

# Auranofin and Related Heterometallic Gold(I)-Thiolates as Potent Inhibitors of Methicillin-Resistant *Staphylococcus aureus* Bacterial Strains

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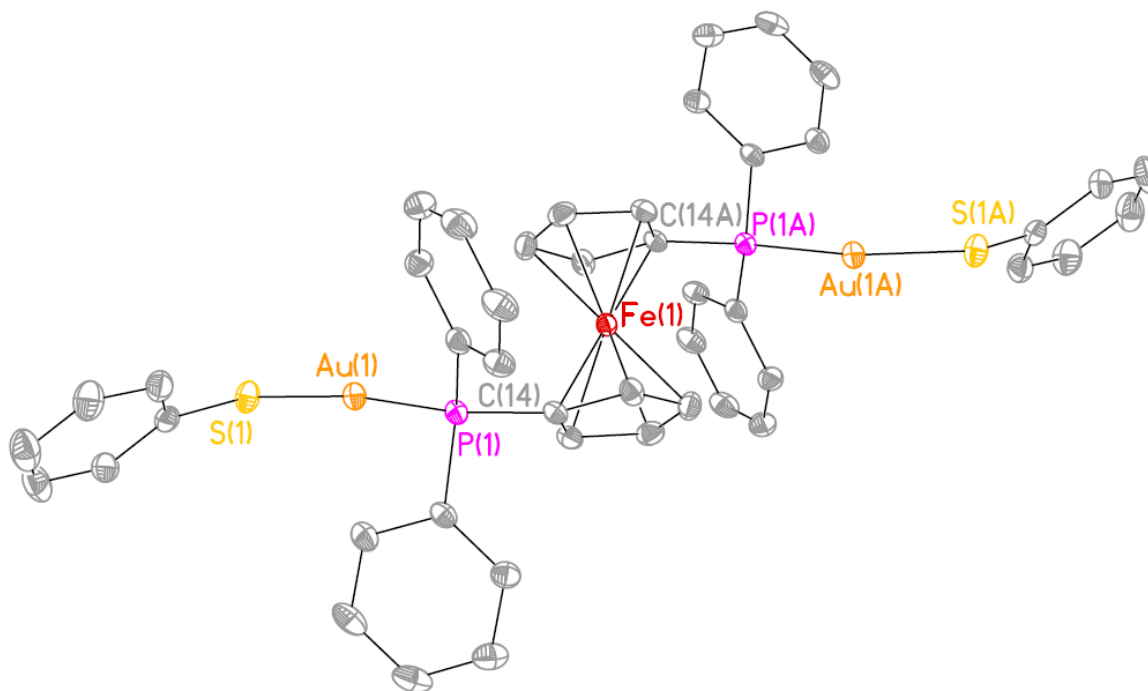
## Supplementary Material

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## 1. Crystallographic Data for Compounds **3a** and **3d**

Single crystals of **3a** and **3d** (see details below) were mounted on a glass fiber in a random orientation. Data collection was performed at room temperature on a Kappa CCD diffractometer using graphite monochromated Mo-K $\alpha$  radiation ( $\lambda=0.71073$  Å). Space group assignments were based on systematic absences, E statistics and successful refinement of the structures. The structures were solved by direct methods with the aid of successive difference Fourier maps and were refined using the SHELXTL 6.1 software package. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to ideal positions and refined using a riding model. Details of the crystallographic data are given in Table S1 (below). These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif). (CCDC 977988 for compound **3a**, and 977989 for compound **3d**). **3a**: Crystals of **3a** (orange prisms with approximate dimensions 0.25 x 0.23 x 0.23 mm) were obtained from a solution of **3a** in CH<sub>2</sub>Cl<sub>2</sub> by slow diffusion of Et<sub>2</sub>O at RT. **3d**: Crystals of **3d** (orange prisms with approximate dimensions 0.25 x 0.24 x 0.22 mm) were obtained from a solution of **3d** in CH<sub>2</sub>Cl<sub>2</sub> by slow diffusion of Et<sub>2</sub>O at RT.



