SUPPLEMENTARY INFORMATION

Elaboration of molecular glues that target TRIM21 into TRIMTACs that degrade protein aggregates

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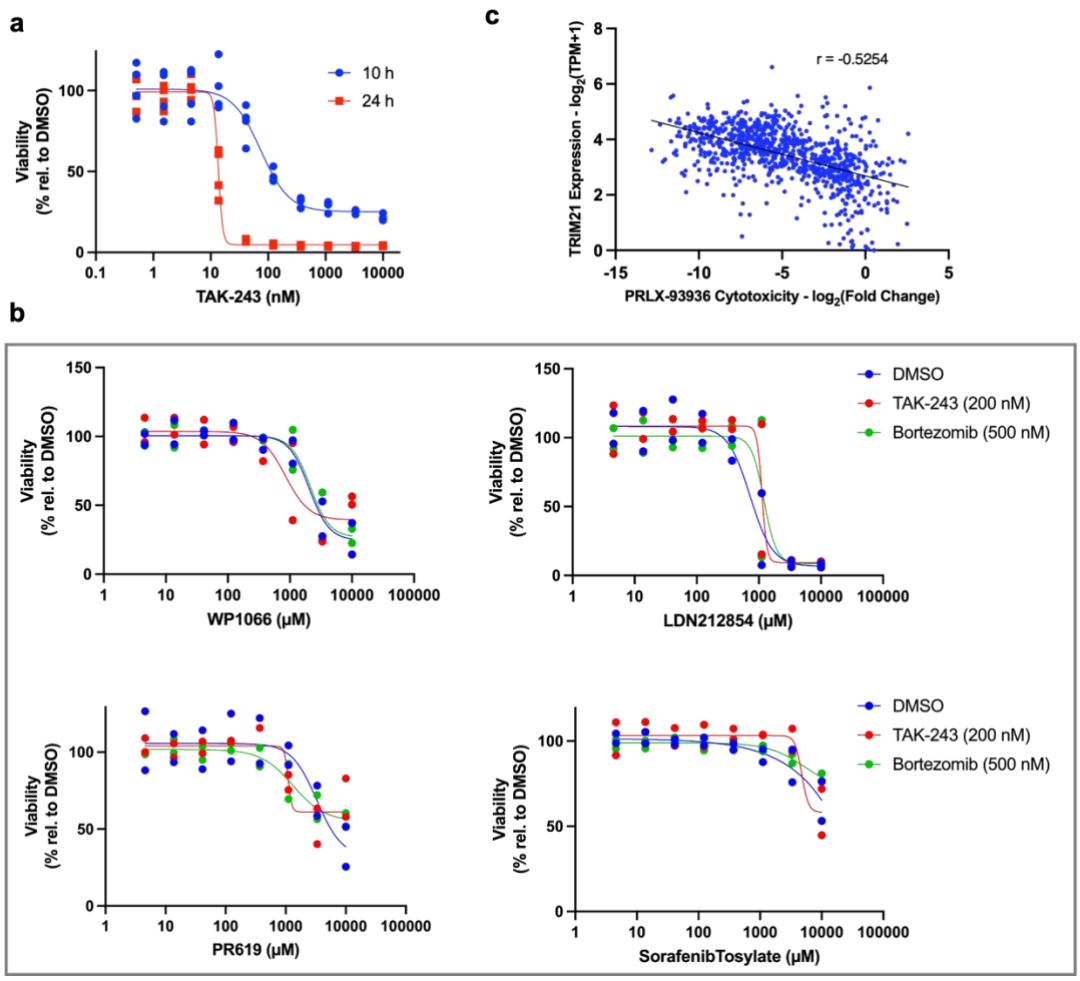
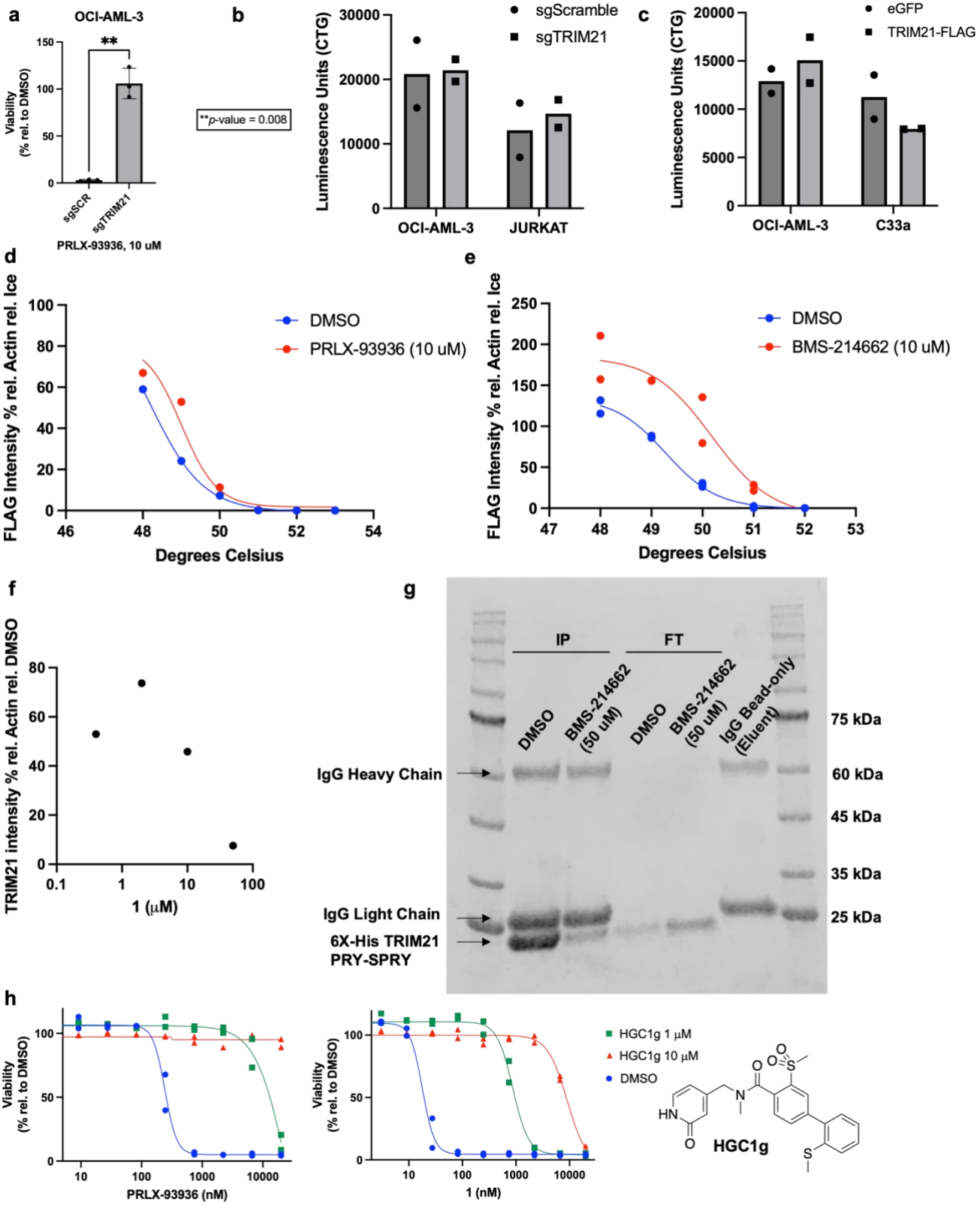
SUPPLEMENTARY FIGURES

Supplementary Figure 1



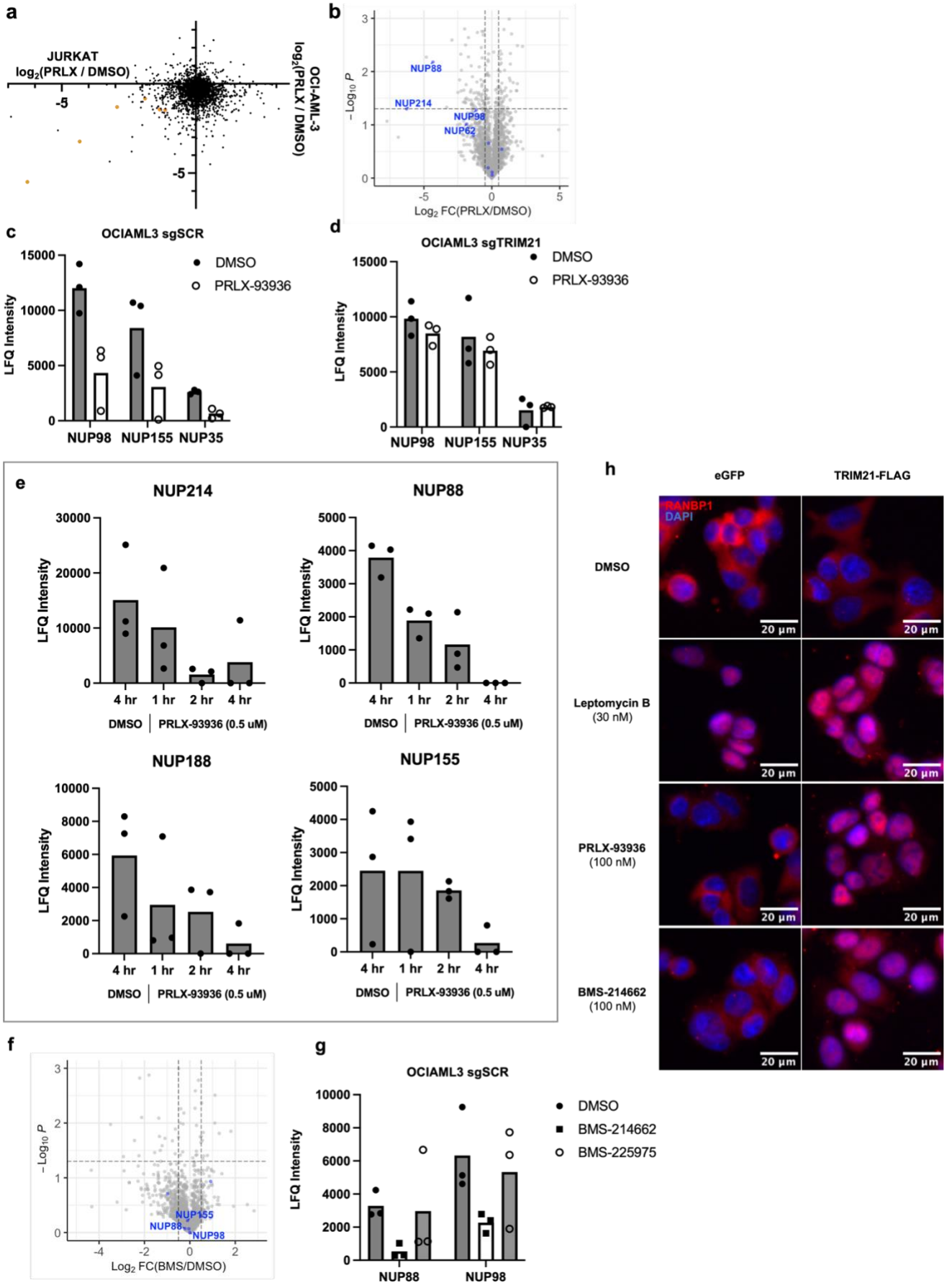
Supplementary Figure 1 a) Cell viability (CellTiter-Glo) following treatment of OCI-AML-3 cells with TAK-243 at the indicated concentrations for either 10 h (blue) or 24 h (red). These data informed selection of 20 nM TAK-243 for our rescue screen in Fig. 1b. n=1 independent experiment with 2 wells/condition. **b)** Cell viability (CellTiter-Glo) for the four additional hits that proved to be false positives and did not show suppression of cytotoxicity upon retest in OCI-AML-3 cells. n=2 independent experiment with points representing mean of 2 wells/condition. **c)** Pearson correlation of PRLX-93936 cytotoxicity expressed as log_2fold change (PRISM) and TRIM21 transcript level expressed as log_2(Transcripts per million+1) across the cancer cell lines available within DepMap (www.depmap.org). n=859 cell lines. A cytotoxicity value of 0 indicates no effect, while more negative numbers reflect more potent cytotoxic effects. Source data are provided as Source Data files.

Supplementary Figure 2



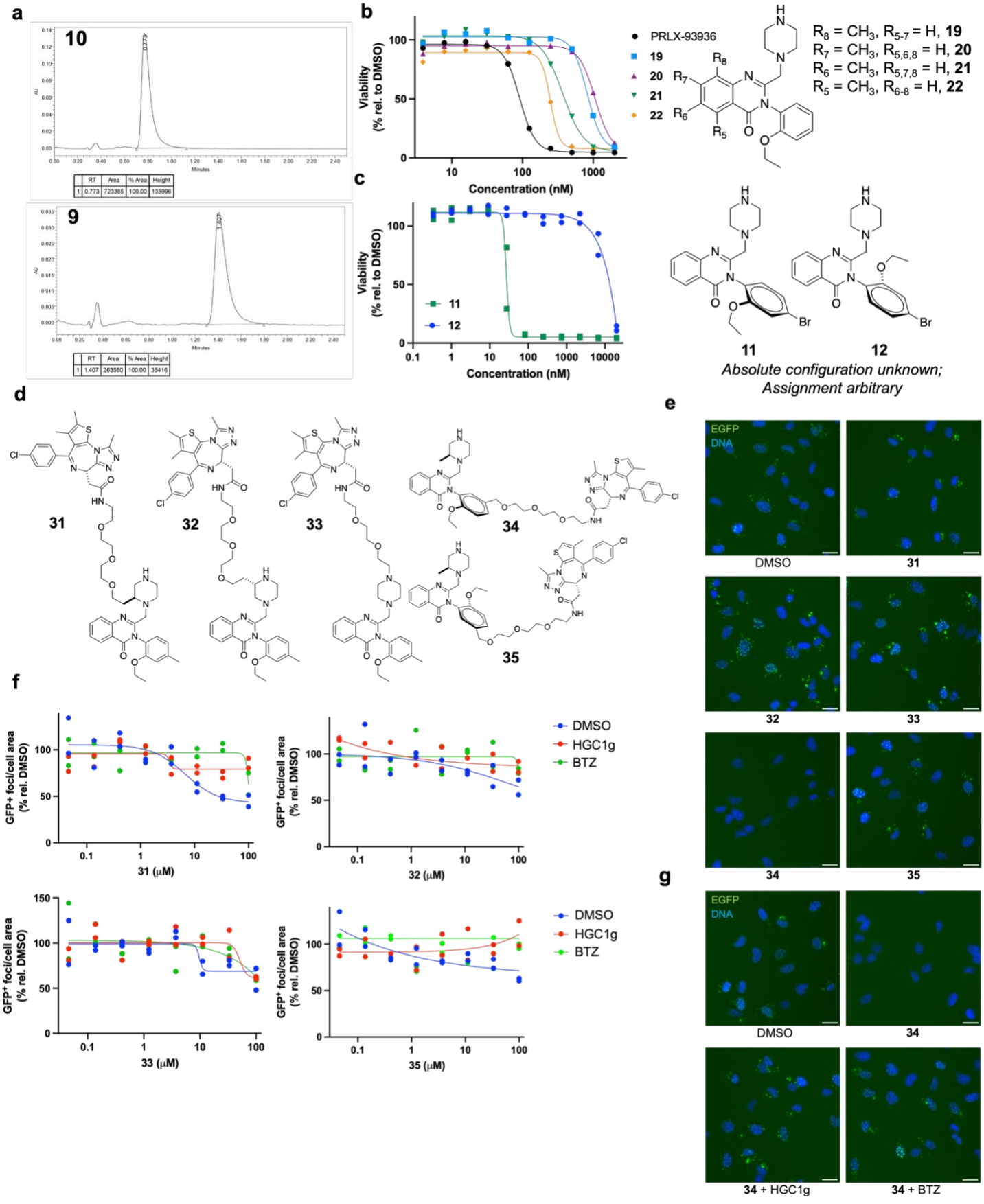
Supplementary Figure 2. a) Cell viability measurements of OCI-AML-3 treated with PRLX-93936 (10 μM) for 24 hours. Bars represent mean of n=3 independent experiments and error bars represent standard deviation. *P* = 0.0080 (Welch's *t*-test, two-sided). **b)** Cell viability measurements of WT or TRIM21 KO OCI-AML-3 or JURKAT cells treated with DMSO for 24 hours. n=2 independent runs are shown. **c)** Cell viability measurements of OCI-AML-3 or C33A cells expressing EGFP or TRIM21 and treated with DMSO for 24 hrs. Points represent mean of 16 wells from n=2 independent experiments. **d)** Quantification of Western Blot from Fig. 3J by Densitometry showing thermal stabilization of cellular TRIM21-FLAG by PRLX-93936. FLAG bands normalized to Actin then normalized to ice-treated control. Representative of n=1 independent experiment. **e)** Quantification of Western Blot from Fig. 3k by Densitometry showing thermal stabilization of cellular TRIM21-FLAG by BMS-214662. Normalization as in Fig. S2d. Representative of n=2 independent experiments. **f)** Quantification of Western Blot from Fig. 3l by Densitometry as in Fig. S2d. Representative of n=1 independent experiments. **g)** Immunoprecipitation assay in which recombinant 6x-His TRIM21 PRY-SPRY captured on IgG resin is displaced in the presence of BMS-214662. Representative of n=1 independent experiments. **h)** Viability of OCI-AML-3 cells (CellTiter-Glo) treated with the indicated concentrations of PRLX-93936 (left) or **1** (right) plus the indicated concentrations of established TRIM21 ligand HGC1g. (n=2 independent experiments, each with at least 3 wells per concentration). Source data are provided as Source Data files.

Supplementary Figure 3



Supplementary Figure 3. Further proteomic characterization of PRLX-93936 and BMS-214662. **a)** Label-free LC/MSMS quantitation (LFQ) of protein levels following PRLX-93936 treatment (500 nM, 6 hr) in JURKAT cells (x-axis) and OCI-AML-3 cells (y-axis), with alterations in nucleoporin proteins highlighted in orange. This expanded version of Figure 4a shows all 4 quadrants. Each point represents the mean of n=3 independent replicates. **b)** Volcano plot highlighting alterations in protein levels following treatment with PRLX-93936 (500 nM, 6 hr) in JURKAT cells. FC = fold change. Nucleoporin proteins colored in blue. **c,d)** LFQ intensity values for specific nucleoporins in both sgSCR (c) and sgTRIM21 (d) OCI-AML-3 cells. **e)** Individual LFQ values for the n=3 independent samples averaged to produce the heatmap shown in Fig. 4f. **f)** Volcano plot as in b highlighting alterations in protein levels following treatment with BMS-214662 (1 μM, 4 hr) in OCI-AML-3 TRIM21 KO cells. **g)** LFQ intensity values for specific nucleoporins in both OCI-AML-3 cells treated with BMS-214662 (black squares) or BMS-225975 (1 μM, 4 hr), the N-methylated analog of BMS-214662 that lacks TRIM21-dependent cell killing (open circles). Scatter and volcano plot points represent mean of n=3 independent replicates. Volcano plot *P*-values derived from two-sided t-tests, no correction for multiple comparisons. Bar graph points represent one of n=3 independent replicates. **h)** Representative immunofluorescence images for RANBP1 as in Fig. 4m, but now false colored with RANBP1 red and DAPI blue. Source data are provided as Source Data files.

Supplementary Figure 4



Supplementary Figure 4: a) Analytical chiral SFC traces for **9** and **10**, the separated atropisomers of PRLX-93936, following 4 d at RT in ethanol. No racemization is observed. **b)** Viability (CellTiter-Glo) of OCI-AML-3 cells following 24 h treatment with the indicated concentrations of the drawn PRLX-93936 analogs. Mean of N=3 independent biological replicates are shown, individual biological replicates shown in Supplementary Table 2. **c)** Viability (CellTiter-Glo) of OCI-AML-3 cells following 24 hours of treatment with the indicated concentrations of the enantiomeric PRLX-93936 analogs **11** and **12**. N=2 independent replicates are shown. **d)** Structures of all candidate PROTACs assessed. Absolute configuration of the chiral axis of **34**/**35** is unknown, and the assignment is arbitrary. **e)** Representative colored images from Fig 6d of an A549 PML-EGFP-BRD4(BD2) clone expressing TRIM21-FLAG treated with indicated compounds for 8 hrs. **31**-**35** each 10 μM. Nuclei are marked with Hoechst (DNA). Representative of n=1 independent experiments. Scale bar (white) = 20 μm. **f)** Quantification of EGFP foci in an A549 PML-EGFP-BRD4(BD2) clone expressing TRIM21-FLAG pre-treated with indicated compounds for 2 hrs before treatment with indicated concentrations of **31**, **32**, **33**, or **35** for 8 hrs. Experiments representative of n=2 (**35**) or n=1 (**31**, **32**, **33**) independent experiments, each containing 2 independent wells and >100 quantified cells per dose. **g)** Representative colored images from Figure 4F as in (e). **34**, 10 μM; HGC1g, 10 μM; BTZ, Bortezomib, 2 μM. Representative of n=2 independent experiments and >100 quantified cells per dose. Scale bar (white) = 20 μm. Source data are provided as Source Data files.

Supplementary Table 1. Small molecule screening data

Category	Parameter	Description
Assay	Type of assay	Comparative Cell Viability Assay
	Target	Phenotypic screen (no target)
	Primary measurement	Cell Viability
	Key reagents	CellTiter-Glo (Promega, G7570), TAK-243 (Medchem Express, HY-100487)
	Assay protocol	Methods Section – "High-Throughput Chemical Screen"
	Additional comments	The goal was to find molecules whose cell killing was lost following pharmacological UBA1 (Uniprot, P22314) inhibition.
Library	Library size	1754
	Library composition	Bioactive Small Molecules
	Source	Multiple commercial library vendors
	Additional comments	
Screen	Format	384-well plate
	Concentration(s) tested	6 μM, 0.1% DMSO
	Plate controls	32 DMSO-treated wells
	Reagent/ compound dispensing system	JANUS (Revvity), EL406 (Agilent)
	Detection instrument and software	SynergyNEO2 Plate Reader (Gen5 3.03.14)
	Assay validation/QC	None performed
	Correction factors	None performed
	Normalization	Normalized to DMSO-treated controls within same plate
	Additional comments	
Post-HTS analysis	Hit criteria	>50% reduction in normalized cell viability in DMSO pre-treated well AND >30% increase in normalized cell viability with TAK-243 treatment relative to DMSO-treated control
	Hit rate	0.3%
	Additional assay(s)	Validation of hits in 8-point dose across ~3 log units
	Confirmation of hit purity and structure	Hit validation performed with separately purchased small molecule stocks. SAR studies with newly-synthesized analogs also strongly support hit authenticity.
	Additional comments	

Supplementary Table 2. Evaluation of PRLX-93936 analogs.

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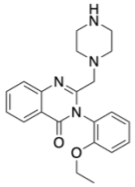
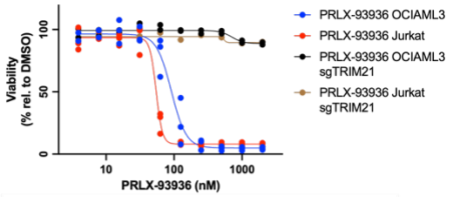
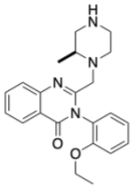
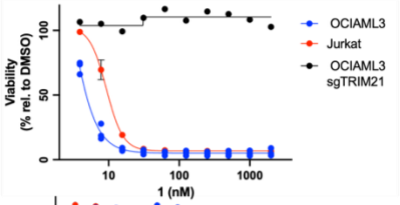
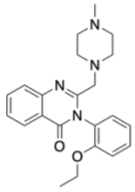
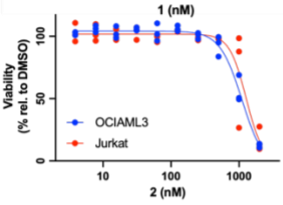
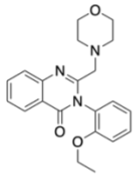
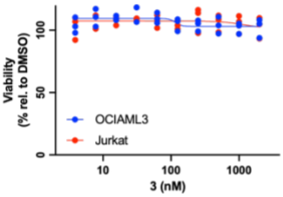
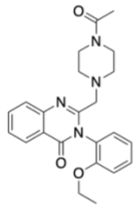
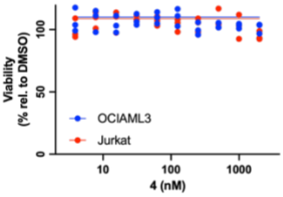
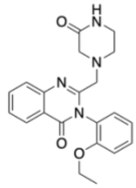
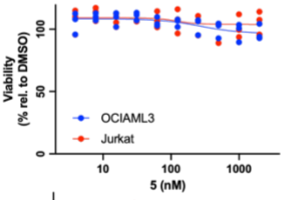
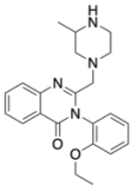
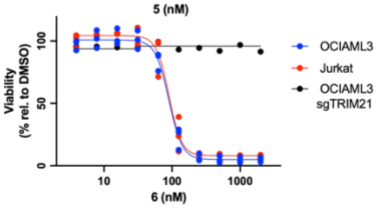
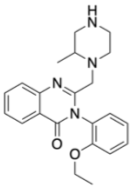
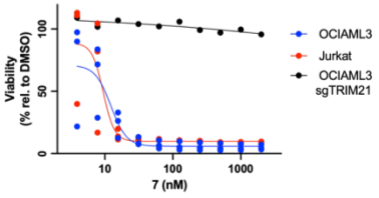
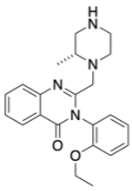
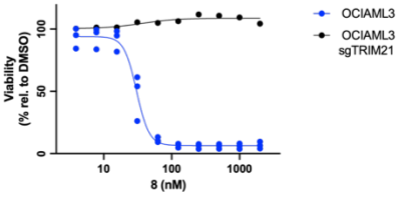
PRLX-93936		54	91	>2,000	
1		9	3	>2,000	
2		1277	1111	>2,000	
3		>2,000	>2,000	n.t.	
4		>2,000	>2,000	n.t.	
5		>2,000	>2,000	n.t.	
6		90	90	>2,000	
7		9	12	>2,000	
8		n.t.	30	>2,000	

Supplementary Table 2, continued. Evaluation of PRLX-93936 analogs.

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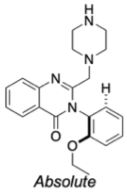
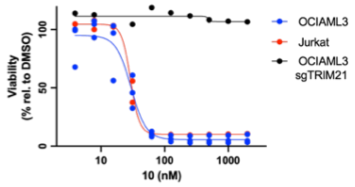
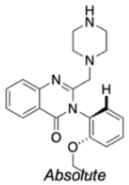
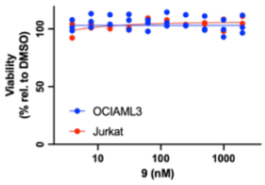
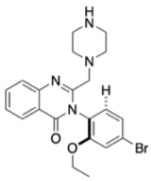
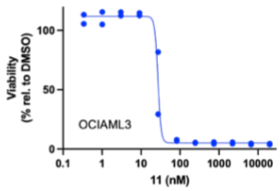
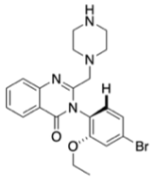
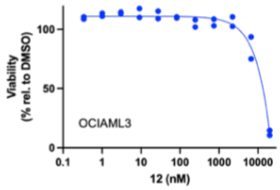
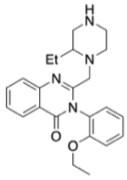
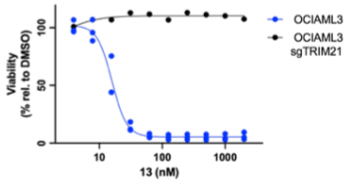
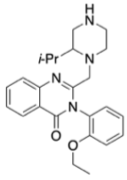
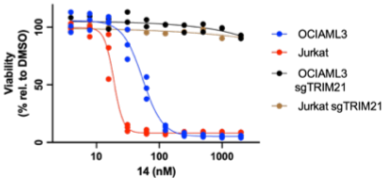
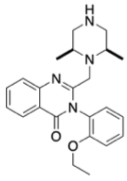
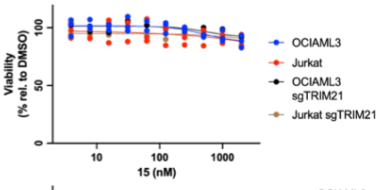
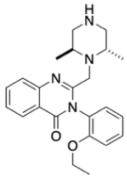
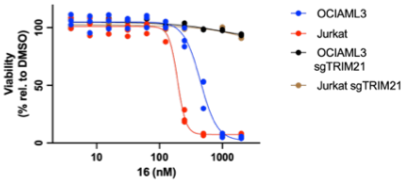
9	 *Absolute configuration unknown*	29	30	>2,000	
10	 *Absolute configuration unknown*	>2,000	>2000	n.t.[c]	
11	 *Absolute configuration unknown*	n.t.	27	n.t.	
12	 *Absolute configuration unknown*	n.t.	>10,000	n.t.	
13		n.t.	16	>2,000	
14		19	54	>2,000	
15		>2,000	>2,000	n.t.	
16		194	448	>2,000	

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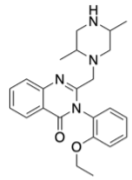
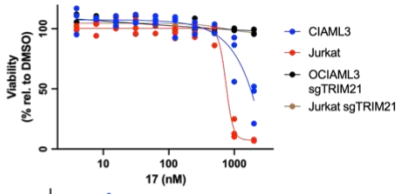
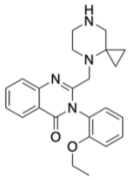
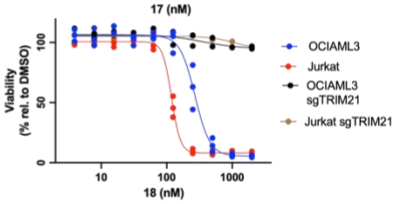
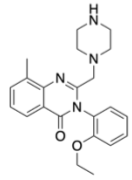
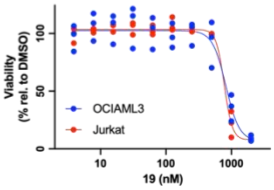
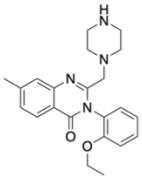
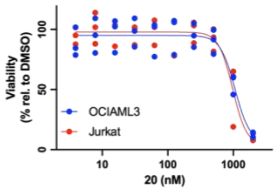
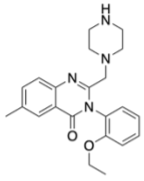
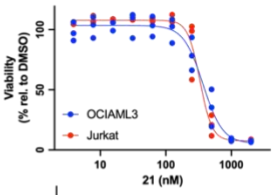
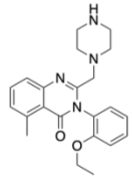
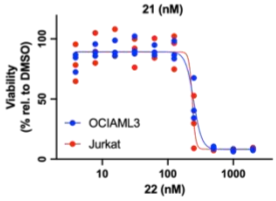
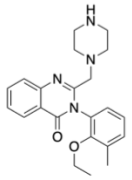
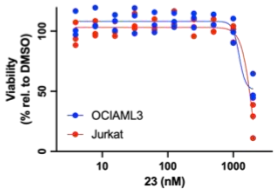
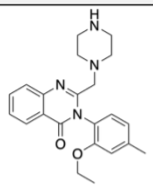
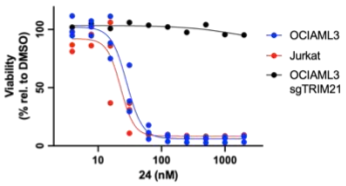
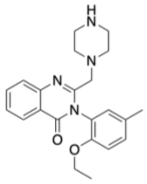
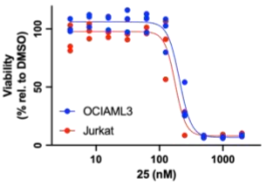
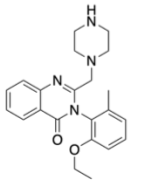
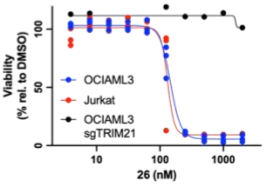
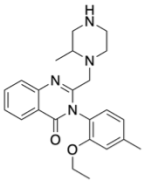
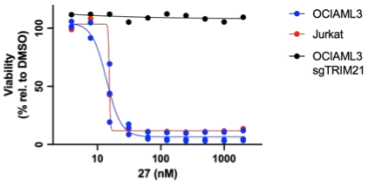
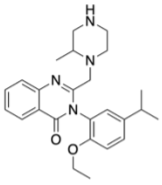
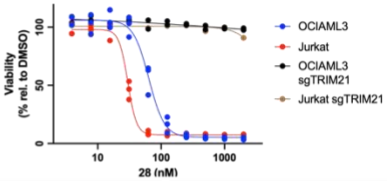
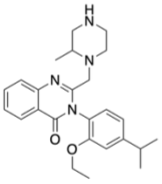
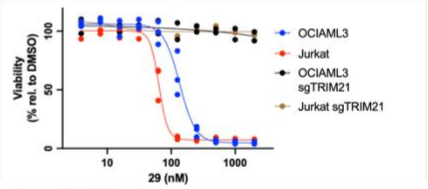
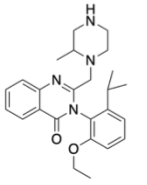
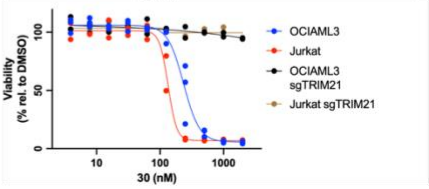
17		745	1735[d]	n.t.	
18		118	270	>2,000	
19		777	822	n.t.	
20		974	1063	n.t.	
21		332	371	n.t.	
22		236	248	n.t.	
23		1792[d]	1977[d]	n.t.	

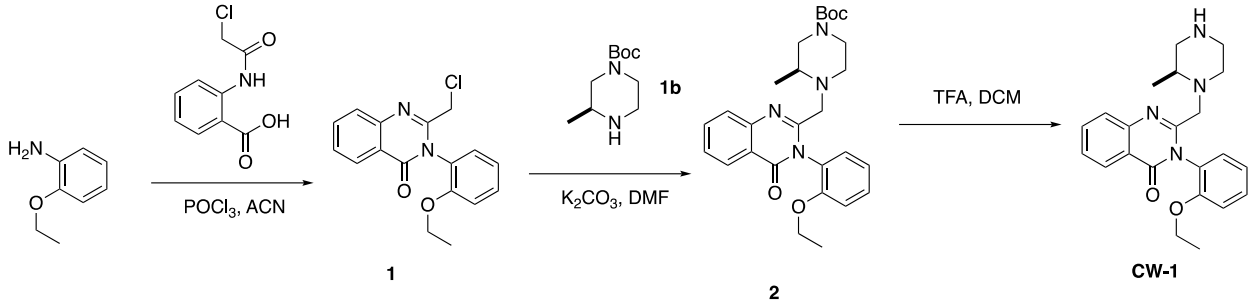
Supplementary Table 2, continued. Evaluation of PRLX-93936 analogs.

		Jurkat (EC_{50}, nM)[a]	OCIAML-3 (EC_{50},nM)[a]	TRIM21 KO (EC_{50},nM)[b]	
24		23	28	>2,000	
25		177	206	n.t.	
26		132	146	>2,000	
27		15	14	>2,000	
28		30	64	>2,000	
29		64	135	>2,000	
30		134	235	>2,000	

[a]EC_{50} values are the average of three independent runs in OCI-AML-3 or JURKAT cells as shown at right. [b]See figure legend at right for whether OCIAML3 TRIM21 KO cells and/or JURKAT TRIM21 KO cells were used. In most instances, one experiment showing the average of at least two independent wells is shown. [c]n.t., not tested. [d]Absolute EC_{50} estimated based on incomplete curve fits, see graphs at right.

Supplementary Note 1: Chemical characterization data for synthesized small molecules

CW-1



To a solution of the indicated aniline (200 mg, 1.46 mmol, 190.84 µL) and indicated chloroacetamide (311.44 mg, 1.46 mmol) in ACN (3 mL) was added $POCl_3$ (670.65 mg, 4.37 mmol, 407.69 µL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed the aniline was consumed and 37% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 15% Ethyl acetate/ Petroleum ether gradient @ 60 mL/min) to afford ***Compound 1*** (400 mg, 1.27 mmol, 87.16% yield) as a red oil. MS-ESI (m/z) calcd for $C_{17}H_{15}ClN_2O_2$ $[M+H]^+$: 315.1/317.1 Found 315.1/317.1.

To a solution of **Compound 1** (100 mg, 317.70 µmol) and **Compound 1b** (76.35 mg, 381.24 µmol) in DMF (2 mL) was added K_2CO_3 (131.72 mg, 953.09 µmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 1** was consumed and 43% of desired compound was detected. The reaction mixture was diluted with H_2O 10 mL and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 20% Ethyl acetate/Petroleum ether gradient @ 50 mL/min) (SiO_2, Petroleum ether: Ethyl acetate = 5:1, Rf (P1) = 0.40) to afford **Compound 2** (80 mg, 167.16 µmol, 52.62% yield) as a pale yellow oil. MS-ESI (m/z) calcd for $C_{27}H_{34}N_4O_4$ $[M+H]^+$:479.2/480.2 Found 479.3/480.3.

To a solution of **Compound 2** (80 mg, 167.16 µmol) in DCM (1 mL) was added TFA (307.00 mg, 2.69 mmol, 0.2 mL). The mixture was stirred at 20°C for 1 hr. LC-MS showed **Compound 2** was consumed and 71% of desired compound was detected. The reaction mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5%-40% B over 8.0 min) to afford **CW-1** (67.99 mg, 138.05 µmol, 82.59% yield, 100% purity, TFA salt) as a colourless gum.

Spectrum:

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.19 - 8.28 (m, 1 H) 7.84 - 7.97 (m, 1 H) 7.78 (dd, *J*=8.13, 2.00 Hz, 1 H) 7.56 - 7.63 (m, 1 H) 7.48 - 7.56 (m, 1 H) 7.37 (td, *J*=7.41, 1.56 Hz, 1 H) 7.23 (br d, *J*=8.50 Hz, 1 H) 7.14 (td, *J*=7.63, 1.25 Hz, 1 H) 4.03 - 4.22 (m, 2 H) 3.75 -

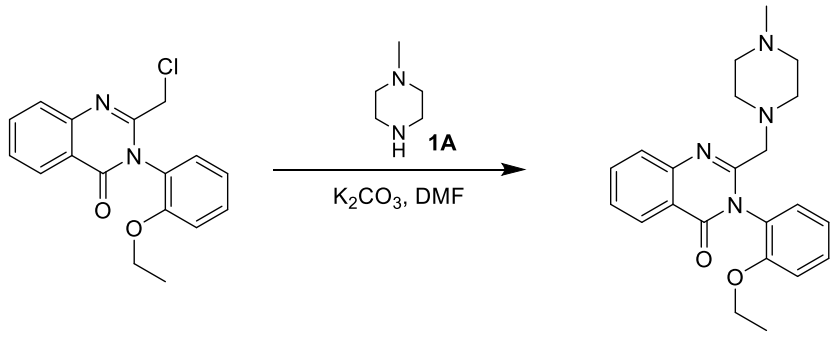
3.96 (m, 1 H) 3.37 -3.28 (m, 1 H) 3.15 - 3.24 (m, 1 H) 3.06 - 3.15 (m, 1 H) 2.74 - 3.04 (m, 3 H) 2.64 - 2.74 (m, 1 H) 2.51 - 2.64 (m, 1 H) 1.22 (td, *J*=7.00, 2.88 Hz, 3 H) 0.75 (dd, *J*=6.32, 1.69 Hz, 3 H).

^{13}C NMR (METHANOL-d_4, 101 MHz): δ ppm 162.3, 162.0, 154.9, 154.2, 154.0, 153.9, 146.6, 134.8, 129.3, 127.3, 127.2, 126.7, 126.6, 126.4, 125.4, 120.7, 120.5, 113.0, 112.9, 64.2, 64.0, 52.5, 48.5, 43.2, 43.1, 13.9, 13.8, 13.6, 13.5

LCMS (ESI+): *m*/*z* 379.2 (M+H)

HRMS (TOF MS ES+): calcd for $C_{22}H_{27}N_4O_2$ $[M+H]^+$: 379.2134 Found 379.2119

CW-2

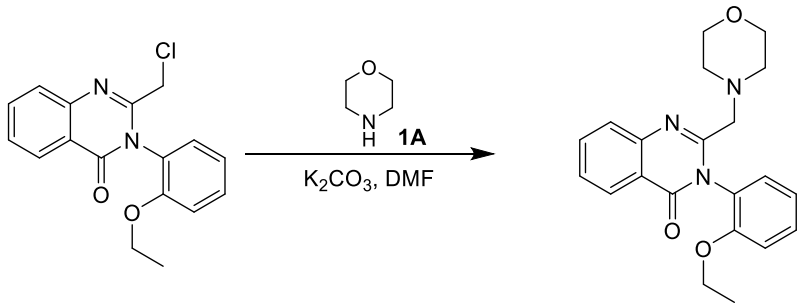


1 **CW-2**

To a solution of **Compound 1** (100 mg, 317.70 μmol) and N-methylpiperazine (**1A)** (31.82 mg, 317.70 μmol, 35.24 μL) in DMF (2 mL) was added K_2CO_3 (131.72 mg, 953.09 μmol). The mixture was stirred at 80°C for 2 hrs. LC-MS showed **Compound 1** was consumed and 32% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*3um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 40% B over 8.0 min) to afford **CW-2** (50 mg, 101.52 μmol, 31.96% yield, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.24 (dd, J = 1.1, 8.0 Hz, 1H), 7.93 - 7.86 (m, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.42 (dd, J = 1.5, 7.8 Hz, 1H), 7.24 (d, J = 7.9 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 4.21 - 4.03 (m, 2H), 3.50 - 3.35 (m, 4H), 3.15 - 2.82 (m, 6H), 2.68 - 2.47 (m, 3H), 1.21 (t, J = 7.0 Hz, 3H).**LCMS** (ESI+): *m/z* 379.2 (M+H)

CW-3



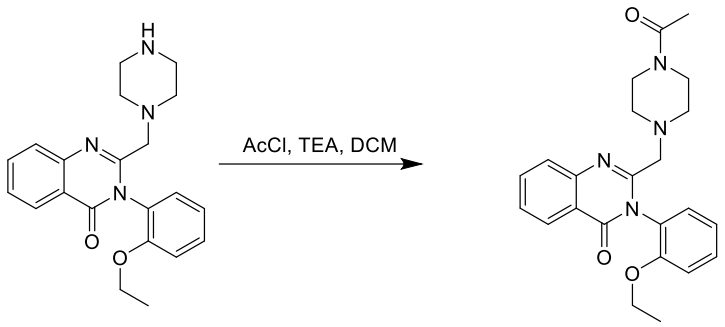
1 **CW-3**

To a solution of **Compound 1** (90 mg, 285.93 µmol) and **Compound 1A** (99.00 mg, 1.14 mmol, 0.1 mL) in DMF (2 mL) was added K_2CO_3 (118.55 mg, 857.78 µmol). The mixture was stirred at 80°C for 2 hrs. LC-MS showed **Compound 1** was consumed and 46% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*3um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 35% B over 8.0 min) to afford **CW-3** (110.49 mg, 229.74 µmol, 80.35% yield, 99.69% purity, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.21 - 8.30 (m, 1 H), 7.83 - 7.99 (m, 2 H), 7.56 - 7.69 (m, 2 H), 7.40 (dd, J=7.75, 1.50 Hz, 1 H), 7.29 (br d, J=8.50 Hz, 1 H), 7.20 (br t, J=7.63 Hz, 1 H), 4.32 (br d, J=16.88 Hz, 1 H), 4.16 - 4.24 (m, 1 H), 4.06 - 4.14 (m, 1 H), 4.05 (br s, 5 H), 3.32 - 3.69 (m, 4 H), 1.22 (t, J=6.94 Hz, 3 H)

LCMS (ESI+): *m*/*z* 366.2 (M+H)

CW-4



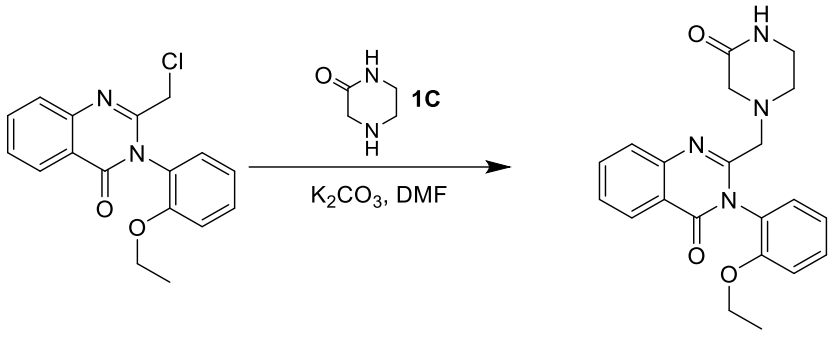
1 **CW-4**

To a solution of **Compound 1** (90 mg, 246.95 µmol; see CW-9/CW-10 below) in DCM (1 mL) was added TEA (74.97 mg, 740.86 µmol, 103.12 µL) and AcCl (38.77 mg, 493.91 µmol, 35.12 µL) at 20°C. The mixture was stirred at 20°C for 1 hr under N_2. LC-MS showed **Compound 1** was consumed and 97% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by Prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*3um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 35% B over 8.0 min) to afford **CW-4** (116.07 mg, 222.02 µmol, 89.90% yield, 99.56% purity, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.31 - 8.24 (m, 1H), 7.98 - 7.91 (m, 1H), 7.90 - 7.86 (m, 1H), 7.68 - 7.62 (m, 1H), 7.62 - 7.55 (m, 1H), 7.40 (dd, J = 1.4, 7.7 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H), 4.30 - 4.21 (m, 1H), 4.20 - 4.04 (m, 2H), 4.02 - 3.78 (m, 5H), 3.51 - 3.34 (m, 4H), 2.14 (s, 3H), 1.22 (t, J = 6.9 Hz, 3H)

LCMS (ESI+): *m*/*z* 407.2 (M+H)

CW-5



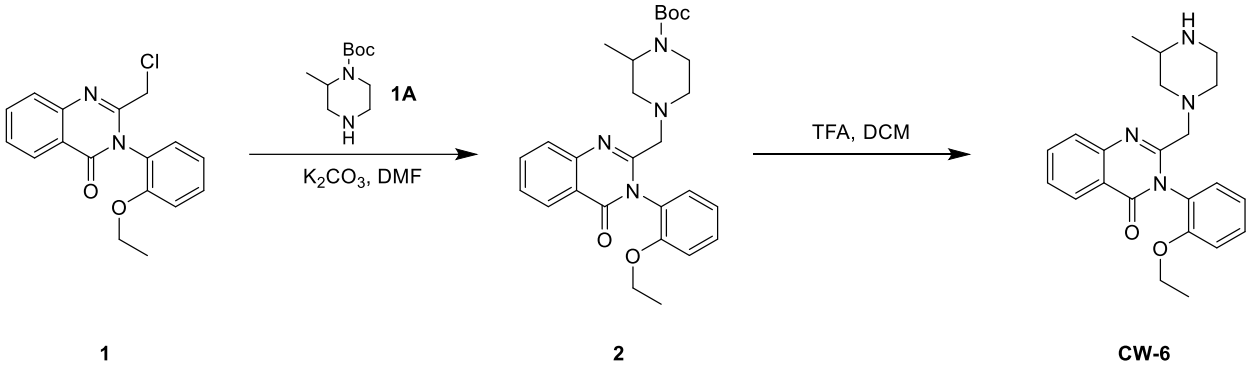
1 **CW-5**

To a solution of **Compound 1** (100 mg, 317.70 μmol) and **Compound 1C** (34.99 mg, 349.47 μmol) in DMF (2 mL) was added K_2CO_3 (131.72 mg, 953.09 μmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 1** was consumed and 22% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 35% B over 8.0 min) to afford **CW-5** (43.6 mg, 86.89 μmol, 27.35% yield, 98.14% purity, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz):δ ppm 8.22 - 8.29 (m, 1 H), 7.88 - 7.98 (m, 1 H), 7.81 - 7.86 (m, 1 H), 7.63 (t, J=7.38 Hz, 1 H), 7.52 - 7.59 (m, 1 H), 7.39 (dd, J=7.75, 1.50 Hz, 1 H), 7.25 (d, J=8.25 Hz, 1 H), 7.16 (t, J=7.57 Hz, 1 H), 4.05 - 4.19 (m, 2 H), 3.93 - 4.00 (m, 1 H), 3.80 - 3.87 (m, 1 H), 3.57 (s, 2 H), 3.45 (t, J=5.44 Hz, 2 H), 3.12 - 3.26 (m, 2 H), 1.22 (t, J=7.00 Hz, 3 H)

LCMS (ESI+): *m*/*z* 379.2 (M+H)

CW-6



1 2 CW-6

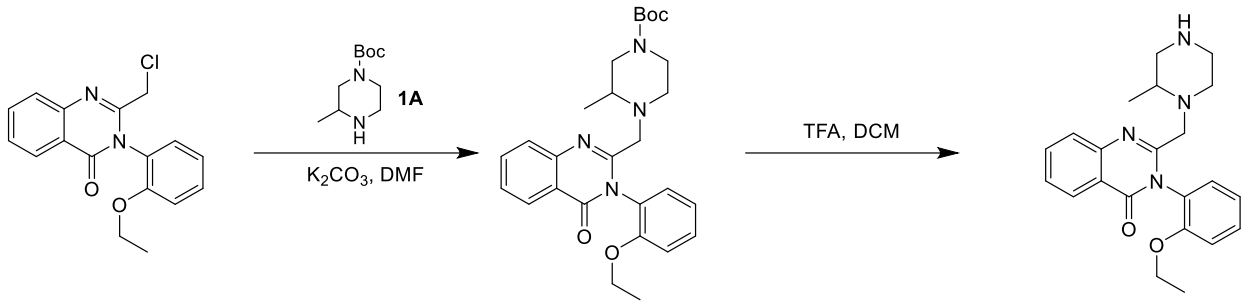
To a solution of **Compound 1** (100 mg, 317.70 µmol) and **Compound 1A** (63.63 mg, 317.70 µmol) in DMF (2 mL) was added K_2CO_3 (131.72 mg, 953.09 µmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 1** was consumed and 32% of desired compound was detected. The reaction mixture was diluted with H_2O 5 mL and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 2*** (150 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{27}H_{34}N_4O_4$ $[M+H]^+$: 479.2 Found 479.3.

To a solution of **Compound 2** (150 mg, 313.43 µmol) in DCM (2 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL). The mixture was stirred at 20°C for 1.5 hrs. LC-MS showed **Compound 2** was consumed and 50% of desired compound was detected. The reaction mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 10% - 40% B over 8.0 min). The LCMS purity was not high enough, then the residue was purified by Prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [H_2O (10mM NH_4HCO_3) - ACN]; gradient: 10% - 50% B over 8.0 min) to afford **CW-6** (29.24 mg, 59.37 µmol, 18.94% yield, 100% purity, TFA salt) as a colorless gum.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.22 (d, J=8.00 Hz, 1 H), 7.83 - 7.95 (m, 1 H), 7.77 (d, J=8.13 Hz, 1 H), 7.58 (t, J=7.57 Hz, 1 H), 7.49 (t, J=7.88 Hz, 1 H), 7.36 (d, J=7.63 Hz, 1 H), 7.18 (d, J=8.25 Hz, 1 H), 7.06 - 7.15 (m, 1 H), 4.01 - 4.16 (m, 2 H), 3.32 - 3.39 (m, 1 H), 3.16 - 3.27 (m, 1 H), 2.71 - 2.80 (m, 1 H), 2.57 - 2.71 (m, 2 H), 2.47 (br d, J=11.01 Hz, 1 H), 2.29 - 2.38 (m, 1 H), 1.96 - 2.07 (m, 1 H), 1.69 (td, J=10.47, 4.19 Hz, 1 H), 1.20 (t, J=6.94 Hz, 3 H), 0.92 (d, J=6.50 Hz, 3 H)

LCMS (ESI+): *m*/*z* 379.2 (M+H)

CW-7



1 **2** **CW-7**

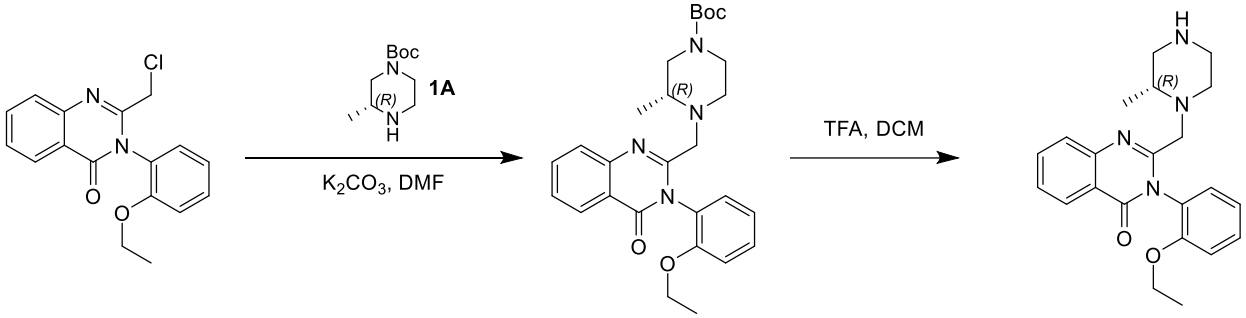
To a solution of **Compound 1** (100.00 mg, 317.70 μmol) and **Compound 1A** (63.63 mg, 317.70 μmol) in DMF (2 mL) was added K_2CO_3 (131.72 mg, 953.09 μmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed 4% of **Compound 1** was remained and 13% of desired compound was detected. The reaction mixture was diluted with H_2O 5 mL and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 20% Ethyl acetate/Petroleum ether gradient @ 50 mL/min) to afford ***Compound 2*** (80 mg, 167.16 μmol, 52.62% yield) as a yellow oil. MS-ESI (m/z) calcd for $C_{27}H_{34}N_4O_4$ $[M+H]^+$: 479.2 Found 479.4.

To a solution of **Compound 2** (80 mg, 167.16 μmol) in DCM (1 mL) was added TFA (307.00 mg, 2.69 mmol, 0.2 mL). The mixture was stirred at 20°C for 1 hr. LC-MS showed **Compound 2** was consumed and 35% of desired compound was detected. The reaction mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (column: WePure Biotech XP tC18 150*40*7um; mobile phase: [H_2O (10mM NH_4HCO_3) - ACN]; gradient: 10% - 40% B over 8.0 min) to afford **CW-7** (4.98 mg, 9.81 μmol, 5.87% yield, 97.0% purity, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz):δ ppm 8.22 (br d, J=7.88 Hz, 1 H), 7.83 - 7.91 (m, 1 H), 7.77 (br d, J=8.13 Hz, 1 H), 7.57 (br t, J=7.44 Hz, 1 H), 7.49 (br t, J=7.82 Hz, 1 H), 7.27 - 7.38 (m, 1 H), 7.15 - 7.23 (m, 1 H), 7.06 - 7.15 (m, 1 H), 4.02 - 4.19 (m, 2 H), 3.67 - 3.95 (m, 1 H), 3.02 - 3.22 (m, 1 H), 2.57 - 2.89 (m, 4 H), 2.12 - 2.42 (m, 3 H), 1.13 - 1.27 (m, 3 H), 0.54 - 0.65 (m, 3 H)

LCMS (ESI+): *m*/*z* 379.3 (M+H)

CW-8



To a solution of **Compound 1** (100 mg, 317.70 µmol) and **Compound 1A** (95.44 mg, 476.55 µmol) in DMF (2 mL) was added K_2CO_3 (131.72 mg, 953.09 µmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 1** was consumed and 34% of desired compound was detected. The reaction mixture was diluted with H_2O 3 mL and extracted with EtOAc (3 mL * 3). The combined organic layers were washed with brine (3 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 2*** (150 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{27}H_{34}N_4O_4$ $[M+H]^+$: 479.3 Found 479.3.

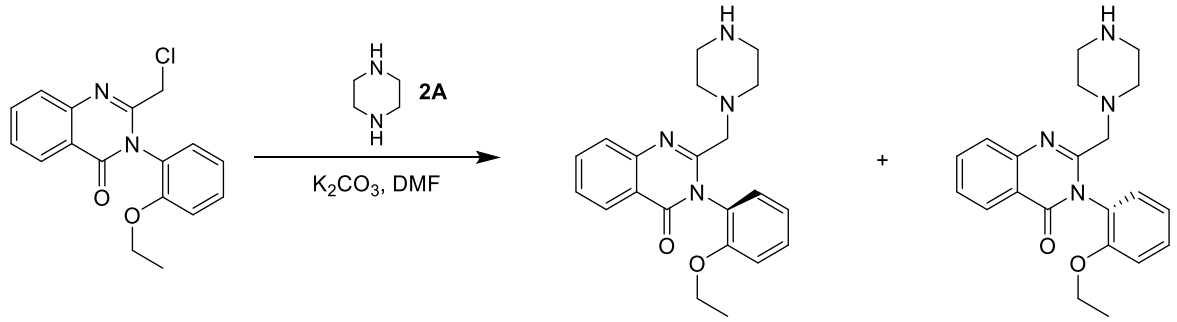
To a solution of **Compound 2** (150 mg, 313.43 µmol) in DCM (2 mL) was added TFA (714.76 mg, 6.27 mmol, 465.64 µL). The mixture was stirred at 20°C for 1 hr. LC-MS showed **Compound 2** was consumed and 74% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by Prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 40% B over 8.0 min) to afford **CW-8** (80.56 mg, 156.84 µmol, 50.04% yield, 95.88% purity, TFA salt) as a pale yellow gum.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.27 - 8.19 (m, 1H), 7.94 - 7.84 (m, 1H), 7.79 (dd, J = 3.3, 8.1 Hz, 1H), 7.63 - 7.56 (m, 1H), 7.56 - 7.49 (m, 1H), 7.37 (dt, J = 1.4, 7.5 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.18 - 7.10 (m, 1H), 4.21 - 4.05 (m, 2H), 3.99 - 3.75 (m, 1H), 3.41 - 3.33 (m, 1H), 3.25 - 3.17 (m, 1H), 3.12 (br d, J = 11.4 Hz, 1H), 3.05 - 2.94 (m, 2H), 2.94 - 2.84 (m, 1H), 2.79 - 2.68 (m, 1H), 2.66 - 2.53 (m, 1H), 1.22 (dt, J = 2.9, 6.9 Hz, 3H), 0.77 (dd, J = 1.9, 6.4 Hz, 3H)

^{13}C NMR (METHANOL-d_4, 101 MHz): δ ppm 162.3, 162.0, 154.9, 153.9, 146.6, 134.9, 134.8, 130.9, 130.8, 129.3, 127.4, 127.3, 126.7, 126.5, 126.4, 120.7, 113.0, 112.9, 64.2, 64.1, 52.8, 52.6, 48.5, 43.1, 13.9, 13.8, 13.6, 13.5

LCMS (ESI+): *m/z* 379.2 (M+H)
HRMS (TOF MS ES+): calcd for $C_{22}H_{27}N_4O_2$ $[M+H]^+$: 379.2134 Found 379.2119

CW-9 & CW-10



2 **CW-9** **CW-10**

To a solution of **Compound 2** (100 mg, 317.70 µmol) and **Compound 2A** (27.36 mg, 317.70 µmol) in DMF (2 mL) was added K_2CO_3 (131.72 mg, 953.09 µmol). The mixture was stirred at 80°C for 2 hrs. LC-MS showed **Compound 2** was consumed and 29% of desired compound was detected. The reaction mixture was filtered. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5%-38% B over 8.0 min). The residue was purified by SFC (column: REGIS (s, s) WHELK-O1 (250mm*30mm, 5um); mobile phase: [CO_2-EtOH (0.1% NH_3H_2O)]; B%:50%, isocratic elution mode) to afford **CW-10** (15.2 mg, 41.25 µmol, 75.17% yield, 98.91% purity) as a pale yellow solid and **CW-9** (13.9 mg, 37.63 µmol, 68.56% yield, 98.65% purity) as a pale yellow solid.

CW-9 spectra

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.23 (dd, *J*=8.00, 1.00 Hz, 1 H) 7.84 - 7.95 (m, 1 H) 7.77 (d, *J*=7.75 Hz, 1 H) 7.54 - 7.63 (m, 1 H) 7.45 - 7.53 (m, 1 H) 7.31 - 7.40 (m, 1 H) 7.15 - 7.24 (m, 1 H) 7.11 (td, *J*=7.63, 1.13 Hz, 1 H) 3.95 - 4.24 (m, 2 H) 3.32 - 3.38 (m, 1 H) 3.19 - 3.26 (m, 1 H) 2.54 - 2.81 (m, 4 H) 2.14 - 2.41 (m, 4 H) 1.20 (t, *J*=6.94 Hz, 3 H)

LCMS (ESI+): *m*/*z* 365.2 (M+H)

Specific Rotation: $[a]^{20\ ^\circ C}_{589\ nm}$ = -80.2° ± 3.6 (c = 0.0640 g/100 mL, methanol)

CW-10 spectra

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.18 - 8.28 (m, 1 H) 7.83 - 7.92 (m, 1 H) 7.73 - 7.80 (m, 1 H) 7.55 - 7.61 (m, 1 H) 7.45 - 7.54 (m, 1 H) 7.37 (dd, J=7.69, 1.56 Hz, 1 H) 7.19 (d, J=8.25 Hz, 1 H) 7.11 (t, J=7.63 Hz, 1 H) 4.03 - 4.16 (m, 2 H) 3.33 - 3.38 (m, 1 H) 3.20 - 3.25 (m, 1 H) 2.63 - 2.75 (m, 4 H) 2.16 - 2.39 (m, 4 H) 1.20 (t, J=7.00 Hz, 3 H)

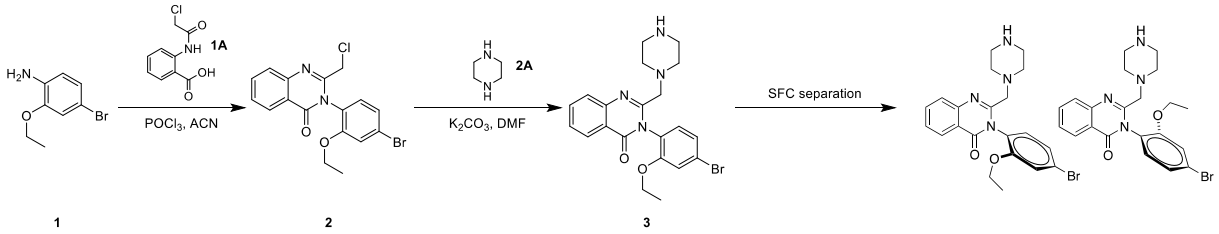
^{13}C NMR (METHANOL-d_4, 101 MHz) δ ppm 162.4, 154.3, 146.9, 134.7, 130.6, 129.8, 127.1, 126.7, 126.3, 125.3, 120.7, 120.2, 112.5, 63.9, 52.9, 48.2, 44.6, 13.6

LCMS (ESI+): *m*/*z* 365.2 (M+H)

HRMS (TOF MS ES+): calcd for $C_{21}H_{25}N_4O_2$ $[M+H]^+$: 365.1977 Found 365.1972.

Specific Rotation: $[a]^{20\ ^\circ C}_{589\ nm}$ = +83.2° ± 2.3 (c = 0.1010 g/100 mL, methanol)

CW-11 and CW-12



To a solution of **Compound 1** (300 mg, 1.39 mmol) and **Compound 1A** (296.59 mg, 1.39 mmol) in ACN (5 mL) was added $POCl_3$ (1.06 g, 6.94 mmol, 647.08 µL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 1** was consumed and 23% of desired compound was detected. The reaction mixture was diluted with $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (10 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 15% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to afford ***Compound 2*** (280 mg, 711.27 µmol, 51.23% yield) as a yellow solid. MS-ESI (m/z) calcd for $C_{17}H_{14}BrClN_2O_2$ $[M+H]^+$: 395.0/393.0 Found 395.1/393.1. To a solution of **Compound 2** (280 mg, 711.27 µmol) and **Compound 2A** (122.53 mg, 1.42 mmol) in DMF (4 mL) was added K_2CO_3 (294.90 mg, 2.13 mmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 2** was consumed and 40% of desired compound was detected. The reaction mixture was filtered. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 10% - 45% B over 8.0 min) to afford ***Compound 3*** (270 mg, 484.43 µmol, 68.11% yield, 100% purity) as a white solid. MS-ESI (m/z) calcd for $C_{21}H_{23}BrN_4O_2$ $[M+H]^+$: 443.1/445.1 Found 443.2/445.2. **Compound 3** (200 mg) was separated by SFC (column: REGIS (s,s) WHELK-O1 (250mm*30mm, 5um); mobile phase: [CO_2 - EtOH (0.1% NH_3H_2O)]; B%: 50%, isocratic elution mode) to afford ***CW-11*** (73.56 mg, 165.66 µmol, 36.72% yield, 99.84% purity) as a white solid.

^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 8.22 (d, J=8.00 Hz, 1 H) 7.84 - 7.93 (m, 1 H) 7.76 (d, J=8.13 Hz, 1 H) 7.58 (t, J=7.57 Hz, 1 H) 7.36 - 7.39 (m, 1 H) 7.35 (br d, J=1.75 Hz, 2 H) 3.99 - 4.19 (m, 2 H) 3.37 (d, J=13.88 Hz, 1 H) 3.14 - 3.28 (m, 1 H) 2.67 (t, J=4.82 Hz, 4 H) 2.15 - 2.35 (m, 4 H) 1.15 - 1.23 (m, 3 H)

LCMS (ESI+): *m*/*z* 443.2/445.2 (M+H)

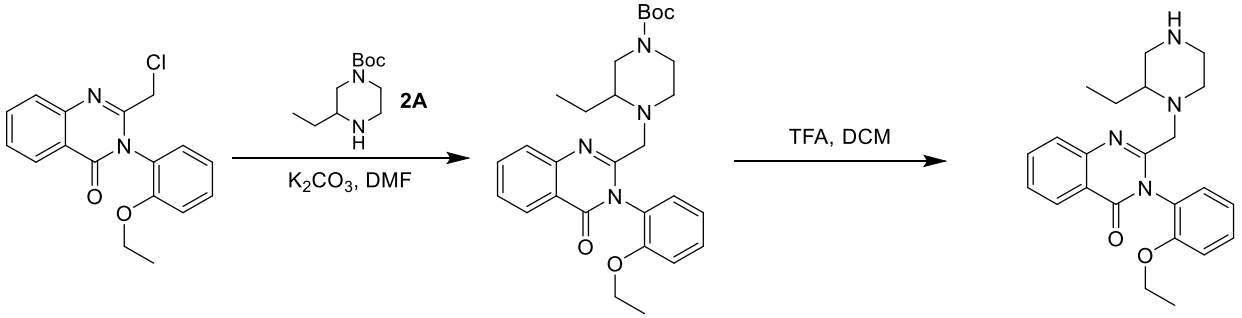
CW-12 (62.49 mg, 140.67 µmol, 31.18% yield, 99.80% purity) as a white solid.

^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 8.15 - 8.26 (m, 1 H) 7.82 - 7.93 (m, 1 H) 7.76 (d, J=8.13 Hz, 1 H) 7.58 (td, J=7.57, 1.25 Hz, 1 H) 7.34 - 7.39 (m, 1 H) 7.24 - 7.34 (m, 2 H) 4.01 - 4.17 (m, 2 H) 3.35 - 3.40 (m, 1 H) 3.17 - 3.26 (m, 1 H) 2.55 - 2.76 (m, 4 H) 2.17 - 2.35 (m, 4 H) 1.20 (t, J=6.94 Hz, 3 H)

LCMS (ESI+): *m*/*z* 443.2/445.2 (M+H)

The absolute configuration of CW-11 and CW-12 is uncertain.

CW-13



2 **3** **CW-13**

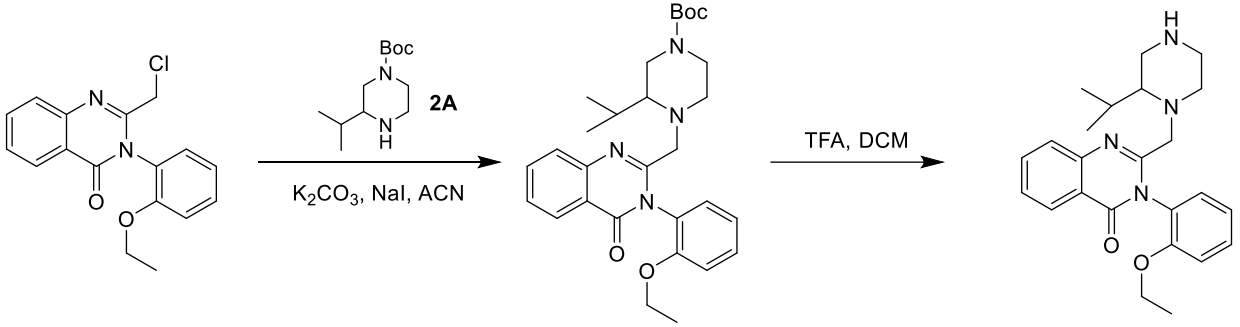
To a solution of **Compound 2** (100 mg, 317.70 μmol) and **Compound 2A** (68.08 mg, 317.70 μmol) in DMF (2 mL) was added K_2CO_3 (131.72 mg, 953.09 μmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 2** was consumed and 25% of desired compound was detected. The reaction mixture was diluted with H_2O 5 mL and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 20% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to afford ***Compound 3*** (70 mg, 142.10 μmol, 44.73% yield) as a pale yellow oil. MS-ESI (m/z) calcd for $C_{28}H_{36}N_4O_4$ $[M+H]^+$: 493.3 Found 493.33.

To a solution of **Compound 3** (70 mg, 142.10 μmol) in DCM (1 mL) was added TFA (614.00 mg, 5.38 mmol, 0.4 mL). The mixture was stirred at 20°C for 1 hr. LC-MS showed **Compound 3** was consumed and 76% of desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 10% - 40% B over 8.0 min) to afford ***CW-13*** (34.31 mg, 66.55 μmol, 46.83% yield, 98.24% purity, TFA salt) as a colourless gum.

