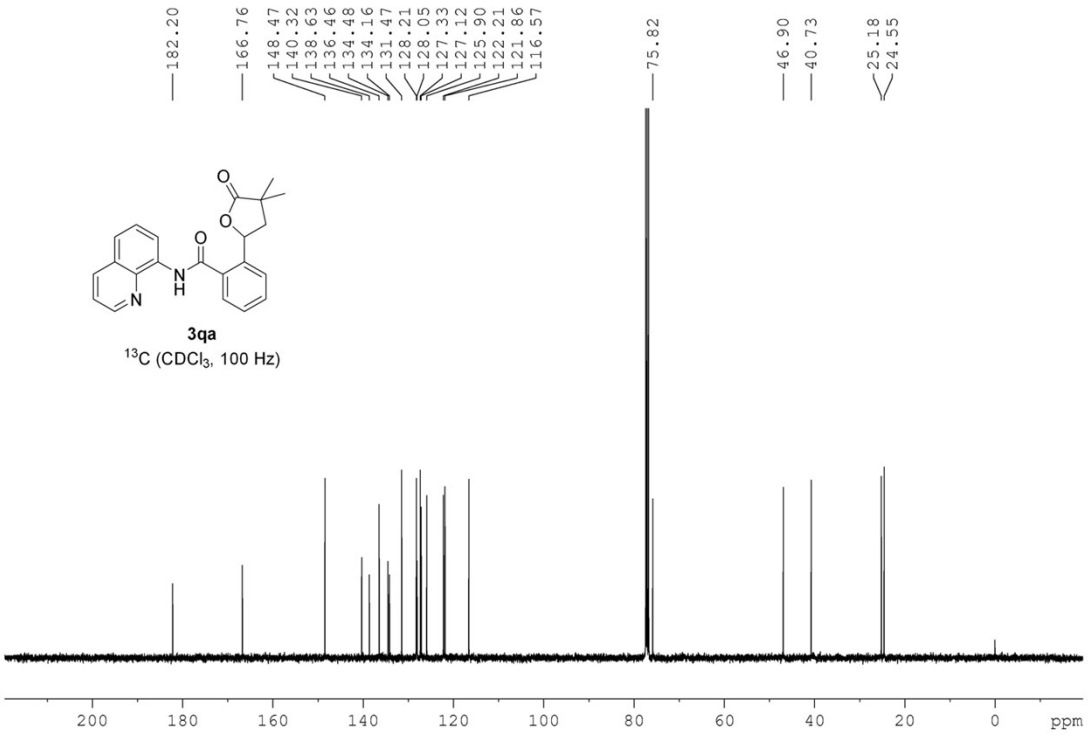
HRMS Spectra of **3pa**



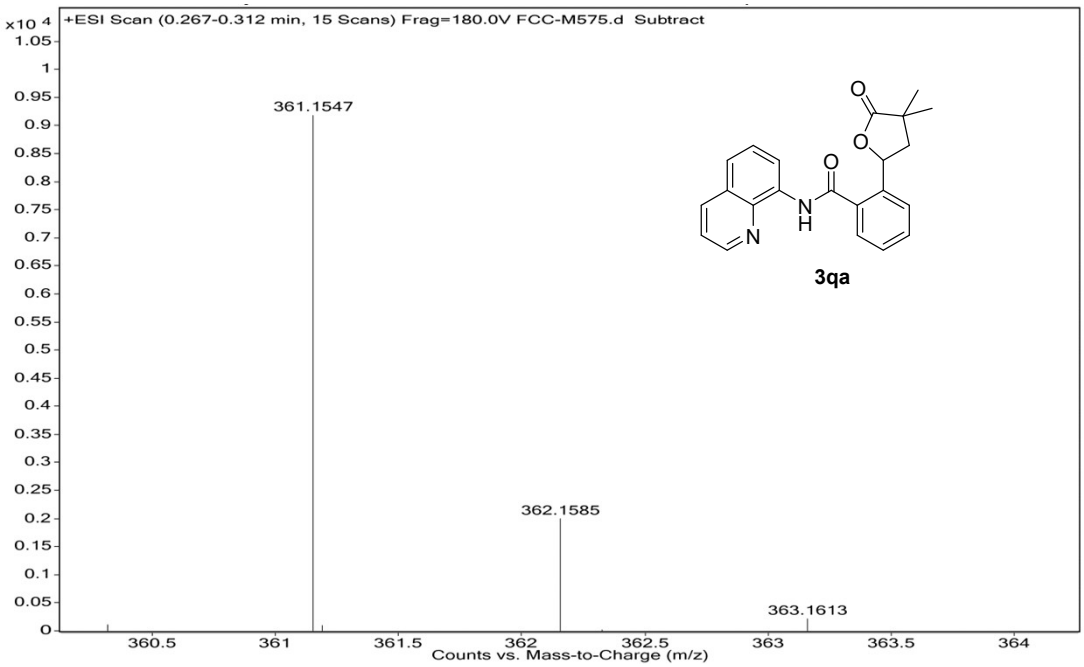
^{1}H NMR Spectra of **3qa**



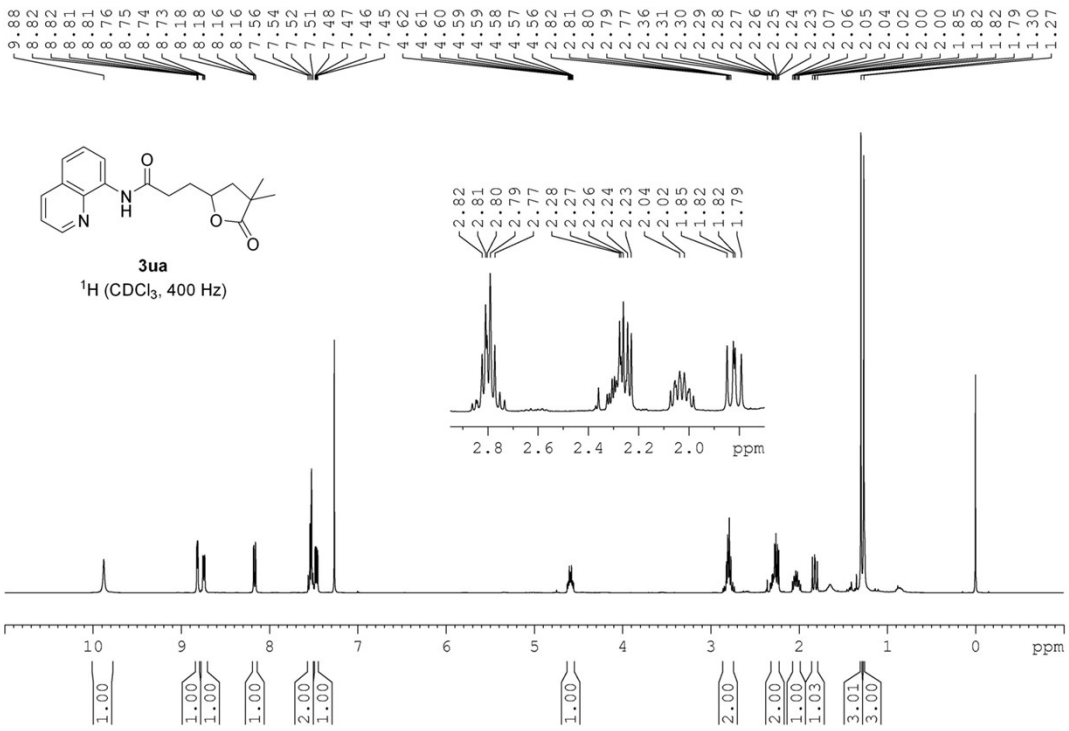
