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Synthesis, structure and *in vitro* biological evaluation of new lupane and dammarane triterpenoids fused with pyrazine heterocycle

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Contents

General experimental

All reagents and solvents were purchased from commercial sources and used without further purification.

MS analysis was performed on Bruker MicroTOF and Shimadzu MALDI-TOF Axima Resonance apparatus. The TLC analysis was carried out on silica gel plates (Merck TLC Silica gel 60 F254) in chloroform-methanol mixture using UV light for detection. Column chromatography was performed on silica gel Acros organics (0.06-0.20 mm, pore diameter ca. 6 nm) with chloroform-methanol mixture eluation. ^{1}H and $^{13}C\{^{1}H\}$ spectra were recorded with Bruker 400 MHz WB Avance III spectrometer. ^{1}H and $^{13}C\{^{1}H\}$ chemical shifts were determined using residual signals of the deuterated solvents (DMSO-d_6) at 298 K and were referenced to $SiMe_4$.

To a solution of triterpenoid **1,3,4** or **5** (2 mmol) in morpholine (20 ml), elemental sulfur (18 mmol) and ethylenediamine (10 mmol) were added at room temperature, and the mixture was heated under reflux for 1.5 h. After cooling, the mixture was poured into water and extracted with AcOEt (50 ml × 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Column chromatography of the residue on silica gel (hexane/AcOEt) and then crystallization from AcOEt afforded products **2,6-8** as colourless crystals.

(1*R*,3a*R*,5a*R*,5b*R*,13a*R*)-1-Isopropenyl-3a,5a,5b,8,8,13a-hexamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,13,13a,13b,14,15,15a,15b-octadecahydro-1*H*-

cyclopenta[7,8]phenanthro[1,2-*g*]quinoxaline 2: yield 70%; m.p. 210-213 °C; HRMS (ESI) *m/z* 461.3909 $[M + H]^+$ (calc. $C_{32}H_{48}N_2$ *M* 460.3818).

(2*S*)-6-Methyl-2-[(1*S*,3a*R*,3b*R*,11a*R*)-3a,3b,6,6,11a-pentamethyl-2,3,3a,3b,4,5,5a,6,11,11a,11b,12,13,13a-tetradecahydro-1*H*-cyclopenta[5,6]naphtho-[1,2-*g*]quinoxalin-1-yl]hept-5-en-2-ol 6: yield 89%; m.p. 146-147 °C; HRMS (ESI) *m/z* 479.4010 $[M + H]^+$ (calc. $C_{32}H_{50}N_2O$ *M* 478.3923).

(5*S*)-5-Methyl-5-[(1*S*,3a*R*,3b*R*,11a*R*)-3a,3b,6,6,11a-pentamethyl-2,3,3a,3b,4,5,5a,6,11,11a,11b,12,13,13a-tetradecahydro-1*H*-cyclopenta[5,6]naphtho-[1,2-*g*]quinoxalin-1-yl]dihydrofuran-2(3*H*)-one 7: yield 86%; m.p. 240-242 °C; HRMS (ESI) *m/z* 451.3341 $[M + H]^+$ (calc. $C_{29}H_{42}N_2O_2$ *M* 450.3246).

(1*S*,3a*R*,3b*R*,11a*R*)-1-[(2*S*,5*R*)-5-Isopropyl-2,5-dimethyltetrahydrofuran-2-yl]-3a,3b,6,6,11a-pentamethyl-2,3,3a,3b,4,5,5a,6,11,11a,11b,12,13,13a-tetradecahydro-1*H*-cyclopenta[5,6]naphtho[1,2-*g*]quinoxaline 8: yield 74%; m.p. 197-200 °C; HRMS (ESI) *m/z* 493.4171 $[M + H]^+$ (calc. $C_{33}H_{52}N_2O$ *M* 492.4080).

NMR spectral data of compounds 2, 6 – 8

NMR measurements were performed on a Bruker Avance III-400 instrument at ambient temperature. ^{1}H NMR (400.13 MHz, $CDCl_3$) and ^{13}C NMR(100.61 MHz, $CDCl_3$)

1D NMR spectra.

Figure S1 Spectrum ^{1}H NMR of Compound 2.

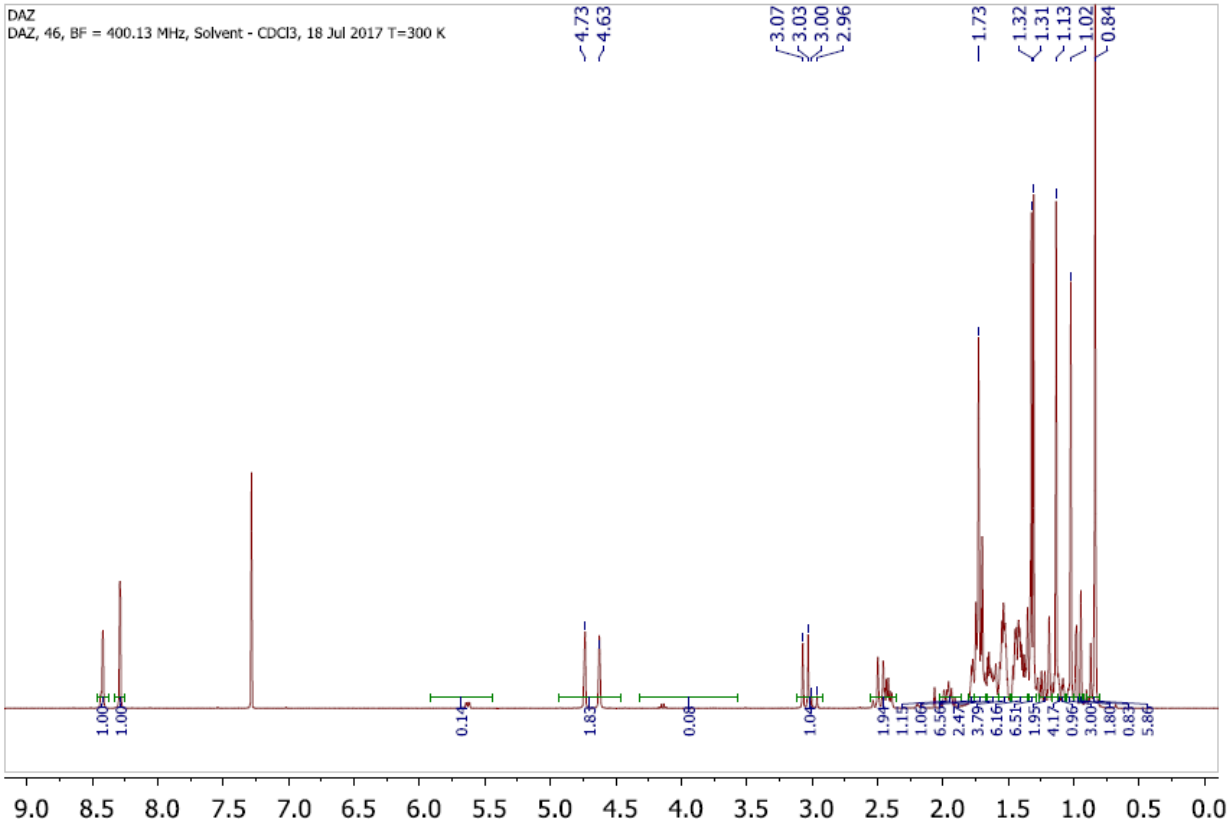


Figure S2 Spectrum ^{13}C NMR of Compound 2.

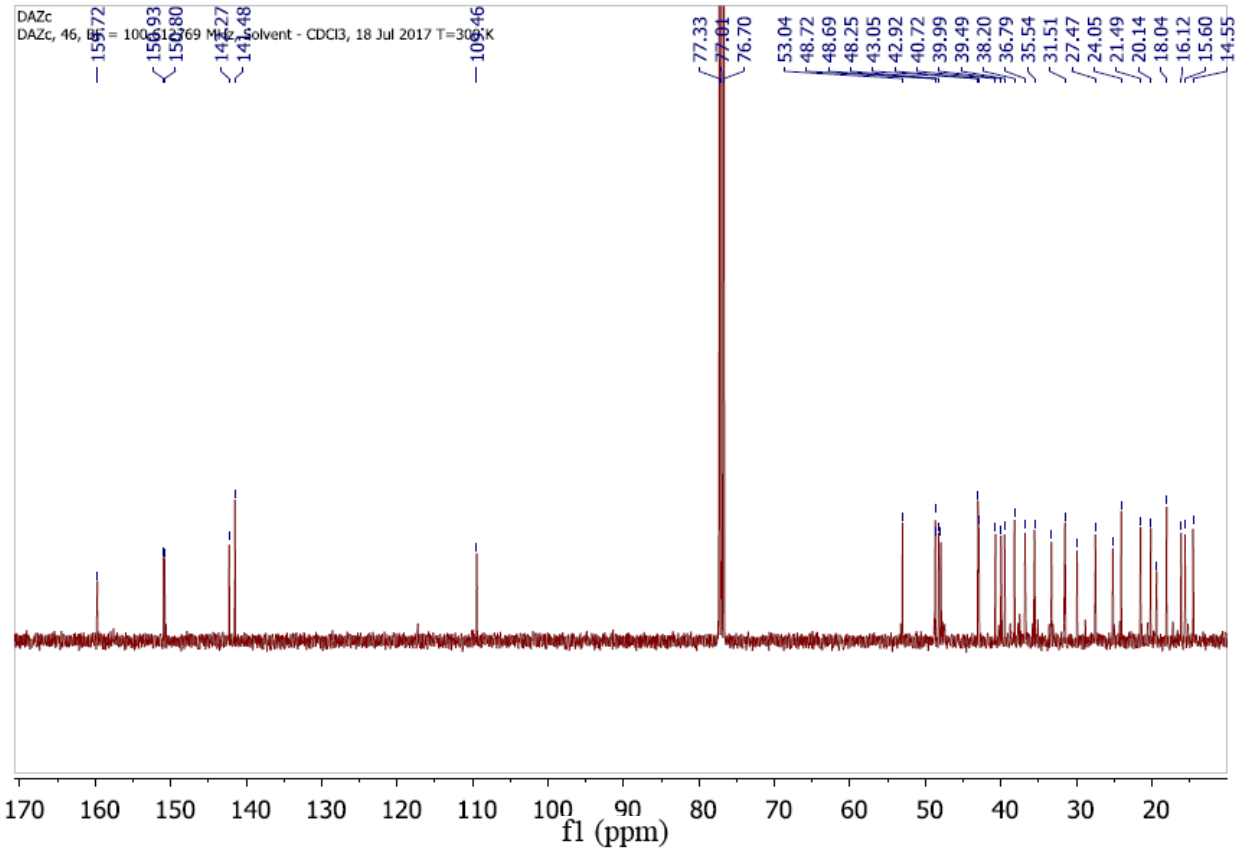


Figure S3 DEPT of Compound 2.

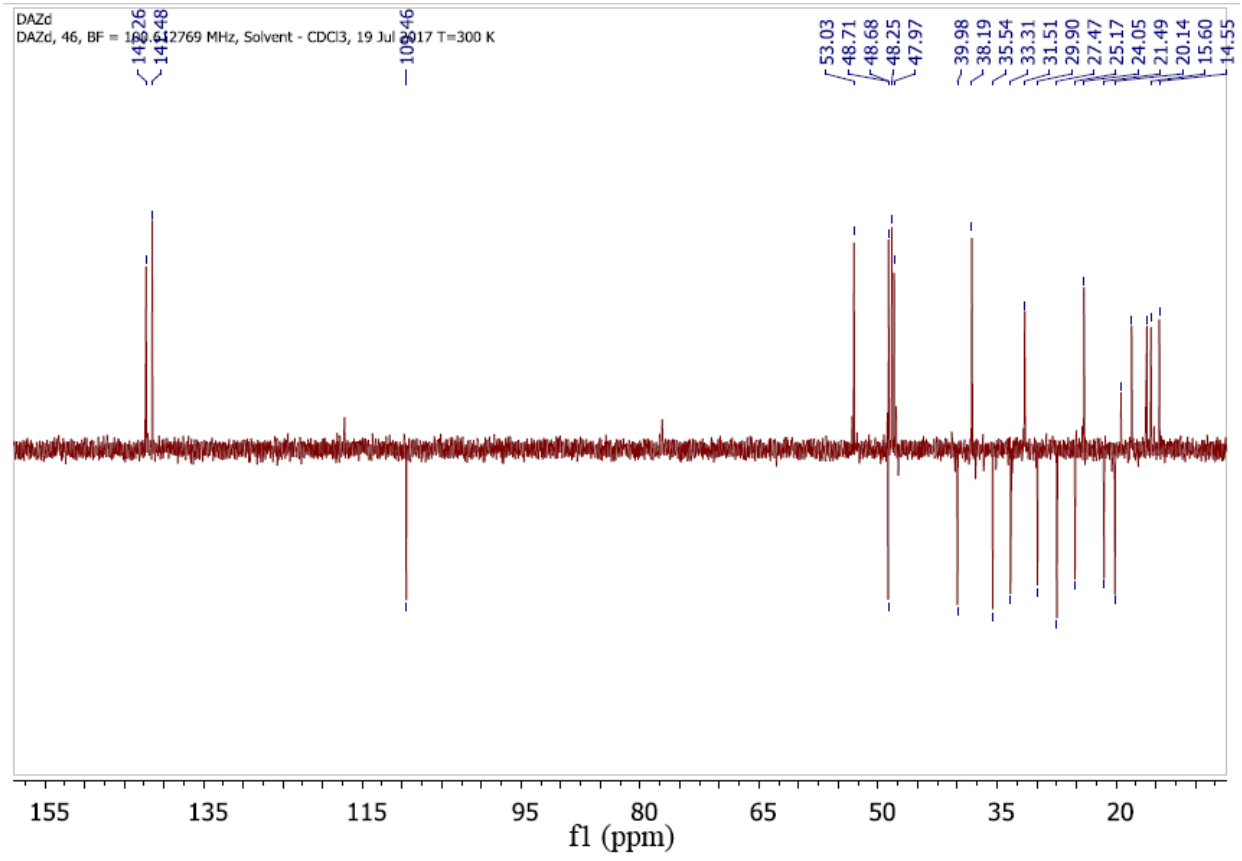


Figure S4 Spectrum ^{1}H NMR of Compound 6.

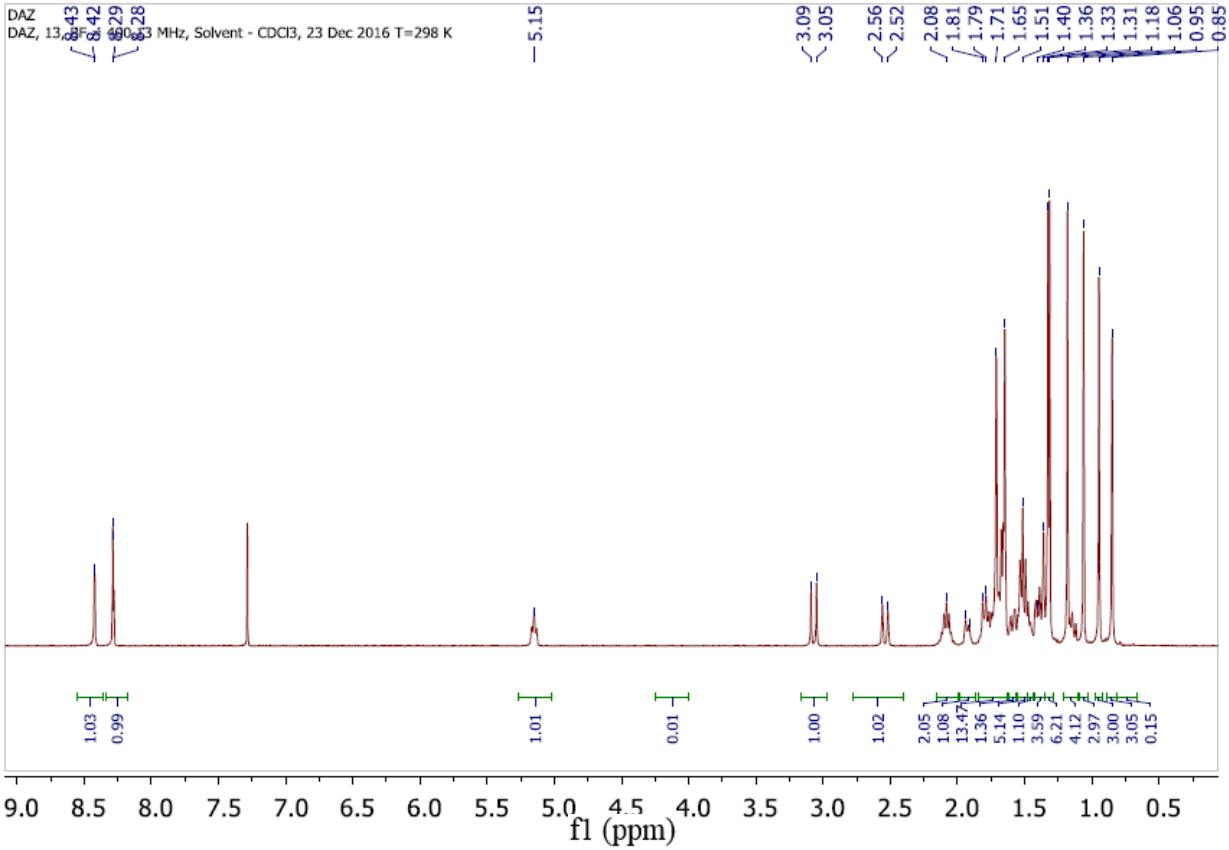


Figure S5 Spectrum ^{13}C NMR of Compound 6.

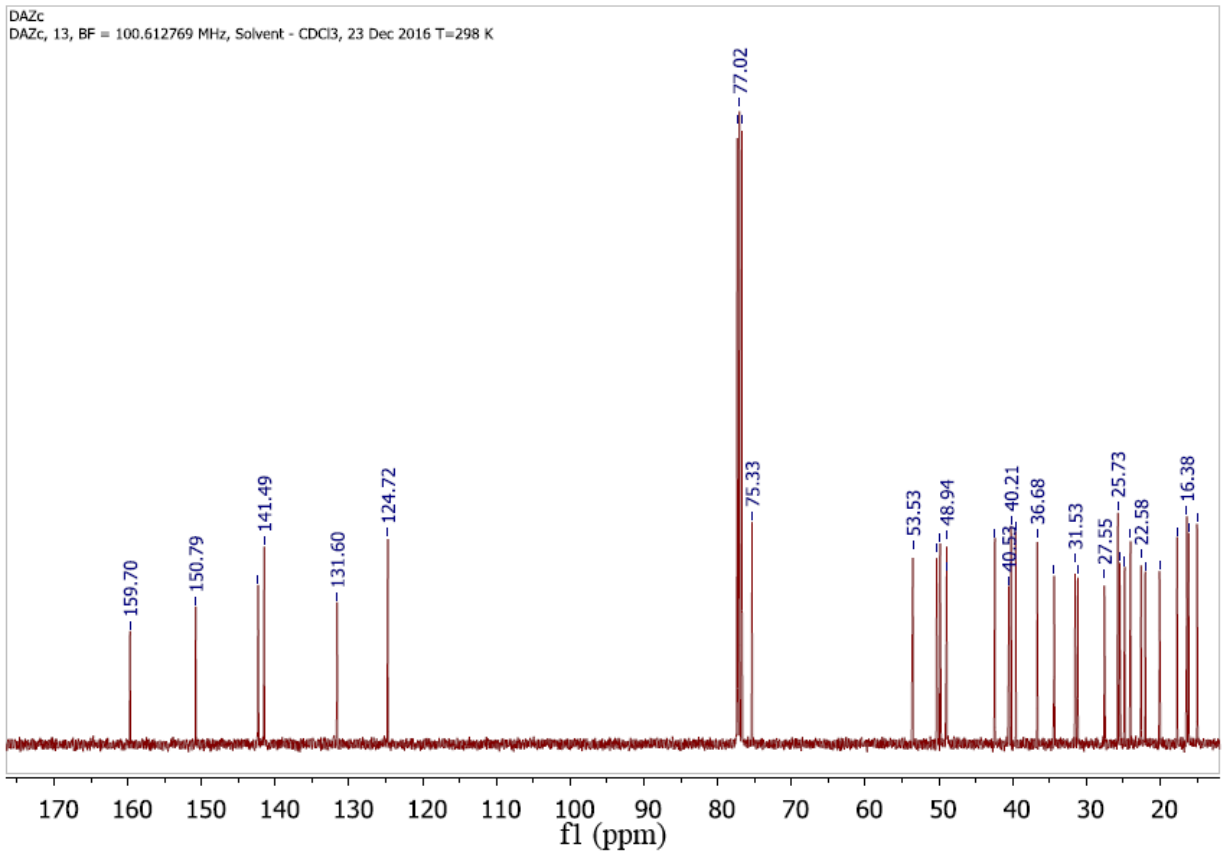


Figure S6 DEPT of Compound 6.

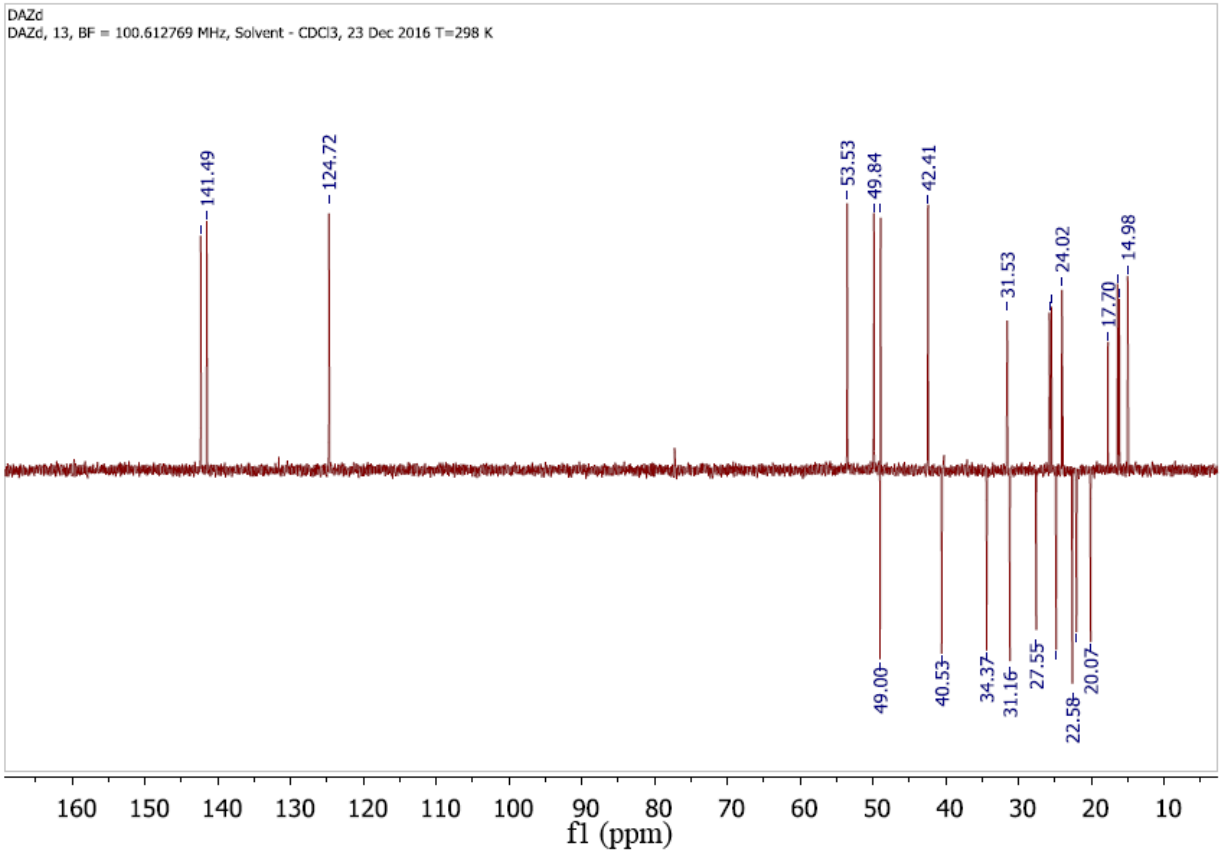


Figure S7 Spectrum ^{1}H NMR of Compound 7.