^{1}H NMR (METHANOL-*d*$_4$, 400 MHz): δ ppm 8.23 (d, J=8.00 Hz, 1 H), 7.83 - 7.94 (m, 1 H), 7.78 (br d, J=8.38 Hz, 1 H), 7.49 - 7.62 (m, 2 H), 7.37 (ddd, J=7.69, 4.57, 1.63 Hz, 1 H), 7.24 (d, J=8.25 Hz, 1 H), 7.15 (tdd, J=7.61, 7.61, 2.22, 1.06 Hz, 1 H), 4.01 - 4.22 (m, 2 H), 3.67 - 3.88 (m, 1 H), 3.35 - 3.55 (m, 1 H), 3.10 - 3.21 (m, 2 H), 2.88 - 3.07 (m, 2 H), 2.53 - 2.86 (m, 3 H), 1.41 - 1.58 (m, 1 H), 1.10 - 1.30 (m, 4 H), 0.68 - 0.81 (m, 3 H)

LCMS (ESI+): *m*/*z* 393.1 (M+H)

CW-14



2 **3A** **CW-14**

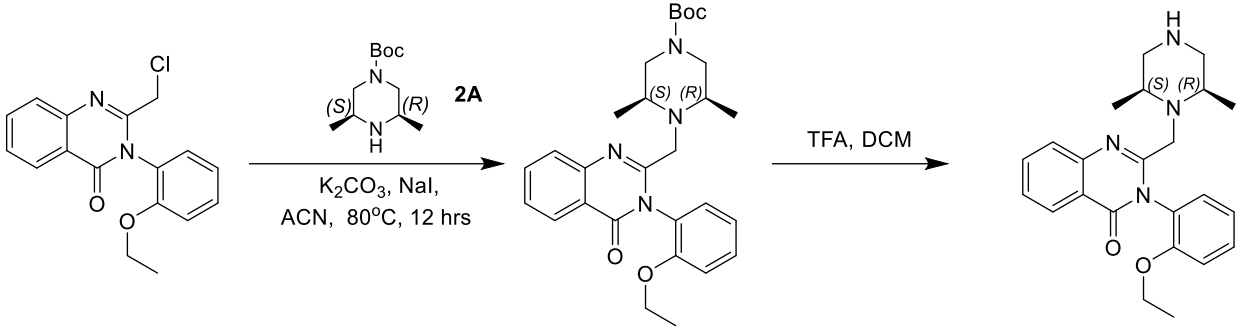
To a solution of **Compound 2** (80 mg, 254.16 µmol) and **Compound 2A** (69.64 mg, 304.99 µmol) in ACN (1 mL) was added NaI (7.62 mg, 50.83 µmol) and K_2CO_3 (105.38 mg, 762.47 µmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 2** was consumed and 67% of desired compound was detected. The reaction mixture was diluted with H_2O 5 mL and extracted with EtOAc (5 mL * 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 3A*** (100 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{29}H_{38}N_4O_4$ $[M+H]^+$: 507.3 Found 507.3.

To a solution of **Compound 3A** (100 mg, 197.38 µmol) in DCM (1 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL). The mixture was stirred at 20°C for 2 hrs. LC-MS showed **Compound 3A** was consumed and 68% of desired compound was detected. The reaction mixture was filtered. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 40% B over 8.0 min) to afford **CW-14** (86.79 mg, 166.73 µmol, 84.47% yield, 100% purity, TFA salt) as a pale yellow gum.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.22 (d, J=7.88 Hz, 1 H), 7.83 - 7.96 (m, 1 H), 7.77 (d, J=8.00 Hz, 1 H), 7.48 - 7.63 (m, 2 H), 7.35 (ddd, J=17.48, 7.72, 1.31 Hz, 1 H), 7.24 (dd, J=8.25, 4.25 Hz, 1 H), 7.15 (td, J=7.54, 3.44 Hz, 1 H), 3.99 - 4.21 (m, 2 H), 3.44 - 3.82 (m, 2 H), 3.33 - 3.42 (m, 1 H), 3.12 - 3.29 (m, 2 H), 2.55 - 3.04 (m, 4 H), 2.10 - 2.32 (m, 1 H), 1.22 (q, J=6.96 Hz, 3 H), 0.91 (dd, J=6.88, 3.00 Hz, 3 H), 0.65 (dd, J=14.38, 6.88 Hz, 3 H)

LCMS (ESI+): *m*/*z* 407.2 (M+H)

CW-15



2 **4** **CW-15**

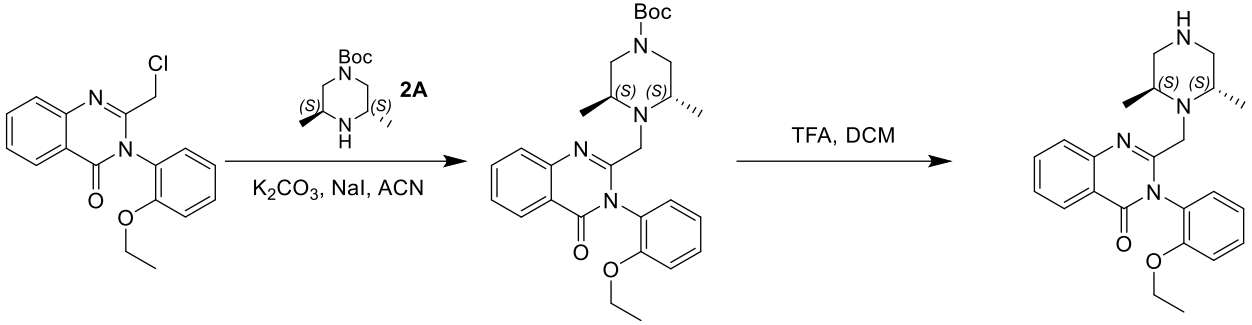
To a solution of **Compound 2** (90 mg, 285.93 μmol) and **Compound 2A** (73.53 mg, 343.11 μmol) in ACN (2 mL) was added NaI (8.57 mg, 57.19 μmol) and K_2CO_3 (118.55 mg, 857.78 μmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 2** was consumed and 54% of desired compound was detected. The reaction mixture was diluted with H_2O 10 mL and extracted with EtOAc (10 mL * 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 4*** (100 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{28}H_{36}N_4O_4$ $[M+H]^+$: 493.3 Found 493.3.

To a solution of **Compound 4** (100 mg, 203.00 μmol) in DCM (1 mL) was added TFA (307.00 mg, 2.69 mmol, 0.2 mL). The mixture was stirred at 20°C for 3 hrs. LC-MS showed 19% of **Compound 4** was remained and 35% of desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 40% B over 8.0 min) to afford **CW-15** (21.7 mg, 42.50 μmol, 20.94% yield, 99.20% purity, TFA salt) as a pale yellow gum.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.22 (d, J=7.13 Hz, 1 H), 7.84 - 7.92 (m, 1 H), 7.74 - 7.83 (m, 1 H), 7.50 - 7.61 (m, 2 H), 7.33 (br d, J=7.75 Hz, 1 H), 7.26 (d, J=8.25 Hz, 1 H), 7.16 (t, J=7.57 Hz, 1 H), 4.03 - 4.19 (m, 2 H), 3.88 - 4.02 (m, 2 H), 3.62 - 3.87 (m, 2 H), 3.17 - 3.29 (m, 2 H), 2.67 - 2.83 (m, 2 H), 1.22 (t, J=6.94 Hz, 3 H), 1.05 - 1.17 (m, 6 H)

LCMS (ESI+): *m/z* 393.2 (M+H)

CW-16



2 **3** **CW-16**

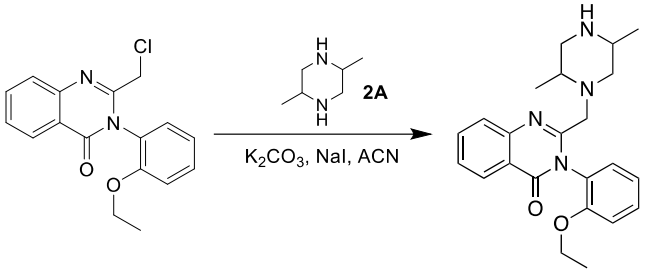
To a solution of **Compound 2** (80 mg, 254.16 μmol) and **Compound 2A** (65.36 mg, 304.99 μmol) in ACN (1 mL) was added NaI (7.62 mg, 50.83 μmol) and K_2CO_3 (105.38 mg, 762.47 μmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 2** was consumed and 73% of desired compound was detected. The reaction mixture was diluted with H_2O 10 mL and extracted with EtOAc (10 mL * 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 3*** (100 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{28}H_{36}N_4O_4$ $[M+H]^+$: 493.3 Found 493.3.

To a solution of **Compound 3** (100 mg, 203.00 μmol) in DCM (1 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL). The mixture was stirred at 20°C for 2 hrs. LC-MS showed **Compound 3** was consumed and 70% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 40% B over 8.0 min) to afford **CW-16** (44.16 mg, 87.10 μmol, 42.90% yield, 99.90% purity, TFA salt) as a pale yellow gum.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.23 (br d, J=7.88 Hz, 1 H), 7.84 - 7.94 (m, 1 H), 7.71 - 7.83 (m, 1 H), 7.59 (td, J=7.35, 3.94 Hz, 1 H), 7.47 - 7.56 (m, 1 H), 7.33 - 7.43 (m, 1 H), 7.23 (d, J=8.38 Hz, 1 H), 7.15 (t, J=7.57 Hz, 1 H), 4.00 - 4.25 (m, 2 H), 3.77 - 3.98 (m, 1 H), 3.77 (br s, 1 H), 2.88 - 3.13 (m, 4 H), 2.75 (br d, J=6.75 Hz, 2 H), 1.22 (dt, J=9.60, 7.02 Hz, 3 H), 0.92 (br d, J=5.75 Hz, 6 H)

LCMS (ESI+): *m*/*z* 393.2 (M+H)

CW-17



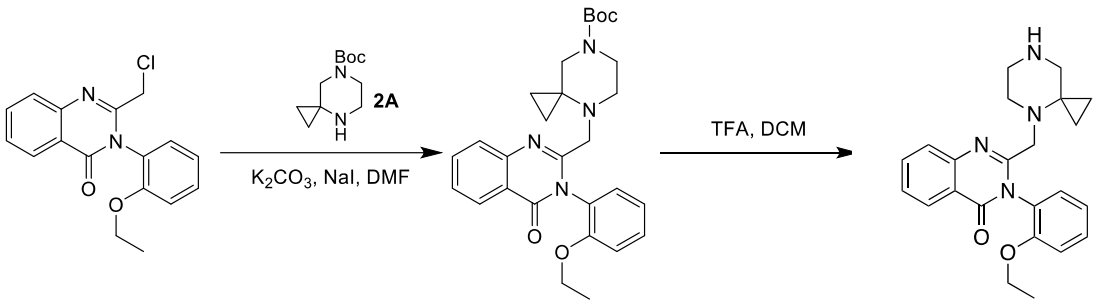
2

To a solution of **Compound 2** (60 mg, 190.62 μmol) and **Compound 2A** (26.12 mg, 228.74 μmol) in ACN (1 mL) was added K_2CO_3 (79.03 mg, 571.85 μmol) and NaI (5.71 mg, 38.12 μmol). The mixture was stirred at 80°C for 1 hr. LC-MS and HPLC showed **Compound 2** was consumed and 42% of desired compound was detected. The reaction mixture was filtered. The residue was purified by Prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 10% - 40% B over 8.0 min) to afford ***CW-17*** (33.21 mg, 65.26 μmol, 34.23% yield, 99.53% purity, TFA) as a white solid.

^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 8.27 - 8.19 (m, 1H), 7.93 - 7.85 (m, 1H), 7.78 (br d, J = 8.3 Hz, 1H), 7.63 - 7.48 (m, 2H), 7.44 - 7.32 (m, 1H), 7.26 - 7.19 (m, 1H), 7.18 - 7.10 (m, 1H), 4.21 - 4.03 (m, 2H), 4.00 - 3.78 (m, 1H), 3.65 - 3.37 (m, 1H), 3.26 (br d, J = 14.8 Hz, 1H), 3.17 - 3.11 (m, 1H), 2.99 - 2.65 (m, 2H), 2.60 - 2.38 (m, 2H), 1.36 - 1.10 (m, 6H), 1.03 - 0.65 (m, 3H)

LCMS (ESI+): *m*/*z* 393.2 (M+H)

CW-18



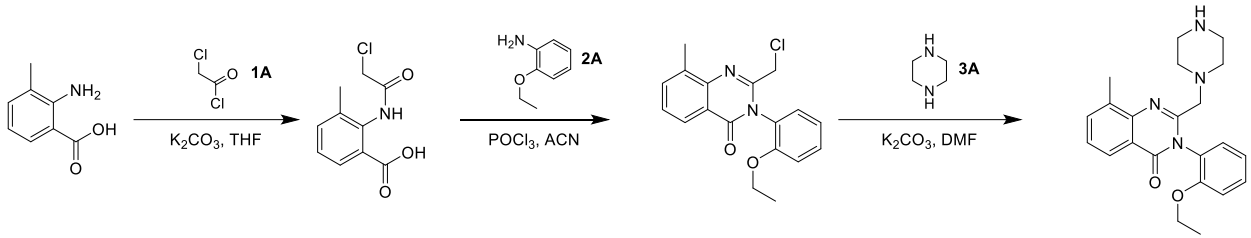
To a solution of **Compound 2** (100 mg, 317.70 μmol) and **Compound 2A** (80.93 mg, 381.24 μmol) in DMF (2 mL) was added K_2CO_3 (131.73 mg, 953.09 μmol) and NaI (4.76 mg, 31.77 μmol). The mixture was stirred at 50°C for 1 hr. LC-MS showed **Compound 2** was consumed and 33% of desired compound was detected. The reaction mixture was diluted with H_2O (2 mL) and extracted with EtOAc (2 mL * 3). The combined organic layers were washed with brine (3 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 3*** (120 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{28}H_{34}N_4O_4$ $[M+H]^+$: 491.3 Found 491.3. To a solution of **Compound 3** (120 mg, 244.60 μmol) in DCM (1 mL) was added TFA (557.79 mg, 4.89 mmol, 363.38 μL). The mixture was stirred at 20°C for 1 hr. LC-MS and HPLC showed **Compound 3** was consumed and 53% of desired compound was detected. The reaction mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 40% B over 8.0 min) to afford ***CW-18*** (46.04 mg, 86.26 μmol, 35.26% yield, 94.52% purity, TFA) as a yellow solid.

Spectrum:

^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 8.22 (d, J = 8.0 Hz, 1H), 7.94 - 7.86 (m, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.56 - 7.49 (m, 1H), 7.27 (dd, J = 1.4, 7.6 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.13 - 7.07 (m, 1H), 4.06 (q, J = 6.9 Hz, 2H), 3.92 - 3.72 (m, 2H), 3.26 - 3.15 (m, 2H), 3.07 - 2.87 (m, 4H), 1.21 (t, J = 7.0 Hz, 3H), 0.44 (br s, 2H), 0.05 (br s, 2H)

LCMS (ESI+): *m*/*z* 391.2 (M+H)

CW-19



To a solution of **Compound 1** (500 mg, 3.31 mmol) and **Compound 1A** (410.94 mg, 3.64 mmol, 289.80 µL) in THF (5 mL) was added K_2CO_3 (1.37 g, 9.92 mmol). The mixture was stirred at 70°C for 1 hr. LC-MS showed **Compound 1** was consumed and 72% of desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to remove solvent to afford ***Compound 2*** (1 g, crude) as a black solid. MS-ESI (m/z) calcd for $C_{10}H_{10}ClNO_3$ $[M+H]^+$: 228.0/230.0 Found 228.1/230.1.

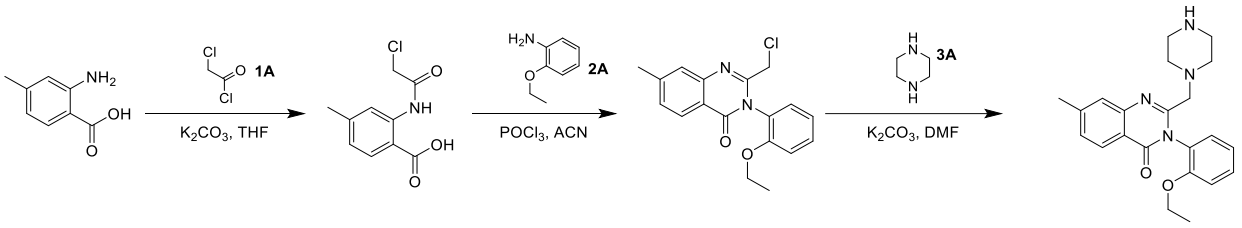
To a solution of **Compound 2** (500 mg, 2.20 mmol) and **Compound 2A** (301.30 mg, 2.20 mmol, 287.50 µL) in ACN (10 mL) was added $POCl_3$ (1.01 g, 6.59 mmol, 614.19 µL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 2** was consumed and 34% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The reaction mixture was diluted with saturated $NaHCO_3$ solution 20 mL and extracted with EtOAc (20 mL * 3), the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 10% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to afford ***Compound 3*** (400 mg, 1.22 mmol, 55.39% yield) as a yellow solid. MS-ESI (m/z) calcd for $C_{18}H_{17}ClN_2O_2$ $[M+H]^+$: 329.1/331.1 Found 328.9/330.9.

To a solution of **Compound 3** (150 mg, 456.22 µmol) in DMF (1 mL) was added K_2CO_3 (189.16 mg, 1.37 mmol) and **Compound 3A** (78.59 mg, 912.43 µmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 3** was consumed and 32% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 10%-40% B over 8.0 min) to afford **CW-19** (143.55 mg, 291.30 µmol, 63.85% yield, 99.94% purity, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.02 - 8.10 (m, 1 H), 7.73 (d, J=6.75 Hz, 1 H), 7.49 - 7.57 (m, 1 H), 7.45 (t, J=7.63 Hz, 1 H), 7.39 (dd, J=7.75, 1.63 Hz, 1 H), 7.23 (d, J=8.25 Hz, 1 H), 7.14 (td, J=7.60, 1.06 Hz, 1 H), 4.02 - 4.21 (m, 2 H), 3.44 - 3.59 (m, 2 H), 3.08 - 3.21 (m, 4 H), 2.67 - 2.94 (m, 4 H), 2.61 - 2.67 (m, 3 H), 1.21 (t, J=7.00 Hz, 3 H)

LCMS (ESI+): *m/z* 379.2 (M+H)

CW-20



To a solution of **Compound 1** (1 g, 6.62 mmol) and **Compound 1A** (821.88 mg, 7.28 mmol, 579.60 µL) in THF (20 mL) was added K_2CO_3 (2.74 g, 19.85 mmol). The mixture was stirred at 70°C for 1 hr. LC-MS showed **Compound 1** was consumed and 96% of desired compound was detected. The reaction mixture was filtered and the filtrate was dried under vacuum to afford ***Compound 2*** (1.42 g, crude) as a yellow solid. MS-ESI (m/z) calcd for $C_{10}H_{10}ClNO_3$ $[M+H]^+$: 228.0/230.0 Found 227.8/229.6.

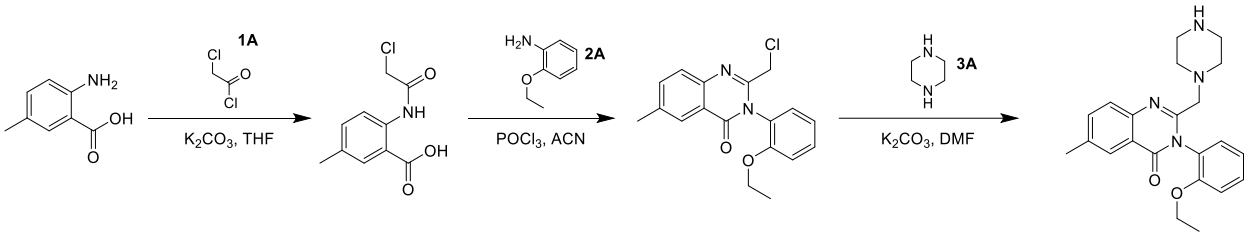
To a solution of **Compound 2** (700 mg, 3.07 mmol) and **Compound 2A** (421.82 mg, 3.07 mmol, 402.50 µL) in ACN (20 mL) was added $POCl_3$ (1.41 g, 9.22 mmol, 859.87 µL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 2** was consumed and 37% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with EtOAc 10 mL and then was poured into saturated Na_2CO_3 solution to pH = 8 ~ 9, the mixture was extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @80 mL/min) to afford ***Compound 3*** (500 mg, 1.49 mmol, 48.47% yield, 98% purity) as a yellow solid. MS-ESI (m/z) calcd for $C_{18}H_{17}ClN_2O_2$ $[M+H]^+$:329.1/331.0 Found 329.1/331.1.

To a solution of **Compound 3** (200 mg, 608.29 µmol) and **Compound 3A** (62.87 mg, 729.94 µmol) in DMF (2 mL) was added K_2CO_3 (252.21 mg, 1.82 mmol). The mixture was stirred at 80°C for 1 hr. LC-MS and HPLC showed **Compound 3** was consumed and 27% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 10% - 40% B over 8.0 min) to afford **CW-20** (99.35 mg, 197.33 µmol, 32.44% yield, 97.82% purity, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.12 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 7.56 - 7.48 (m, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.39 (dd, J = 1.4, 7.7 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.14 (dt, J = 0.9, 7.6 Hz, 1H), 4.24 - 3.98 (m, 2H), 3.52 - 3.37 (m, 2H), 3.10 (br d, J = 4.6 Hz, 4H), 2.67 (br dd, J = 4.6, 12.2 Hz, 2H), 2.55 (s, 5H), 1.21 (t, J = 7.0 Hz, 3H)

LCMS (ESI+): *m/z* 379.2 (M+H)

CW-21



To a solution of **Compound 1** (1 g, 6.62 mmol) in THF (20 mL) was added K_2CO_3 (2.74 g, 19.85 mmol) was added **Compound 1A** (821.88 mg, 7.28 mmol, 579.60 µL) at 20°C. The mixture was stirred at 70°C for 1 hr. LC-MS showed **Compound 1** was consumed and 97% of desired compound was detected. The reaction mixture was filtered to afford ***Compound 2*** (1.4 g, crude) as a yellow solid. MS-ESI (m/z) calcd for $C_{10}H_{10}ClNO_3$ $[M+H]^+$:228.0/230.0 Found 227.8/230.0.

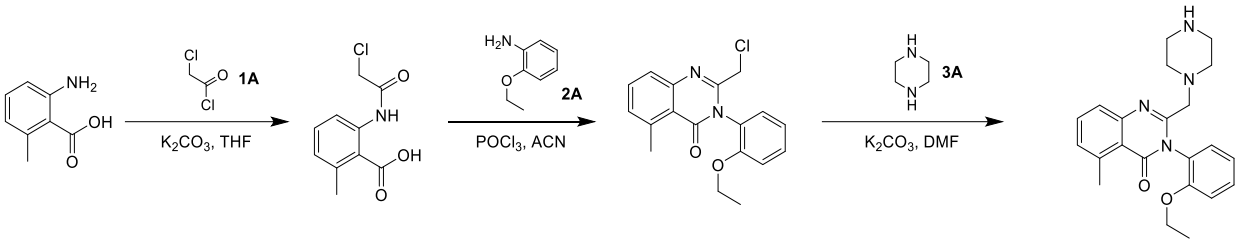
To a solution of **Compound 2** (700 mg, 3.07 mmol) and **Compound 2A** (464.00 mg, 3.38 mmol, 442.75 µL) in ACN (10 mL) was added $POCl_3$ (1.41 g, 9.22 mmol, 859.87 µL). The mixture was stirred at 80°C for 7 hrs. LC-MS showed **Compound 2** was consumed and 39% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with EtOAc 10 mL and then was poured into saturated Na_2CO_3 solution to pH = 8 ~ 9, the mixture was extracted with EtOAc (10 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to afford ***Compound 3*** (450 mg, 1.34 mmol, 43.62% yield, 98% purity) as a yellow solid. MS-ESI (m/z) calcd for $C_{18}H_{17}ClN_2O_2$ $[M+H]^+$: 329.1/331.0 Found 329.1/331.0.

To a solution of **Compound 3** (150 mg, 456.22 µmol) and **Compound 3A** (47.16 mg, 547.46 µmol) in DMF (2 mL) was added K_2CO_3 (189.15 mg, 1.37 mmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 3** was consumed and 64% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient; 10% - 40% B over 8.0 min) to afford **CW-21** (123.62 mg, 250.63 µmol, 54.94% yield, 99.85% purity, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.03 (s, 1H), 7.79 - 7.66 (m, 2H), 7.53 (t, J = 7.9 Hz, 1H), 7.40 (dd, J = 1.3, 7.8 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 4.29 - 3.95 (m, 2H), 3.61 - 3.41 (m, 2H), 3.22 - 3.08 (m, 4H), 2.86 - 2.57 (m, 4H), 2.51 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H)

LCMS (ESI+): *m/z* 379.2 (M+H)

CW-22



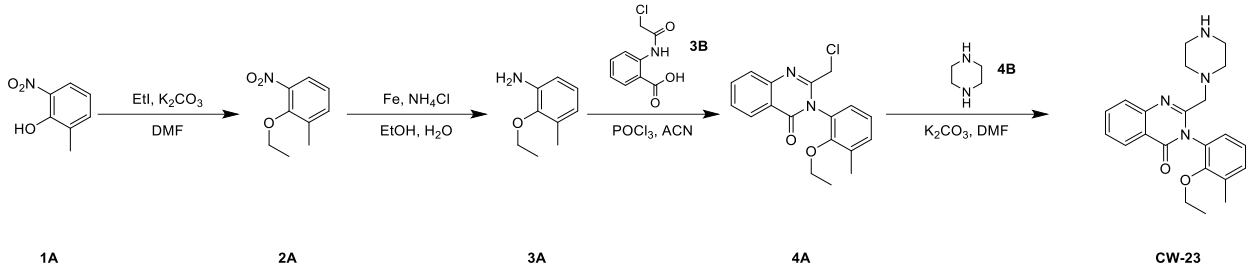
To a solution of **Compound 1** (500 mg, 3.31 mmol) and **Compound 1A** (410.94 mg, 3.64 mmol, 289.80 µL) in THF (5 mL) was added K_2CO_3 (1.37 g, 9.92 mmol). The mixture was stirred at 70°C for 1 hr. LC-MS showed **Compound 1** was consumed and 92% of desired compound was detected. The reaction mixture was filtered and concentrated under reduced pressure to afford ***Compound 2*** (1 g, crude) as a white solid. MS-ESI (m/z) calcd for $C_{10}H_{10}ClNO_3$ $[M+H]^+$: 228.0/230.0 Found 228.2/230.2.

To a solution of **Compound 2** (500 mg, 2.20 mmol) and **Compound 2A** (301.30 mg, 2.20 mmol, 287.50 µL) in ACN (10 mL) was added $POCl_3$ (1.01 g, 6.59 mmol, 614.18 µL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 2** was consumed and 54% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The reaction mixture was diluted with saturated $NaHCO_3$ solution 20 mL and extracted with EtOAc (20 mL * 3), the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 10% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to afford ***Compound 3*** (100 mg, 304.14 µmol, 13.85% yield) as a white solid. MS-ESI (m/z) calcd for $C_{18}H_{17}ClN_2O_2$ $[M+H]^+$: 329.1/331.0 Found 328.9/330.9.

To a solution of **Compound 3** (100 mg, 304.14 µmol) in DMF (2 mL) was added K_2CO_3 (126.10 mg, 912.43 µmol) and **Compound 3A** (52.39 mg, 608.29 µmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 3** was consumed and 33% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 10% - 40% B over 8.0 min) to afford **CW-22** (49.06 mg, 99.48 µmol, 32.71% yield, 99.86% purity, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 7.66 - 7.79 (m, 1 H), 7.57 - 7.64 (m, 1 H), 7.48 - 7.55 (m, 1 H), 7.33 - 7.43 (m, 2 H), 7.23 (d, J=8.25 Hz, 1 H), 7.14 (td, J=7.60, 1.06 Hz, 1 H), 4.04 - 4.22 (m, 2 H), 3.41 - 3.51 (m, 2 H), 3.13 (t, J=5.13 Hz, 4 H), 2.80 (s, 3 H), 2.67 - 2.77 (m, 2 H), 2.55 - 2.65 (m, 2 H), 1.23 (t, J=6.94 Hz, 3 H)
LCMS (ESI+): *m/z* 379.2 (M+H)

CW-23



To a solution of **Compound 1A** (900 mg, 5.88 mmol) and EtI (1.10 g, 7.05 mmol, 564.08 µL) in DMF (20 mL) was added K_2CO_3 (2.44 g, 17.63 mmol). The mixture was stirred at 80°C for 2 hrs. TLC (SiO_2, Petroleum ether: Ethyl acetate=5:1, Rf (P1) =0.43) indicated **Compound 1A** was consumed and one major new spot with larger polarity was detected. The reaction mixture was diluted with H_2O 20 mL and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 2A*** (1 g, crude) as a yellow oil.

To a solution of **Compound 2A** (1.10 g, 6.07 mmol) in EtOH (40 mL) and H_2O (10 mL) was added Fe (1.02 g, 18.21 mmol) and NH_4Cl (1.62 g, 30.36 mmol). The mixture was stirred at 80°C for 1 hr. TLC (SiO_2, Petroleum ether: Ethyl acetate=5:1, Rf (P1) = 0.41) indicated **Compound 2A** was consumed and one major new spot with larger polarity was detected. The reaction mixture was filtered and then the mixture was poured into saturated $NaHCO_3$ solution to pH = 8 ~ 9, then the mixture was extracted with EtOAc (10 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue to afford ***Compound 3A*** (600 mg, crude) as a yellow oil.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ ppm 6.73 - 6.63 (m, 1H), 6.55 - 6.48 (m, 1H), 6.35 (d, J = 7.4 Hz, 1H), 4.70 (s, 2H), 3.76 (q, J = 7.0 Hz, 2H), 2.13 (s, 3H), 1.31 (t, J = 7.0 Hz, 3H)

MS-ESI (m/z) calcd for $C_9H_{13}NO$ $[M+H]^+$: 152.1 Found 152.5.

To a solution of **Compound 3A** (150 mg, 702.19 µmol) and **Compound 3B** (106.17 mg, 702.19 µmol) in ACN (3 mL) was added $POCl_3$ (323.01 mg, 2.11 mmol, 196.36 µL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 3A** was consumed and 59% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with EtOAc 5 mL and then was poured into saturated Na_2CO_3 solution to pH = 8 ~ 9, the mixture was extracted with EtOAc (5 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~8% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to afford ***Compound 4A*** (140 mg, 400.25 µmol, 57.00% yield, 94% purity) as a yellow solid. MS-ESI (m/z) calcd for $C_{18}H_{17}ClN_2O_2$ $[M+H]^+$: 329.1/331.0 Found 329.1/331.2.

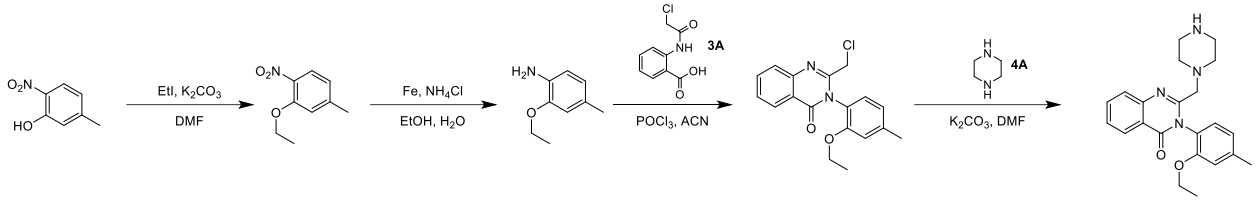
To a solution of **Compound 4A** (140 mg, 425.80 µmol) and **Compound 4B** (55.01 mg, 638.70 µmol) in DMF (2 mL) was added K_2CO_3 (176.54 mg, 1.28 mmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 4A** was consumed and 32% of desired

compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 40% B over 8.0 min) to afford **CW-23** (47.57 mg, 96.41 μmol, 22.64% yield, 99.81% purity, TFA salt) as a pale blue solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.26 (dd, J = 0.8, 7.9 Hz, 1H), 7.96 - 7.86 (m, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.46 - 7.36 (m, 1H), 7.30 - 7.18 (m, 2H), 4.06 - 3.86 (m, 1H), 3.74 - 3.58 (m, 1H), 3.47 (s, 2H), 3.20 - 3.03 (m, 4H), 2.76 - 2.64 (m, 2H), 2.61 - 2.47 (m, 2H), 2.40 (s, 3H), 1.01 (t, J = 7.1 Hz, 3H)

LCMS (ESI+): *m*/*z* 379.1 (M+H)

CW-24



To a solution of **Compound 1** (1 g, 6.53 mmol) and EtI (1.22 g, 7.84 mmol, 626.76 µL) in DMF (20 mL) was added K_2CO_3 (2.71 g, 19.59 mmol) at 20°C. The mixture was stirred at 80°C for 2 hrs. TLC (SiO_2, Petroleum ether: Ethyl acetate=5:1, Rf (P1) = 0.35, plate1) indicated **Compound 1** was consumed and one major new spot with larger polarity was detected. The reaction mixture was diluted with H_2O 20 mL and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue to afford **Compound 2** (1.1 g, crude) as a yellow oil.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ ppm 7.76 (d, *J* = 8.3 Hz, 1H), 7.16 (s, 1H), 6.89 (dd, *J* = 0.8, 8.3 Hz, 1H), 4.18 (q, *J* = 6.9 Hz, 2H), 2.37 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H)

MS-ESI (m/z) calcd for $C_9H_{11}NO_3$ $[M+H]^+$: 182.0 Found 182.4

To a solution of **Compound 2** (1.1 g, 6.07 mmol) in EtOH (40 mL) and H_2O (10 mL) was added Fe (1.02 g, 18.21 mmol) and NH_4Cl (1.62 g, 30.36 mmol). The mixture was stirred at 80°C for 1 hr. TLC (SiO_2, Petroleum ether: Ethyl acetate=5:1, Rf (P1) = 0.43, plate1) indicated **Compound 2** was consumed and one major new spot with larger polarity was detected. The reaction mixture was filtered and then the mixture was poured into saturated $NaHCO_3$ solution to pH = 8~9, then the mixture was extracted with EtOAc (10 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford **Compound 3** (620 mg, crude) as a yellow oil.

^{1}H NMR (DMSO-*d*$_6$, 400 MHz): δ ppm 6.59 (s, 1H), 6.54 - 6.49 (m, 1H), 6.49 - 6.44 (m, 1H), 4.40 (br s, 2H), 3.96 (q, J = 6.9 Hz, 2H), 2.15 (s, 3H), 1.32 (t, *J* = 6.9 Hz, 3H)

MS-ESI (m/z) calcd for $C_9H_{13}NO$ $[M+H]^+$: 152.1 Found 152.5

To a solution of **Compound 3** (150 mg, 702.19 µmol) and **Compound 3A** (106.17 mg, 702.19 µmol) in ACN (3 mL) was added $POCl_3$ (323.01 mg, 2.11 mmol, 196.36 µL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 3** was consumed and 61% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with EtOAc 5 mL and then was poured into saturated Na_2CO_3 solution to pH = 8~9, the mixture was extracted with EtOAc (5 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~8% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) (SiO_2, Petroleum ether: Ethyl acetate=3:1, Rf (P1) = 0.51, plate1) to afford **Compound**

4 (140 mg, 417.28 μmol, 59.43% yield, 98% purity) as a yellow solid. MS-ESI (m/z) calcd for $C_{18}H_{17}ClN_2O_2$ $[M+H]^+$: 329.1/331.0 Found 329.0/331.0.
To a solution of **Compound 4** (140 mg, 425.80 μmol) and **Compound 4A** (55.01 mg, 638.70 μmol) in DMF (2 mL) was added K_2CO_3 (176.54 mg, 1.28 mmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 4** was consumed and 34% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5%-40% B over 8.0 min) to afford **CW-24** (87.8 mg, 177.65 μmol, 41.72% yield, 99.65% purity, TFA salt) as a pale blue solid.

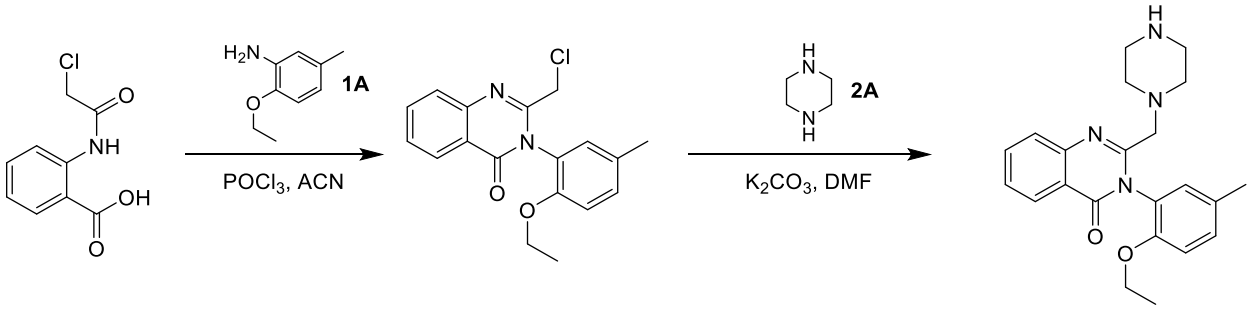
^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.29 - 8.19 (m, 1H), 7.94 - 7.84 (m, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.63 - 7.54 (m, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.05 (s, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 4.20 - 4.00 (m, 2H), 3.48 - 3.36 (m, 2H), 3.10 (t, *J* = 5.1 Hz, 4H), 2.73 - 2.61 (m, 2H), 2.59 - 2.49 (m, 2H), 2.45 (s, 3H), 1.20 (t, *J* = 6.9 Hz, 3H)

^{13}C NMR (METHANOL-d_4, 101 MHz): δ ppm 162.3, 153.8, 153.5, 146.6, 141.7, 134.8, 129.4, 127.3, 126.7, 126.4, 122.3, 121.1, 120.7, 113.6, 64.0, 49.0, 43.1, 20.4, 13.6

LCMS (ESI+): *m*/*z* 379.2 (M+H)

HRMS (TOF MS+): calcd for $C_{22}H_{27}N_4O_2$ $[M+H]^+$: 379.2134 Found 379.2119

CW-25



1 **2** **CW-25**

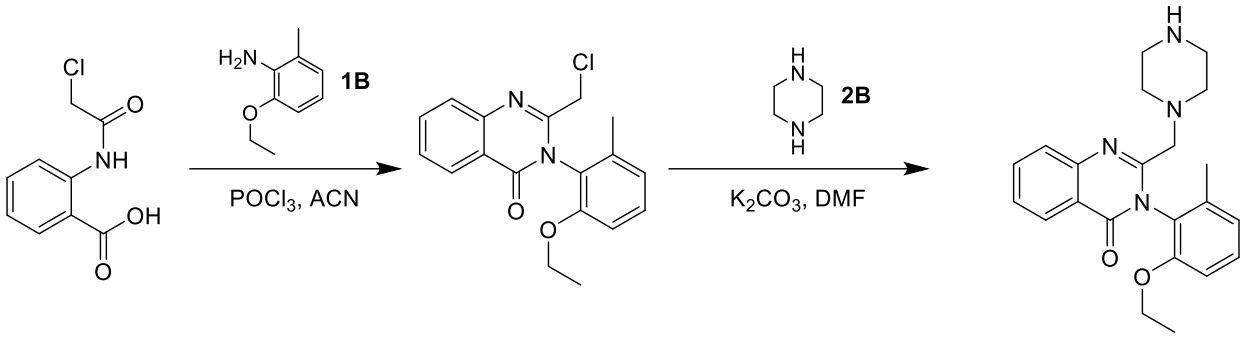
To a solution of **Compound 1** (150 mg, 702.19 μmol) and **Compound 1A** (106.17 mg, 702.19 μmol) in ACN (3 mL) was added $POCl_3$ (323.01 mg, 2.11 mmol, 196.36 μL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed 11% of **Compound 1** remained and 40% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The reaction mixture was diluted with H_2O 10 mL and extracted with EtOAc (10 mL * 3), the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to afford ***Compound 2*** (100 mg, 304.14 μmol, 43.31% yield) as a pale yellow solid. MS-ESI (m/z) calcd for $C_{18}H_{17}ClN_2O_2$ $[M+H]^+$: 329.1/331.0 Found 329.1/331.1.

To a solution of **Compound 2** (100 mg, 304.14 μmol) and **Compound 2A** (52.39 mg, 608.29 μmol) in DMF (2 mL) was added K_2CO_3 (126.10 mg, 912.43 μmol). The mixture was stirred at 80°C for 0.5 hr. LC-MS showed **Compound 2** was consumed and 37% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 5% - 40% B over 8.0 min) to afford **CW-25** (65.27 mg, 132.38 μmol, 43.53% yield, 99.89% purity, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.24 (d, J=7.88 Hz, 1 H), 7.84 - 7.95 (m, 1 H), 7.75 - 7.82 (m, 1 H), 7.60 (t, J=7.57 Hz, 1 H), 7.33 (br d, J=8.38 Hz, 1 H), 7.22 (d, J=1.88 Hz, 1 H), 7.11 (d, J=8.38 Hz, 1 H), 3.98 - 4.17 (m, 2 H), 3.38 - 3.60 (m, 2 H), 3.00 - 3.18 (m, 4 H), 2.48 - 2.82 (m, 4 H), 2.38 (s, 3 H), 1.19 (t, J=7.00 Hz, 3 H)

LCMS (ESI+): *m*/*z* 379.2 (M+H)

CW-26



1A **2A** **CW-26**

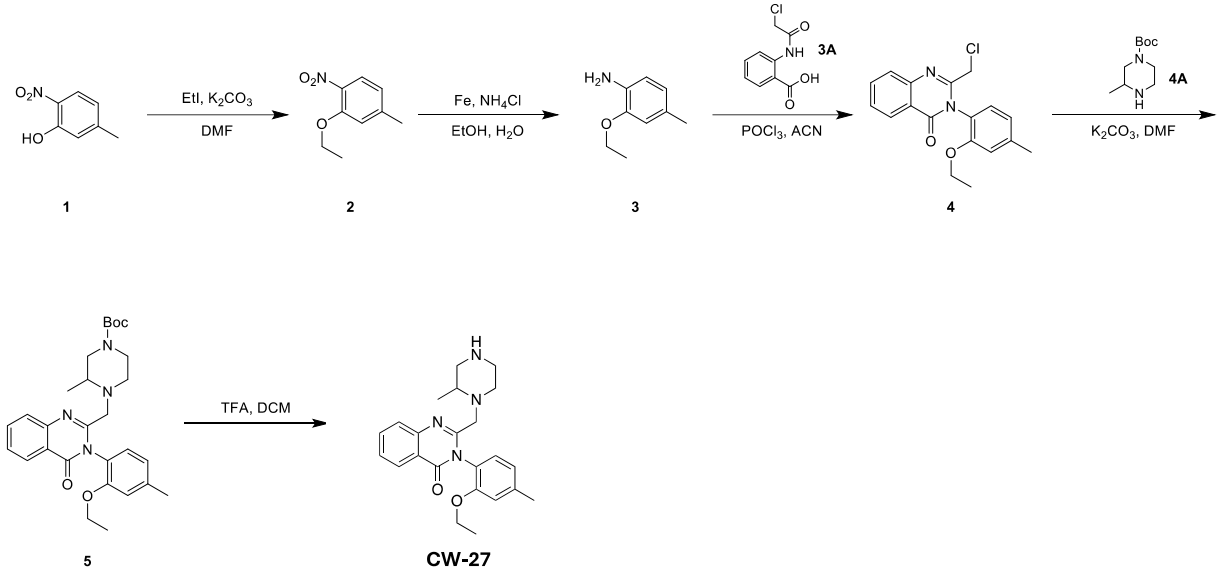
To a solution of **Compound 1A** (150.00 mg, 702.19 μmol) and **Compound 1B** (106.17 mg, 702.19 μmol) in ACN (3 mL) was added $POCl_3$ (323.01 mg, 2.11 mmol, 196.36 μL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed 11% of **Compound 1A** was remained and 67% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The reaction mixture was diluted with H_2O 10 mL and extracted with EtOAc (10 mL * 3), the combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 10% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to afford ***Compound 2A*** (100 mg, 304.14 μmol, 43.31% yield) as a pale yellow solid. MS-ESI (m/z) calcd for $C_{18}H_{17}ClN_2O_2$ $[M+H]^+$: 329.1/331.1 Found 329.1/331.2.

To a solution of **Compound 2A** (100 mg, 304.14 μmol) and **Compound 2B** (52.39 mg, 608.29 μmol) in DMF (2 mL) was added K_2CO_3 (126.10 mg, 912.43 μmol). The mixture was stirred at 80°C for 0.5 hr. LC-MS showed **Compound 2A** was consumed and 33% of desired compound was detected. The reaction mixture was filtered. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA)-ACN]; gradient: 5%-40% B over 8.0 min) to afford **CW-26** (60.05 mg, 121.93 μmol, 40.09% yield, 100% purity, TFA salt) as a white solid.

^{1}H NMR (METHANOL-d_4, 400 MHz): δ ppm 8.25 (dd, J=7.94, 1.06 Hz, 1 H), 7.85 - 7.94 (m, 1 H), 7.76 - 7.84 (m, 1 H), 7.55 - 7.66 (m, 1 H), 7.42 (t, J=8.00 Hz, 1 H), 7.05 (t, J=7.50 Hz, 2 H), 3.95 - 4.25 (m, 2 H), 3.32 - 3.54 (m, 2 H), 3.12 (br s, 4 H), 2.67 - 2.92 (m, 2 H), 2.36 - 2.57 (m, 2 H), 2.17 (s, 3 H), 1.19 (t, J=7.00 Hz, 3 H)

LCMS (ESI+): *m*/*z* 379.2 (M+H)

CW-27



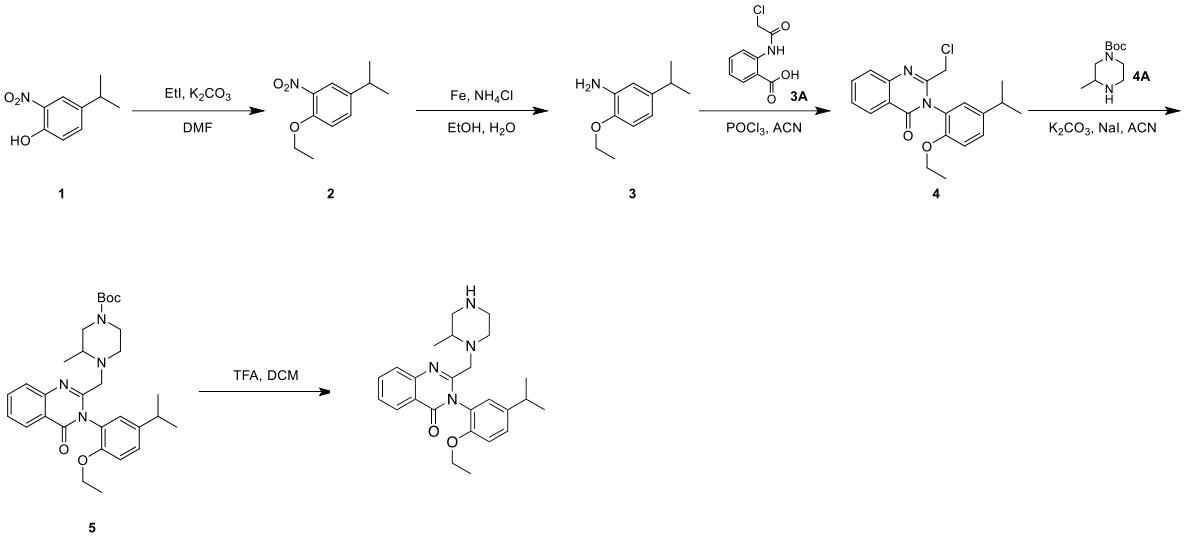
To a solution of **Compound 1** (1 g, 6.53 mmol) and EtI (1.22 g, 7.84 mmol, 626.76 µL) in DMF (40 mL) was added K_2CO_3 (2.71 g, 19.59 mmol) at 20°C. The mixture was stirred at 80°C for 2 hrs. LC-MS showed **Compound 1** was consumed and 27% of desired compound was detected. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 2*** (1 g, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_9H_{11}NO_3$ $[M+H]^+$: 182.1 Found 182.4. To a solution of **Compound 2** (1 g, 5.52 mmol) in EtOH (20 mL) and H_2O (5 mL) was added Fe (924.65 mg, 16.56 mmol) and NH_4Cl (1.48 g, 27.60 mmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 2** was consumed and 76% of desired compound was detected. The reaction mixture was filtered and then the mixture was poured into saturated $NaHCO_3$ solution to pH = 8 ~ 9, then the mixture was extracted with EtOAc (10 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 3*** (700 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_9H_{13}NO$ $[M+H]^+$: 152.1 Found 152.5. To a solution of **Compound 3** (150 mg, 702.19 µmol) and **Compound 3A** (106.17 mg, 702.19 µmol) in ACN (3 mL) was added $POCl_3$ (323.01 mg, 2.11 mmol, 196.36 µL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 3** was consumed and 51% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with EtOAc 5 mL and then was poured into saturated Na_2CO_3 solution to pH = 8 ~ 9, the mixture was extracted with EtOAc (5 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~8% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to afford ***Compound 4*** (120 mg, 357.67 µmol, 50.94% yield, 98% purity) as a yellow solid. MS-ESI (m/z) calcd for $C_{18}H_{17}ClN_2O_2$ $[M+H]^+$: 329.1/331.1 Found 329.2/331.2. To a solution of **Compound 4** (120 mg, 364.97 µmol) and **Compound 4A** (87.71 mg, 437.97 µmol) in DMF (2 mL) was added K_2CO_3 (151.32 mg, 1.09 mmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed

Compound 4 was consumed and 28% of desired compound was detected. The reaction mixture was diluted with H_2O 2 mL and extracted with EtOAc (2 mL * 3). The combined organic layers were washed with brine (3 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~8% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to afford ***Compound 5*** (120 mg, 204.63 μmol, 56.07% yield, 84% purity) as a yellow oil. MS-ESI (m/z) calcd for $C_{28}H_{36}N_4O_4$ $[M+H]^+$: 493.3 Found 493.2. To a solution of **Compound 5** (120 mg, 243.60 μmol) in DCM (2 mL) was added TFA (555.52 mg, 4.87 mmol, 361.90 μL). The mixture was stirred at 20°C for 1 hr. LC-MS showed **Compound 5** was consumed and 82% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by Prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 10% - 40% B over 10.0 min) to afford ***B-27*** (31.36 mg, 61.40 μmol, 88.86% yield, 99.17% purity, TFA) as a yellow gum.

^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 8.27 - 8.18 (m, 1H), 7.93 - 7.83 (m, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.27 - 7.17 (m, 1H), 7.05 (s, 1H), 6.96 (d, J = 7.9 Hz, 1H), 4.18 - 4.03 (m, 2H), 4.00 - 3.66 (m, 1H), 3.38 - 3.32 (m, 1H), 3.25 - 3.16 (m, 1H), 3.12 (br d, J = 12.4 Hz, 1H), 3.04 - 2.93 (m, 2H), 2.92 - 2.83 (m, 1H), 2.82 - 2.69 (m, 1H), 2.61 (br t, J = 11.4 Hz, 1H), 2.50 - 2.41 (m, 3H), 1.24 - 1.16 (m, 3H), 0.84 - 0.70 (m, 3H)

LCMS (ESI+): *m*/*z* 393.2 (M+H)

CW-28



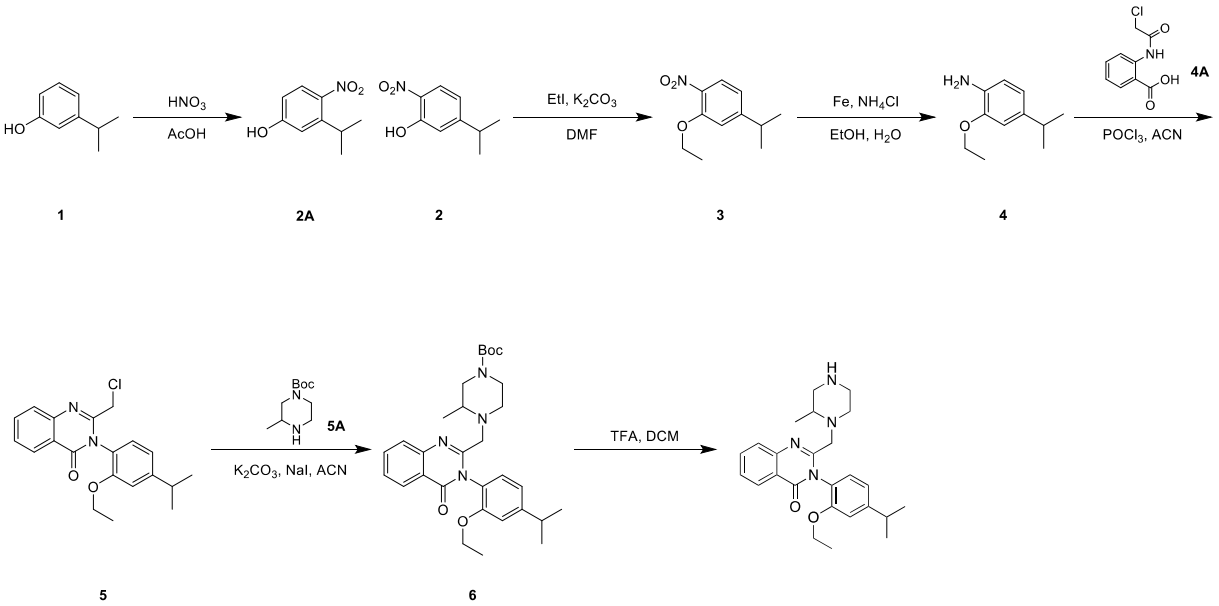
To a solution of **Compound 1** (200 mg, 1.10 mmol) and EtI (206.59 mg, 1.32 mmol, 105.94 µL) in DMF (3 mL) was added K_2CO_3 (457.66 mg, 3.31 mmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 1** was consumed and 33% of desired compound was detected. The reaction mixture was diluted with H_2O 3 mL and extracted with EtOAc (3 mL * 3). The combined organic layers were washed with brine (5 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 2*** (240 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{11}H_{15}NO_3$ $[M+H]^+$: 210.1 Found 210.2. To a solution of **Compound 2** (240 mg, 1.15 mmol) in EtOH (1.2 mL) and H_2O (0.3 mL) was added Fe (192.16 mg, 3.44 mmol) and NH_4Cl (306.77 mg, 5.74 mmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 2** was consumed and 90% of desired compound was detected. The reaction mixture was filtered and the filtrate was poured into saturated $NaHCO_3$ solution to pH = 8 ~ 9 and extracted with EtOAc (3 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 3*** (180 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{11}H_{17}NO$ $[M+H]^+$: 180.1 Found 180.2. To a solution of **Compound 3** (100 mg, 468.13 µmol) and **Compound 3A** (100.70 mg, 561.75 µmol) in ACN (2 mL) was added $POCl_3$ (215.34 mg, 1.40 mmol, 130.90 µL). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 3** was consumed and 51% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with EtOAc 3 mL and then the mixture was poured into saturated Na_2CO_3 solution to pH = 8 ~ 9, the mixture was extracted with EtOAc (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to afford ***Compound 4*** (90 mg, 234.56 µmol, 50.11% yield, 93% purity) as a yellow oil. MS-ESI (m/z) calcd for $C_{20}H_{21}ClN_2O_2$ $[M+H]^+$: 357.1/359.1 Found 357.2/359.2. To a solution of **Compound 4** (70 mg, 196.16 µmol) and **Compound 4A** (47.14 mg, 235.40 µmol,) in ACN (2 mL) was added K_2CO_3 (81.33 mg, 588.49 µmol) and NaI (5.88 mg, 39.23 µmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 4** was consumed and 48% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O 2 mL and extracted with EtOAc (2 mL * 3). The combined

organic layers were washed with brine (5 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 5*** (80 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{30}H_{40}N_4O_4$ $[M+H]^+$: 521.3 Found 521.4. To a solution of **Compound 5** (80 mg, 153.65 µmol) in DCM (2 mL) was added TFA (350.39 mg, 3.07 mmol, 228.27 µL). The mixture was stirred at 20°C for 1 hr. LC-MS and HPLC showed **Compound 5** was consumed and 60% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by Prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 15% - 45% B over 8.0 min) to afford ***CW-28*** (36.93 mg, 69.08 µmol, 44.96% yield, 100% purity, TFA) as a pale yellow gum.

^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 8.23 (dd, J = 1.4, 7.9 Hz, 1H), 7.93 - 7.85 (m, 1H), 7.78 (br d, J = 7.9 Hz, 1H), 7.64 - 7.55 (m, 1H), 7.39 (dd, J = 1.8, 8.5 Hz, 1H), 7.24 (dd, J = 2.3, 9.3 Hz, 1H), 7.18 - 7.11 (m, 1H), 4.17 - 4.01 (m, 2H), 4.01 - 3.76 (m, 1H), 3.35 - 3.16 (m, 2H), 3.14 - 3.05 (m, 1H), 3.01 - 2.89 (m, 3H), 2.78 (br d, J = 12.6 Hz, 1H), 2.71 - 2.45 (m, 2H), 1.34 - 1.24 (m, 6H), 1.20 (dt, J = 2.4, 7.0 Hz, 3H), 0.78 - 0.64 (m, 3H)

LCMS (ESI+): *m*/*z* 421.3 (M+H)

CW-29



To a solution of **Compound 1** (1 g, 7.34 mmol, 1.01 mL) in AcOH (10 mL) was added HNO_3 (810 mg, 8.36 mmol, 578.57 µL, 65% purity) at 0°C. The mixture was stirred at 20°C for 1 hr. LC-MS showed **Compound 1** was consumed and 45% of desired compound was detected. The reaction mixture was poured into saturated $NaHCO_3$ solution (20 mL) and extracted with EtOAc (10 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~3% Ethyl acetate/Petroleum ether gradient @ 80mL/min) to afford ***Compound 2*** (330 mg, 1.78 mmol, 24.31% yield, 98% purity) as a yellow oil. MS-ESI (m/z) calcd for $C_9H_{11}NO_3$ [M-H]: 180.1 Found 180.5. **^{1}H NMR** (DMSO-*d*6 400MHz): δ ppm 10.78 (br s, 1H), 7.85 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 1.5 Hz, 1H), 6.89 (dd, J = 1.6, 8.6 Hz, 1H), 2.90 (td, J = 6.9, 13.8 Hz, 1H), 1.18 (d, J = 6.9 Hz, 6H) ***Compound 2A*** (450 mg, 2.31 mmol, 31.46% yield, 93% purity) as a yellow oil. MS-ESI (m/z) calcd for $C_9H_{11}NO_3$ [M-H]: 180.0 Found 180.5

Spectrum:
^{1}H NMR ET88248-523-P1C DMSO-*d*6 400MHz

δ ppm 10.66 (s, 1H), 7.80 (d, J = 8.9 Hz, 1H), 6.88 (d, J = 2.6 Hz, 1H), 6.74 (dd, J = 2.6, 8.9 Hz, 1H), 3.45 (td, J = 6.8, 13.6 Hz, 1H), 1.23 - 1.18 (m, 6H)

To a solution of **Compound 2** (300 mg, 1.66 mmol) and EtI (387.36 mg, 2.48 mmol, 198.64 µL) in DMF (2 mL) was added K_2CO_3 (686.50 mg, 4.97 mmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 2** was consumed and 28% of desired compound was detected. The reaction mixture was diluted with H_2O 3 mL and extracted with EtOAc (3 mL * 3). The combined organic layers were washed with brine (5 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 3***

(320 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{11}H_{15}NO_3$ $[M+H]^+$: 210.1 Found 210.5. To a solution of **Compound 3** (220 mg, 1.05 mmol) in EtOH (4 mL) and H_2O (1 mL) was added Fe (176.15 mg, 3.15 mmol) and NH_4Cl (281.21 mg, 5.26 mmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 3** was consumed and 81% of desired compound was detected. The reaction mixture was filtered and then poured into saturated Na_2CO_3 solution (5 mL) and extracted with EtOAc (3 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give ***Compound 4*** (180 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{11}H_{17}NO$ $[M+H]^+$: 180.1 Found 180.2. To a solution of **Compound 4** (100 mg, 468.13 µmol) and **Compound 4A** (100.70 mg, 561.75 µmol) in ACN (2 mL) was added $POCl_3$ (215.34 mg, 1.40 mmol, 130.90 µL). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 4** was consumed and 32% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with EtOAc 3 mL and then poured into saturated Na_2CO_3 solution to pH = 8 ~ 9, the mixture was extracted with EtOAc (3 mL * 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to afford ***Compound 5*** (70 mg, 190.28 µmol, 40.65% yield, 97% purity) as a yellow oil. MS-ESI (m/z) calcd for $C_{20}H_{21}ClN_2O_2$ $[M+H]^+$: 357.1/359.1 Found 357.1/359.1. To a solution of **Compound 5** (50 mg, 140.12 µmol) and **Compound 5A** (33.67 mg, 168.14 µmol) in ACN (2 mL) was added K_2CO_3 (58.10 mg, 420.35 µmol) and NaI (4.20 mg, 28.02 µmol). The mixture was stirred at 80°C for 1 hr. LC-MS showed **Compound 5** was consumed and 49% of desired compound was detected. The reaction mixture was diluted with H_2O (1 mL) and extracted with EtOAc (2 mL * 3). The combined organic layers were washed with brine (2 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 6*** (70 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{30}H_{40}N_4O_4$ $[M+H]^+$: 521.3 Found 521.4. To a solution of **Compound 6** (70 mg, 134.44 µmol) in DCM (2 mL) was added TFA (306.60 mg, 2.69 mmol, 199.74 µL). The mixture was stirred at 20°C for 1 hr. LC-MS and HPLC showed **Compound 6** was consumed and 67% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by Prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 15% - 45% B over 8.0 min) to afford ***CW-29*** (21.06 mg, 39.23 µmol, 29.18% yield, 99.58% purity, TFA) as a pale yellow gum.

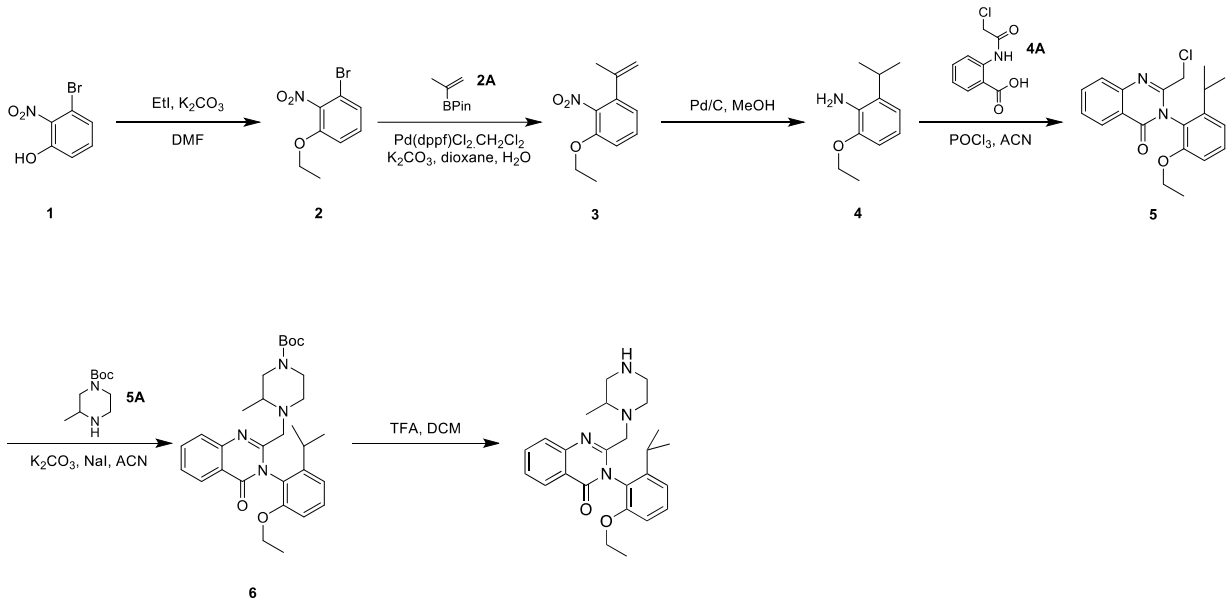
Spectrum:

^{1}H NMR (METHANOL-*d*4 400MHz)

δ ppm 8.23 (d, J = 8.0 Hz, 1H), 7.93 - 7.84 (m, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.63 - 7.55 (m, 1H), 7.31 - 7.22 (m, 1H), 7.08 (s, 1H), 7.03 (br d, J = 8.0 Hz, 1H), 4.21 - 4.03 (m, 2H), 3.97 - 3.74 (m, 1H), 3.38 - 3.15 (m, 2H), 3.10 (br d, J = 11.6 Hz, 1H), 3.04 - 2.92 (m, 2H), 2.88 - 2.76 (m, 1H), 2.76 - 2.59 (m, 2H), 2.58 - 2.47 (m, 1H), 1.32 (d, J = 6.9 Hz, 6H), 1.21 (dt, J = 2.9, 7.0 Hz, 3H), 0.76 - 0.69 (m, 3H)

LCMS (ESI+): *m*/*z* 421.3 (M+H)

CW-30



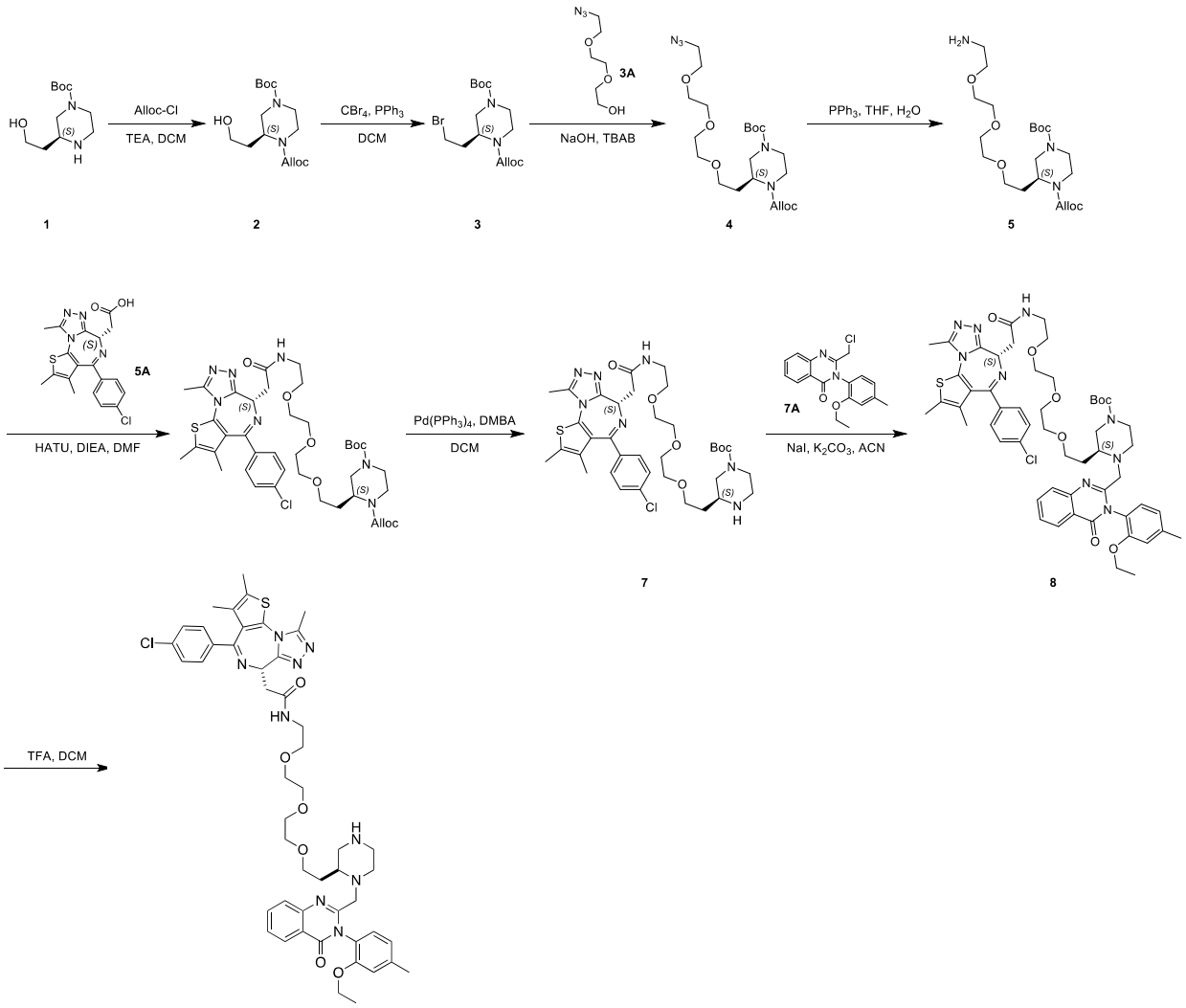
To a solution of **Compound 1** (1 g, 4.59 mmol) and EtI (858.50 mg, 5.50 mmol, 440.26 µL) in DMF (20 mL) was added K_2CO_3 (1.90 g, 13.76 mmol). The mixture was stirred at 80°C for 12 hrs. TLC showed **Compound 1** was consumed and one major new spot with lower polarity was detected. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (50 mL * 1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 2*** (1.1 g, crude) as a yellow oil. **^{1}H NMR** (DMSO-*d*6 400MHz): δ ppm 7.52 - 7.44 (m, 1H), 7.40 - 7.34 (m, 2H), 4.21 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H). To a solution of **Compound 2** (1.1 g, 4.47 mmol) and **Compound 2**A (901.47 mg, 5.36 mmol) in dioxane (20 mL) and H_2O (4 mL) was added $Pd(dppf)Cl_2.CH_2Cl_2$ (365.08 mg, 447.05 µmol) and K_2CO_3 (1.85 g, 13.41 mmol). The mixture was stirred at 80°C for 12 hrs under N_2. LC-MS showed **Compound 2** was consumed and 47% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to afford ***Compound 3*** (900 mg, 4.34 mmol, 97.15% yield) as a yellow oil. MS-ESI (m/z) calcd for $C_{11}H_{13}NO_3$ $[M+H]^+$: 208.1 Found 208.4. **^{1}H NMR** (DMSO-*d*6 400MHz): δ ppm 7.49 (t, J = 8.1 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 5.21 (s, 1H), 4.91 (s, 1H), 4.17 (q, J = 7.0 Hz, 2H), 2.01 (s, 3H), 1.28 (t, J = 6.9 Hz, 3H). To a solution of **Compound 3** (500 mg, 2.41 mmol) in MeOH (10 mL) was added Pd/C (300 mg, 10% purity) at 25°C. The mixture was stirred at 25°C for 4 hrs under H_2 at 15psi. LC-MS showed **Compound 3** was consumed and 84% of desired compound was detected. The reaction mixture was filtered and then dried under vacuum to afford ***Compound 4*** (350 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{11}H_{17}NO$ $[M+H]^+$: 180.1 Found 180.4. To a solution of **Compound 4** (100 mg, 468.13 µmol) and **Compound 4A** (100.70 mg, 561.75 µmol) in ACN (3 mL) was added $POCl_3$ (215.34 mg, 1.40 mmol, 130.90 µL). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 4** was consumed and 55% of desired

compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with EtOAc (3 mL) and then poured into saturated Na_2CO_3 solution to pH = 8 ~ 9, the mixture was extracted with EtOAc (3 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~5% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to afford ***Compound 5*** (90 mg, 237.08 μmol, 50.64% yield, 94% purity) as a yellow solid. MS-ESI (m/z) calcd for $C_{20}H_{21}ClN_2O_2$ $[M+H]^+$: 357.1/359.1 Found 357.2/359.2. To a solution of **Compound 5** (80 mg, 224.19 μmol) and **Compound 5**A (44.90 mg, 224.19 μmol) in ACN (2 mL) was added K_2CO_3 (92.95 mg, 672.56 μmol) and NaI (3.36 mg, 22.42 μmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 5** was consumed and 48% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to afford ***Compound 6*** (60 mg, 102.56 μmol, 45.75% yield, 89% purity) as a yellow oil. MS-ESI (m/z) calcd for $C_{30}H_{40}N_4O_4$ $[M+H]^+$: 521.3 Found 521.4. To a solution of **Compound 6** (60 mg, 115.24 μmol) in DCM (1 mL) was added TFA (262.80 mg, 2.30 mmol, 171.20 μL). The mixture was stirred at 20°C for 1 hr. LC-MS and HPLC showed **Compound 6** was consumed and 88% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by Prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 15% - 45% B over 8.0 min) to afford ***CW-30*** (26.06 mg, 48.75 μmol, 42.30% yield, 100% purity, TFA) as a white solid.

