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SI 1. HPLC-DAD (280 nm) chromatogram of alkaloid extract from *Cinchona pubescens*

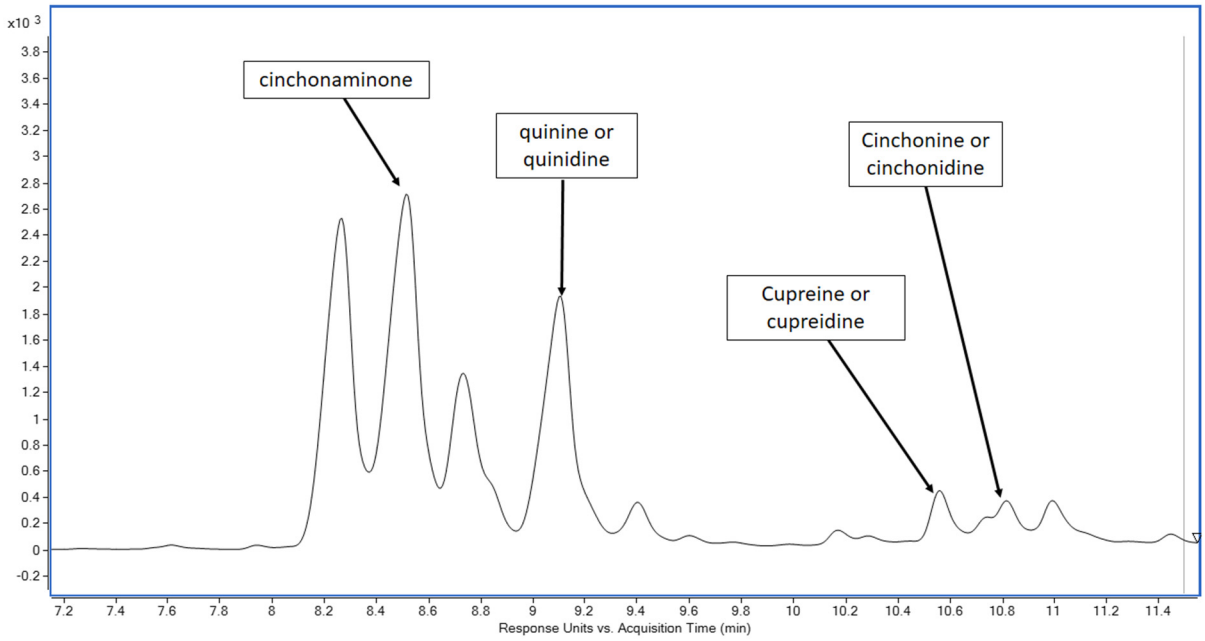
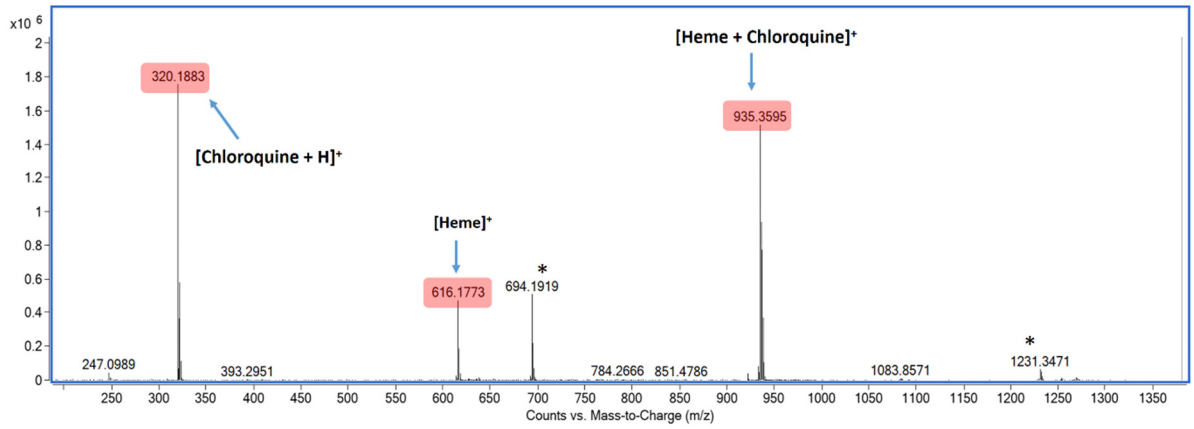


Figure S1 HPLC-DAD (280 nm) chromatogram of alkaloid extract from Cinchona pubescens

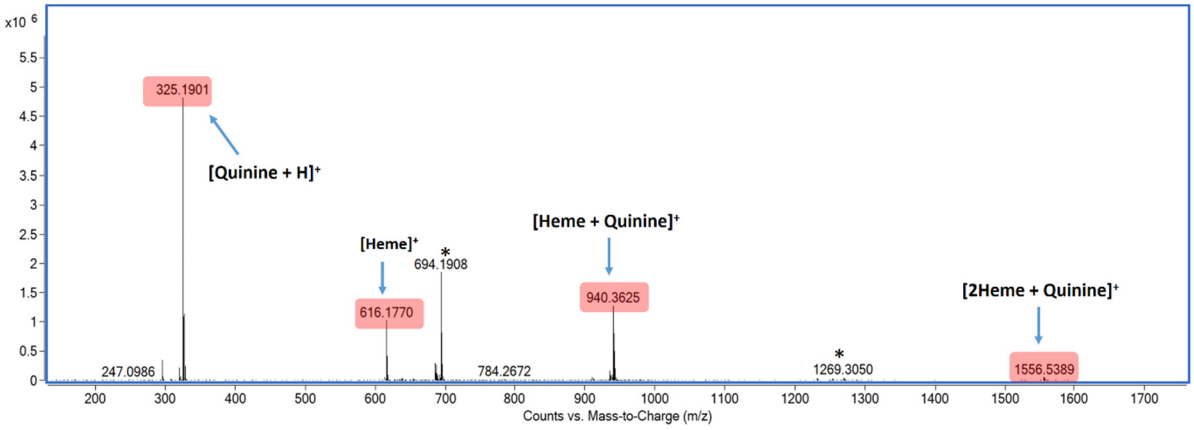
SI 2. ESI (+) HRMS spectra of antimalarial drugs with heme-Fe(III)

Figure S2. ESI (+) HRMS spectra of antimalarial drugs with heme-Fe(III)

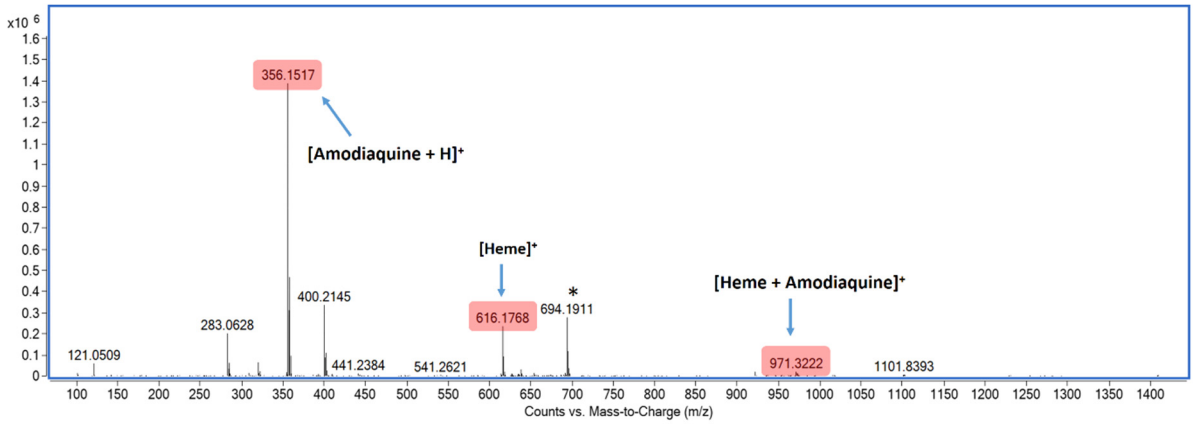
ESI (+) spectrum of mixture chloroquine diphosphate - heme



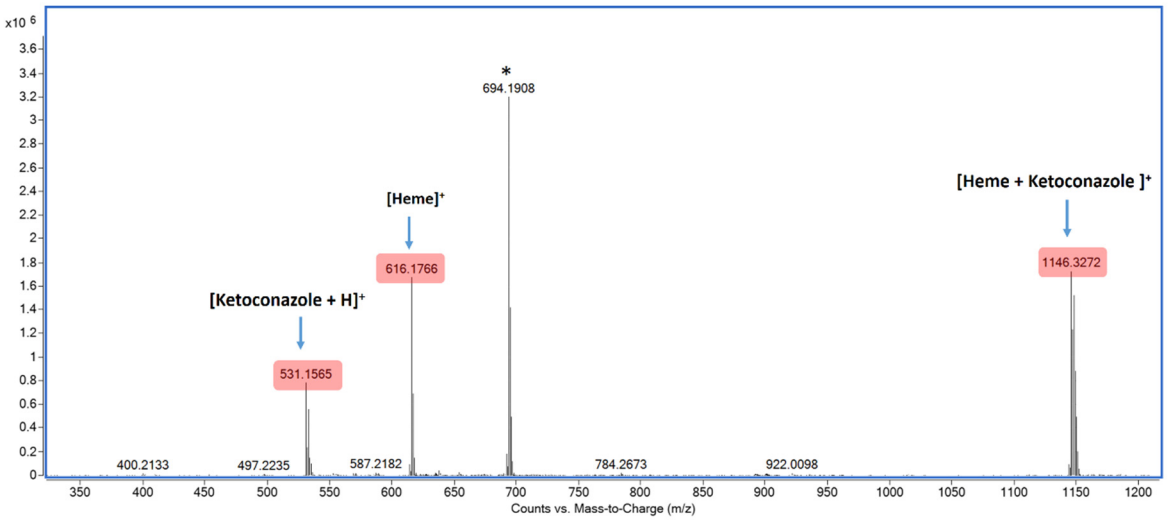
ESI (+) spectrum of mixture quinine - heme



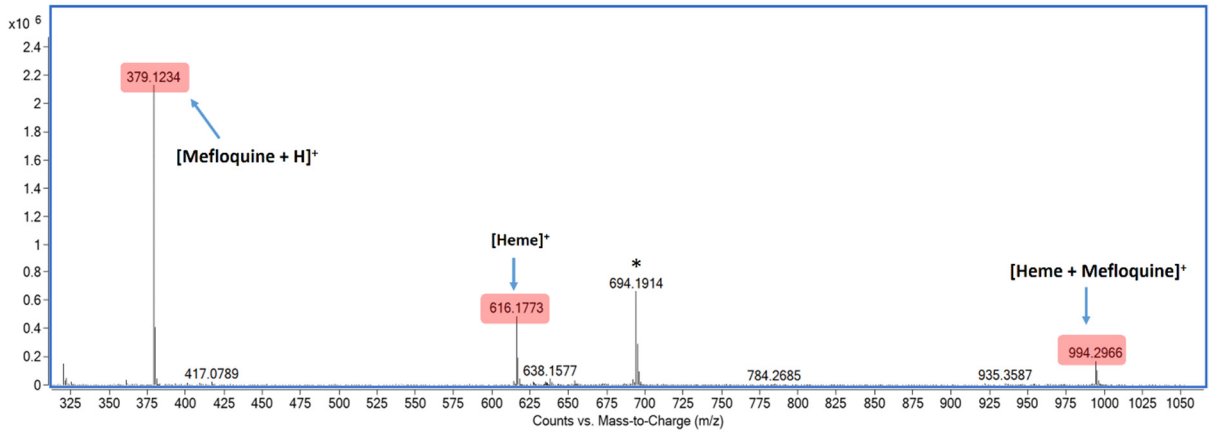
ESI (+) spectrum of mixture amodiaquine - heme



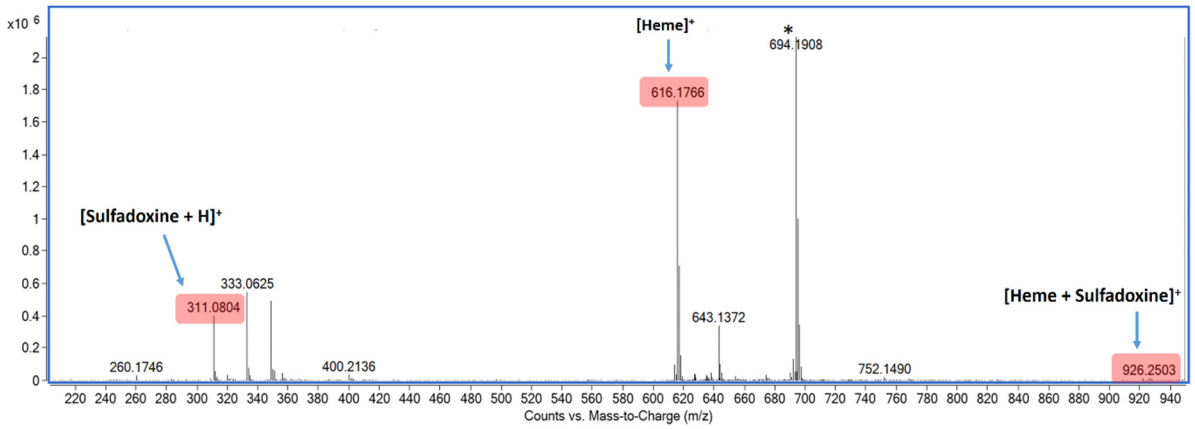
ESI (+) spectrum of mixture ketoconazole - heme



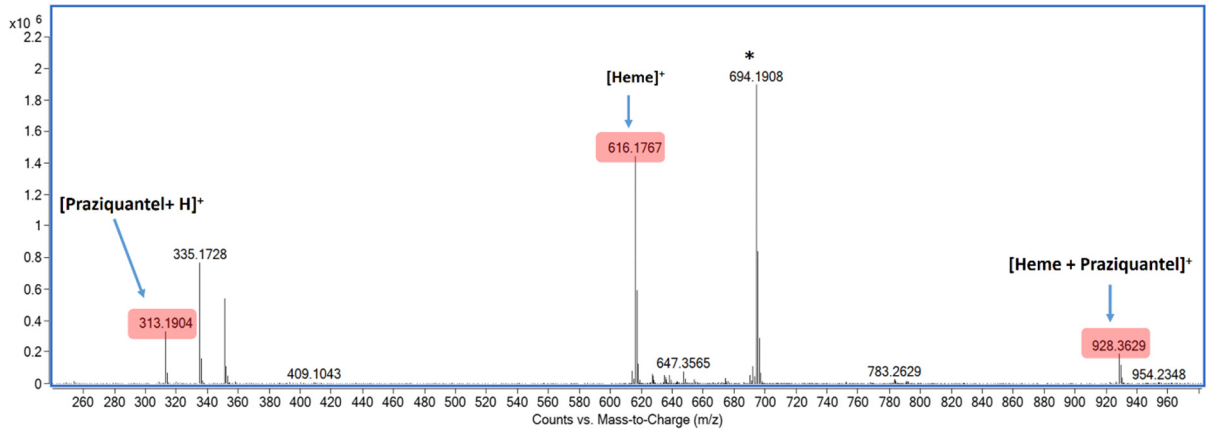
ESI (+) spectrum of mixture mefloquine - heme