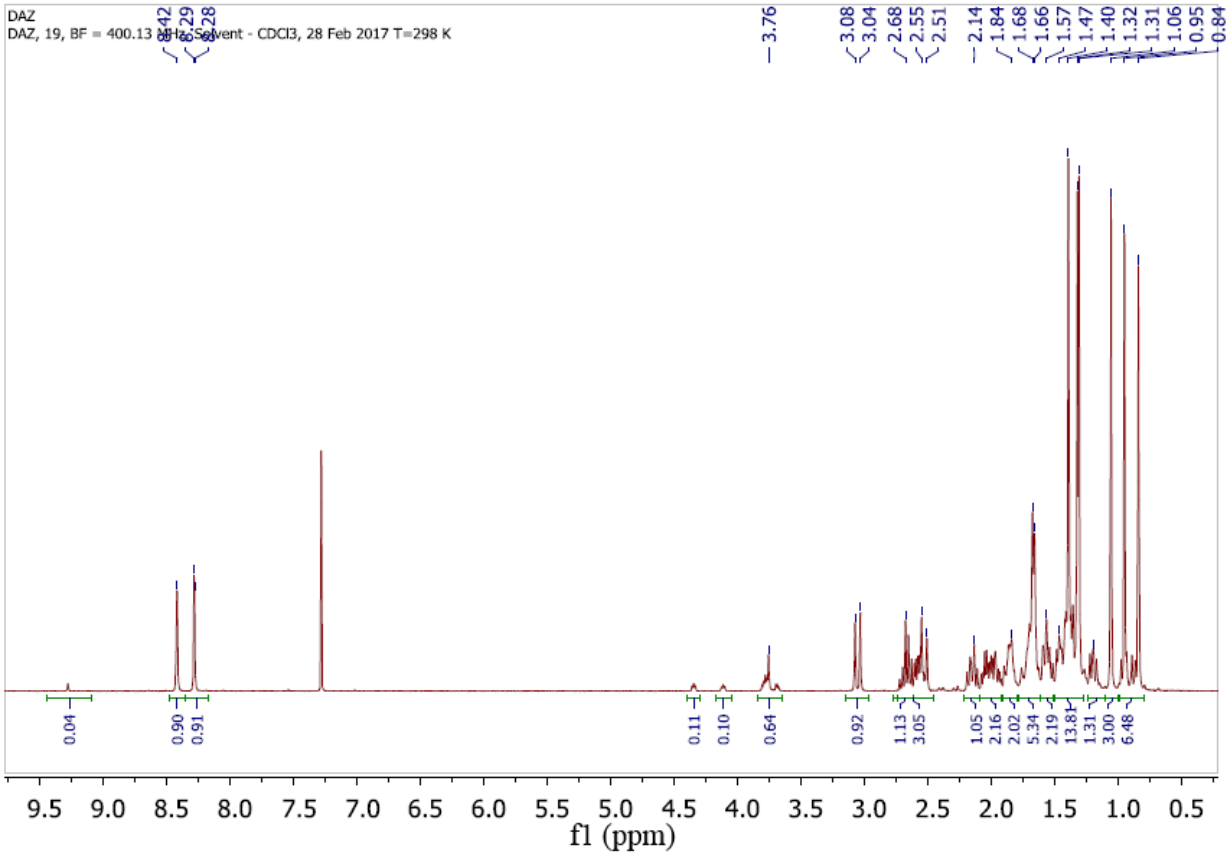


Figure S8 Spectrum ^{13}C NMR of Compound 7.

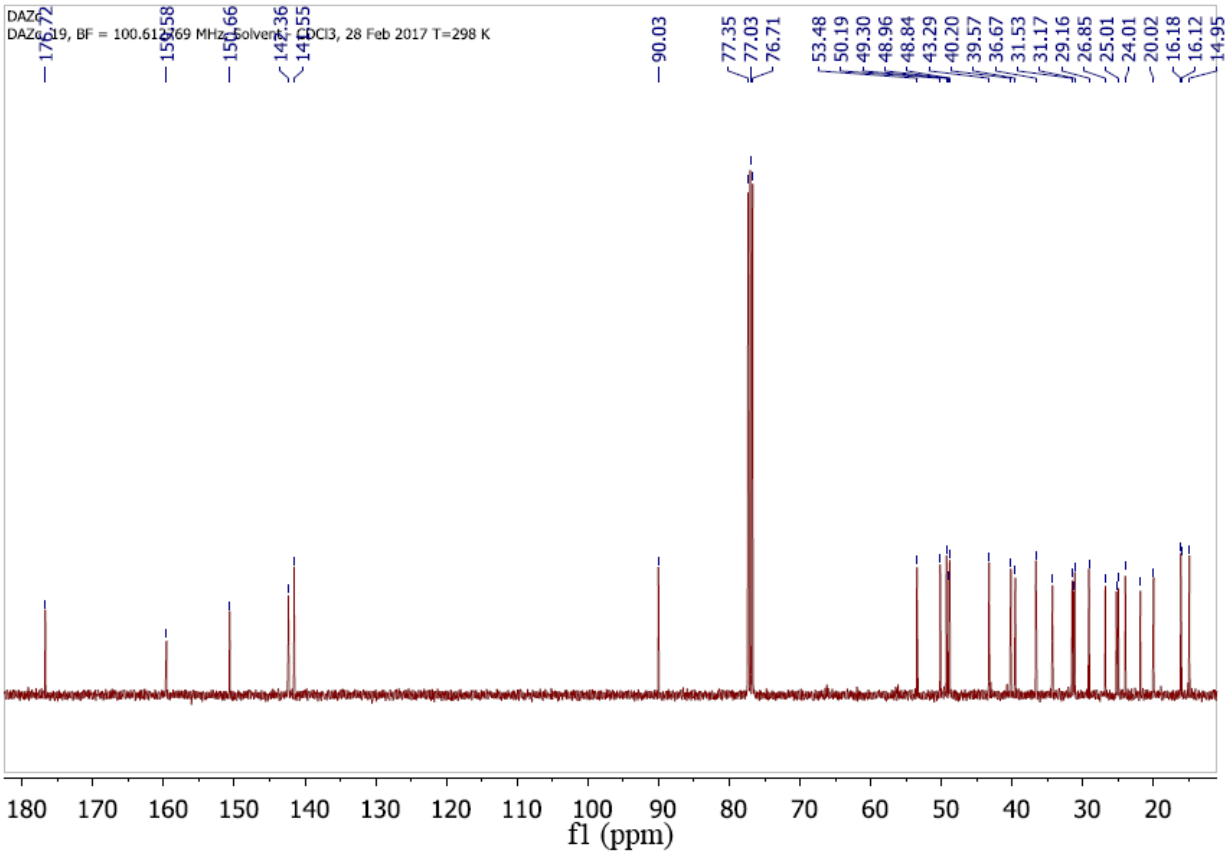


Figure S9 DEPT Compound 7.

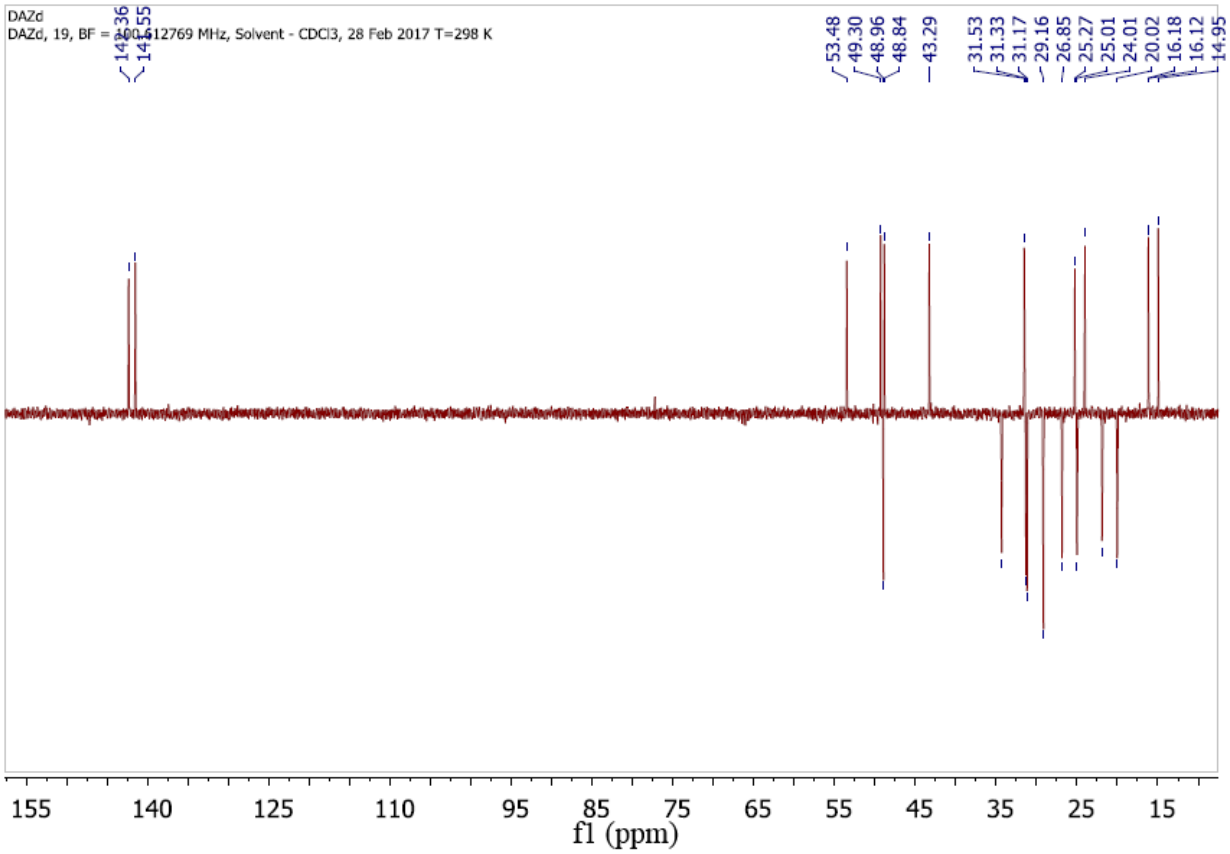


Figure S10 Spectrum ^{1}H NMR of Compound 8.

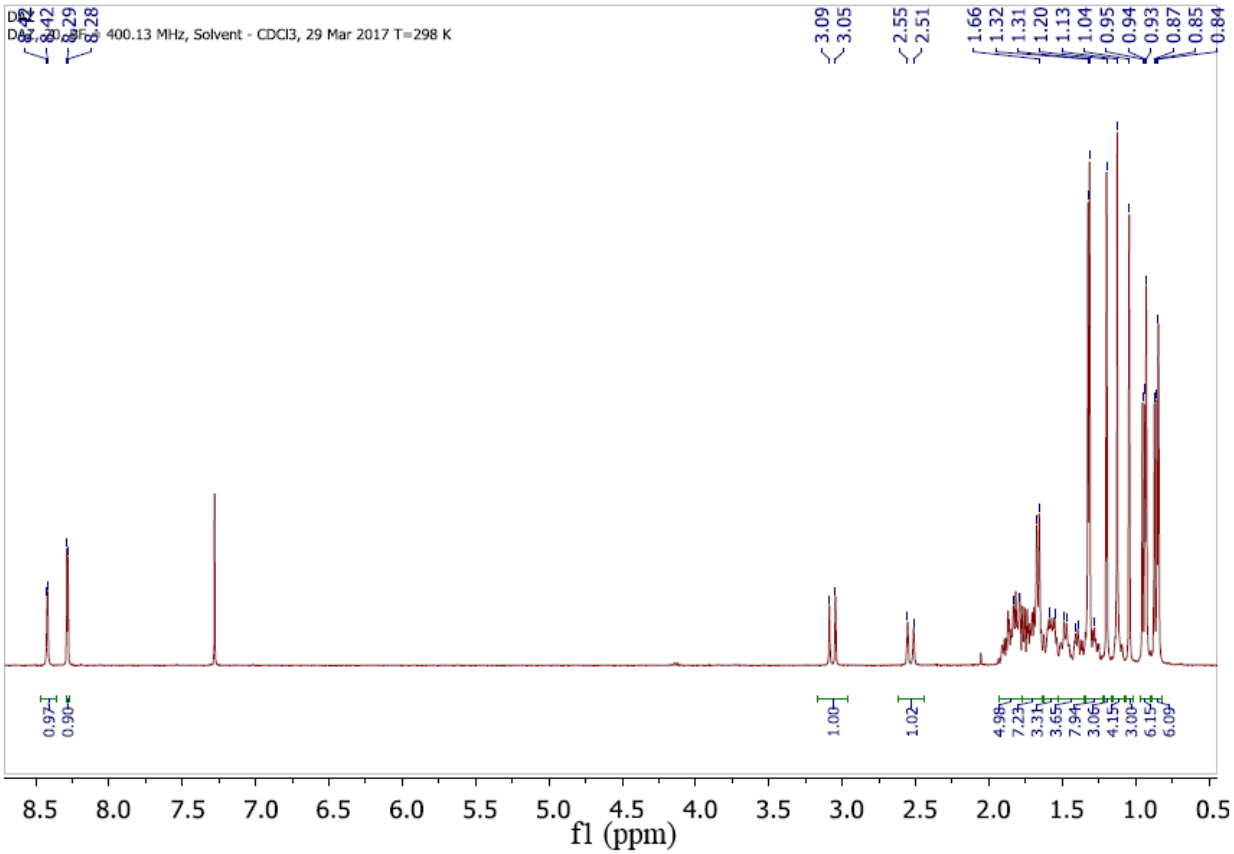


Figure S11 Spectrum ^{13}C NMR of Compound 8

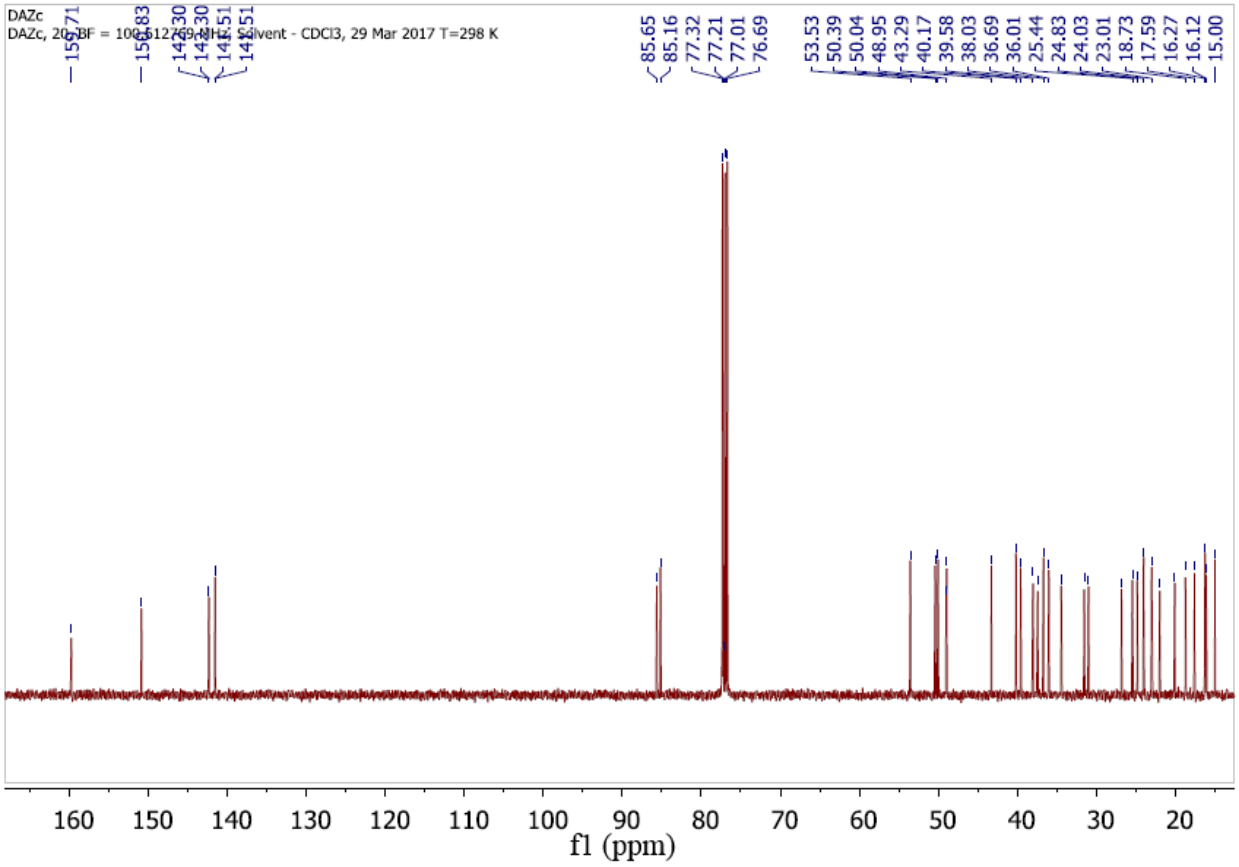
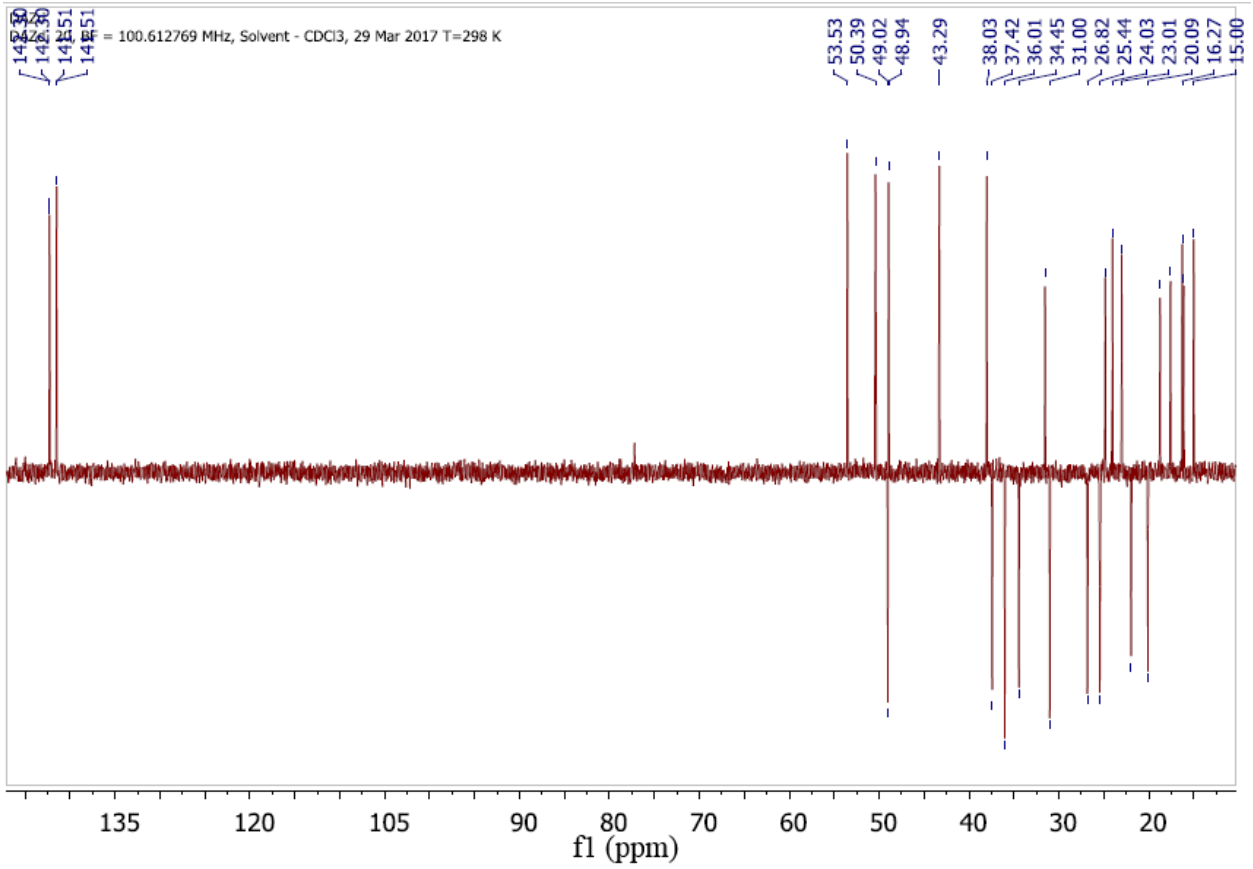


Figure S12 DEPT Compound 8.



2D NMR spectra.

Fig S13. COSY Compound (2)

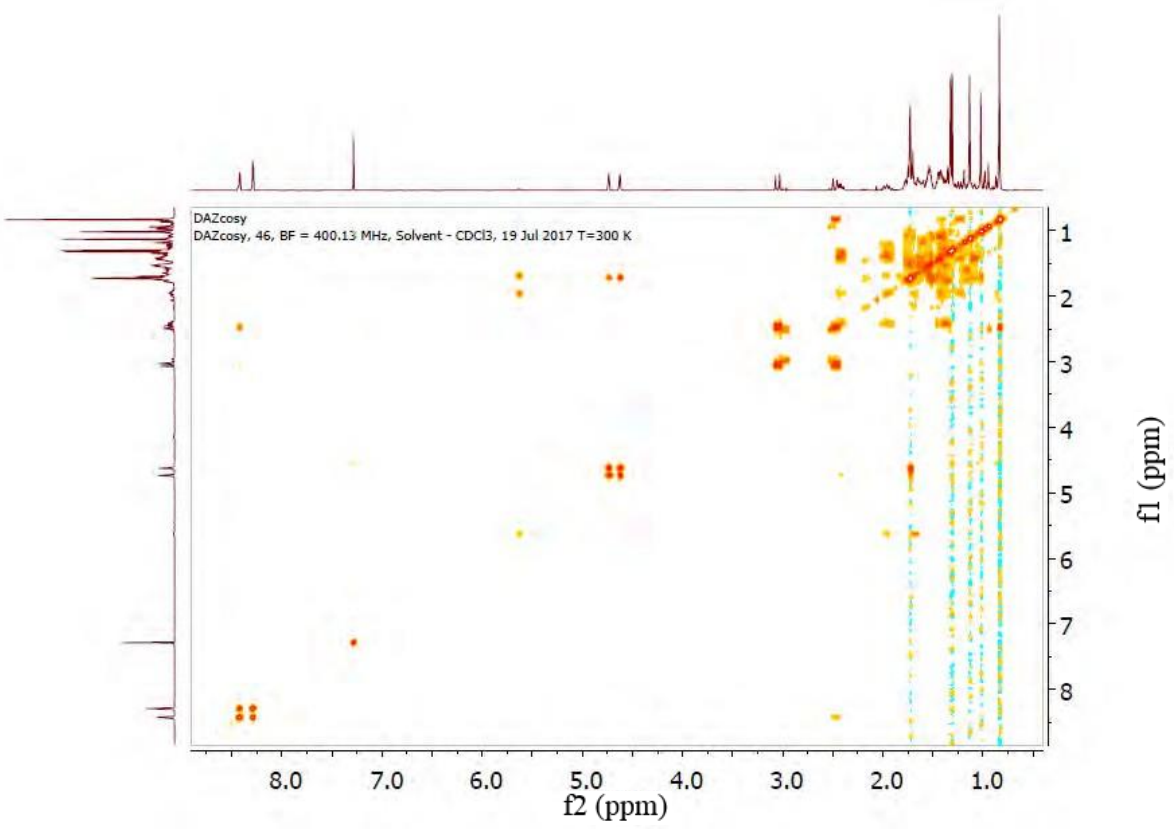


Figure S14 NOESYof Compound 2.