^{13}C NMR Spectra of **3qa**



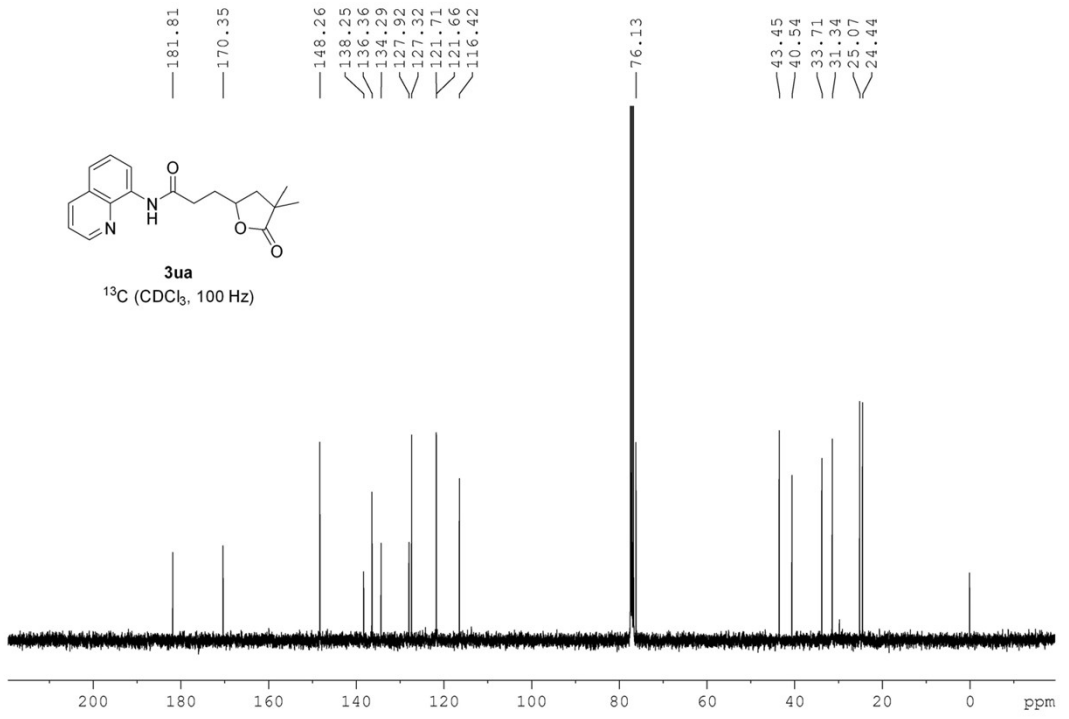
HRMS Spectra of **3qa**



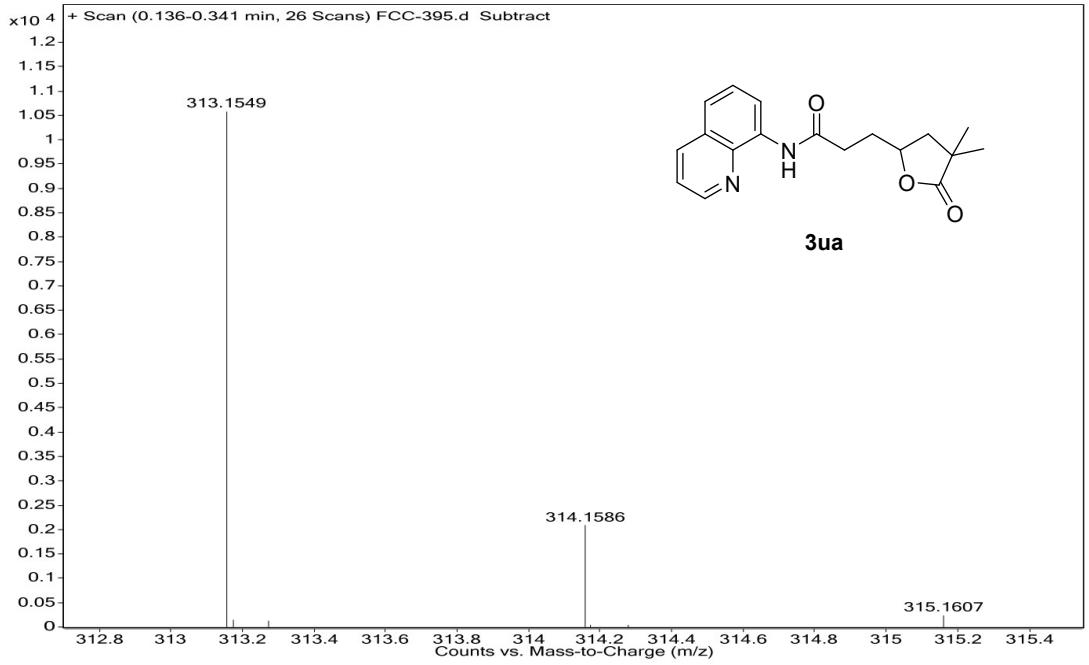
^{1}H NMR Spectra of **3ua**



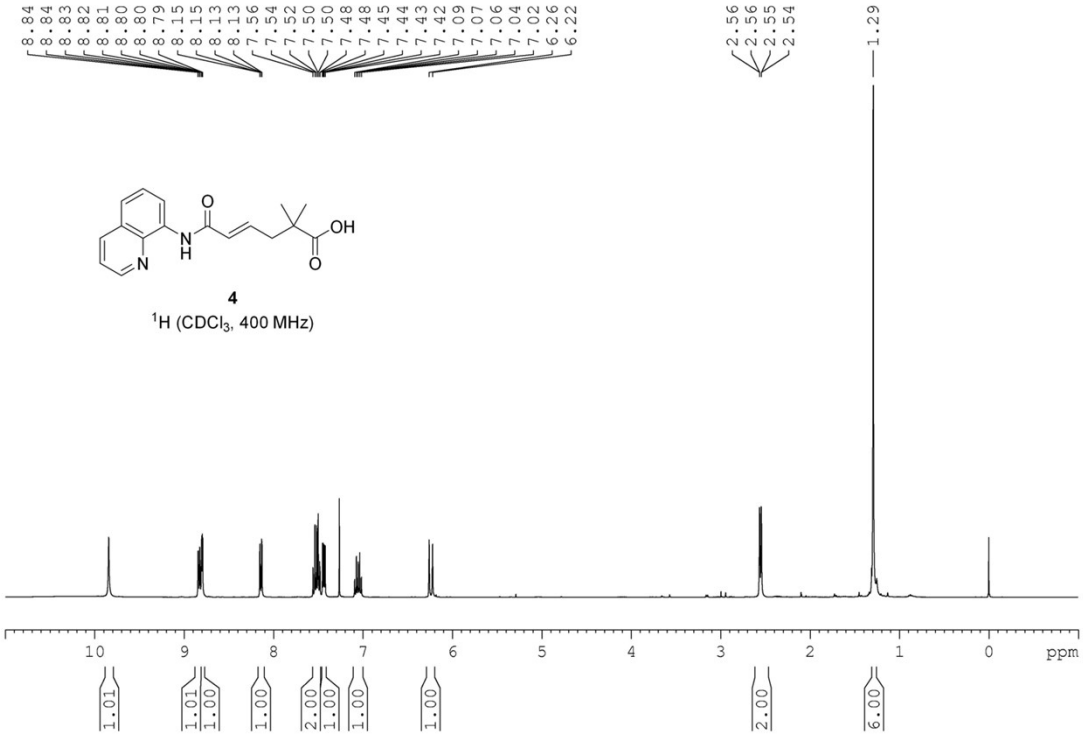