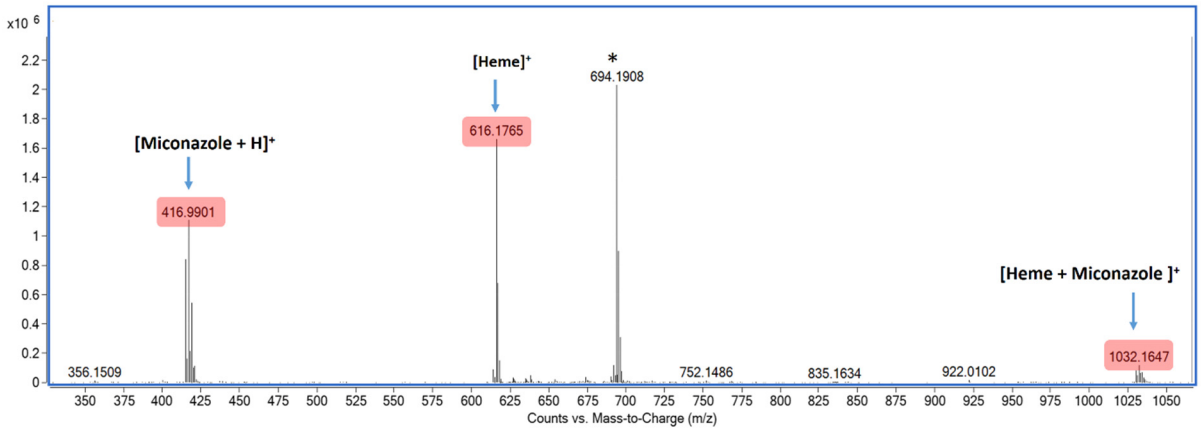
ESI (+) spectrum of sulfadoxine - heme



ESI (+) spectrum of mixture praziquantel - heme

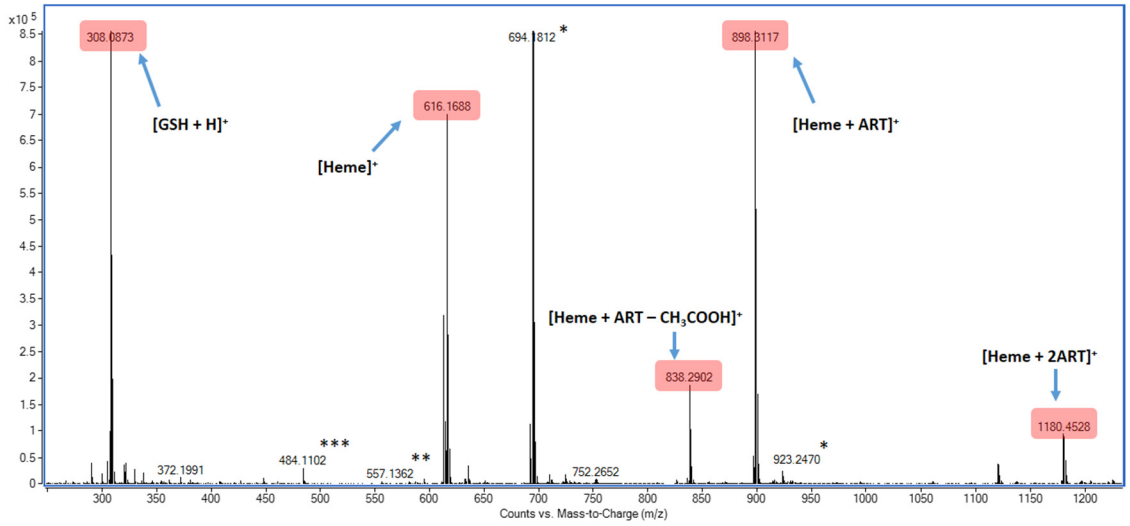


ESI (+) spectrum of mixture miconazole - heme



SI 3. ESI (+) HRMS spectrum of artemisinin - Fe(II) heme

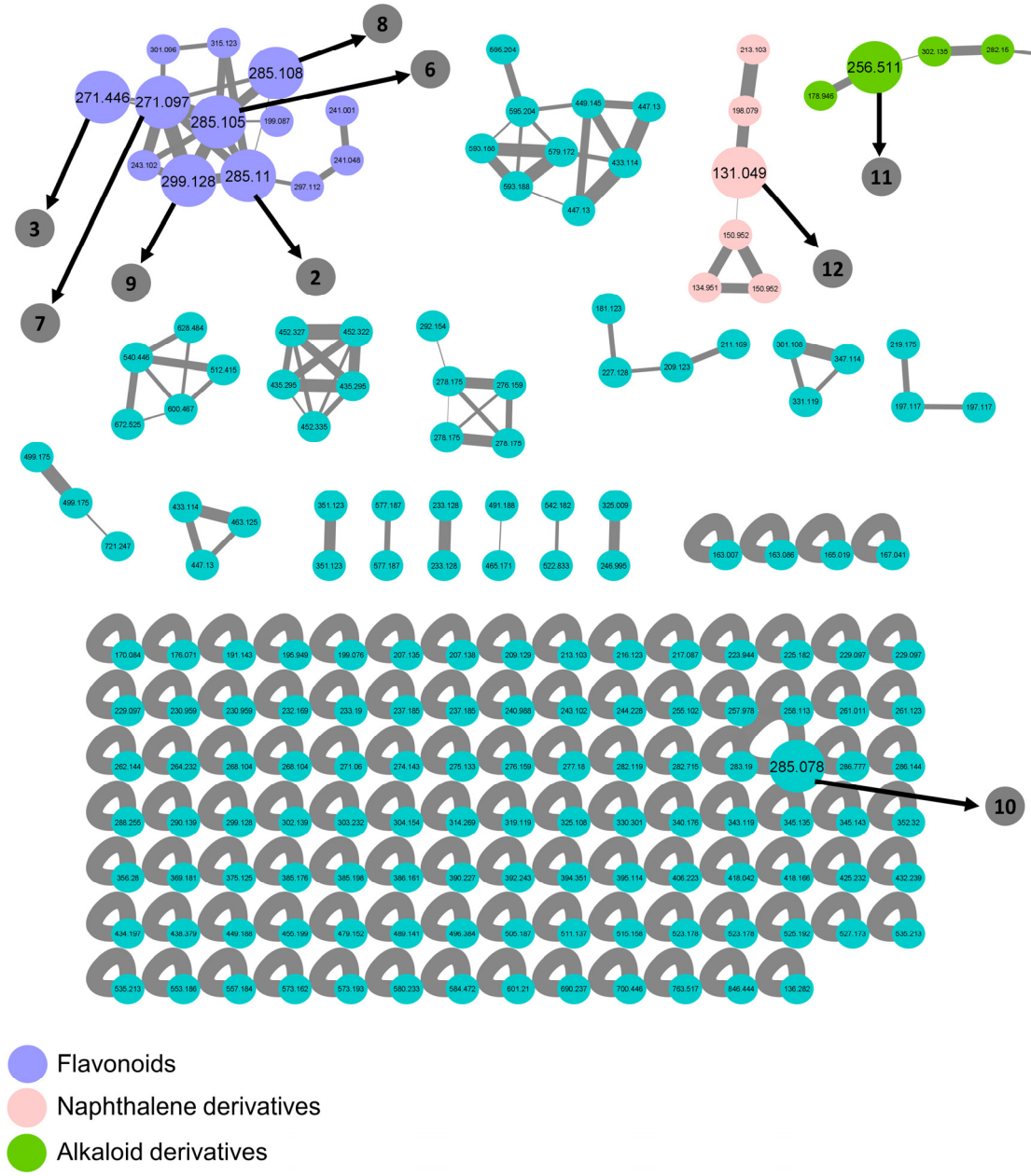
Figure S3. ESI (+) HRMS spectrum of artemisinin - Fe(II) heme



*Heme adducts with DMSO, GSH or heme dimers ($[2heme - H]^+$, $[2heme + 37Cl]^+$); ** fragment of heme following loss of CH_2-COOH; *** fragment GSSG following loss of γ-glutamate.

SI 4. Molecular network of ethyl acetate extract from *Piper coruscans*

Figure S4. Molecular network of ethyl acetate extract from *Piper coruscans*



SI 5. Experimental

Materials

Antimalarial drugs, reagents and solvents were acquired from Sigma-Aldrich (France) or other providers when specified: chloroquine diphosphate salt, quinine chloride, amodiaquine dihydrochloride dehydrate, miconazole nitrate salt, ketoconazole, sulfadoxine ≥ 95 % (TLC), praziquantel, mefloquine hydrochloride and artemisinin, Tween 20, citric acid, ACS reagent, ≥99.5%, LCMS-grade acetonitrile, LCMS-grade methanol, n-octanol for analysis (Carlo ERBA reagents, France), n-heptane for analyses (Scharlau), ethyl acetate for analyses (VWR chemical), n-butanol for analyses (EMSURE® ACS,ISO), methanol for analyses (EMSURE® ACS,ISO), water Milli-Q. NMR of compounds was carried in deutered solvents ($CDCl_3$, CD_3CN or MeOD). Deionized water was obtained from a Milli-Q instrument (Millipore, France).

Extraction of alkaloidic extract from *Cinchona pubescens* Vahl (Rubiaceae) was carried in December 2011 in the Pharmacognosy laboratory at Paris-Saclay University (France), as described in Durango *et al* [1].

Known compounds were identified based on literature spectral data. Aurentiacin (**1**) [2] ; stercurensin, (**2**) [3,4]; cardamomin, (**3**) [4,5]; strobopinin 7-methyl ether (**4**) [6]; 5-hydroxy-7-methoxy-6,8-dimethyl flavanone (**5**) [7]; desmethoxymatteucinol (**6**) [8]; alpinetin, (**7**) [4,9]; pinocembrin, (**8**) [10]; dimethyl cryptostrobin, (**9**) [11]; *N*-Benzoyltyrarnine methyl ether, (**11**) [12,13]; 1*H*-inden-1-one (**12**) [14,15].

Analyses

$[\alpha]_D$ analyses were carried used Atago™ Polarimetre Polax-2L carried at λ = 589 at a temperature of 16 °C. All compounds were yellow pale. For **4**, $[\alpha]_D$ + 7.02 (c 0.02 in MeOH); for **5**, $[\alpha]_D$ + 3.34 (c 0.01 in MeOH); for **6**, $[\alpha]_D$ + 3.51 (c 0.01 in MeOH); for **10**, $[\alpha]_D$ + 7.38 (c 0.02 in MeOH); for **9**, $[\alpha]_D$ + 7.02 (c 0.02 in MeOH); and for **11**, $[\alpha]_D$ + 10.03 (c 0.03 in MeOH).

Positive (+) HRMS $[M + H]^+$ was performed in 6530 Accurate-Mass QToF LC/MS instrument (Agilent Technologies). (+) HRMS $[M + H]^+$ for **1** *m/z* 299.1228 (calcd for $C_{18}H_{18}O_4$ 298.3153); (+) HRMS $[M + H]^+$ for **2** *m/z* 285.1101 (calcd for $C_{17}H_{16}O_4$ 284.1115); (+) HRMS $[M + H]^+$ for **3** *m/z* 271.0943 (calcd for $C_{16}H_{14}O_4$ 271.0930); (+) HRMS $[M + H]^+$ for **4** *m/z* 285.1109 (calcd for $C_{17}H_{16}O_4$ 284.1063); (+) HRMS $[M + H]^+$ for **5** *m/z* 299.1274 (calcd for $C_{18}H_{18}O_4$ 298.1253); (+) HRMS $[M + H]^+$ for **6** *m/z* 285.1101 (calcd for $C_{17}H_{16}O_4$ 284.1115); (+) HRMS $[M + H]^+$ for **7** *m/z* 271.4951 (calcd for $C_{16}H_{14}O_4$ 271.4958); (+) HRMS $[M + H]^+$ for **8** *m/z* 285.1088 (calcd for $C_{17}H_{16}O_4$ 284.1117); (+) HRMS $[M + H]^+$ for **9** *m/z* 299.1270

(calcd for $C_{18}H_{18}O_4$ 298.1271); (+) HRMS $[M + H]^+$ for **10** *m*/*z* 285.1109 (calcd for $C_{17}H_{16}O_4$ 285.1108); (+) HRMS $[M + H]^+$ for **11** *m*/*z* 256.1334 (calcd for $C_{16}H_{17}NO_2$ 255.1342); (+) HRMS $[M + H]^+$ for **12** *m*/*z* 131.0476 (calcd for C_9H_6O 131.0478).

NMR analyses were performed on a NMR Avance Bruker 500 MHz and 600 MHz CryoProbe for all compounds. Results were carried on Bruker TopSpin Software/NMR Data Analysis.

NMR analyses of compound 10 (ethyl 5-cinnamoyl-4,5-dihydroxy-3-methyl-4,5-dihydrofuran-2-carboxylate): Compound **10** was obtained as a yellow, amorphous powder; UV (MeOH), λmax = 280 nm. (+) HREMS indicated a $[M + H]^+$ ion peak at *m*/*z* 285.1109, consistent with the molecular formula $C_{17}H_{16}O_4$. This product is obtained through the spontaneous fragmentation of compound **10** in the MS source corresponding at $[C_{17}H_{18}O_6 – H_2O_2]^+$. Suggested pathway is proposed in Figure 1. NMR analyses accounted for structure **a**. Double-bond equivalent (DBE) value for this structure is 9. Analysis of ^{1}H NMR spectra and correlating its information with that of ^{13}C NMR spectrum resulted to the identification of two aromatic rings (cinnamoyl and furan moieties). The ^{13}C NMR spectrum (CD_3OD) showed 17 signals arising from two carbonyls, four sp^2 quaternary carbons, eight sp^2 methines, one methyl and one carboxylate group (SI4). In the ^{1}H NMR spectrum, characteristic protons of an α, β unsaturated ketone were observed at δ_H 6.77 (1H, d, *J* = 15.93) and 6.23 (1H, d, *J* = 15.93), typical signals of a cinnamoyl moiety, corroborated in COSY (Figure 2). Methine proton is observed at δ_H 3.80 (1H, s) in furan cycle. For the ester group, the methylene proton at δ_H 4.19, (2H, m) correlated in COSY with methyl proton at δ_H 1.27 (3H, t, *J* = 7.1). In addition, it correlated in HMBC with the quaternary carbons C-6′ at δ_C 171.9 and C-2′ at δ_C 151.3 (Figure 2). Location of the quaternary sp^2 carbon at C-5′ in furan cycle was evidenced by HMBC J^3 correlation of H-8 (cinnamoyl moiety) and J^2 correlation with H-4′. Connection between the furan and cinnamoyl moieties was also corroborated by J^3 correlation of H-4′ with carbonyl at C-9 (δ_C 200.8). Location of carbonyl at C-6′ in ester group was evidenced by the correlation in HMBC J^3 with H7′ and correlations in J^4 of H-4′, H-9′. The methyl at δ_H 1.97 (3H, s) and the carboxylate substitutions were observed in *meta* and *ortho* of the oxygen bridge in the furan cycle respectively.

