Supporting Information

Sesquiterpenoids and hexanorcucurbitacin from *Aquilaria malaccensis* agarwood with anti-inflammatory effects by inhibiting STAT1/AKT/MAPK/NLRP3 pathway

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1. Plant material

The agarwood chips of *A. malaccensis* was purchased from Industrial Plantation Co. (Vientiane, Laos) in January 2010. A voucher specimen (AM-2010-01) was authenticated by Professor Jeong Hill Park (Natural Products Research Institute, Seoul National University) and deposited at the Herbarium of the Natural Product Research Institute, Seoul National University, Korea.

2. Extraction and isolation

The agarwood chips of *A. malaccencis* (9.0 kg) was ground and extracted with 70% MeOH under reflux (20 L X 3h, 3 times). The solvent was evaporated under reduced pressure to obtain a crude extract (864 g), which was suspended in water and successively partitioned with diethyl ether, EtOAc, *n*-BuOH, achieving 225, 155, and 289 g of residue, respectively.

The diethyl ether fraction (30 g) was applied on a silica gel column (230-400 mesh, 300 g), eluted with *n*-hexane/EtOAc (gradient 40:1 → 1:1, v/v) to obtain 7 fractions (DE1-DE7). Fraction DE2 was separated by a silica gel column chromatography (CC) (*n*-hexane/EtOAc, gradient 20:1 to 8:2, v/v) to afford 4 fractions (DE2.1-DE2.4). Fraction DE2.3 was applied to a silica gel CC, eluted with *n*-hexane/EtOAc (95:5 to 7:3, v/v) to obtain 3 fractions (DE2.3.1-DE2.3.3). Fraction DE2.3.2 was separated by semi-preparative RP-HPLC (MeOH/H_2O, 65:35, v/v) to give **10** (4.29 mg) and **12** (30.4). Fraction DE3 (3.36 g) was further subjected to a silica gel CC (*n*-hexane/EtOAc, gradient 95:5 to 7:3, v/v) to achieve 9 sub-fractions (DE3.1-DE3.9). Fraction DE3.3 (450 mg) was subjected to semi-preparative RP-HPLC (MeOH/H_2O, 65:35, v/v) and then purified by Sephadex LH-20 CC (MeOH) to yield **14** (72.9 mg). Fraction DE3.4 (237 mg) was applied to a Sephadex LH-20 CC (MeOH) to furnish 5 sub-fractions (DE3.4.1-DE3.4.5). Fraction 3.4.3 (81.7 mg) was further isolated by using semi-preparative RP-HPLC (CH_3CN/H_2O, 45:55, v/v) to obtain **2** (3.5 mg), and **8** (23.5 mg), respectively. Compounds **9** (4.5 mg) and **15** (4.8 mg) were obtained from fraction DE3.4.5

(71.5 mg) by semi-preparative RP-HPLC (MeOH/H_2O, 65:35, v/v). Fraction DE3.5 was loaded on a Sephadex LH-20 CC (MeOH) to give 5 sub-fractions (DE3.5.1-DE3.5.5). By using semi-preparative RP-HPLC (MeOH/H_2O, 65:35, v/v), compounds **4** (6.7 mg) and **13** (15.8 mg) were obtained from fraction DE3.5.3 (118.2 mg) and DE3.5.4 (87.2 mg), respectively. Fraction DE4 (7.6 g) was applied to a silica gel CC (*n*-hexane/EtOAc, gradient 95:5 to 1:1, v/v) to obtain 10 sub-fractions (DE4.1 – DE4.10). Compounds **1** (1.0 mg) and **3** (3.3 mg) were obtained from fraction DE4.5 (96.8 mg) by semi-preparative RP-HPLC (CH_3CN/H_2O, 35:65, v/v). Fraction DE4.6 (781 mg) was isolated and purified by semi-preparative RP-HPLC (MeOH/H_2O, 65:35, v/v) to obtain **5** (2.08 mg), and **11** (10.3 mg). .

The EtOAC fraction (51.5 g) was separated by a silica gel CC (*n*-hexane/EtOAc, gradient 200:1 to 1:1, v/v) to afford 5 fractions (EA1-EA5). Fraction EA2 (20 g) was continuously fractionated by a silica gel CC (*n*-hexane/EtOAc, gradient 95:5 to 1:1, v/v) to achieve 17 fractions (EA2.1-EA2.17). Fraction EA2.10 was separated to a Sephadex LH-20 (MeOH) column to yield 3 fractions (EA2.10.1-EA2.10.3). Compounds **6** (5.19 mg) and **7** (2.6 mg) were achieved from fractions EA2.10.1 by semi-preparative RP-HPLC (MeOH/H_2O, 65:35, v/v). By crystallization method in MeOH, compound **16** (125.8 mg) was obtained from fraction EA2.14.

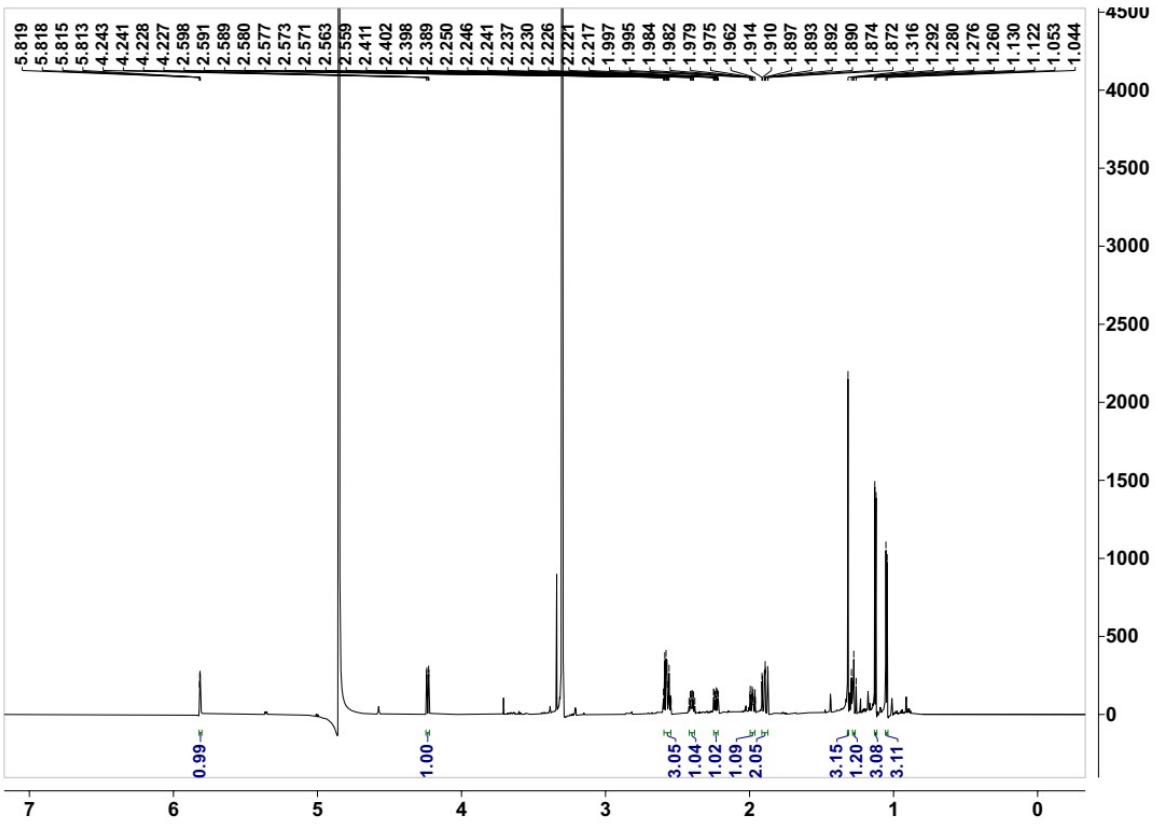


Figure S1. ^{1}H NMR spectrum of compound **1** in CD_3OD (800 MHz)

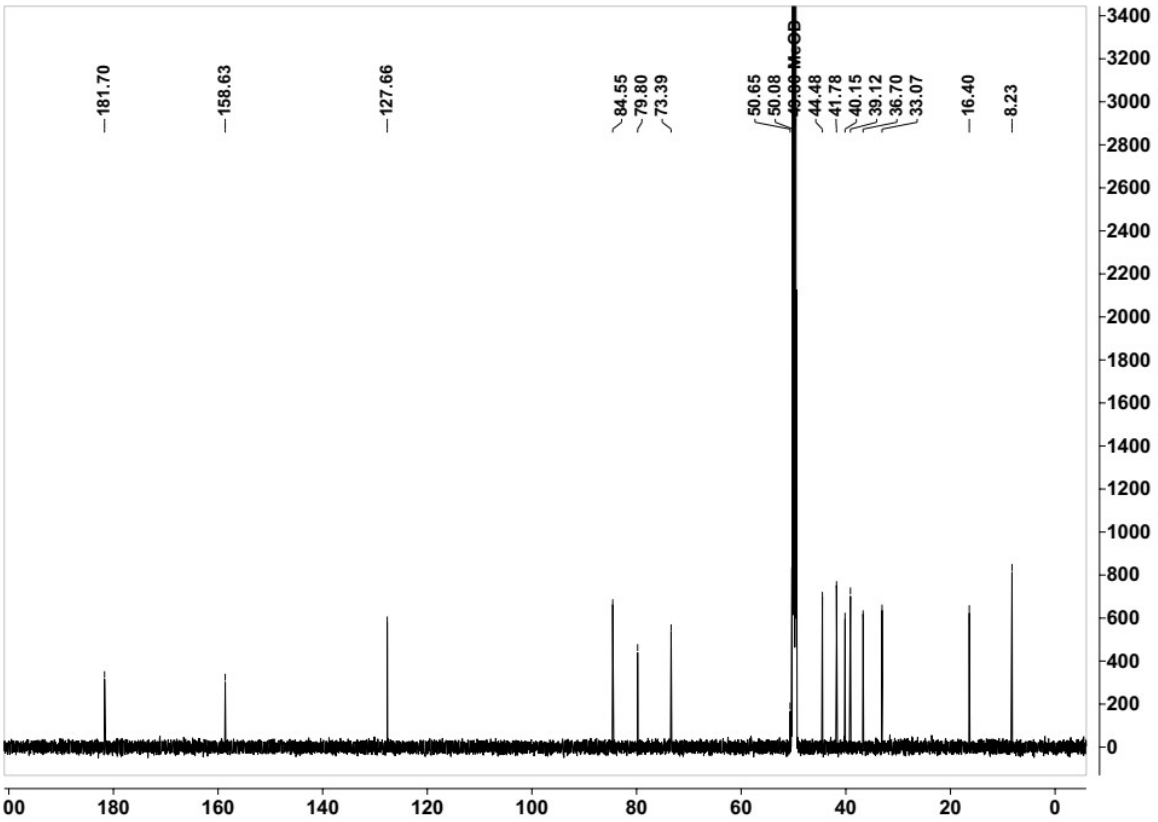


Figure S2. ^{13}C NMR spectrum of compound 1 in CD_3OD (800 MHz)

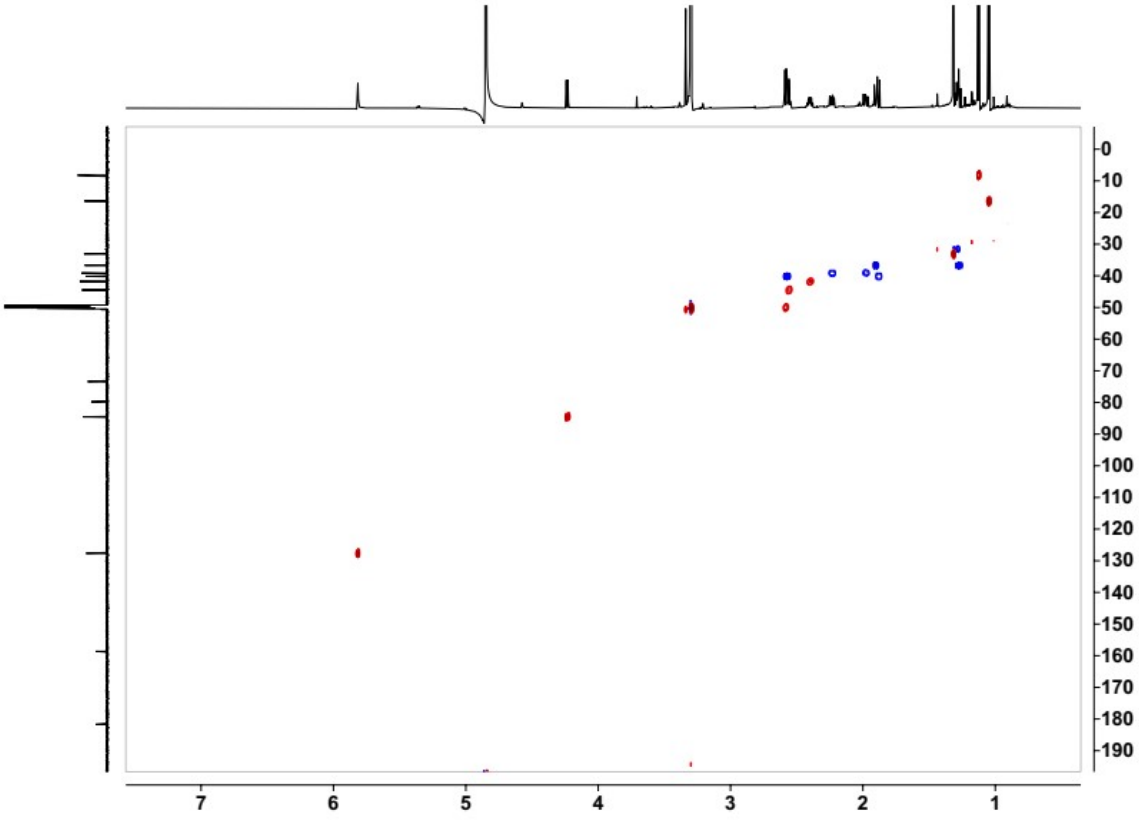


Figure S3: HSQC spectrum of compound **1** in CD_3OD (800 MHz)

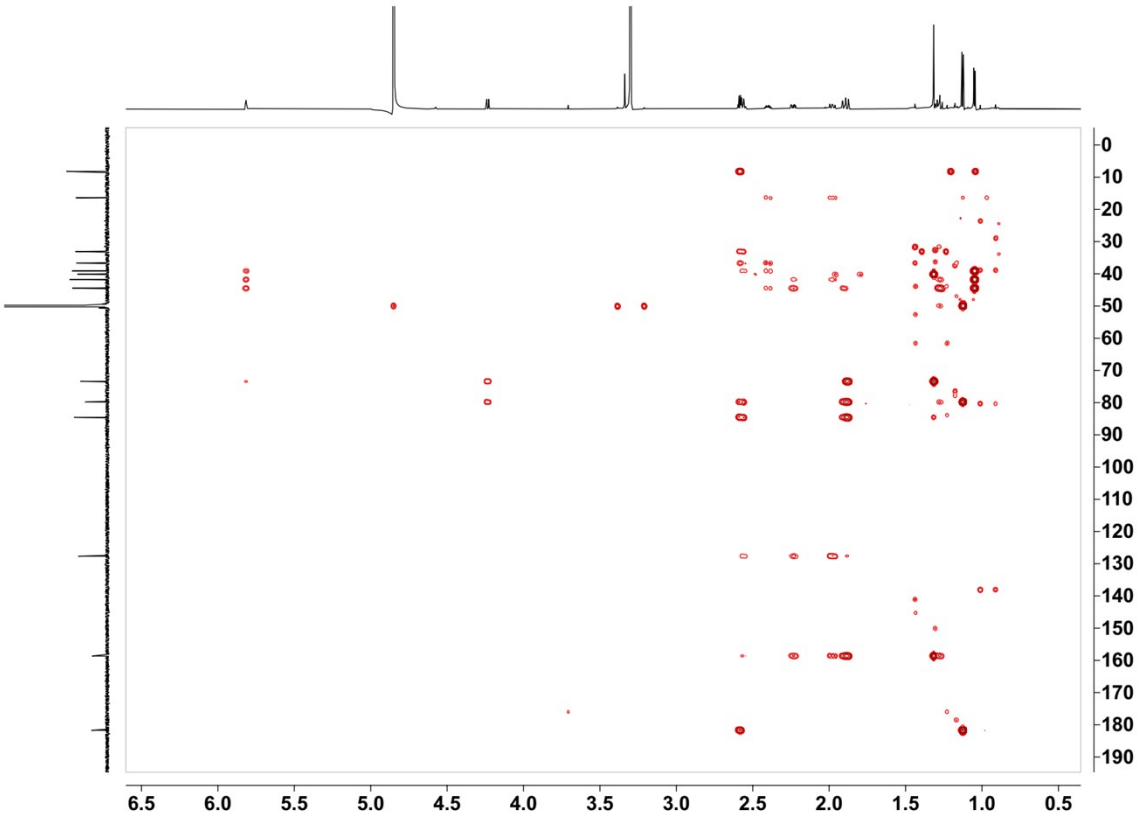


Figure S4: HMBC spectrum of compound **1** in CD_3OD (800 MHz)

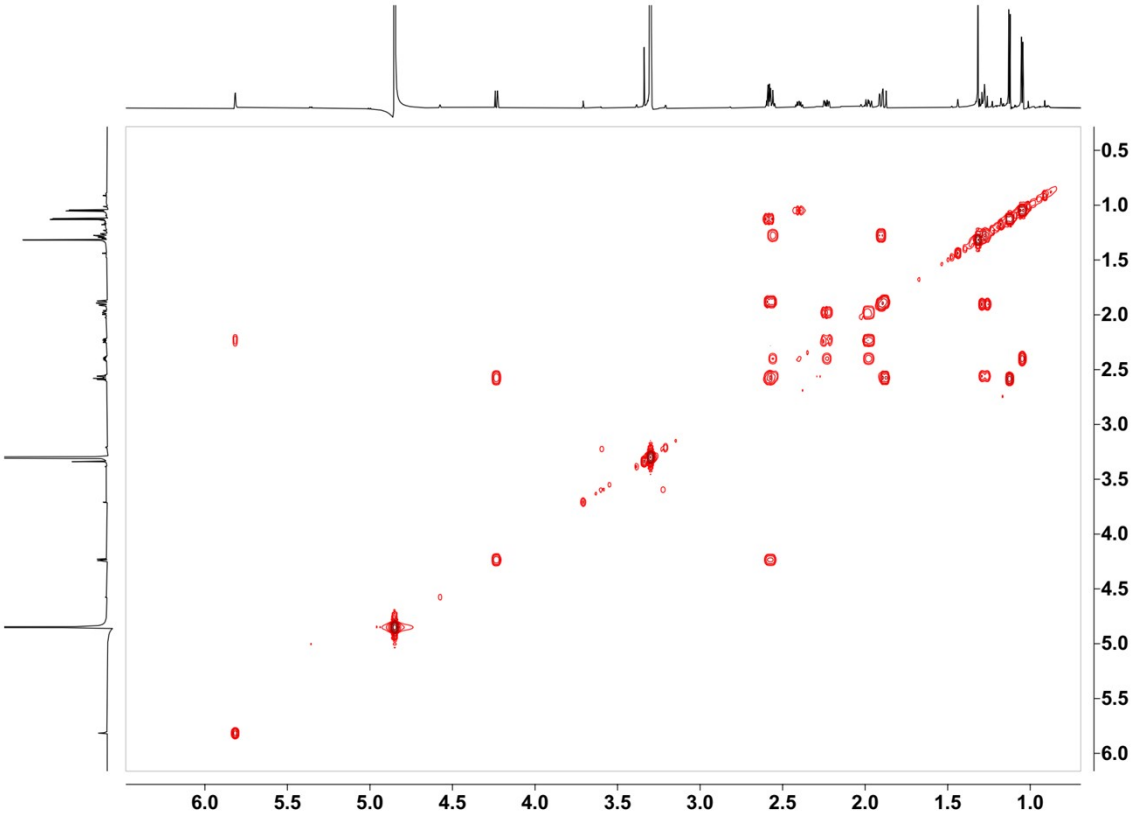


Figure S5: COSY spectrum of compound **1** in CD_3OD (800 MHz)

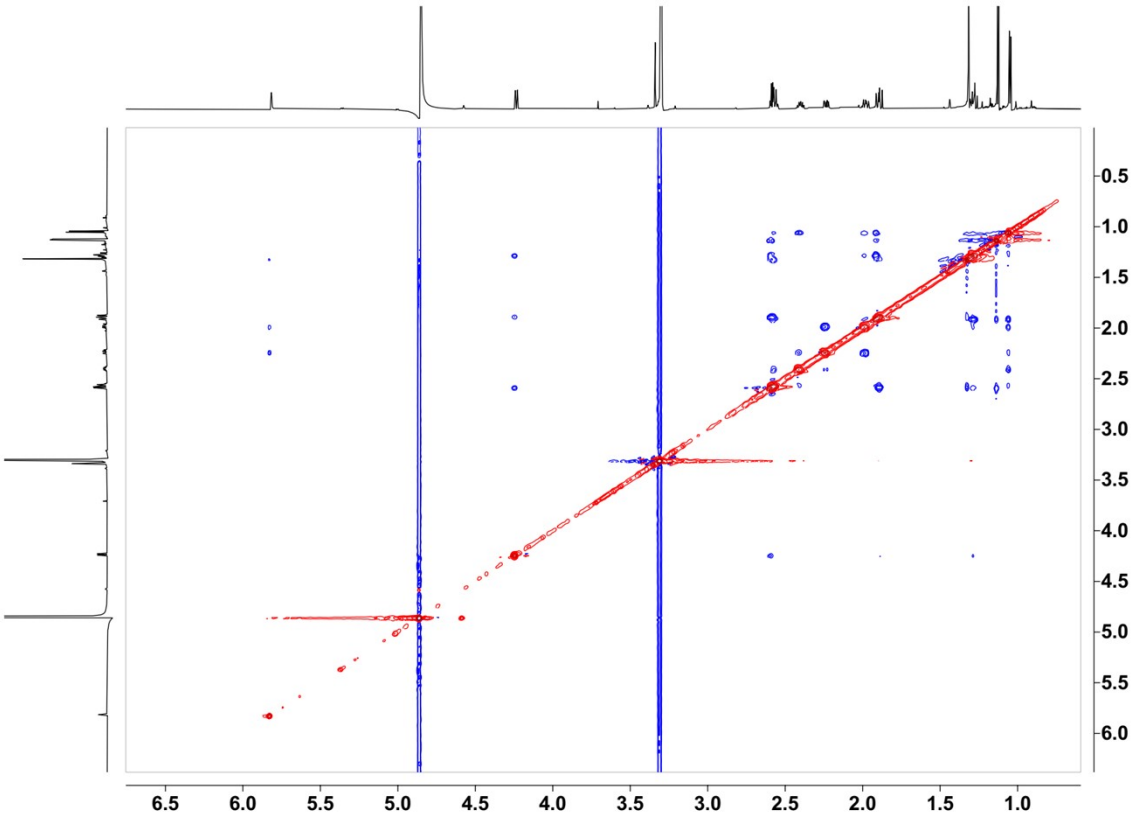
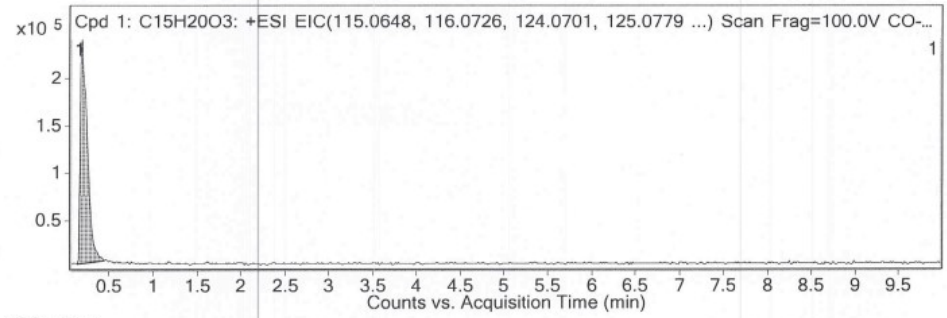


