

Phytochemical Investigation and Anti-Inflammatory Activity of the Leaves of *Machilus japonica* var. *kusanoi*

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Table S1. Inhibitory effects of crude extracts from the leaves of *M. japonica* var. *kusanoi* on superoxide anion generation and elastase release in fMLP/CB-induced human neutrophils.

37

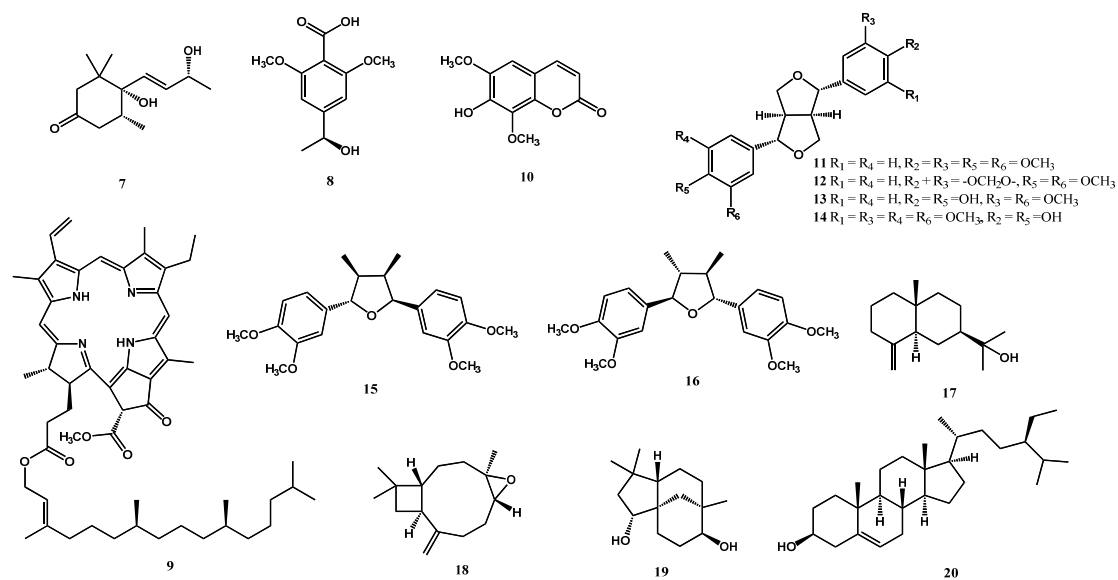


Figure S1. Structures of known compounds 7–20.

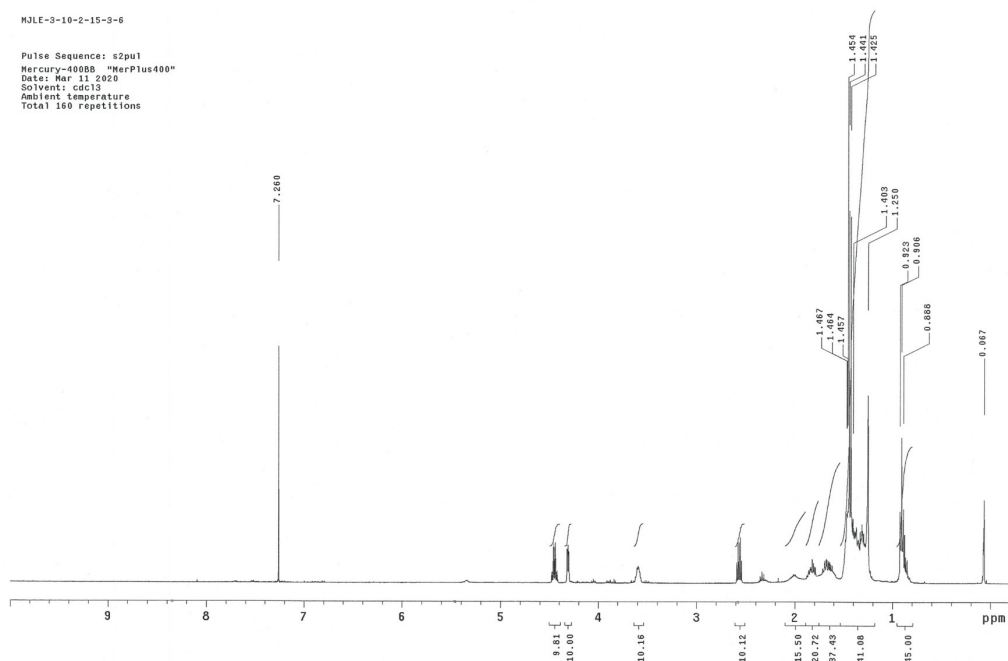


Figure S2. ¹H NMR spectrum of (400 MHz, CDCl₃) spectrum of 1

MJLE-3-10-2-15-3-6

Pulse Sequence: s2pu1
Mercury-400SB "MerPlus400"
Date: Mar 11 2020
Solvent: cdcl3
Ambient temperature
Total 2888 repetitions

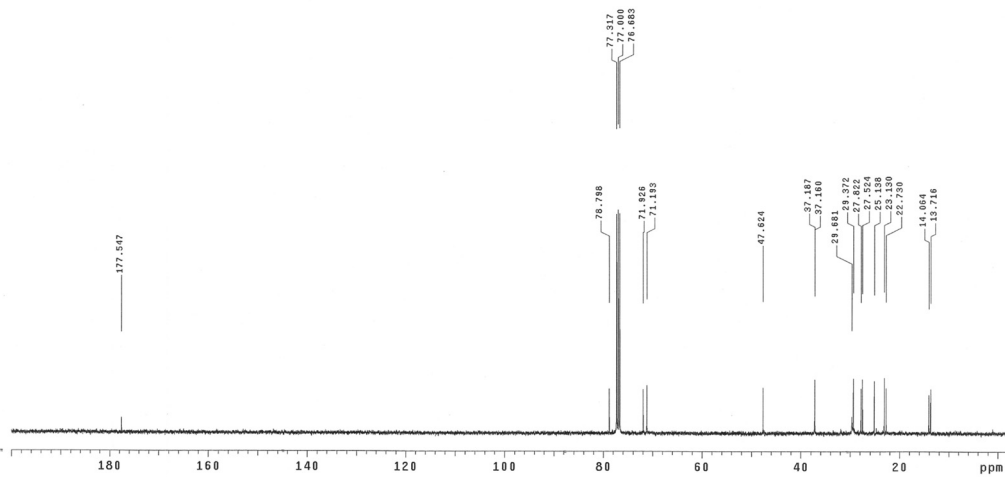


Figure S3. ^{13}C NMR spectrum of (100 MHz, CDCl_3) spectrum of **1**

MJLE-3-10-2-15-3-6

Pulse Sequence: DEPT

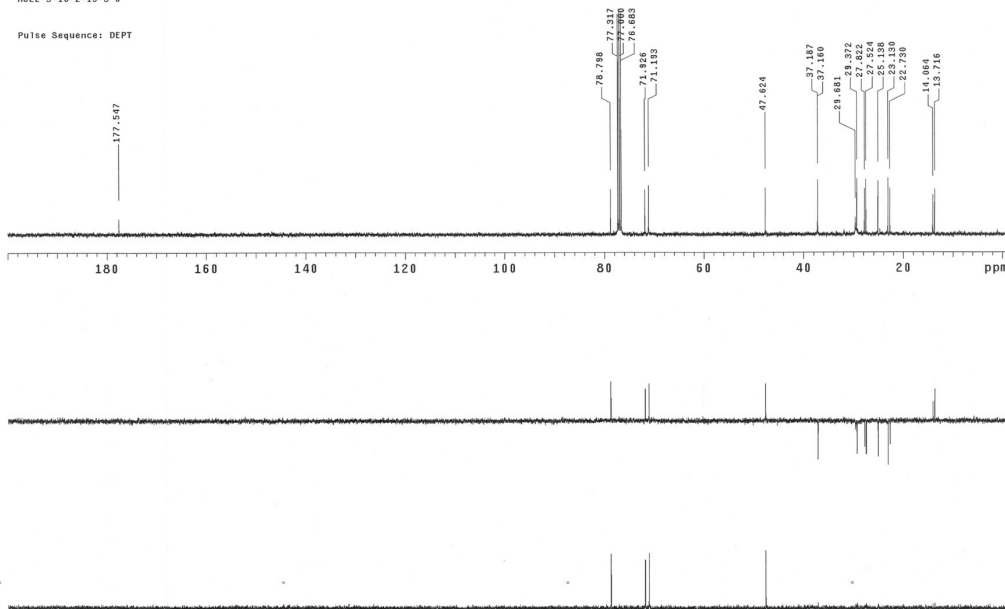


Figure S4. DEPT spectrum of **1**

MJLE-3-10-2-15-3-6

exp14 gCOSY

```
date      Mar 11 2020  hs  FLAGS  nn
solvent   cdc13      sspu1   y
sample    hsg1v1      1212
ACQUISITION  SPECIAL
sw        6410.3  temp  not used
at        0.150  gain  24
np        1920   spin  0
fd        not used  f2 PROCESSING  0
ss        32     sb   -0.075
dl        1.000  sbs  not used
nt        20     fn   4096
2D ACQUISITION  F1 PROCESSING
sw1       6410.3  sb1  -0.020
n1        160    sbc1 not used
d2        0      procl 1p
PRESATURATION 0      fn1  4096
satmode      n      DISPLAY
wet          n      sp      -82.4
TRANSMITTER  n      wp      4091.5
tn           H1    sp1    -82.4
frrq        400  wp1    4091.5
tor         366.0  rf1    892.3
tpwr        56    rfp    0
pw          11.800  rf11   892.3
GRADIENTS    1012  PLOT  0
gz1v1e      0.001000  wc    140.0
gTE         1.000    sc    5.0
gStab       0.000500  wc2   140.0
DECOUPLER   C13    vc    100
dn          nnn    th    7
dm          nnn    at   cdc av  7
```

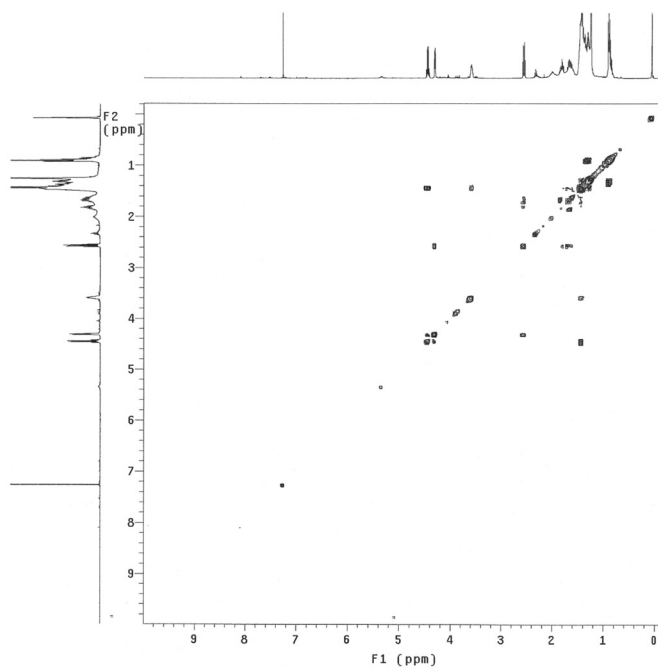


Figure S5. COSY spectrum of **1**

Pulse Sequence: gHSQC

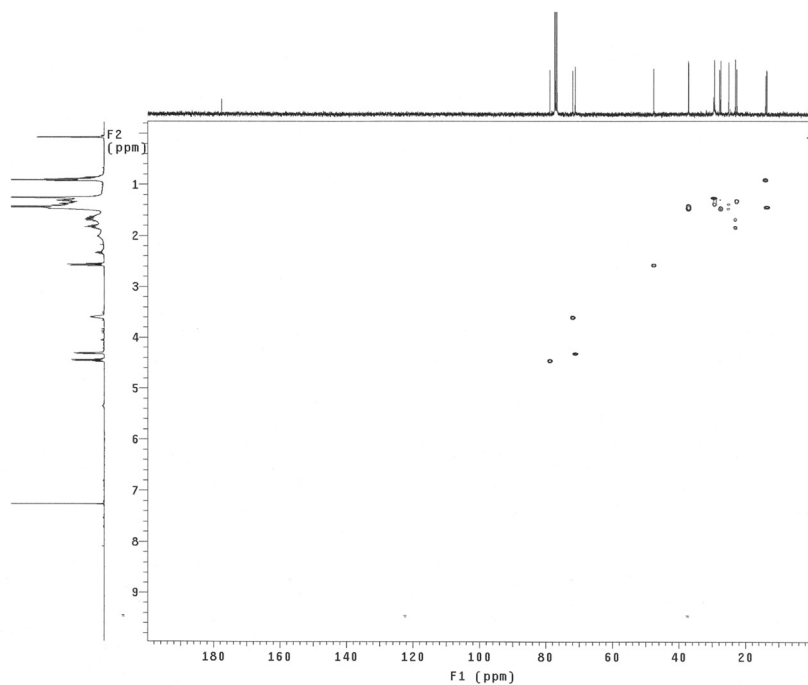


Figure S6. HSQC spectrum of **1**

Pulse Sequence: gHMBC

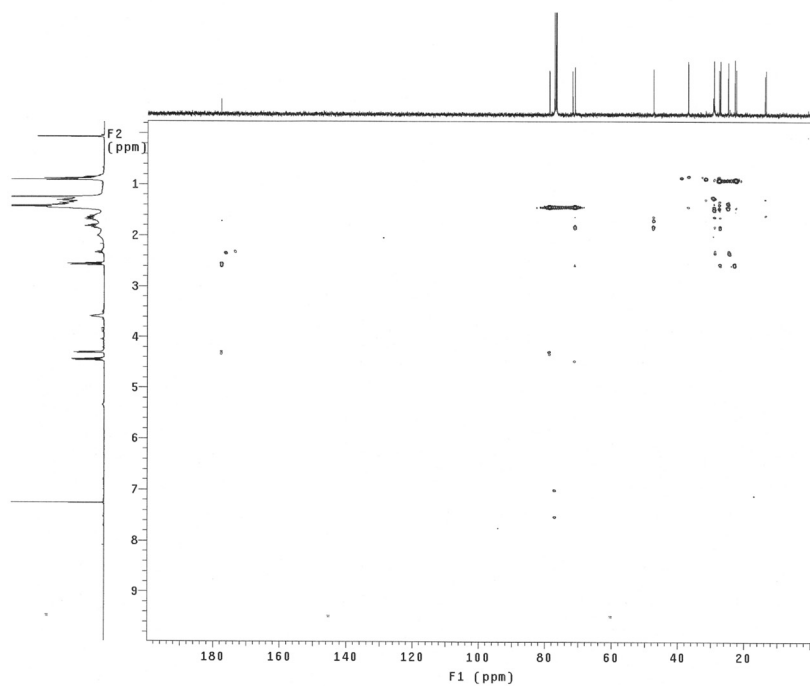


Figure S7. HMBC spectrum of 1

NJLE-3-10-2-15-3-6
exp15 NOESY

```
date      Mar 11 2020   hs      FLAGS      nn
solvent   cdc13             spul1     y
sample    PFOF1g           y
ACQUISITION  hsglv1       1212
sw        8810.3      SPECIAL   not used
at        0.150    temp      not used
np        1920     gain     24
fb        not used  spin     0
ss        32      F2 PROCESSING 0
d1        1.000    pf       0.069
nt        16     gfs     not used
2D ACQUISITION  F1 PROCESSING 4096
ni        6410.3   F1
TRANSMITTER  H1     proc1   not used
tn        400.001  f1
sfrq      386.0    DISPLAY
tpwr      55     sp       -82.4
pw        11.900  wp       4081.5
mixN      NOESY   0.600   cp1     -82.4
PRESATURATION  rff1   802.3
satmode   n     rfp     0
wet       n     rf11   802.3
dm        DECOUPLER C13     PLOT
          nnn    wc      140.0
          wc2   140.0
          sc2   5.0
          vs    2852
          ln     5
          al   cdc ph
```

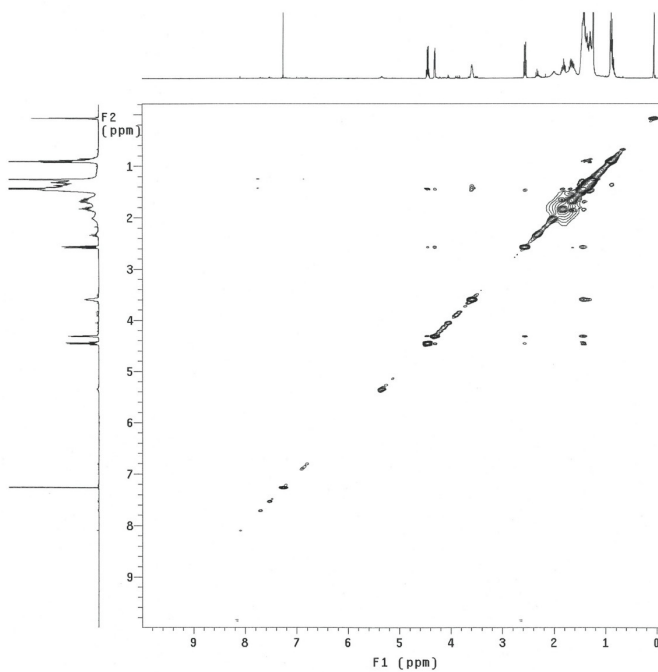


Figure S8. NOESY spectrum of 1

[Mass Spectrum]
Data: 3091 Date: 11-Mar-2020 15:29
Instrument: MStation
Sample: MJLE-3-10-2-15-3-6
Note: --
Inlet: Reservoir Ion Mode: EI+
Spectrum Type: Normal Ion [MF-Linear]
RT: 1.42 min Scan#: 18
BP: m/z 57 Int.: 10683552 (10683552)
Output m/z range: 50 to 350 Cut Level: 2.50 %

