Supporting Information

Structure-Based Design of 5′-Substituted 1,2,3-Triazolylated Oseltamivir Derivatives as Potent Influenza Neuraminidase Inhibitors

Pengfei Wang, Babayemi O. Oladejo, Chenning Li, Lifeng Fu, Shanshan Zhang, Jianxun Qi, Xun Lv*, and Xuebing Li*

*lixb@im.ac.cn

Contents

**Table S1.** X-ray Crystallographic Data Collection and Refinement Statistics[a]

Parameter	N5-**1e**
Data collection	
Space group	P4
Cell dimensions	
a, b, c (Å)	109.06, 109.06, 71.15
α, β, γ (°)	90, 90, 90
Resolution (Å)	50.00-2.20 (2.28-2.20)
R_{merge}	0.083 (0.235)
I/σI	21.1（7.1）
Completeness(%)	95.6 (82.3)
Redundancy	5.4 (5.1)
Refinement	
Resolution(Å)	32.37- 2.20
No. of reflections	40762
R_{work}/R_{free}	0.2085/0.2361
No. of atoms	
Protein	6126
Ligand/ion	62
Water	78
B factors	
Protein	39.5
Ligand/ion	42.5
Water	35.8
RMSDs	
Bond length (Å)	0.009
Bond angle (°)	1.215
Ramachandran plot	
Favored (%)	95.41
Allowed (%)	4.21
Disallowed (%)	0.38

[a] Values in parentheses are for the highest-resolution shell. $R_{merge} = \Sigma_{hkl} \Sigma_i |I_i(hkl) - <I(hkl)>|/\Sigma_{hkl} \Sigma_i I_i(hkl)$, where $I_i(hkl)$ is the observed intensity and $<I(hkl)>$ is the average intensity of multiple observations of symmetry-related reflections; I, the intensity of a reflection; σI, the standard deviation of intensity; B factor, a mix of thermal displacement and disorder.

# NMR and MS Spectra

## ¹H NMR of 5a (500 MHz, CDCl₃)
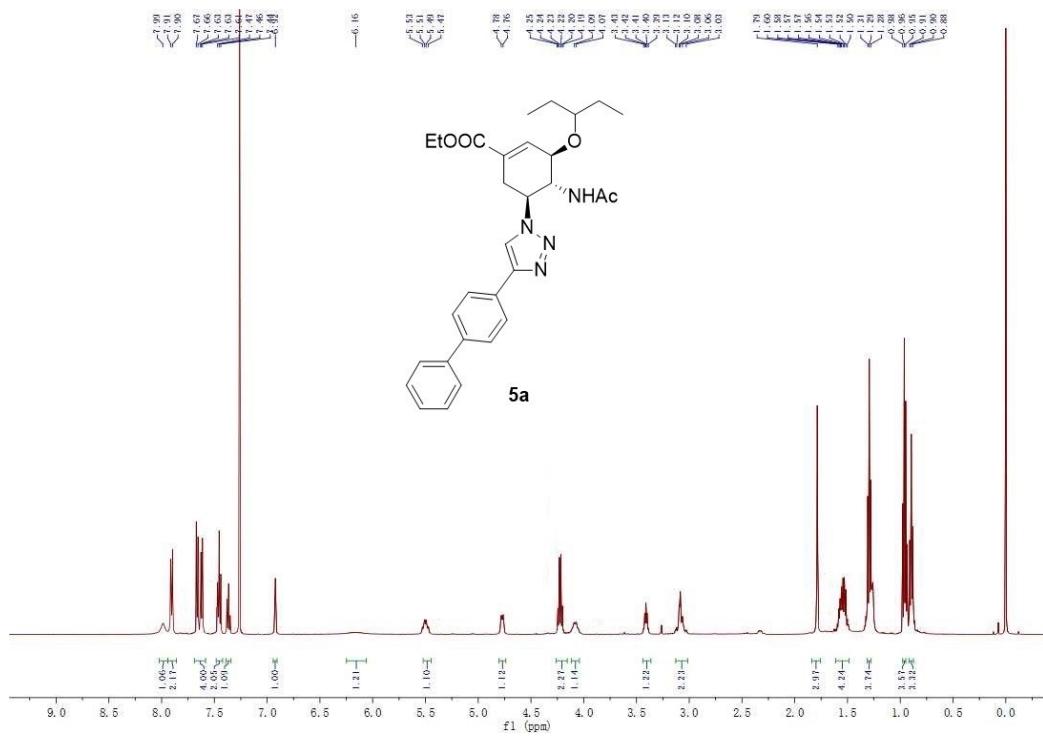

ESIMS of 5a
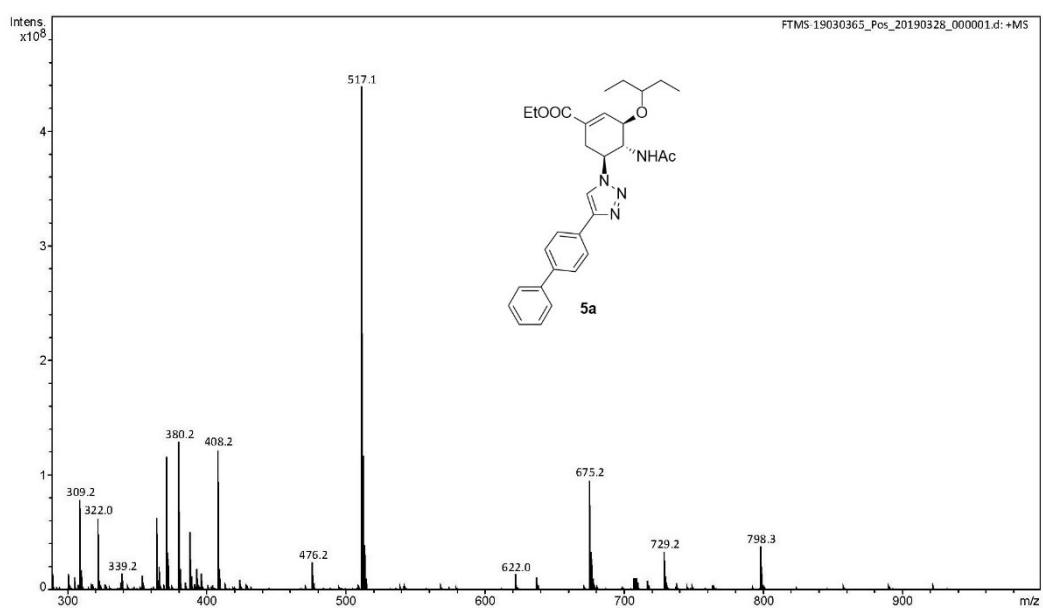
# ¹H NMR of 5b (500 MHz, CDCl₃)
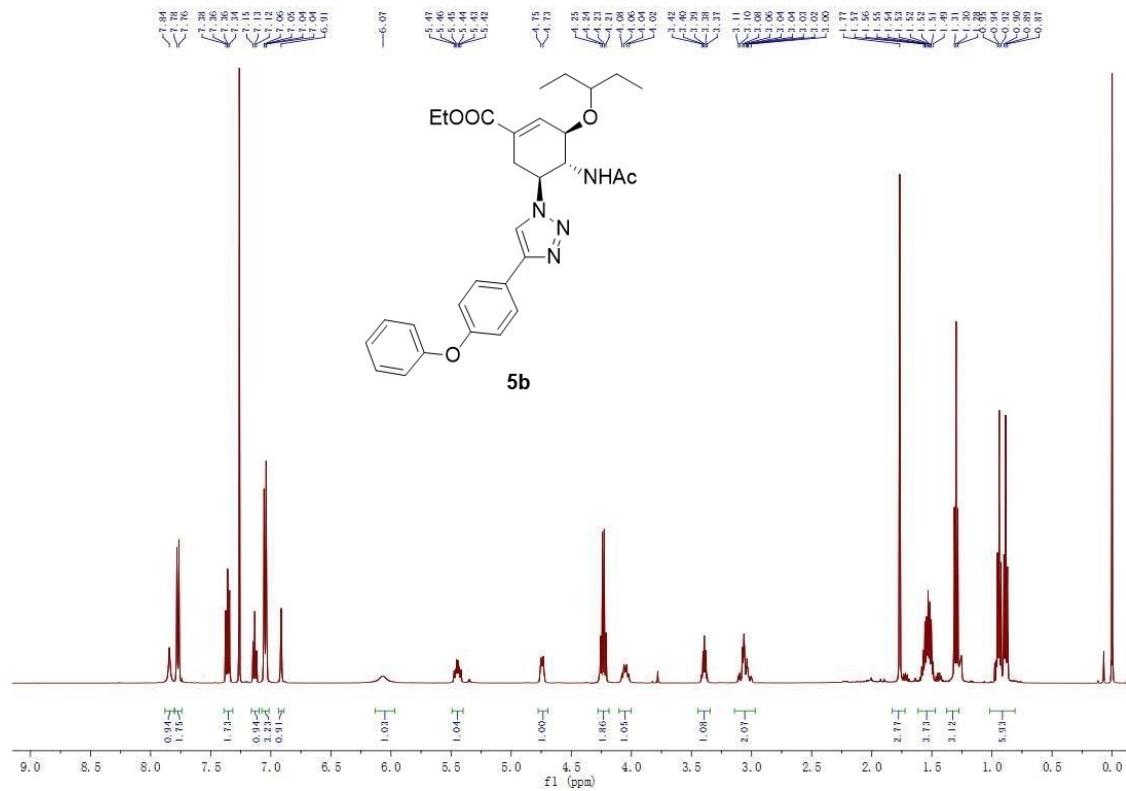
ESIMS of 5b
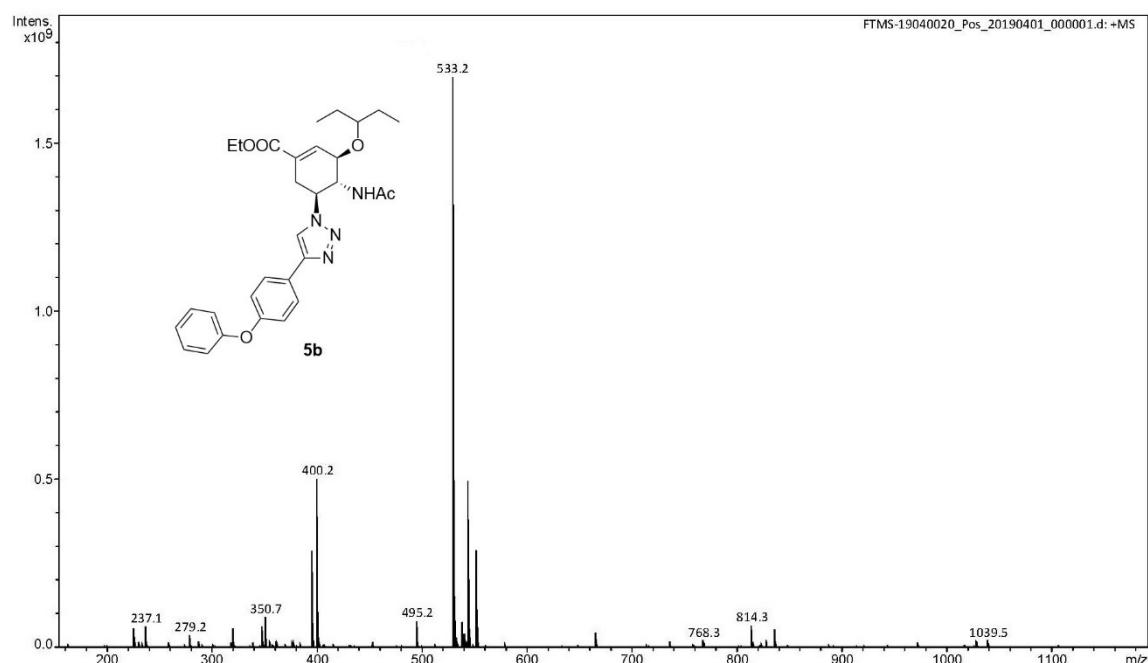
^{1}H NMR of 5c (500 MHz, CDCl$_3$)

HR-ESIMS of 5c

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
521.27696	16762716	C 29 H 37 N 4 O 5	100.00	521.27585	-1.1	-2.1	12.1	13.5	even	ok
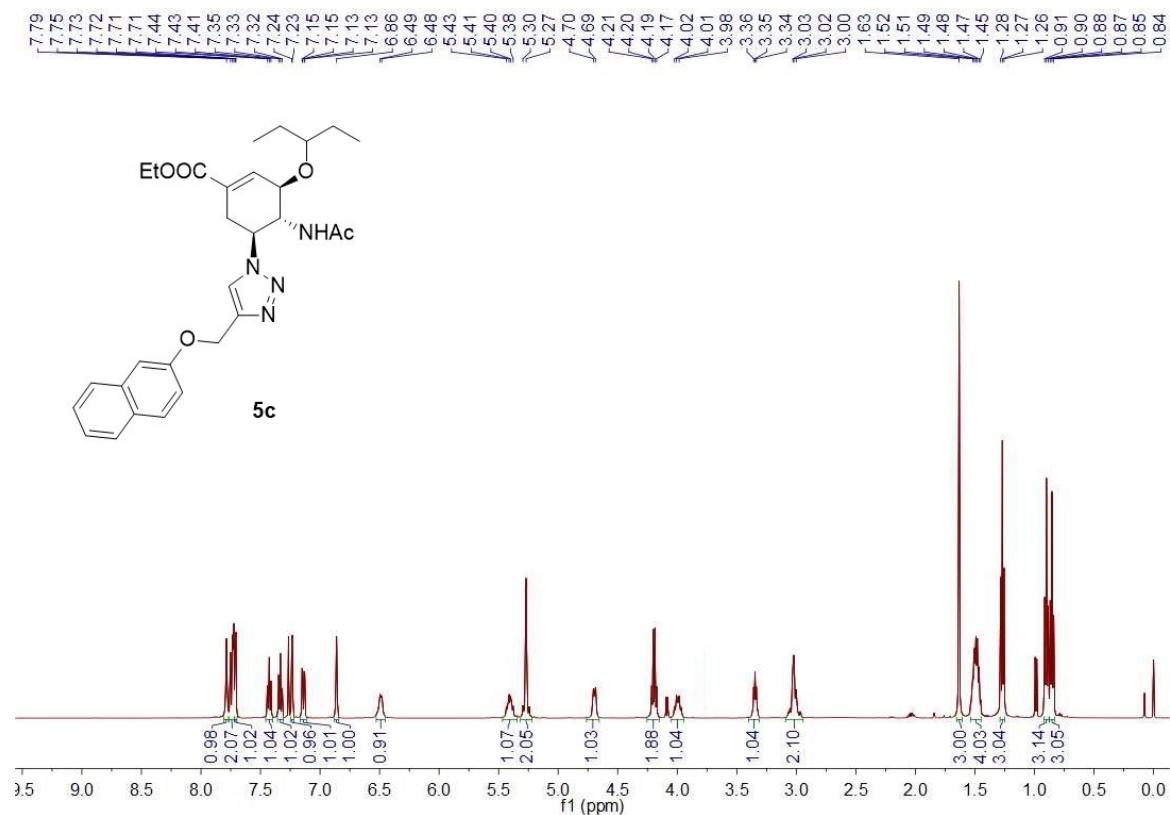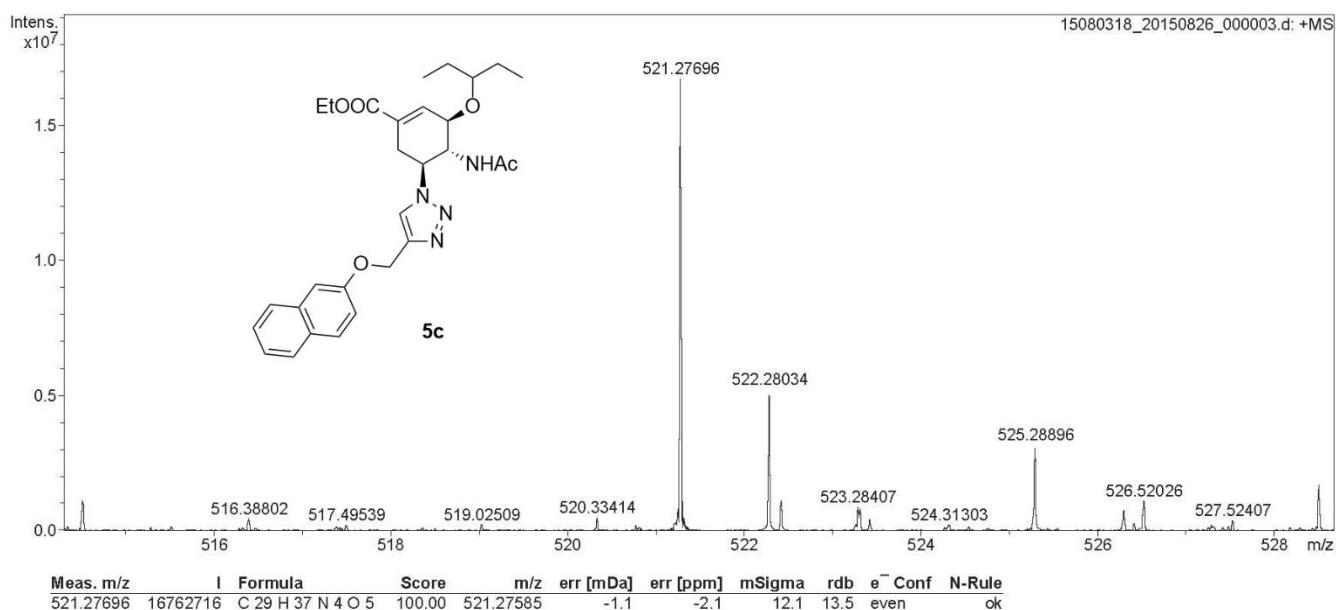
¹H NMR of 5d (500 MHz, CDCl₃)

HR-ESIMS of 5d

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
455.26509	163635872	C 25 H 35 N 4 O 4	100.00	455.26528	0.2	0.4	8.2	10.5	even	ok
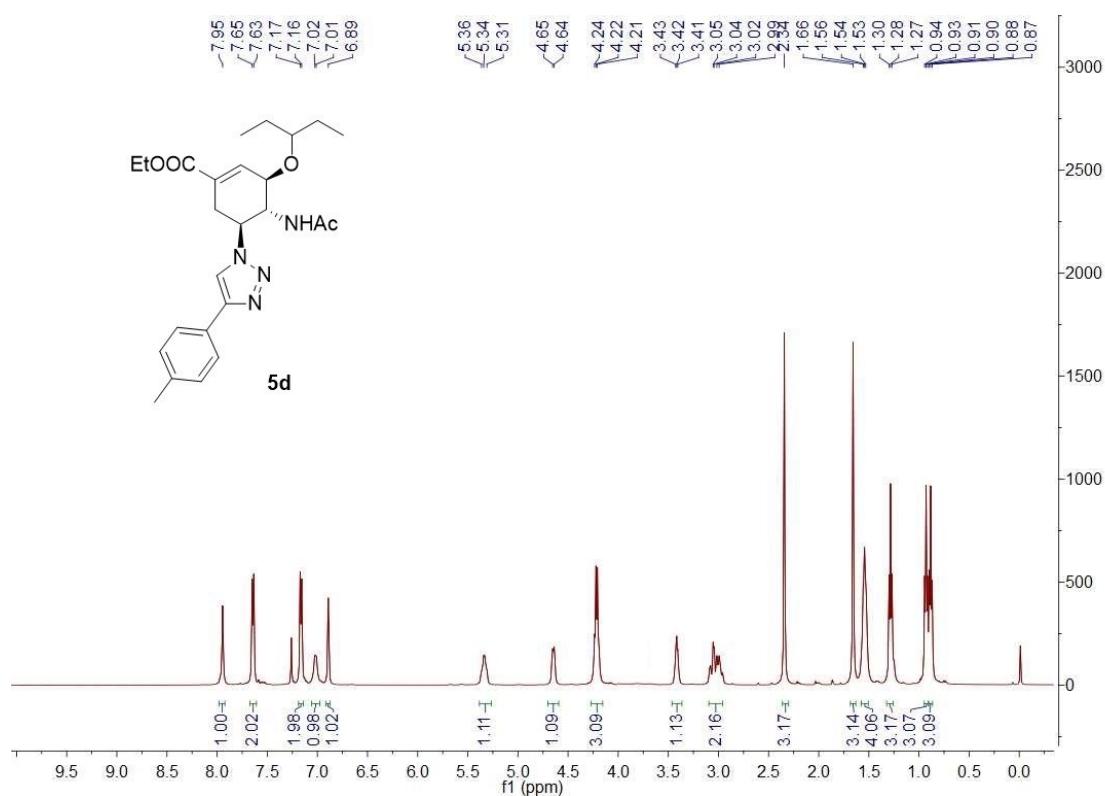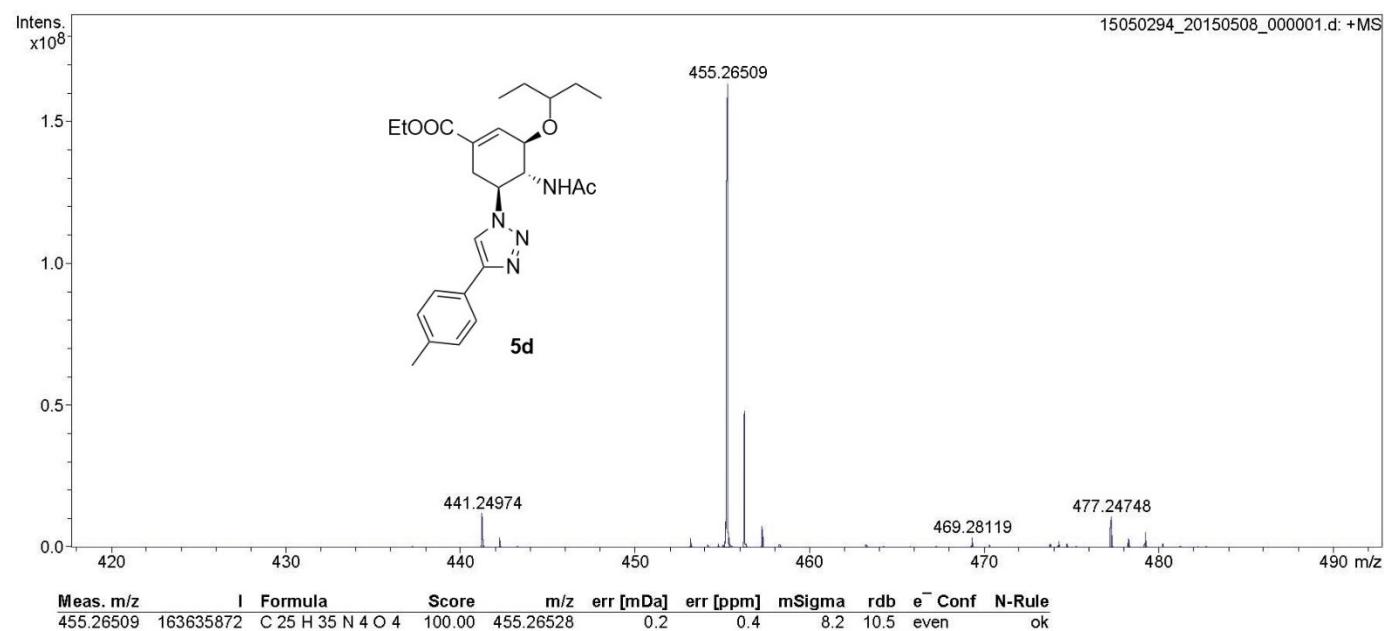
^{1}H NMR of 5e (500 MHz, CDCl$_3$)

HR-ESIMS of 5e

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
441.24931	90295112	C 24 H 33 N 4 O 4	100.00	441.24963	0.3	0.7	4.0	10.5	even	ok
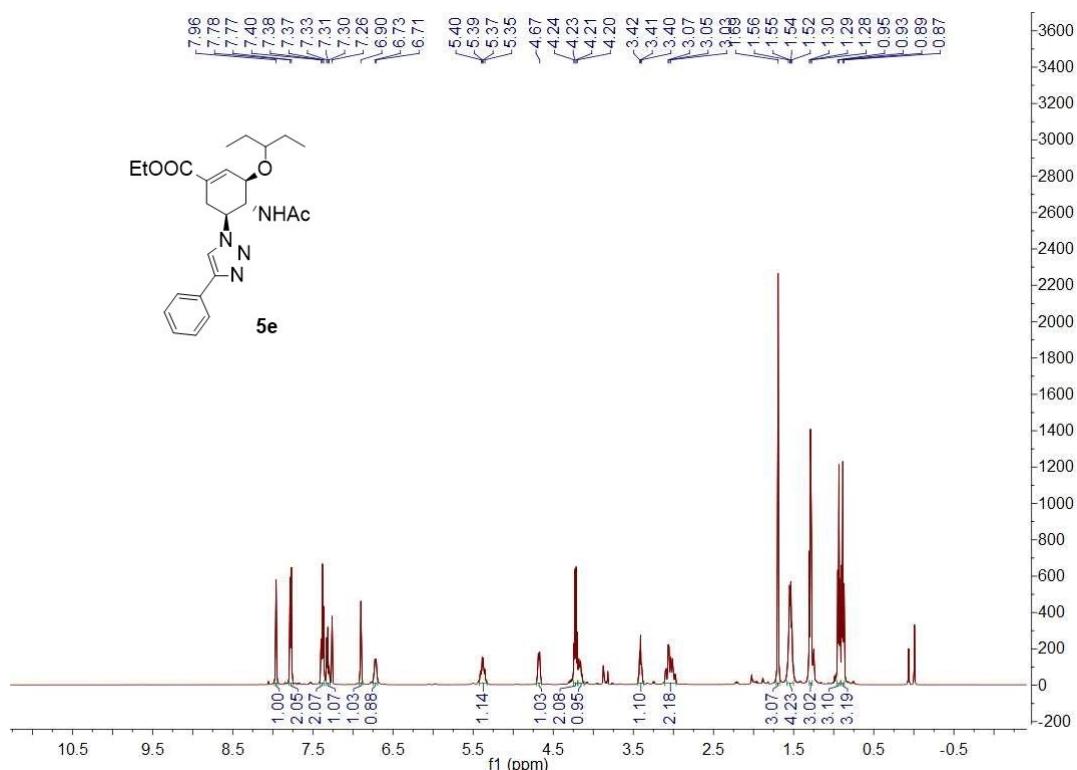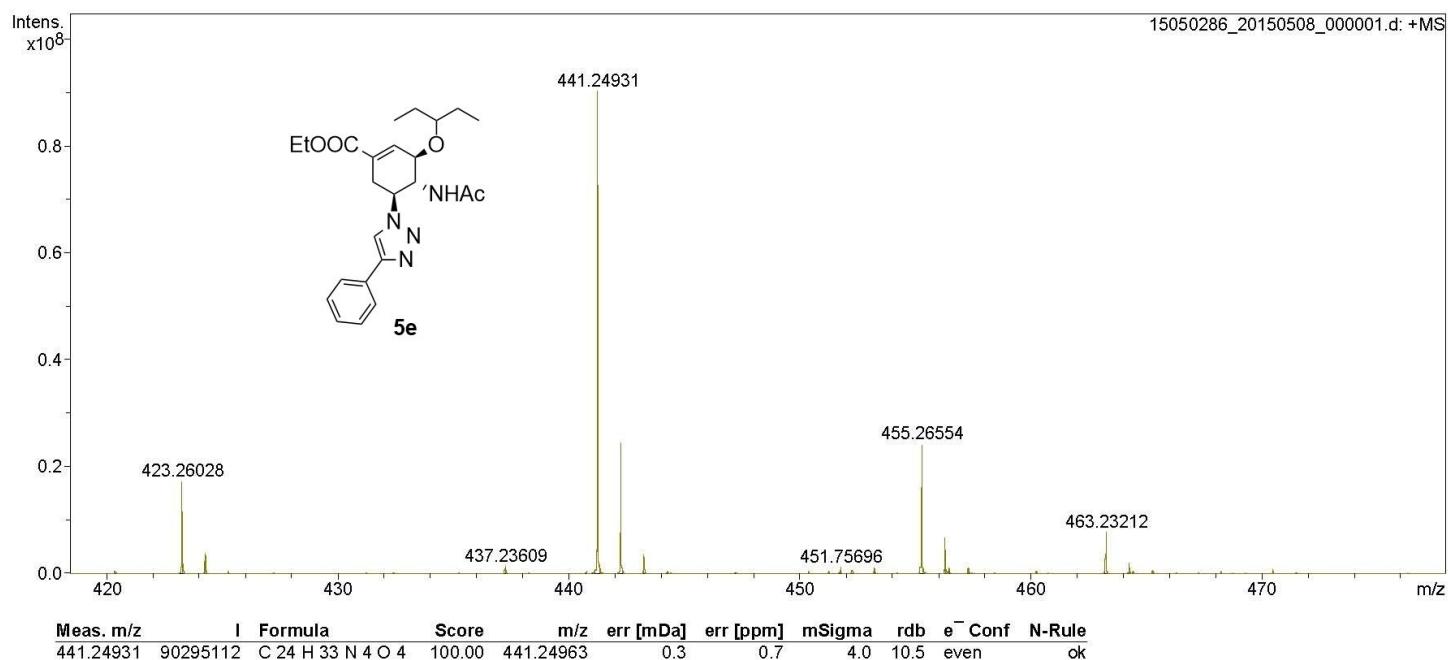
^{1}H NMR of 5f (500 MHz, CDCl$_3$)

HR-ESIMS of 5f

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e$^-$ Conf	N-Rule
499.25440	143098176	C 26 H 35 N 4 O 6	100.00	499.25511	0.7	1.4	4.6	11.5	even	ok
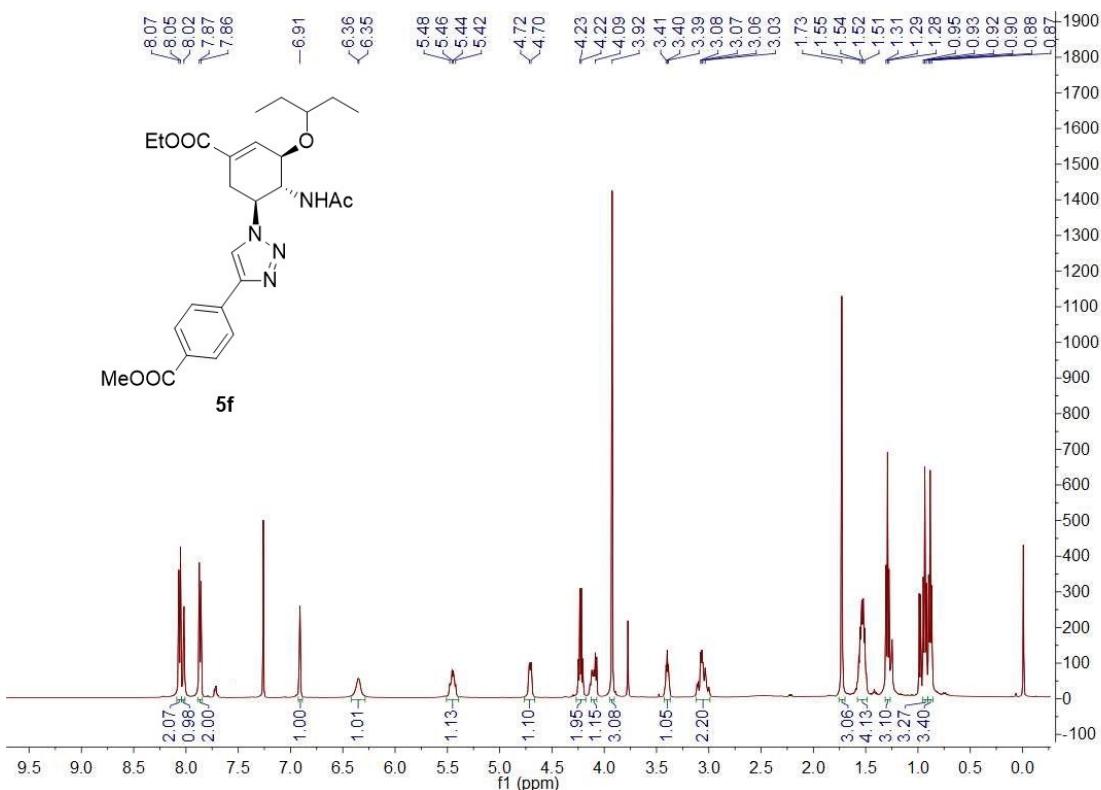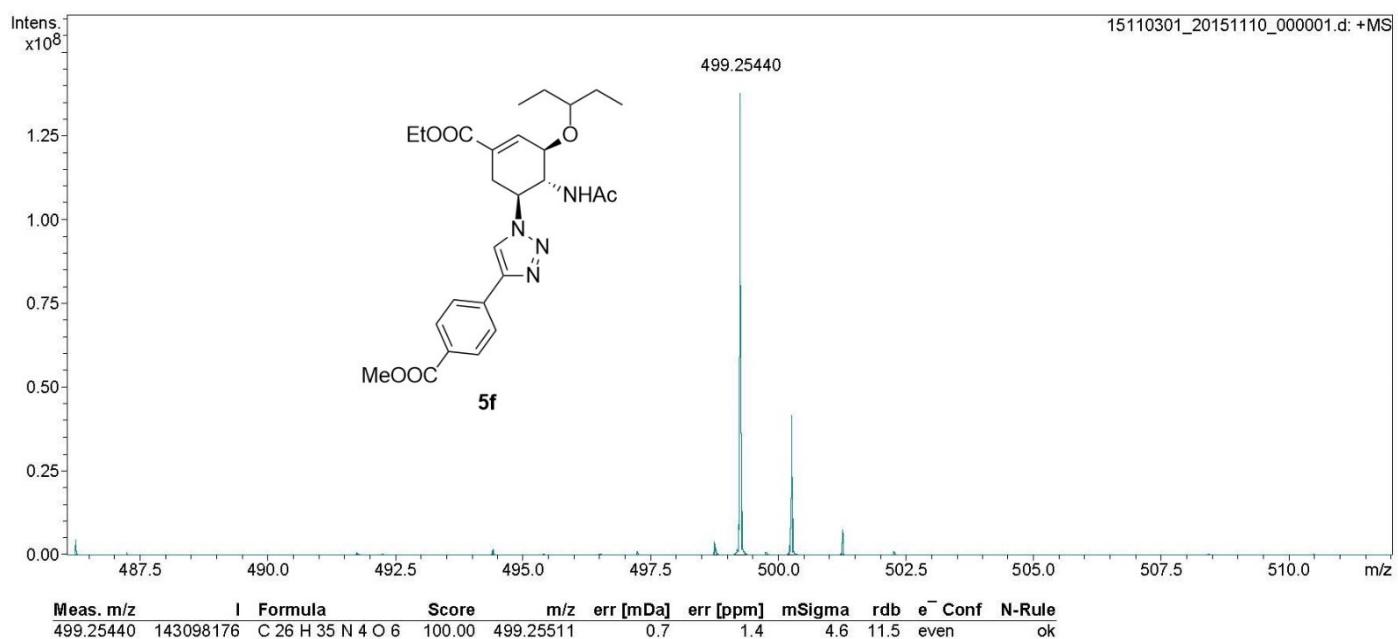
^{1}H NMR of 5g (500 MHz, CDCl$_3$)

HR-ESIMS of 5g

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
499.25508	188816608	C 26 H 35 N 4 O 6	100.00	499.25511	0.0	0.1	7.2	11.5	even	ok

¹H NMR of 5h (500 MHz, CDCl₃)

¹H NMR of 5h (500 MHz, CDCl₃)

5h

HR-ESIMS of 5h

HR-ESIMS of 5h

+ESI Scan (2.769 min) Frag=130.0V 1.d

* 521.2376

1019.5105

301.1422

767.3532
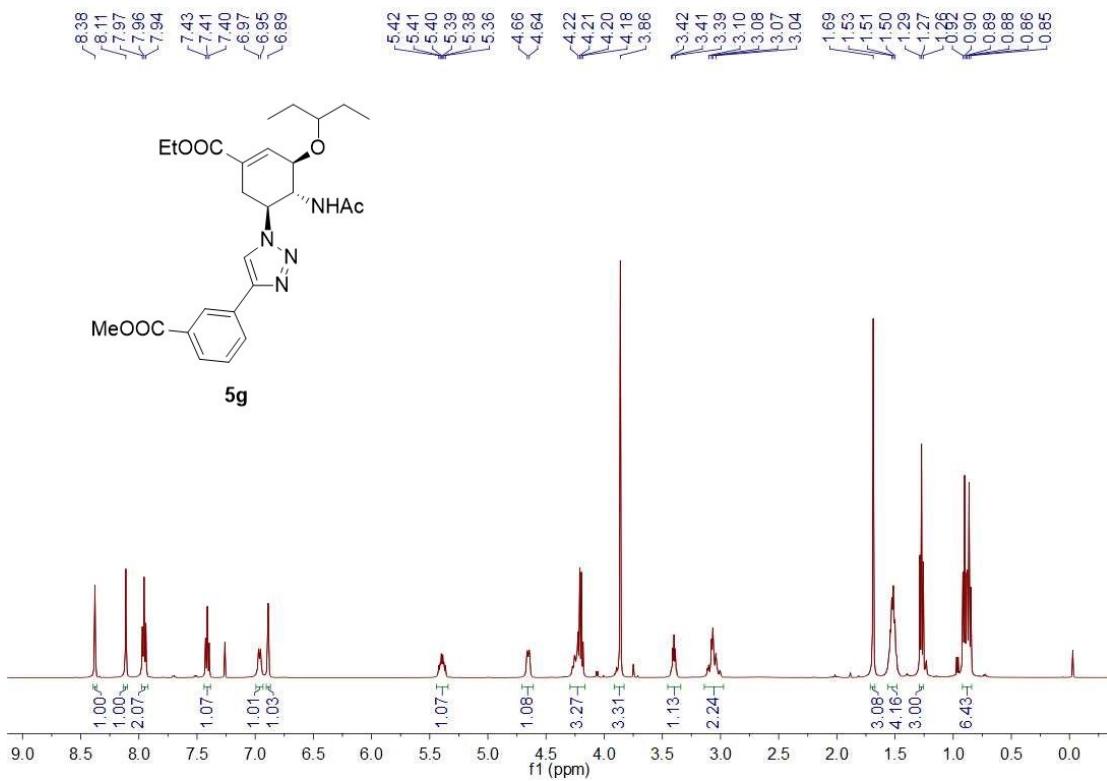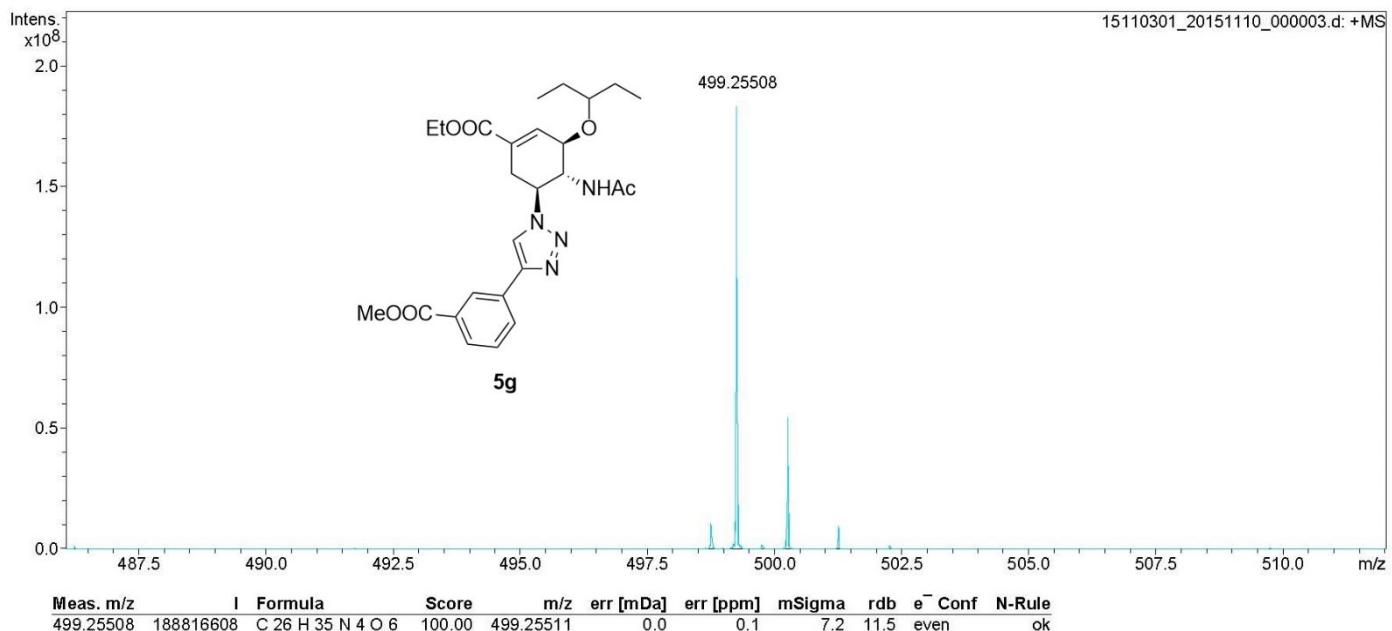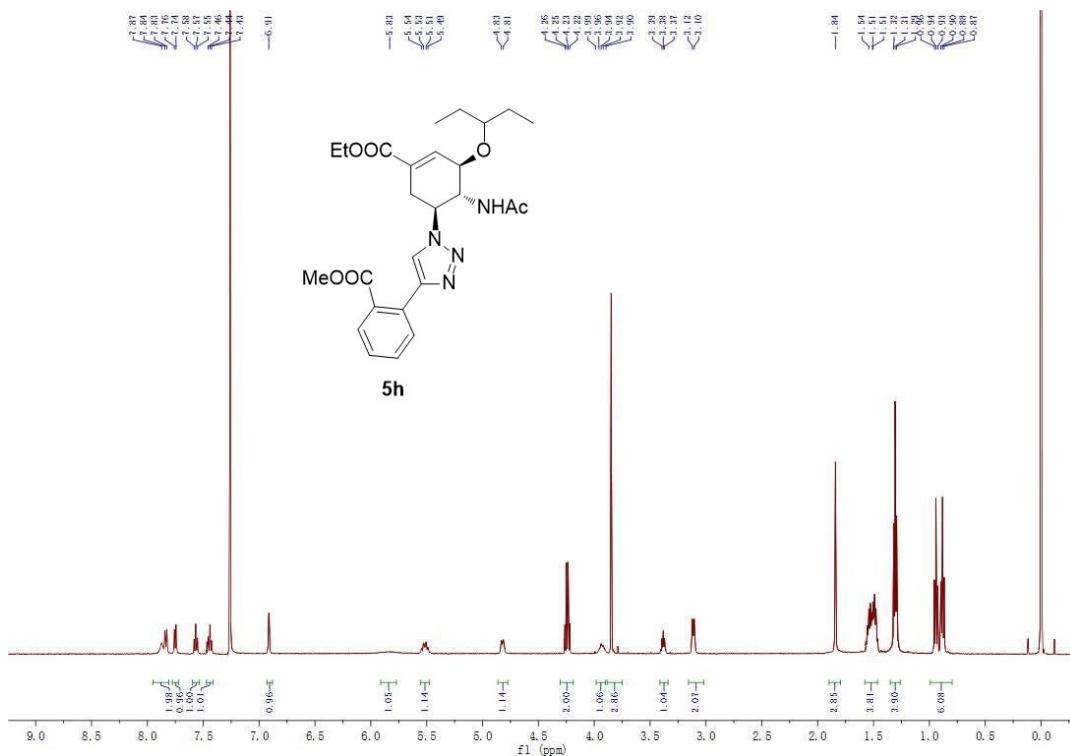
5h
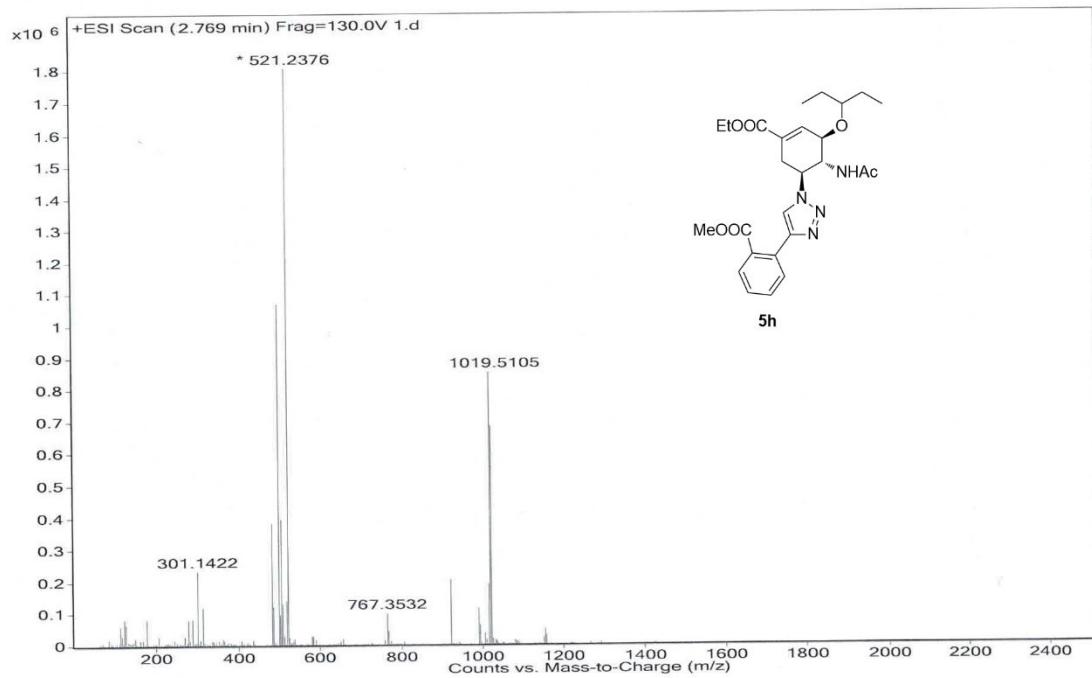
^{1}H NMR of 5i (500 MHz, CDCl$_3$)
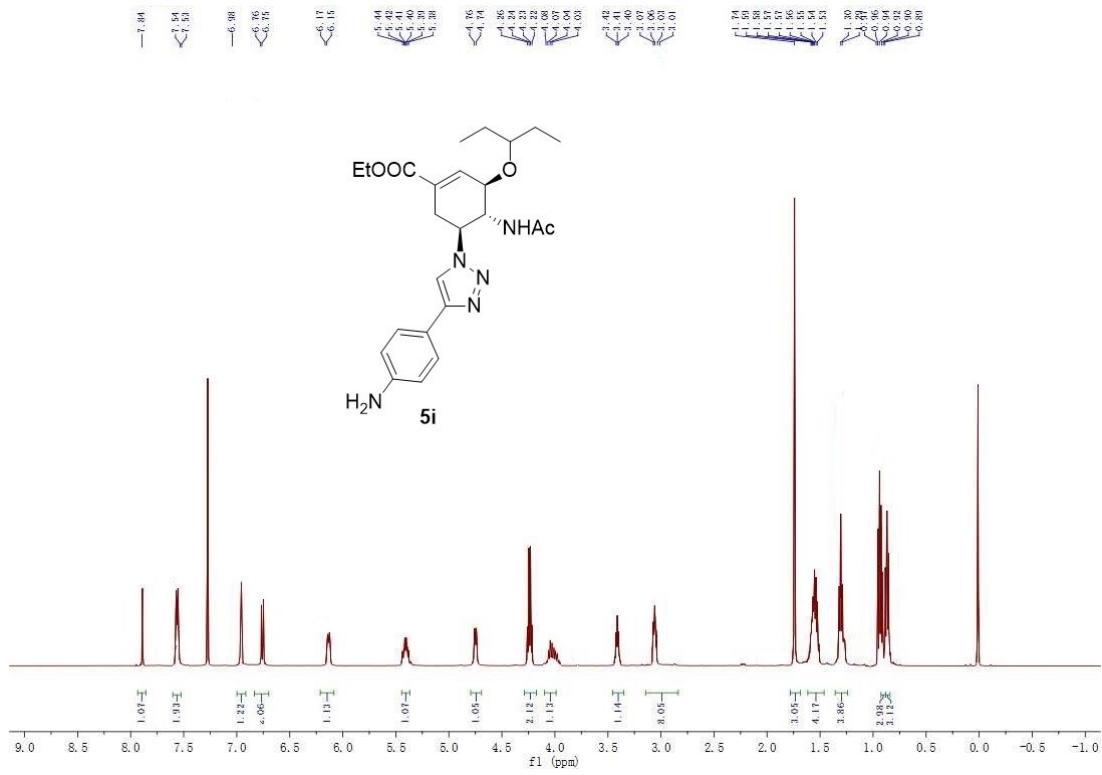
ESIMS of 5i