Figure S6: NOESY spectrum of compound **1** in CD_3OD (800 MHz)

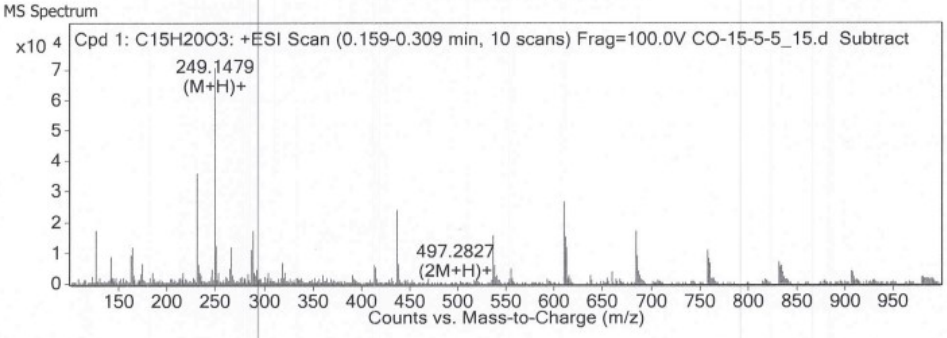
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C15H20O3	0.192	248.1407	70577	C15H20O3	248.1412	-2.06

Compound Label	RT	Algorithm	Mass
Cpd 1: C15H20O3	0.192	Find By Formula	248.1407

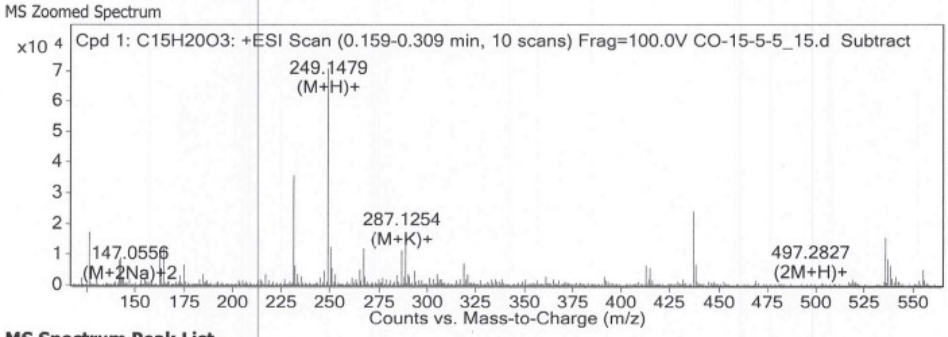


MS Spectrum



Qualitative Compound Report

MS Zoomed Spectrum



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
147.0556	147.0598	-28.94	2	187	C15 H20 Na2 O3	(M+2Na)+2
231.1375	231.138	-2.05	1	35872	C15 H19 O2	(M+H)+[-H2O]
248.1365	248.1407	-17.04		1181	C15 H20 O3	M*+
248.1648	248.1645	1.27		584	C15 H22 N O2	(M+NH4)+[-H2O]
249.1479	249.1485	-2.45		70577	C15 H21 O3	(M+H)+
266.1662	266.1751	-33.46	1	1339	C15 H24 N O3	(M+NH4)+
271.135	271.1305	16.68	1	608	C15 H20 Na O3	(M+Na)+
287.1254	287.1044	73.06	1	10956	C15 H20 K O3	(M+K)+
497.2827	497.2898	-14.3	1	448	C30 H41 O6	(2M+H)+
517.2287	517.2351	-12.38	1	379	C30 H38 K O5	(2M+K)+[-H2O]

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Figure S7: MS spectrum of compound **1**

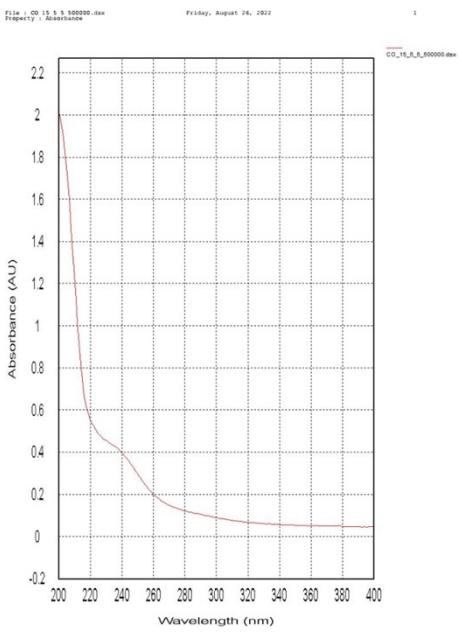


Figure S8: UV spectrum of compound **1**

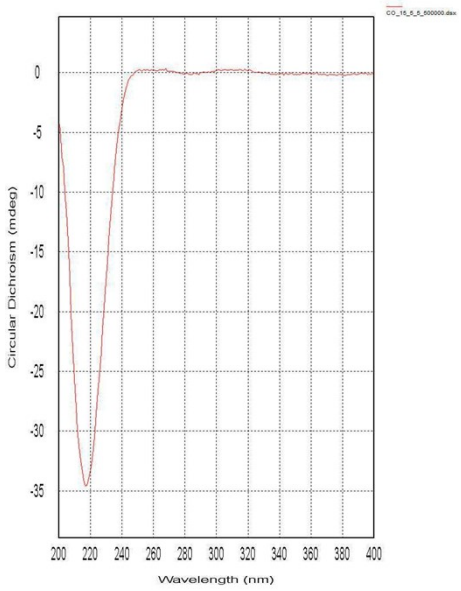


Figure S9: CD spectrum of compound **1**

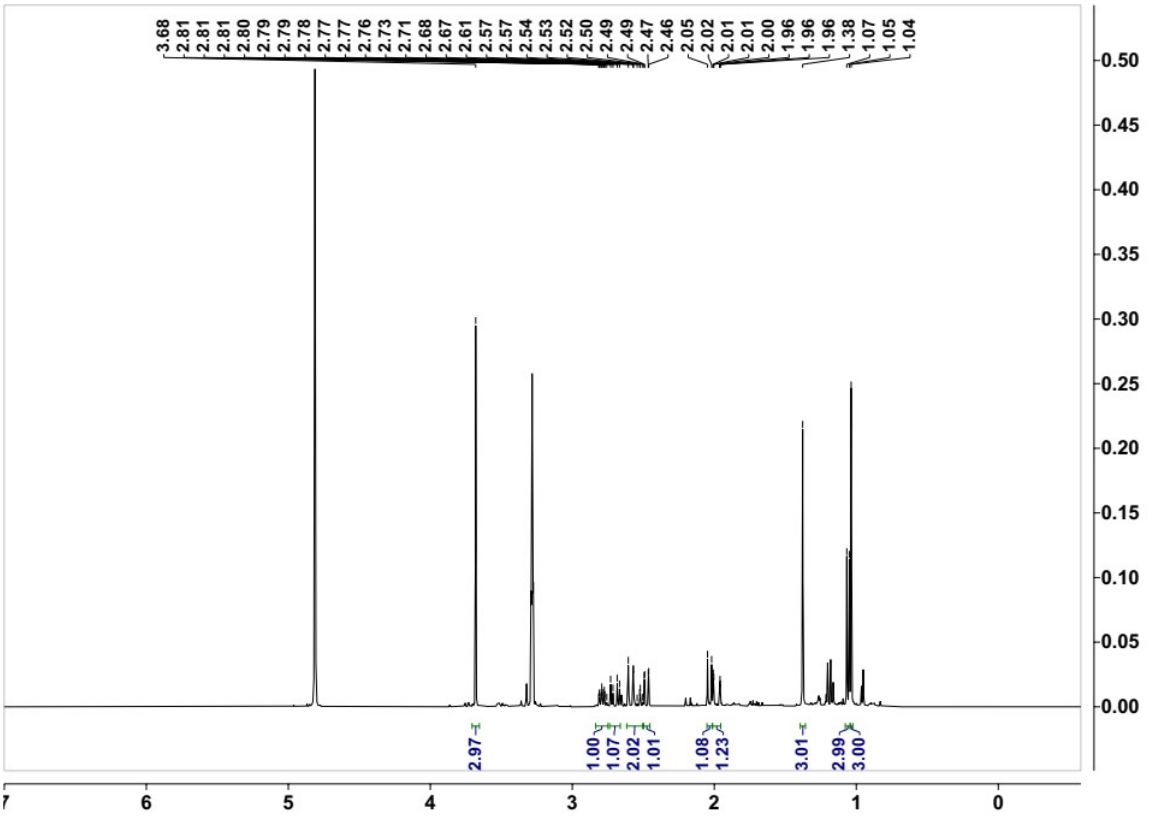


Figure S10: ^{1}H NMR spectrum of compound **2** in CD_3OD (400 MHz)

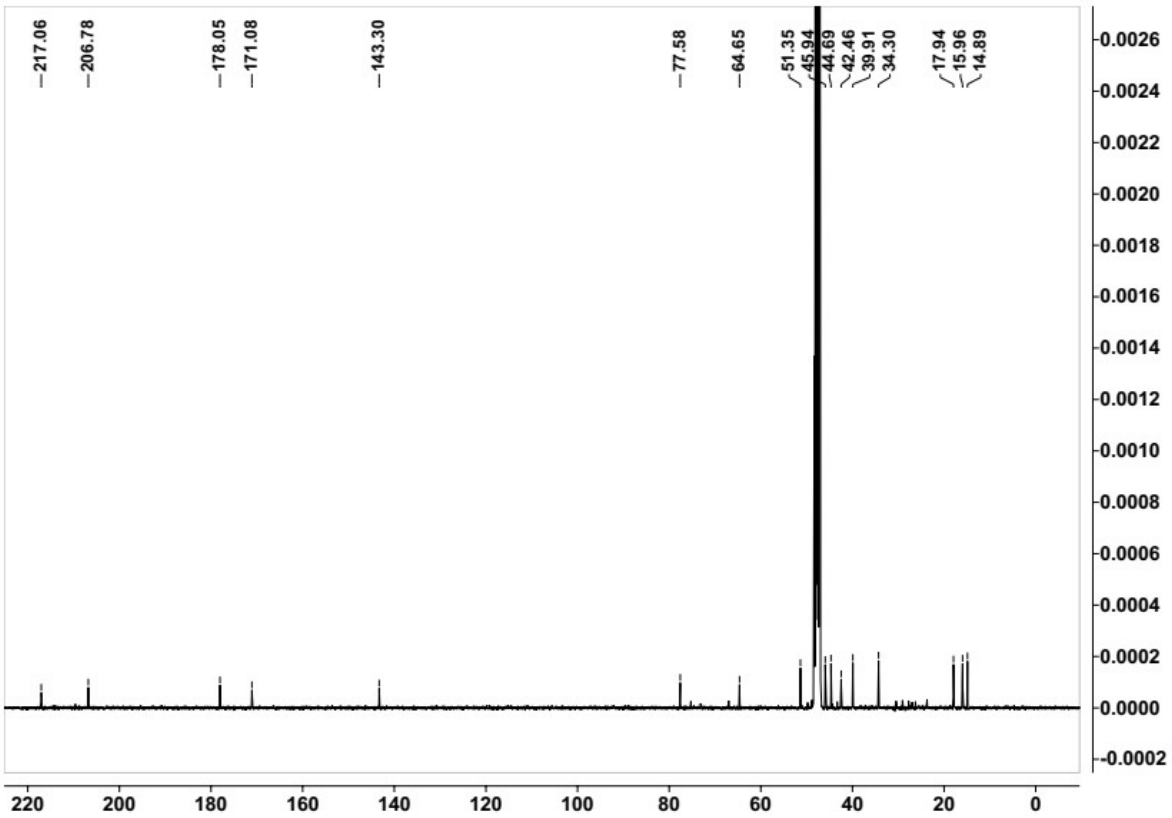


Figure S11: ^{13}C NMR spectrum of compound **2** in CD_3OD (400 MHz)

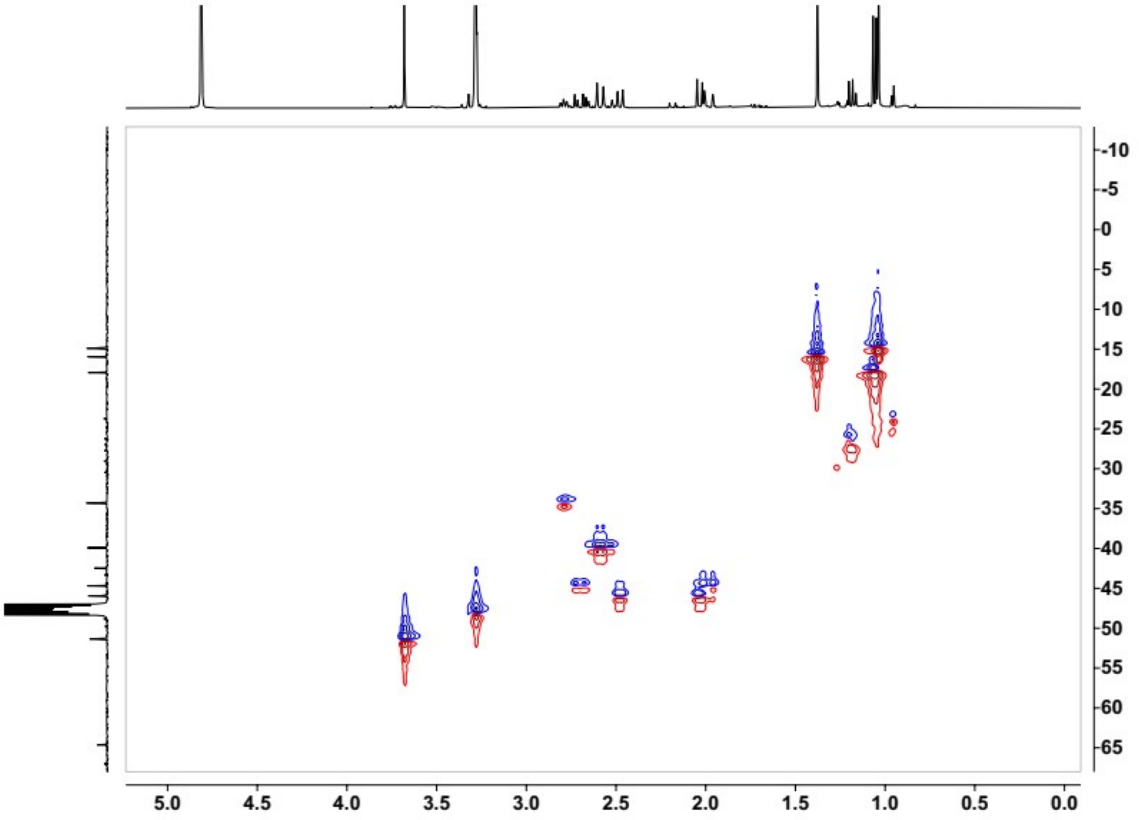


Figure S12: HSQC spectrum of compound **2** in CD_3OD (400 MHz)

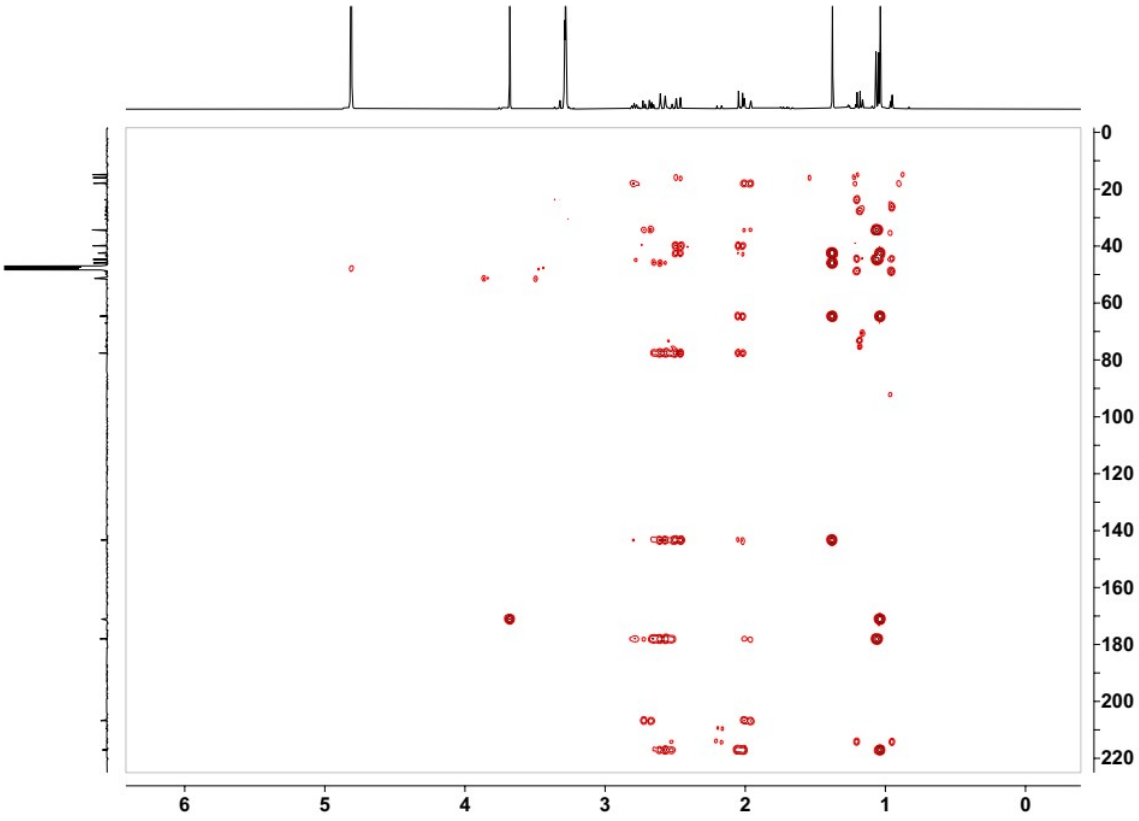


Figure S13: HMBC spectrum of compound **2** in CD_3OD (400 MHz)

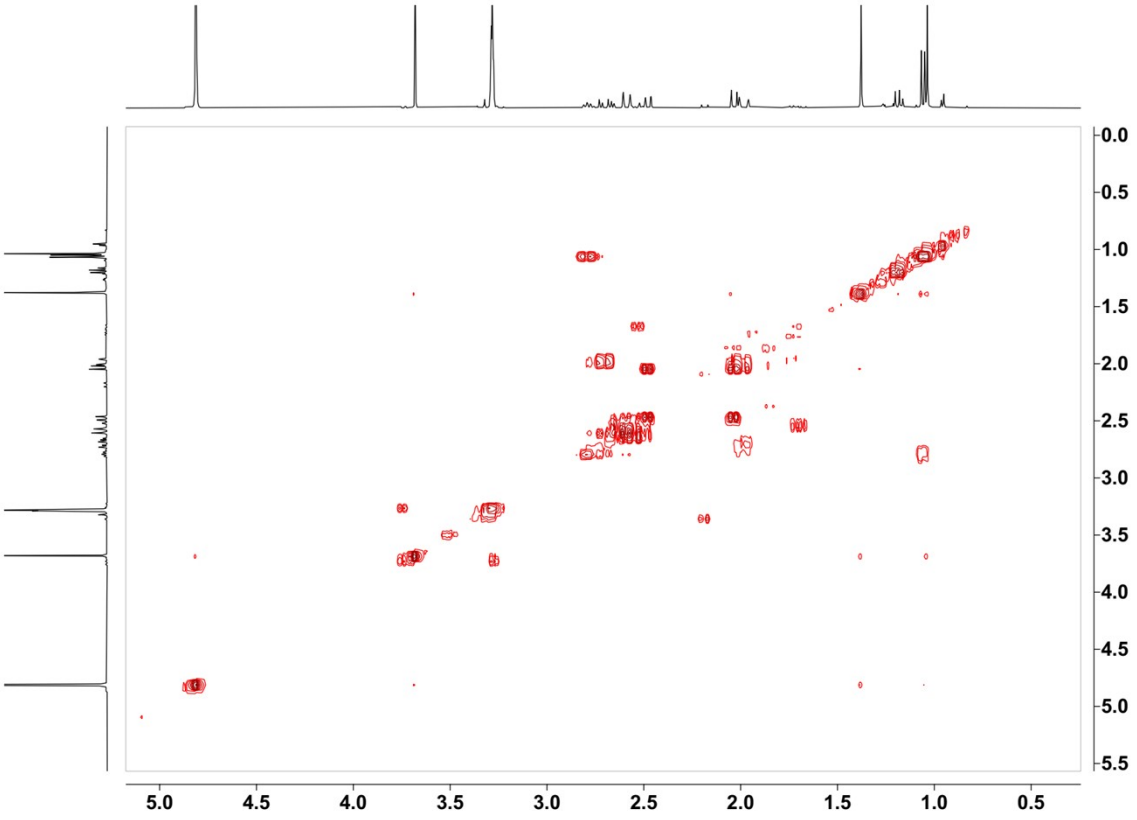


Figure S14: COSY spectrum of compound **2** in CD_3OD (400 MHz)