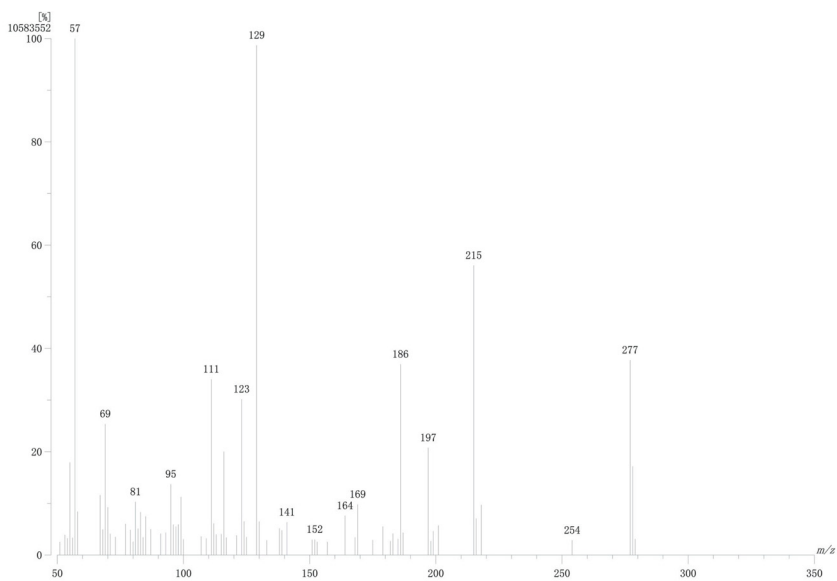


Figure S9. EIMS spectrum of 1

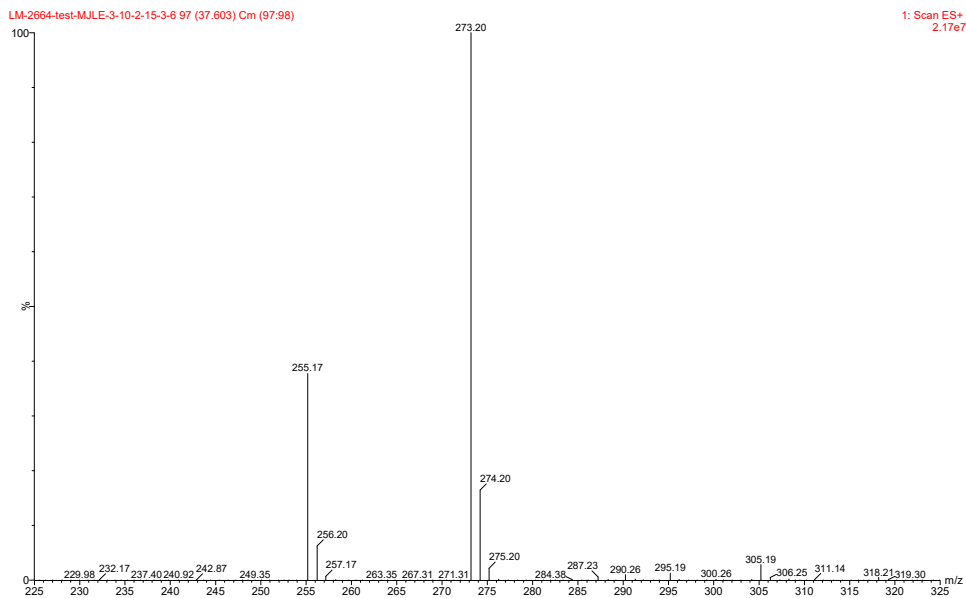
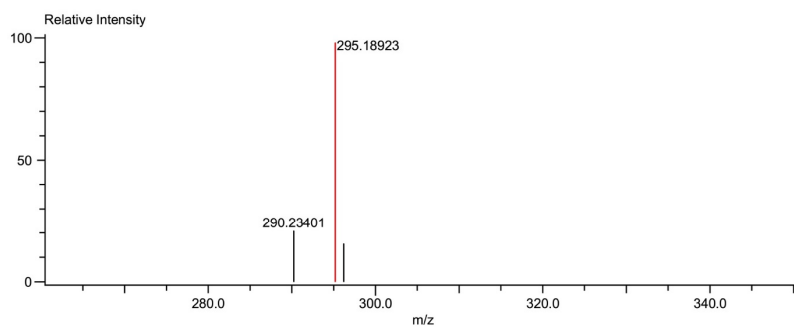


Figure S10. ESIMS spectrum of 1

Data: MJLE-3-10-2-15-3-6
Comment:
Description:
Ionization Mode: ESI+
History: Average(MS[1] 0.37..0.38)

Acquired: 2/7/2020 1:58:58 PM
Operator: AccuTOF
m/z Calibration File: 20200102-1TFANa...
Created: 2/7/2020 2:02:24 PM
Created by: AccuTOF

Charge number: 1 Tolerance: 250.00[ppm], 200.00 .. 200.00... Unsaturation Number: -100.5 .. 200.0 (...
Element: ¹²C: 15 .. 15, ¹H: 28 .. 29, ²³Na: 0 .. 2, ¹⁶O: 4 .. 4



Mass	Intensity	Calc. Mass	Mass Difference [mDa]	Mass Difference [ppm]	Possible Formula
295.18923	13277.94	295.18853	0.70	2.36	¹² C ₁₅ ¹ H ₂₈ ²³ Na ₁ ¹⁶ O ₄

Figure S11. HRESIMS spectrum of 1

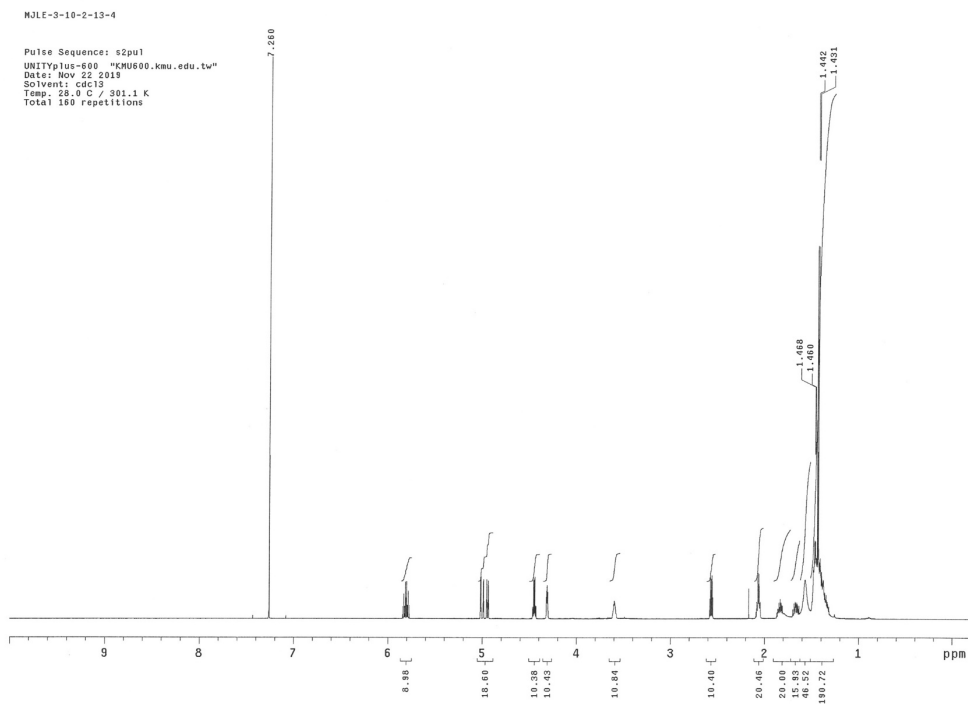


Figure S12. ¹H NMR spectrum of (600 MHz, CDCl₃) spectrum of 2

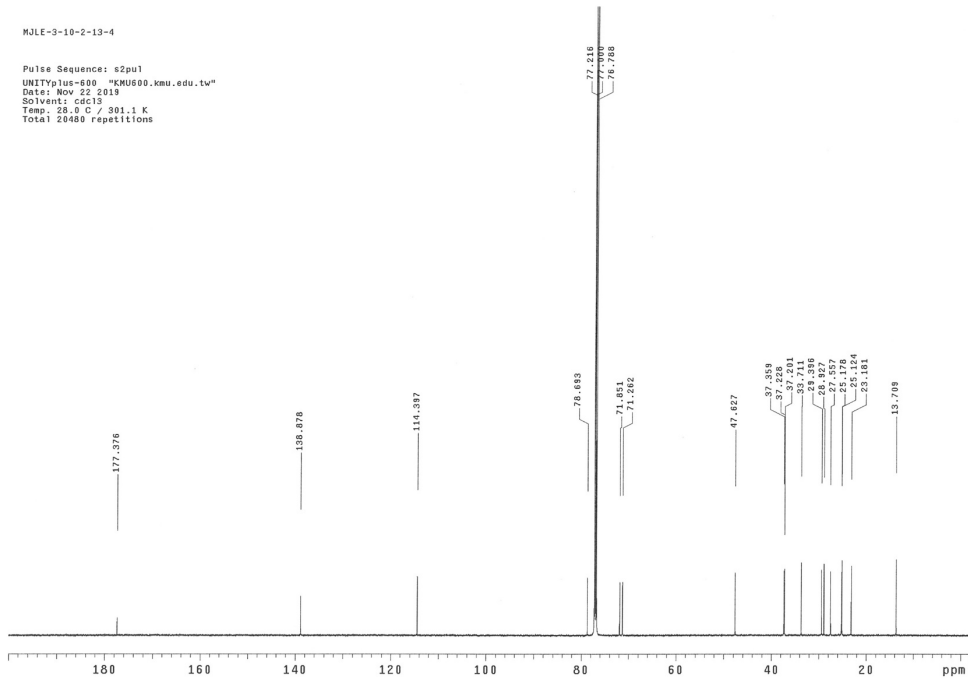


Figure S13. ^{13}C NMR spectrum of (150 MHz, CDCl_3) spectrum of **2**

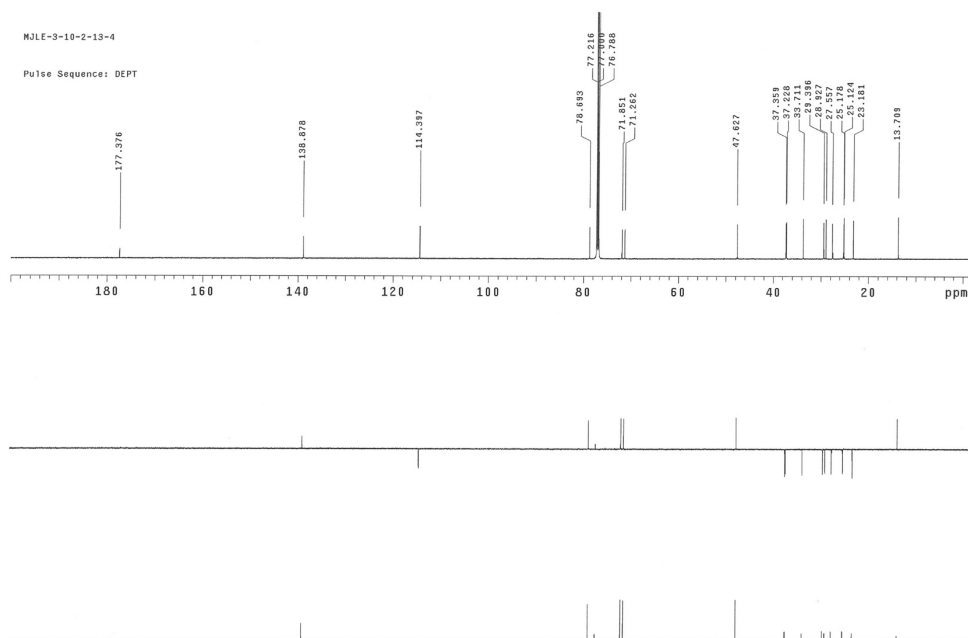


Figure S14. DEPT spectrum of **2**

```

M3LE-3-10-2-13-4
exp14 qCOSY
SAMPLE          FLAGS
date Nov 22 2019 hs nn
solvent cdc13  sspul y
sample          hsjlv1 5352
ACQUISITION     SPECIAL
sv 9542.0 tempo 28.0
at 0.150 gain 50
np 2862 spfn not used
fb 4000 F2 PROCESSING
ss 32 sb -0.075
d1 1.000 sbs not used
nt 40 fn 4096
2D ACQUISITION  F1 PROCESSING
sv1 9542.0 sb1 -0.017
n1 160 sb1 not used
d2 0 procl lp
PRESATURATION  n fn1 4096
satmode
wet n sp DISPLAY
tn TRANSMITTER wp -120.5
tn H1 sp1 -122.7
ffq 597.257 wp1 6089.5
tof 597.2 rf1 1192.1
tpwr 58 rfp 0
pw 12.000 rf11 1194.3
GRADIENTS      rf1 0
gz1v1e 4464 PLOT
gtE 0.001000 wc 140.0
Edratio 1.0000 zc 5.0
gstab 0.000500 wc2 140.0
DECOUPLER      sc2 5.0
dn C13 vs 4000
dm nnn th 8
at cdc av

```

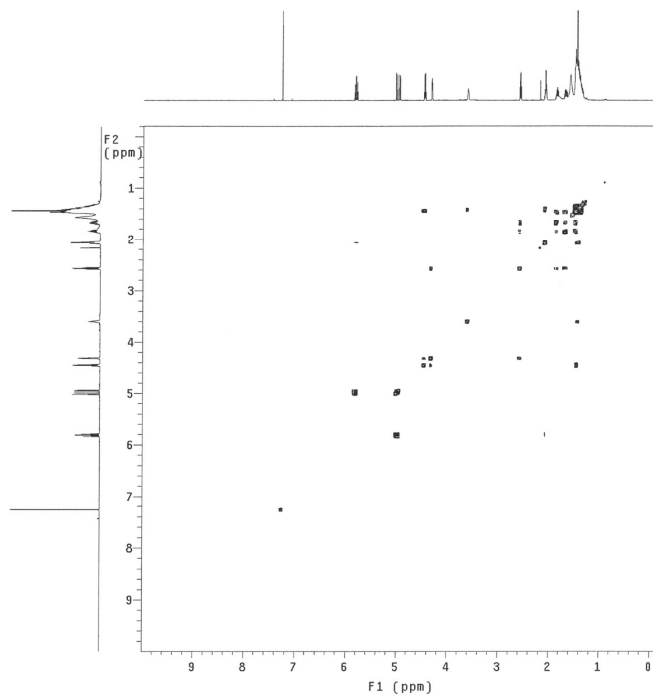


Figure S15. COSY spectrum of 2

```

M3LE-3-10-2-13-4
Pulse Sequence: gHSQCAD

```

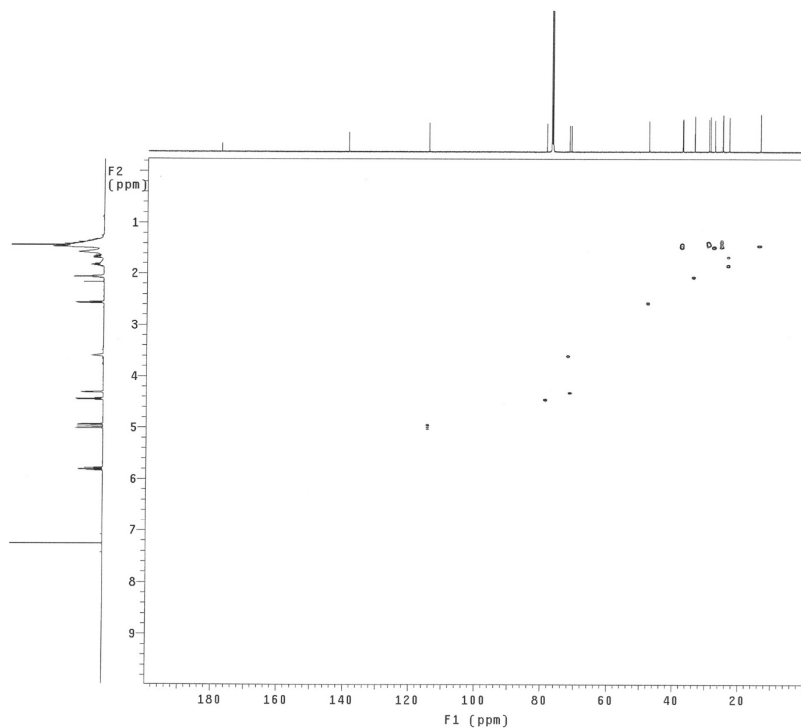


Figure S16. HSQC spectrum of 2

NJLE-3-10-2-13-4
Pulse Sequence: gHMBCAD

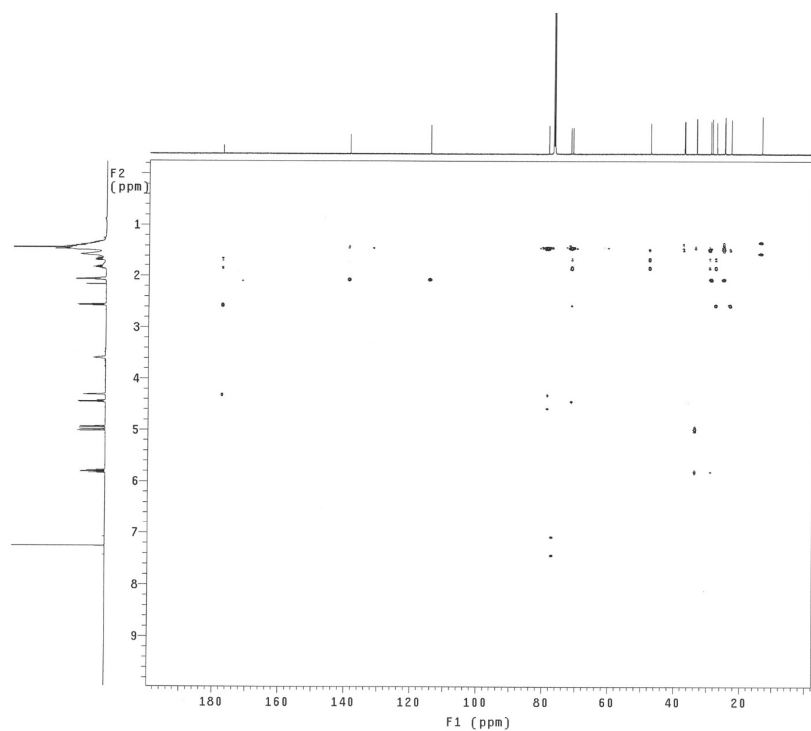


Figure S17. HMBC spectrum of 2

NJLE-3-10-2-13-4
exp15 NOESY

```

SAMPLE          hs   FLAGS   nn
date Nov 22 2019
solvent cdc13  sspul   y
sample PFG1q  hsglvq  y
ACQUISITION    SPECIAL 5352
sw 9542.0
at 0.150 temp 28.0
np 2052 gn 40
fb 4000 spin 0
se 32 f2 PROCESSING 0
st 1.500 gf 0.069
nt 40 gfs not used
2D ACQUISITION fn 4096
sw1 9542.0 f1 PROCESSING 0
nt 150 gf1 0.015
TRANSMITTER h1 gf1 not used
ln h1 proc1 lg
tfrq 597.257 fn1 4096
tpwr 30 sp DISPLAY -119.5
pw 12.000 wp 6089.5
NOESY sp1 -121.6
mixN 0.600 wp1 6089.5
PRESATURATION rf1 1181.0
satmode n rfp 0
wet n rfp1 1184.1
DECOUPLER rf1 0
dn C13 wc PLOT 140.0
dm nmn sc 5.0
sc2 140.0
sc2 5.0
ve 422
ln 4
a1 ph