Figure S5-1. Suggested MS source decomposition pathway for compound **10**.

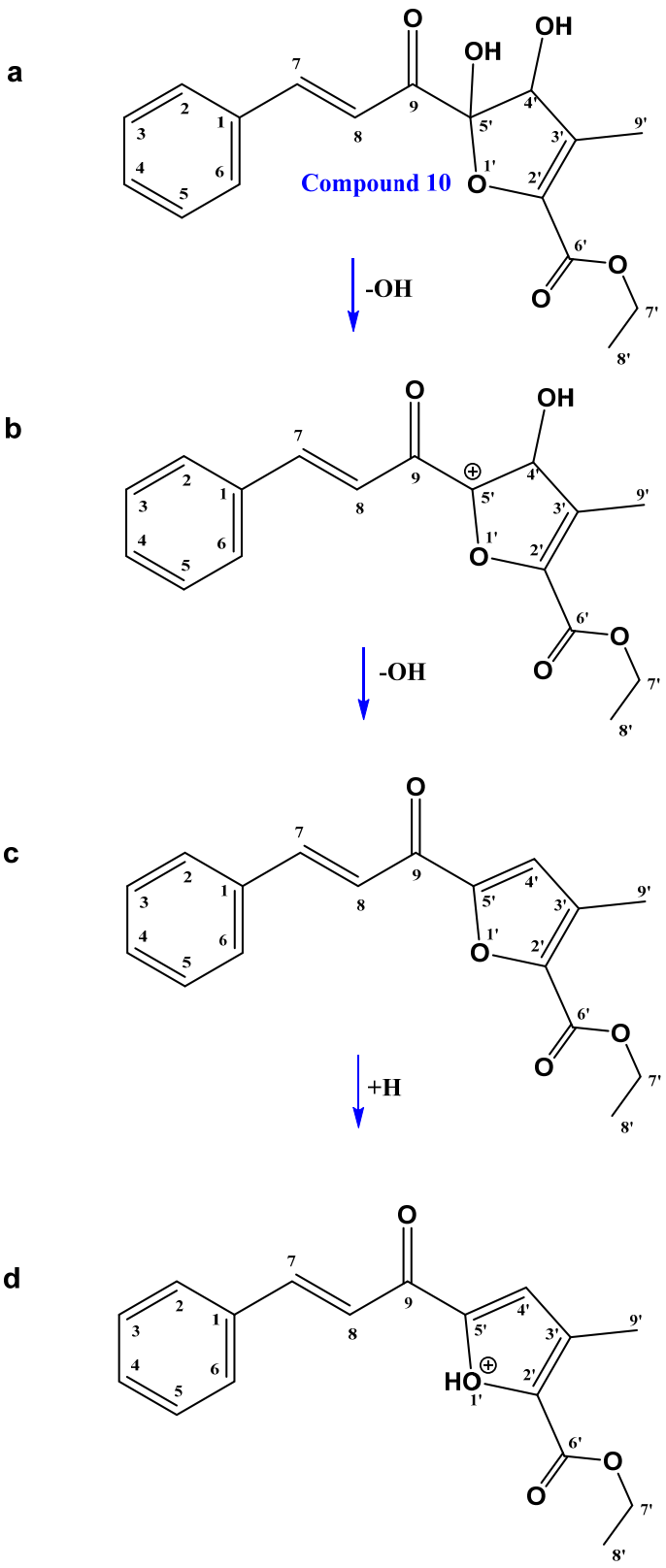
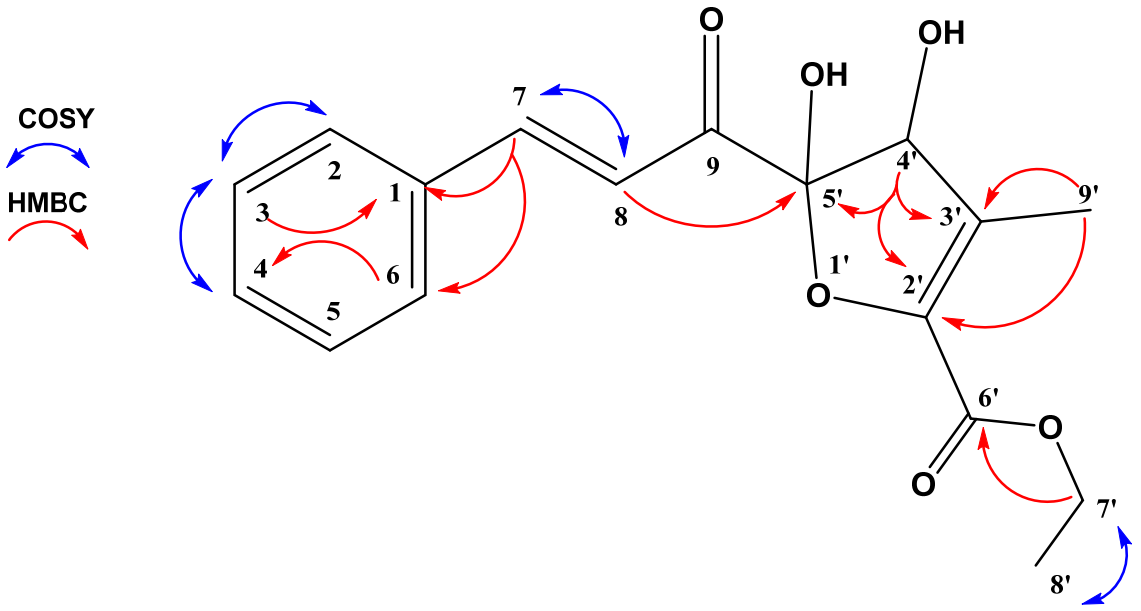


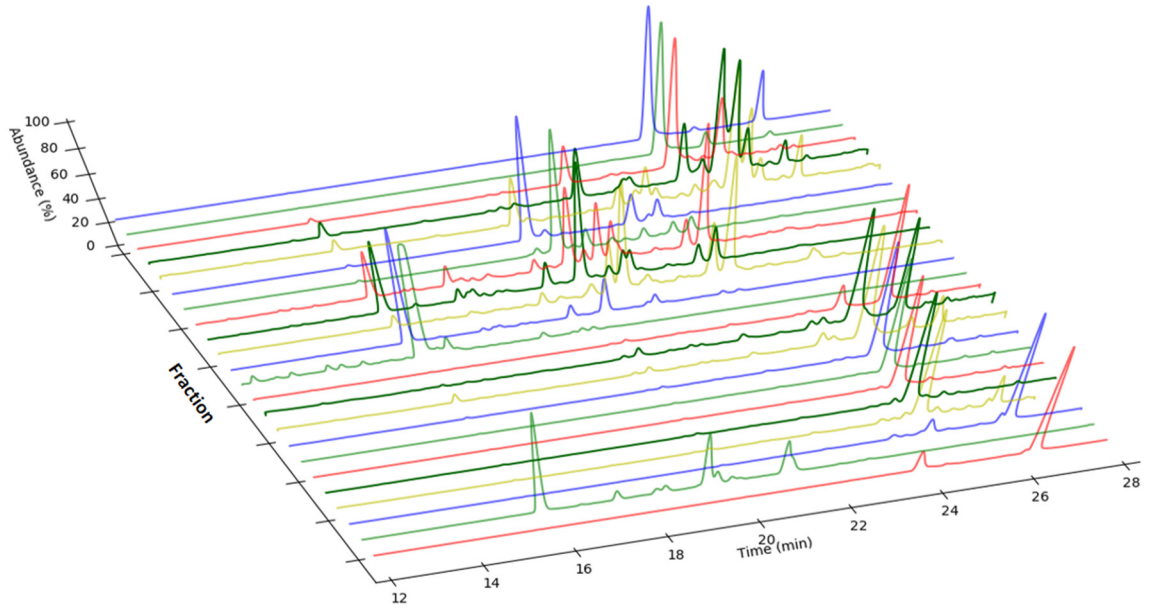
Figure S5-2: Main HMBC and COSY correlations for compound **10**.



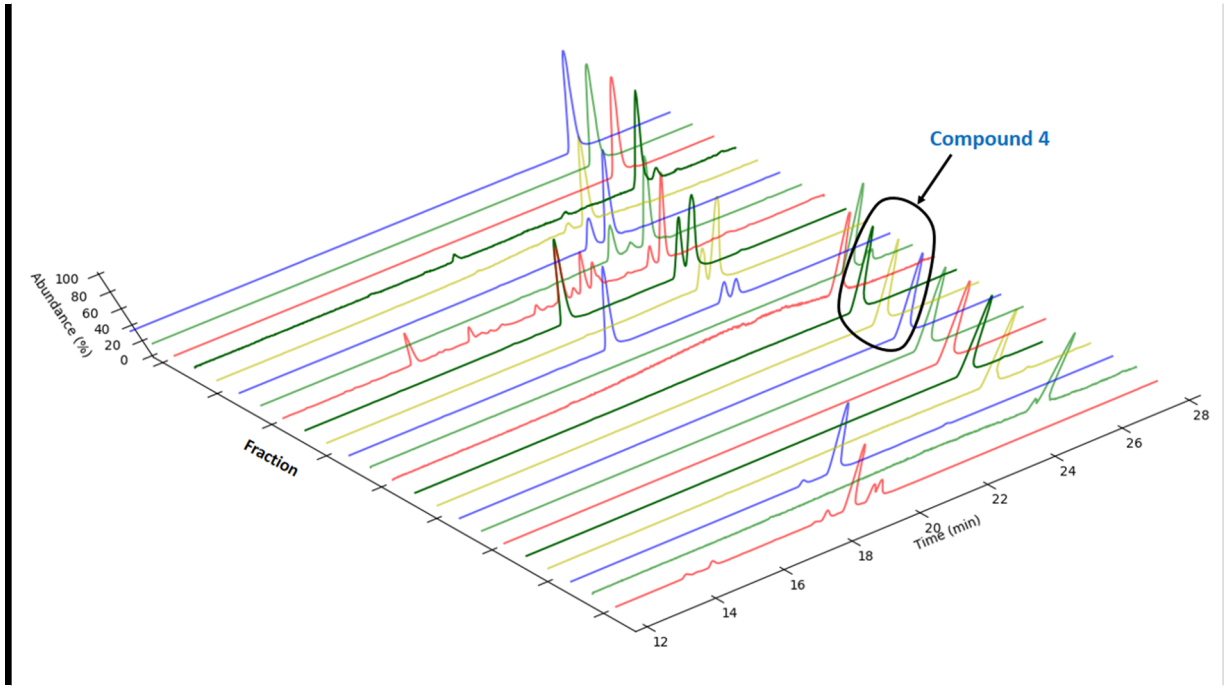
SI 6. CPC fractograms of cyclohexane extract (PCC) from *P. coruscans*

Figure S6. CPC fractograms of cyclohexane extract (PCC) from *P. coruscans*

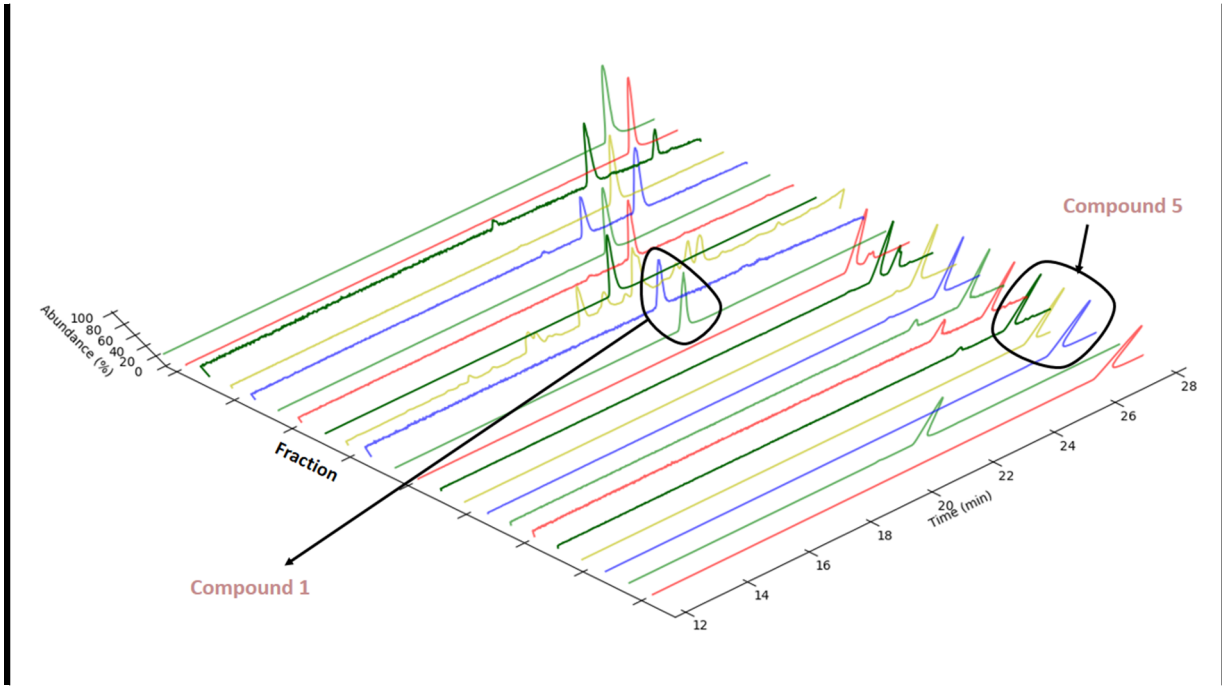
Total CPC UV fractogram at 280 nm. Fraction volume is 0,5 ml.



CPC fractogram at *m*/*z* 285 (mass of compound **4**). Fraction volume is 0,5 ml.