^{13}C NMR Spectra of **3ua**



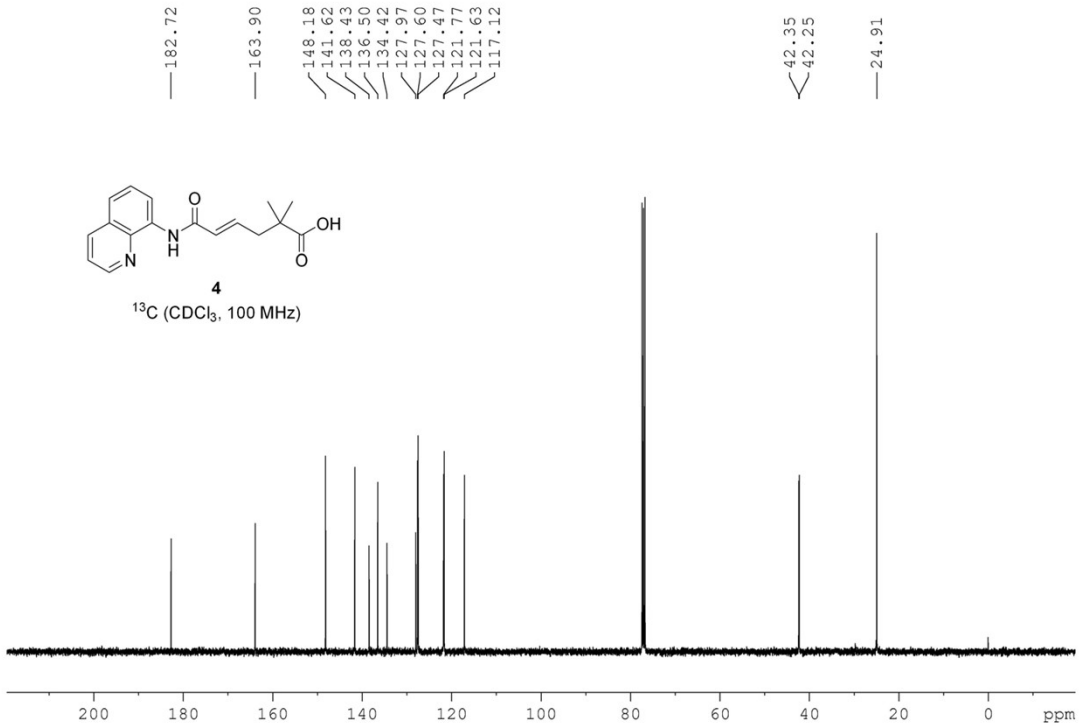
HRMS Spectra of **3ua**



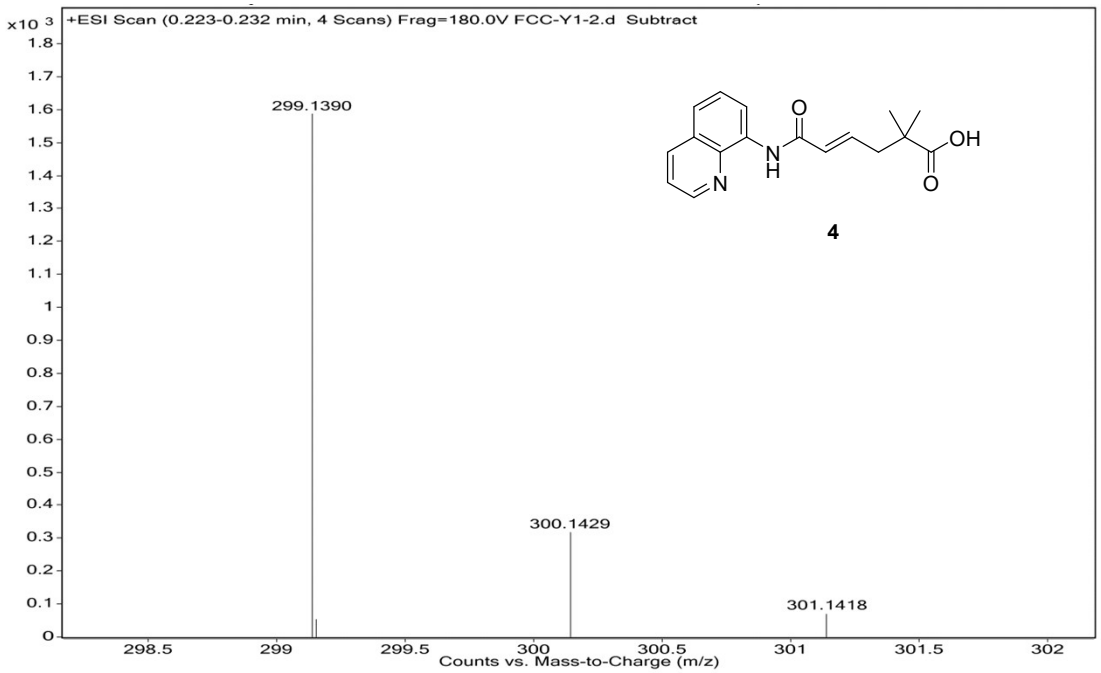
^{1}H NMR Spectra of **4**