```

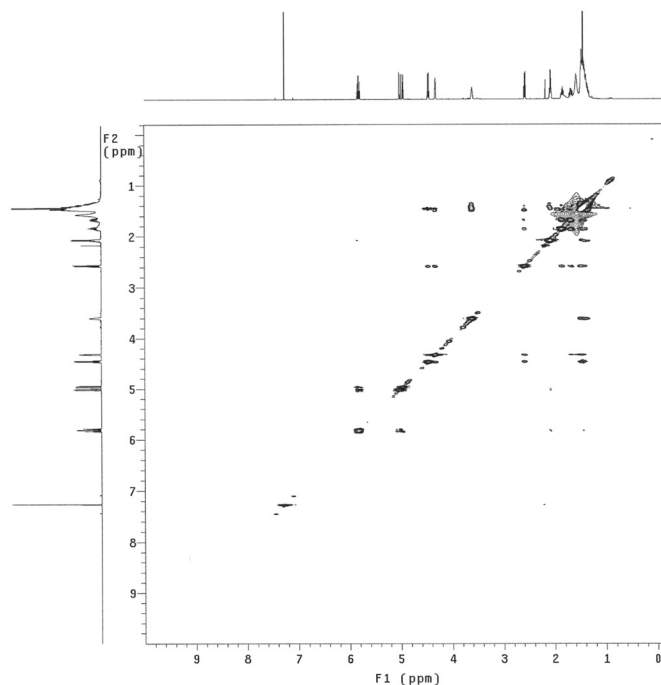


Figure S18. NOESY spectrum of 2

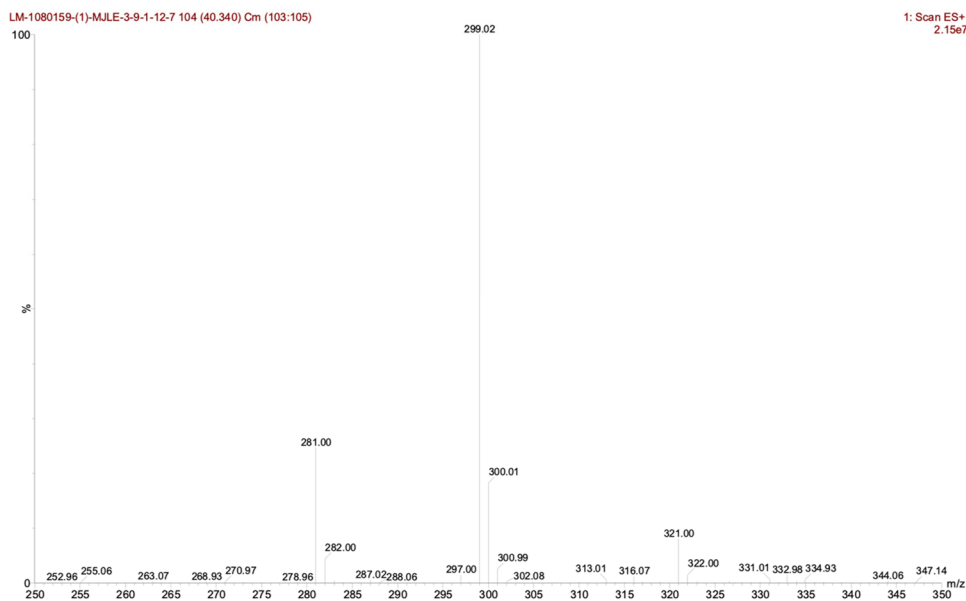


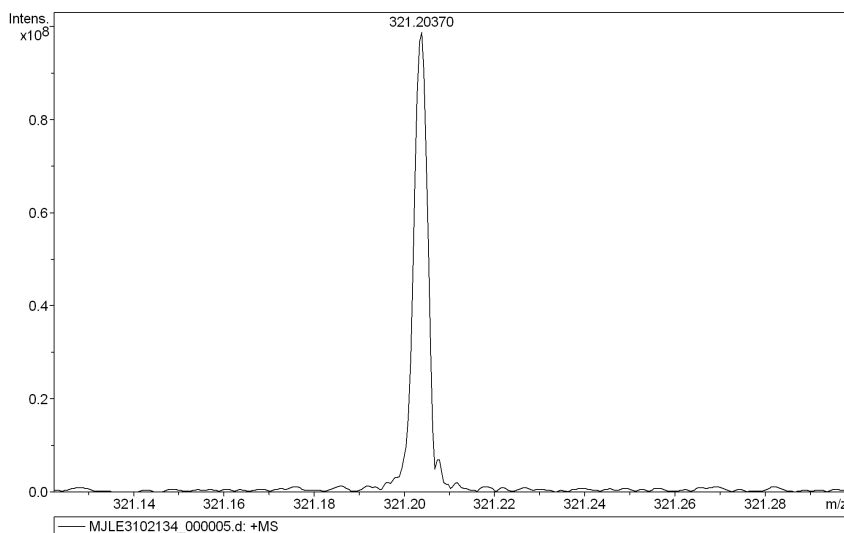
Figure S19. ESIMS spectrum of 2

Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name D:\Data\7\MJLE3102134_000005.d
 Method broadband first signal
 Sample Name MJLE-3-10-2-13-4
 Comment ESI Positive

12/31/2019 3:14:11 PM
 Operator: YU HSIAO-CHING
 Instrument: BRUKER FT-MS solariX



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e ⁻ Conf	N-Rule
321.20370	1	C 17 H 30 Na O 4	100.00	321.20363	-0.07	-0.23	18.8	2.5	even	ok