^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 8.23 (br d, J = 7.9 Hz, 1H), 7.96 - 7.85 (m, 1H), 7.80 (br d, J = 8.1 Hz, 1H), 7.64 - 7.55 (m, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.19 - 7.10 (m, 1H), 7.08 - 7.01 (m, 1H), 4.17 - 3.97 (m, 2H), 3.79 - 3.60 (m, 1H), 3.36 - 3.21 (m, 2H), 3.19 - 3.10 (m, 1H), 3.08 - 2.88 (m, 3H), 2.85 - 2.51 (m, 3H), 1.33 - 1.26 (m, 3H), 1.23 - 1.07 (m, 6H), 0.90 - 0.65 (m, 3H)

LCMS (ESI+): *m*/*z* 421.3 (M+H)

CW-31



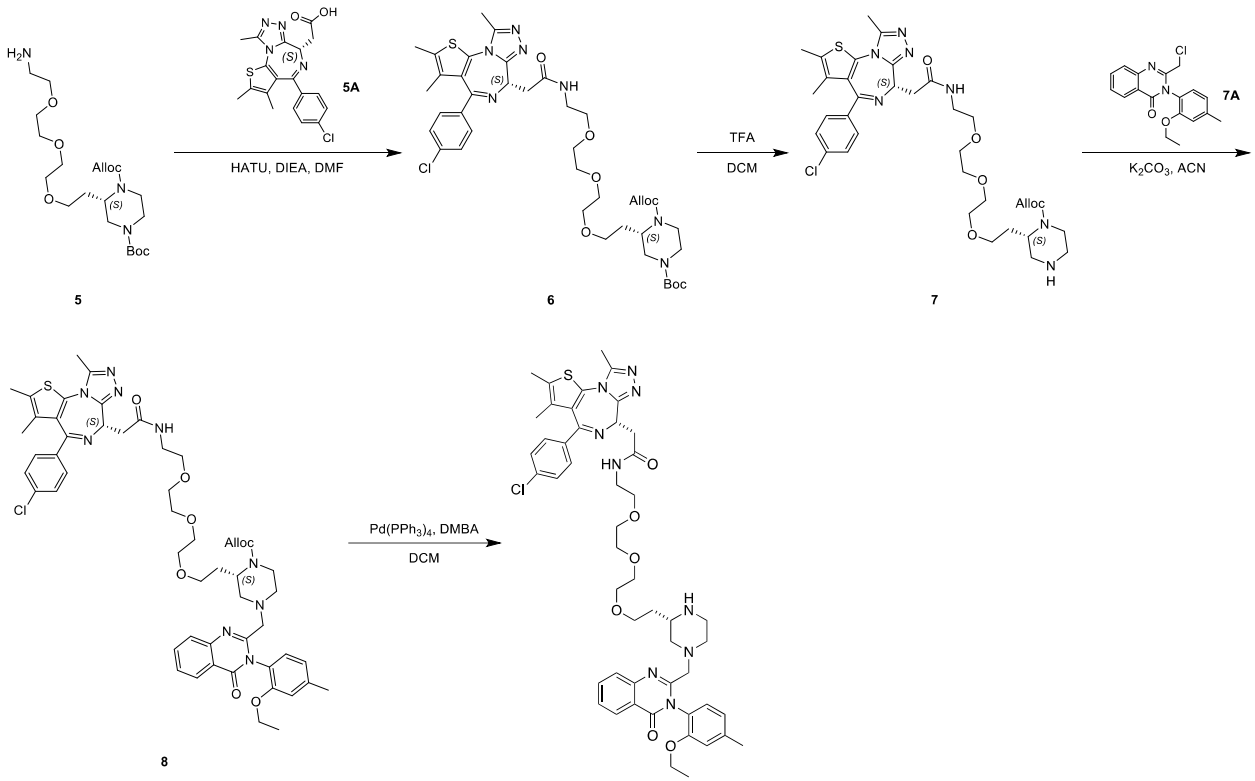
To a solution of **Compound 1** (6 g, 26.05 mmol) and TEA (5.52 g, 54.58 mmol, 7.60 mL, 2.09 eq) in DCM (60 mL) was added Alloc-Cl (3.45 g, 28.66 mmol, 3.04 mL) at 0°C, then the mixture was stirred at 0°C for 1 hr. LCMS showed 9% of **Compound 1** was remained and 48% of desired product was detected. The reaction was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to afford ***Compound 2*** (4.69 g, 14.92 mmol, 57.26% yield) as a colourless oil. MS-ESI (m/z) calcd for $C_{15}H_{26}N_2O_5$ [M+H] $^+$: 315.2 Found 315.3. **^{1}H NMR** (CHLOROFORM-*d*6 400MHz): δ ppm 5.87 - 6.02 (m, 1 H), 5.21 - 5.37 (m, 2 H), 4.63 (br s, 2 H), 4.36 (br s, 1 H) ,3.84 - 4.09 (m, 3 H), 3.59 - 3.73 (m, 1 H), 3.40 (br s, 1 H), 3.11 (br s, 1 H), 2.99 (td, J=12.76, 3.38 Hz, 1 H), 2.85 (br d, J=1.38 Hz, 1 H), 1.79 -

1.93 (m, 1 H), 1.73 (br d, J=2.00 Hz, 1 H), 1.47 (s, 9 H). To a solution of **Compound 2** (3 g, 9.54 mmol) in DCM (30 mL) was added CBr_4 (4.11 g, 12.41 mmol) and PPh_3 (3.25 g, 12.41 mmol) at 0°C, then the mixture was stirred at 0°C for 1 hr. TLC showed **Compound 2** was consumed and desired product was detected. The reaction was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to afford ***Compound 3*** (2.9 g, 6.23 mmol, 65.25% yield, 81% purity) as a yellow oil. MS-ESI (m/z) calcd for $C_{15}H_{25}BrN_2O_4$ [M+H-100] $^+$: 277.1/279.1 Found 277.2/279.2. To a solution of **Compound 3** (2.9 g, 7.69 mmol) in NaOH (6 M, 55.77 mL) was added **Compound 3A** (1.35 g, 7.69 mmol) and TBAB (247.80 mg, 768.67 μmol) at 20°C and the reaction was stirred at 20°C for 12 hrs. LCMS showed **Compound 3** was consumed and desired product was detected. The reaction was quenched with H_2O (50 mL), extracted with EtOAc (50 mL * 3), the organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20~30% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to afford ***Compound 4*** (1.56 g, 3.31 mmol, 43.04% yield, 100% purity) as a colourless oil. MS-ESI (m/z) calcd for $C_{21}H_{37}N_5O_7$ [M+H] $^+$: 472.3 Found 472.3. To a solution of **Compound 4** (160 mg, 339.31 μmol) in THF (1.5 mL) and H_2O (1.5 mL) was added PPh_3 (266.99 mg, 1.02 mmol) at 20°C, then the mixture was stirred at 70°C for 2 hrs. LCMS showed **Compound 4** consumed and 41% of desired product was detected. 2 mL 1M HCl was added into the reaction, then stirred at 20°C for 1 hr, then extracted with EtOAc (3 mL * 2), the organic layer was discarded, the aqueous layer was basified with saturated Na_2CO_3 solution to pH = 8, then extracted with EtOAc (3 mL * 3), the organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under vacuum to afford ***Compound 5*** (115 mg, crude) as a colourless oil and it was used directly without further purification. MS-ESI (m/z) calcd for $C_{21}H_{39}N_3O_7$ [M+H] $^+$: 446.3 Found 446.2. To a solution of **Compound 5** (115 mg, 258.11 μmol) and **Compound 5A** (103.47 mg, 258.11 μmol) in DMF (2 mL) was added HATU (98.14 mg, 258.11 μmol) and DIEA (66.72 mg, 516.22 μmol, 89.92 μL) at 20°C, then the mixture was stirred at 20°C for 0.5 hr. LCMS showed **Compound 5** was consumed and 12% of desired product was detected. The reaction was filtered. The filtrate was purified by Prep-HPLC (TFA condition, column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 35% - 65% B over 8.0 min) to afford ***Compound 6*** (105 mg, 119.87 μmol, 46.44% yield, 94.57% purity) as a pale yellow solid. MS-ESI (m/z) calcd for $C_{40}H_{54}ClN_7O_8S$ [M+H] $^+$: 828.3 Found 828.2. To a solution of **Compound 6** (95 mg, 114.68 μmol) in DCM (2 mL) was added DMBA (44.76 mg, 286.69 μmol) and Pd $(PPh_3)_4$ (13.25 mg, 11.47 μmol) at 20°C, then the mixture was stirred at 20°C for 12 hrs under N_2. LCMS showed **Compound 6** was consumed and 17% of desired product was detected. The reaction was concentrated under vacuum. The residue was purified by Prep-HPLC (TFA condition, column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 15% - 65% B over 8.0 min) to afford ***Compound 7*** (85 mg, 99.03 μmol, 86.35% yield, TFA) as a yellow liquid. MS-ESI (m/z) calcd for $C_{36}H_{50}ClN_7O_6S$ [M+H] $^+$:744.3/745.3/746.3 Found 744.3/745.3/746.2. To a solution of **Compound 7** (65 mg, 75.73 μmol, TFA) and **Compound 7A** (29.88 mg, 90.87 μmol) in ACN (1 mL) was added K_2CO_3 (31.40 mg, 227.18 μmol) and NaI (1.14 mg, 7.57 μmol) at 20°C, then the mixture was stirred at 80°C for 12 hrs. LCMS showed 35% of **Compound 7** was remained and 26% of desired product was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 30% - 70% B over 8.0 min) to afford ***Compound 8*** (50 mg) as a yellow liquid. MS-ESI (m/z) calcd for $C_{54}H_{66}ClN_9O_8S$ [M+H] $^+$:1036.4 Found 1036.4. To a solution of **Compound 8** (50 mg, 48.23 μmol) in DCM (1 mL) was added TFA (307.00 mg, 2.69 mmol, 0.2 mL) at 20°C, then the mixture was stirred at 20°C for 1 hr. LCMS showed **Compound 8** was consumed and 54% of desired product was detected. The reaction mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 30% - 50% B over 10.0 min) to afford ***CW-31*** (12.15 mg, 11.41 μmol, 23.65% yield, 98.64% purity, TFA) as a colorless gum.

^{1}H NMR (HLOROFORM-*d*6 400MHz): δ ppm 8.28 (br d, J=7.88 Hz, 1 H) 8.05 - 8.18 (m, 1 H) 7.72 - 7.89 (m, 2 H) 7.49 - 7.56 (m, 1 H) 7.43 (br dd, J=7.88, 3.25 Hz, 2 H) 7.32 - 7.37 (m, 2 H) 7.02 - 7.12 (m, 1 H) 6.84 - 6.95 (m, 2 H) 4.60 - 4.90 (m, 1 H) 3.95 - 4.19 (m, 2 H) 3.68 - 3.92 (m, 2 H) 3.52 - 3.67 (m, 12 H) 3.46 - 3.52 (m, 3 H) 3.17 - 3.45 (m, 8 H) 2.57 - 2.78 (m, 3 H) 2.37 - 2.48 (m, 6 H) 1.73 - 1.94 (m, 2 H) 1.70 (s, 3 H) 1.21 (t, J=6.88 Hz, 3 H)

LCMS (ESI+): *m*/*z* 936.3 (M+H)

CW-32



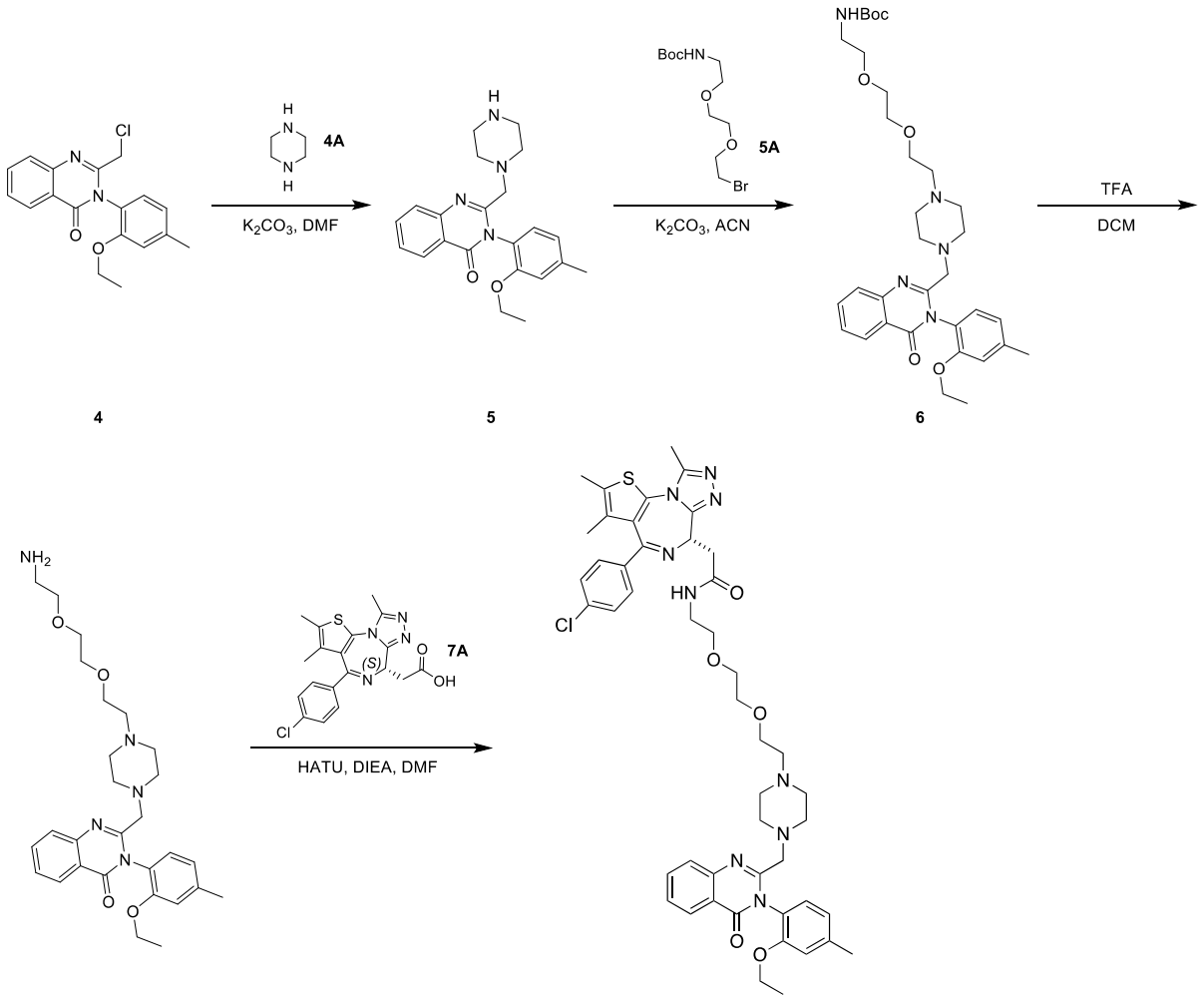
To a solution of **Compound 5** (115 mg, 258.11 μmol) and **Compound 5A** (103.47 mg, 258.11 μmol) in DMF (2 mL) was added HATU (98.14 mg, 258.11 μmol) and DIEA (66.72 mg, 516.22 μmol, 89.92 μL) at 20°C, then the mixture was stirred at 20°C for 0.5 hr. LCMS showed **Compound 5** was consumed and 12% of desired product was detected. The reaction was filtered. The filtrate was purified by Prep-HPLC (TFA condition, column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 35% - 65% B over 8.0 min) to afford ***Compound 6*** (105 mg, 119.87 μmol, 46.44% yield, 94.57% purity) as a pale yellow solid. MS-ESI (m/z) calcd for $C_{40}H_{54}ClN_7O_8S$ [M+H] $^+$: 828.3 Found 828.2. To a solution of **Compound 6** (20 mg, 24.14 μmol) in DCM (1 mL) was added TFA (307.00 mg, 2.69 mmol) at 20°C, then the mixture was stirred at 20°C for 1 hr. LCMS showed **Compound 6** was consumed and 75% of desired product was detected. The reaction was concentrated under vacuum to afford ***Compound 7*** (20 mg, crude, TFA) as a yellow liquid and it was used directly without further purification. MS-ESI (m/z) calcd for $C_{35}H_{46}ClN_7O_6S$ [M+H] $^+$:728.3 /729.3/730.3 Found 728.2/729.2/730.2. To a solution of **Compound 7** (20 mg, 23.74 μmol, TFA) and **Compound 7A** (15.61 mg, 47.49 μmol) in ACN (1 mL)

was added K_2CO_3 (9.84 mg, 71.23 μmol) at 20°C, then the mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 7** was consumed and 39% of desired compound was detected. The reaction mixture was diluted with H_2O (3 mL) and extracted with EtOAc (3 mL *3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 8*** (20 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{53}H_{62}ClN_9O_8S$ $[M+H]^+$:1020.4/1021.4 Found 1020.4/1021.4. To a solution of **Compound 8** (20 mg, 19.60 μmol) in DCM (1 mL) was added DMBA (7.65 mg, 48.99 μmol) and Pd $(PPh_3)_4$ (2.26 mg, 1.96 μmol). The mixture was stirred at 20°C for 2 hrs under N_2. LC-MS showed **Compound 8** was consumed and 30% of desired compound was detected. The reaction mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 20% - 60% B over 8.0 min) to afford ***CW-32*** (11.27 mg, 10.56 μmol, 53.88% yield, 98.43% purity, TFA) as a colorless gum.

^{1}H NMR (CHLOROFORM-*d* 400MHz): δ ppm 8.24 - 8.32 (m, 1 H), 7.80 - 7.88 (m, 1 H), 7.71 - 7.79 (m, 2 H), 7.46 - 7.56 (m, 1 H), 7.30 - 7.45 (m, 4 H), 6.96 - 7.13 (m, 1 H), 6.77 - 6.94 (m, 2 H), 4.71 (t, J=7.00 Hz, 1 H), 3.94 - 4.16 (m, 2 H), 3.81 - 3.94 (m, 1 H), 3.70 - 3.78 (m, 2 H), 3.49 - 3.69 (m, 16 H), 3.34 - 3.49 (m, 3 H), 3.13 - 3.33 (m, 3 H), 2.65 (d, J=9.38 Hz, 3 H), 2.33 - 2.48 (m, 6 H), 2.07 - 2.31 (m, 1 H), 1.74 - 1.87 (m, 1 H), 1.69 (s, 3 H), 1.11 - 1.28 (m, 3 H)

LCMS (ESI+): *m*/*z* 936.3 (M+H)

CW-33



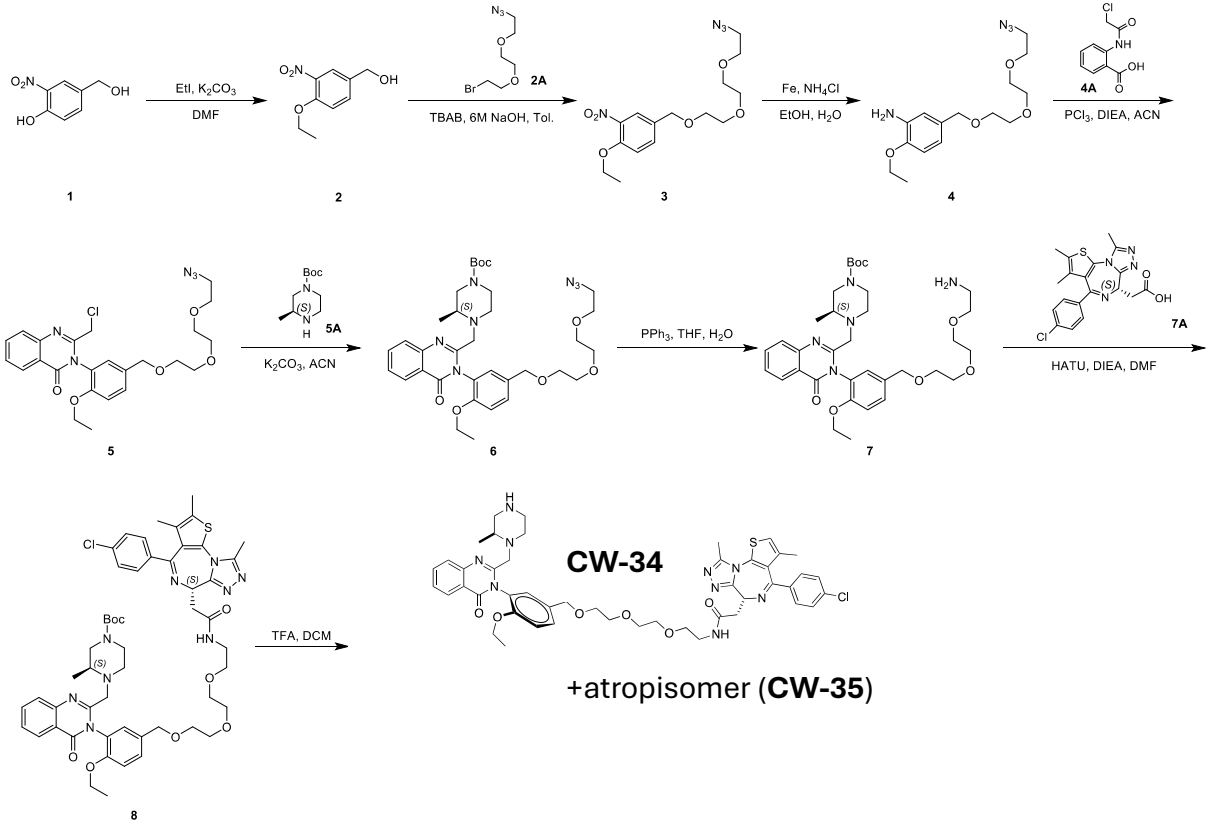
To a solution of **Compound 4** (150 mg, 456.22 µmo) and **Compound 4A** (78.59 mg, 912.43 µmol) in DMF (2 mL) was added K_2CO_3 (189.15 mg, 1.37 mmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 4** was consumed and 37% of desired compound was detected. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL * 3). The combined organic layers were washed with brine (5 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 10% Dichloromethane: Methanol gradient @ 40 mL/min) to afford ***Compound 5*** (140 mg, 369.91 µmol, 81.08% yield) as a yellow solid. MS-

ESI (m/z) calcd for $C_{22}H_{26}N_4O_2$ [M+H] $^+$: 379.2 Found 379.2. To a solution of **Compound 5** (110 mg, 290.65 µmol) and **Compound 5A** (108.89 mg, 348.78 µmol) in ACN (2 mL) was added K_2CO_3 (120.51 mg, 871.94 µmol). The mixture was stirred at 80°C for 2 hrs. LC-MS showed **Compound 5** was consumed and 87% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL * 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 6*** (170 mg, crude) as a yellow solid. MS-ESI (m/z) calcd for $C_{33}H_{47}N_5O_6$ [M+H] $^+$: 610.3 Found 610.4. To a solution of **Compound 6** (170 mg, 278.80 µmol) in DCM (1 mL) was added TFA (1.30 g, 11.44 mmol, 850.00 µL). The mixture was stirred at 20°C for 12 hrs. LC-MS showed **Compound 6** was consumed and 88% of desired compound was detected. The reaction mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 10% - 45% B over 8.0 min) to afford ***Compound 7*** (110 mg, 176.38 µmol, 63.26% yield, TFA) as a colourless solid. MS-ESI (m/z) calcd for $C_{28}H_{39}N_5O_4$ [M+H] $^+$: 510.3 Found 510.3. To a solution of **Compound 7** (100 mg, 196.22 µmol) and **Compound 7A** (94.39 mg, 235.46 µmol) in DMF (1 mL) was added HATU (89.53 mg, 235.46 µmol) and DIEA (76.08 mg, 588.65 µmol, 102.53 µL). The mixture was stirred at 20°C for 1 hr. LC-MS showed **Compound 7** was consumed and 25% of desired compound was detected. The reaction mixture was filtered. The filtrate was purified by Prep-HPLC (column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 15% - 65% B over 8.0 min) to afford ***C-33*** (70.54 mg, 69.77 µmol, 35.56% yield, 99.55% purity, TFA) as a pale yellow solid.

^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 8.16 - 8.24 (m, 1 H) 7.81 - 7.90 (m, 1 H) 7.74 (d, J=8.13 Hz, 1 H) 7.53 - 7.60 (m, 1 H) 7.37 - 7.48 (m, 4 H) 7.18 - 7.29 (m, 1 H) 6.99 - 7.08 (m, 1 H) 6.88 - 6.97 (m, 1 H) 4.58 - 4.67 (m, 1 H) 3.97 - 4.15 (m, 2 H) 3.79 - 3.85 (m, 2 H) 3.68 (s, 4 H) 3.56 - 3.63 (m, 2 H) 3.32 - 3.52 (m, 10 H) 3.27 (br d, J=1.00 Hz, 2 H) 2.72 - 2.86 (m, 2 H) 2.68 - 2.71 (m, 3 H) 2.57 - 2.65 (m, 2 H) 2.40 - 2.46 (m, 6 H) 1.69 (d, J=2.38 Hz, 3 H) 1.17 (t, J=6.94 Hz, 3 H)

LCMS (ESI+): *m*/*z* 892.2 (M+H)

CW-34 and CW-35



To a solution of **Compound 1** (10 g, 59.12 mmol) and K_2CO_3 (24.51 g, 177.37 mmol) in DMF (100 mL) was added EtI (10.14 g, 65.04 mmol, 5.20 mL) at 20°C, then the reaction was stirred at 80°C for 1 hr. LC-MS showed **Compound 1** was consumed and 32% of desired product was detected. The reaction was quenched with H_2O (100 mL), extracted with EtOAc (100 mL * 3), the organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to afford ***Compound 2*** (11.6 g, 58.83 mmol, 99.50% yield) as a yellow solid. MS-ESI (m/z) calcd for $C_9H_{11}NO_4$ [M-H]: 196.1 Found 196.1. **^{1}H NMR** (CHLOROFORM-*d* 400MHz): δ ppm 7.82 (d, *J*=2.00 Hz, 1 H), 7.51 (dd, *J*=8.57, 2.06 Hz, 1 H), 7.05 (d, *J*=8.50 Hz, 1 H), 4.67 (s, 2 H), 4.18 (q, *J*=7.00 Hz, 2 H), 1.47 (t, *J*=7.00 Hz, 3 H). To a solution of **Compound 2** (1 g, 5.07 mmol) in Tol. (5 mL) was added **Compound 2A** (1.21 g, 5.07 mmol) and NaOH (6 M, 10 mL), TBAB (163.48 mg, 507.13 µmol) at 20°C and the reaction was stirred at 20°C for 12 hrs. LC-MS showed **Compound 2** was consumed and 61% of desired compound was detected. The reaction was quenched with H_2O (10 mL), extracted with EtOAc (10 mL * 3), the organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash ® Silica Flash Column,

Eluent of 30% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to afford ***Compound 3*** (1 g, 2.82 mmol, 55.65% yield) as a colourless oil.

^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 7.75 - 7.80 (m, 1 H), 7.53 - 7.59 (m, 1 H), 7.23 (d, J=8.63 Hz, 1 H), 4.54 (s, 2 H), 4.17 - 4.23 (m, 2 H), 3.52 - 3.85 (m, 10 H), 3.36 (t, J=4.88 Hz, 2 H), 1.42 (t, J=6.94 Hz, 3 H). To a solution of **Compound 3** (500 mg, 1.41 mmol) in EtOH (10 mL) and H_2O (2 mL) was added Fe (236.39 mg, 4.23 mmol) and NH_4Cl (226.43 mg, 4.23 mmol). The mixture was stirred at 80°C for 0.5 hr. LC-MS showed **Compound 3** was consumed and 74% of desired compound was detected. The reaction mixture was filtered and diluted with H_2O (20 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (20 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 30% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to afford ***Compound 4*** (650 mg, 2.00 mmol, 71.01% yield) as a yellow oil. MS-ESI (m/z) calcd for $C_{15}H_{24}N_4O_4$ $[M+H]^+$: 325.2 Found 325.4. To a solution of **Compound 4** (217.32 mg, 1.02 mmol) in ACN (6 mL) was added DIEA (143.44 mg, 1.11 mmol, 193.31 µL). Then PCl_3 (152.42 mg, 1.11 mmol) was added at 20°C. The mixture was stirred at 20°C for 0.1 hr. Then **Compound 4A** (300 mg, 924.86 µmol) in ACN (6 mL) was added. The mixture was stirred at 60°C for 12 hrs. LC-MS showed **Compound 4** was consumed and 48% of desired compound was detected. The reaction mixture was diluted with $NaHCO_3$ (5 mL) and extracted with EtOAc (3 mL * 3). The combined organic layers were washed with brine (10 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 50% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to afford ***Compound 5*** (260 mg, 517.97 µmol, 56.01% yield) as a pale yellow solid. MS-ESI (m/z) calcd for $C_{24}H_{28}ClN_5O_5$ $[M+H]^+$: 502.2/504.2 Found 502.1/504.1. To a solution of **Compound 5** (140 mg, 278.91 µmol) and **Compound 5A** (55.86 mg, 278.91 µmol) in ACN (3 mL) was added K_2CO_3 (115.64 mg, 836.72 µmol). The mixture was stirred at 80°C for 12 hrs. LC-MS showed **Compound 5** was consumed and 87% of desired compound was detected. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL * 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash ® Silica Flash Column, Eluent of 30% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to afford ***Compound 6*** (180 mg, 270.36 µmol, 96.94% yield) as a yellow oil. MS-ESI (m/z) calcd for $C_{34}H_{47}N_7O_7$ $[M+H]^+$: 666.4 Found 666.5. To a solution of **Compound 6** (120 mg, 180.24 µmol) in THF (2 mL) and H_2O (2 mL) was added PPh_3 (141.82 mg, 540.72 µmol). The mixture was stirred at 80°C for 2 hrs. LC-MS showed **Compound 6** was consumed and 35% of desired compound was detected. 2 mL 2M HCl was added into the reaction, then stirred at 20°C for 1 hr, then extracted with EtOAc (5 mL * 2), the organic layer was discarded, the aqueous layer was basified with saturated Na_2CO_3 solution to pH = 8, then extracted with EtOAc (5 mL * 3), the organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under vacuum to afford ***Compound 7*** (80 mg, 125.04 µmol, 69.38% yield) as a yellow oil. MS-ESI (m/z) calcd for $C_{34}H_{49}N_5O_7$ $[M+H]^+$: 640.4 Found 640.3. To a solution of **Compound 7** (80 mg, 125.04 µmol) and **Compound 7A** (50.13 mg, 125.04 µmol) in DMF (2 mL) was added HATU (57.05 mg, 150.05 µmol) and DIEA (48.48 mg, 375.13 µmol, 65.34 µL). The mixture was stirred at 20°C for 0.5 hr. LC-MS showed **Compound 7** was consumed and 25% of desired compound was detected. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 mL * 3). The combined organic layers were washed with brine (5 mL * 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford ***Compound 8*** (120 mg, crude) as a yellow oil. MS-ESI (m/z) calcd for $C_{53}H_{64}ClN_9O_8S$ $[M+H]^+$:

1022.4/1023.4 Found 1022.5/1023.5. To a solution of **Compound 8** (120 mg, 117.34 µmol) in DCM (2 mL) was added TFA (767.50 mg, 6.73 mmol, 0.5 mL). The mixture was stirred at 20°C for 1 hr. LC-MS showed **Compound 8** was consumed and 54% of desired compound was detected. The reaction mixture was concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100* 30mm* 5um; mobile phase: [H_2O (0.1% TFA) - ACN]; gradient: 30% - 50% B over 10.0 min) to afford ***CW-34*** (23.55 mg, 21.76 µmol, 18.54% yield, 95.77% purity, TFA) as a white solid. ***CW-35*** (28.62 mg, 27.19 µmol, 23.17% yield, 98.47% purity, TFA) as a white solid.

CW-34 Spectrum:

^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 8.18 - 8.25 (m, 1 H), 7.84 - 7.92 (m, 1 H), 7.74 (d, J=8.00 Hz, 1 H), 7.53 - 7.62 (m, 1 H), 7.34 - 7.52 (m, 6 H), 7.17 (d, J=8.50 Hz, 1 H), 4.64 (dd, J=8.69, 5.44 Hz, 1 H), 4.51 - 4.60 (m, 2 H), 4.00 - 4.19 (m, 2 H), 3.80 (d, J=14.51 Hz, 1 H), 3.71 (s, 4 H), 3.64 (br d, J=4.38 Hz, 4 H), 3.54 - 3.60 (m, 2 H), 3.38 - 3.49 (m, 3 H), 3.20 - 3.30 (m, 2 H), 3.08 - 3.20 (m, 2 H), 2.91 - 3.03 (m, 1 H), 2.68 - 2.77 (m, 4 H), 2.53 - 2.66 (m, 3 H), 2.46 (s, 3 H), 1.70 (s, 3 H), 1.19 (t, J=6.94 Hz, 3 H), 0.72 - 0.84 (m, 3 H)

^{13}C NMR (METHANOL-d_4 101 MHz): δ ppm 171.4, 165.0, 162.0, 155.6, 154.3, 154.0, 146.6, 136.8, 136.4, 134.8, 132.2, 130.2, 130.0, 128.5, 127.4, 126.6, 126.5, 120.6, 112.8, 71.8, 70.4, 70.1, 69.9, 69.4, 64.3, 53.6, 48.5, 43.1, 39.1, 37.2, 13.6, 13.1, 11.6, 10.2

LCMS (ESI+): *m*/*z* 922.3 (M+H).

HRMS (TOF MS ES+): calcd for $C_{48}H_{57}ClN_9O_6S$ $[M+H]^+$: 922.3841 Found 922.3840

CW-35 Spectrum:

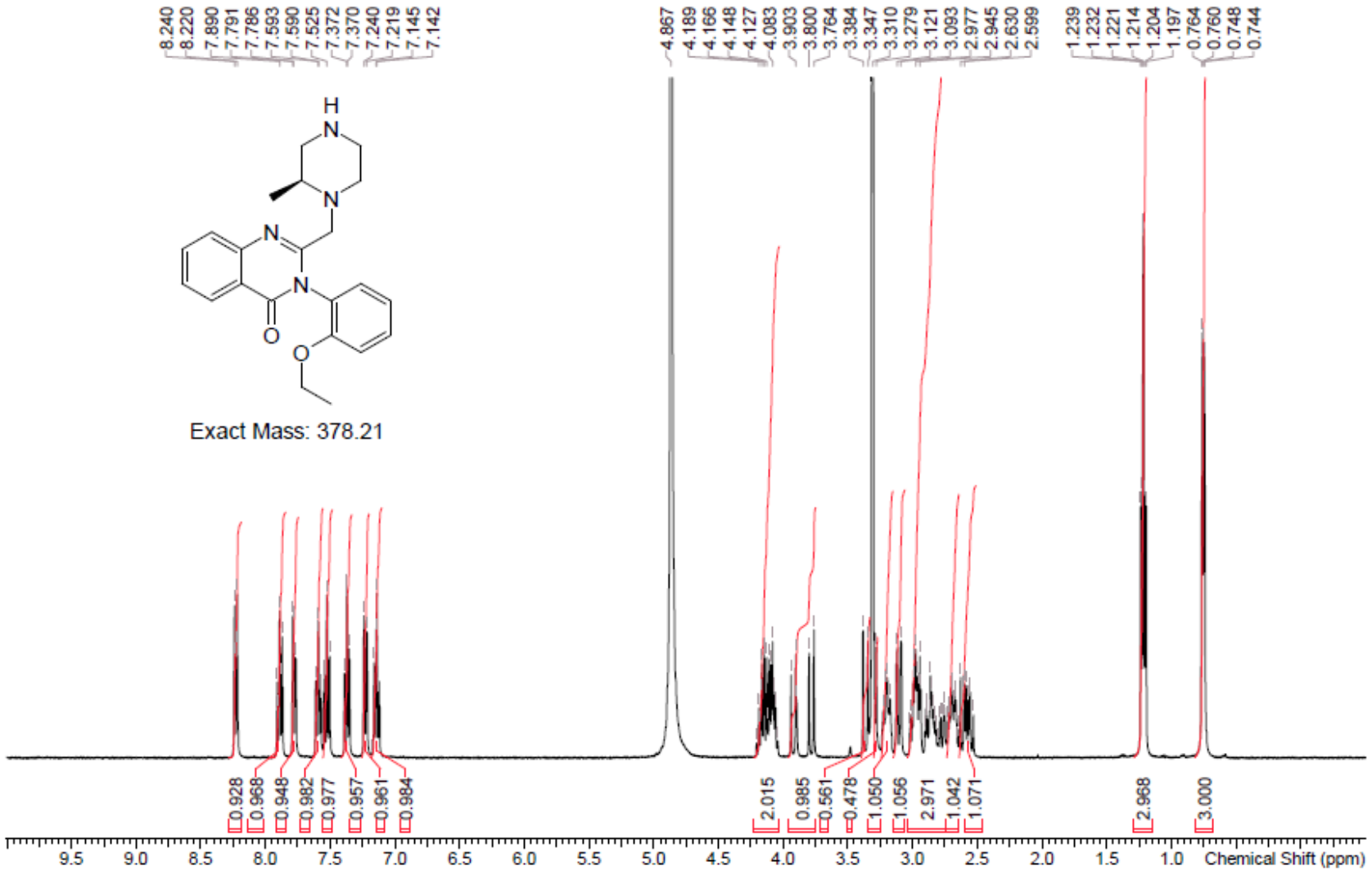
^{1}H NMR (METHANOL-*d*4 400MHz): δ ppm 8.20 (d, J=8.13 Hz, 1 H), 7.84 - 7.92 (m, 1 H), 7.75 (d, J=8.13 Hz, 1 H), 7.58 (t, J=7.50 Hz, 1 H), 7.36 - 7.50 (m, 6 H), 7.16 (d, J=8.50 Hz, 1 H), 4.49 - 4.66 (m, 3 H), 4.00 - 4.15 (m, 2 H), 3.78 (br d, J=13.88 Hz, 1 H), 3.74 (s, 4 H), 3.60 - 3.69 (m, 4 H), 3.56 (t, J=5.38 Hz, 2 H), 3.37 - 3.49 (m, 3 H), 3.34 (br d, J=6.00 Hz, 1 H), 3.15 - 3.27 (m, 2 H), 2.98 - 3.10 (m, 2 H), 2.88 - 2.98 (m, 1 H), 2.53 - 2.74 (m, 6 H), 2.45 (s, 3 H), 1.70 (s, 3 H), 1.20 (t, J=7.00 Hz, 3 H), 0.60 (d, J=6.13 Hz, 3 H)

LCMS (ESI+): *m*/*z* 922.3 (M+H).

Supplementary Note 2: Compiled spectral data for synthesized small molecules

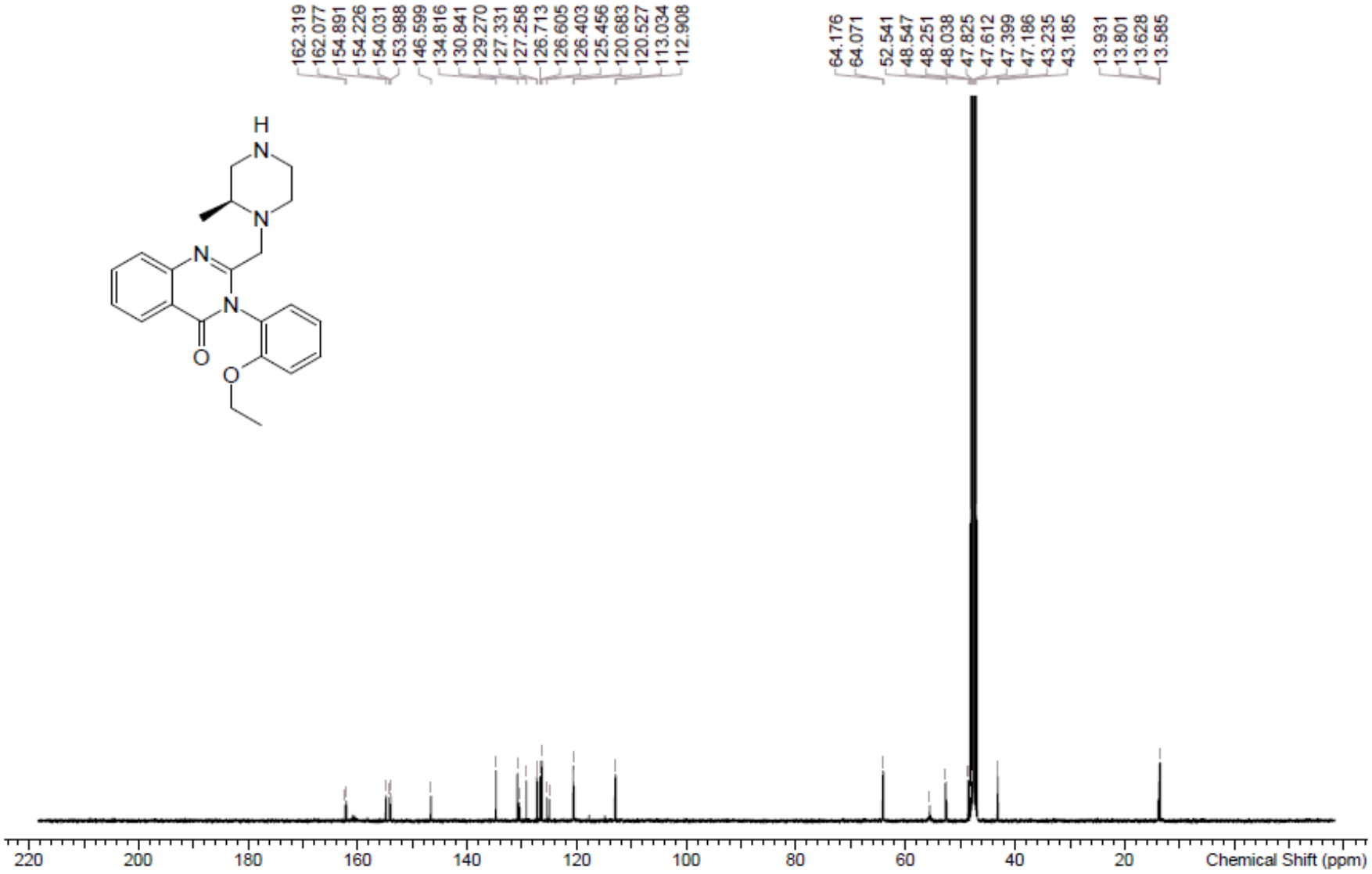
CW-1

^{1}H NMR: (400 MHz, CD_3OD)



CW-1

^{13}C NMR (101 MHz, CD_3OD)



CW-1
LC-MS

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                  Column Temp: 40 °C
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                  Mobile Phase:B:ACN
                  Flow Rate: 0.8ml/min
                  Time              B%              Flow(ml/min)
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                  0.40              5                    0.8
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                  3.85              95                   0.8
                  3.86              5                    0.8
                  4.50              5                    0.8
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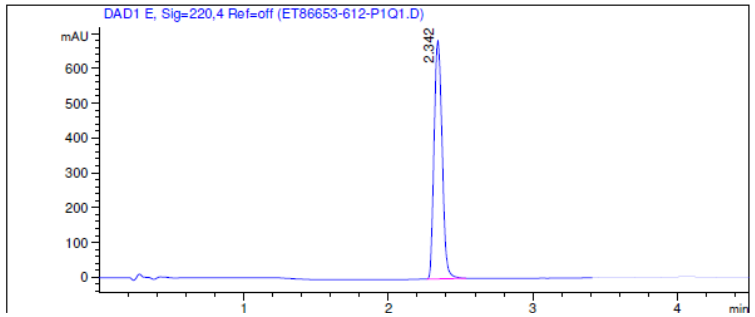

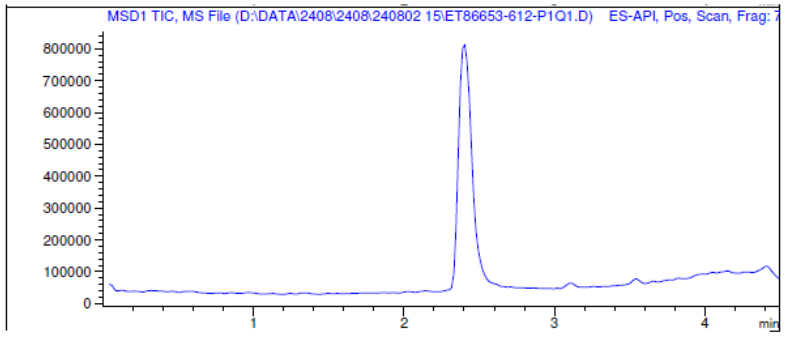

Report

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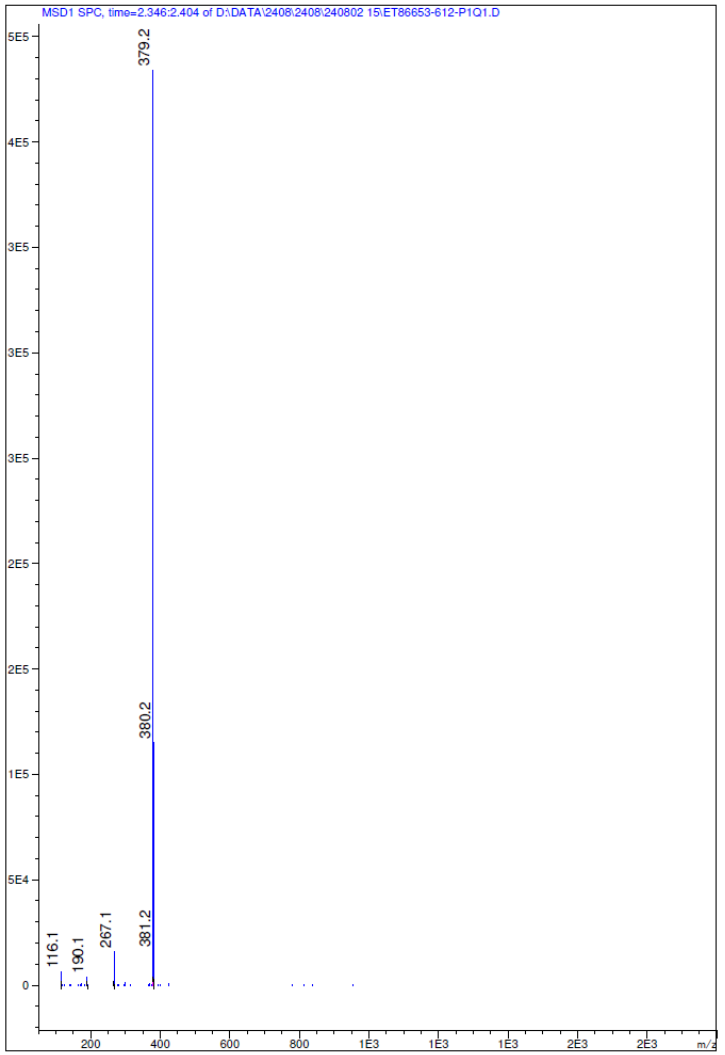
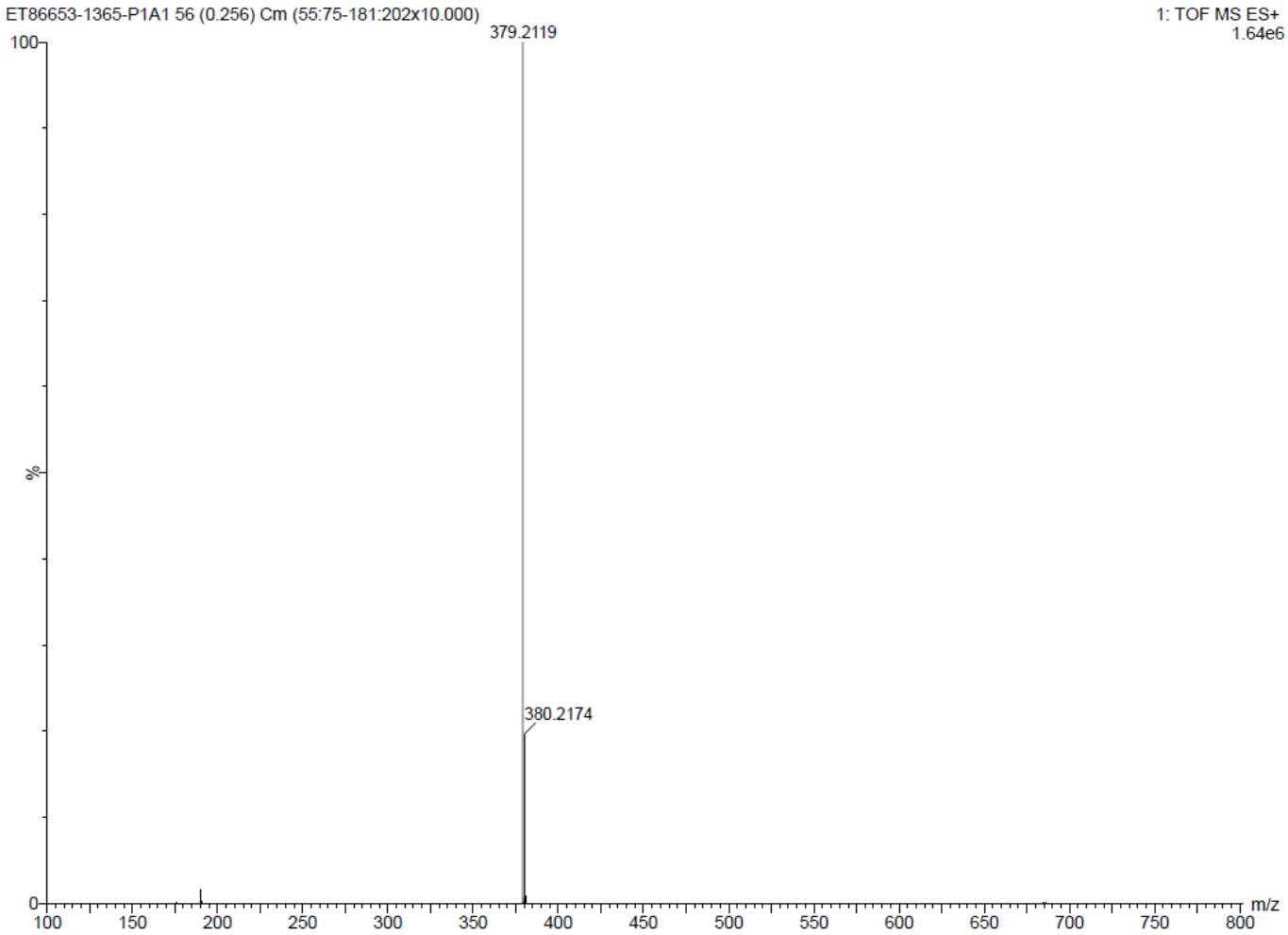


CW-1
HRMS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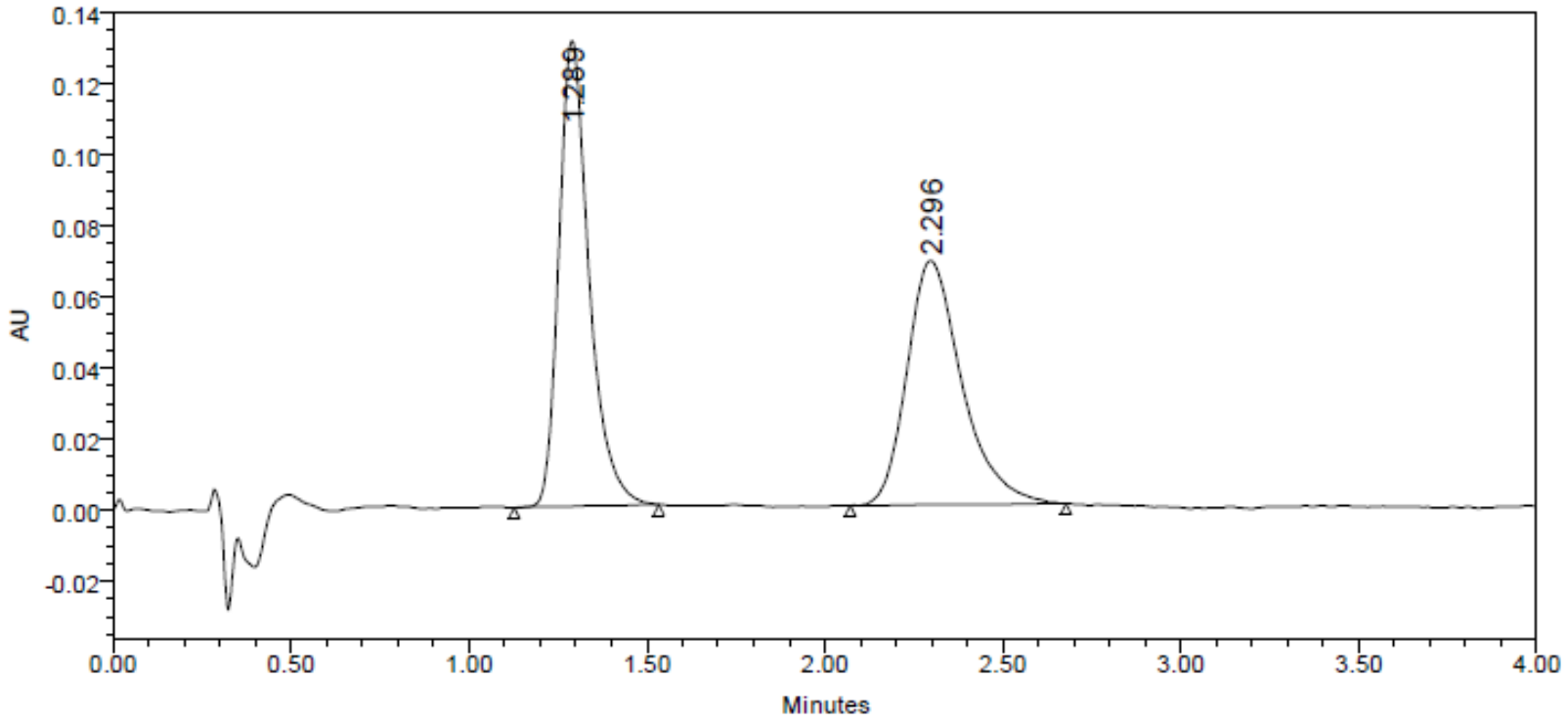
CW-1
Chiral HPLC



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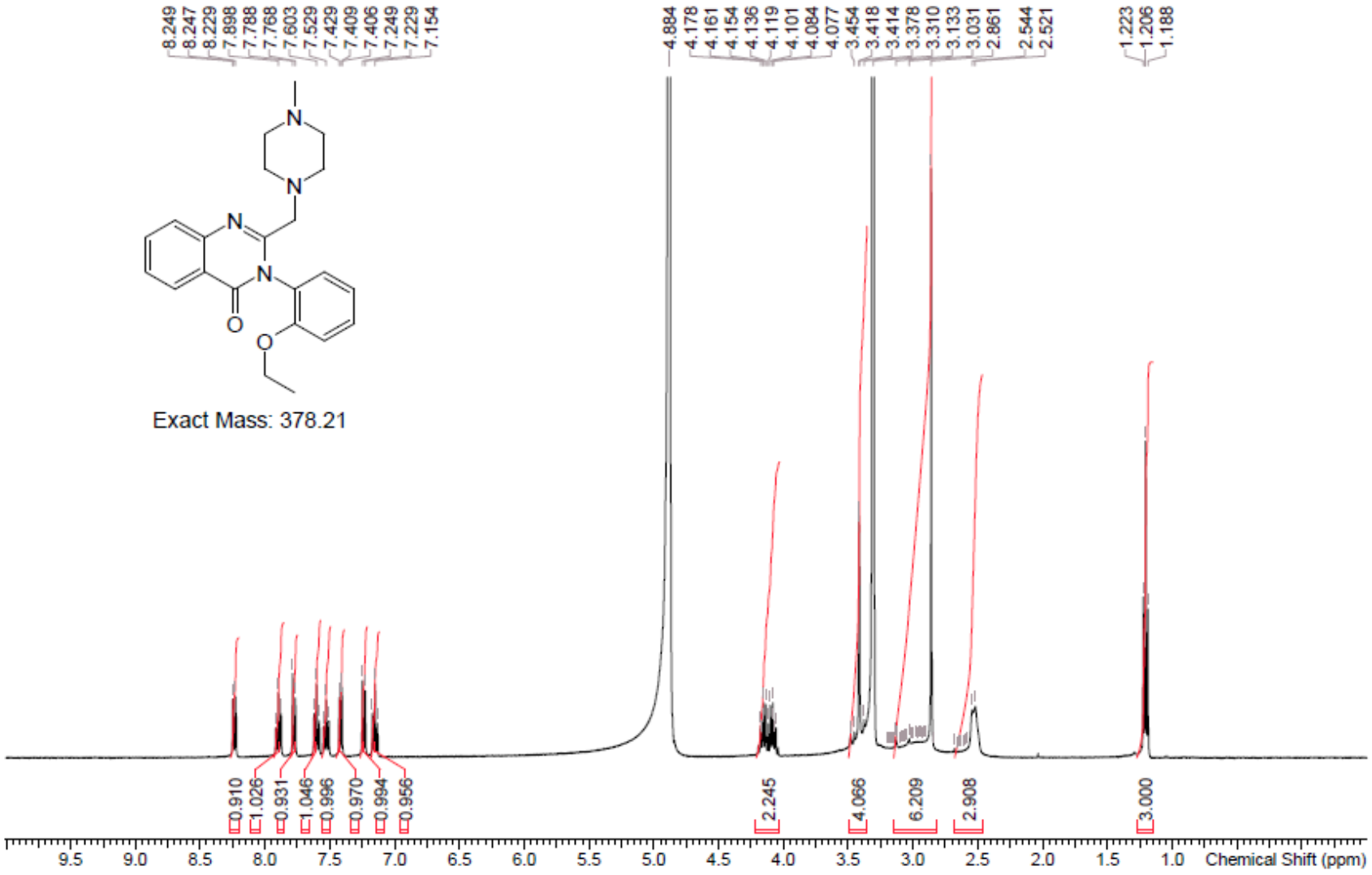
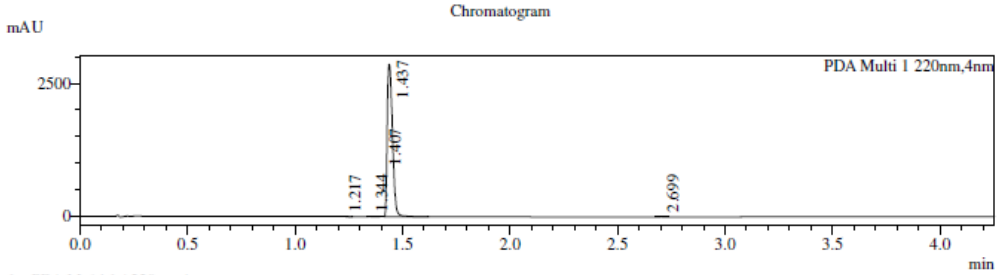
CW-2

^{1}H NMR: (400 MHz, CD_3OD)



CW-2
LC-MS



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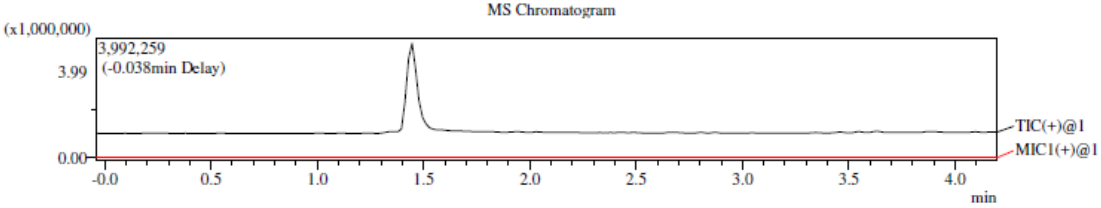

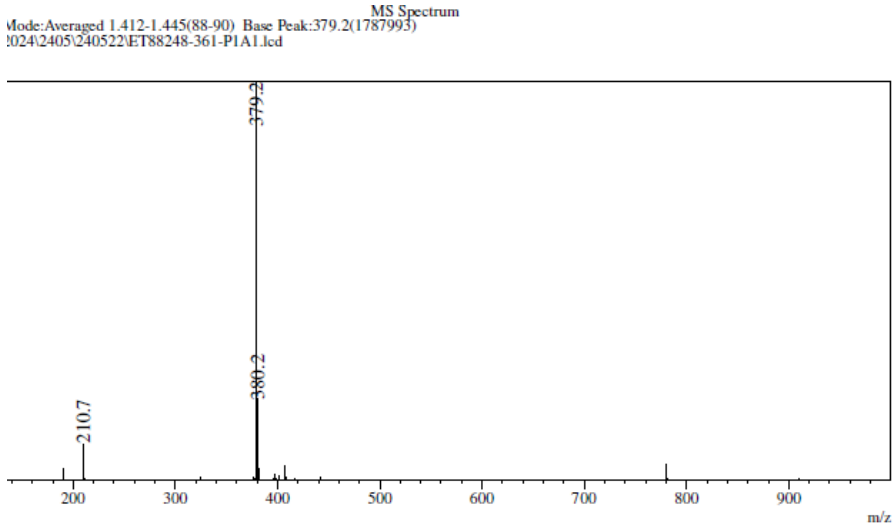

Integration Result

Peak Table

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Total						

PDA Ch1 220nm

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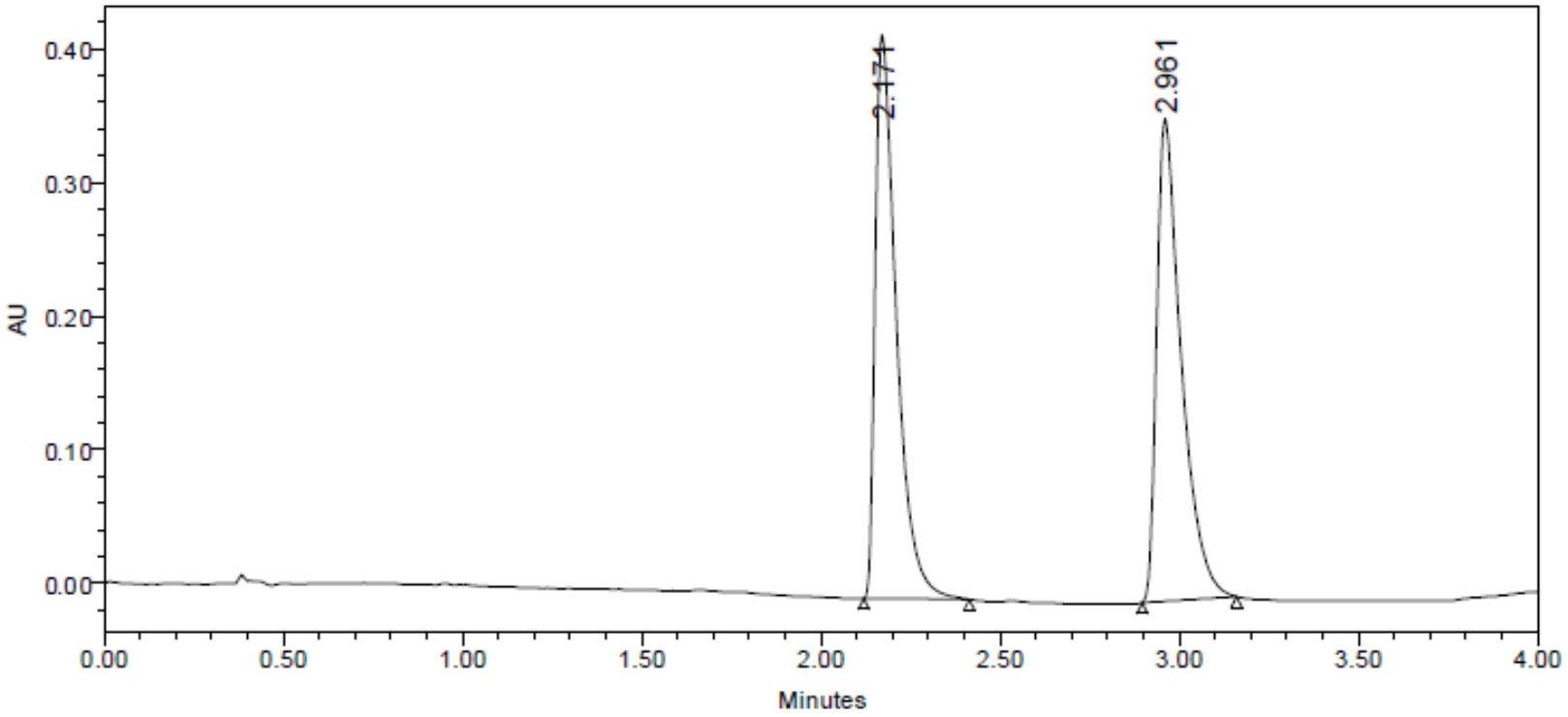
CW-2
Chiral HPLC



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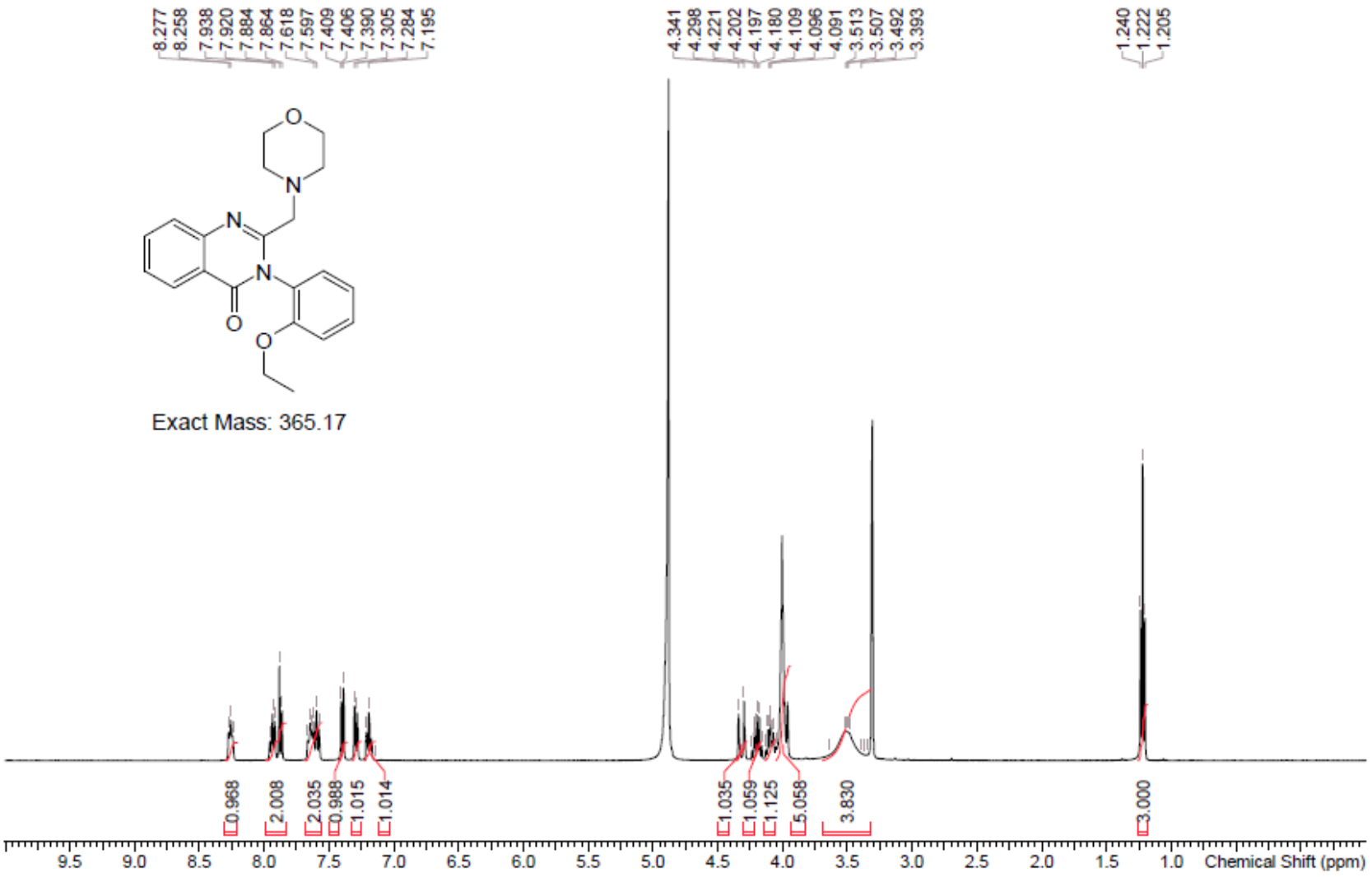
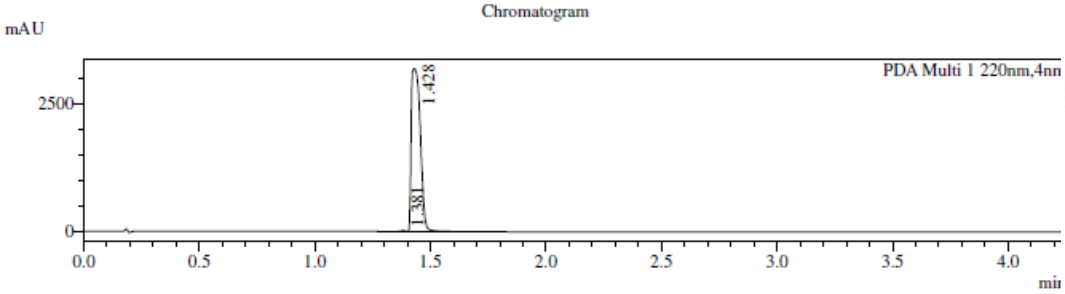
CW-3
^{1}H NMR (400 MHz, CD_3OD



CW-3
LC-MS



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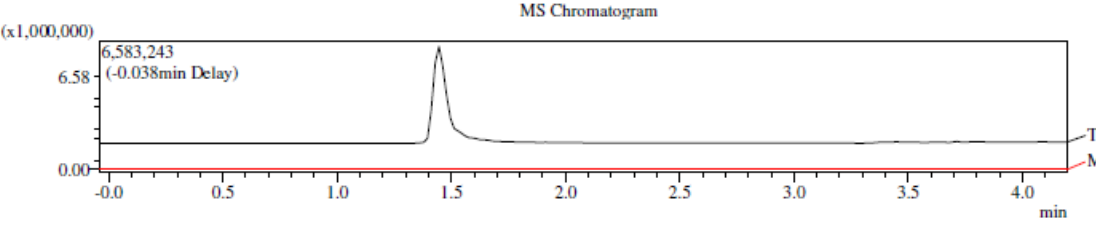

