Supplementary Material (SM)

Natural-product-inspired Design and Synthesis of Thiolated Coenzyme Q Analogs as Promising Agents against Gram-positive Bacterial Strains: Insights into Structure-activity Relationship, Activity Profile, Mode of Action, and Molecular Docking

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Contents

Code of Strains	Isolate	Specimens	MIC values (µg/mL)	
			CoQ1	CoQ2
S2	MRSA	Blood	39.06	39.06
S4	MRSA	Blood	39.06	39.06
S5	MRSA	Blood	19.53	19.53
S10	MRSA	Blood	19.53	19.53
S12	MRSA	Blood	19.53	19.53
S18	MRSA	Blood	19.53	19.53
SA1	MRSA	Blood	78.12	625.00
SA2	MRSA	Blood	39.06	78.12
SA3	MRSA	Blood	39.06	39.06
SA4	MRSA	Blood	19.53	19.53
SA5	MRSA	Blood	9.76	19.53
SA6	MRSA	Blood	9.76	19.53
SA11	MRSA	Blood	78.12	78.12
SA14	MRSA	Blood	19.53	19.53
SA15	MRSA	Blood	19.53	19.53
SA16	MRSA	Blood	39.06	78.12
SA17	MRSA	Blood	39.06	78.12
SA18	MRSA	Blood	39.06	78.12
SA19	MRSA	Blood	39.06	39.06
SA20	MRSA	Blood	19.53	19.53