Figure S20. HRESIMS spectrum of 2

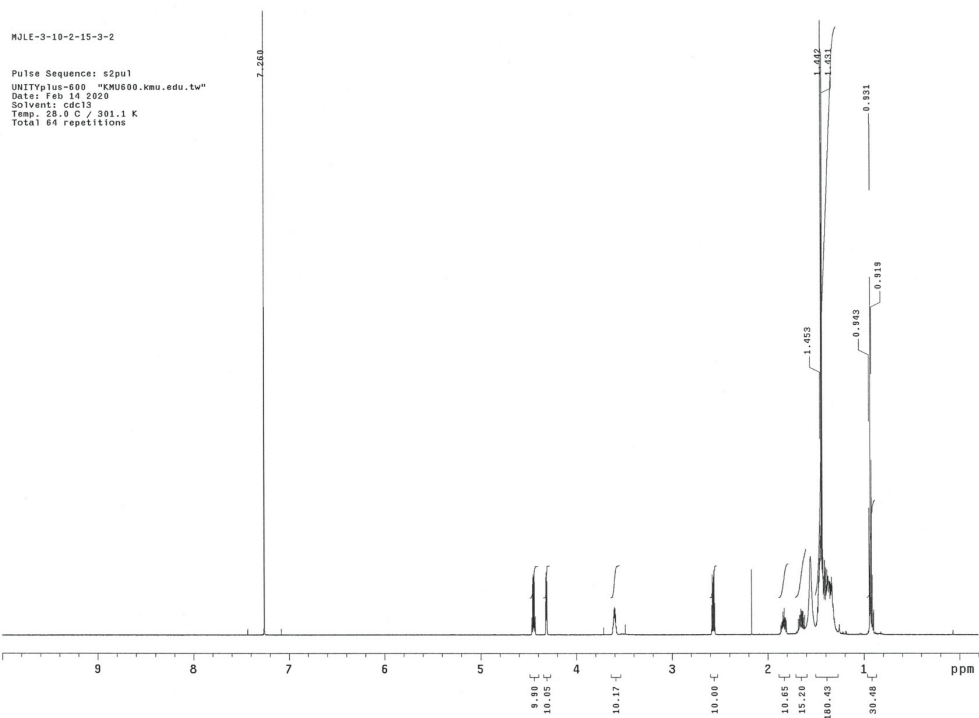


Figure S21. ^1H NMR spectrum of (600 MHz, CDCl_3) spectrum of **3**

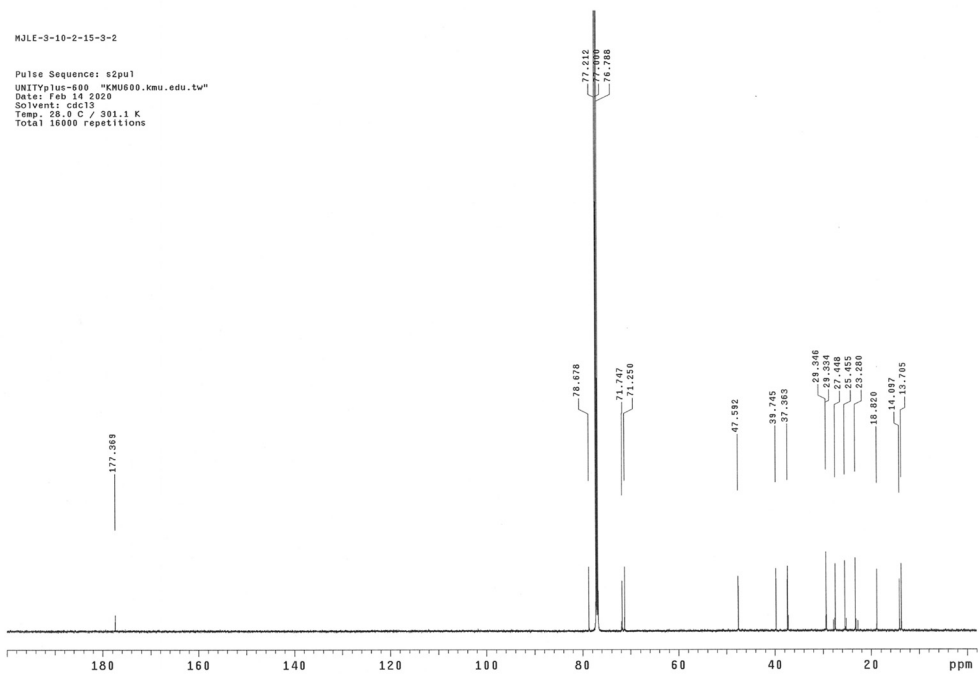


Figure S22. ^{13}C NMR spectrum of (150 MHz, CDCl_3) spectrum of **3**

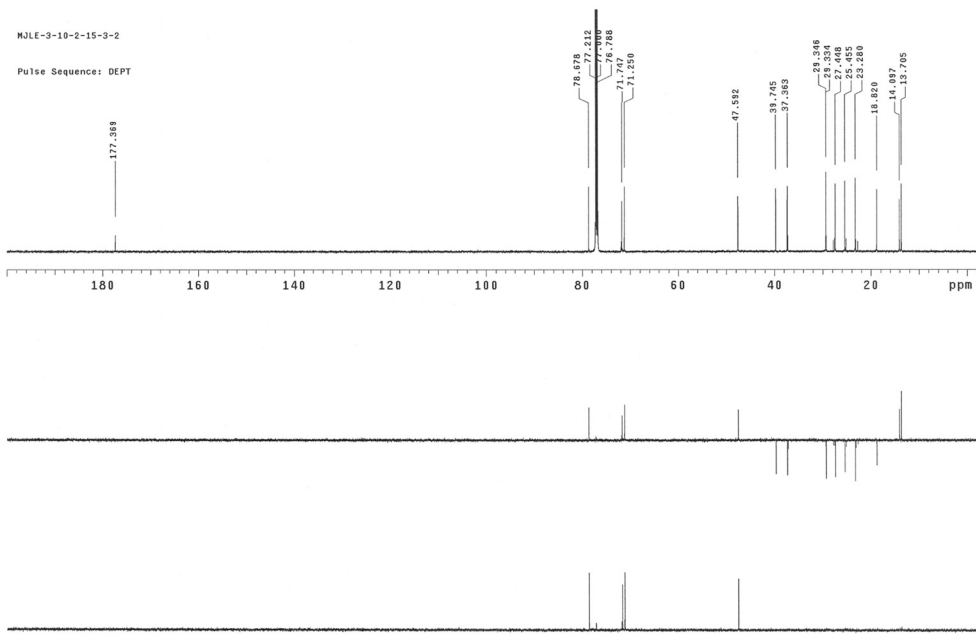


Figure S23. DEPT spectrum of 3

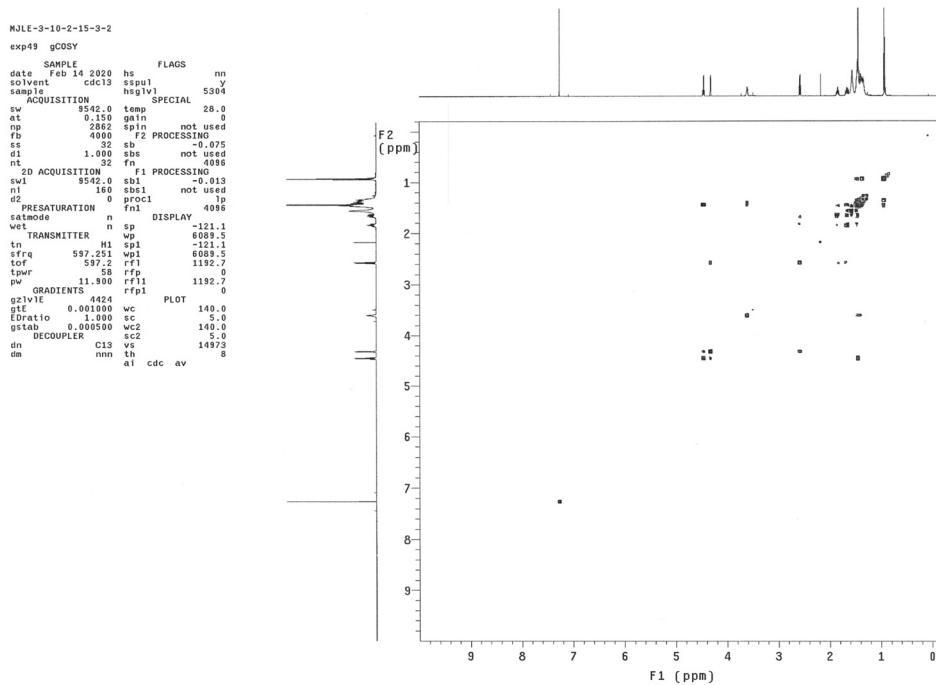


Figure S24. COSY spectrum of 3

NJLE-3-10-2-15-3-2
Pulse Sequence: gHSQCAD

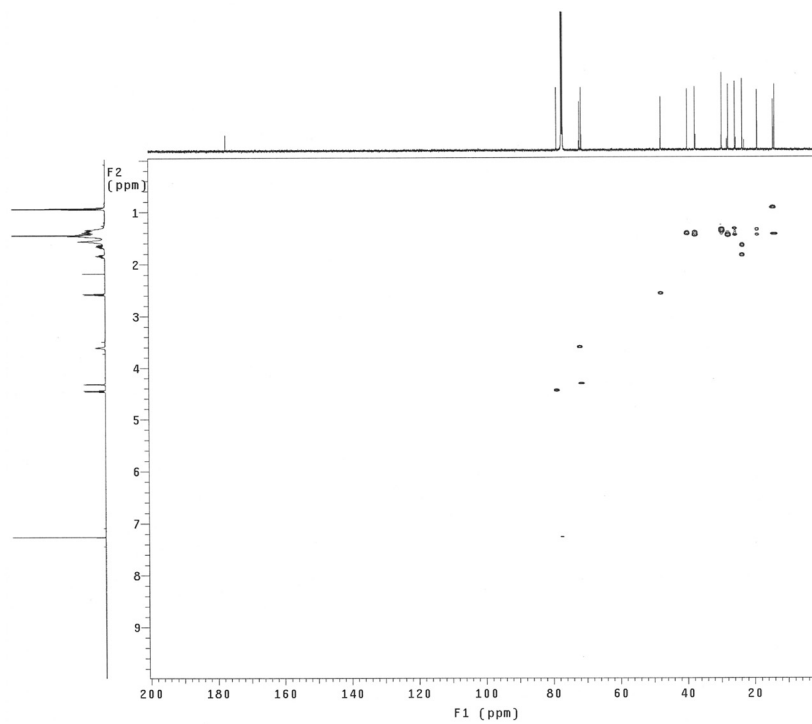


Figure S25. HSQC spectrum of 3

NJLE-3-10-2-15-3-2
Pulse Sequence: gHMBCAD

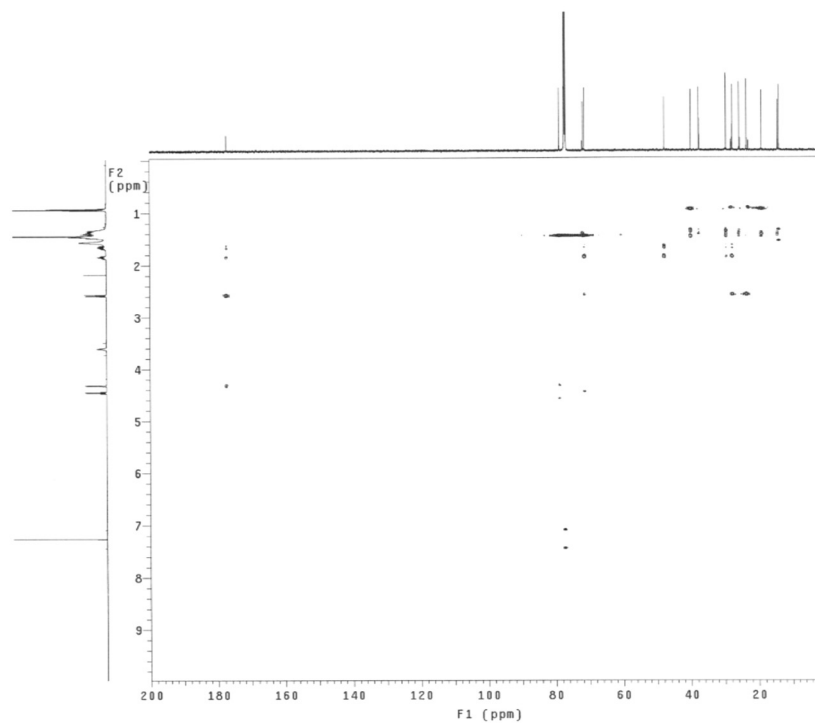


Figure S26. HMBC spectrum of 3

MJLE-3-10-2-15-3-2
exp50 NOESY

```

SAMPLE          hs      FLAGS      nn
date    Feb 14 2020  sspul      y
solvent  cdc13      PFG1g      0
sample  PFG1g
ACQUISITION  hsg1v1  5304
sw      9542.0      SPECIAL  28.0
at      0.150      temp    28.0
np      2862      gain    0
fb      4000      sp1n    not used
ss      32        F2 PROCESSING
dt      1.500      gf      0.069
nt      32        gfs     not used
2D ACQUISITION  tn      4096
sw1     9542.0      F1 PROCESSING
ni      160      gf1     0.014
TRANSMITTER  m1      procl   not used
tn      597.251    fn1     4096
tof     597.2
tpr     58        sp      -121.1
pw      11.900    wp1     6089.5
mixN    NOESY    0.600   sp1     -121.1
PRESATURATION  n      rfp     0
satmode  n      rfp     0
wet      DECOUPLER  n      rfp1    1192.7
dn       C13      min     PLOT
dm       mm      wc      140.0
          sc      5.0
          wc2     140.0
          sc2     5.0
          vs      350
          tn      2
          al      cdc ph

```

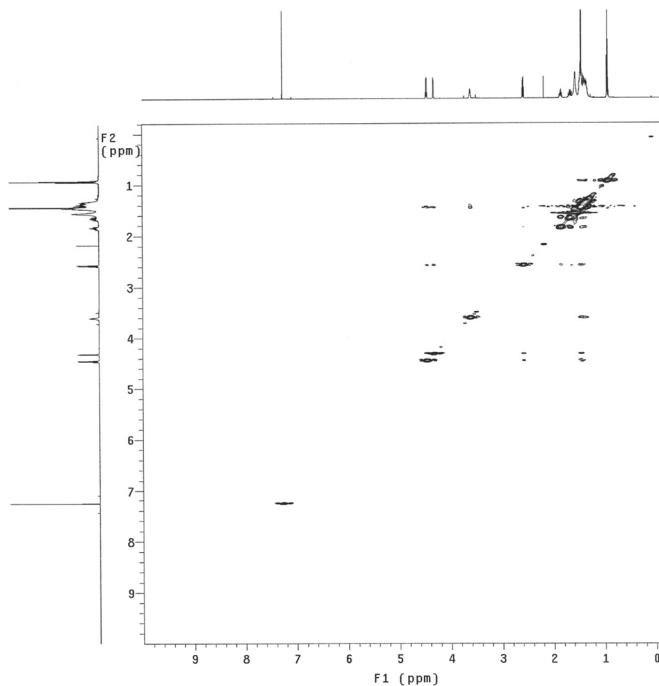


Figure S27. NOESY spectrum of 3

[Mass Spectrum]
Data : 3082 Date : 11-Mar-2020 15:43
Instrument : MStation
Sample : MJLE-3-10-2-15-3-2
Note : -
Inlet : Reservoir Ion Mode : EI+
Spectrum Type : Normal Ion [MF-Linear]
RT : 2.17 min Scan# : 27
BP : m/z 57 Int. : 129751 (13605376)
Output m/z range : 50 to 320 Cut Level : 2.00 %

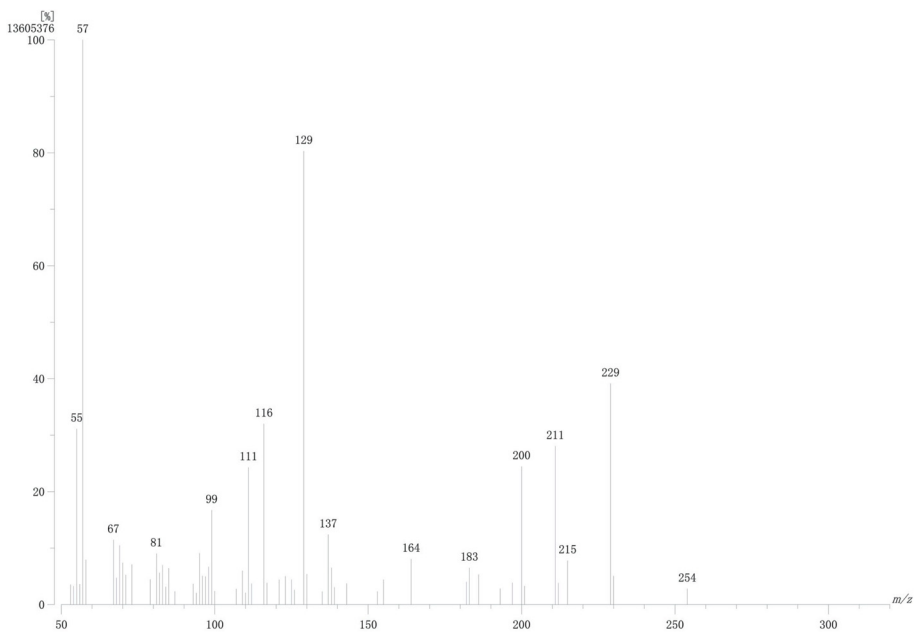


Figure S28. EIMS spectrum of 1

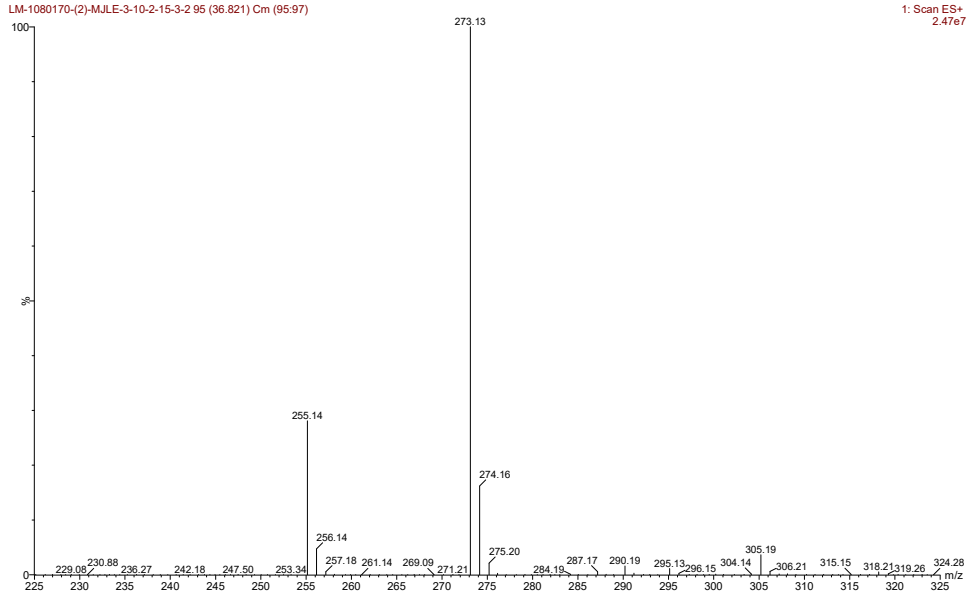
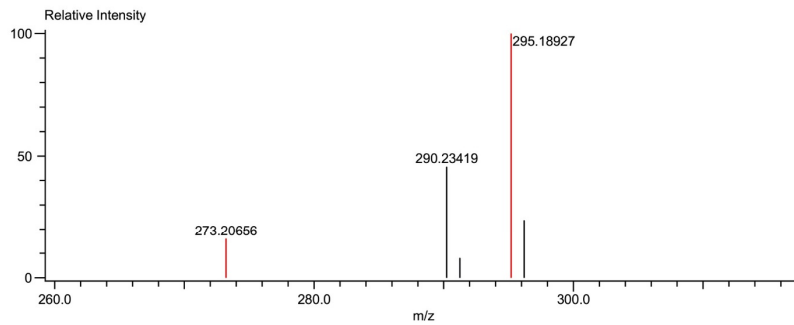


Figure S29. ESIMS spectrum of 3

Data: MJLE-3-10-2-15-3-2
 Comment:
 Description:
 Ionization Mode: ESI+
 History: Average(MS[1]) 0.38..0.39

Acquired: 12:00:00 AM
 Operator: AccuTOF
 m/z Calibration File: 20200102-1TFANA...
 Created: 2/7/2020 2:00:40 PM
 Created by: AccuTOF

Charge number: 1
 Tolerance: 250.00[ppm], 200.00 .. 200.00
 Unsaturation Number: -100.5 .. 200.0 (...)
 Element: ¹²C:15 .. 15, ¹H:28 .. 29, ²³Na:0 .. 2, ¹⁶O:4 .. 4



Mass	Intensity	Calc. Mass	Mass Difference [mDa]	Mass Difference [ppm]	Possible Formula
273.20656	1360.64	273.20658	-0.02	-0.07	¹² C ₁₅ ¹ H ₂₉ ¹⁶ O ₄
295.18927	8664.71	295.18853	0.74	2.52	¹² C ₁₅ ¹ H ₂₈ ²³ Na ¹⁶ O ₄

Figure S30. HRESIMS spectrum of 3

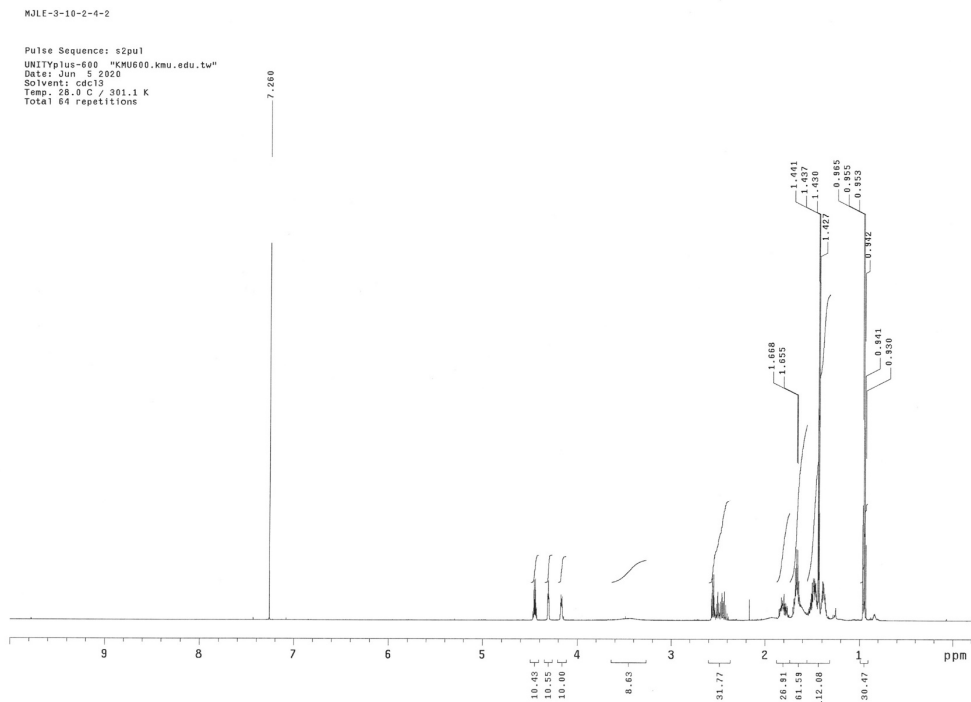


Figure S31. ^1H NMR spectrum of (600 MHz, CDCl_3) spectrum of **4**

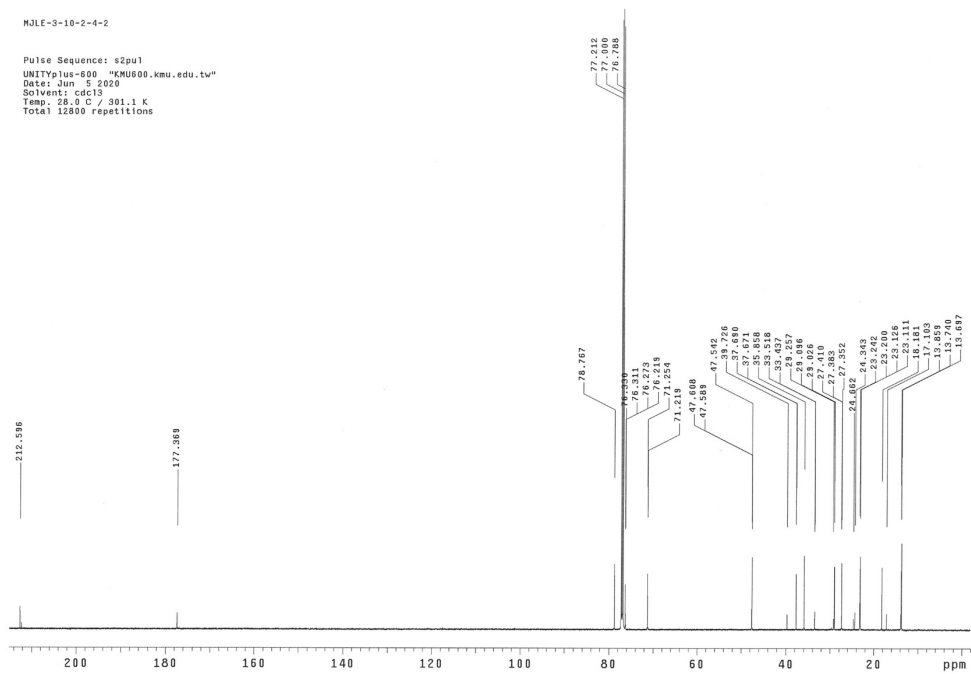


Figure S32. ^{13}C NMR spectrum of (150 MHz, CDCl_3) spectrum of **4**

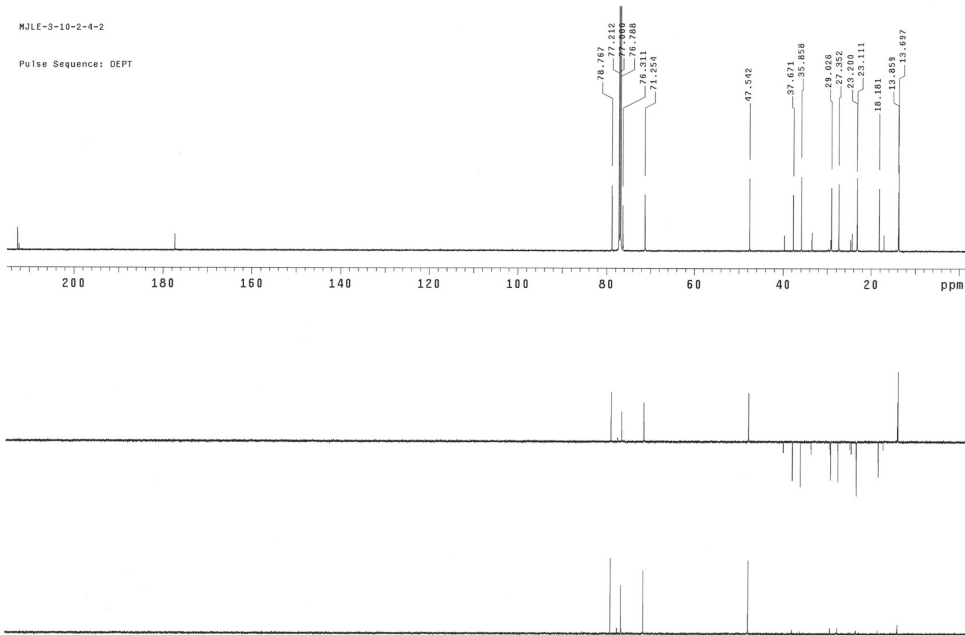


Figure S33. DEPT spectrum of 4

MJLE-3-10-2-4-2

exp14 gCOSY

SAMPLE		hs	FLAGS	nn
date	Jun 5 2020	hs		
solvent	cdcl3	spsol		y
sample		hsplvl		5304
ACQUISITION		SPECIAL		
sw	9542.0	temp		26.0
at	0.150	gain		46
rp	2862	spin		not used
fb	4000	F2	PROCESSING	
ss	32	sb		-0.075
d1	1.000	sbs		not used
nt	32	fn		4096
2D ACQUISITION		F1 PROCESSING		
sw1	9542.0	sb1		-0.013
n1	160	sbs1		not used
dc	0	procl1		lp
PRESATURATION		f1		
satmode	n	sp	DISPLAY	
wet			-120.6	
TRANSMITTER		wp		
tn	H1	sp1		6088.5
sfrq	597.251	wp1		6088.5
tof	597.2	rf1		1187.5
tpwr	58	rfp		0
pw	11.900	rf1f1		1187.5
GRADIENTS		rfp1		
gz1v1e	4424		PLOT	
g1e	0.001800	wc		140.0
Edratio	1.000	sc		5.0
g5tab	0.000500	wc2		140.0
		sc2		5.0
dm	CL3	ve		165
de	mm	ln		8
		at	cdc	av