¹H NMR of 5j (500 MHz, CDCl₃)

¹H NMR of 5j (500 MHz, CDCl₃)

HR-ESIMS of 5j

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
456.26028	274799968	C 24 H 34 N 5 O 4	100.00	456.26053	0.2	0.5	15.2	10.5	even	ok
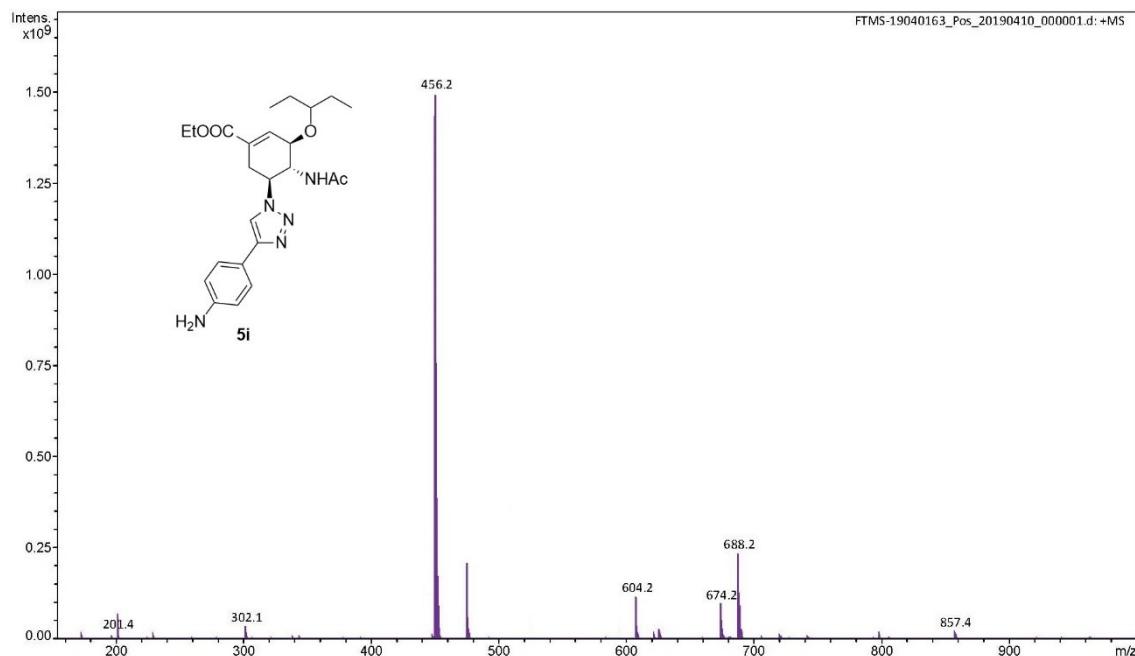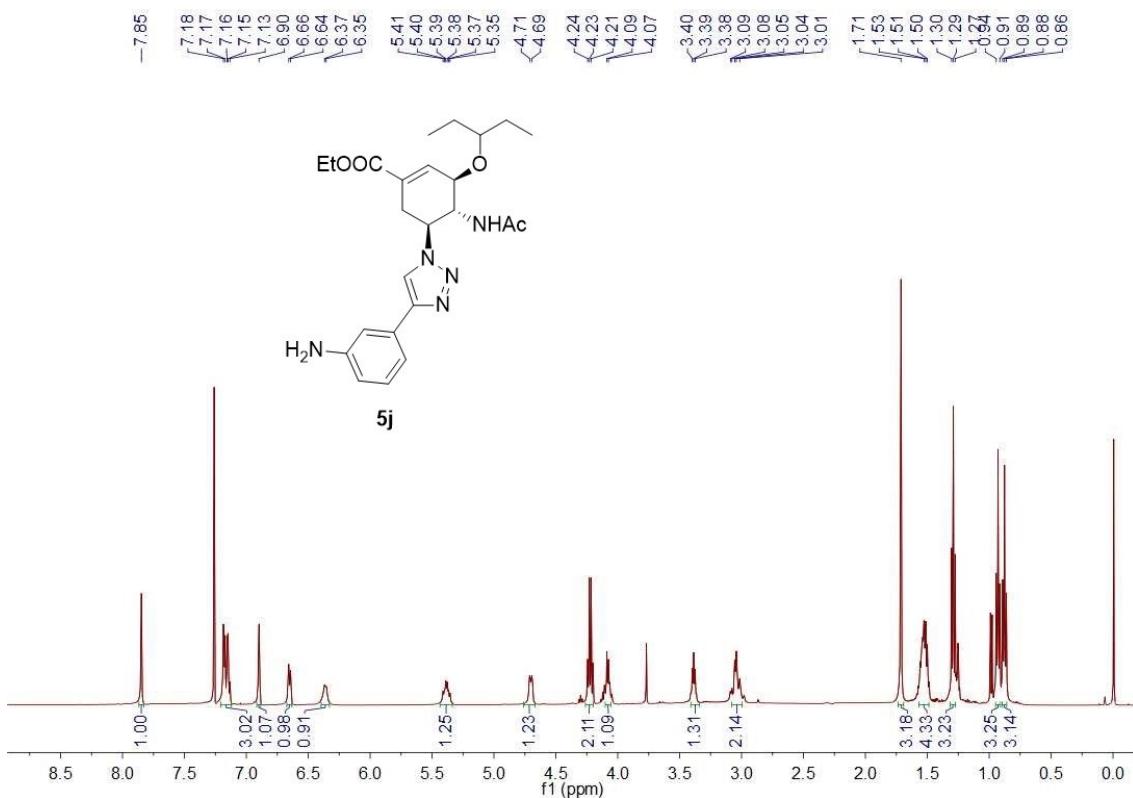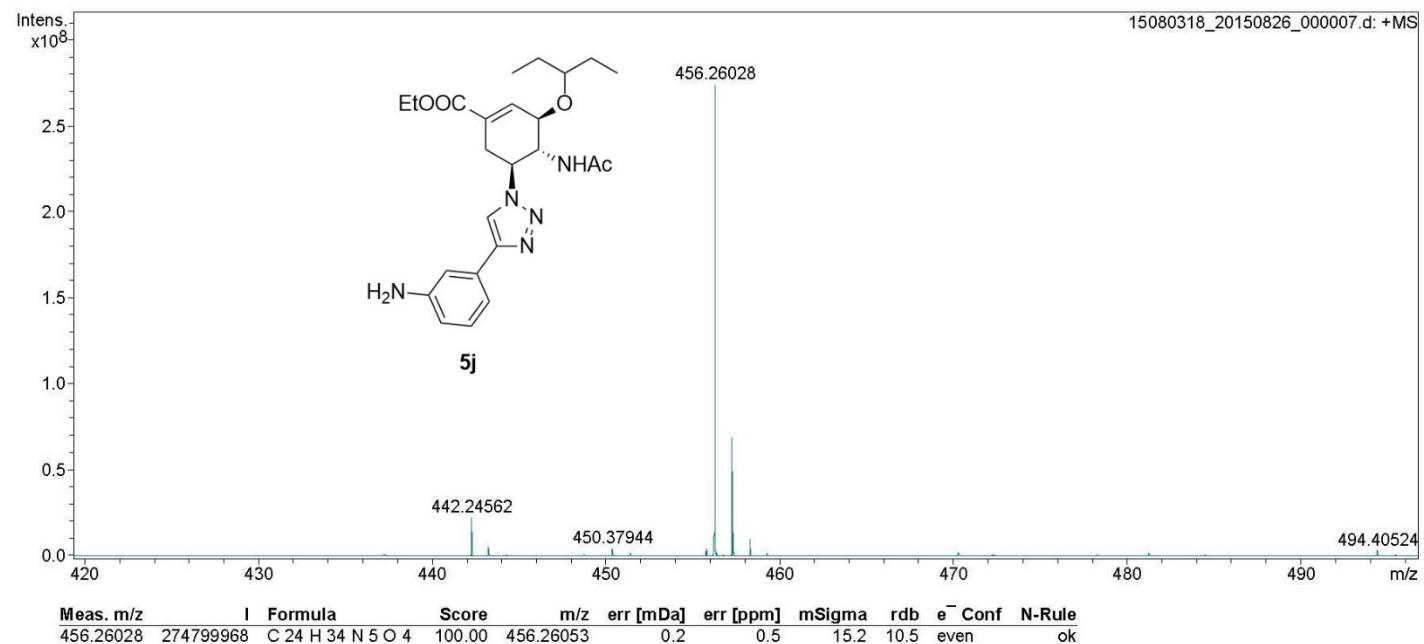
^{1}H NMR of 5k (500 MHz, CDCl$_3$)

HR-ESIMS of 5k

+ESI Scan (2.560 min) Frag=130.0V 2.d Subtract (2)

456.2609 (M+H)+

478.2426

Counts vs. Mass-to-Charge (m/z)
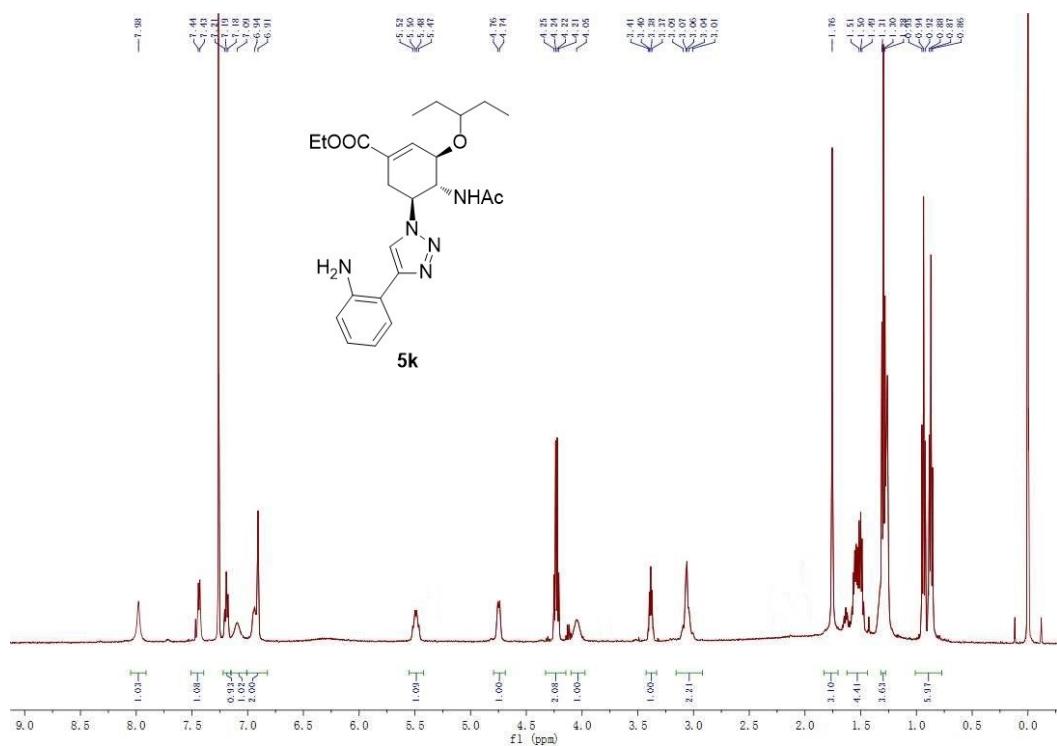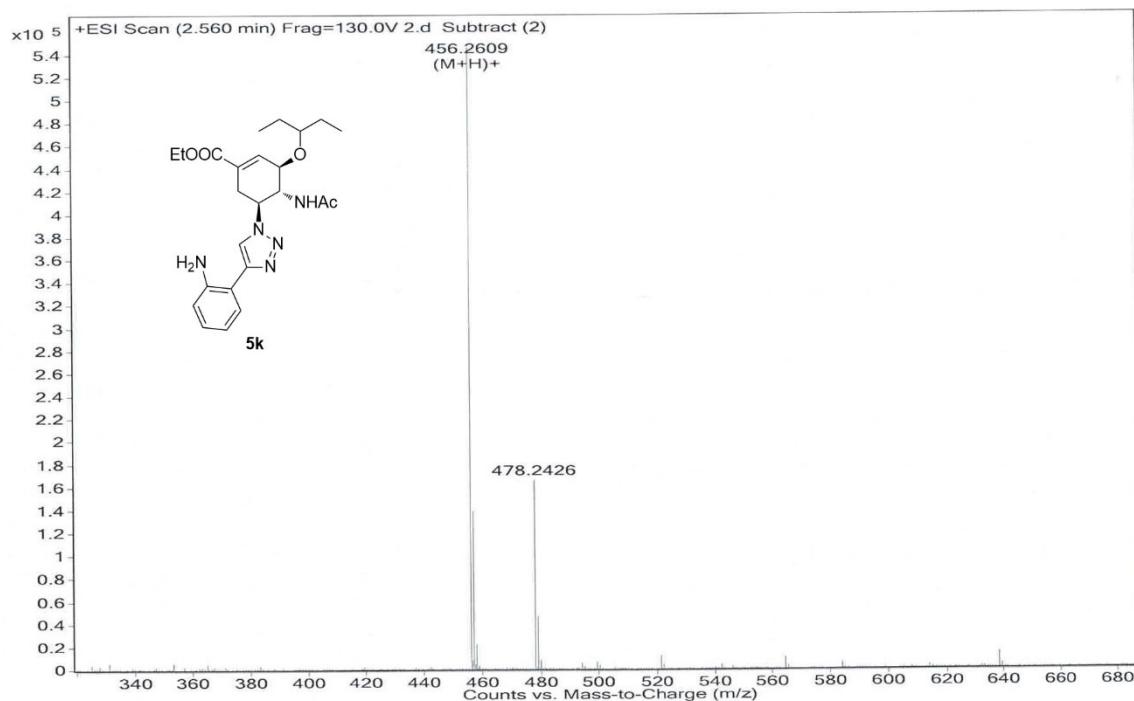
^{1}H NMR of 5l (500 MHz, CDCl$_3$)
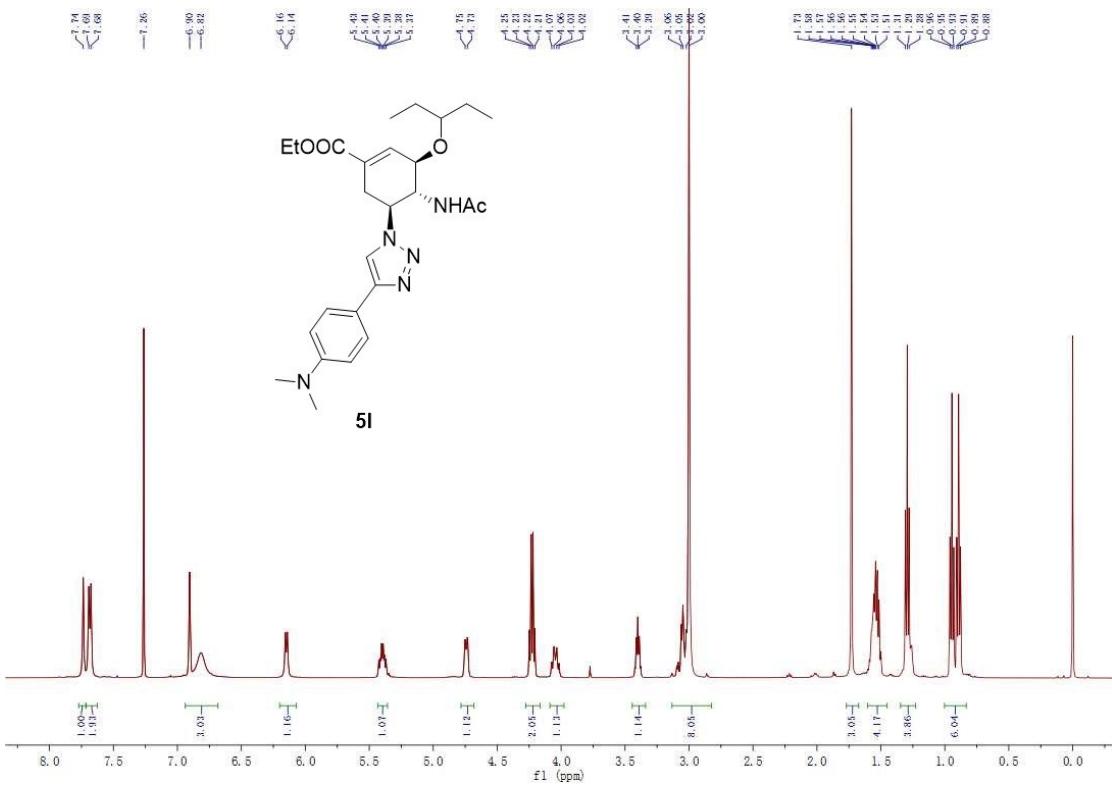
ESIMS of 5l
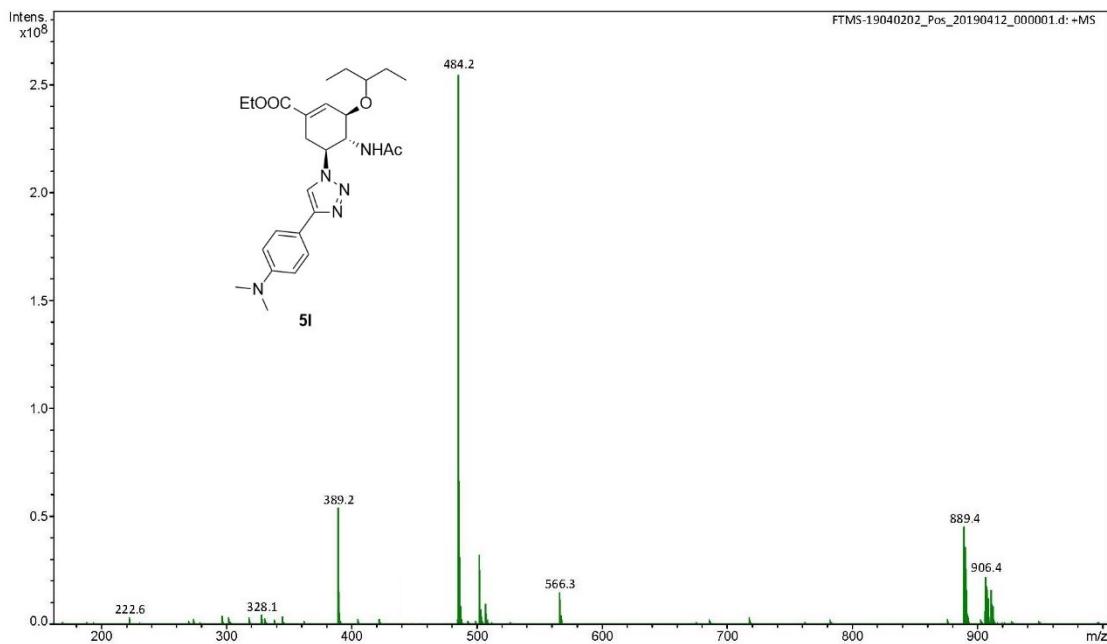
^{1}H NMR of 5m (500 MHz, CDCl$_3$)
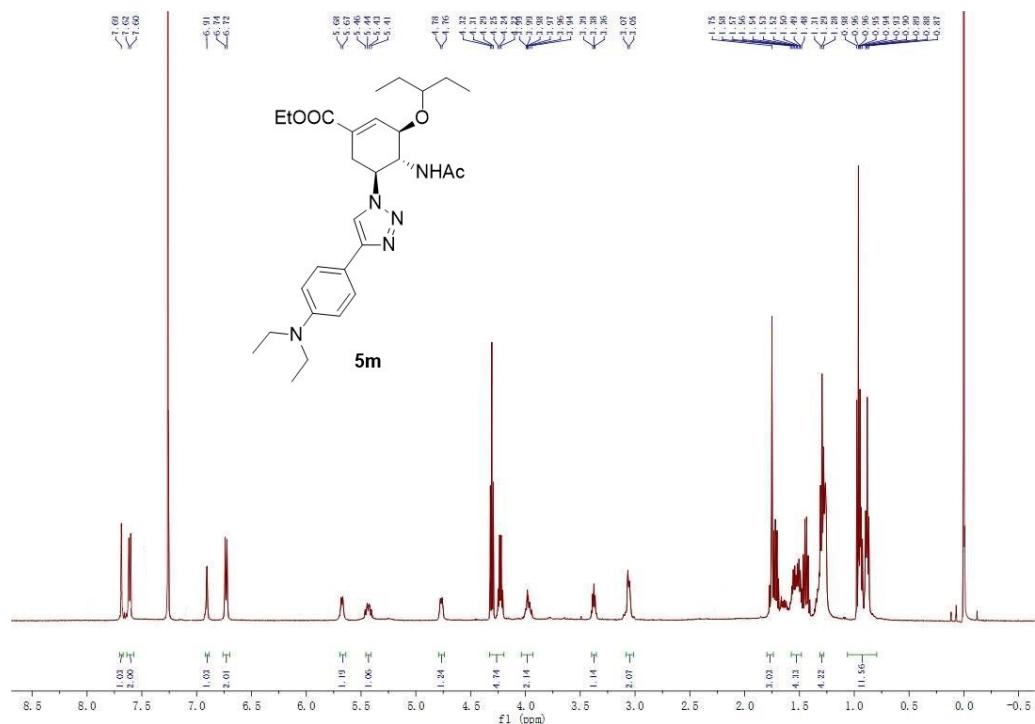

ESIMS of 5m
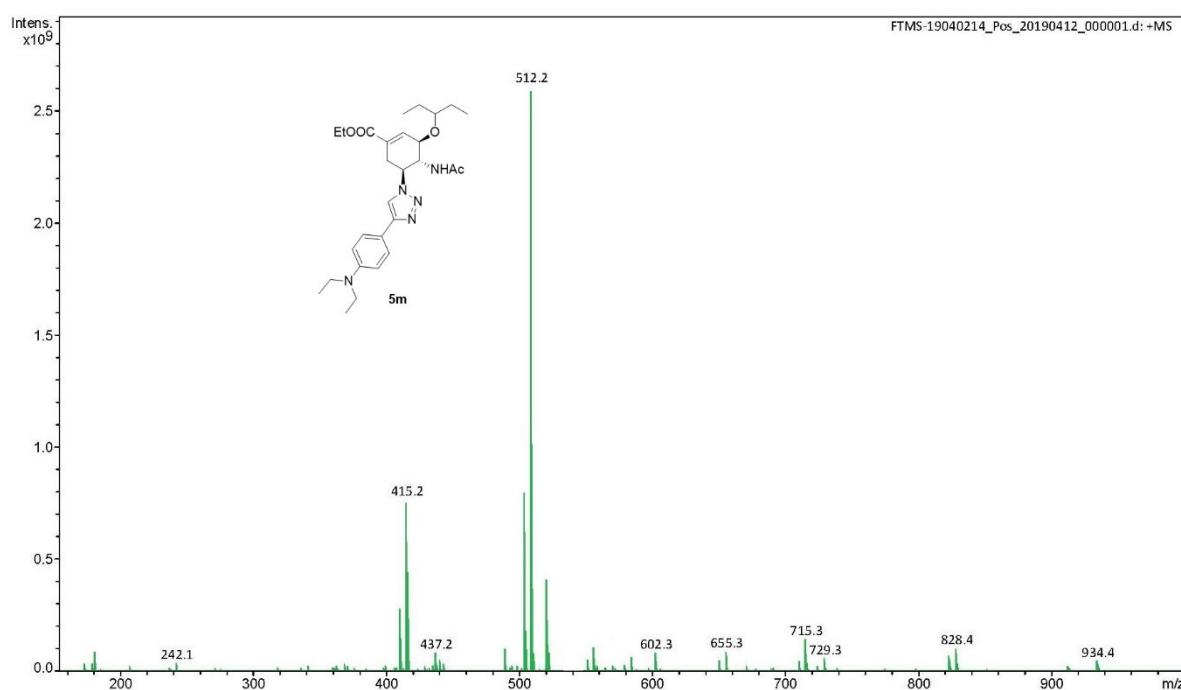
# ¹H NMR of 5n (500 MHz, CDCl₃)

HR-ESIMS of 5n

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
672.36072	25670274	C 34 H 50 N 5 O 9	100.00	672.36030	-0.4	-0.6	4.4	12.5	even	ok
694.34307	92786656	C 34 H 49 N 5 Na O 9	100.00	694.34225	-0.8	-1.2	7.9	12.5	even	ok
710.31682	49930212	C 34 H 49 K N 5 O 9	100.00	710.31619	-0.6	-0.9	14.5	12.5	even	ok
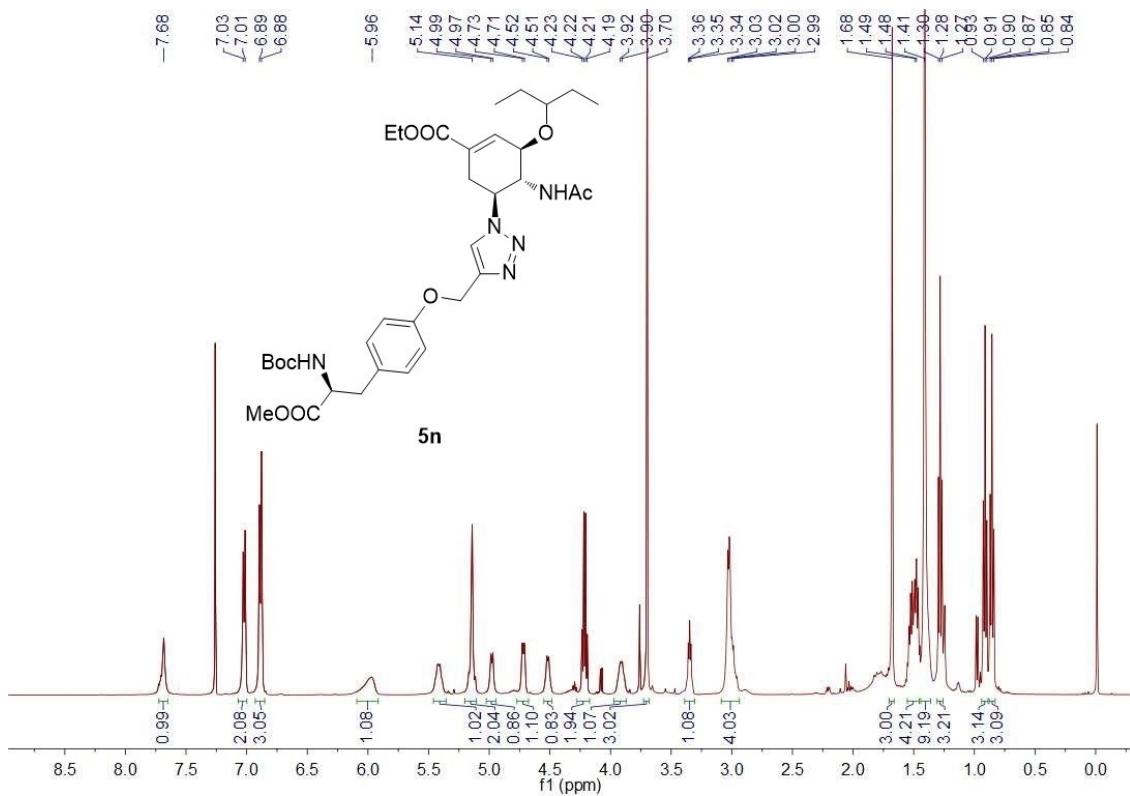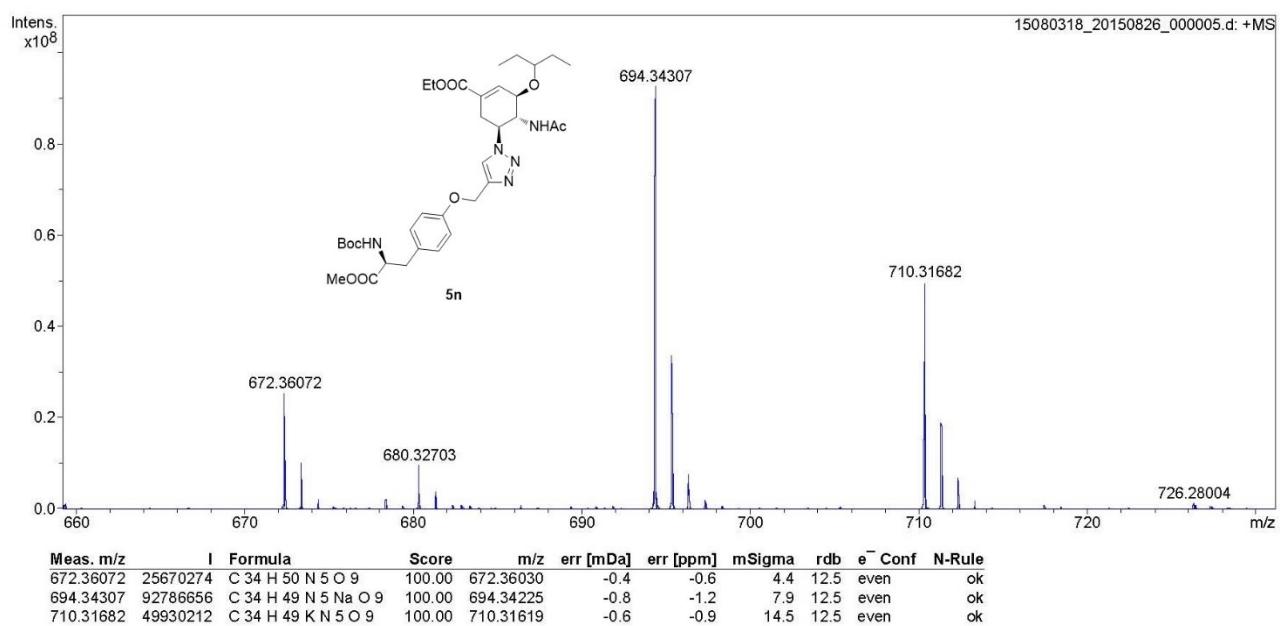
^{1}H NMR of 6e (500 MHz, CDCl$_3$)

HR-ESIMS of 6e

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
441.24940	87108832	C 24 H 33 N 4 O 4	100.00	441.24963	0.2	0.5	5.6	10.5	even	ok
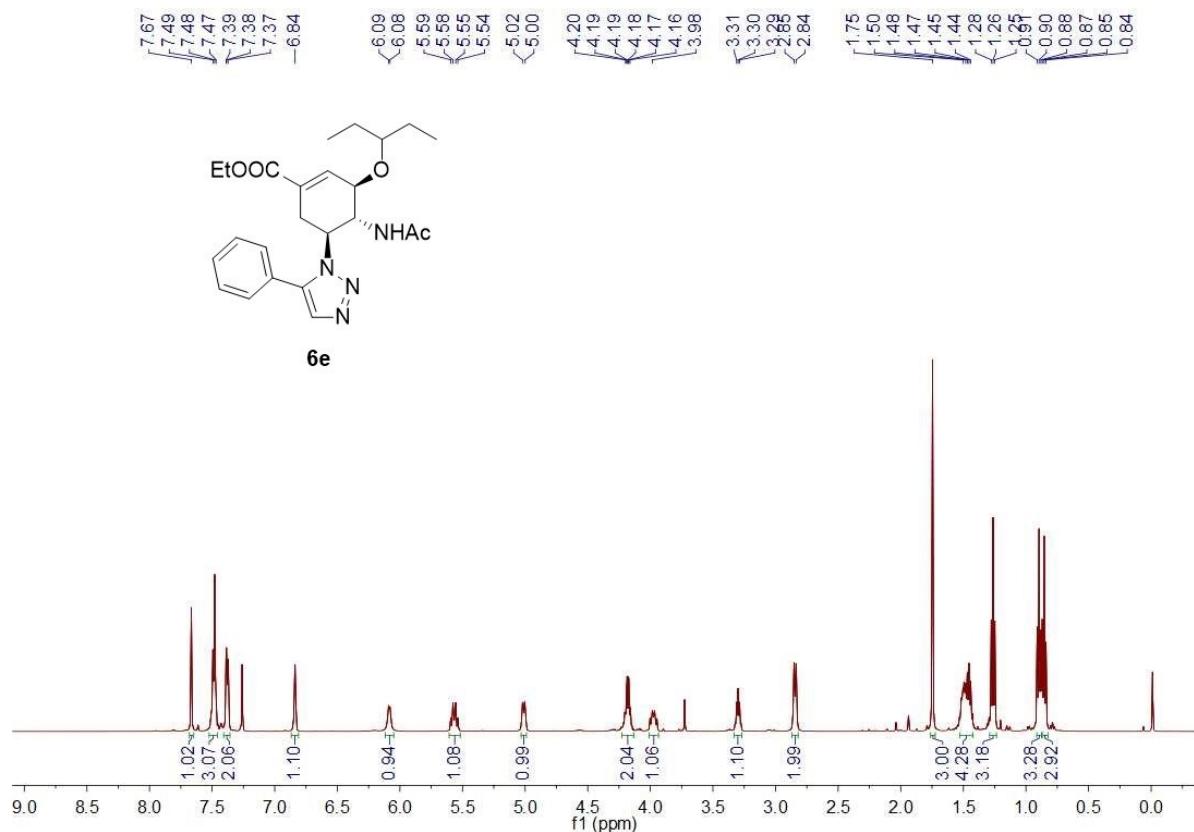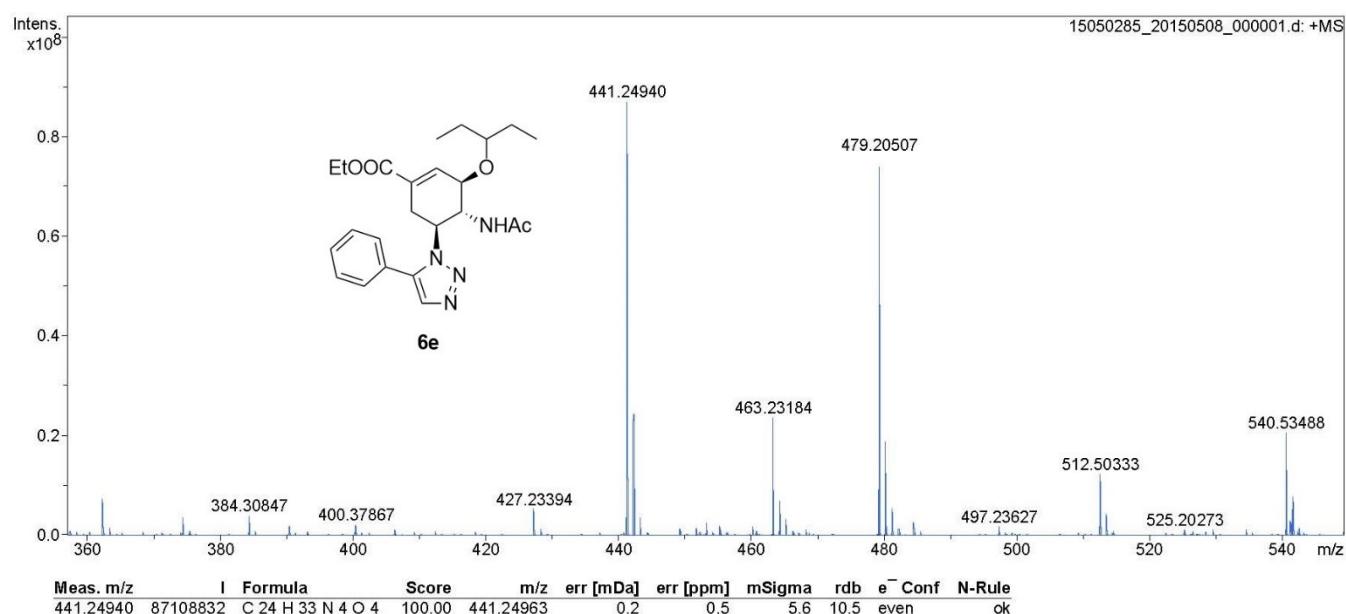
^{1}H NMR of 6f (500 MHz, CDCl$_3$)

HR-ESIMS of 6f

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e$^-$ Conf	N-Rule
499.25371	193139120	C 26 H 35 N 4 O 6	100.00	499.25511	1.4	2.8	9.0	11.5	even	ok

^{1}H NMR of 6g (500 MHz, CDCl$_3$)

HR-ESIMS of 6g

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e$^-$ Conf	N-Rule
499.25566	141718880	C 26 H 35 N 4 O 6	100.00	499.25511	-0.5	-1.1	4.5	11.5	even	ok
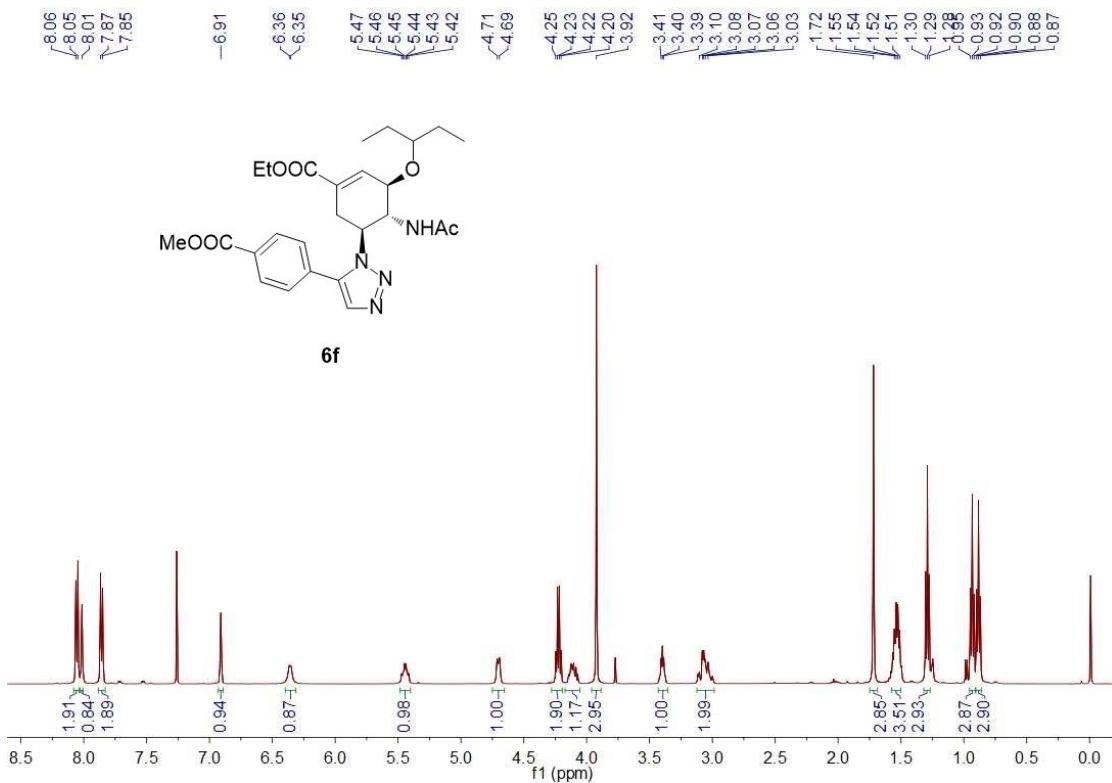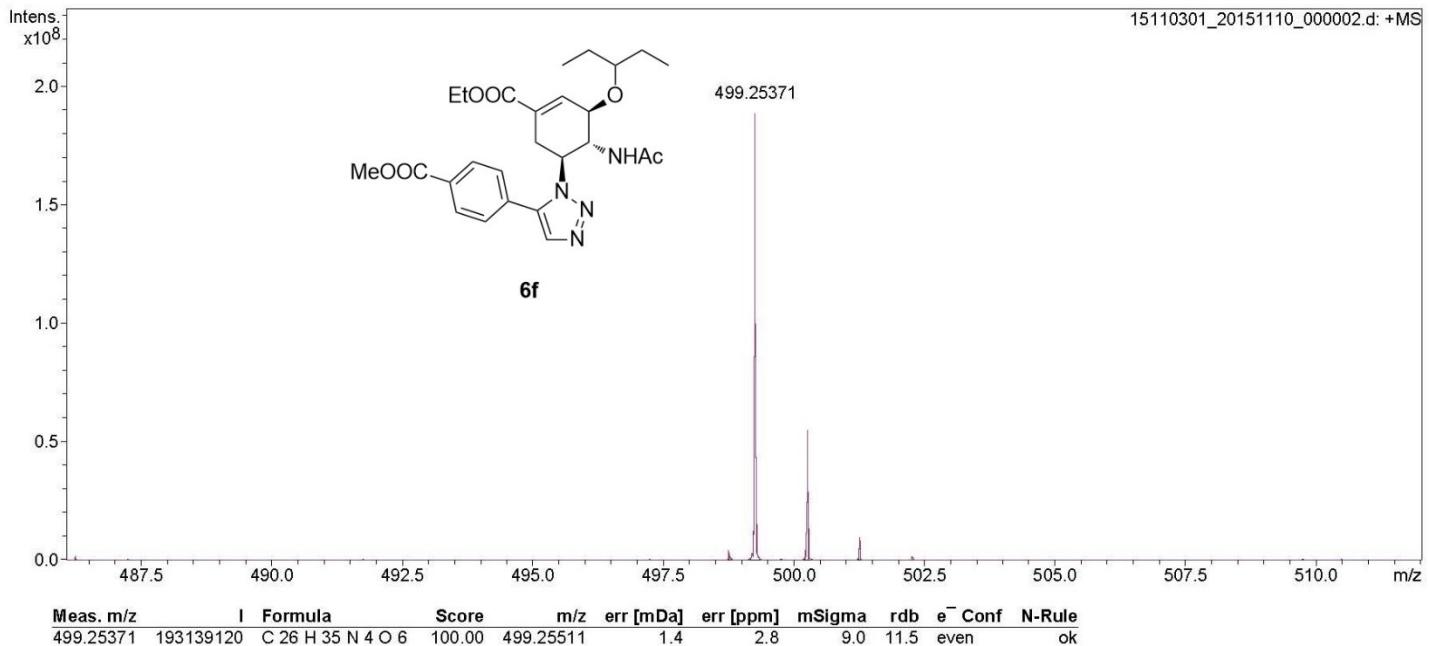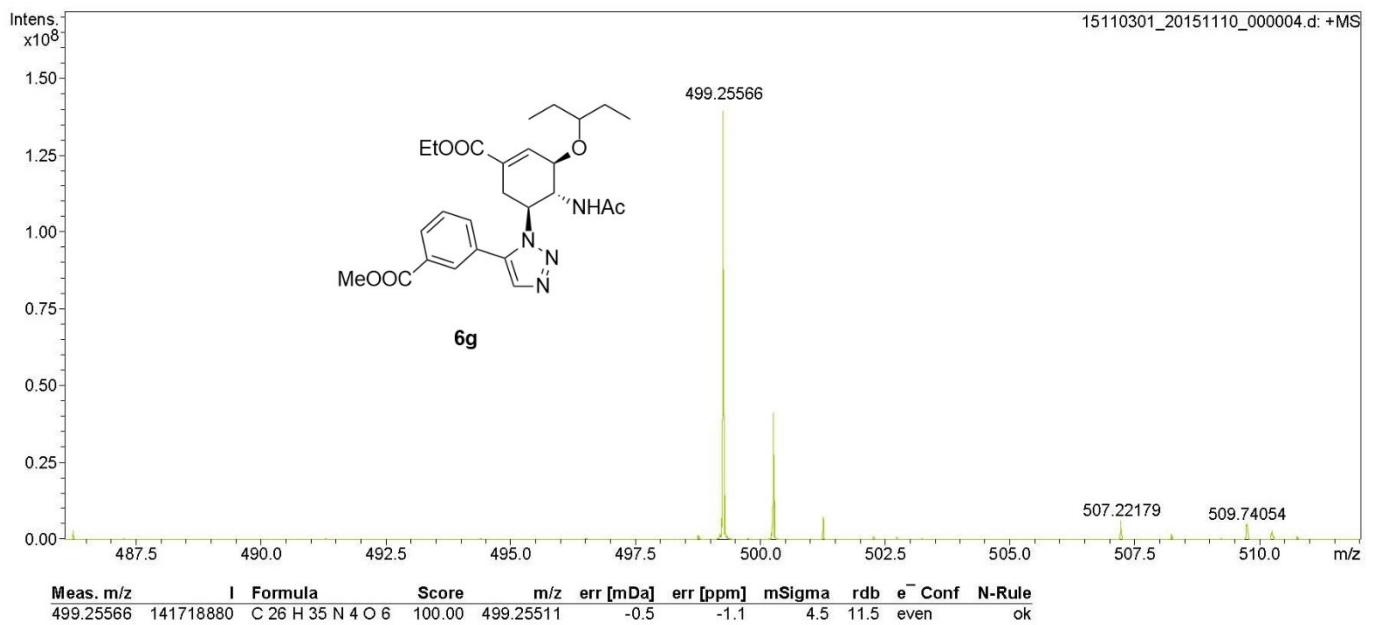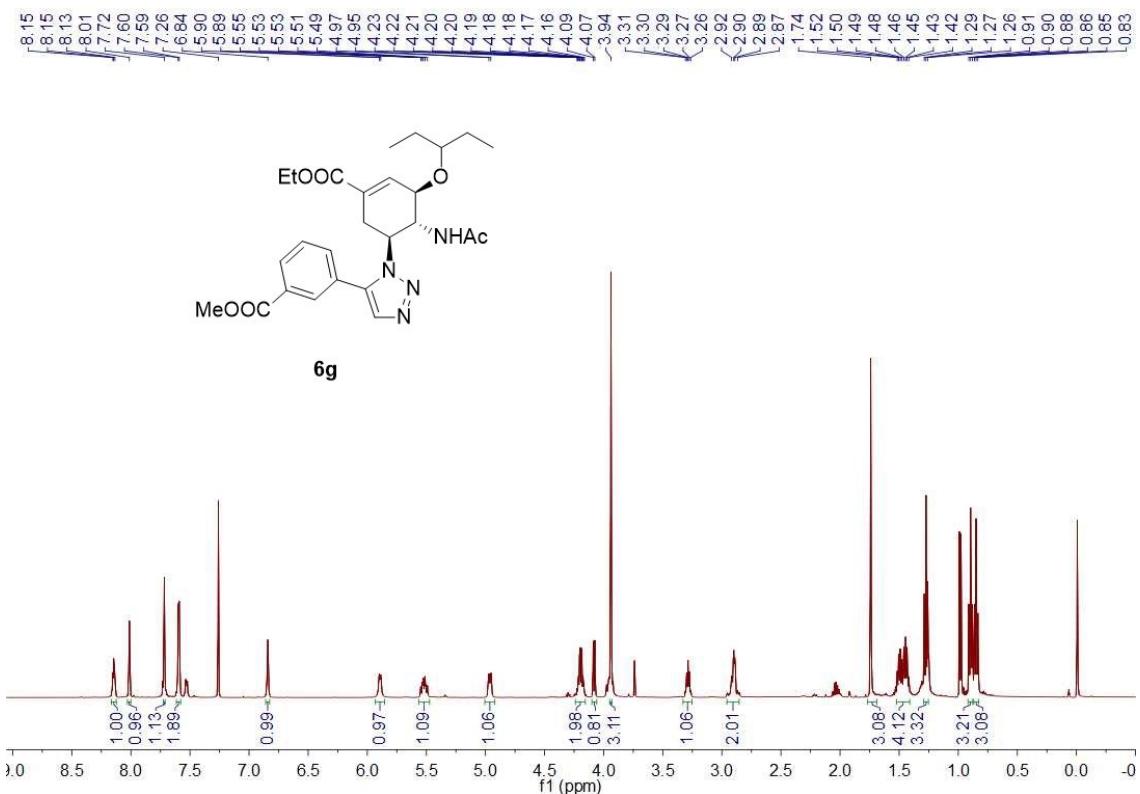
^{1}H NMR of 6h (500 MHz, CDCl$_3$)
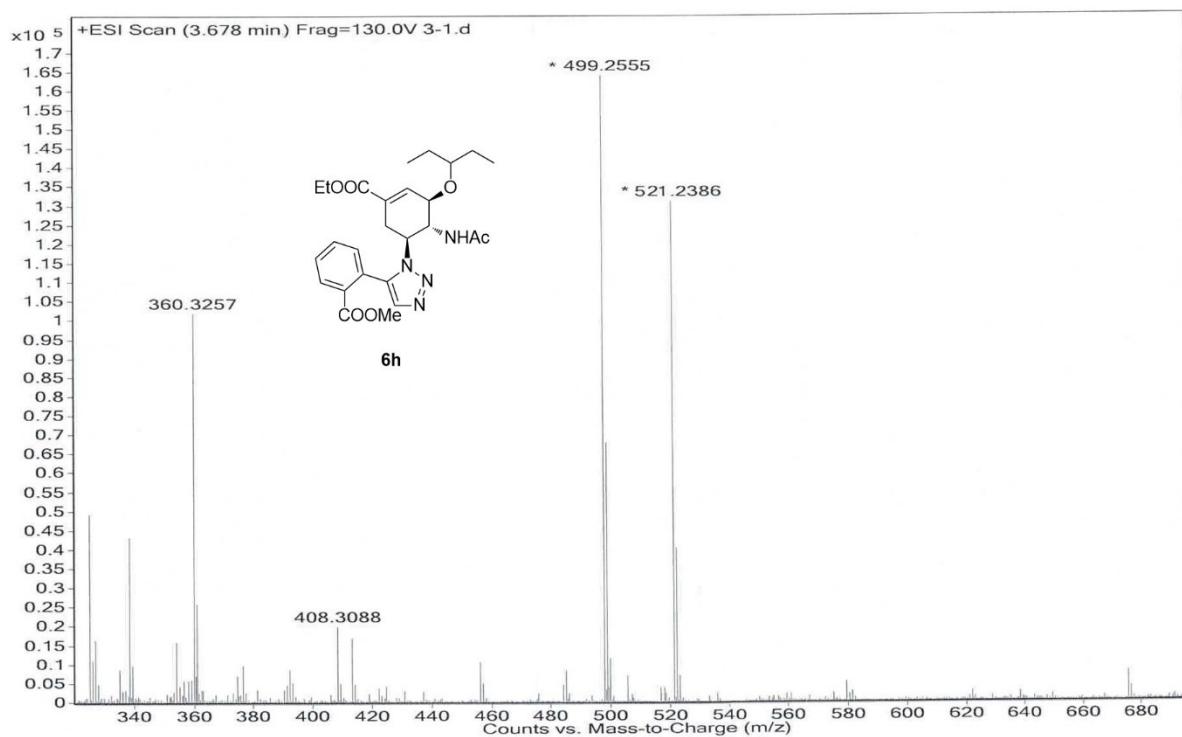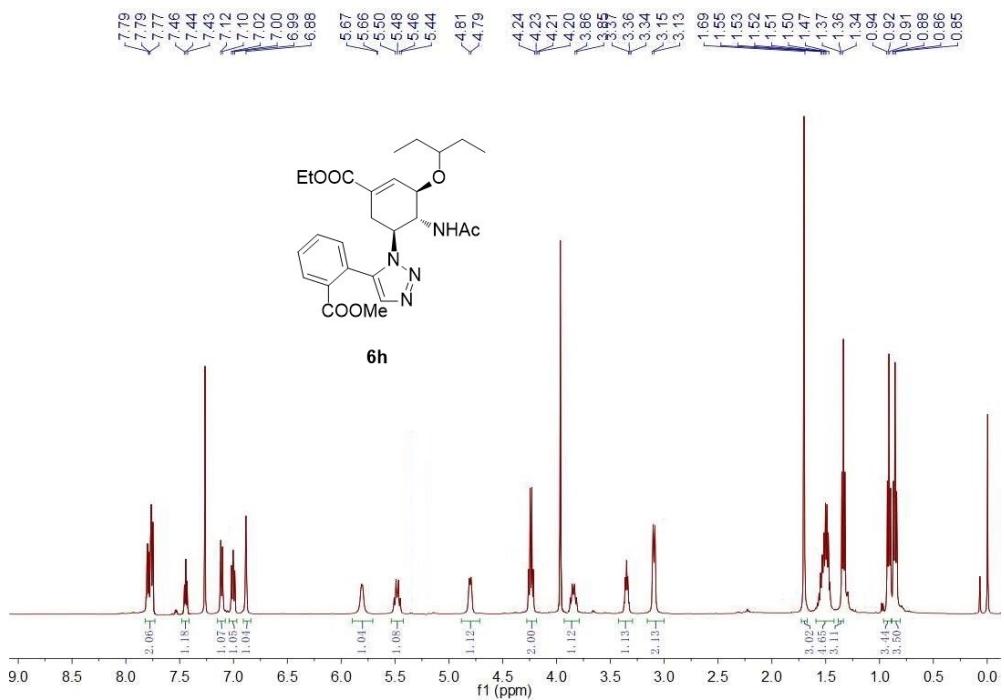
HR-ESIMS of 6h