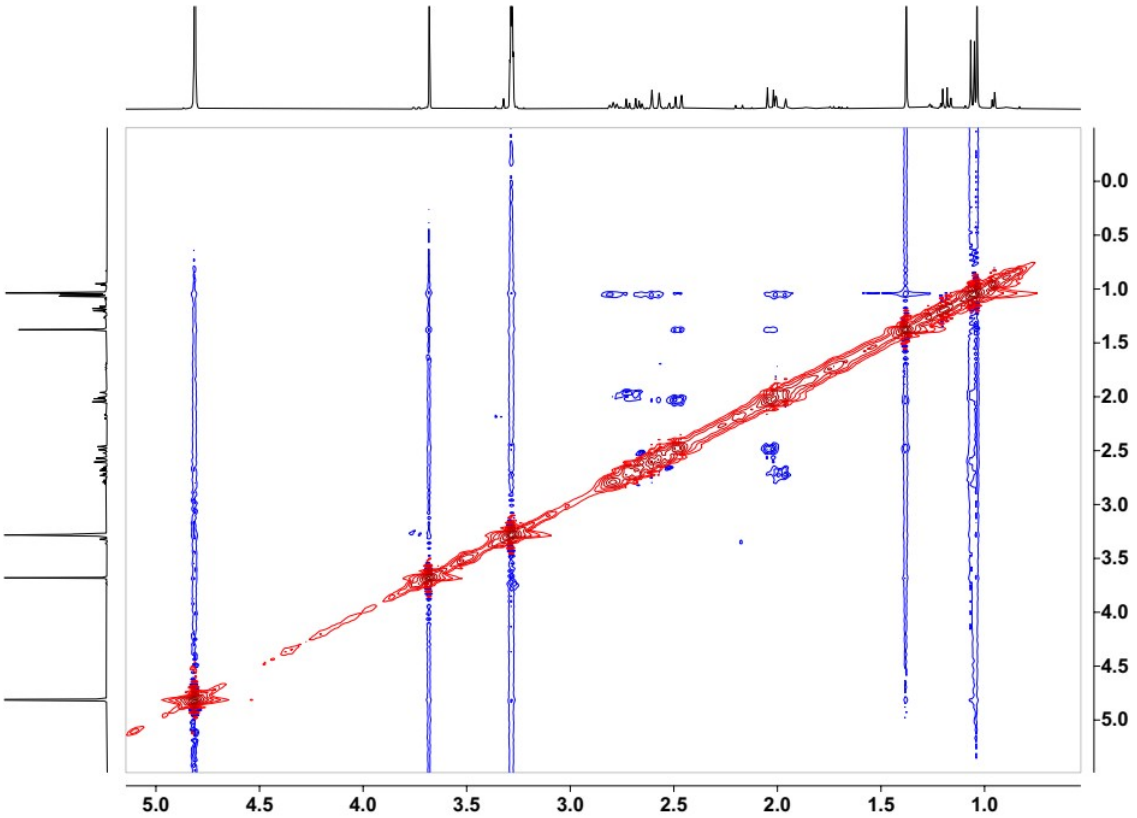
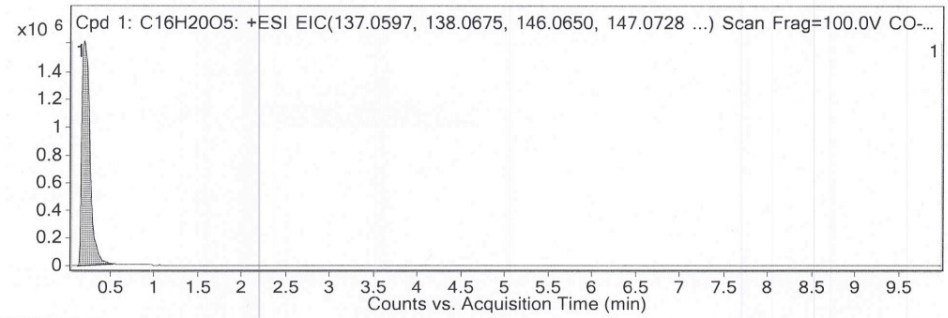


Figure S15: NOESY spectrum of compound **2** in CD_3OD (400 MHz)

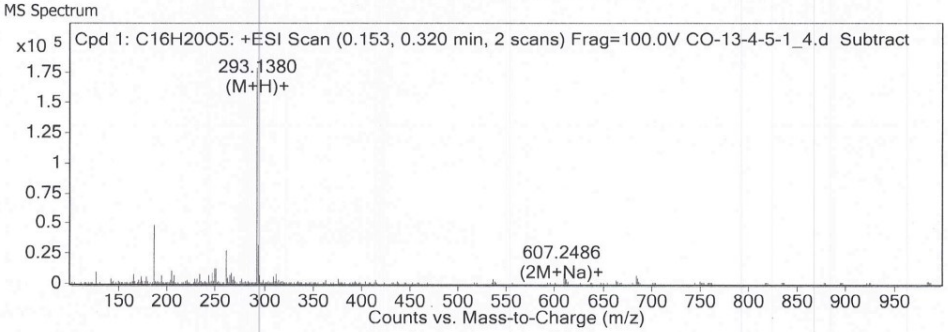
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C16H20O5	0.203	292.1307	178996	C16H20O5	292.1311	-1.17

Compound Label	RT	Algorithm	Mass
Cpd 1: C16H20O5	0.203	Find By Formula	292.1307

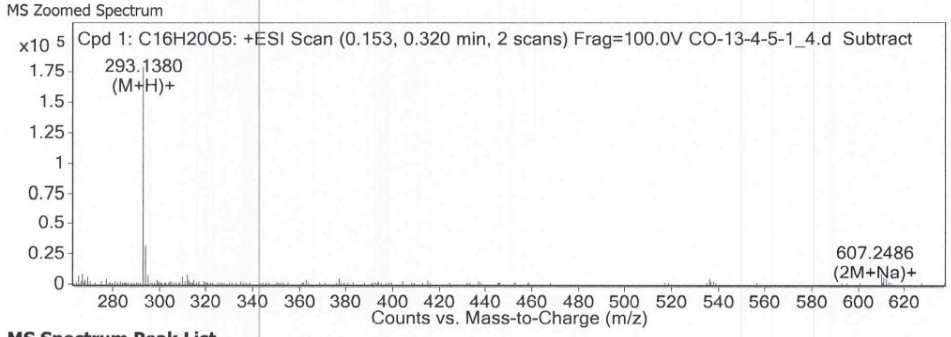


MS Spectrum



Qualitative Compound Report

MS Zoomed Spectrum



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
293.138	293.1384	-1.19		178996	C16 H21 O5	(M+H)+
294.1424	294.1418	2.22		31580	C16 H21 O5	(M+H)+
294.2901				1580		
295.1482	295.1441	14.01		6587	C16 H21 O5	(M+H)+
310.1668	310.1649	6.26	1	5618	C16 H24 N O5	(M+NH4)+
311.1655	311.1682	-8.71	1	1851	C16 H24 N O5	(M+NH4)+
312.1717	312.1705	3.61	1	2263	C16 H24 N O5	(M+NH4)+
315.1194	315.1203	-2.98	1	2555	C16 H20 Na O5	(M+Na)+
331.096	331.0942	5.45	1	1084	C16 H20 K O5	(M+K)+
607.2486	607.2514	-4.61	1	366	C32 H40 Na O10	(2M+Na)+

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Figure S16: MS spectrum of compound **2**

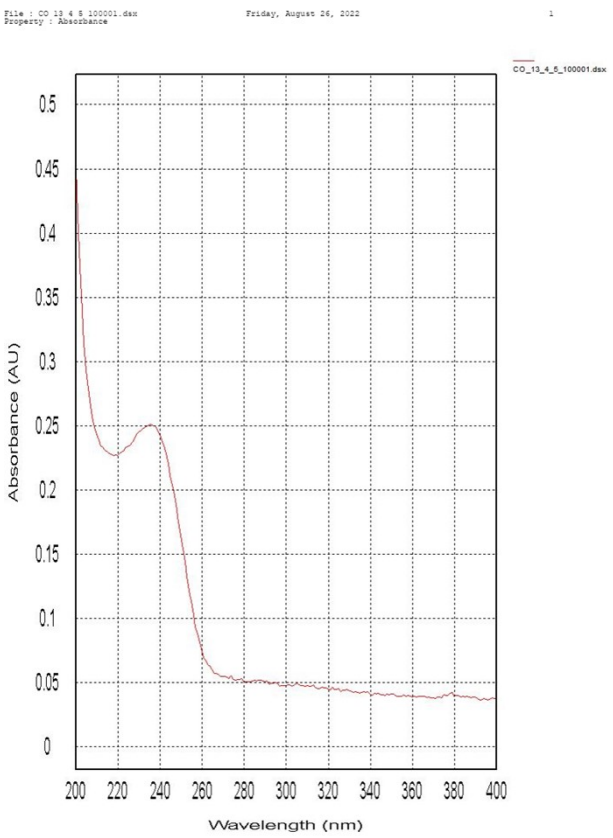


Figure S17: UV spectrum of compound **2**

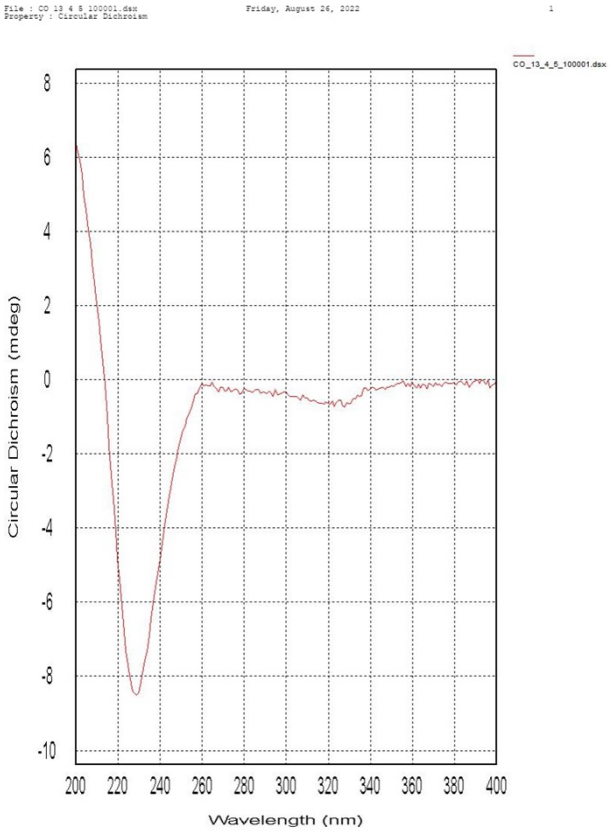


Figure S18: Experimental ECD spectrum of compound **2**

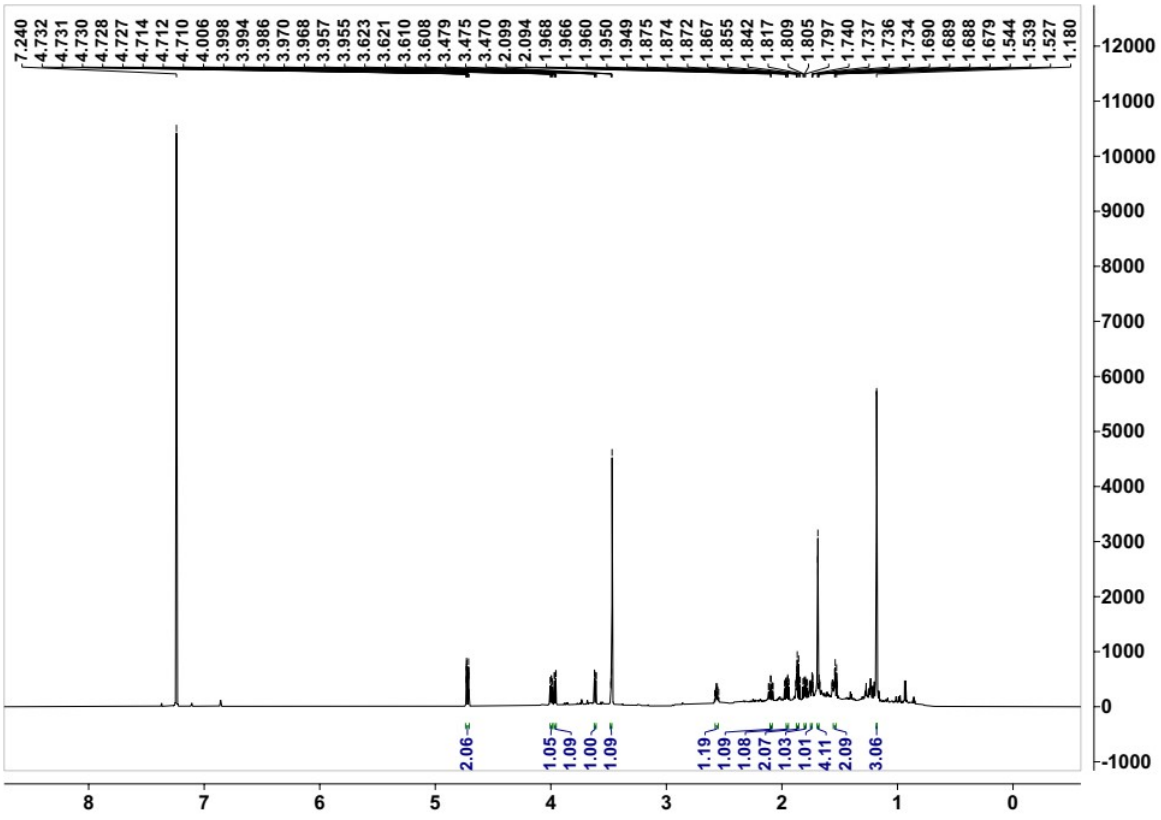


Figure S19: ^{1}H NMR spectrum of compound **3** in $CDCl_3$ (800 MHz)

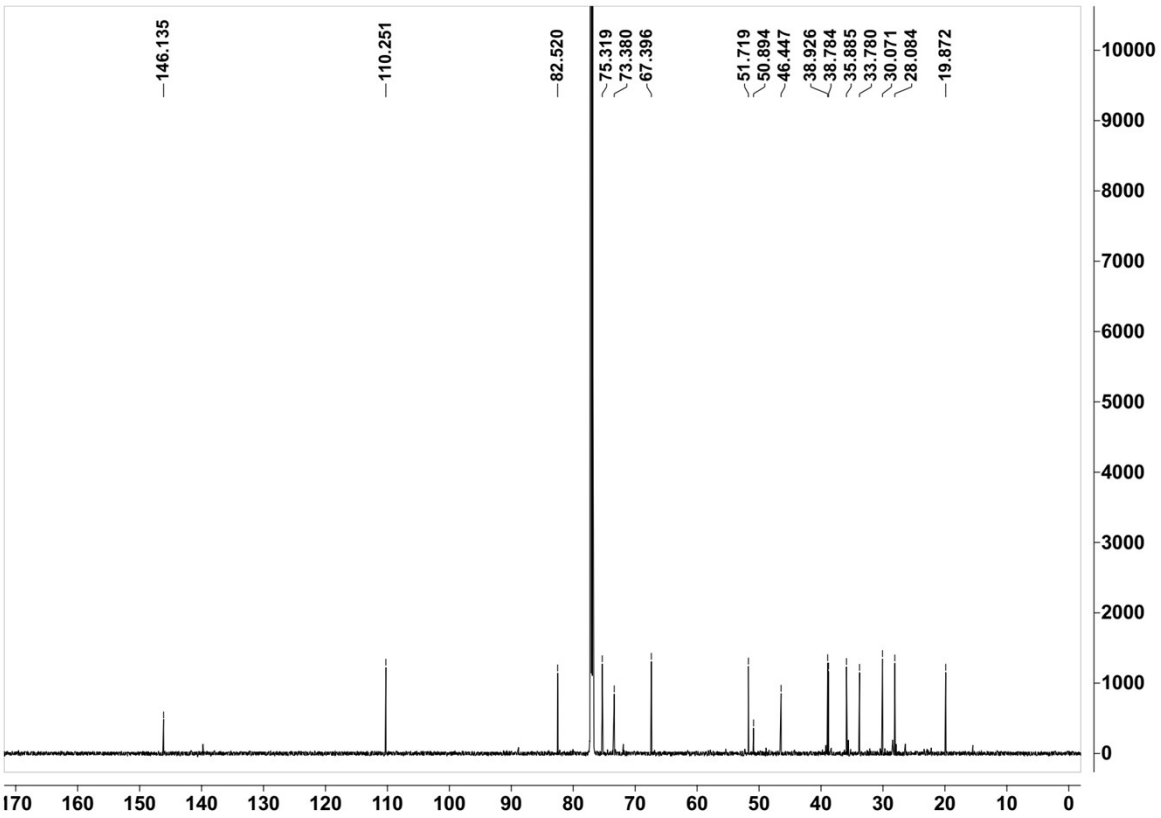


Figure S20: ^{13}C NMR spectrum of compound **3** in $CDCl_3$ (800 MHz)

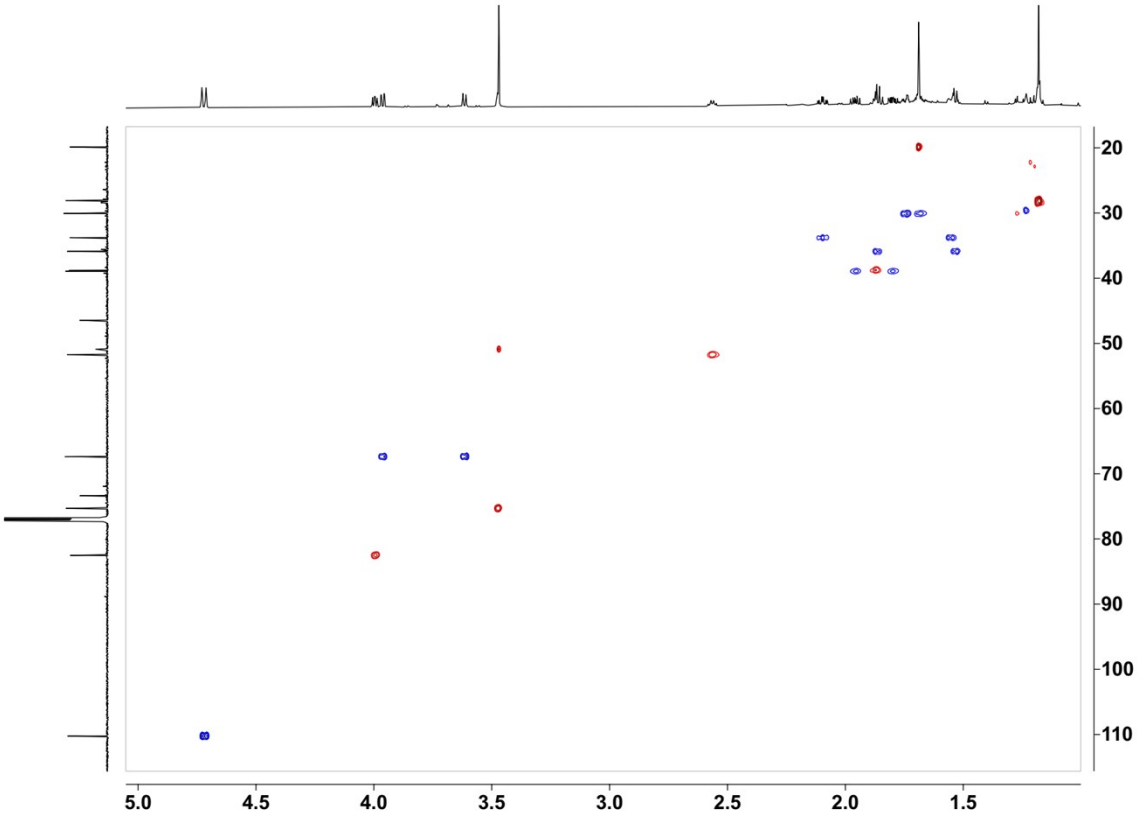


Figure S21: HSQC spectrum of compound **3** in $CDCl_3$ (800 MHz)

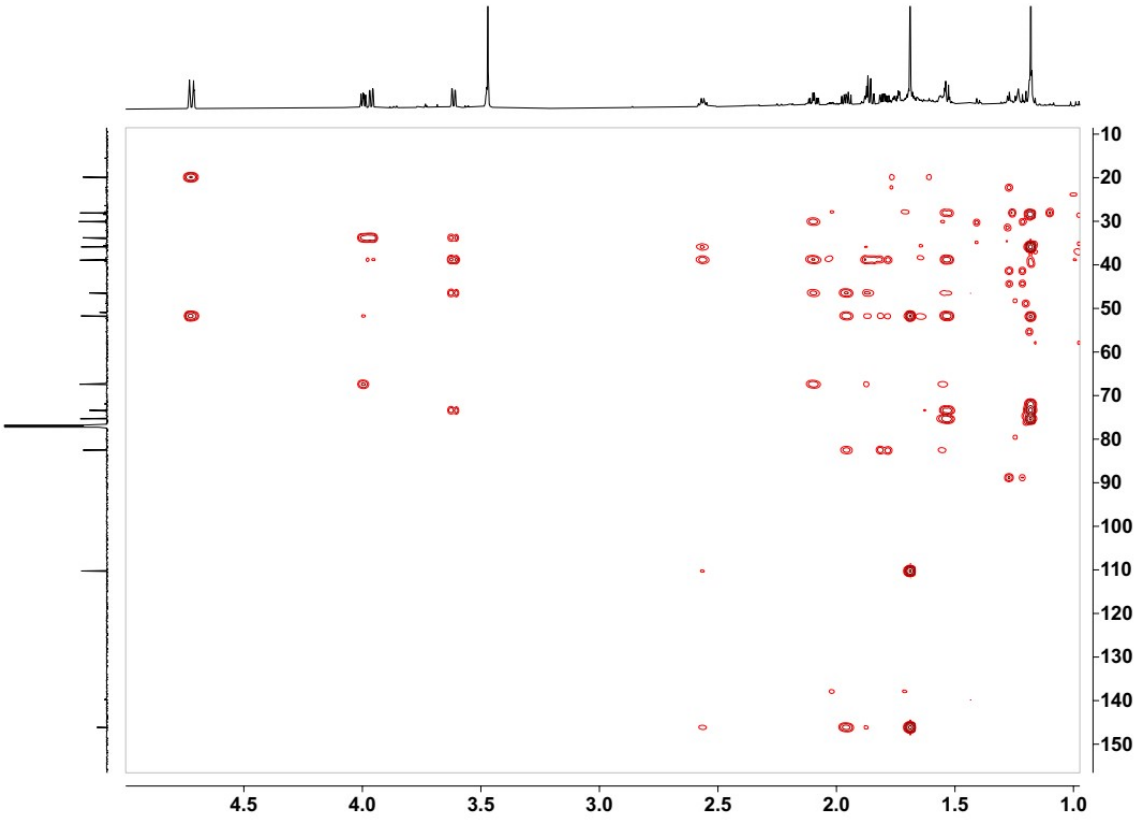


Figure S22: HMBC spectrum of compound **3** in $CDCl_3$ (800 MHz)

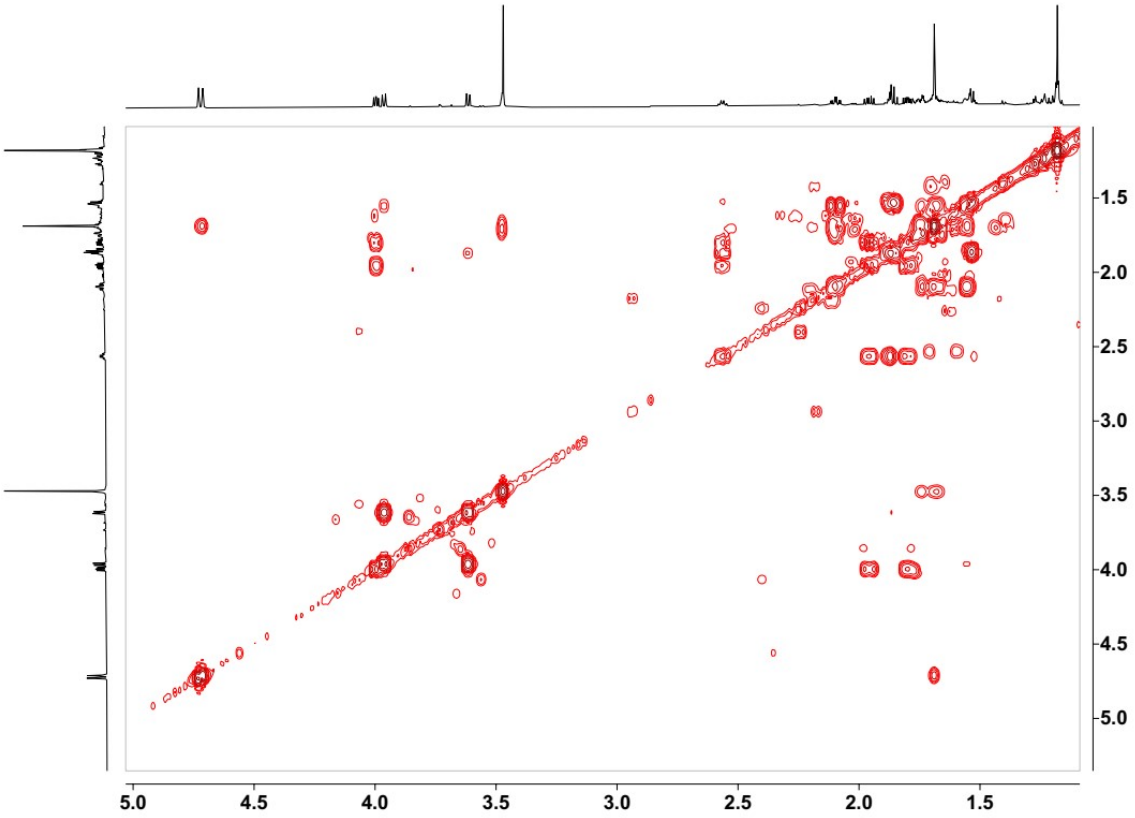


Figure S23: COSY spectrum of compound **3** in $CDCl_3$ (800 MHz)