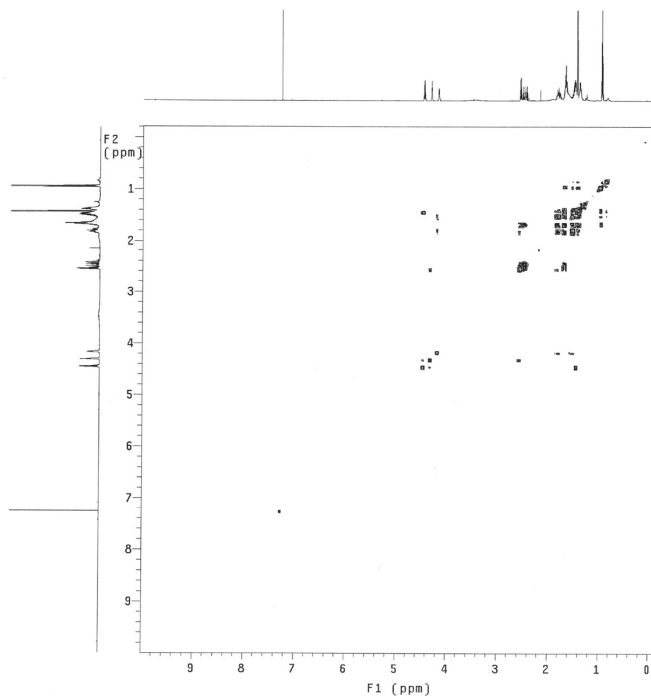


Figure S34. COSY spectrum of 4

hJLT-2-1U-2-9-2
Pulse Sequence: gHSQCAD

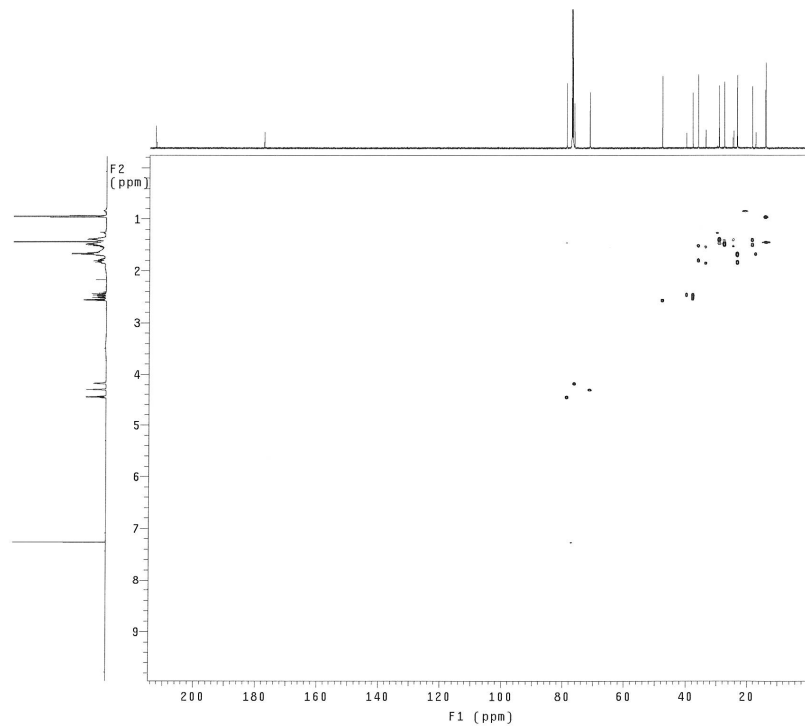


Figure S35. HSQC spectrum of **4**

hJLT-2-1U-2-9-2
Pulse Sequence: gHMBCAD

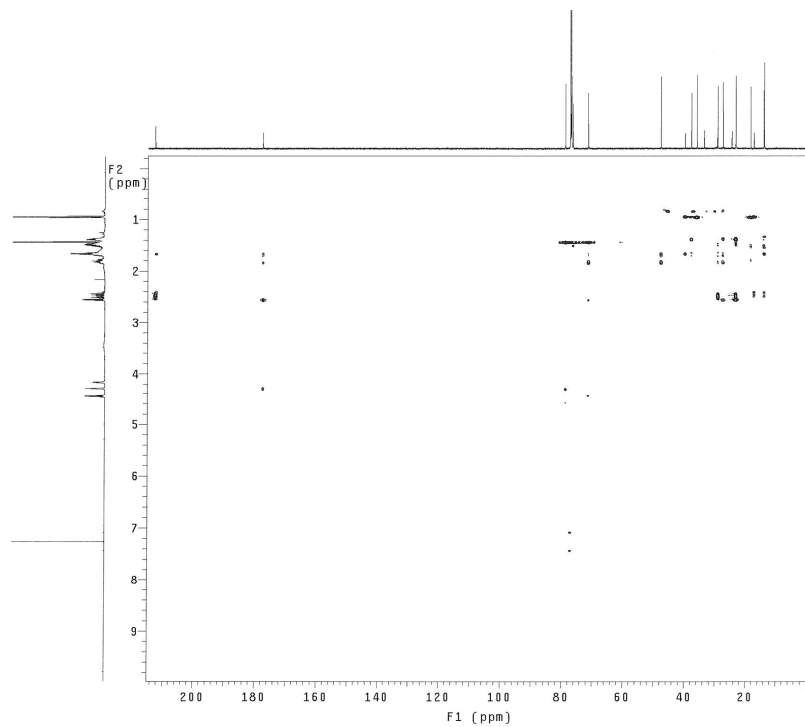


Figure S36. HMBC spectrum of **4**

MJLE-3-10-2-4-2

exp15 NOESY

```
SAMPLE          FLAGS      nn
date Jun 5 2020  hs          y
solvent cdcl3      sspu1     y
sample          pfgf1g     y
ACQUISITION     hsa1v1     5304
sv              9542.0    SPECIAL  28.0
at              0.150    temp     42
nd              2862    gain     not used
fb              4000    spfm     not used
se              32      F2 PROCESSING
d1              1.500    gf       0.069
nt              32      gfs      not used
nt              32      gf       not used
2D ACQUISITION  f1 F1 PROCESSING 4096
swi             9542.0    f1
ni              160    gf1     0.013
tn TRANSMITTER  hf1     not used
sfrq           537.251  fn1
topf           537.2    DISPLAY 4096
lpwr           58      sp       -120.6
pw            11.900    wp       6089.5
mi4M          NOESY    sp1     -120.6
PRESATURATION rf1     6089.5
satmode       n      rfp     1187.5
wet           n      rfp1    1187.5
DECOUPLER     C13    rfp1    0
dn            nnn     wc       140.0
            sc       3.0
            wc2     140.0
            sc2     5.0
            vs     350
            th
            at cdc ph 5
```

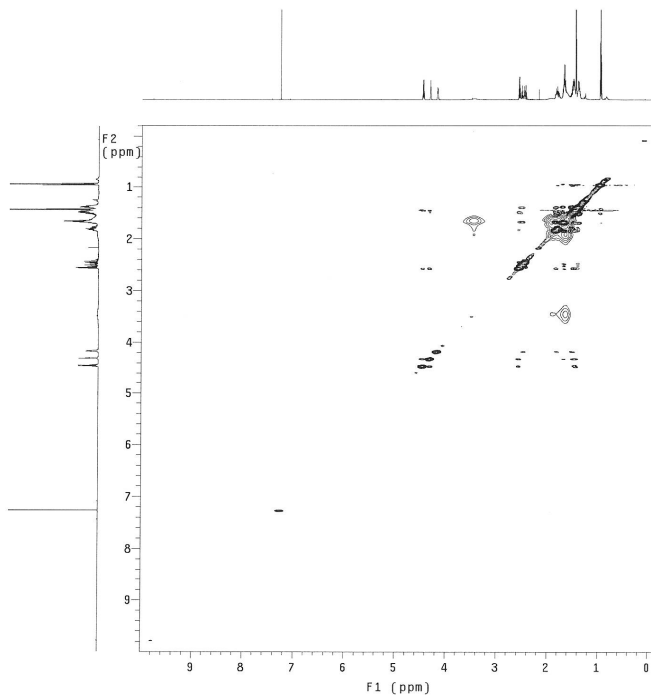


Figure S37. NOESY spectrum of 4

LM-1090073-(1)-MJLE-3-10-2-4-2 76 (29.391) Cm (76)

1: Scan ES+
2.19e7

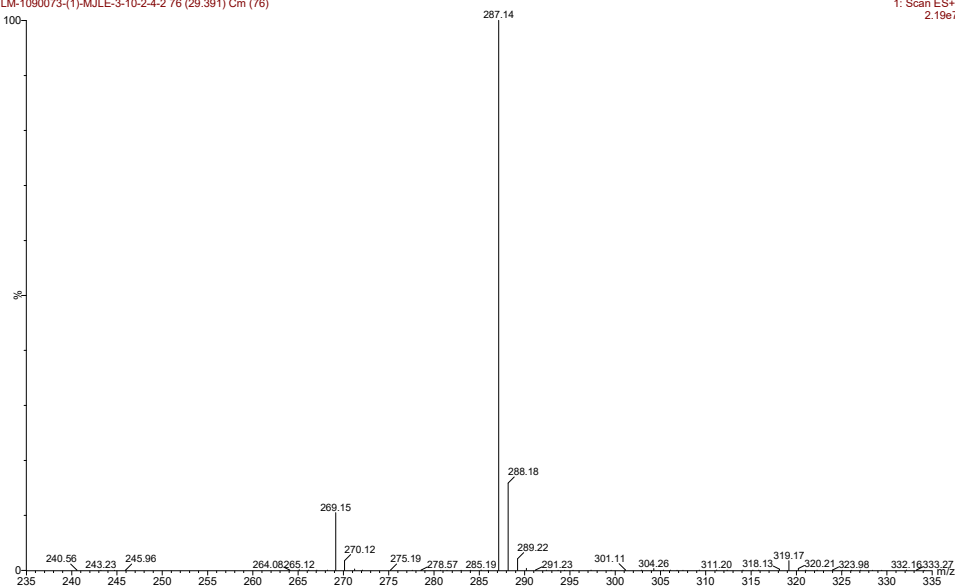


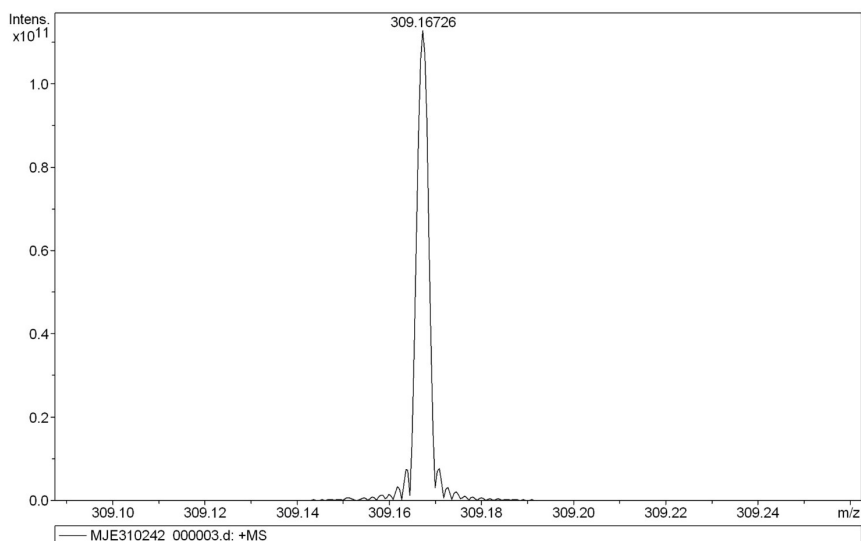
Figure S38. ESIMS spectrum of 4

Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name D:\Data\7\MJE310242_000003.d
Method broadband first signal
Sample Name MJLE-3-10-2-4-2
Comment ESI Positive

6/30/2020 2:47:28 PM
Operator: YU HSIAO-CHING
Instrument: BRUKER FT-MS solariX



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e ⁻ Conf	N-Rule
309.16726	1	C 15 H 26 Na O 5	100.00	309.16725	-0.02	-0.06	11.5	2.5	even	ok