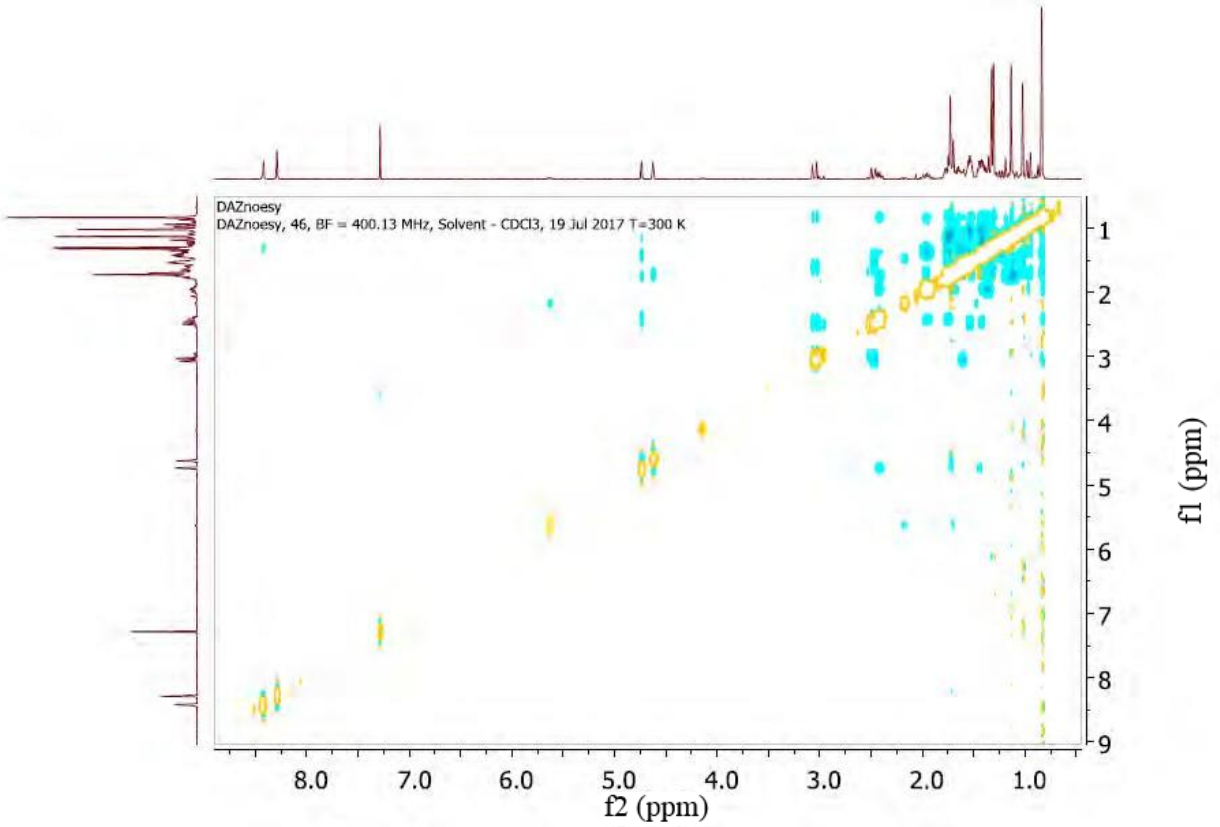


Figure S15 Spectrum HSQC Compound 2.

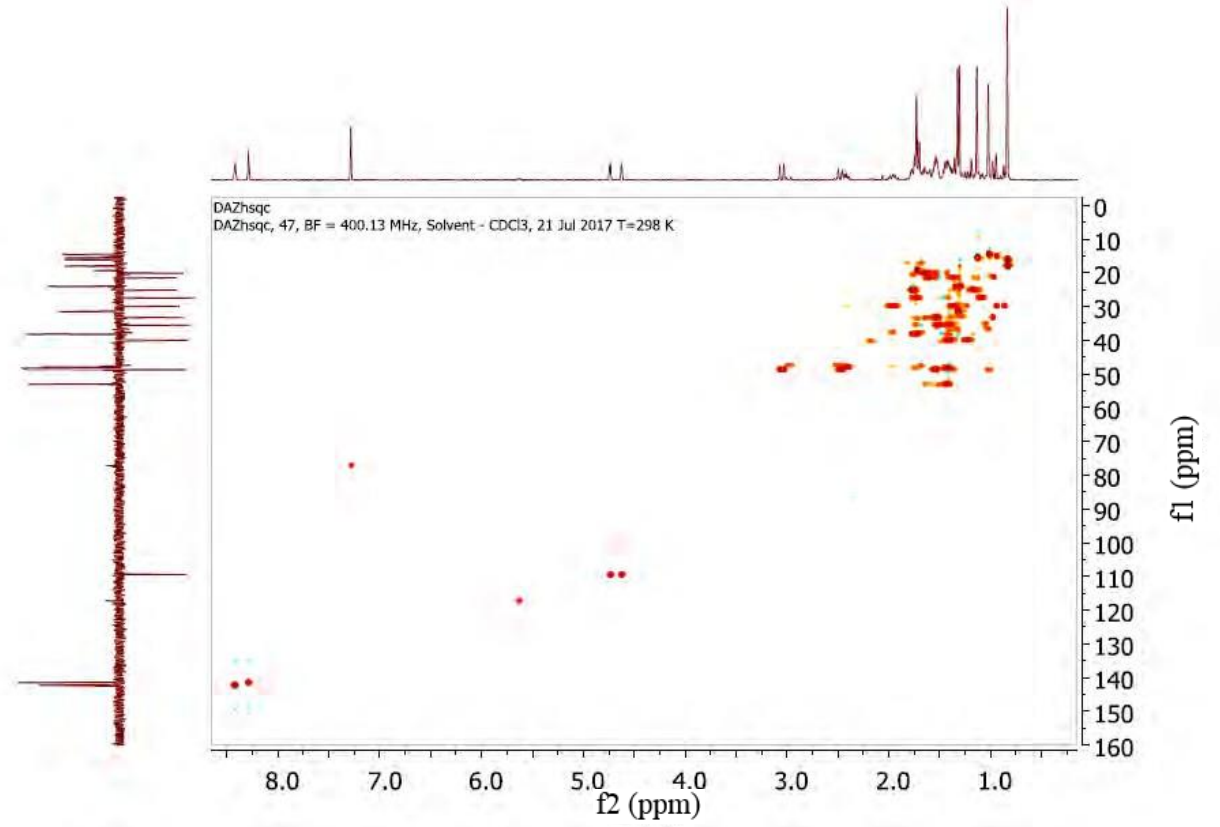


Figure S16 HMBC of Compound 2.

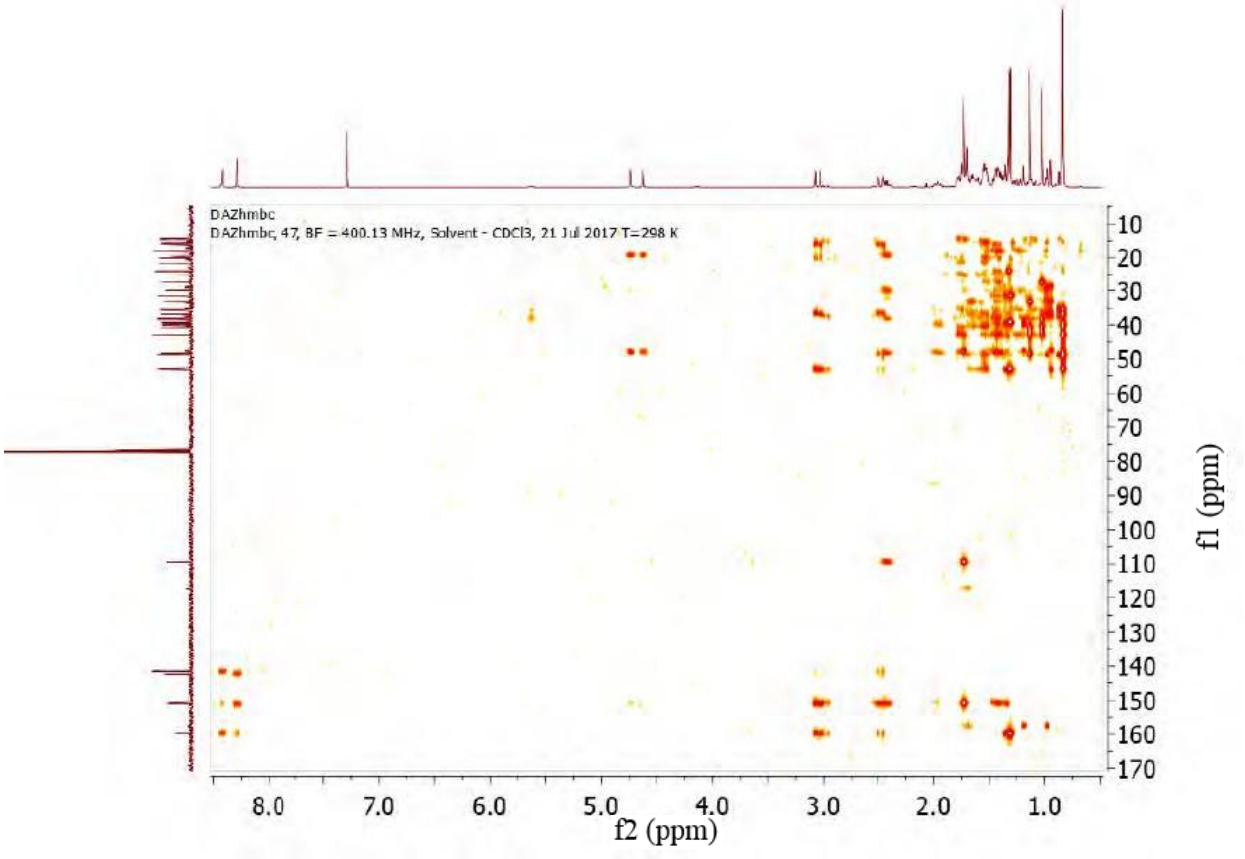


Figure S17 COSYof Compound 6.

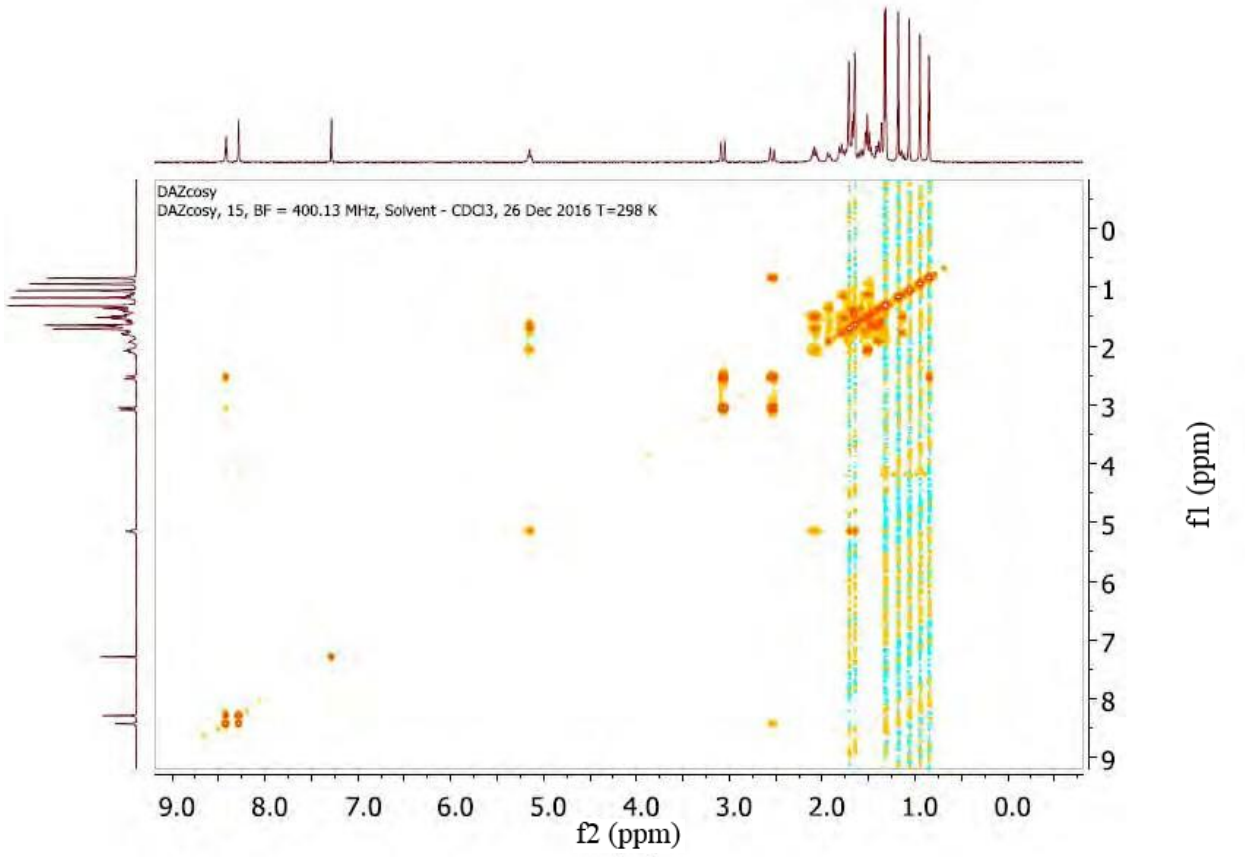


Figure S18 NOESY of Compound 6.

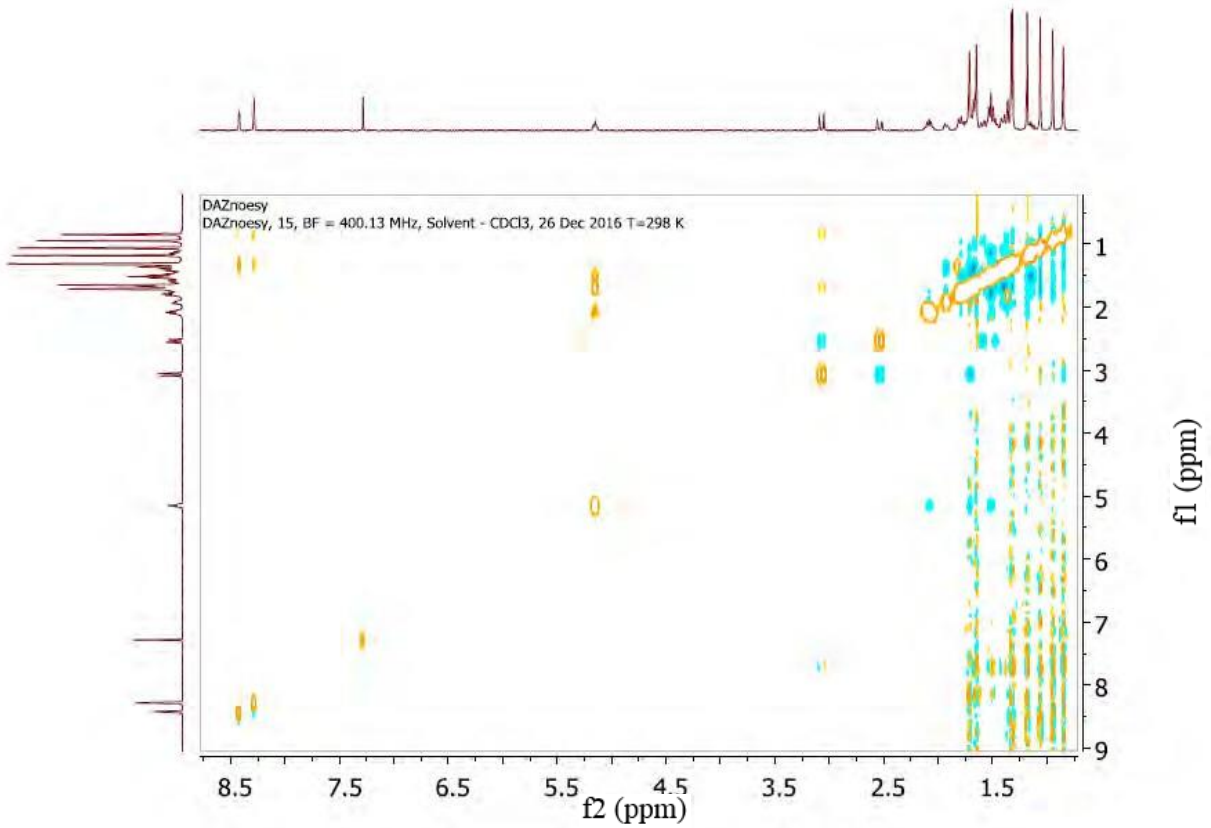


Figure S19 Spectrum HSQC of Compound 6

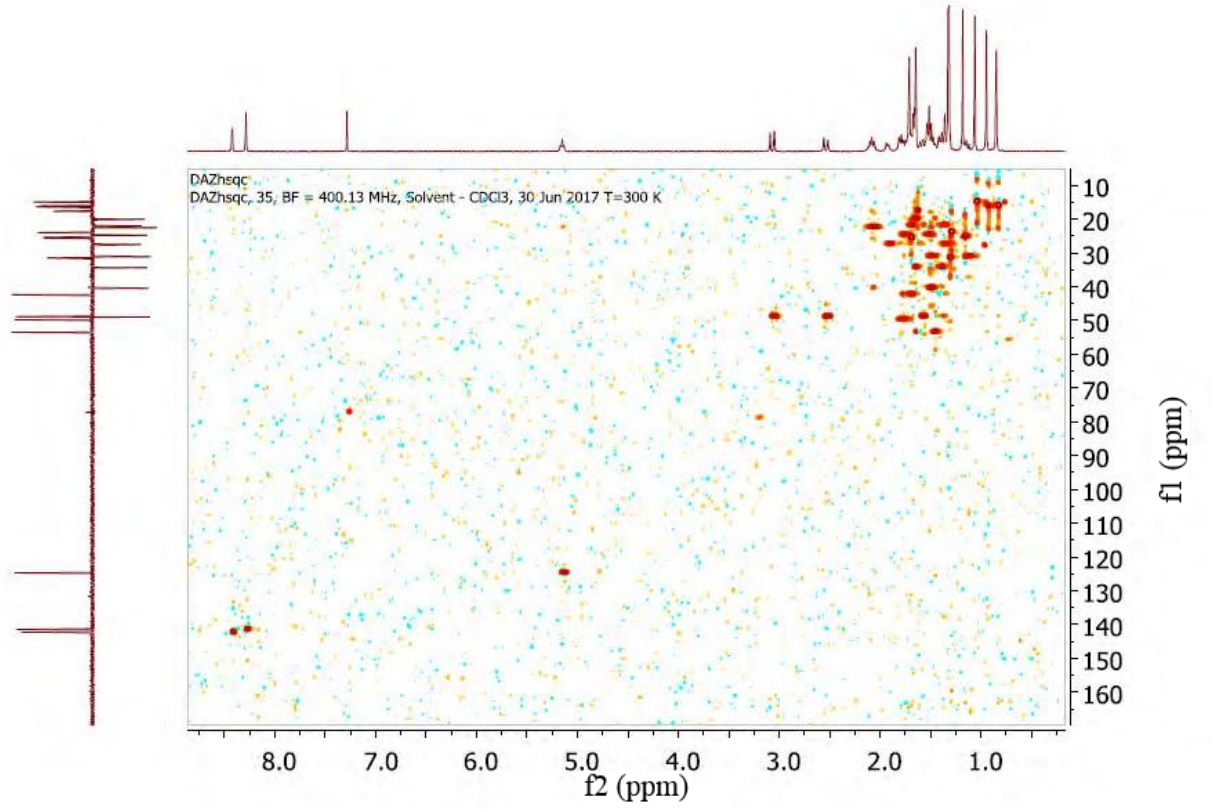


Figure S20 Spectrum HMBC of Compound 6.

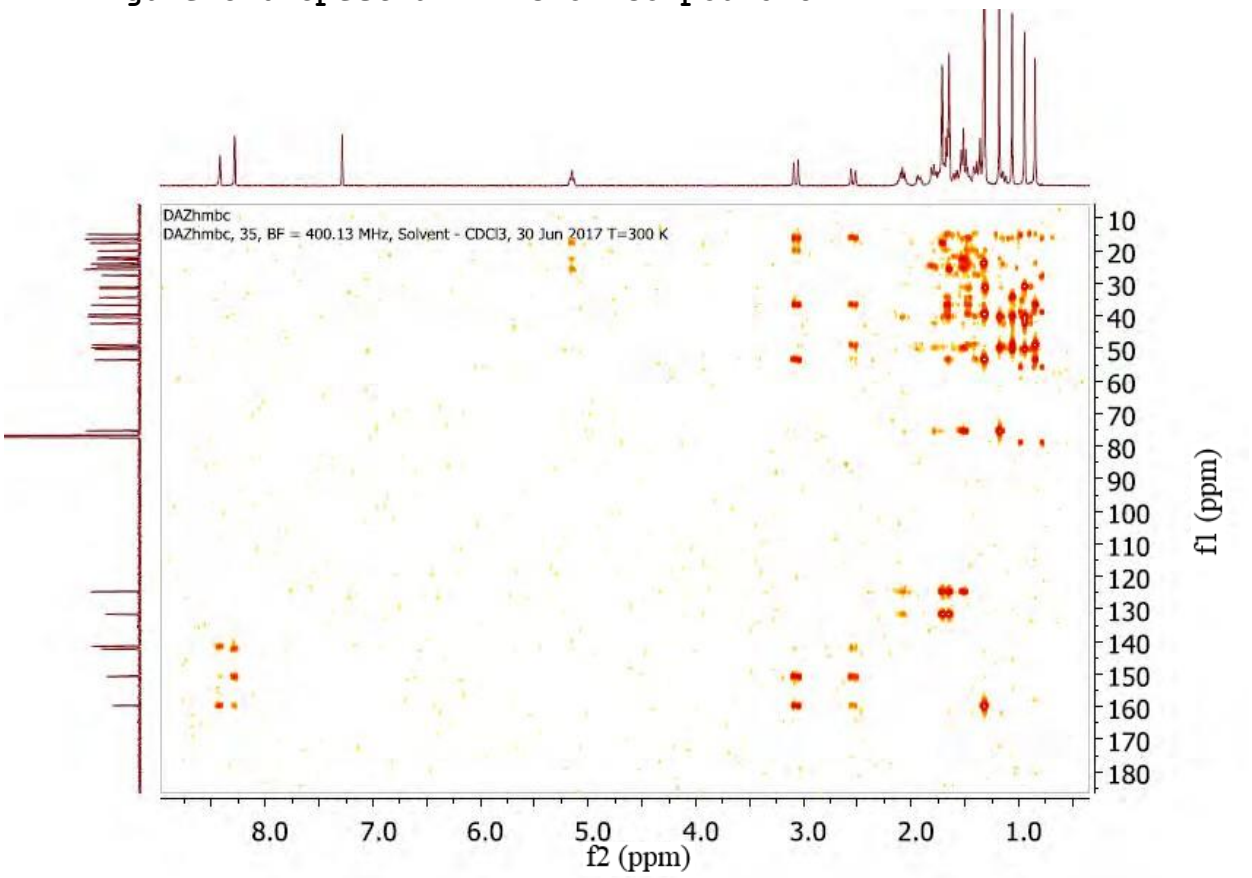


Figure S21 COSY of Compound 7.