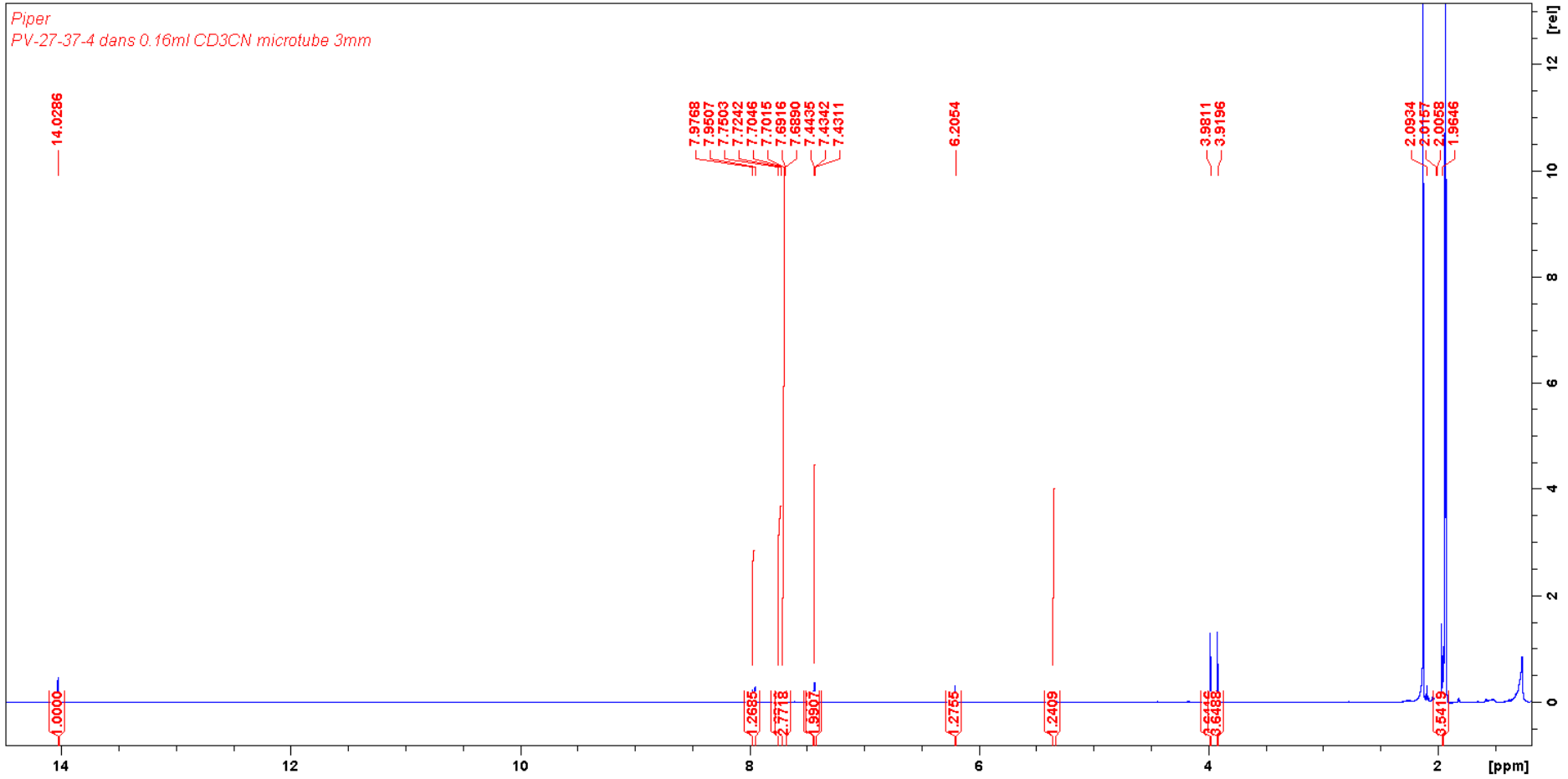
CPC fractogram at *m*/*z* 299 (mass of compounds **1** and **5**). Fraction volume is 0,5 ml.



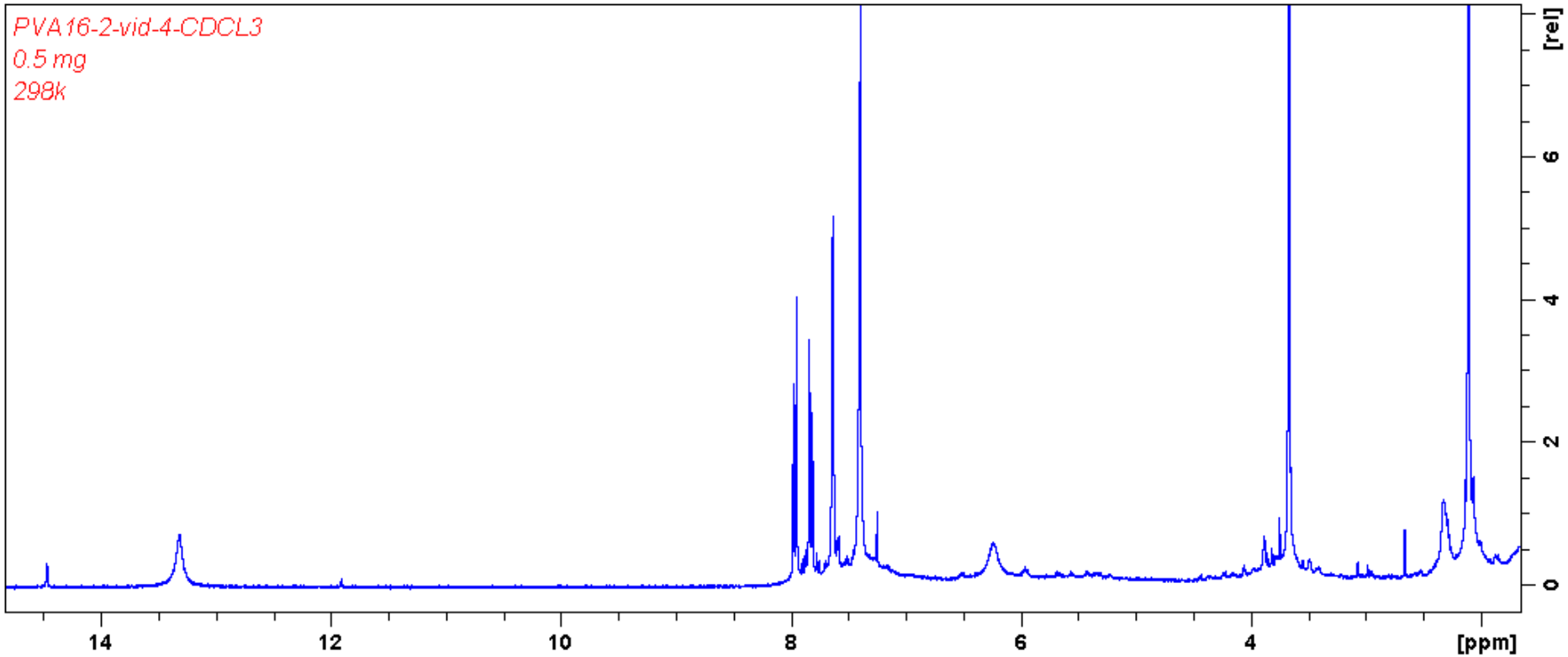
SI 7. Proton NMR of known compounds isolated for *P. coruscans*

Figure S7. Proton NMR of known compounds isolated for *P. coruscans*

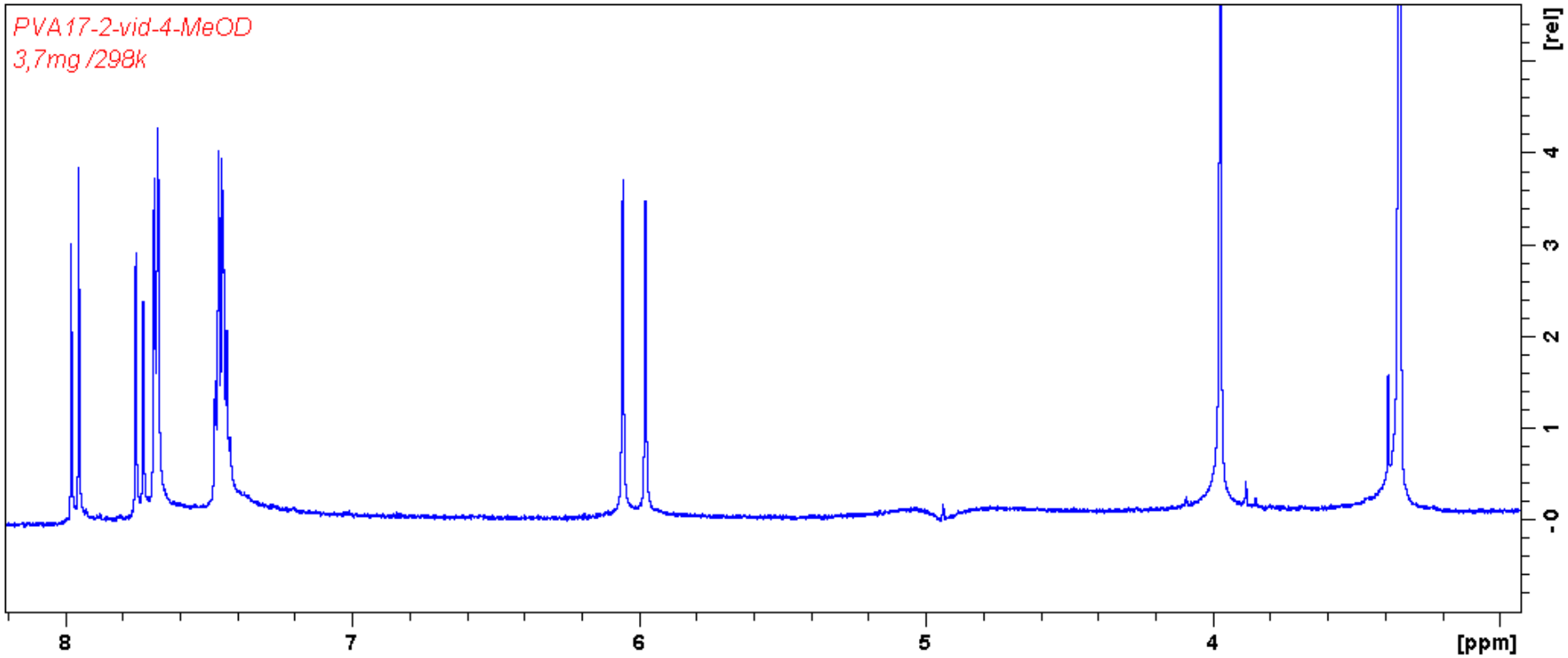
^{1}H NMR for compound **1** in CD_3CN



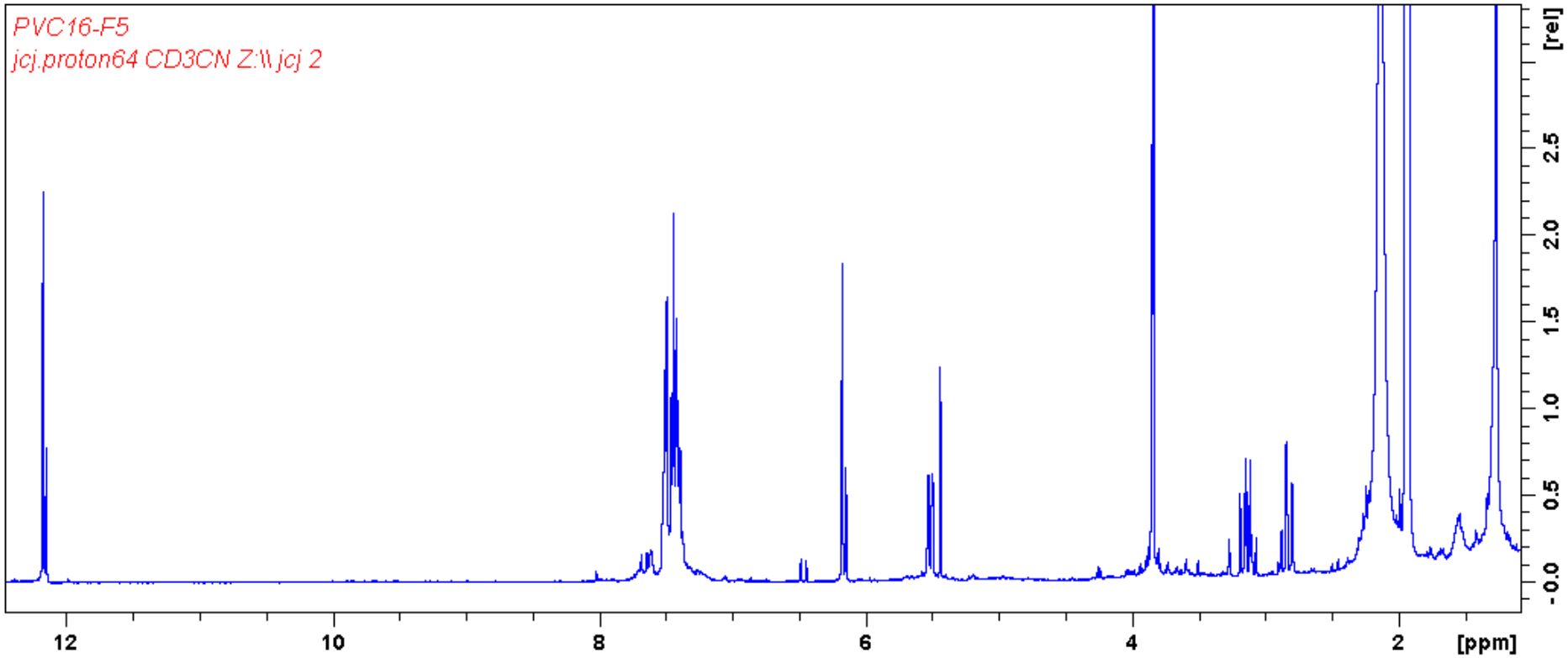
^{1}H NMR for compound **2** in $CDCl_3$



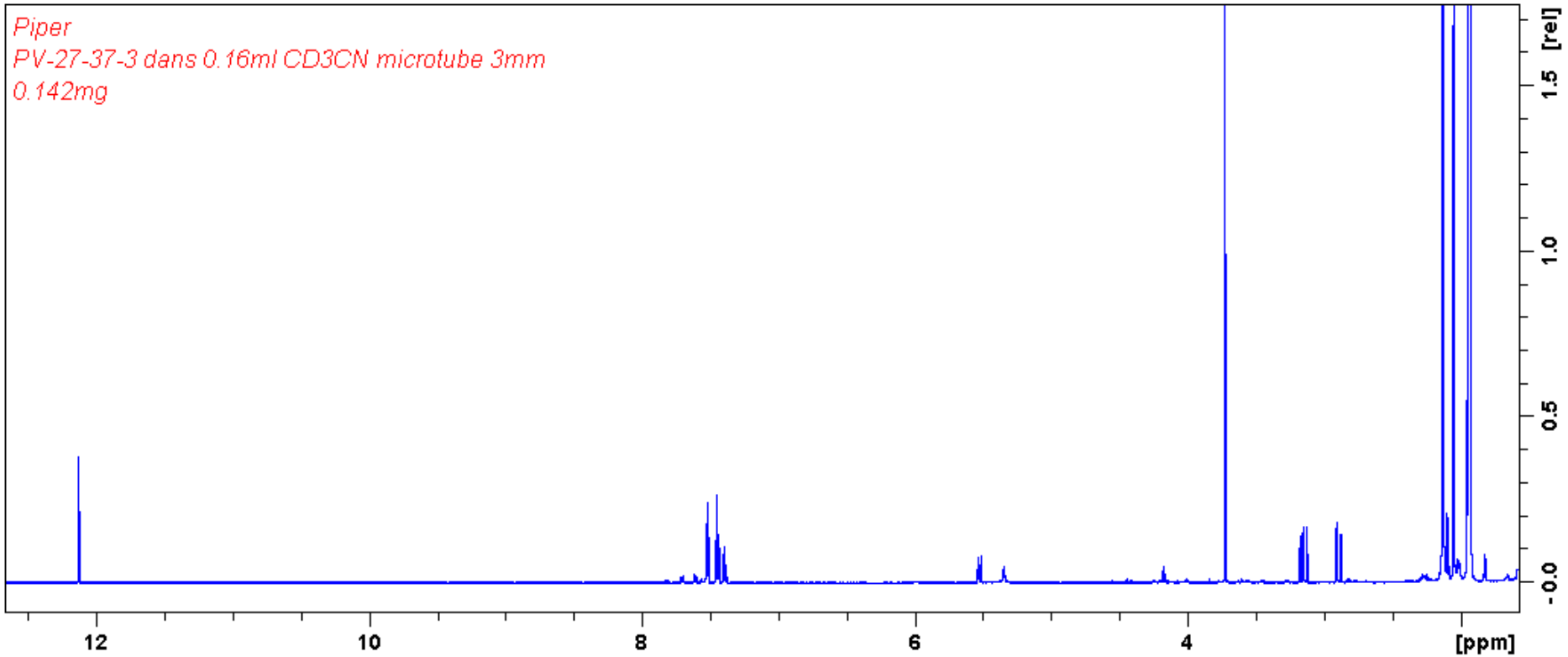
^{1}H NMR for compound **3** in $CDCl_3$