**Figure S1.** Crystal structure of **3a**.

**Table S1.** Crystal Data and Structure Refinement for Complexes **3a** and **3d**.

Compound	<b>3a</b> [ <b>{AuSPh}</b> ]( $\mu$ -DPPF)]	<b>3d</b> [ <b>{AuSthiazoline}</b> ] <sub>2</sub> ( $\mu$ -DPPF)]
formula	C <sub>46</sub> H <sub>38</sub> Au <sub>2</sub> FeP <sub>2</sub> S <sub>2</sub>	C <sub>40</sub> H <sub>36</sub> Au <sub>2</sub> FeN <sub>2</sub> P <sub>2</sub> S <sub>4</sub>
fw	1161.61	1184.67
T [K]	293 (2)	293(2)
$\lambda$ (MoK $\alpha$ )[Å]	0.71073	0.71073
crystal system	Triclinic	Monoclinic
space group	P-1	P2(1)/c
<i>a</i> [Å]	8.6320(17)	10.8500(7)
<i>b</i> [Å]	10.140(2)	9.5950(3)
<i>c</i> [Å]	13.014(3)	19.8390(13)
$\alpha$ [°]	101.87(3)	90
$\beta$ [°]	106.29(3)	105.962(2)
$\gamma$ [°]	105.48(3)	90
<i>V</i> [Å <sup>3</sup> ]	1004.1(3)	1985.72(19)
<i>Z</i>	1	2
<i>D</i> <sub>calcd</sub> (g cm <sup>-3</sup> )	1.929	1.981
$\mu$ (mm <sup>-1</sup> )	7.860	8.053
GOF	1.134	1.049
R <sub>1</sub> [ <i>I</i> > 2 $\sigma$ ]	0.0328	0.0582
wR <sub>2</sub> (all data)	0.085	0.1861

**Table S2.** Selected bond lengths [Å] and angles [°] for complexes **3a** and **3d**.

<b>3a</b>		<b>3d</b>	
Au(1)-P(1)	2.2546(14)	Au(1)-P(1)	2.259(3)
Au(1)-S(1)	2.3000(16)	Au(1)-S(1)	2.307(3)
Fe-C	2.032(4)-2.063(5)	Fe-C	2.025(15) -2.050(15)
S-C(41)	1.783(6)	S-C(1)	1.761(14)
P(1)-C(14)	1.781(5)	P(1)-C(12)	1.788(12)
P(1)-C(31)	1.826(5)	P(1)-C(31)	1.815(13)
P(1)-C(21)	1.827(5)	P(1)-C(21)	1.810(13)
P(1)-Au(1)-S(1)	171.33(5)	C(1)-N(1)	1.273(18)
C(14)-Fe(1)-C(14A)	180.0(3)	C(1)-S(2)	1.759(16)
C(41)-S(1)-Au(1)	100.93(19)	N(1)-C(3)	1.44(2)
		S(2)-C(2)	1.82(2)
		C(2)-C(3)	1.41(3)
		P(1)-Au(1)-S(1)	177.75(11)
		C(14)-Fe(1)-(C14A)	179.999(2)
		C(1)-S(1)-Au(1)	104.0(5)

## 2. DFT Studies for compounds **4a** and **4d**

The calculations have been performed using the hybrid density functional method B3LYP, as implemented in Gaussian09. Geometries were optimized with the 6-31G(d,p) basis set for the C, N, P, S, and H elements and the SDD pseudopotential for the iron and gold centers. Frequency calculations have been done at the same level of theory as the geometry optimizations to confirm the nature of the stationary points.