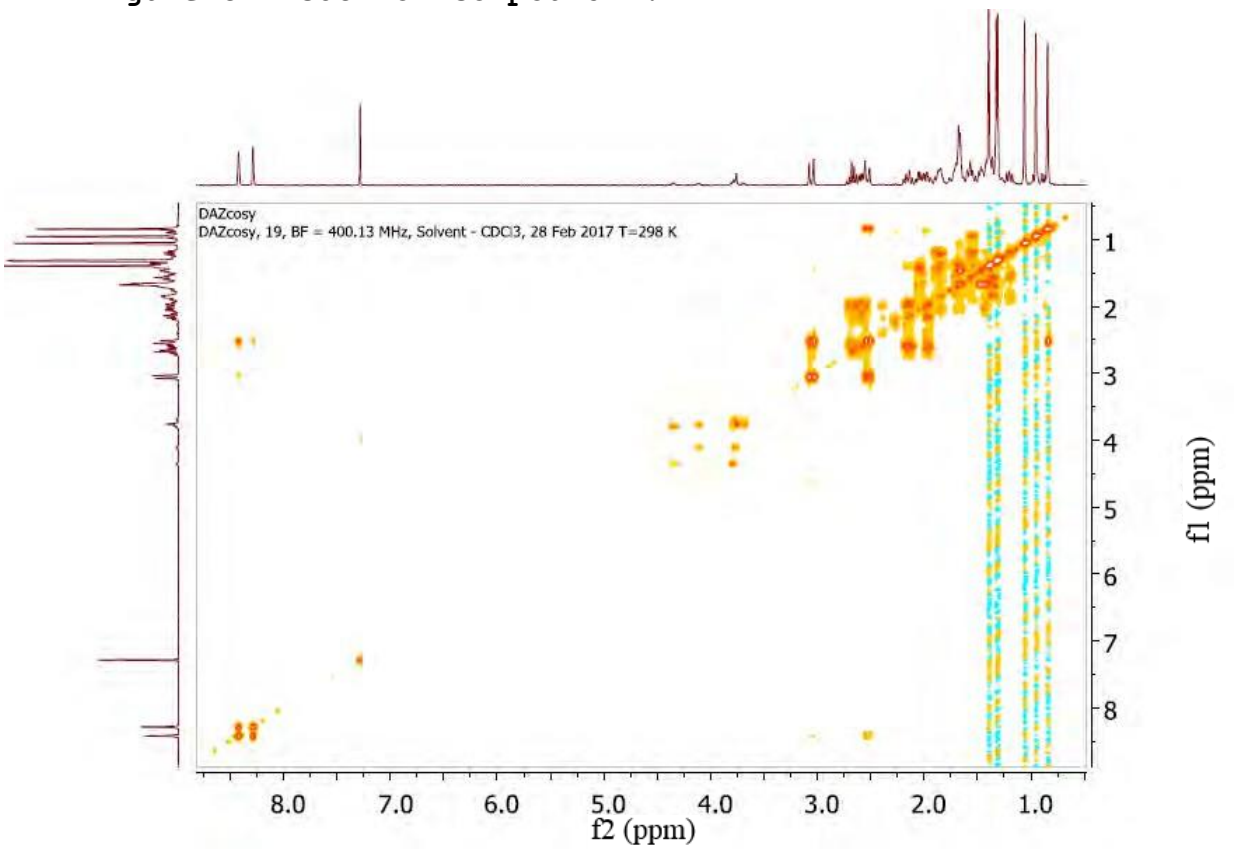


Figure S22 NOESY of Compound 7.

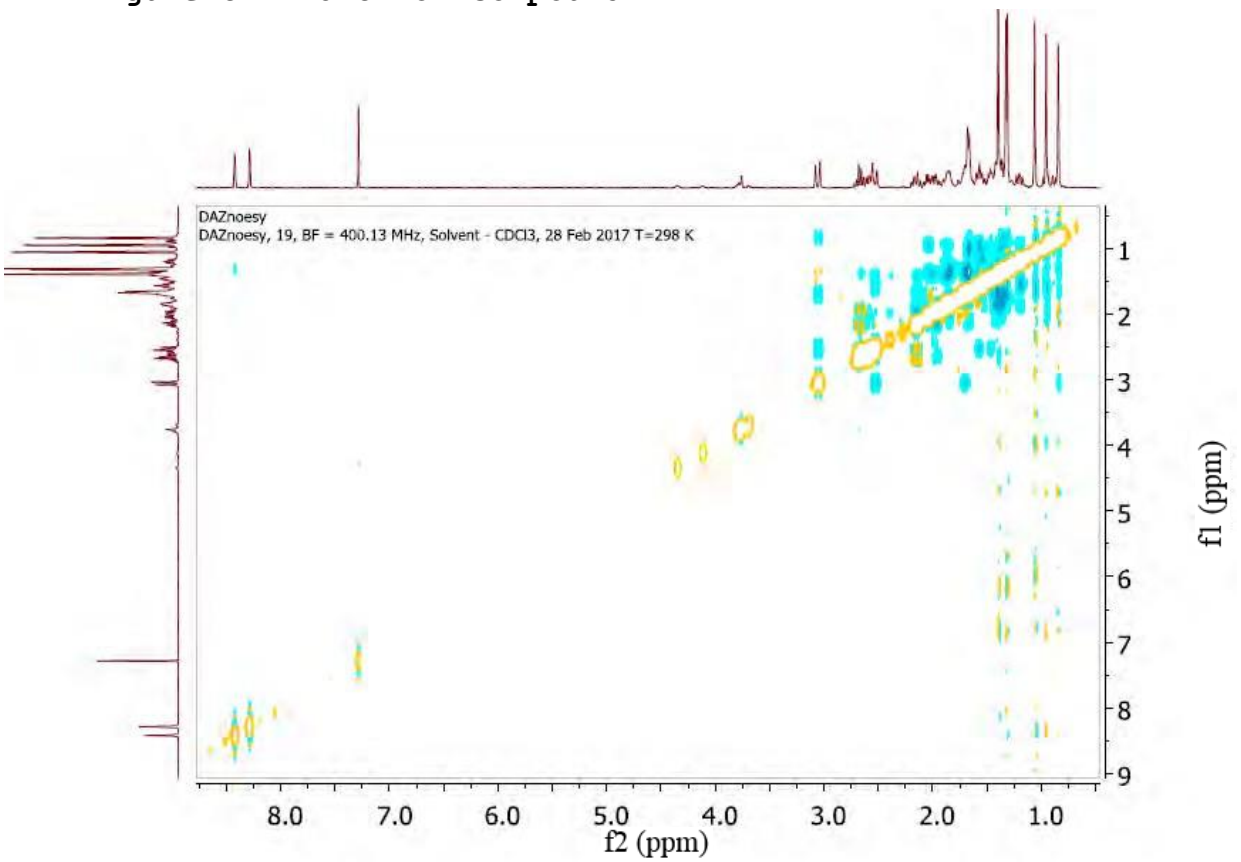


Figure S23 Spectrum HSQC of Compound 7.

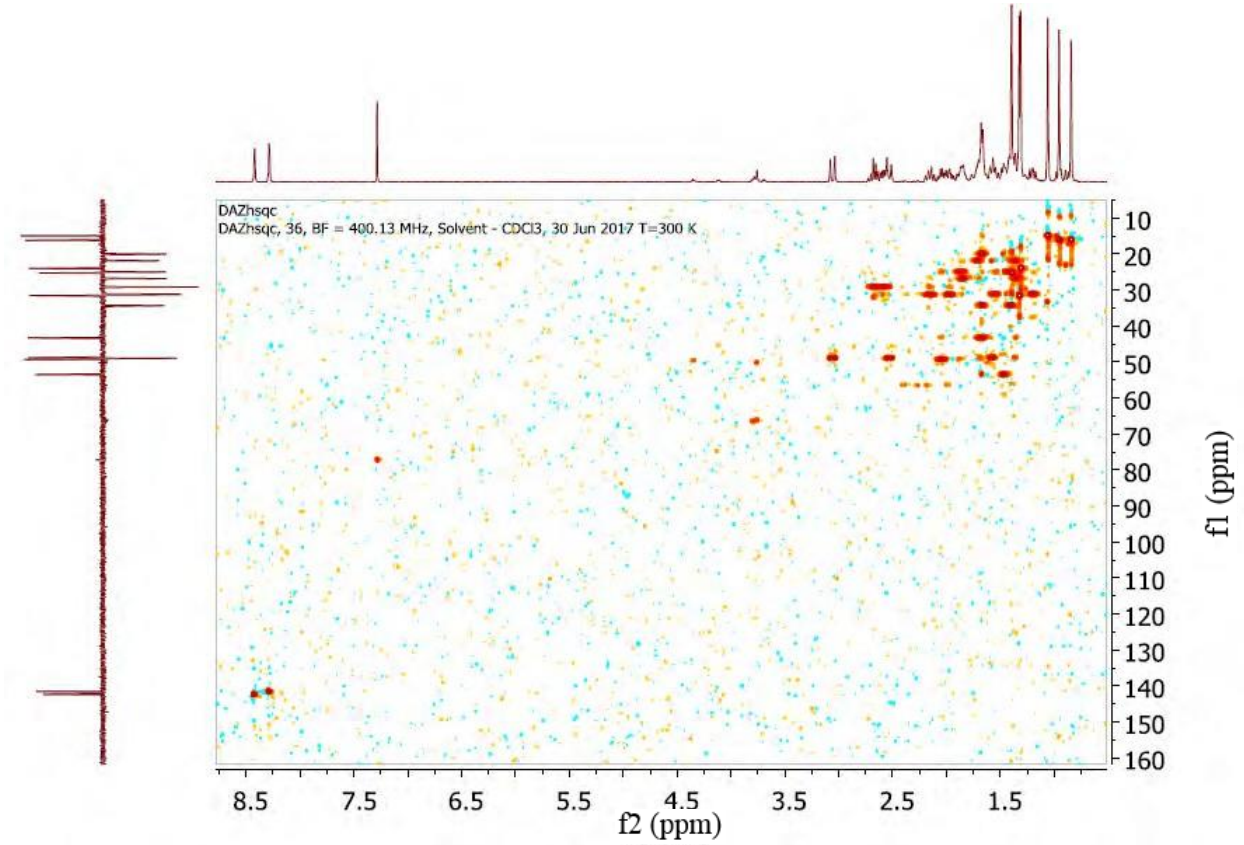


Figure S24 HMBC of Compound 7.

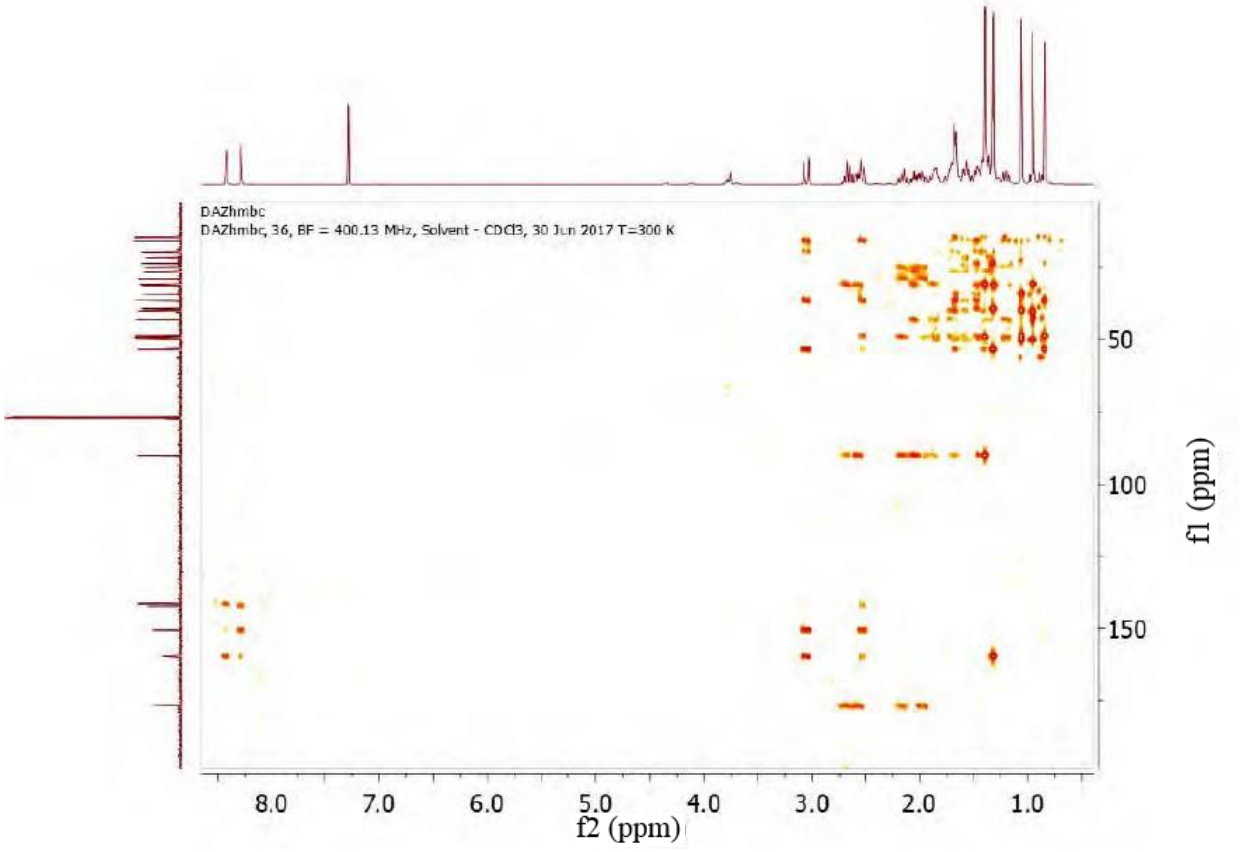


Figure S25 COSY of Compound 8.

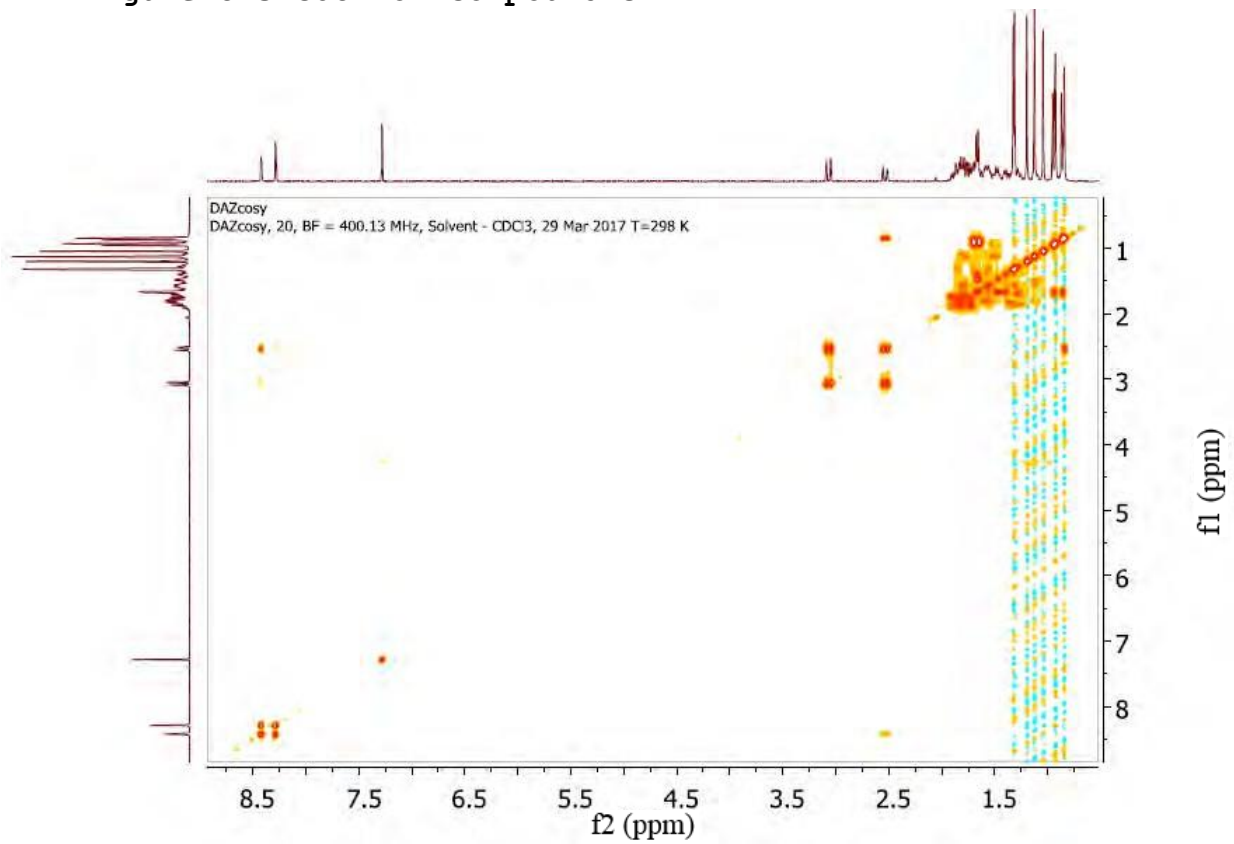


Figure S26 NOESY of Compound 8.

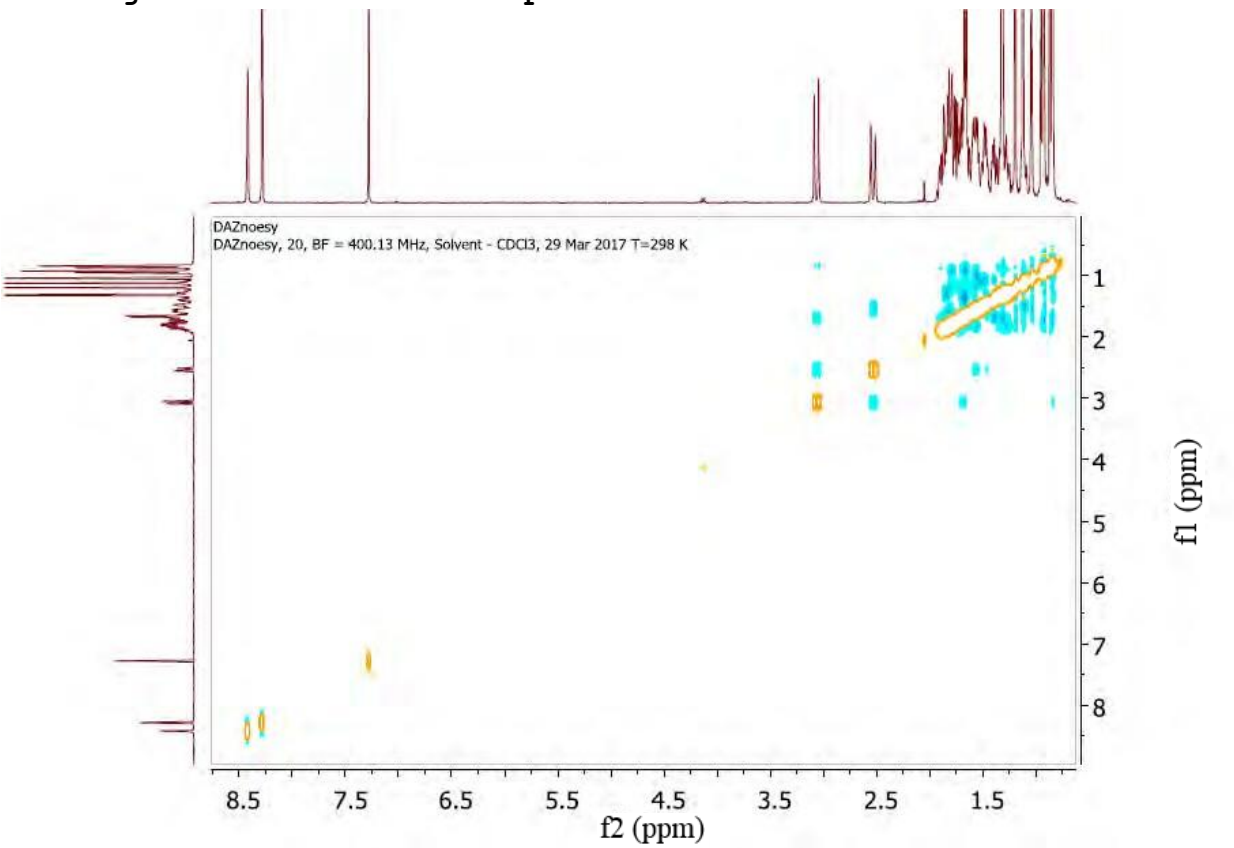


Figure S27 Spectrum HSQC of Compound 8.