Table S1. Properties and MIC results of the 20 clinically obtained MRSA

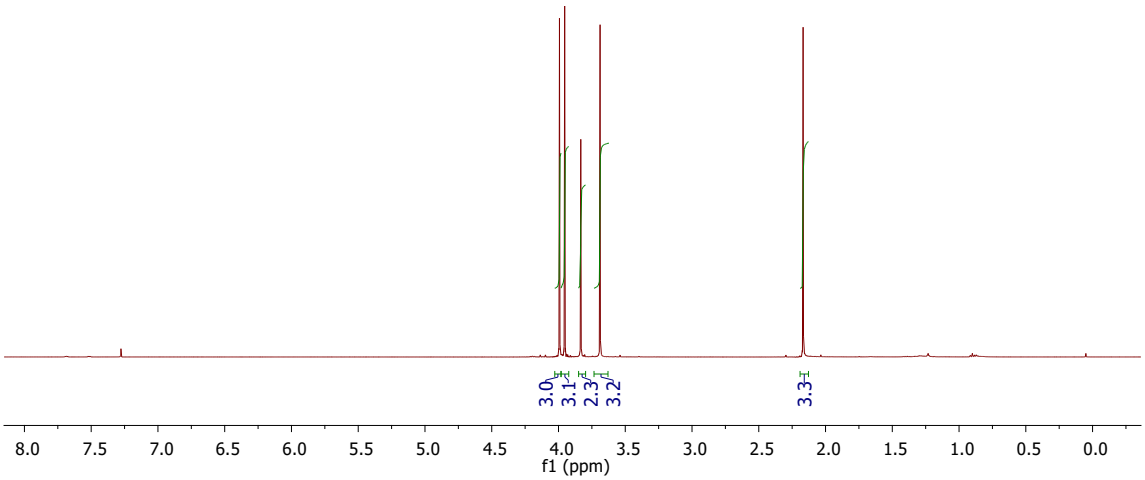

Figure S1: ^{1}H NMR (500 MHz) spectrum of the **CoQ1** in $CDCl_3$-*d1*

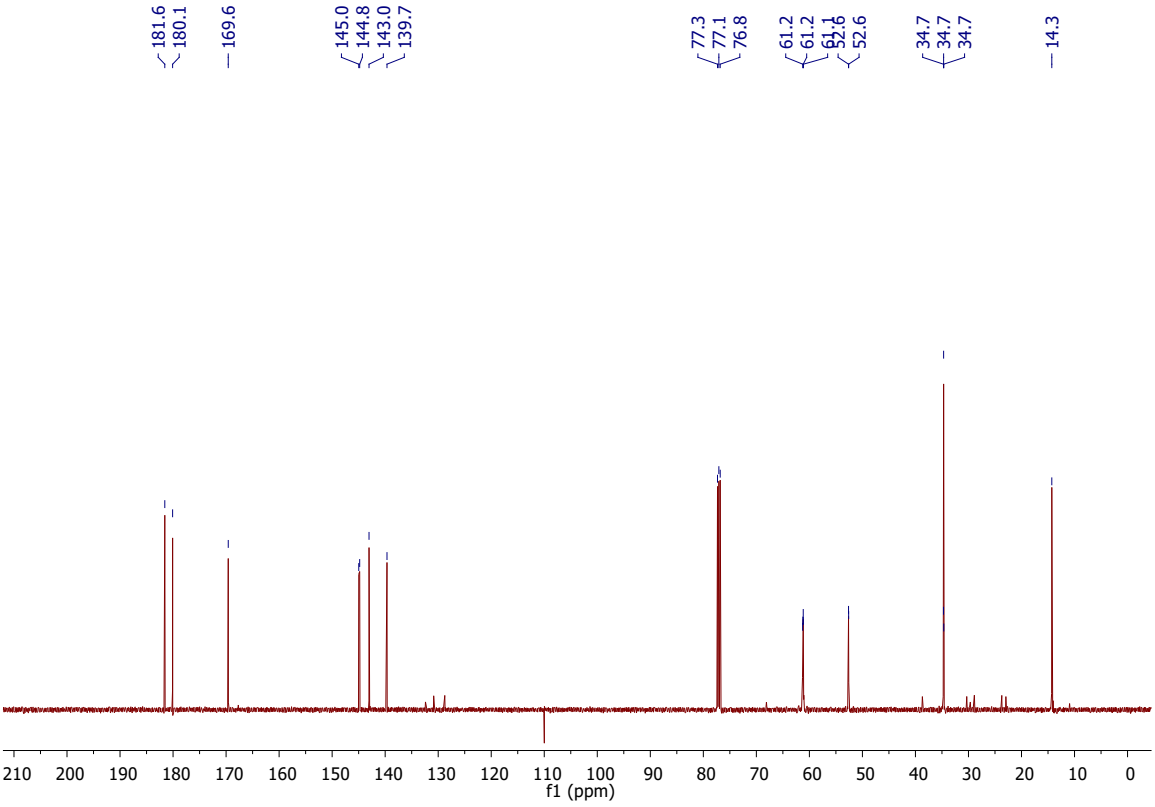

Figure S2: ^{13}C NMR (125 MHz) spectrum of the **CoQ1** in $CDCl_3$-*d1*

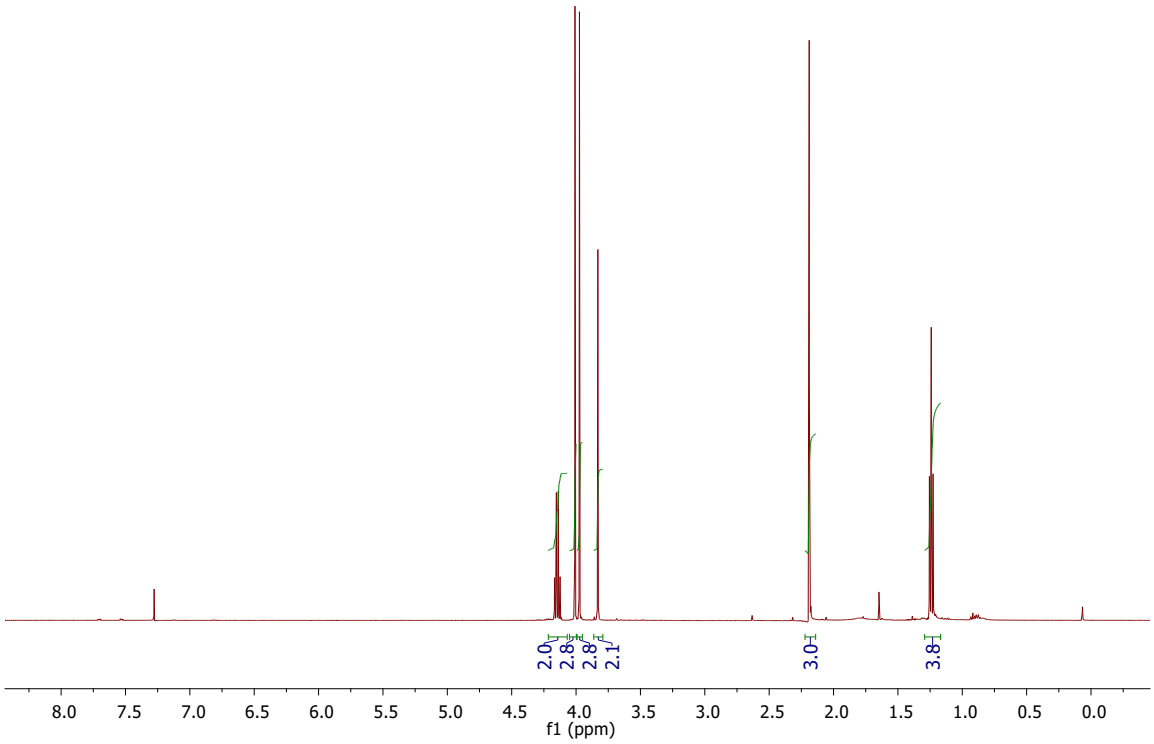

Figure S3: ^{1}H NMR (500 MHz) spectrum of the **CoQ2** in $CDCl_3$-*d1*

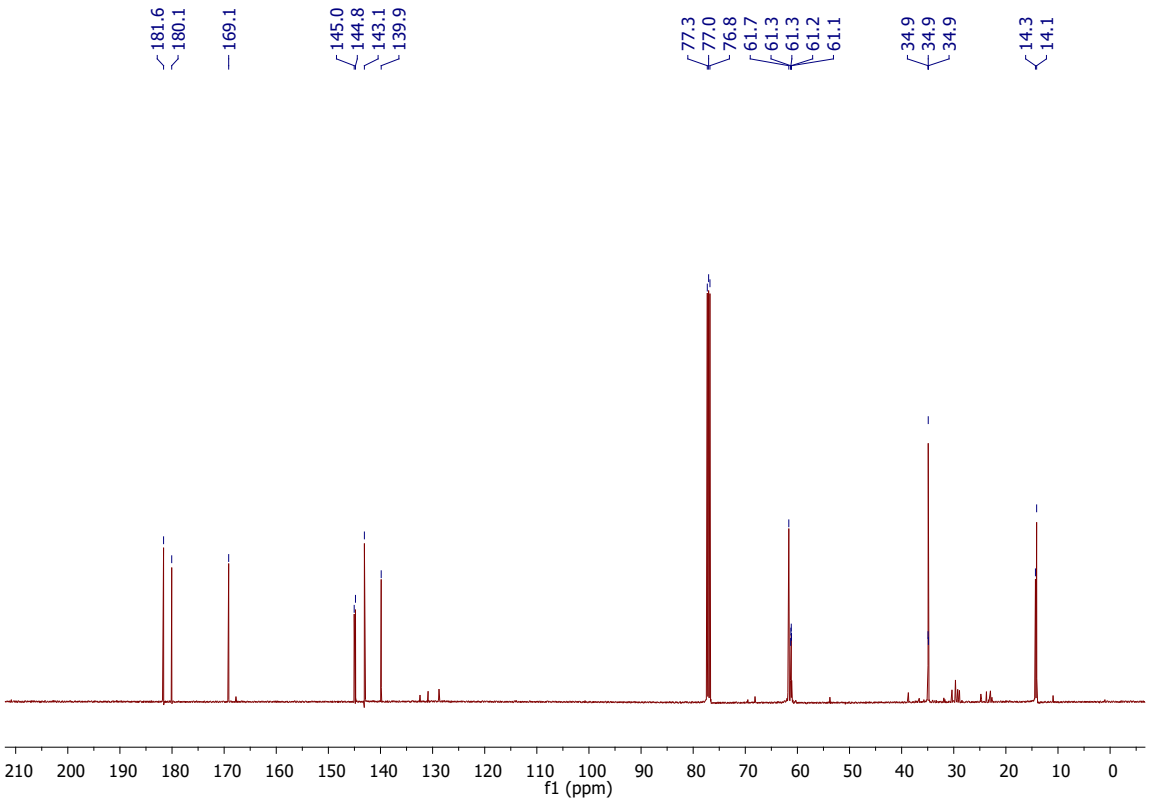

Figure S4: ^{13}C NMR (125 MHz) spectrum of the **CoQ2** in $CDCl_3$-*d1*

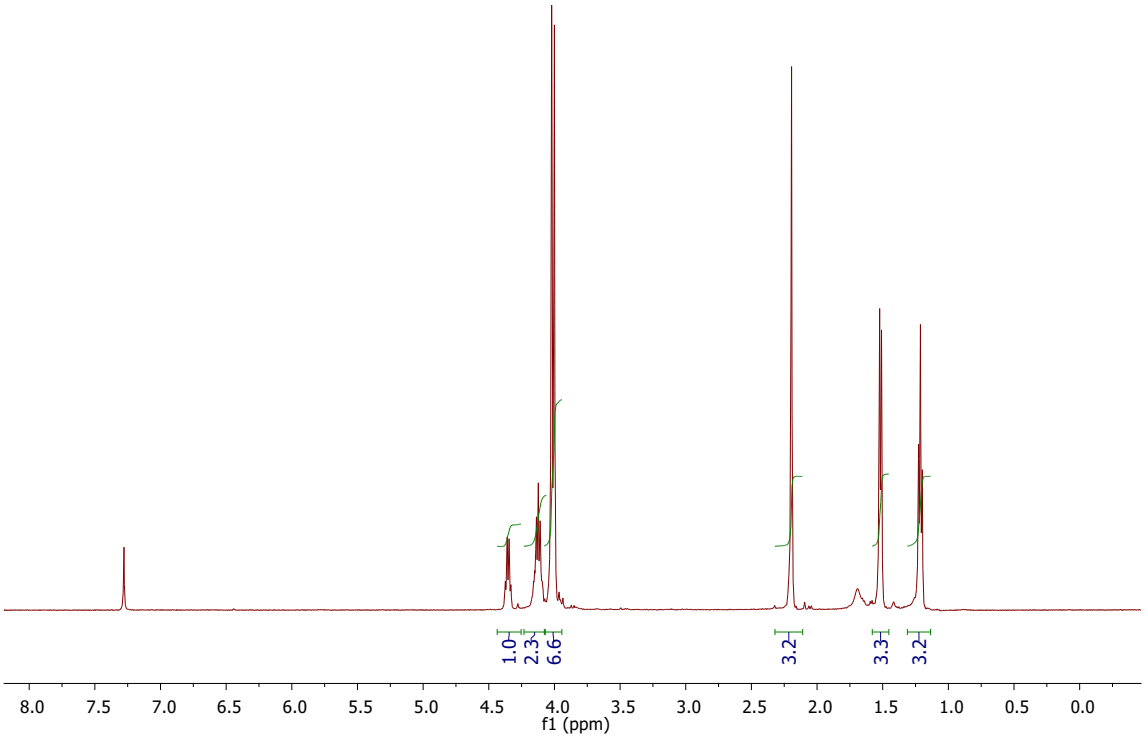

Figure S5: ^{1}H NMR (500 MHz) spectrum of the **CoQ3** in $CDCl_3$-*d1*

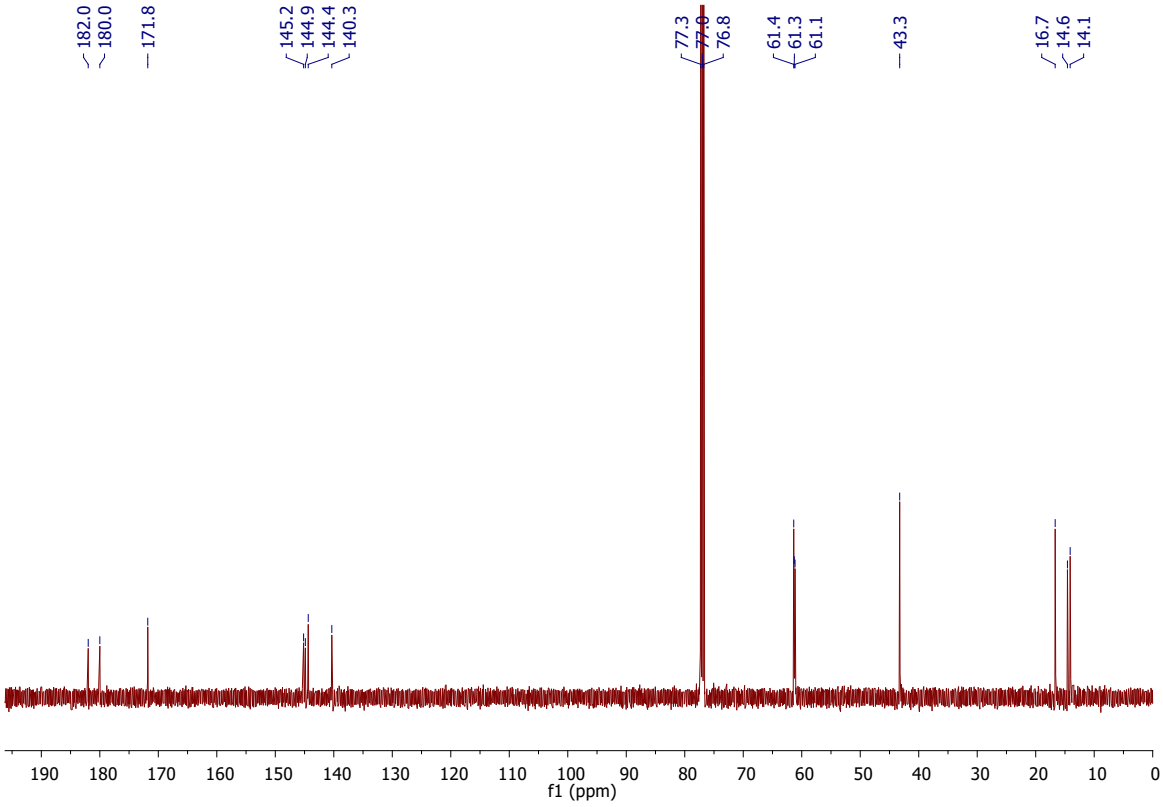

Figure S6: ^{13}C NMR (125 MHz) spectrum of the **CoQ3** in $CDCl_3$-*d1*

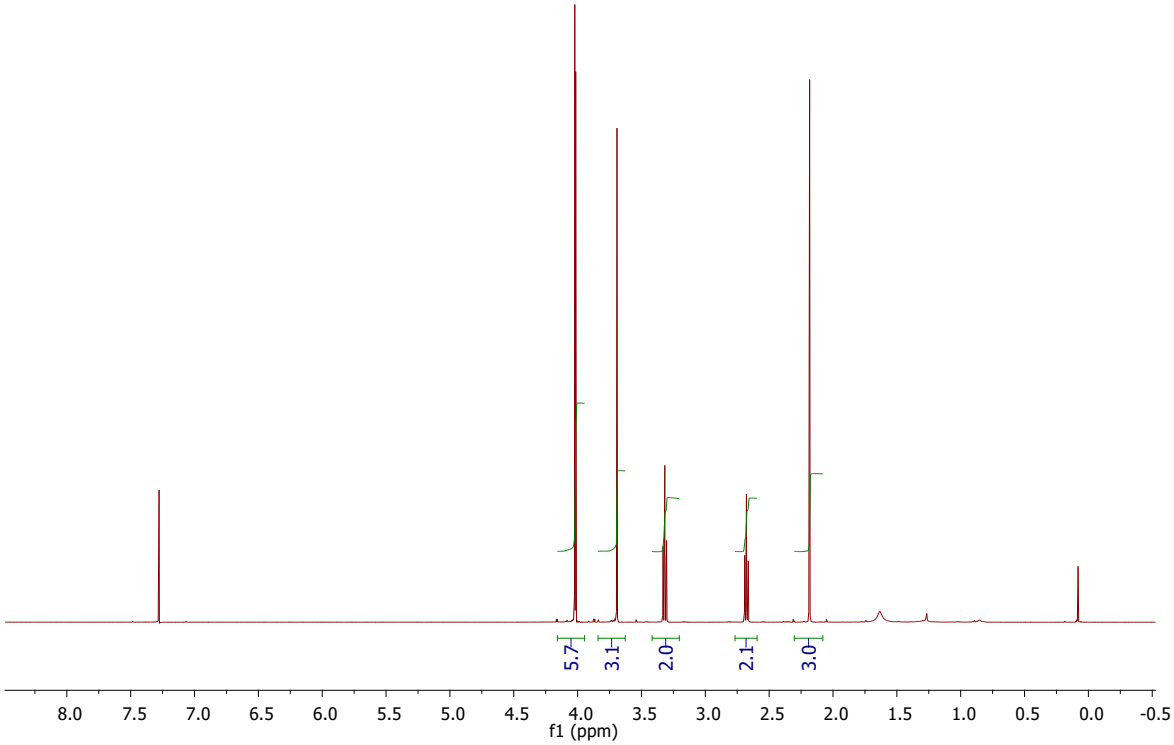

Figure S7: ^{1}H NMR (500 MHz) spectrum of the **CoQ4** in $CDCl_3$-*d1*