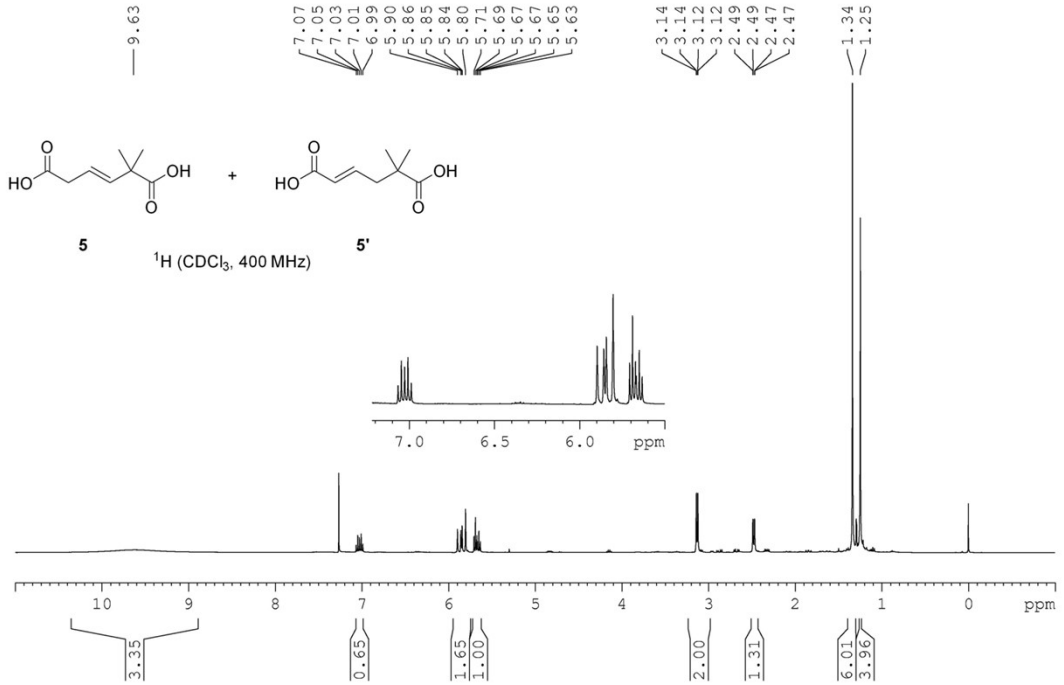
^{13}C NMR Spectra of **4**



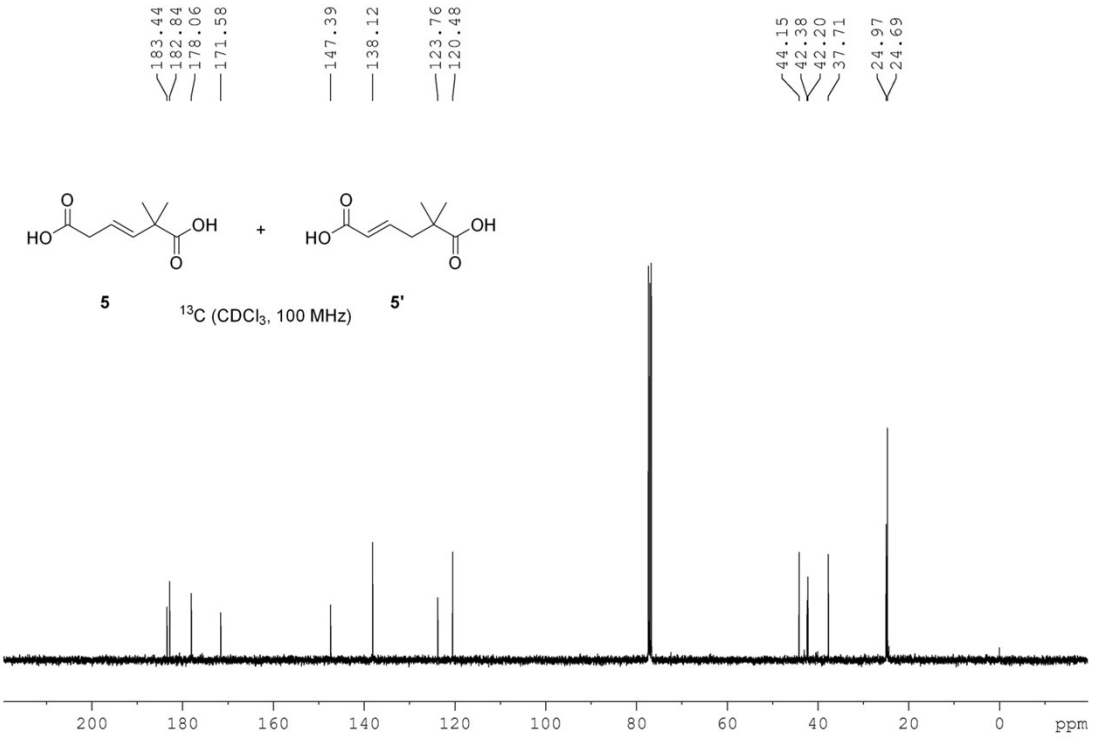
HRMS Spectra of **4**



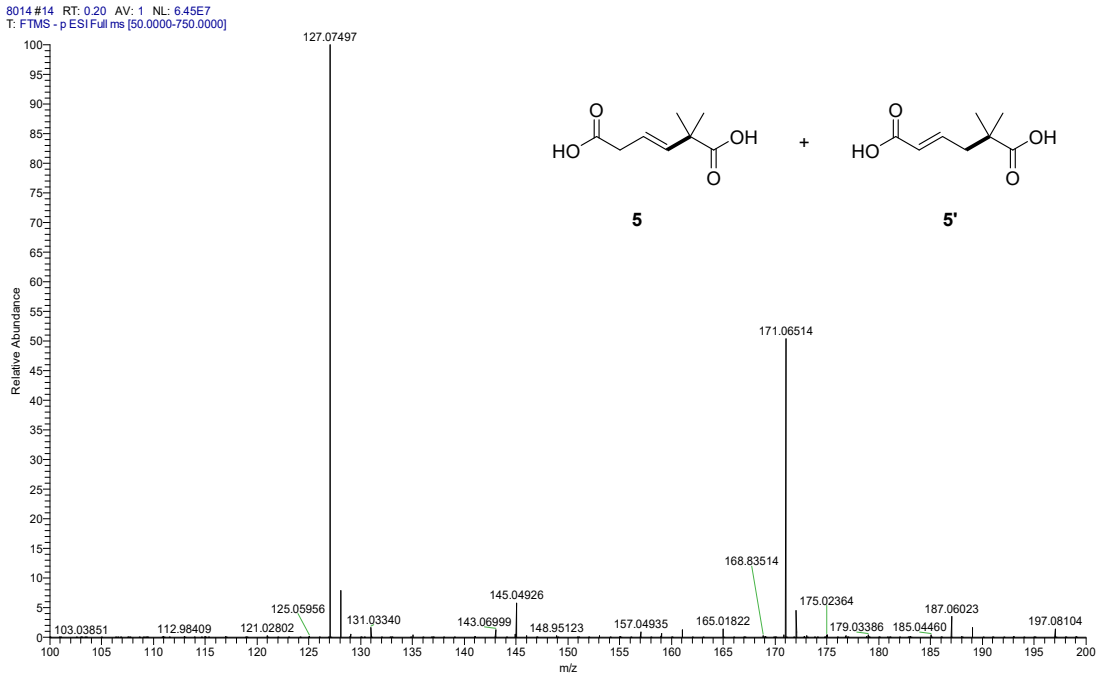
^{1}H NMR Spectra of **5**