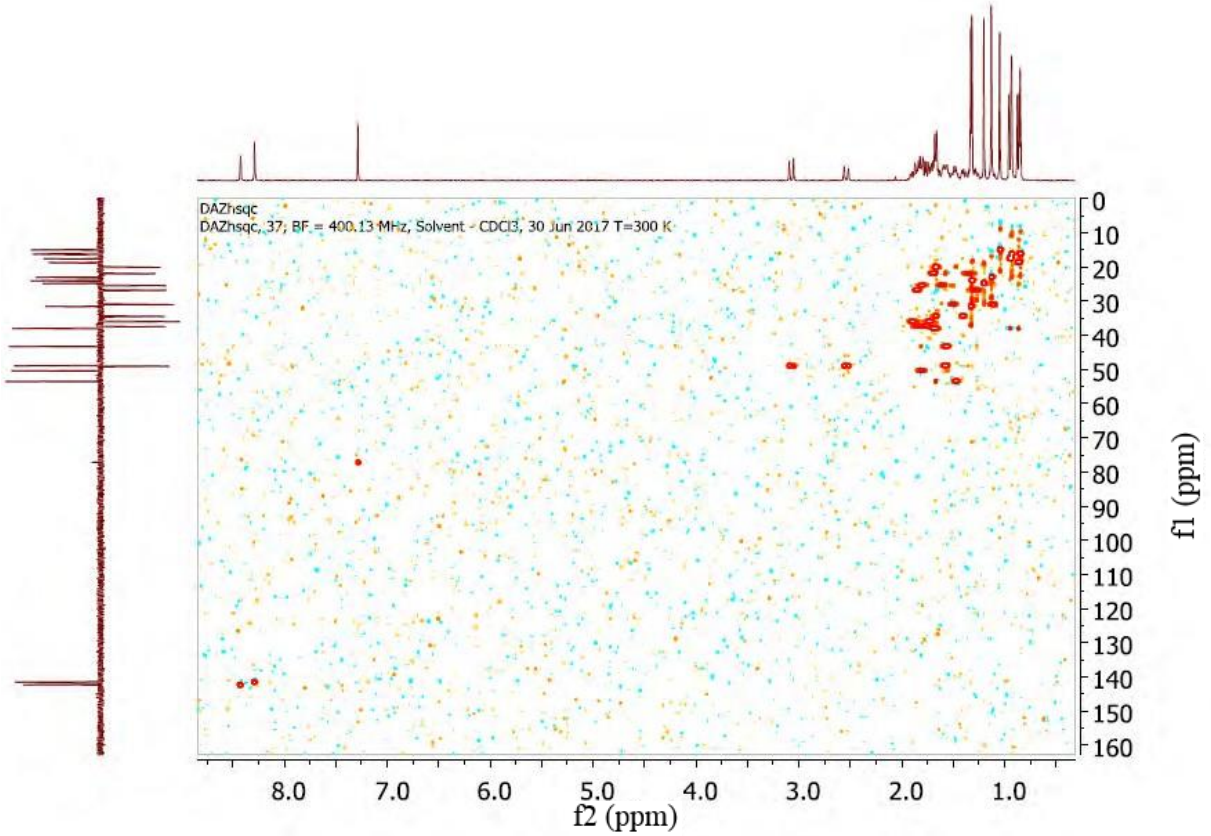
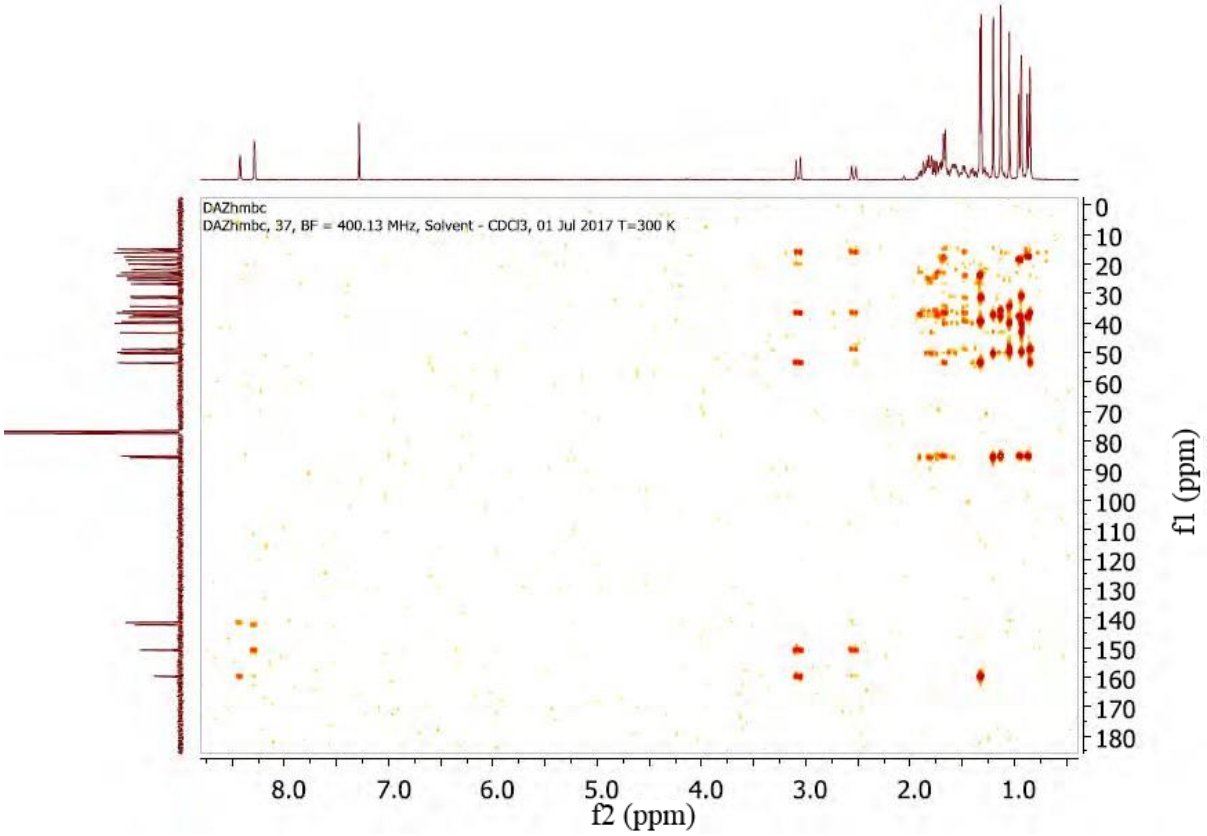


Figure S28 HMBC of Compound 8.



According to 2D NMR spectral data the pyrazine proton bonded to C-3' at 8.42 ppm has a scalar interaction through 6 bonds with the pseudoaxial proton Hα bonded with C-1 (δ 2.53 ppm), which is easily detected in the COSY spectrum, and the pseudoequatorial proton Hβ bonded with C-1 (δ 3.06 ppm) has a spatial interaction with protons of C-19 methyl group, which is confirmed by the corresponding cross-peak in the NOESY spectrum. These assignments are consistent with the known data on the identification of these proton signals for pyrazine derivatives condensed with ring A.[24,29]

Figure S29 HMBC correlations in pyrazino terpenes 2,6.

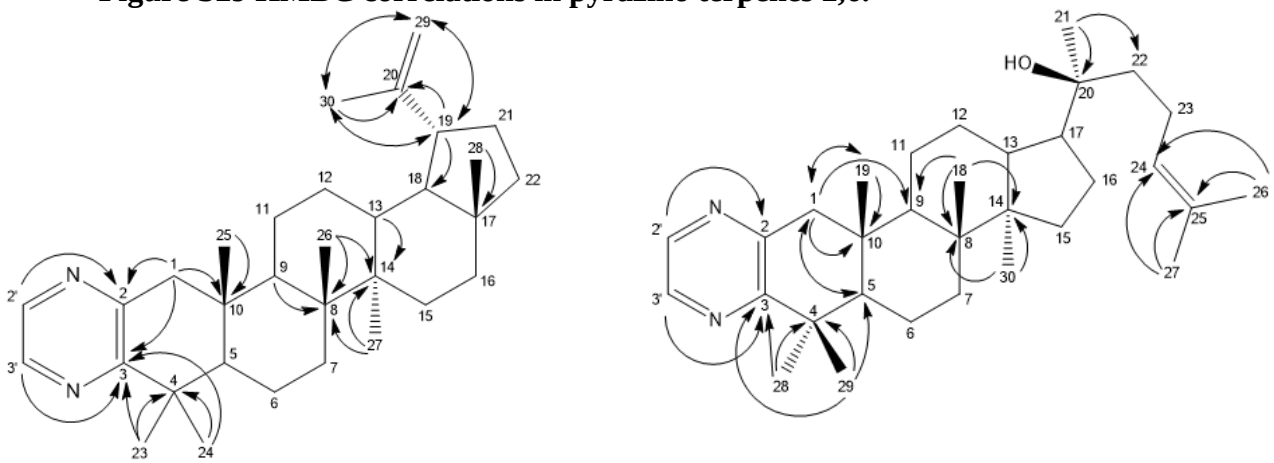


Table S1. The ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100MHz, $CDCl_3$) data assignments (in ppm) for **2,6-8**

Atom	Compound **2**		Compound **6**		Compound **7**		Compound **8**	
	δ_C	δ_H(J, Hz)	δ_C	δ_H(J, Hz)	δ_C	δ_H(J, Hz)	δ_C	δ_H(J, Hz)
1β 1α	48.7	3.05d (16.7) 2.48d (16.0)	49.0	3.07d (16.3) 2.54d (16.3)	48.8	3.06d (16.6) 2.53d (16.8)	49.0	3.07d (16.9) 2.54d (16.5)
2	151.0*		150.8		150.7		150.8	
3	159.7		159.7		159.6		159.7	
4	39.5		39.6		39.6		39.6	
5	53.0		53.5		53.5		53.5	
6	20.1		24.8		25.3		25.4	
7	33.3		31.2		31.2		31.0	
8	40.7		50.3		49.3		50.0	
9	48.7		49.0		49.0		48.9	
10	36.8		36.7		36.7		36.7	
11	21.5		22.0		22.0		21.9	
12	25.2		20.1		20.0		20.1	
13	38.2		42.4		43.3		43.3	
14	42.9		40.2		40.2		40.2	
15	27.5		34.4		34.3		34.4	
16	35.5		27.6		26.5		26.8	
17	43.0		49.8		50.2		50.4	
18	48.2		15.0	1.06	14.9	1.06	15.0	1.04
19	48.0		16.1	0.85	16.1	0.84	16.1	0.84
20	150.8*		75.3		90.0		85.6	
21	29.9		25.5	1.18	25.0	1.40	24.8	1.20
22α 22β	40.0		40.5	1.51t(8.4)	31.5	1.97m 2.15m	37.4	1.81m 1.76m
23α 23 β	31.5	1.33	22.6	2.08t(7.4)	29.2	2.58m 2.67m	36.0	1.89m 1.73m
24	24.1	1.31	124.7	5.15tt(7.0,1.4)	176.7		85.1	
25	16.2	0.84	131.6				38.0	1.67m
26	15.6	1.13	17.7	1.71			17.6	0.95d(6.8)
27	14.6	1.02	25.7.	1.65			18.8	0.87d(6.9)
28	18.1	0.84	31.5	1.33	31.3	1.33	31.5	1.32
29b 29a	109.5	4.72 dd(9.1,2.1) 4.61 ddd (11.1,1.2, 1.0)	24.0	1.31	24.0	1.31	24.0	1.31
30	19.4	1.73	16.4	0.95	16.2	0.95	16.3	0.93
31								1.13
2'	141.5	8.29 d(2.4)	141.5	8.28d(2.5)	141.5	8.28d(2.1)	141.5	8.28d(2.4)
3'	142.3	8.42 d(2.1)	142.3	8.42dd (2.5,0.7)	142.4	8.42 br.s	142.3	8.42 dd (2.4,0.7)

Mass-spectra

The HR-ESI mass-spectra were obtained on a BRUKER maxis spectrometer equipped with an electrospray ionization (ESI) source; methanol was used as the solvent. The instrument was operated in positive mode using an m/z range of 50–1200. The capillary voltage of the ion source was set at 4000 V The nebulizer gas pressure was 1.0 bar, and the drying gas flow was 4.0 dm^3 min^{-1}

Figure S30 The HR-ESI mass-spectrum of Compound 2(AZ-21).

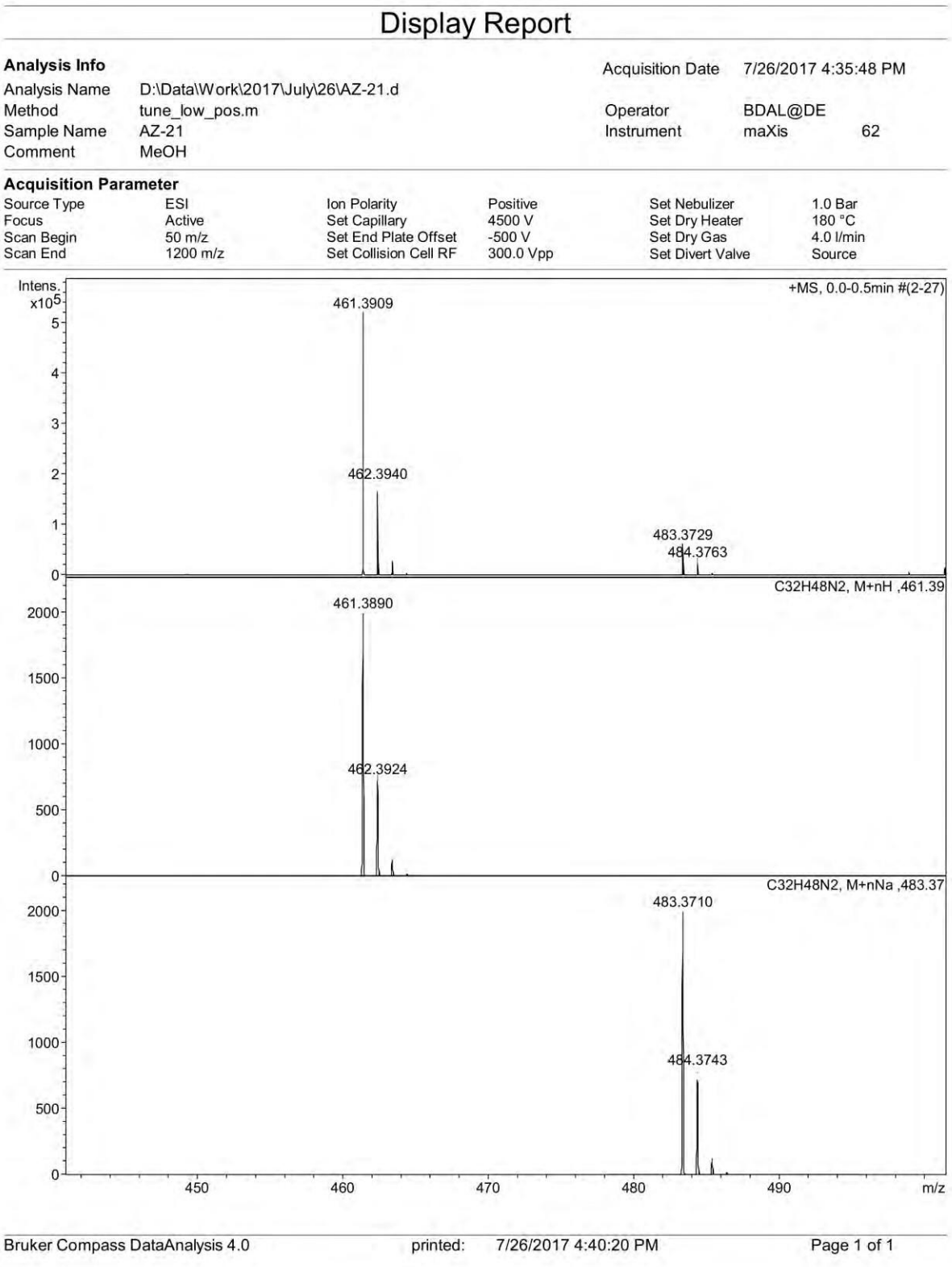


Figure S31 The HR-ESI mass-spectrum of Compound 6. (AZ 12)

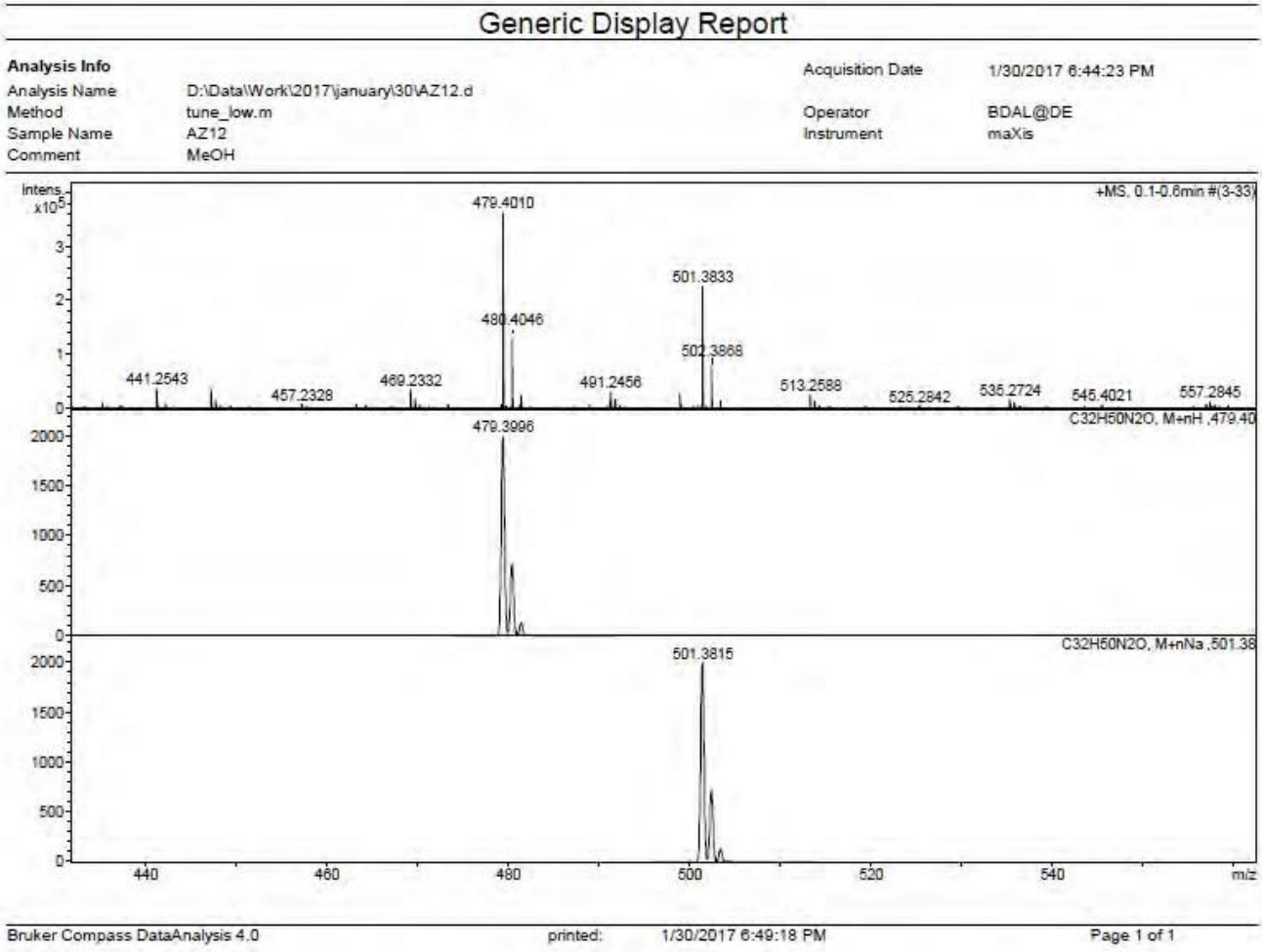


Figure S32 The HR-ESI mass-spectrum of Compound 7 (AZ-23).

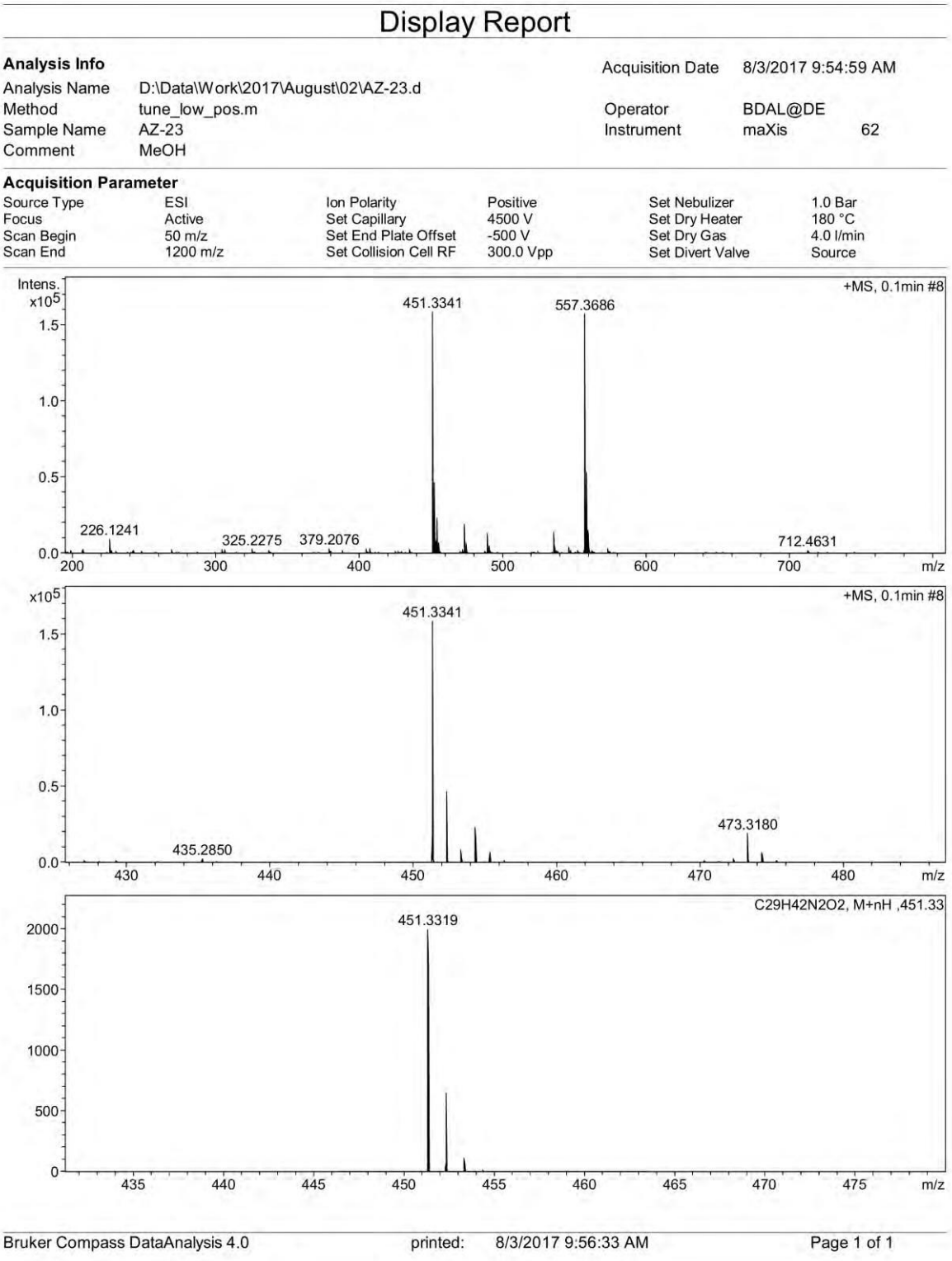
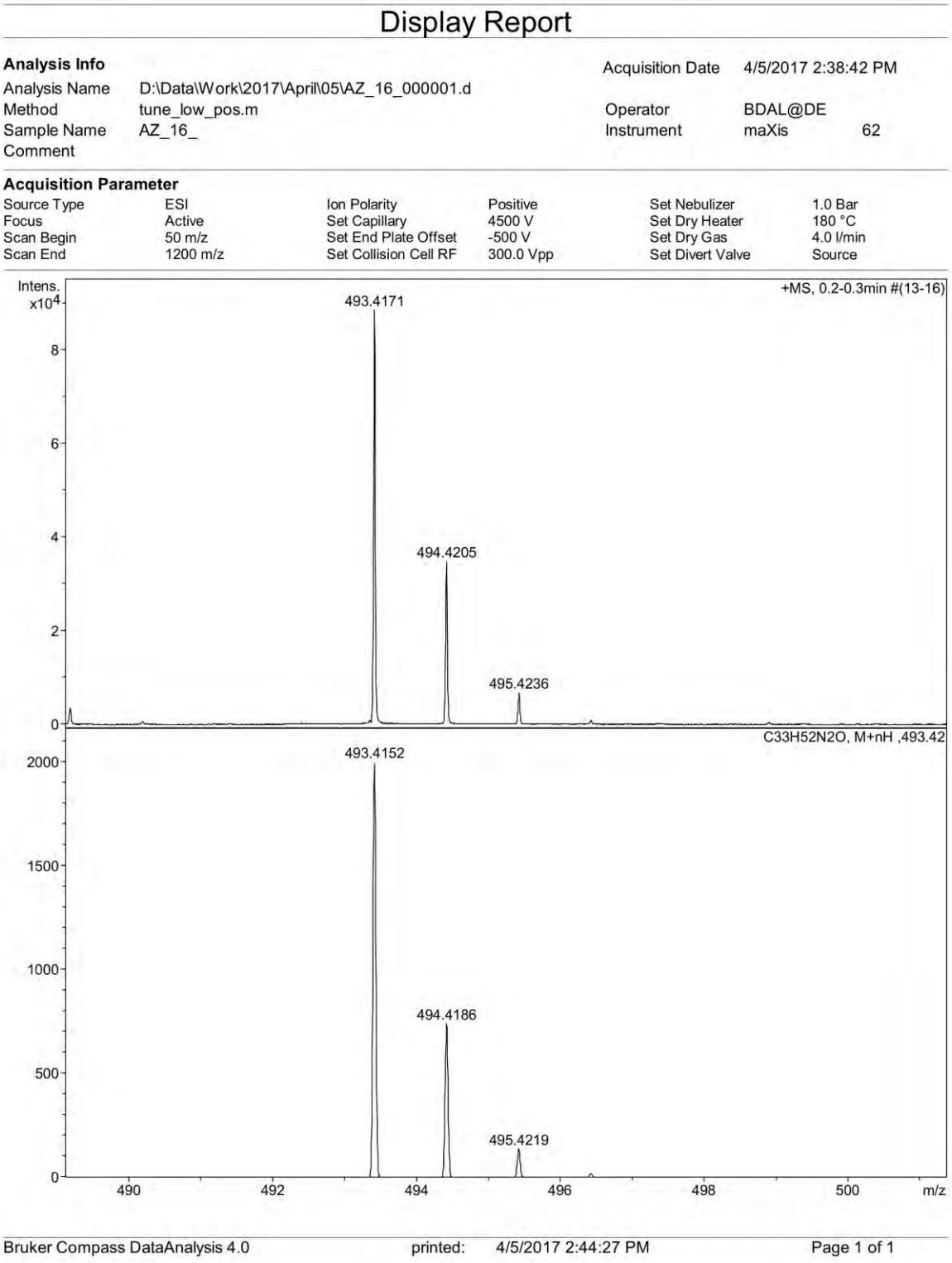


Figure S33 The HR-ESI mass-spectrum of Compound 8 (AZ 16).