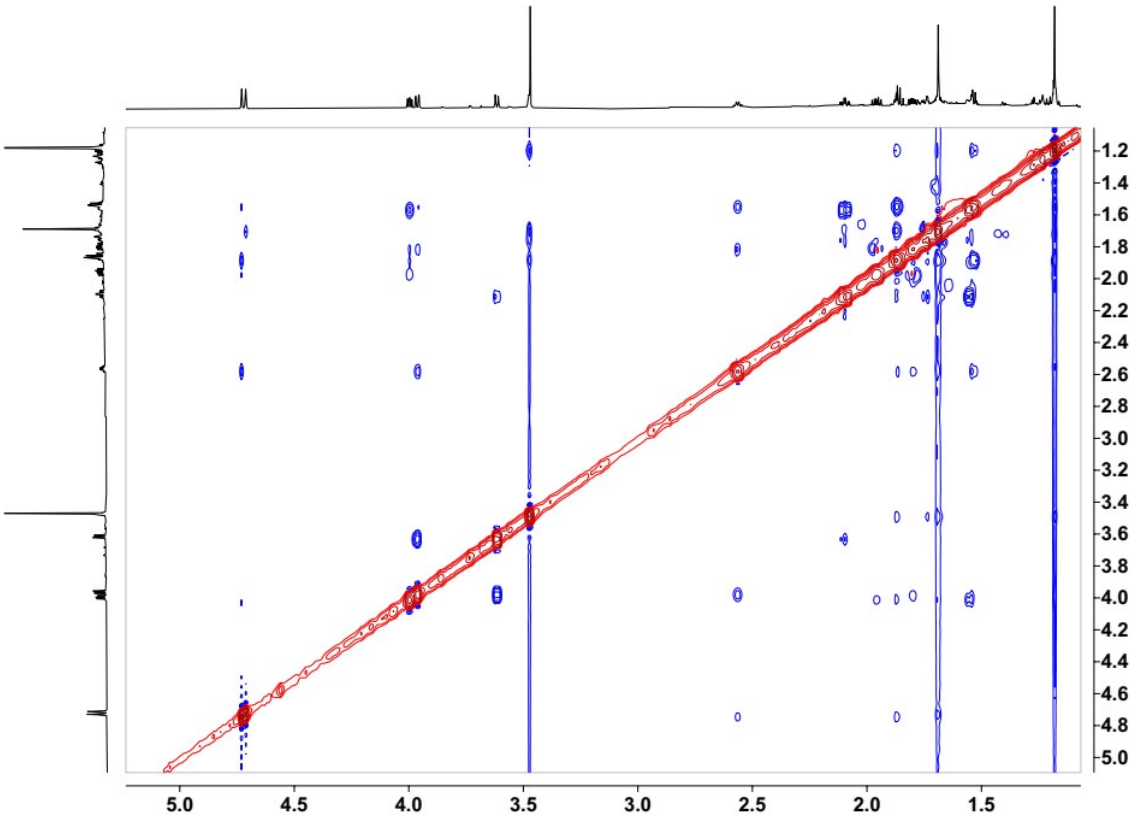
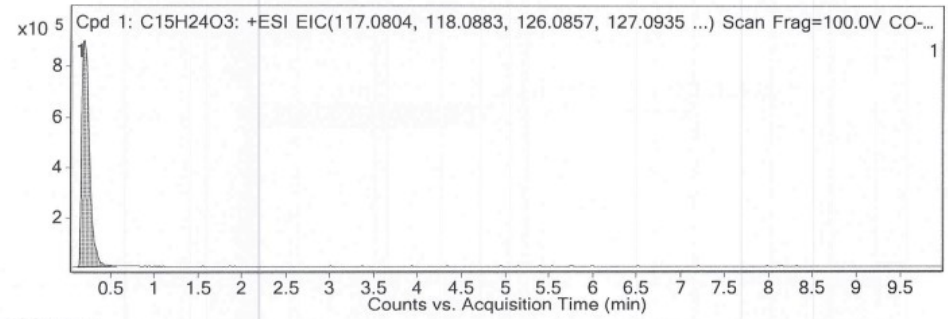


Figure S24: NOESY spectrum of compound **3** in $CDCl_3$ (800 MHz)

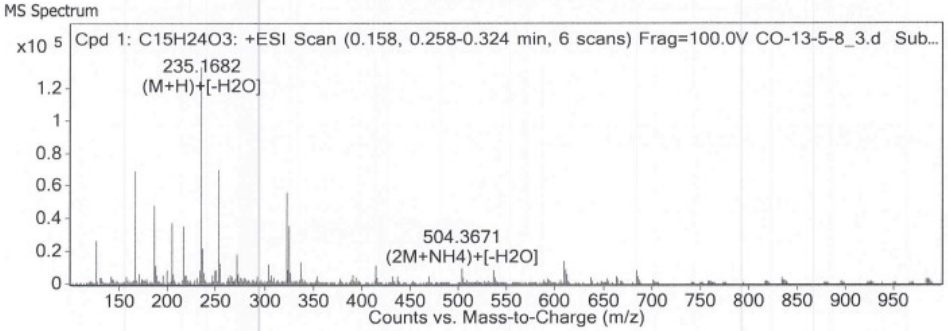
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C15H24O3	0.208	252.1715	69994	C15H24O3	252.1725	-4.19

Compound Label	RT	Algorithm	Mass
Cpd 1: C15H24O3	0.208	Find By Formula	252.1715

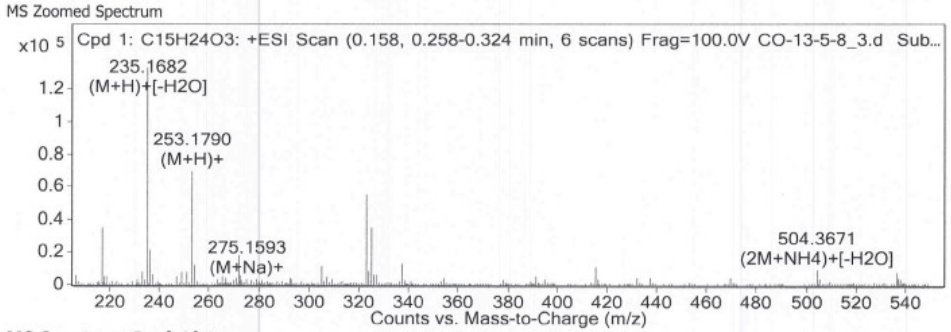


MS Spectrum



Qualitative Compound Report

MS Zoomed Spectrum



MS Spectrum Peak List

m/z	Calc m/z	Diff(ppm)	z	Abund	Formula	Ion
235.1682	235.1693	-4.63		132643	C15 H23 O2	(M+H)+[-H2O]
236.1721	236.1727	-2.18		21277	C15 H23 O2	(M+H)+[-H2O]
253.179	253.1798	-3.33	1	69994	C15 H25 O3	(M+H)+
254.1825	254.1832	-2.86	1	11933	C15 H25 O3	(M+H)+
270.2037	270.2064	-9.85	1	2785	C15 H28 N O3	(M+NH4)+
275.1593	275.1618	-8.98	1	3833	C15 H24 Na O3	(M+Na)+
487.34	487.3418	-3.77	1	643	C30 H47 O5	(2M+H)+[-H2O]
504.3671	504.3684	-2.5	1	9511	C30 H50 N O5	(2M+NH4)+[-H2O]
509.32	509.3237	-7.32	1	2150	C30 H46 Na O5	(2M+Na)+[-H2O]
525.2942	525.2977	-6.58	1	546	C30 H46 K O5	(2M+K)+[-H2O]

--- End Of Report ---

Figure S25: MS spectrum of compound **3**

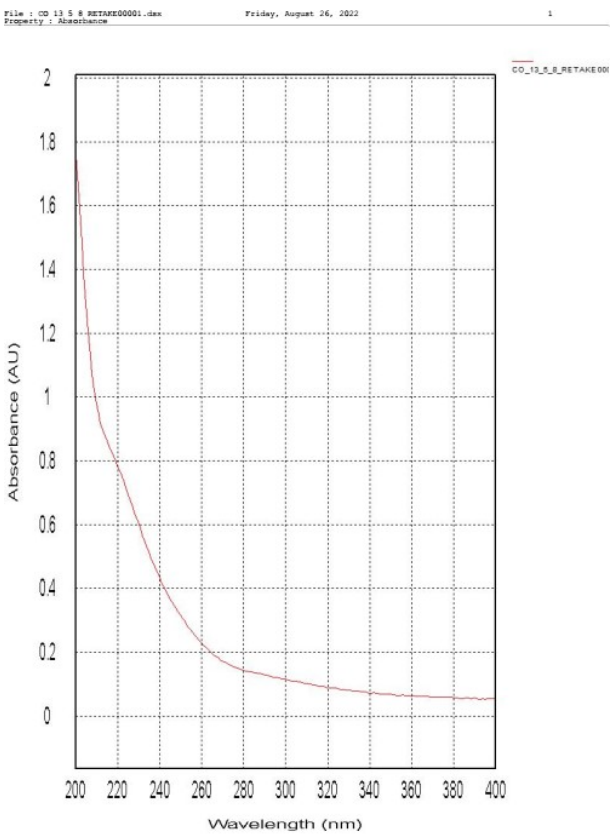


Figure S26: UV spectrum of compound **3**

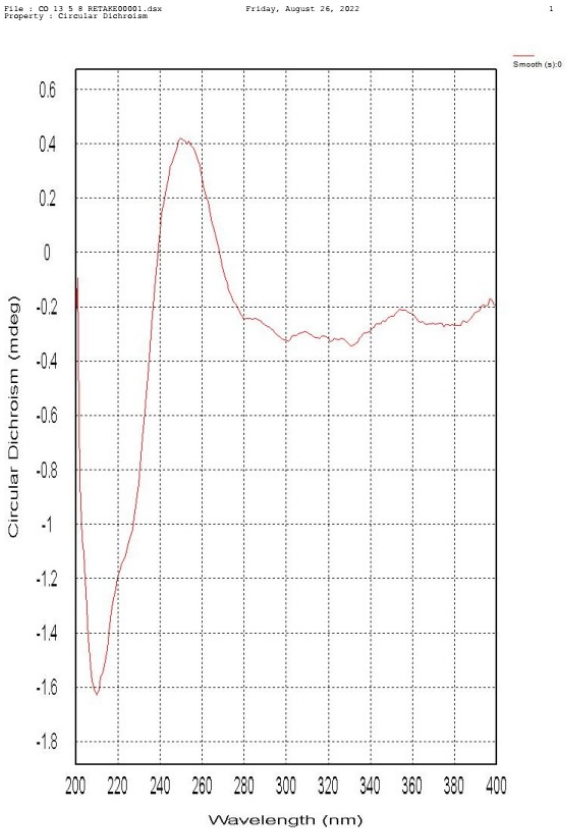


Figure S27: Experimental ECD spectrum of compound **3**

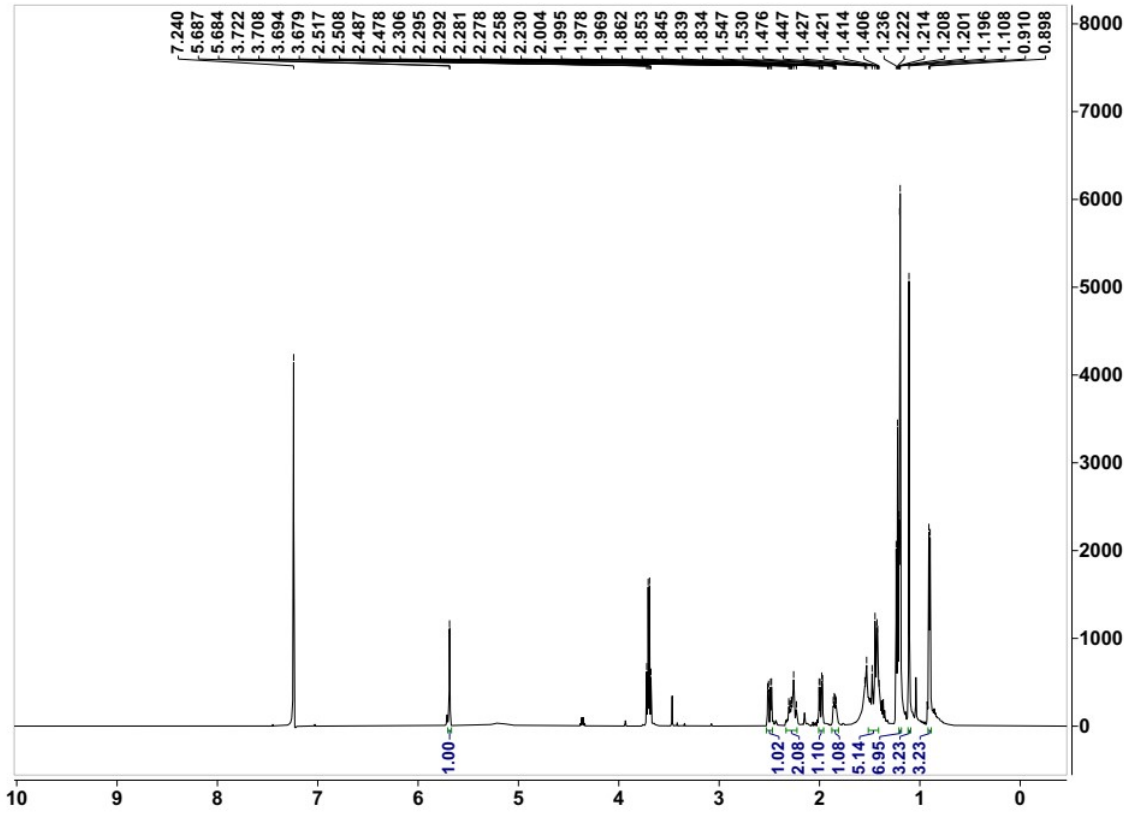


Figure S28: ^{1}H NMR spectrum of compound **4** in $CDCl_3$ (500 MHz)

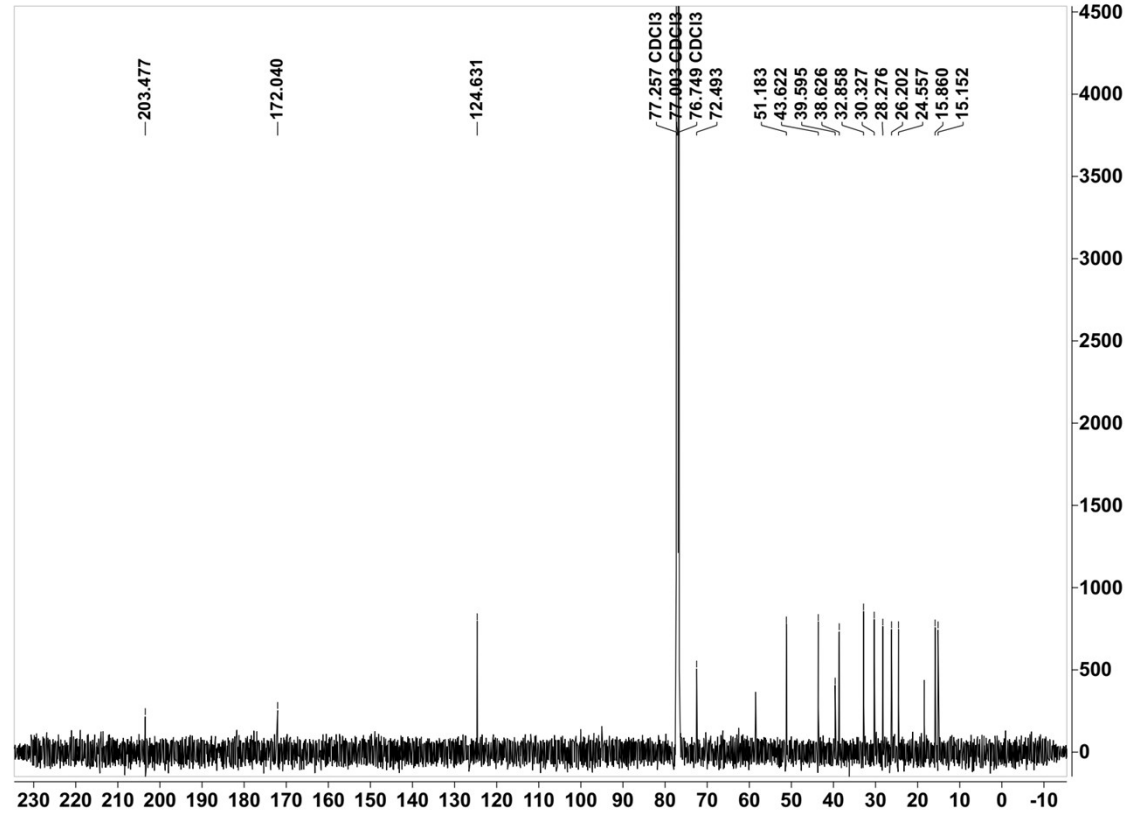


Figure S29: ^{13}C NMR spectrum of compound **4** in $CDCl_3$ (500 MHz)

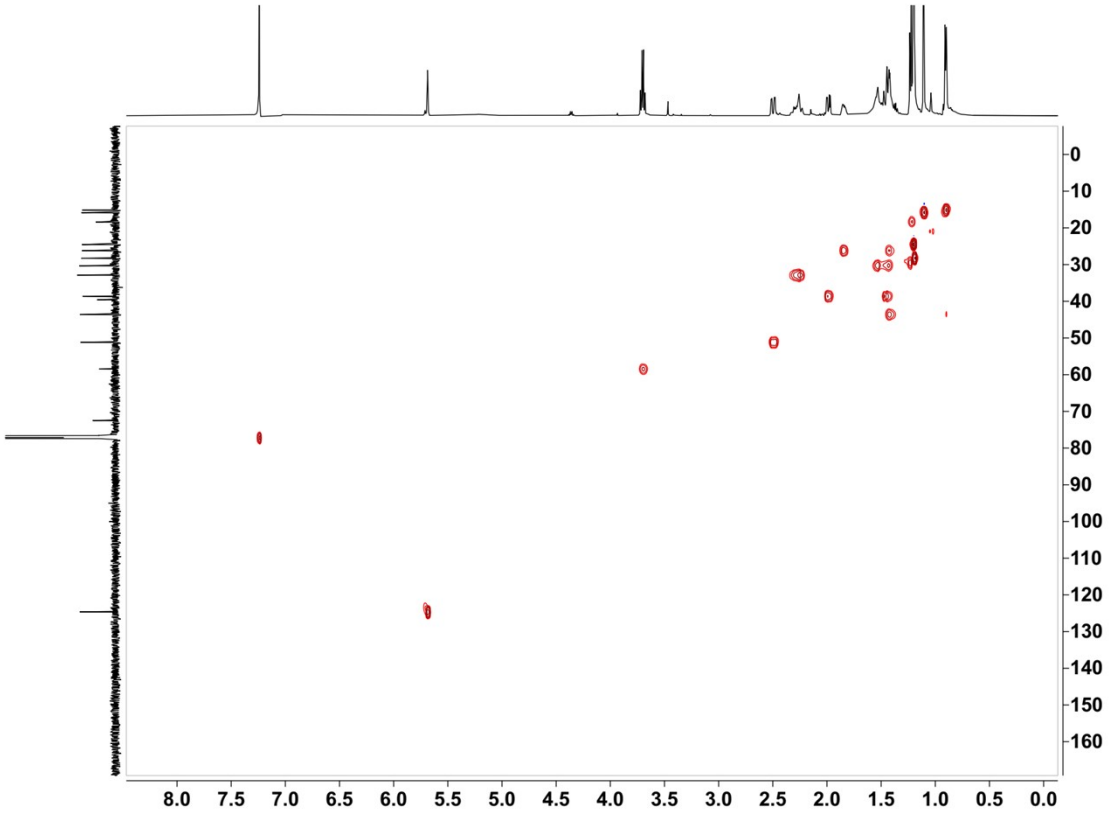


Figure S30: HSQC spectrum of compound **4** in $CDCl_3$ (500 MHz)

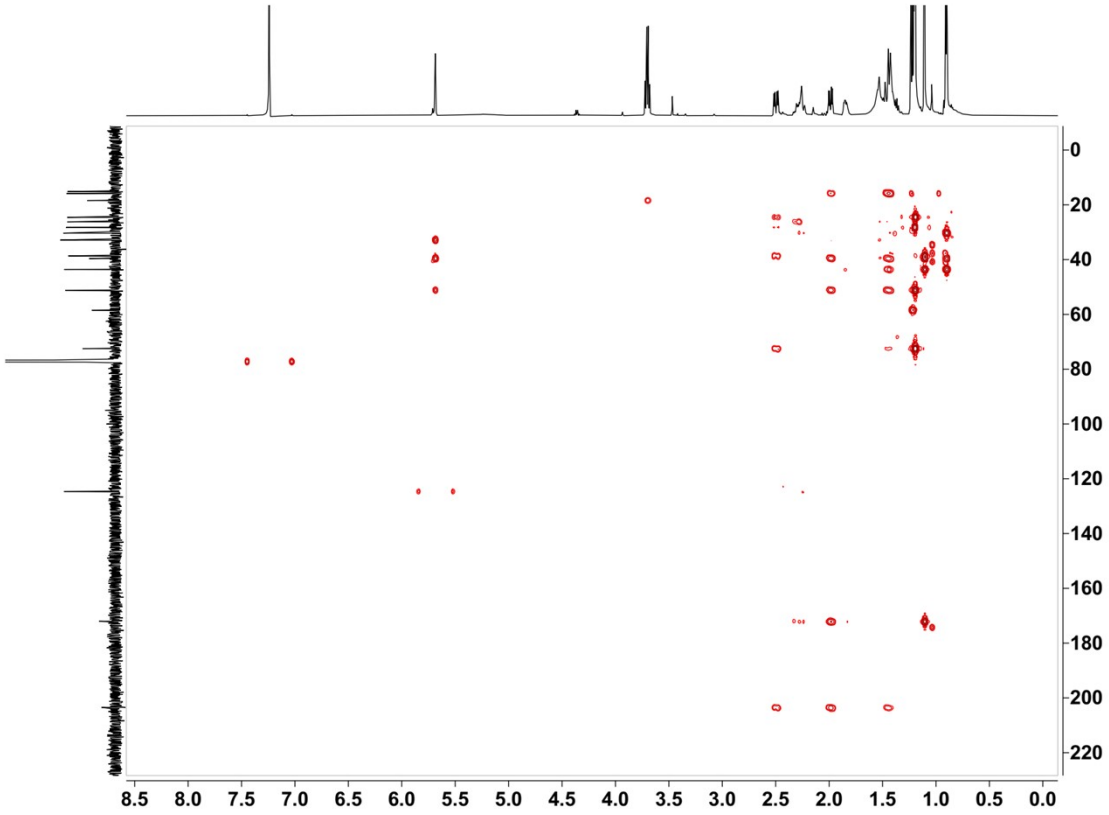


Figure S31: HMBC spectrum of compound **4** in $CDCl_3$ (500 MHz)