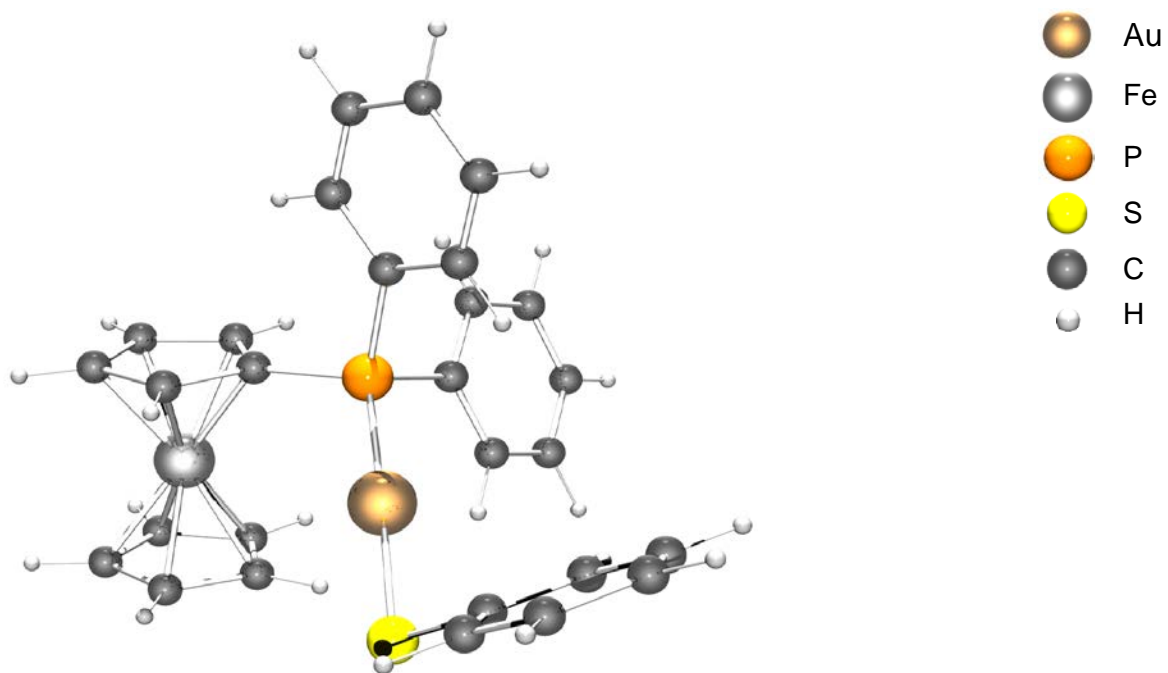


Figure S2. Optimized structure of 4a.

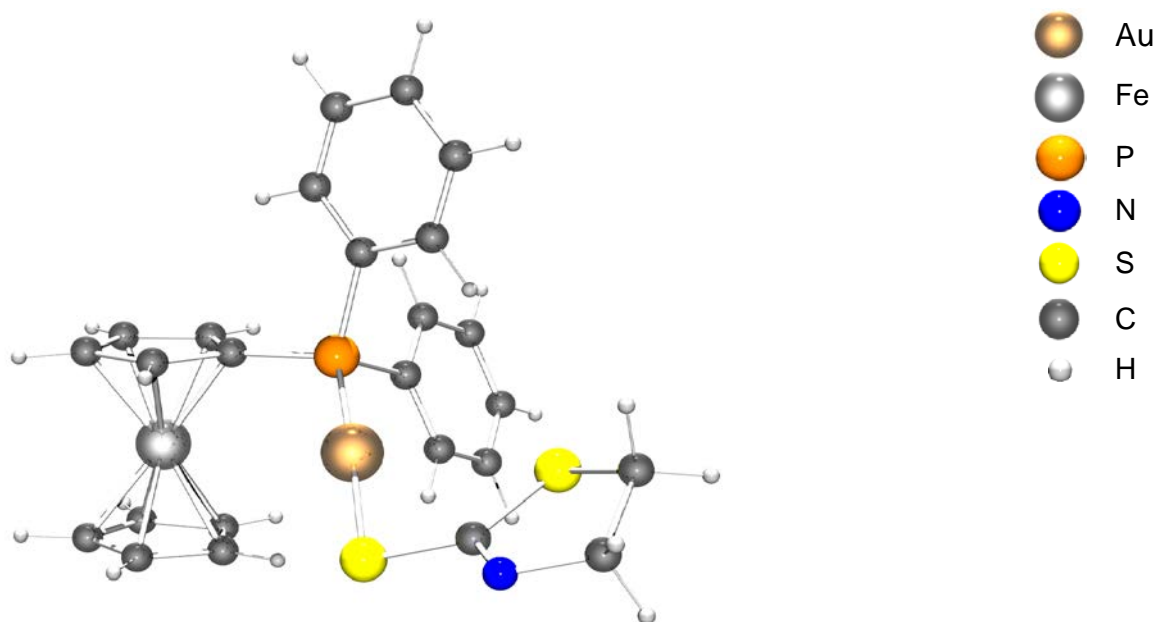


Figure S3. Optimized structure of 4d.

**Table S3.** Selected structural parameters of complexes **4a** and **4d** obtained from DFT calculations and the comparison with experimental values of **3a** and **3d**. Bond lengths in Å and angles in °.