X-ray crystal data of compounds.

1. X-ray crystal data of Compound 2 (adz3)

Adz3CCDC 1812486

Summary of Data CCDC 1812486

Compound Name:
Formula: C32 H48 N2
Unit Cell Parameters: a 14.42840(18) b 12.00295(14) c 23.1544(2) P21

Table S2 Compound 2 (adz 3)

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) adz3

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: adz3

Bond precision: C-C = 0.0033 A Wavelength=1.54184

Cell: a=14.42840(18) b=12.00295(14) c=23.1544(2)
alpha=90 beta=90.5465(11) gamma=90
Temperature: 100 K

	Calculated	Reported
Volume	4009.77(8)	4009.78(8)
Space group	P 21	P 1 21 1
Hall group	P 2yb	P 2yb
Moiety formula	C32 H48 N2	C32 H48 N2
Sum formula	C32 H48 N2	C32 H48 N2
Mr	460.72	460.72
Dx,g cm-3	1.145	1.145
Z	6	6
Mu (mm-1)	0.487	0.487
F000	1524.0	1524.0
F000'	1527.62	
h,k,lmax	17,14,28	17,14,28
Nref	15208[7994]	14964
Tmin,Tmax	0.900,0.943	0.774,1.000
Tmin'	0.847	

Correction method= # Reported T Limits: Tmin=0.774 Tmax=1.000
AbsCorr = MULTI-SCAN

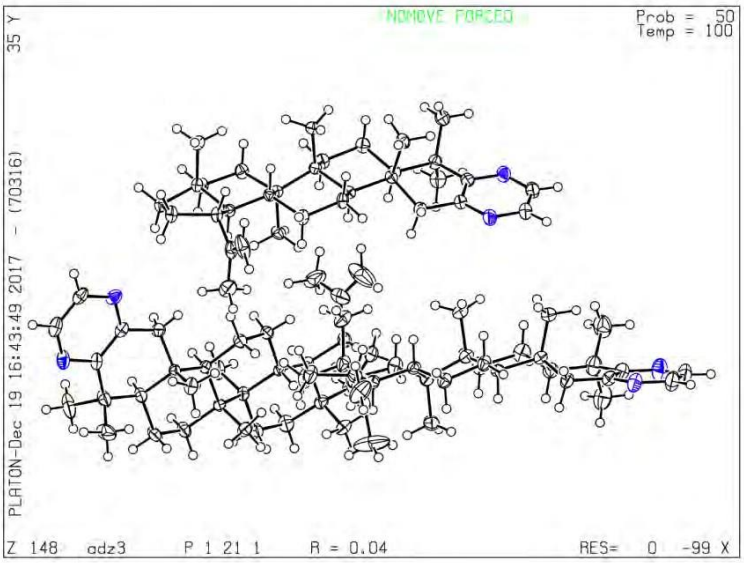
Data completeness= 1.87/0.98 Theta(max)= 69.995

R(reflections)= 0.0408(13933) wR2(reflections)= 0.1064(14964)

S = 1.043 Npar= 940

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Datablock adz3 - ellipsoid plot



2. X-ray crystal data of Compound 6 (adz5)

Adz5CCDC 1813229

Summary of Data CCDC 1813229

Compound Name:
Formula: C32 H50 N2 O1
Unit Cell Parameters: a 6.97320(10) b 11.8087(2) c 33.8433(8) P212121
Table S3 Compound 6 (adz5)

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) adz5

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: adz5

Bond precision: C-C = 0.0031 A Wavelength=1.54184

Cell: a=6.9732(1) b=11.8087(2) c=33.8433(8)
alpha=90 beta=90 gamma=90
Temperature: 100 K

	Calculated	Reported
Volume	2786.81(9)	2786.81(9)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C32 H50 N2 O	C32 H50 N2 O
Sum formula	C32 H50 N2 O	C32 H50 N2 O
Mr	478.74	478.74
Dx,g cm-3	1.141	1.141
Z	4	4
Mu (mm-1)	0.511	0.511
F000	1056.0	1056.0
F000'	1058.61	
h,k,lmax	8,14,41	8,14,41
Nref	5512[3170]	5485
Tmin,Tmax	0.885,0.941	0.623,1.000
Tmin'	0.849	

Correction method= # Reported T Limits: Tmin=0.623 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 1.73/1.00 Theta(max)= 72.290

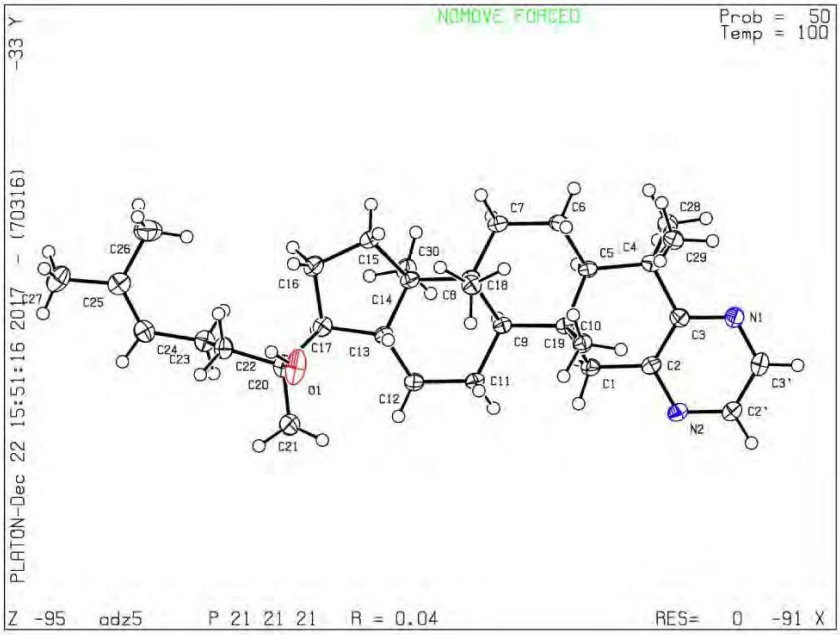
R(reflections)= 0.0411(5145) wR2(reflections)= 0.1043(5485)

S = 1.046 Npar= 325

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

PLATON version of 13/12/2017; check.def file version of 12/12/2017

Datablock adz5 - ellipsoid plot



3. X-ray crystal data of Compound 7 (adz-2) .

Summary of Data CCDC 1812773

Compound Name:
Formula: C29 H42 N2 O2
Unit Cell Parameters: a 12.6984(12) b 15.0386(14) c 13.5944(15) P21

Table S4. Compound 7 (adz-2) .

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) 2

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: 2

Bond precision: C-C = 0.0033 A Wavelength=0.71073

Cell: a=12.6984(12) b=15.0386(14) c=13.5944(15)
alpha=90 beta=108.824(12) gamma=90
Temperature: 100 K

	Calculated	Reported
Volume	2457.2(5)	2457.2(4)
Space group	P 21	P 1 21 1
Hall group	P 2yb	P 2yb
Moiety formula	C29 H42 N2 O2	C29 H42 N2 O2
Sum formula	C29 H42 N2 O2	C29 H42 N2 O2
Mr	450.65	450.64
Dx,g cm-3	1.218	1.218
Z	4	4
Mu (mm-1)	0.076	0.076
F000	984.0	984.0
F000'	984.37	
h,k,lmax	15,18,17	15,18,17
Nref	10160[5281]	8346
Tmin,Tmax	0.980,0.991	0.681,1.000
Tmin'	0.974	

Correction method= # Reported T Limits: Tmin=0.681 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 1.58/0.82 Theta(max)= 26.497

R(reflections)= 0.0367(7747) wR2(reflections)= 0.0885(8346)

S = 1.029 Npar= 607

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

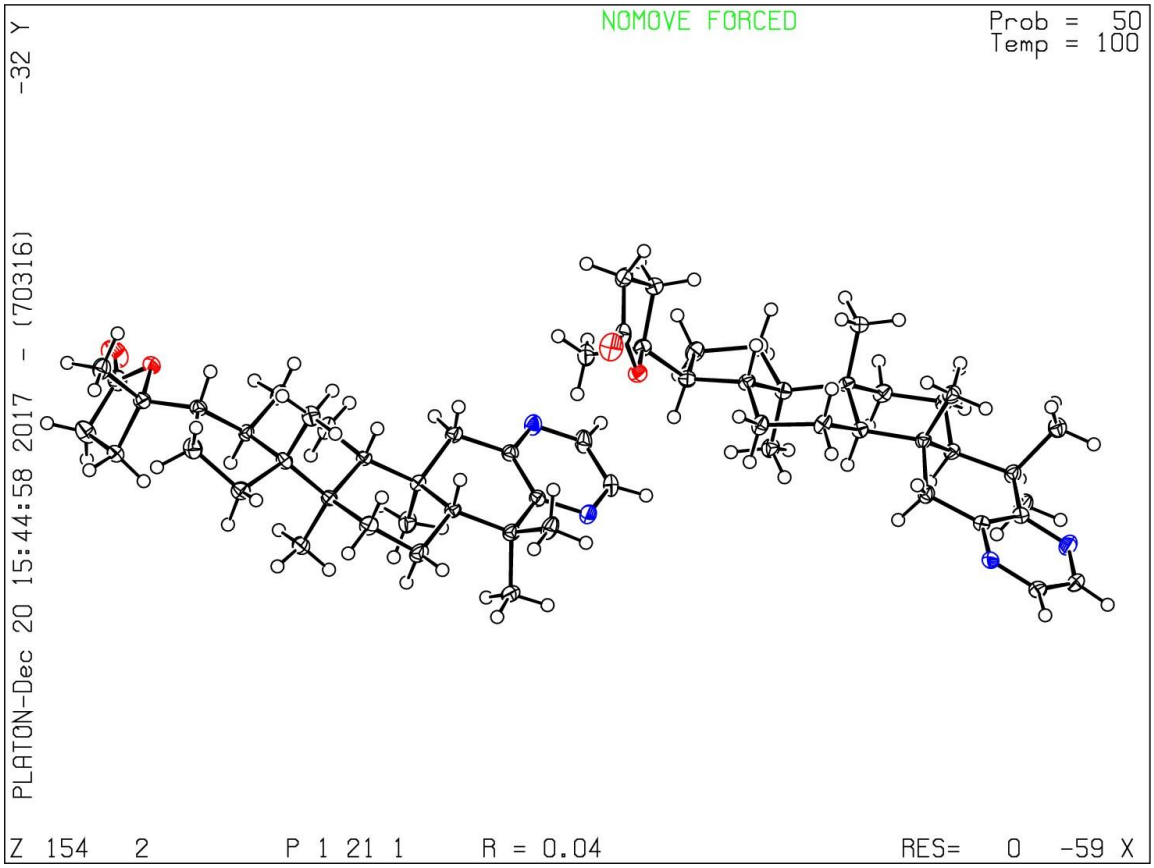

NOMOVE FORCED
Prob = 50
Temp = 100
-32 Y
PLATON-Dec 20 15:44:58 2017 - (70316)
Z 154 2
P 1 21 1
R = 0.04
RES= 0 -59 X

Table S5 Crystal data and structure refinement for compounds **2(adz3), 6(adz5), 7(adz2)**

Identification code	Compound **2** (adz3)	Compound **6** (adz5)	Compound 7 (adz 2)
Empirical formula	$C_{32}H_{48}N_2$	$C_{32}H_{50}N_2O$	$C_{29}H_{42}N_2O_2$
Formula weight	460.72	478.74	450.64
Crystal system	monoclinic	orthorhombic	monoclinic
Space group	$P2_1$	$P2_12_12_1$	$P2_1$
a/Å	14.42840(18)	6.97320(10)	12.6984(12)
b/Å	12.00295(14)	11.8087(2)	15.0386(14)
c/Å	23.1544(2)	33.8433(8)	13.5944(15)
α/°	90	90	90
β/°	90.5465(11)	90	108.824(12)
γ/°	90	90	90
Volume/Å^3	4009.78(8)	2786.81(9)	2457.2(4)
Z	6	4	4
ρ_{calc}g/cm^3	1.145	1.141	1.218
μ/mm^{-1}	0.487	0.511	0.076
F(000)	1524.0	1056.0	984.0
Crystal size/mm^3	0.34 × 0.18 × 0.12	0.32 × 0.20 × 0.12	0.34 × 0.22 × 0.12
Radiation	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.126 to 139.99	7.93 to 144.58	5.982 to 52.994
Index ranges	-17 ≤ h ≤ 17, -14 ≤ k ≤ 14, -28 ≤ l ≤ 19	-8 ≤ h ≤ 8, -14 ≤ k ≤ 14, -41 ≤ l ≤ 41	-15 ≤ h ≤ 15, -18 ≤ k ≤ 18, -14 ≤ l ≤ 17
Reflections collected	43055	52955	11308
Independent reflections	14964 [R_{int} = 0.0434, R_{sigma} = 0.0426]	5485 [R_{int} = 0.0700, R_{sigma} = 0.0287]	8346 [R_{int} = 0.0179, R_{sigma} = 0.0386]

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

Table S6 LAST.CIF of Compound 2 (adz3)

data_adz3
_audit_creation_date 2017-12-19
_
List of Runs (angles in degrees, time in seconds):

```
   # Type     Start     End       Width     t~exp~  \w      \q      \k      \f       Frames
------------------------------------------------------------------------------
-------------------------------------------------
1  \w  -81.00  -56.00 0.50  0.20   --  -41.35  -15.00   -50
                                          46.00
2  \w  -83.00  -28.00 0.50  0.20   --  -41.35  116.00   -110
                                          58.00
3  \w  -104.00 -56.00 0.50  0.20   --  -41.35-155.00    -96
                                          33.00
4  \w  1.00    31.00  0.50  0.20   --  -41.35   15.00    60
                                          123.00
5  \w  -23.00  2.00   0.50  0.20   --  -41.35  116.00   -50
                                          58.00
6  \w  40.00   86.00  0.50  0.20   --  41.35-120.00      92
                                          123.00
7  \w  10.00   35.00  0.50  0.20   --  41.35-120.00      50
                                          123.00
8  \w  45.00   70.00  0.50  0.20   --  41.35-164.00      50
                                               64.00
9  \w  14.00   39.00  0.50  0.20   --  41.35   -15.00   -50
                                          46.00
10 \w  90.00   116.00 0.50  0.55   --  101.00-116.00-    52
                                          147.00
11 \w  37.00   87.00  0.50  0.55   --  101.00-116.00-    100
                                          147.00
12 \w  96.00   121.00 0.50  0.55   --  101.00    15.00   50
                                          123.00
13 \w  29.00   96.00  0.50  0.55   --  101.00  -15.00   -134
                                          46.00
14 \w  111.00  149.00 0.50  0.55   --  101.00     120.00-76
                                          151.00
15 \w  100.00  125.00 0.50  0.55   --  101.00  116.00   -50
                                          58.00
16 \w  75.00   113.00 0.50  0.55   --  101.00-120.00     76
                                          123.00
17 \w  -101.00 -29.00 0.50  0.20   --  -41.35  -43.00   -144
                                          60.00
18 \w  -53.00  -28.00 0.50  0.20   --  -41.35     120.00-50
                                          151.00
19 \w  -93.00  -68.00 0.50  0.20   --  -41.35  138.00   -50
                                          60.00
20 \w  58.00   83.00  0.50  0.20   --  41.35     15.00   50
```

```
                                                    123.00
21 \w  -1.00   49.00  0.50  0.20   --   41.35       -32.00100
                                                     60.00
22 \w  62.00   155.00 0.50  0.55   --   101.00  145.00  -186
                                                    90.00
23 \w  105.00  156.00 0.50  0.55   --   101.00    17.00-  102
                                                    120.00
24 \w  67.00   105.00 0.50  0.55   --   101.00      -96.0076
                                                    120.00
25 \w  37.00   88.00  0.50  0.55   --   101.00-117.00     102
                                                     60.00
26 \w  31.00   63.00  0.50  0.55   --   101.00      -96.0064
                                                    120.00
27 \w  39.00   91.00  0.50  0.55   --   101.00     -42.00-104
                                                    150.00
28 \w  66.00   91.00  0.50  0.55   --   101.00-164.00     50
                                                     64.00
29 \w  63.00   89.00  0.50  0.55   --   101.00-120.00     52
                                                    123.00
30 \w  -95.00  -67.00 0.50  0.20   --   -41.35      -43.0056
                                                     90.00
31 \w  -111.00 -85.00 0.50  0.20   --   -41.35     -21.00-52
                                                    180.00
32 \w  -99.00  -17.00 0.50  0.20   --   -41.35  -77.00  -164
                                                    90.00
33 \w  -104.00 -43.00 0.50  0.20   --   -41.35     -32.00-122
                                                    180.00
34 \w  -55.00  -18.00 0.50  0.20   --   -41.35    43.00-  74
                                                    120.00
35 \w  -76.00  -51.00 0.50  0.20   --   -41.35     -21.00-50
                                                    180.00
36 \w  -57.00  -31.00 0.50  0.20   --   -41.35      -43.0052
                                                     90.00
37 \w  6.00    59.00  0.50  0.20   --   41.35       -77.00106
                                                    150.00
38 \w  65.00   91.00  0.50  0.20   --   41.35       155.0052
                                                      5.00
39 \w  56.00   81.00  0.50  0.20   --   41.35     32.00  -50
                                                     60.00
40 \w  23.00   49.00  0.50  0.20   --   41.35      -54.00-52
                                                    180.00
41 \w  61.00   106.00 0.50  0.20   --   41.35     32.00-  90
                                                    180.00
42 \w  48.00   74.00  0.50  0.55   --   101.00      -87.0052
                                                    120.00
43 \w  30.00   115.00 0.50  0.55   --   101.00     -17.00-170
                                                    150.00
44 \w  40.00   130.00 0.50  0.55   --   101.00-145.00     180
                                                    120.00
45 \w  92.00   124.00 0.50  0.55   --   101.00    50.00  -64
```

```
                                                  60.00
46 \w  94.00   130.00 0.50  0.55   --  101.00-145.00     72
                                       60.00
47 \w  38.00   104.00 0.50  0.55   --  101.00  -42.00  -132
                                      90.00
48 \w  78.00   151.00 0.50  0.55   --  101.00   77.00   146
                                       30.00
49 \w  85.00   117.00 0.50  0.55   --  101.00   59.00   64
                                      120.00
50 \w  94.00   124.00 0.50  0.55   --  101.00   25.00   60
                                       90.00
51 \w  56.00   115.00 0.50  0.55   --  101.00  -68.00  -118
                                      90.00
52 \w  57.00   83.00  0.50  0.55   --  101.00     -59.0052
                                      120.00
53 \w  40.00   109.00 0.50  0.55   --  101.00    -96.00-138
                                      120.00
54 \w  80.00   122.00 0.50  0.55   --  101.00 68.00 -30.00 84
55 \w  97.00   149.00 0.50  0.55   --  101.00 42.00 150.00 104
56 \w  46.00   72.00  0.50  0.55   --  101.00-     30.00  52
                                        50.00
57 \w  83.00   117.00 0.50  0.55   --  101.00-     30.00  68
                                        50.00
58 \w  80.00   129.00 0.50  0.55   --  101.00-     0.00   98
                                        87.00
59 \w  64.00   116.00 0.50  0.55   --  101.00-117.00-     104
                                      120.00
60 \w  38.00   102.00 0.50  0.55   --  101.00     -33.00128
                                       30.00
61 \w  87.00   153.00 0.50  0.55   --  101.00  117.00  -132
                                      30.00
62 \w   37.00 107.00 0.50  0.55   --  101.00    -77.00-140
                                      120.00
63 \w   81.00 155.00 0.50  0.55   --  101.00   96.00   148
                                       0.00
```