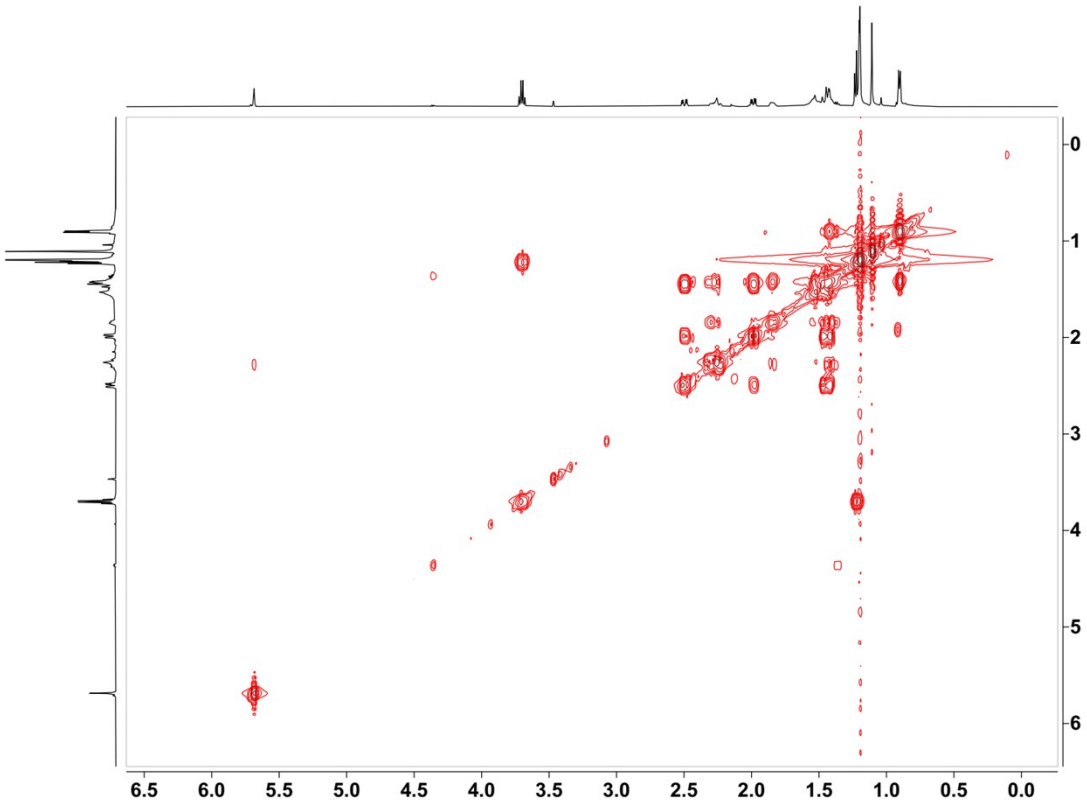


Figure S32: COSY spectrum of compound **4** in $CDCl_3$ (500 MHz)

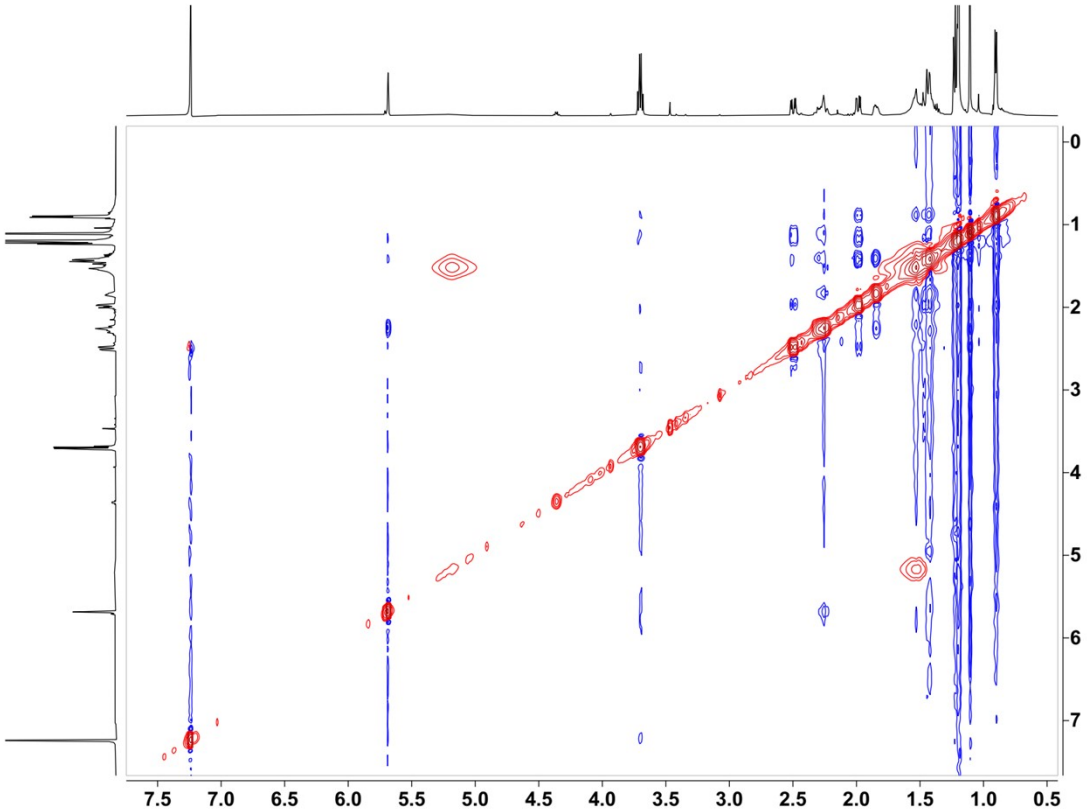
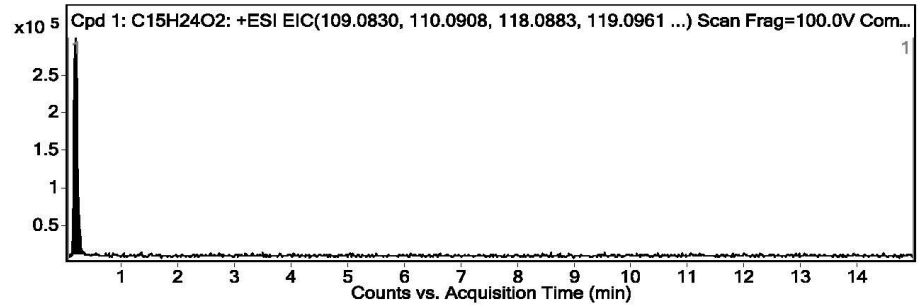


Figure S33: NOESY spectrum of compound **4** in $CDCl_3$ (500 MHz)

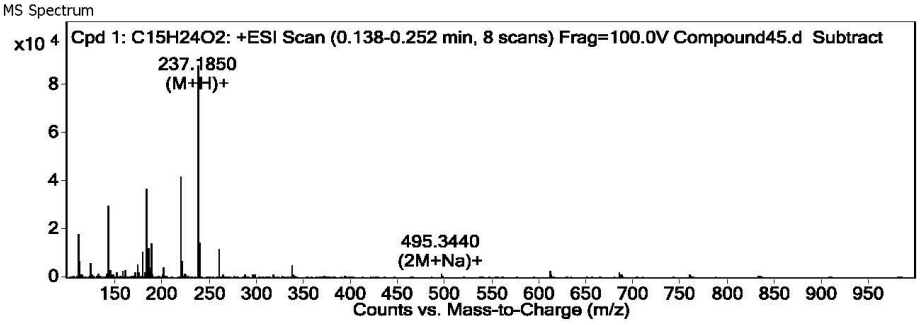
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C15H24O2	0.187	236.1777	88199	C15H24O2	236.1776	0.38

Compound Label	RT	Algorithm	Mass
Cpd 1: C15H24O2	0.187	Find By Formula	236.1777

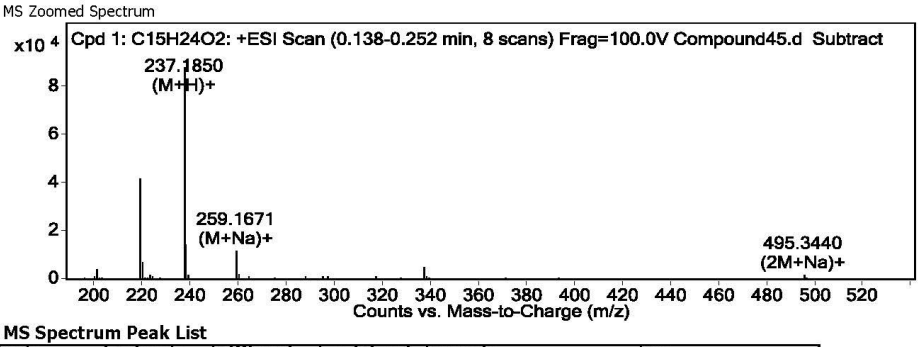


MS Spectrum



Qualitative Compound Report

MS Zoomed Spectrum



MS Spectrum Peak List

m/z	Calc m/z	Diff(ppm)	z	Abund	Formula	Ion
219.1744	219.1743	0.07	1	42232	C15 H23 O	(M+H)+[-H2O]
220.1776	220.1777	-0.6	1	7100	C15 H23 O	(M+H)+[-H2O]
236.1775	236.1771	1.84		87	C15 H24 O2	M*+
237.185	237.1849	0.4		88199	C15 H25 O2	(M+H)+
238.1889	238.1883	2.36		14826	C15 H25 O2	(M+H)+
259.1671	259.1669	1.02	1	11999	C15 H24 Na O2	(M+Na)+
275.1412	275.1408	1.51	1	934	C15 H24 K O2	(M+K)+
472.3757	472.3785	-5.93	1	98	C30 H50 N O3	(2M+NH4)+[-H2O]
495.344	495.3445	-0.89	1	1806	C30 H48 Na O4	(2M+Na)+
511.3188	511.3184	0.68	1	56	C30 H48 K O4	(2M+K)+

--- End Of Report ---

Figure S34: MS spectrum of compound **4**

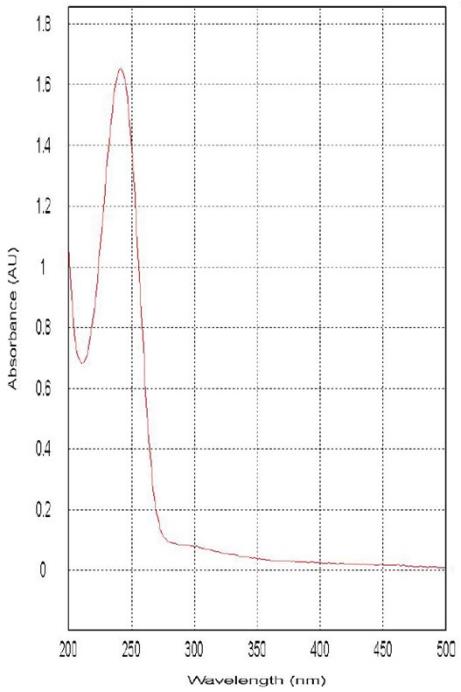


Figure S35: UV spectrum of compound **4**

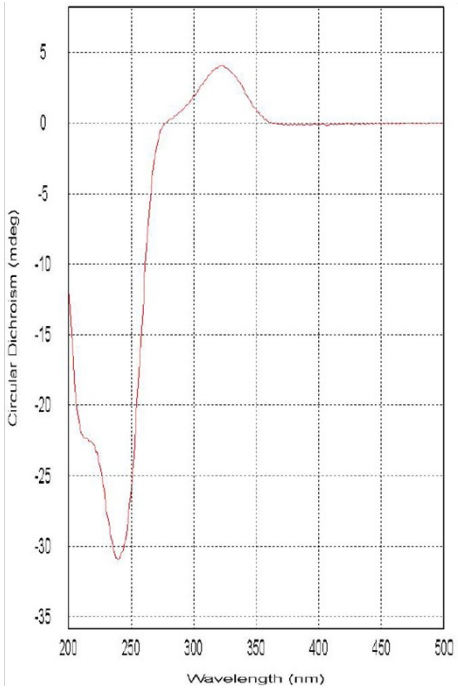


Figure S36: Experimental ECD spectrum of compound **4**

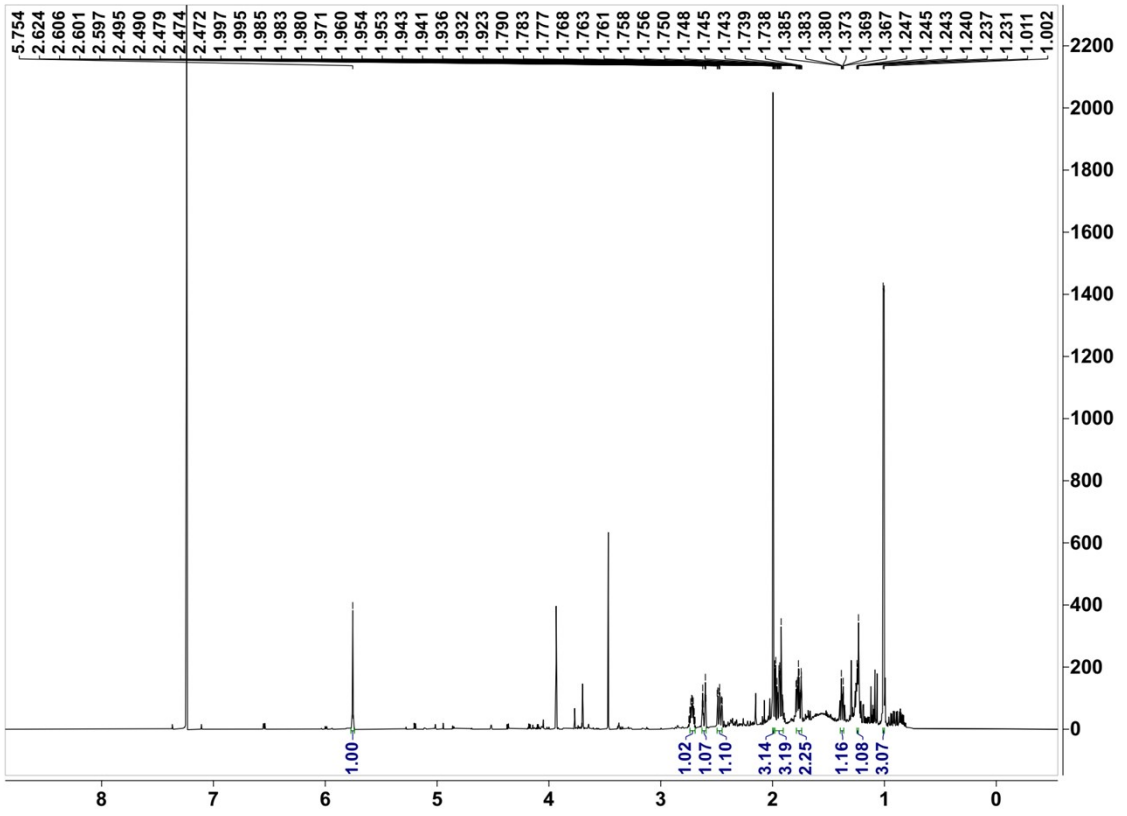


Figure S37: ^{1}H NMR spectrum of compound **5** in $CDCl_3$ (800 MHz)

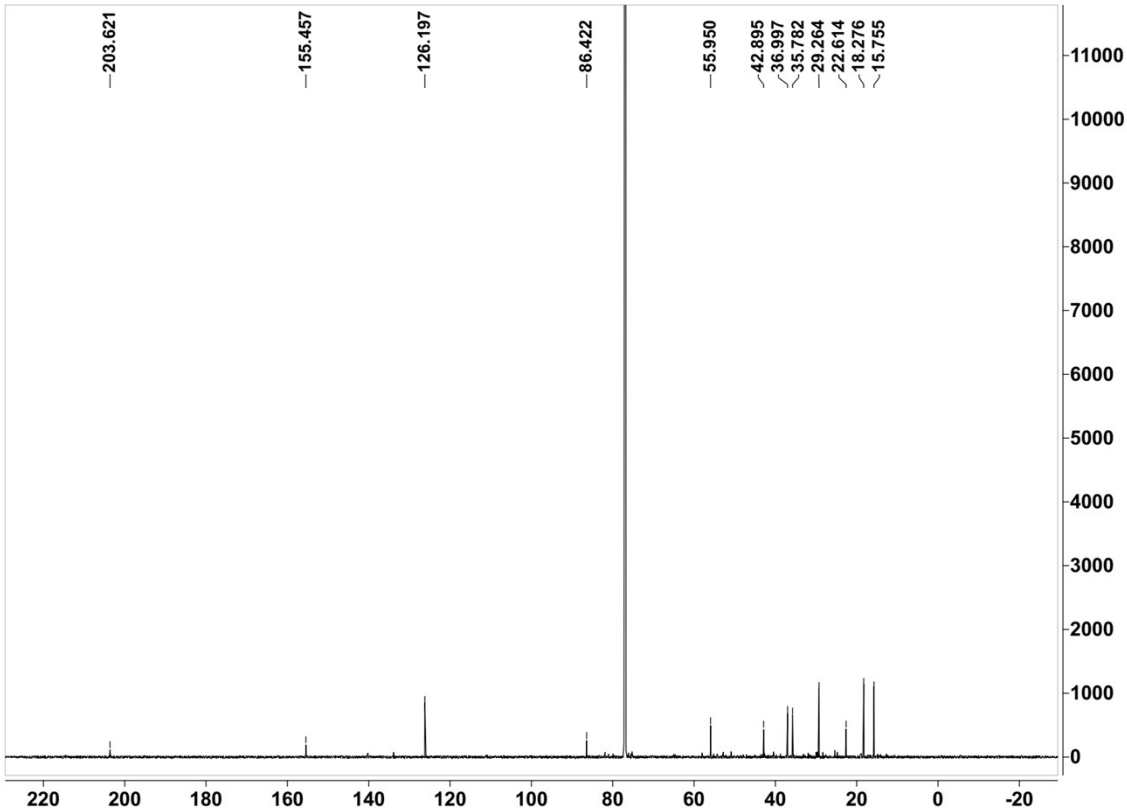


Figure S38: ^{13}C NMR spectrum of compound **5** in $CDCl_3$ (800 MHz)

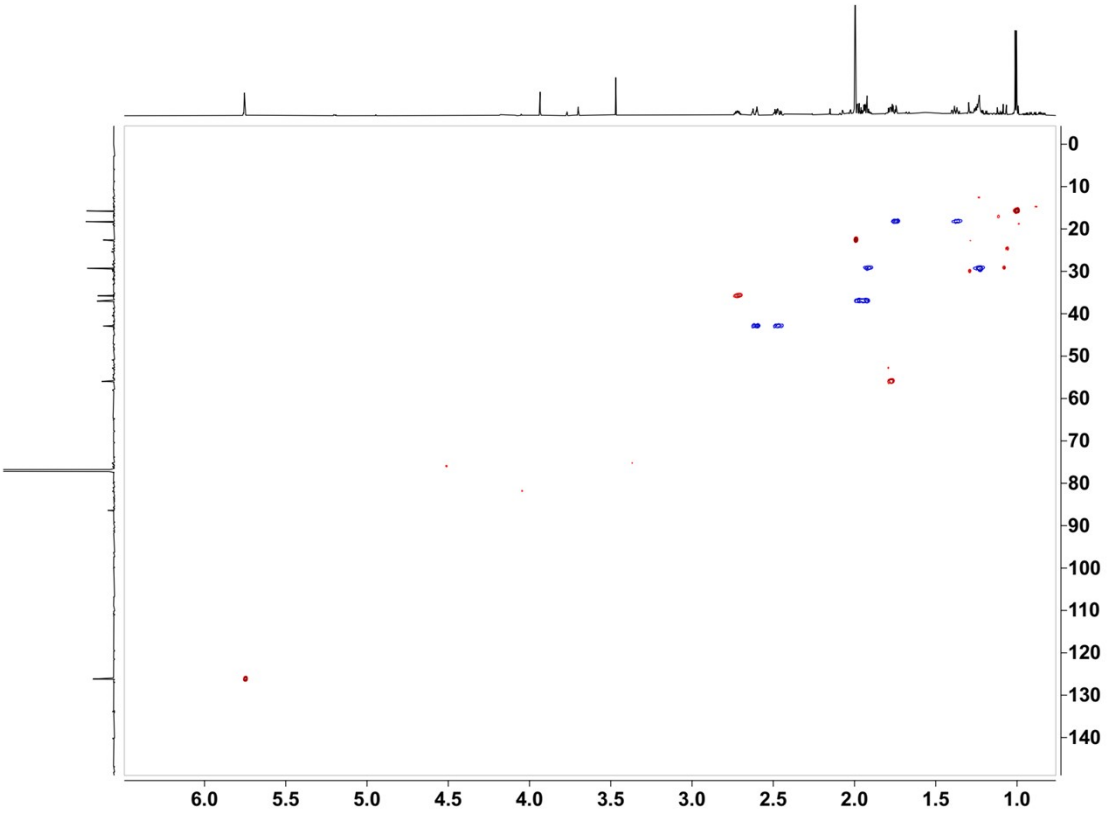


Figure S39: HSQC spectrum of compound **5** in $CDCl_3$ (800 MHz)

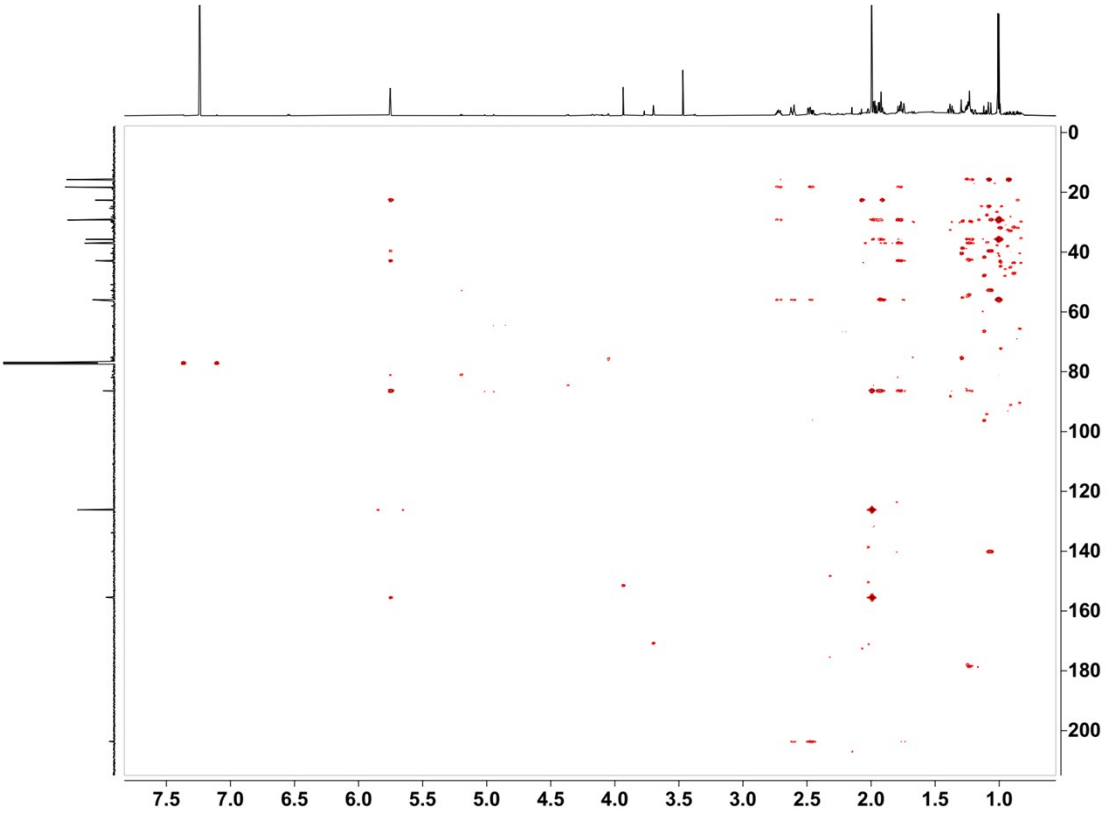


Figure S40: HMBC spectrum of compound **5** in $CDCl_3$ (800 MHz)