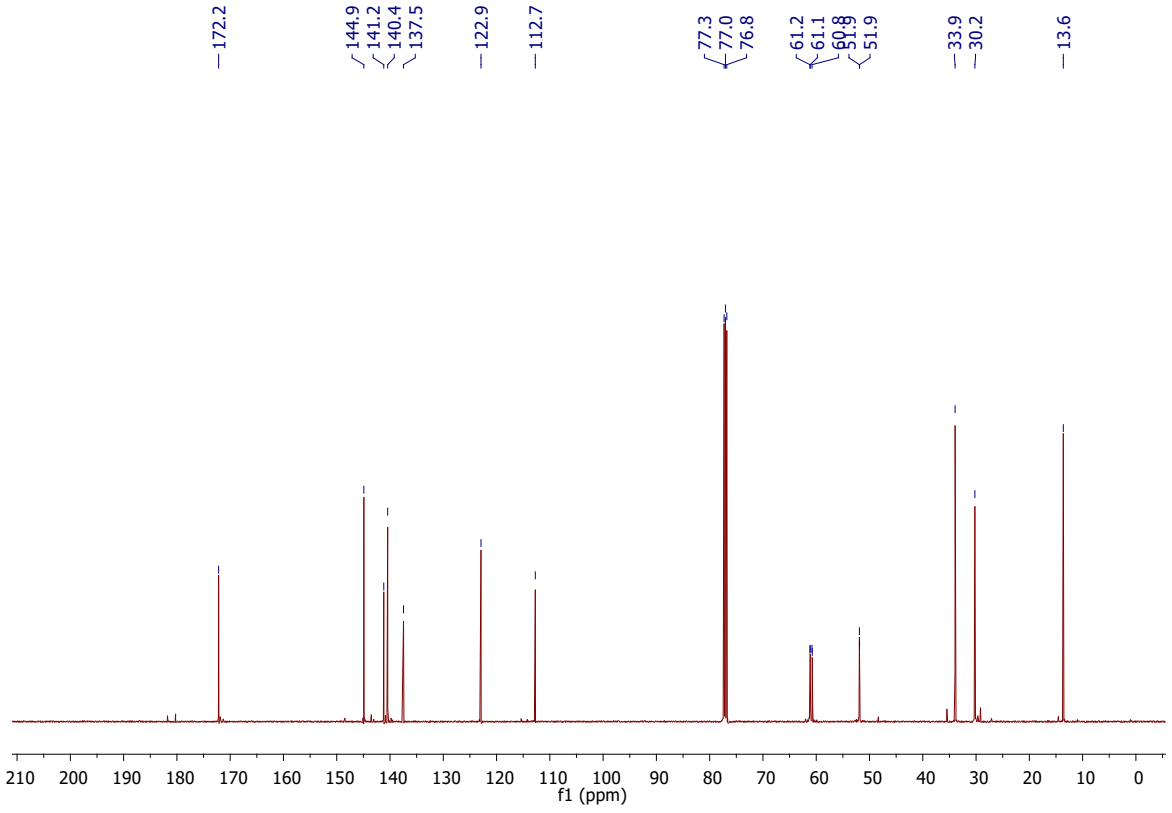

Figure S8: ^{13}C NMR (125 MHz) spectrum of the **CoQ4** in $CDCl_3$-*d1*

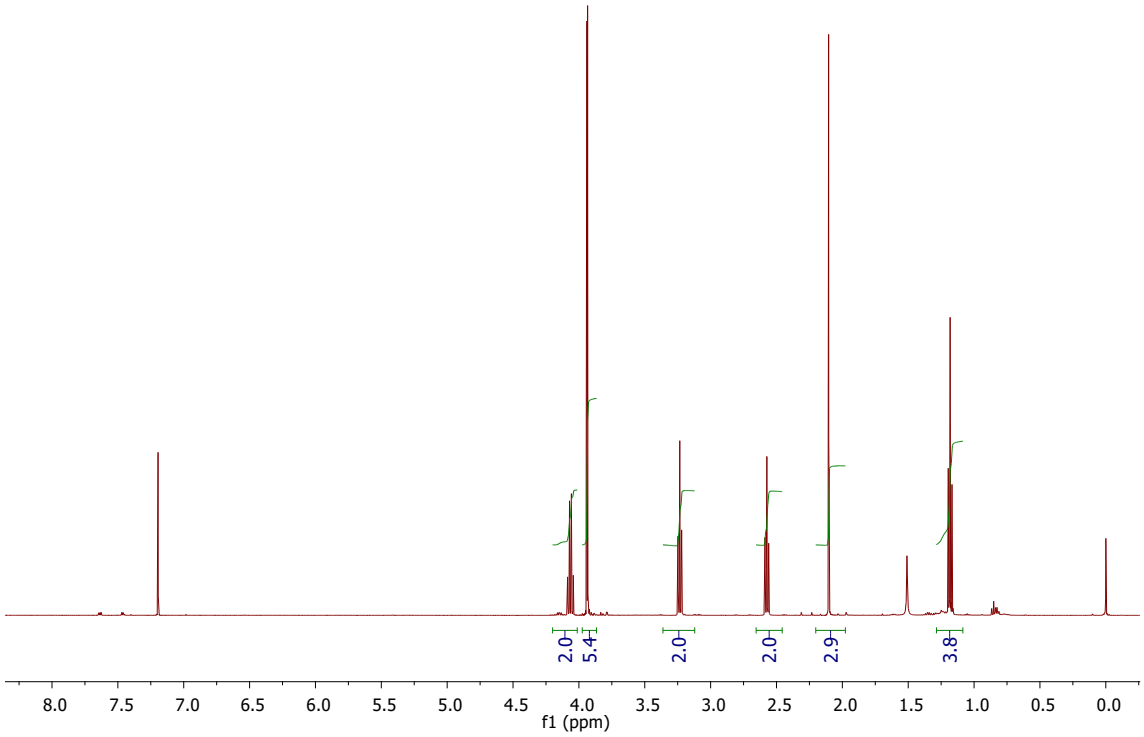

Figure S9: ^{1}H NMR (500 MHz) spectrum of the **CoQ5** in $CDCl_3$-*d1*

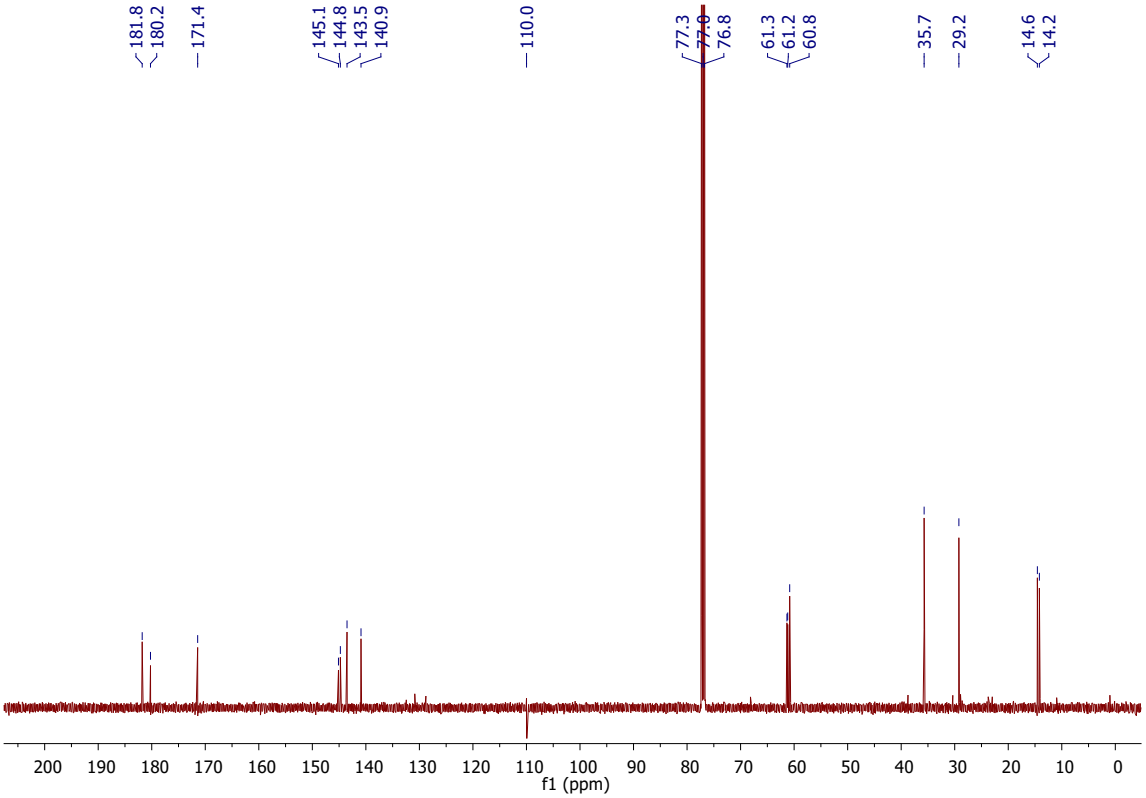

Figure S10: ^{13}C NMR (125 MHz) spectrum of the **CoQ5** in $CDCl_3$-*d1*

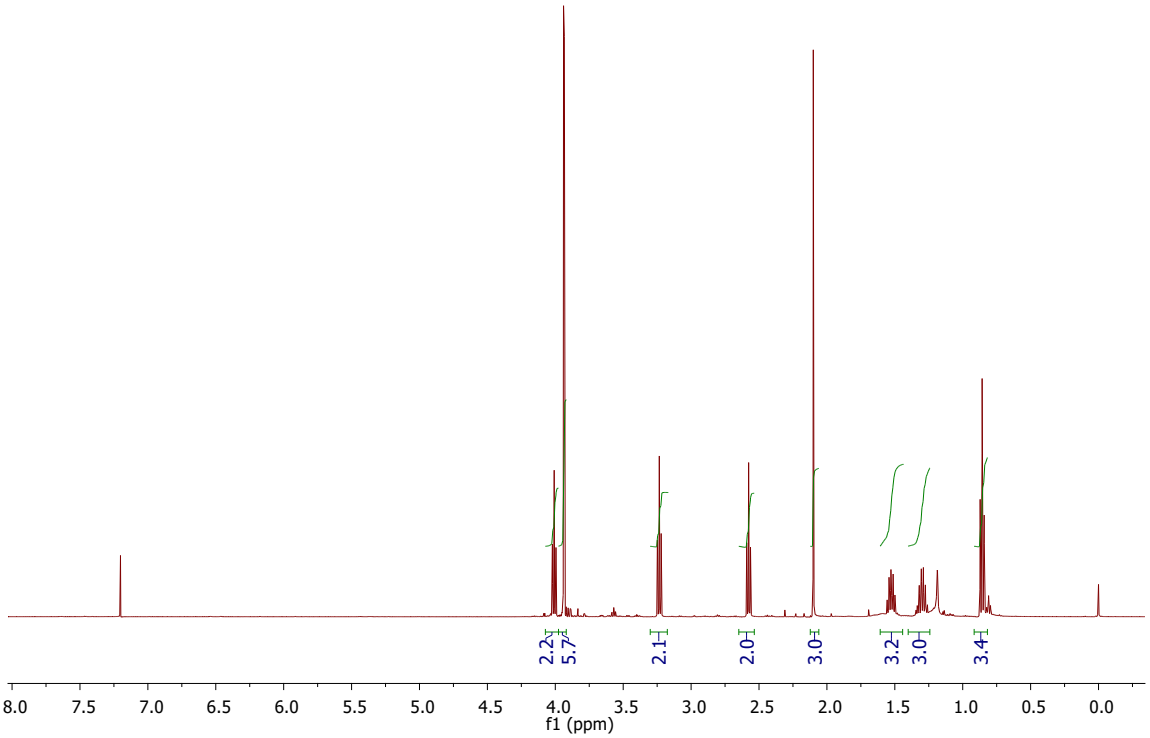

Figure S11: ^{1}H NMR (500 MHz) spectrum of the **CoQ6** in $CDCl_3$-*d1*

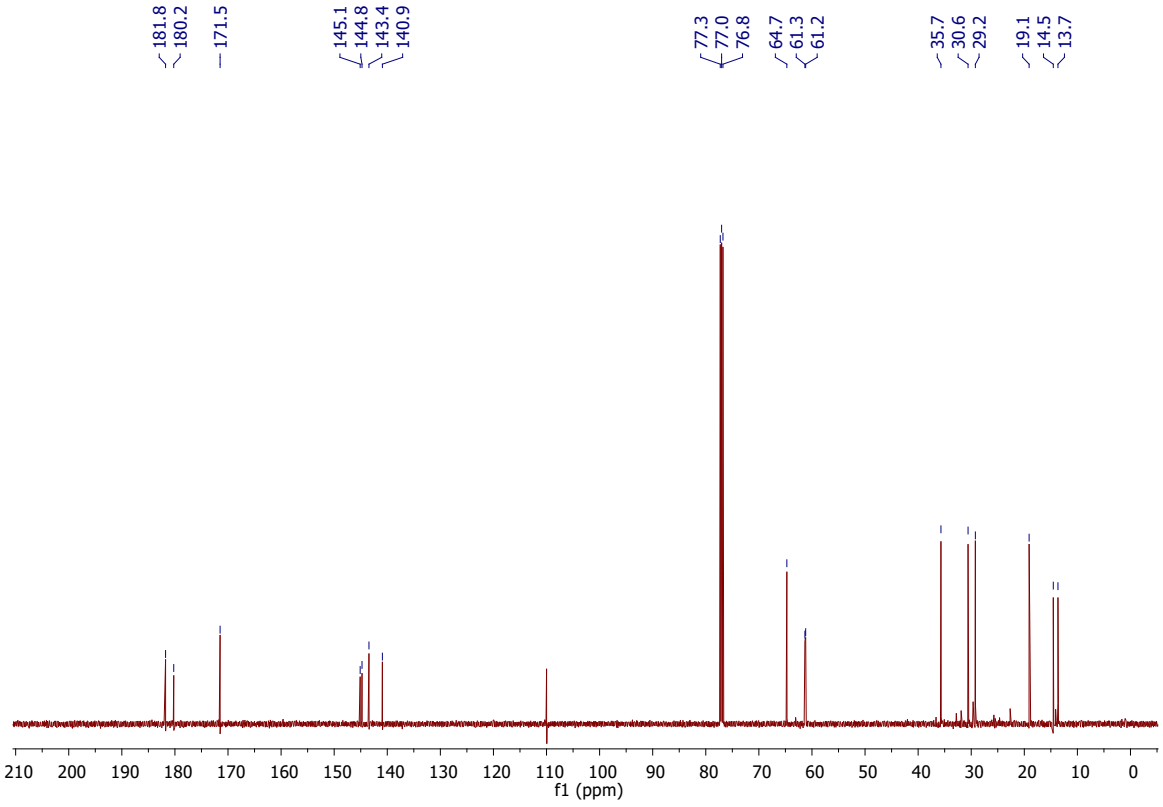

Figure S12: ^{13}C NMR (125 MHz) spectrum of the **CoQ6** in $CDCl_3$-*d1*

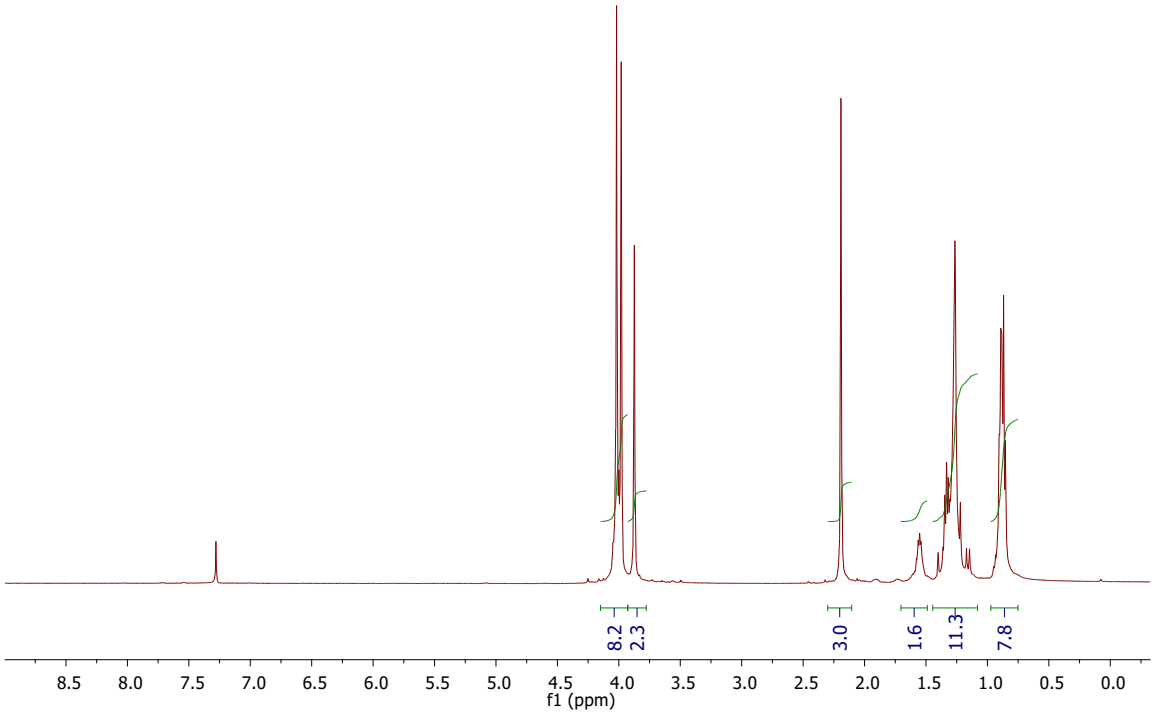

Figure S13: ^{1}H NMR (500 MHz) spectrum of the **CoQ7** in $CDCl_3$-*d1*

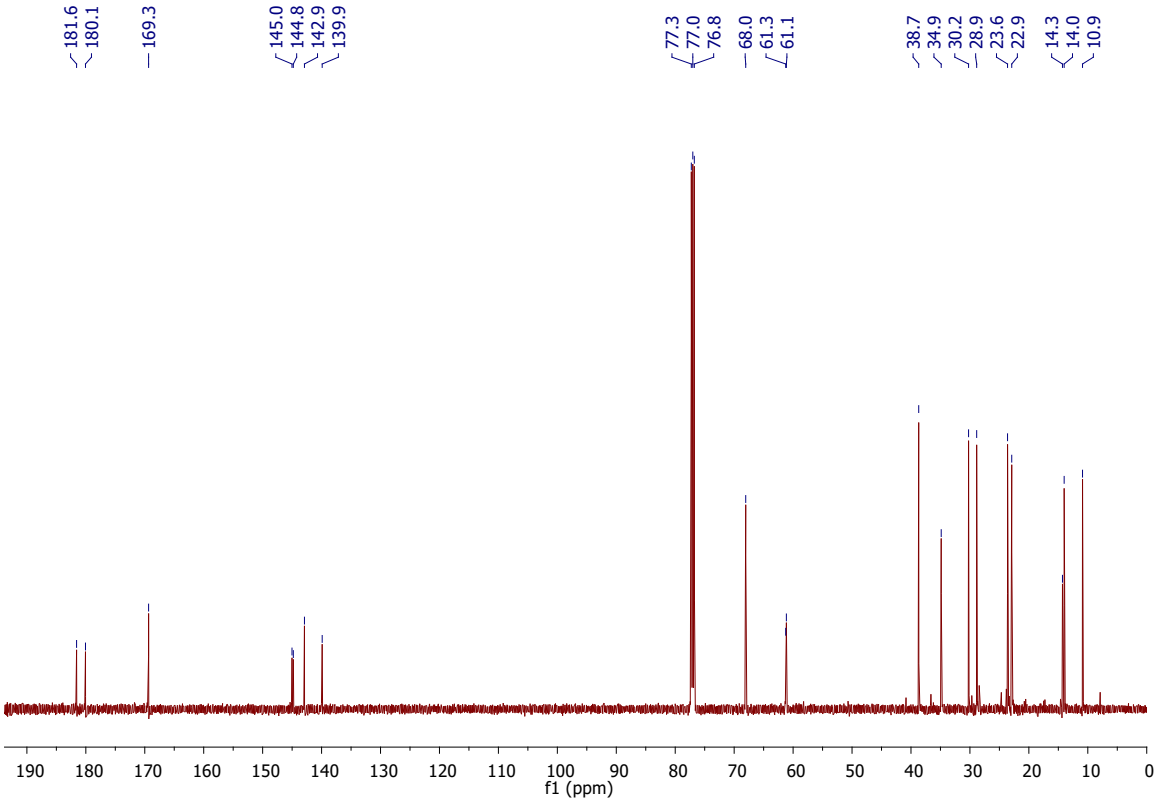

Figure S14: ^{13}C NMR (125 MHz) spectrum of the **CoQ7** in $CDCl_3$-*d1*

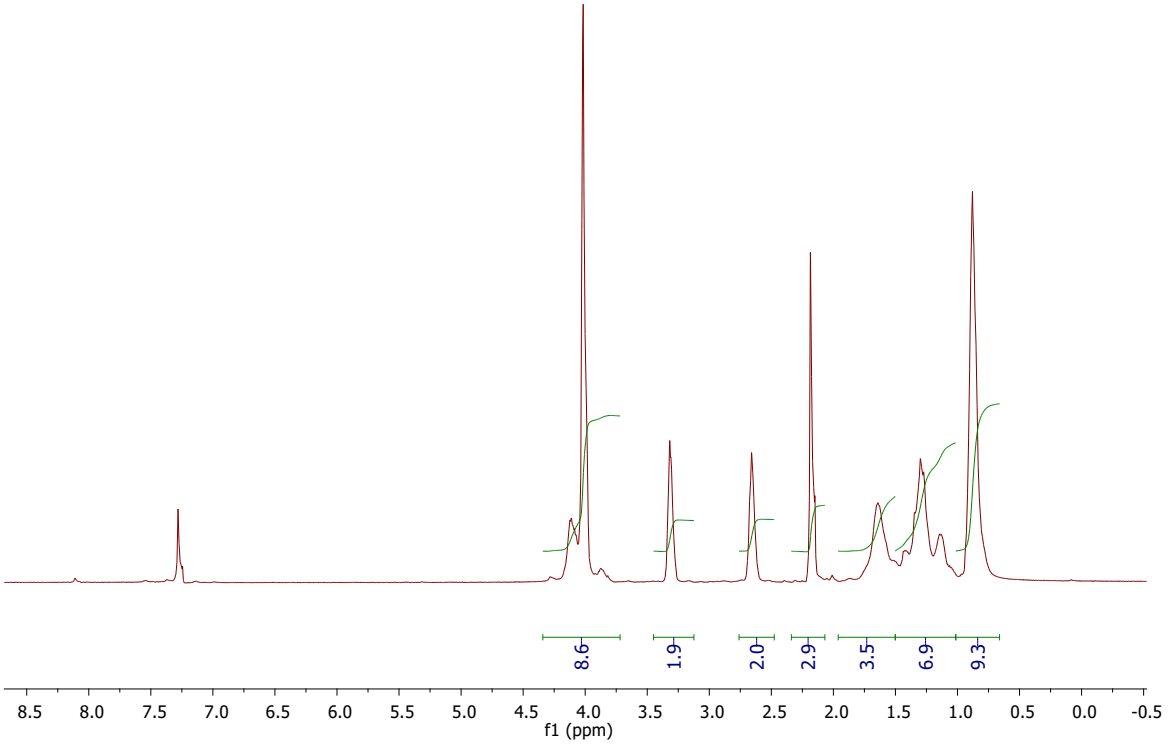