Table S7 LAST.CIF of Compound 6 (adz5)

data_adz5
_audit_creation_date 2017-12-22
_audit_creation_method

List of Runs (angles in degrees, time in seconds):

```
  # Type    Start     End      Width    t~exp~  \w     \q     \k     \f       Frames
-------------------------------------------------------------------------------
-------------------------------------------------
1   \w  -13.00 14.00  0.50  1.56   --  -41.35 95.00 55.00  54
2   \w  -72.00 -46.00 0.50  1.56   --  -41.35 95.00 55.00  52
3   \w  -76.00 -25.00 0.50  1.56   --  -41.35-     42.00  102
                                          69.00
4   \w  -72.00 -22.00 0.50  1.56   --  -41.35-     179.00 100
```

5	\w	-4.00	21.00	0.50	1.56	--	41.35	61.00 - 69.00	42.00	50
6	\w	-12.00	50.00	0.50	1.56	--	41.35	61.00 - 95.00	-54.00	124
7	\w	63.00	88.00	0.50	1.56	--	41.35	61.00	-42.00	50
8	\w	-8.00	18.00	0.50	1.56	--	41.35	61.00 - 69.00	179.00	52
9	\w	38.00	63.00	0.50	1.56	--	41.35	69.00	174.00	50
10	\w	73.00	104.00	0.50	6.22	--	101.00	61.00 - 69.00	179.00	62
11	\w	90.00	155.00	0.50	6.22	--	101.00	69.00	174.00	130
12	\w	37.00	108.00	0.50	6.22	--	101.00	61.00 - 95.00	42.00	142
13	\w	95.00	120.00	0.50	6.22	--	101.00	95.00	55.00	50
14	\w	119.00	150.00	0.50	6.22	--	101.00	61.00	-42.00	62
15	\w	34.00	108.00	0.50	6.22	--	101.00	61.00 - 95.00	-54.00	148
16	\w	-40.00	1.00	0.50	1.56	--	-41.35	32.00	30.00	82
17	\w	-54.00	4.00	0.50	1.56	--	-41.35	43.00	60.00	116
18	\w	-39.00	-14.00	0.50	1.56	--	-41.35	61.00	-42.00	50
19	\w	-23.00	33.00	0.50	1.56	--	41.35	61.00 - 32.00	0.00	112
20	\w	119.00	156.00	0.50	6.22	--	101.00	33.00	-60.00	74
21	\w	92.00	155.00	0.50	6.22	--	101.00	33.00	-30.00	126
22	\w	86.00	142.00	0.50	6.22	--	101.00	50.00 - 120.00		112
23	\w	42.00	107.00	0.50	6.22	--	101.00	-42.00 - 30.00		130
24	\w	89.00	157.00	0.50	6.22	--	101.00	42.00 - 90.00		136
25	\w	92.00	123.00	0.50	6.22	--	101.00	25.00 - 120.00		62
26	\w	-59.00	-34.00	0.50	1.56	--	-41.35	61.00 - 42.00		-50
27	\w	-46.00	-19.00	0.50	1.56	--	4.00	129.00 - 109.54		54
28	\w	-42.00	-17.00	0.50	1.56	--	24.00	151.00 - 124.78		50
29	\w	-43.00	-18.00	0.50	1.56	--	24.00	153.00 - 105.33		50
30	\w	-3.00	22.00	0.50	1.56	--	28.00	96.00 - 38.69		-50
31	\w	-3.00	22.00	0.50	1.56	--	28.00	96.00 - 145.61		50
32	\w	2.00	27.00	0.50	1.56	--	32.00	91.00	80.26	50
33	\w	2.00	27.00	0.50	1.56	--	32.00	91.00	26.05	50
34	\w	9.00	34.00	0.50	1.56	--	36.00	84.00	-86.55	50
35	\w	10.00	35.00	0.50	1.56	--	36.00	83.00	135.98	50
36	\w	10.00	35.00	0.50	1.56	--	36.00	83.00	38.97	50

```
37  \w  -53.00 -17.00 0.50  1.56  --  -41.35 65.00 -90.00 72
38  \w  -97.00 -12.00 0.50  1.56  --  -41.35 138.0 60.00  170
                                          0
39  \w  -13.00 13.00  0.50  1.56  --  -41.35 61.00 -42.00 52
40  \w  -66.00 -28.00 0.50  1.56  --  -41.35 138.0 30.00  76
                                          0
41  \w  44.00  70.00  0.50  1.56  --  41.35  -     150.00 52
                                          89.00
42  \w  -24.00 38.00  0.50  1.56  --  41.35  -     150.00 124
                                          89.00
43  \w  19.00  44.00  0.50  1.56  --  44.00  79.00        50
                                          146.17
44  \w  19.00  44.00  0.50  1.56  --  44.00  81.00        50
                                          171.55
45  \w  19.00  44.00  0.50  1.56  --  44.00  80.00        50
                                               23.49
46  \w  18.00  44.00  0.50  1.56  --  44.00  82.00        52
                                               87.84
47  \w  19.00  44.00  0.50  1.56  --  44.00  80.00        50
                                          158.49
48  \w  19.00  44.00  0.50  1.56  --  44.00  80.00       -50
                                          69.61
49  \w  19.00  44.00  0.50  1.56  --  44.00  81.00       -50
                                          58.14
50  \w  19.00  44.00  0.50  1.56  --  44.00  80.00-148.1 50
51  \w  18.00  43.00  0.50  1.56  --  44.00  82.00       -50
                                          16.90
52  \w  18.00  43.00  0.50  1.56  --  44.00  82.00       -50
                                          39.33
53  \w  19.00  44.00  0.50  1.56  --  44.00  81.00-106.07 50
54  \w  18.00  43.00  0.50  1.56  --  44.00  82.00        50
                                               47.43
55  \w  34.00  63.00  0.50  1.56  --  52.00  76.00        58
                                          136.35
56  \w  28.00  55.00  0.50  1.56  --  52.00  76.00       -54
                                          44.78
57  \w  28.00  54.00  0.50  1.56  --  52.00  75.00-135.44 52
58  \w  31.00  63.00  0.50  1.56  --  56.00  76.00     - 64
                                          2.91
59  \w  34.00  59.00  0.50  1.56  --  56.00  77.00        50
                                               80.05
60  \w  41.00  67.00  0.50  1.56  --  60.00  73.00        52
                                          154.76
61  \w  100.00 125.00 0.50  1.56  --  60.00  77.00        50
                                          114.89
62  \w  35.00  61.00  0.50  1.56  --  60.00  77.00        52
                                          114.89
63  \w  35.00  61.00  0.50  1.56  --  60.00  77.00        52
                                               46.26
64  \w  95.00  122.00 0.50  1.56  --  60.00  76.00-145.82 54
```

```
65  \w  36.00  62.00  0.50  1.56  --  60.00 76.00-145.8252
66  \w  103.00 128.00 0.50  1.56  --  64.00 67.00      -50
                                          72.94
67  \w  44.00  70.00  0.50  1.56  --  64.00 65.00       52
                                                68.06
68  \w  42.00  68.00  0.50  1.56  --  64.00 77.00-118.0052
69  \w  43.00  89.00  0.50  1.56  --  64.00 67.00      -92
                                          72.94
70  \w  103.00 128.00 0.50  1.56  --  64.00 75.00      -50
                                          48.37
71  \w  75.00  111.00 0.50  1.56  --  64.00 65.00       72
                                                68.06
72  \w  41.00  67.00  0.50  1.56  --  64.00 75.00      -52
                                          48.37
73  \w  45.00  90.00  0.50  1.56  --  68.00 73.00       90
                                                10.37
74  \w  46.00  82.00  0.50  1.56  --  68.00 74.00       72
                                          179.89
75  \w  45.00  72.00  0.50  1.56  --  68.00 74.00       54
                                          126.83
76  \w  105.00 131.00 0.50  1.56  --  68.00 73.00       52
                                                10.37
77  \w  49.00  105.00 0.50  6.22  --  72.00 74.00      -112
                                          10.20
78  \w  51.00  102.00 0.50  6.22  --  72.00 66.00       102
                                                86.62
79  \w  54.00  124.00 0.50  6.22  --  76.00 71.00-108.24140
80  \w  55.00  80.00  0.50  6.22  --  76.00 67.00-157.3950
81  \w  54.00  80.00  0.50  6.22  --  76.00 69.00       52
                                          160.03
82  \w  64.00  90.00  0.50  6.22  --  80.00 59.00-133.4352
83  \w  59.00  99.00  0.50  6.22  --  80.00 71.00       80
                                          105.19
84  \w  65.00  92.00  0.50  6.22  --  84.00 68.00      -54
                                          53.36
85  \w  63.00  105.00 0.50  6.22  --  88.00 76.00       84
                                                42.71
86  \w  65.00  92.00  0.50  6.22  --  88.00 72.00      -54
                                          46.89
87  \w  105.00 151.00 0.50  6.22  --  92.00 75.00       92
                                                7.69
88  \w  68.00  97.00  0.50  6.22  --  92.00 75.00       58
                                                7.69
89  \w  70.00  124.00 0.50  6.22  --  92.00 71.00      -108
                                          43.74
90  \w  81.00  107.00 0.50  6.22  --  101.00-96.00-     52
                                          180.00
91  \w  41.00  124.00 0.50  6.22  --  101.00-145.00-    166
                                          150.00
92  \w  31.00  57.00  0.50  6.22  --  101.00-96.00-     52
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									180.00	
93	\w	85.00	136.00	0.50	6.22	--	101.00	59.00		102
									120.00	
94	\w	61.00	110.00	0.50	6.22	--	101.00	-33.00-		98
									150.00	
95	\w	81.00	107.00	0.50	6.22	--	101.00	68.00	-180.00	52
96	\w	127.00	154.00	0.50	6.22	--	101.00	59.00		54
									150.00	
97	\w	99.00	130.00	0.50	6.22	--	101.00	-145.00		62
								150.00		
98	\w	83.00	109.00	0.50	6.22	--	101.00	59.00		52
								150.00		
99	\w	40.00	66.00	0.50	6.22	--	101.00	-145.00		52
								150.00		
100	\w	132.00	157.00	0.50	6.22	--	101.00	77.00	-180.00	50
101	\w	76.00	120.00	0.50	6.22	--	101.00	77.00		88
									150.00	
102	\w	76.00	157.00	0.50	6.22	--	101.00	77.00		162
									30.00	
103	\w	79.00	105.00	0.50	6.22	--	101.00	77.00	-180.00	52
104	\w	114.00	140.00	0.50	6.22	--	101.00	63.00-		52
									151.78	
105	\w	81.00	107.00	0.50	6.22	--	101.00	63.00-		52
									151.78	
106	\w	50.00	76.00	0.50	6.22	--	101.00	-68.00-		52
									180.00	
107	\w	90.00	117.00	0.50	6.22	--	101.00	-87.00		-54
									30.00	
108	\w	76.00	153.00	0.50	6.22	--	101.00	77.00-		154
									120.00	
109	\w	127.00	156.00	0.50	6.22	--	101.00	77.00-		58
									150.00	
110	\w	38.00	104.00	0.50	6.22	--	101.00	-50.00		-132
									60.00	
111	\w	76.00	102.00	0.50	6.22	--	101.00	77.00-		52
									150.00	
112	\w	84.00	139.00	0.50	6.22	--	101.00	59.00		110
									30.00	
113	\w	34.00	110.00	0.50	6.22	--	101.00	-25.00		-152
									60.00	
114	\w	84.00	110.00	0.50	6.22	--	101.00	59.00		-52
									30.00	
115	\w	80.00	132.00	0.50	6.22	--	101.00	117.00-		104
									120.00	
116	\w	76.00	122.00	0.50	6.22	--	101.00	77.00		-92
									30.00	
117	\w	116.00	157.00	0.50	6.22	--	101.00	68.00		82
									60.00	
118	\w	37.00	95.00	0.50	6.22	--	101.00	-117.00		-116
								90.00		

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119 \w  40.00  129.00 0.50  6.22   --  101.00-145.00-    178
                                       120.00
120 \w  119.00 151.00 0.50  6.22   --  101.00 77.00 120.00 64
121 \w  76.00  102.00 0.50  6.22   --  101.00 77.00 120.00 52
122 \w  80.00  106.00 0.50  6.22   --  101.00 68.00 60.00  52
123 \w  76.00  102.00 0.50  6.22   --  101.00 77.00 60.00  52
124 \w  37.00  122.00 0.50  6.22   --  101.00-     -60.00 170
                                          68.00
125 \w  132.00 157.00 0.50  6.22   --  101.00 77.00 -90.00 50
126 \w  108.00 155.00 0.50  6.22   --  101.00 96.00 -30.00 94
127 \w  71.00  116.00 0.50  6.22   --  101.00-     -60.00 90
                                       117.00
128 \w  38.00  64.00  0.50  6.22   --  101.00-     -60.00 52
                                       117.00
129 \w  76.00  157.00 0.50  6.22   --  101.00 77.00 90.00  162
130 \w  76.00  110.00 0.50  6.22   --  101.00 77.00 -90.00 68
131 \w  82.00  154.00 0.50  6.22   --  101.00 68.00 0.00   144
132 \w  118.00 157.00 0.50  6.22   --  101.00 145.0 -30.00 78
                                          0
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Table S8 LAST.CIF of Compound 7 (adz 2)

data_2
_audit_creation_date 2017-12-20
_publ_section_references
;
1. Fixed Uiso
At 1.2 times of:
All C(H) groups, All C(H,H) groups
At 1.5 times of:
All C(H,H,H) groups
2.a Ternary CH refined with riding coordinates:
C9A(H9A), C5A(H5A), C13A(H13A), C17A(H17A), C5(H5), C9(H9), C13(H13), C17(H17)
2.b Secondary CH2 refined with riding coordinates:
C15A(H15A,H15B), C16A(H16A,H16B), C1A(H1AA,H1AB), C12A(H12A,H12B), C6A(H6AA, H6AB), C7A(H7AA,H7AB), C11A(H11A,H11B), C22A(H22A,H22B), C23A(H23A,H23B), C6(H6A,H6B), C7(H7A,H7B), C15(H15C,H15D), C11(H11C,H11D), C1(H1A,H1B), C23(H23C,H23D), C22(H22C,H22D), C16(H16C,H16D), C12(H12C,H12D)
2.c Aromatic/amide H refined with riding coordinates:
C3A'(H3A'), C2A'(H2A'), C2'(H2'), C3'(H3')
2.d Idealised Me refined as rotating group:
C26A(H26A,H26B,H26C), C19A(H19A,H19B,H19C), C25A(H25A,H25B,H25C), C18A(H18A, H18B,H18C), C27A(H27A,H27B,H27C), C21A(H21A,H21B,H21C), C26(H26D,H26E,H26F), C19(H19D,H19E,H19F), C18(H18D,H18E,H18F), C21(H21D,H21E,H21F), C27(H27D,H27E,
H27F), C25(H25D,H25E,H25F)
C14A C -0.03852(17) -0.00752(15) -0.44805(19) 0.0154(5) Uani 1 1 d . . . . .
N2A N -0.37813(16) -0.32597(14) -0.83517(17) 0.0214(4) Uani 1 1 d . . . . .
N1A N -0.49148(15) -0.18974(14) -0.96643(16) 0.0201(4) Uani 1 1 d . . . . .
O2A O 0.24305(12) -0.17073(11) -0.25049(13) 0.0186(4) Uani 1 1 d . . . . .

C9A C -0.13734(17) -0.11238(14) -0.59159(18) 0.0130(5) Uani 1 1 d . . . . .
H9A H -0.1877 -0.1185 -0.5504 0.016 Uiso 1 1 calc R . . . .
C15A C 0.02408(19) 0.07894(15) -0.4053(2) 0.0192(5) Uani 1 1 d . . . . .
H15A H -0.0276 0.1264 -0.4049 0.023 Uiso 1 1 calc R . . . .
H15B H 0.0698 0.0974 -0.4466 0.023 Uiso 1 1 calc R . . . .
C3A C -0.41494(17) -0.17145(16) -0.87450(18) 0.0157(5) Uani 1 1 d . . . . .
C16A C 0.09685(19) 0.05520(16) -0.2937(2) 0.0214(5) Uani 1 1 d . . . . .
H16A H 0.0604 0.0728 -0.2441 0.026 Uiso 1 1 calc R . . . .
H16B H 0.1683 0.0850 -0.2761 0.026 Uiso 1 1 calc R . . . .
C5A C -0.30170(18) -0.05977(15) -0.73985(18) 0.0148(5) Uani 1 1 d . . . . .
H5A H -0.3424 -0.0631 -0.6897 0.018 Uiso 1 1 calc R . . . .
C1A C -0.27465(19) -0.22048(15) -0.7050(2) 0.0178(5) Uani 1 1 d . . . . .
H1AA H -0.2219 -0.2692 -0.6858 0.021 Uiso 1 1 calc R . . . .
H1AB H -0.3117 -0.2164 -0.6529 0.021 Uiso 1 1 calc R . . . .
C13A C 0.05550(18) -0.07669(15) -0.40606(18) 0.0151(5) Uani 1 1 d . . . . .
H13A H 0.1093 -0.0669 -0.4429 0.018 Uiso 1 1 calc R . . . .
C8A C -0.09008(17) -0.01552(15) -0.56902(19) 0.0148(5) Uani 1 1 d . . . . .
C17A C 0.11237(18) -0.04836(15) -0.29255(19) 0.0164(5) Uani 1 1 d . . . . .
H17A H 0.0704 -0.0742 -0.2504 0.020 Uiso 1 1 calc R . . . .
C10A C -0.21109(17) -0.13318(15) -0.70541(18) 0.0137(5) Uani 1 1 d . . . . .
C4A C -0.39174(18) -0.07303(16) -0.84809(19) 0.0172(5) Uani 1 1 d . . . . .
C2A C -0.35915(18) -0.24010(16) -0.80818(19) 0.0163(5) Uani 1 1 d . . . . .
C20A C 0.23455(18) -0.07309(15) -0.24234(19) 0.0173(5) Uani 1 1 d . . . . .
C12A C 0.01323(19) -0.17176(16) -0.42925(19) 0.0208(5) Uani 1 1 d . . . . .
H12A H -0.0379 -0.1853 -0.3916 0.025 Uiso 1 1 calc R . . . .
H12B H 0.0752 -0.2130 -0.4068 0.025 Uiso 1 1 calc R . . . .
C6A C -0.2514(2) 0.03391(16) -0.7267(2) 0.0230(5) Uani 1 1 d . . . . .
H6AA H -0.2025 0.0397 -0.7684 0.028 Uiso 1 1 calc R . . . .
H6AB H -0.3103 0.0776 -0.7509 0.028 Uiso 1 1 calc R . . . .
C3A' C -0.51095(18) -0.27560(17) -0.9917(2) 0.0223(5) Uani 1 1 d . . . . .
H3A' H -0.5639 -0.2905 -1.0548 0.027 Uiso 1 1 calc R . . . .
C26A C -0.3595(2) -0.03046(17) -0.9377(2) 0.0233(5) Uani 1 1 d . . . . .
H26A H -0.2911 -0.0560 -0.9400 0.035 Uiso 1 1 calc GR . . . .
H26B H -0.3501 0.0325 -0.9263 0.035 Uiso 1 1 calc GR . . . .
H26C H -0.4173 -0.0413 -1.0023 0.035 Uiso 1 1 calc GR . . . .
O1A O 0.36871(15) -0.26949(13) -0.26337(19) 0.0387(5) Uani 1 1 d . . . . .
C19A C -0.14557(18) -0.14621(18) -0.78154(19) 0.0223(5) Uani 1 1 d . . . . .
H19A H -0.1204 -0.0895 -0.7977 0.034 Uiso 1 1 calc GR . . . .
H19B H -0.1927 -0.1734 -0.8442 0.034 Uiso 1 1 calc GR . . . .
H19C H -0.0826 -0.1839 -0.7504 0.034 Uiso 1 1 calc GR . . . .
C7A C -0.1861(2) 0.05136(15) -0.6133(2) 0.0216(5) Uani 1 1 d . . . . .
H7AA H -0.2363 0.0481 -0.5726 0.026 Uiso 1 1 calc R . . . .
H7AB H -0.1558 0.1111 -0.6065 0.026 Uiso 1 1 calc R . . . .
C25A C -0.50039(19) -0.02929(17) -0.8449(2) 0.0239(5) Uani 1 1 d . . . . .
H25A H -0.5565 -0.0350 -0.9116 0.036 Uiso 1 1 calc GR . . . .
H25B H -0.4873 0.0326 -0.8278 0.036 Uiso 1 1 calc GR . . . .
H25C H -0.5250 -0.0582 -0.7932 0.036 Uiso 1 1 calc GR . . . .
C11A C -0.04608(19) -0.18211(16) -0.5463(2) 0.0210(5) Uani 1 1 d . . . . .
H11A H -0.0791 -0.2409 -0.5595 0.025 Uiso 1 1 calc R . . . .
H11B H 0.0086 -0.1778 -0.5821 0.025 Uiso 1 1 calc R . . . .

C18A C -0.00190(19) 0.00529(18) -0.6209(2) 0.0241(6) Uani 1 1 d . . . . .
H18A H 0.0294 0.0630 -0.5992 0.036 Uiso 1 1 calc GR . . . .
H18B H -0.0358 0.0046 -0.6951 0.036 Uiso 1 1 calc GR . . . .
H18C H 0.0559 -0.0387 -0.6009 0.036 Uiso 1 1 calc GR . . . .
C24A C 0.34025(19) -0.19337(17) -0.2640(2) 0.0244(6) Uani 1 1 d . . . . .
C2A' C -0.45454(19) -0.34256(17) -0.9267(2) 0.0232(6) Uani 1 1 d . . . . .
H2A' H -0.4704 -0.4013 -0.9475 0.028 Uiso 1 1 calc R . . . .
C27A C -0.12670(18) -0.01898(17) -0.39368(19) 0.0200(5) Uani 1 1 d . . . . .
H27A H -0.0931 -0.0092 -0.3204 0.030 Uiso 1 1 calc GR . . . .
H27B H -0.1565 -0.0782 -0.4054 0.030 Uiso 1 1 calc GR . . . .
H27C H -0.1855 0.0233 -0.4213 0.030 Uiso 1 1 calc GR . . . .