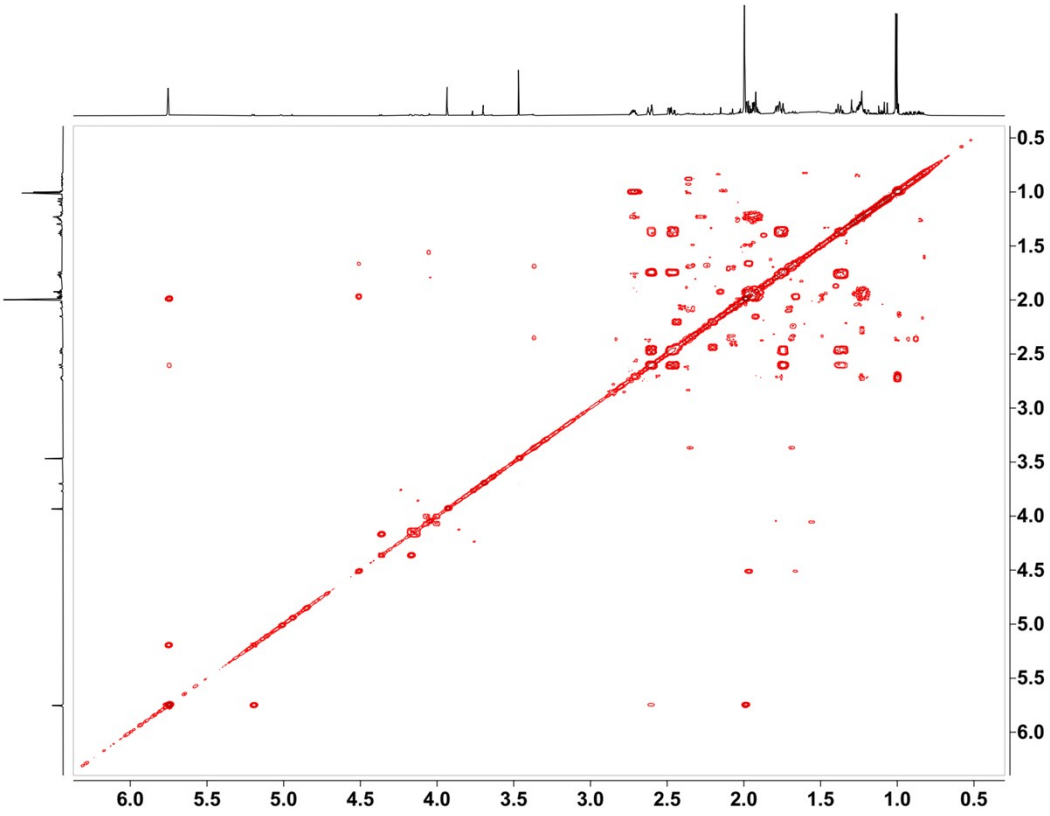


Figure S41: COSY spectrum of compound **5** in $CDCl_3$ (800 MHz)

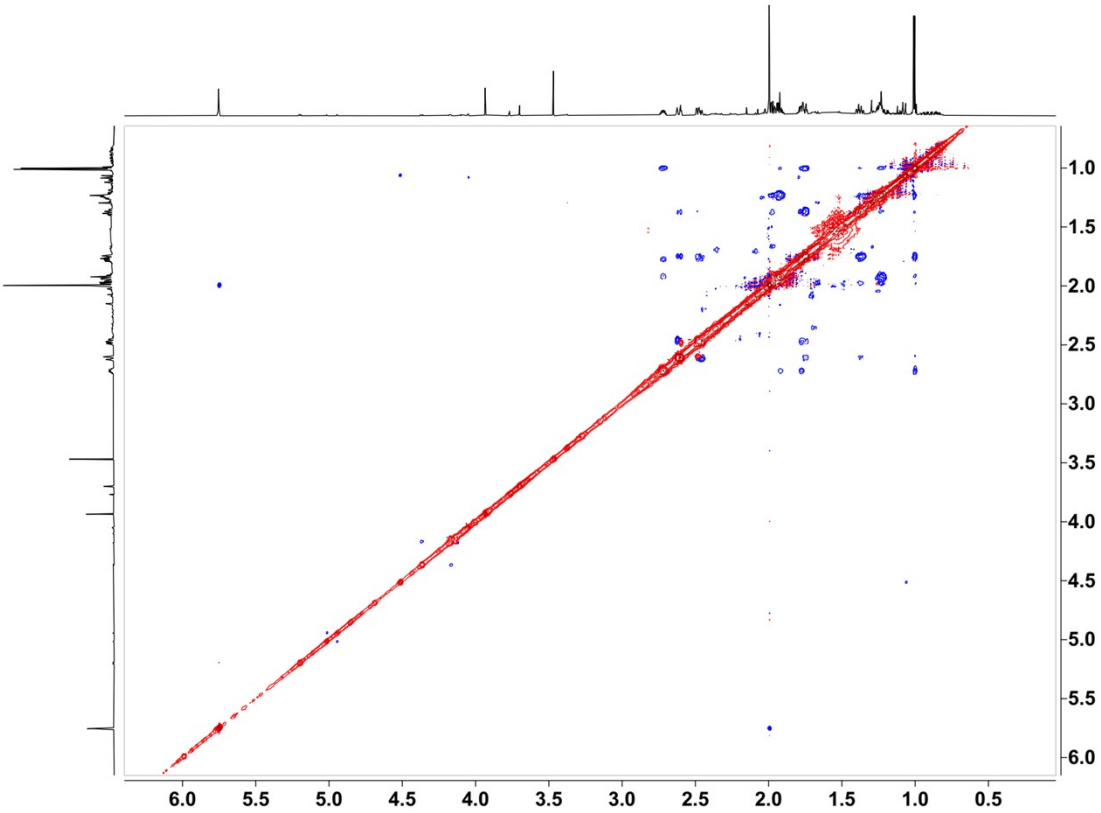
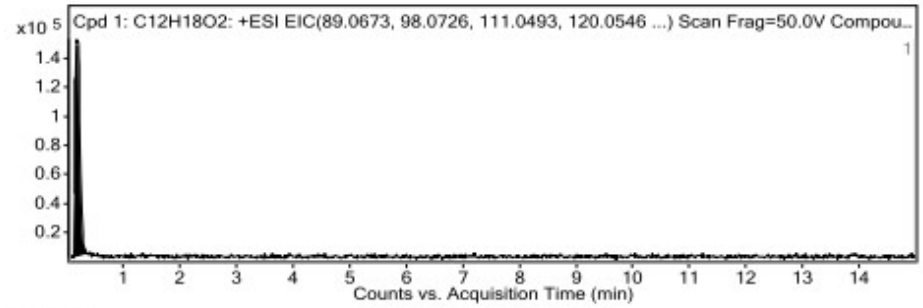


Figure S42: NOESY spectrum of compound **5** in $CDCl_3$ (800 MHz)

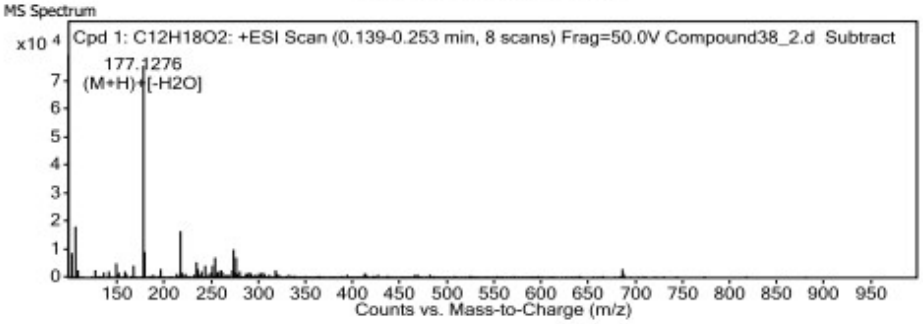
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C12H18O2	0.172	194.1309	75519	C12H18O2	194.1307	1.08

Compound Label	RT	Algorithm	Mass
Cpd 1: C12H18O2	0.172	Find By Formula	194.1309

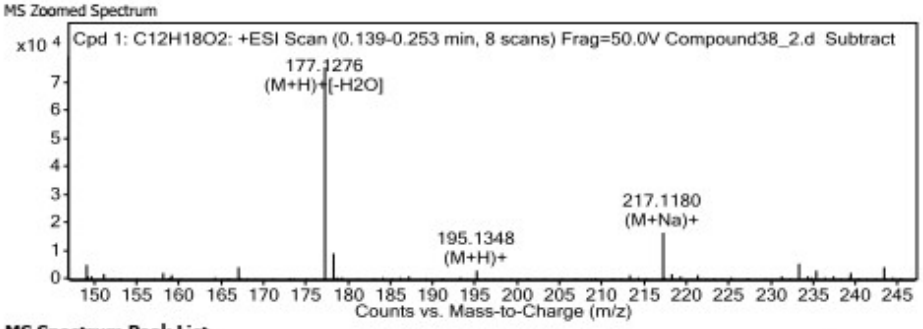


MS Spectrum



Qualitative Compound Report

MS Zoomed Spectrum



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
175.9558				475		
177.1276	177.1274	1.32		75519	C12 H17 O	(M+H)+[-H2O]
178.1305	178.1308	-1.61		9340	C12 H17 O	(M+H)+[-H2O]
178.5861				769		
179.1338	179.1337	0.81		920	C12 H17 O	(M+H)+[-H2O]
195.1348	195.138	-15.98	1	3130	C12 H19 O2	(M+H)+
196.1376	196.1414	-19.43	1	600	C12 H19 O2	(M+H)+
199.1132	199.1093	19.45	1	55	C12 H16 Na O	(M+Na)+[-H2O]
217.118	217.1199	-8.99	1	16707	C12 H18 Na O2	(M+Na)+
218.121	218.1233	-10.69	1	2247	C12 H18 Na O2	(M+Na)+

--- End Of Report ---

Figure S43: MS spectrum of compound **5**

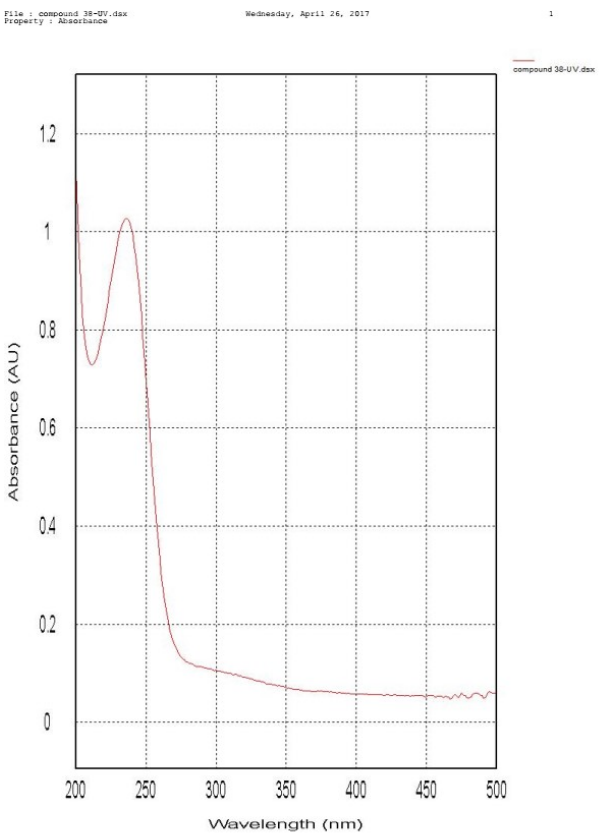


Figure S44: UV spectrum of compound **5**

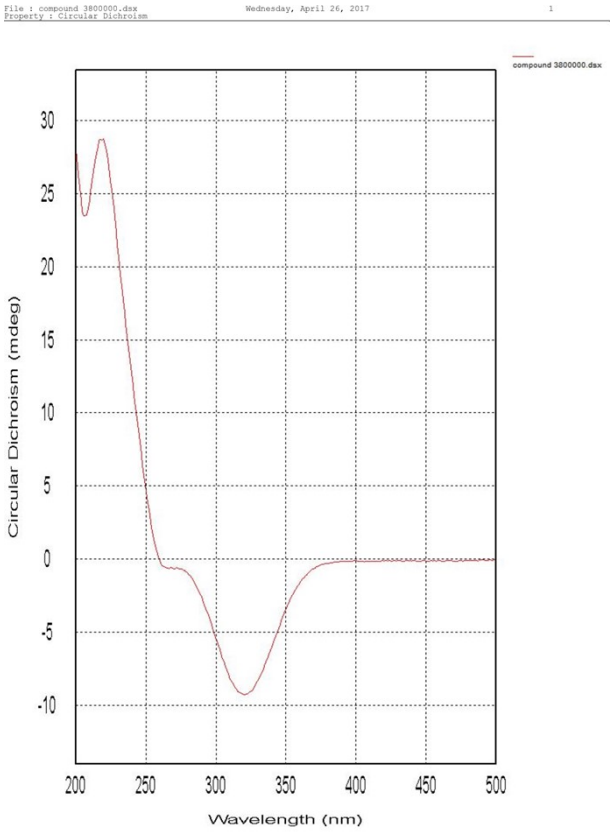


Figure S45: Experimental ECD spectrum of compound **5**

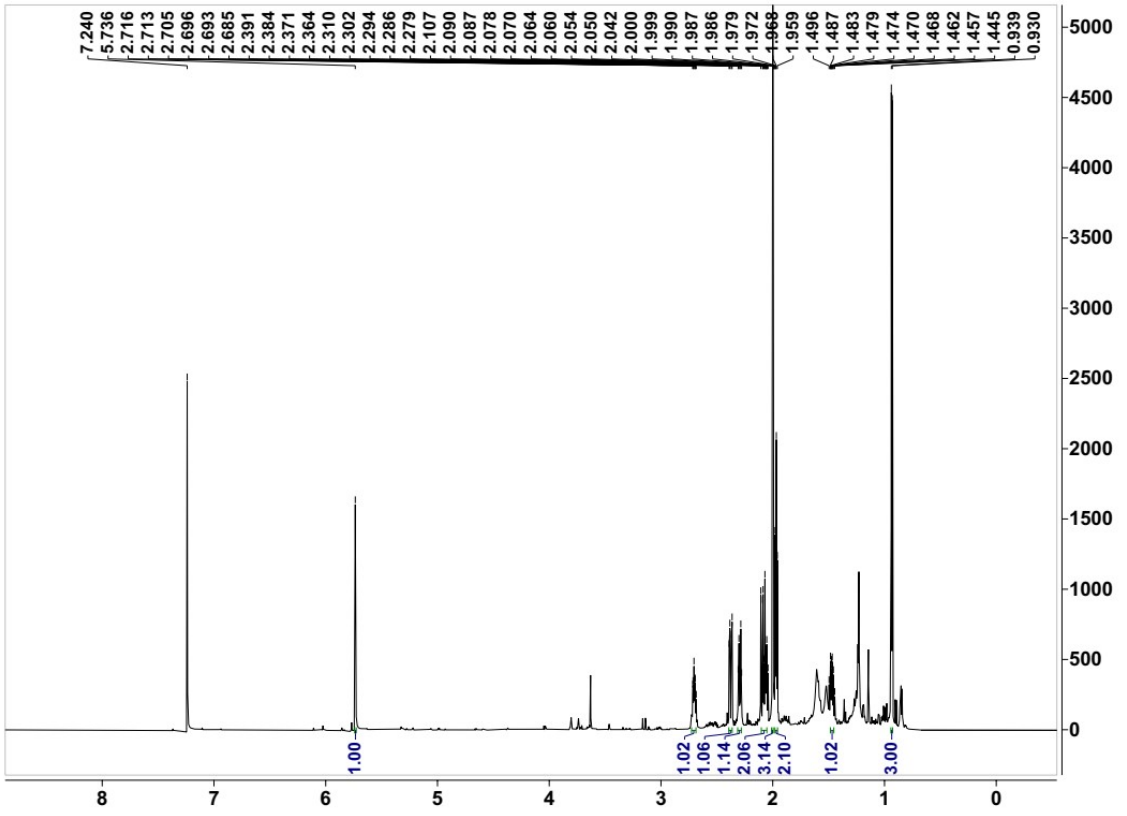


Figure S46: ^{1}H NMR spectrum of compound **6** in $CDCl_3$ (800 MHz)

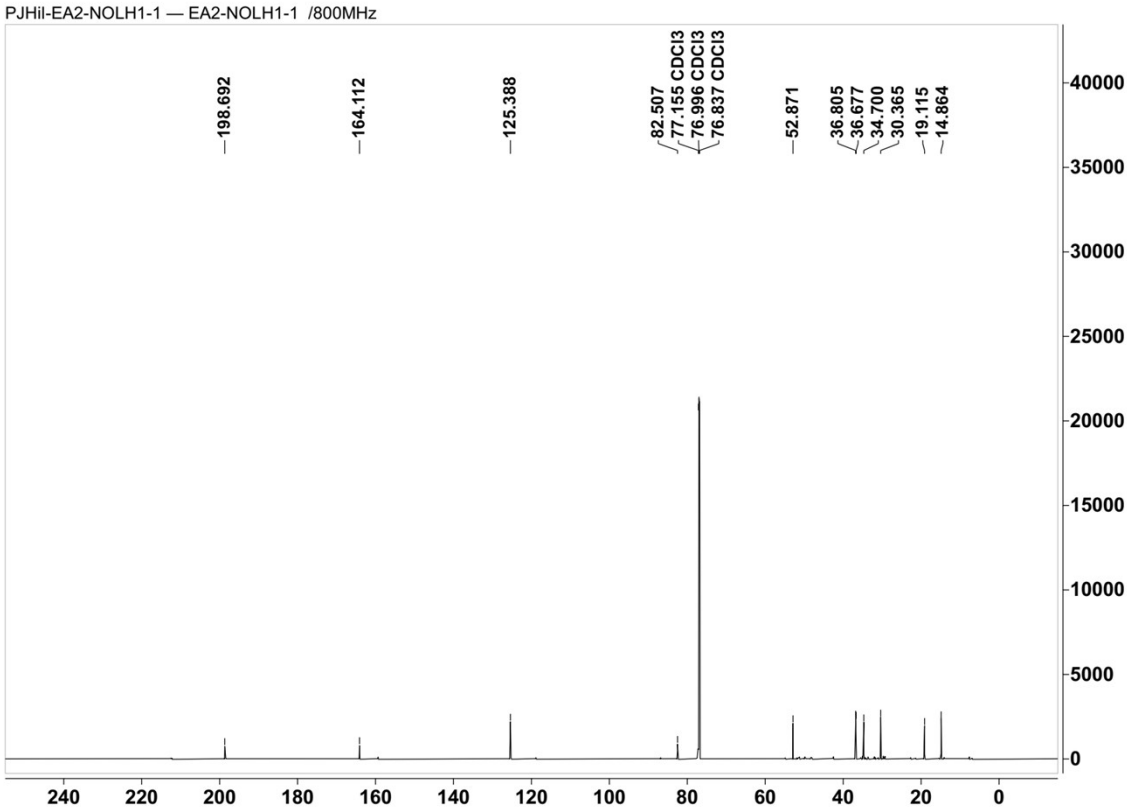


Figure S47: ^{13}C NMR spectrum of compound **6** in $CDCl_3$ (800 MHz)

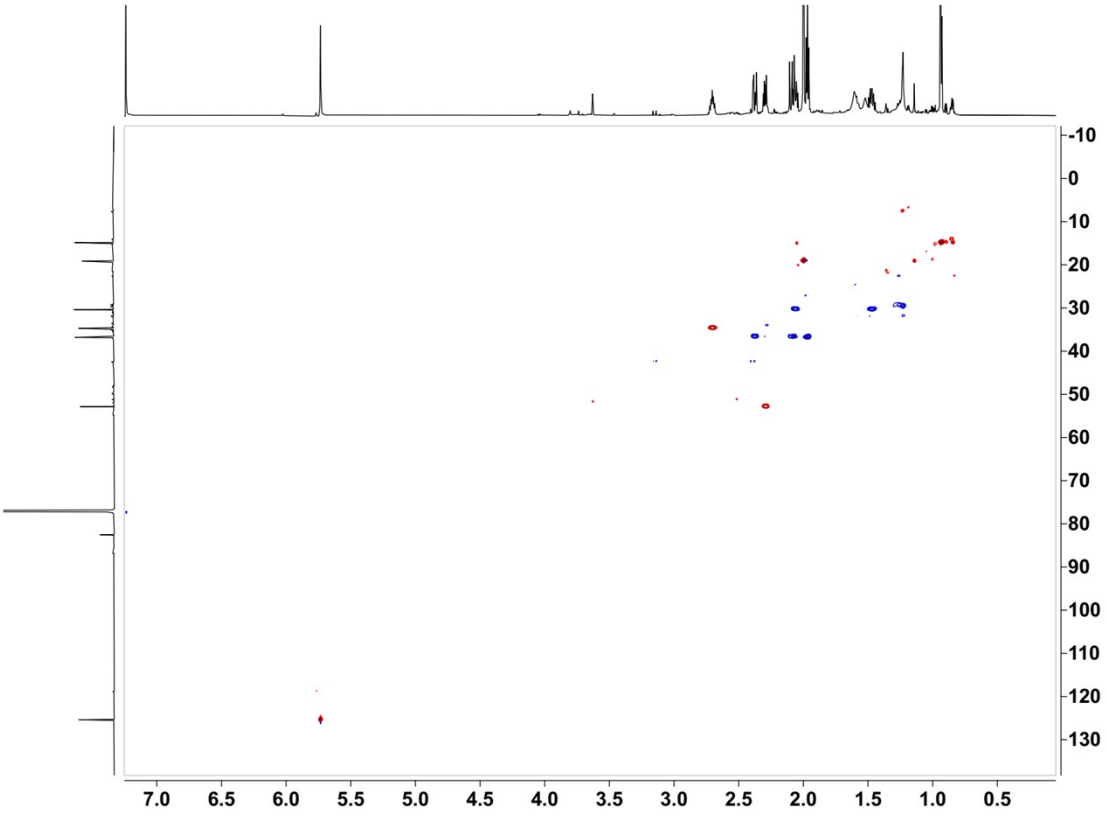


Figure S48: HSQC spectrum of compound **6** in $CDCl_3$ (800 MHz)