Figure S15: ^{1}H NMR (500 MHz) spectrum of the **CoQ8** in $CDCl_3$-*d1*

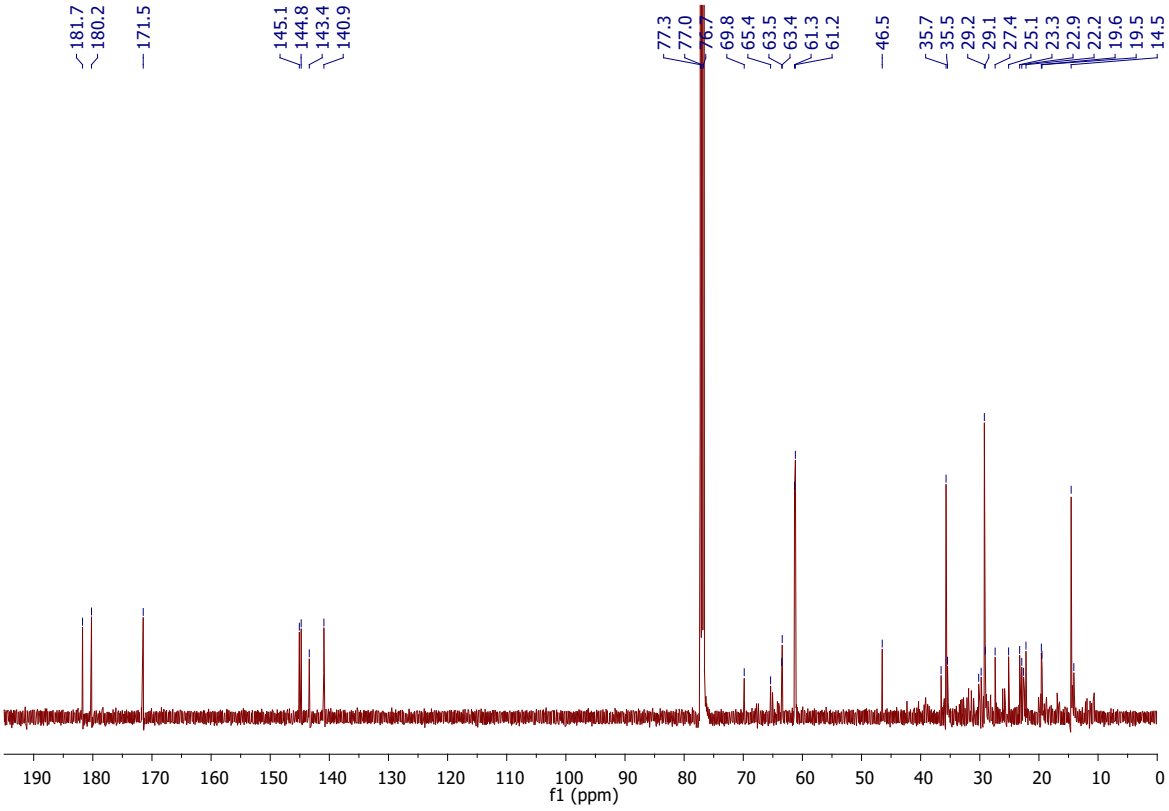

Figure S16: ^{13}C NMR (125 MHz) spectrum of the **CoQ8** in $CDCl_3$-*d1*

Crystallographic data of **CoQ1**

Computing details

Data collection: Bruker Instrument Service v2013.12.0.0 (Bruker AXS); cell refinement: APEX2 v2014.9-0 (Bruker AXS); data reduction: SAINT V8.34A (Bruker AXS); program(s) used to solve structure: SHELXTL V6.14 (Bruker AXS); program(s) used to refine structure: SHELXTL V6.14 (Bruker AXS); molecular graphics: Mercury (Macrae et al., 2006); software used to prepare material for publication: PLATON V1.16 (Spek, 2009), SHELXTL V6.14 (Bruker AXS).

Crystal data

$C_{12}H_{14}O_6S$
$M_r = 286.29$
Monoclinic, $P2_1/n$
$a = 3.9584$ (5) Å
$b = 23.942$ (3) Å
$c = 13.7731$ (15) Å
$\beta = 91.887$ (8)°
$V = 1304.6$ (3) $Å^3$
$Z = 4$
$F(000) = 600$
$D_x = 1.458$ Mg m^{-3}