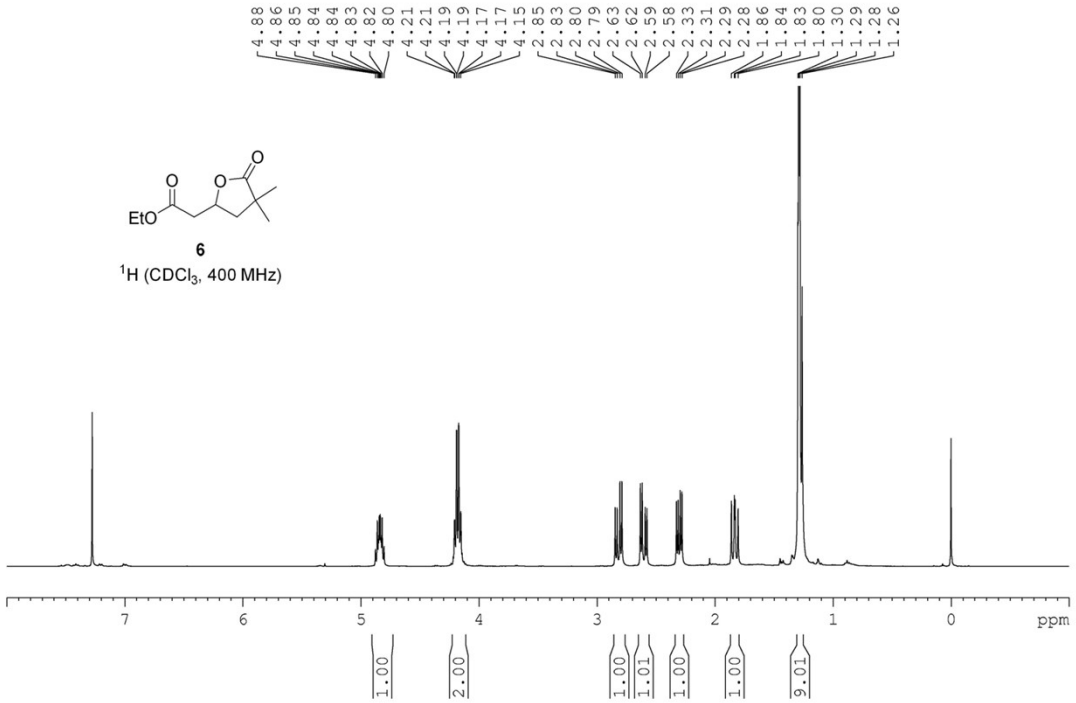
^{13}C NMR Spectra of **5**



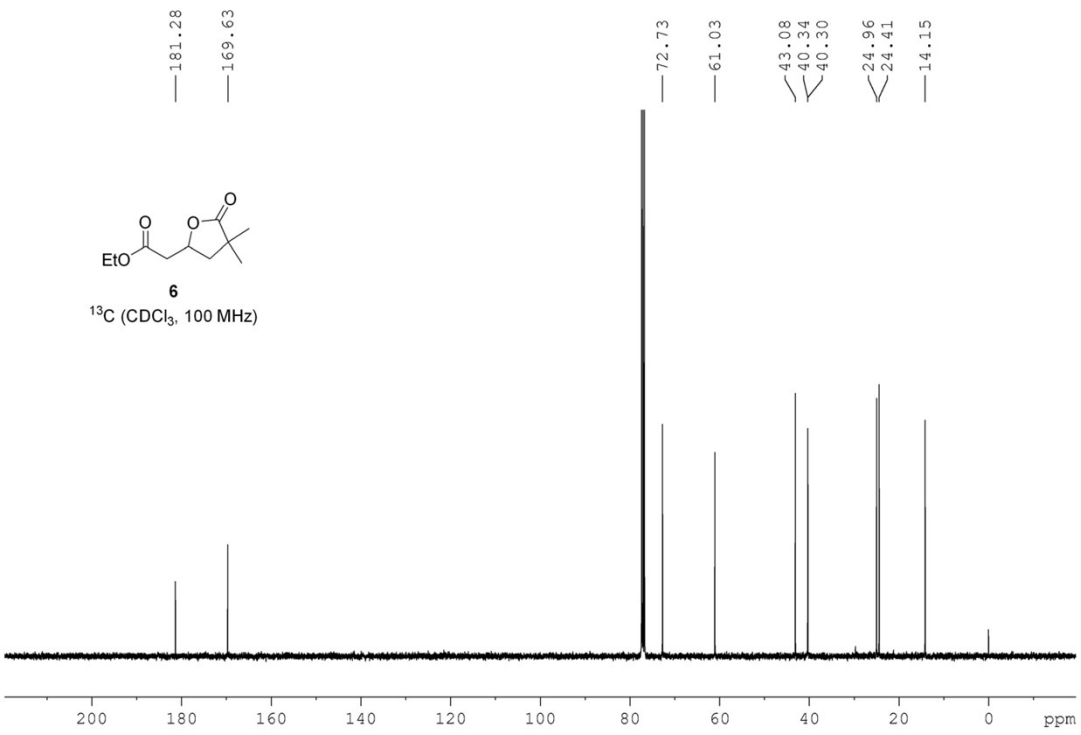
HRMS Spectra of **5**



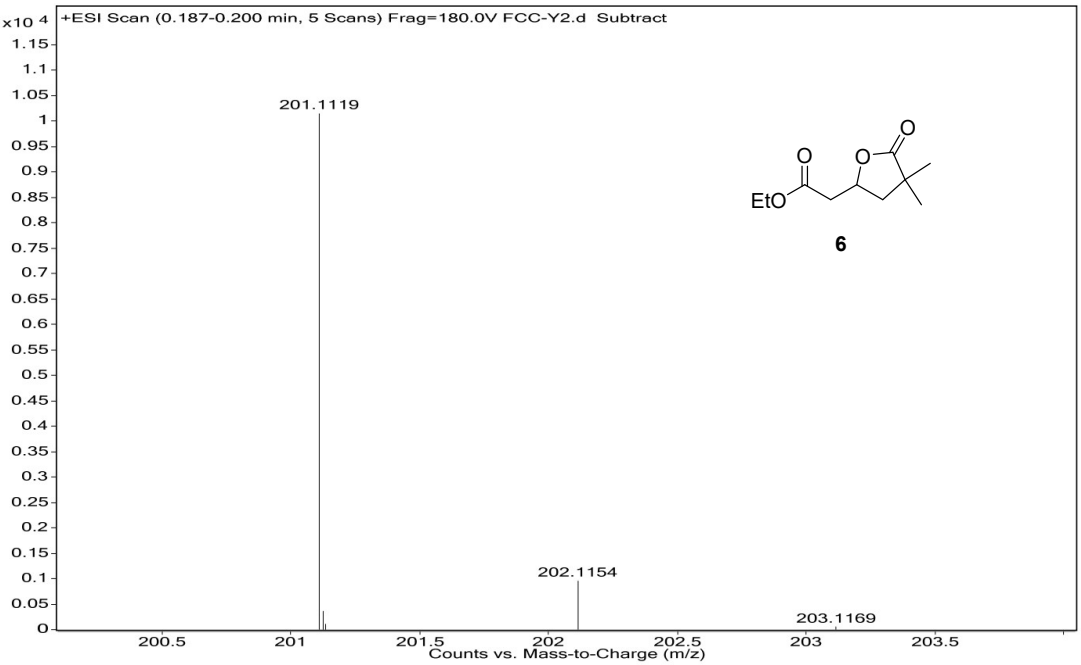
^{1}H NMR Spectra of **6**