Figure S39. HRESIMS spectrum of 4

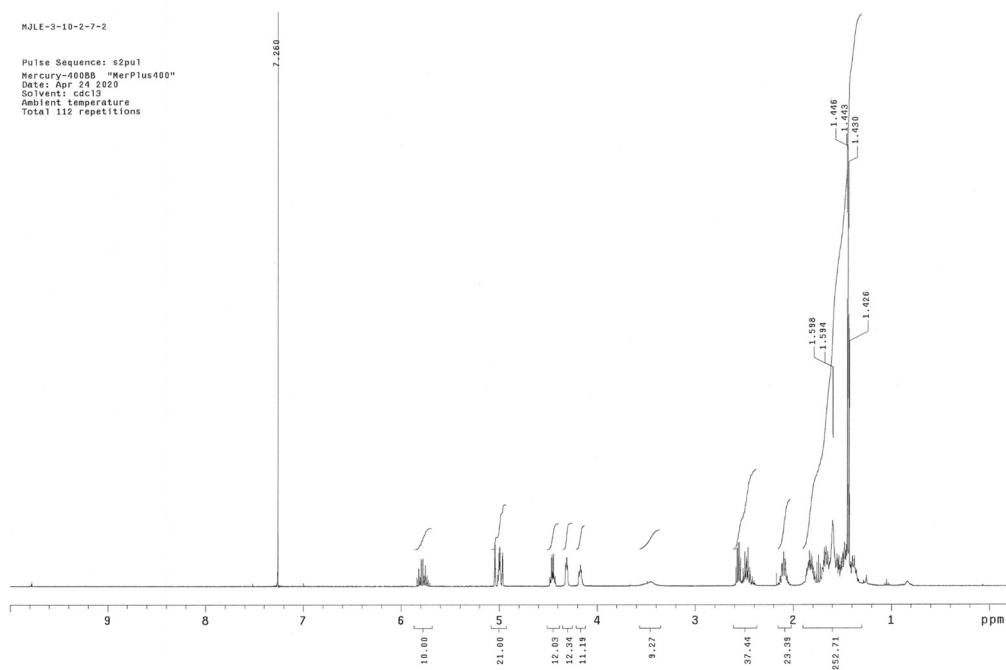


Figure S40. ¹H NMR spectrum of (400 MHz, CDCl₃) spectrum of 5

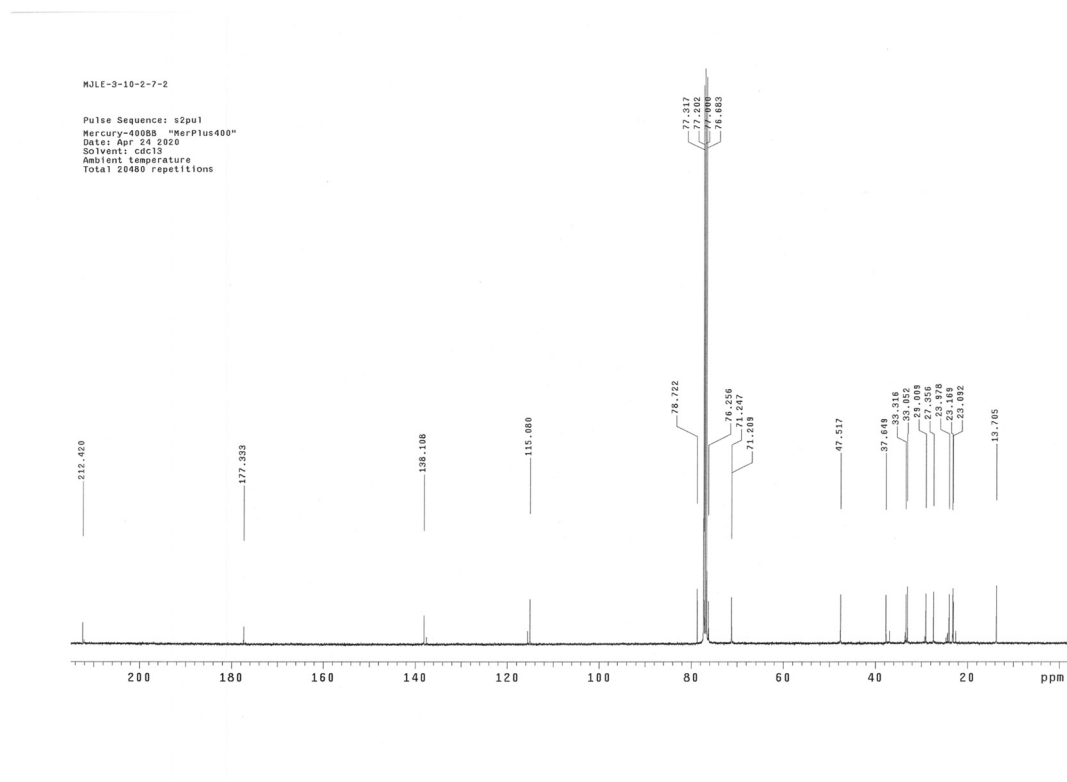


Figure S41. ^{13}C NMR spectrum of (100 MHz, CDCl_3) spectrum of **5**

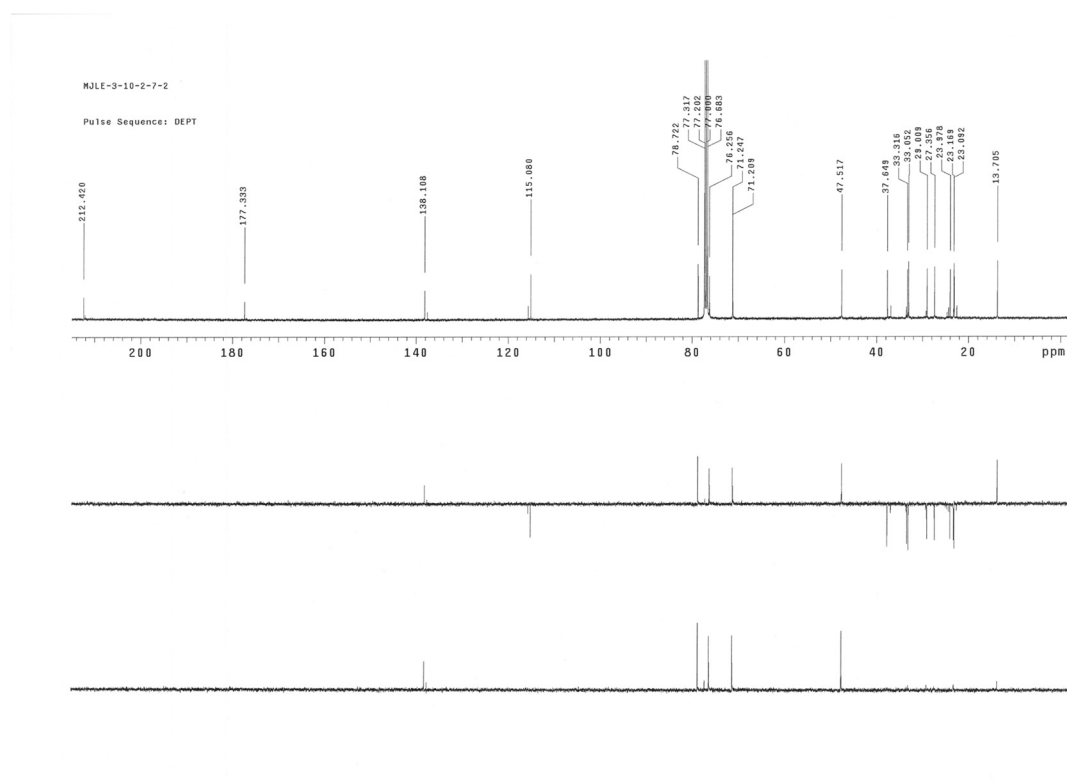


Figure S42. DEPT spectrum of **5**

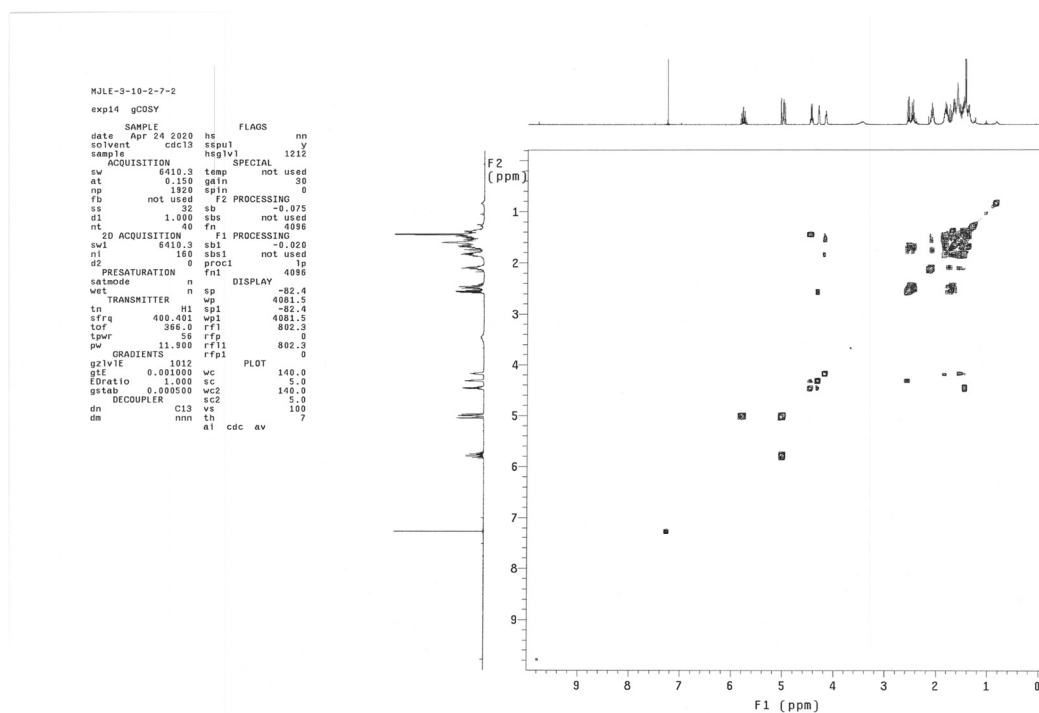


Figure S43. COSY spectrum of 5

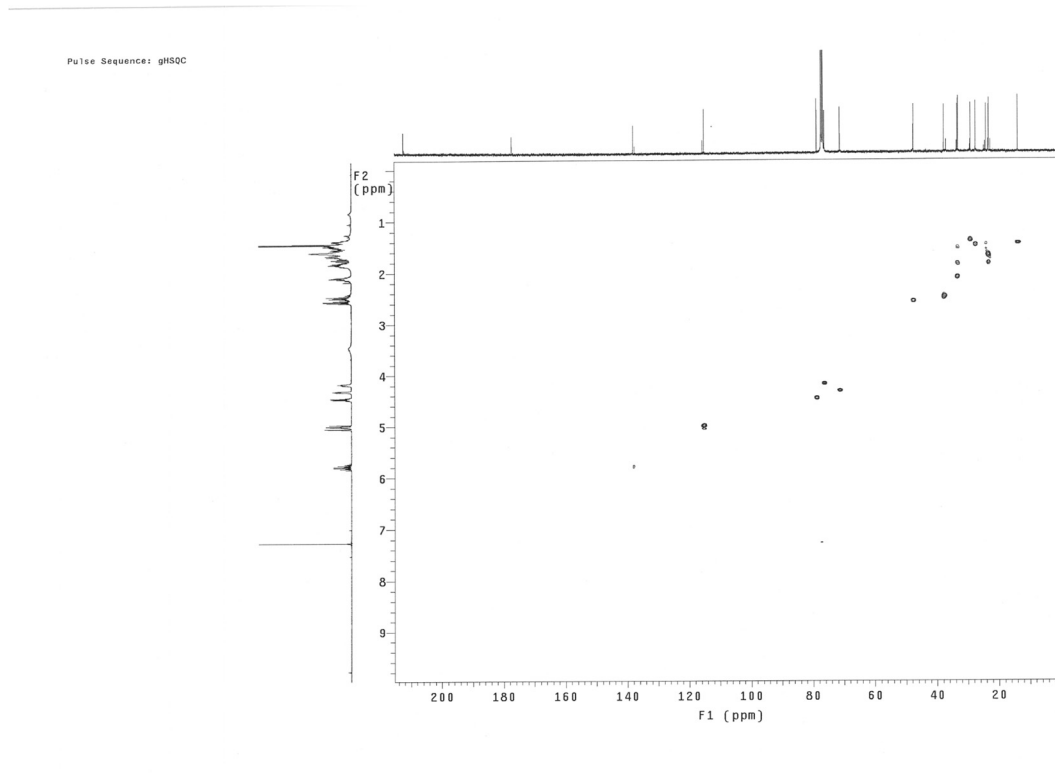


Figure S44. HSQC spectrum of 5

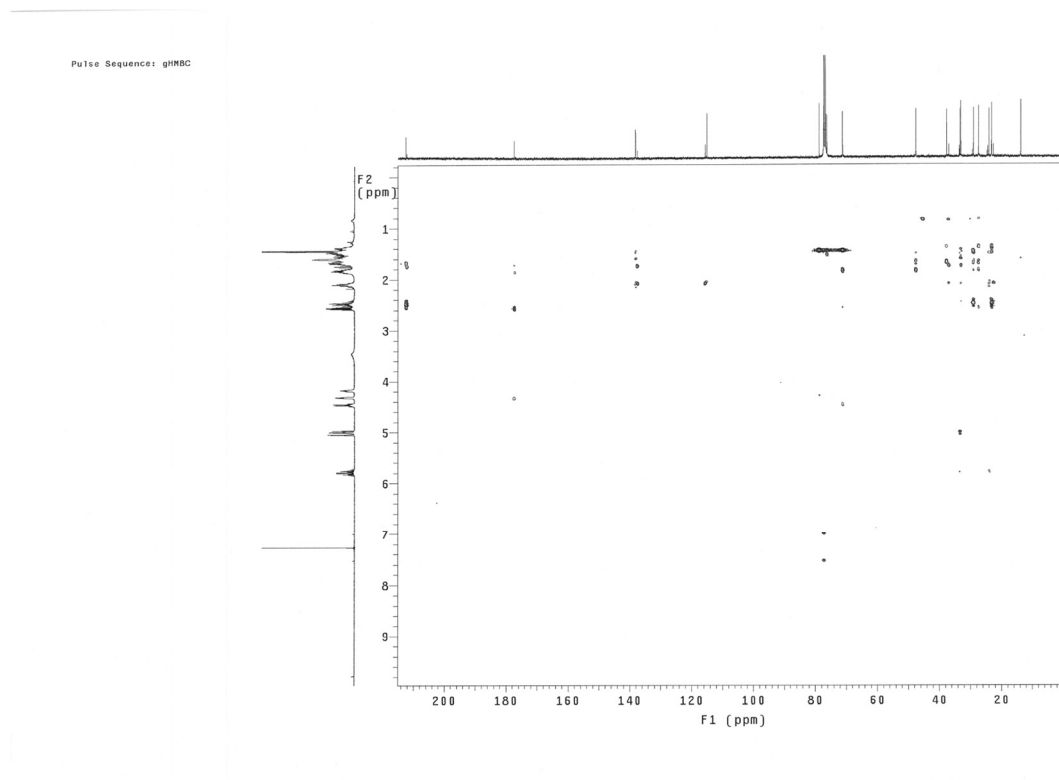


Figure S45. HMBC spectrum of 5

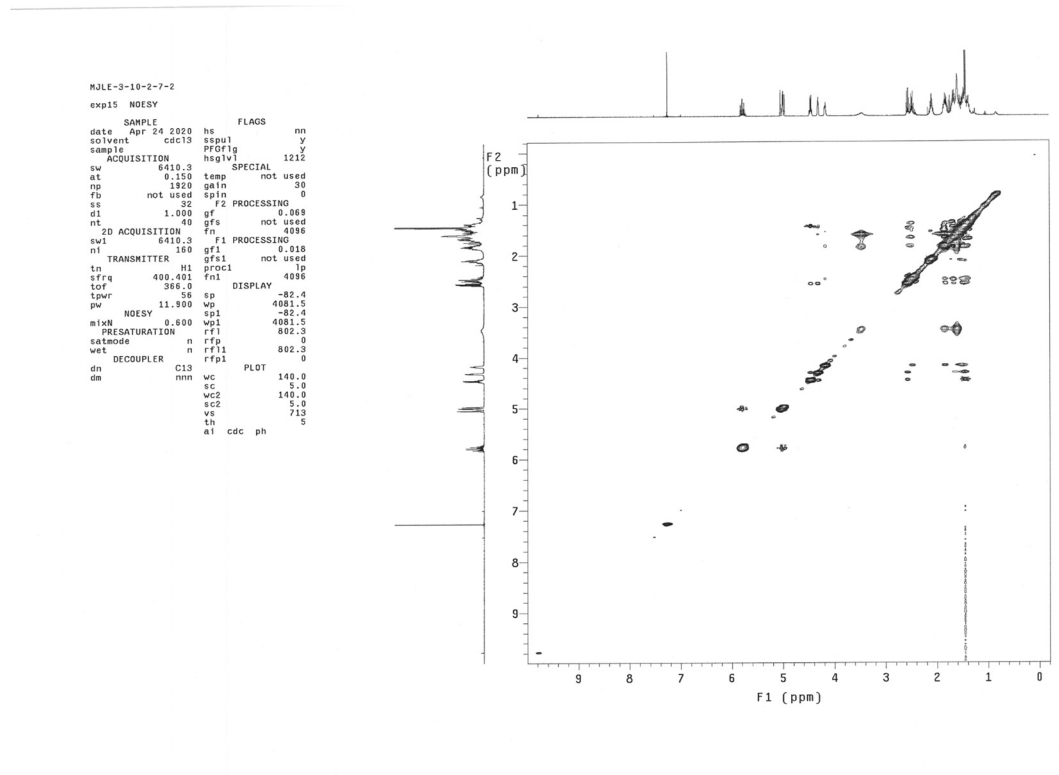


Figure S46. NOESY spectrum of 5

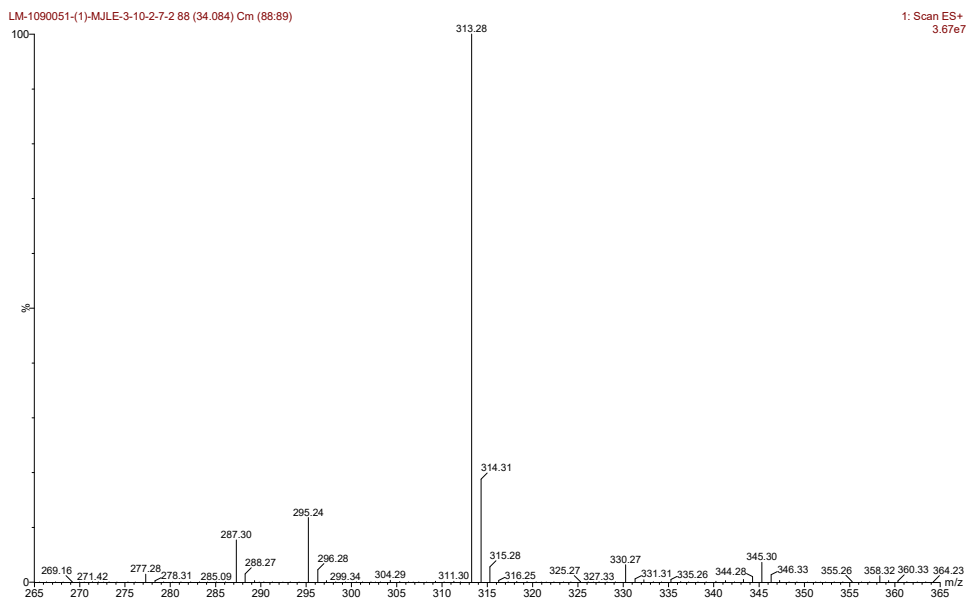


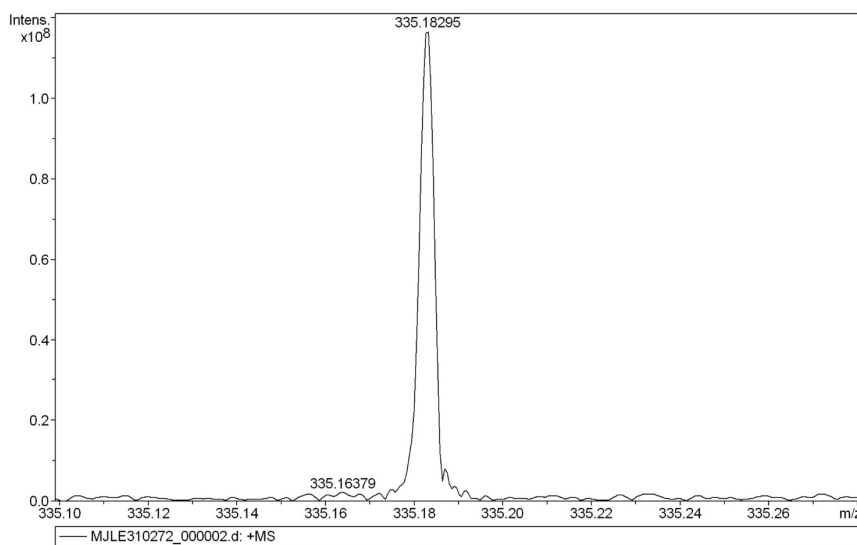
Figure S47. ESIMS spectrum of 5

Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name D:\Data\7\MJLE310272_000002.d
 Method broadband first signal
 Sample Name MJLE-3-10-2-7-2
 Comment ESI Positive

5/14/2020 4:18:37 PM
 Operator: YU HSIAO-CHING
 Instrument: BRUKER FT-MS solariX



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e ⁻ Conf	N-Rule
335.18295	1	C 17 H 28 Na O 5	100.00	335.18290	-0.05	-0.16	17.2	3.5	even	ok