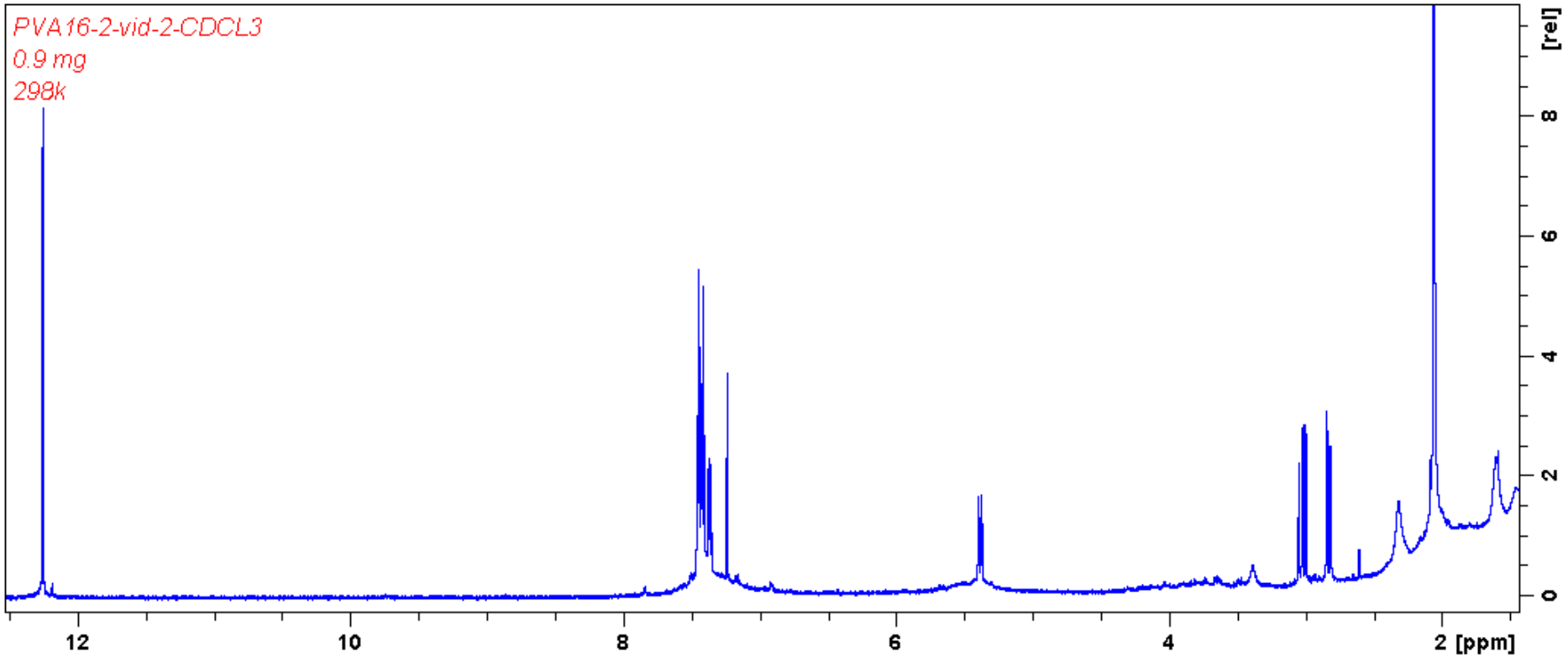
^{1}H NMR for compound **4** in CD_3CN



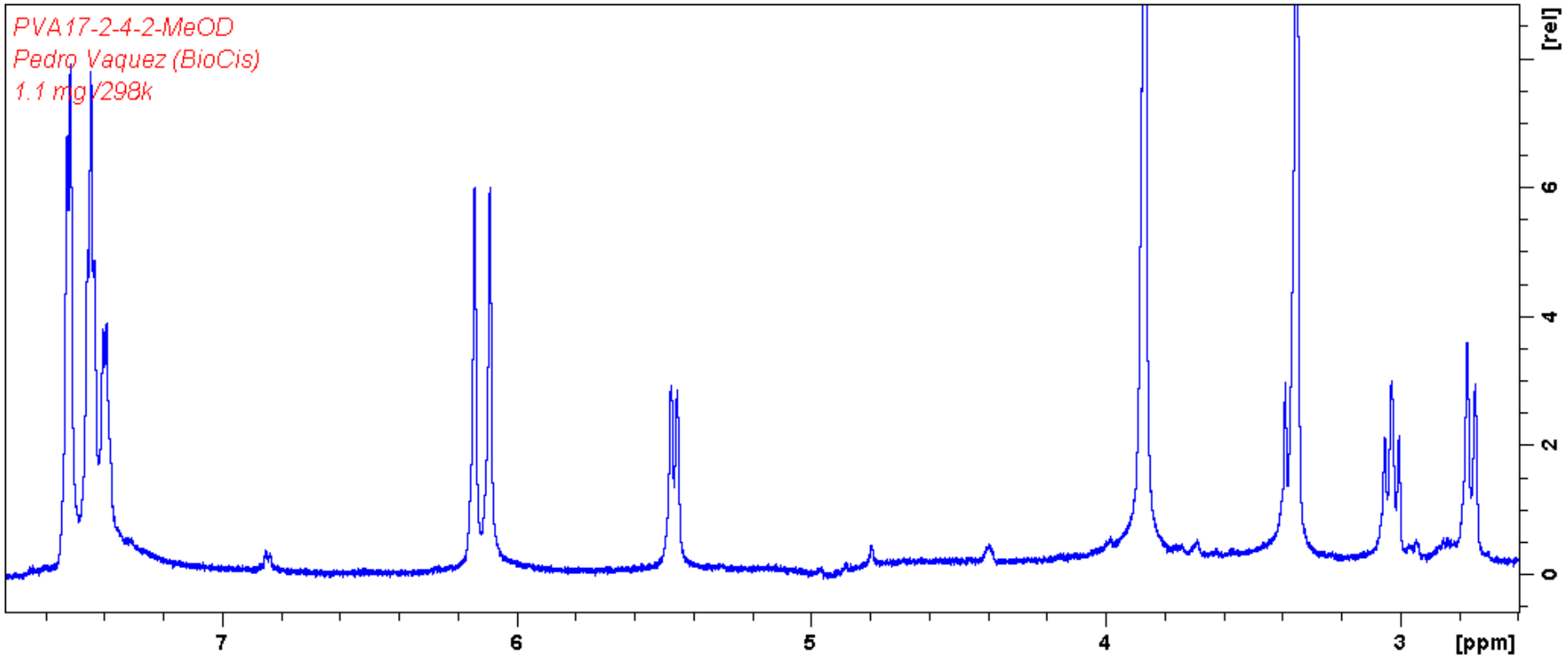
^{1}H NMR for compound **5** in CD_3CN



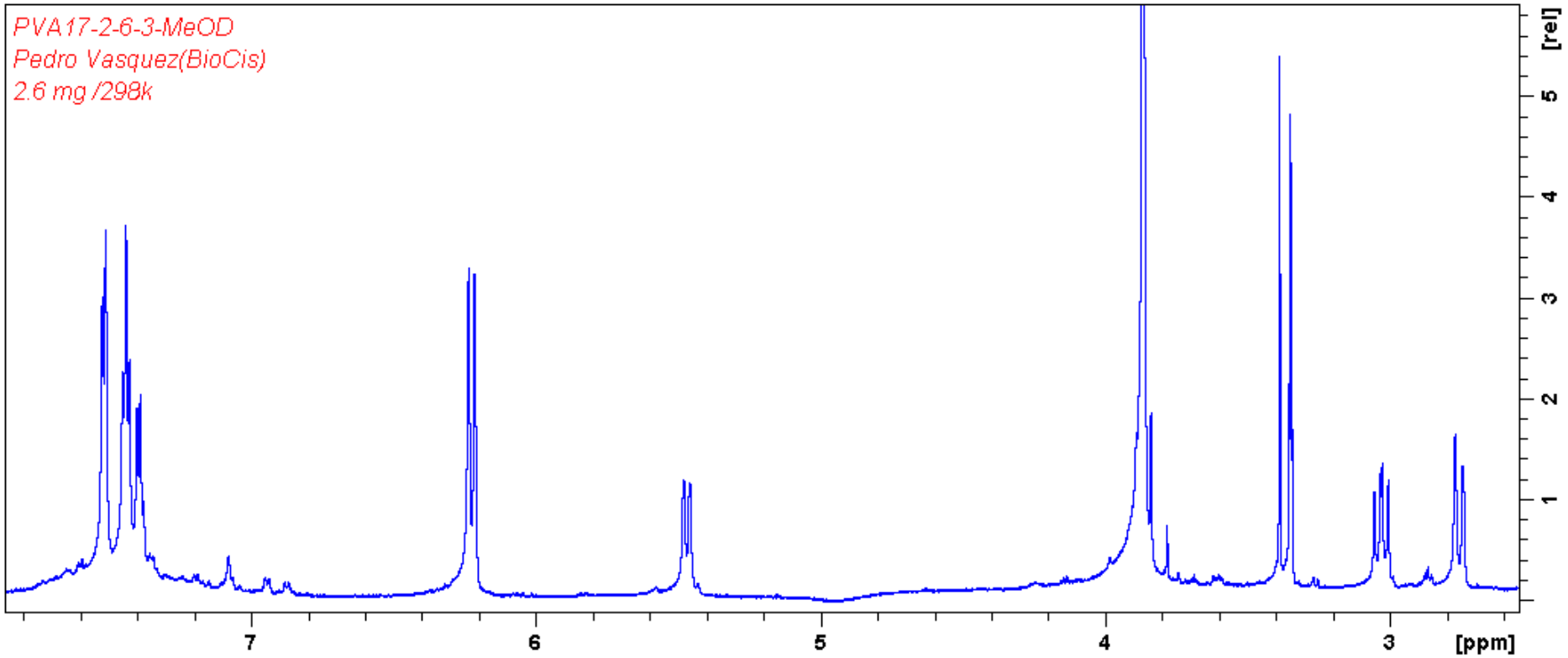
^{1}H NMR for compound **6** in $CDCl_3$