¹H NMR of 6i (500 MHz, CDCl₃)
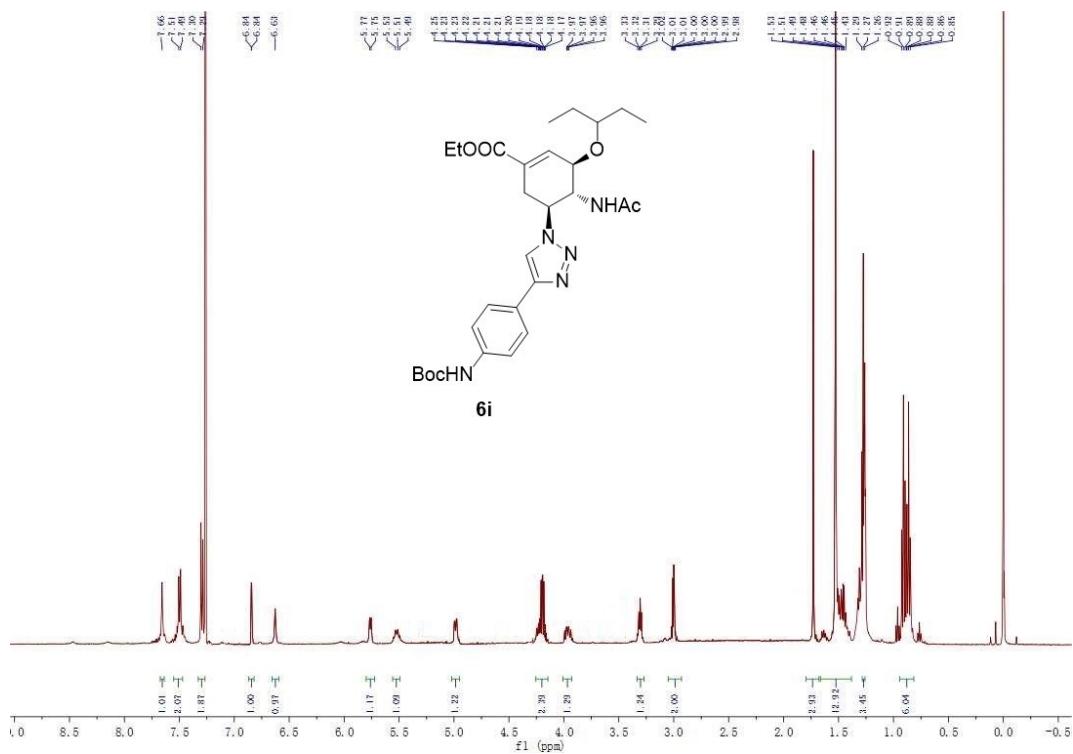
# ESIMS of 6i
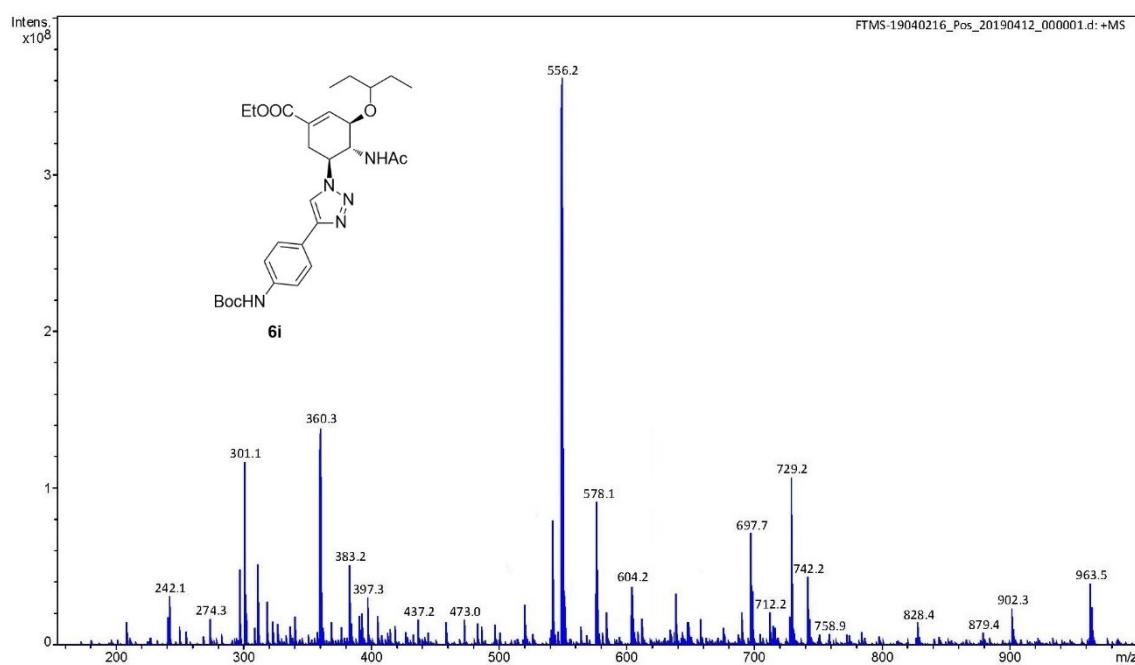
¹H NMR of 6j (500 MHz, CDCl₃)

HR-ESIMS of 6j

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
556.31399	13758877	C 29 H 42 N 5 O 6	100.00	556.31296	-1.0	-1.8	5.6	11.5	even	ok
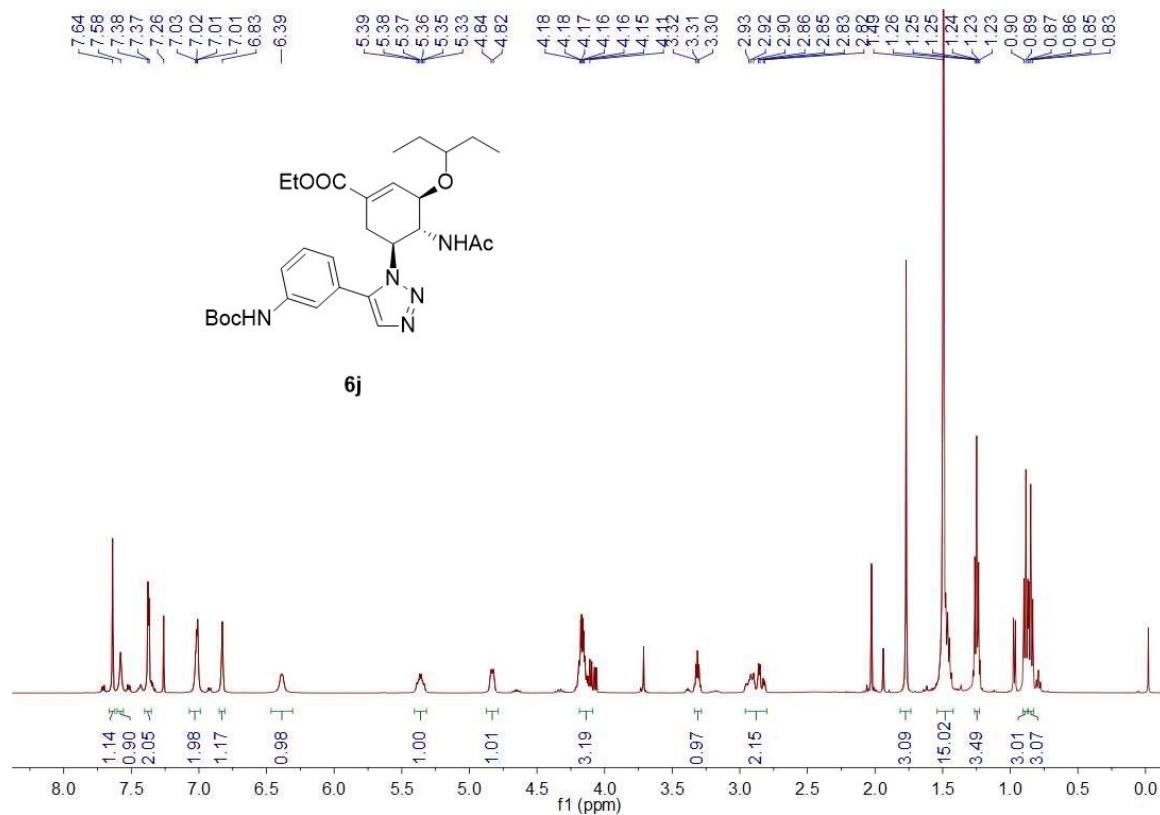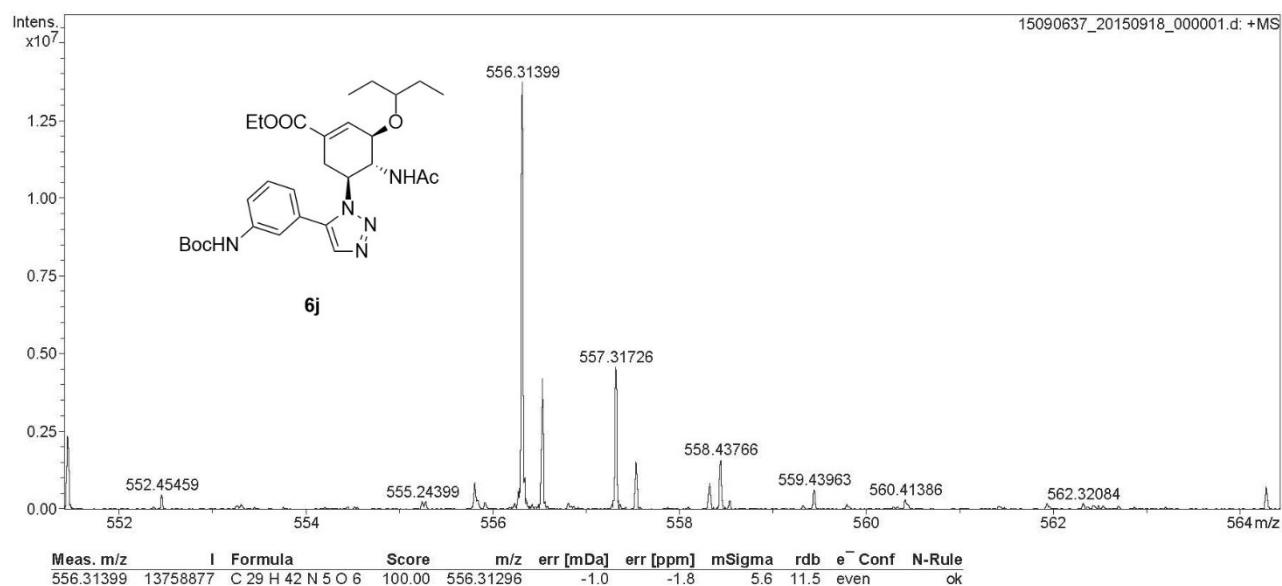
^{1}H NMR of 6k (500 MHz, CDCl$_3$)

HR-ESIMS of 6k

+ESI Scan (2.620 min) Frag=130.0V 4-1.d

456.2609

478.2429
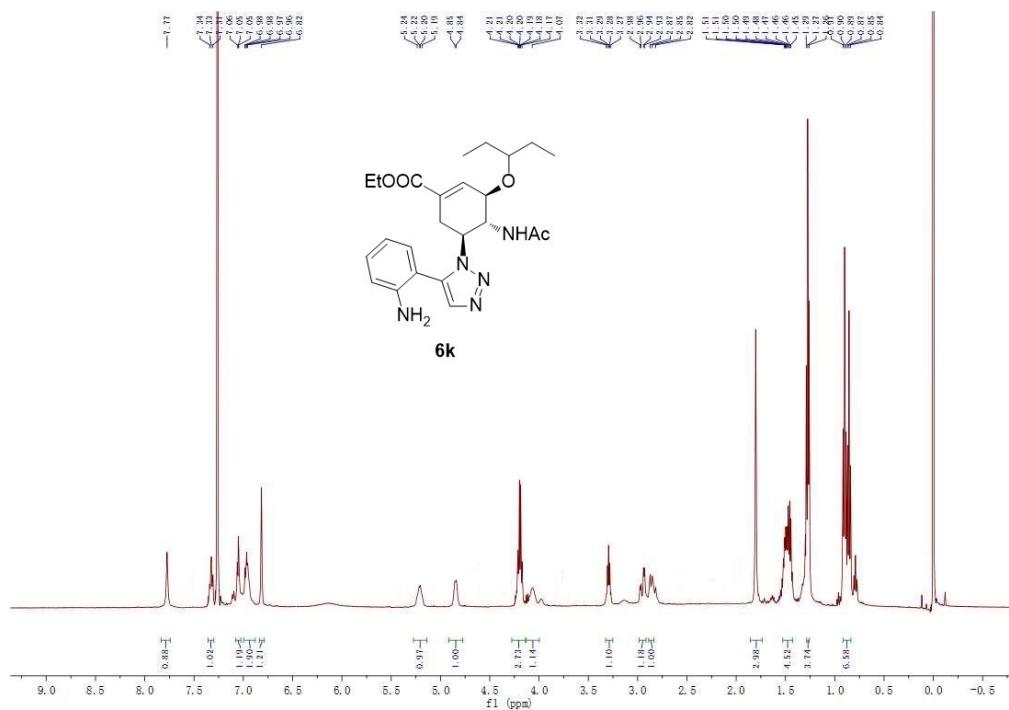
¹H NMR of 6l (500 MHz, CDCl₃)
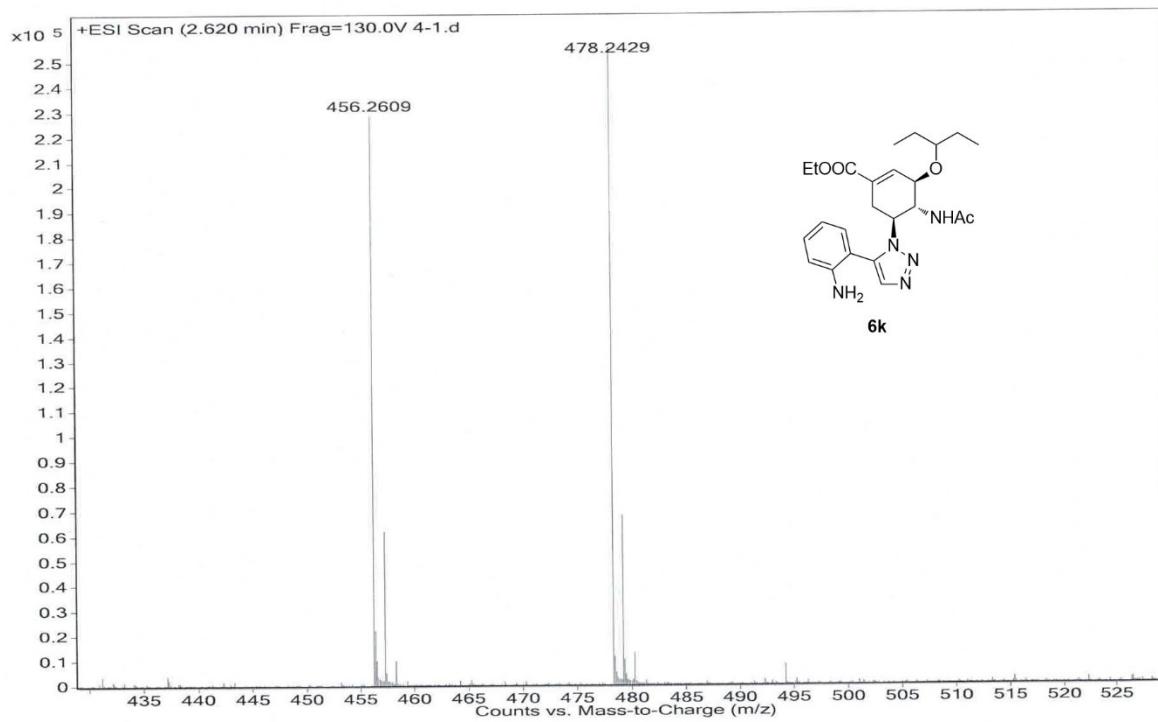
¹H NMR of 6l (500 MHz, CDCl₃)
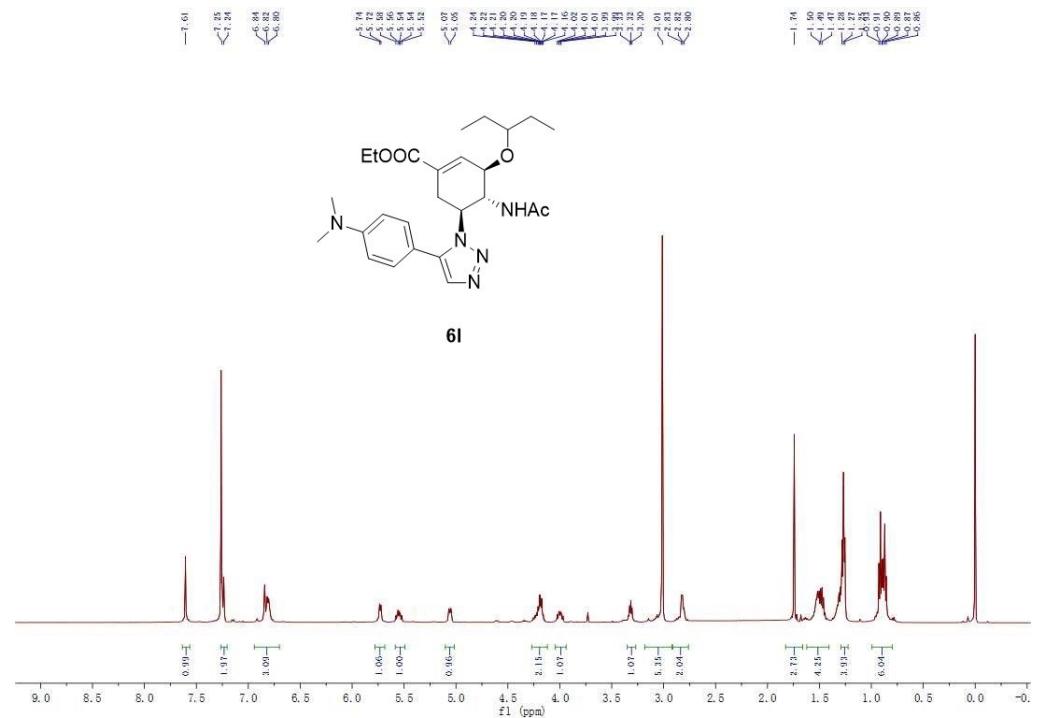
ESIMS of 6l
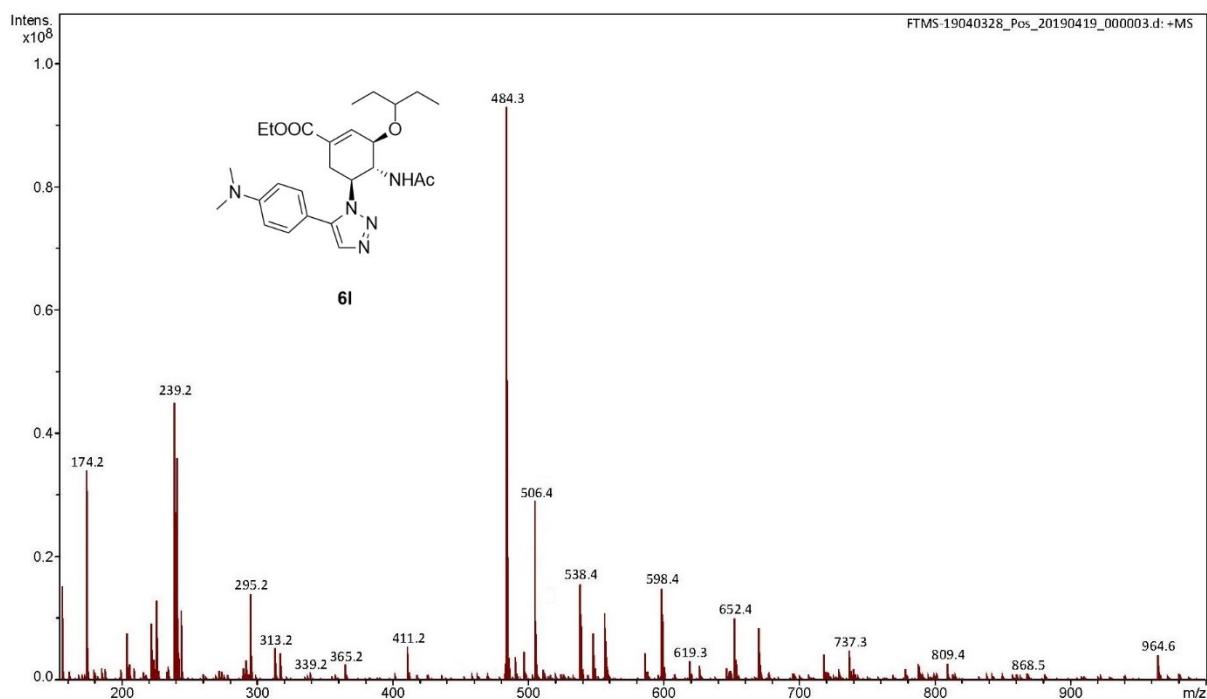
ESIMS of 6l

^{1}H NMR of 6m (500 MHz, CDCl$_3$)
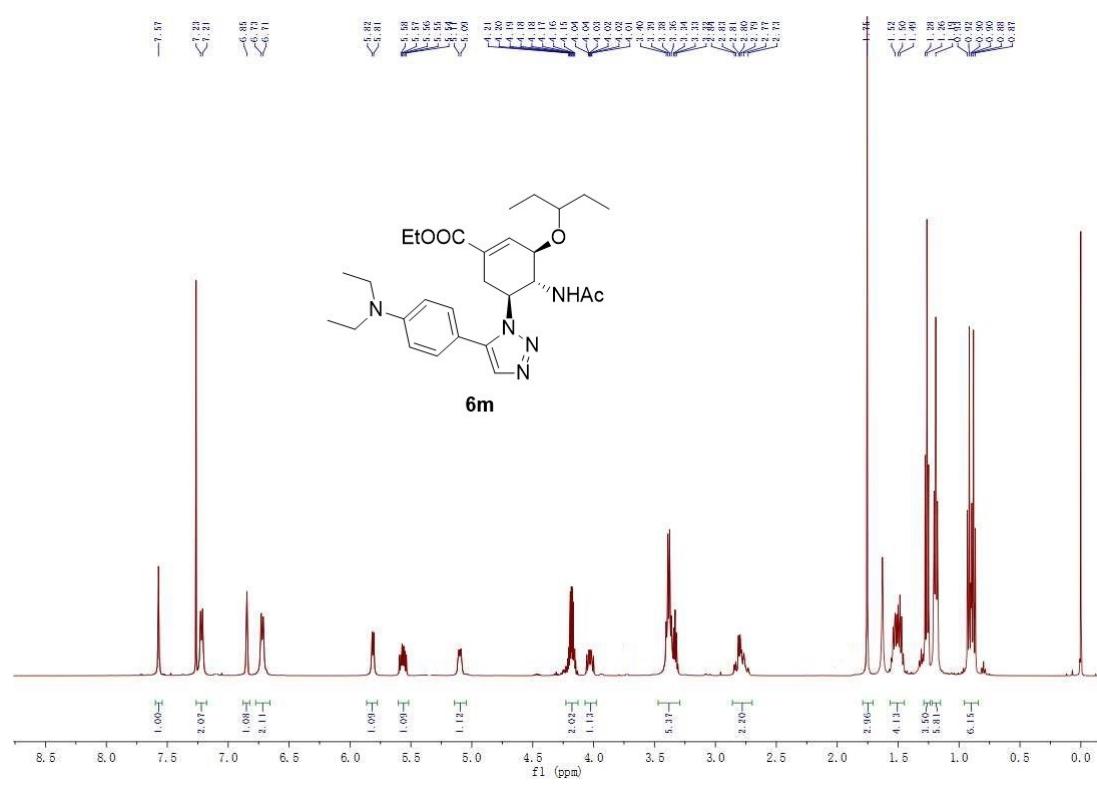
ESIMS of 6m
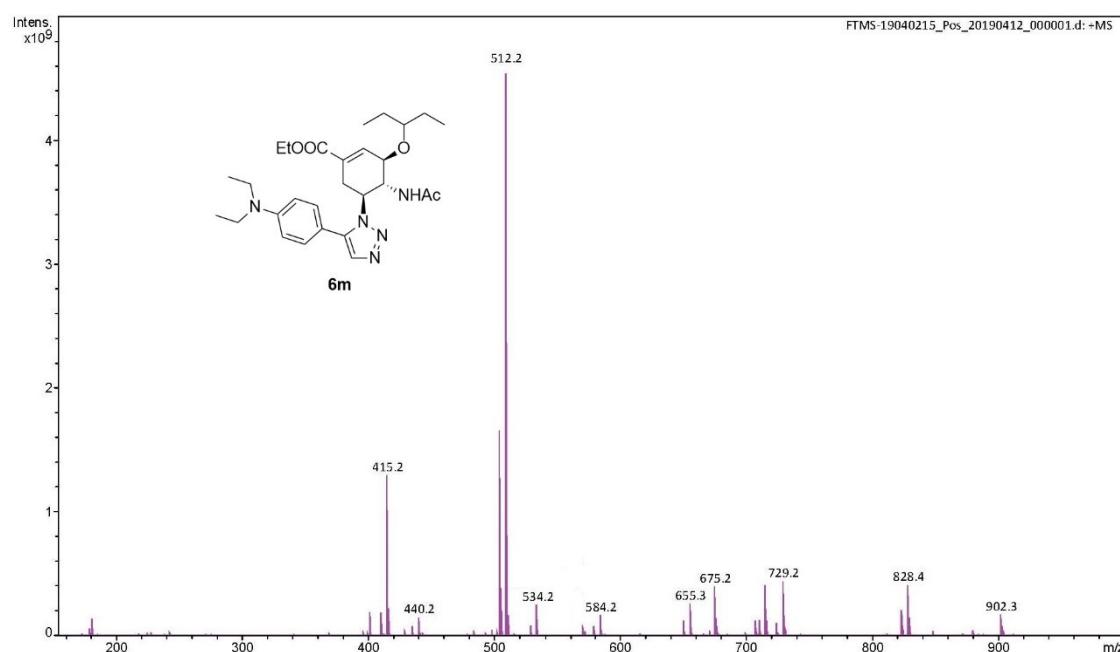
^{1}H NMR of 6n (500 MHz, CDCl$_3$)

HR-ESIMS of 6n

| Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
672.36018	23743106	C 34 H 50 N 5 O 9	100.00	672.36030	0.1	0.2	6.3	12.5	even	ok
694.34244	12200879	C 34 H 49 N 5 Na O 9	100.00	694.34225	-0.2	-0.3	10.7	12.5	even	ok
710.31616	6986031	C 34 H 49 K N 5 O 9	100.00	710.31619	0.0	0.0	19.1	12.5	even	ok
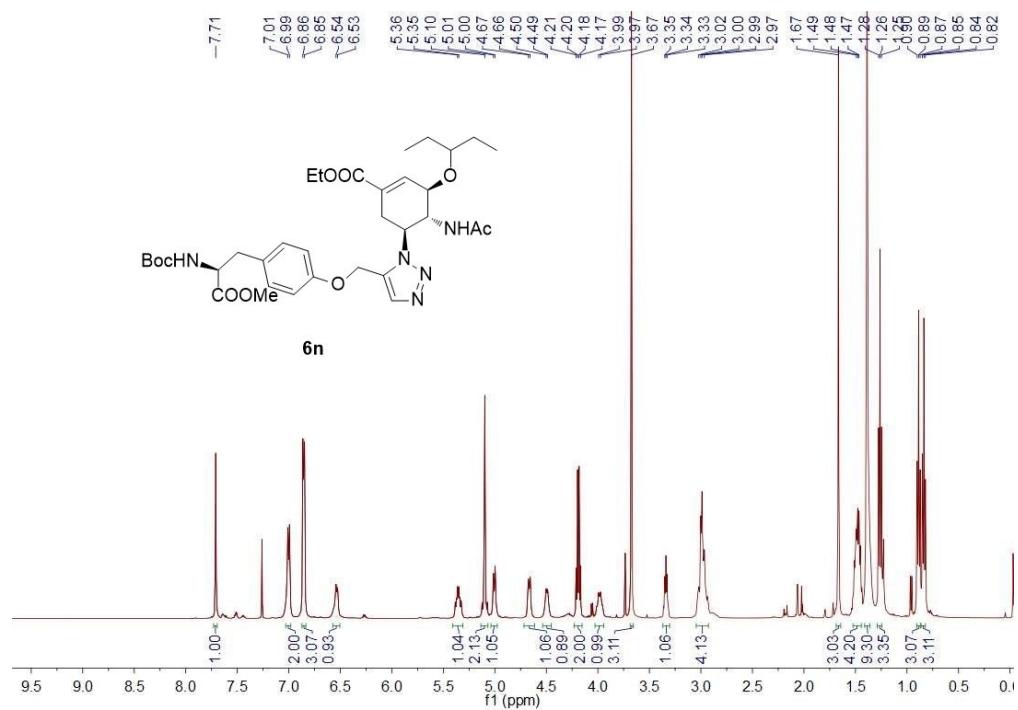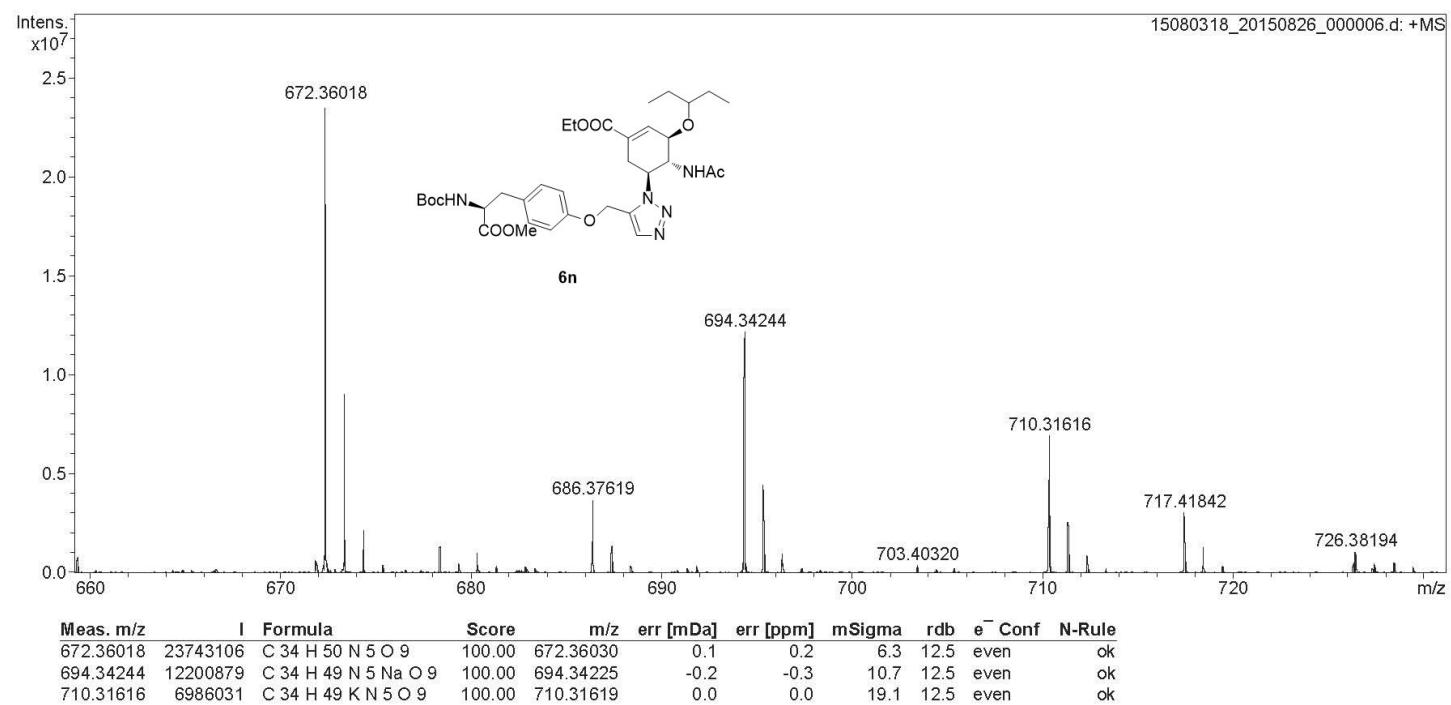
# ¹H NMR of 1a (500 MHz, CD₃OD)
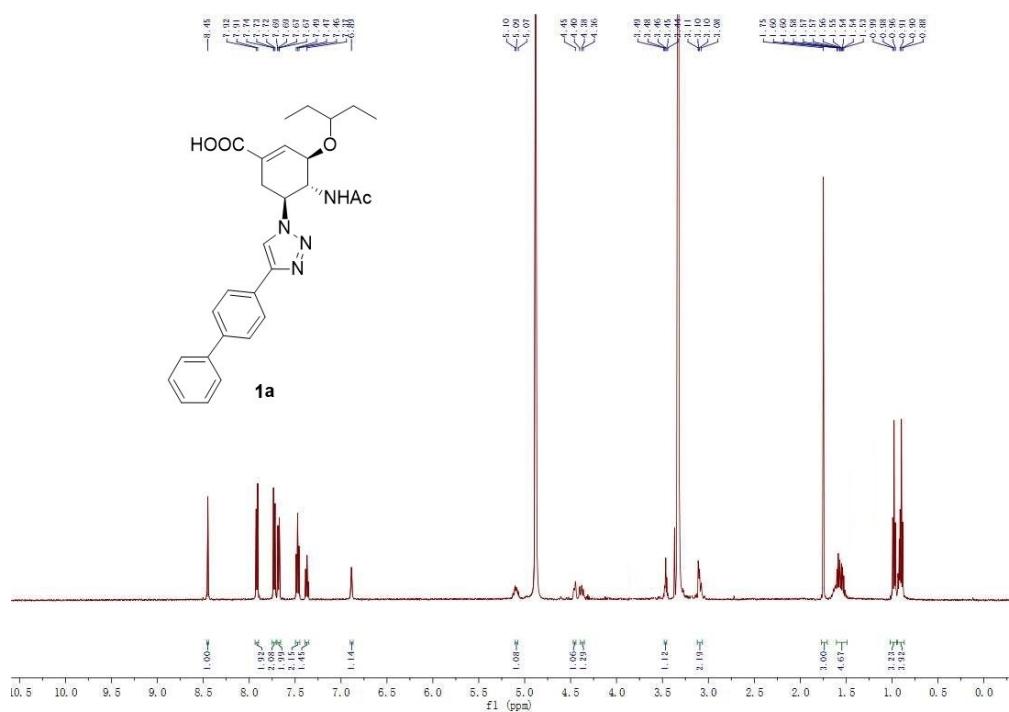
¹³C NMR of 1a (500 MHz, CD₃OD)

HR-ESIMS of 1a


Meas. m/z	#	Ion Formula	Score	m/z	err [ppm]	Mean err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
489.249657	1	C28H33N4O4	100.00	489.249632	-0.1	-1.1	13.4	15.0	even	ok
511.231798	1	C28H32N4NaO4	100.00	511.231576	-0.4	-1.8	11.6	15.0	even	ok
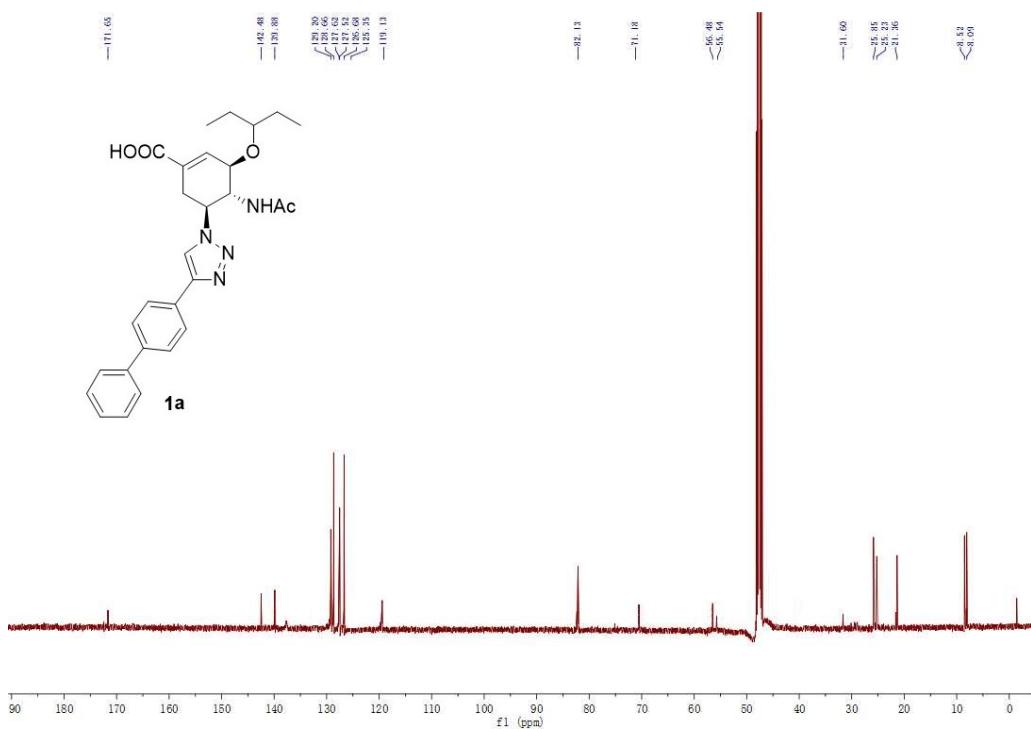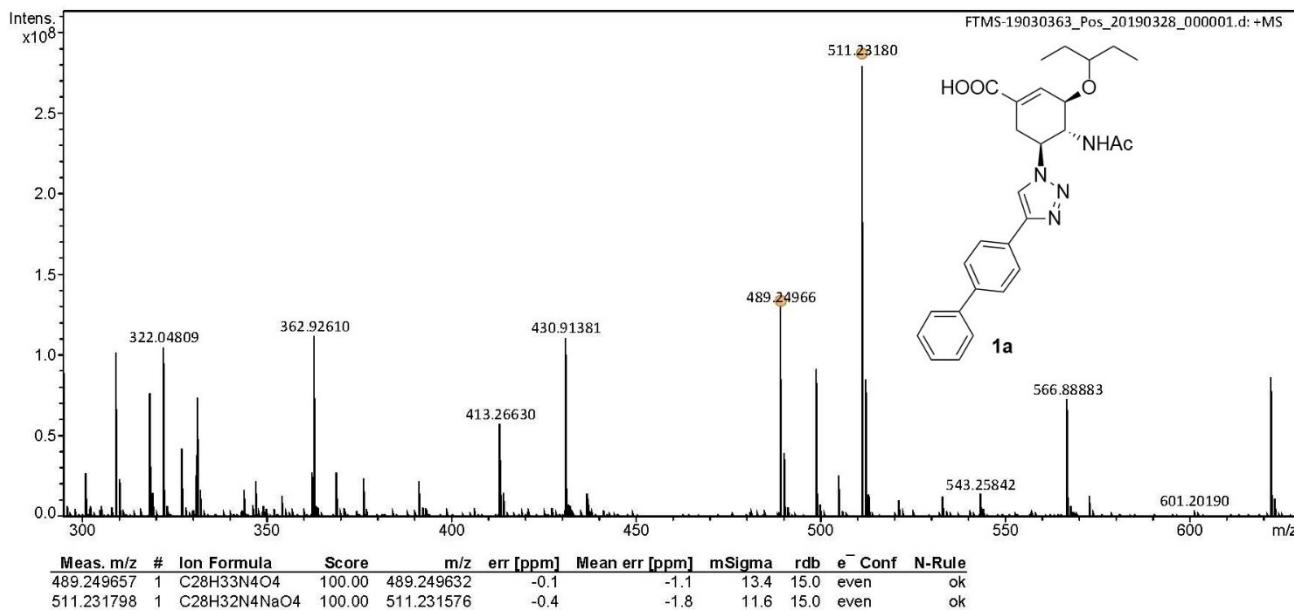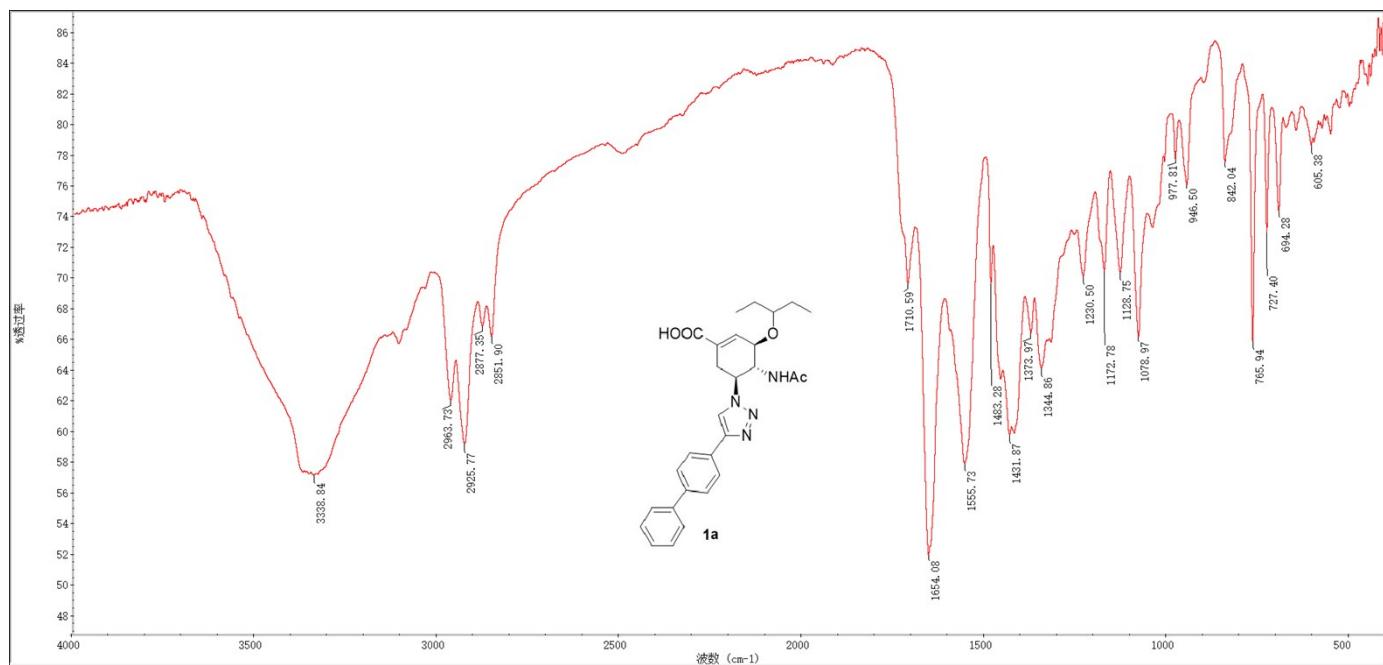
IR of 1a