Mo Kα radiation, $\lambda = 0.71073$ Å
Cell parameters from 2473 reflections
$\theta = 2.3–21.1°$
$\mu = 0.27$ mm^{-1}
$T = 293$ K
Plate, red
0.51 × 0.06 × 0.05 mm

Data collection

Bruker APEX II QUAZAR three-circle diffractometer
Radiation source: microfocus sealed tube, ImuS Multilayer QUAZAR mirrors monochromator
Detector resolution: 8.3333 pixels mm^{-1}
φ and ω scans
$\theta_{max} = 25.0°$, $\theta_{min} = 1.7°$
$h = -4 \rightarrow 4$
$k = -28 \rightarrow 28$
$l = -16 \rightarrow 16$
Absorption correction: multi-scan SADABS V2014/4 (Bruker AXS)
$T_{min} = 0.87$, $T_{max} = 0.99$
18184 measured reflections
2291 independent reflections
1555 reflections with $I > 2\sigma(I)$
$R_{int} = 0.078$

Refinement

Refinement on F_2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.049$
$wR(F^2) = 0.124$
$S = 1.04$
2291 reflections
176 parameters
0 restraints
Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0386P)^2 + 1.4745P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.015$
$\Delta\rho_{max} = 0.25$ e $Å^{-3}$
$\Delta\rho_{min} = -0.21$ e $Å^{-3}$

Special details

Geometry. All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

Geometric parameters (Å, º) for **CoQ1**

S1—C4	1.761 (3)	C3—C2	1.485 (4)
S1—C3	1.803 (3)	C3—H3A	0.97
O3—C11	1.218 (4)	C3—H3B	0.97
O4—C10	1.365 (4)	C8—C7	1.490 (5)
O4—C12	1.446 (4)	C6—H6A	0.96
O1—C2	1.318 (4)	C6—H6B	0.96
O1—C1	1.444 (4)	C6—H6C	0.96
O5—C8	1.344 (4)	C12—H12A	0.96
O5—C9	1.413 (4)	C12—H12B	0.96
O6—C7	1.209 (4)	C12—H12C	0.96
O2—C2	1.188 (4)	C9—H9A	0.96
C10—C8	1.337 (4)	C9—H9B	0.96
C10—C11	1.473 (4)	C9—H9C	0.96
C11—C4	1.497 (4)	C1—H1A	0.96
C4—C5	1.343 (4)	C1—H1B	0.96
C5—C7	1.486 (5)	C1—H1C	0.96
C5—C6	1.495 (4)		

C4—S1—C3	100.42 (15)	O6—C7—C5	120.5 (3)
C10—O4—C12	115.5 (3)	O6—C7—C8	120.0 (3)
C2—O1—C1	118.8 (3)	C5—C7—C8	119.4 (3)