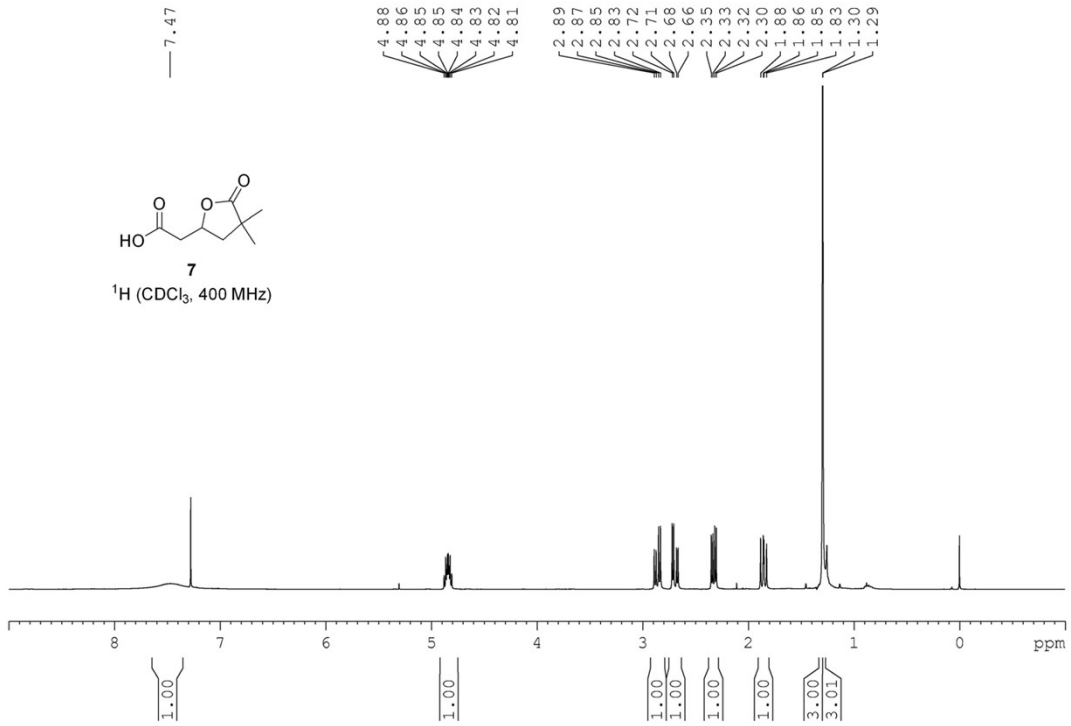
^{13}C NMR Spectra of **6**



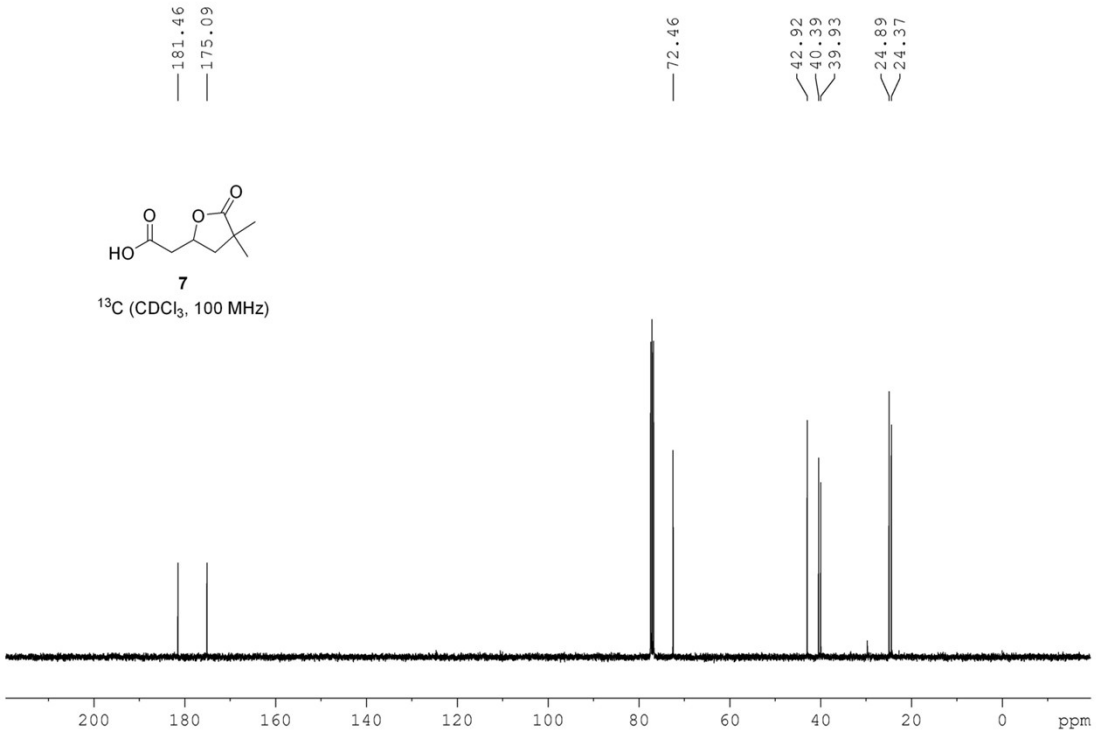
HRMS Spectra of **6**



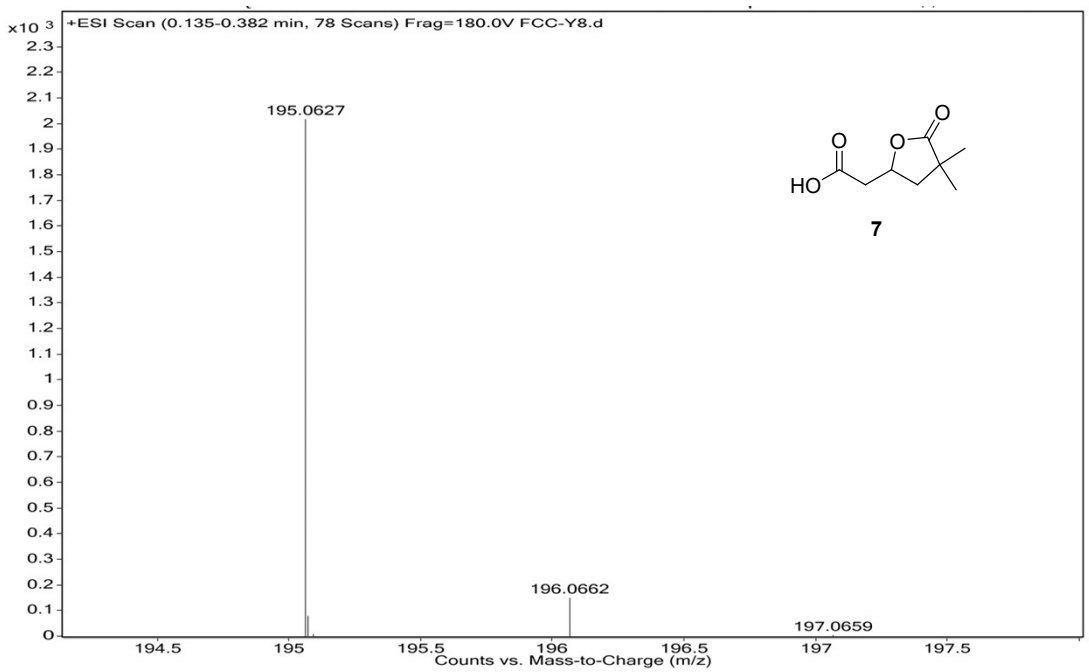