^{1}H NMR of 1b (500 MHz, CD$_3$OD)
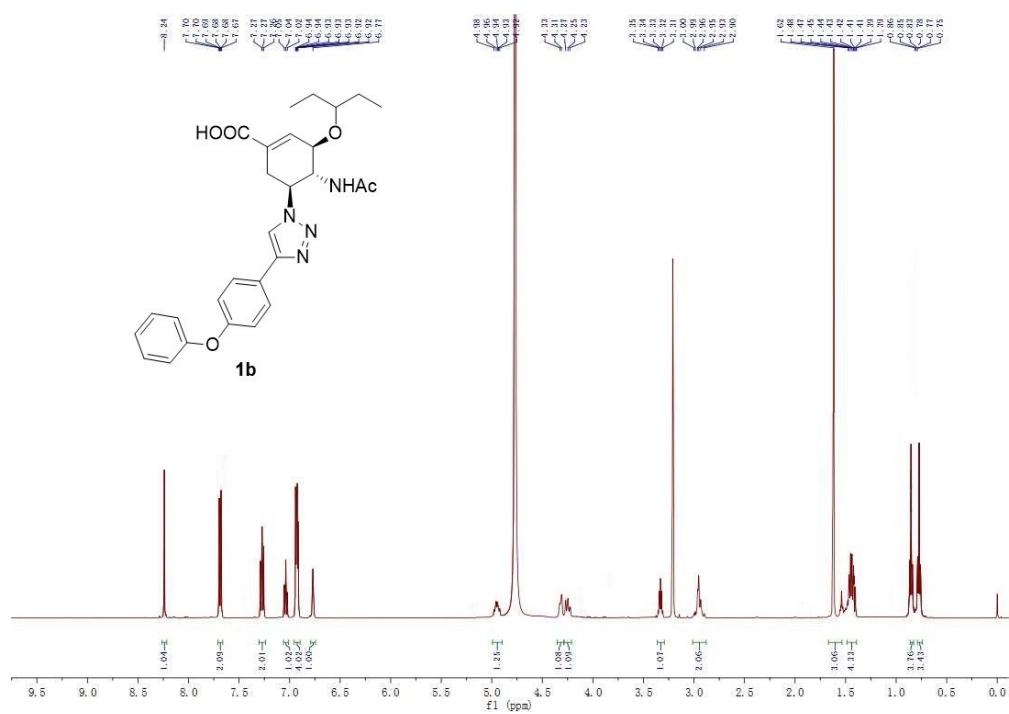
# ^{13}C NMR of 1b (500 MHz, CD$_3$OD)

HR-ESIMS of 1b

Meas. m/z	#	Ion Formula	Score	m/z	err [ppm]	Mean err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
503.229591	1	C28H31N4O5	100.00	503.229994	0.8	-2.8	20.2	15.0	even	ok
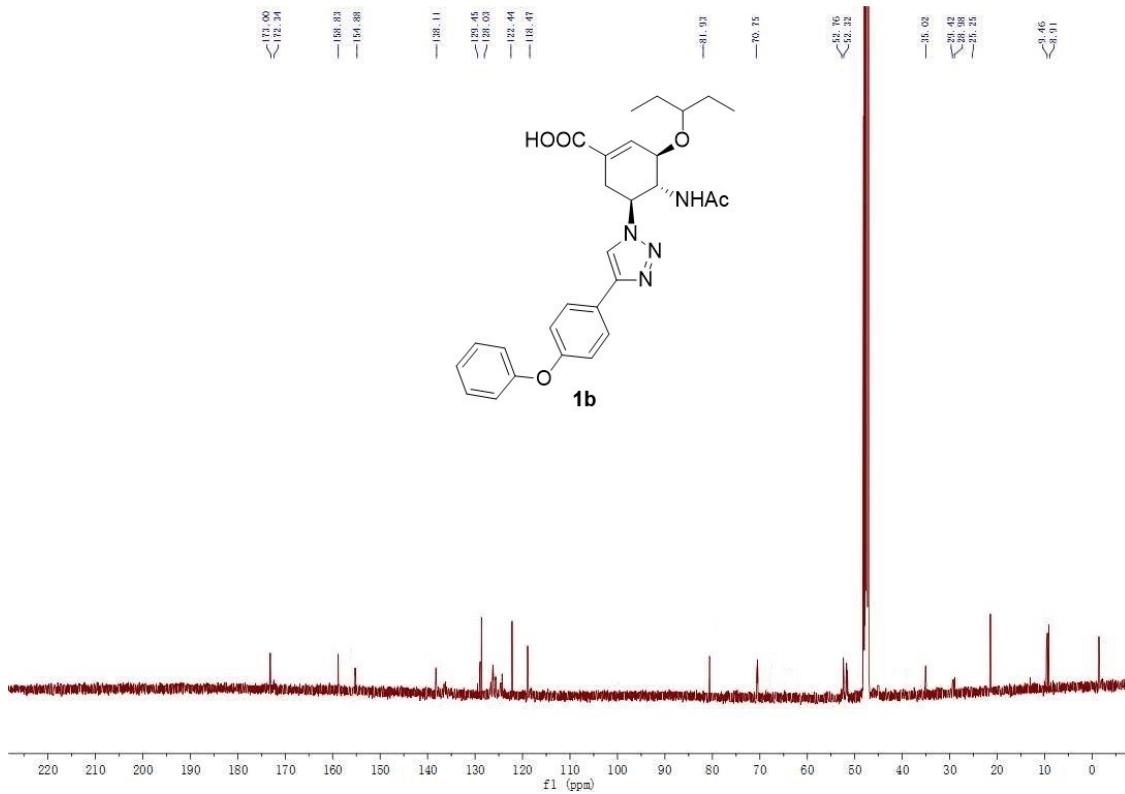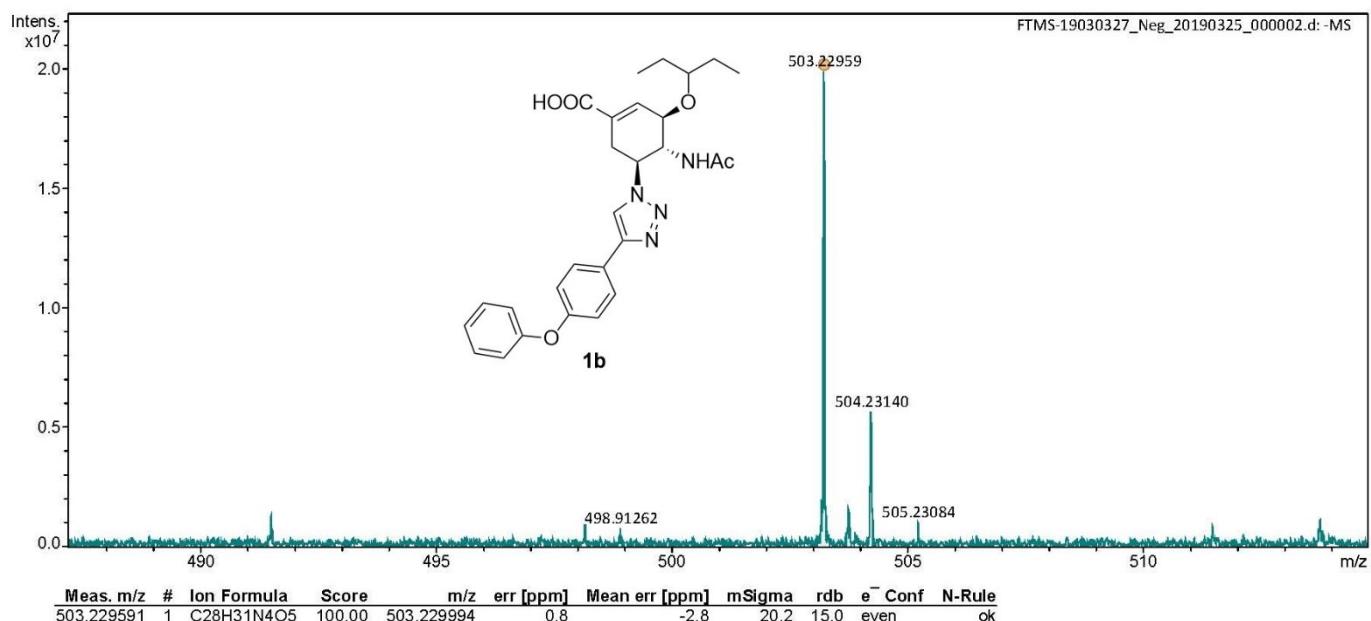
IR of 1b

¹H NMR of 1c (500 MHz, CD₃OD)
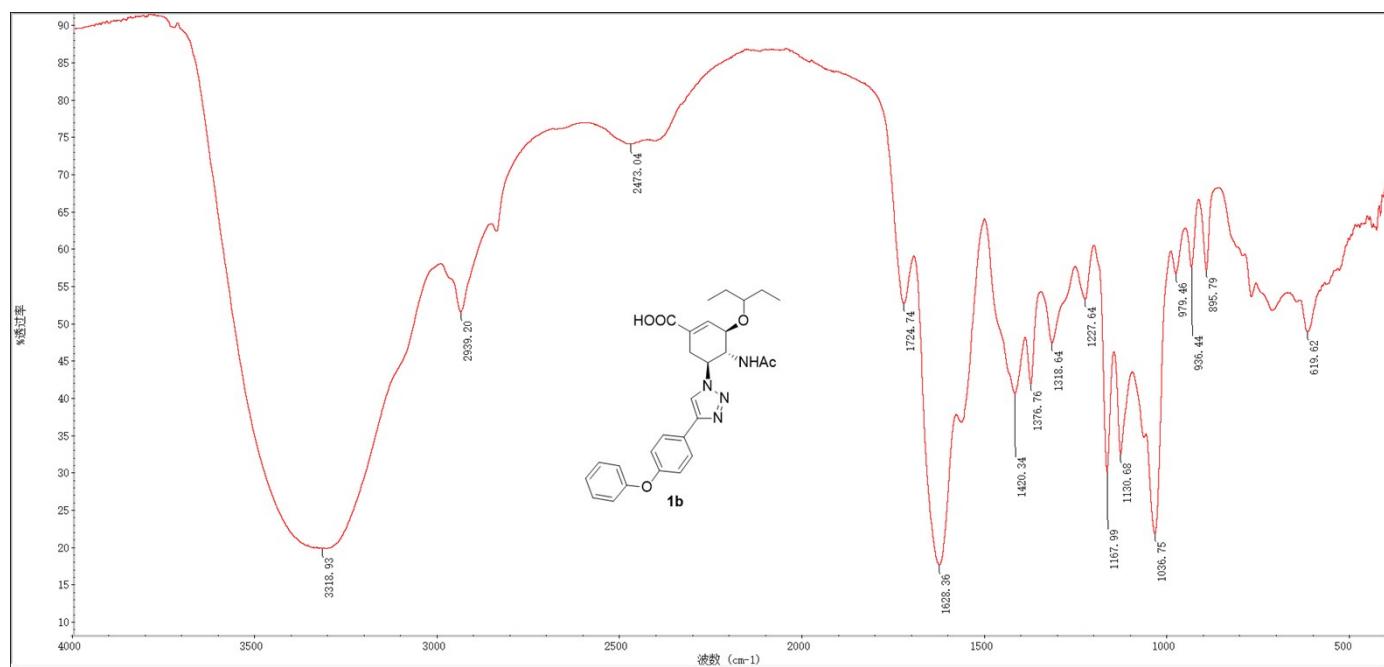
¹H NMR of 1c (500 MHz, CD₃OD)
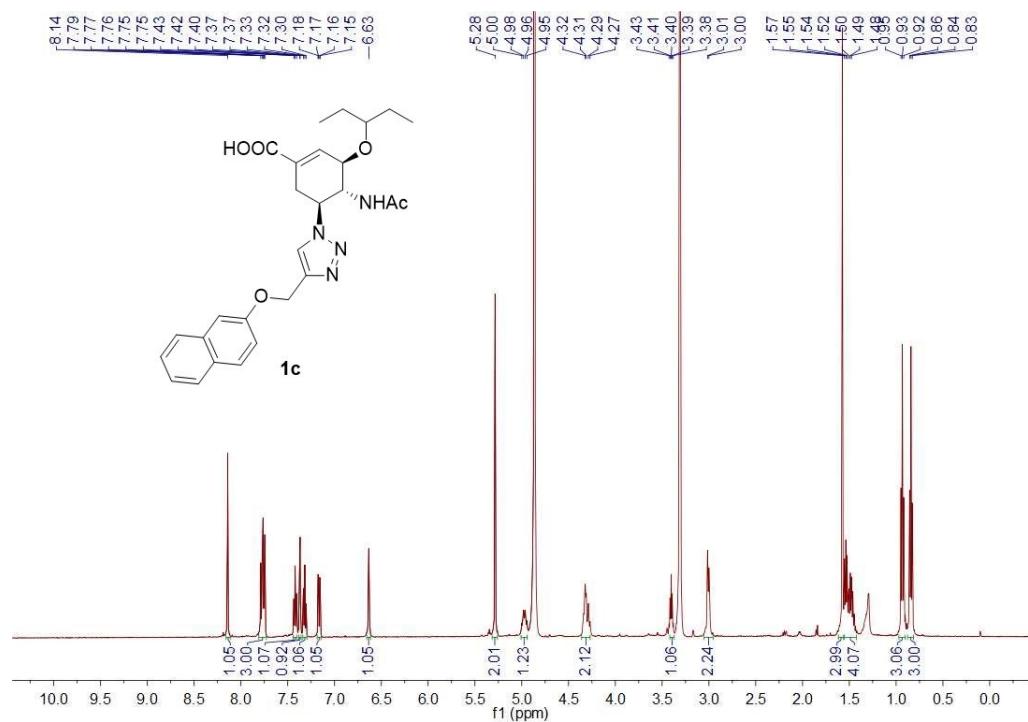
¹³C NMR of 1c (500 MHz, CD₃OD)

HR-ESIMS of 1c

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
493.24512	1122853	C 27 H 33 N 4 O 5	100.00	493.24455	-0.6	-1.2	49.8	13.5	even	ok
515.22682	62045444	C 27 H 32 N 4 Na O 5	100.00	515.22649	-0.3	-0.6	10.8	13.5	even	ok
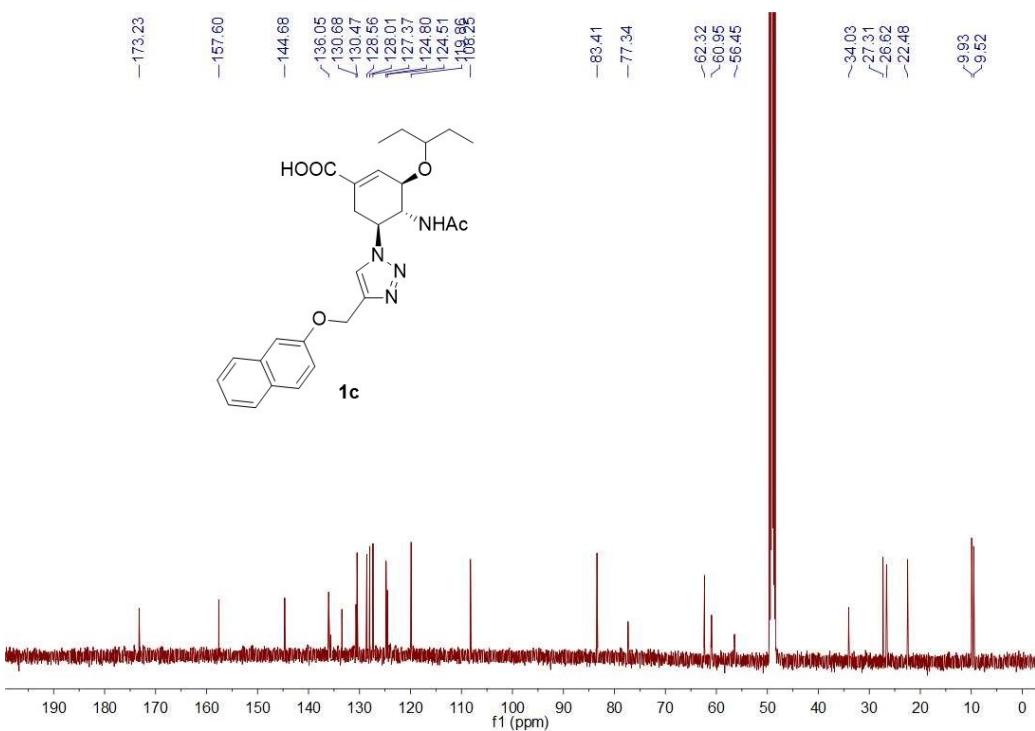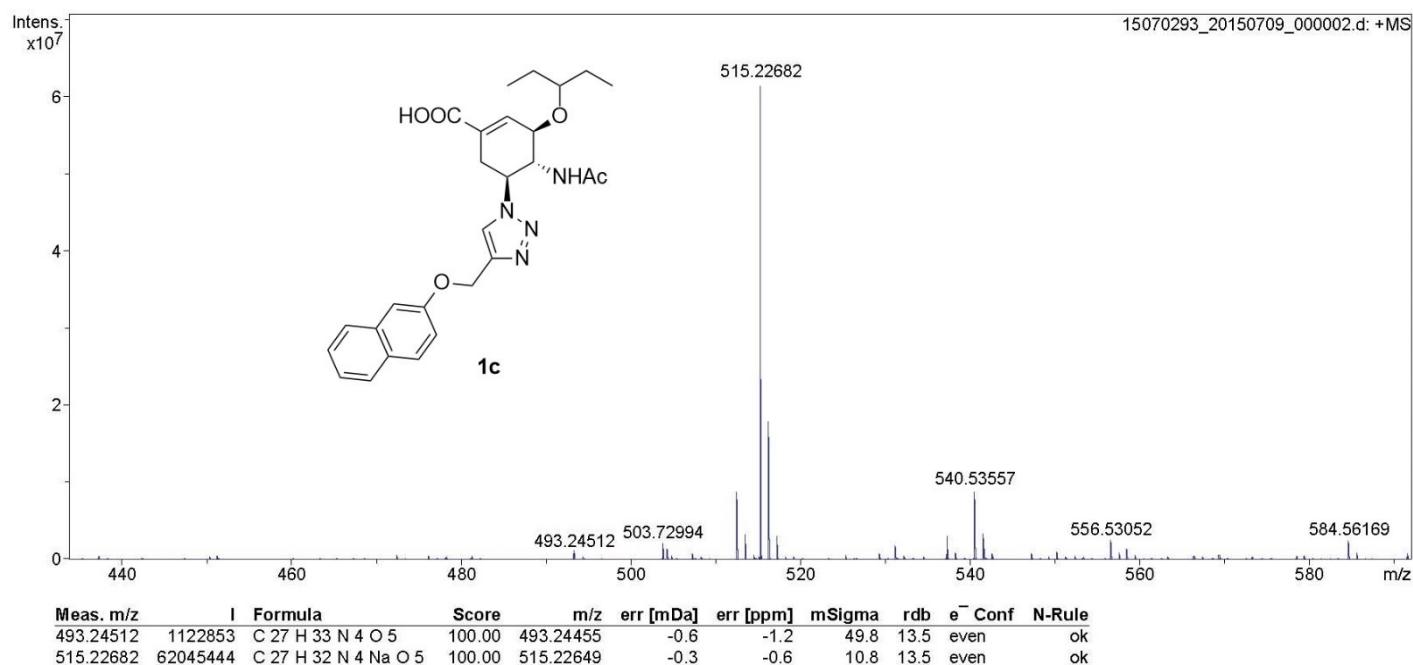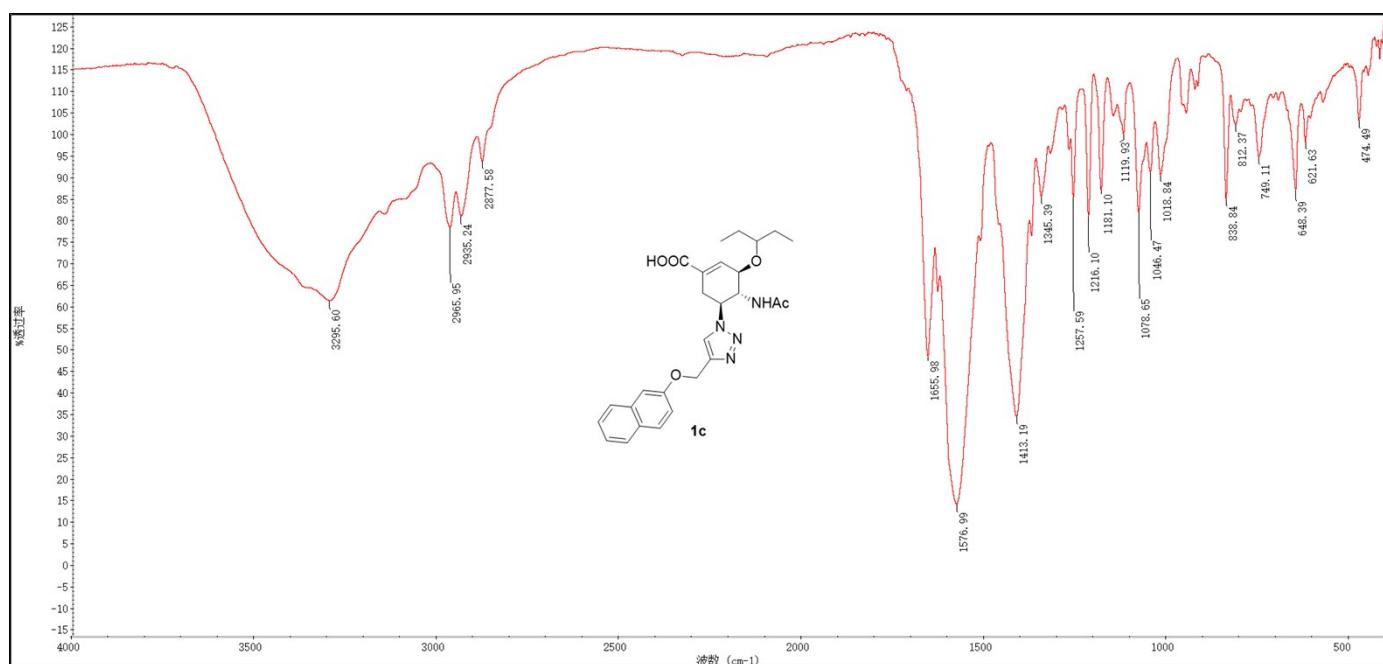
IR of 1c

^{1}H NMR of 1d (500 MHz, CD$_3$OD)
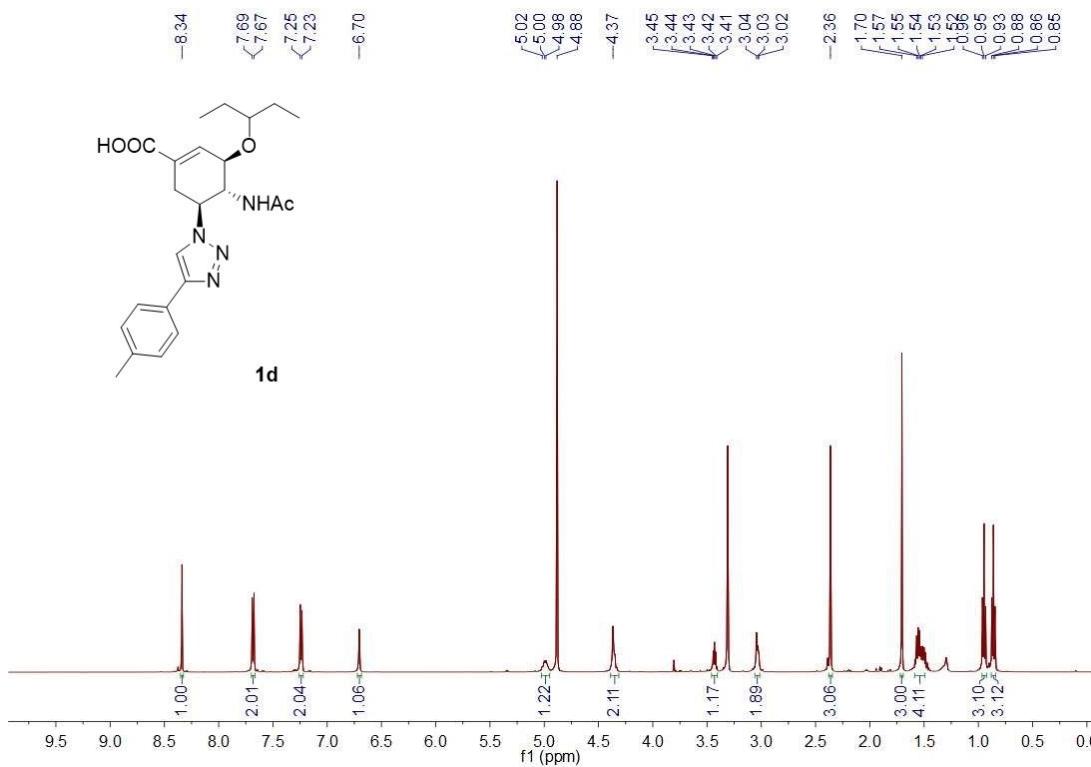
# ^{13}C NMR of 1d (500 MHz, CD$_3$OD)

HR-ESIMS of 1d

15010350_20150112_000001.d: +MS

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
427.23395	78180848	C 23 H 31 N 4 O 4	100.00	427.23398	0.0	0.1	3.0	10.5	even	ok
449.21590	49347400	C 23 H 30 N 4 Na O 4	100.00	449.21593	0.0	0.1	8.8	10.5	even	ok
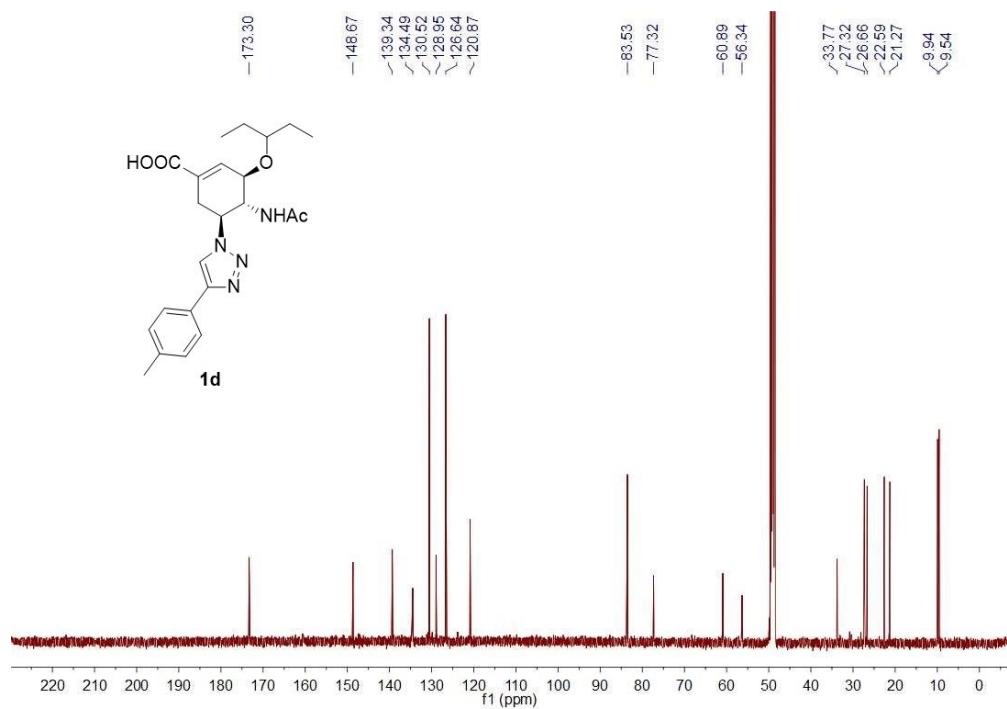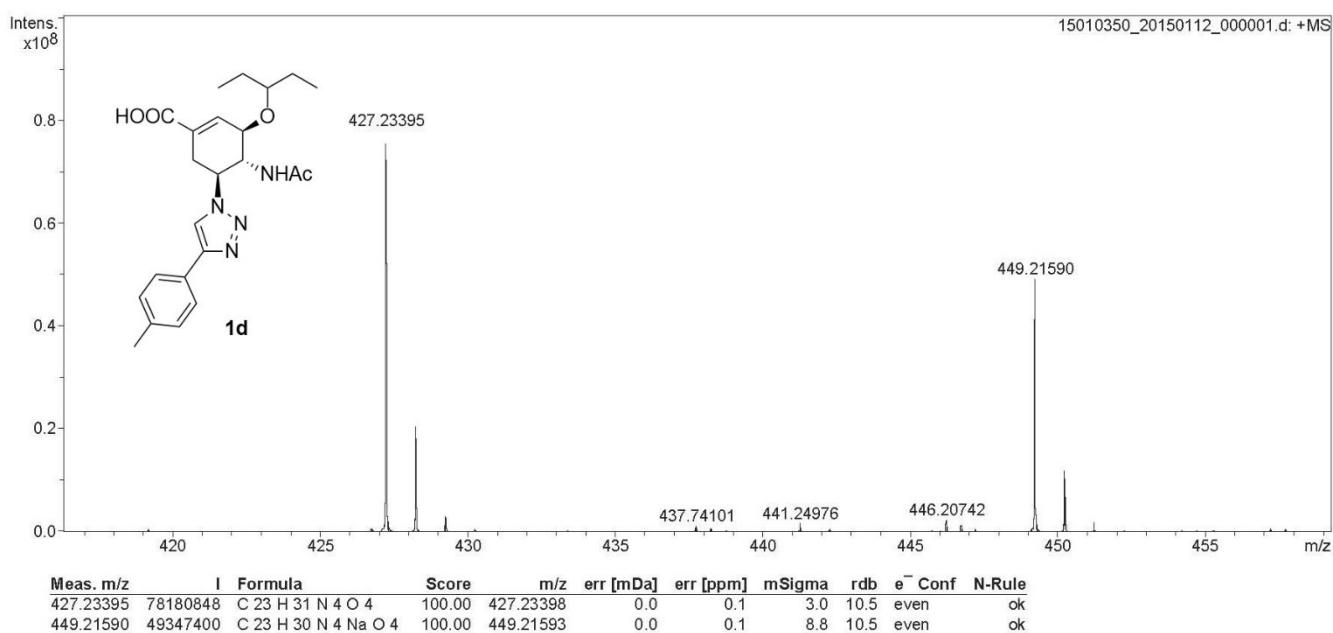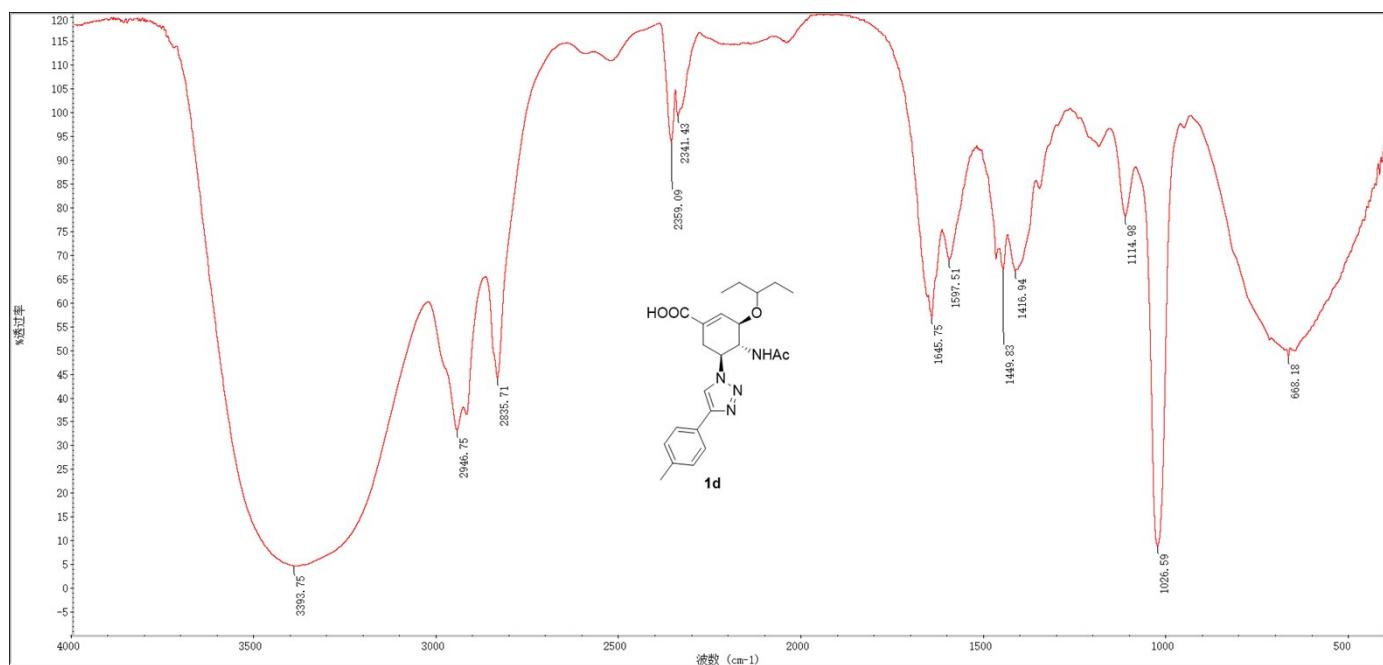
IR of 1d

^{1}H NMR of 1e (500 MHz, CD$_3$OD)
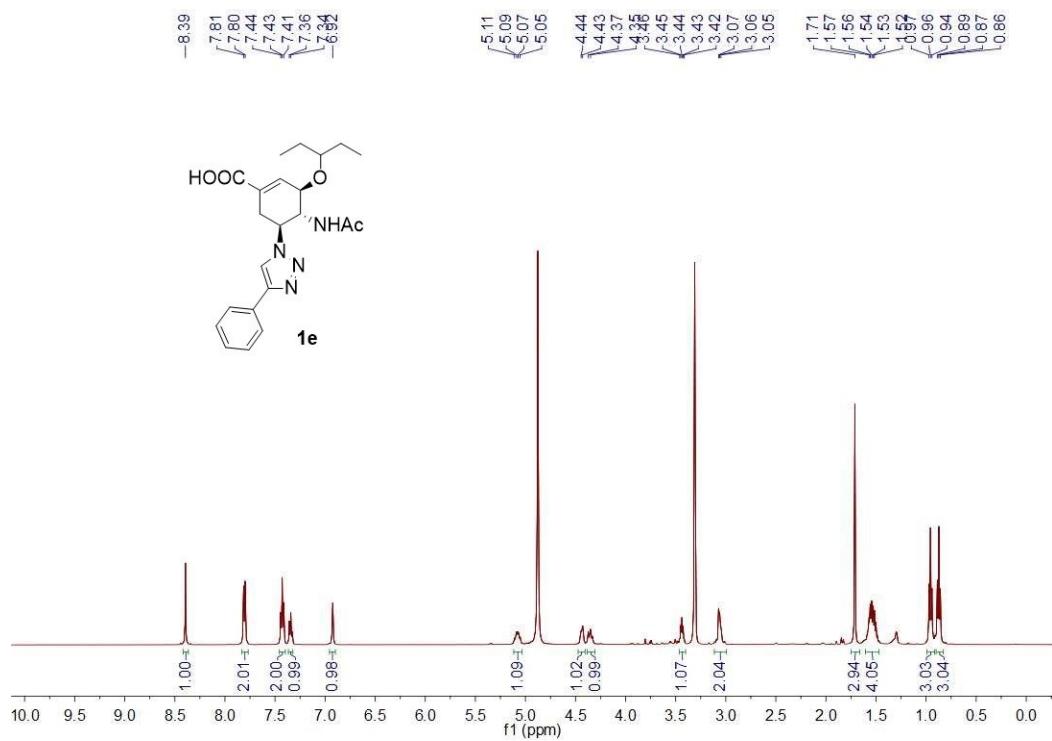
^{13}C NMR of 1e (500 MHz, CD$_3$OD)

HR-ESIMS of 1e

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
413.21785	61575136	C 22 H 29 N 4 O 4	100.00	413.21833	0.5	1.2	10.9	10.5	even	ok
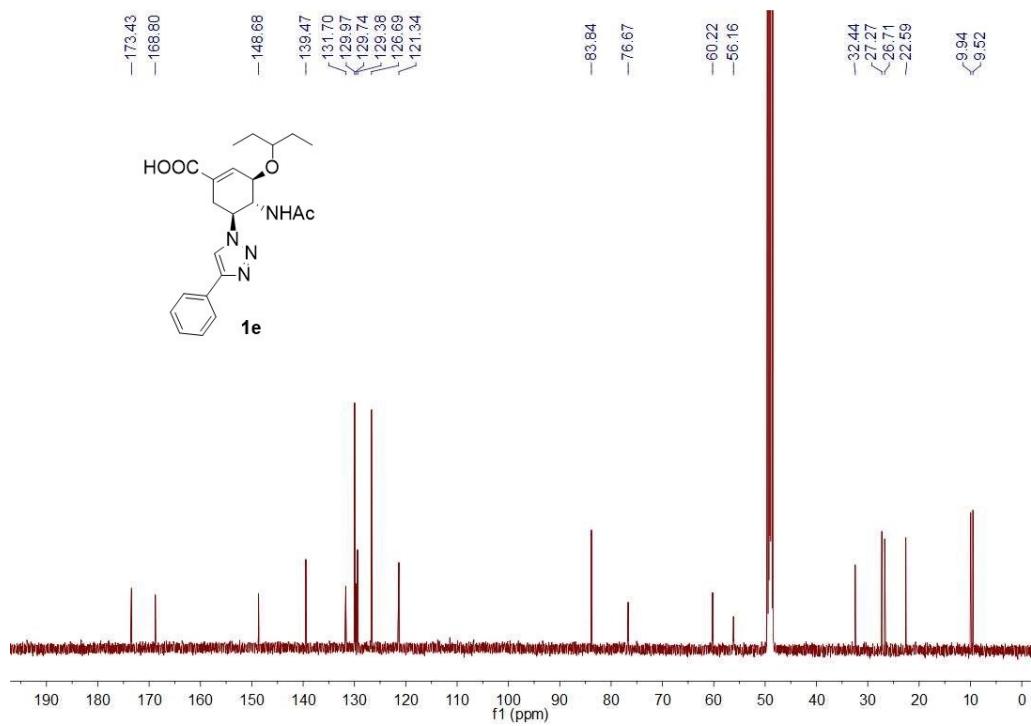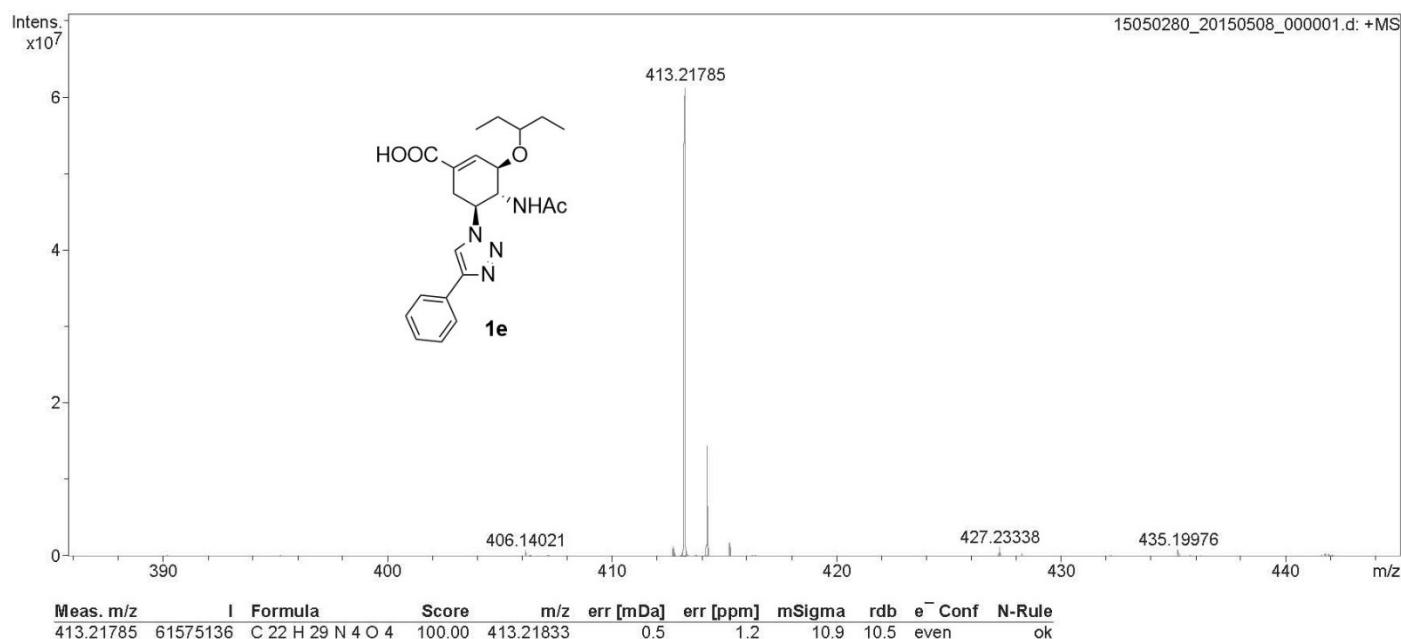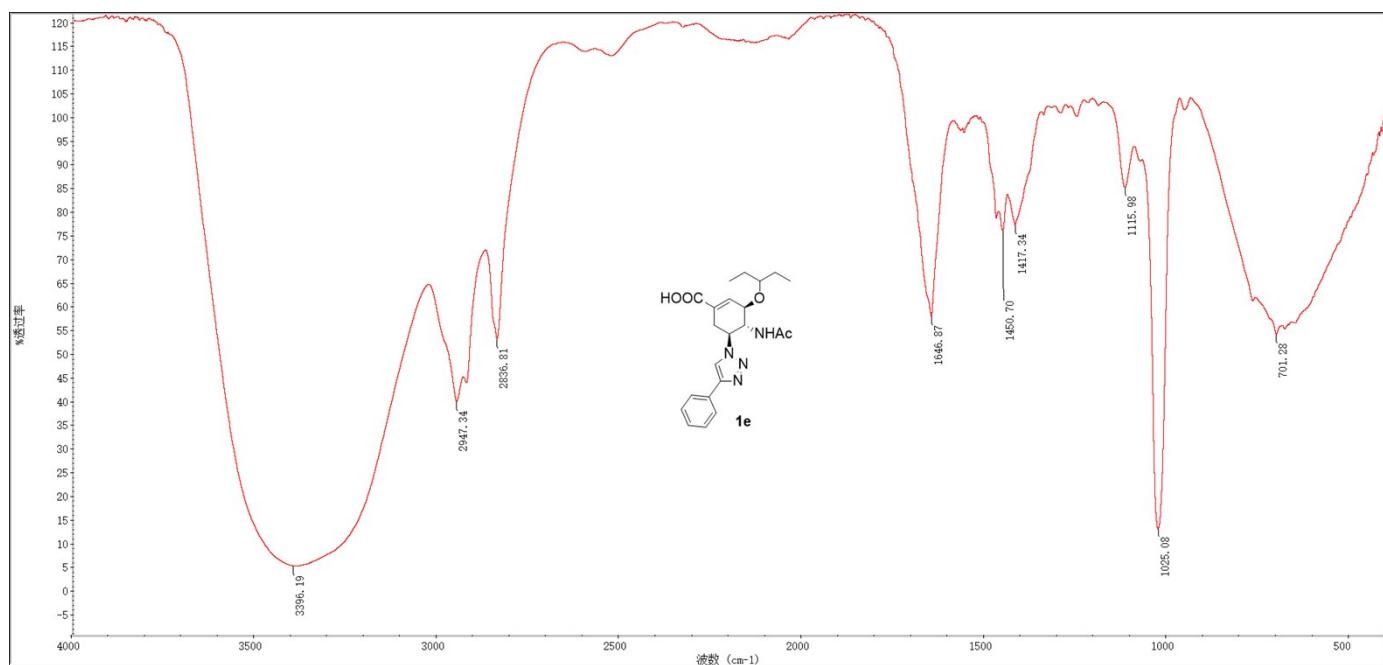
IR of 1e