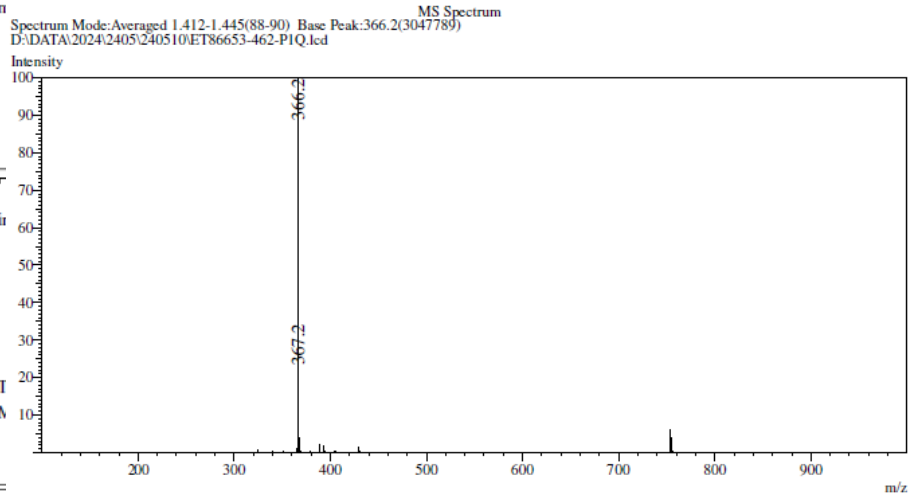

Integration Result

Peak Table

ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

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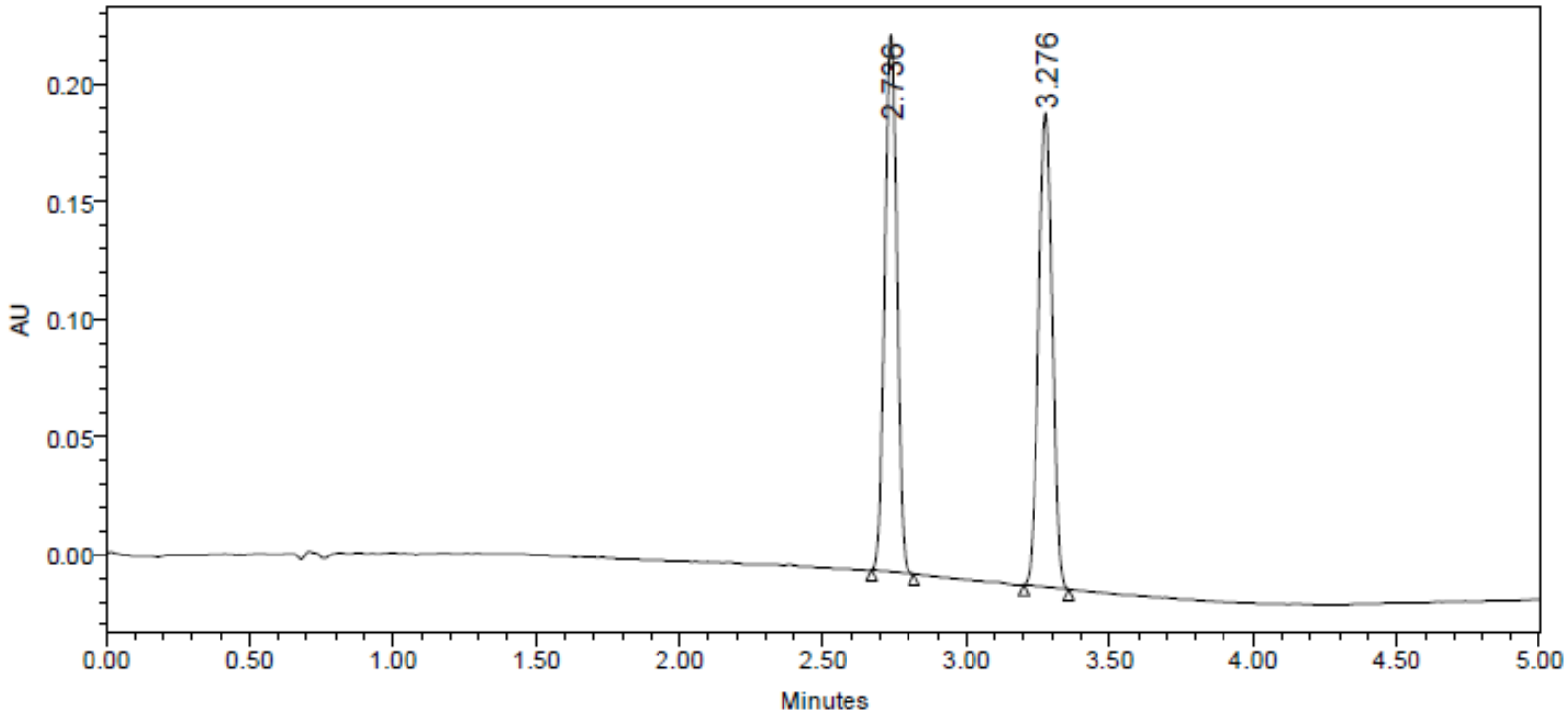
CW-3
Chiral HPLC



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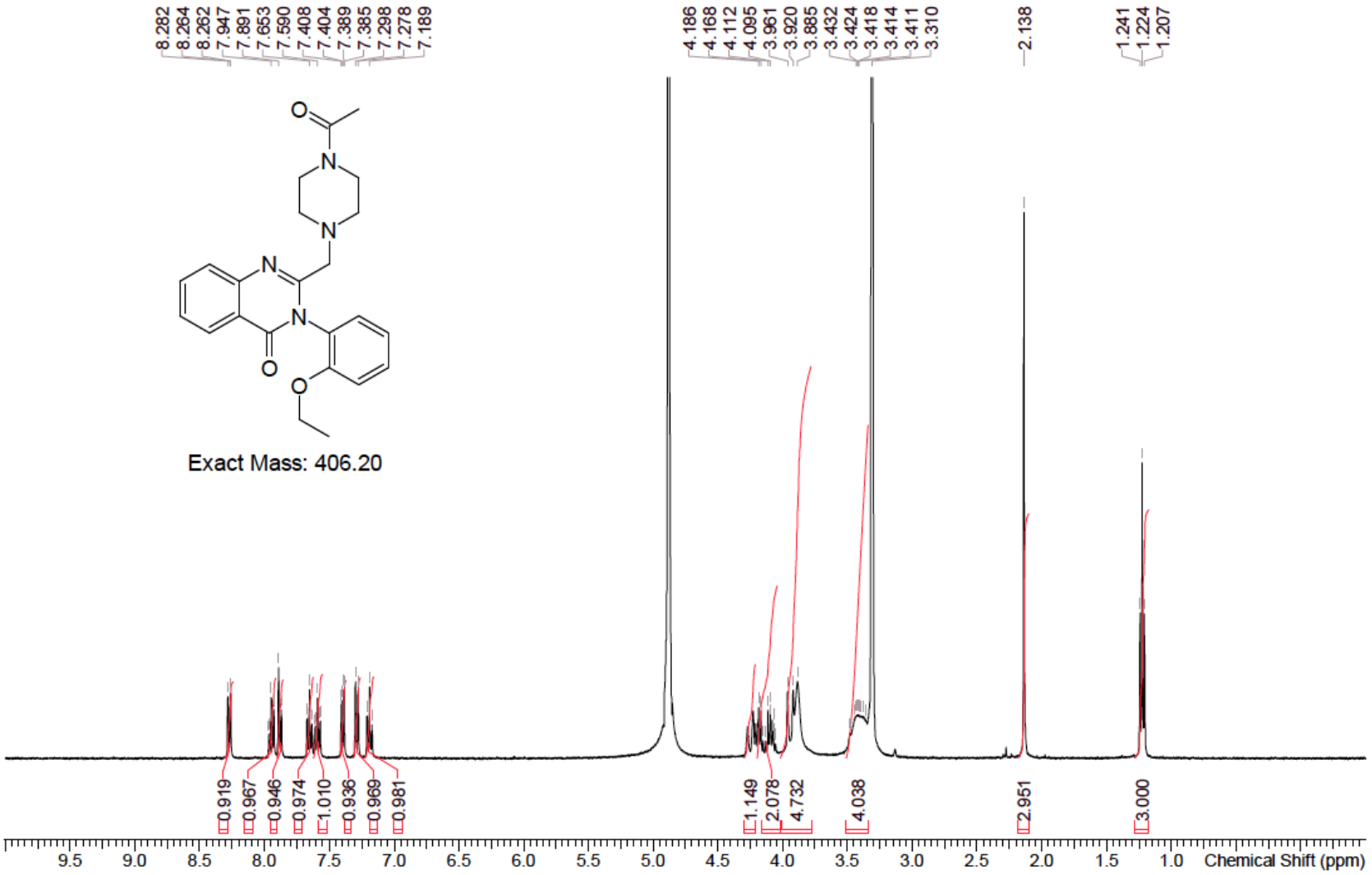
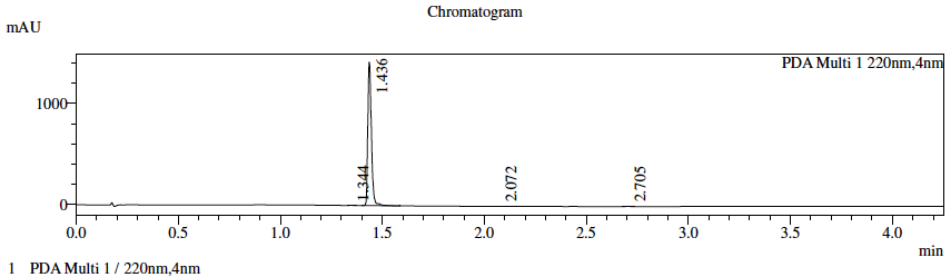
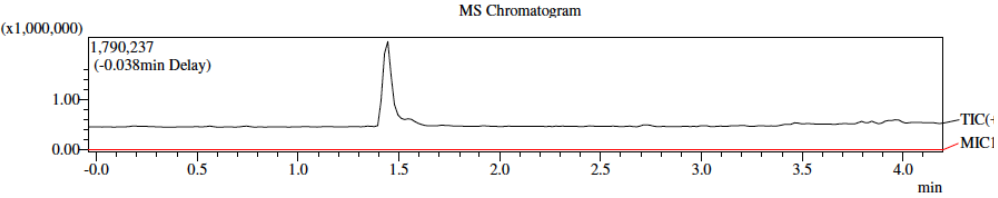
CW-4
^{1}H NMR: (400 MHz, CD_3OD)

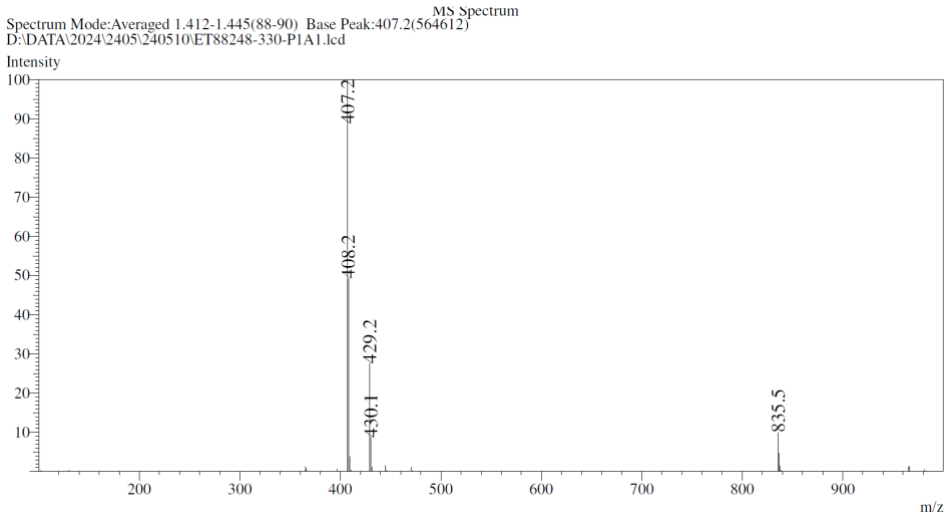


CW-4
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

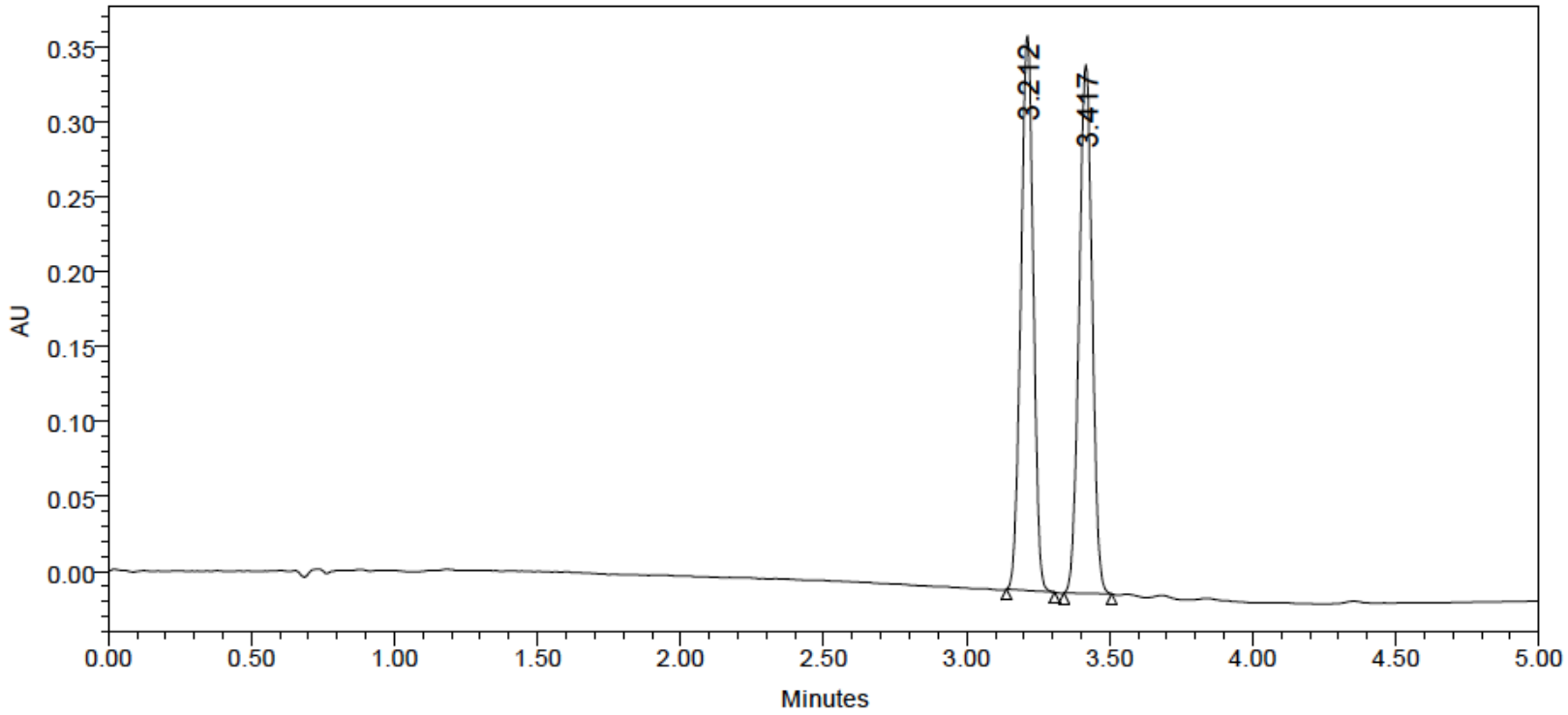
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.344	0.029	--	1597	1581	0.090
2	1.436	0.033	2.948	1416984	1740545	99.565
3	2.072	0.035	18.664	1283	1540	0.088
4	2.705	0.037	17.652	3386	4489	0.257
Total					1748154	100.000

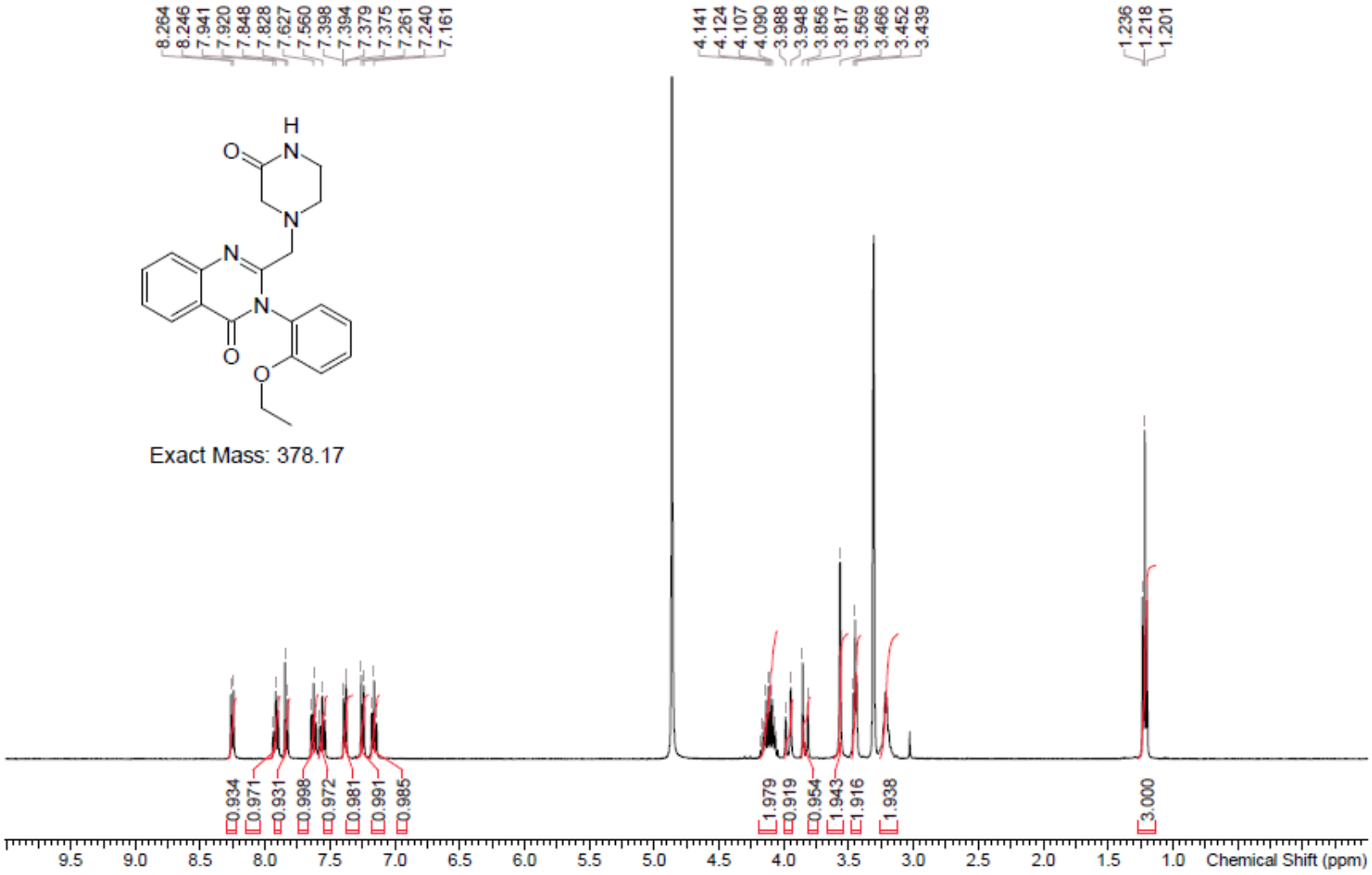
CW-4
Chiral HPLC



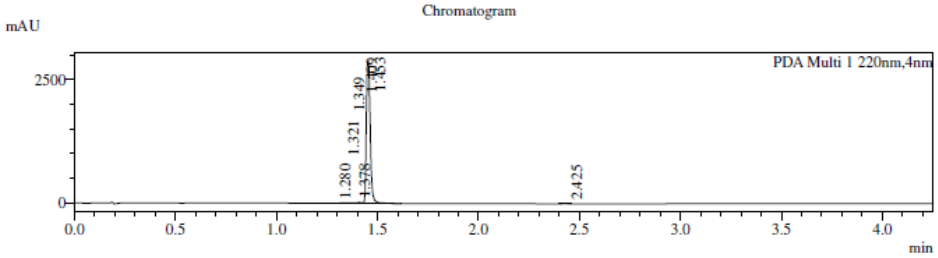
	RT	Area	% Area	Height
1	3.212	1119354	49.91	370175
2	3.417	1123434	50.09	352455

CW-5

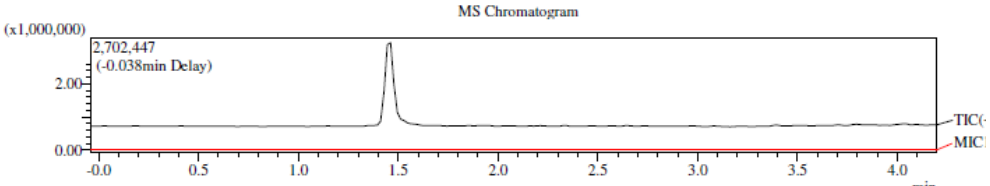
^{1}H NMR (400 MHz, CD_3OD)

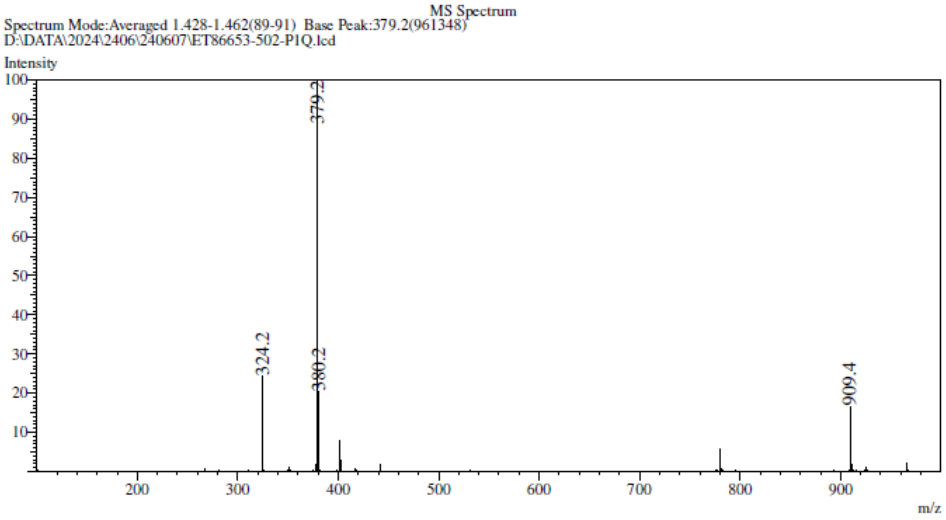


CW-5
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

ELSD

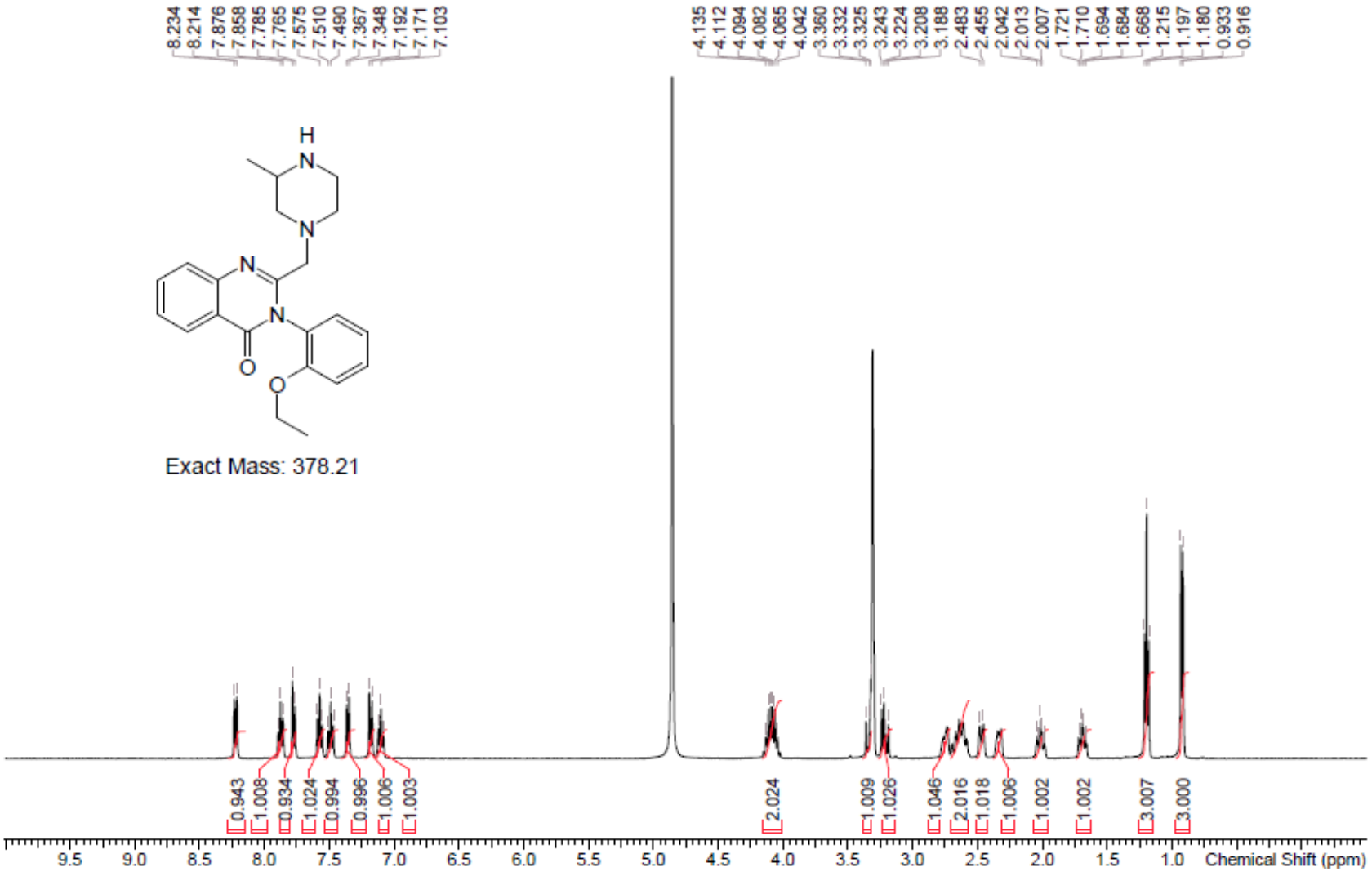
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

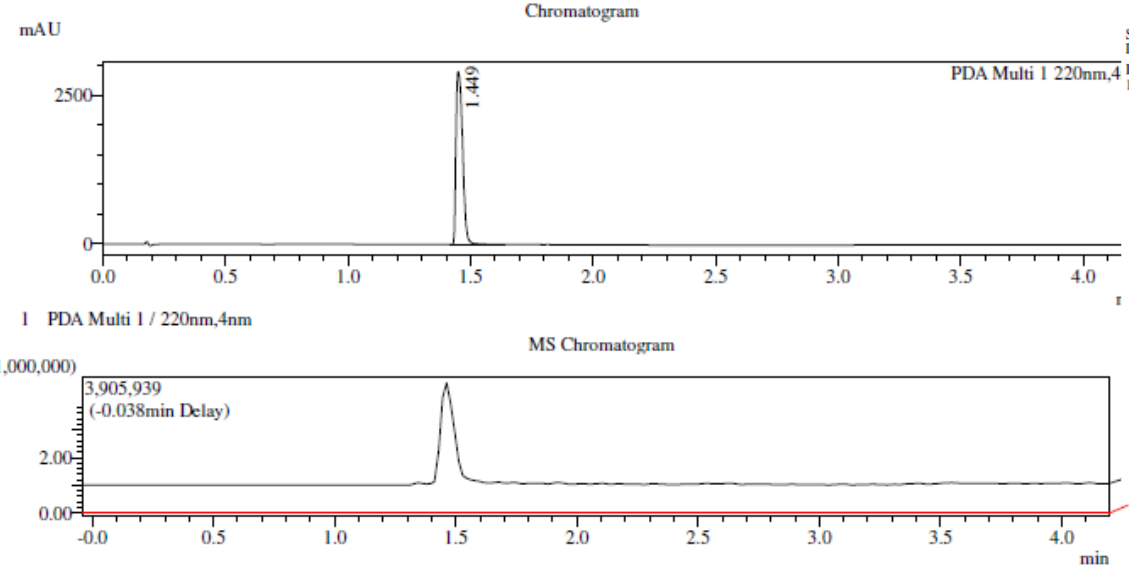
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.280	0.035	--	1829	2317	0.058
2	1.321	0.045	1.038	7878	9605	0.240
3	1.349	0.070	0.477	9246	12275	0.307
4	1.378	0.089	0.374	11758	17505	0.437
5	1.409	0.063	0.407	18756	30047	0.751
6	1.453	0.034	0.906	2892782	3927334	98.144
7	2.425	0.044	24.752	1517	2503	0.063
Total					4001587	100.000

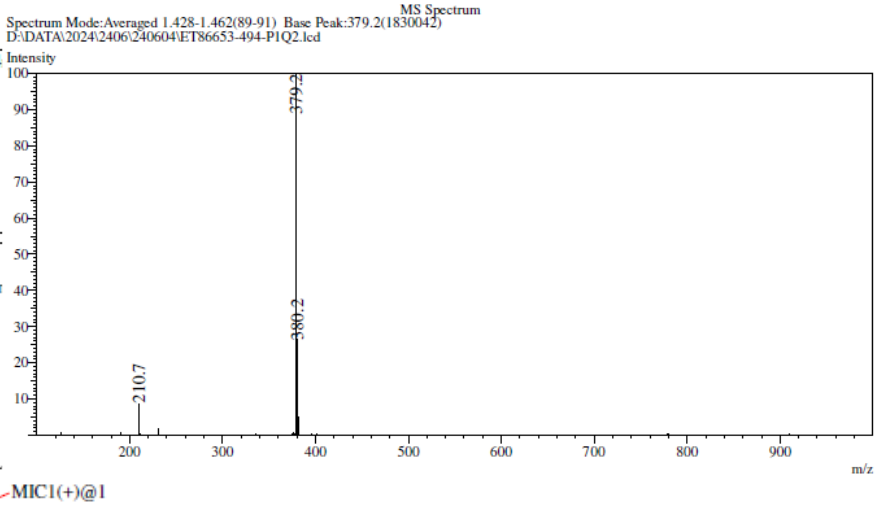
CW-6

^{1}H NMR: (400 MHz, CD_3OD)



CW-6
LC-MS





Integration Result

Peak Table

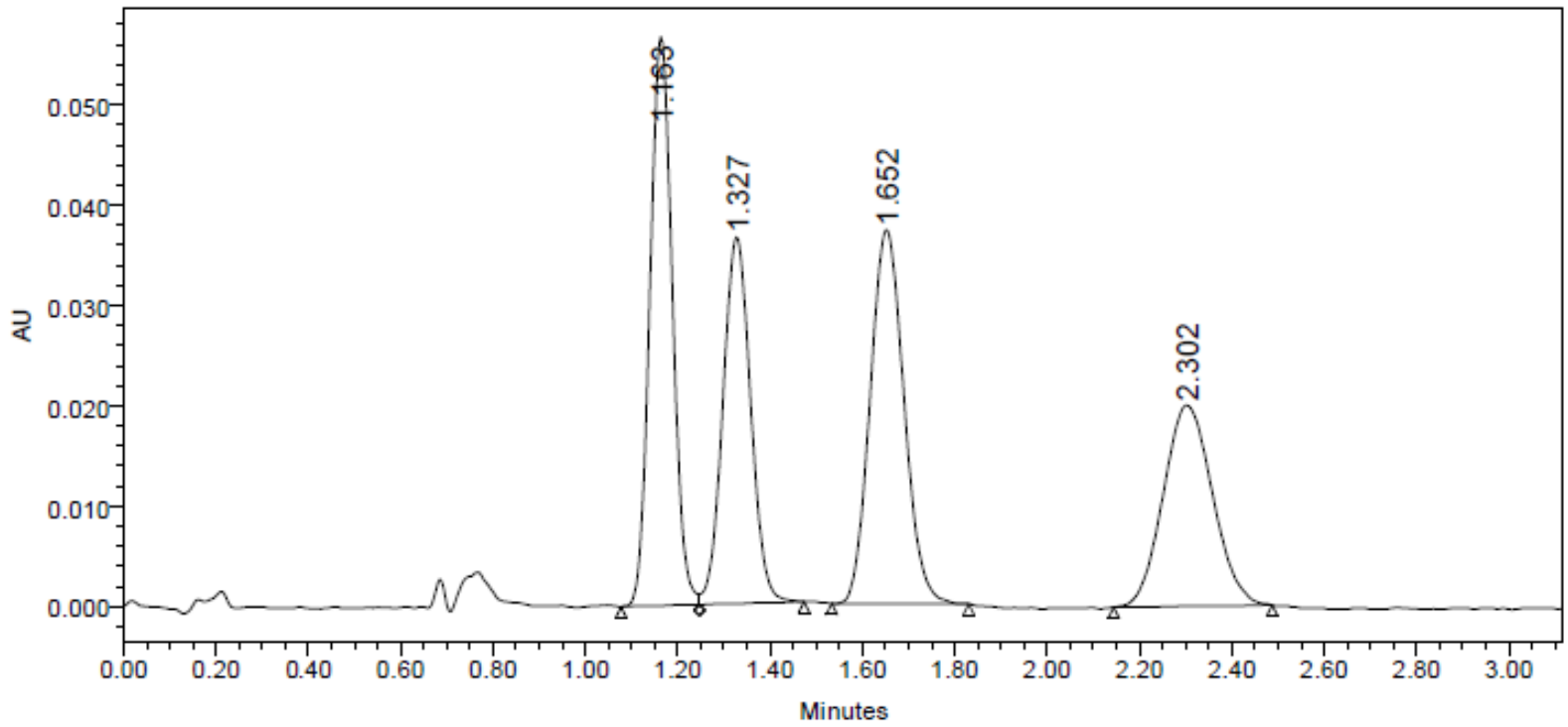
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

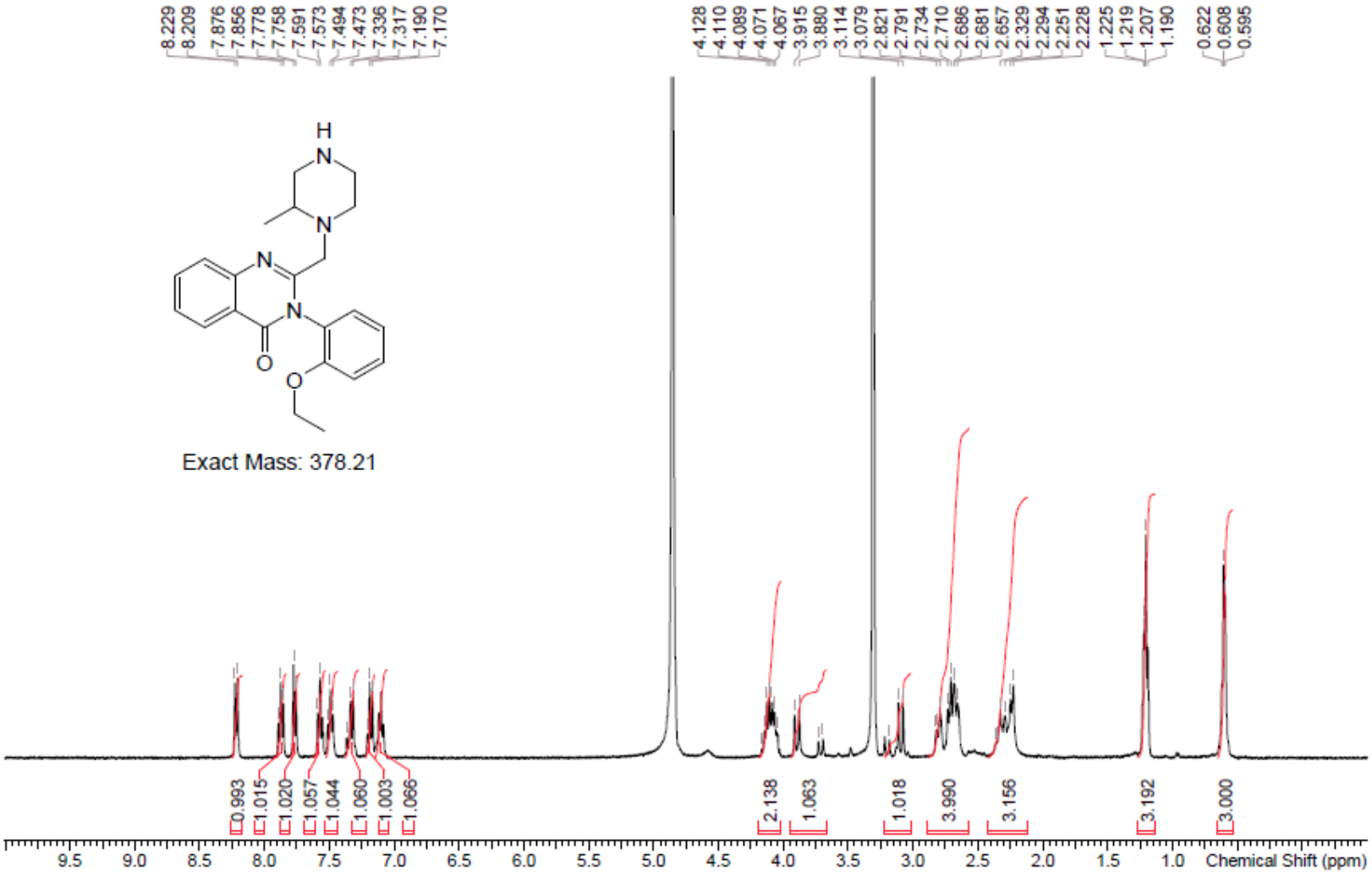
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.449	0.048	--	2900677	5464399	100.000
Total					5464399	100.000

CW-6
Chiral HPLC

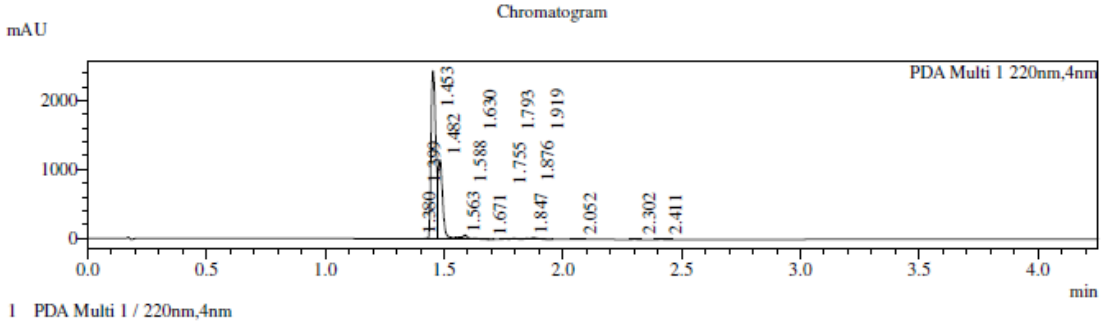


	RT	Area	% Area	Height
1	1.163	191291	28.02	56659
2	1.327	152676	22.36	36519
3	1.652	189664	27.78	37290
4	2.302	149057	21.83	20040

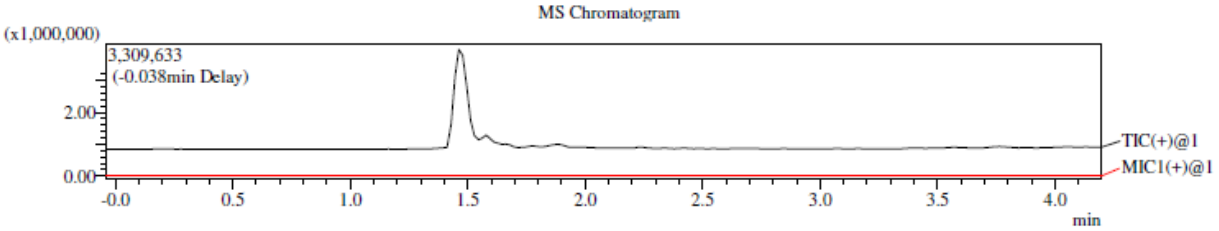
CW-7
^{1}H NMR (400 MHz, CD_3OD)



CW-7
LC-MS



1 PDA Multi 1 / 220nm,4nm



Integration Result

Peak Table

ELSD

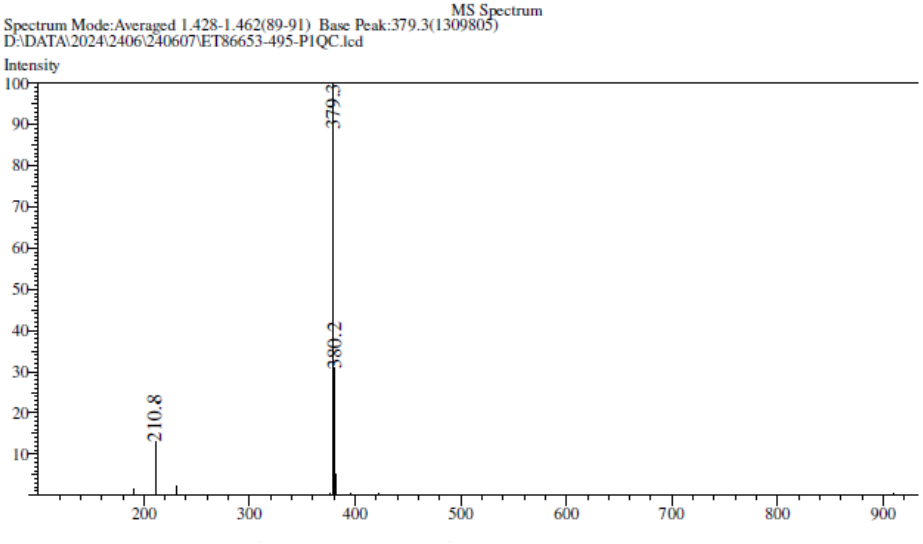
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

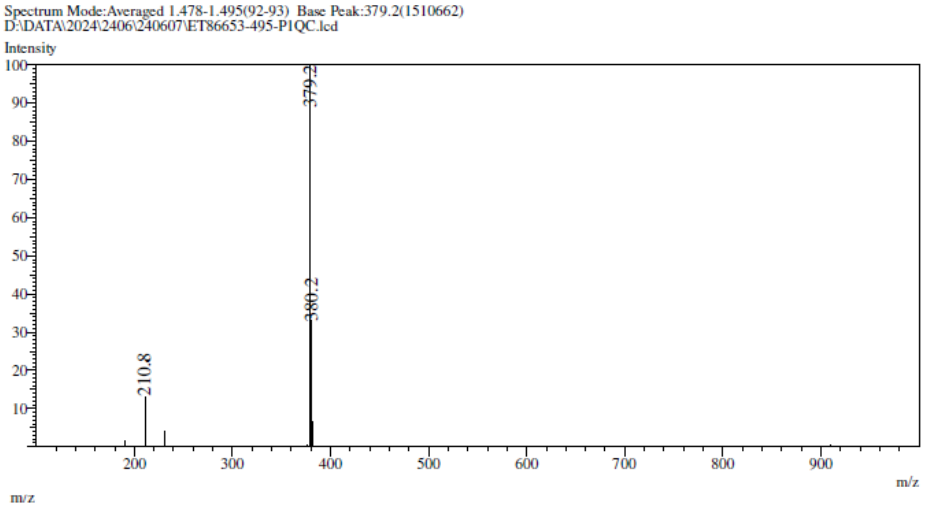
PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.380	0.431	--	1752	1703	0.033
2	1.399	0.054	0.078	2843	2708	0.053
3	1.453	0.041	1.128	2438772	3382237	66.361
4	1.482	0.066	0.544	1145077	1561892	30.645
5	1.563	0.068	1.211	16391	16052	0.315
6	1.588	0.036	0.478	47316	57800	1.134
7	1.630	0.036	1.178	1712	2103	0.041
8	1.671	0.036	1.119	1770	2312	0.045
9	1.755	0.041	2.187	2734	3421	0.067
10	1.793	0.041	0.935	7449	10877	0.213
11	1.847	0.043	1.269	8086	9435	0.185
12	1.876	0.042	0.679	19203	31616	0.620
13	1.919	0.060	0.842	5445	6635	0.130
14	2.052	0.037	2.724	1970	2652	0.052
15	2.302	0.033	7.124	1455	1705	0.033
16	2.411	0.050	2.623	1900	3592	0.070
Total					5096739	100.000

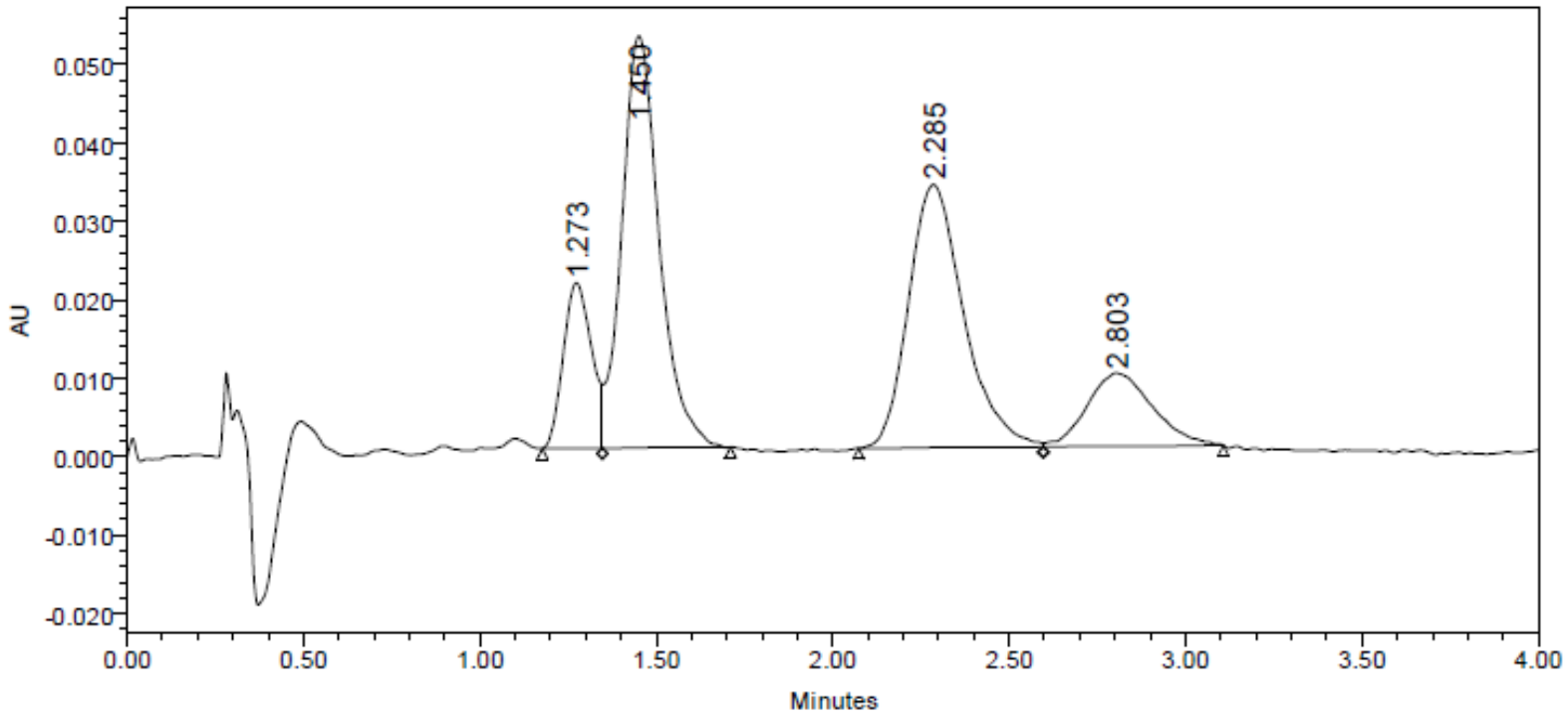
MS Peak Table MIC1

CW-7
LC-MS continued



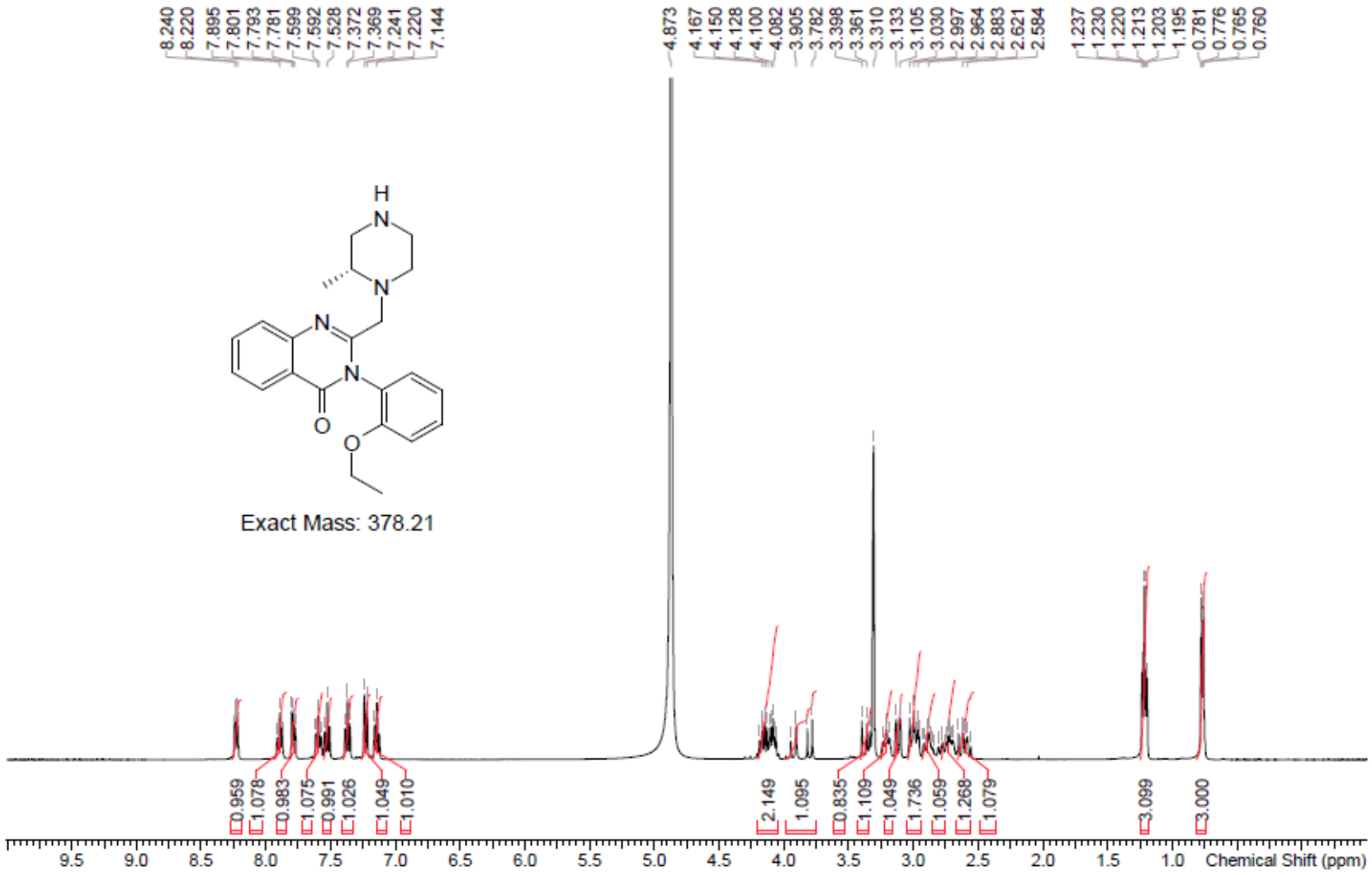


CW-7
Chiral HPLC

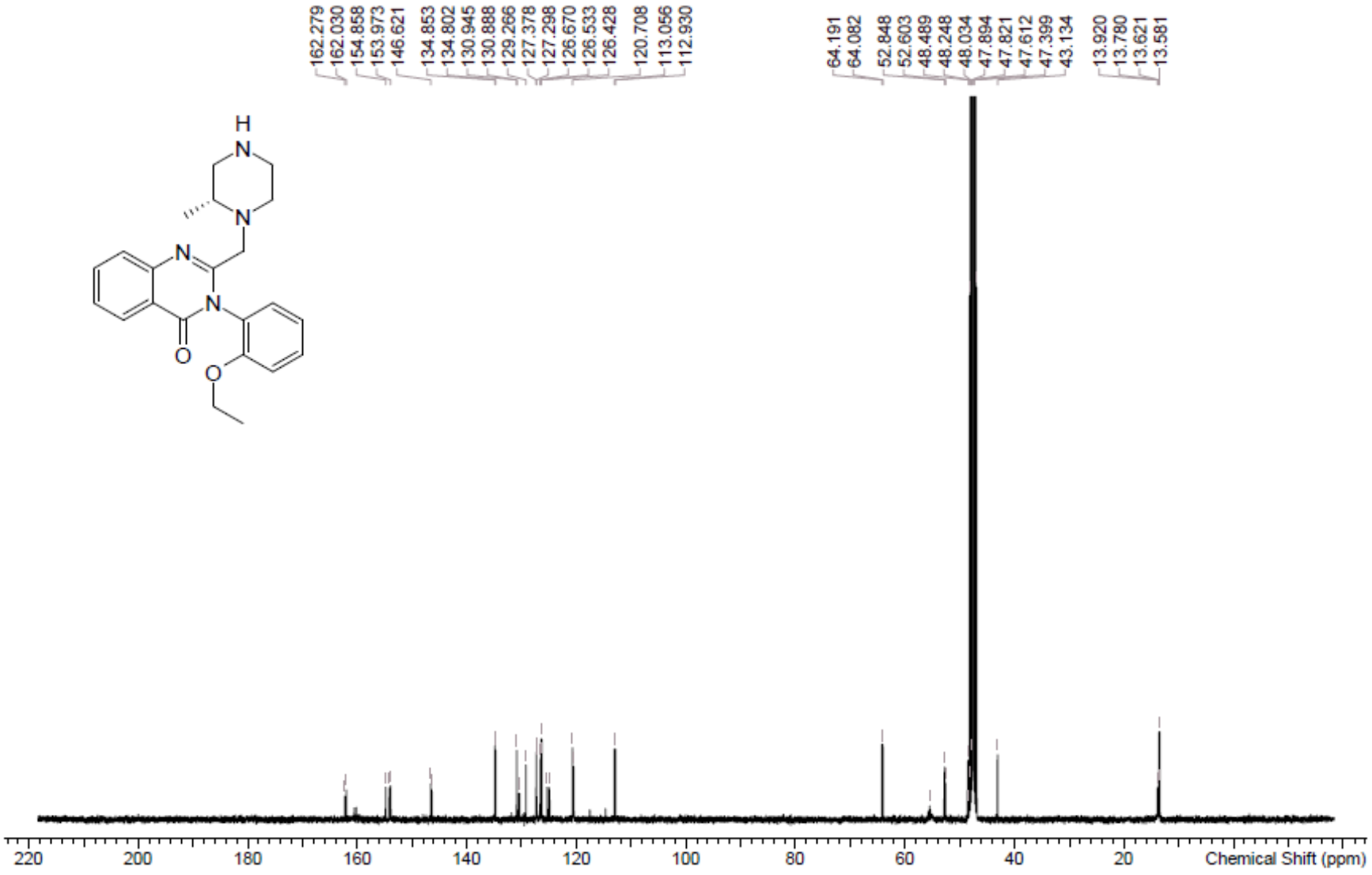


	RT	Area	% Area	Height
1	1.273	117793	11.87	21152
2	1.450	388891	39.20	52521
3	2.285	364914	36.78	33580
4	2.803	120506	12.15	9338

CW-8
^{1}H NMR: (400 MHz, CD_3OD)

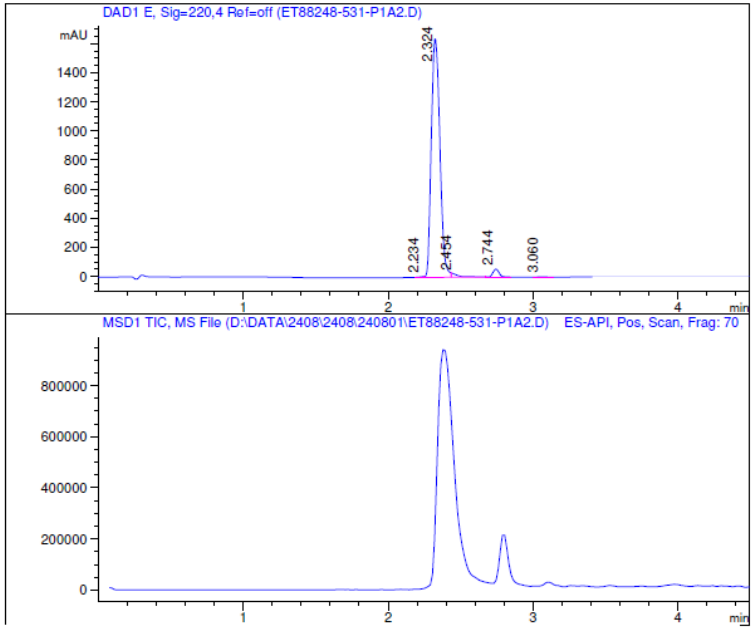


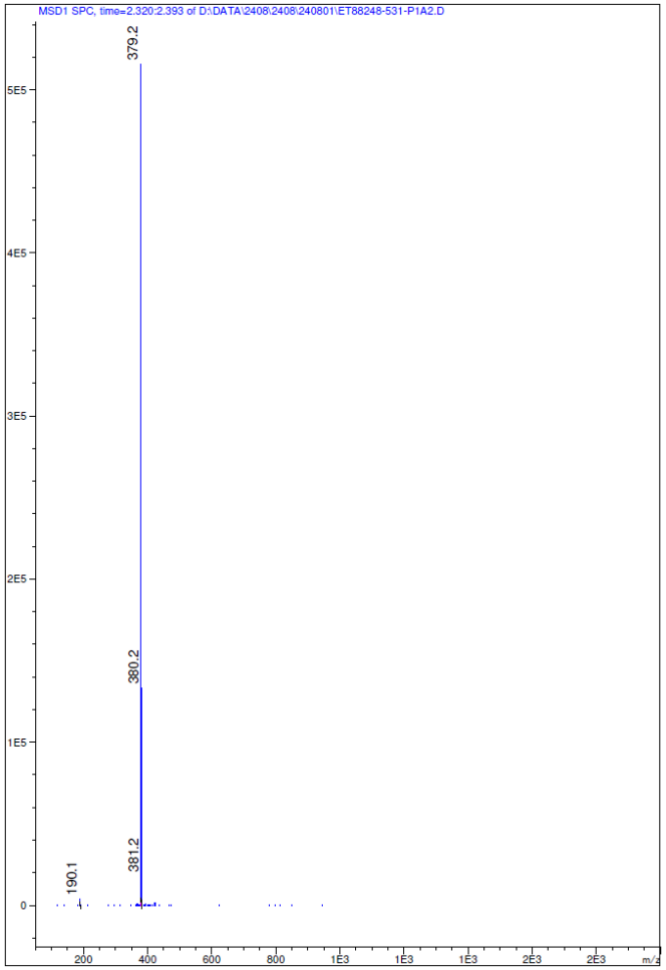
CW-8
^{13}C NMR: (101 MHz, CD_3OD)



CW-8
LC-MS

```
Method Info     ->Instrument:Agilent 1200 HPLC
                  MSD:6120 single quadrupole MSD
                  Column:XBridge C18,2.1*50mm, 5μm
                  Column Temp: 40 °C
                  Mobile Phase:A:H2O+10mM NH4HCO3
                  Mobile Phase:B:ACN
                  Flow Rate: 0.8ml/min
                  Time                B%              Flow(ml/min)
                  0.00                5                   0.8
                  0.40                5                   0.8
                  3.40                95                  0.8
                  3.85                95                  0.8
                  3.86                5                   0.8
                  4.50                5                   0.8
```

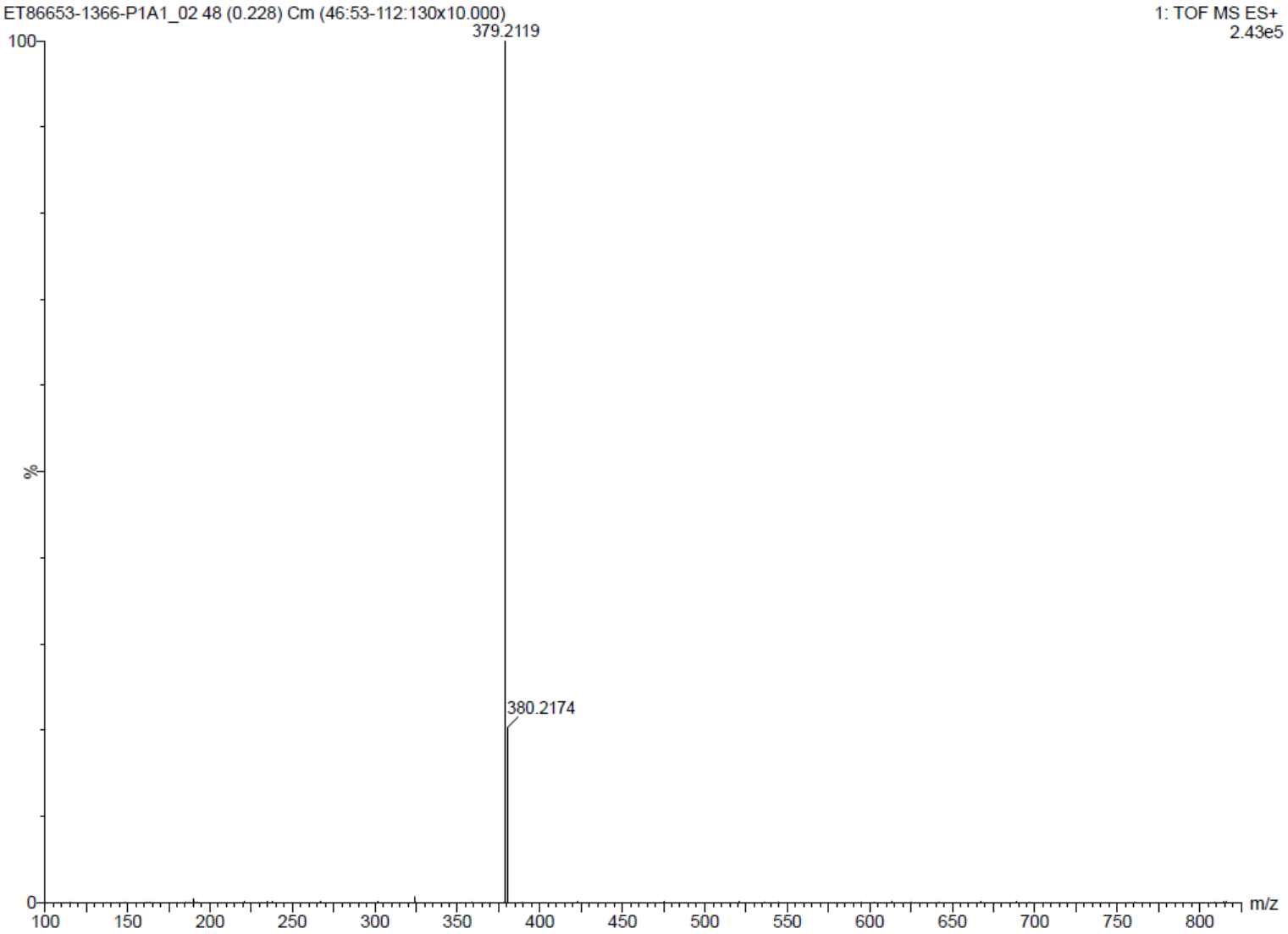




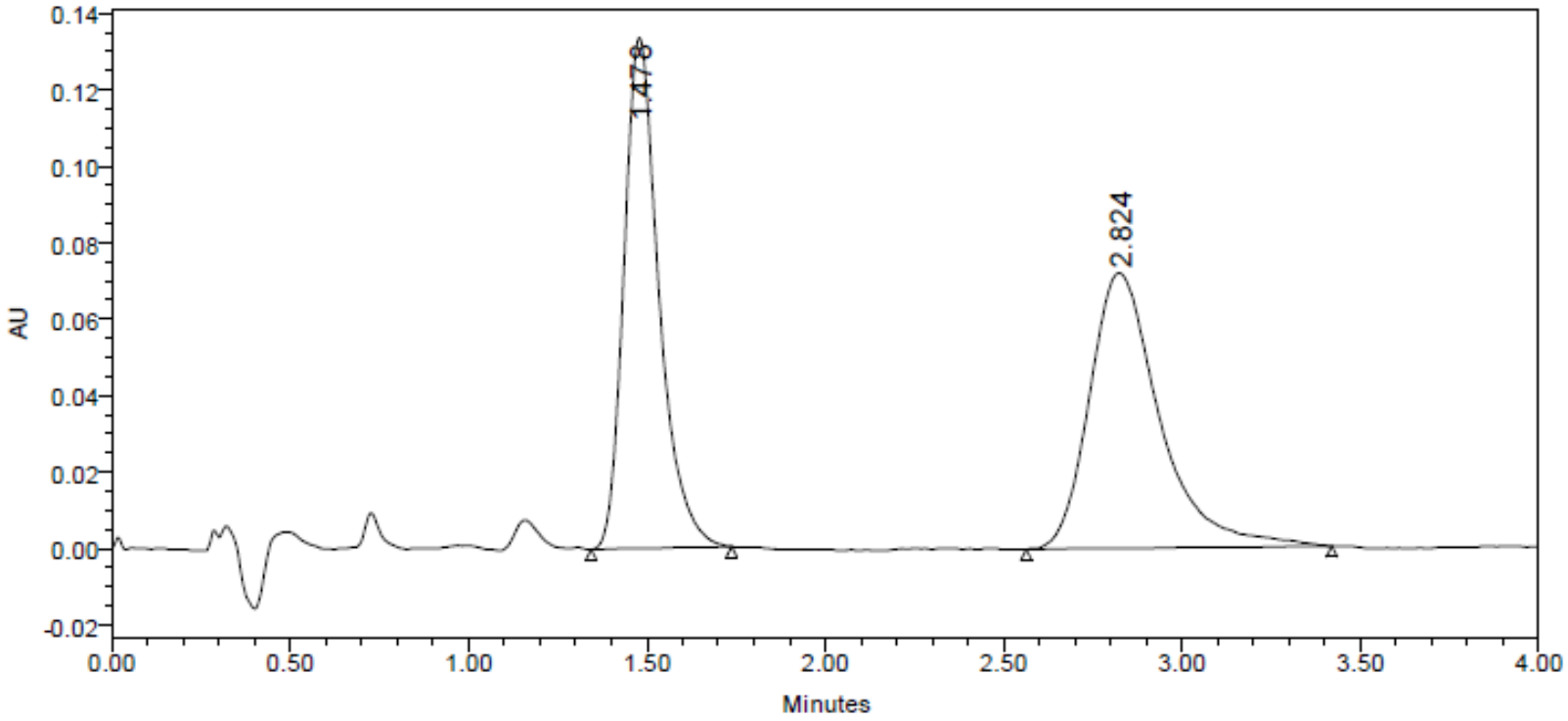
Signal 1 :DAD1 E, Sig=220,4 Ref=off

Peak #	RT [min]	Height	Height %	Width [min]	Area	Area %
1	2.234	5.419	0.312	0.030	11.332	0.161
2	2.324	1650.220	95.061	0.068	6766.576	95.881
3	2.454	23.633	1.361	0.062	108.632	1.539
4	2.744	54.834	3.159	0.047	165.096	2.339
5	3.060	1.856	0.107	0.047	5.598	0.079

CW-8
HRMS


ET86653-1366-P1A1_02 48 (0.228) Cm (46:53-112:130x10.000)
1: TOF MS ES+
2.43e5
379.2119
380.2174
100
%
0
m/z
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800