C21A C 0.2738(2) -0.05133(18) -0.1268(2) 0.0240(6) Uani 1 1 d . . . . .
H21A H 0.2277 -0.0817 -0.0938 0.036 Uiso 1 1 calc GR . . . .
H21B H 0.2690 0.0117 -0.1176 0.036 Uiso 1 1 calc GR . . . .
H21C H 0.3496 -0.0702 -0.0961 0.036 Uiso 1 1 calc GR . . . .
C22A C 0.31520(18) -0.03693(16) -0.2963(2) 0.0197(5) Uani 1 1 d . . . . .
H22A H 0.2777 -0.0276 -0.3700 0.024 Uiso 1 1 calc R . . . .
H22B H 0.3490 0.0185 -0.2651 0.024 Uiso 1 1 calc R . . . .
C23A C 0.4014(2) -0.11106(17) -0.2777(2) 0.0273(6) Uani 1 1 d . . . . .
H23A H 0.4281 -0.1172 -0.3366 0.033 Uiso 1 1 calc R . . . .
H23B H 0.4642 -0.0993 -0.2159 0.033 Uiso 1 1 calc R . . . .
O2 O -0.73435(12) -0.16950(11) -0.72259(13) 0.0190(4) Uani 1 1 d . . . . .
C8 C -1.04192(18) -0.34050(15) -1.05989(18) 0.0147(5) Uani 1 1 d . . . . .
N2 N -1.35423(15) -0.04370(13) -1.33182(16) 0.0192(4) Uani 1 1 d . . . . .
C5 C -1.21779(18) -0.30041(16) -1.26303(19) 0.0160(5) Uani 1 1 d . . . . .
H5 H -1.1573 -0.2817 -1.2884 0.019 Uiso 1 1 calc R . . . .
O1 O -0.75408(15) -0.09031(13) -0.59045(16) 0.0318(5) Uani 1 1 d . . . . .
N1 N -1.44018(16) -0.18133(14) -1.47185(17) 0.0238(5) Uani 1 1 d . . . . .
C6 C -1.18874(19) -0.39658(16) -1.2259(2) 0.0185(5) Uani 1 1 d . . . . .
H6A H -1.2380 -0.4166 -1.1888 0.022 Uiso 1 1 calc R . . . .
H6B H -1.1991 -0.4352 -1.2855 0.022 Uiso 1 1 calc R . . . .
C14 C -0.91265(18) -0.33181(16) -1.00706(19) 0.0162(5) Uani 1 1 d . . . . .
C3 C -1.36164(18) -0.19742(17) -1.38022(19) 0.0180(5) Uani 1 1 d . . . . .
C9 C -1.08599(17) -0.24456(15) -1.09507(18) 0.0140(5) Uani 1 1 d . . . . .
H9 H -1.0409 -0.2243 -1.1372 0.017 Uiso 1 1 calc R . . . .
C13 C -0.88589(18) -0.26903(15) -0.91212(18) 0.0156(5) Uani 1 1 d . . . . .
H13 H -0.9236 -0.2929 -0.8653 0.019 Uiso 1 1 calc R . . . .
C17 C -0.76017(18) -0.28179(16) -0.85846(19) 0.0171(5) Uani 1 1 d . . . . .
H17 H -0.7214 -0.2440 -0.8945 0.021 Uiso 1 1 calc R . . . .
C10 C -1.20888(18) -0.23769(15) -1.17011(18) 0.0152(5) Uani 1 1 d . . . . .
C20 C -0.71018(18) -0.26333(16) -0.74271(19) 0.0169(5) Uani 1 1 d . . . . .
C7 C -1.06834(19) -0.40197(16) -1.1548(2) 0.0188(5) Uani 1 1 d . . . . .
H7A H -1.0197 -0.3869 -1.1946 0.023 Uiso 1 1 calc R . . . .
H7B H -1.0522 -0.4628 -1.1310 0.023 Uiso 1 1 calc R . . . .
C15 C -0.85043(18) -0.41618(16) -0.9558(2) 0.0196(5) Uani 1 1 d . . . . .
H15C H -0.8915 -0.4475 -0.9175 0.024 Uiso 1 1 calc R . . . .
H15D H -0.8386 -0.4559 -1.0075 0.024 Uiso 1 1 calc R . . . .
C11 C -1.05650(18) -0.17979(16) -1.00279(19) 0.0184(5) Uani 1 1 d . . . . .
H11C H -1.0955 -0.1978 -0.9553 0.022 Uiso 1 1 calc R . . . .
H11D H -1.0825 -0.1208 -1.0282 0.022 Uiso 1 1 calc R . . . .

C4 C -1.32401(18) -0.29415(16) -1.35923(19) 0.0177(5) Uani 1 1 d . . . . .
C1 C -1.22491(18) -0.14122(15) -1.21101(19) 0.0173(5) Uani 1 1 d . . . . .
H1A H -1.2382 -0.1035 -1.1583 0.021 Uiso 1 1 calc R . . . .
H1B H -1.1563 -0.1215 -1.2209 0.021 Uiso 1 1 calc R . . . .
C26 C -1.4226(2) -0.34991(17) -1.3499(2) 0.0233(6) Uani 1 1 d . . . . .
H26D H -1.4020 -0.4116 -1.3421 0.035 Uiso 1 1 calc GR . . . .
H26E H -1.4857 -0.3422 -1.4114 0.035 Uiso 1 1 calc GR . . . .
H26F H -1.4414 -0.3306 -1.2903 0.035 Uiso 1 1 calc GR . . . .
C19 C -1.29854(18) -0.25428(17) -1.11812(19) 0.0196(5) Uani 1 1 d . . . . .
H19D H -1.3685 -0.2308 -1.1614 0.029 Uiso 1 1 calc GR . . . .
H19E H -1.2773 -0.2253 -1.0517 0.029 Uiso 1 1 calc GR . . . .
H19F H -1.3057 -0.3170 -1.1089 0.029 Uiso 1 1 calc GR . . . .
C2 C -1.31807(17) -0.12822(16) -1.31075(19) 0.0163(5) Uani 1 1 d . . . . .
C18 C -1.09690(19) -0.38153(17) -0.9839(2) 0.0201(5) Uani 1 1 d . . . . .
H18D H -1.0596 -0.4359 -0.9558 0.030 Uiso 1 1 calc GR . . . .
H18E H -1.1739 -0.3937 -1.0204 0.030 Uiso 1 1 calc GR . . . .
H18F H -1.0913 -0.3405 -0.9284 0.030 Uiso 1 1 calc GR . . . .
C23 C -0.74384(19) -0.25282(17) -0.5799(2) 0.0225(5) Uani 1 1 d . . . . .
H23C H -0.8043 -0.2593 -0.5514 0.027 Uiso 1 1 calc R . . . .
H23D H -0.6738 -0.2633 -0.5252 0.027 Uiso 1 1 calc R . . . .
C2' C -1.43176(18) -0.02947(17) -1.4237(2) 0.0220(5) Uani 1 1 d . . . . .
H2' H -1.4585 0.0279 -1.4411 0.026 Uiso 1 1 calc R . . . .
C22 C -0.75790(19) -0.31597(16) -0.67027(19) 0.0201(5) Uani 1 1 d . . . . .
H22C H -0.8357 -0.3302 -0.7043 0.024 Uiso 1 1 calc R . . . .
H22D H -0.7167 -0.3706 -0.6474 0.024 Uiso 1 1 calc R . . . .
C21 C -0.58397(18) -0.27126(18) -0.7096(2) 0.0227(5) Uani 1 1 d . . . . .
H21D H -0.5556 -0.2300 -0.7488 0.034 Uiso 1 1 calc GR . . . .
H21E H -0.5640 -0.3307 -0.7223 0.034 Uiso 1 1 calc GR . . . .
H21F H -0.5528 -0.2580 -0.6369 0.034 Uiso 1 1 calc GR . . . .
C27 C -0.85434(18) -0.29920(17) -1.08468(19) 0.0200(5) Uani 1 1 d . . . . .
H27D H -0.8608 -0.3439 -1.1367 0.030 Uiso 1 1 calc GR . . . .
H27E H -0.7771 -0.2882 -1.0480 0.030 Uiso 1 1 calc GR . . . .
H27F H -0.8890 -0.2453 -1.1173 0.030 Uiso 1 1 calc GR . . . .
C16 C -0.73930(19) -0.38110(17) -0.8823(2) 0.0205(5) Uani 1 1 d . . . . .
H16C H -0.6820 -0.3847 -0.9152 0.025 Uiso 1 1 calc R . . . .
H16D H -0.7158 -0.4157 -0.8187 0.025 Uiso 1 1 calc R . . . .
C12 C -0.93122(18) -0.17534(16) -0.94301(19) 0.0189(5) Uani 1 1 d . . . . .
H12C H -0.8926 -0.1481 -0.9863 0.023 Uiso 1 1 calc R . . . .
H12D H -0.9185 -0.1391 -0.8812 0.023 Uiso 1 1 calc R . . . .
C3' C -1.47314(19) -0.09701(17) -1.4935(2) 0.0243(6) Uani 1 1 d . . . . .
H3' H -1.5255 -0.0838 -1.5574 0.029 Uiso 1 1 calc R . . . .
C25 C -1.2955(2) -0.32914(18) -1.4544(2) 0.0237(5) Uani 1 1 d . . . . .
H25D H -1.2356 -0.2948 -1.4634 0.036 Uiso 1 1 calc GR . . . .
H25E H -1.3597 -0.3240 -1.5154 0.036 Uiso 1 1 calc GR . . . .
H25F H -1.2736 -0.3904 -1.4435 0.036 Uiso 1 1 calc GR . . . .
C24 C -0.74559(17) -0.16199(18) -0.6276(2) 0.0217(5) Uani 1 1 d . . . . .
C14A 0.0165(10) 0.0124(11) 0.0174(12) -0.0025(10) 0.0057(9) -0.0015(9)
N2A 0.0207(9) 0.0172(10) 0.0224(11) -0.0019(10) 0.0013(9) -0.0006(8)
N1A 0.0172(9) 0.0233(11) 0.0180(11) 0.0012(9) 0.0029(8) 0.0007(8)
O2A 0.0187(7) 0.0149(8) 0.0210(9) 0.0007(8) 0.0048(7) -0.0027(7)

C9A 0.0148(10) 0.0102(10) 0.0134(12) -0.0002(10) 0.0039(9) 0.0011(8)
C15A 0.0228(11) 0.0132(11) 0.0208(13) -0.0004(11) 0.0060(10) 0.0005(9)
C3A 0.0144(9) 0.0175(11) 0.0158(12) 0.0000(11) 0.0056(9) 0.0002(9)
C16A 0.0235(11) 0.0168(12) 0.0229(14) -0.0060(11) 0.0059(11) -0.0025(10)
C5A 0.0166(10) 0.0133(11) 0.0141(12) 0.0011(10) 0.0043(9) 0.0013(9)
C1A 0.0205(11) 0.0121(12) 0.0175(13) 0.0009(10) 0.0016(10) 0.0007(9)
C13A 0.0158(10) 0.0139(11) 0.0143(12) -0.0012(10) 0.0032(9) -0.0005(9)
C8A 0.0163(10) 0.0117(11) 0.0160(12) -0.0005(10) 0.0047(9) -0.0014(9)
C17A 0.0192(10) 0.0149(11) 0.0155(12) -0.0012(10) 0.0059(10) -0.0029(9)
C10A 0.0147(10) 0.0132(11) 0.0126(12) -0.0006(10) 0.0035(9) 0.0019(9)
C4A 0.0179(10) 0.0149(11) 0.0177(13) 0.0019(10) 0.0041(10) 0.0022(9)
C2A 0.0161(10) 0.0163(11) 0.0165(12) 0.0007(10) 0.0055(9) 0.0006(9)
C20A 0.0209(11) 0.0133(11) 0.0166(13) -0.0011(10) 0.0045(10) -0.0029(9)
C12A 0.0225(11) 0.0126(11) 0.0207(13) 0.0001(11) -0.0023(10) 0.0030(10)
C6A 0.0257(12) 0.0151(12) 0.0224(14) 0.0041(11) -0.0002(11) 0.0008(10)
C3A' 0.0154(10) 0.0263(14) 0.0214(13) -0.0035(12) 0.0006(10) -0.0032(10)
C26A 0.0270(12) 0.0205(13) 0.0178(13) 0.0053(11) 0.0009(10) -0.0034(10)
O1A 0.0339(10) 0.0209(10) 0.0637(15) -0.0008(11) 0.0189(10) 0.0031(8)
C19A 0.0185(11) 0.0328(15) 0.0163(13) -0.0051(11) 0.0063(10) -0.0006(10)
C7A 0.0262(12) 0.0089(11) 0.0242(14) 0.0001(11) 0.0008(11) -0.0010(9)
C25A 0.0207(11) 0.0229(13) 0.0224(14) 0.0004(12) -0.0008(10) 0.0079(10)
C11A 0.0221(11) 0.0127(11) 0.0219(13) -0.0040(11) -0.0014(10) 0.0045(9)
C18A 0.0229(11) 0.0317(15) 0.0164(13) 0.0008(12) 0.0046(10) -0.0093(11)
C24A 0.0213(11) 0.0240(14) 0.0268(15) -0.0009(12) 0.0063(11) -0.0014(10)
C2A' 0.0206(11) 0.0186(13) 0.0258(14) -0.0065(12) 0.0010(11) -0.0018(10)
C27A 0.0192(10) 0.0232(13) 0.0185(13) -0.0043(11) 0.0072(10) -0.0009(10)
C21A 0.0235(11) 0.0273(14) 0.0186(13) -0.0034(12) 0.0031(10) -0.0040(10)
C22A 0.0188(10) 0.0199(12) 0.0192(13) 0.0015(11) 0.0044(10) -0.0047(10)
C23A 0.0220(11) 0.0251(14) 0.0362(16) -0.0016(13) 0.0113(12) -0.0032(11)
O2 0.0223(8) 0.0158(8) 0.0184(9) -0.0002(8) 0.0058(7) 0.0000(7)
C8 0.0176(10) 0.0141(11) 0.0123(12) 0.0007(10) 0.0046(9) 0.0006(9)
N2 0.0158(9) 0.0182(10) 0.0221(11) 0.0047(9) 0.0041(8) -0.0007(8)
C5 0.0173(10) 0.0173(12) 0.0128(12) 0.0001(10) 0.0042(9) -0.0008(9)
O1 0.0325(10) 0.0274(10) 0.0341(11) -0.0097(9) 0.0087(9) 0.0064(8)
N1 0.0245(10) 0.0232(11) 0.0189(11) 0.0012(10) 0.0001(9) -0.0007(9)
C6 0.0226(11) 0.0154(12) 0.0148(13) -0.0025(10) 0.0023(10) -0.0003(9)
C14 0.0181(10) 0.0140(11) 0.0168(12) -0.0018(11) 0.0062(10) 0.0001(9)
C3 0.0172(10) 0.0206(12) 0.0156(12) 0.0020(11) 0.0045(10) -0.0024(9)
C9 0.0168(10) 0.0131(11) 0.0125(12) -0.0022(10) 0.0053(9) 0.0005(9)
C13 0.0184(10) 0.0145(11) 0.0131(12) -0.0009(10) 0.0043(9) 0.0005(9)
C17 0.0180(10) 0.0158(12) 0.0176(12) 0.0006(10) 0.0060(10) 0.0003(9)
C10 0.0168(10) 0.0154(11) 0.0127(12) -0.0009(10) 0.0038(9) -0.0009(9)
C20 0.0167(10) 0.0146(11) 0.0189(13) 0.0009(10) 0.0050(9) 0.0019(9)
C7 0.0229(11) 0.0134(11) 0.0193(13) -0.0005(11) 0.0056(10) 0.0027(9)
C15 0.0213(11) 0.0153(11) 0.0217(14) -0.0016(11) 0.0062(10) 0.0031(9)
C11 0.0205(10) 0.0169(12) 0.0155(12) -0.0018(11) 0.0028(10) 0.0056(9)
C4 0.0189(11) 0.0166(11) 0.0152(12) -0.0016(10) 0.0022(10) -0.0007(9)
C1 0.0183(10) 0.0144(12) 0.0165(13) -0.0011(10) 0.0017(10) -0.0001(9)
C26 0.0231(12) 0.0220(13) 0.0220(14) -0.0006(11) 0.0033(11) -0.0037(10)
C19 0.0185(11) 0.0234(13) 0.0174(13) 0.0014(11) 0.0065(10) 0.0019(10)

C2 0.0160(10) 0.0172(11) 0.0160(13) 0.0018(10) 0.0055(9) -0.0010(9)
C18 0.0205(11) 0.0205(12) 0.0187(13) 0.0043(11) 0.0055(10) -0.0024(10)
C23 0.0177(11) 0.0307(15) 0.0176(13) 0.0032(12) 0.0035(10) 0.0006(10)
C2' 0.0179(11) 0.0212(13) 0.0246(14) 0.0084(12) 0.0036(10) 0.0003(10)
C22 0.0194(11) 0.0199(13) 0.0195(13) 0.0035(11) 0.0041(10) -0.0010(9)
C21 0.0170(10) 0.0296(14) 0.0204(14) -0.0030(12) 0.0047(10) -0.0009(10)
C27 0.0191(11) 0.0246(13) 0.0165(13) -0.0013(11) 0.0059(10) 0.0004(10)
C16 0.0198(11) 0.0210(12) 0.0197(13) 0.0005(11) 0.0049(10) 0.0050(10)
C12 0.0203(10) 0.0144(11) 0.0184(13) -0.0026(11) 0.0011(10) 0.0013(9)
C3' 0.0215(12) 0.0254(14) 0.0207(14) 0.0079(12) -0.0008(11) -0.0012(10)
C25 0.0271(12) 0.0255(13) 0.0155(13) -0.0038(12) 0.0026(10) 0.0003(11)
C24 0.0130(10) 0.0278(14) 0.0225(14) -0.0025(12) 0.0032(10) 0.0021(10)

REM Highest difference peak 0.220, deepest hole -0.190, 1-sigma level
0.041
Q1 1 -0.2533 -0.0950 -0.7215 11.00000 0.05 0.22
Q2 1 -0.1170 -0.0642 -0.5833 11.00000 0.05 0.21
Q3 1 -1.1471 -0.2414 -1.1279 11.00000 0.05 0.20
Q4 1 -1.0664 -0.2899 -1.0799 11.00000 0.05 0.20
Q5 1 -1.2804 -0.2997 -1.2981 11.00000 0.05 0.20
Q6 1 -0.2428 -0.1778 -0.7025 11.00000 0.05 0.20
Q7 1 -0.3982 -0.1216 -0.8577 11.00000 0.05 0.19
Q8 1 -0.9827 -0.3381 -1.0361 11.00000 0.05 0.18
Q9 1 -1.2202 -0.1897 -1.1946 11.00000 0.05 0.18
Q10 1 -0.7535 -0.2789 -0.7996 11.00000 0.05 0.18
Q11 1 -0.0587 -0.0156 -0.5099 11.00000 0.05 0.18
Q12 1 -1.3389 -0.2473 -1.3613 11.00000 0.05 0.18
Q13 1 -0.1365 0.0166 -0.5869 11.00000 0.05 0.18
Q14 1 -1.0654 -0.3754 -1.0987 11.00000 0.05 0.18
Q15 1 -0.3467 -0.0677 -0.7968 11.00000 0.05 0.17
Q16 1 -1.2149 -0.2676 -1.2190 11.00000 0.05 0.17
Q17 1 0.0072 -0.0408 -0.4273 11.00000 0.05 0.17
Q18 1 0.0824 -0.0711 -0.3463 11.00000 0.05 0.17
Q19 1 0.1773 -0.0617 -0.2685 11.00000 0.05 0.17
Q20 1 -0.3891 -0.2026 -0.8384 11.00000 0.05 0.17
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Biology

Investigation of cytotoxicity *in vitro* on the MDCK cells. Cytotoxicity of compounds was studied in experiments on the MDCK cells that were incubated for 48 h at 36°C at 5% CO_2). A series of three-fold dilution in concentrations from 300 to 3 μg ml^{-1} on the Eagle's essential medium (MEM) was prepared from the compounds under study and the microtetrazolium test was performed in 96-well plates. The cell monolayer was washed twice with saline (0.9% NaCl) and 100 μl of MTT solution [3-(4,5-dimethylthiazole-2)-2,5-diphenyltetrazolium bromide] were added in each well at a concentration 0.5 μg ml^{-1} in a phosphate–buffered saline. The plates were incubated for 1 h at 36°C, then the liquid was removed and formazam was dissolved in dimethyl sulfoxide (0.1 ml per well). The optical density in the wells was measured on a spectrophotometer Victor 2 1440 at the wavelength 535 nm. The results obtained were used for calculating the concentration of the compound resulting in death of 50% cells in the culture (*CC*50).

Estimation of antiviral activity *in vitro*. Monolayer MDCK was infected along the following protocol: in each well of plates was added 100 μl of the compound dissolved in MEM and the plates were incubated for 1 h at 36°C at 5% CO2. Cells were infected with 100 μl of influenza virus A/Puerto Rico/8/34 (H1N1) (m.o.i. 0.01), and the plates were kept for 24 h at 36°C at 5% CO2. The virus titer was determined after 24 h on the MDCK cells. The culture liquid was used for the preparation of the series of 10-fold dilutions, cells were infected with the dilutions, and the plates were incubated for 48 h at 36°C at 5% CO2. After 48 h from each well 100 μl of culture fluid was sampled and placed in the round-bottom plate where the hemagglutination reaction was performed. To this end the same amount of 1% suspension of chicken erythrocytes in saline was added into the wells with the samples of culture fluid . The results were checked after 40 min incubation at room temperature. The infectious titer of the virus was considered as a reciprocal to the maximum virus dilution that caused a complete erythrocytes agglutination. The decrease in the infectious titer of the virus indicated the antiviral activity of compounds. The data obtained were used for the calculation of the 50% effective concentration of the compound, or the substance concentration that caused the two-fold decrease in the virus titer (*IC*50), and then the selectivity index was calculated, *SI*=*CC*50/*IC*50.

Investigation of cytotoxicity *in vitro* on cell lines. Human cervical cancer cells HeLa, liver cancer cell line Hep G2 and normal lung fibroblasts WI-38 were obtained from ATCC collection and then were stored in the cryobank until present experiments. The cells were cultivated in DMEM medium. The medium was supplemented with 10% FBS, L-glutamine (250

mg dm^{-3}), penicillin (100 U ml^{-1}), streptomycin (100 mg dm^{-3}). Cells were kept under standard cell culture conditions at 37 ◦C and 5% CO_2 in a humid environment and subcultured twice per week following standard trypsinization protocols. MTT cell viability assay: Cell viability was assessed by 3-(4,5-dimethylthiozol-2-yl)-2,5- diphenyltetrazolium bromide (MTT) assays to determine cytotoxicity concentrations of the studied agents. In these assays 5.0 10^3 MCF-7 cells in medium were added per well to 96-well plates, and grown for 24 h. The cells (70–80% confluent) were treated with compounds in concentrations of 1–60 μM for 48 h in cell culture medium. Cells used as control were incubated solely with the maximum used amount of the diluent DMFA (0,1%). After incubation for 48 h, MTT solution (5 mg ml^{-1}) was added and the cells were incubated for 4 h. The concentration leading to inhibition of viability was determined by measuring absorbance at 570 nm, using a microplate reader, as an indicator used to measure of MTT reductase activity. The viability of treated cells was expressed as a percentage relative to the viability of control vehicle-treated cells. Each experiment was performed in independently repeated at least three times.

Analysis of the cell cycle of HepG2 cells incubated with compounds 2,6-8. HepG2 cells were incubated in 6 well plates for 2 days in a medium with the addition of 10% FBS and the tested compounds at a concentration of IC50, then treated successively with Versen solution (2 ml) and 0.25% trypsin solution, after exposure at 37°C for 1 min they were suspended in 2 ml of a medium. The cells were centrifuged at 1500 rpm for 3 min, washed with PBS (2 × 3 ml), treated with 70% EtOH (0.5 ml) and stored at –20°C. Before an experiment the cells were washed with PBS (2×3 ml) and suspended in 1 ml of PBS, then 200 μL of RNase A (200 μg ml^{-1}), and after incubation at 37°C for 30 min 100 μl of propidium iodide (1 mg ml^{-1}) were added, after which the cells were kept at 20°C for 45 min. Analysis was performed on a BD FACSAria flow cytofluorometer in FL1 mode.

Figure S34. Antiproliferative activity of compounds 2,6,7,8 on human cervical cancer cells HeLa (a), liver cancer cells Hep G2 (b) and normal lung fibroblasts cells WI-38(c).