¹H NMR of 1f (500 MHz, CD₃OD)
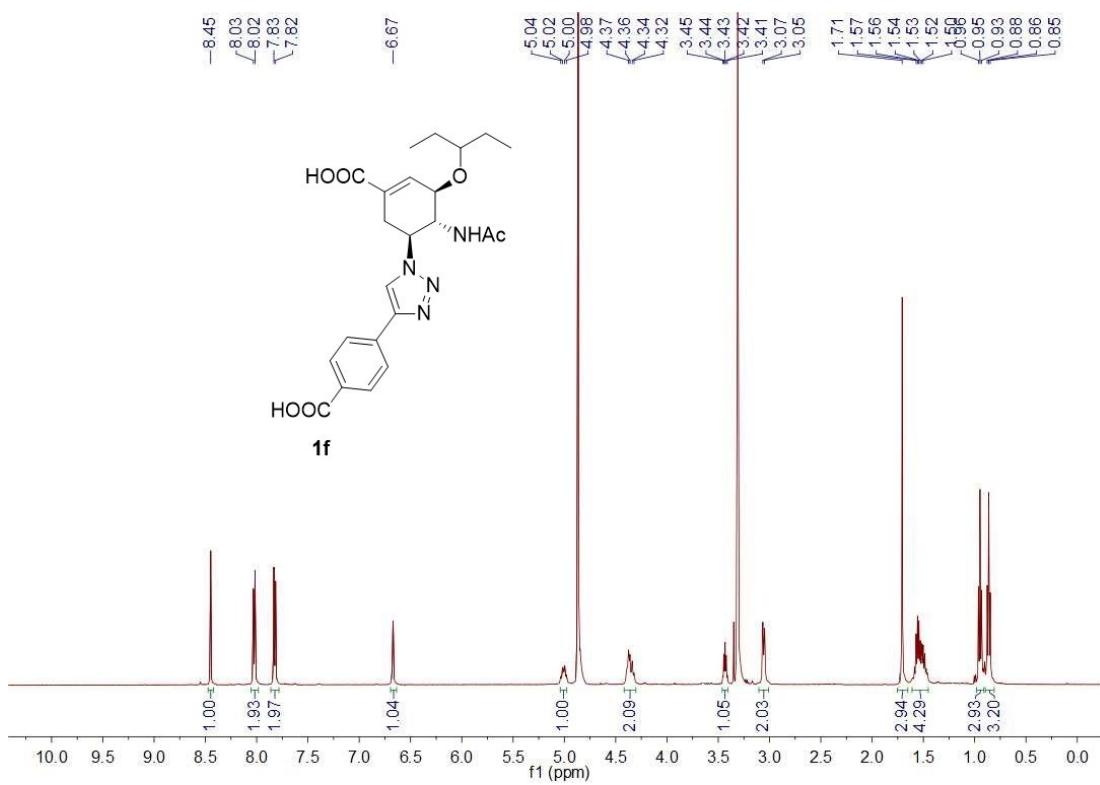

**¹³C NMR of 1f (500 MHz, CD₃OD)**

HR-ESIMS of 1f

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
457.20878	18827234	C 23 H 29 N 4 O 6	100.00	457.20816	-0.6	-1.4	6.6	11.5	even	ok
479.19037	68660808	C 23 H 28 N 4 Na O 6	100.00	479.19011	-0.3	-0.6	14.1	11.5	even	ok
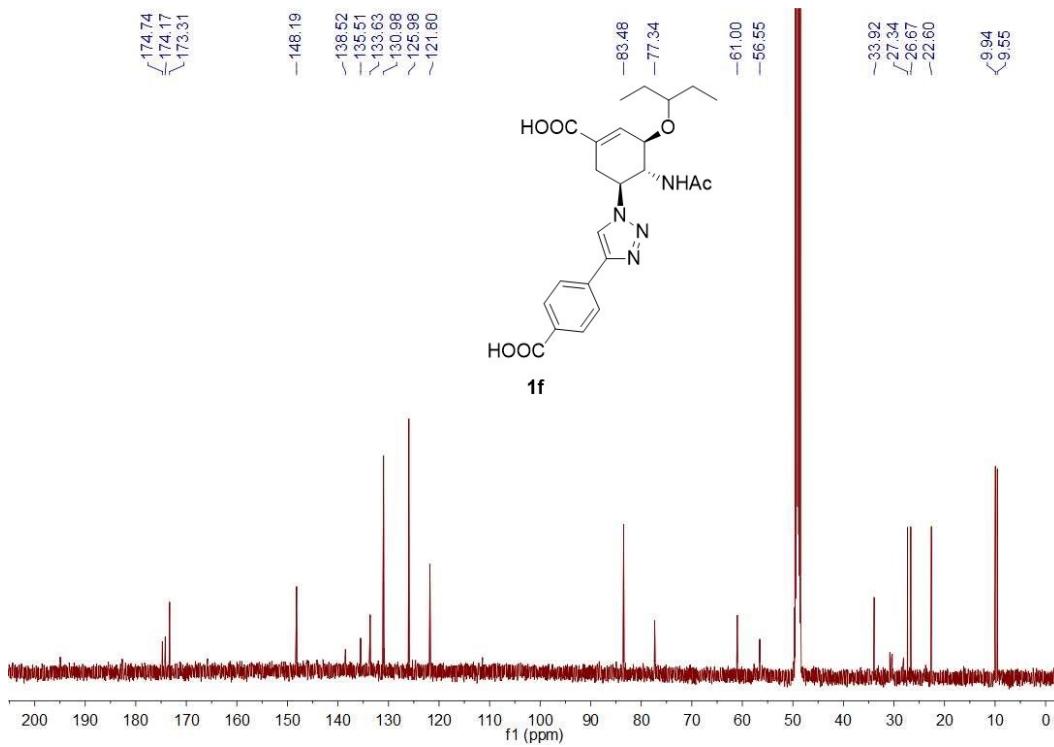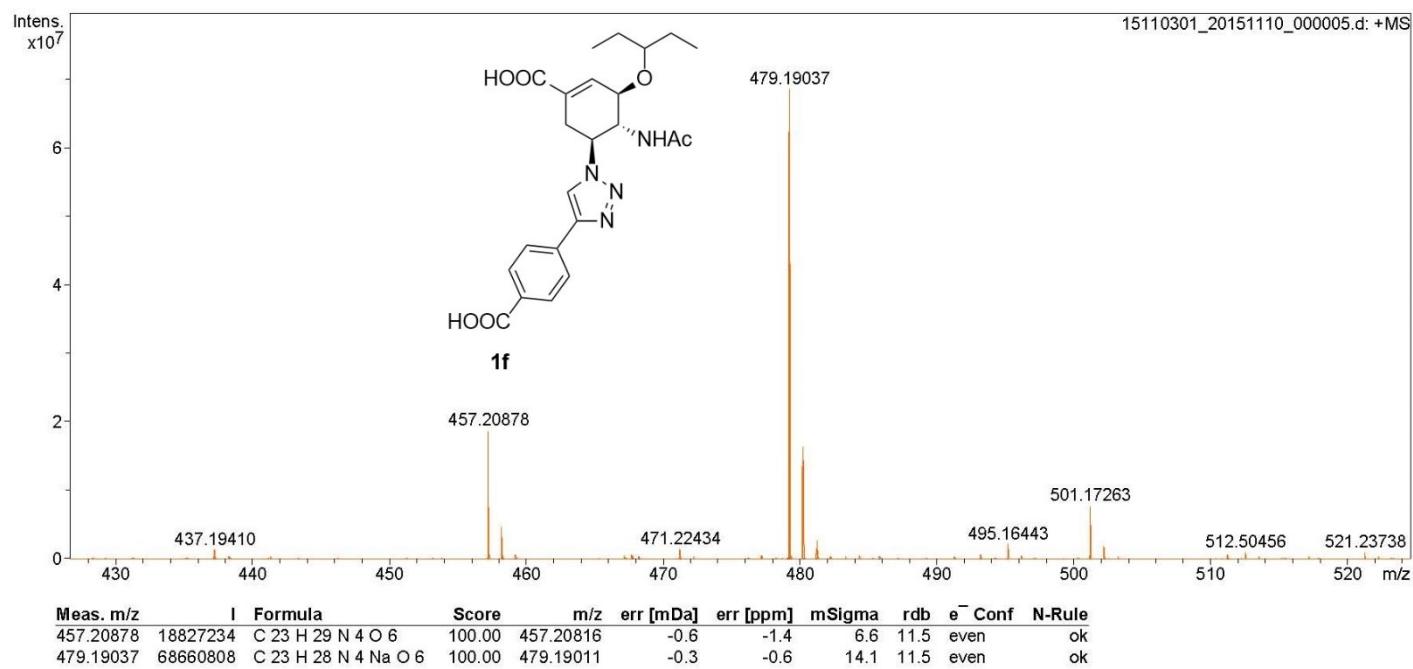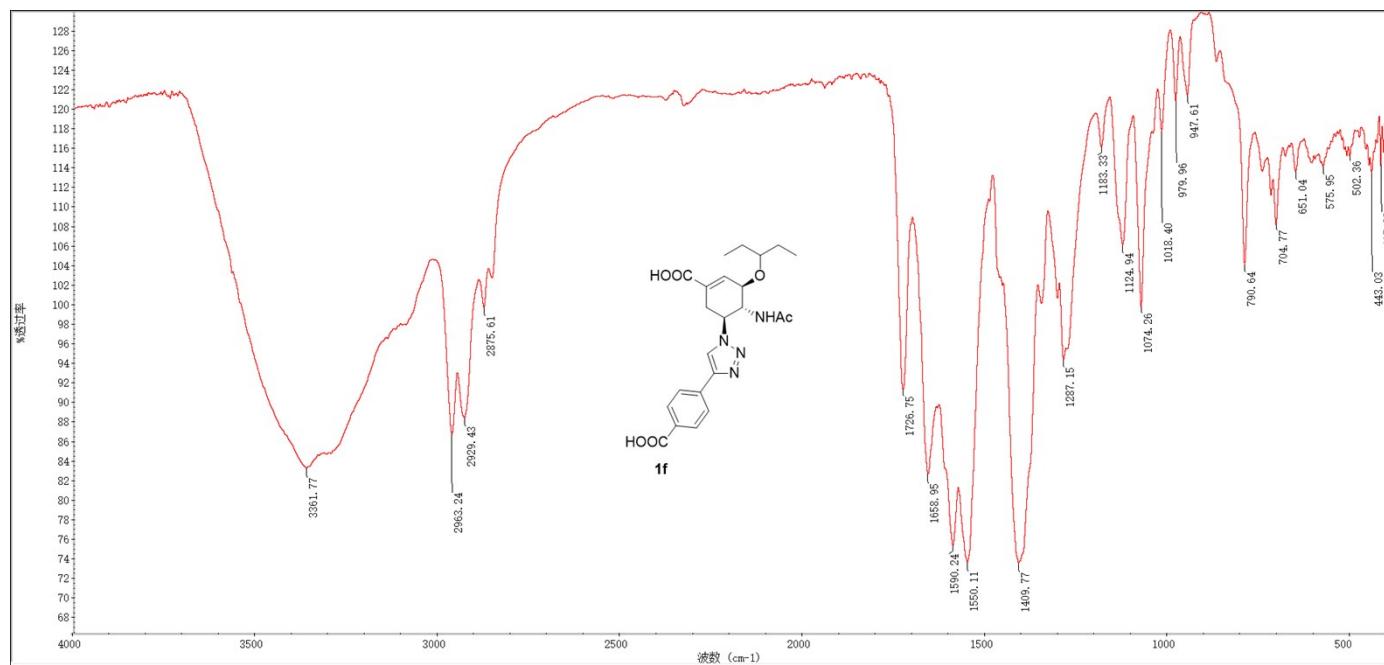
IR of 1f

^{1}H NMR of 1g (500 MHz, CD$_3$OD)
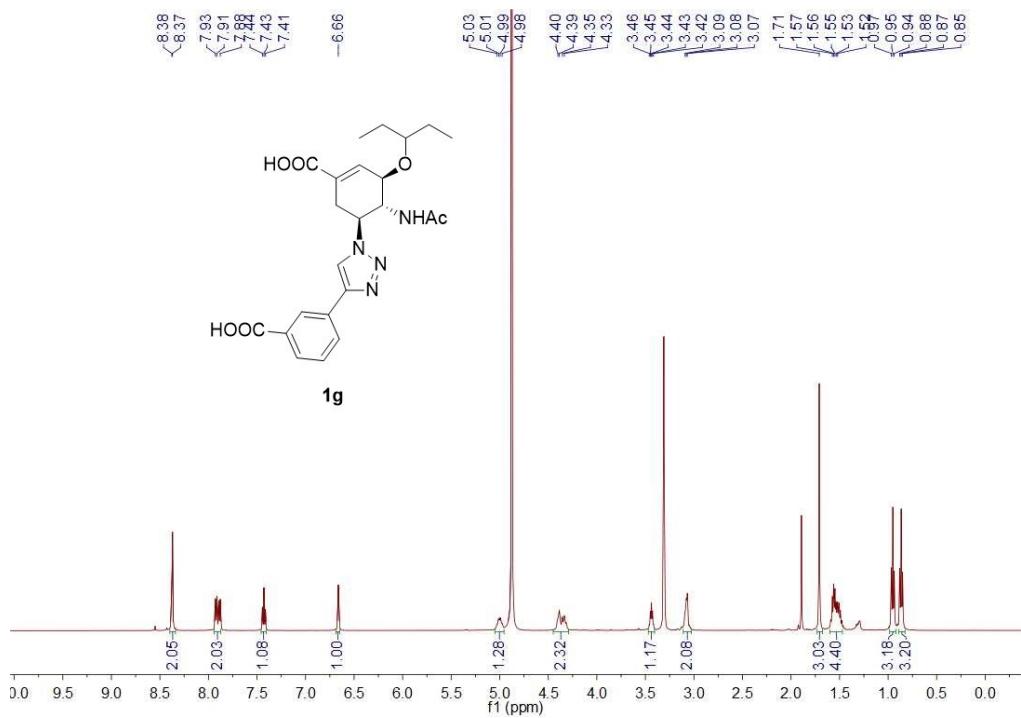
^{13}C NMR of 1g (500 MHz, CD$_3$OD)

HR-ESIMS of 1g

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
457.20916	53168828	C 23 H 29 N 4 O 6	100.00	457.20816	-1.0	-2.2	10.5	11.5	even	ok
479.19089	11656764	C 23 H 28 N 4 Na O 6	100.00	479.19011	-0.8	-1.6	19.8	11.5	even	ok
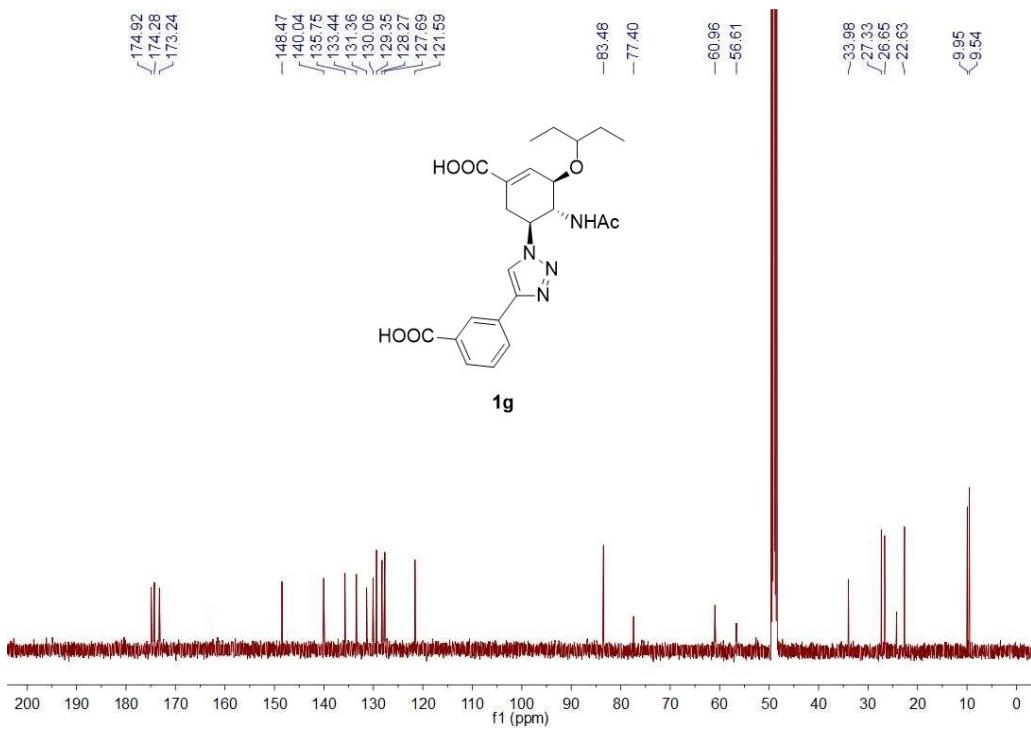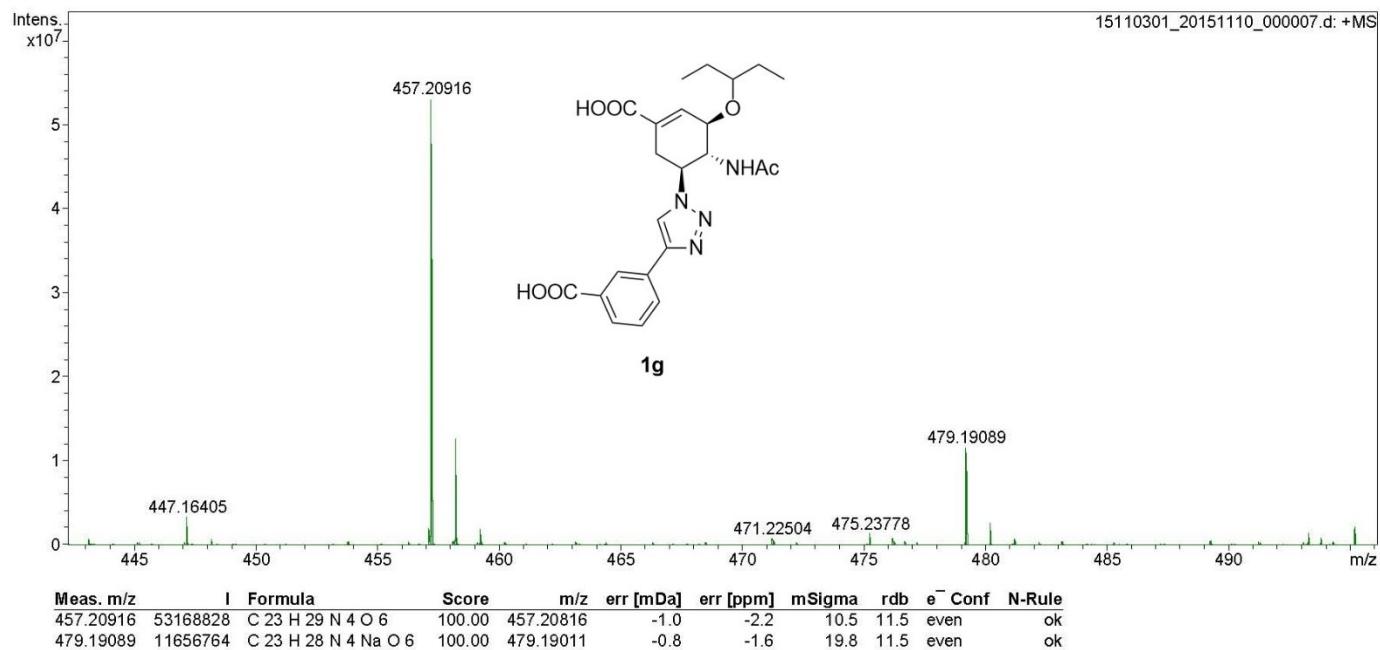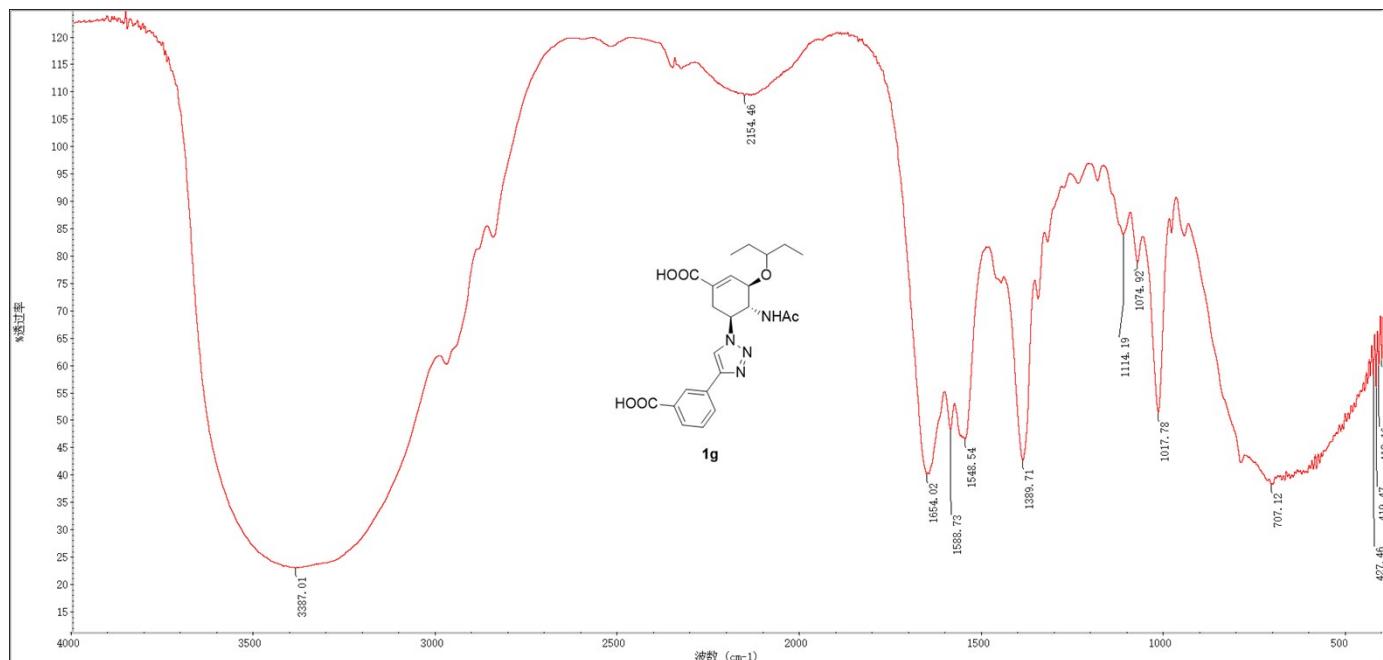
IR of 1g

^{1}H NMR of 1h (500 MHz, CD$_3$OD)
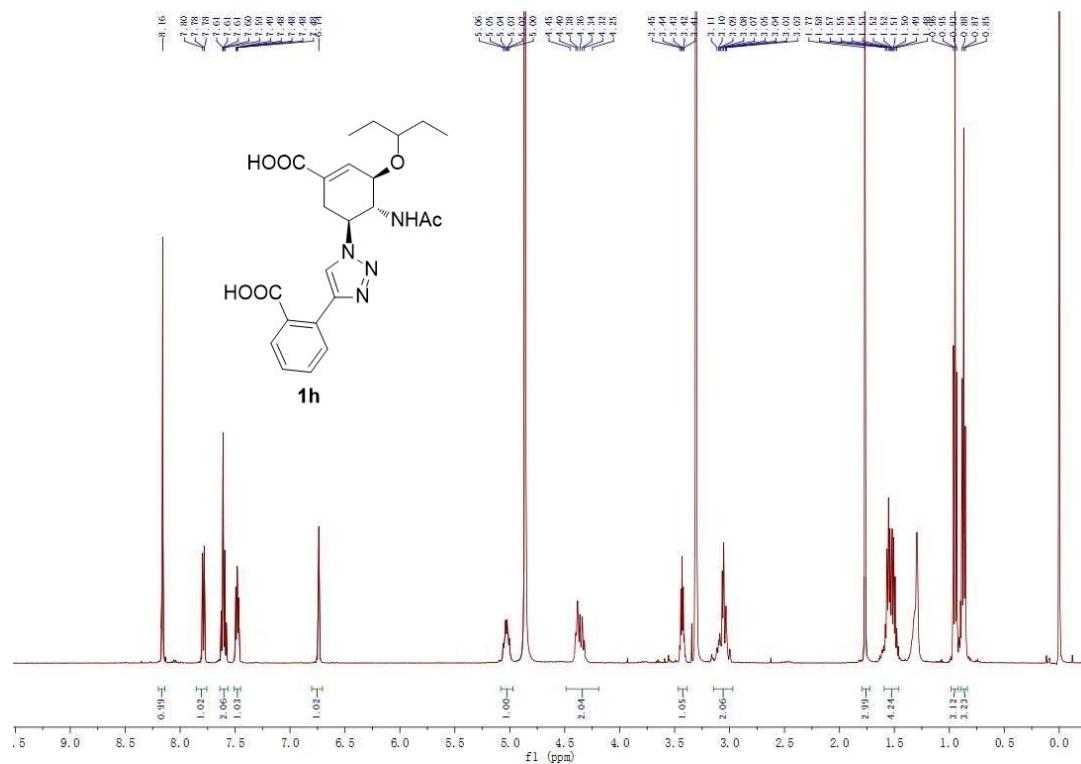
^{13}C NMR of 1h (500 MHz, CD$_3$OD)
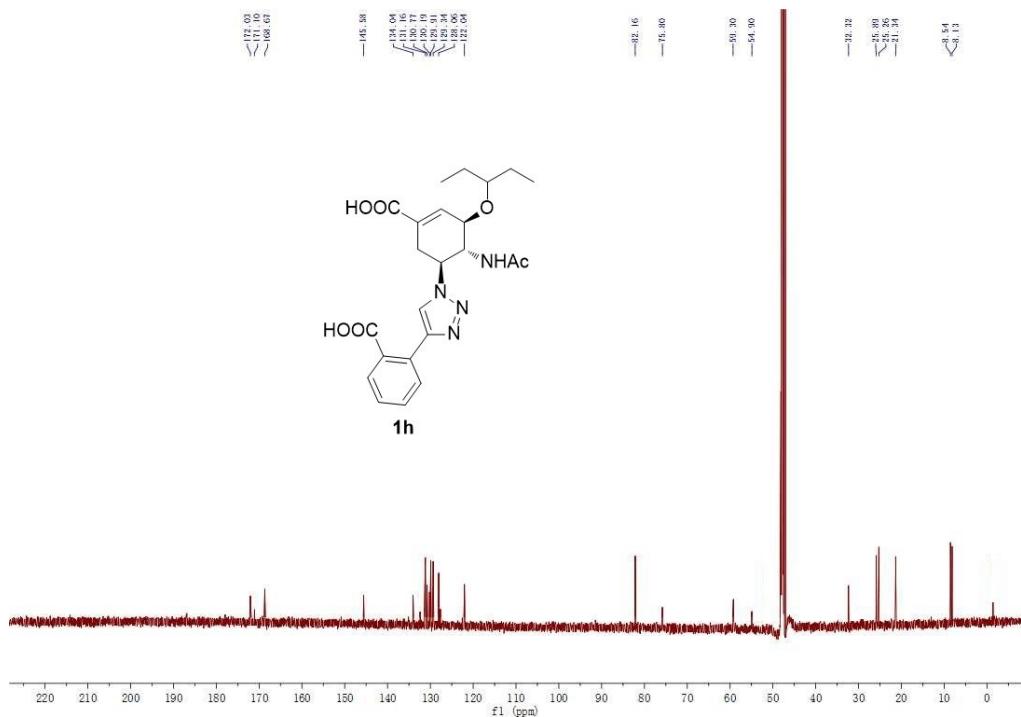
HR-ESIMS of 1h
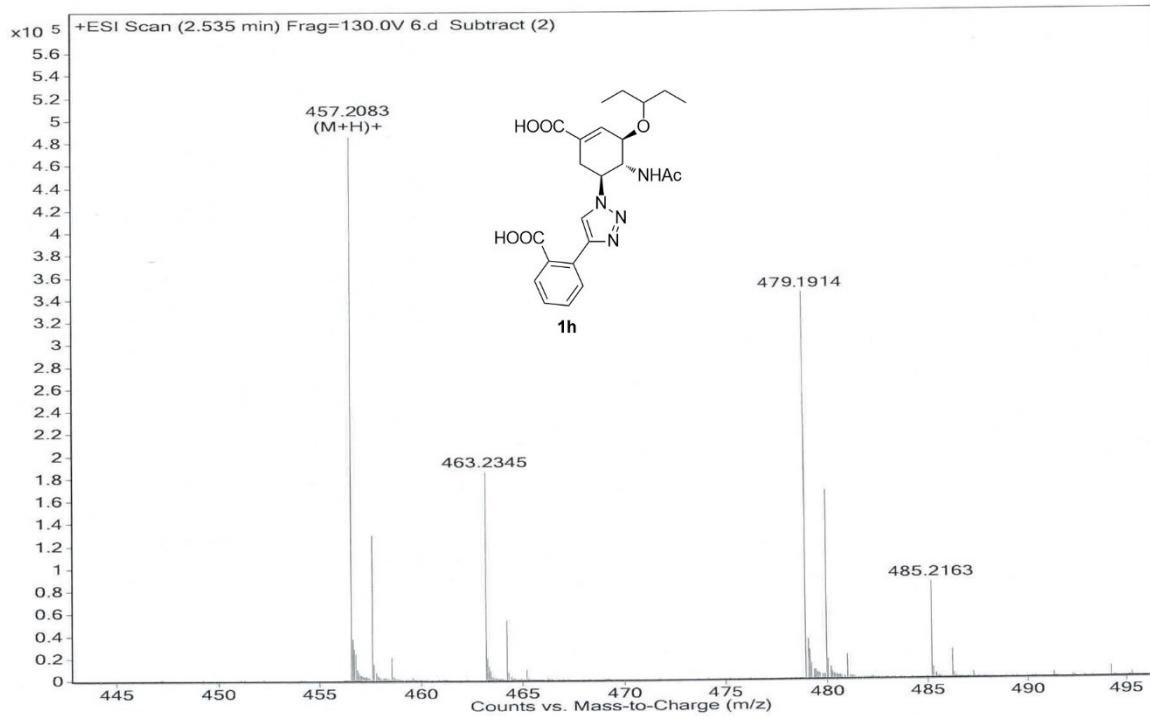
IR of 1h
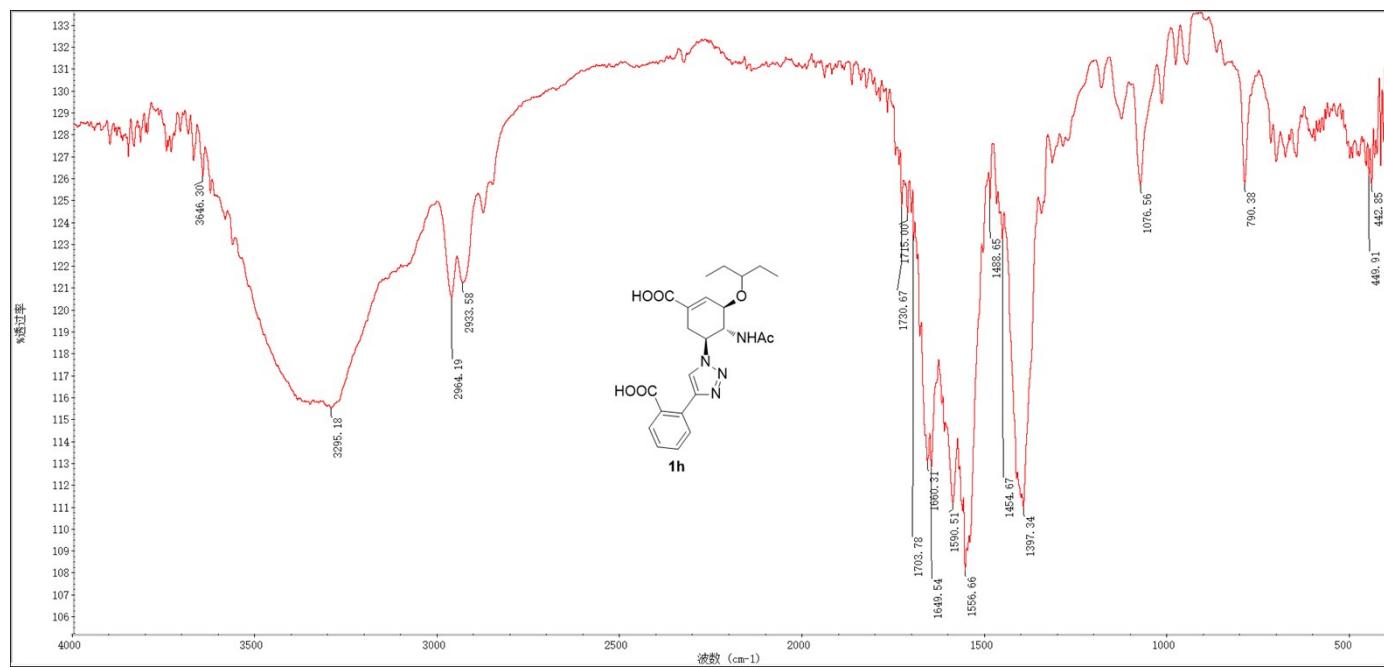
^{1}H NMR of 1i (500 MHz, CD$_3$OD)
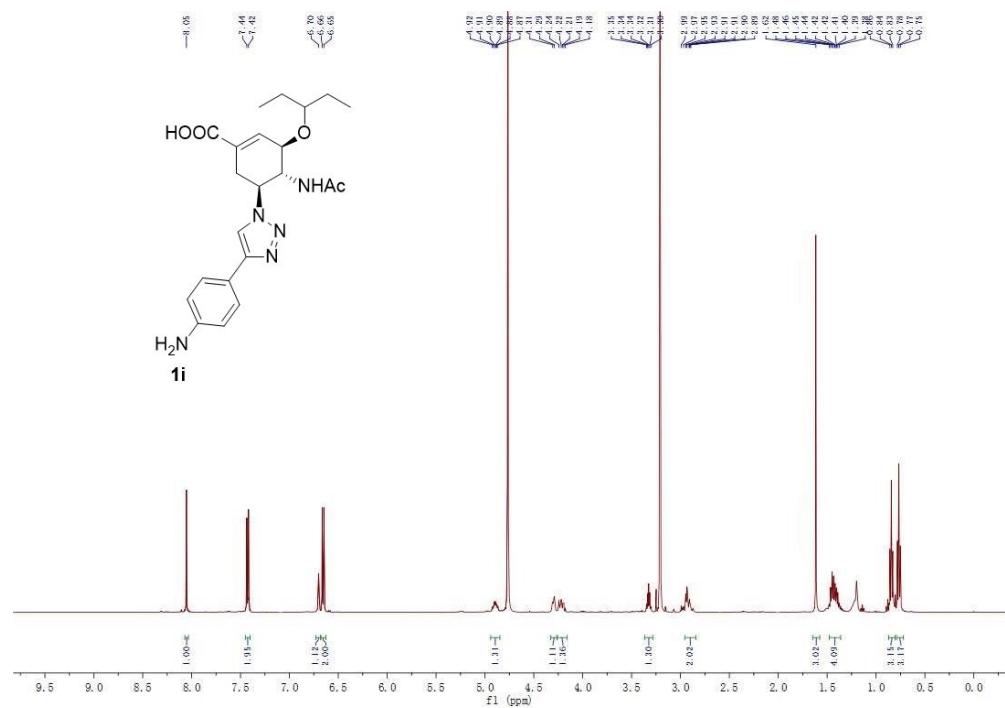
^{13}C NMR of 1i (500 MHz, CD$_3$OD)

HR-ESIMS of 1i

FTMS-19030364_Pos_20190328_000001.d: +MS

Meas. m/z	#	Ion Formula	Score	m/z	err [ppm]	Mean err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
428.229191	1	C22H30N5O4	100.00	428.229231	0.1	-1.0	15.1	11.0	even	ok
450.211363	1	C22H29N5NaO4	100.00	450.211175	-0.4	-1.5	15.4	11.0	even	ok
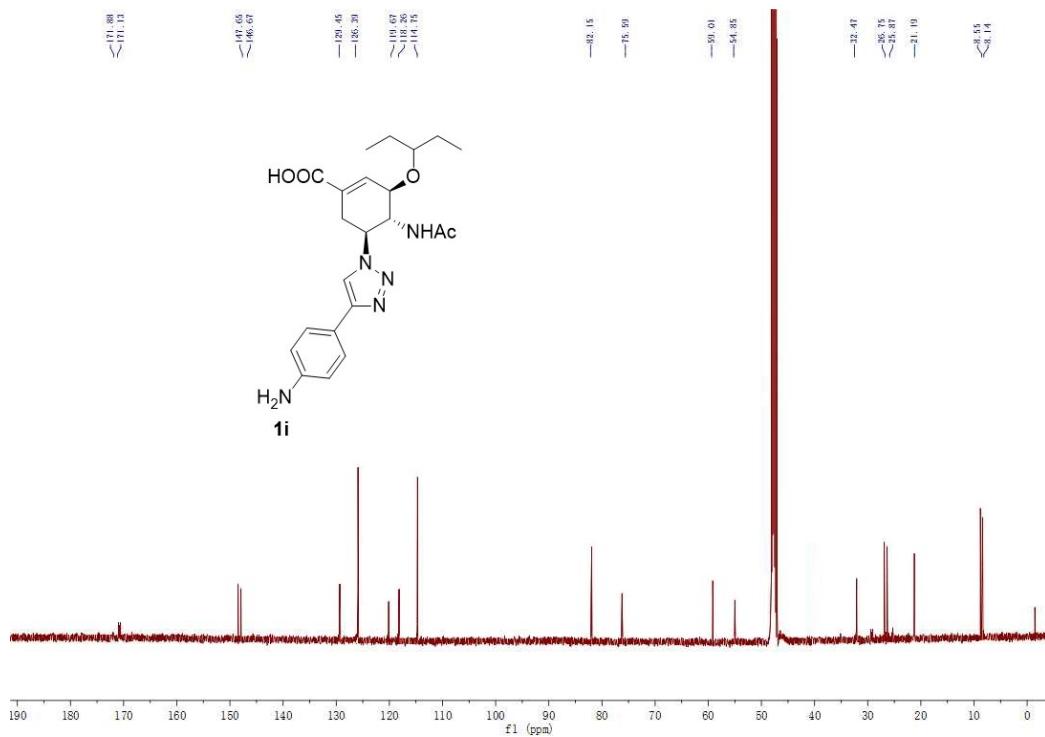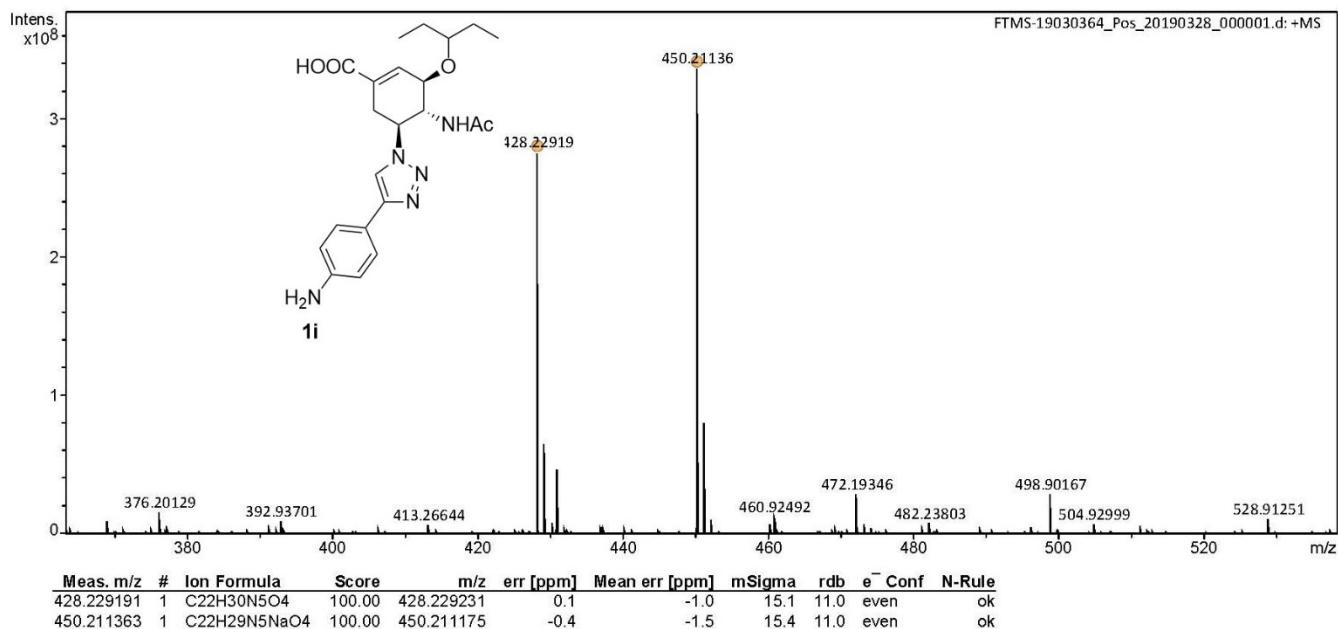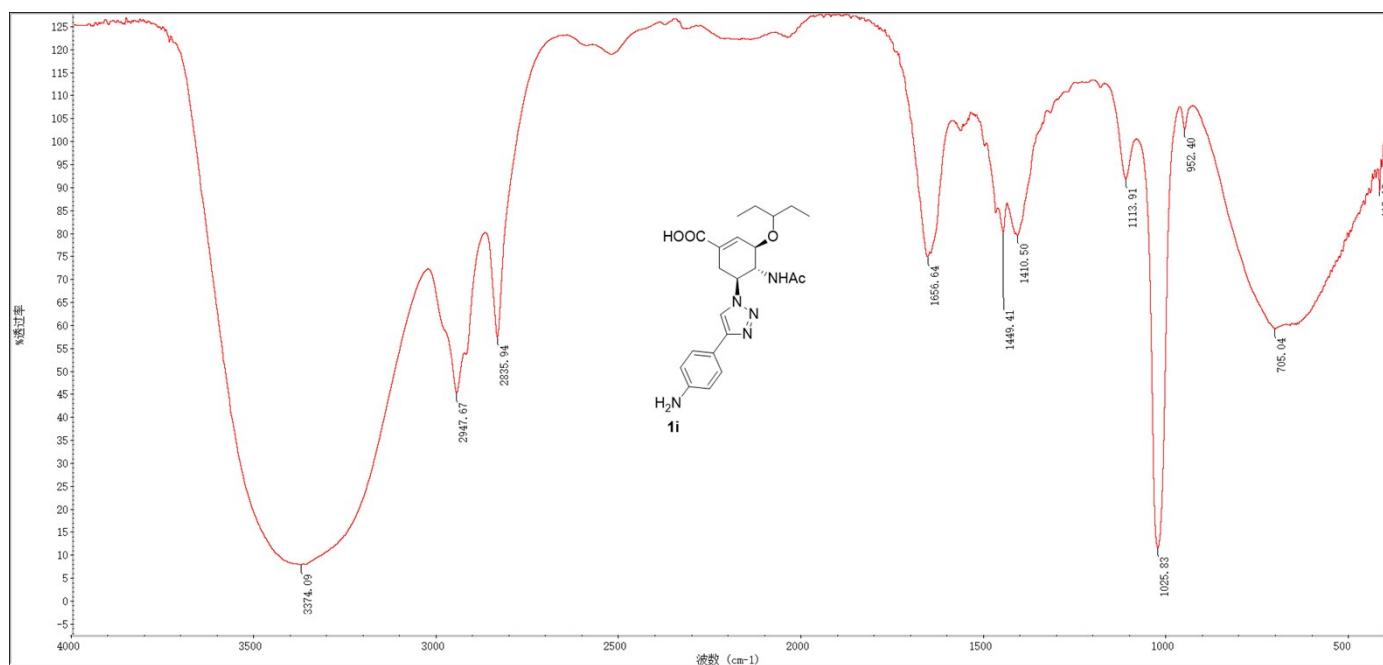
IR of 1i

^{1}H NMR of 1j (500 MHz, CD$_3$OD)
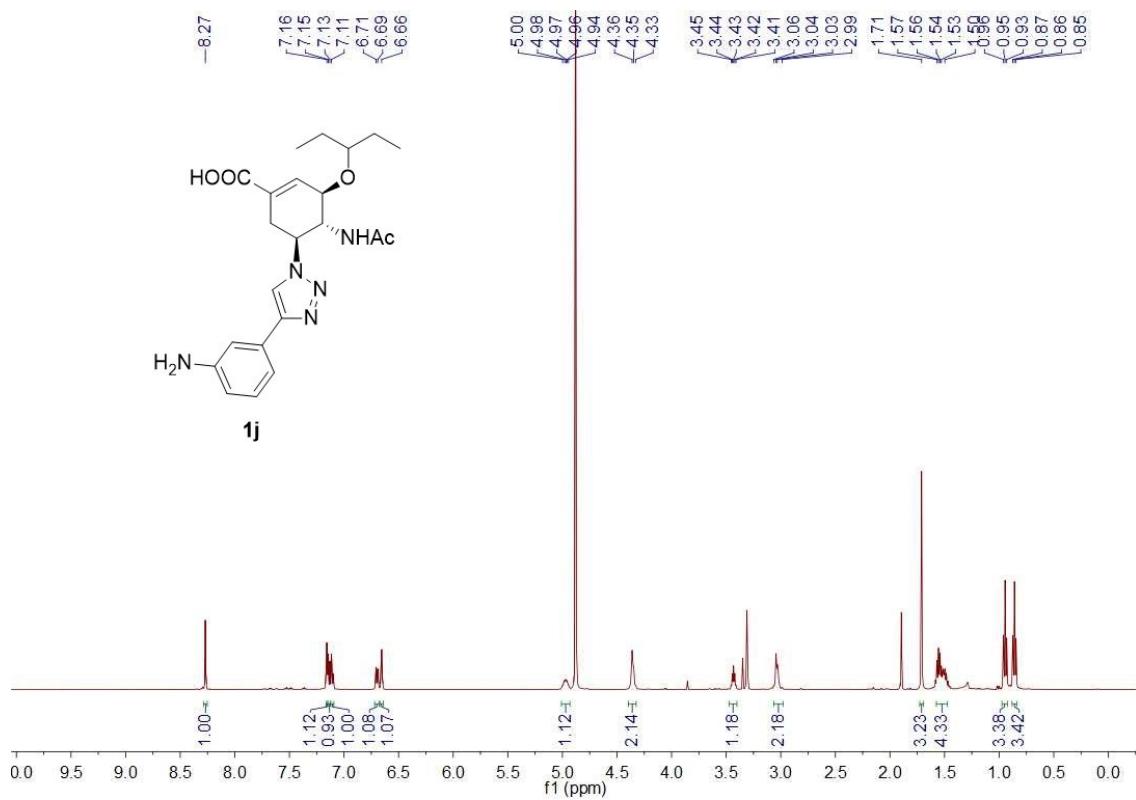
^{13}C NMR of 1j (500 MHz, CD$_3$OD)

HR-ESIMS of 1j

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
428.22947	2663501	C 22 H 30 N 5 O 4	100.00	428.22923	-0.2	-0.6	34.5	10.5	even	ok
450.21159	1268105	C 22 H 29 N 5 Na O 4	100.00	450.21118	-0.4	-0.9	45.1	10.5	even	ok
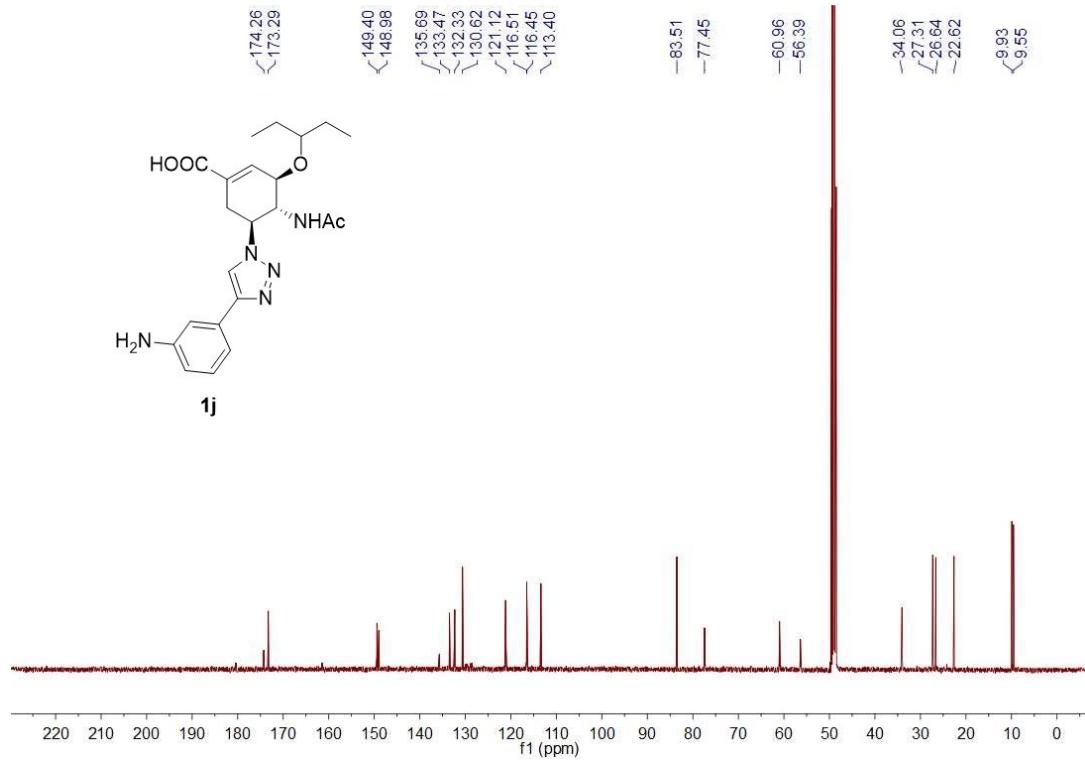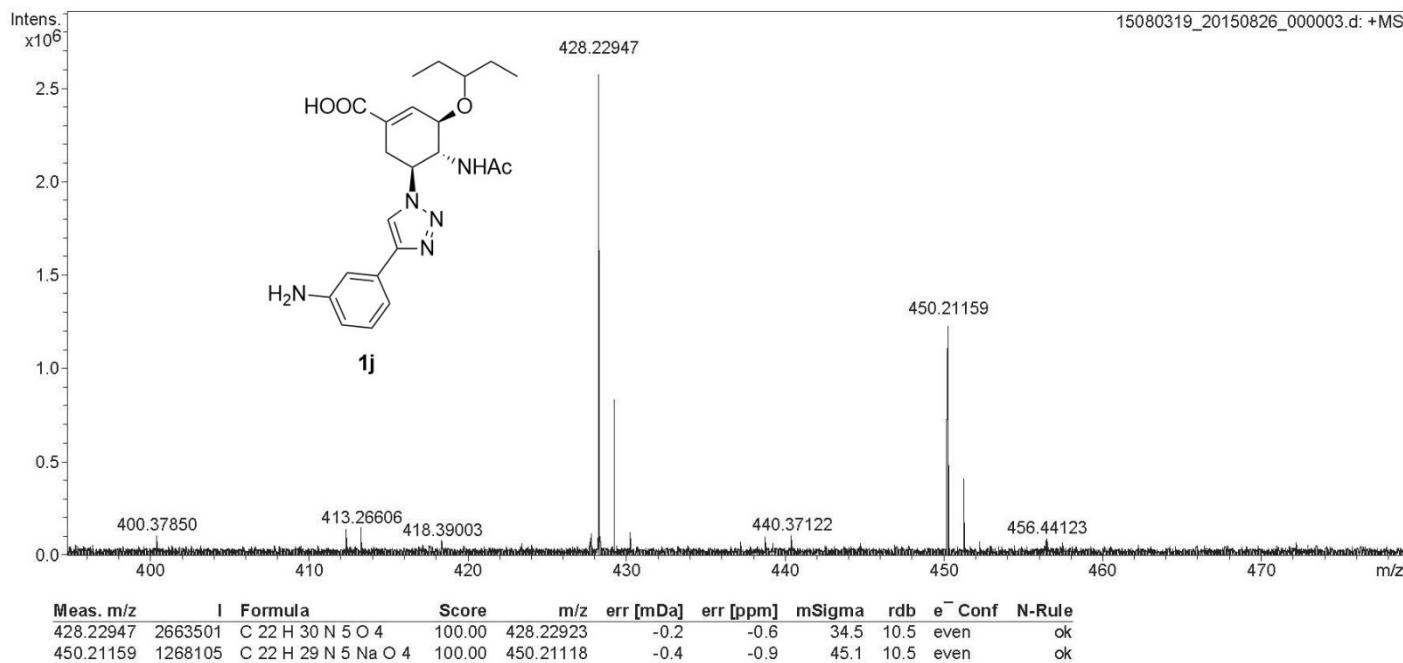
IR of 1j