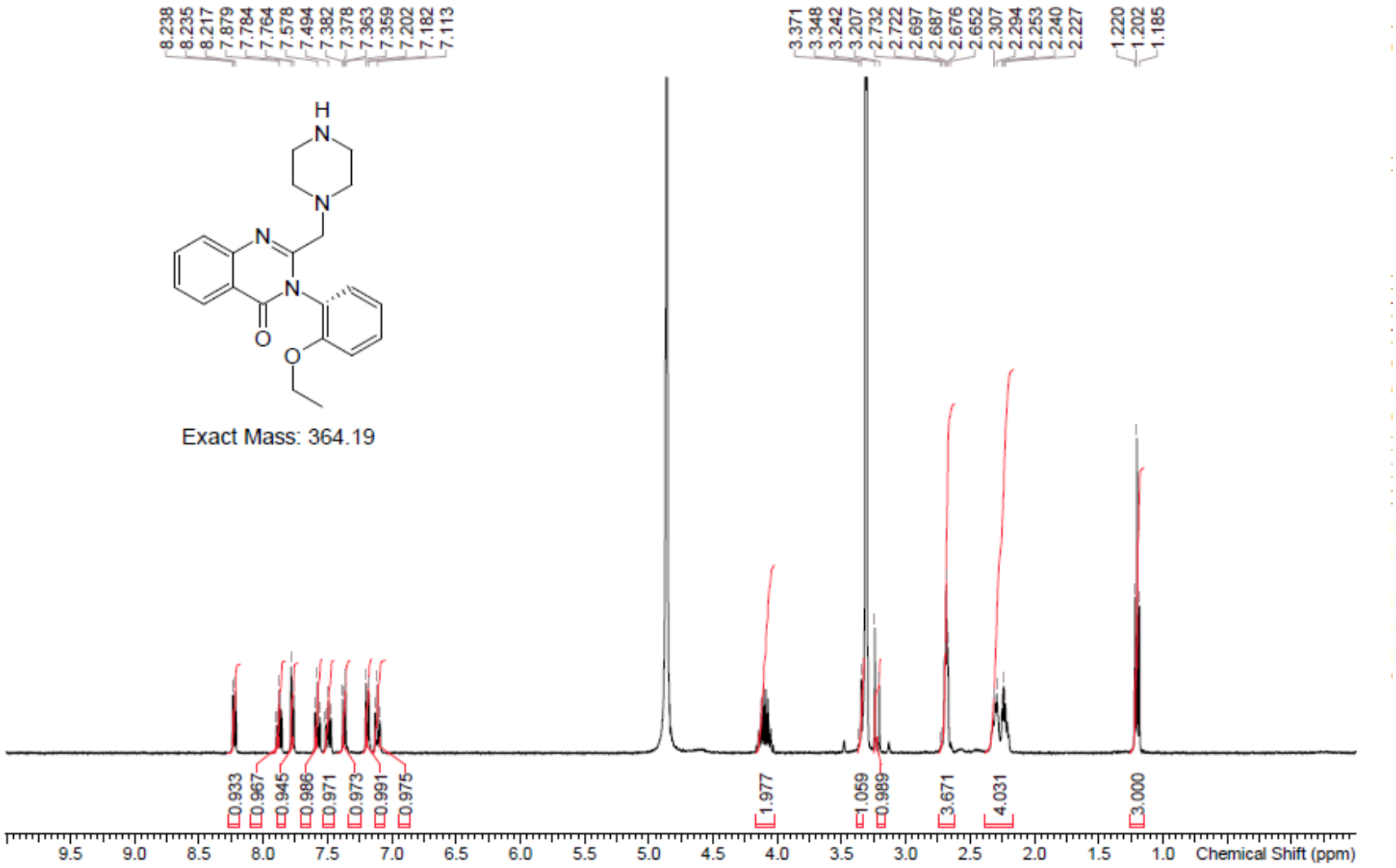
CW-8
Chiral HPLC



	RT	Area	% Area	Height
1	1.478	913097	48.08	133649
2	2.824	986105	51.92	72001

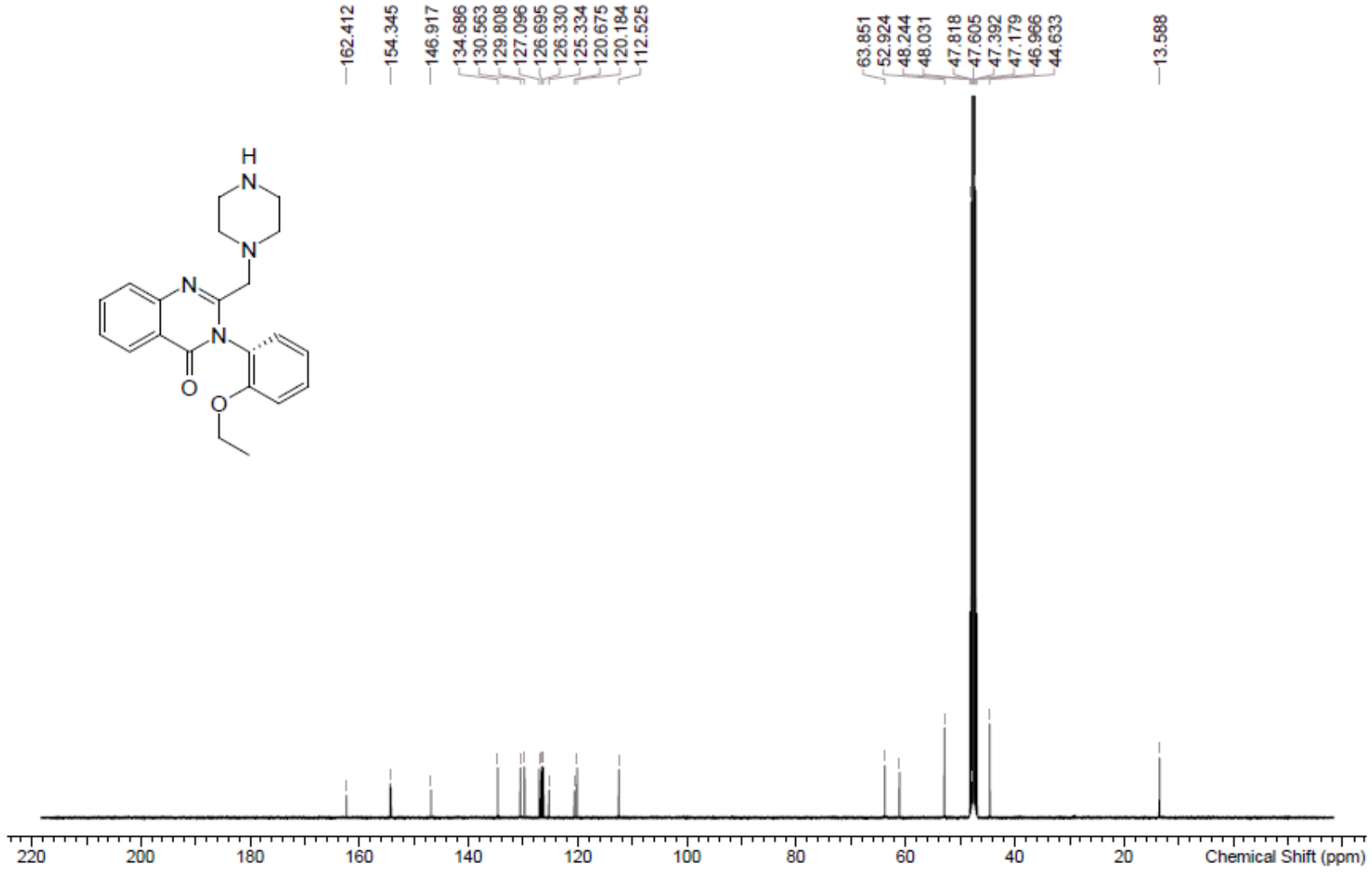
CW-9

^{1}H NMR: (400 MHz, CD_3OD)

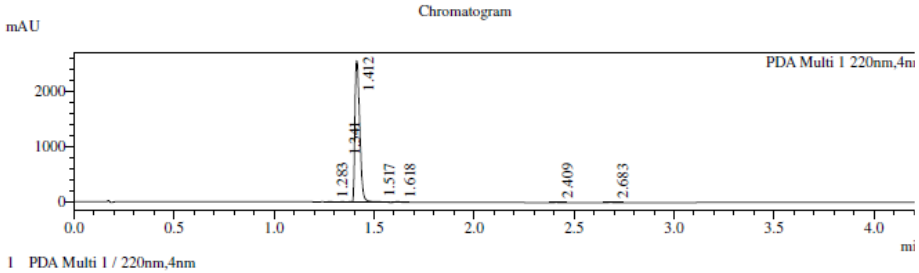


CW-9

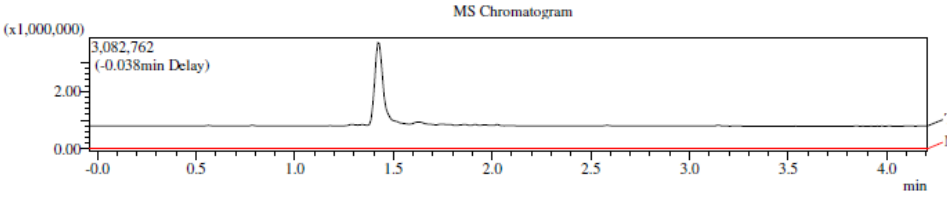
^{13}C NMR (101 MHz, CD_3OD)



CW-9
LC-MS



1 PDA Multi 1 / 220nm,4nm



Integration Result

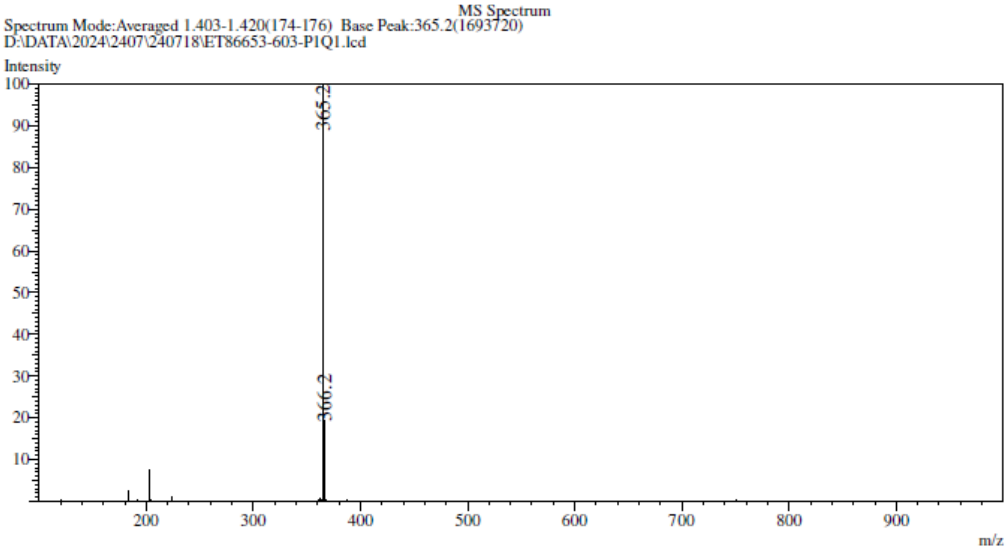
Peak Table

ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

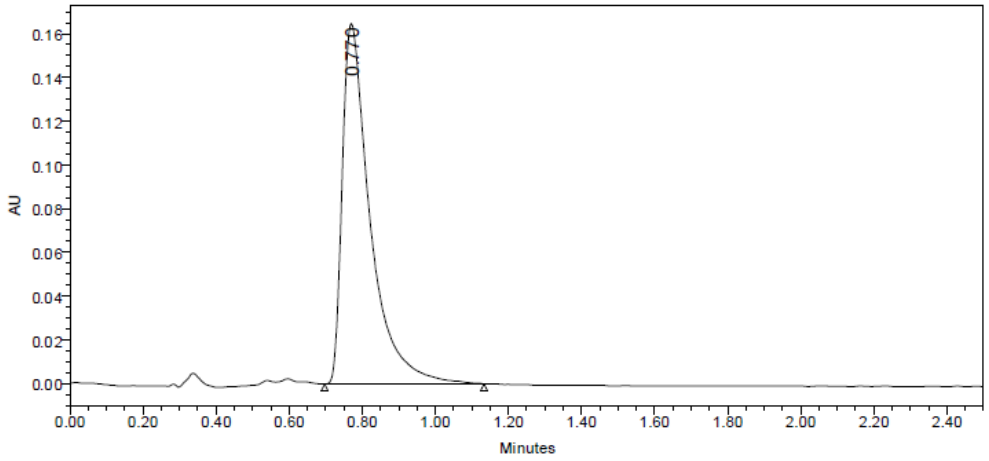
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.283	0.047	--	2355	3830	0.089
2	1.341	0.031	1.488	3786	4118	0.095
3	1.412	0.044	1.907	2555041	4270677	98.919
4	1.517	0.058	2.042	9923	16999	0.394
5	1.618	0.041	2.011	7384	11359	0.263
6	2.409	0.047	17.890	1625	3049	0.071
7	2.683	0.044	6.032	4474	7306	0.169
Total					4317338	100.000



CW-9
HRMS


ET86653-1361-P1A1 19 (0.169) Cm (19:23-106x10.000)
1: TOF MS ES+
1.51e6
365.1972
366.2013
183.1021
100
%
0
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
m/z

CW-9
Chiral HPLC



	RT	Area	% Area	Height
1	0.770	872897	100.00	164941

CW-9
Specific Rotation

Solvent : MeOH

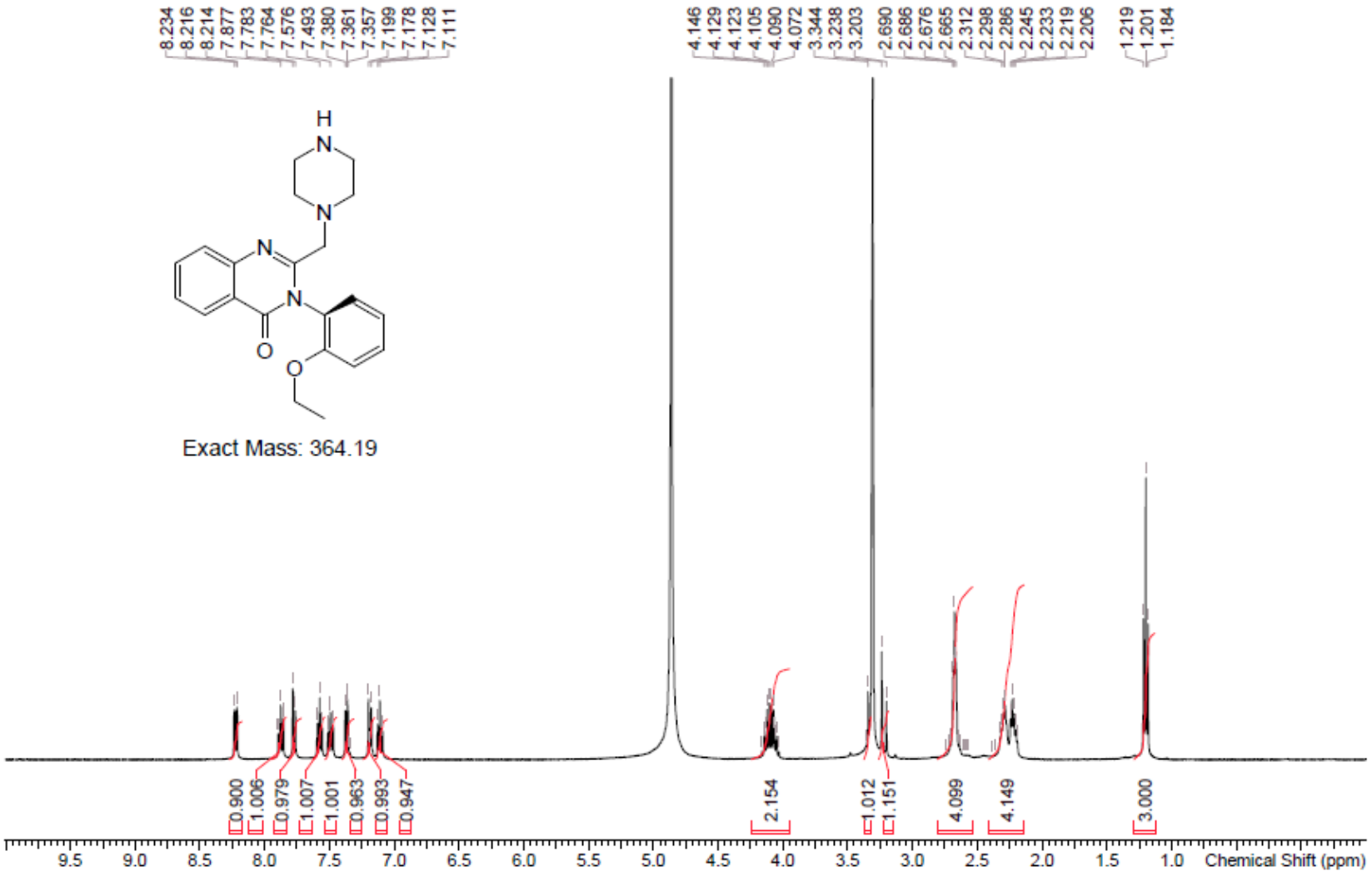
Set Temperature : 20.0°C

N	Avg.	Std.Dev.	%RSD	Min	Max
3	-80.2	3.6	-4.48	-84.4	-78.1

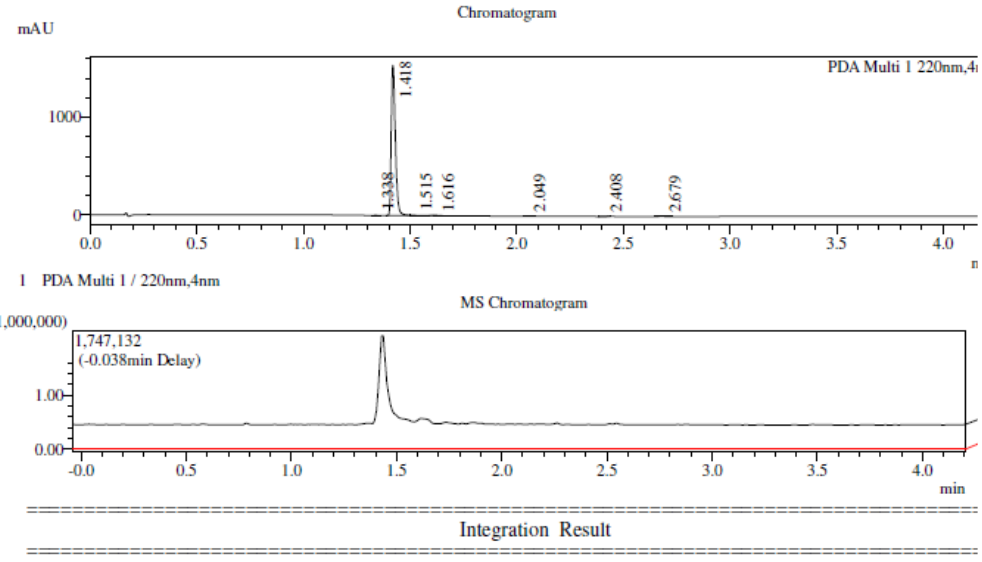
S.No	Result	Scale	OR °Arc	WLG.nm	Lg.mm	Conc.g/100mL	Temp
1	-84.4	SR	-0.027	589	50	0.0640	20.0°C
2	-78.1	SR	-0.025	589	50	0.0640	20.0°C
3	-78.1	SR	-0.025	589	50	0.0640	20.0°C

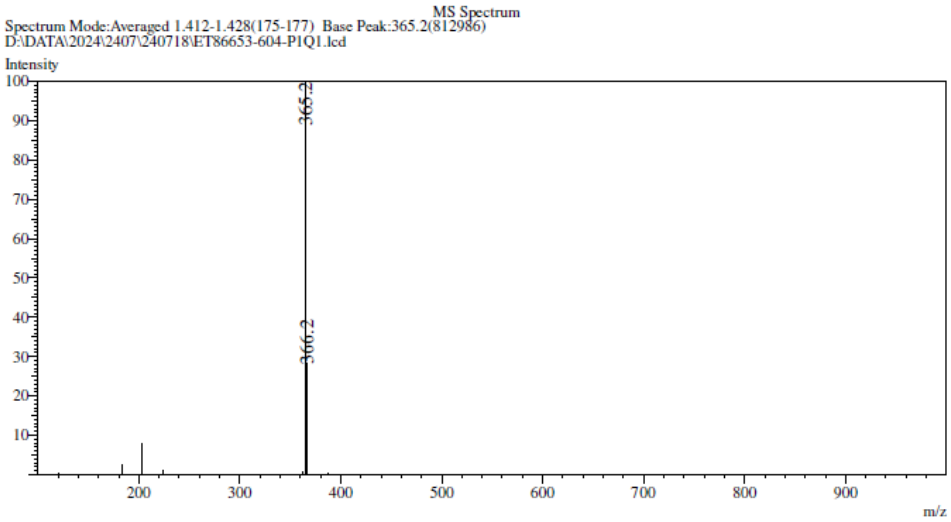
CW-10

^{1}H NMR: (400 MHz, CD_3OD)



CW-10
LC-MS





Integration Result

Peak Table

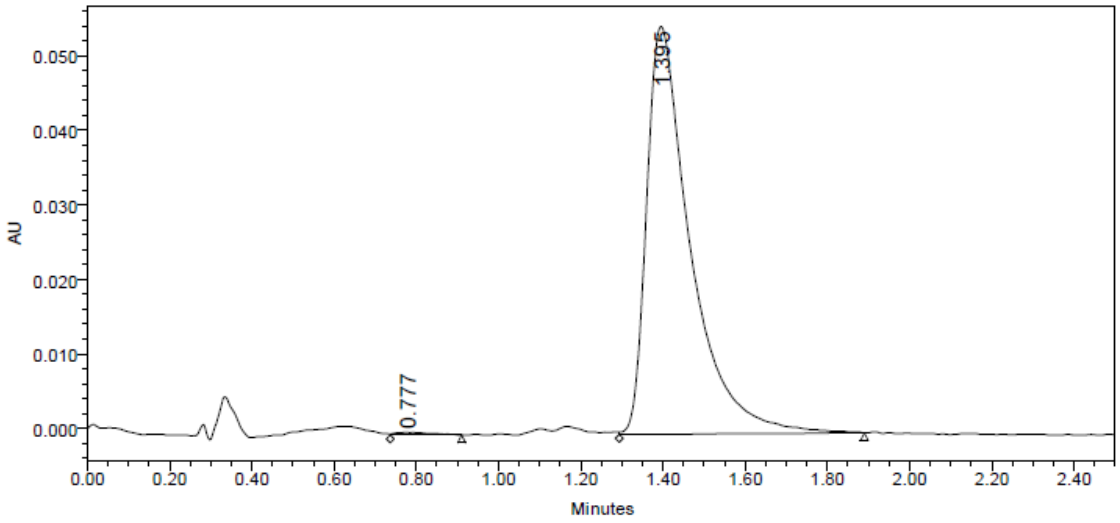
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.338	0.028	--	1282	1214	0.058
2	1.418	0.036	2.498	1540825	2071781	98.658
3	1.515	0.059	2.008	4923	8278	0.394
4	1.616	0.042	1.992	6183	9673	0.461
5	2.049	0.038	10.767	1169	1636	0.078
6	2.408	0.044	8.771	1783	2757	0.131
7	2.679	0.046	6.049	2694	4624	0.220
Total					2099964	100.000

CW-10
Chiral HPLC



	RT	Area	% Area	Height
1	0.777	2218	0.55	348
2	1.395	404471	99.45	54735

CW-10
Specific Rotation

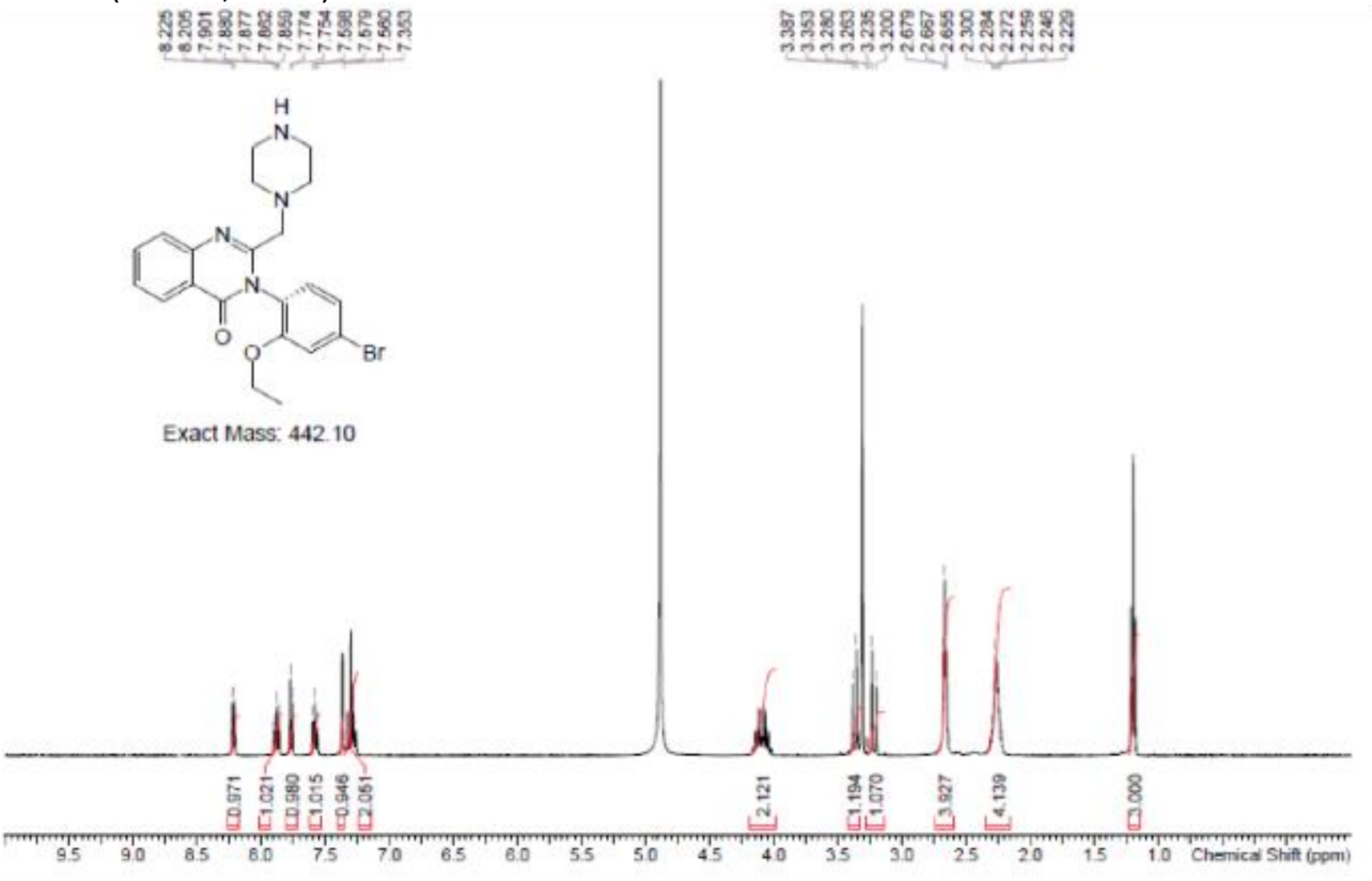
Solvent : MeOH

Set Temperature : 20.0°C

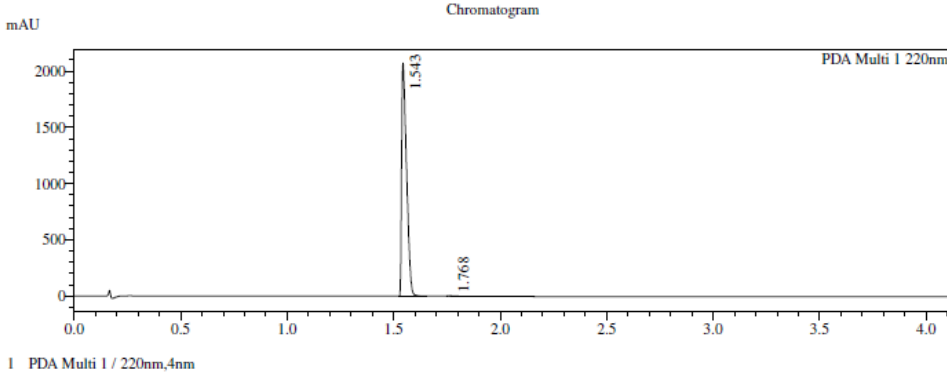
N	Avg.	Std.Dev.	%RSD	Min	Max
3	83.8	2.3	2.74	81.2	85.1

S.No	Result	Scale	OR °Arc	WLG.nm	Lg.mm	Conc.g/100mL	Temp
1	81.2	SR	0.041	589	50	0.1010	20.0°C
2	85.1	SR	0.043	589	50	0.1010	20.0°C
3	85.1	SR	0.043	589	50	0.1010	20.0°C

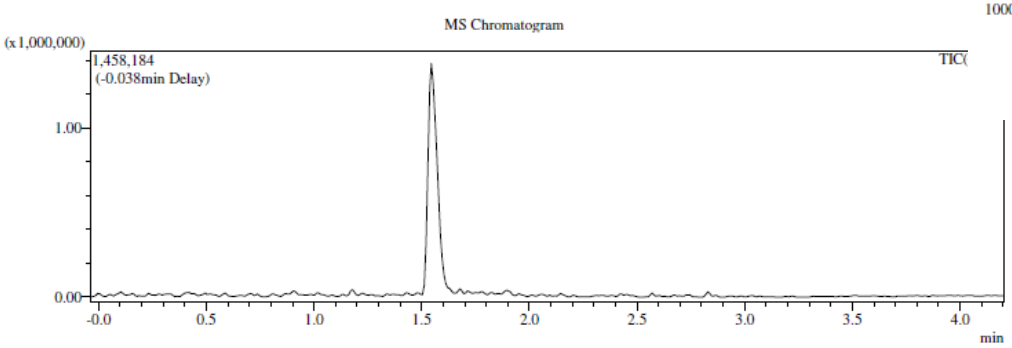
CW-11
^{1}H NMR: (400 MHz, CD_3OD)

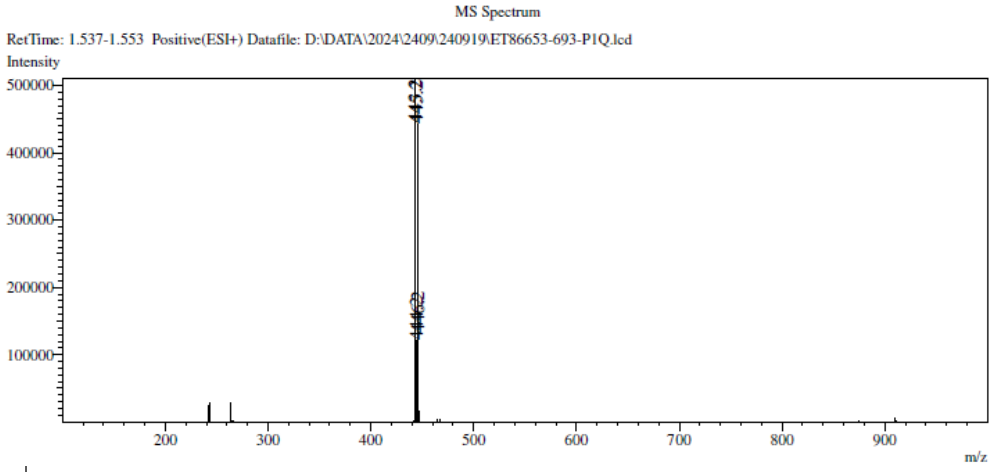


CW-11
LC-MS



1 PDA Multi 1 / 220nm,4nm





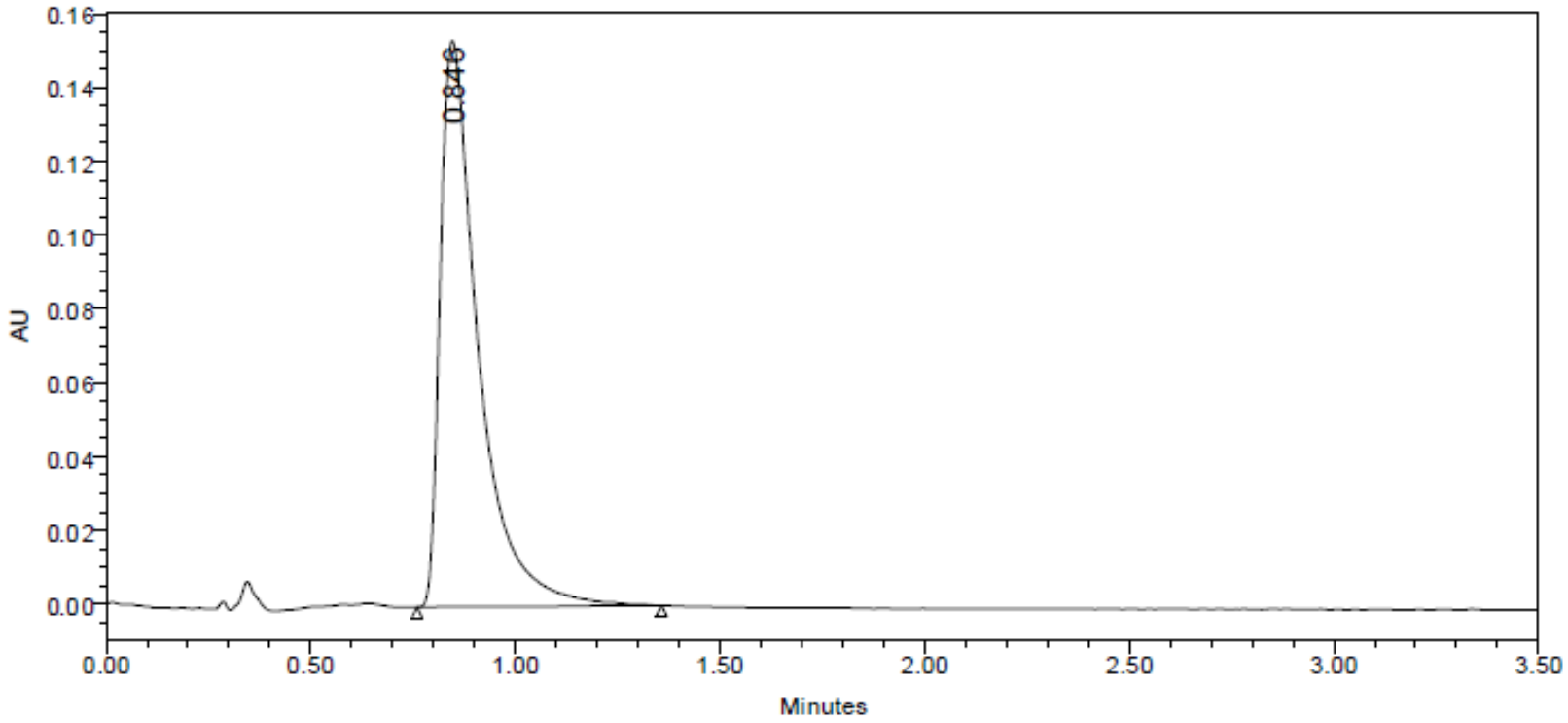
Integration Result

ELSD

PDA Ch1 220nm

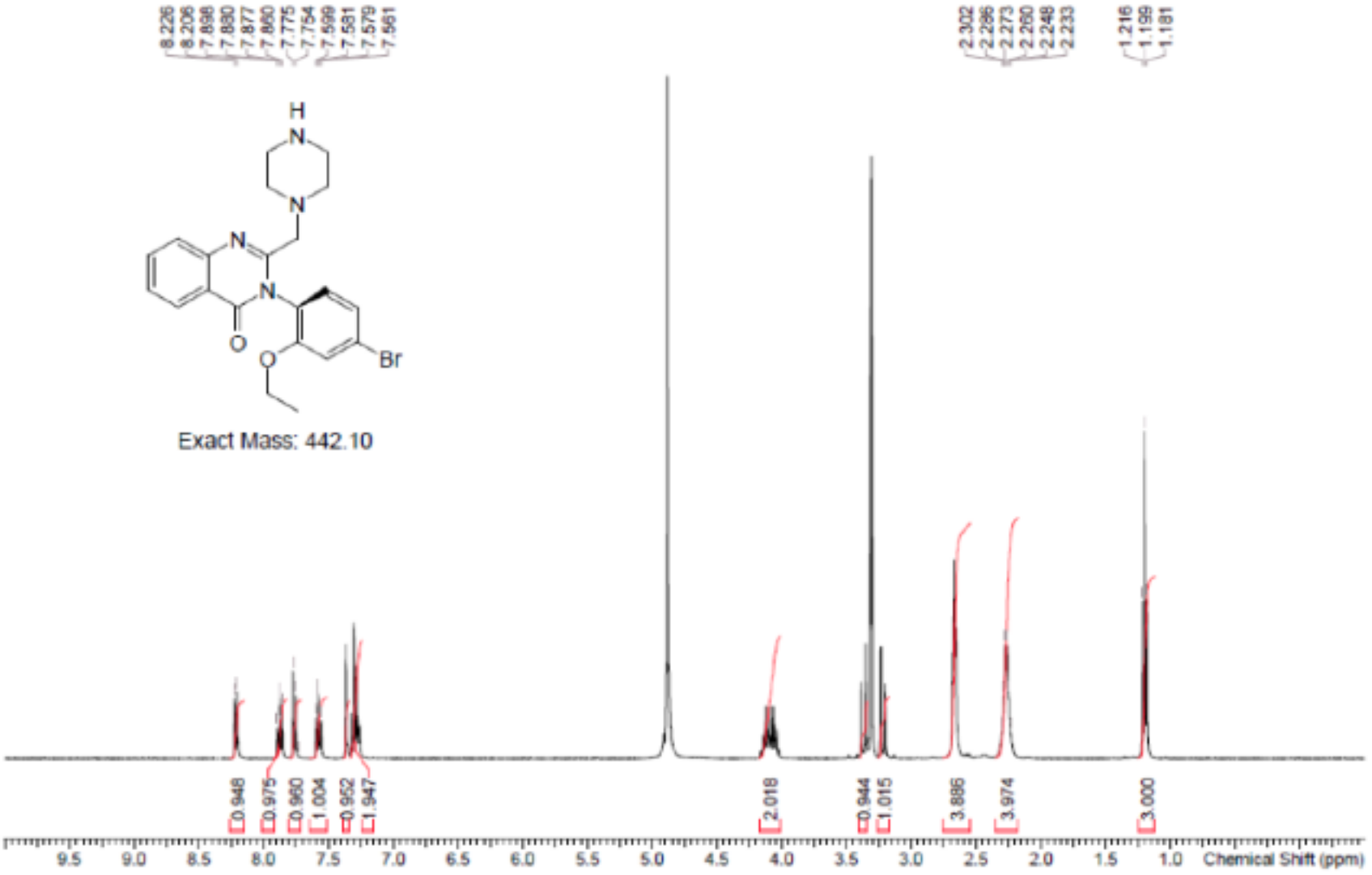
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	1.543	0.046	2071710	99.778	3348934	99.844
2	1.768	0.030	4618	0.222	5245	0.156

CW-11
Chiral HPLC

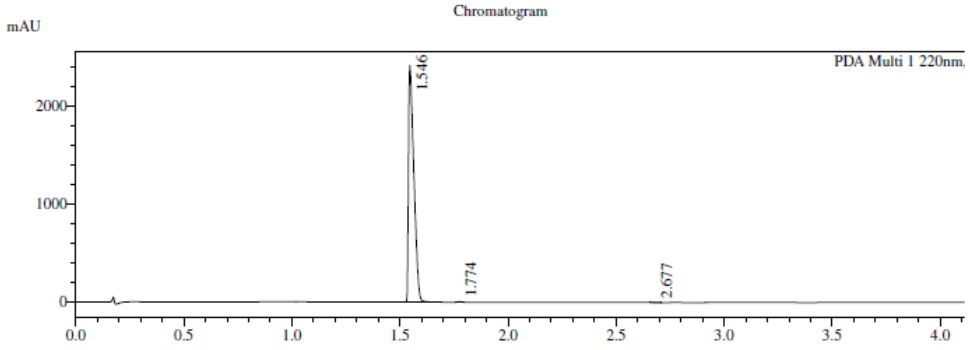


	RT	Area	% Area	Height
1	0.846	999502	100.00	153493

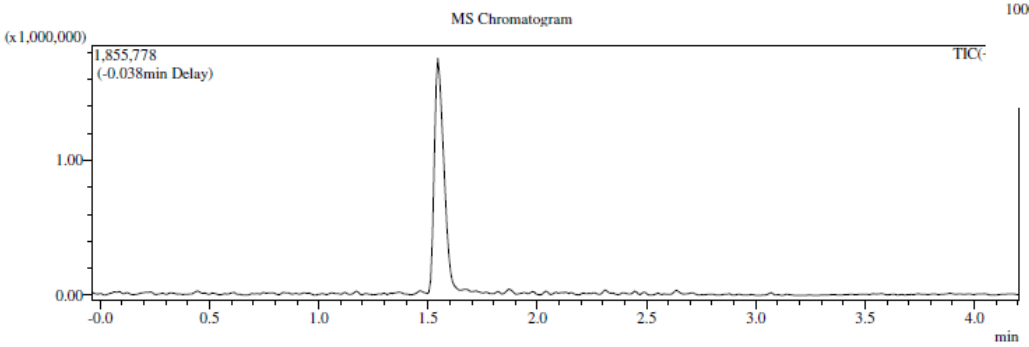
CW-12
^{1}H NMR: (400 MHz, CD_3OD)

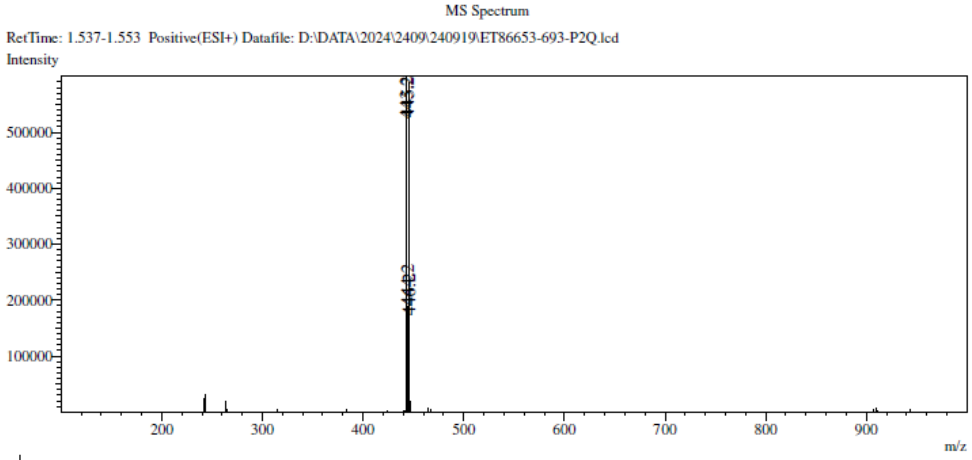


CW-12
LC-MS



1 PDA Multi 1 / 220nm,4nm





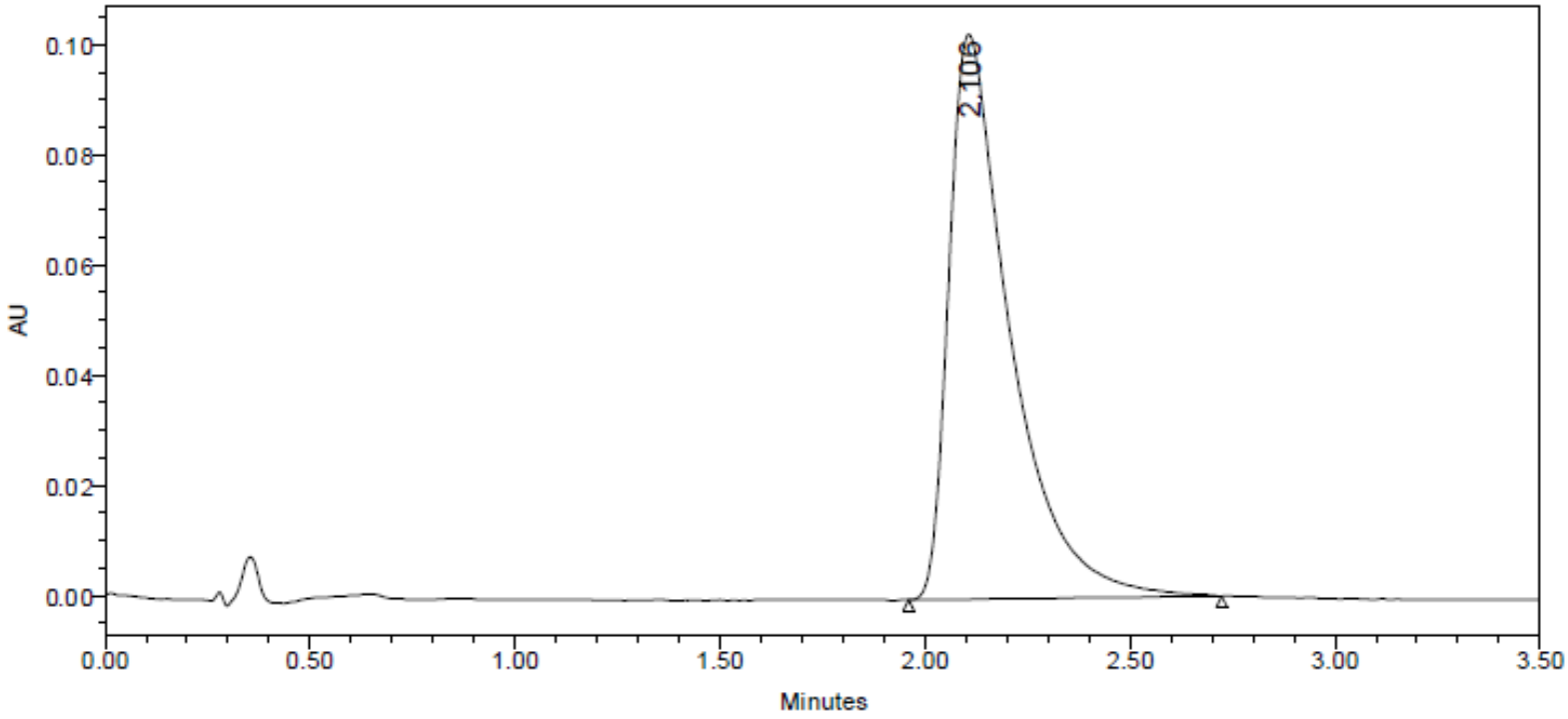
Integration Result

ELSD

PDA Ch1 220nm

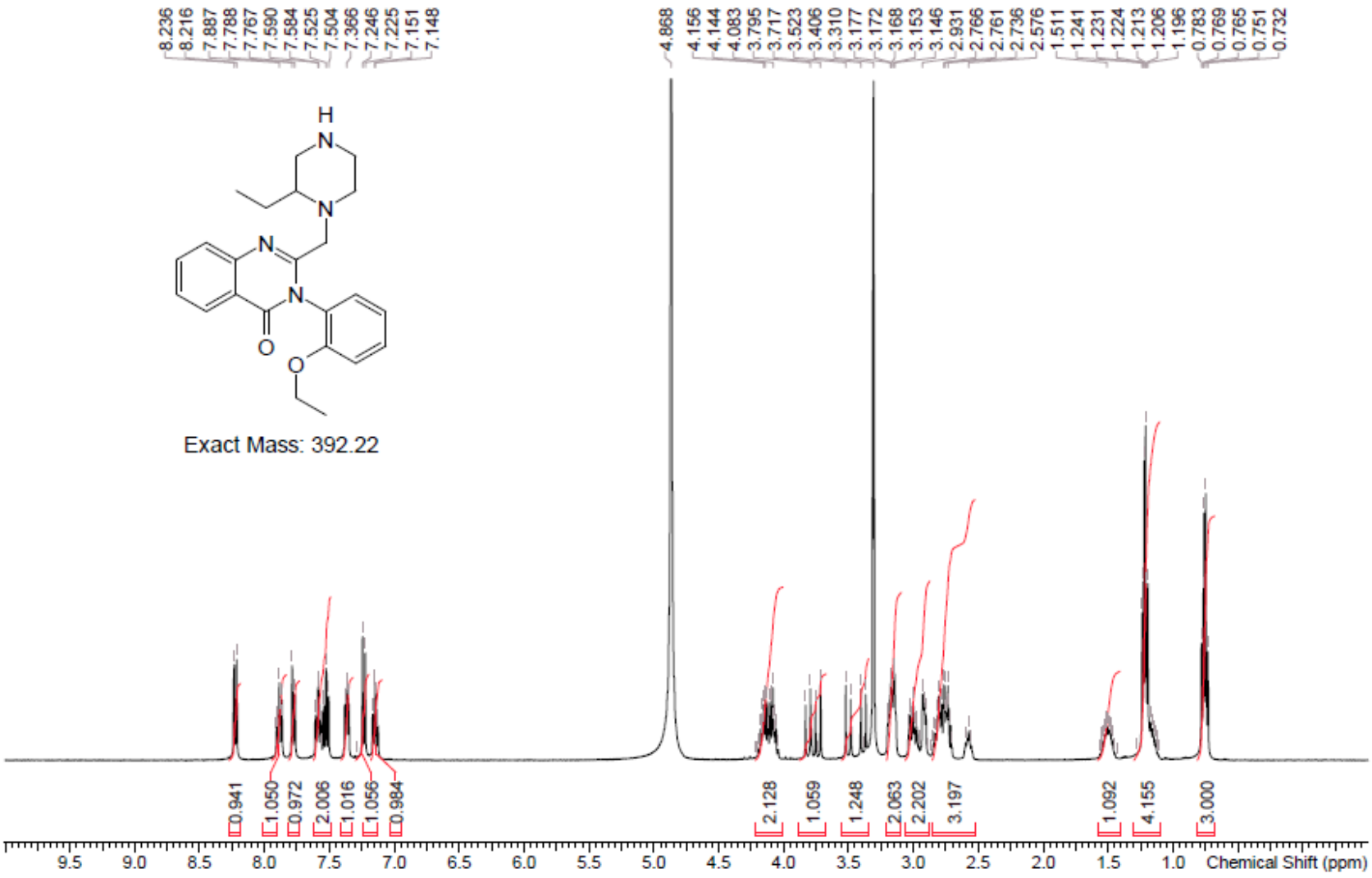
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	1.546	0.050	2418621	99.662	4202013	99.807
2	1.774	0.026	6288	0.259	5700	0.135
3	2.677	0.037	1902	0.078	2438	0.058

CW-12
Chiral HPLC

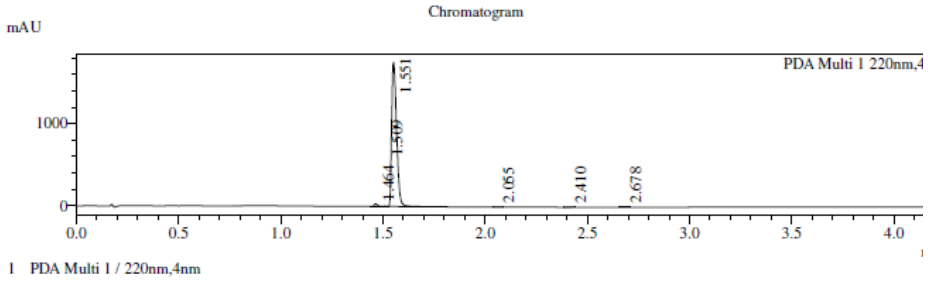


	RT	Area	% Area	Height
1	2.106	1069786	100.00	102575

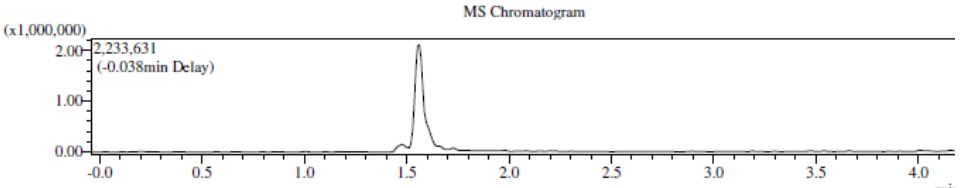
CW-13
^{1}H NMR: (400 MHz, CD_3OD)

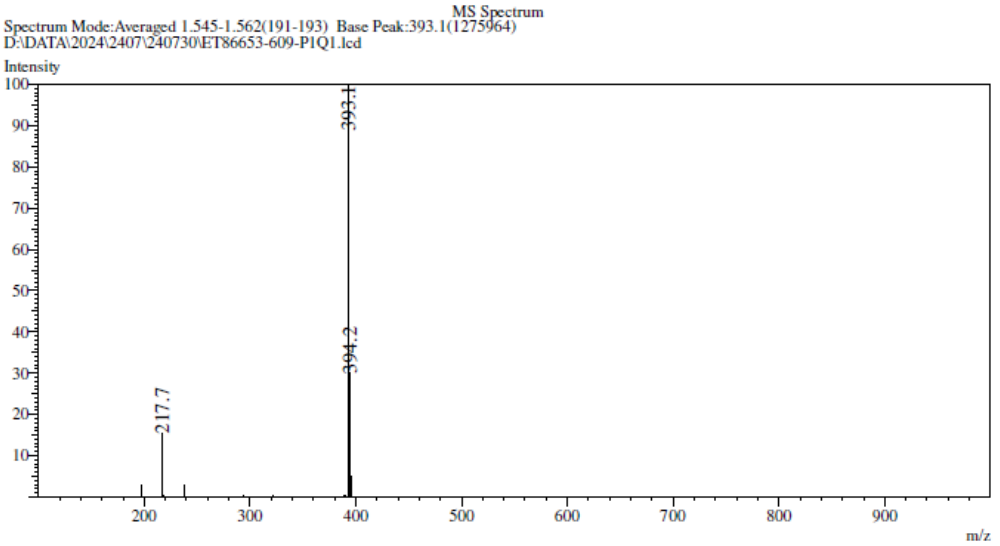


CW-13
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

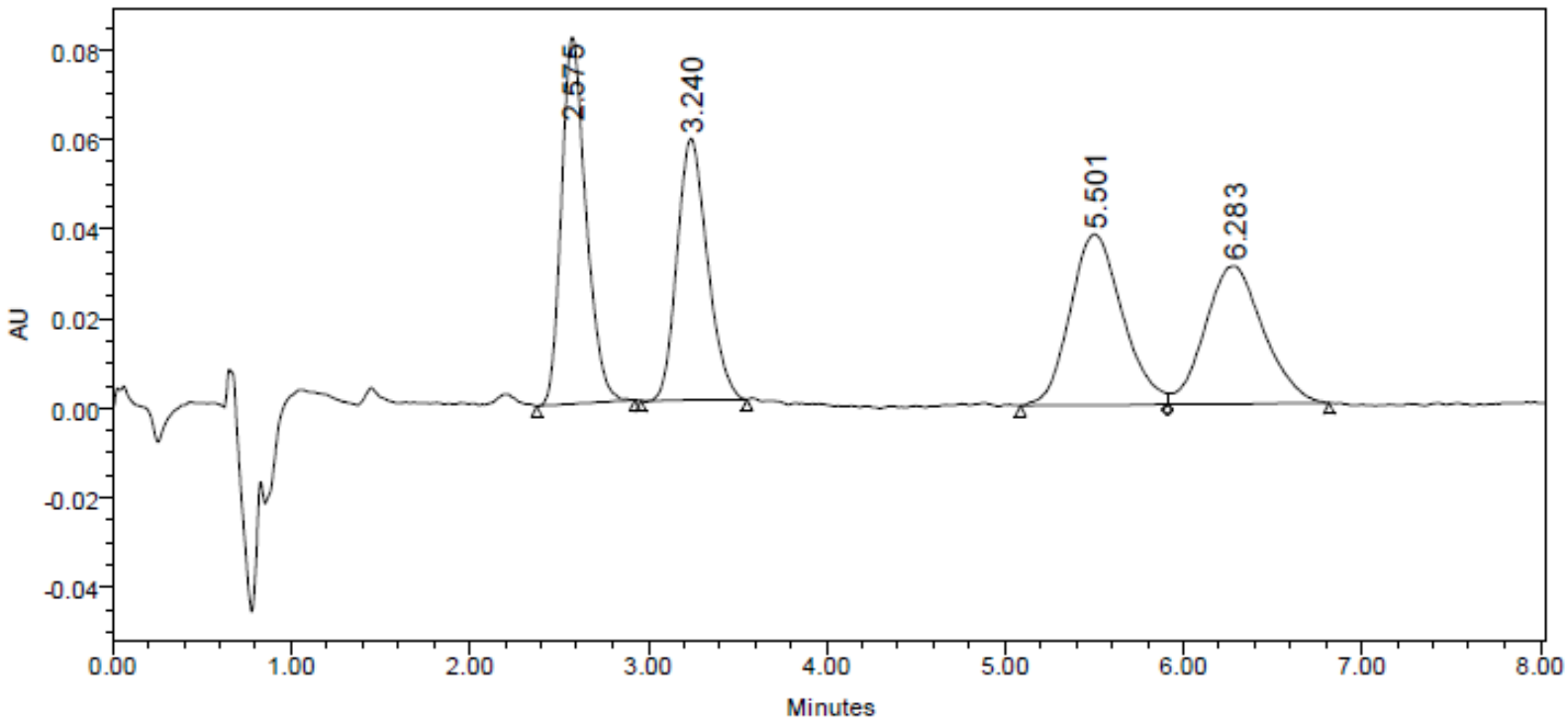
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

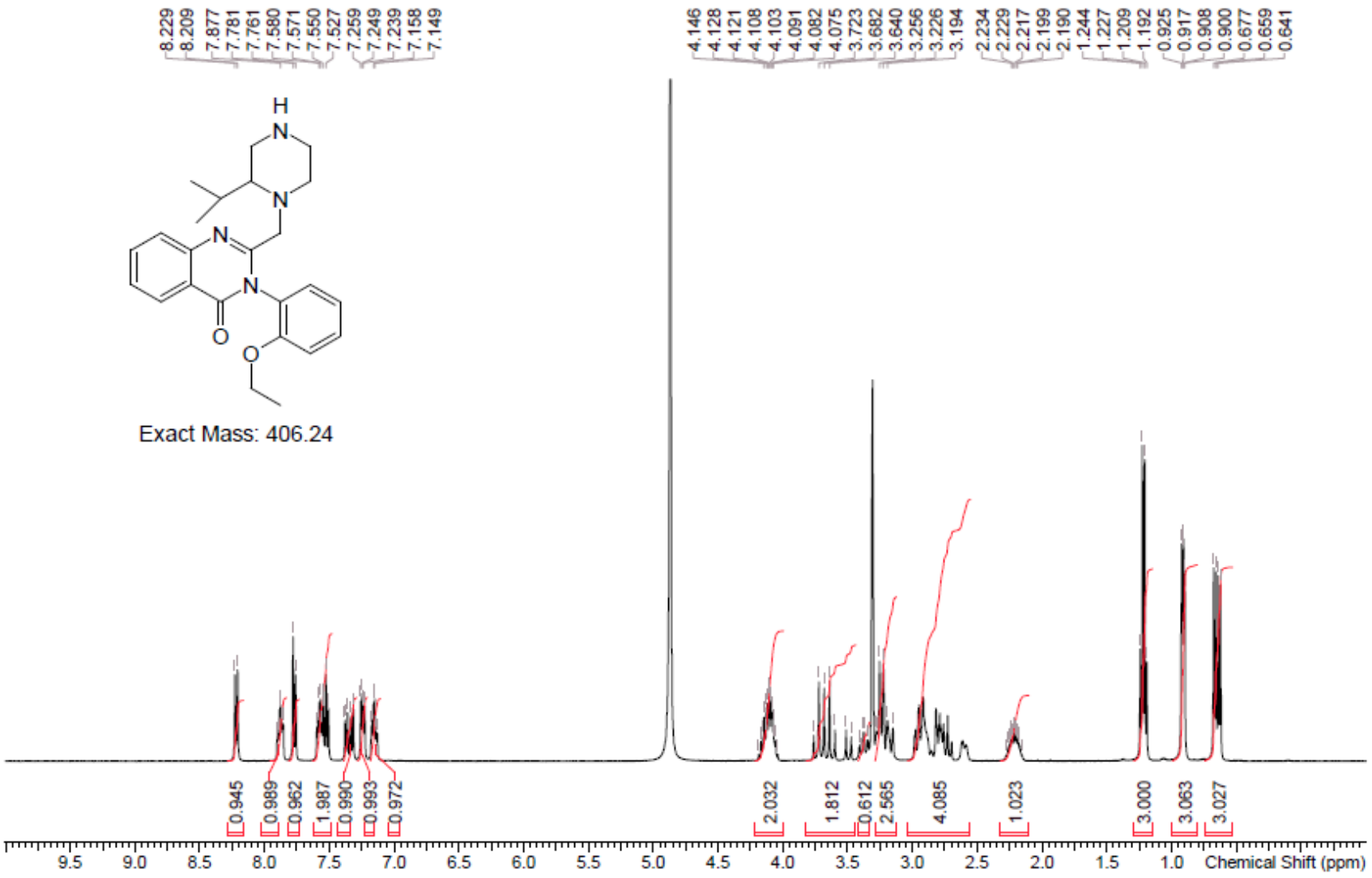
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.464	0.031	--	32740	39159	1.310
2	1.509	0.053	1.079	5409	7523	0.252
3	1.551	0.045	0.853	1753844	2937787	98.248
4	2.055	0.036	12.308	1265	1628	0.054
5	2.410	0.042	8.987	1771	2605	0.087
6	2.678	0.039	6.601	1074	1477	0.049
Total					2990180	100.000

CW-13
Chiral HPLC

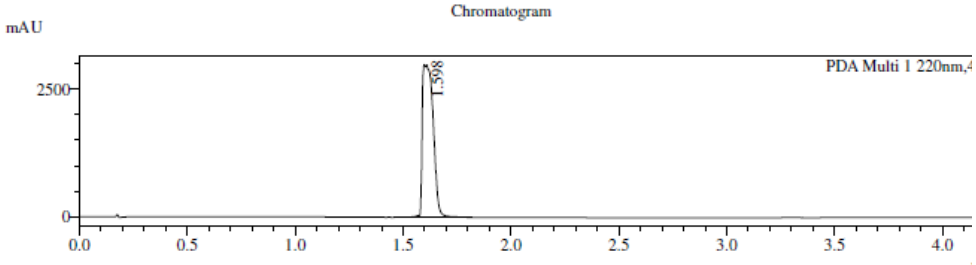


	RT	Area	% Area	Height
1	2.575	784083	26.53	81873
2	3.240	690929	23.38	58410
3	5.501	778349	26.33	38176
4	6.283	702288	23.76	30798

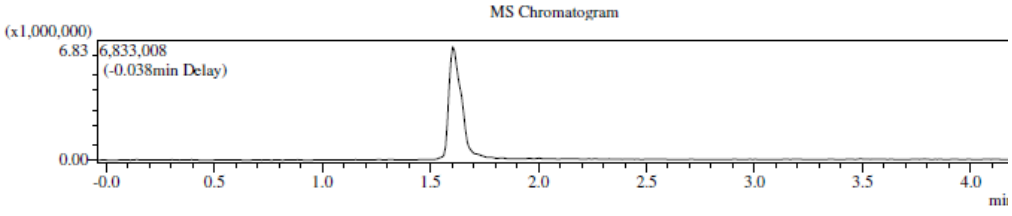
CW-14
^{1}H NMR: (400 MHz, CD_3OD)

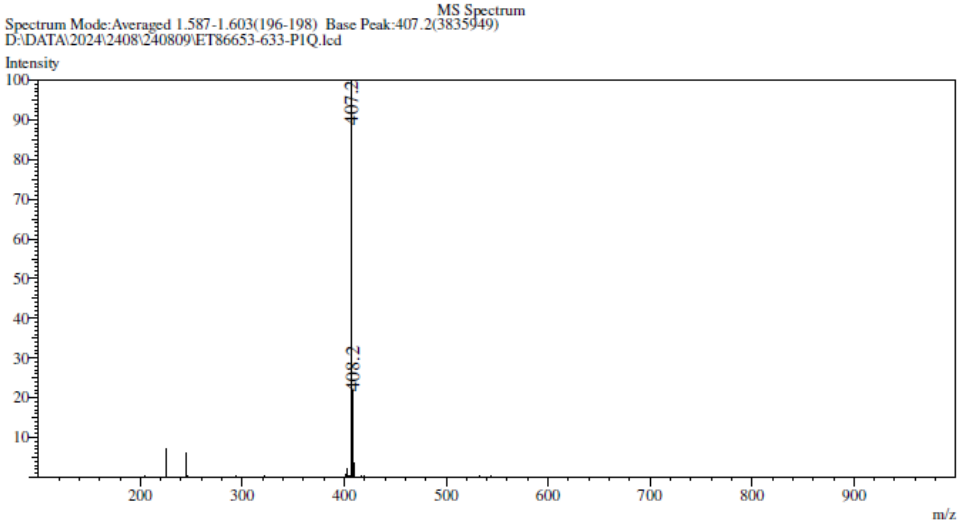


CW-14
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

ELSD

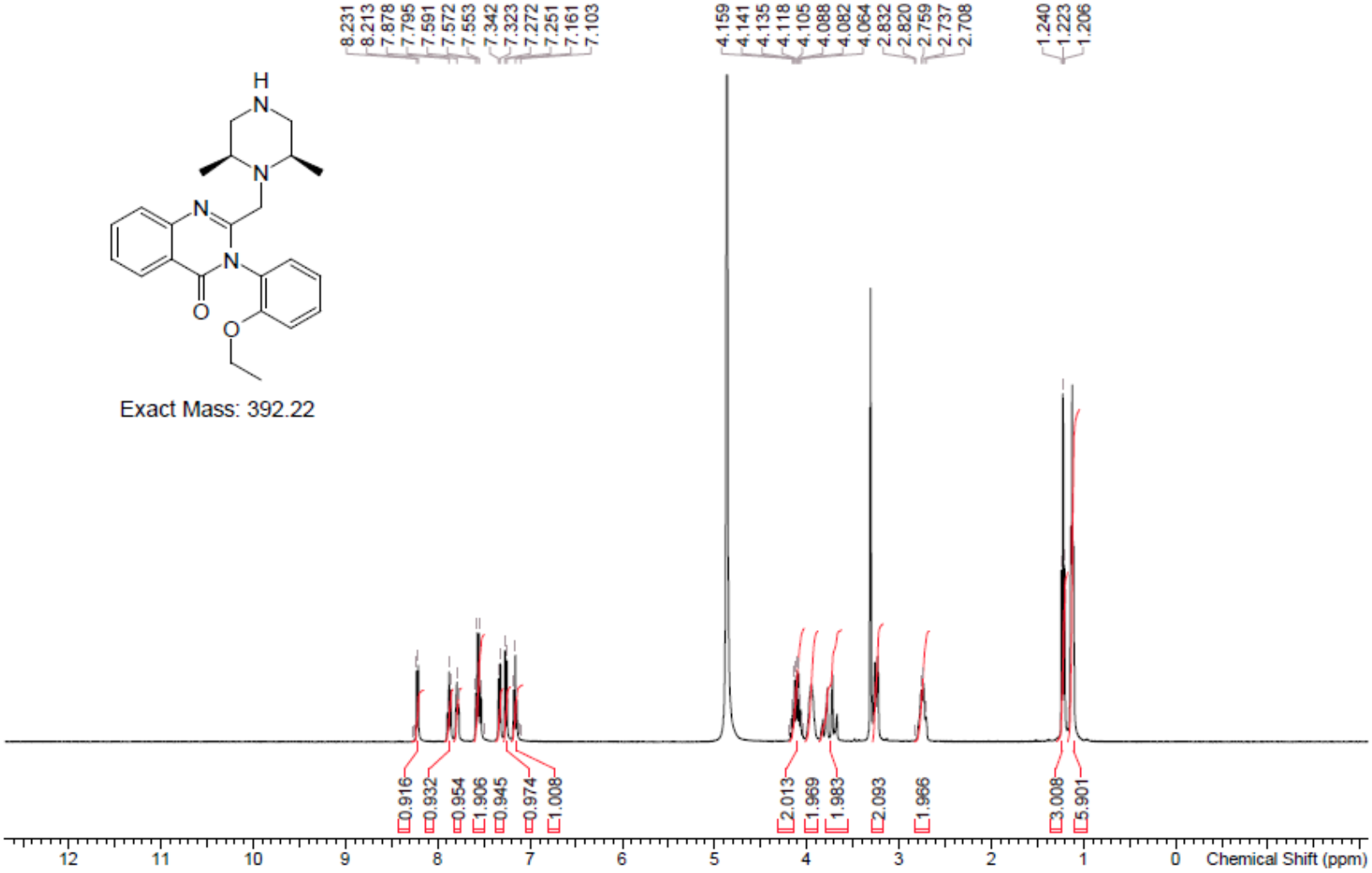
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.598	0.081	--	2981915	10548994	100.000
Total					10548994	100.000

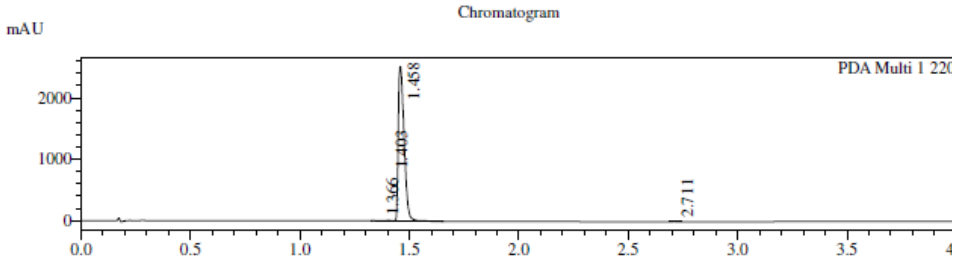
CW-15

^{1}H NMR: (400 MHz, CD_3OD)

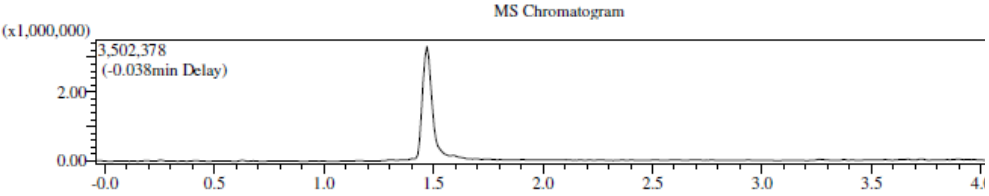


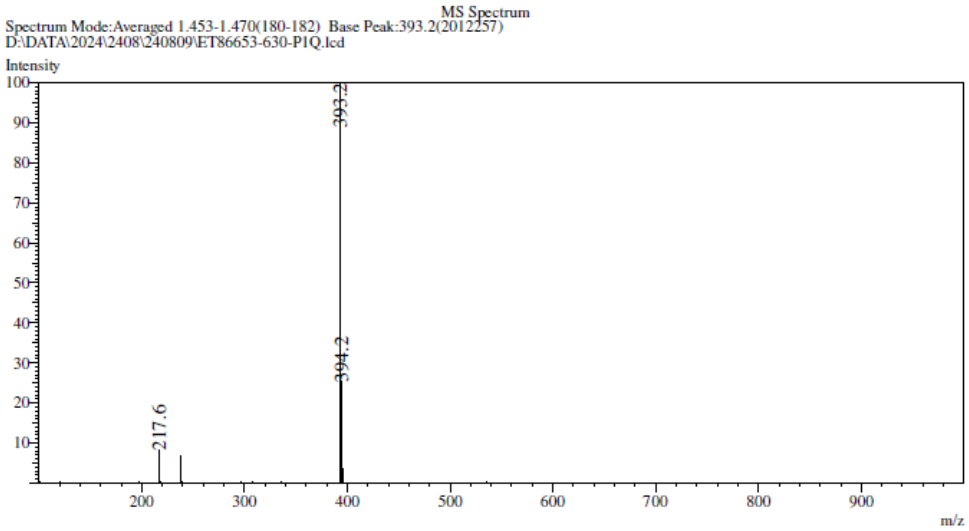
Exact Mass: 392.22

CW-15
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

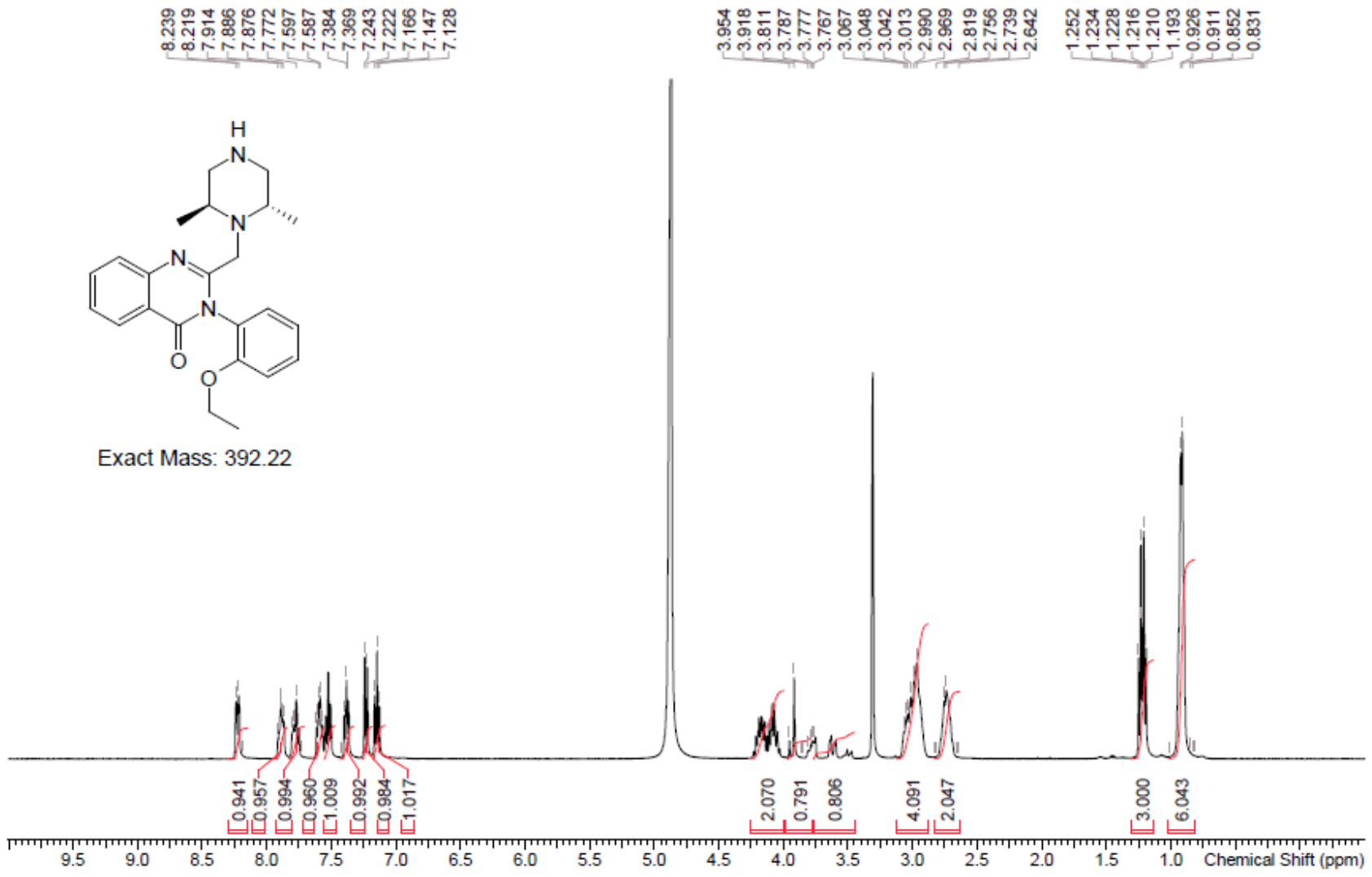
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