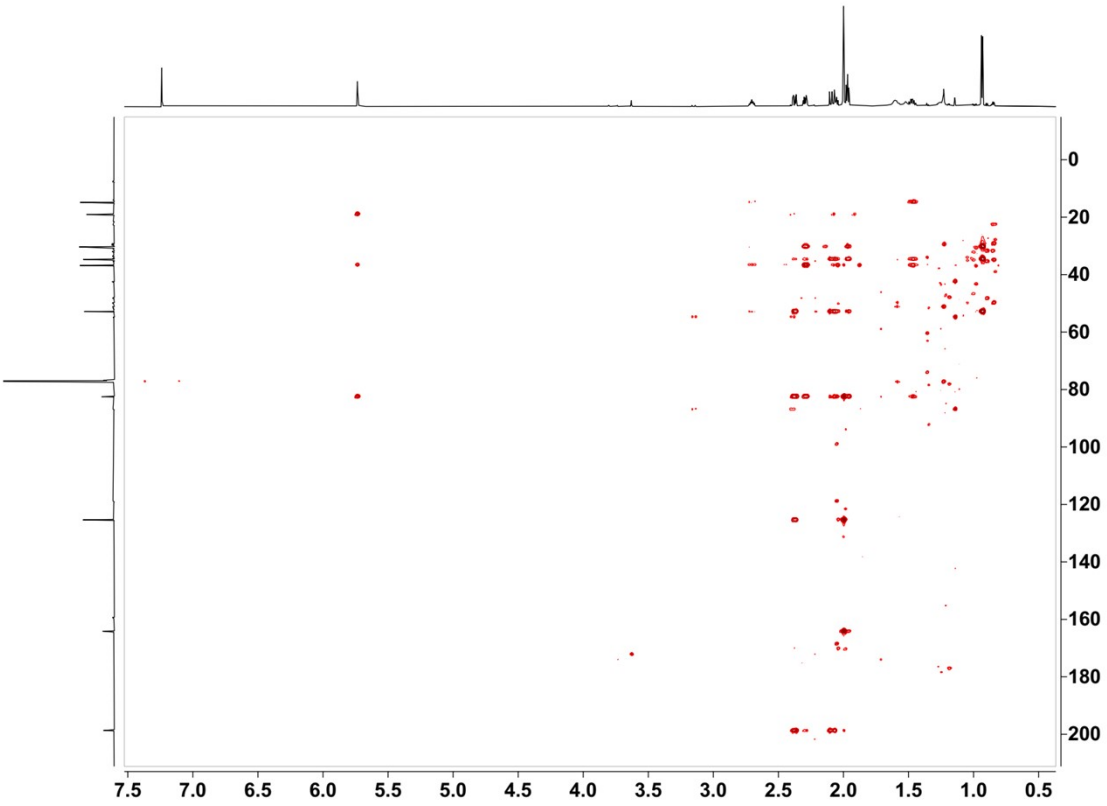


Figure S49: HMBC spectrum of compound **6** in $CDCl_3$ (800 MHz)

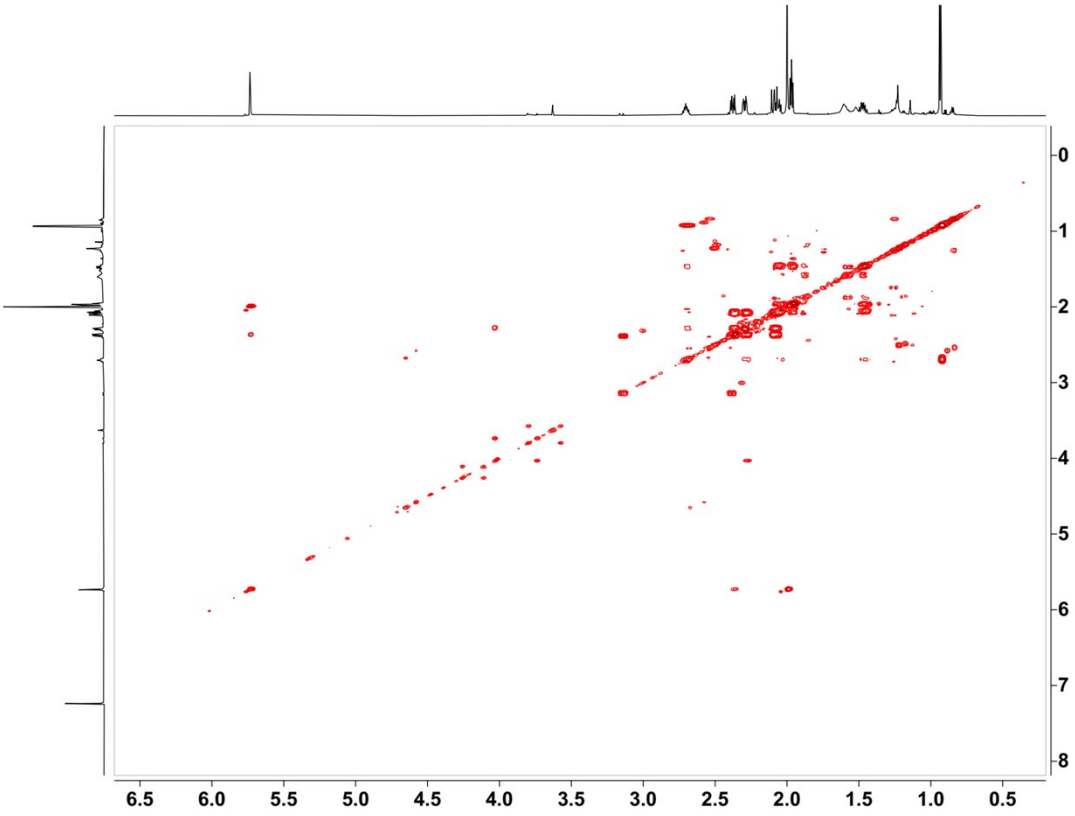


Figure S50: COSY spectrum of compound **6** in $CDCl_3$ (800 MHz)

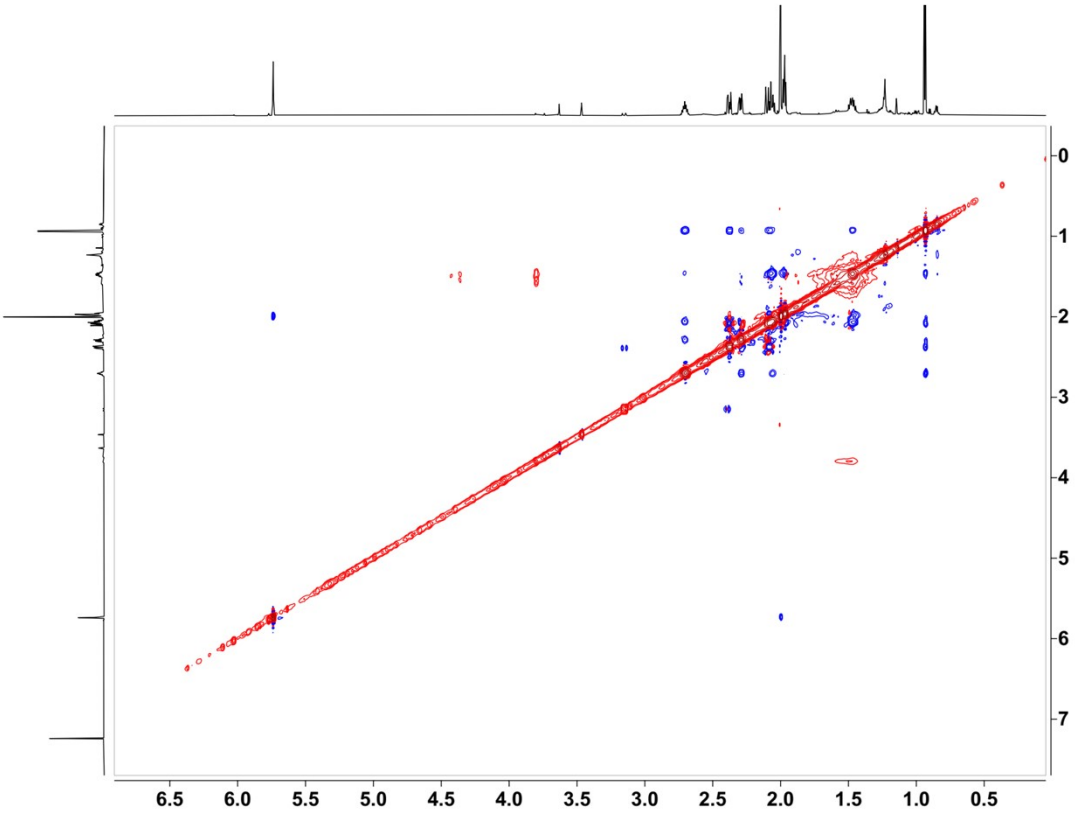
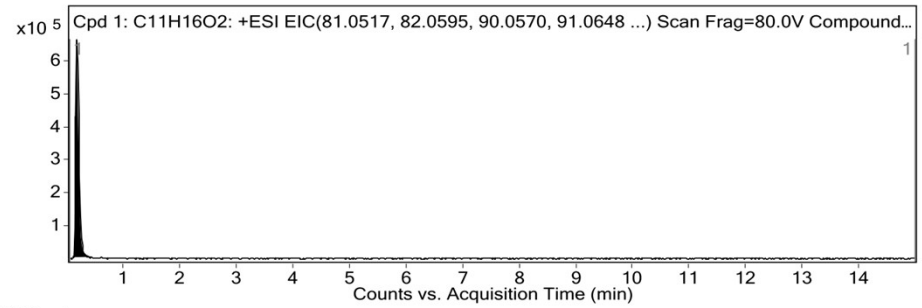


Figure S51: NOESY spectrum of compound **6** in $CDCl_3$ (800 MHz)

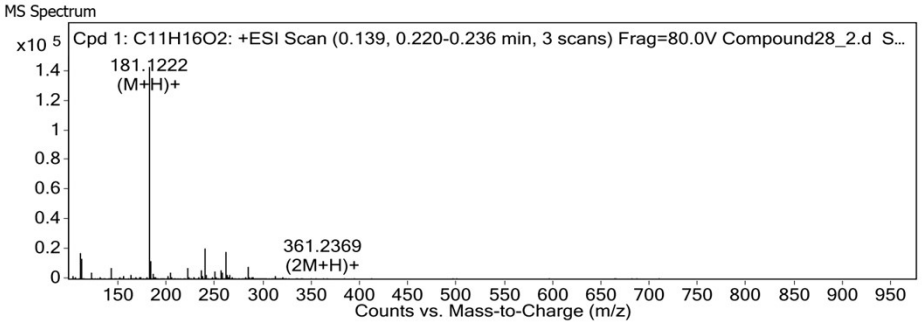
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C11H16O2	0.171	180.1149	142708	C11H16O2	180.115	-0.7

Compound Label	RT	Algorithm	Mass
Cpd 1: C11H16O2	0.171	Find By Formula	180.1149

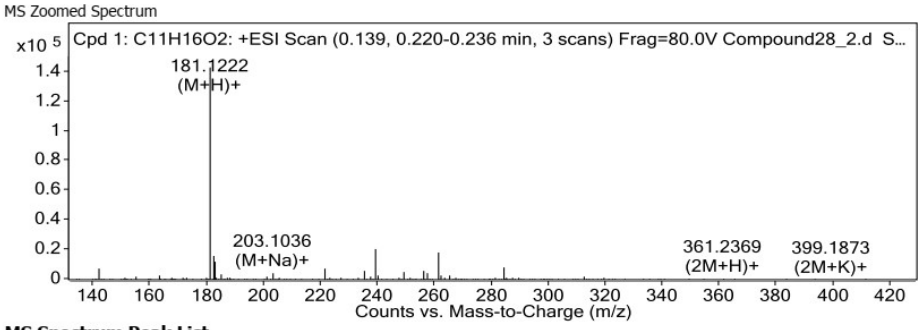


MS Spectrum



Qualitative Compound Report

MS Zoomed Spectrum



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
163.1154	163.1117	22.51	1	3288	C11 H15 O	(M+H)+[-H2O]
180.1011	180.1145	-74.22		374	C11 H16 O2	M*+
181.1222	181.1223	-0.7		142708	C11 H17 O2	(M+H)+
185.0813	185.0937	-66.99		209	C11 H14 Na O	(M+Na)+[-H2O]
201.0628	201.0676	-24.15	1	535	C11 H14 K O	(M+K)+[-H2O]
203.1036	203.1043	-3.16	1	4513	C11 H16 Na O2	(M+Na)+
219.0808	219.0782	11.82	1	268	C11 H16 K O2	(M+K)+
360.2197	360.2295	-27.3	1	194	C22 H32 O4	2M*+
361.2369	361.2373	-1.31	1	728	C22 H33 O4	(2M+H)+
383.2195	383.2193	0.52	1	519	C22 H32 Na O4	(2M+Na)+

--- End Of Report ---

Figure S52: MS spectrum of compound **6**

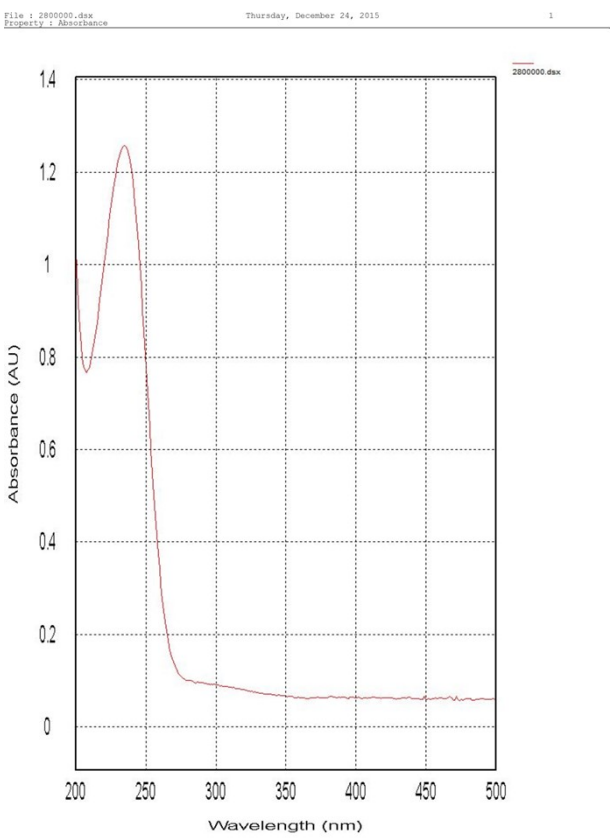


Figure S53: UV spectrum of compound **6**

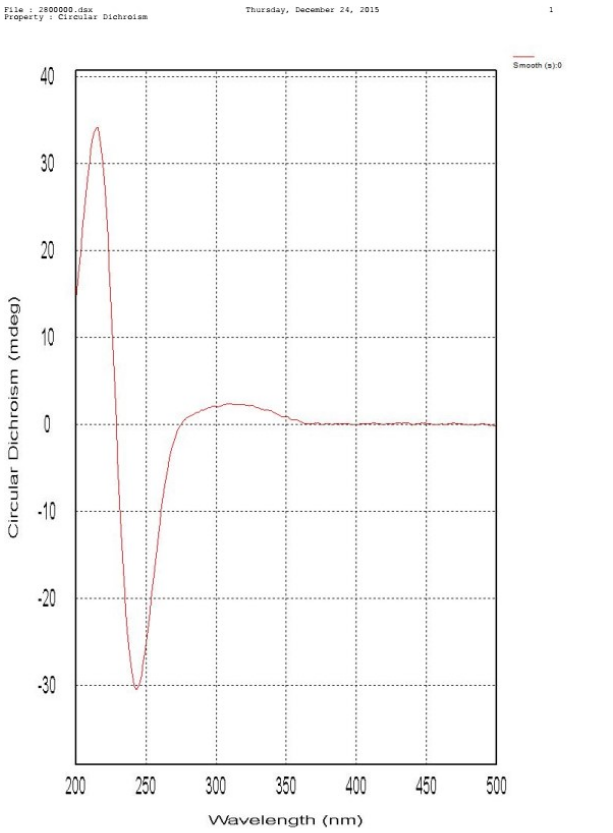


Figure S54: Experimental ECD spectrum of compound **6**

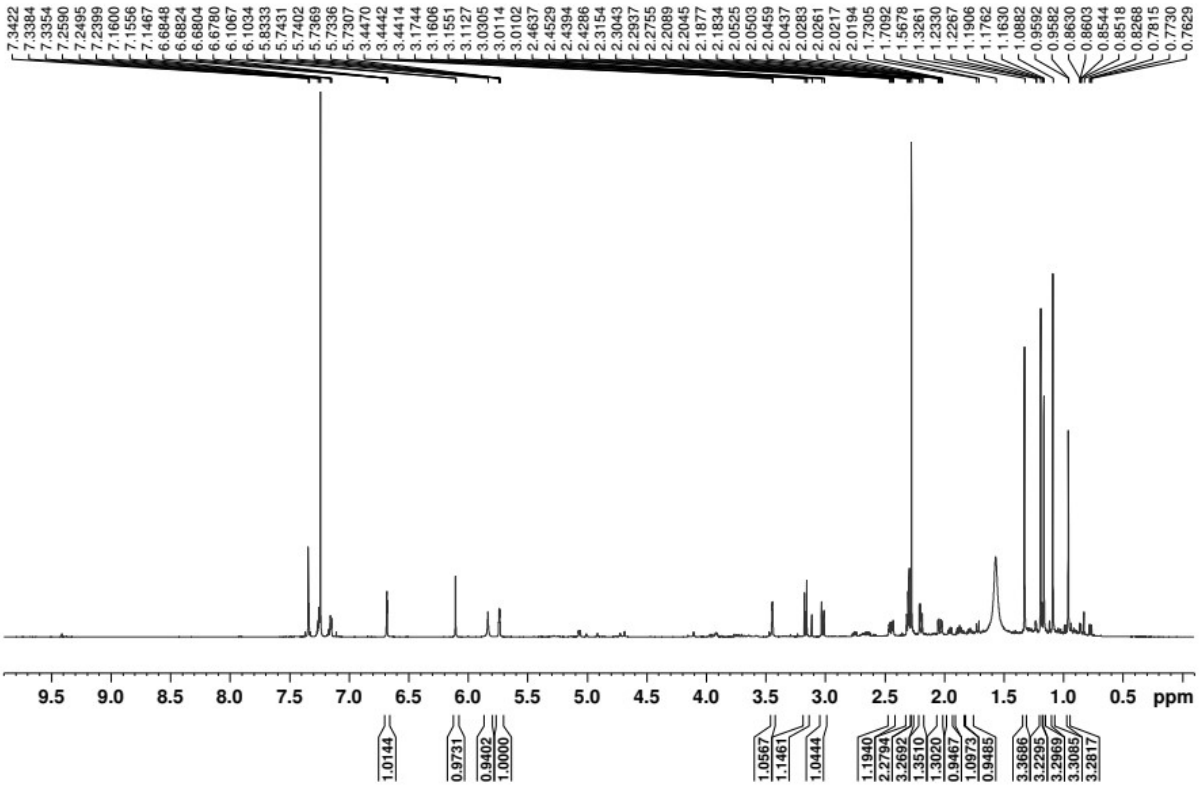


Figure S55: ^{1}H NMR spectrum of compound **7** in $CDCl_3$ (800 MHz)

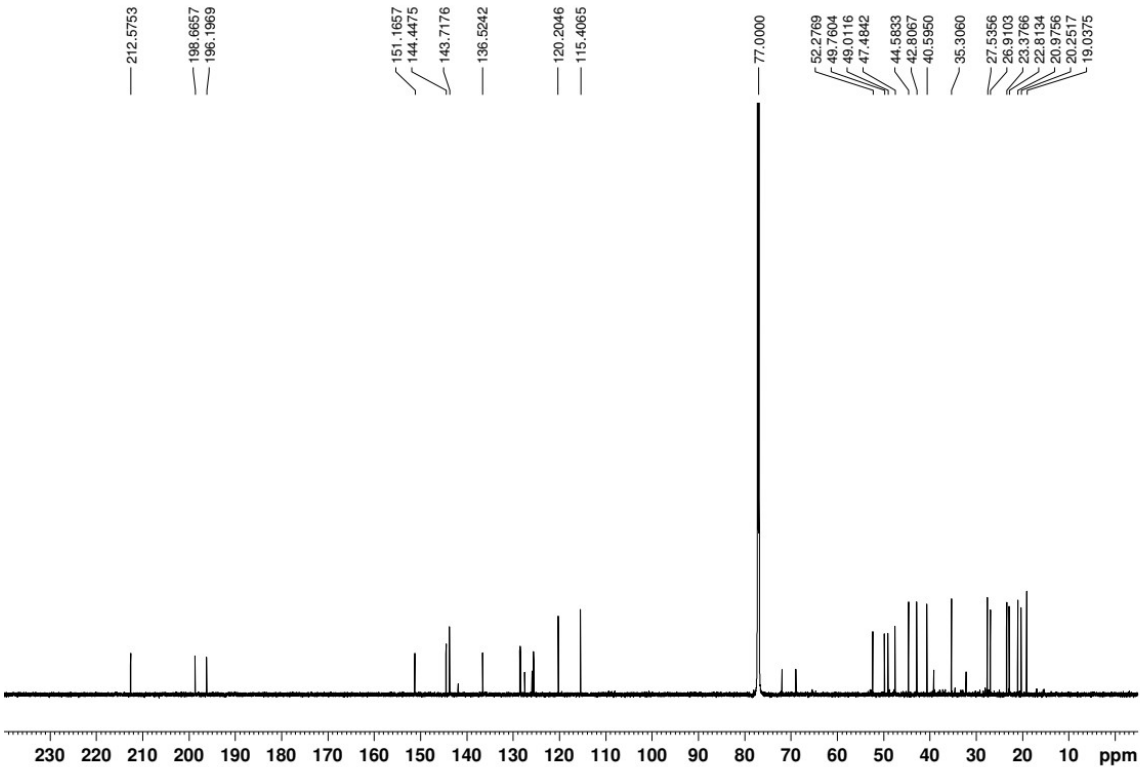


Figure S56: ^{13}C NMR spectrum of compound **7** in $CDCl_3$ (800 MHz)