¹H NMR of 1k (500 MHz, CD₃OD)
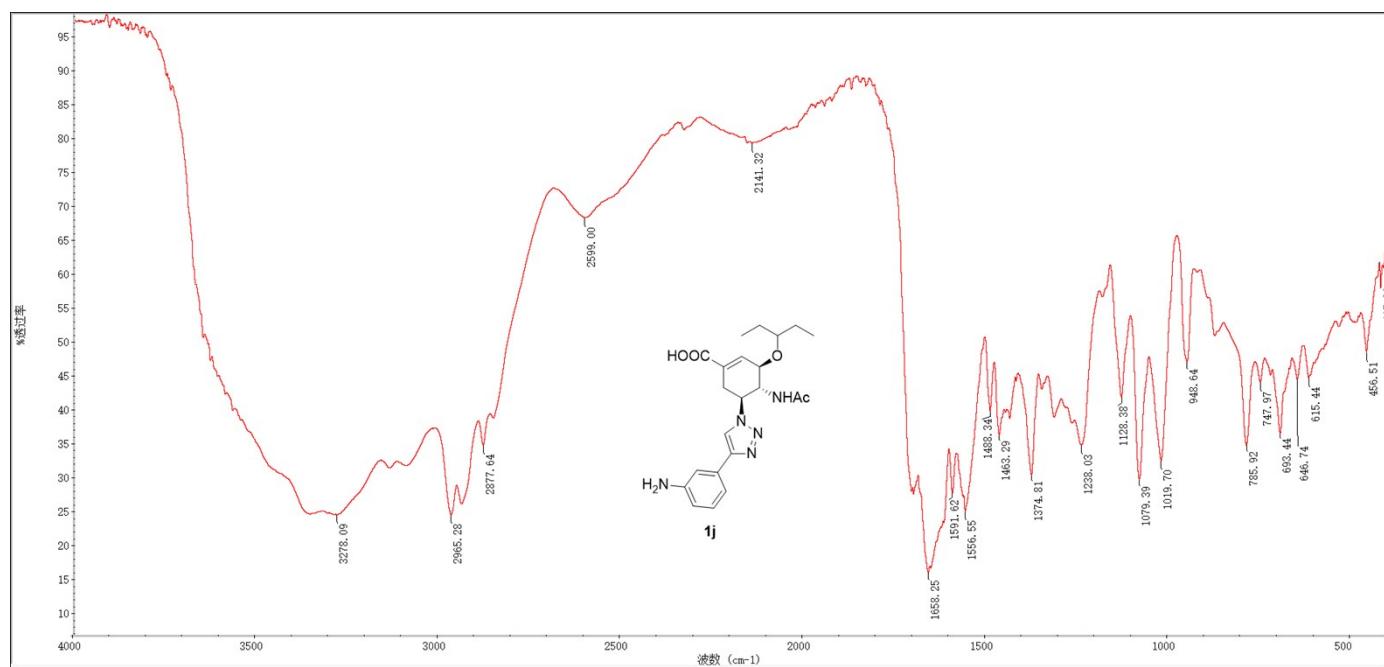
^{1}H NMR of 1k (500 MHz, CD$_3$OD)
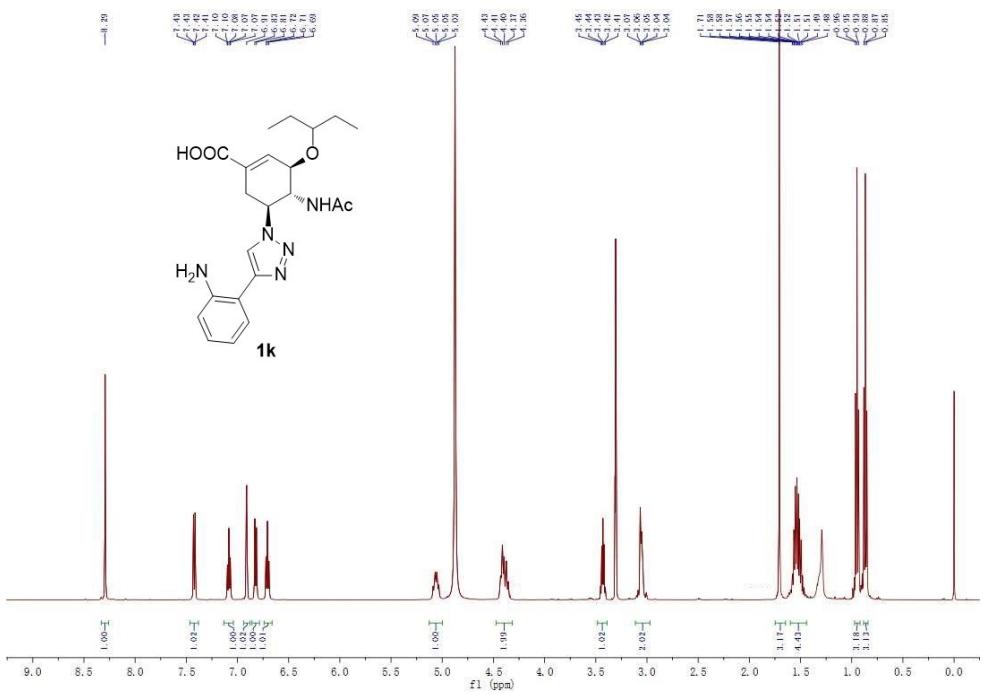
^{13}C NMR of 1k (500 MHz, CD$_3$OD)
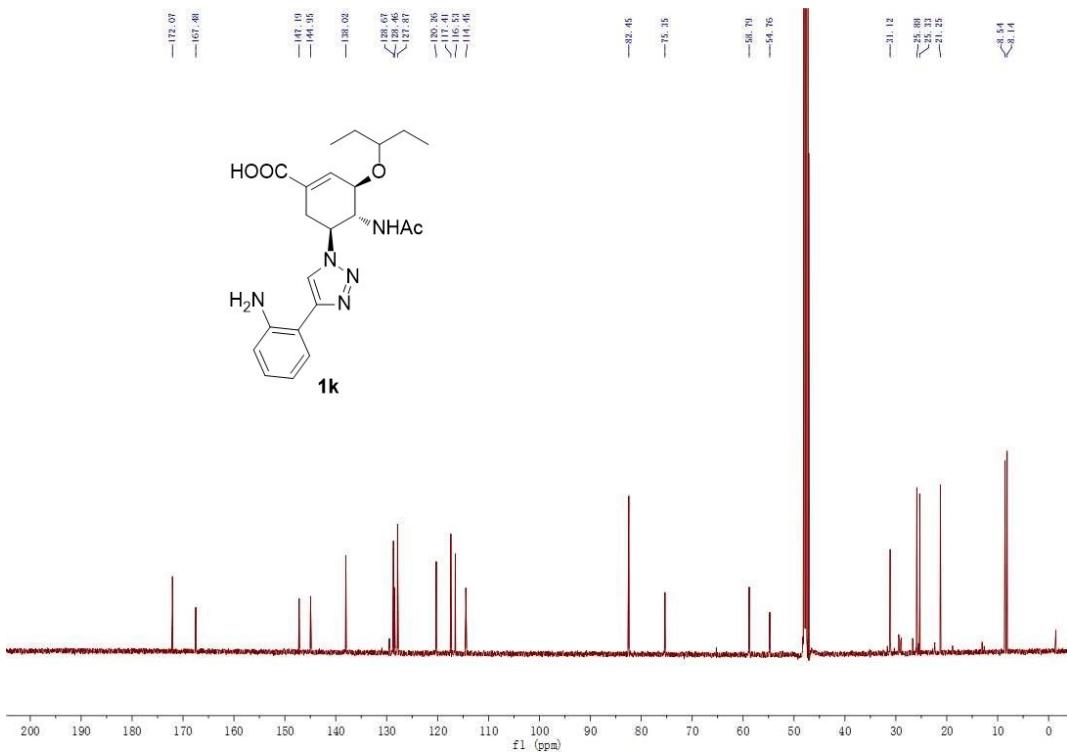
HR-ESIMS of 1k
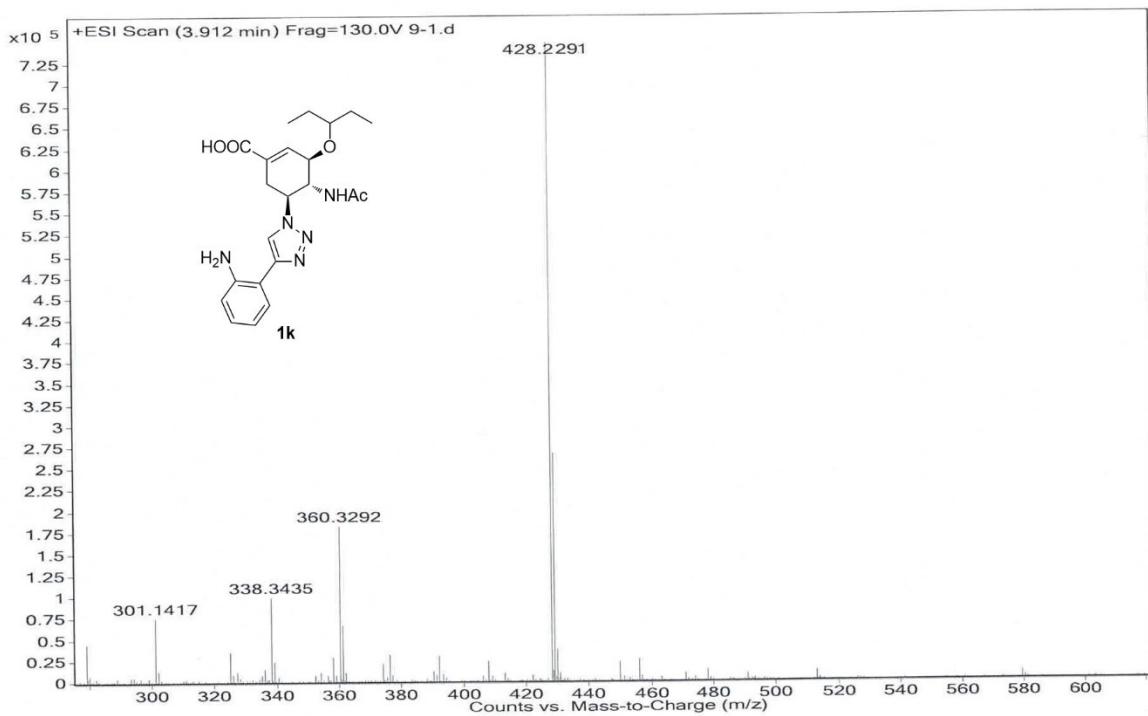
IR of 1k
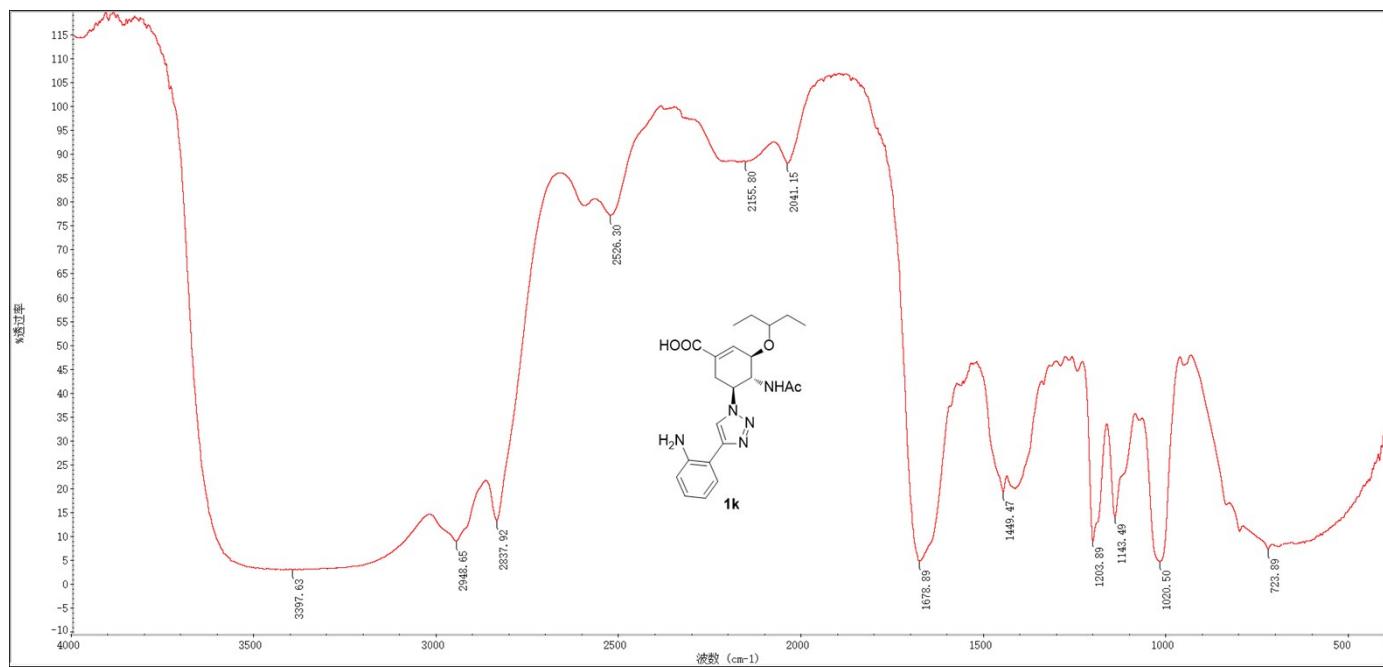
¹H NMR of 1l (500 MHz, CD₃OD)
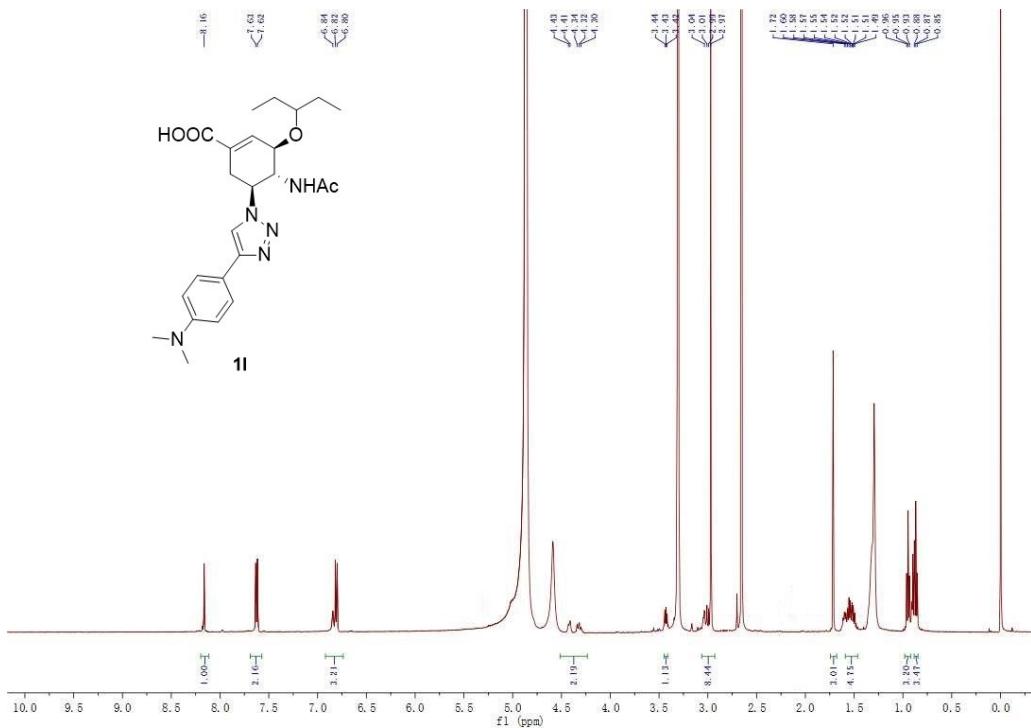
¹³C NMR of 1l (500 MHz, CD₃OD)
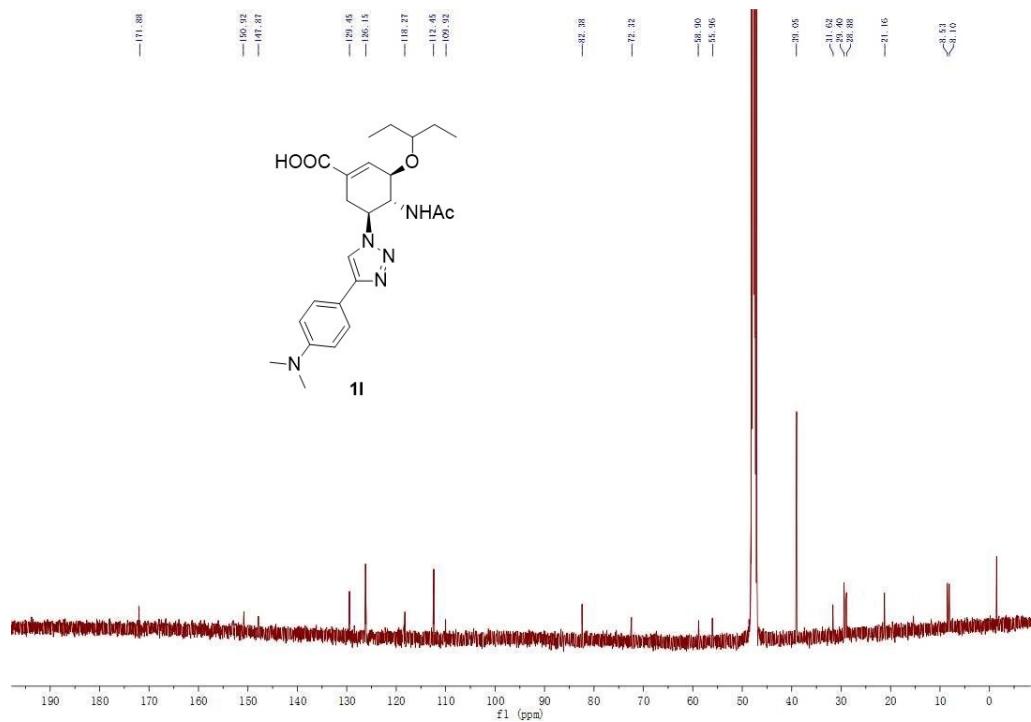
HR-ESIMS of 1l
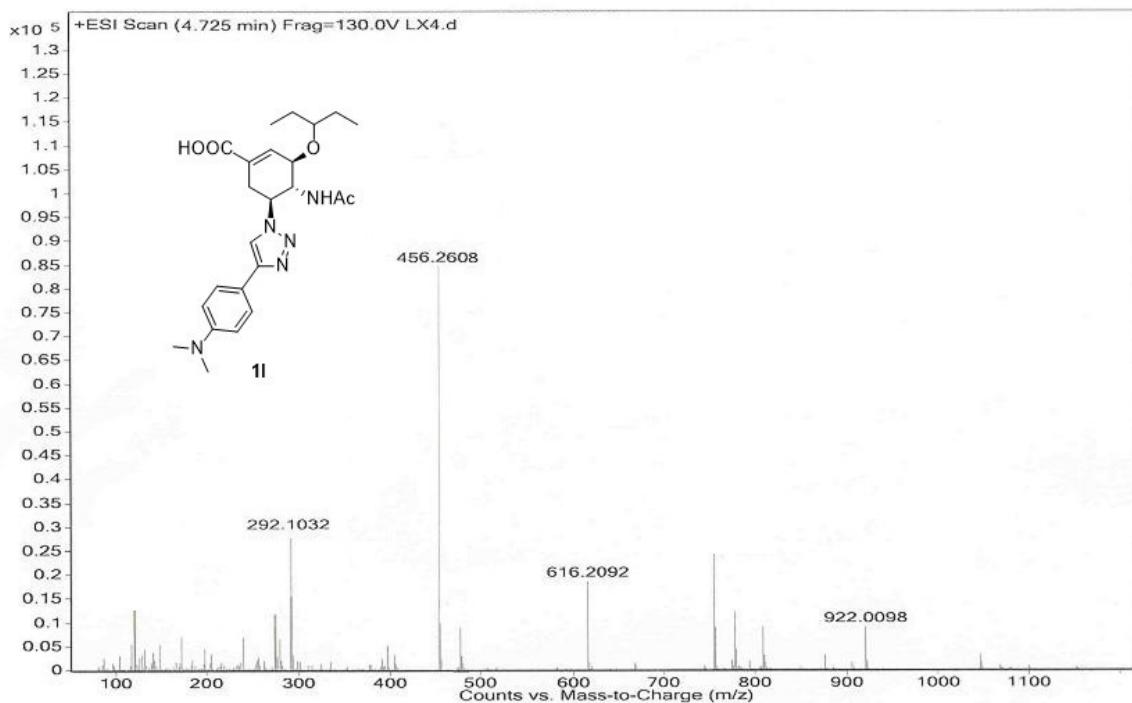
IR of 1l
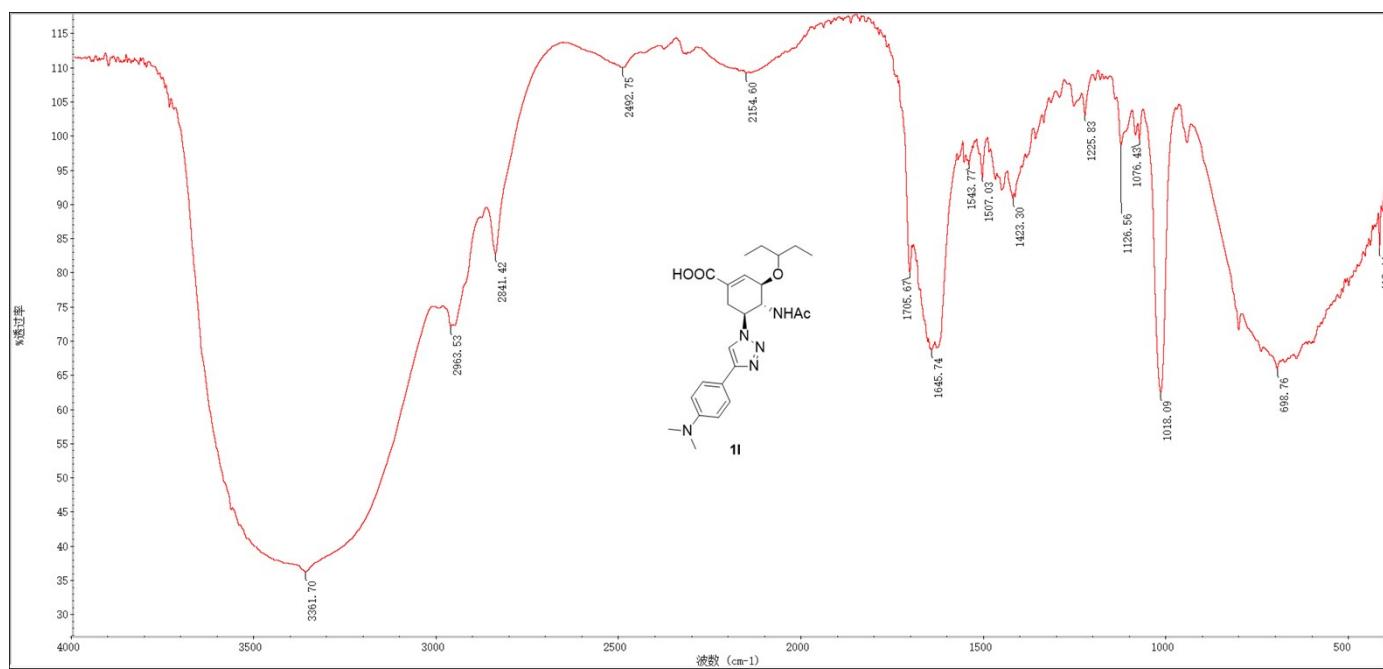
¹H NMR of 1m (500 MHz, CD₃OD)
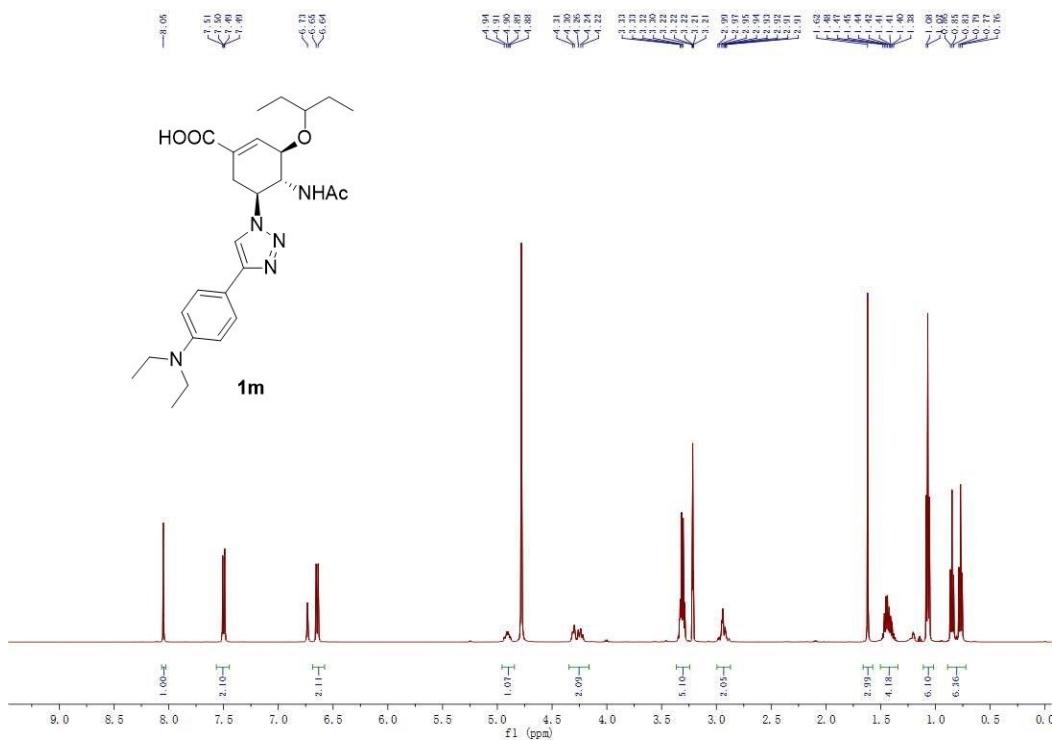
¹³C NMR of 1m (500 MHz, CD₃OD)
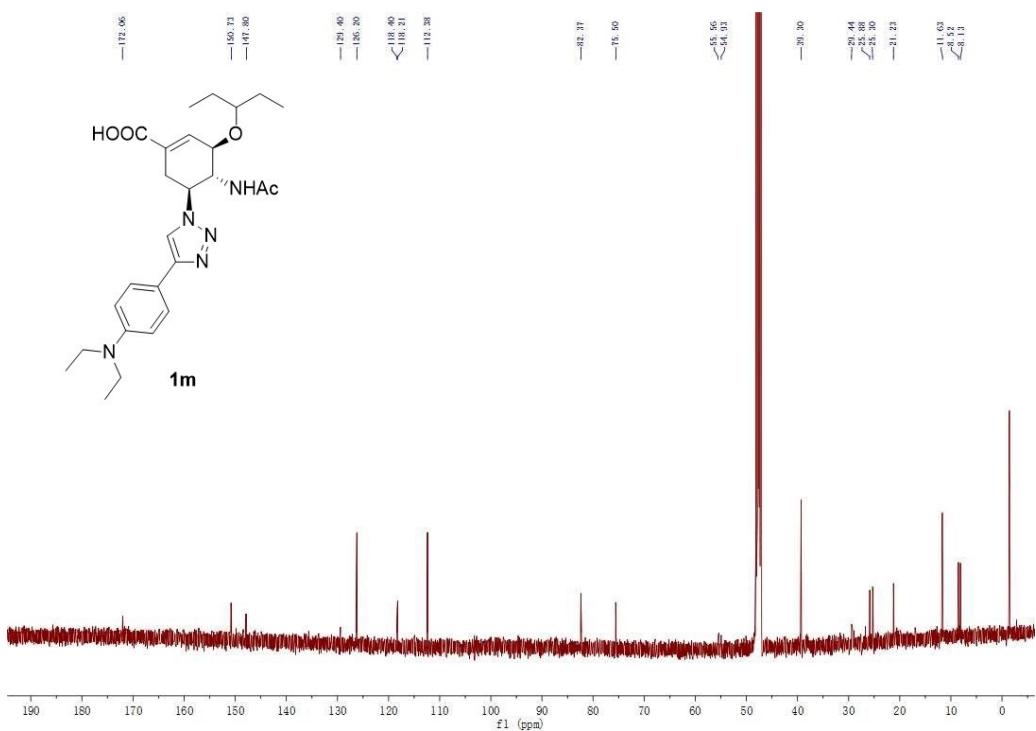
HR-ESIMS of 1m
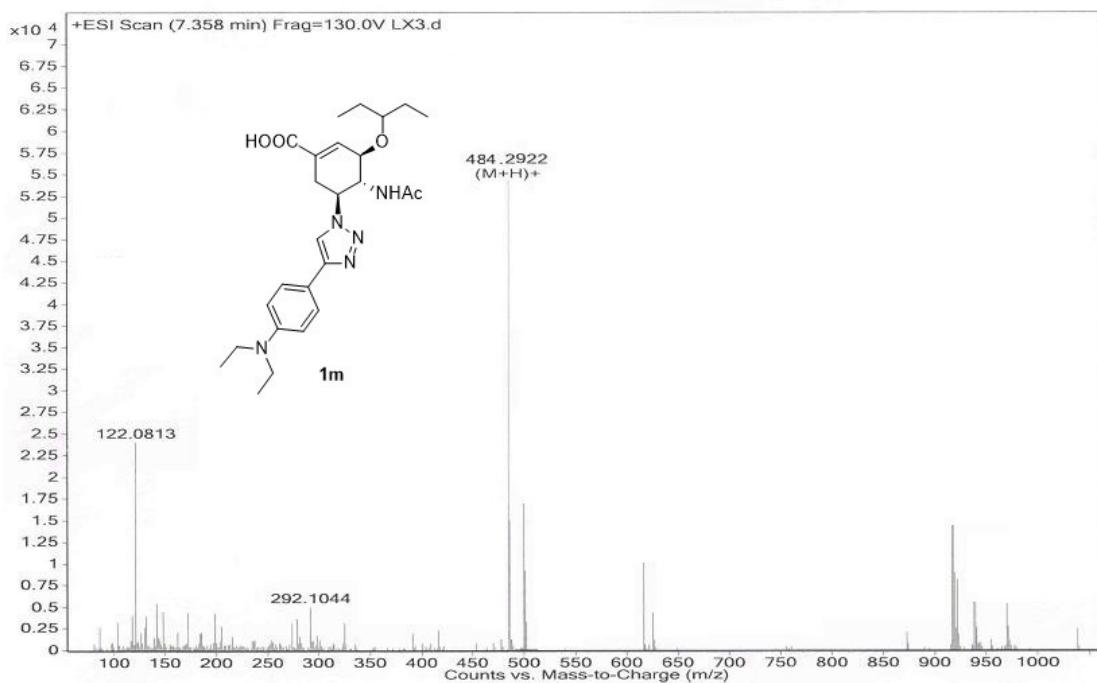
IR of 1m
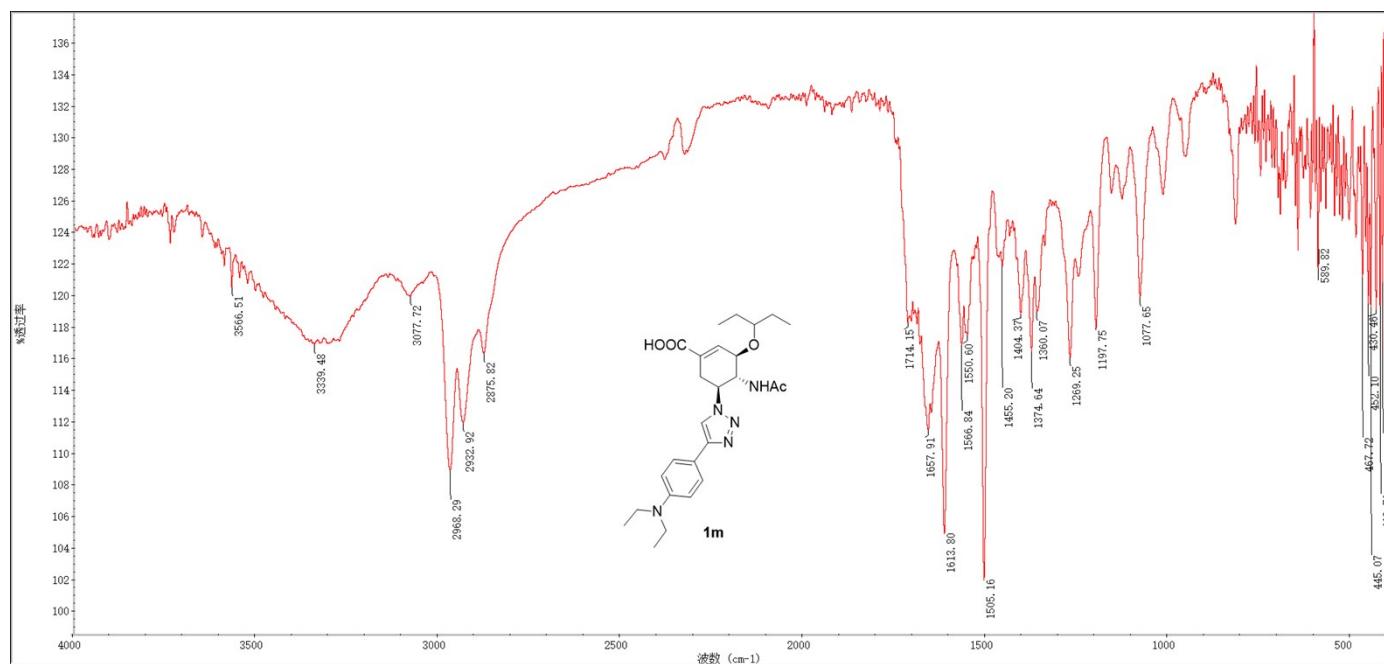
^{1}H NMR of 1n (500 MHz, CD$_3$OD)
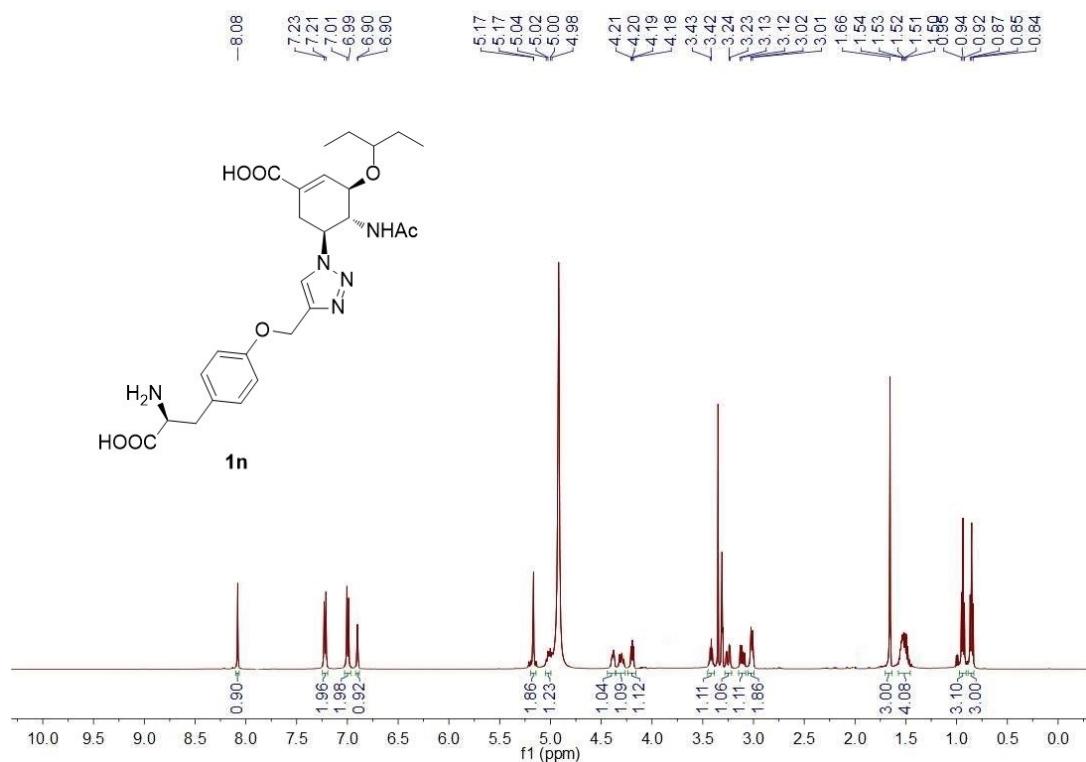
^{13}C NMR of 1n (500 MHz, CD$_3$OD)

HR-ESIMS of 1n

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
530.26065	19968246	C 26 H 36 N 5 O 7	100.00	530.26092	0.3	0.5	10.8	11.5	even	ok
552.24248	18906580	C 26 H 35 N 5 Na O 7	100.00	552.24287	0.4	0.7	20.5	11.5	even	ok
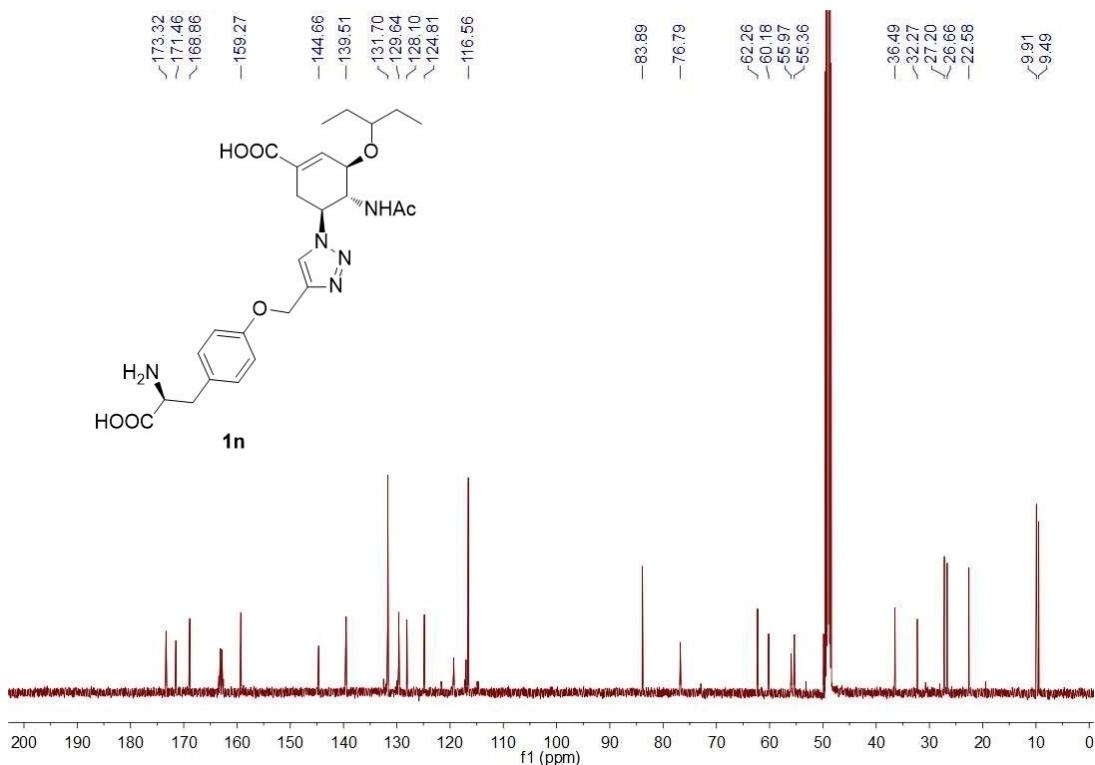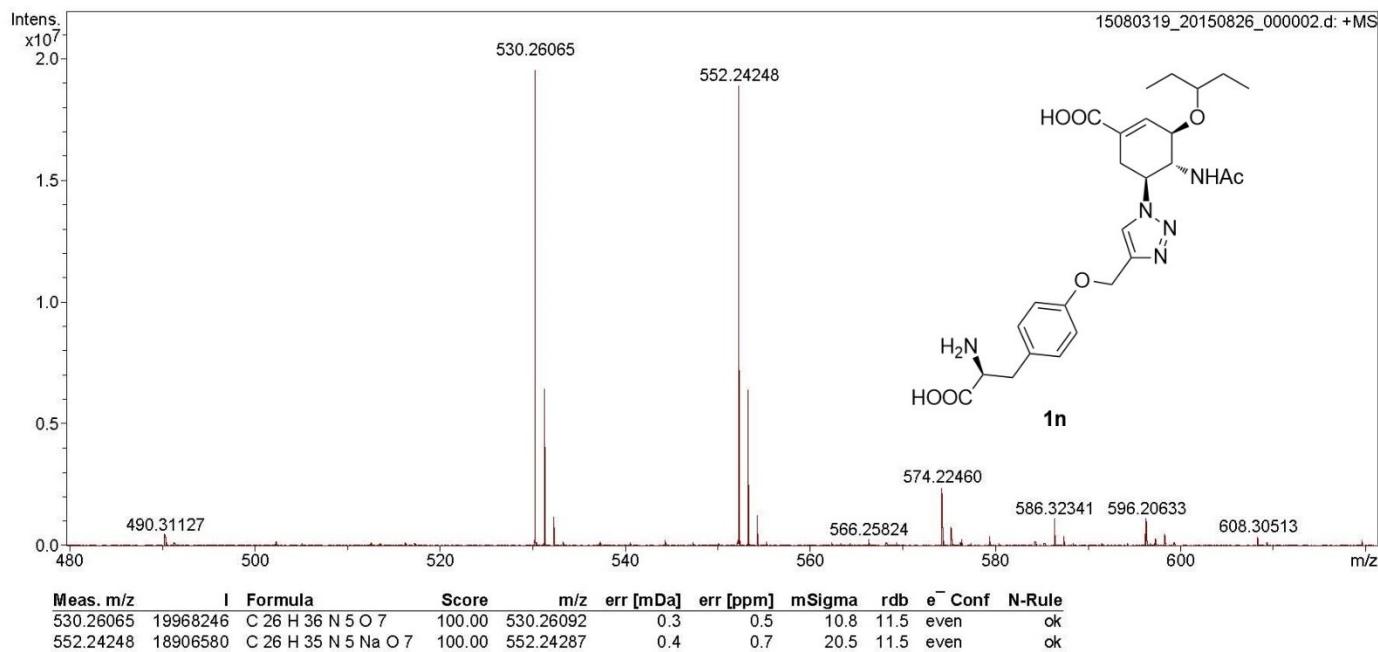
IR of 1n
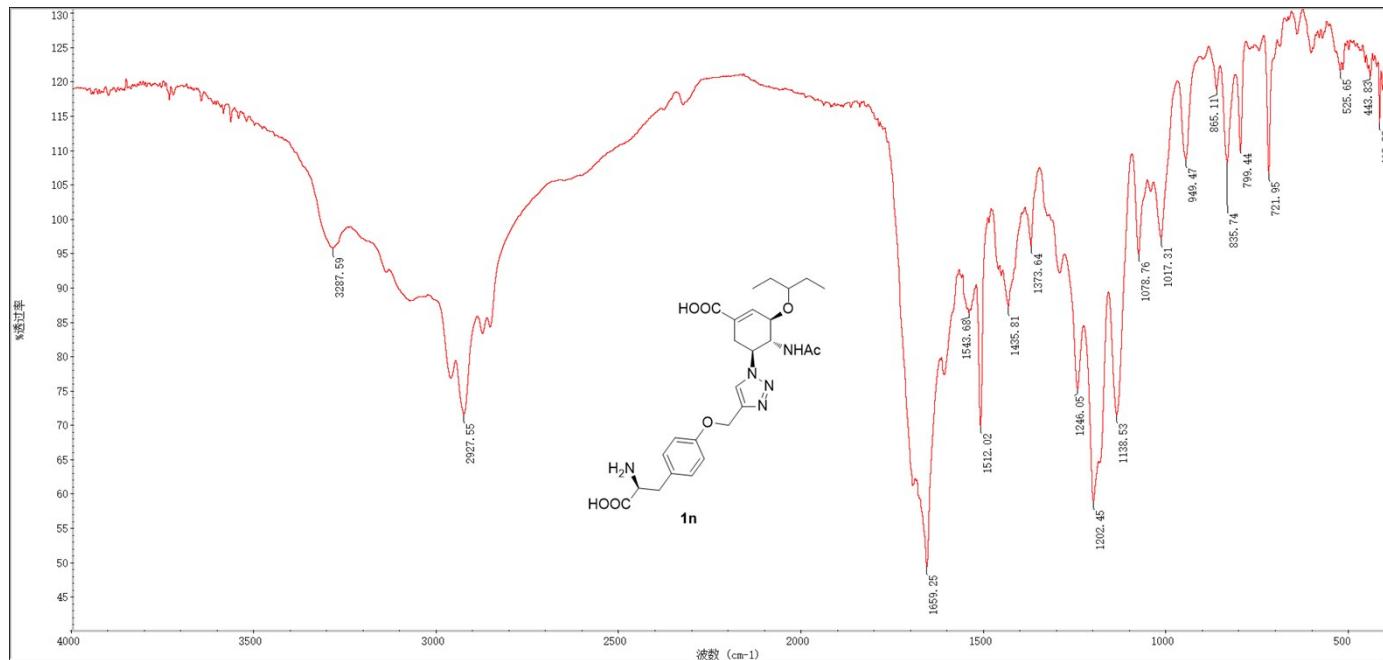
^{1}H NMR of 2e (500 MHz, CD$_3$OD)
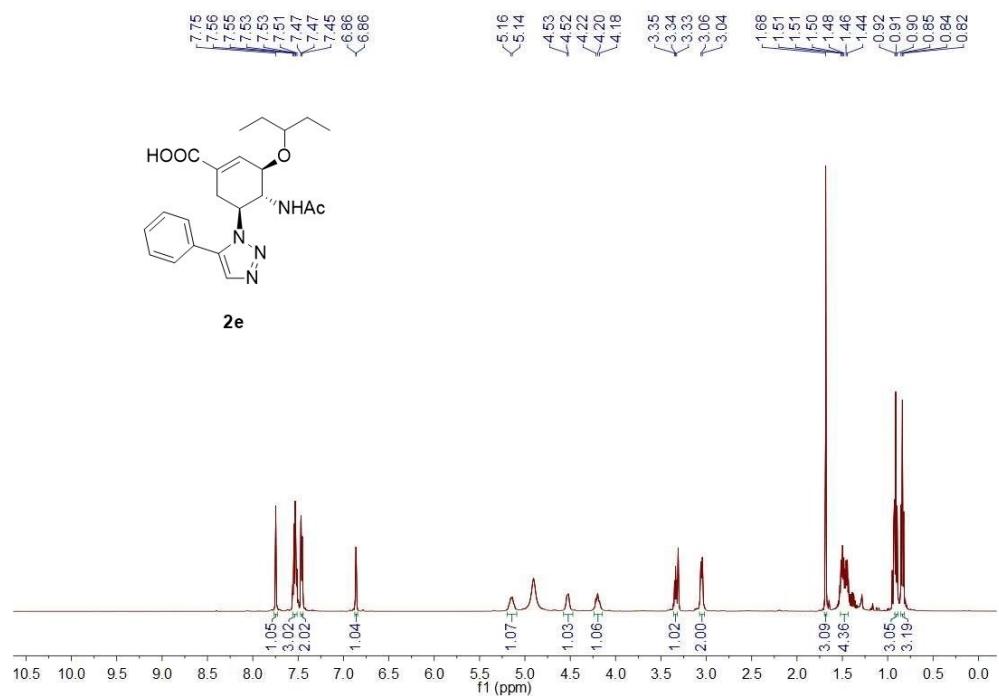
^{13}C NMR of 2e (500 MHz, CD$_3$OD)