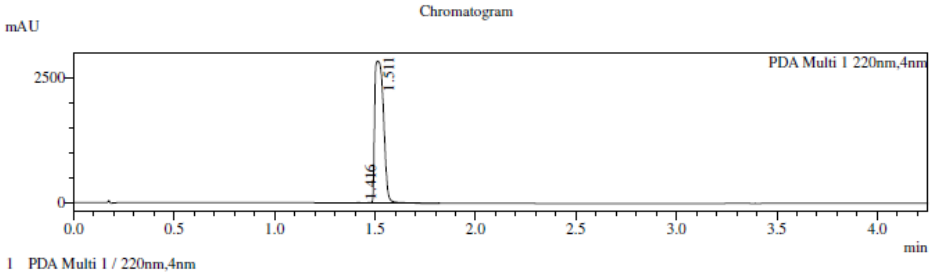
PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.366	0.077	--	7847	19077	0.403
2	1.403	0.051	0.583	10774	14840	0.313
3	1.458	0.050	1.096	2521585	4697830	99.202
4	2.711	0.039	28.166	2838	3885	0.082
Total					4735633	100.000

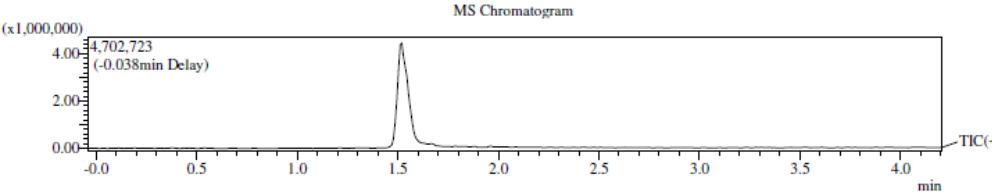
CW-16
^{1}H NMR: (400 MHz, CD_3OD)

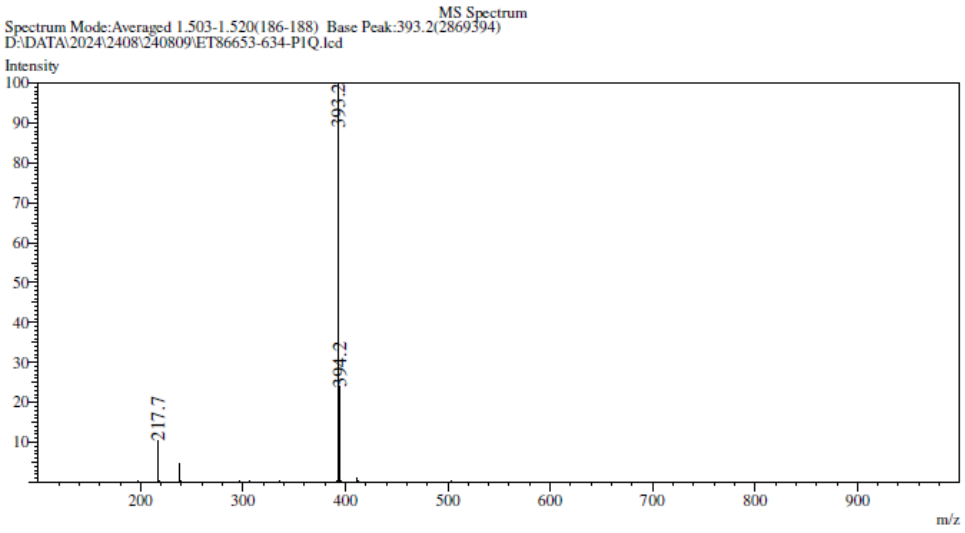


CW-16
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

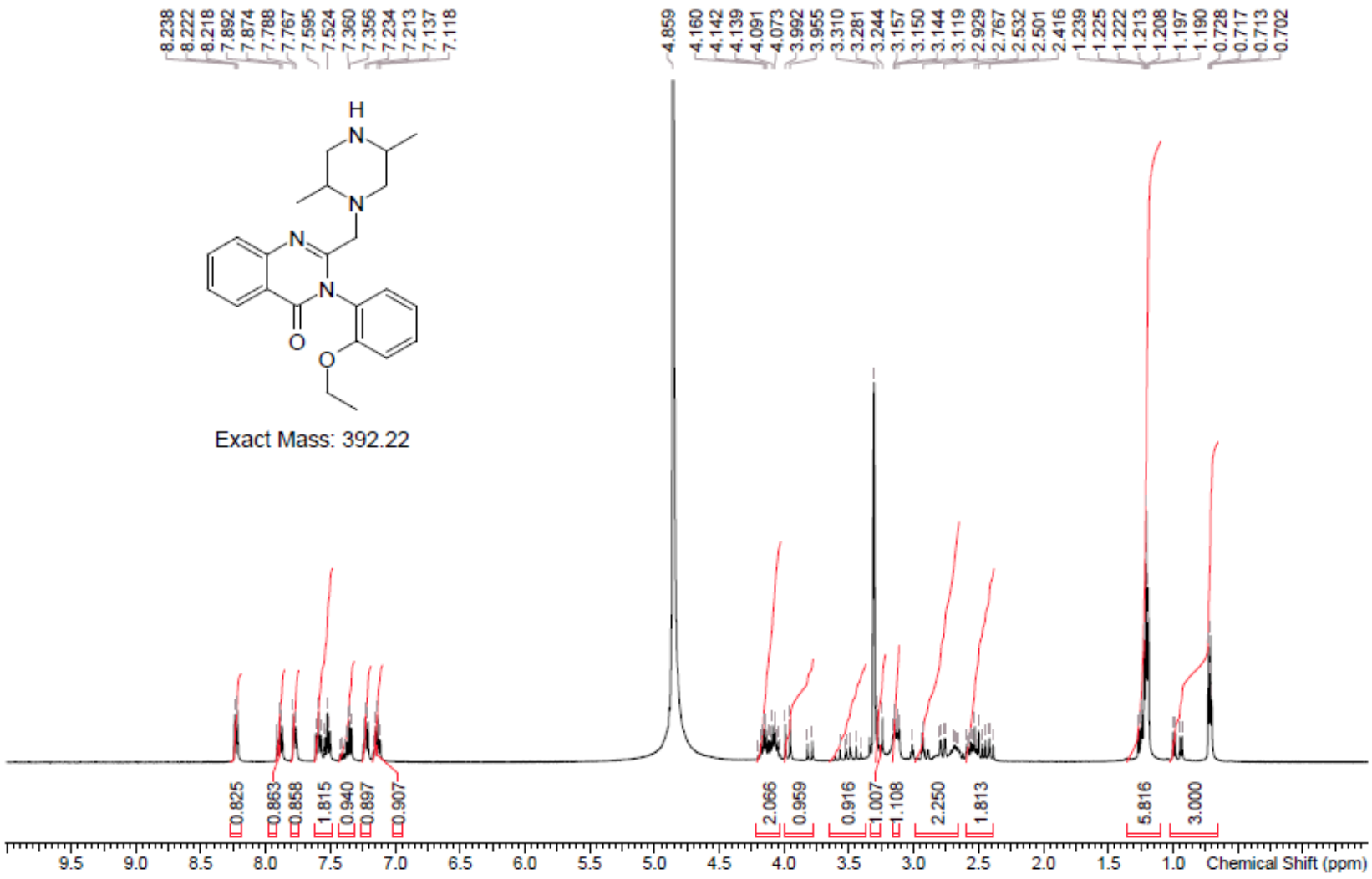
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

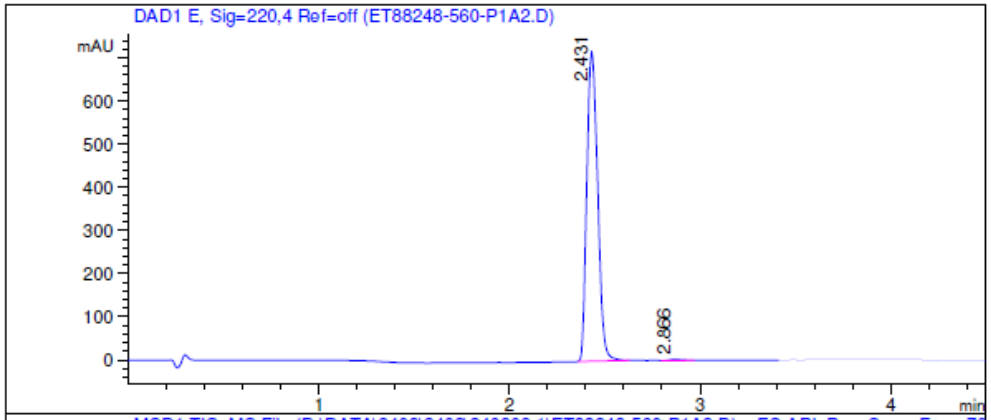
PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.416	0.032	--	7250	8355	0.096
2	1.511	0.072	1.834	2834680	8687244	99.904
Total					8695599	100.000

CW-17
^{1}H NMR: (400 MHz, CD_3OD)



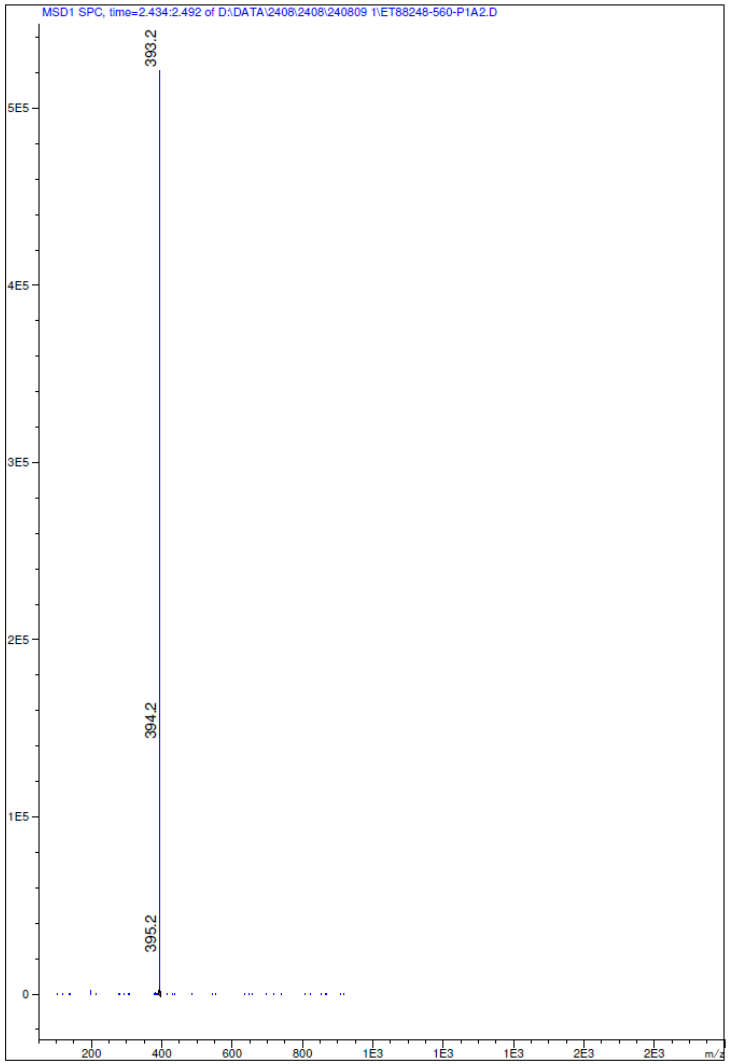
CW-17
LC-MS



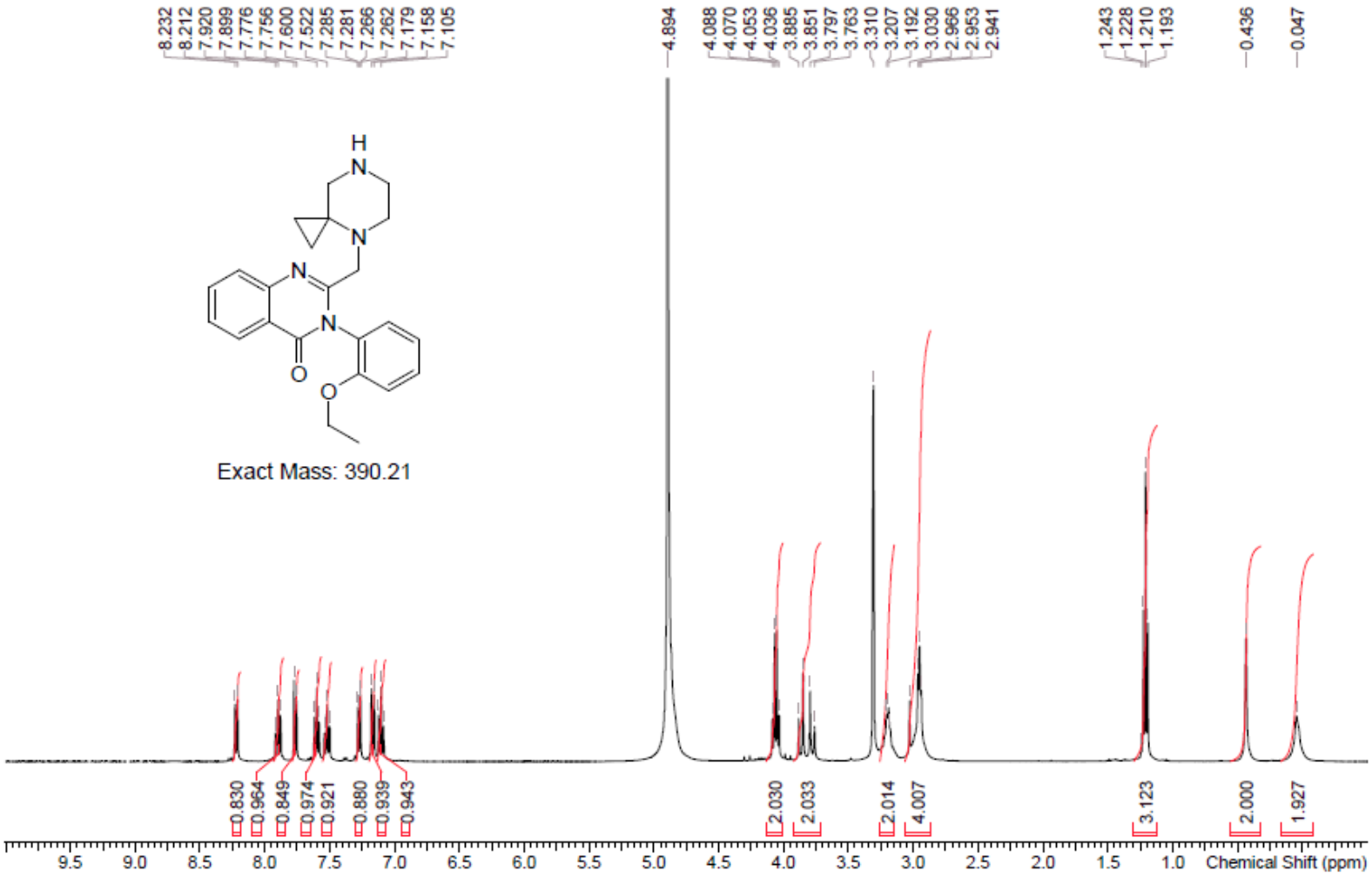
Report

Signal 1 :DAD1 E, Sig=220,4 Ref=off

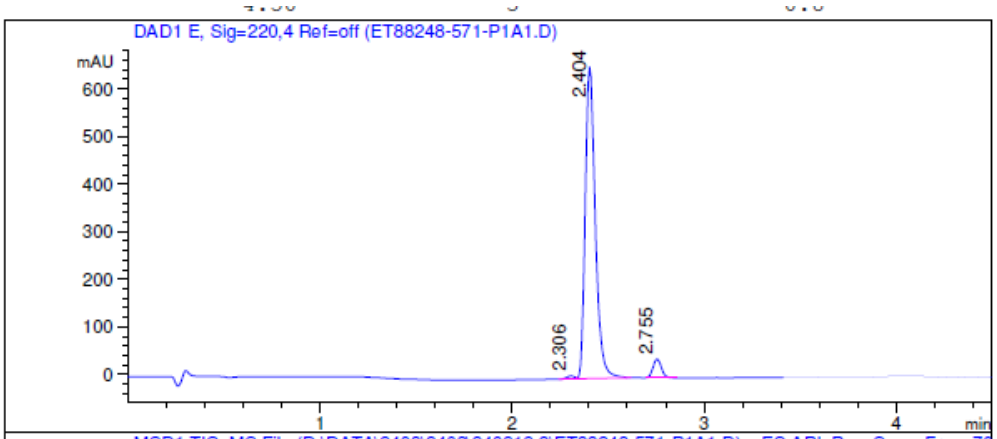
Peak #	RT [min]	Height	Height %	Width [min]	Area	Area %
1	2.431	719.131	99.595	0.066	2832.745	99.535
2	2.866	2.922	0.405	0.067	13.222	0.465

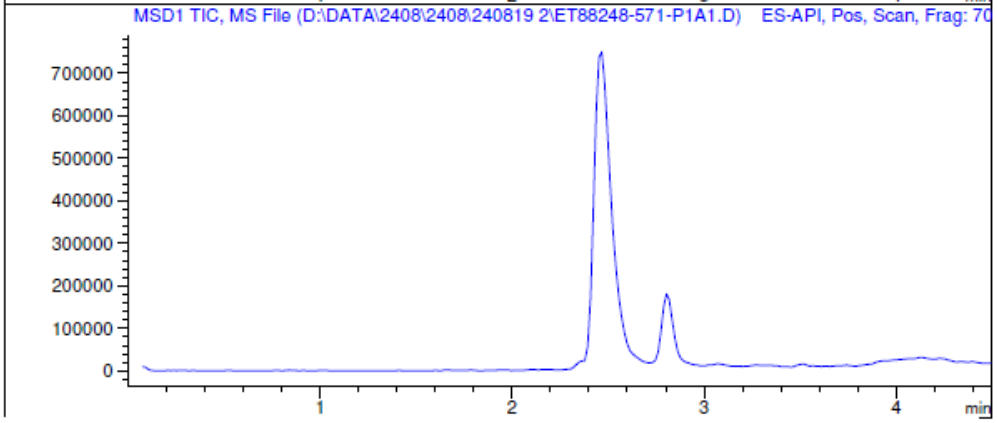


CW-18
^{1}H NMR: (400 MHz, CD_3OD)


8.232
8.212
7.920
7.899
7.776
7.756
7.600
7.522
7.285
7.281
7.266
7.262
7.179
7.158
7.105
4.894
4.088
4.070
4.053
4.036
3.885
3.851
3.797
3.763
3.310
3.207
3.192
3.030
2.966
2.953
2.941
1.243
1.228
1.210
1.193
0.436
0.047
H
N
N
N
N
O
O
Exact Mass: 390.21
0.830
0.964
0.849
0.974
0.921
0.880
0.939
0.943
2.030
2.033
2.014
4.007
3.123
2.000
1.927
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

CW-18
LC-MS

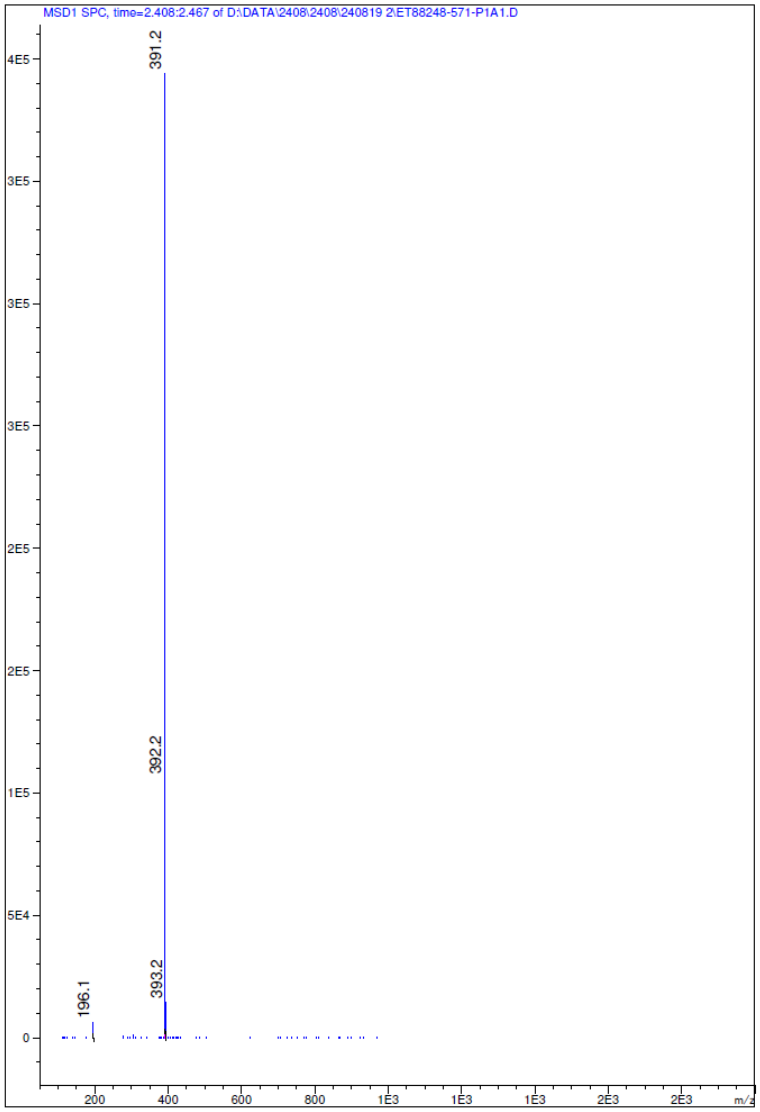




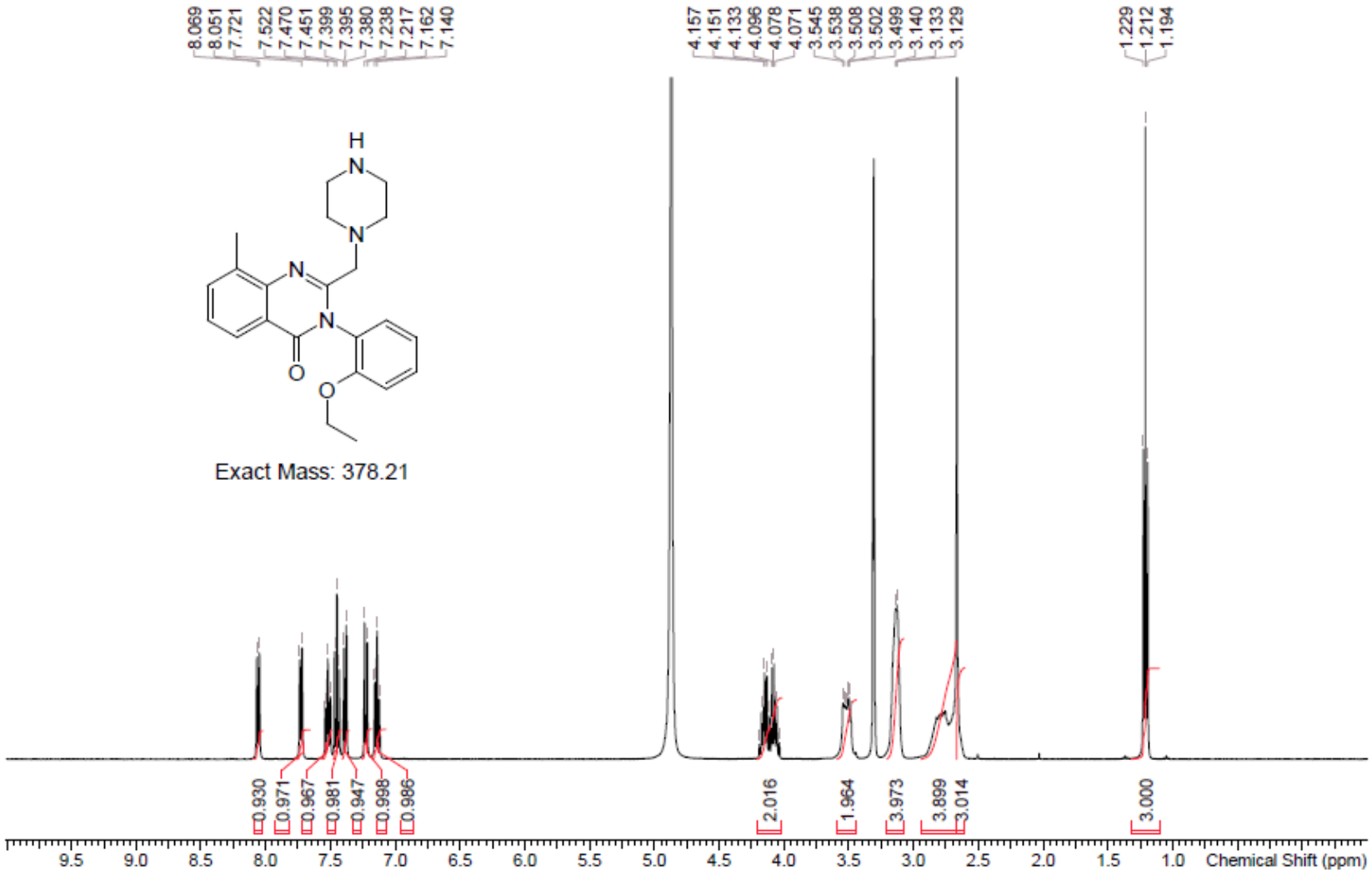
Report

Signal 1 :DAD1 E, Sig=220,4 Ref=off

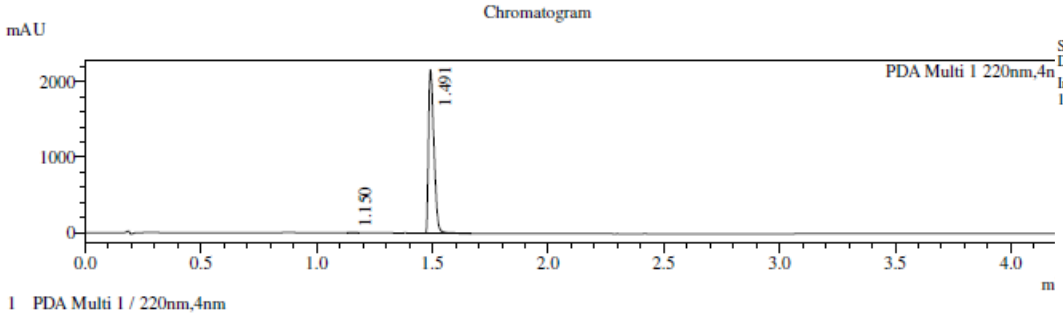
Peak #	RT [min]	Height	Height %	Width [min]	Area	Area %
1	2.306	5.969	0.852	0.046	17.335	0.689
2	2.404	655.382	93.522	0.056	2379.112	94.525



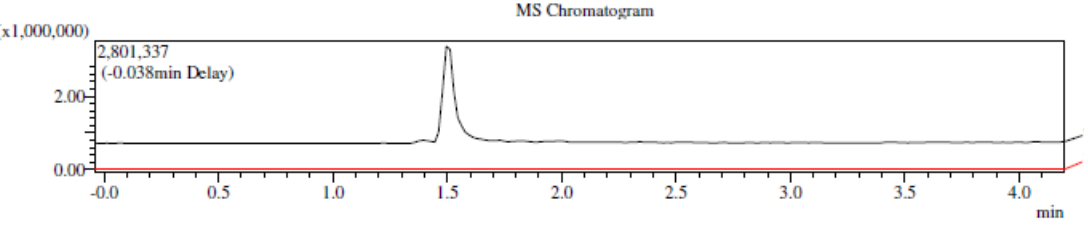
CW-19
^{1}H NMR: (400 MHz, CD_3OD)

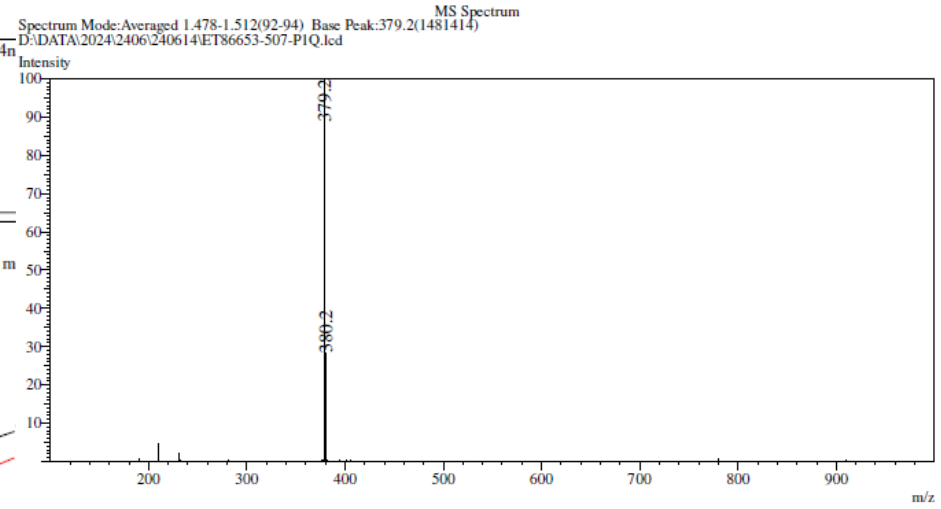

8.069
8.051
7.721
7.522
7.470
7.451
7.399
7.395
7.380
7.238
7.217
7.162
7.140
4.157
4.151
4.133
4.096
4.078
4.071
3.545
3.538
3.508
3.502
3.499
3.140
3.133
3.129
1.229
1.212
1.194
H
N
N
N
N
O
O
Exact Mass: 378.21
0.930
0.971
0.967
0.981
0.947
0.998
0.986
2.016
1.964
3.973
3.899
3.014
3.000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

CW-19
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

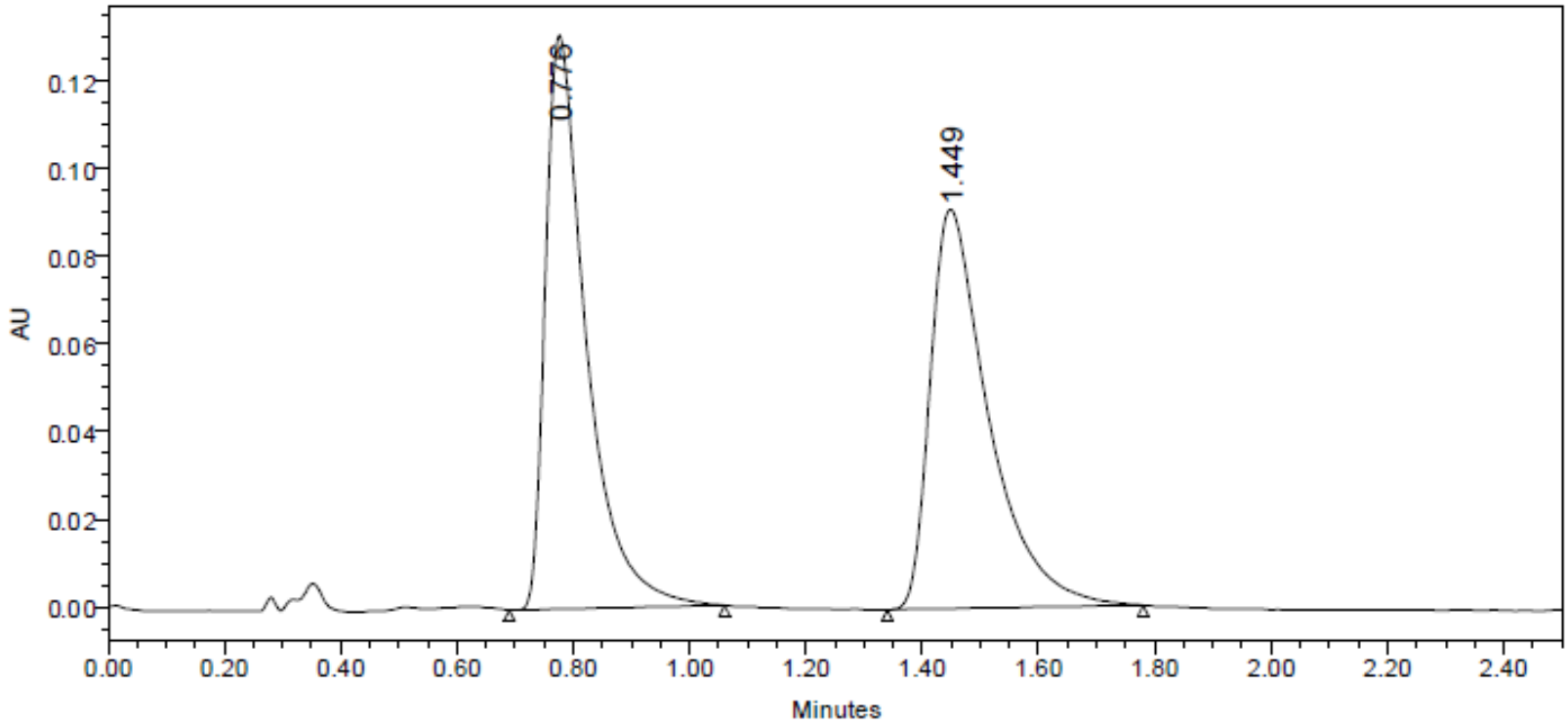
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

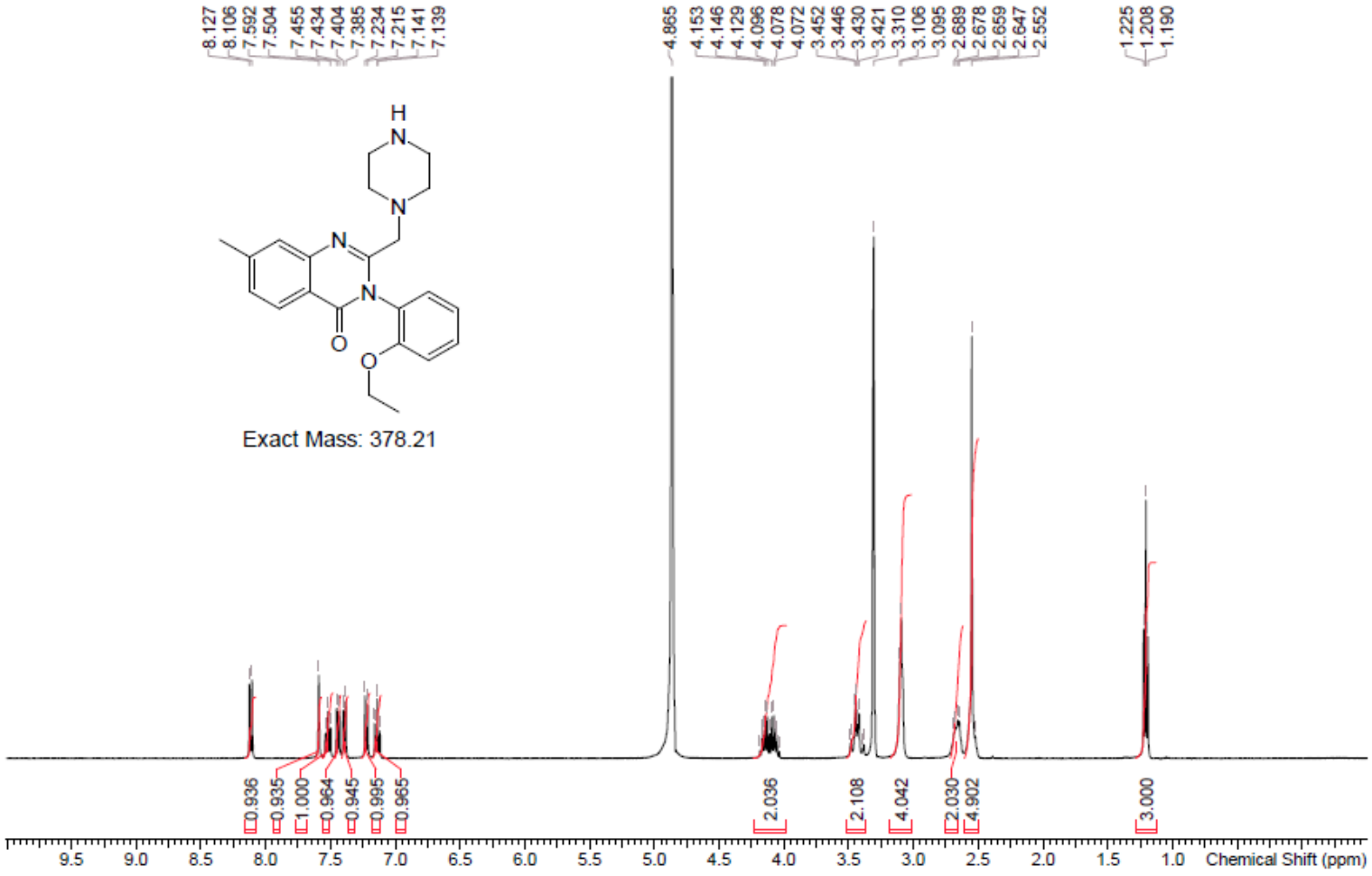
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.150	0.033	--	1646	1960	0.055
2	1.491	0.045	8.670	2170974	3552447	99.945
Total					3554408	100.000

CW-19
Chiral HPLC

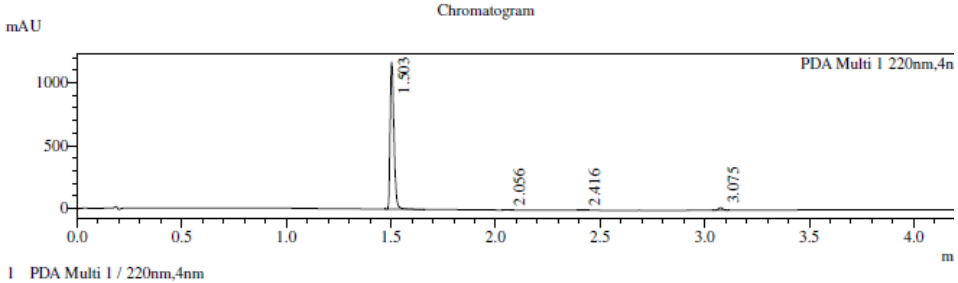


	RT	Area	% Area	Height
1	0.776	641940	50.19	131078
2	1.449	637080	49.81	91228

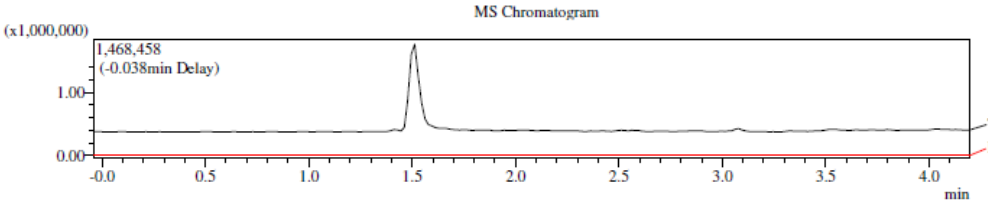
CW-20
^{1}H NMR (400 MHz, CD_3OD)

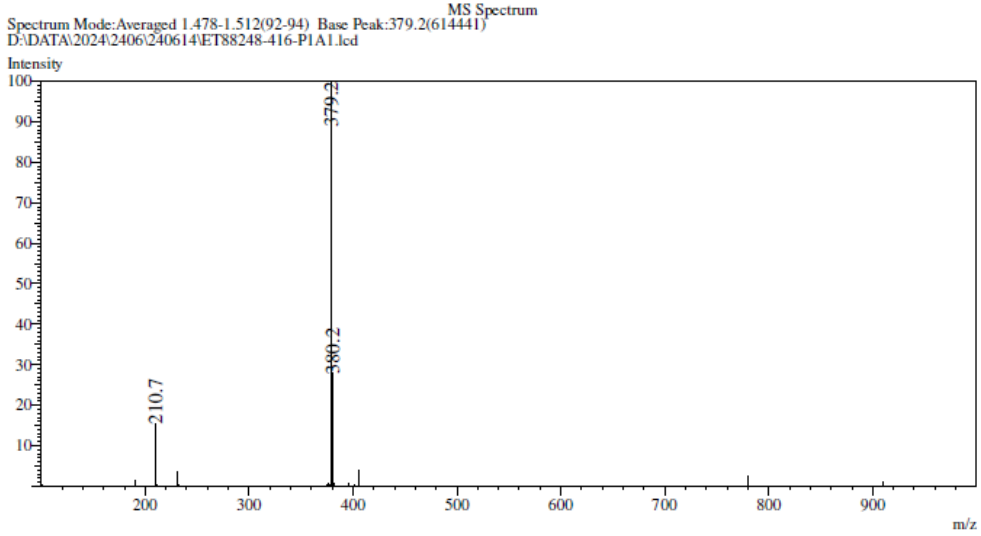


CW-20
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

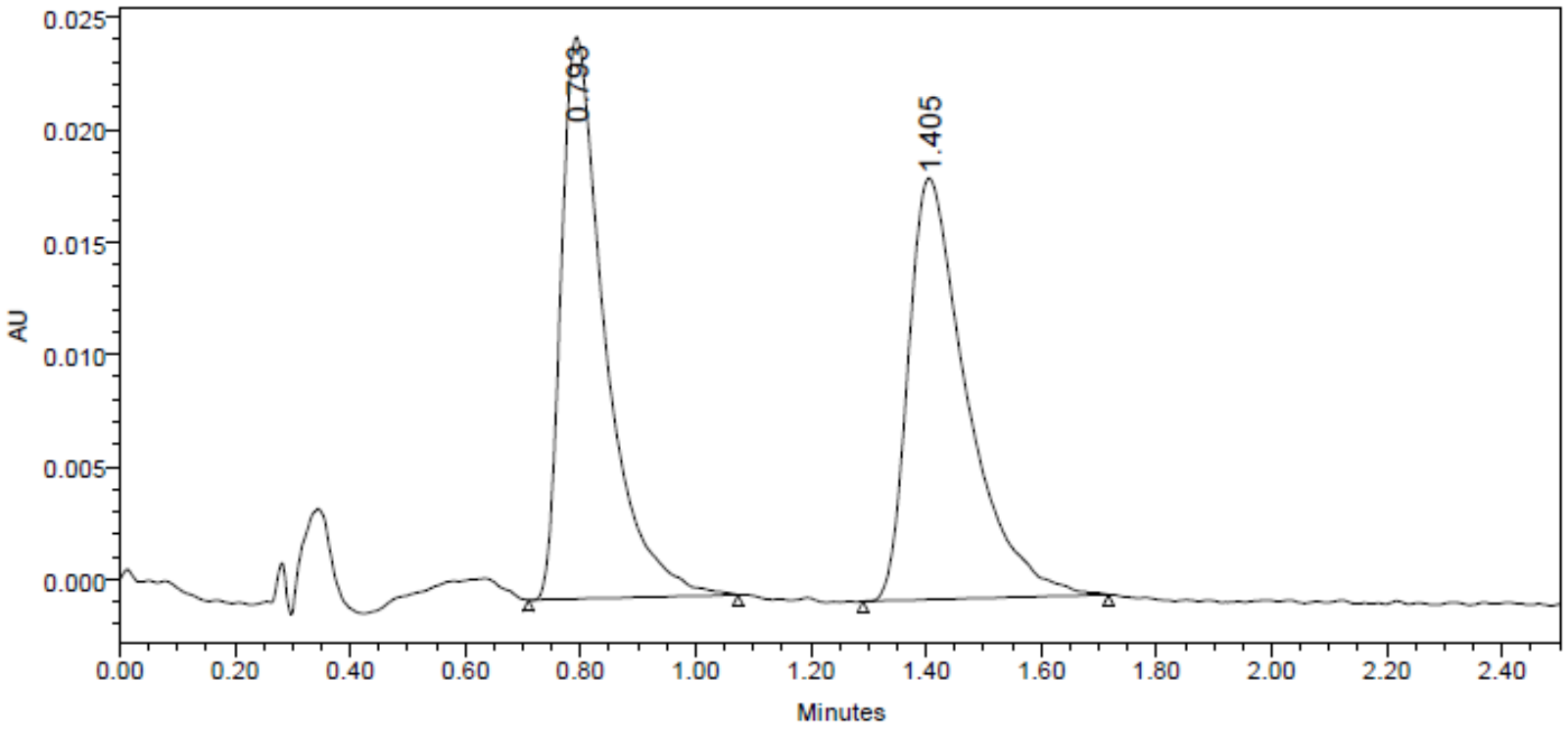
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.503	0.035	--	1169853	1490332	97.826
2	2.056	0.038	15.264	1868	2523	0.166
3	2.416	0.046	8.581	1321	2183	0.143
4	3.075	0.037	15.858	20627	28415	1.865
Total					1523453	100.000

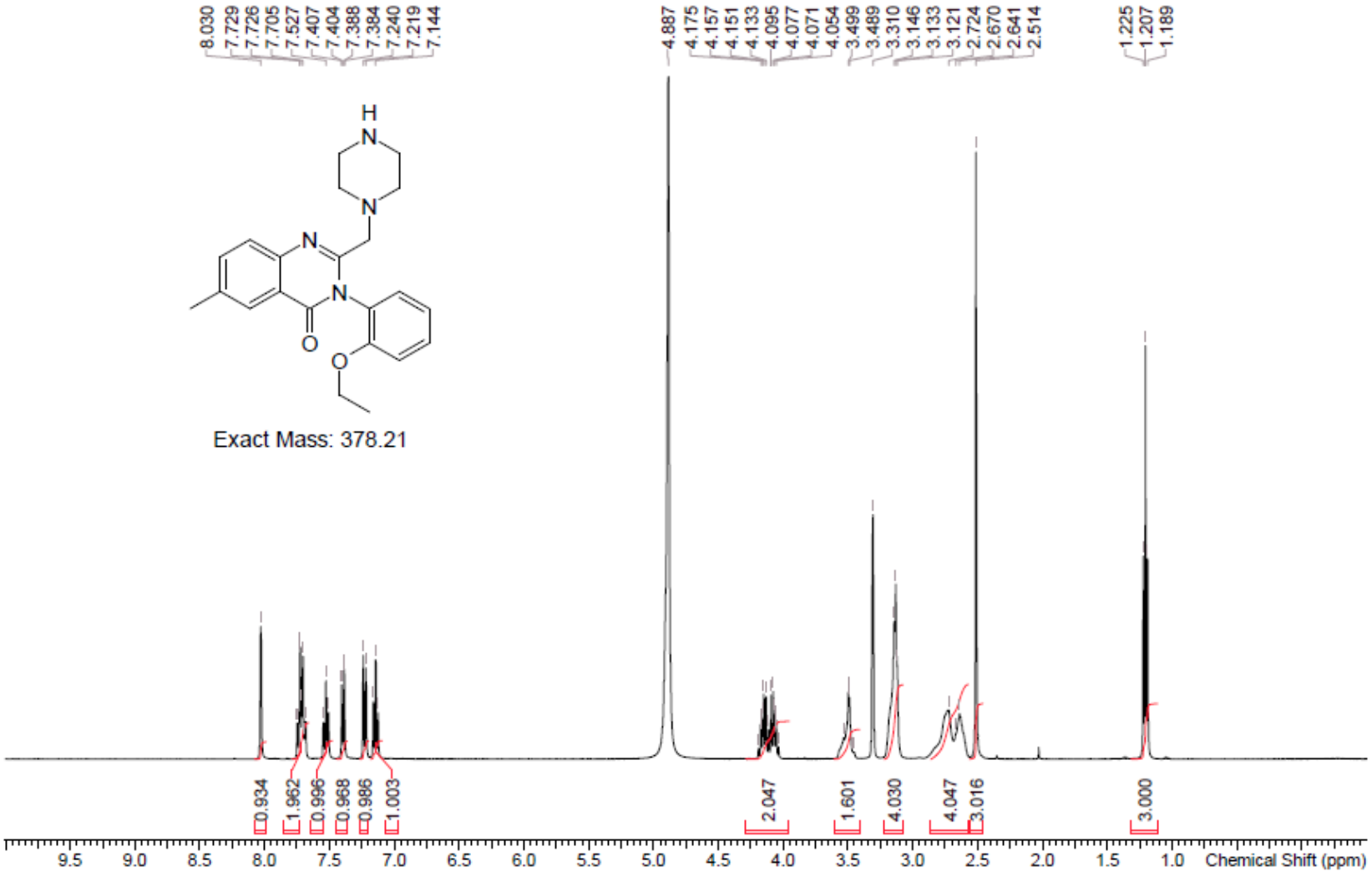
CW-20
Chiral HPLC



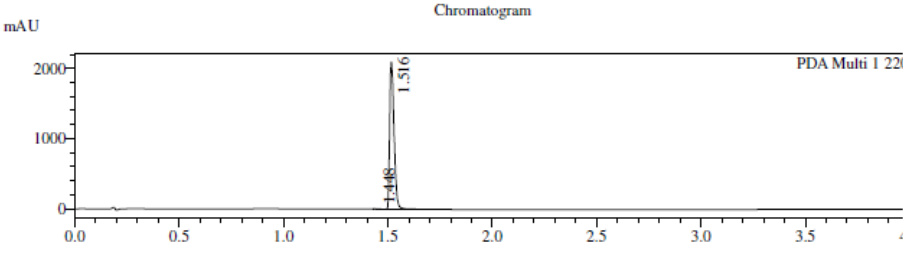
	RT	Area	% Area	Height
1	0.793	132935	50.01	24990
2	1.405	132903	49.99	18749

CW-21

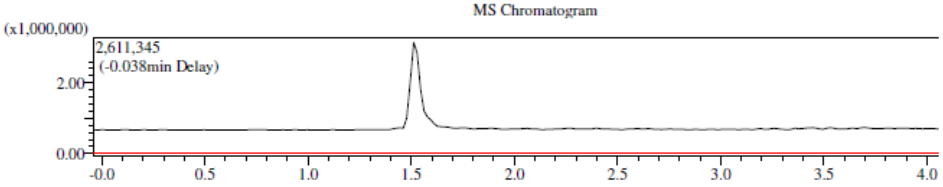
^{1}H NMR (400 MHz, CD_3OD)

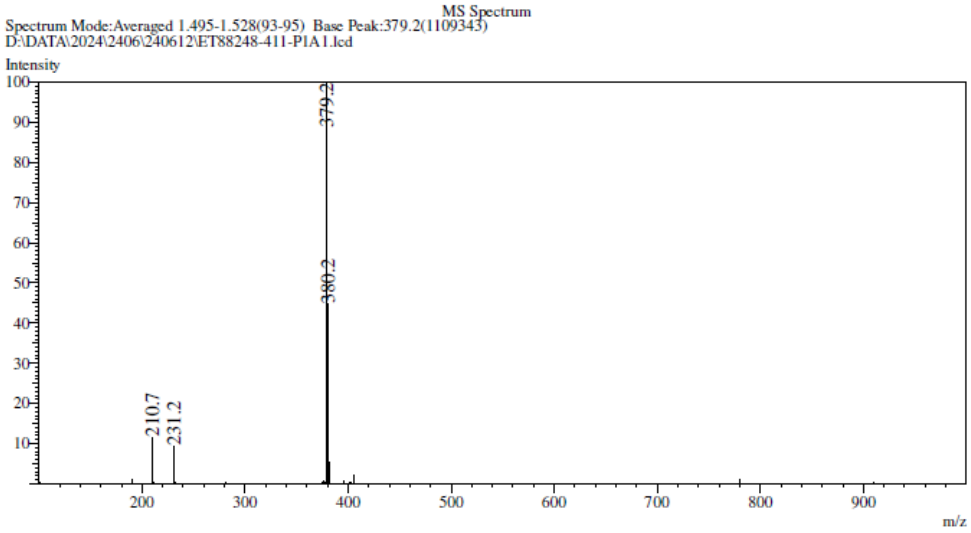


CW-21
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

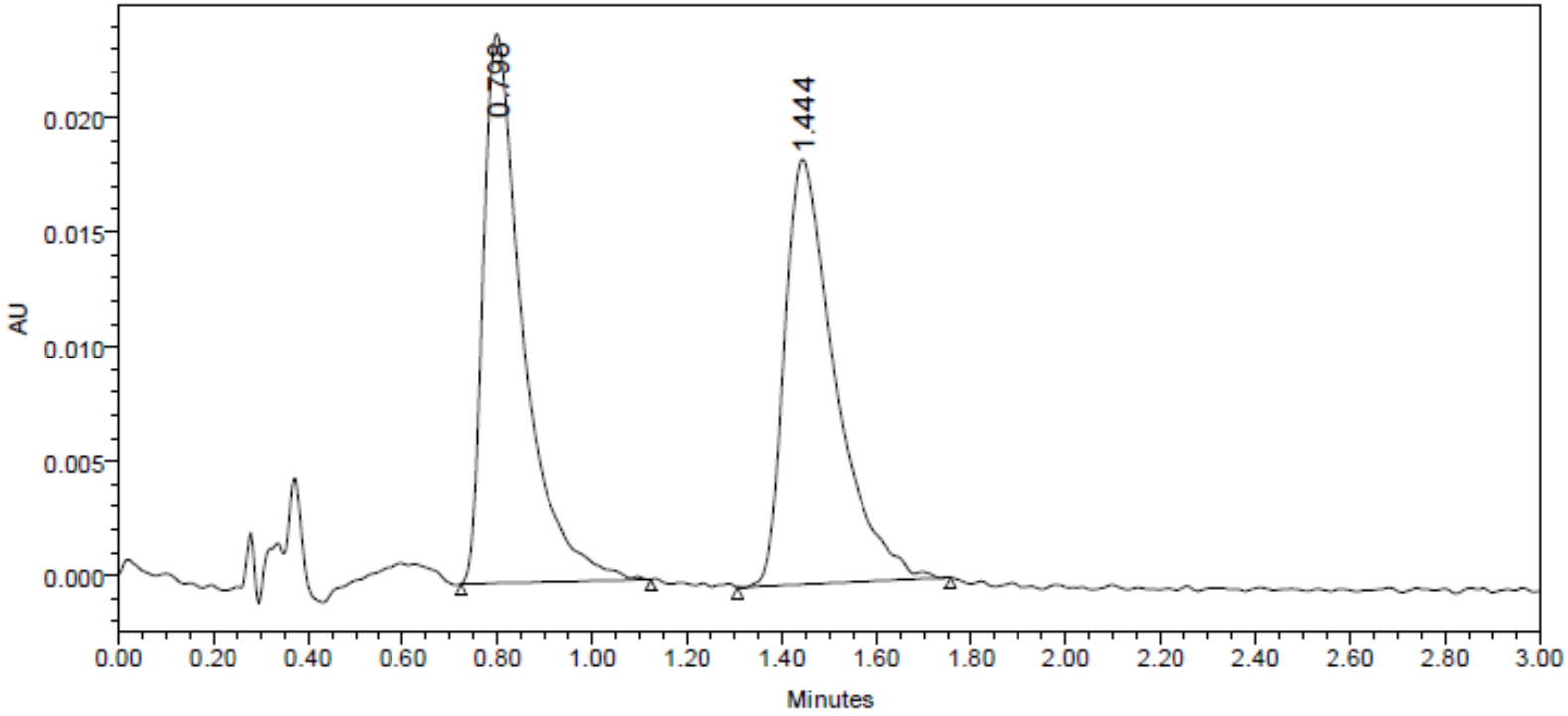
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.448	0.029	--	4258	4377	0.141
2	1.516	0.040	1.945	2100299	3089835	99.859
Total					3094212	100.000

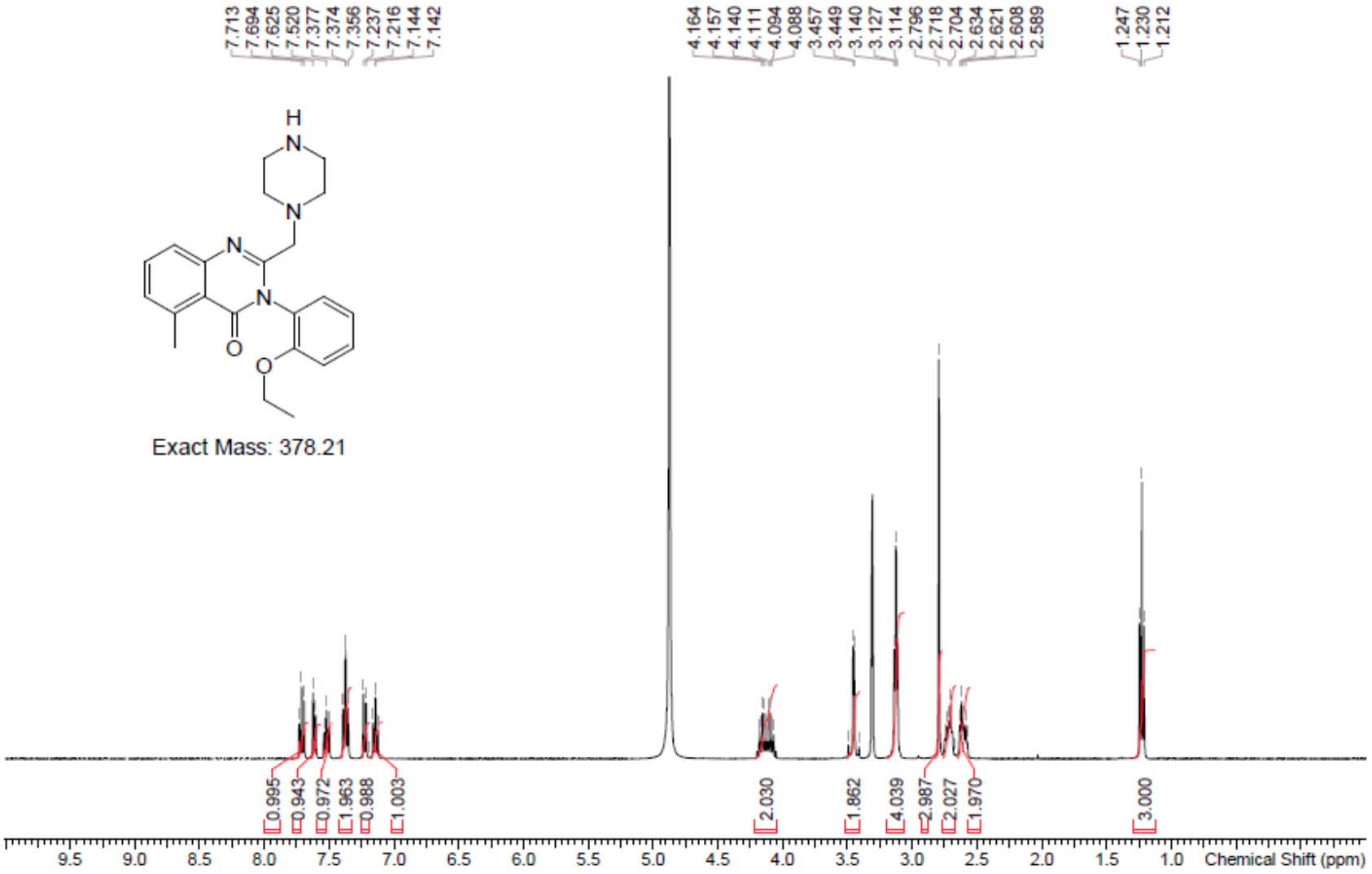
CW-21
Chiral HPLC



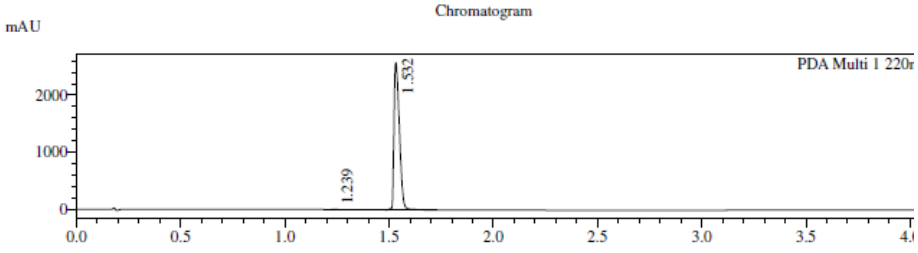
	RT	Area	% Area	Height
1	0.798	139823	50.49	24024
2	1.444	137083	49.51	18573

CW-22

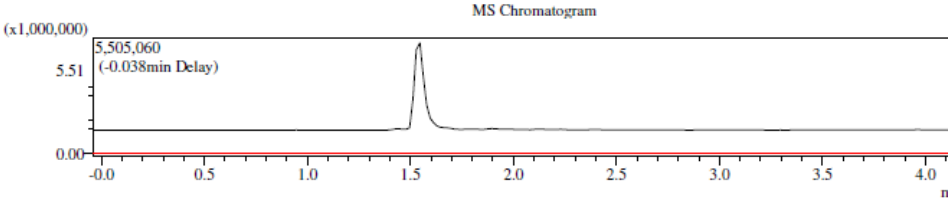
^{1}H NMR (400 MHz, CD_3OD)

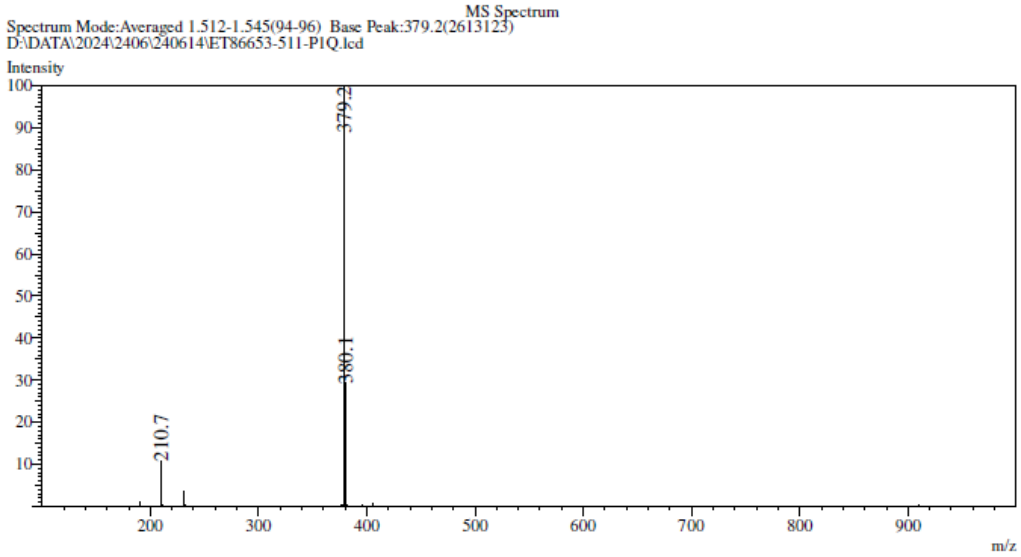


CW-22
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

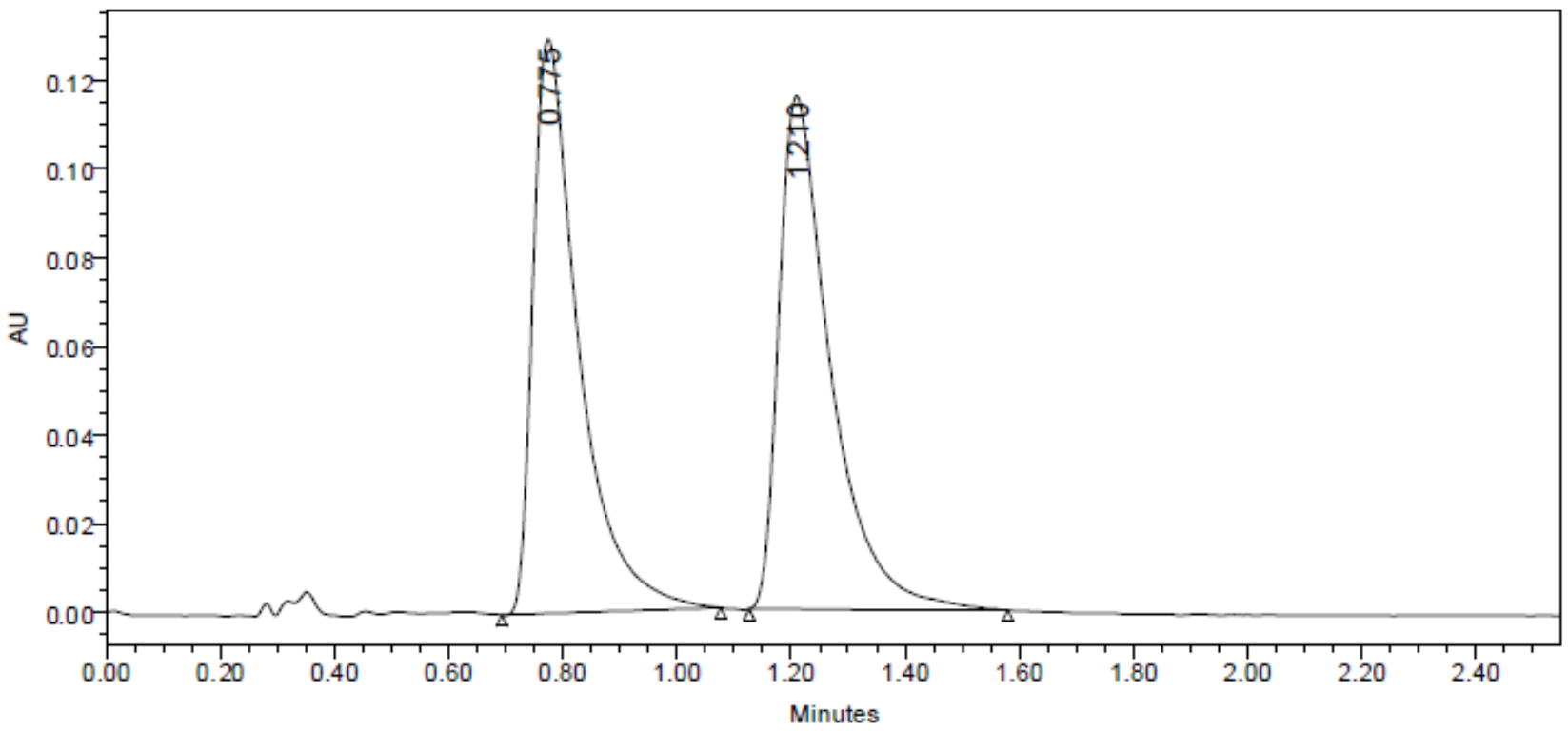
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

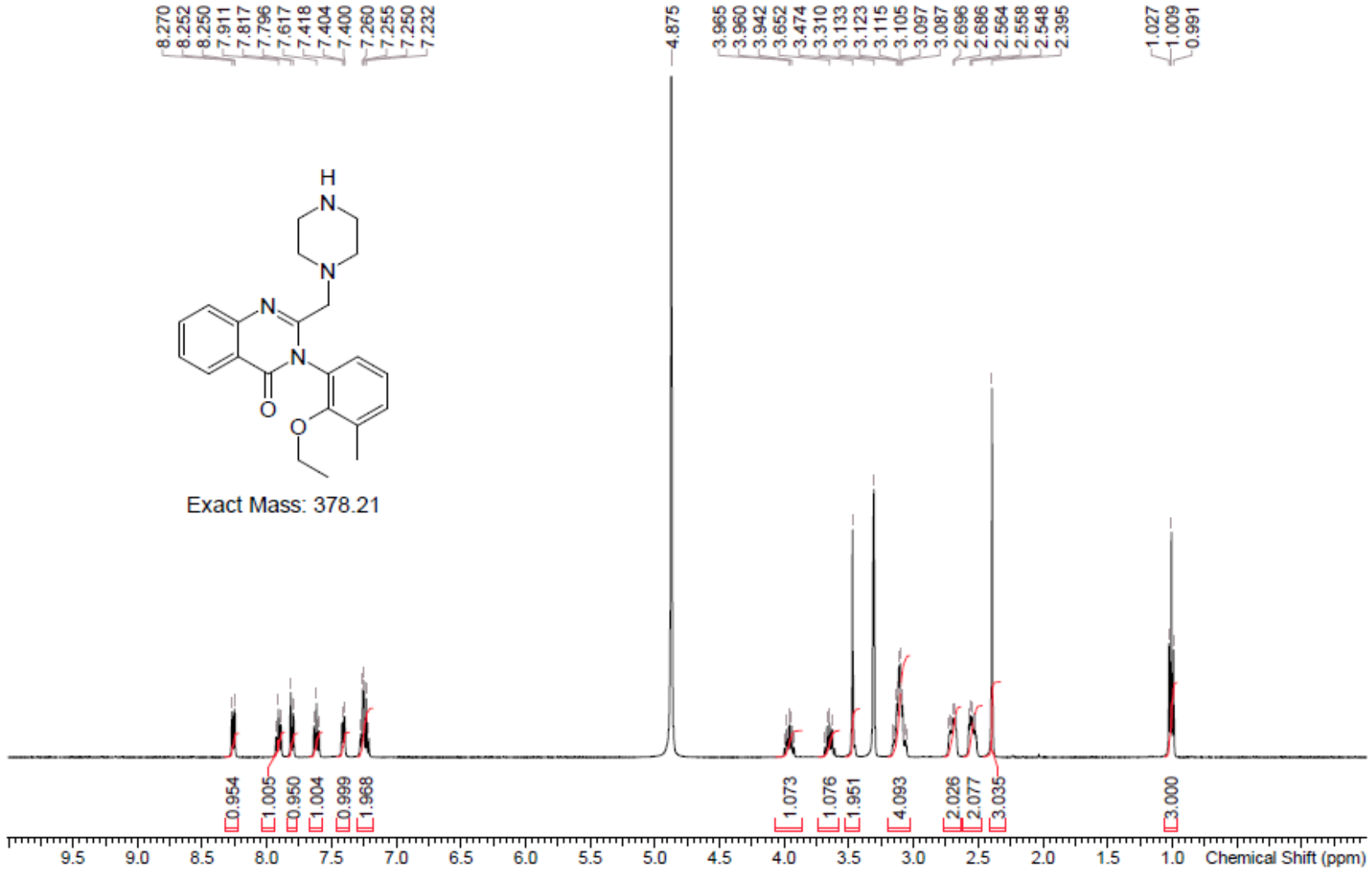
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.239	0.034	--	5129	6150	0.132
2	1.532	0.050	7.013	2581554	4662879	99.868
Total					4669029	100.000