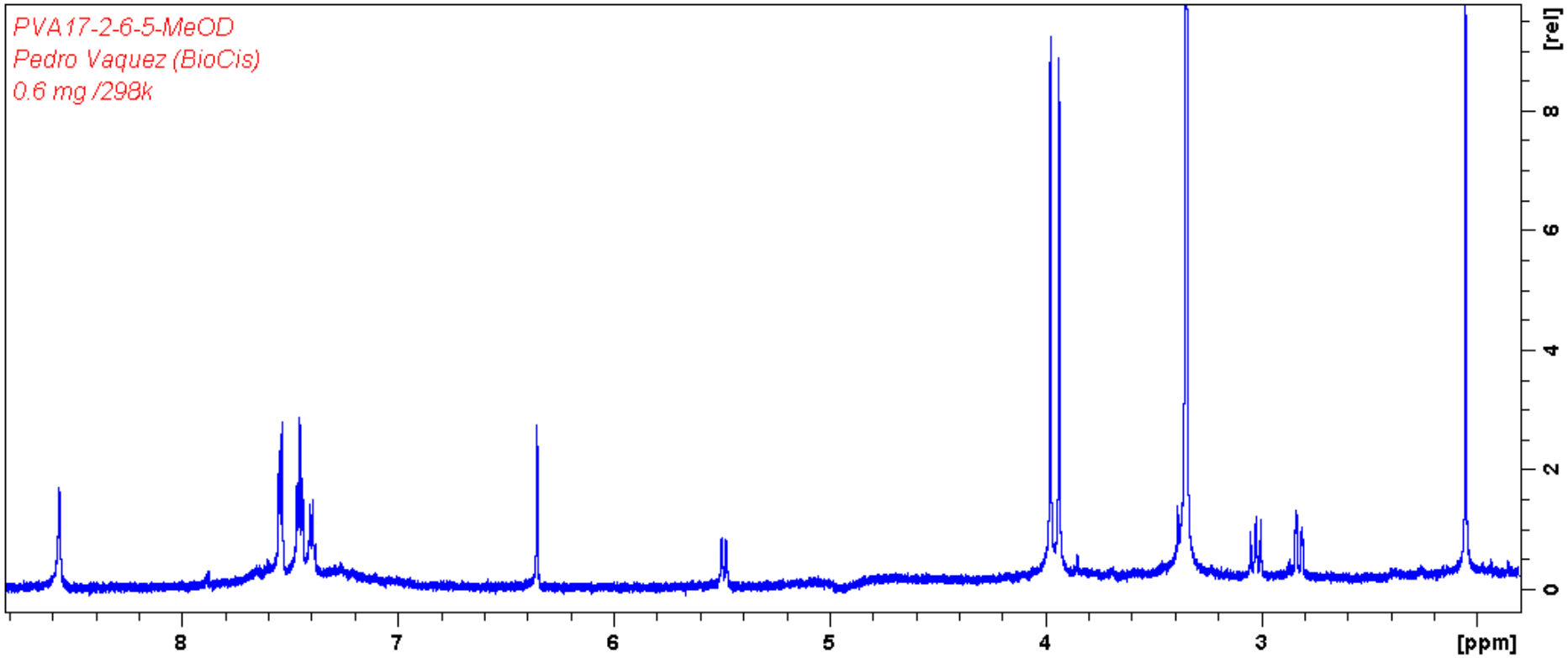
^{1}H NMR for compound **7** in CD_3OD



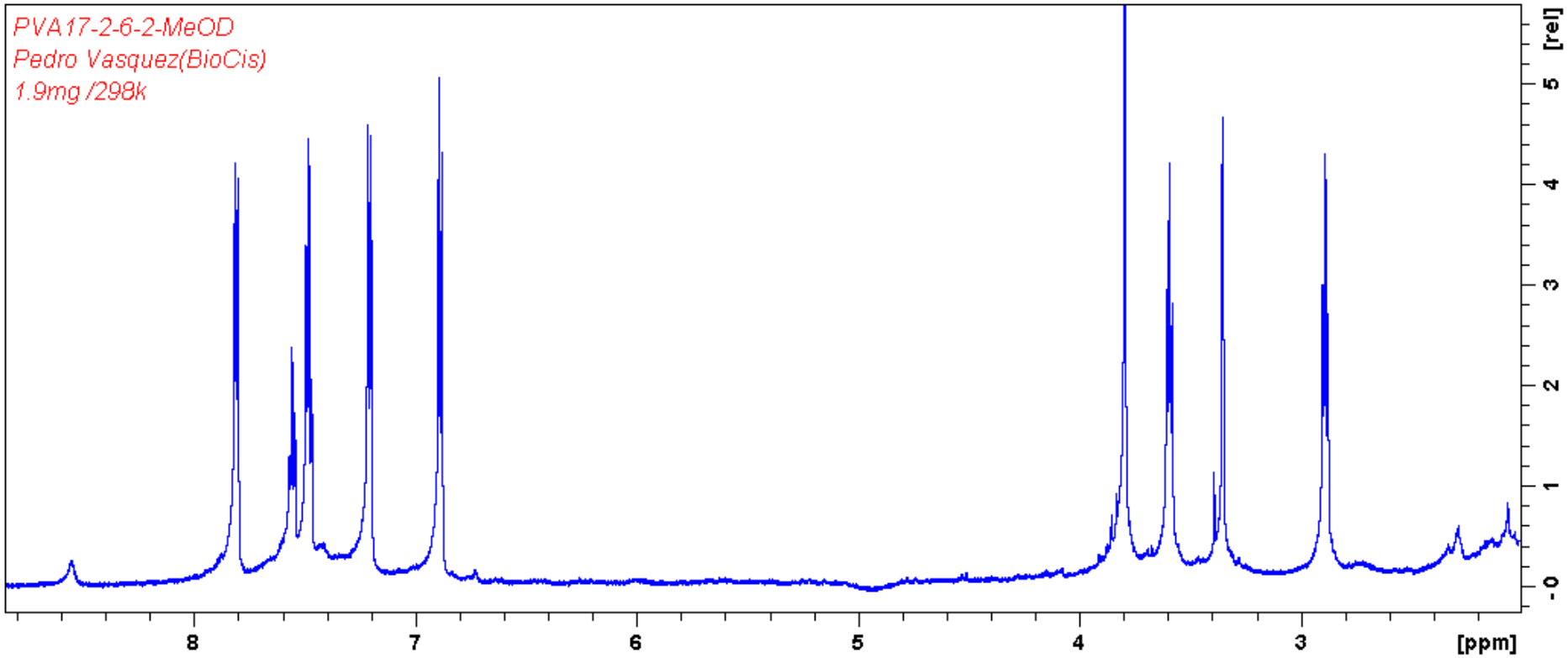
^{1}H NMR for compound **8** in CD_3OD



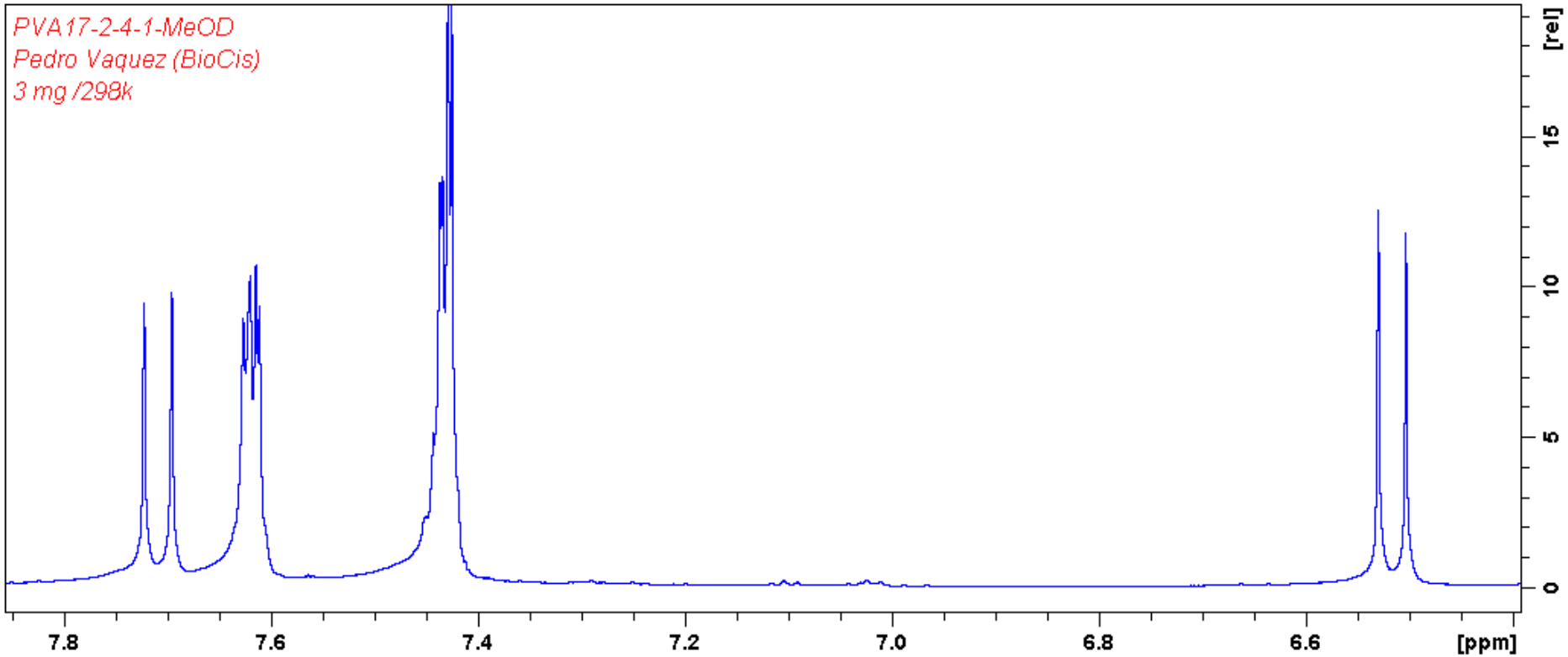
^{1}H NMR for compound **9** in CD_3OD



^{1}H NMR for compound **11** in CD_3OD



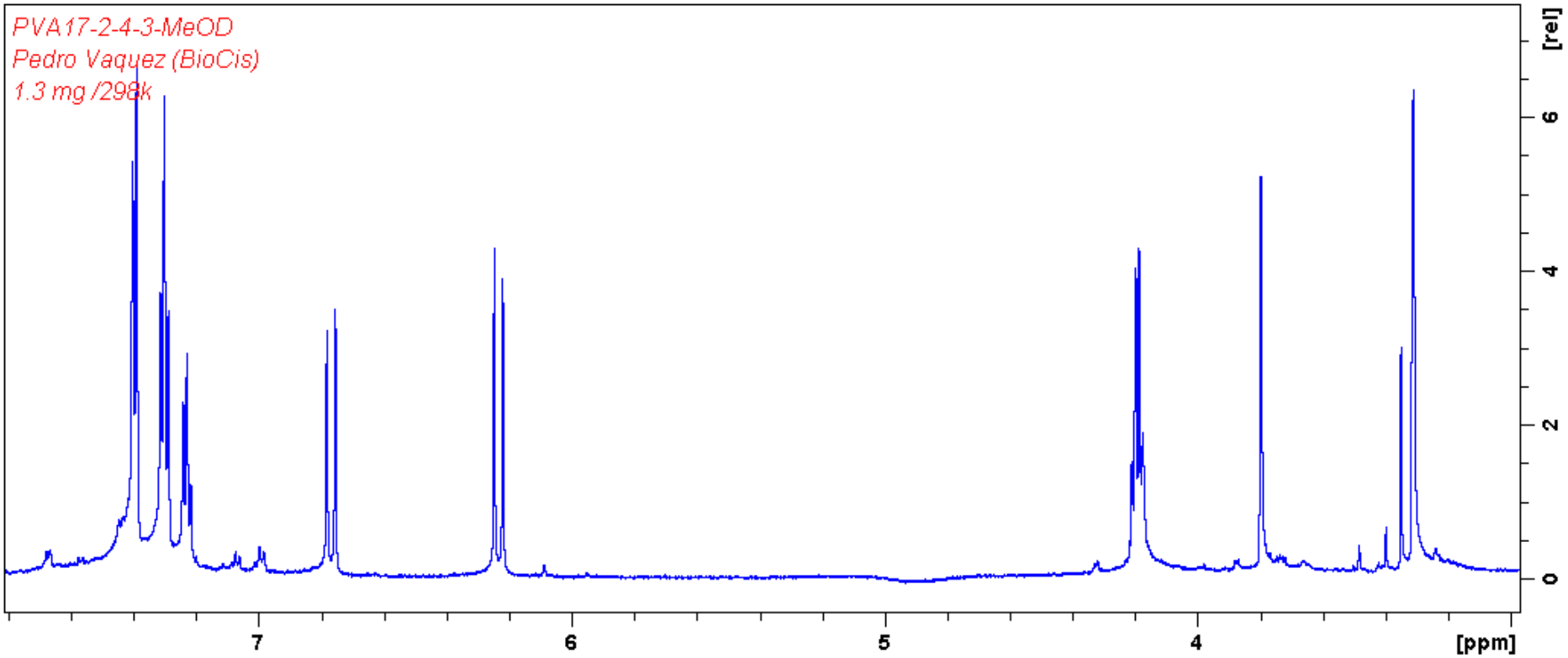
^{1}H NMR for compound **12** in CD_3OD



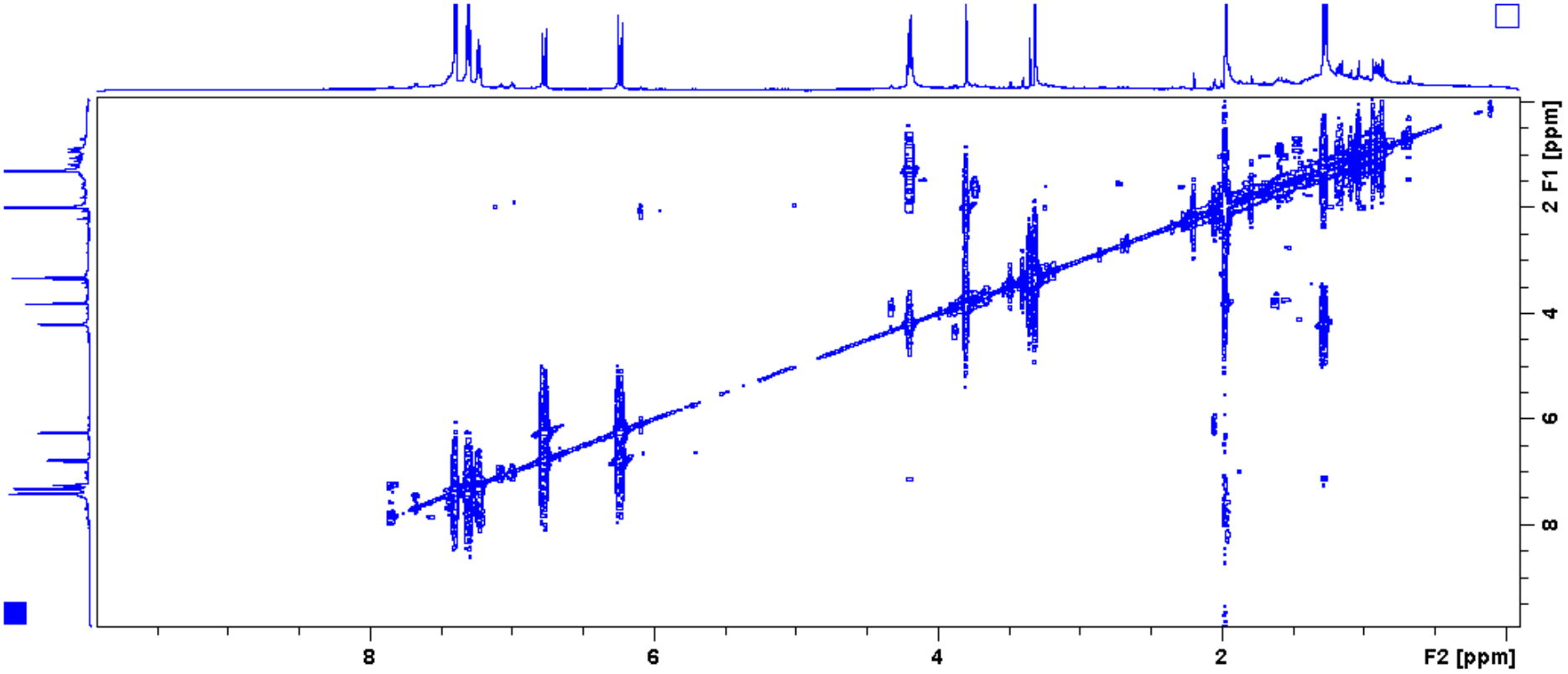
SI 8. 1D and 2D NMR for compound **10**

Figure S8. 1D and 2D NMR for compound **10**

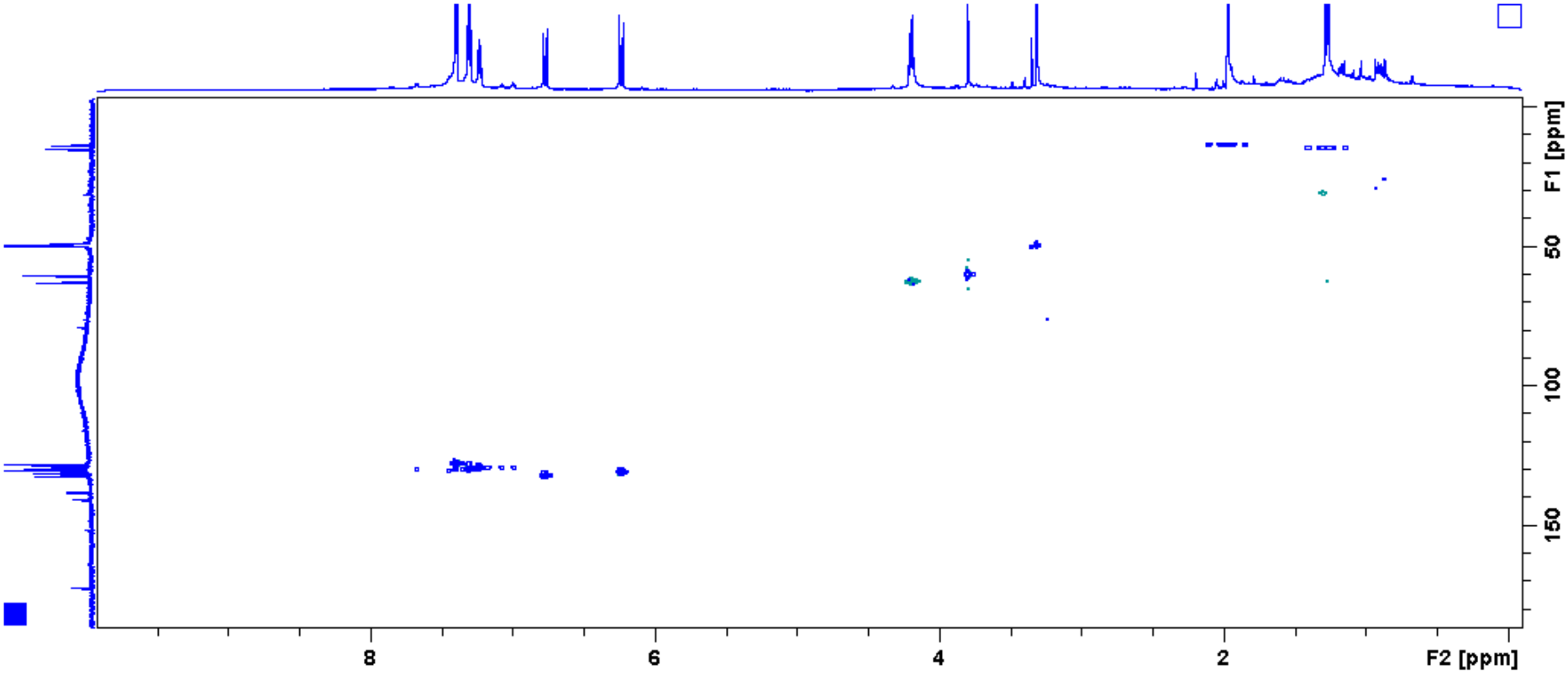
^{1}H NMR for compound **10** in CD_3OD



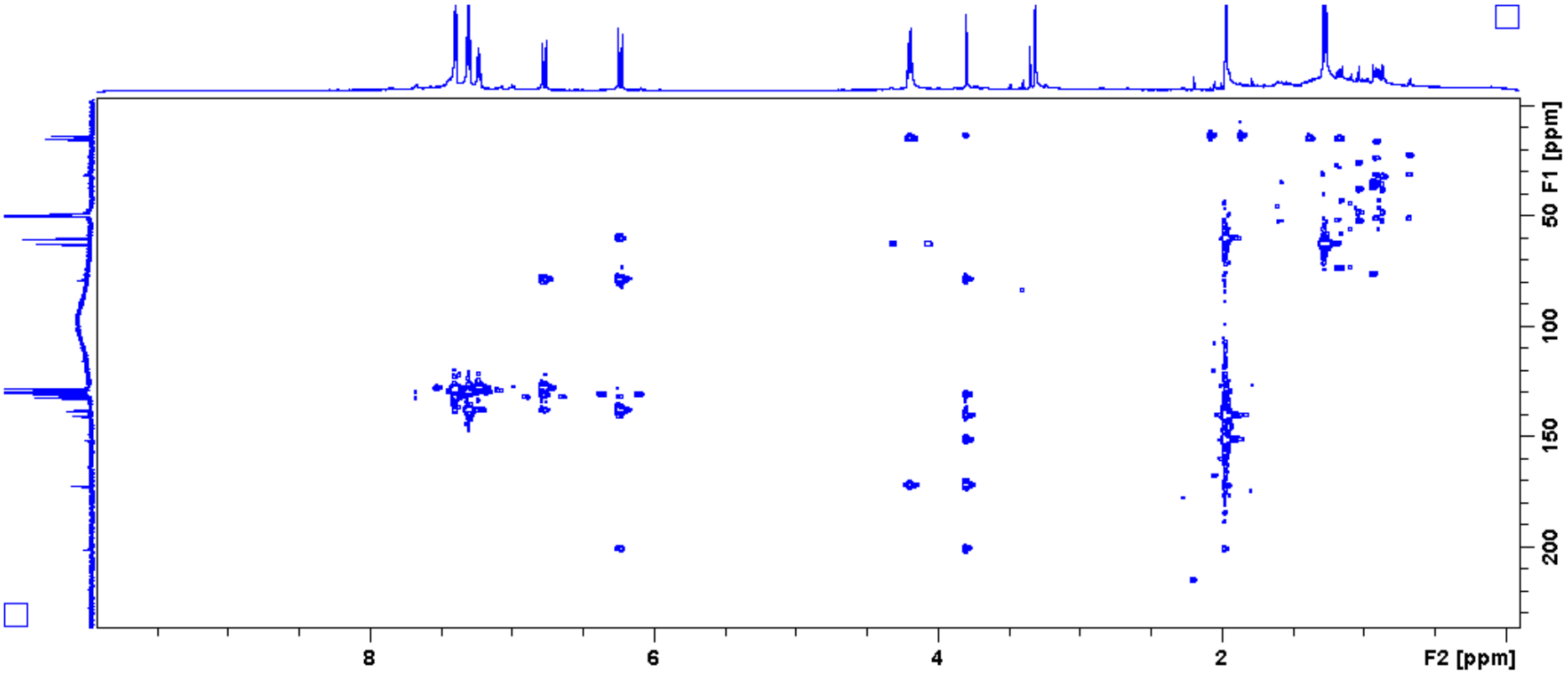
COSY spectrum for compound **10**



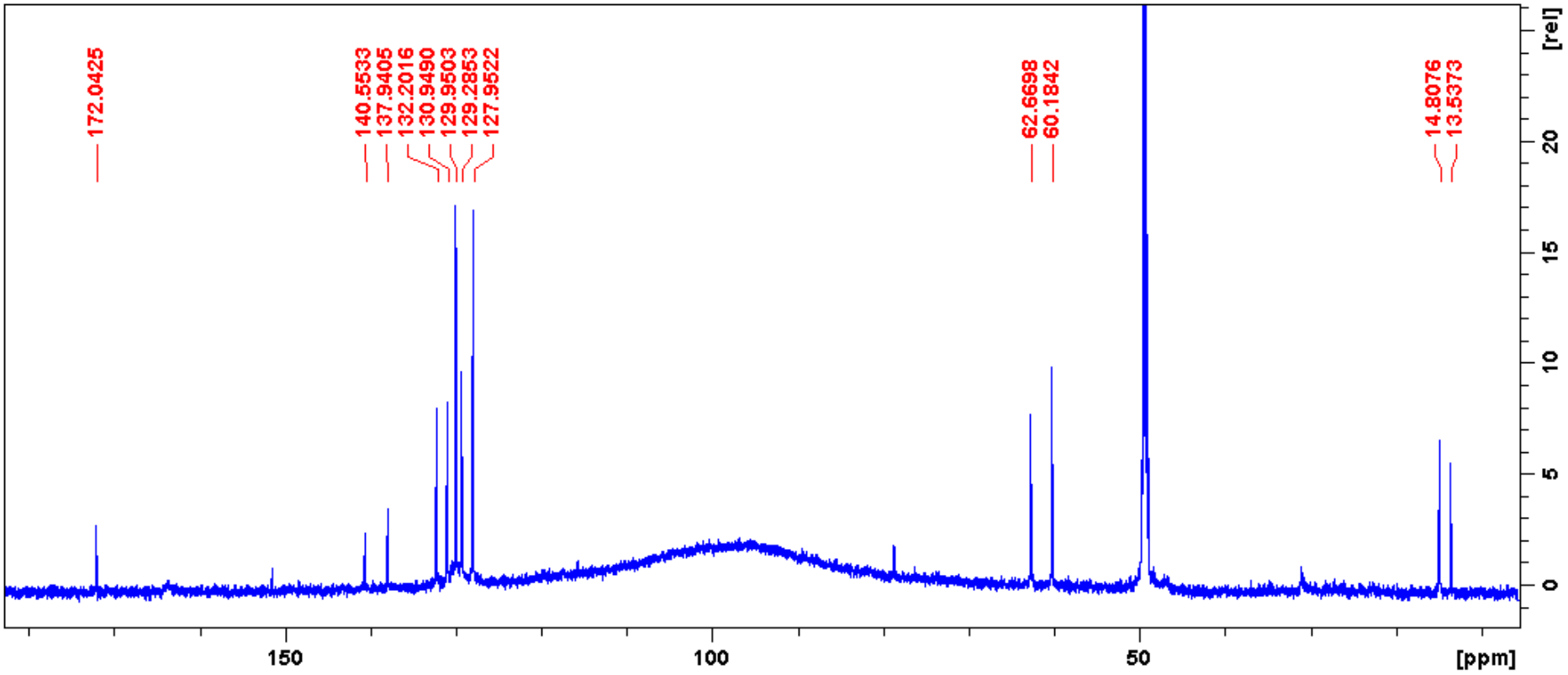
HSQC spectrum for compound **10**



HMBC spectrum for compound **10**



^{13}C NMR spectrum for compound **10**



SI 9. NMR spectroscopic data for isolated compounds

Table S1. NMR spectroscopic data for isolated compounds

NMR spectroscopic data for flavanones **4-9**.

Position	4		5		6		7		8		9	
	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C	δ_H, mult. (*J* in Hz)	δ_C
1												
2	5.51, dd (*2.8, 12.7*)	80.2	5.52, dd (*3.1, 12.7*)	79.6	5.39, dd (2.9, *12.9*)	78.9	5.46, dd (*2.4, 12.6*)	80.5	5.47, dd (*1.9, 13.0*)	80.4	5.49, dd (2.3, *12.6*)	80.2
3	a)3.14, dd (*12.7, 17.2*) b)2.83, dd (*3.2, 17.1*)	43.6	a) 3.15, dd (*12.7, 17.1*) b) 2.89, dd (*3.1, 17.1*)	43.7	b) 3.02, dd (*13.0, 17.1*) a) 2.83, dd (*3.1, 17.0*)	43.7	a) 3.02, dd *(13.0, 16.4)* b) 2.76, dd (*2.3, 16.3*)	46.6	a) 3.03, dd (*13.0, 16.6)* b) 2.76, dd (*2.2, 16.6*)	46.5	a) 3.03, dd (*12.7, 16.9,*) b) 2.83, dd (*2.5, 16.3*)	46.8
4		197.7		199.1		196.6		191.9		191.9		192.9
4a		103.7		105.9		103.1		106.1		106.7		106.4
5		161.2		160.0		159.4		164.6		163.9		166.0
6		106.2		111.8		102.4	6.14, s	94.6	6.23, d (*1.8*)	94.0	6.36, s	90.0
7		166.8		166.2		161.1		167.2		168.4		162.4
8	6.17, s	91.9		110.5		103.2	6.09, s	97.4	6.24, d (*1.8*)	95.1		107.2
8a		162.5		159.0		157.8		166.5		166.8		159.5
1′		140.0		140.1		139.0		140.9		140.5		141.1
2′	7.51, d (*6.8*)	127.4	7.52, d (*7.4*)	127.3	7.45, d (*7.1*)	126.1	7.52, d (*7.2*)	127.4	7.51, d (*7.3*)	127.4	7.55, d (*7.9*)	127.3