HR-ESIMS of 2e

| Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
413.21801	128047696	C 22 H 29 N 4 O 4	100.00	413.21833	0.3	0.8	9.2	10.5	even	ok
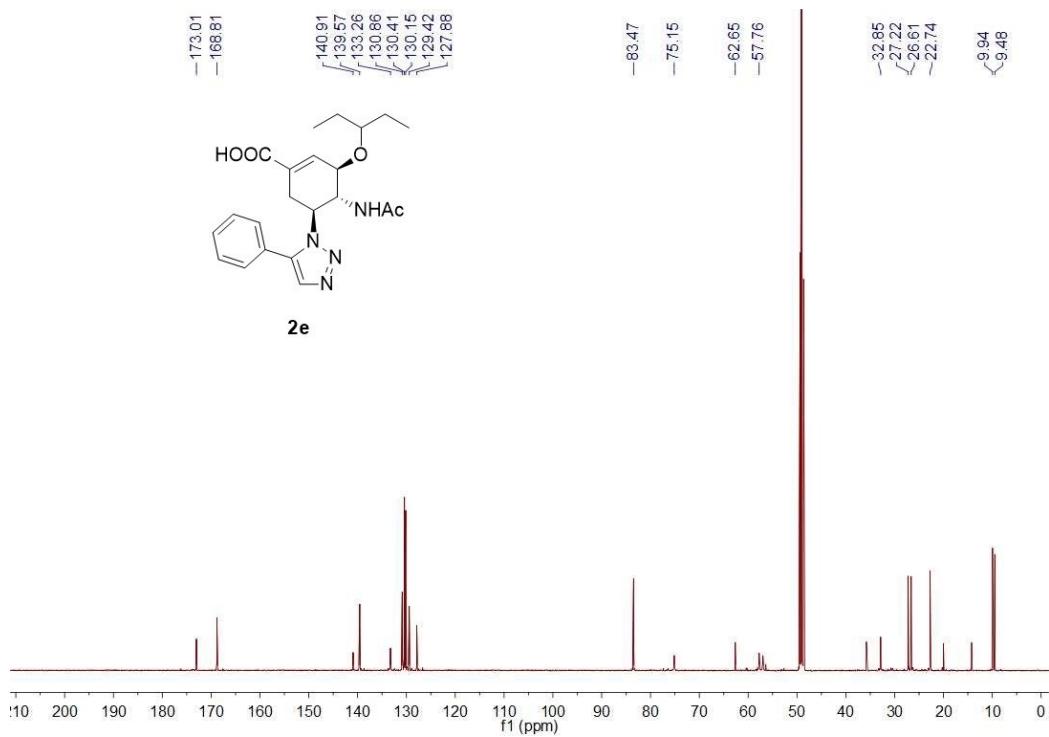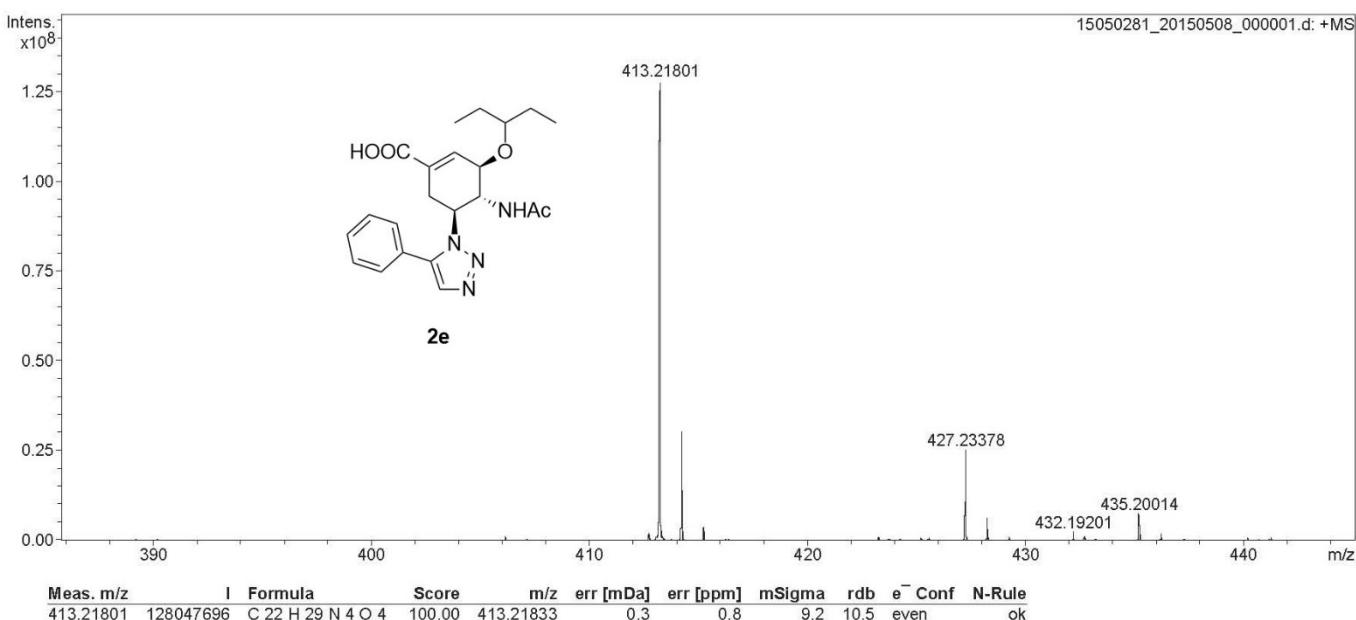
IR of 2e

¹H NMR of 2f (500 MHz, CD₃OD)

¹³C NMR of 2f (500 MHz, CD₃OD)

HR-ESIMS of 2f

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
457.20873	21065850	C 23 H 29 N 4 O 6	100.00	457.20816	-0.6	-1.2	11.8	11.5	even	ok
479.19035	70457016	C 23 H 28 N 4 Na O 6	100.00	479.19011	-0.2	-0.5	14.3	11.5	even	ok
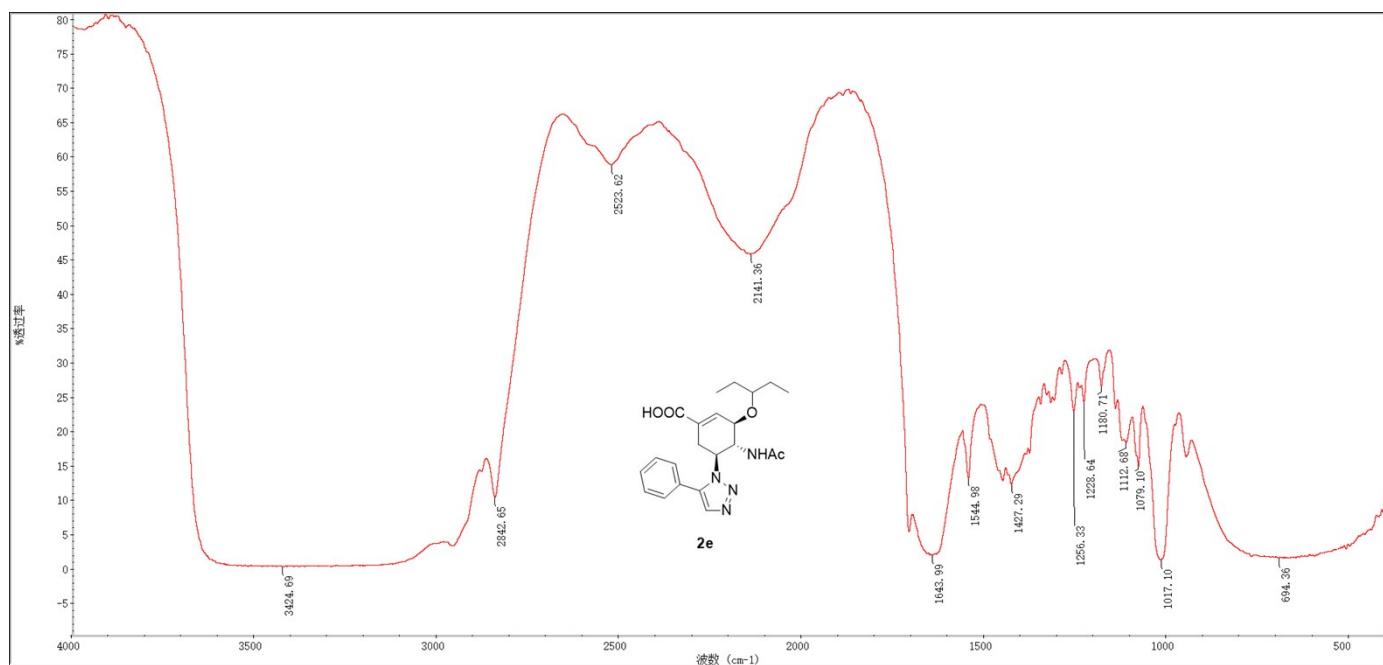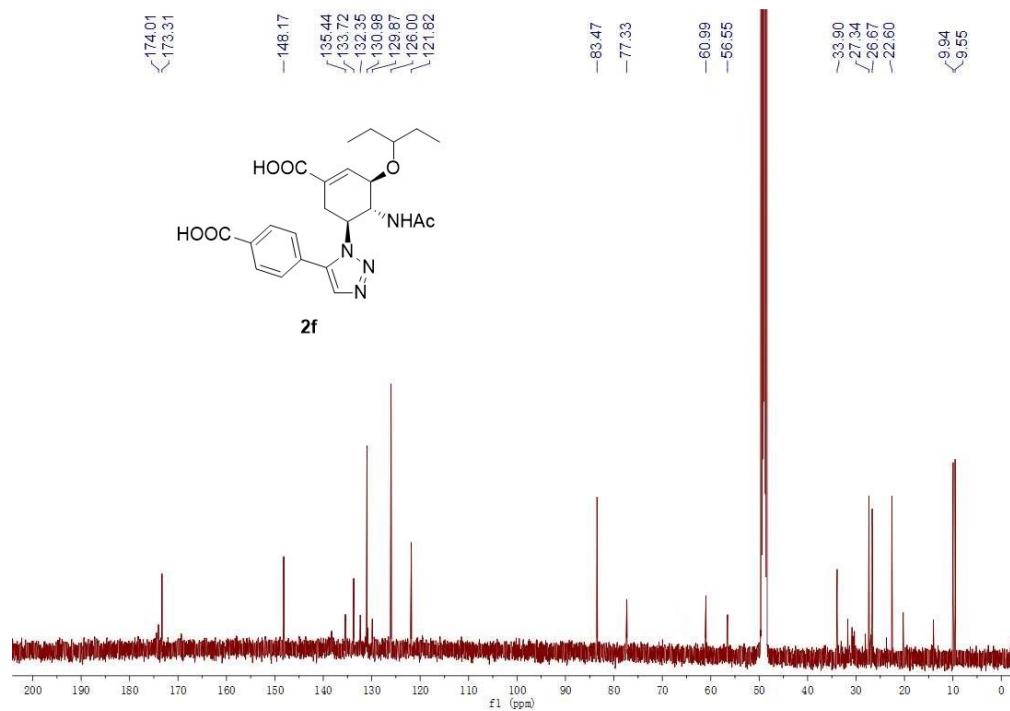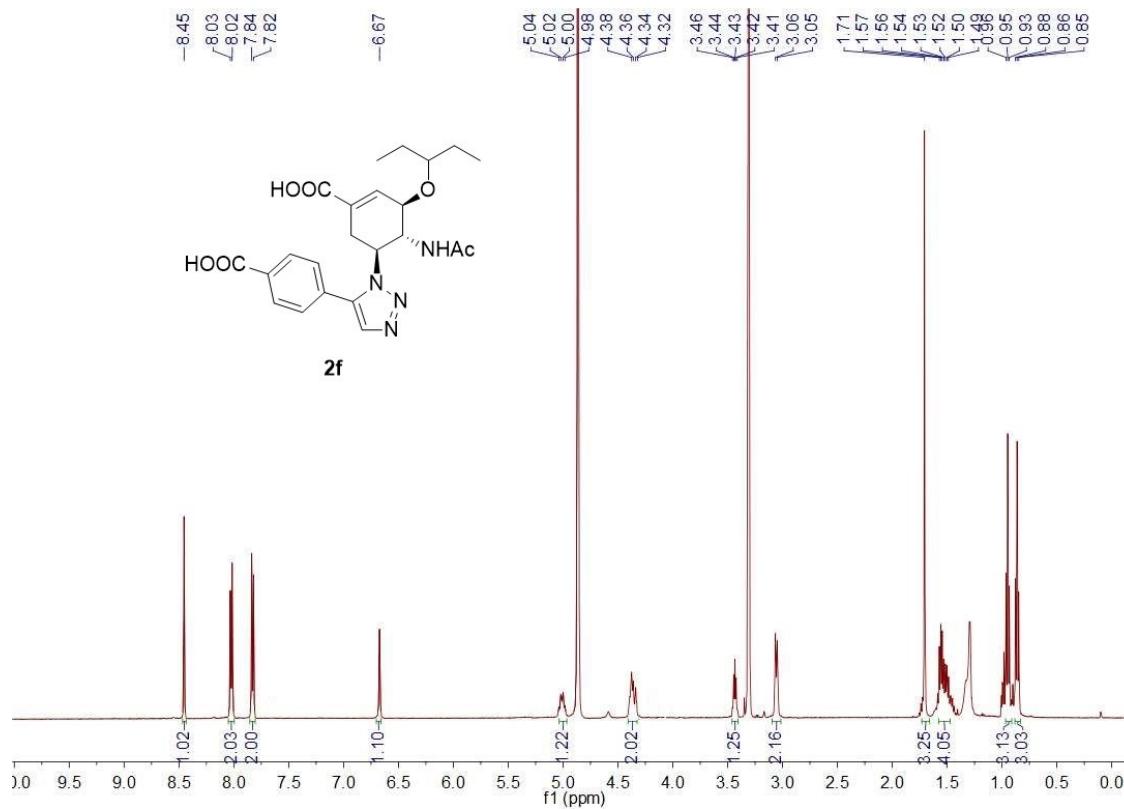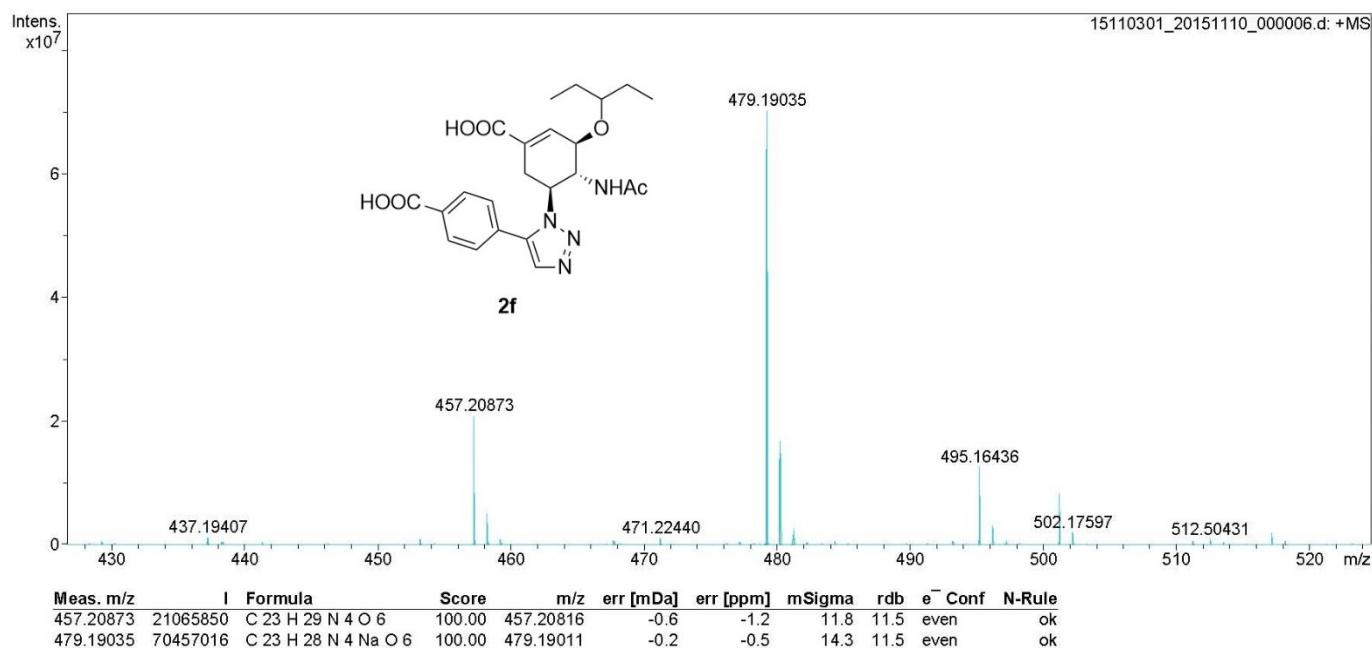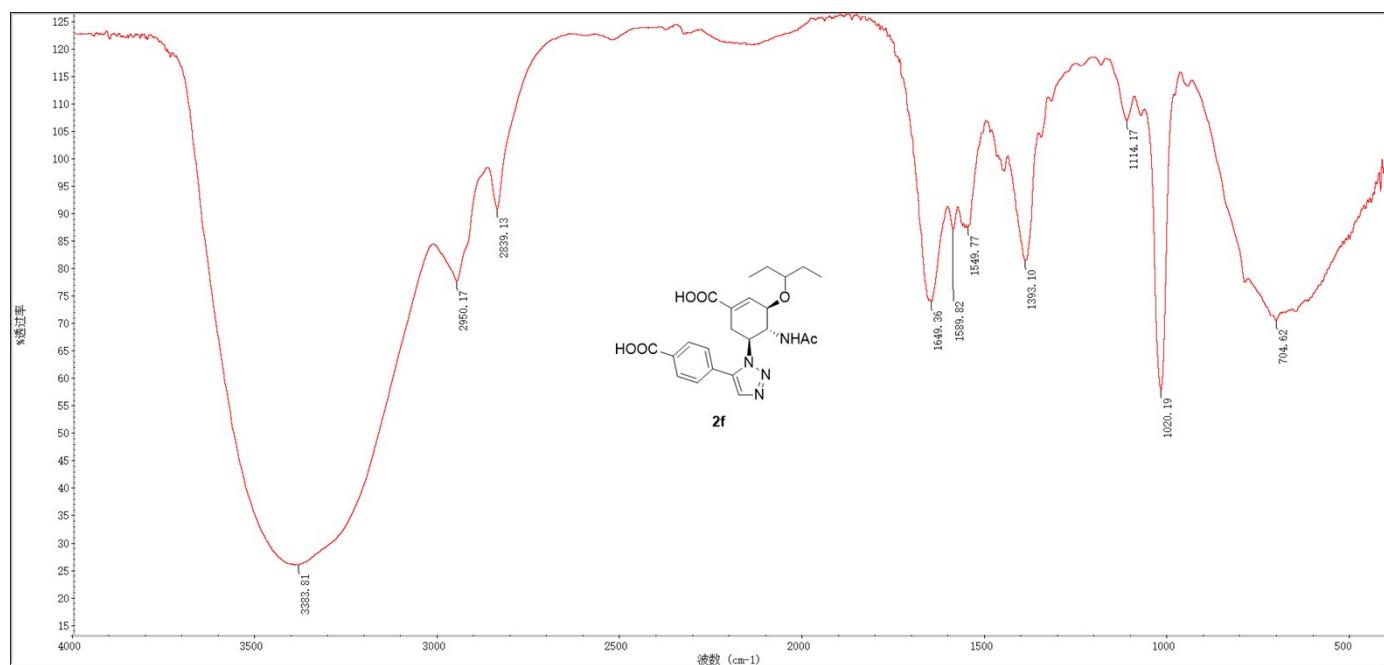
IR of 2f

^{1}H NMR of 2g (500 MHz, CD[3]OD)
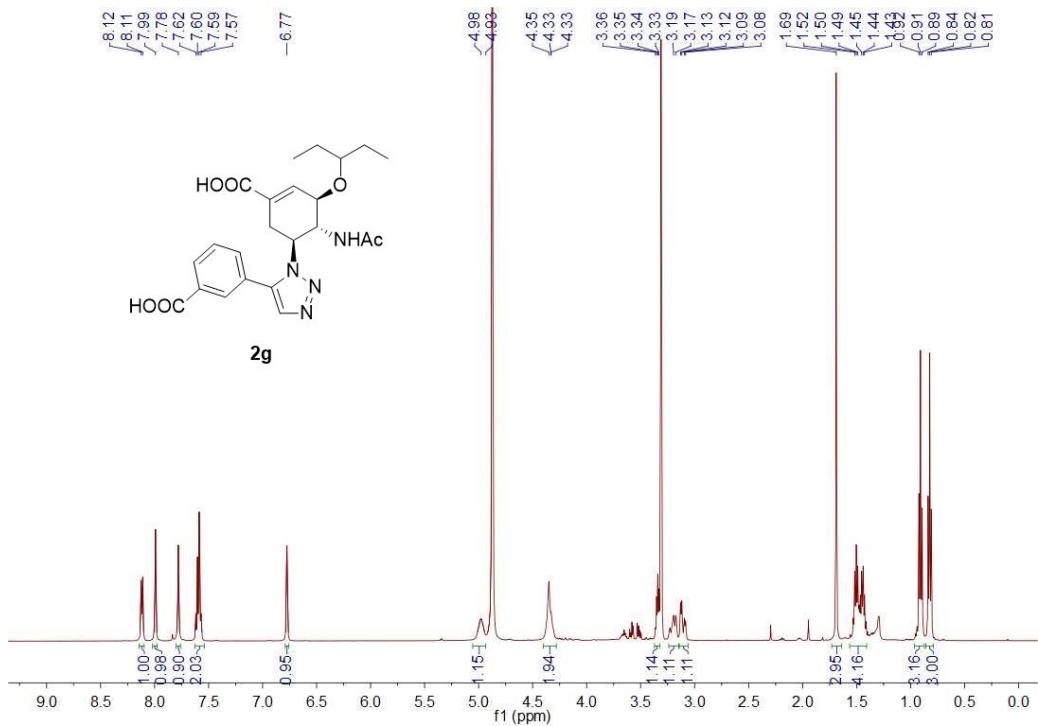
^{13}C NMR of 2g (500 MHz, CD[3]OD)

HR-ESIMS of 2g

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
457.20900	53910728	C 23 H 29 N 4 O 6	100.00	457.20816	-0.8	-1.8	10.9	11.5	even	ok
479.19074	16376330	C 23 H 28 N 4 Na O 6	100.00	479.19011	-0.6	-1.3	10.6	11.5	even	ok
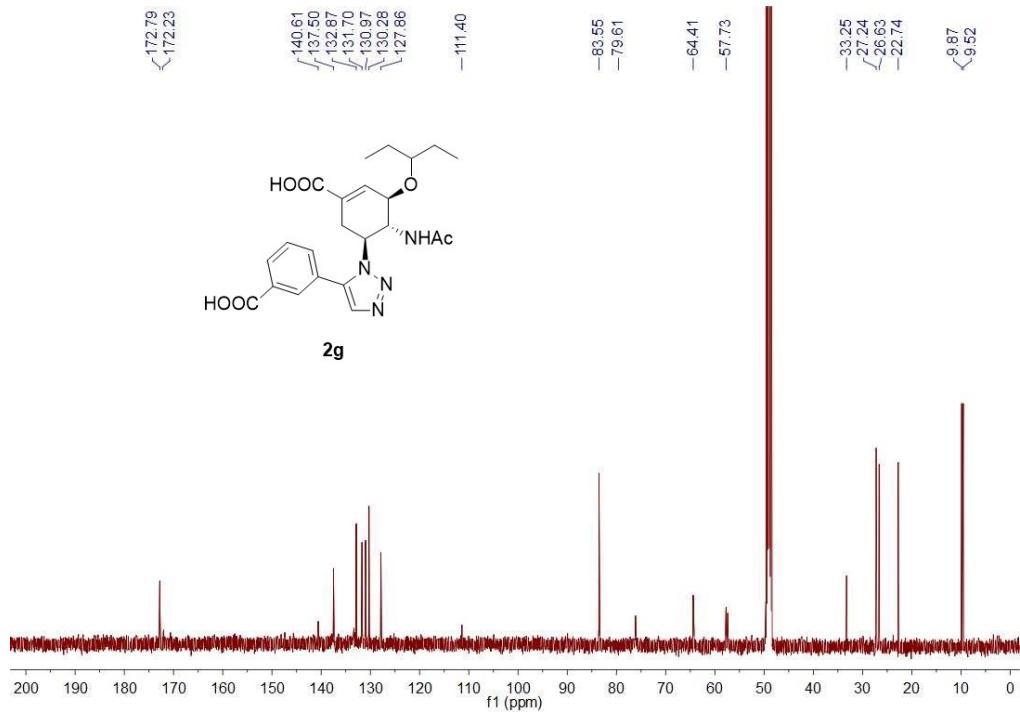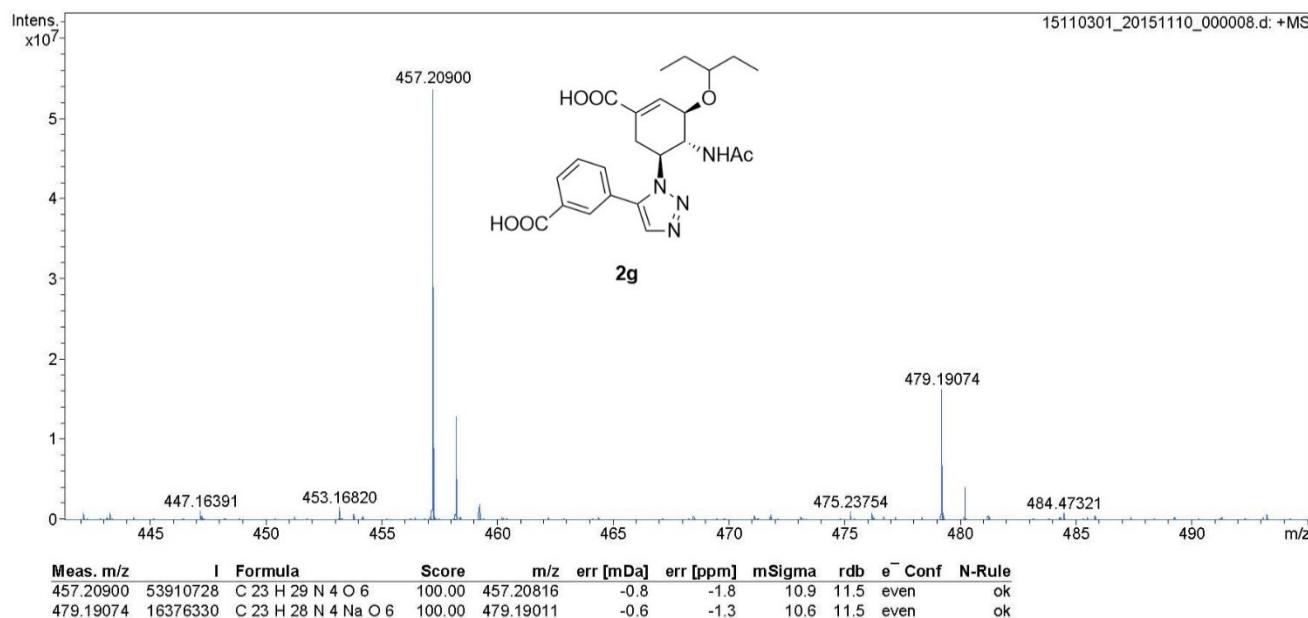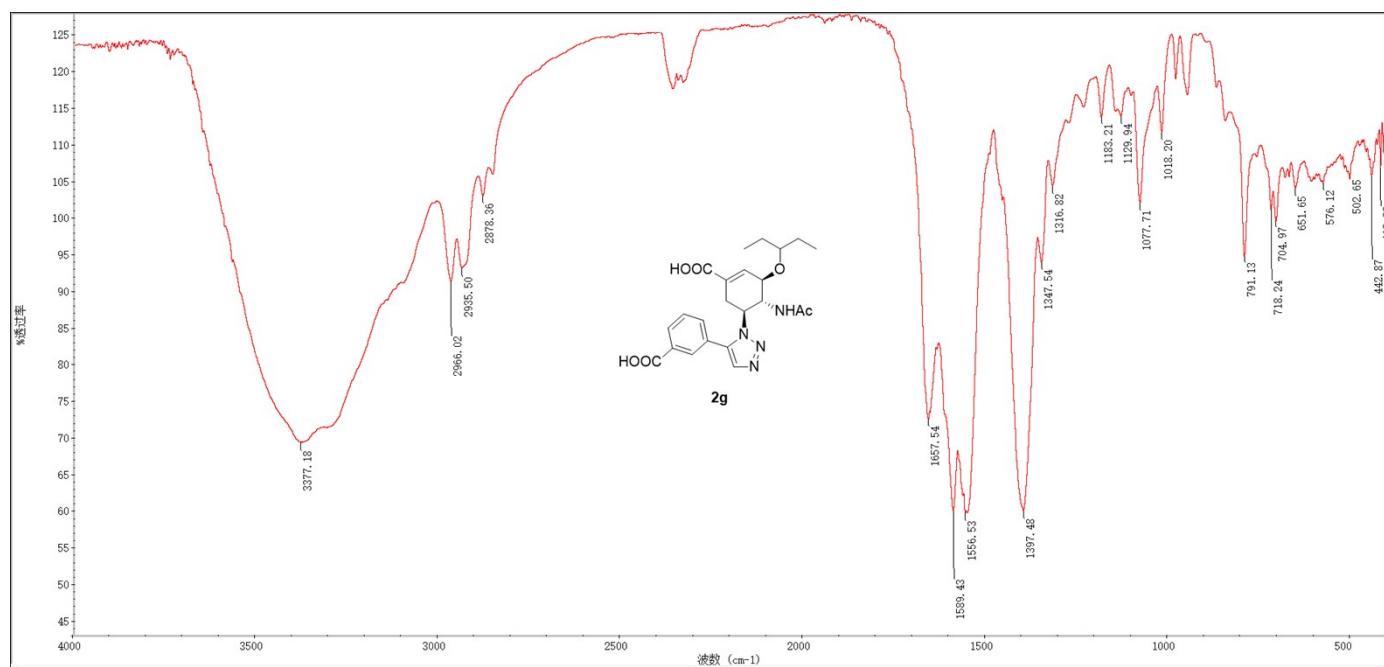
IR of 2g

¹H NMR of 2h (500 MHz, CD₃OD)
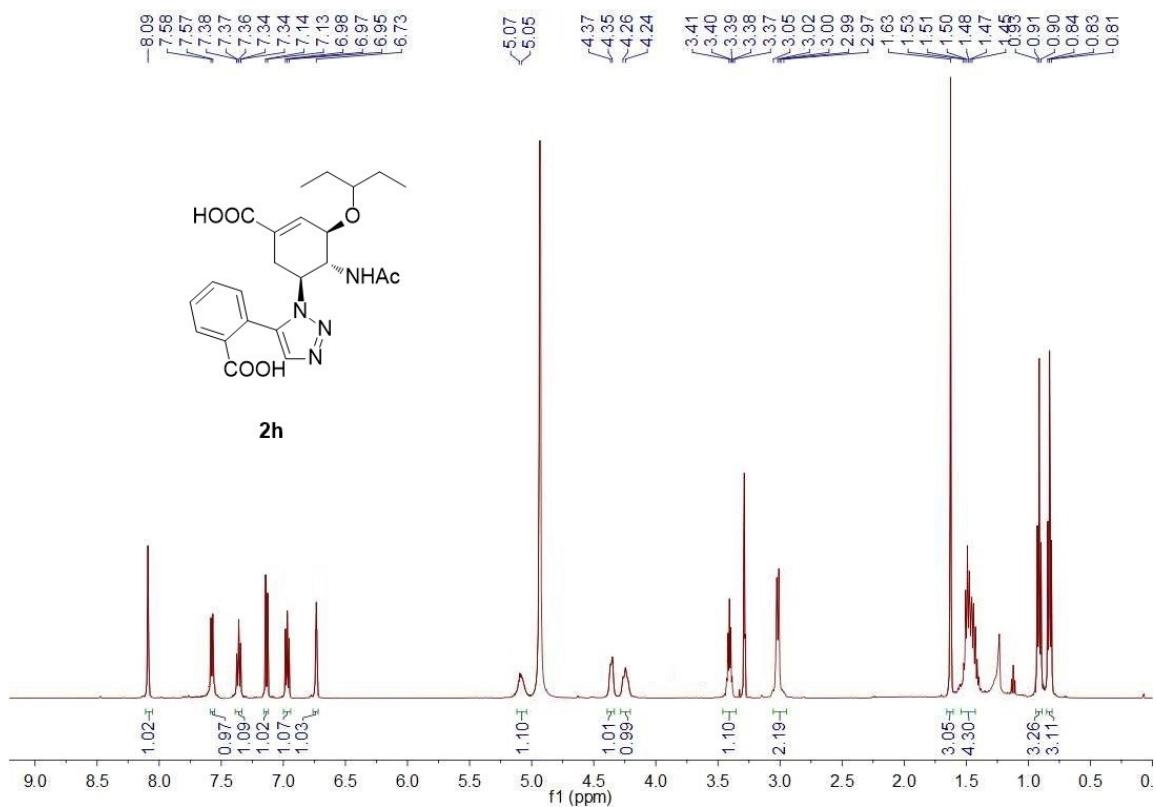
¹³C NMR of 2h (500 MHz, CD₃OD)
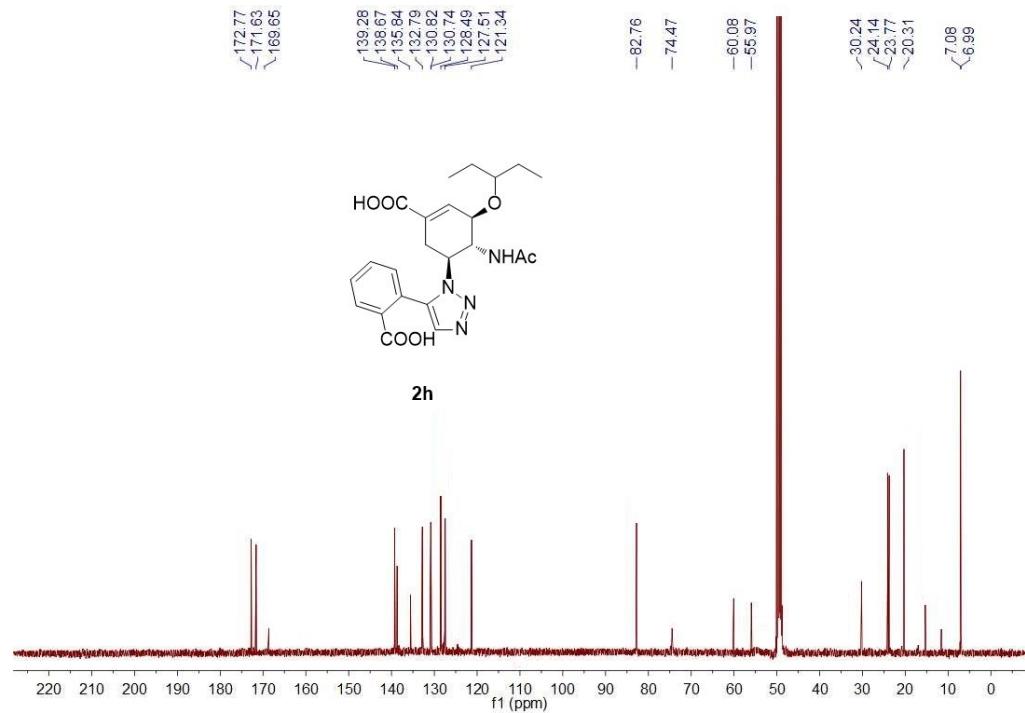
HR-ESIMS of 2h
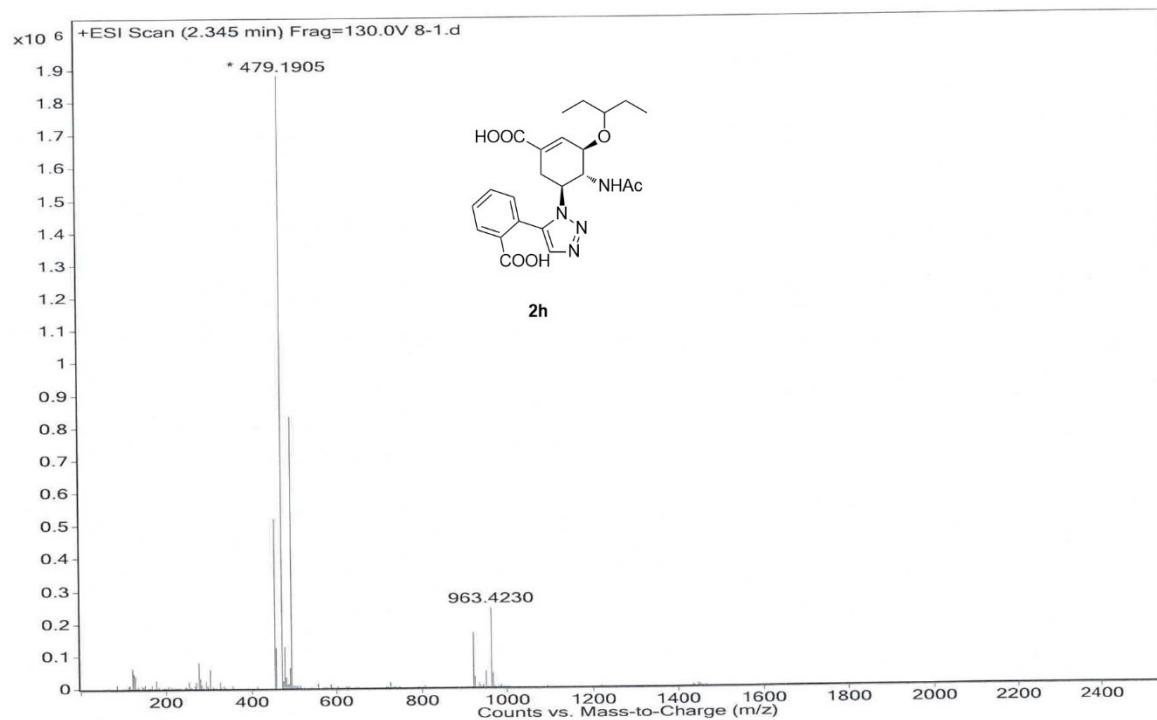
IR of 2h
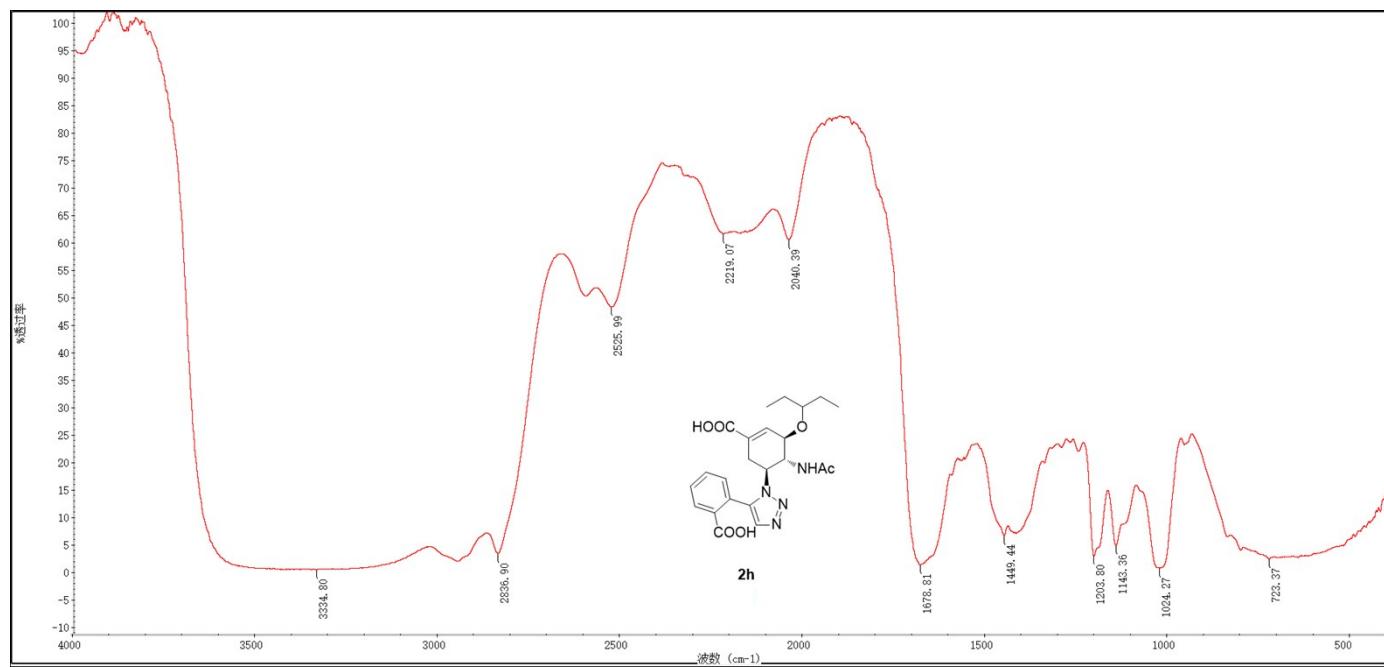
^{1}H NMR of 2i (500 MHz, CD$_3$OD)
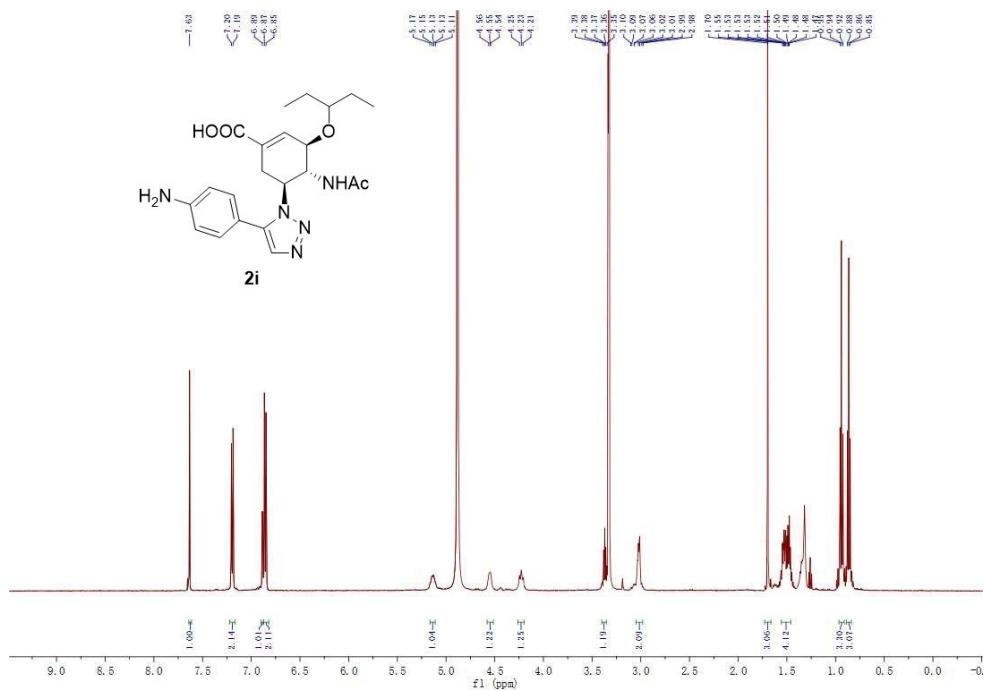
# ^{13}C NMR of 2i (500 MHz, CD$_3$OD)
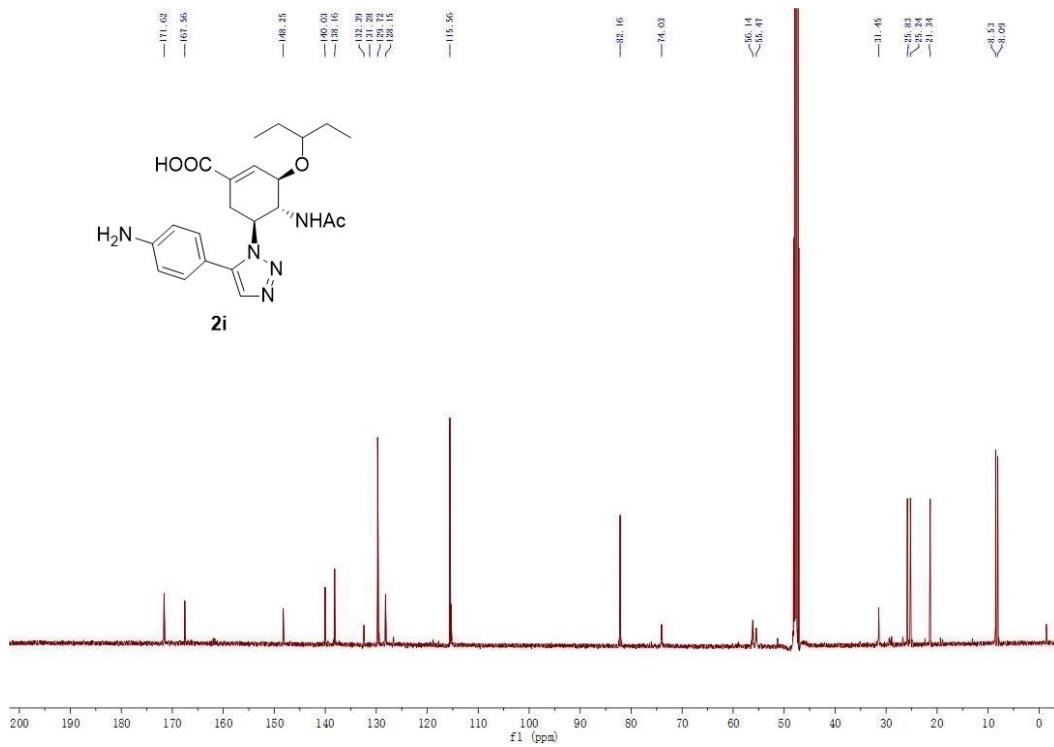
HR-ESIMS of 2i
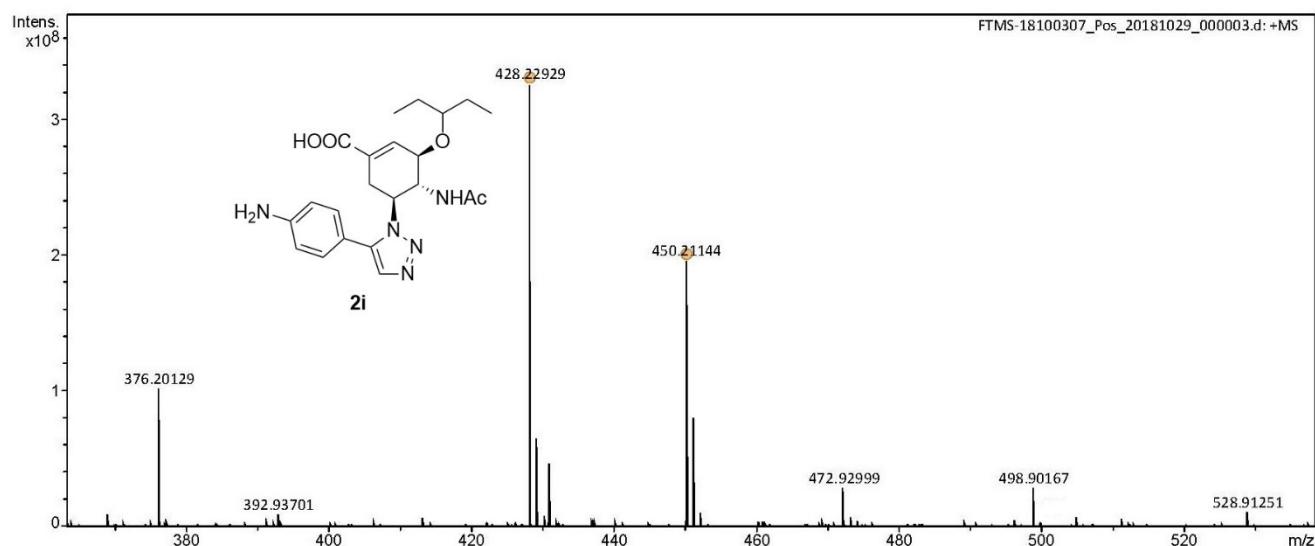