CW-22
Chiral HPLC

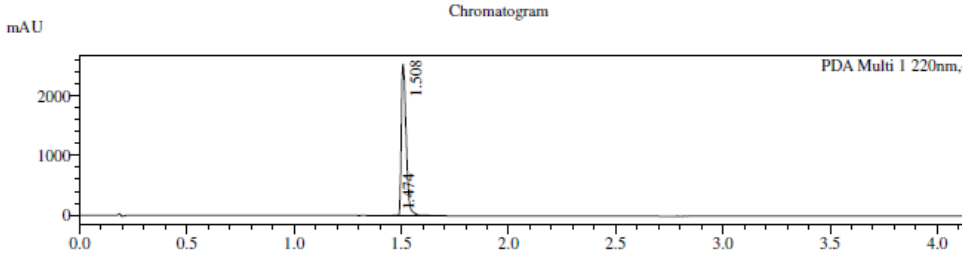


	RT	Area	% Area	Height
1	0.775	723096	49.82	129545
2	1.210	728270	50.18	115775

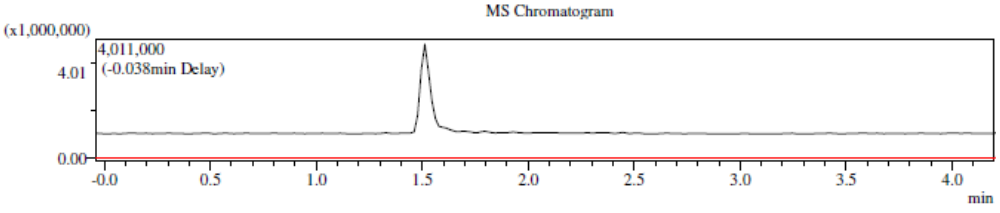
CW-23
^{1}H NMR: (400 MHz, CD_3OD)

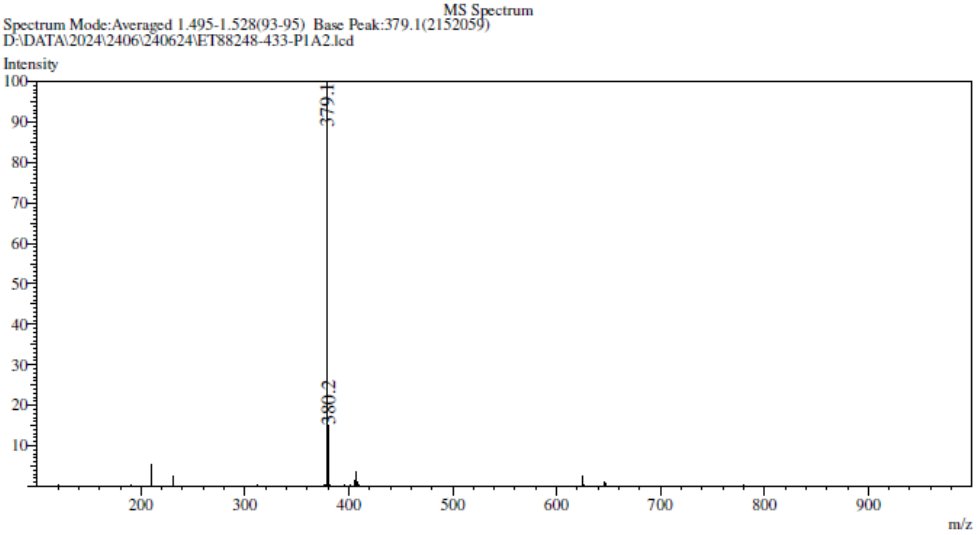


CW-23
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

ELSD

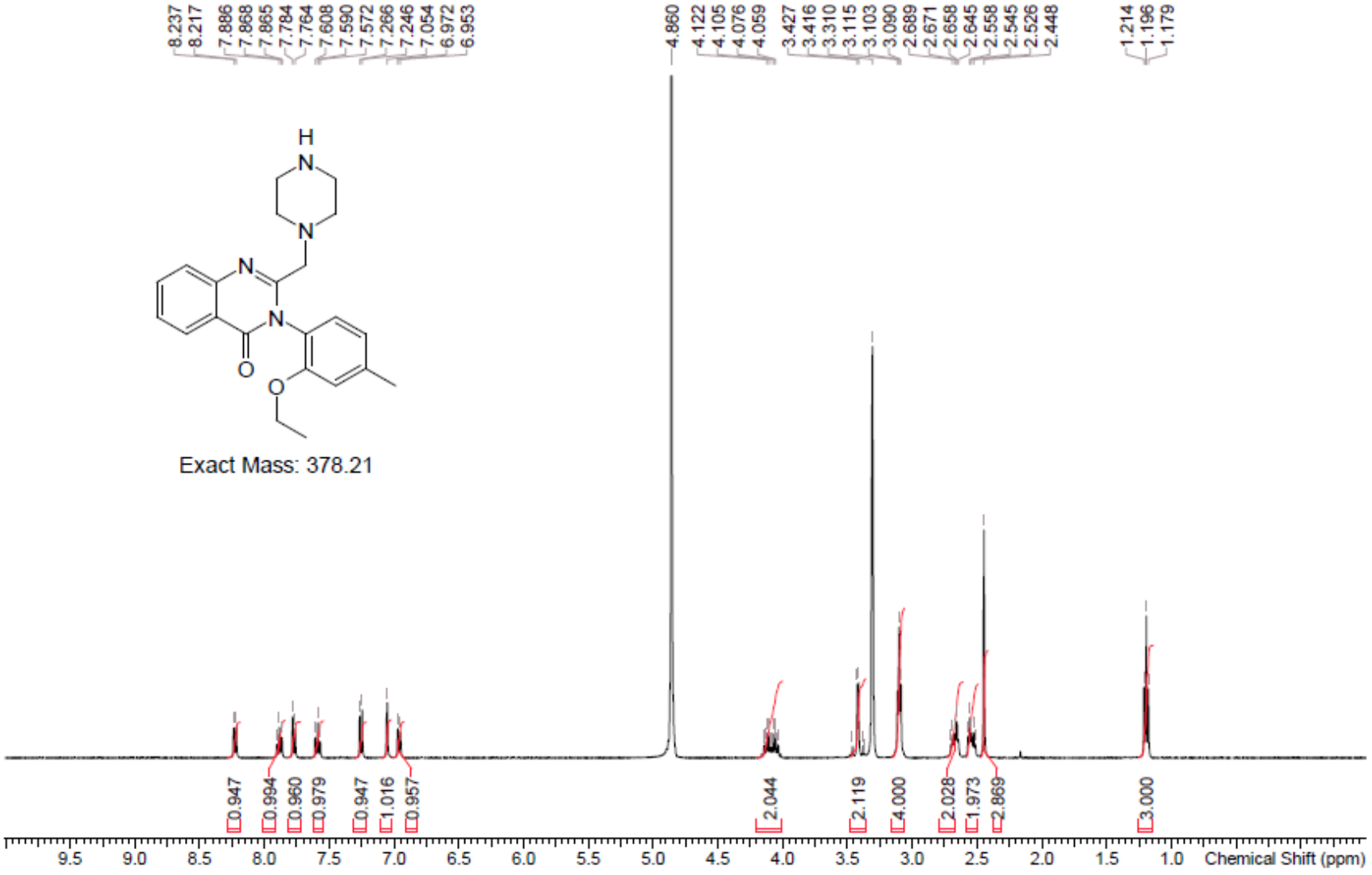
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.474	0.047	--	6947	7309	0.183
2	1.508	0.042	0.764	2542548	3993833	99.817
Total					4001142	100.000

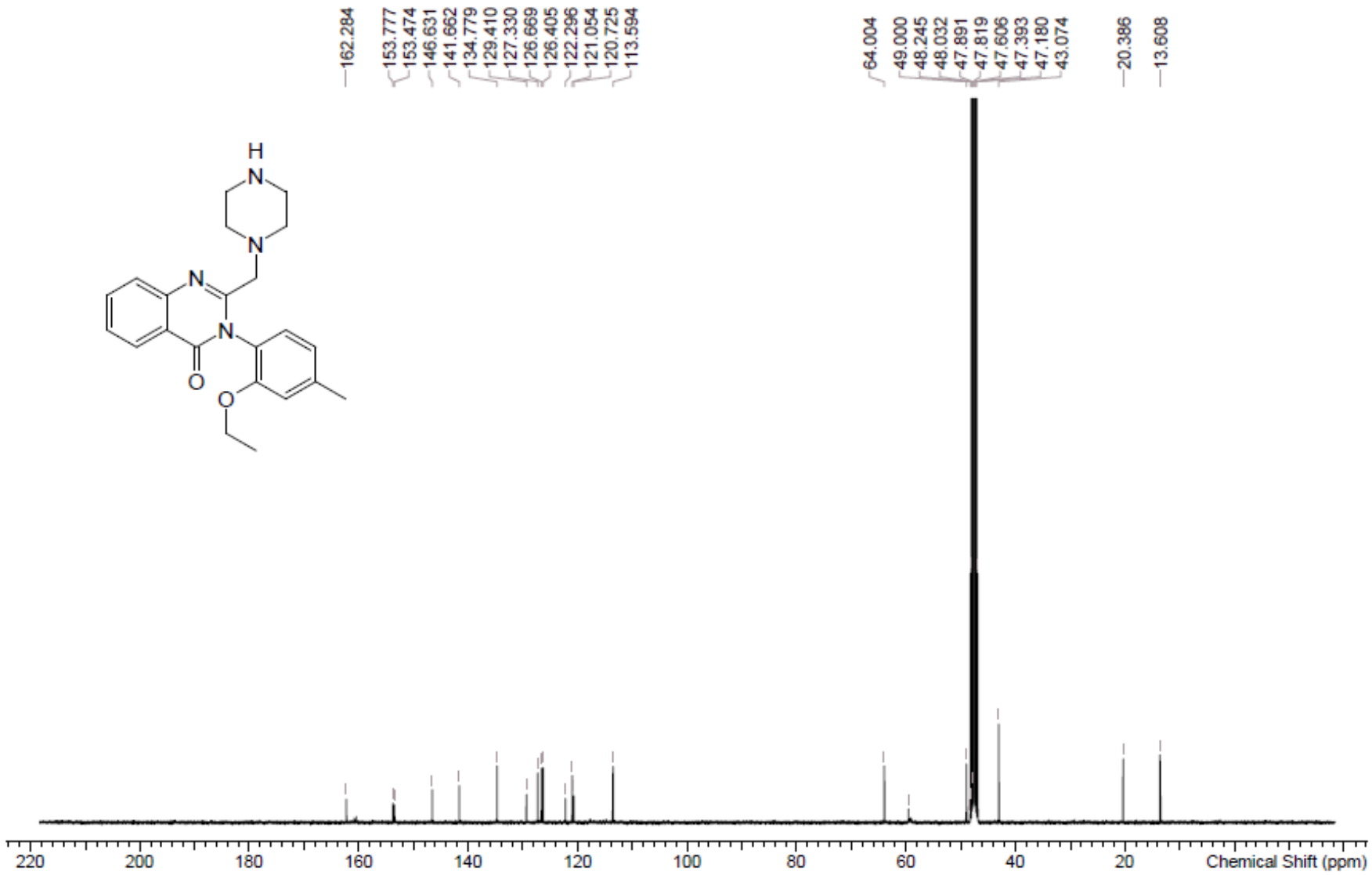
CW-24

^{1}H NMR: (400 MHz, CD_3OD)

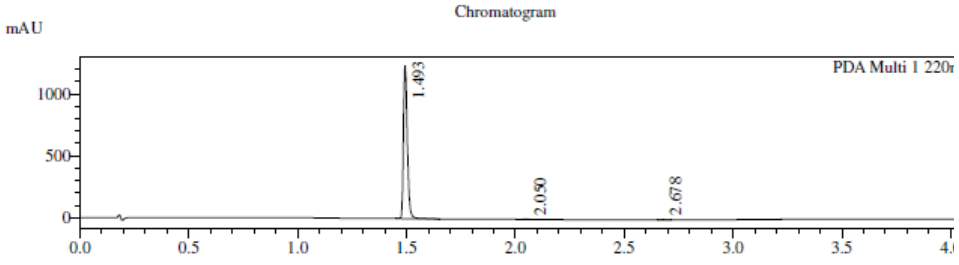


Exact Mass: 378.21

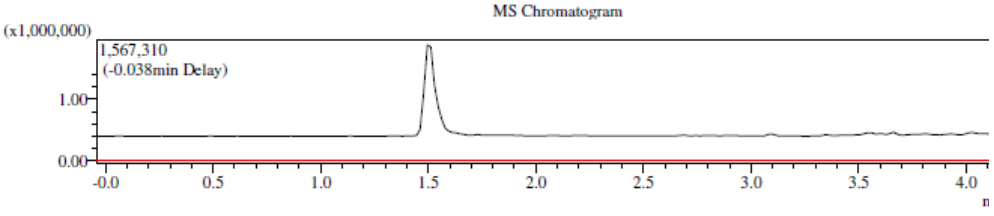
CW-24
^{13}C NMR: (101 MHz, CD_3OD)

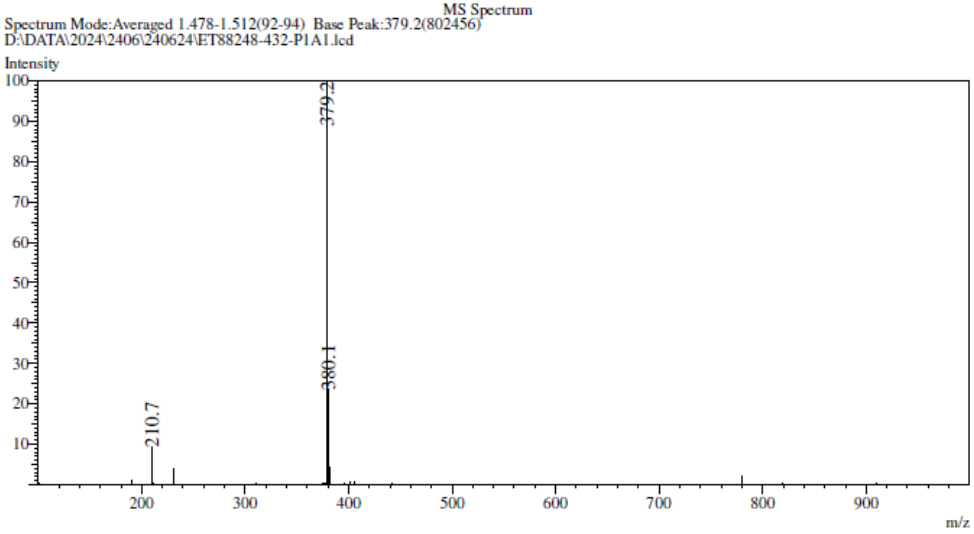


CW-24
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

ELSD

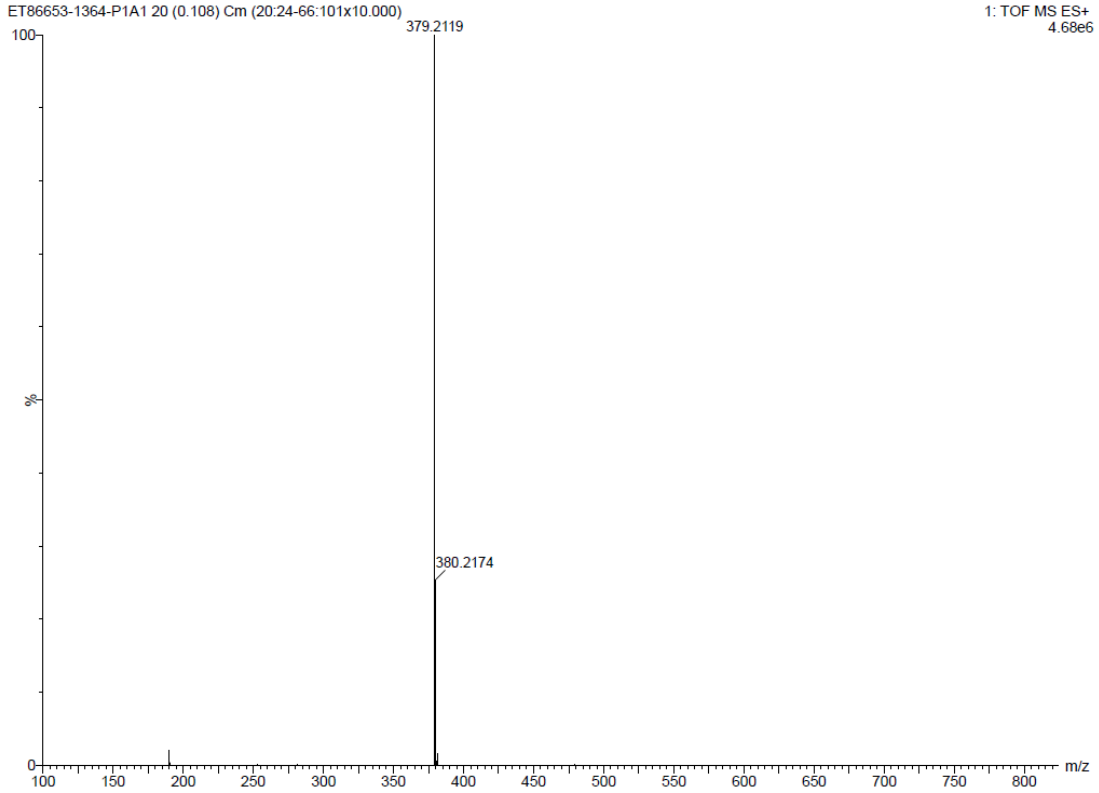
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.493	0.034	--	1237055	1542913	99.651
2	2.050	0.036	15.920	1469	1819	0.117
3	2.678	0.042	16.055	2343	3592	0.232
Total					1548323	100.000

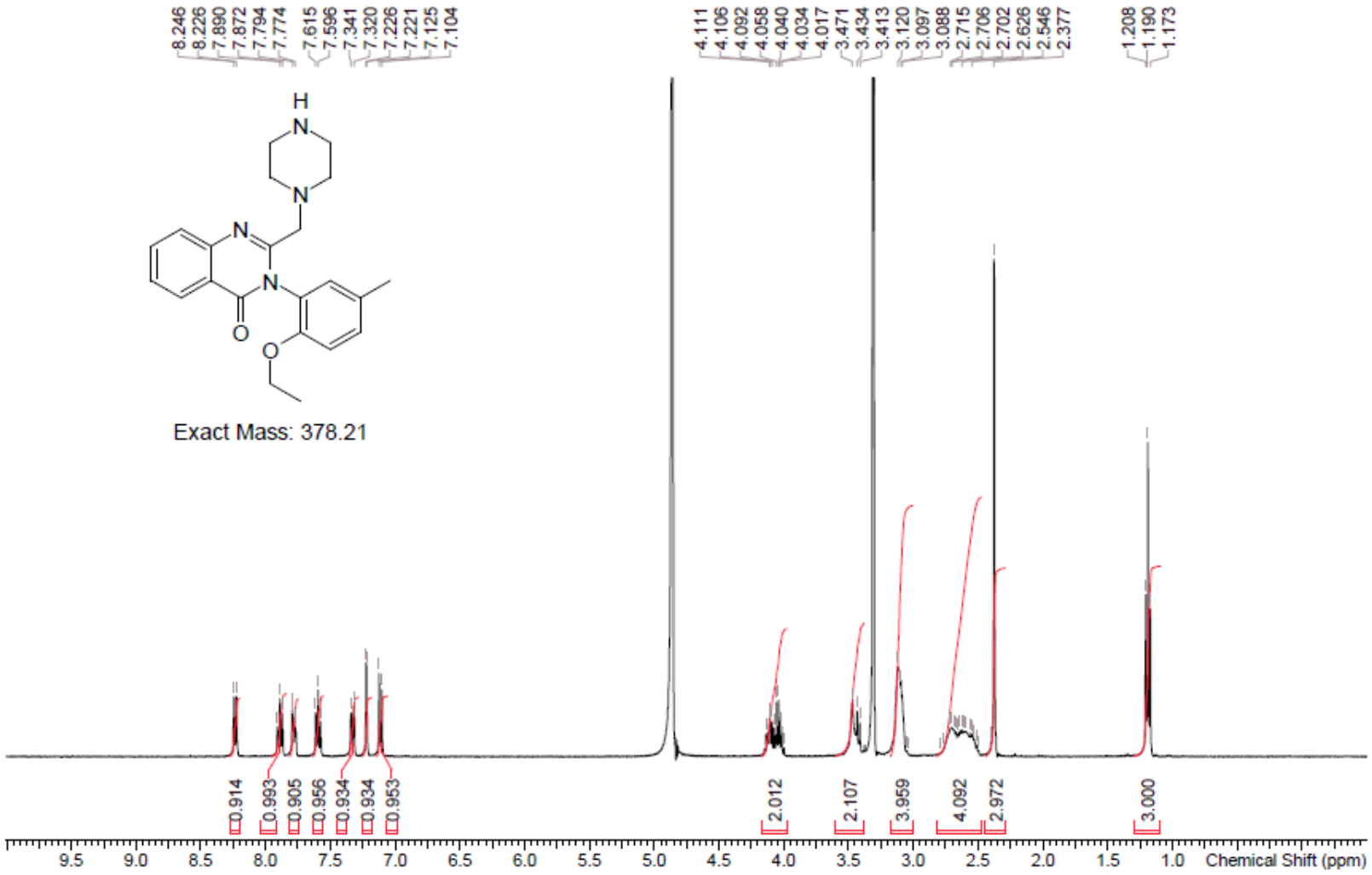
CW-24

HRMS

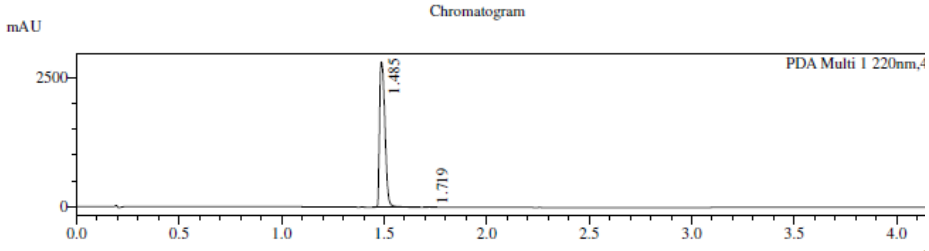

ET86653-1364-P1A1 20 (0.108) Cm (20:24-66:101x10.000)
1: TOF MS ES+
4.68e6
379.2119
380.2174
100
%
0
m/z
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800

CW-25

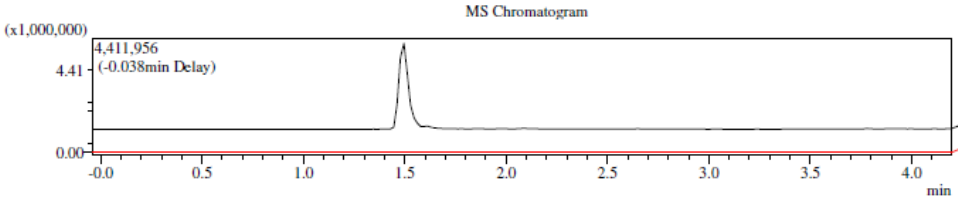
^{1}H NMR (400 MHz, CD_3OD)

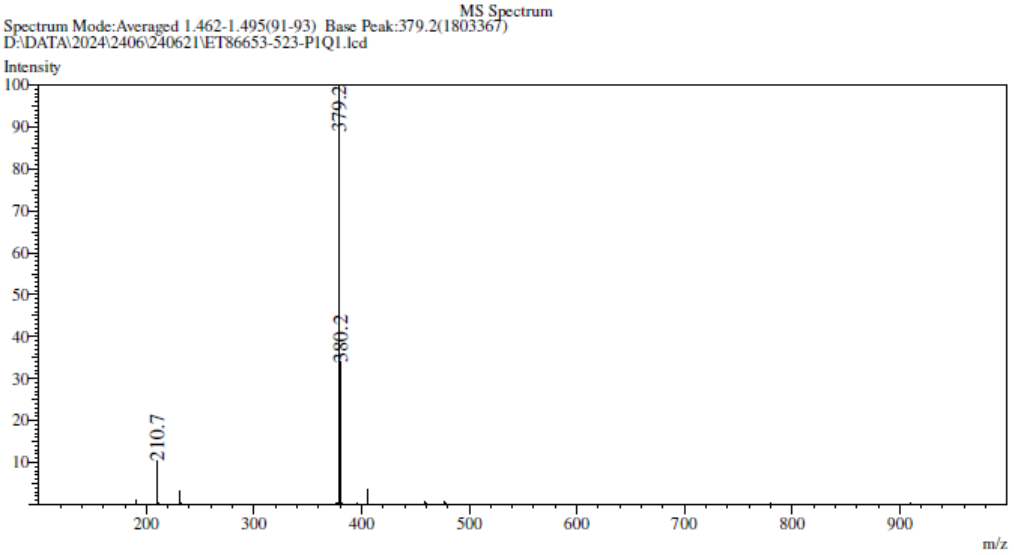


CW-25
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

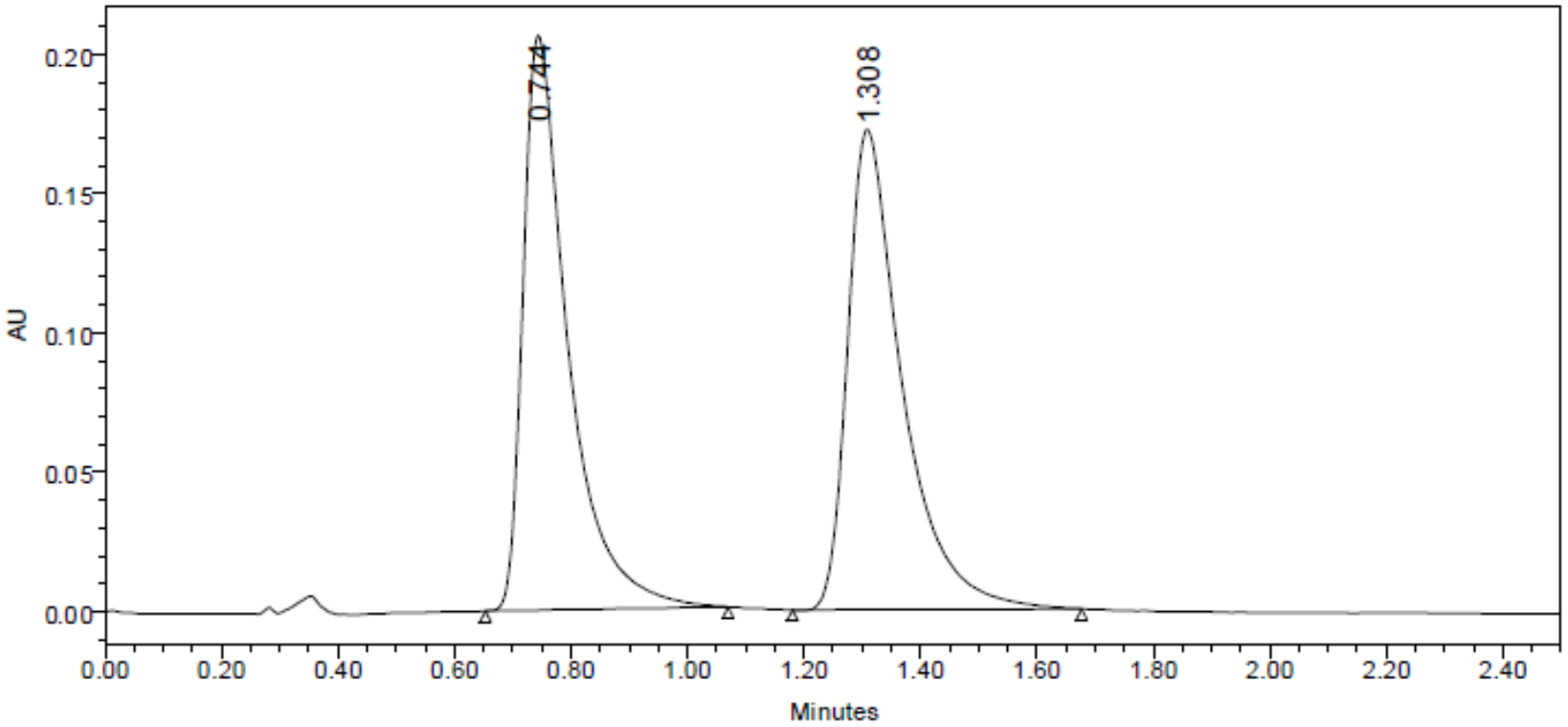
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

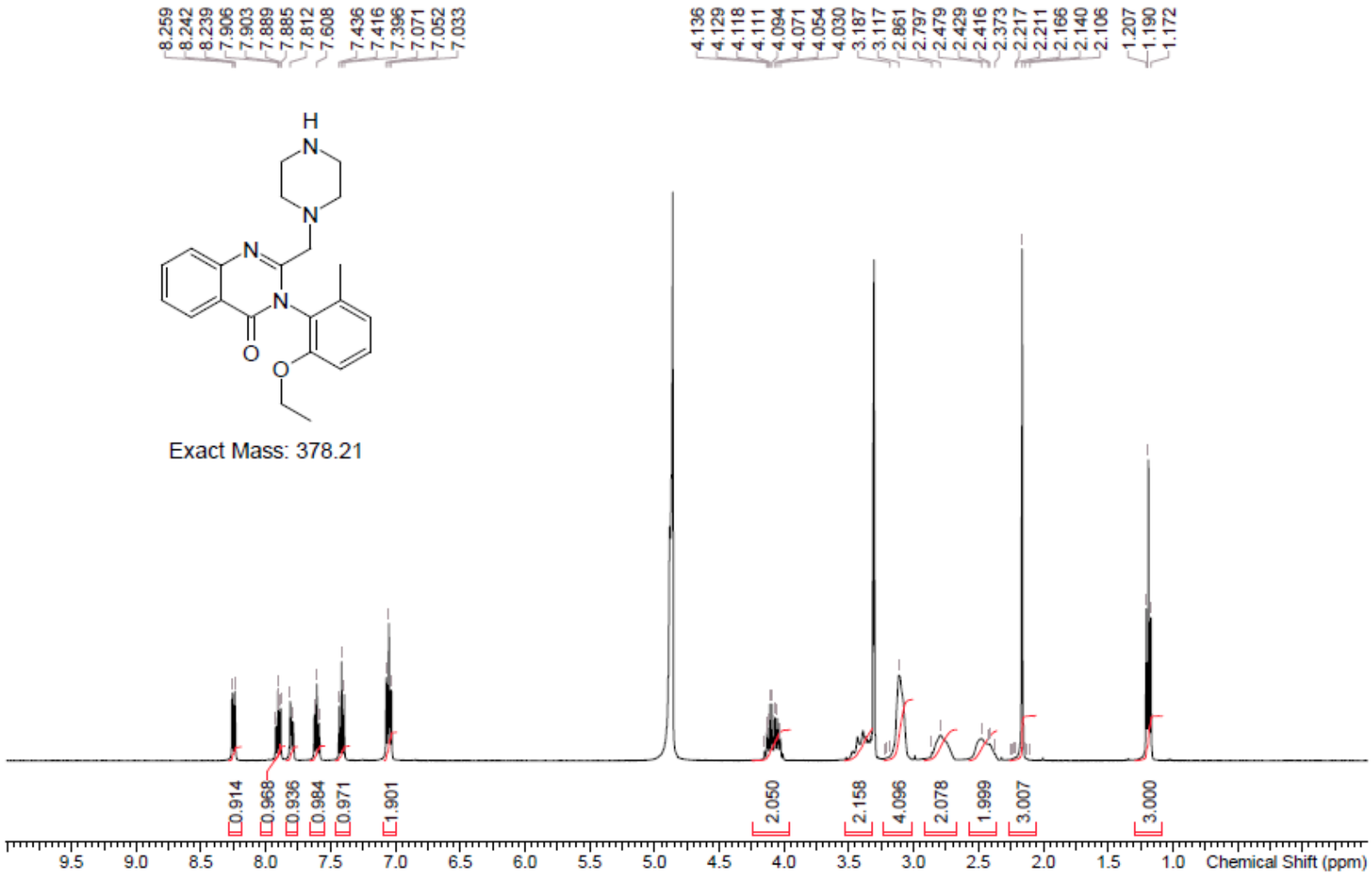
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.485	0.048	--	2808716	5165851	99.899
2	1.719	0.041	5.241	3447	5205	0.101
Total					5171056	100.000

CW-25
Chiral HPLC

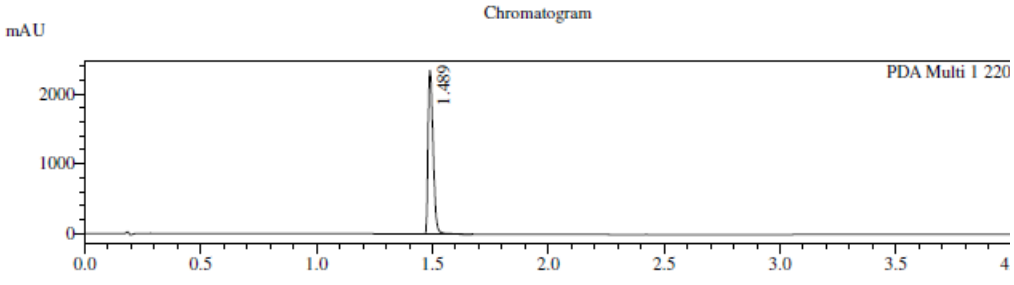


	RT	Area	% Area	Height
1	0.744	1111414	49.74	206467
2	1.308	1123100	50.26	172448

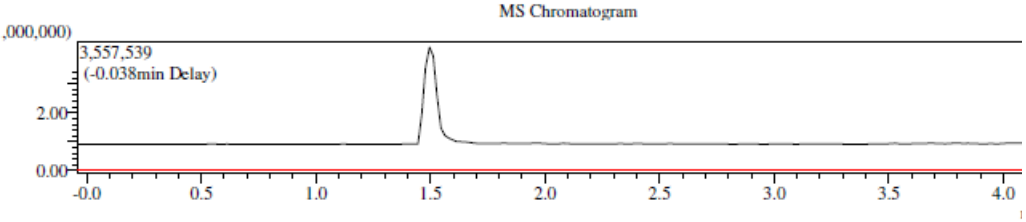
CW-26
^{1}H NMR: (400 MHz, CD_3OD)

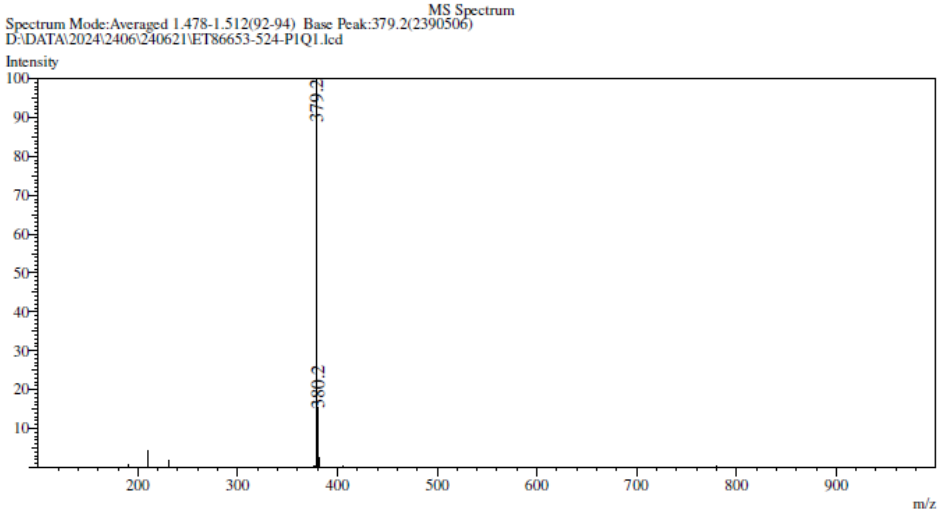


CW-26
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

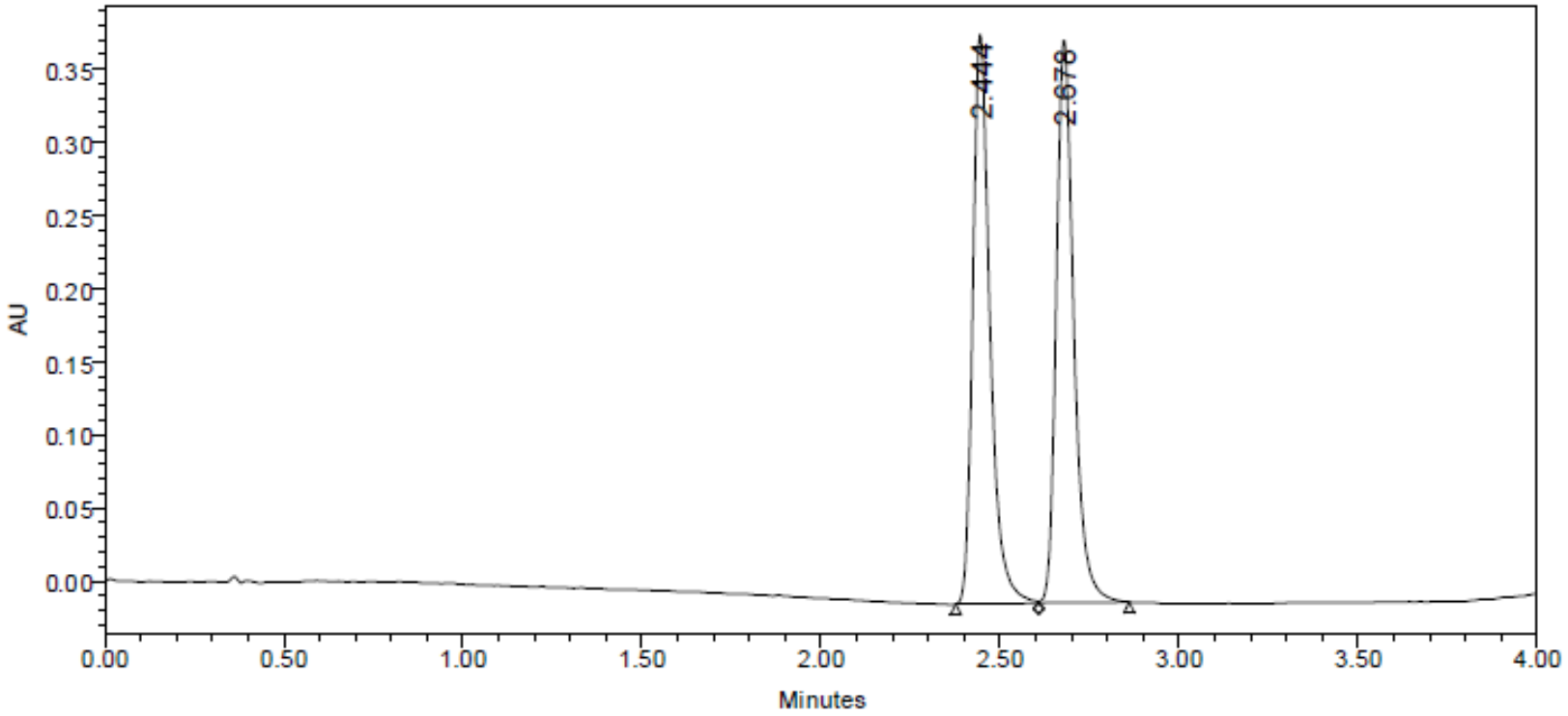
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

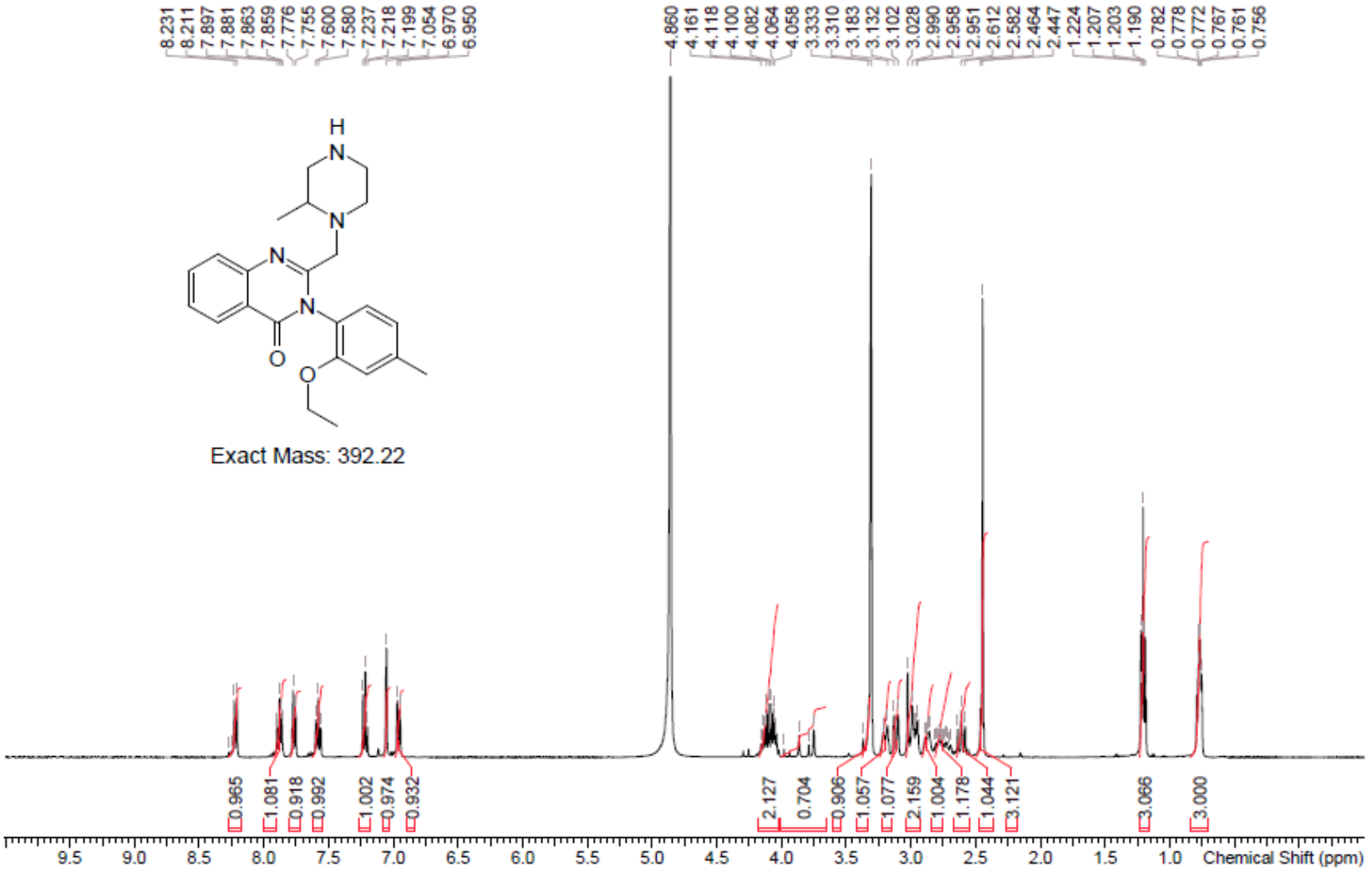
Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.489	0.041	--	2354543	3573185	100.000
Total					3573185	100.000

CW-26
Chiral HPLC

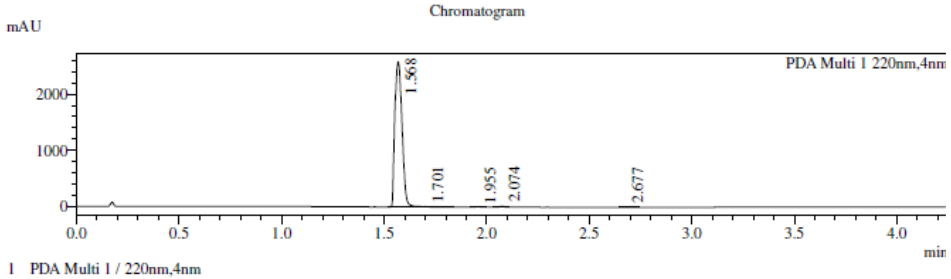


	RT	Area	% Area	Height
1	2.444	1304109	49.97	389506
2	2.678	1305625	50.03	385066

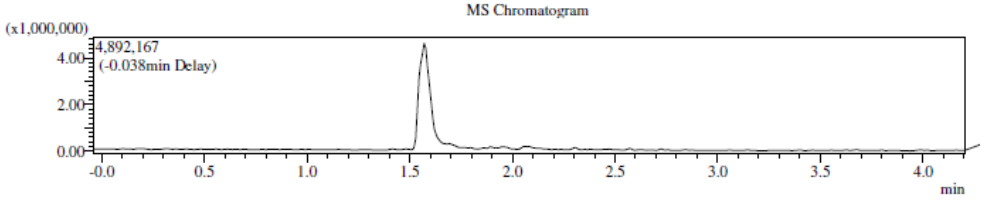
CW-27
^{1}H NMR: (400 MHz, CD_3OD)

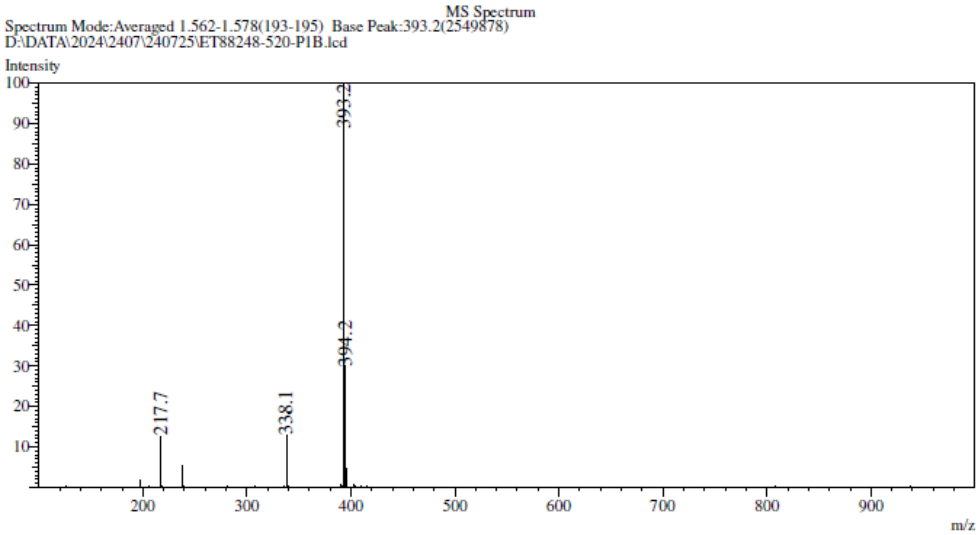


CW-27
LC-MS



1 PDA Multi 1 / 220nm,4nm





Integration Result

Peak Table

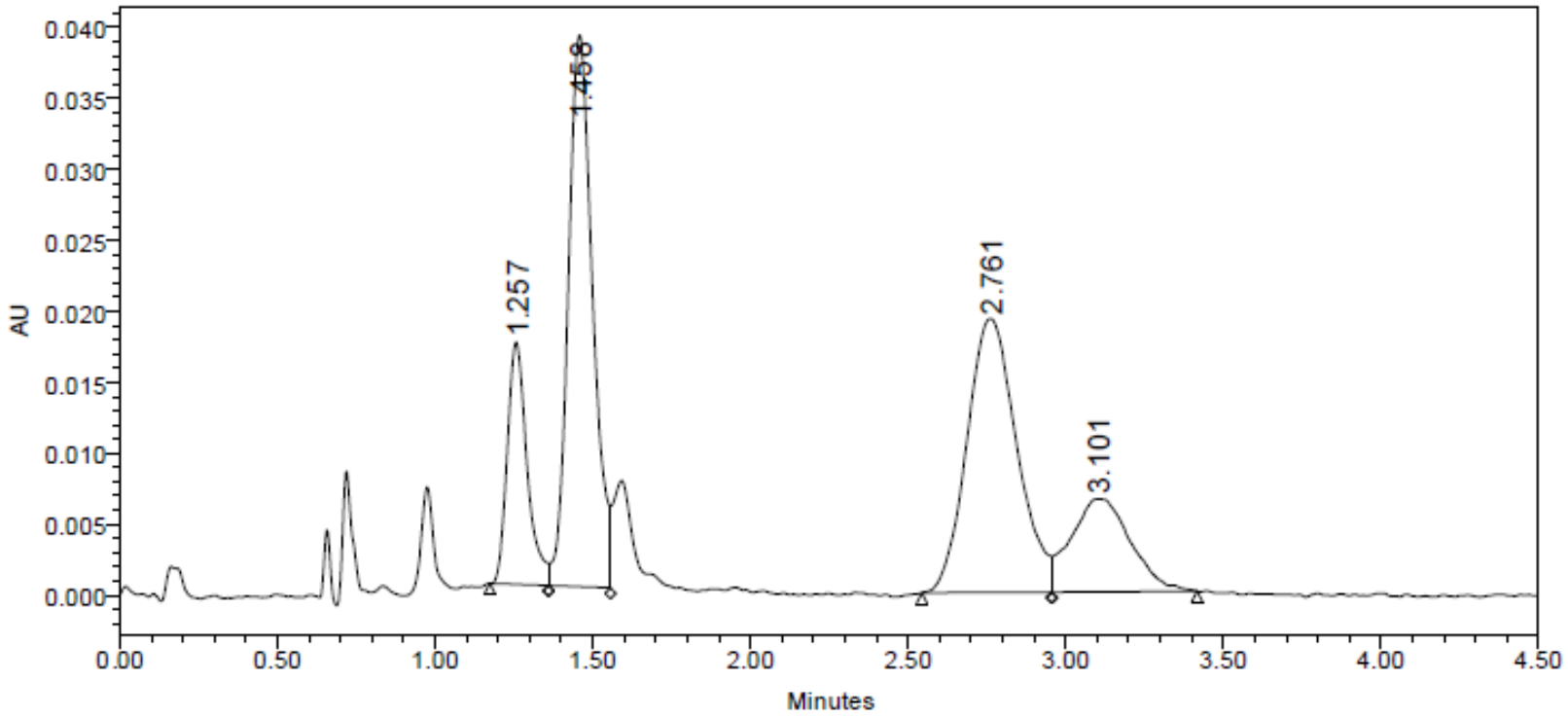
ELSD

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
Total						

PDA Ch1 220nm

Peak#	Ret. Time	USP Width	Resolution	Height	Area	Area%
1	1.568	0.064	--	2587929	6336253	99.177
2	1.701	0.079	1.856	6586	15366	0.241
3	1.955	0.037	4.382	8075	11013	0.172
4	2.074	0.038	3.154	15861	22816	0.357
5	2.677	0.043	14.757	1963	3409	0.053
Total					6388857	100.000

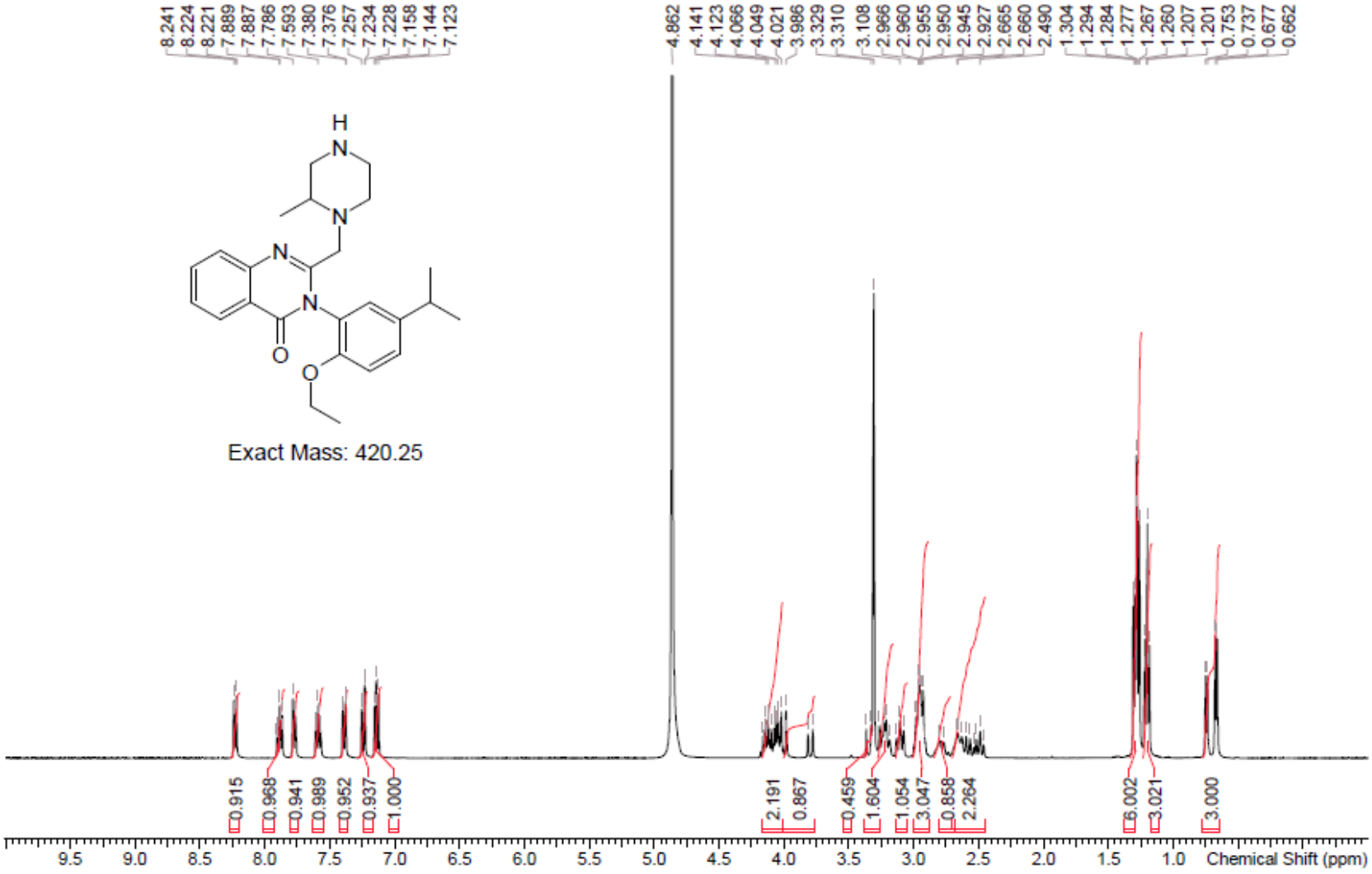
CW-27
Chiral HPLC



	RT	Area	% Area	Height
1	1.257	74573	12.81	17063
2	1.458	209025	35.92	38868
3	2.761	212079	36.44	19272
4	3.101	86292	14.83	6547

CW-28

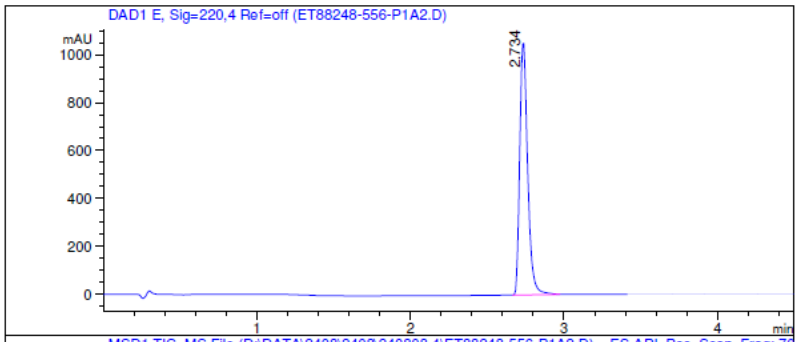
^{1}H NMR: (400 MHz, CD_3OD)

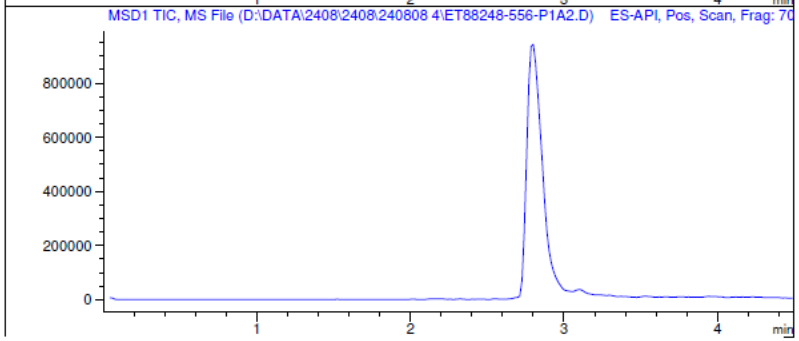


CW-28
LC-MS

Method Info ->Instrument:Agilent 1200 HPLC
MSD:6120 single quadrupole MSD
Column:XBridge C18,2.1*50mm, 5μm
Column Temp: 40 °C
Mobile Phase:A:H2O+10mM NH4HCO3
Mobile Phase:B:ACN
Flow Rate: 0.8ml/min

Time	B%	Flow(ml/min)
0.00	5	0.8
0.40	5	0.8
3.40	95	0.8
3.85	95	0.8
3.86	5	0.8
4.50	5	0.8

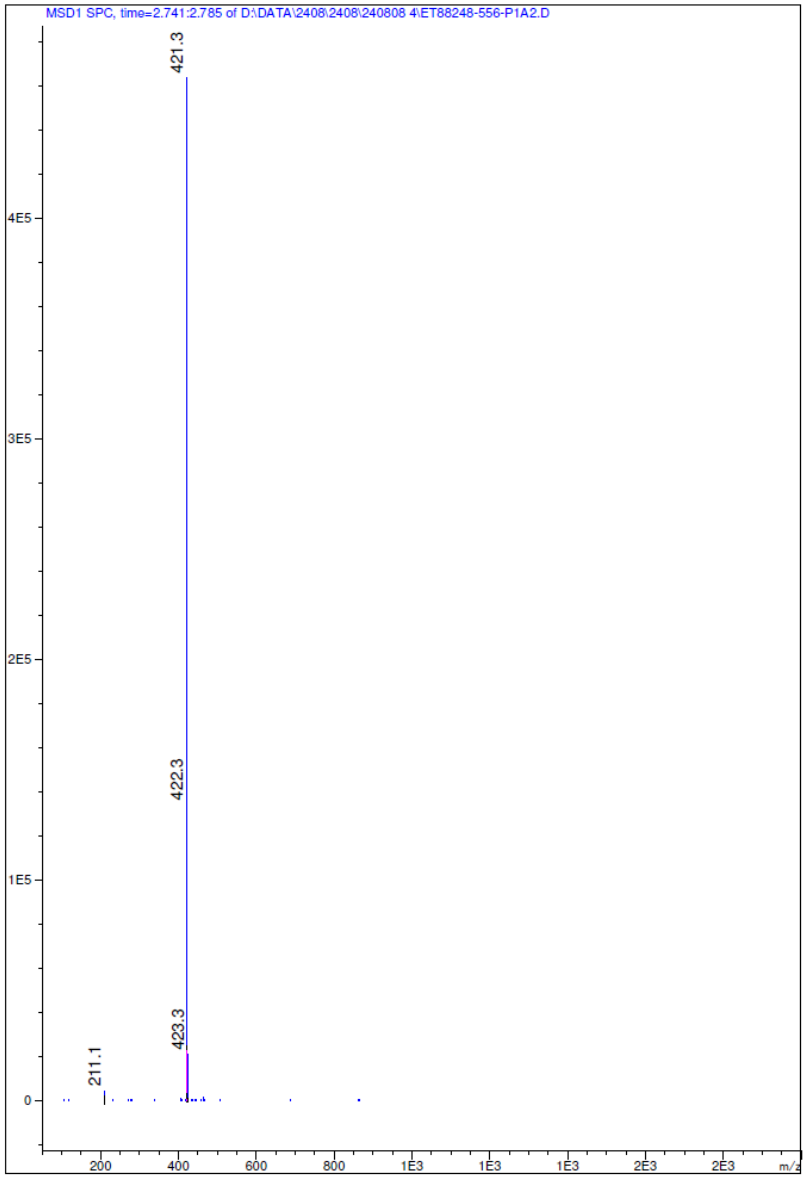




Report

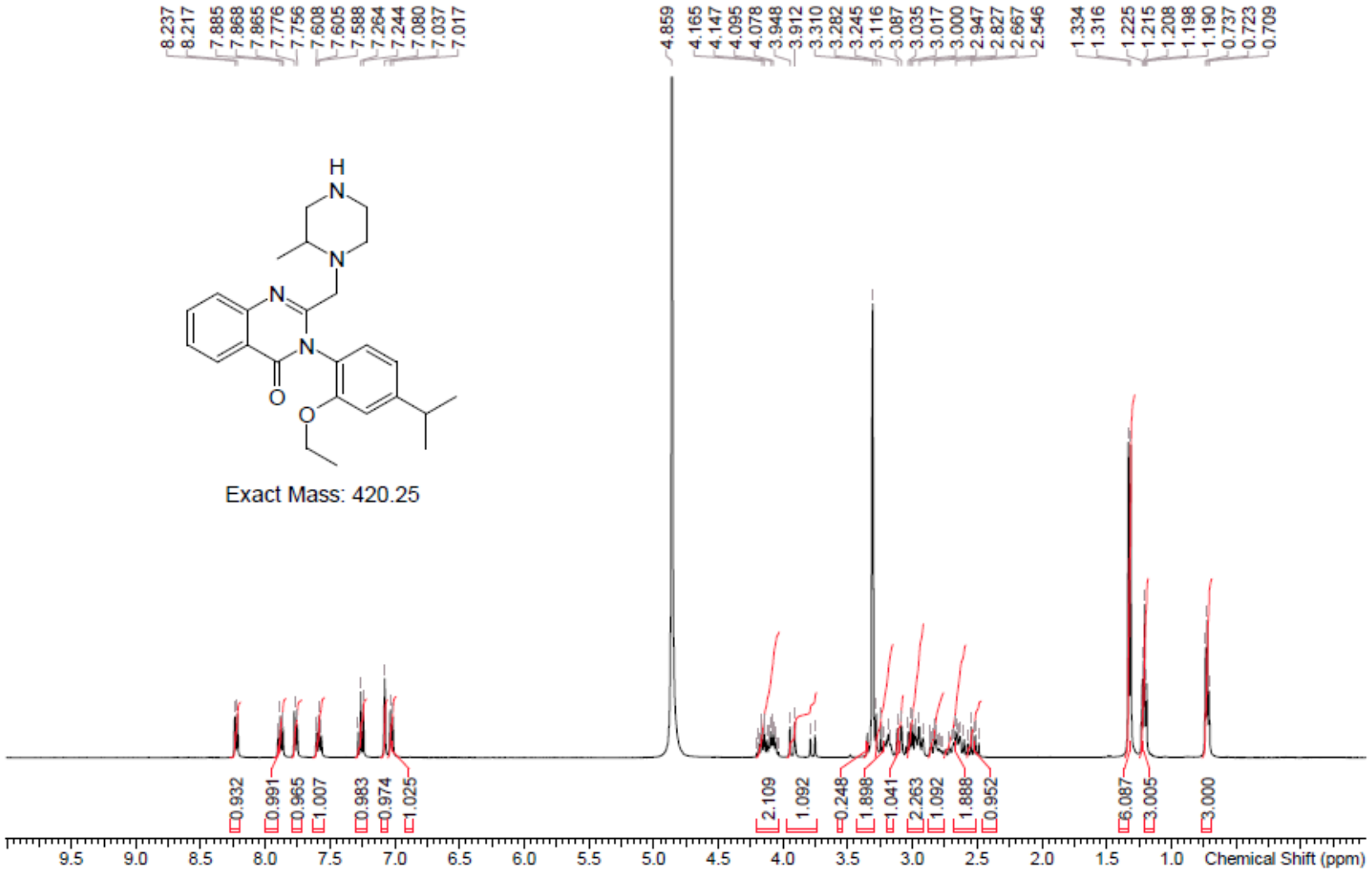
Signal 1 :DAD1 E, Sig=220,4 Ref=off

Peak #	RT [min]	Height	Height %	Width [min]	Area	Area %
1	2.734	1059.530	100.000	0.056	3786.221	100.000

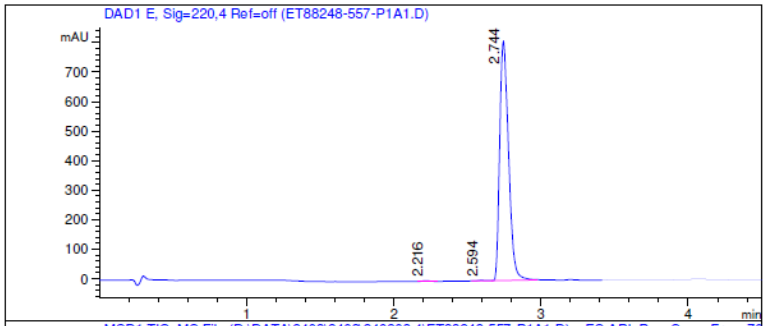


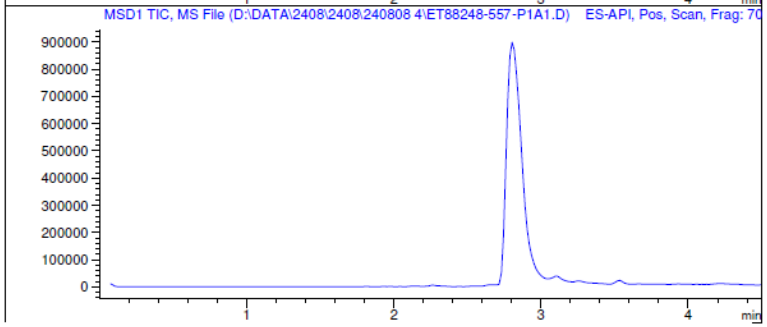
CW-29

^{1}H NMR: (400 MHz, CD_3OD)



CW-29
LC-MS



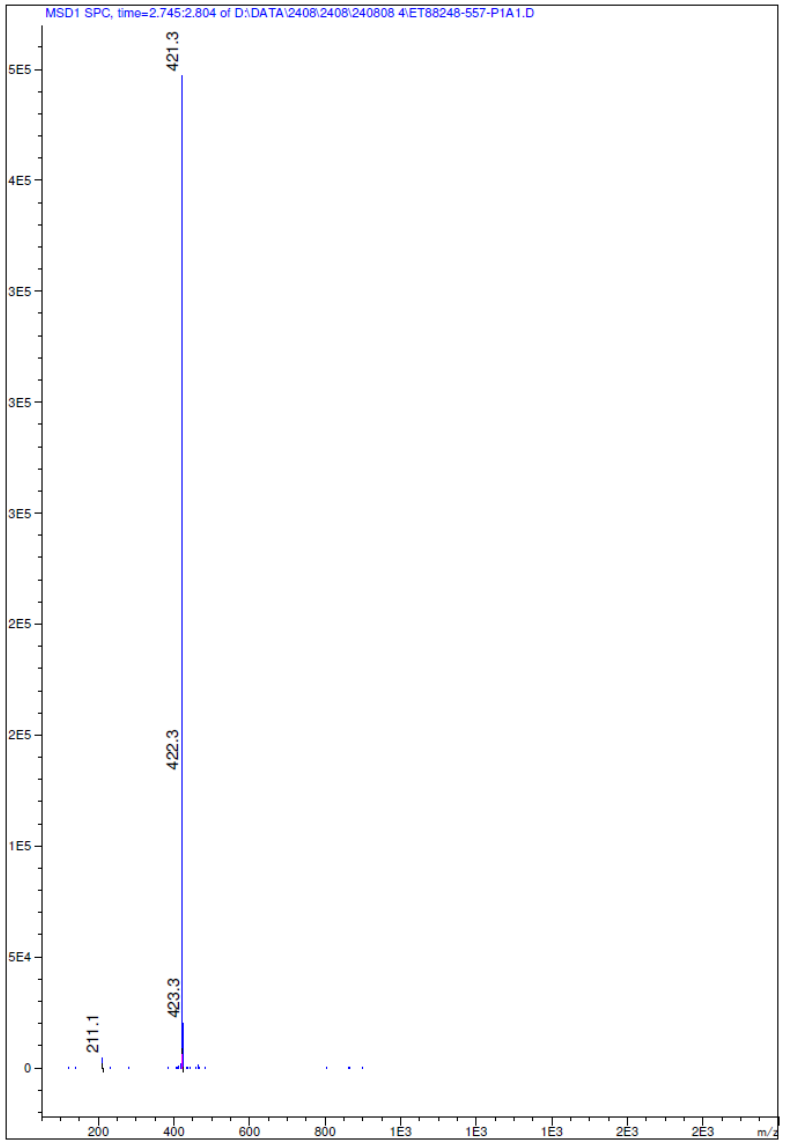


Report

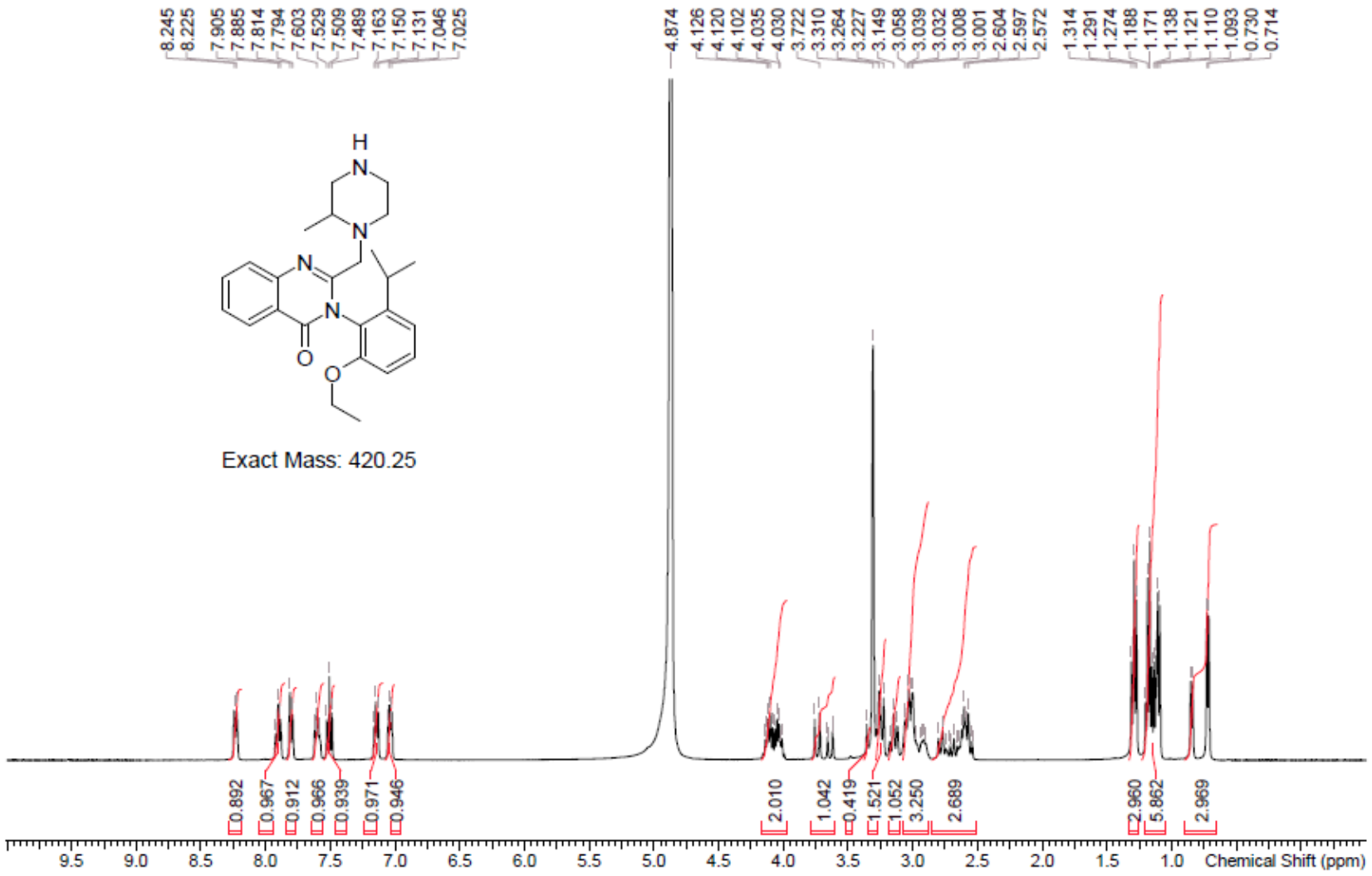
Signal 1 :DAD1 E, Sig=220,4 Ref=off

Peak #	RT [min]	Height	Height %	Width [min]	Area	Area %
1	2.216	2.492	0.305	0.047	7.388	0.217
2	2.594	1.947	0.238	0.053	6.829	0.200