C8—O5—C9	122.5 (3)	C5—C6—H6A	109.5
C8—C10—O4	122.2 (3)	C5—C6—H6B	109.5
C8—C10—C11	120.4 (3)	H6A—C6—H6B	109.5
O4—C10—C11	116.9 (3)	C5—C6—H6C	109.5
O3—C11—C10	120.3 (3)	H6A—C6—H6C	109.5
O3—C11—C4	121.0 (3)	H6B—C6—H6C	109.5
C10—C11—C4	118.7 (3)	O4—C12—H12A	109.5
C5—C4—C11	119.9 (3)	O4—C12—H12B	109.5
C5—C4—S1	121.4 (2)	H12A—C12—H12B	109.5
C11—C4—S1	118.2 (2)	O4—C12—H12C	109.5
C4—C5—C7	119.7 (3)	H12A—C12—H12C	109.5
C4—C5—C6	124.6 (3)	H12B—C12—H12C	109.5
C7—C5—C6	115.7 (3)	O5—C9—H9A	109.5
C2—C3—S1	110.5 (2)	O5—C9—H9B	109.5
C2—C3—H3A	109.5	H9A—C9—H9B	109.5
S1—C3—H3A	109.5	O5—C9—H9C	109.5
C2—C3—H3B	109.5	H9A—C9—H9C	109.5
S1—C3—H3B	109.5	H9B—C9—H9C	109.5
H3A—C3—H3B	108.1	O1—C1—H1A	109.5
C10—C8—O5	129.4 (3)	O1—C1—H1B	109.5
C10—C8—C7	120.1 (3)	H1A—C1—H1B	109.5
O5—C8—C7	110.5 (3)	O1—C1—H1C	109.5
O2—C2—O1	124.1 (3)	H1A—C1—H1C	109.5
O2—C2—C3	125.8 (3)	H1B—C1—H1C	109.5
O1—C2—C3	110.2 (3)		