Figure S48. HRESIMS spectrum of 5

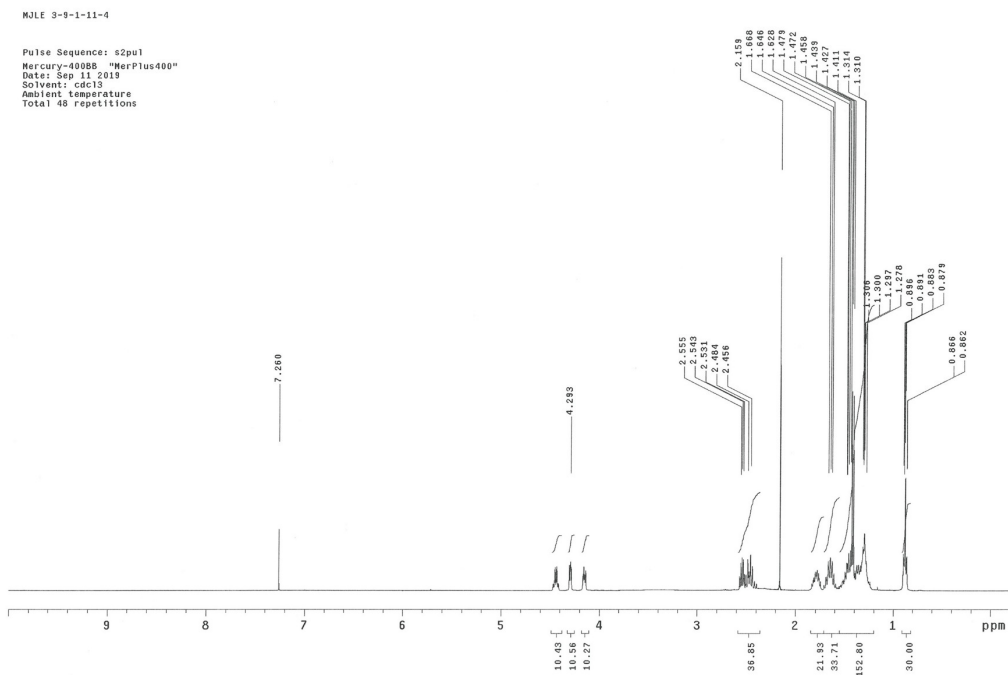


Figure S49. ^1H NMR spectrum of (400 MHz, CDCl_3) spectrum of **6**

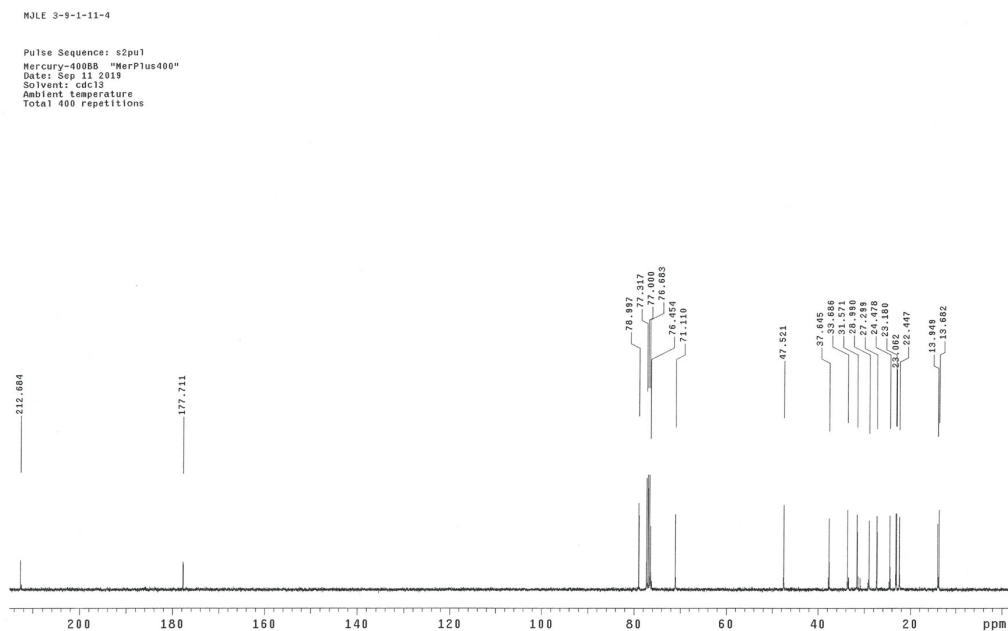


Figure S50. ^{13}C NMR spectrum of (100 MHz, CDCl_3) spectrum of **6**

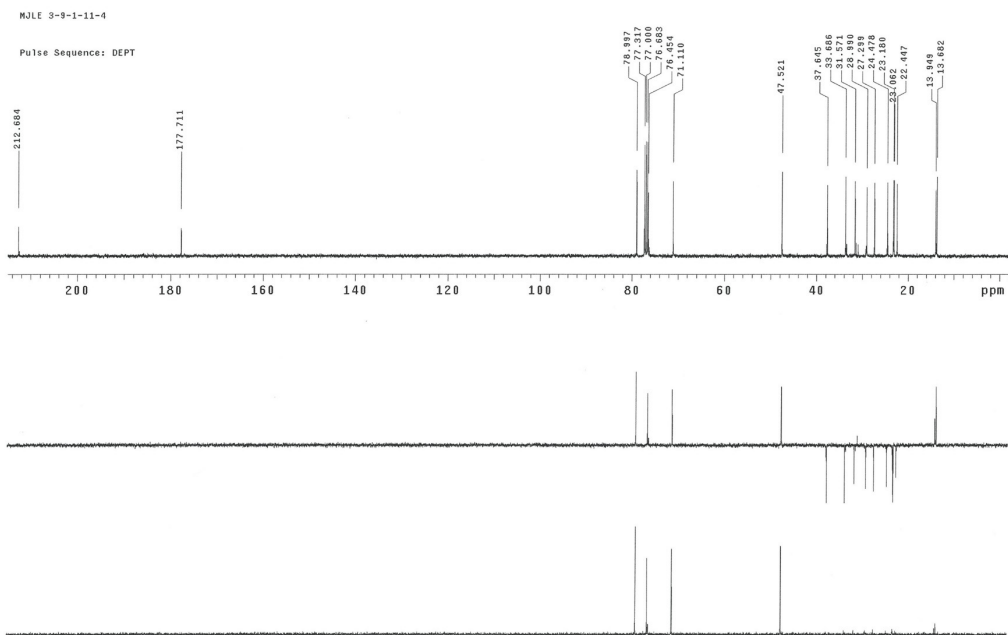


Figure S51. DEPT spectrum of 6

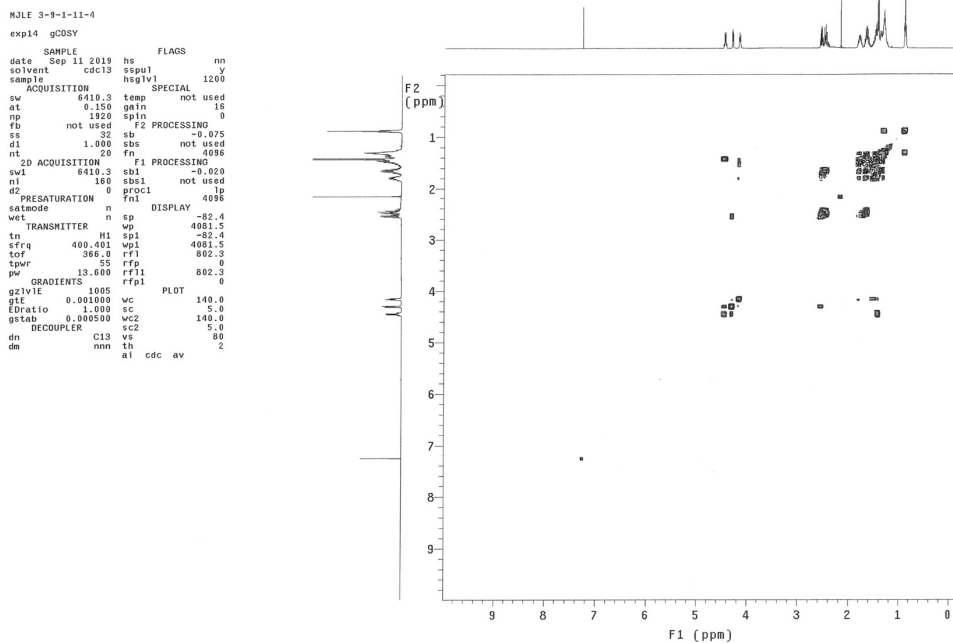


Figure S52. COSY spectrum of 6

Pulse Sequence: gHSQC

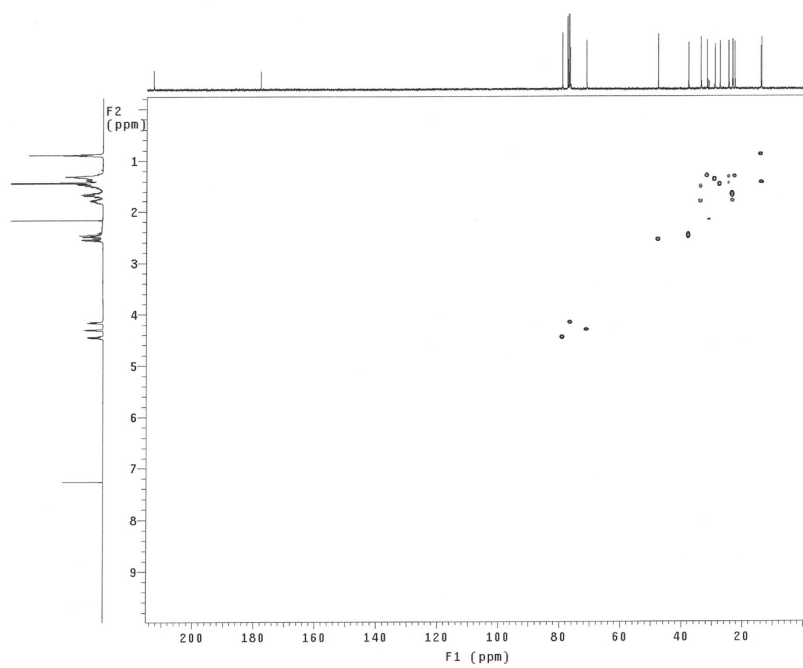


Figure S53. HSQC spectrum of **6**

Pulse Sequence: gHMBC

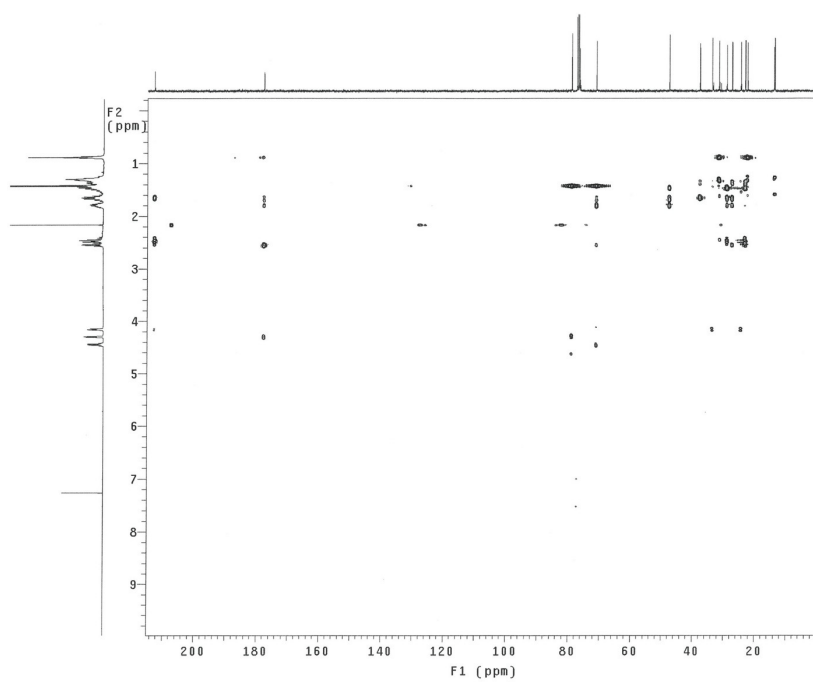


Figure S54. HMBC spectrum of **6**

MJLE 3-9-1-11-4
exp15 NOESY

```
SAMPLE          FLAGS
date Sep 11 2013 hs nn
solvent cdc13 sspul y
sample          y
ACQUISITION    hsgtvl 1200
sw 6410.3 SPECIAL
at 0.150 temp not used
nu 1320 gain 15
fb not used sp1n 0
ss 32 F2 PROCESSING 0
d1 1.000 gf 0.059
nt 16 gfs not used
2D ACQUISITION fn 4056
sw1 6410.3 F1 PROCESSING
n1 180 gfi 0.023
TRANSMITTER    H1 not used
t1 400.401 fni 1p
sfrq 400.401 fni 4056
tcf 366.0 DISPLAY
tpwr 55 sp -82.4
pw 13.600 wp 4081.5
NOESY          sp1 -82.4
mixN 0.600 wp1 4081.5
PRESATURATION  rf1 862.3
satmode n rfp 0
wet DECOUPLER n rf1 862.3
dn DECOUPLER n rfp1 0
dm C13 PLOT
mm wc 140.0
sc sc 5.0
w2 w2 140.0
sc2 sc2 5.0
vs vs 80
th th 4
ai ai cdc ph 4
```

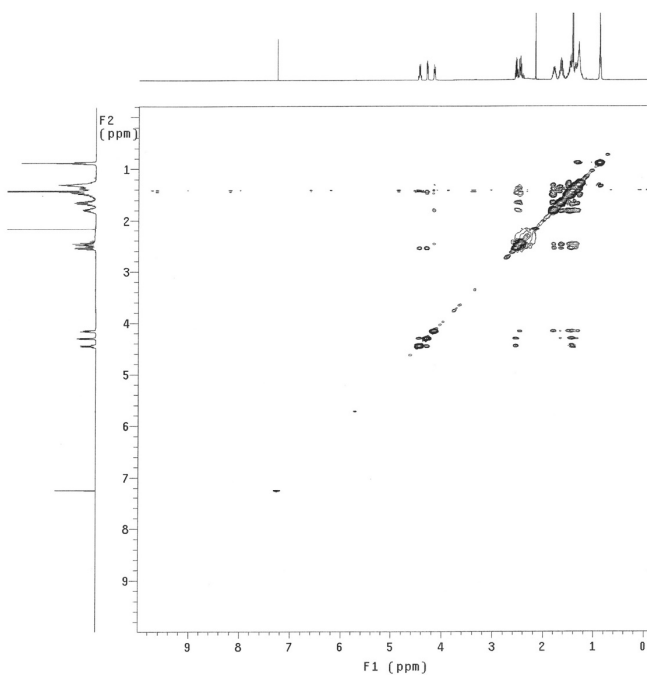


Figure S55. HMBC spectrum of 6

LM-1080131-(9)-MJLE-3-9-1-11-4 95 (36.821) Cm (94.95)

1: Scan ES+
4.92e7

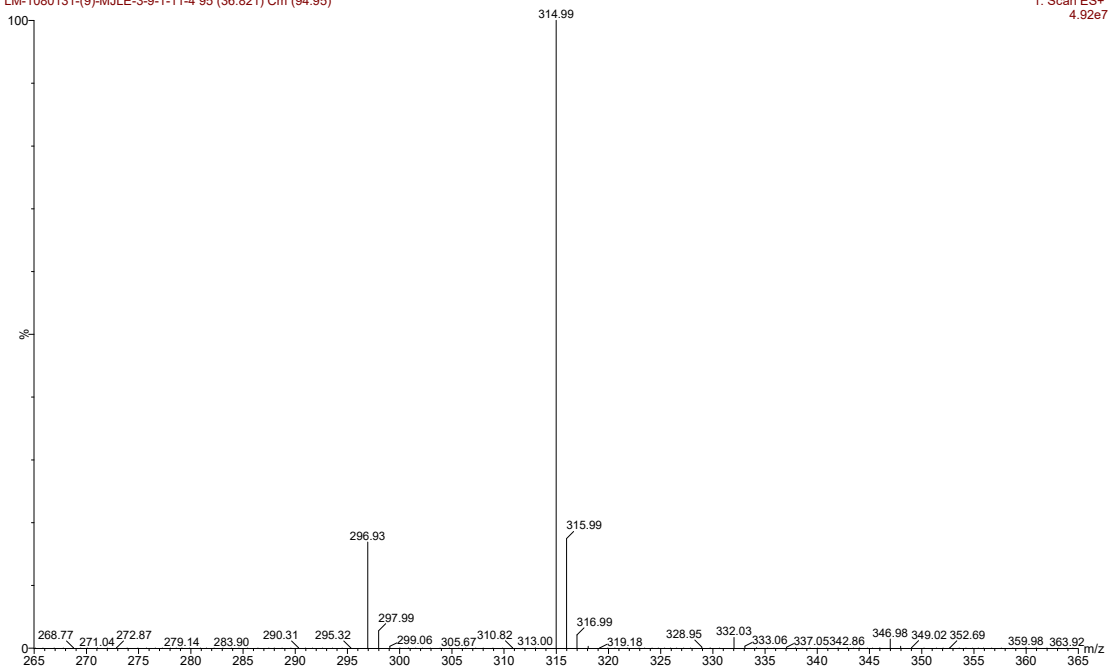


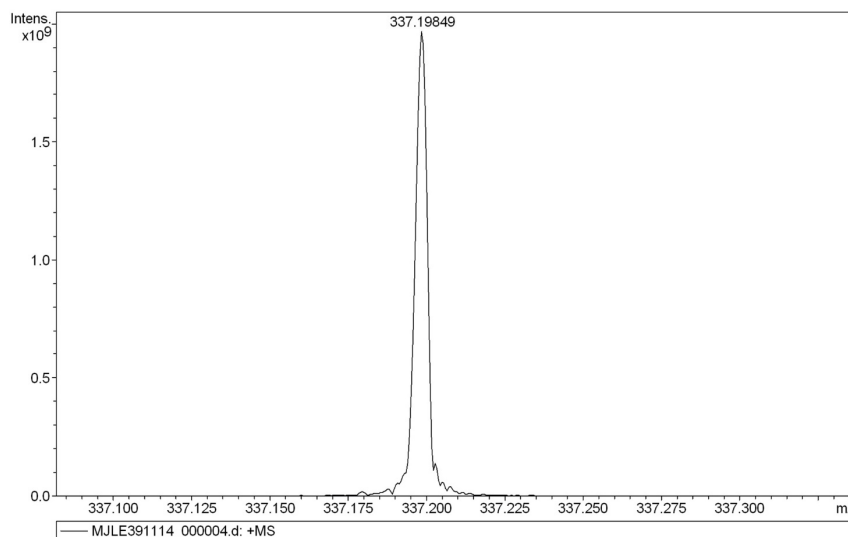
Figure S56. ESIMS spectrum of 6

Mass Spectrum SmartFormula Report

Analysis Info

Analysis Name: D:\Data\7\MJLE391114_000004.d
 Method: broadband first signal
 Sample Name: MJLE-3-9-1-11-4
 Comment: ESI Positive