3′	7.44, t (*7.2*)	129.7	7.44, t (*7.5*)	129.7	7.42, dd (*7.5*)	129.0	7.44, t (*7.0*)	129.8	7.44, t (*7.4*)	129.8	7.46, t (*7.5)*	130.0
4′	7.39, t (*7.1*)	129.7	7.39, t (*7.3*)	129.6	7.36, dd (*7.1*)	128.6	7.40, t (*7.3*)	129.6	7.39, t (*7.1*)	129.7	7.40, t (*7.1*)	129.7
5′	7.44, t (*7.2*)	129.7	7.44, t (7.5)	129.7	7.42, dd (*7.5*)	129.0	7.44, t (*7.0*)	129.8	7.44, t (*7.4*)	129.8	7.46, t (*7.5*)	130.0
6′	7.51, d (*6.7*)	127.4	7.52, d (*7.4*)	127.3	7.45, d (*7.1*)	126.1	7.52, d (*7.2*)	127.4	7.51, d (*7.3*)	127.4	7.55, d (*7.9*)	127.3
O-CH3	3.84, s	7) 56.9	7) 3.72, s	60.8			5) 3.86, s	56.4	5) 3.869, s 7) 3.867, s	56.5 56.5	5) 3.98, s 7) 3.94, s	-56.5 -56.4
OH	12.17, s		5) 12.12		5) 12.25, s							
CH_3	1.94, s	6) 7.1	6) 2.04, s 8) 2.04, s	8.6 8.1	6) 2.060, s 8) 2.055, s	6) 7.2 8) 7.7					2.06, s	8)8.2

NMR spectroscopic data for chalcones **1-3**.

Position	1		2		3	
	δ_H, mult. (*J* in Hz)[a]	δ_C[a]	δ_H, mult. (*J* in Hz)[b]	δ_C[b]	δ_H, mult. (*J* in Hz)[c]	δ_C[c]
1		135.4		135.3		137.3
2	7.70, dd (*1.9, 7.8*)	128.4	7.63, d (*6.5)*	128.5	7.68, d (*6.3)*	129.6
3	7.43, m	130.2	7.40 m	129.0	7.45, m	131.5
4	7.44, m	129.0	7.40 m	130.3	7.47, m	130.3
5	7.43, m	130.2	7.40 m	129.0	7.45, m	131.5
6	7.70, m	128.4	7.63, d (*6.5)*	128.5	7.68, d (*6.3)*	129.6
α	7.97, d (*15.6*)	128.0	7.95, d (*15.5)*	126.4	7.96, d (*15.6)*	129.3
β	7.74, d (*15.6*)	141.6	7.82, d (*15.5)*	143.2	7.74, d (*15.6)*	143.2
9		193.1		194.2		193.1
1′		105.8		109.7		107.0
2′		163.8		162.5		169.1
3′		104.9		110.2	5.98, d (*2.2)*	97.4
4′		164.1		160.7		167.1
5′	6.21, s	87.2	6.23, s	99.8	6.06, d (*2.0)*	92.8
6′		161.6		161.4		165.1
O-CH3	4) 3.92, s 6) 3.99, s	-55.6 -55.9	6′)3.66, s	62.3	6′) 3.97, s	56.7
OH	2′) 14.03	163.8	2′) OH 4′) OH	162.5 160.7	2′) OH 4′) OH	169.1 167.1
CH_3	3′) 1.96, s	6.5	2.1, s	8.1	-	

NMR spectroscopic data for compound **12**

Position	12	
	δ_H, mult. (*J* in Hz)[a]	δ_C[a]
1		170.7
2	6.52, d (*16.0*)	119.6
3	7.71, d (*16.0*)	146.6
4		136.1
5	7.62, dd (*7.6, 4.1*)	129.5
6	7.43, dd (*4.8, 1.6*)	130.3
7	7.62, dd (*7.6, 4.1*)	129.5
8	7.43, dd (*5.18*)	131.7
9		136.1