IR of 2i
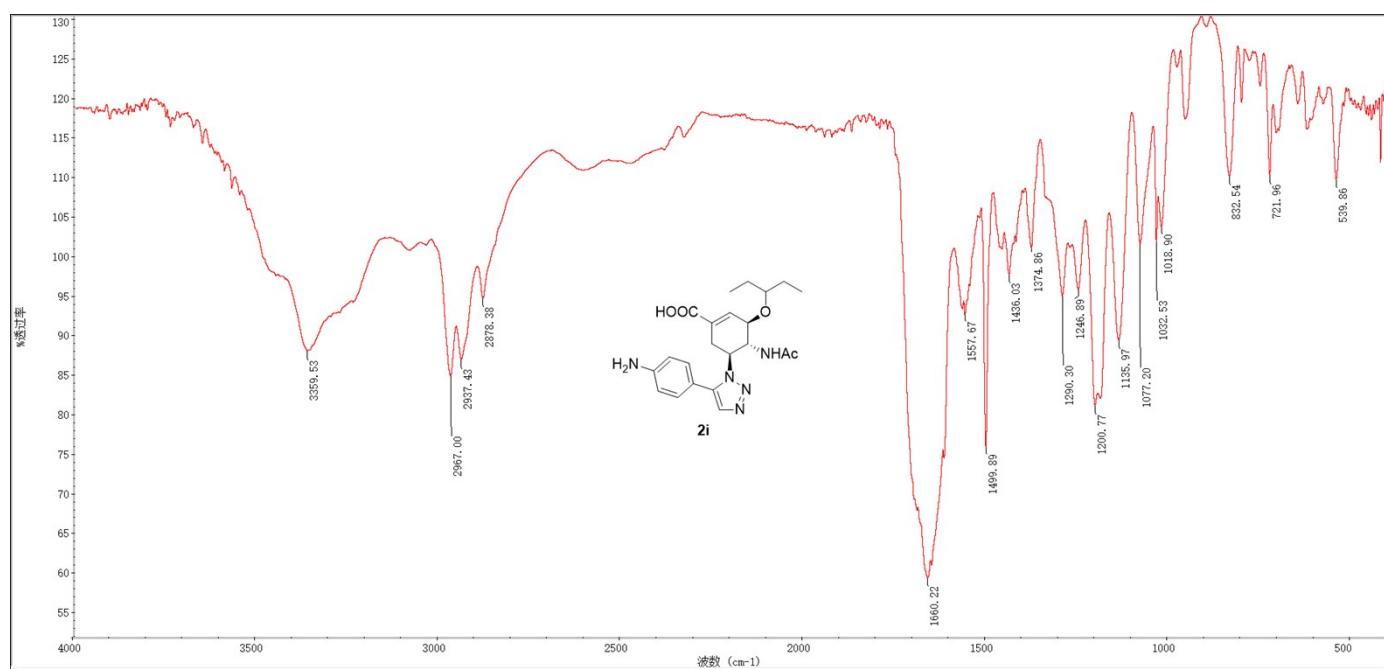
# ¹H NMR of 2j (500 MHz, CD₃OD)
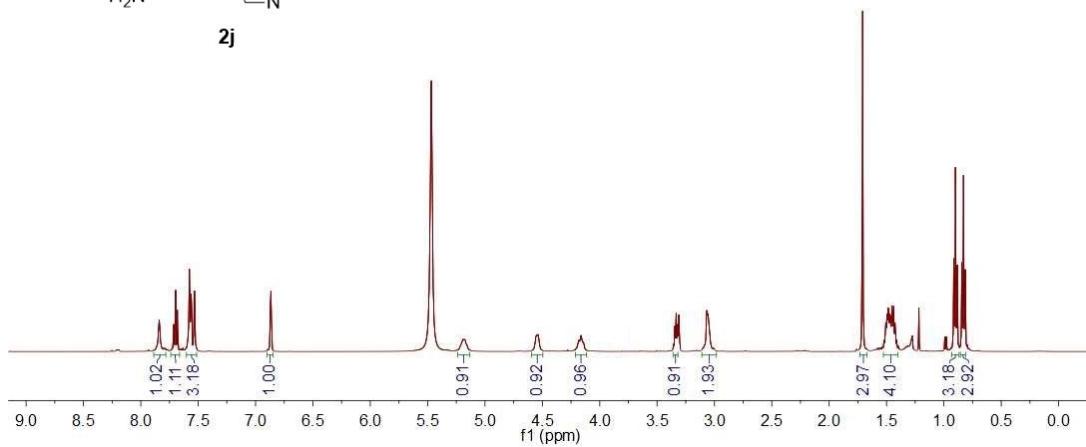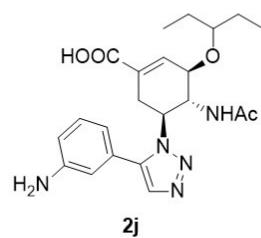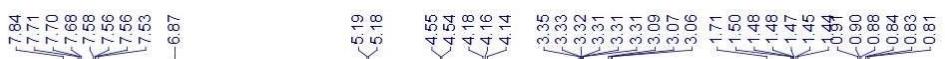
# ¹³C NMR of 2j (500 MHz, CD₃OD)

HR-ESIMS of 2j

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
428.22930	124279728	C 22 H 30 N 5 O 4	100.00	428.22923	-0.1	-0.2	6.7	10.5	even	ok
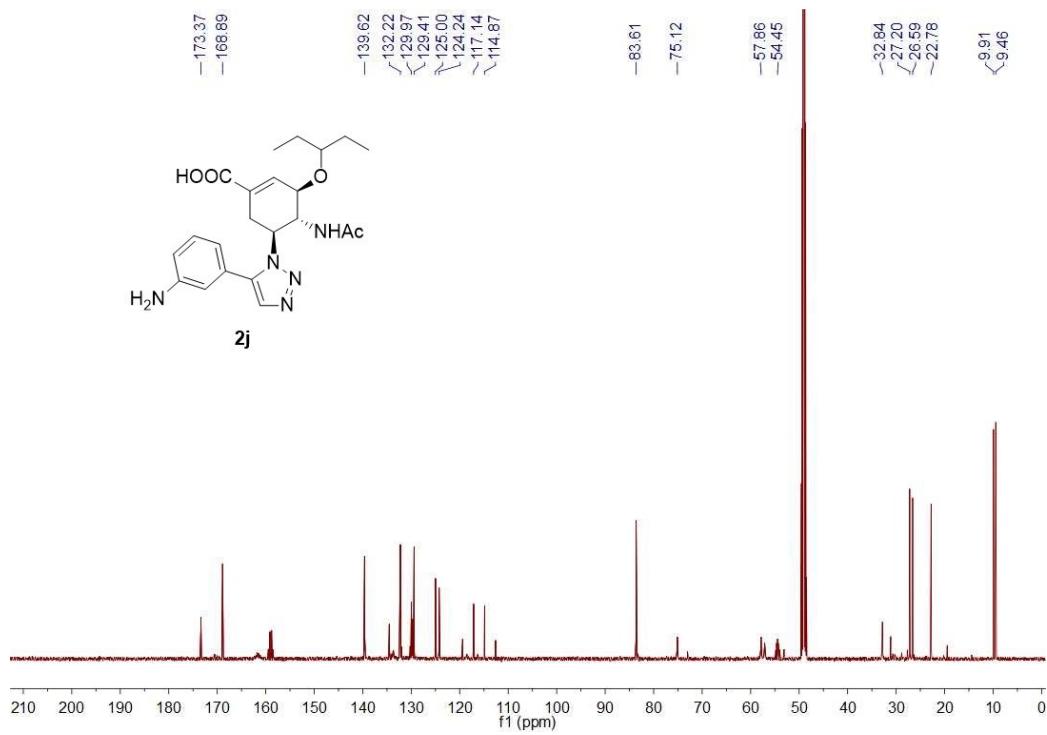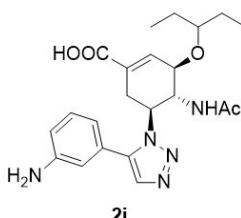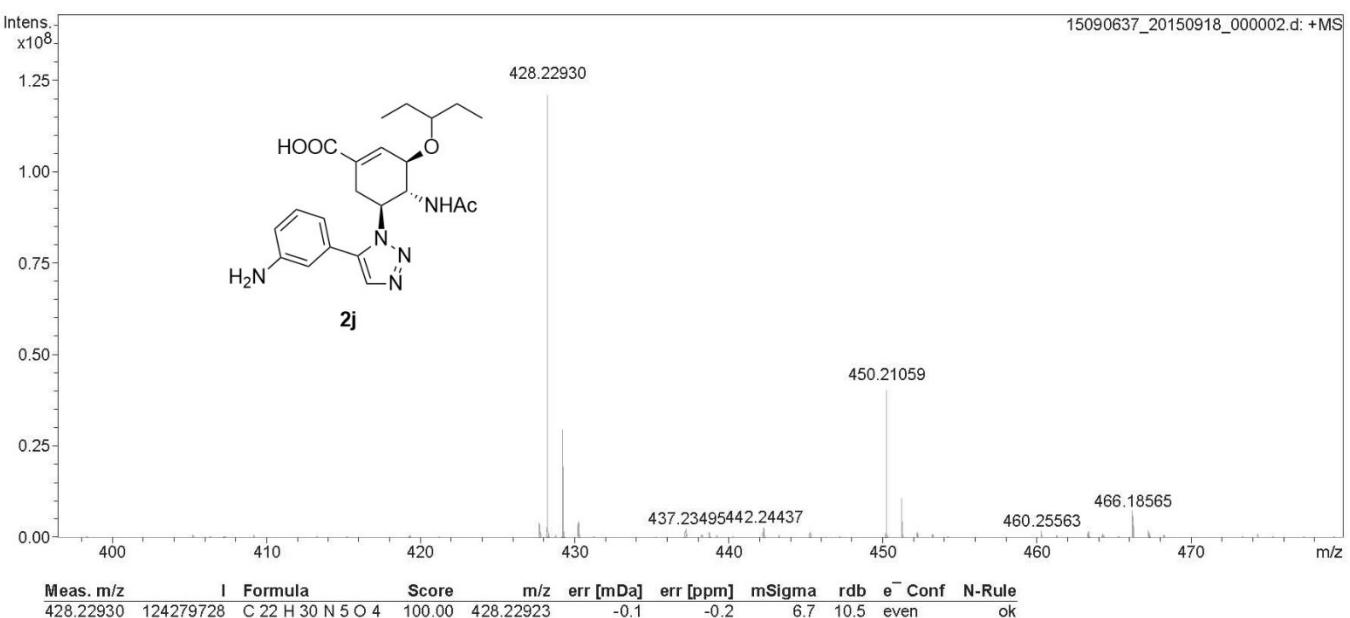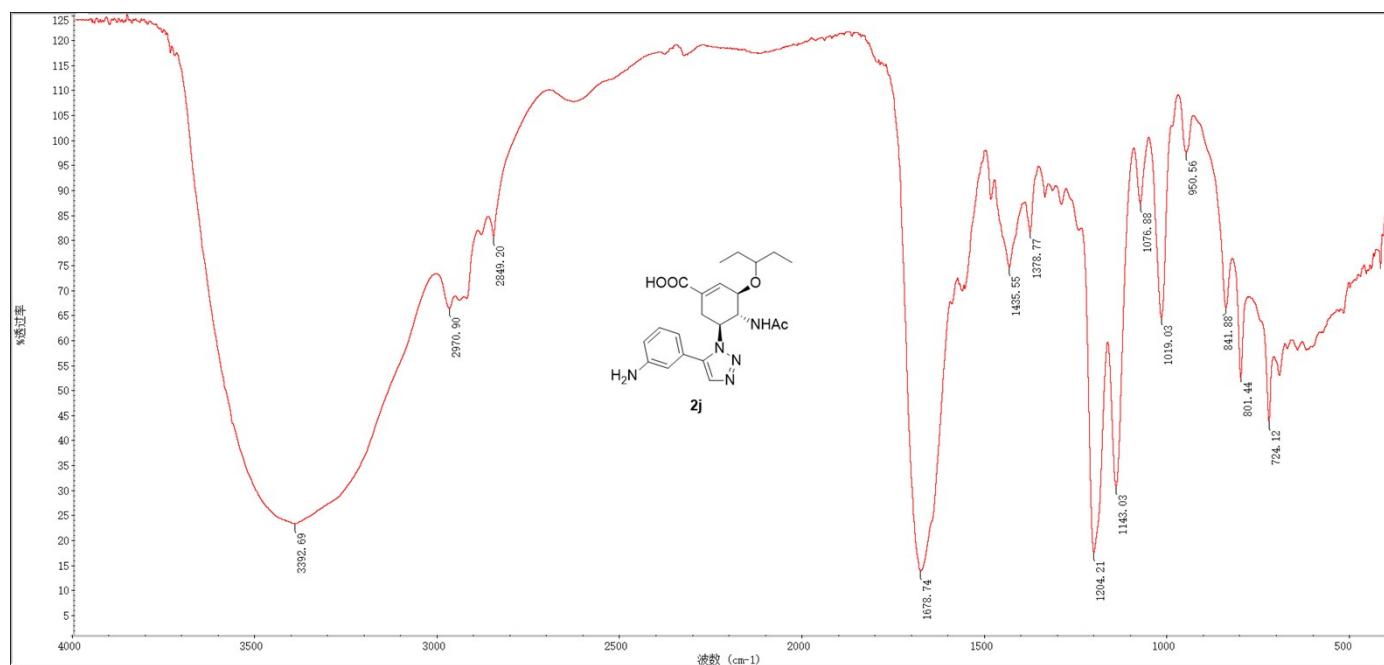
IR of 2j

¹H NMR of 2k (500 MHz, CD₃OD)
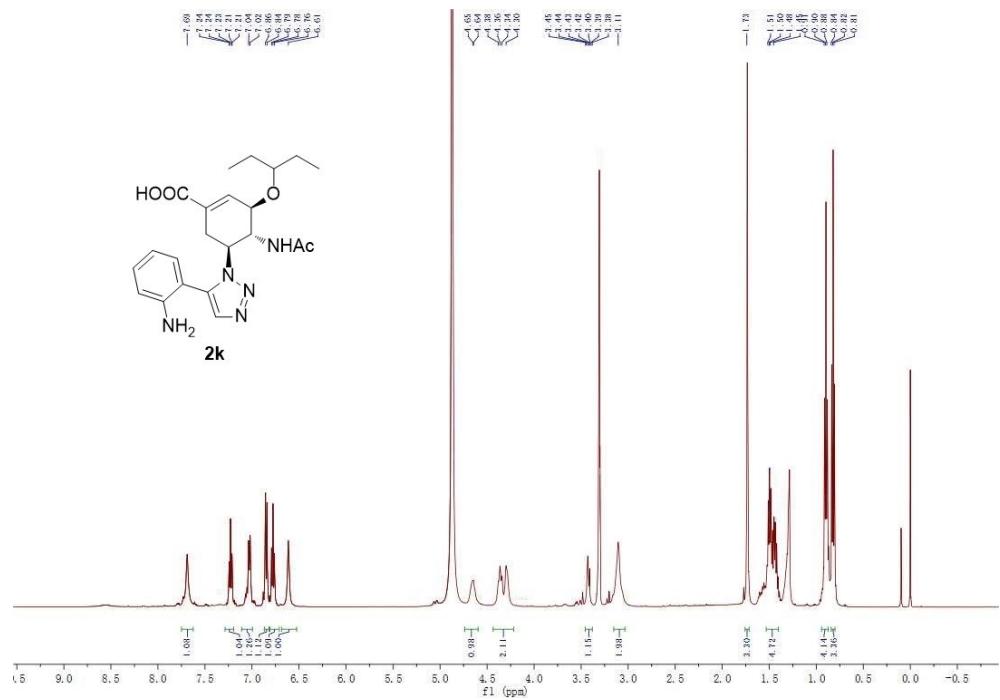
¹³C NMR of 2k (500 MHz, CD₃OD)
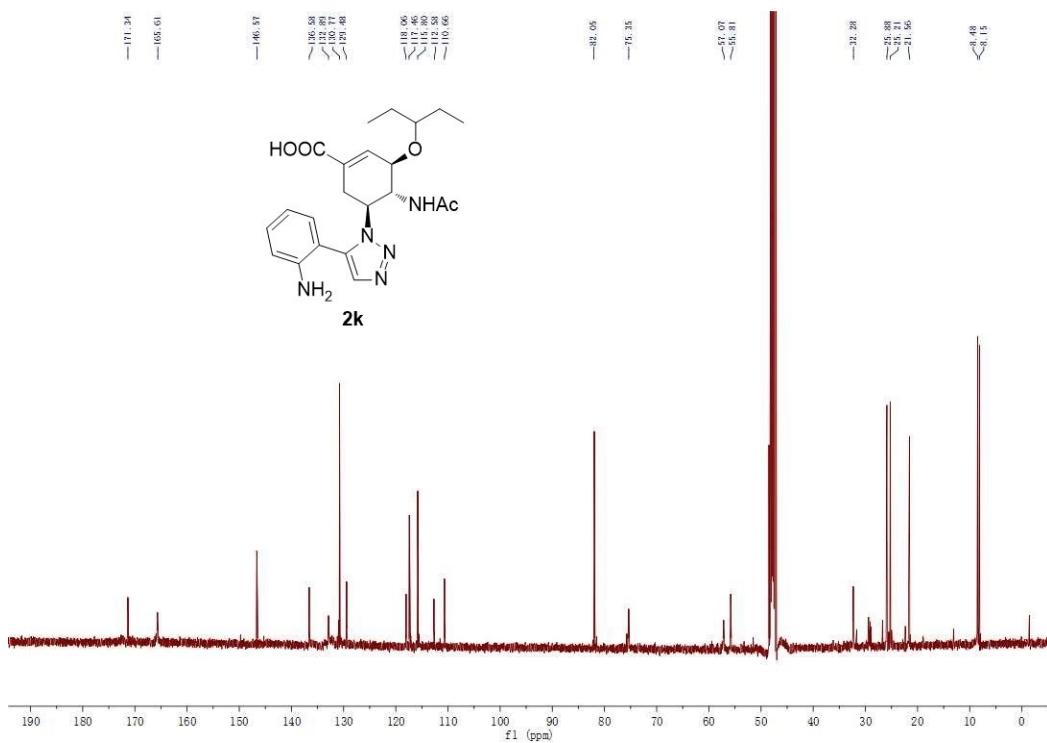
HR-ESIMS of 2k
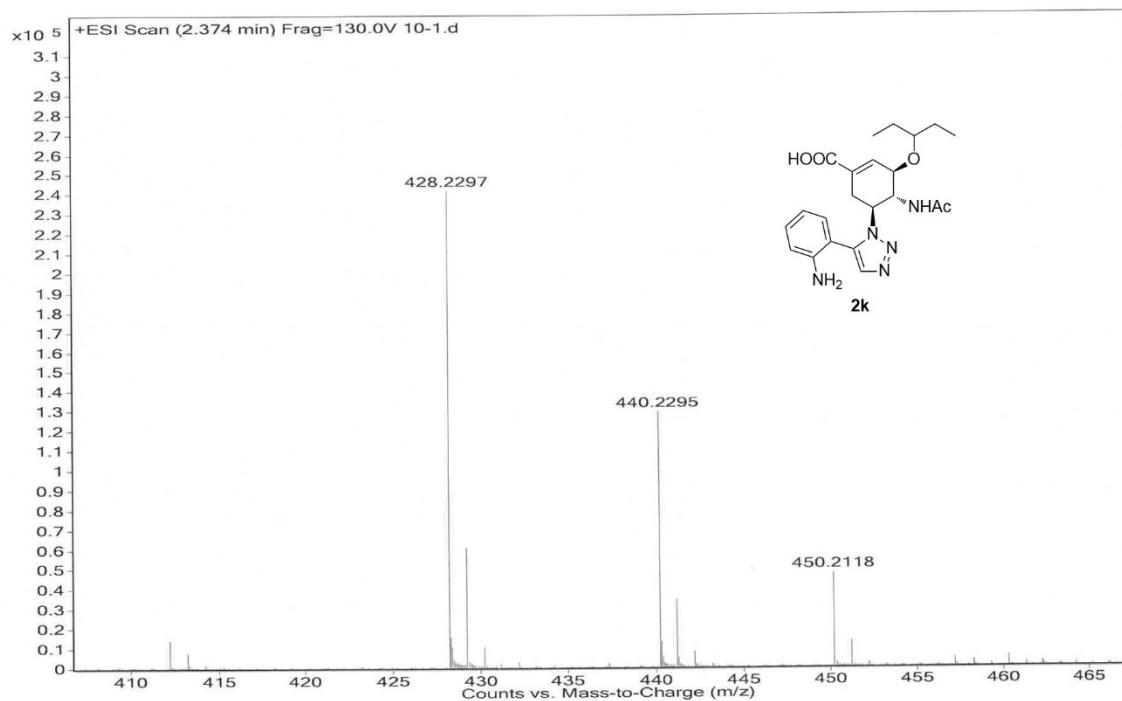
IR of 2k
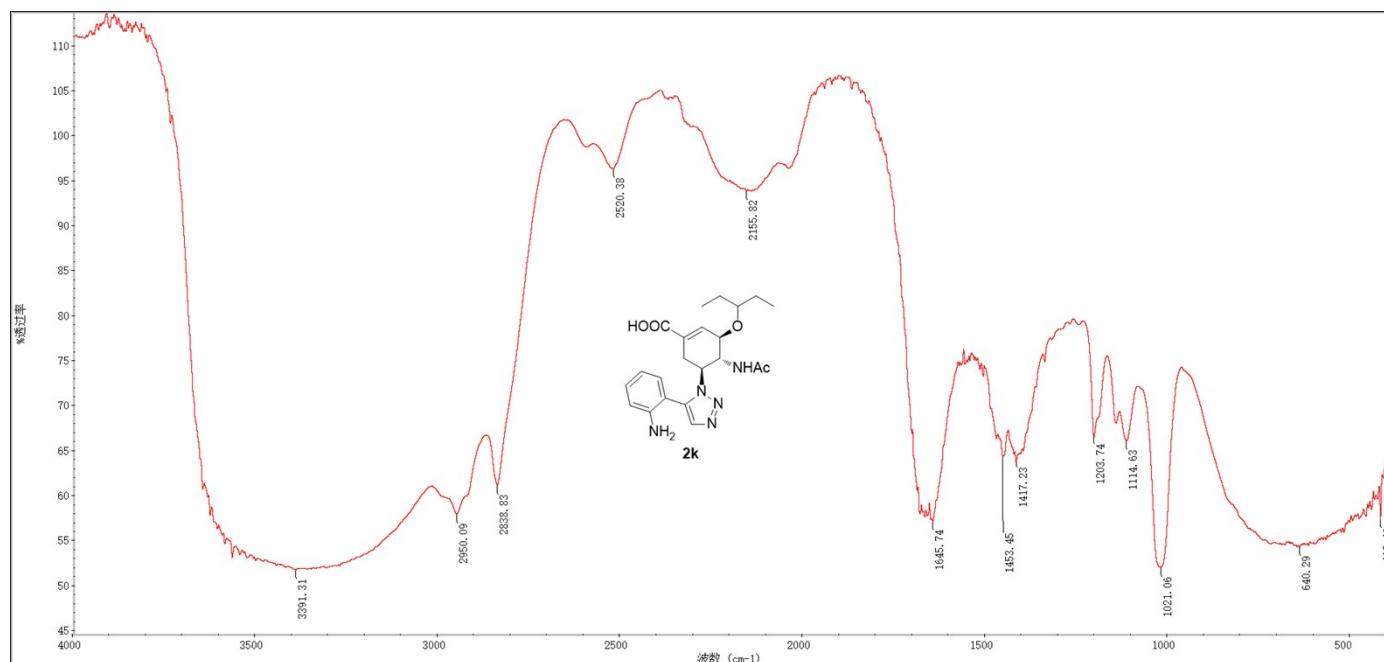
## ¹H NMR of 2l (500 MHz, CD₃OD)
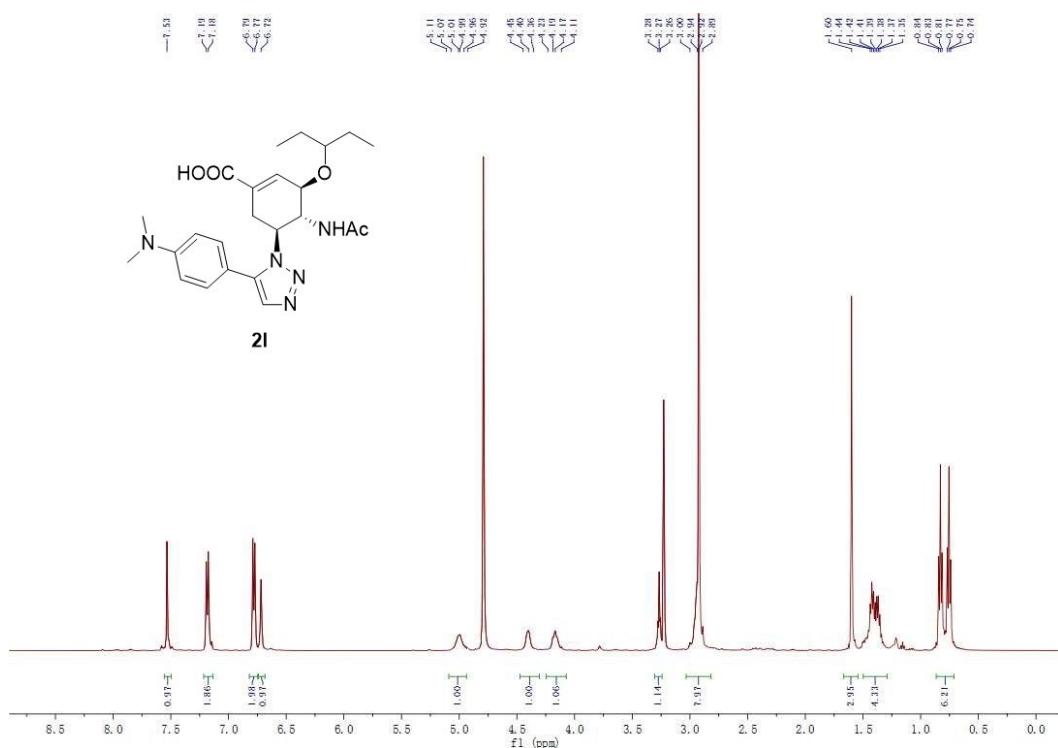

## ¹³C NMR of 2l (500 MHz, CD₃OD)
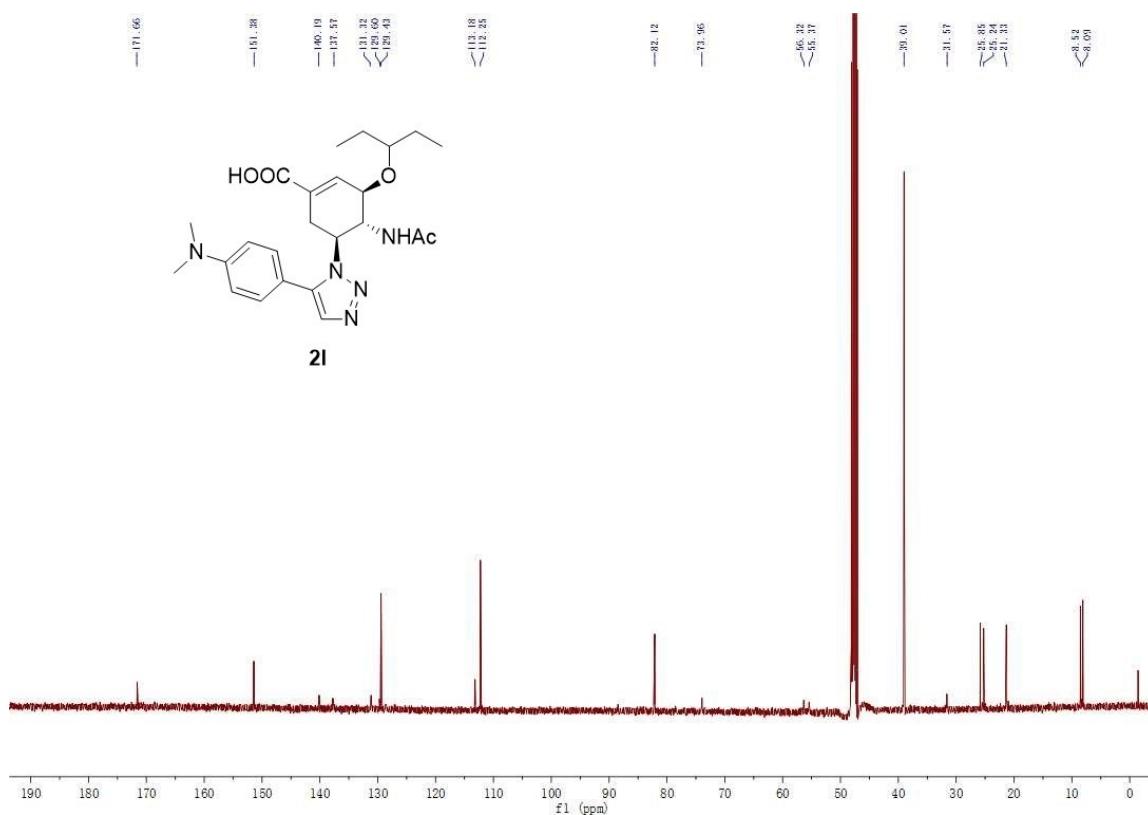
HR-ESIMS of 2l
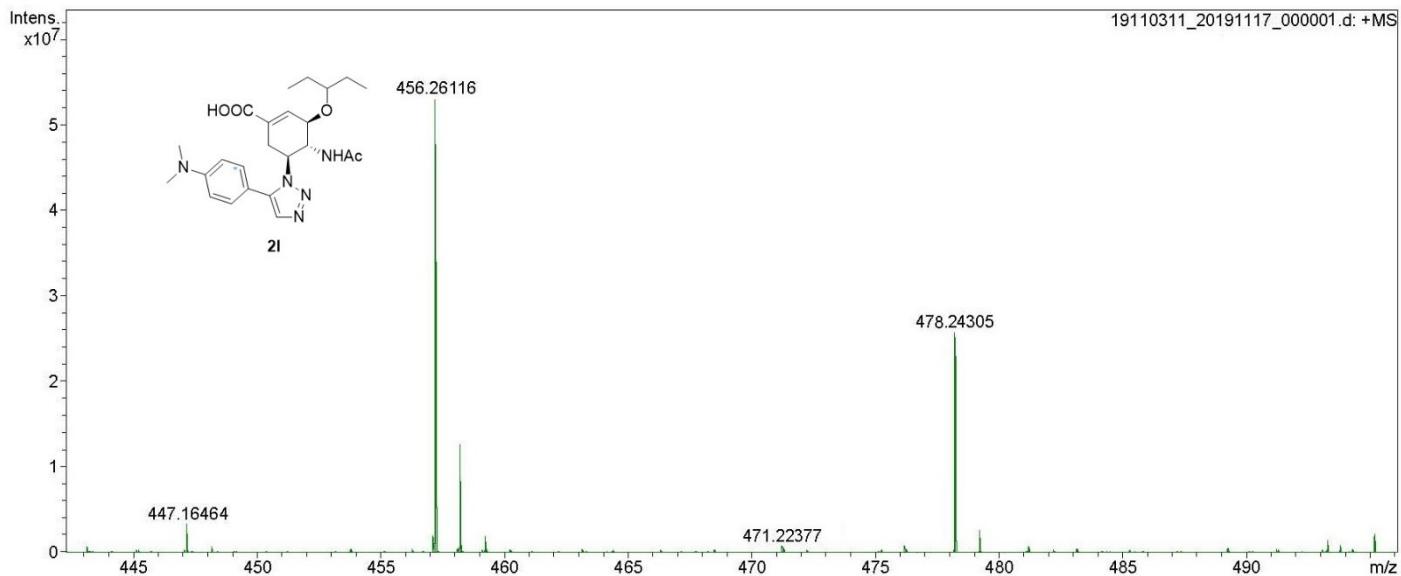

IR of 2l

¹H NMR of 2m (500 MHz, CD₃OD)

¹H NMR of 2m (500 MHz, CD₃OD)
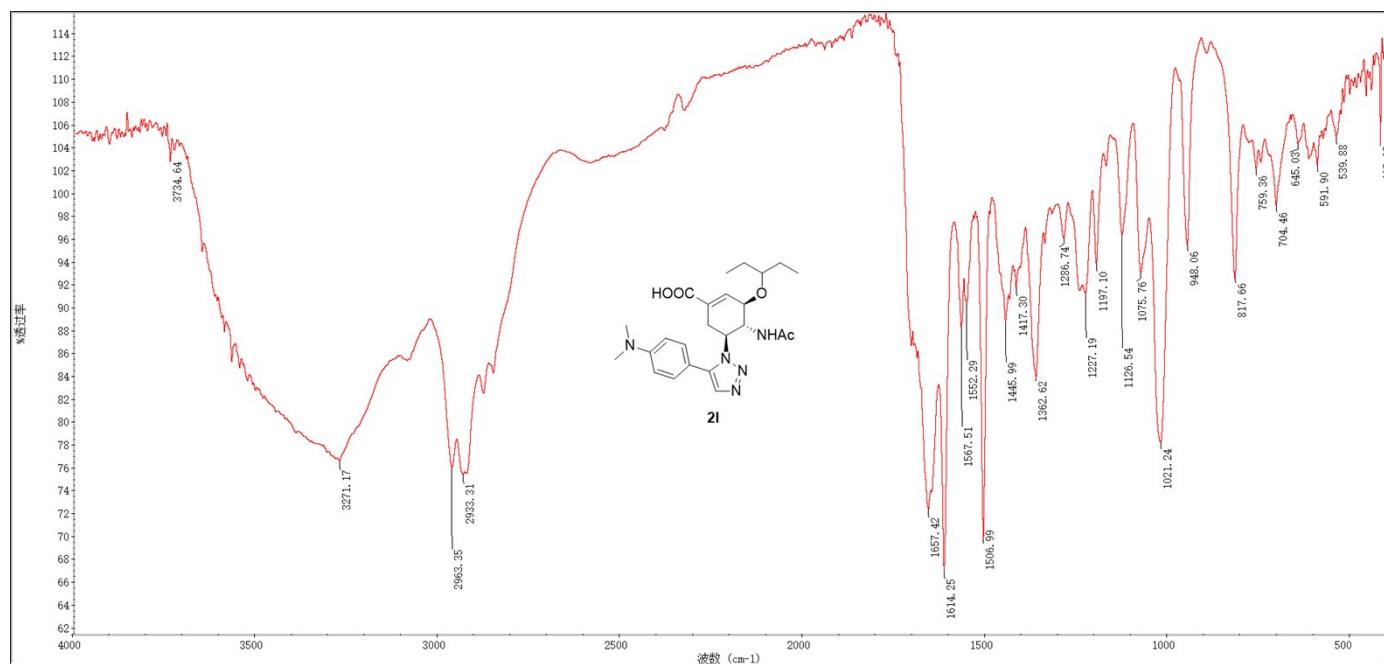
¹³C NMR of 2m (500 MHz, CD₃OD)
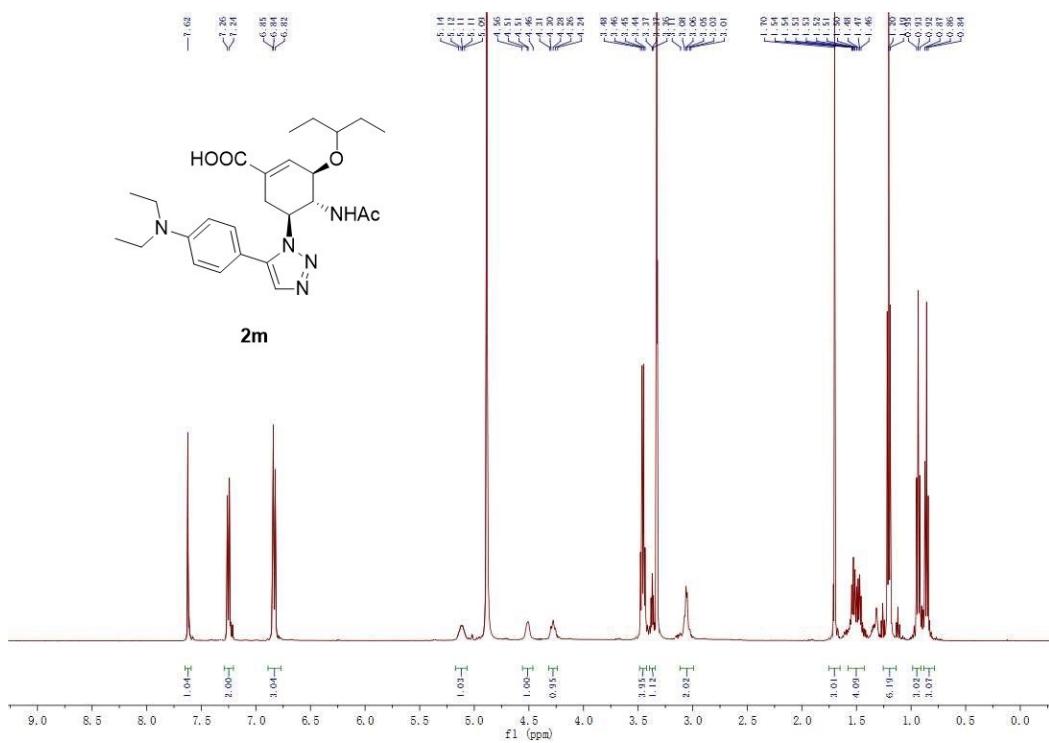
¹³C NMR of 2m (500 MHz, CD₃OD)
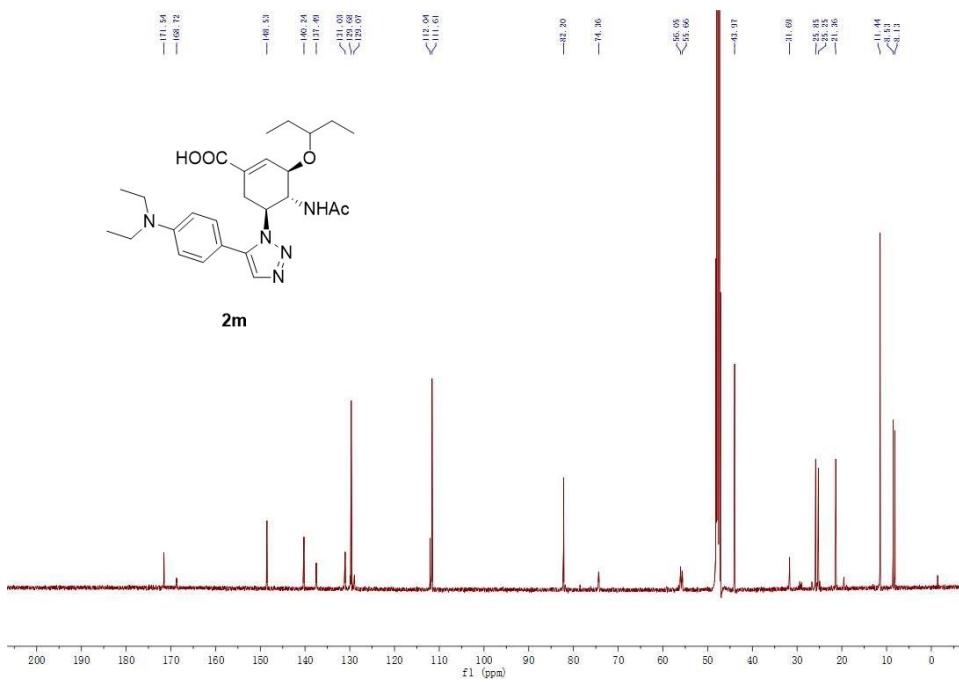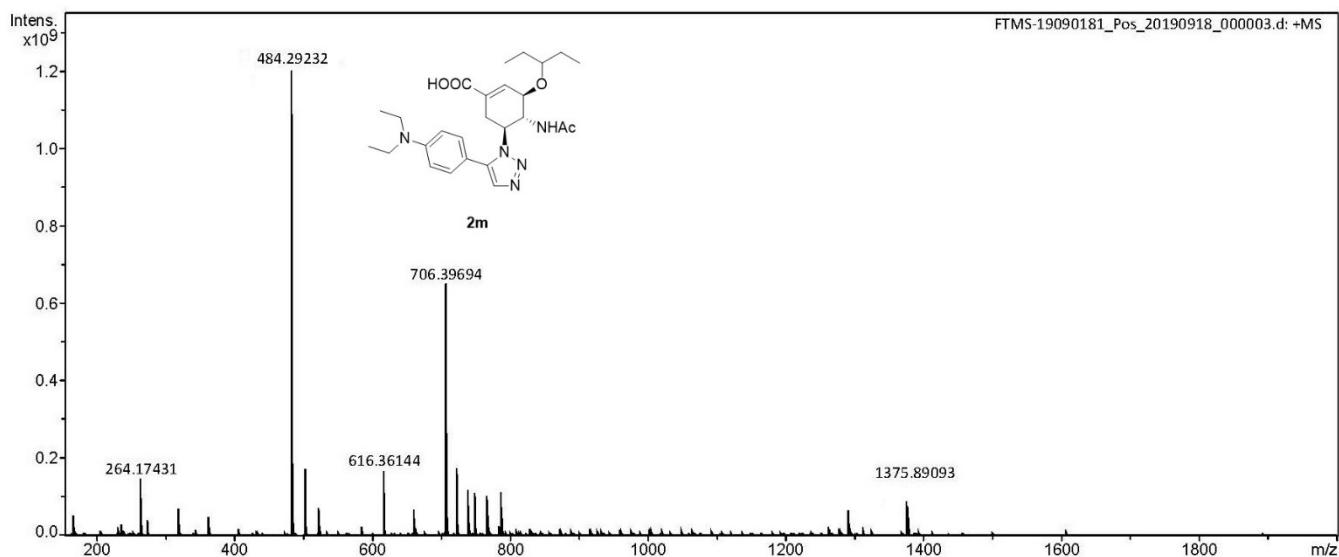
HR-ESIMS of 2m

IR of 2m
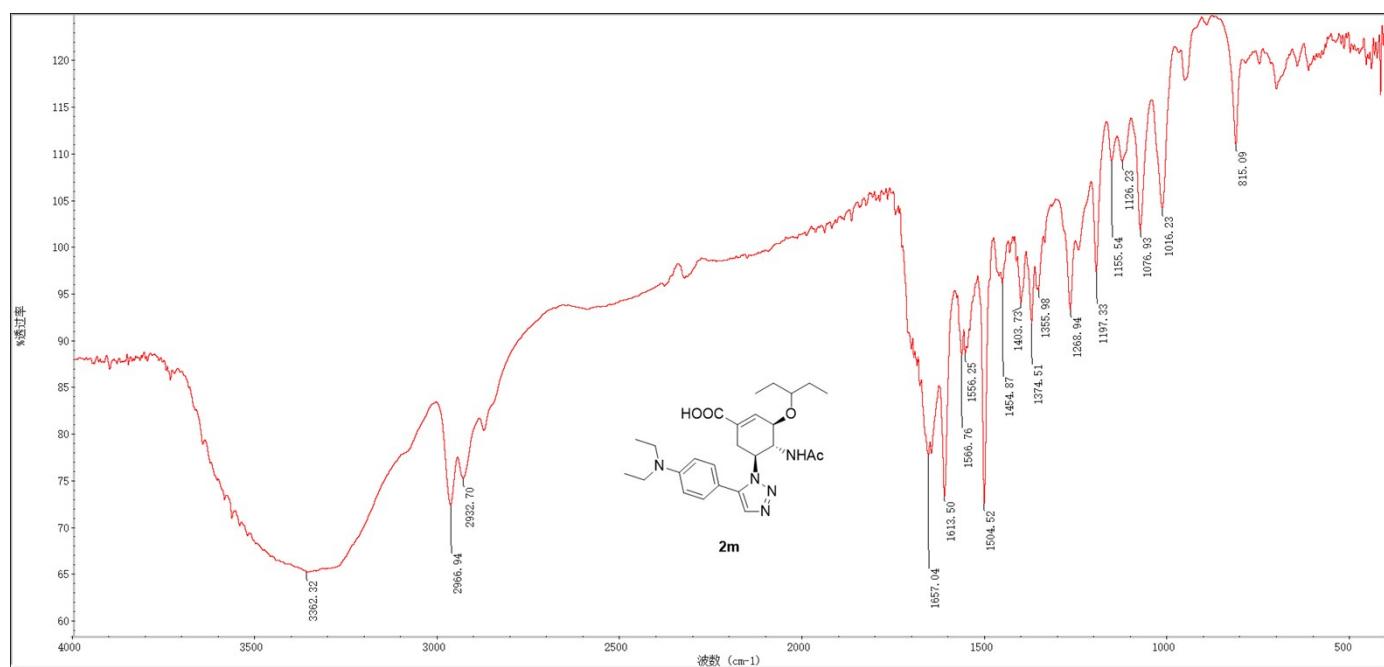
^{1}H NMR of 2n (500 MHz, CD$_3$OD)
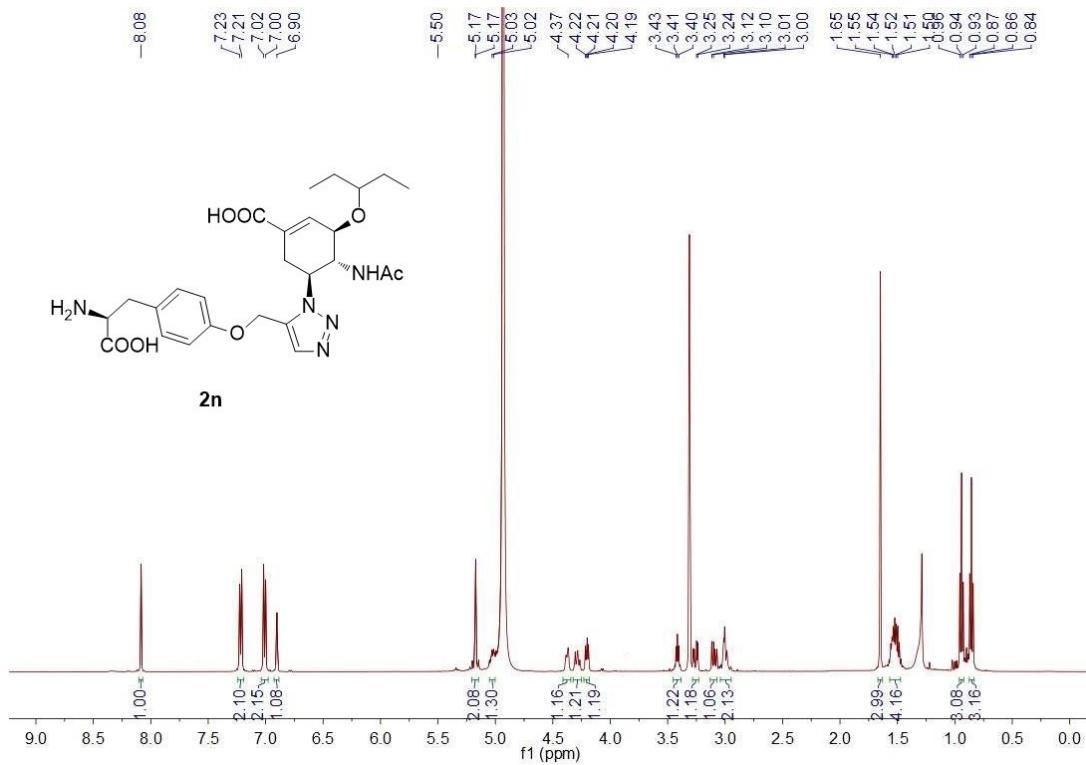

^{13}C NMR of 2n (500 MHz, CD$_3$OD)

HR-ESIMS of 2n

Meas. m/z	I	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
530.26064	122822536	C 26 H 36 N 5 O 7	100.00	530.26092	0.3	0.5	8.0	11.5	even	ok

IR of 2n