^{1}H NMR Spectra of **7**



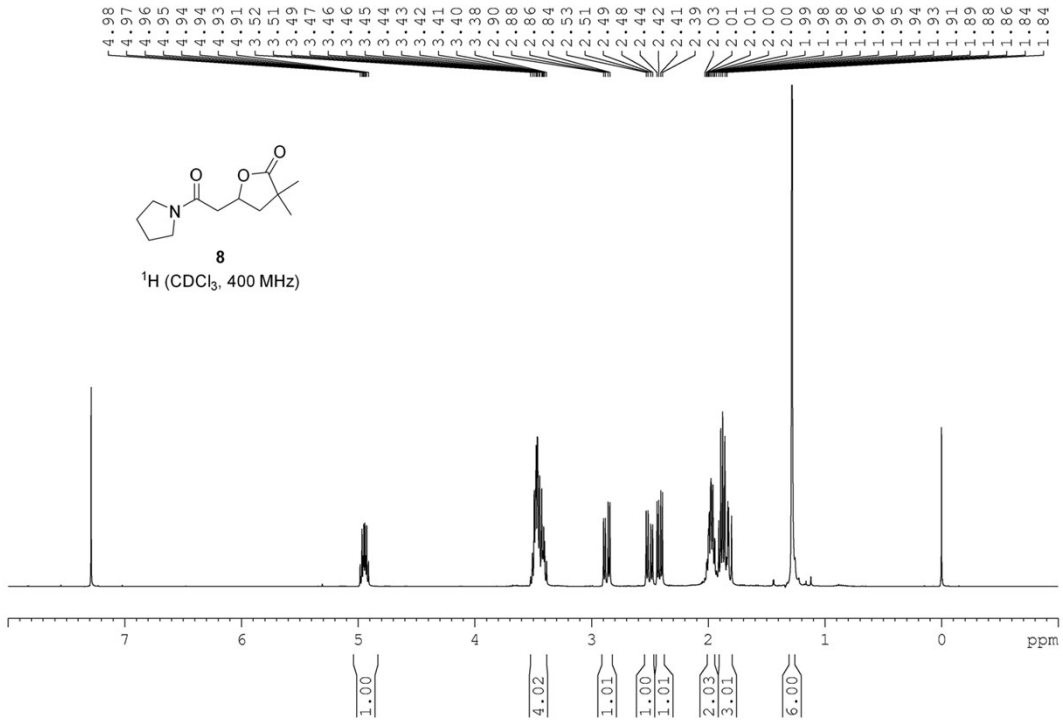
^{13}C NMR Spectra of **7**



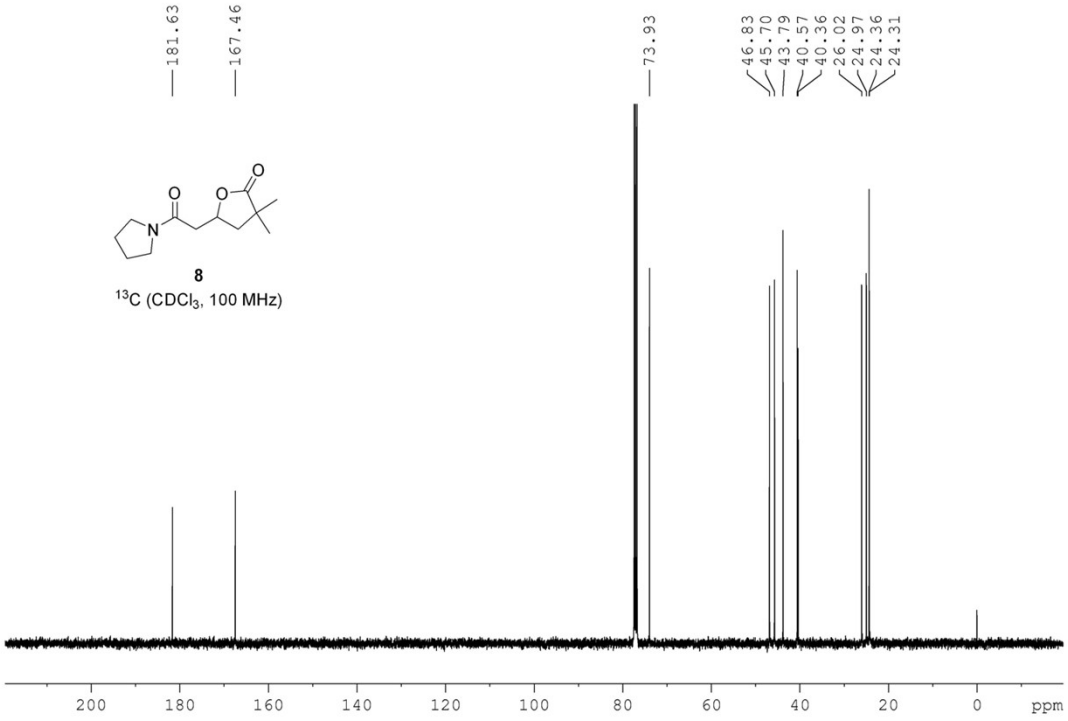
HRMS Spectra of **7**



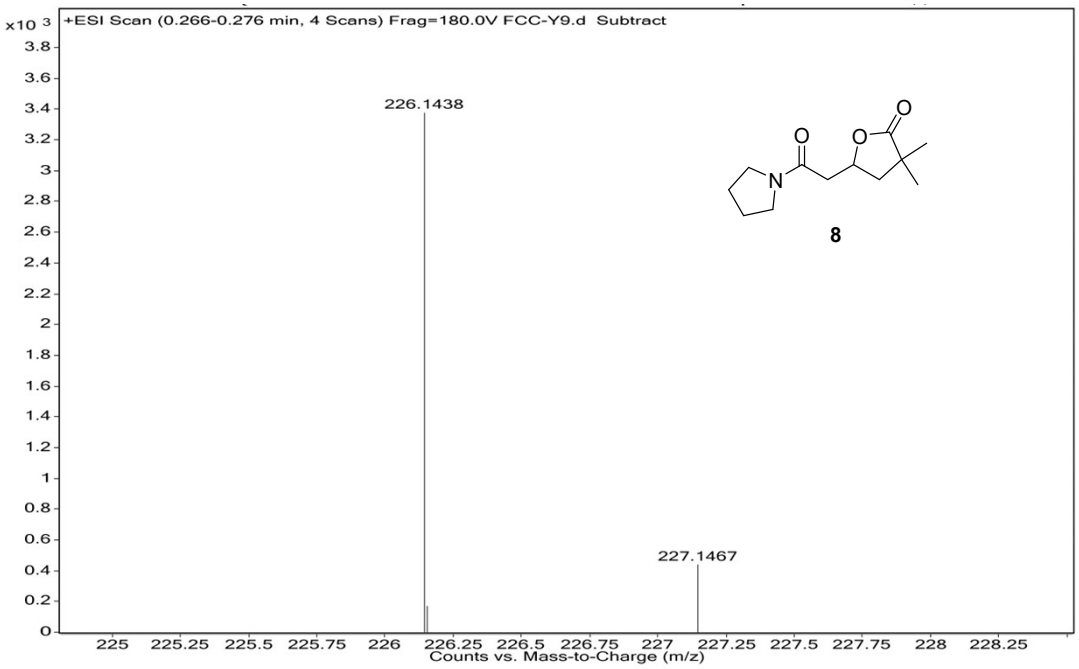