12/31/2019 2:44:51 PM
 Operator: YU HSIAO-CHING
 Instrument: BRUKER FT-MS solariX



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e ⁻ Conf	N-Rule
337.19849	1	C 17 H 30 Na O 5	100.00	337.19855	0.05	0.16	15.9	2.5	even	ok

Figure S57. HRESIMS spectrum of 6

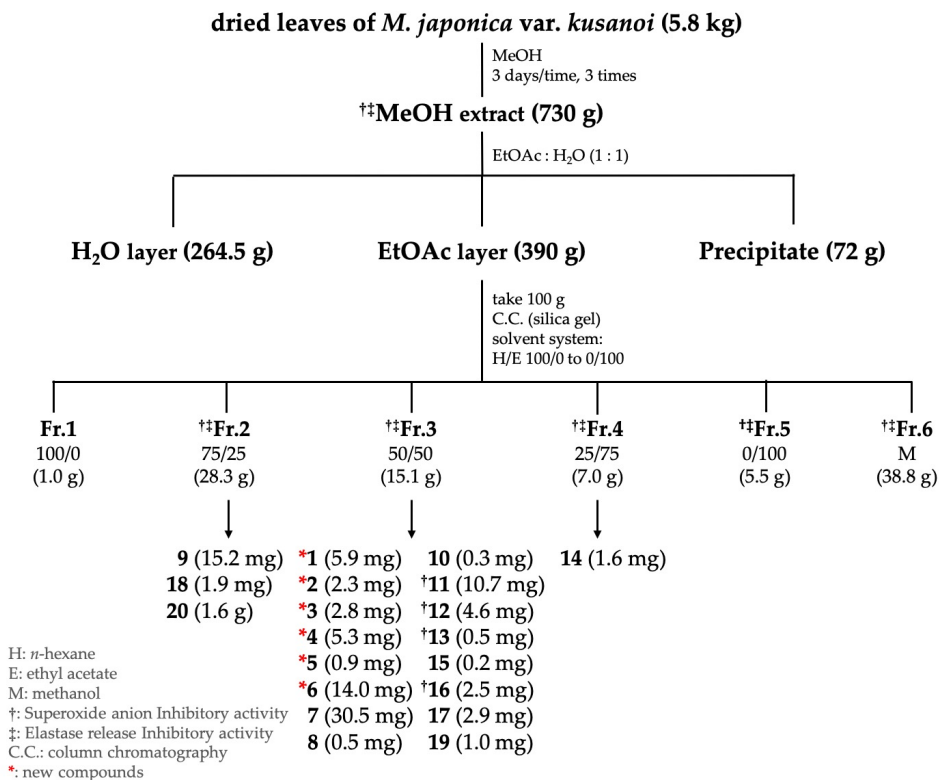


Figure S58. Extraction and isolation of the leaves from *M. japonica* var. *kusanoi*.

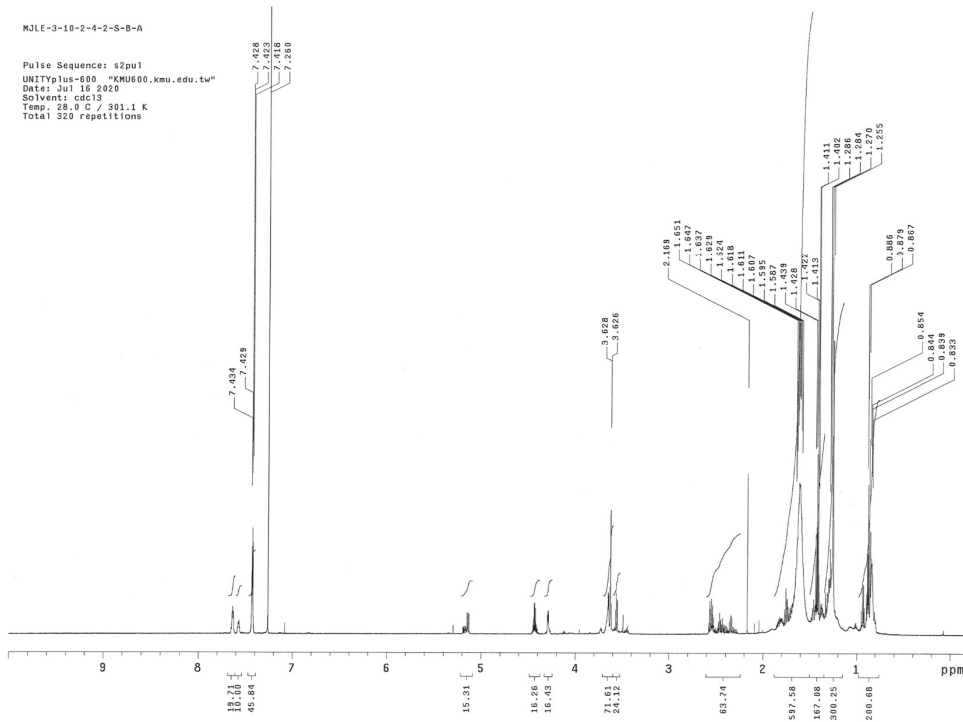


Figure S59. ^1H NMR spectrum of (600 MHz, CDCl_3) spectrum of **4a**

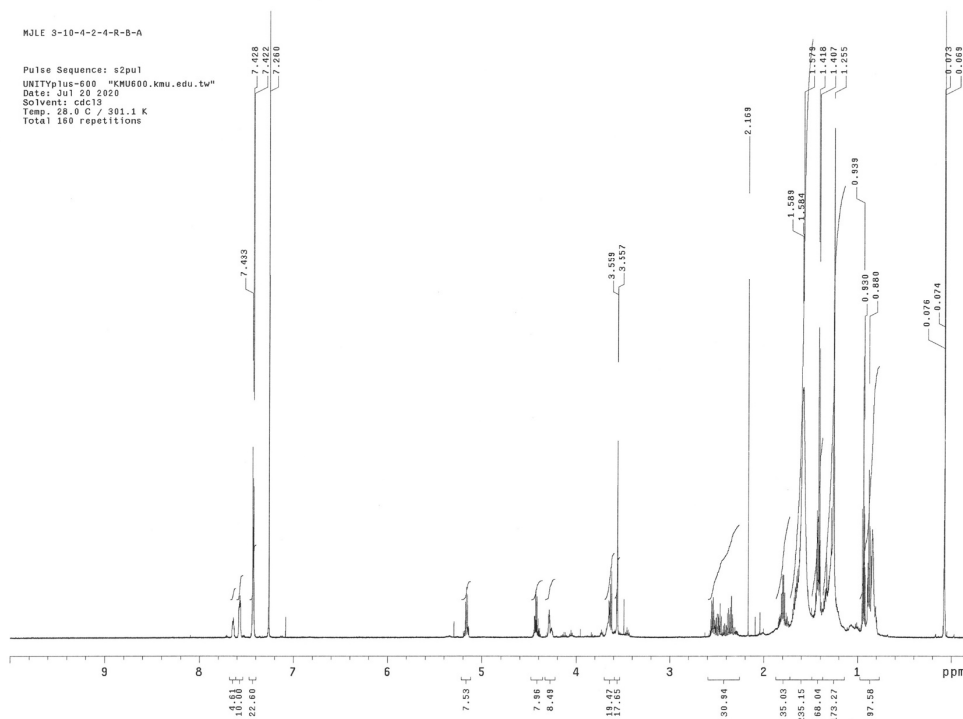


Figure S60. ^1H NMR spectrum of (600 MHz, CDCl_3) spectrum of **4b**

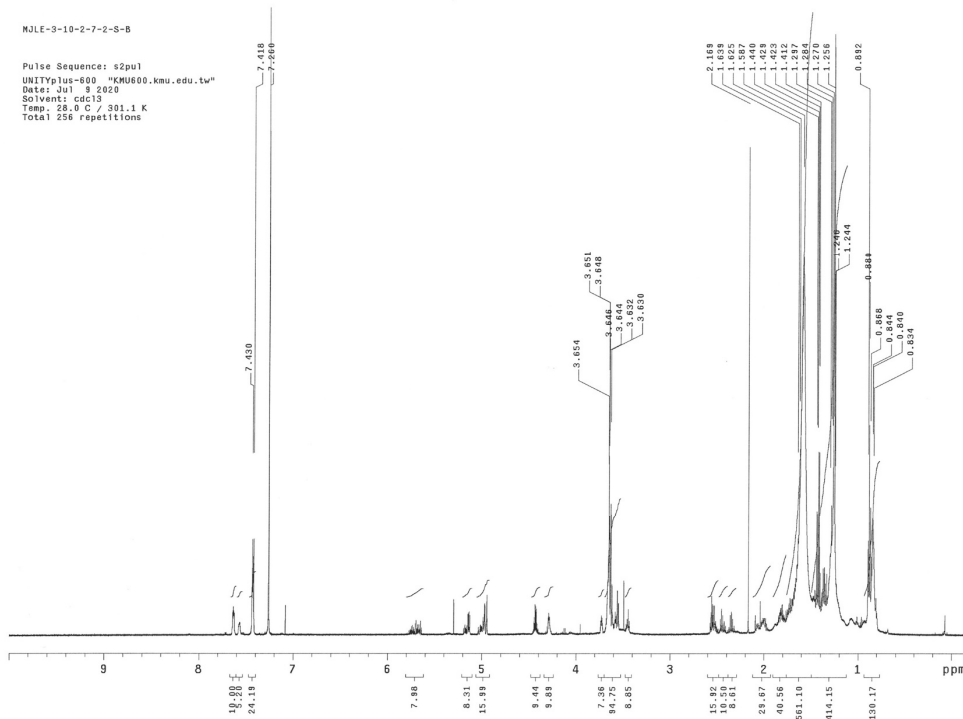


Figure S61. ^1H NMR spectrum of (600 MHz, CDCl_3) spectrum of **5a**

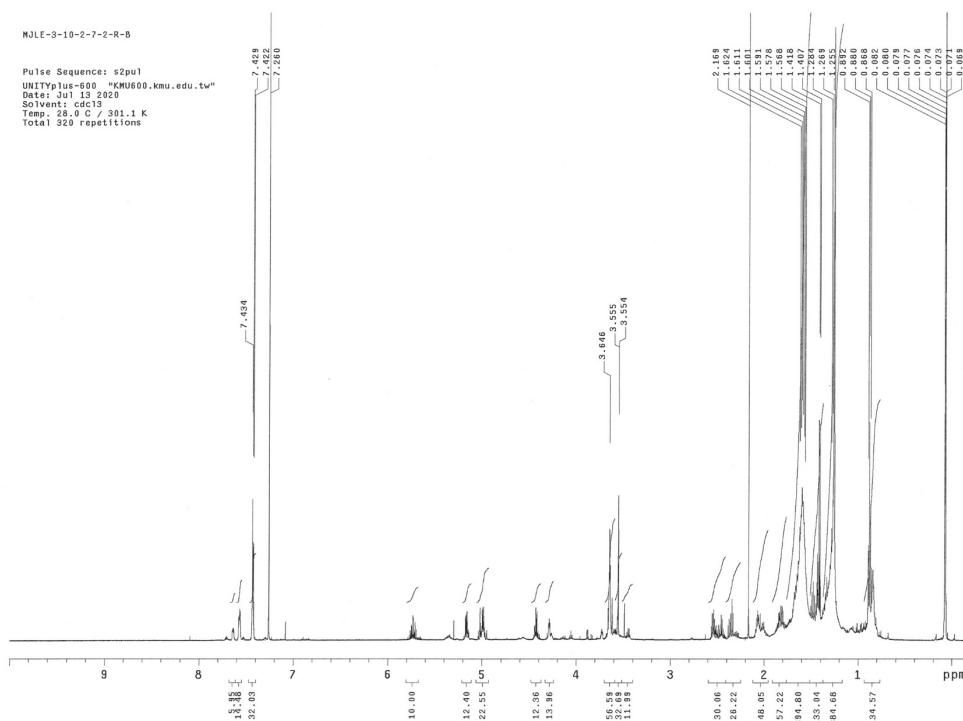


Figure S62. ^1H NMR spectrum of (600 MHz, CDCl_3) spectrum of **5b**

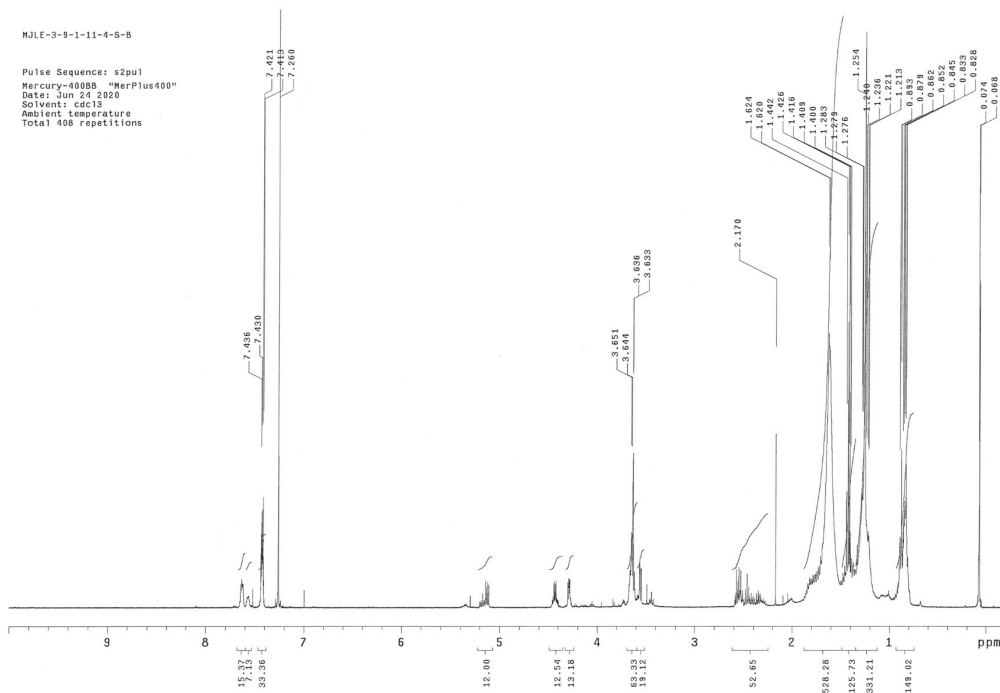


Figure S63. ^1H NMR spectrum of (400 MHz, CDCl_3) spectrum of **6a**

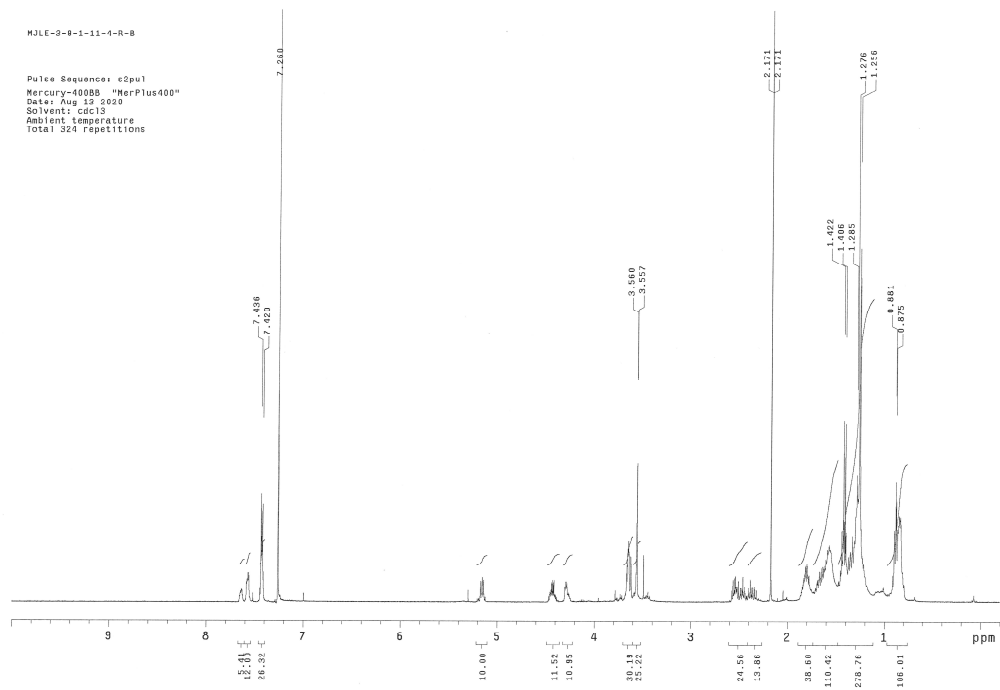


Figure S64. ^1H NMR spectrum of (400 MHz, CDCl_3) spectrum of **6b**

Table S1. Inhibitory effects of crude extracts from the leaves of *M. japonica* var. *kusanoi* on superoxide anion generation and elastase release in fMLP/CB-induced human neutrophils.

Extract (10 µg/mL)	Superoxide anion	Elastase release
	Inh %	Inh %
MJLW-1	36.25 ± 5.65	89.86 ± 4.77
MJLW-2	75.35 ± 5.12	95.00 ± 3.86
MJLW-3	71.13 ± 6.98	64.26 ± 2.58
MJLW-4	94.32 ± 0.89	128.43 ± 5.95
MJLW-5	108.63 ± 1.86	121.81 ± 4.24
MJLE-1	8.88 ± 7.27	17.92 ± 2.03
MJLE-2	103.05 ± 0.80	128.41 ± 0.78
MJLE-3	101.85 ± 1.92	120.57 ± 6.06
MJLE-4 (1 µg/mL)	102.45 ± 0.41	118.19 ± 5.59
MJLE-5	98.28 ± 2.92	117.61 ± 4.35
MJLE-6	110.84 ± 2.02	119.78 ± 5.15

Percentage of inhibition (Inh %) at 10 µg/ml concentration. MJLW: water layer from the leaves of *M. japonica* var.

kusanoi, MJLE: ethyl acetate layer from the leaves of *M. japonica* var. *kusanoi*.