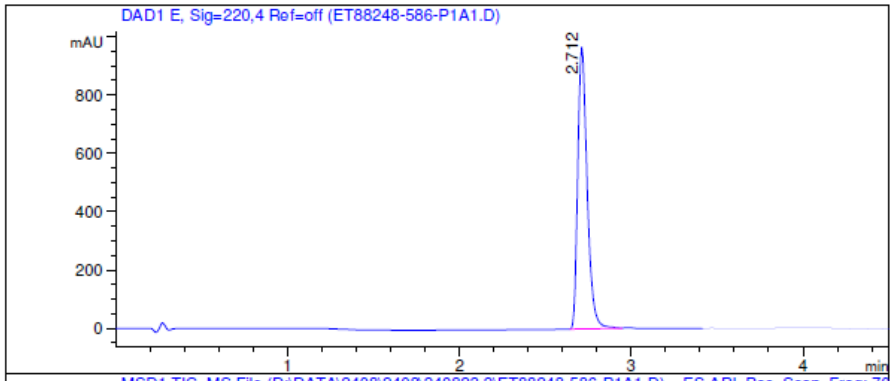
Peak #	RT [min]	Height	Height %	Width [min]	Area	Area %
3	2.744	813.413	99.457	0.067	3395.070	99.583

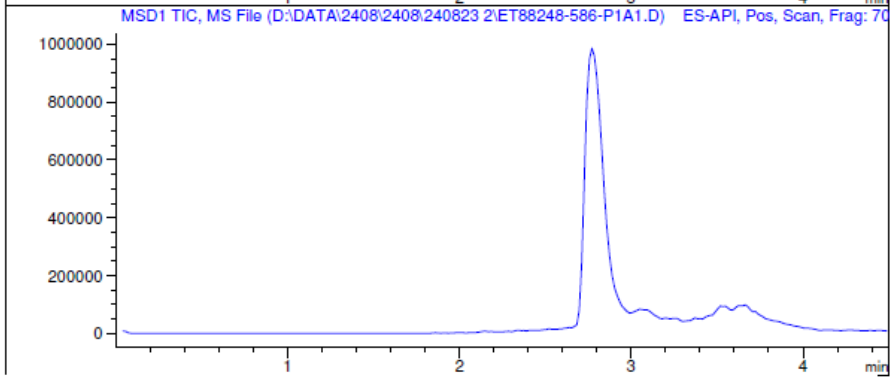


CW-30
^{1}H NMR: (400 MHz, CD_3OD)



CW-30
LC-MS

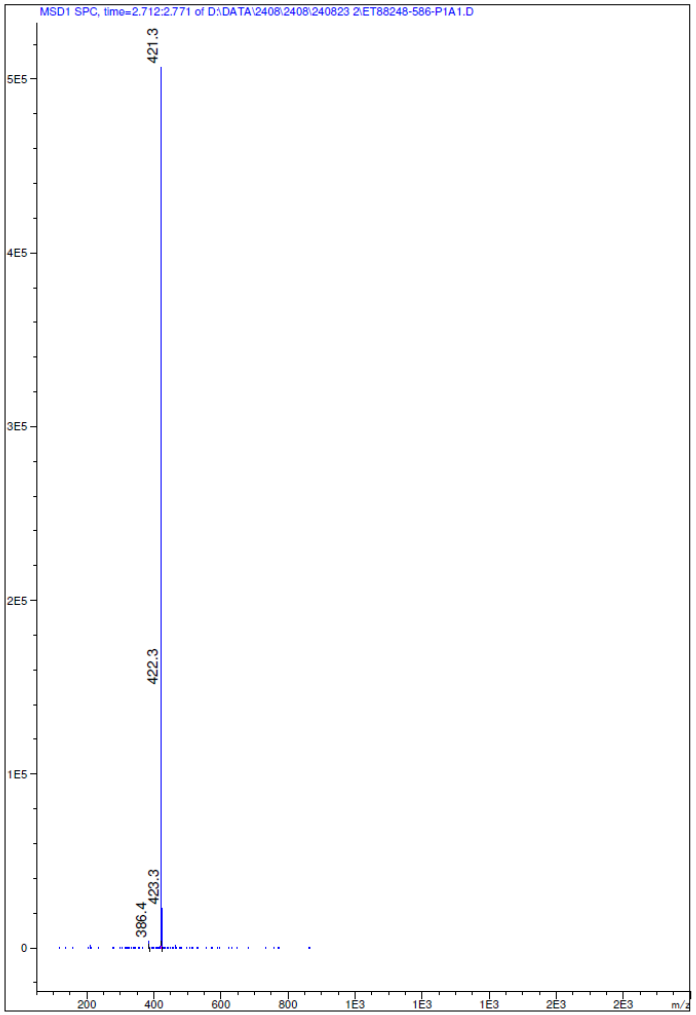




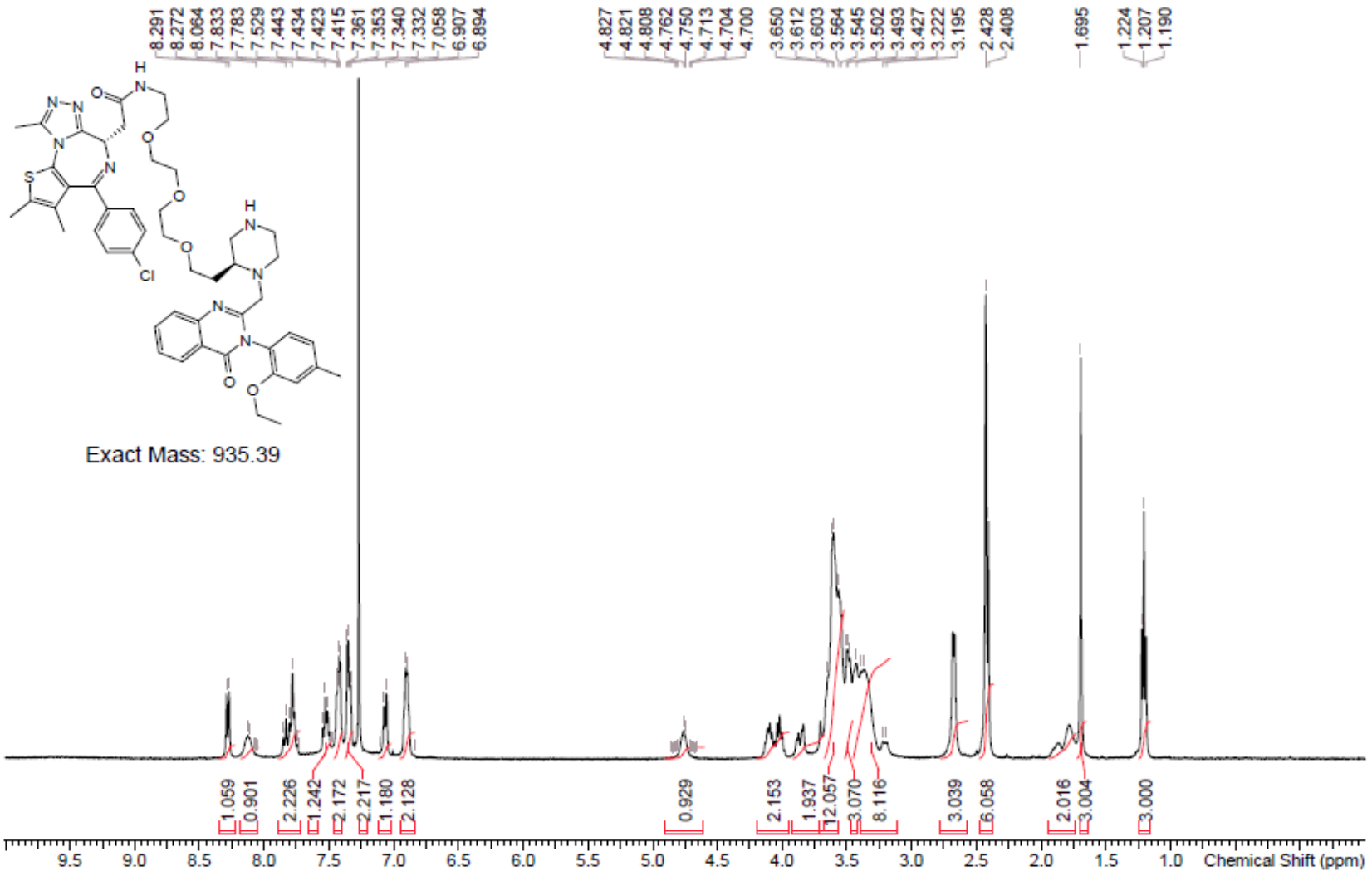
Report

Signal 1 :DAD1 E, Sig=220,4 Ref=off

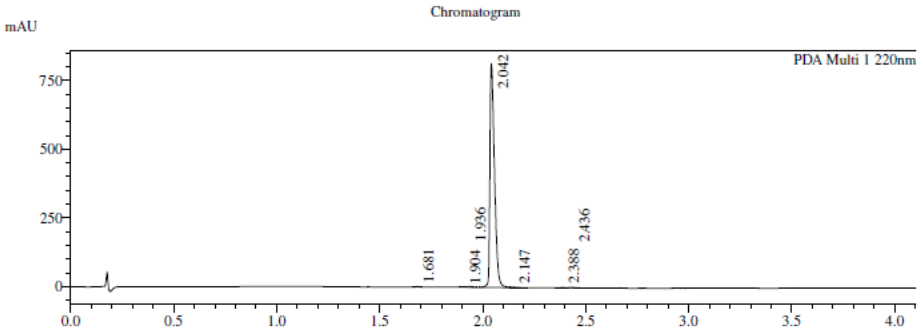
Peak #	RT [min]	Height	Height %	Width [min]	Area	Area %
1	2.712	966.884	100.000	0.058	3686.757	100.000

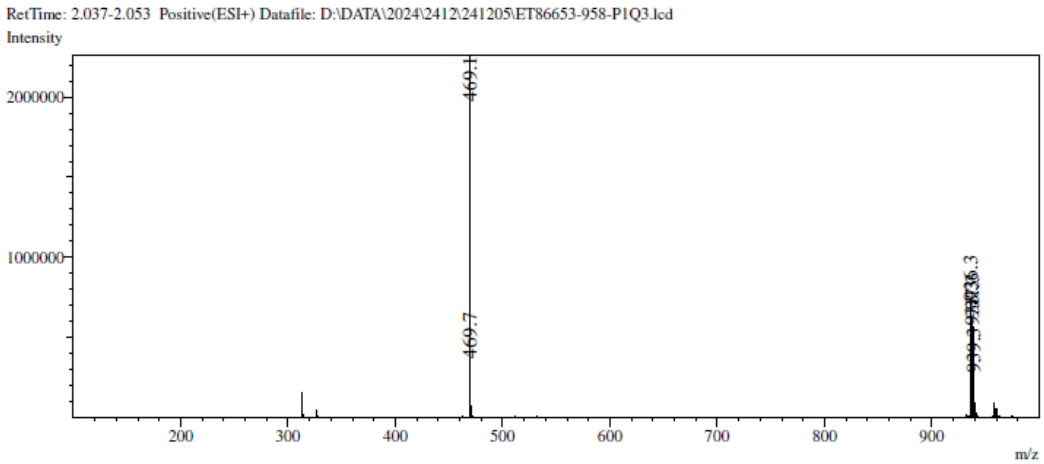


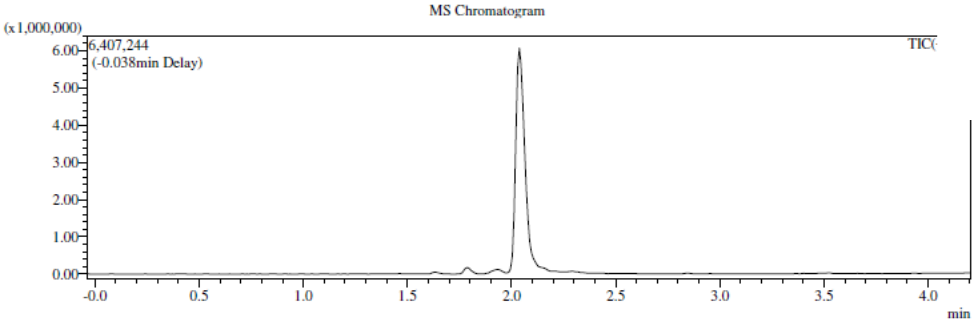
CW-31
^{1}H NMR: (400 MHz, $CDCl_3$)



CW-31
LC-MS







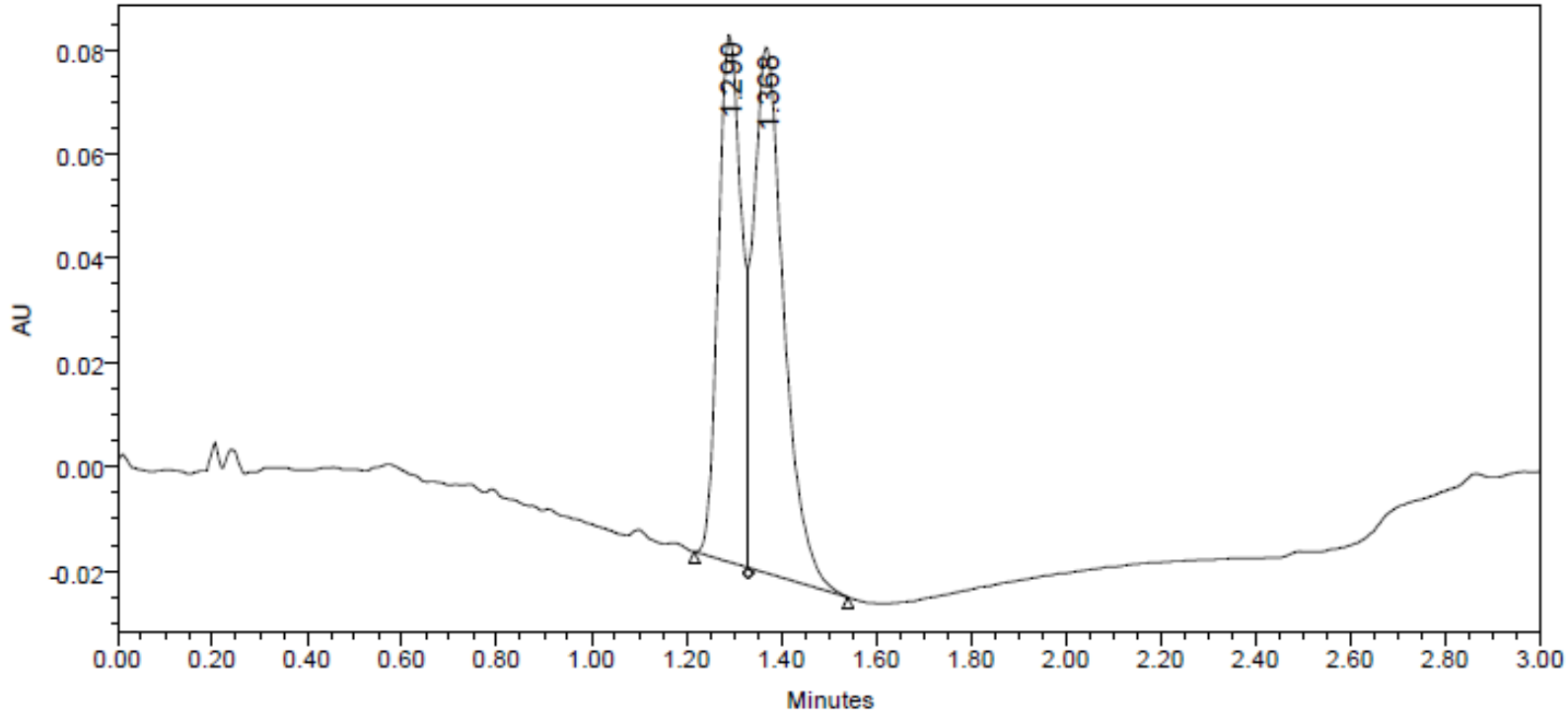
Integration Result

ELSD

PDA Ch1 220nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	1.681	0.031	1864	0.227	2050	0.161
2	1.904	0.036	864	0.105	1095	0.086
3	1.936	0.038	3117	0.379	4597	0.362
4	2.042	0.042	810613	98.638	1253935	98.640
5	2.147	0.101	1729	0.210	3296	0.259
6	2.388	0.061	1617	0.197	3489	0.274
7	2.436	0.036	1999	0.243	2756	0.217

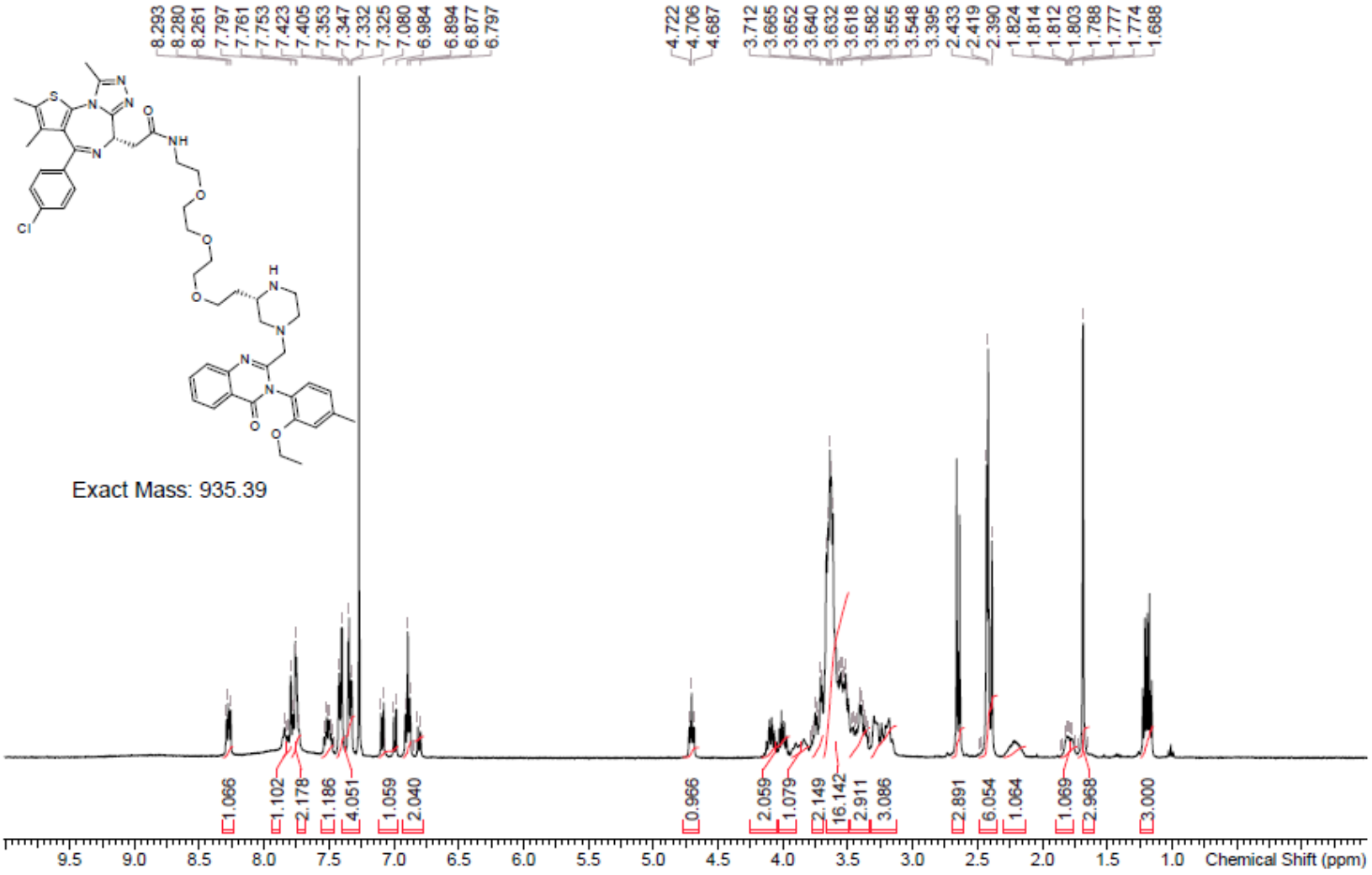
CW-31
Chiral HPLC



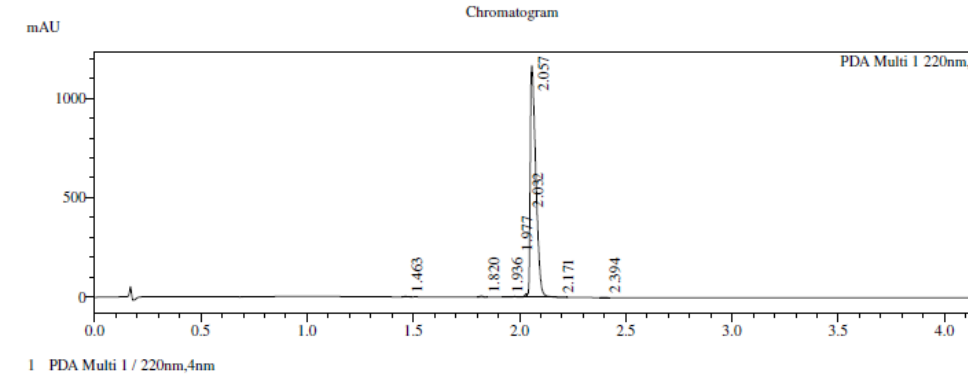
	RT	Area	% Area	Height
1	1.290	347913	43.66	101099
2	1.368	448882	56.34	100960

CW-32

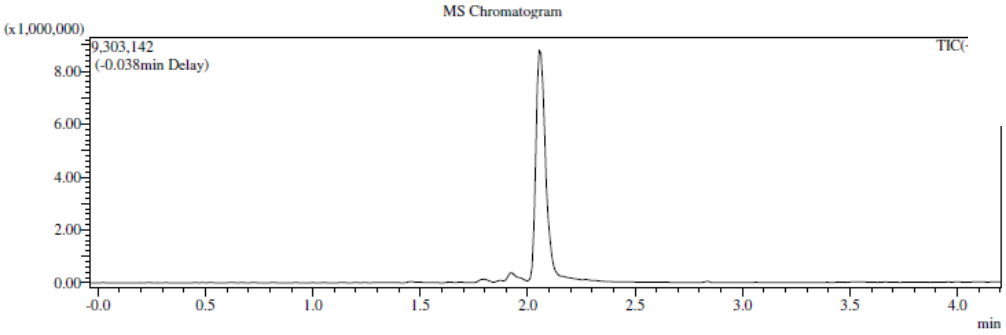
^{1}H NMR: (400 MHz, $CDCl_3$)

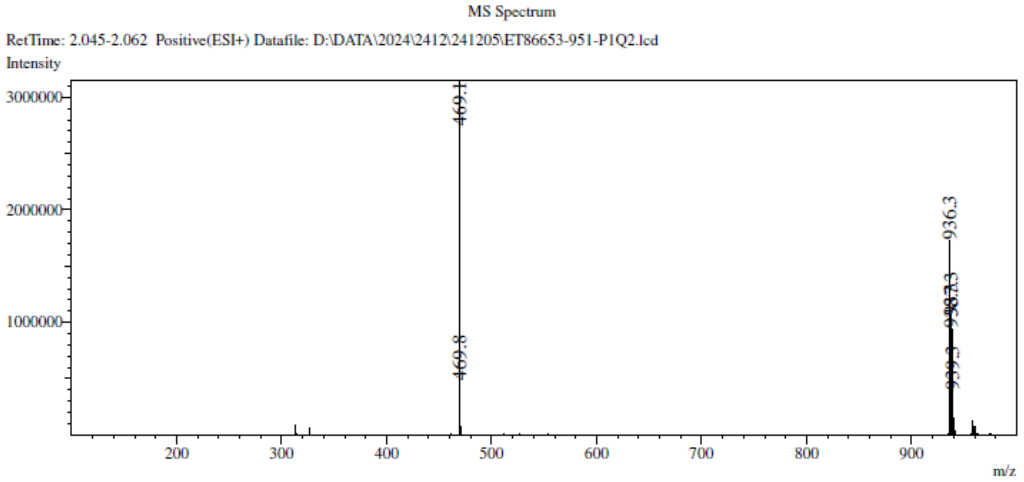


CW-32
LC-MS



1 PDA Multi 1 / 220nm,4nm





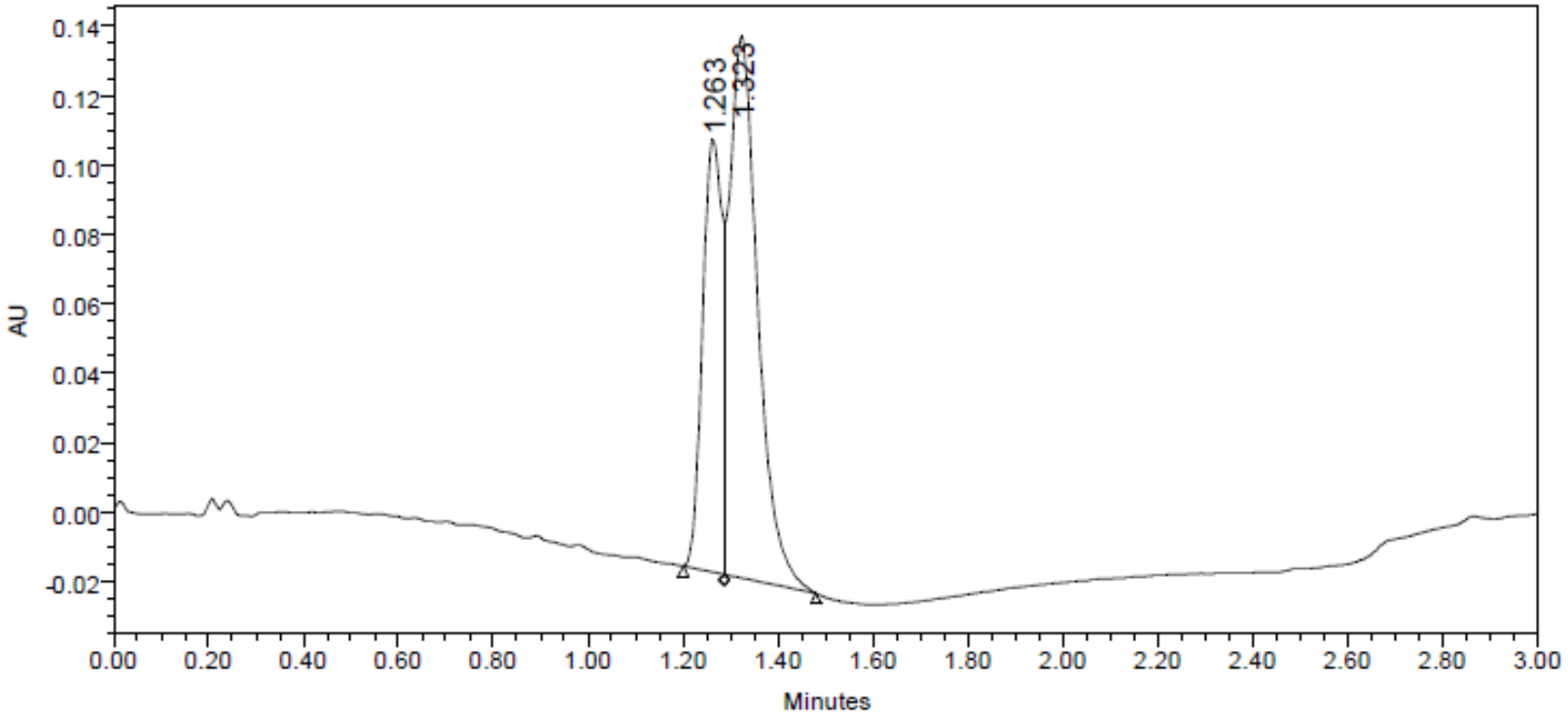
Integration Result

ELSD

PDA Ch1 220nm

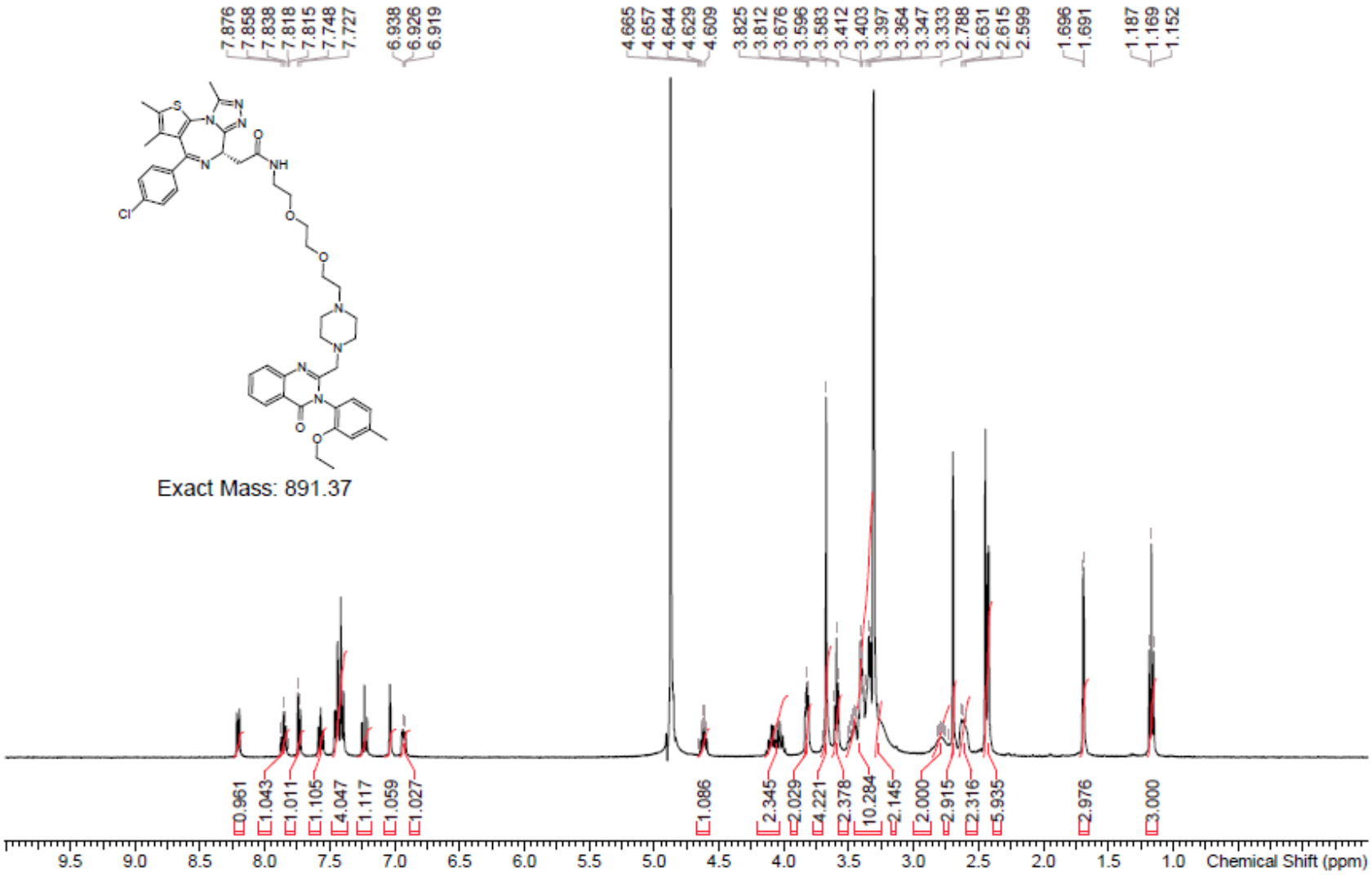
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	1.463	0.029	1905	0.159	2010	0.093
2	1.820	0.030	5163	0.432	5420	0.252
3	1.936	0.039	1189	0.100	1865	0.087
4	1.977	0.032	2817	0.236	3179	0.148
5	2.032	0.081	17177	1.438	14703	0.683
6	2.057	0.051	1162695	97.338	2119573	98.437
7	2.171	0.237	2533	0.212	4991	0.232
8	2.394	0.041	1018	0.085	1490	0.069

CW-32
Chiral HPLC

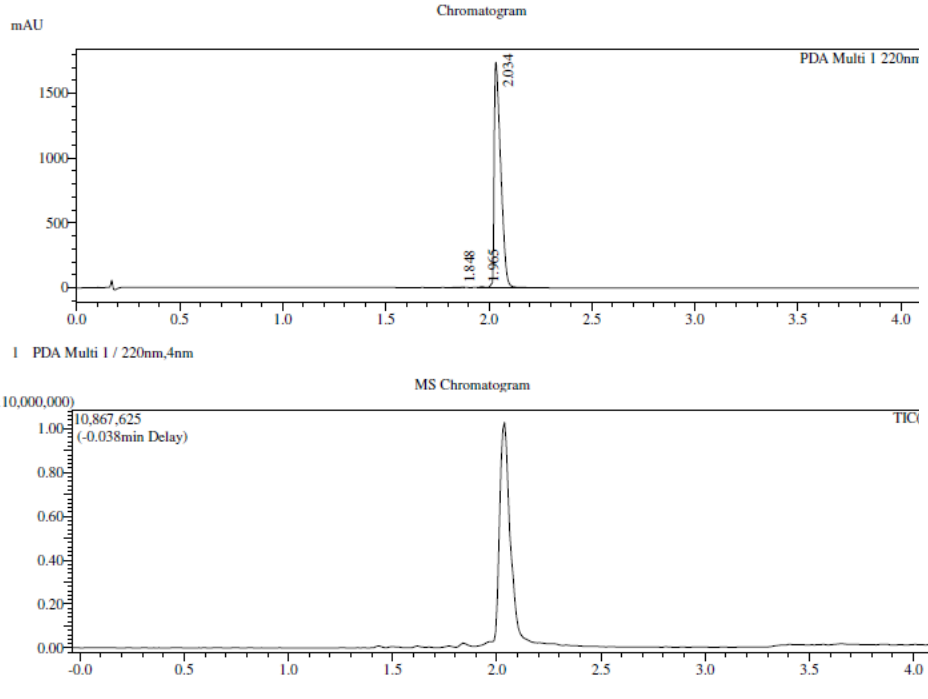


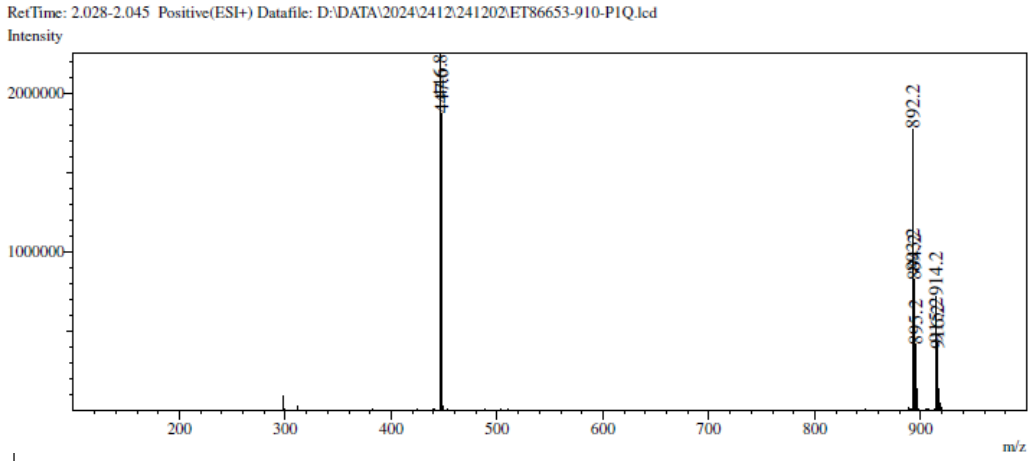
	RT	Area	% Area	Height
1	1.263	349881	34.57	124584
2	1.323	662233	65.43	156336

CW-33
^{1}H NMR: (400 MHz, CD_3OD)



CW-33
LC-MS





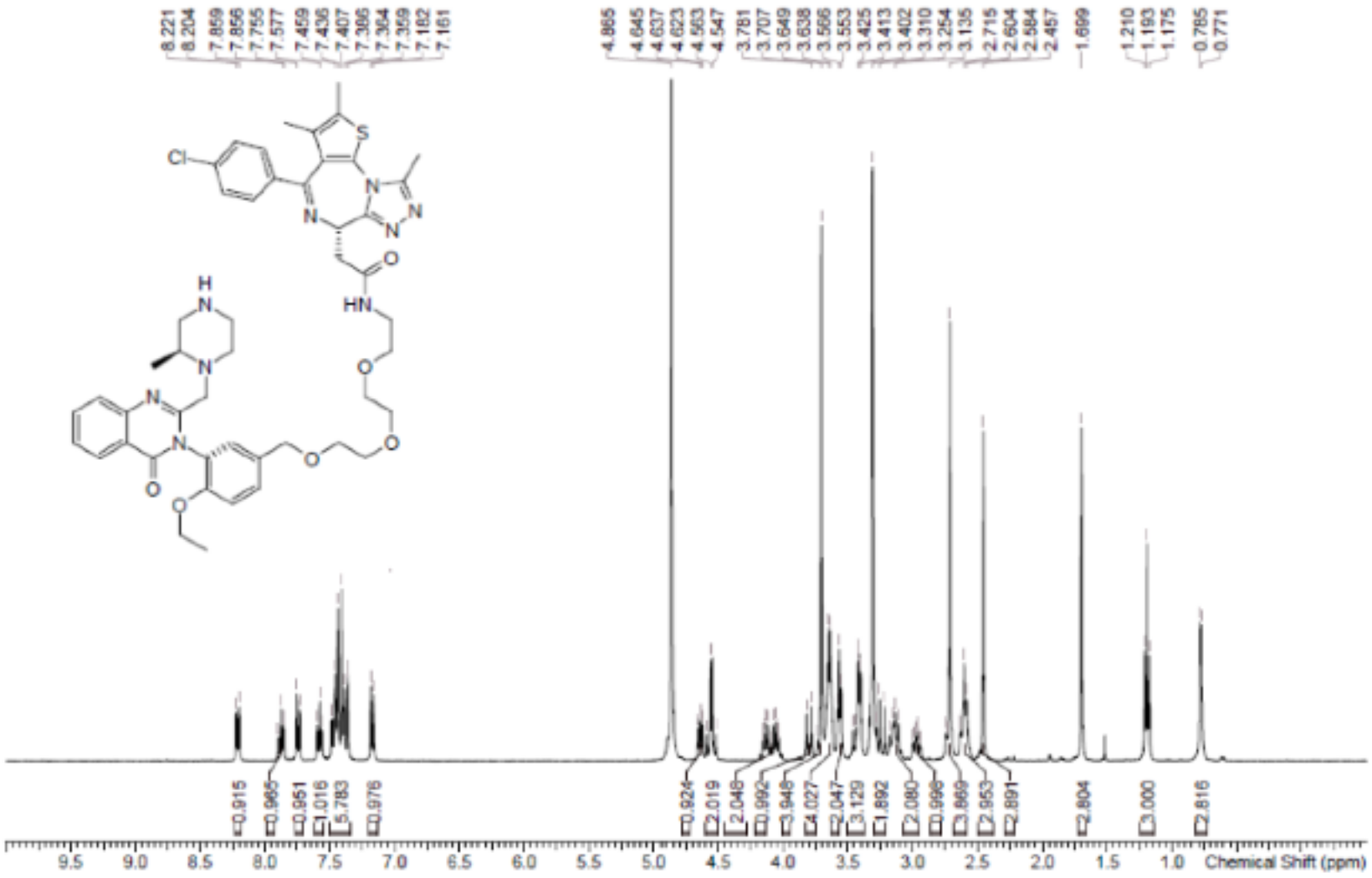
Integration Result

ELSD

PDA Ch1 220nm

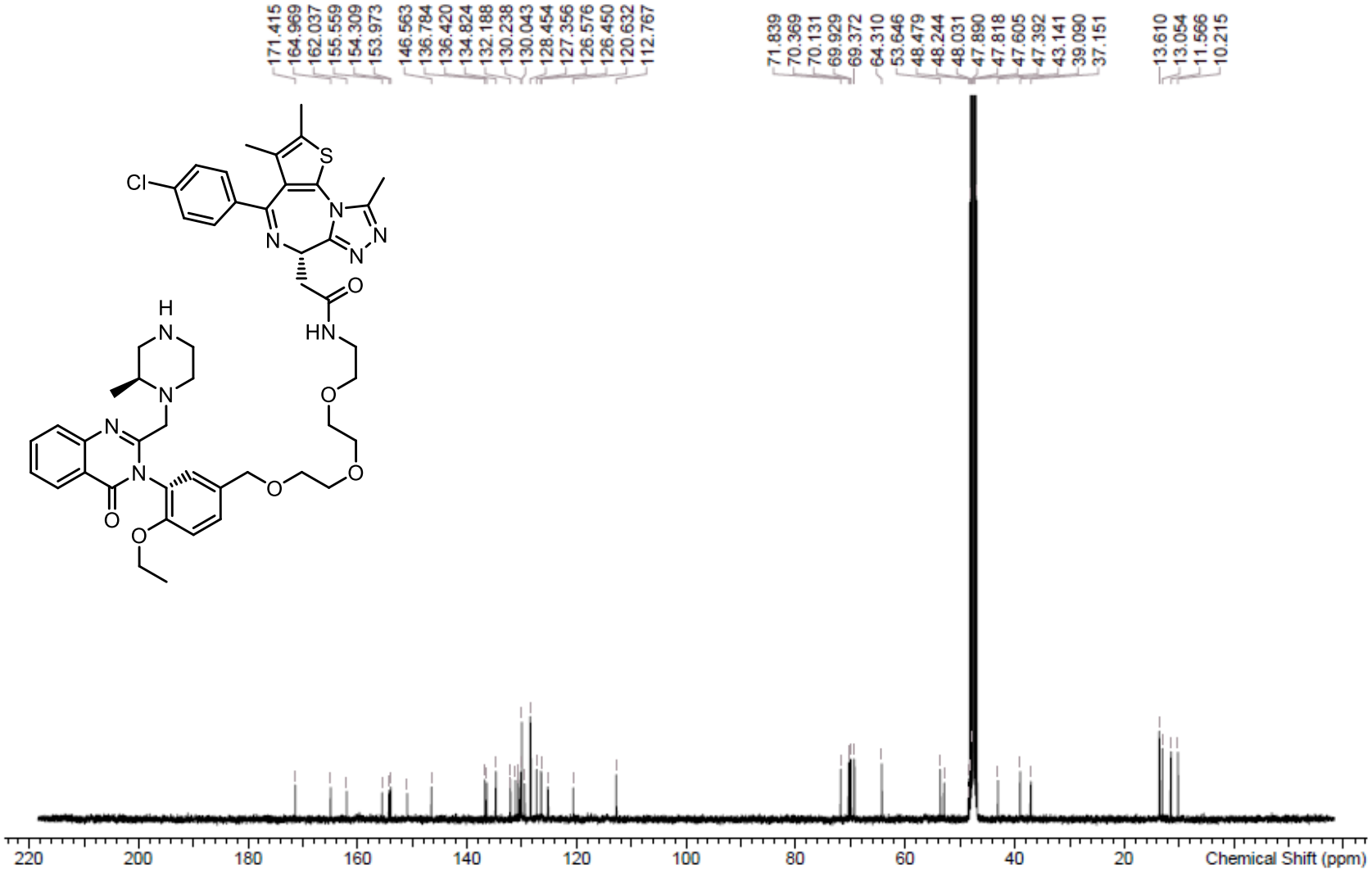
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	1.848	0.046	3543	0.203	5709	0.149
2	1.965	0.039	7795	0.446	11238	0.294
3	2.034	0.061	1736059	99.351	3810840	99.557

CW-34
^{1}H NMR: (400 MHz, CD_3OD)

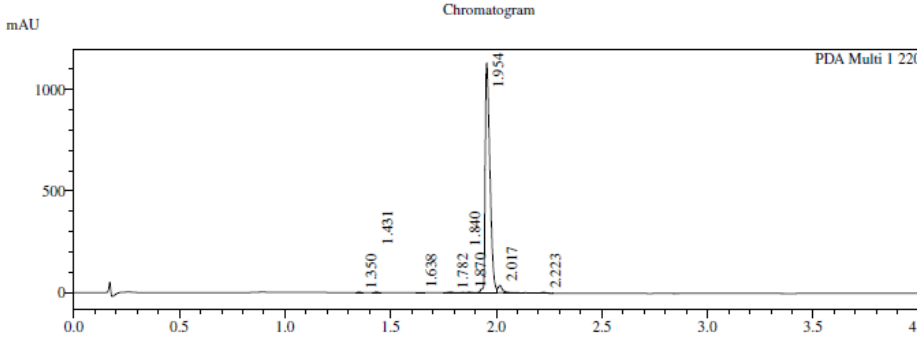


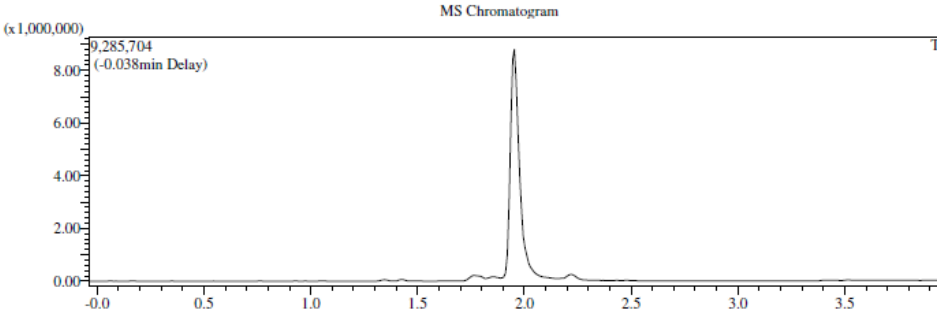
CW-34

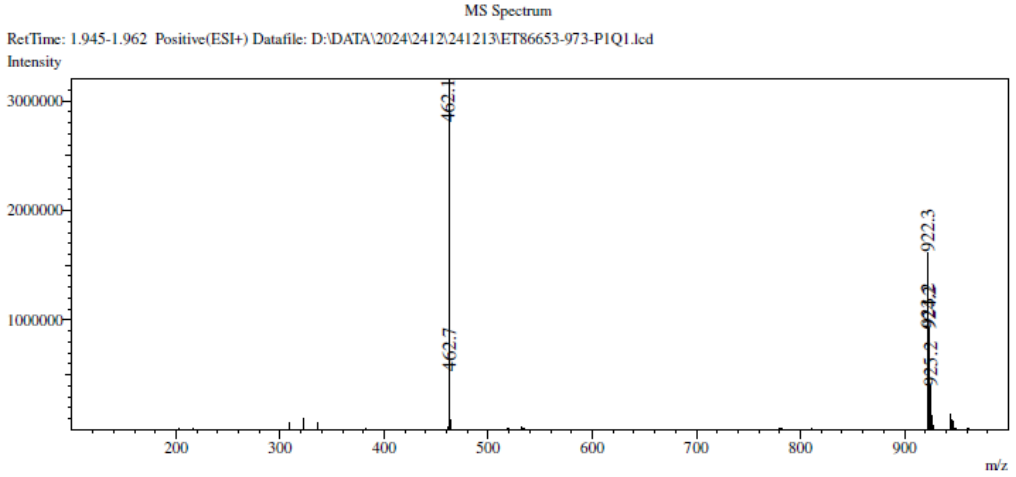
^{13}C NMR (101 MHz, CD_3OD)

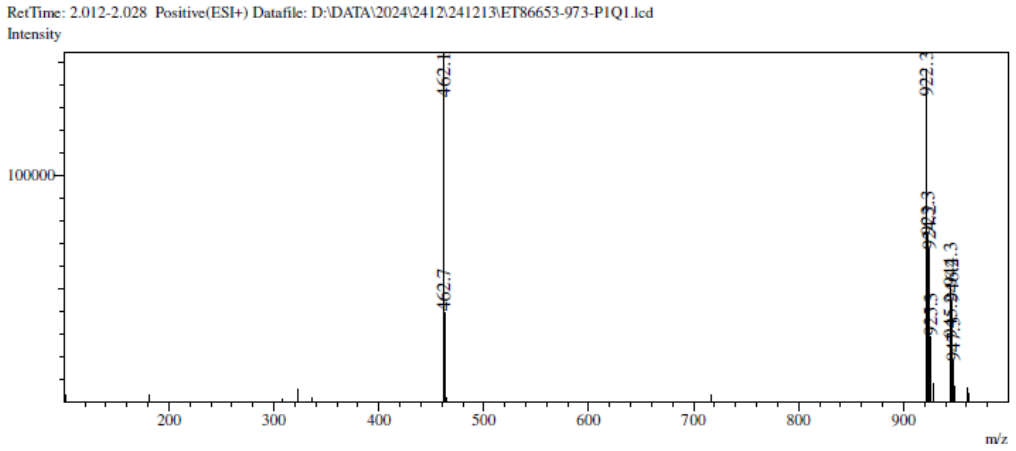


CW-34
LC-MS









Integration Result

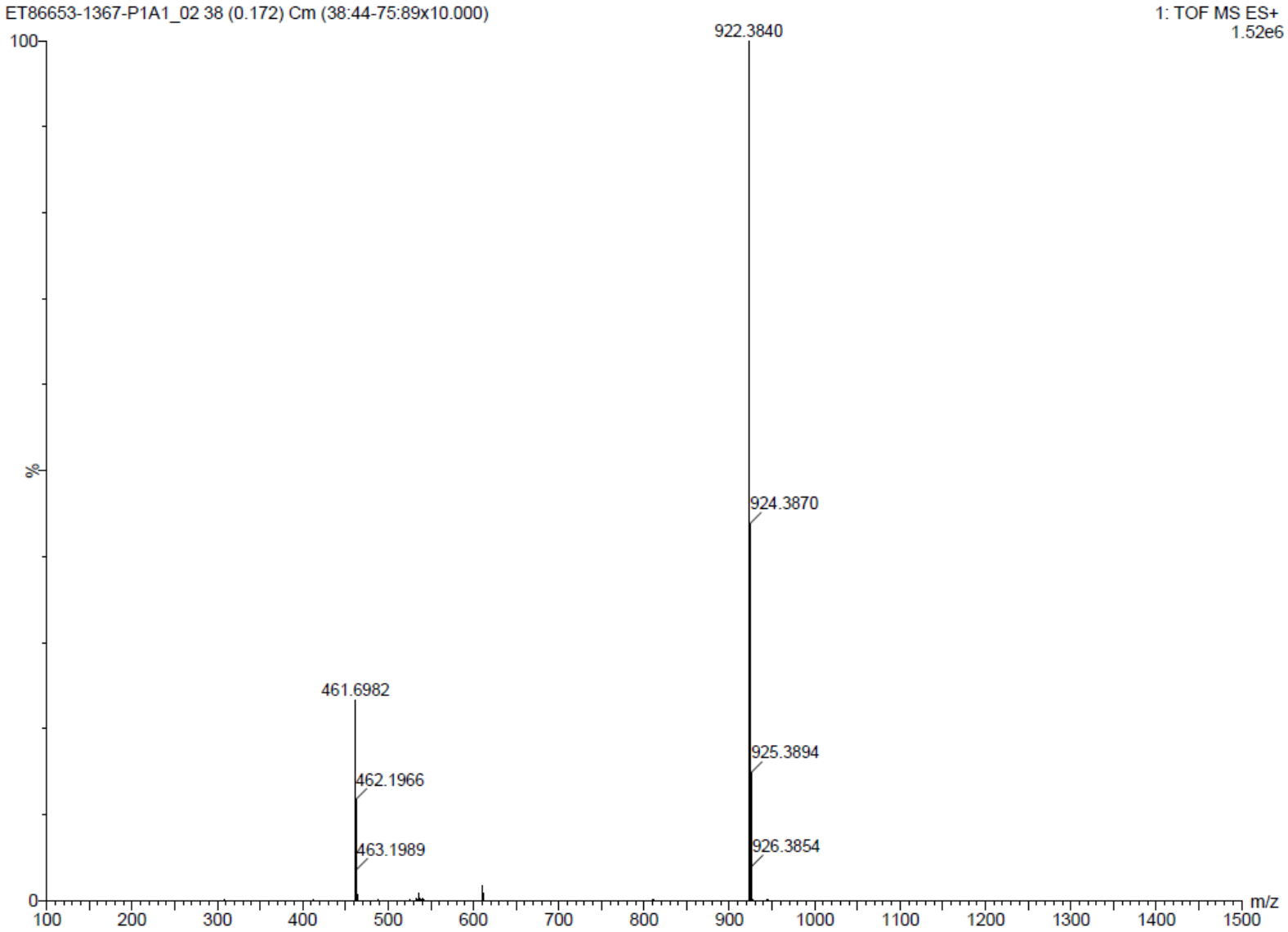
ELSD

PDA Ch1 220nm

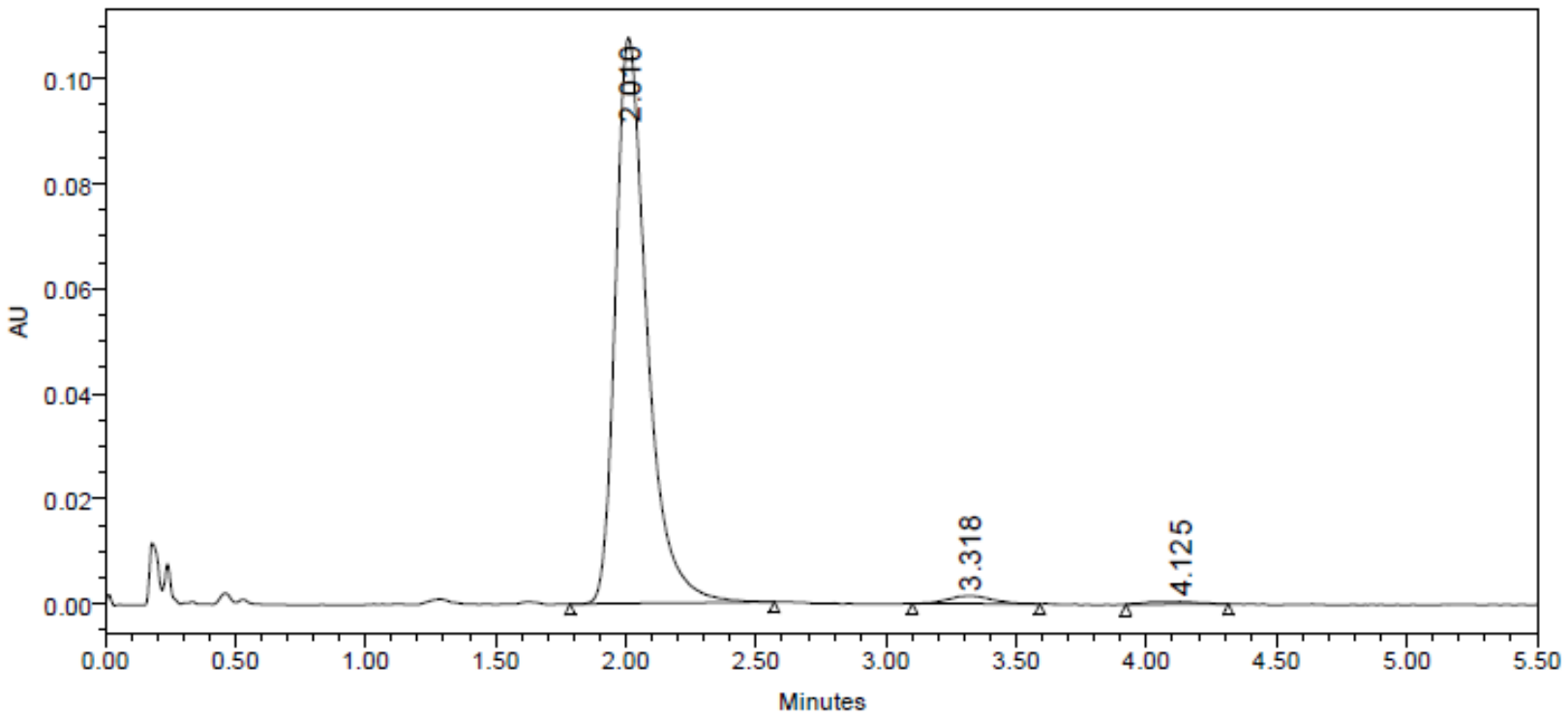
Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	1.350	0.024	2008	0.170	1639	0.089
2	1.431	0.025	3199	0.272	2810	0.153
3	1.638	0.031	891	0.076	968	0.053
4	1.782	0.058	2890	0.245	5279	0.286
5	1.840	0.033	1957	0.166	2131	0.116
6	1.870	0.053	3158	0.268	5078	0.276
7	1.954	0.043	1123909	95.410	1764658	95.773
8	2.017	0.045	36310	3.082	55609	3.018

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
9	2.223	0.033	3660	0.311	4365	0.237

CW-34
HRMS

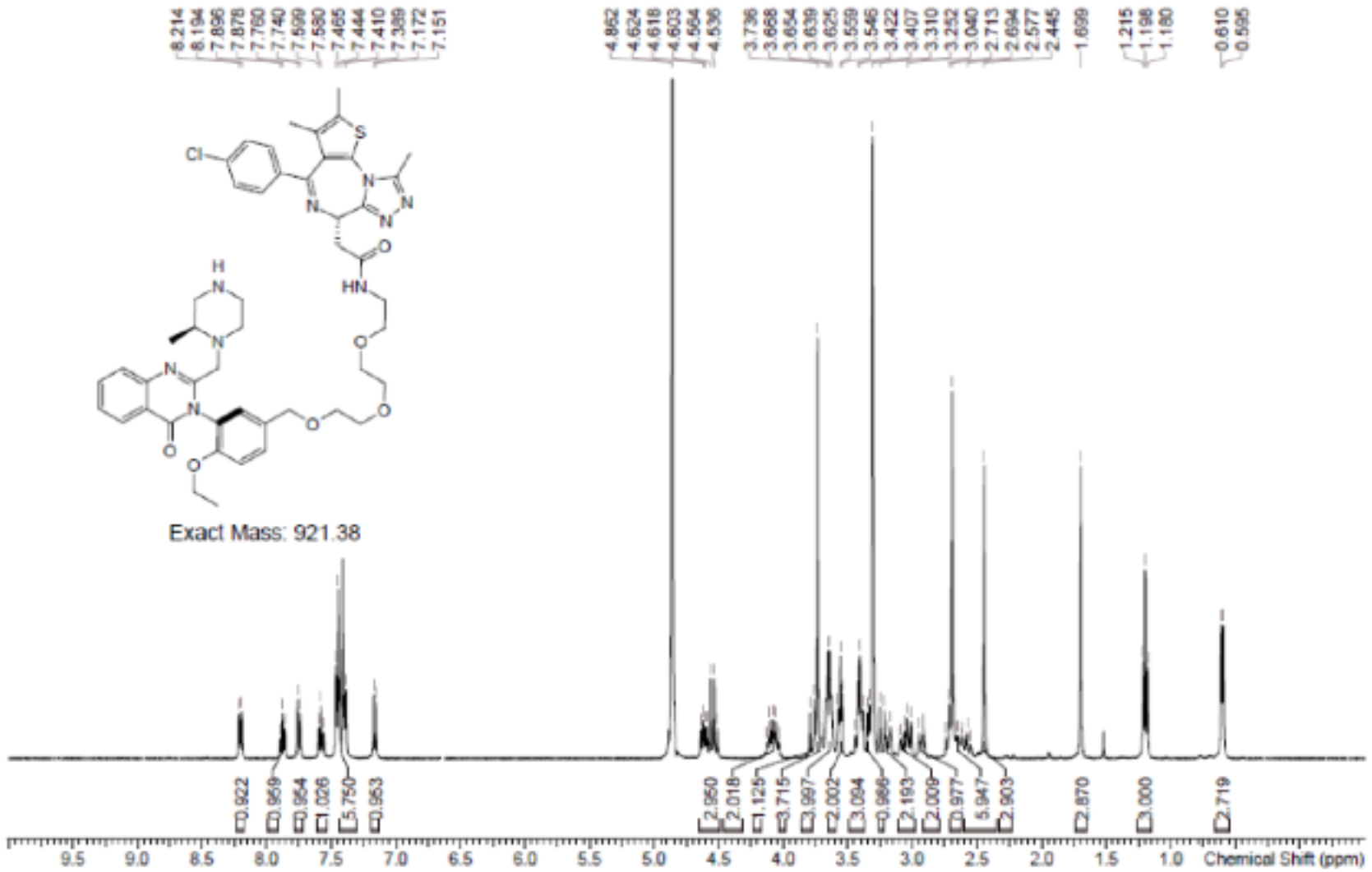

ET86653-1367-P1A1_02 38 (0.172) Cm (38:44-75:89x10.000)
1: TOF MS ES+
1.52e6
100
%
0
922.3840
924.3870
461.6982
925.3894
462.1966
926.3854
463.1989
m/z
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500

CW-34
Chiral HPLC

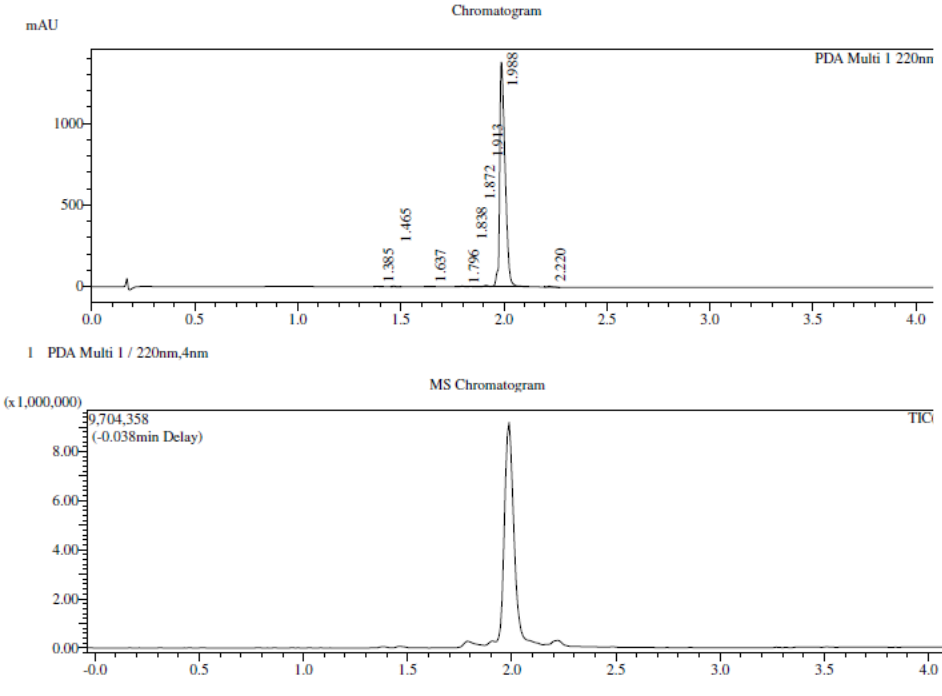


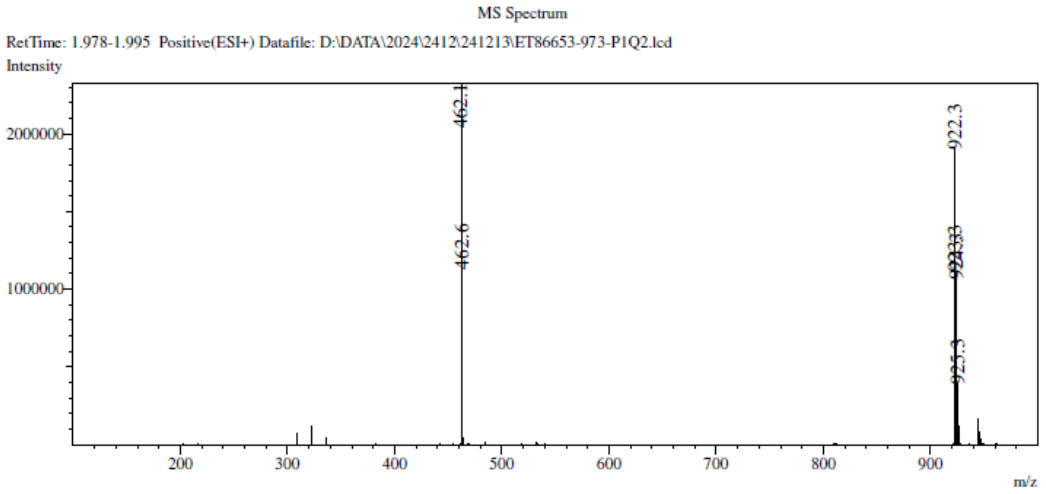
	RT	Area	% Area	Height
1	2.010	910710	97.42	107806
2	3.318	17152	1.83	1481
3	4.125	6939	0.74	517

CW-35
^{1}H NMR: (400 MHz, CD_3OD)



CW-35
LC-MS





Integration Result

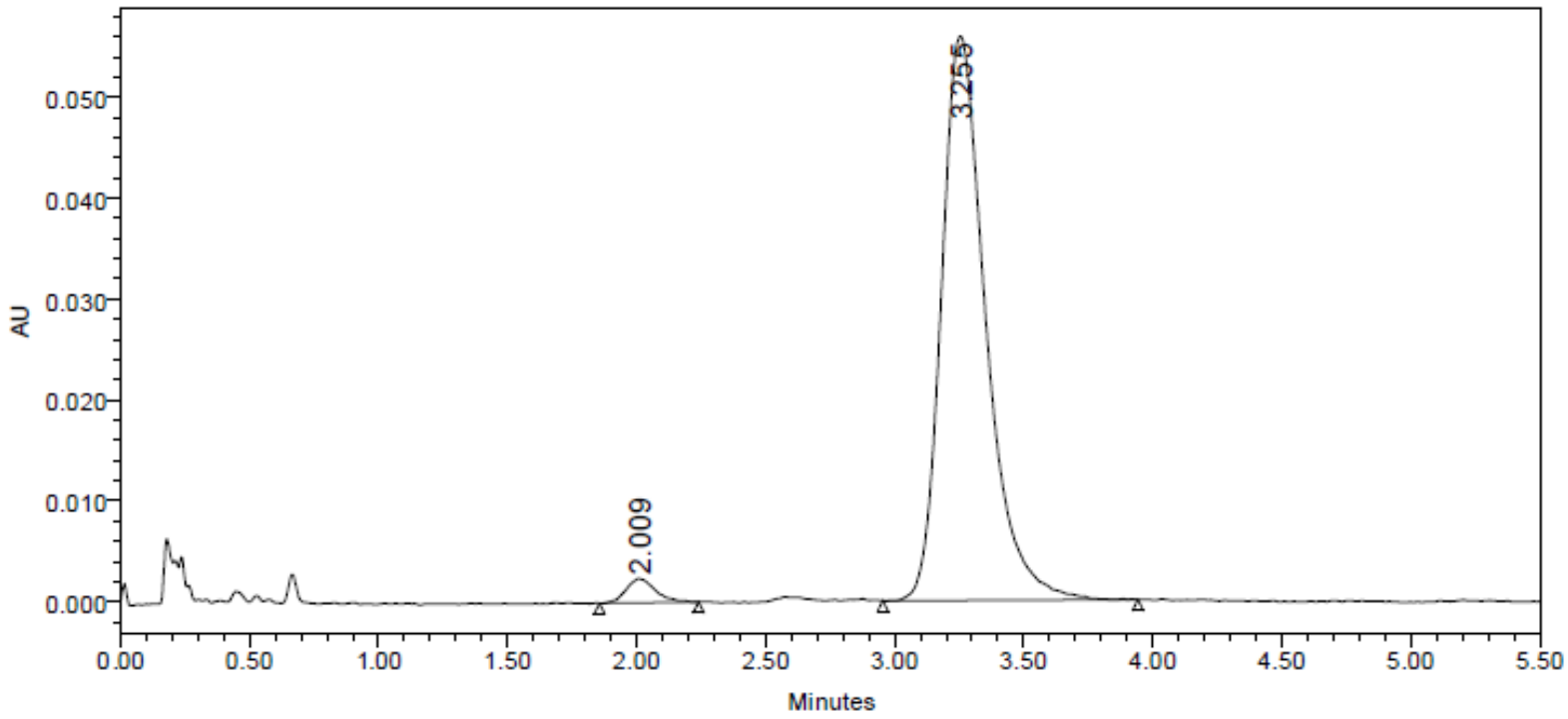
ELSD

PDA Ch1 220nm

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
1	1.385	0.025	2350	0.167	2204	0.086
2	1.465	0.026	3770	0.268	3483	0.136
3	1.637	0.032	1729	0.123	1979	0.077
4	1.796	0.040	3991	0.284	6055	0.236
5	1.838	0.037	3141	0.223	4098	0.160
6	1.872	0.094	1689	0.120	2821	0.110
7	1.913	0.040	8618	0.613	12484	0.487
8	1.988	0.050	1376016	97.859	2521822	98.473

Peak#	Ret. Time	Width	Height	Height%	Area	Area%
9	2.220	0.034	4813	0.342	5973	0.233

CW-35
Chiral HPLC



	RT	Area	% Area	Height
1	2.009	18739	2.73	2382
2	3.255	668172	97.27	55911