^{1}H NMR Spectra of **8**



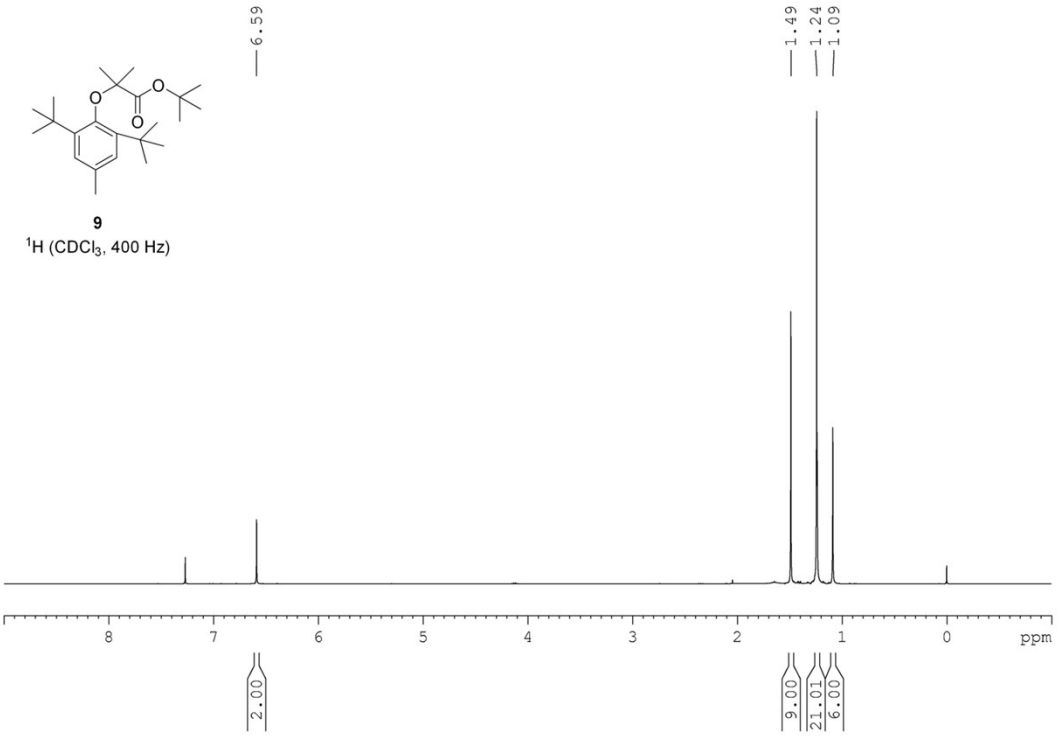
^{13}C NMR Spectra of **8**



HRMS Spectra of **8**



^{1}H NMR Spectra of **9**



^{13}C NMR Spectra of **9**