NMR spectroscopic data for compound **10**

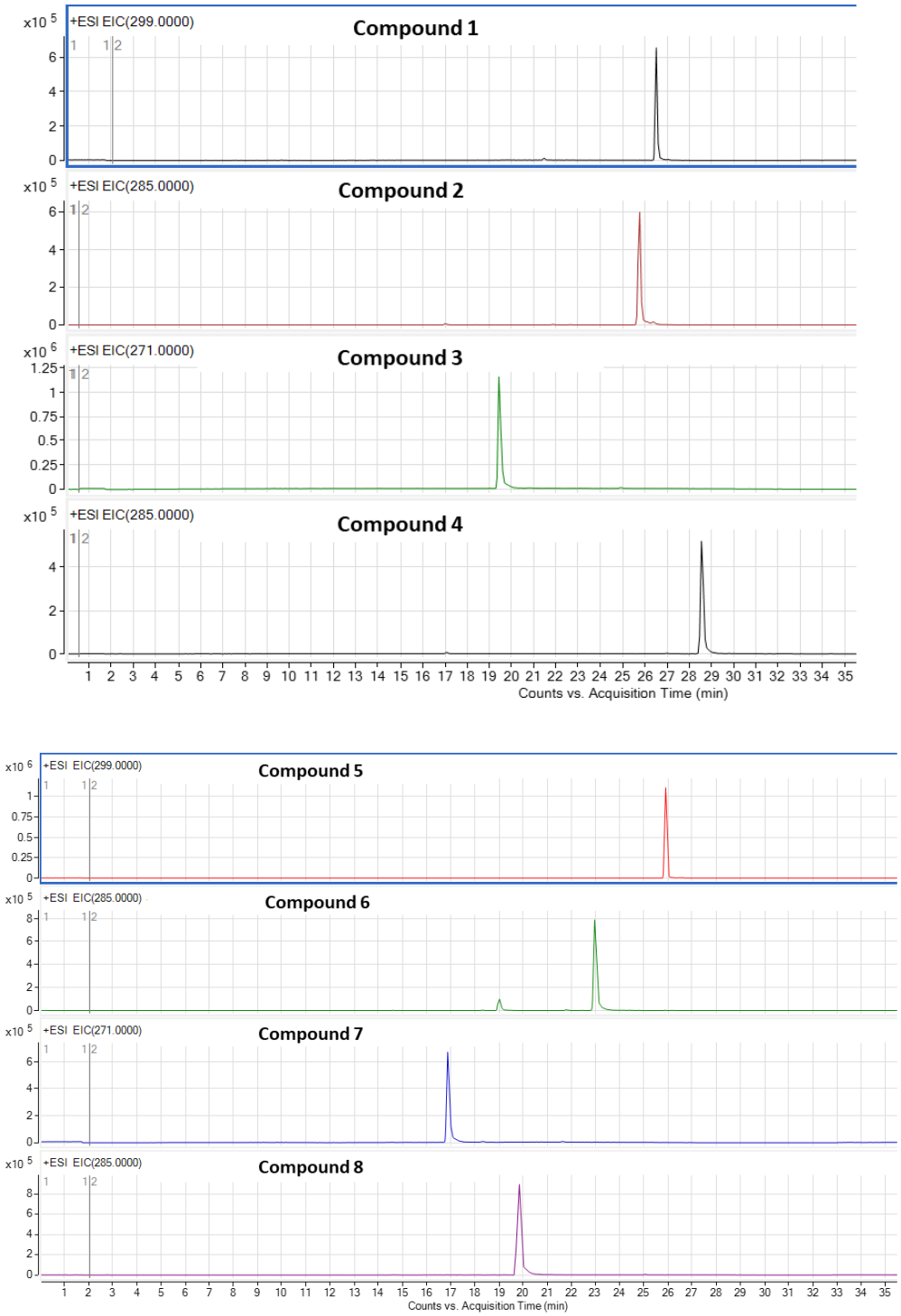
Position	10	
	δ_H, mult. (*J* in Hz)	δ_C
1		137.8
2	7.40, d (*7.7*)	127.9
3	7.30, dd (*7.7, 7.4*)	129.9
4	7.23, t (*7.4, 7.1*)	129.2
5	7.30, dd (*7.7, 7.4*)	129.9
6	7.40, dd (*7.7*)	127.9
7	6.77, d (*15.9*)	132.1
8	6.23, d (*15.9*)	130.9
9		200.8
2′		151.3
3′		140.4
4′	3.80, s	60.0
5′		78.6
6′		171.9
7′	4.19, m	62.5
8′	1.27, t (*7.1*)	14.9
9′	1.97; s	13.5

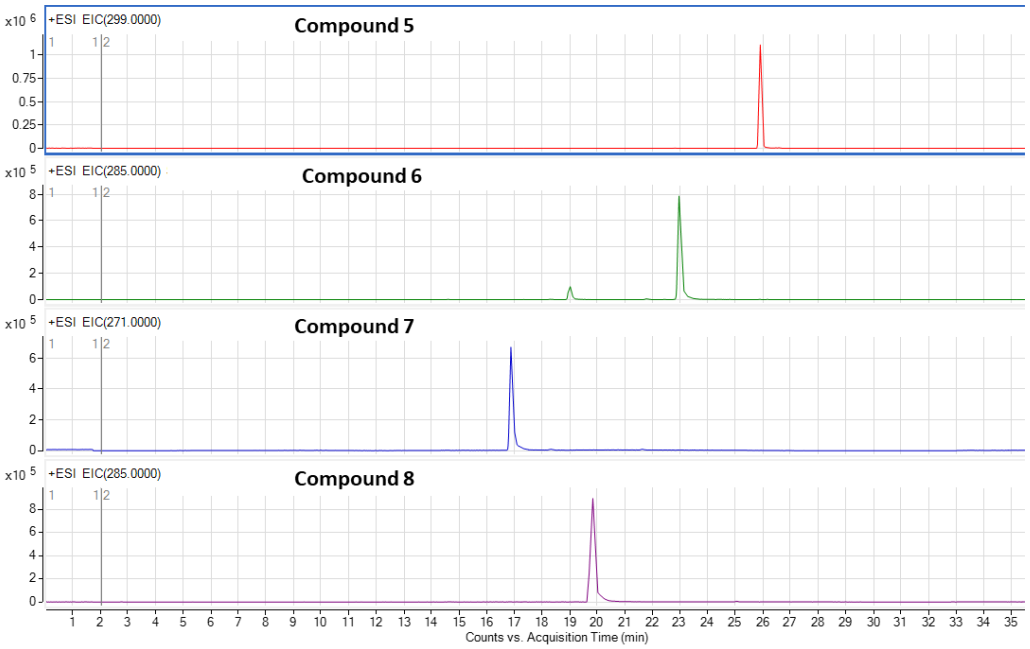
NMR spectroscopic data for compound **11**

Position	11	
	δ_H, mult. (*J* in Hz)	δ_C
1		170.5
2		136.1
3	7.81, d (*7.2*)	128.5
4	7.48, t (*7.6*)	129.8
5	7.55, dd (7.3, *7.4*)	132.9
6	7.48, dd (*7.6*)	129.8
7	7.81, d (*7.2*)	128.5
8	NH	
9	3.59, t (*7.4*)	43.2
10	2.89, t (*7.3*)	36.0
11		132.9
12	7.21, d (*8.5*)	131.1
13	6.88, d (*8.6*)	115.2
14		160.0
15	6.88, d (*8.6*)	115.2
16	7.21, d (*8.5*)	131.1
O-CH$_3$	14) 3.79, s	55.8

SI 10. LCMS of compounds isolated from *P. coruscans*.

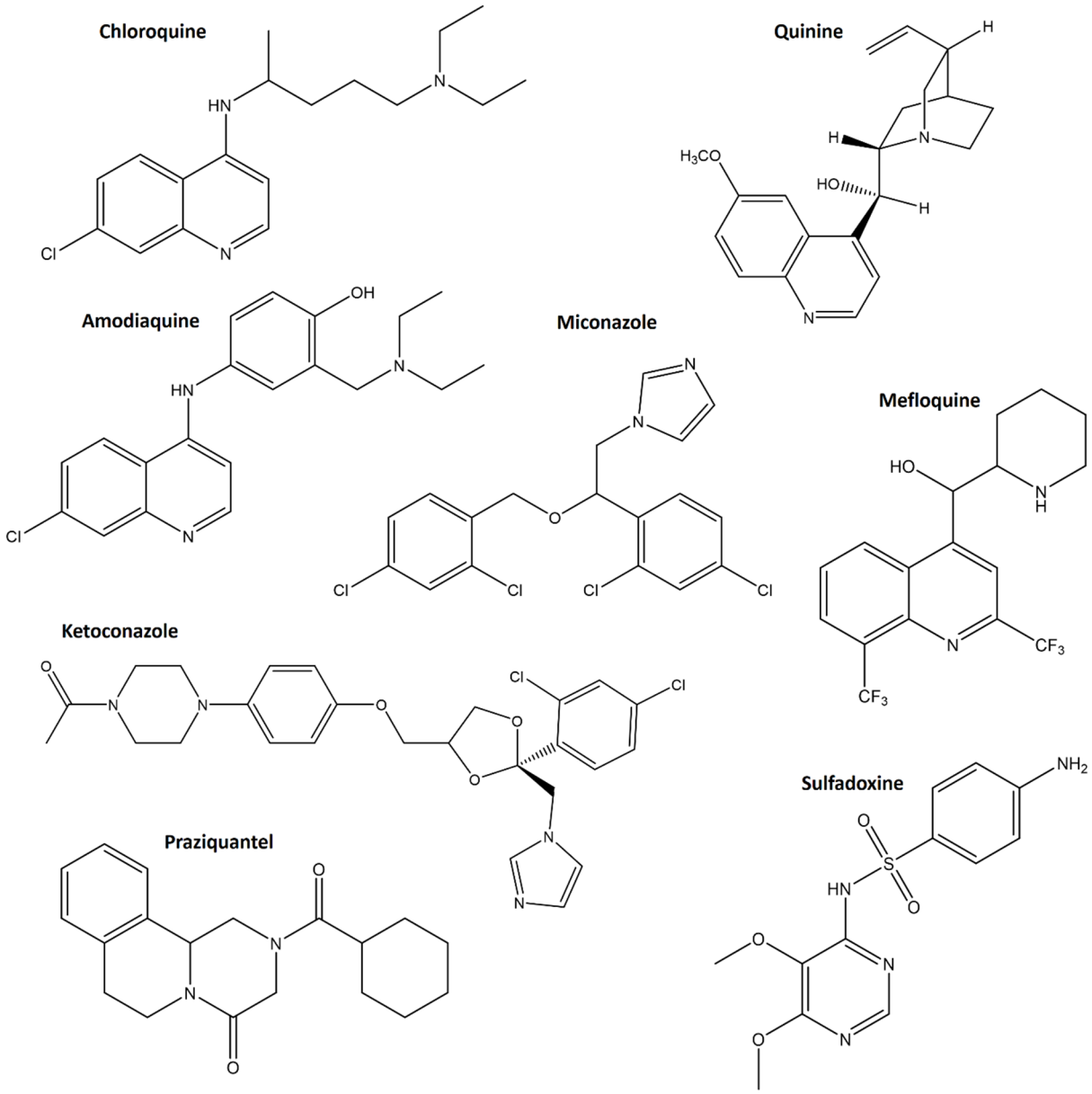
Figure S9. LCMS of compounds isolated from *P. coruscans*.




x10 6
+ESI EIC(299.0000)
Compound 5
x10 5
+ESI EIC(285.0000)
Compound 6
x10 5
+ESI EIC(271.0000)
Compound 7
x10 5
+ESI EIC(285.0000)
Compound 8
Counts vs. Acquisition Time (min)

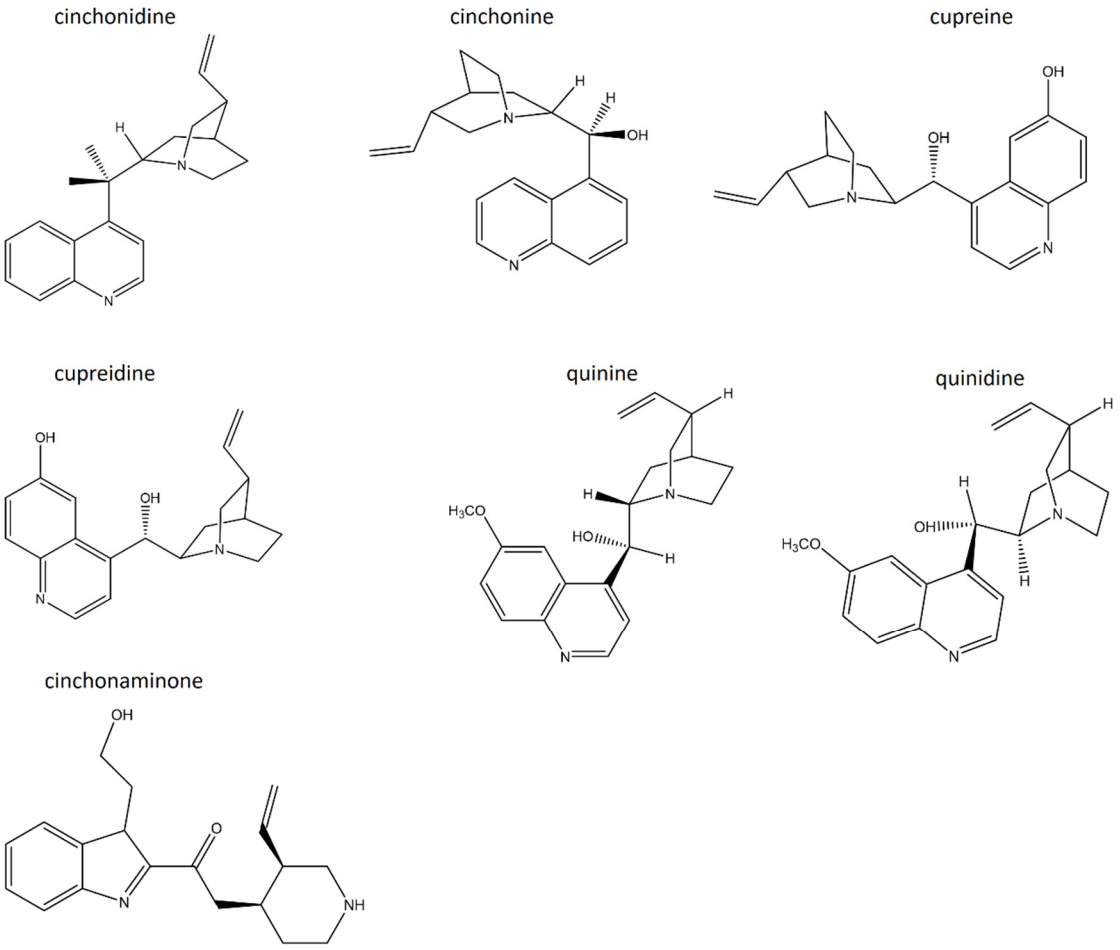
SI 11. Structures of antimalarial drugs

Figure S10. Structures of antimalarial drugs



SI 12. Structures of alkaloids from *C. pubescens*

Figure S11. Structures of alkaloids from *C. pubescens*



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