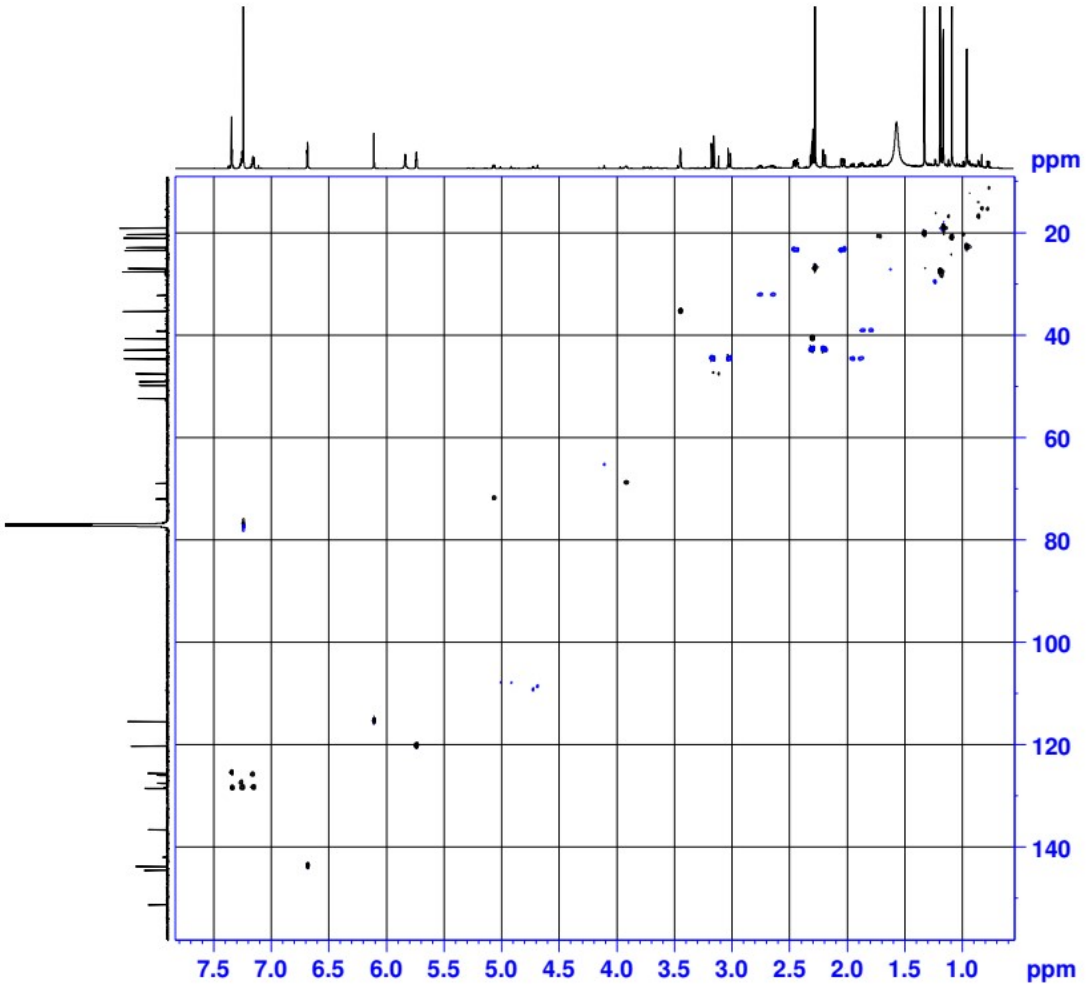


Figure S57: HSQC spectrum of compound **7** in $CDCl_3$ (800 MHz)

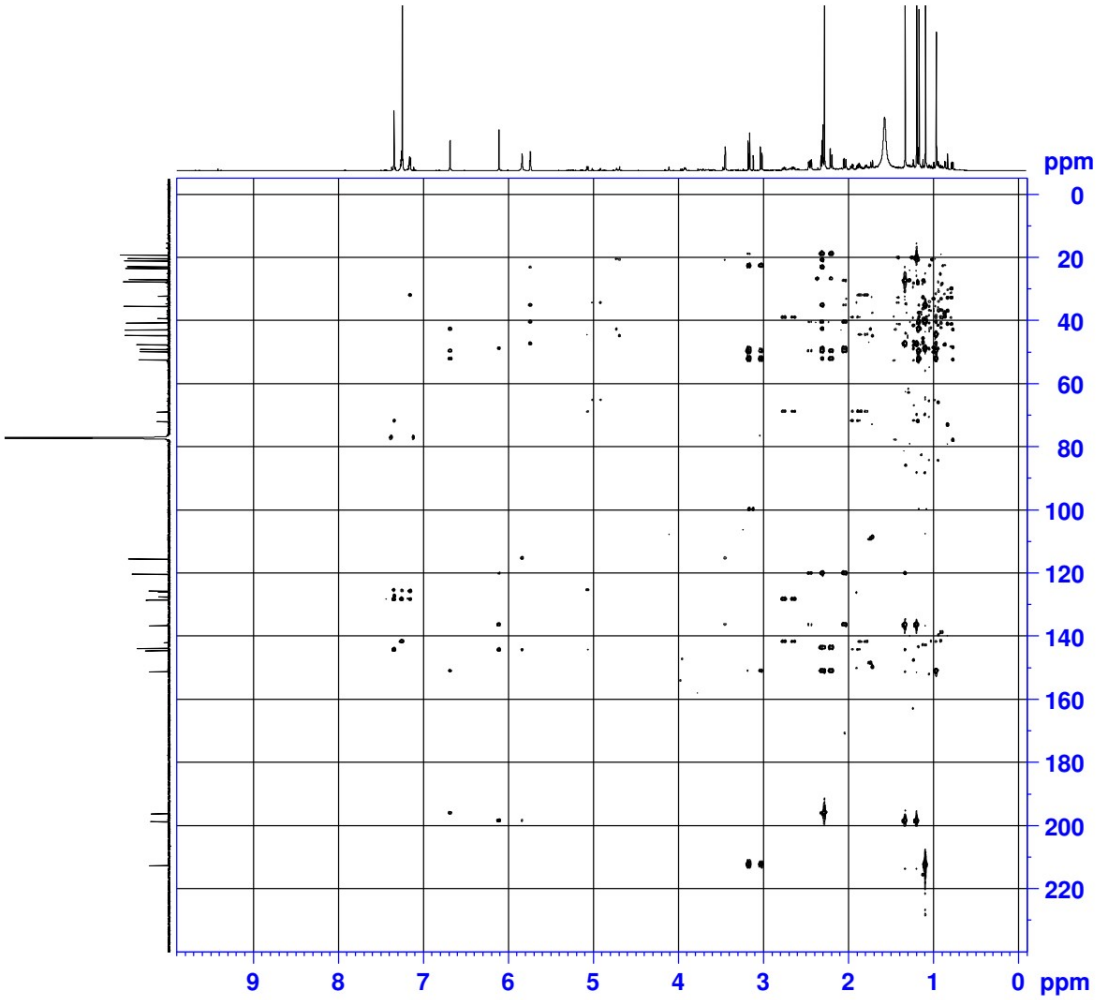


Figure S58: HMBC spectrum of compound **7** in $CDCl_3$ (800 MHz)

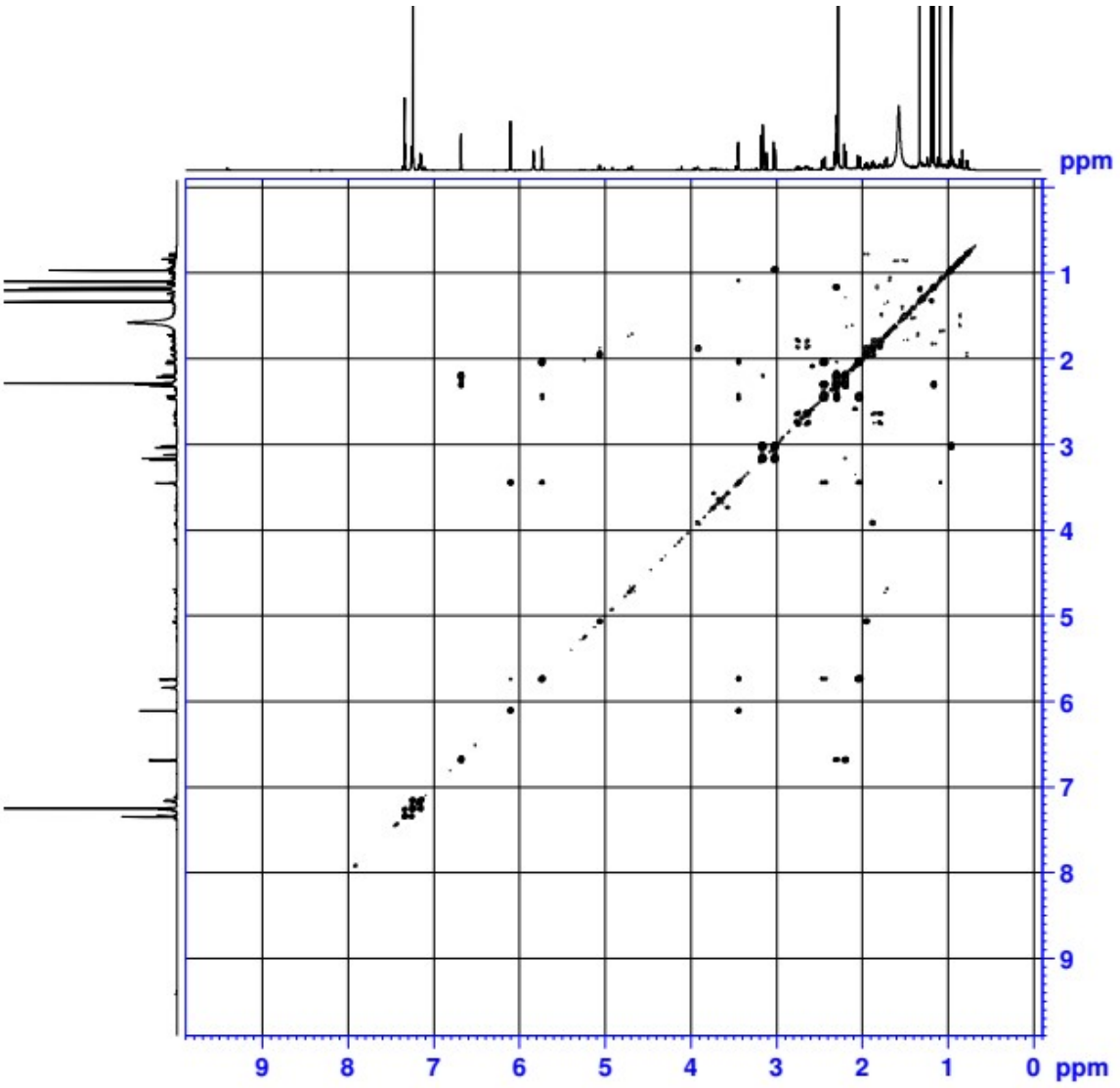


Figure S59: COSY spectrum of compound **7** in $CDCl_3$ (800 MHz)

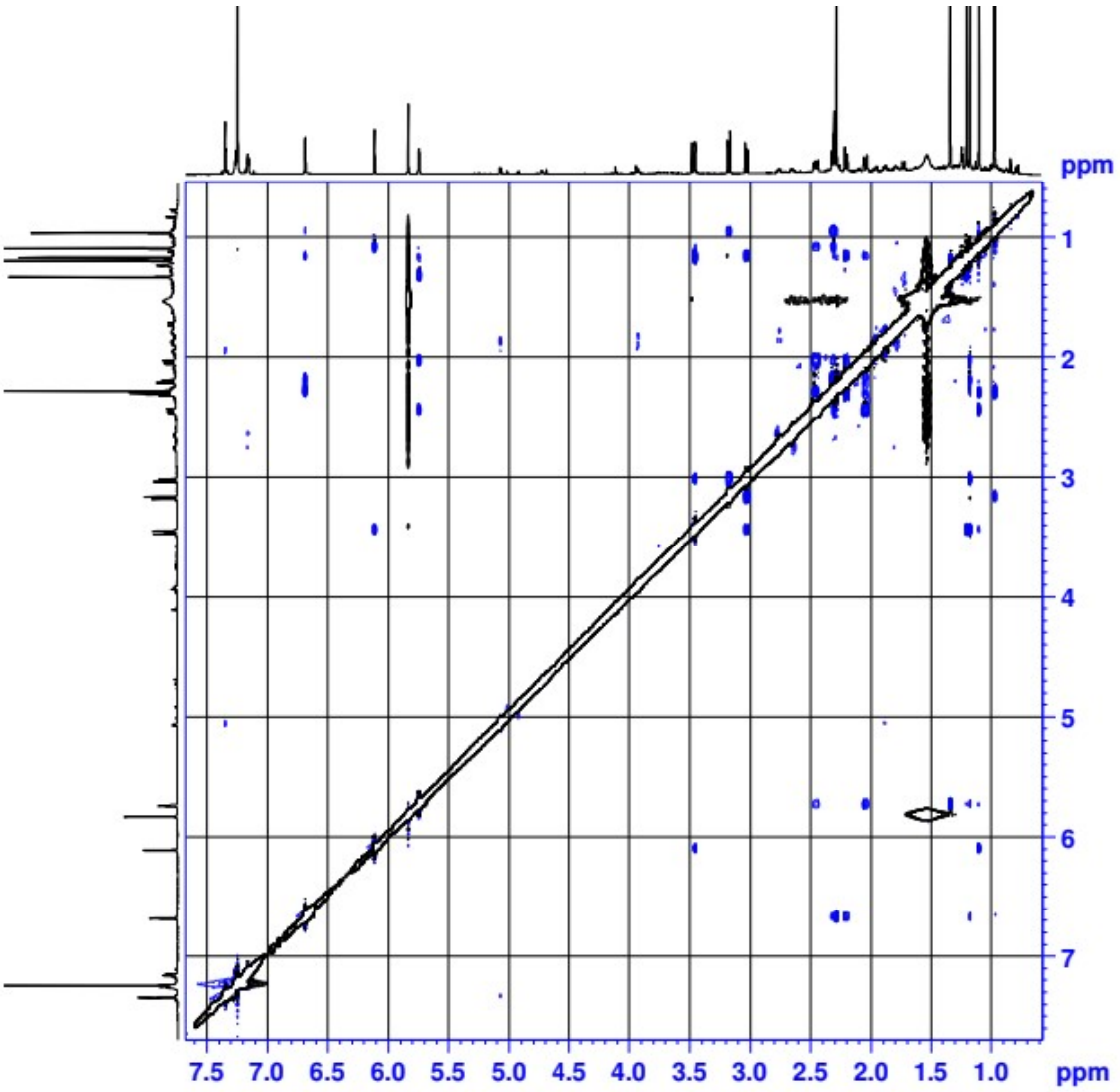
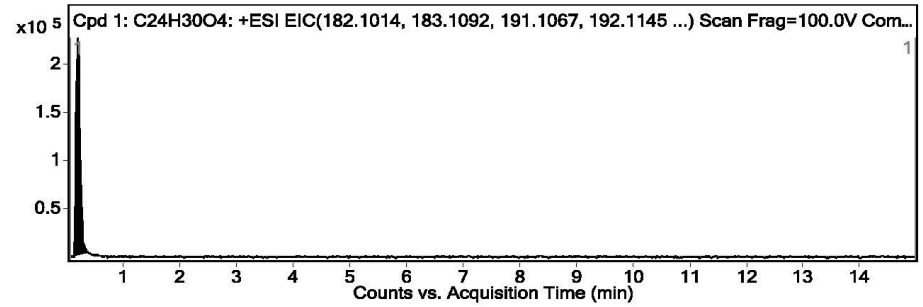


Figure S60: NOESY spectrum of compound **7** in $CDCl_3$ (800 MHz)

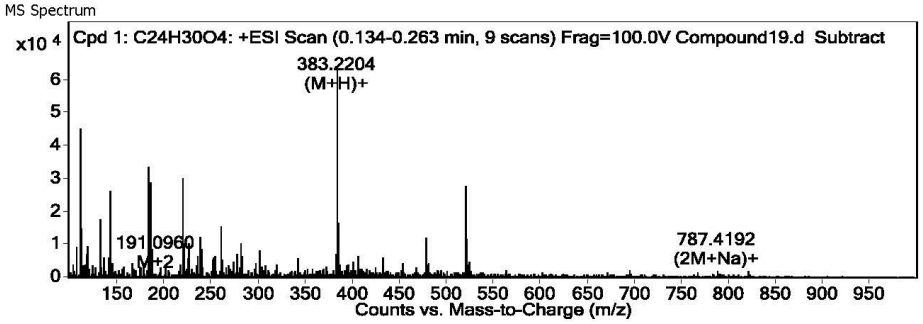
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)
Cpd 1: C24H30O4	0.182	382.2131	64286	C24H30O4	382.2144	-3.31

Compound Label	RT	Algorithm	Mass
Cpd 1: C24H30O4	0.182	Find By Formula	382.2131

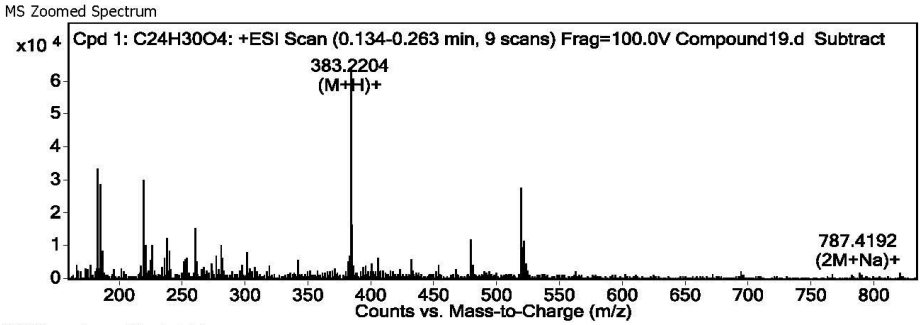


MS Spectrum



Qualitative Compound Report

MS Zoomed Spectrum



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
191.096	191.1067	-55.89	2	1101	C24 H30 O4	M+2
209.1418	209.141	3.58	2	915	C24 H38 N2 O4	(M+2(NH4))+2
382.2131	382.2139	-2.12		7362	C24 H30 O4	M*+
383.2204	383.2217	-3.34		64286	C24 H31 O4	(M+H)+
387.2036	387.1931	27.16		1992	C24 H28 Na O3	(M+Na)+[-H2O]
400.2462	400.2482	-5.2	1	5036	C24 H34 N O4	(M+NH4)+
405.2043	405.2036	1.64	1	6755	C24 H30 Na O4	(M+Na)+
765.4323	765.4361	-5.02	1	1658	C48 H61 O8	(2M+H)+
787.4192	787.418	1.44	1	2100	C48 H60 Na O8	(2M+Na)+
803.3983	803.392	7.93	1	1213	C48 H60 K O8	(2M+K)+

--- End Of Report ---

Figure S61: MS spectrum of compound **7**

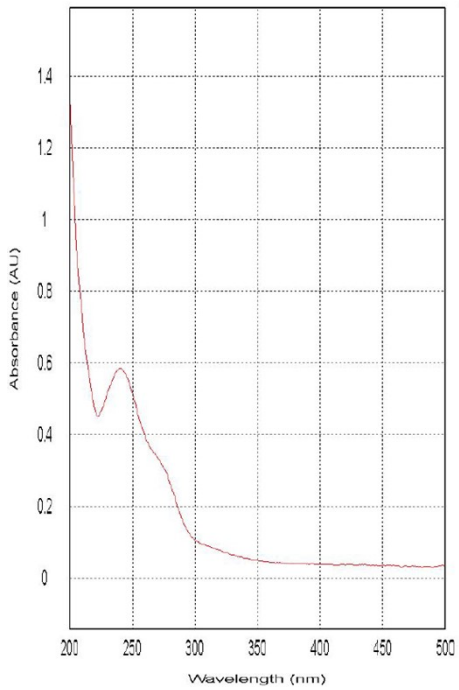


Figure S62: UV spectrum of compound **7**

Table S1. Calculated energy and Boltzmann distribution of compound **1** conformers

Conformers	B3-LYP/6-31G(d,p) Gibbs free energy (298.15 K)		
	Calculated Energy (Hartree)	Relative Energy (kcal/mol)	Boltzmann population (%)
1-1	-885.219441	0.00	10.1
1-2	-885.220566	-0.71	33.2
1-3	-885.218251	0.75	2.9
1-4	-885.220522	-0.68	31.7
1-5	-885.217545	1.19	1.4
1-6	-885.219257	0.12	8.3
1-7	-885.217878	0.98	1.9
1-8	-885.217658	1.12	1.5
1-9	-885.219021	0.26	6.5
1-10	-885.215936	2.20	0.2
1-11	-885.215727	2.33	0.2
1-12	-885.217186	1.42	0.9
1-13	-885.214478	3.11	0.1
1-14	-885.217365	1.30	1.1

Table S2. Calculated energy and Boltzmann distribution of compound **2** conformers

Conformers	B3-LYP/6-31G(d,p) Gibbs free energy (298.15 K)		
	Calculated Energy (Hartree)	Relative Energy (kcal/mol)	Boltzmann population (%)
2-1	-997.300119	0.00	41.2
2-2	-997.300454	-0.21	58.8

Table S3. Calculated energy and Boltzmann distribution of compound **3** conformers

Conformers	B3-LYP/6-31G(d,p) Gibbs free energy (298.15 K)		
	Calculated Energy (Hartree)	Relative Energy (kcal/mol)	Boltzmann population (%)
3-1	-811.191694	0.00	6.3
3-2	-811.192087	-0.25	9.6
3-3	-811.191096	0.38	3.4
3-4	-811.192485	-0.50	14.6
3-5	-811.192292	-0.38	11.9
3-6	-811.191537	0.10	5.4
3-7	-811.192803	-0.70	20.5
3-8	-811.193014	-0.83	25.6
3-9	-811.187355	2.72	0.1
3-10	-811.190739	0.60	2.3
3-11	-811.188199	2.19	0.2
3-12	-811.186854	3.04	0.00
3-13	-811.186101	3.51	0.00
3-14	-811.186448	3.29	0.00
3-15	-811.187265	2.78	0.01

Table S4. Calculated energy and Boltzmann distribution of compound **4** conformers

Conformers	B3-LYP/6-31G(d,p) Gibbs free energy (298.15 K)		
	Calculated Energy (Hartree)	Relative Energy (kcal/mol)	Boltzmann population (%)
4-1	-736.042562	0.00	56.4
4-2	-736.042200	0.23	38.5
4-3	-736.040131	1.53	4.3
4-4	-736.038480	2.56	0.7
4-5	-736.036437	3.84	0.1

Table S5. Calculated energy and Boltzmann distribution of compound **5** conformers

Conformers	B3-LYP/6-31G(d,p) Gibbs free energy (298.15 K)		
	Calculated Energy (Hartree)	Relative Energy (kcal/mol)	Boltzmann population (%)
5-1	-618.1680236	0.00	46.3
5-2	-618.1634657	2.86	0.4
5-3	-618.1639011	2.59	0.6
5-4	-618.1650828	1.85	2.1
5-5	-618.1631341	3.07	0.3
5-6	-618.1631648	3.05	0.3
5-7	-618.1680278	0.00	46.6
5-8	-618.1613847	4.17	0.0
5-9	-618.1603176	4.84	0.0
5-10	-618.1650594	1.86	2.0
5-11	-618.1632614	2.99	0.3
5-12	-618.1645279	2.19	1.1

Table S6. Calculated energy and Boltzmann distribution of compound **6** conformers

Conformers	B3-LYP/6-31G(d,p) Gibbs free energy (298.15 K)		
	Calculated Energy (Hartree)	Relative Energy (kcal/mol)	Boltzmann population (%)
6-1	-578.896092	0.00	86.3
6-2	-578.893187	1.82	4.0
6-3	-578.893831	1.42	7.9
6-4	-578.891596	2.82	0.7
6-5	-578.889059	4.41	0.1
6-6	-578.889994	3.83	0.1
6-7	-578.891598	2.82	0.7
6-8	-578.889727	3.99	0.1
6-9	-578.889340	4.24	0.1

Table S7. Crystal data and structure refinement for **7**

Empirical formula	$C_{25}H_{34}O_5$
Formula weight	414.52
Temperature/K	99.8(7)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	10.0589(2)
b/Å	14.2921(3)
c/Å	15.1181(3)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2173.43(8)
Z	4
ρ_{calc}g/cm^3	1.267
μ/mm^{-1}	0.697
F(000)	896.0
Crystal size/mm^3	0.15 × 0.04 × 0.02
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.514 to 153.356
Index ranges	$-12 \leq h \leq 12$, $-17 \leq k \leq 15$, $-19 \leq l \leq 19$
Reflections collected	21475
Independent reflections	4530 [R_{int} = 0.0390, R_{sigma} = 0.0242]
Data/restraints/parameters	4530/0/280
Goodness-of-fit on F^2	1.067
Final R indexes [I>=2σ (I)]	R_1 = 0.0369, wR_2 = 0.0976
Final R indexes [all data]	R_1 = 0.0382, wR_2 = 0.0987
Largest diff. peak/hole / e Å^{-3}	0.22/-0.24
Flack parameter	-0.01(8)