C12—O4—C10—C8	124.0 (4)	C11—C10—C8—O5	−176.3 (4)
C12—O4—C10—C11	−64.0 (4)	O4—C10—C8—C7	174.2 (3)
C8—C10—C11—O3	165.0 (3)	C11—C10—C8—C7	2.5 (5)
O4—C10—C11—O3	−7.2 (5)	C9—O5—C8—C10	−17.9 (6)
C8—C10—C11—C4	−13.4 (5)	C9—O5—C8—C7	163.3 (3)
O4—C10—C11—C4	174.4 (3)	C1—O1—C2—O2	1.9 (6)
O3—C11—C4—C5	−162.6 (3)	C1—O1—C2—C3	−177.9 (3)
C10—C11—C4—C5	15.8 (5)	S1—C3—C2—O2	−0.1 (5)
O3—C11—C4—S1	9.4 (4)	S1—C3—C2—O1	179.7 (2)
C10—C11—C4—S1	−172.1 (2)	C4—C5—C7—O6	179.6 (4)
C3—S1—C4—C5	−136.1 (3)	C6—C5—C7—O6	−1.9 (5)

C3—S1—C4—C11	52.0 (3)	C4—C5—C7—C8	−4.1 (5)
C11—C4—C5—C7	−7.0 (5)	C6—C5—C7—C8	174.4 (3)
S1—C4—C5—C7	−178.8 (3)	C10—C8—C7—O6	−177.1 (4)
C11—C4—C5—C6	174.7 (3)	O5—C8—C7—O6	1.8 (5)
S1—C4—C5—C6	2.9 (5)	C10—C8—C7—C5	6.5 (5)
C4—S1—C3—C2	175.5 (3)	O5—C8—C7—C5	−174.5 (3)
O4—C10—C8—O5	−4.5 (6)		

Hydrogen-bond geometry (Å, º) for **CoQ1**

D—H···A	D—H	H···A	D···A	D—H···A
C3—H3A···O3	0.97	2.33	2.974 (4)	123
C3—H3B···O3$_{i}$	0.97	2.60	3.425 (4)	143
C9—H9A···O4$_{i}$	0.96	2.65	3.508 (5)	149
C1—H1A···O5$_{ii}$	0.96	2.54	3.456 (5)	160

Symmetry codes: (i) x+1, y, z; (ii) −x+3/2, y+1/2, −z+1/2.

Table S2. Crystallographic data for the **CoQ1**.

Identification code	**CoQ1**
Chemical formula	$C_{12}H_{14}O_6S$
Formula weight (g mol^{-1})	286.29
Temperature (K)	273
Radiation λ (Å)	0.71073
Crystal system	Monoclinic
Space groups, Z	P 1 2$_1$/n 1, 4
Unit cell dimensions (Å)	a = 3.9584(5) b = 23.942(3) c = 13.7731(15) α, γ = 90° β = 91.887(8)°
Volume (Å^3)	1304.6(3)
Crystal sizes (mm)	0.053 x 0.055 x 0.507
dcalc (g cm^{-3})	1.458
Absorption coefficient (mm^{-1})	0.268
Absorption correction, Tmin, Tmax	multi-scan, 0.986 and 0.876
θ_{max}, deg	1.70 to 25.00
Goodness-of-fit on F^2	1.039
Index ranges	-4≤h≤4 -28≤k≤28 -16≤l≤16
Reflections collected	18184
Independent reflections	2291 [R(int) = 0.0781]
Final R indices [I > 2σ(I)]	1555 data R1 = 0.0491 wR2 = 0.1037

R indices (all data)	R1 = 0.0872 wR2 = 0.1244
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2291 / 0 / 176
Largest diff. peak and hole ($eÅ^{-3}$)	0.253 and -0.212

Table S3. Selected bond lengths (Å) for **CoQ1**

S1-C4	1.761(3)	S1-C3	1.803(3)
O3-C11	1.218(4)	O4-C10	1.365(4)
O4-C12	1.446(4)	O1-C2	1.318(4)
O1-C1	1.444(4)	O5-C8	1.344(4)
O5-C9	1.413(4)	O6-C7	1.209(4)
O2-C2	1.188(4)	C3-C2	1.485(4)

Table S4. Selected bond angles (°) for **CoQ1**

C4-S1-C3	100.42(15)	C10-O4-C12	115.5(3)
C2-O1-C1	118.8(3)	C8-O5-C9	122.5(3)
O4-C10-C11	116.9(3)	O5-C8-C7	110.5(3)

Table S5. Selected torsion angles (°) for **CoQ1**

O3-C11-C4-S1	9.4(4)	C12-O4-C10-C11	-64.0(4)
C3-S1-C4-C5	-136.1(3)	O4-C10-C11-O3	-7.2(5)
C3-S1-C4-C11	52.0(3)	O5-C8-C7-O6	1.8(5)
S1-C4-C5-C7	-178.8(3)	C9-O5-C8-C7	163.3(3)
S1-C4-C5-C6	2.9(5)	C1-O1-C2-C3	-177.9(3)
C4-S1-C3-C2	175.5(3)	C1-O1-C2-O2	1.9(6)

Table S6. Hydrogen-bond geometry (Å, °) for **CoQ1**

D-H···A	**Donor-H**	**Acceptor-H**	**Donor-Acceptor**	**Angle**
C3-H3A···O3	0.97	2.33	2.974(4)	123.0
C3-H3B···O3^{i}	0.97	2.60	3.425(4)	143.3
C9-H9A···O4^{i}	0.96	2.65	3.508(5)	148.8
C1-H1A···O5^{ii}	0.96	2.54	3.456(5)	160.4

Symmetry codes: (i) x+1, y, z; (ii) −x+3/2, y+1/2, −z+1/2

ADME data for CoQ3-8

Property/rule	CoQ3	CoQ4	CoQ5	CoQ6	CoQ7	CoQ8
MW	314	300	314	342	384	384
Log P	2.80	2.62	2.31	3.47	3.69	3.62
TPSA Å²	104.20	104.20	104.20	104.20	104.20	104.20
HBA	6	6	6	6	6	6
HBD	0	0	0	0	0	0
Lipinski	Yes, 0 violation	Yes, 0 violation	Yes, 0 violation	Yes, 0 violation	Yes, 0 violation	Yes, 0 violation
Ghose	Yes	Yes	Yes	Yes	Yes	Yes
Veber	Yes	Yes	Yes	Yes	No	No
Egan	Yes	Yes	Yes	Yes	Yes	Yes
Muegge	Yes	Yes	Yes	Yes	Yes	Yes
Leadlikeness	Yes	Yes	Yes	No	No	Yes

Property	CoQ3	CoQ4	CoQ5	CoQ6	CoQ7	CoQ8
BBB permeability	No	No	No	No	No	No
GI absorption	High	High	High	High	High	High
Log *S*	-2.70	-2.07	-2.32	-2.9	-4.2	-4.2
Solubility	Soluble	Soluble	Soluble	Moderately Soluble	Moderately Soluble	Moderately Soluble
Bioavailability score	0.56	0.56	0.56	0.56	0.56	0.56
CYP1A2, CYP2C9, CYP2D6, CYP3A4	No	No	No	No	No	No