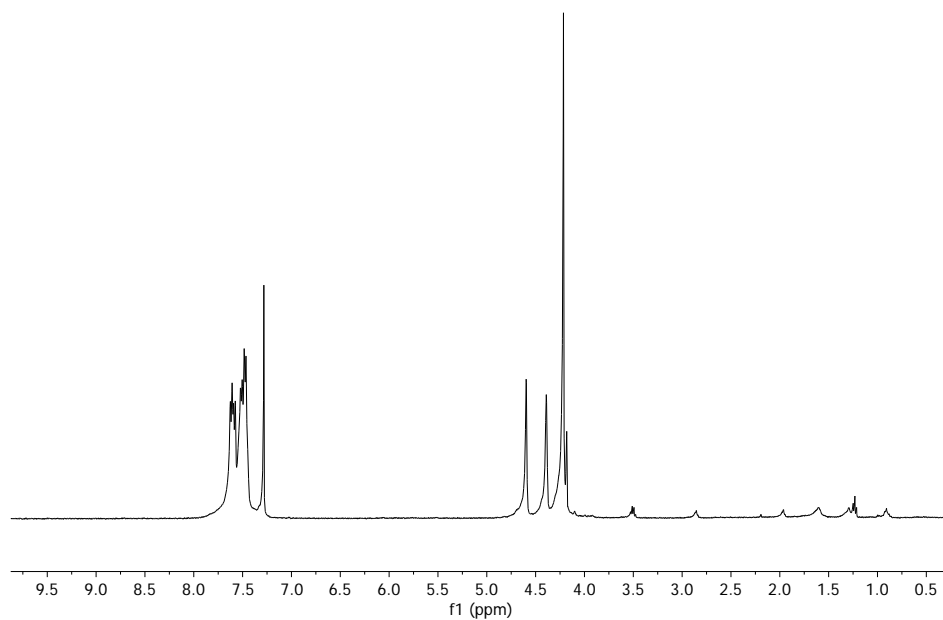
<b>3a</b>		<b>4a</b>	<b>3d</b>		<b>4d</b>
Au(1)-P(1)	2.2546(14)	2.335	Au(1)-P(1)	2.259(3)	2.333
Au(1)-S(1)	2.3000(16)	2.345	Au(1)-S(1)	2.307(3)	2.353
Fe-C	2.032(4)- 2.063(5)	2.070-2.083 1.796	Fe-C	2.025(15)- 2.050(15)	2.070-2.084 1.765
S-C(41)	1.783(6)	178.201	S-C(1)	1.761(14)	177.842
P(1)-Au(1)- S(1)	171.33(5) 180.0(3)	156.270	P(1)-Au(1)- S(1)	177.75(11) 179.999(2)	166.650
C(14)-Fe(1)- C14(1)#			C(14)-Fe(1)- C14(1)#		
C(41)-S(1)- Au(1)	100.93(19)	103.791	C(1)-S(1)- Au(1)	104.0(5)	103.953

**Optimized geometries and cartesian coordinates of stationary points.**

<b>4a</b>			H	0.408445	-0.208660	2.601860	
Charge: 0			C	1.398505	1.136051	3.964722	
Multiplicity: 1			H	1.228247	0.501263	4.829310	
			C	2.057965	2.357866	4.108959	
Fe	3.174301	-1.294432	-0.625860	H	2.407172	2.675770	5.087051
C	2.439271	-3.219095	-0.335296	C	2.255076	3.178325	2.995756
H	1.633419	-3.658183	-0.907181	H	2.755623	4.135950	3.106071
C	2.293533	-2.457363	0.861465	C	1.801676	2.776005	1.739081
H	1.354704	-2.224275	1.344373	H	1.943681	3.429505	0.883775
C	3.590489	-2.026350	1.275263	C	0.025224	2.483243	-0.938494
H	3.810330	-1.407094	2.134249	C	0.887078	3.216346	-1.767461
C	3.828446	-3.263876	-0.661127	H	1.907507	2.880813	-1.923990
C	4.540117	-2.527824	0.334242	C	0.432434	4.372546	-2.404976
H	5.607556	-2.353366	0.352775	H	1.105611	4.931366	-3.048724
Au	-1.108365	-0.664342	0.021466	C	-0.881581	4.805286	-2.220765
P	0.567429	0.959569	-0.063069	H	-1.233743	5.702586	-2.721267
S	-2.745009	-2.342651	0.074728	C	-1.746489	4.076522	-1.401062
C	3.433470	0.761983	-0.645406	H	-2.773693	4.401277	-1.264685
H	3.774516	1.343353	0.199309	C	-1.298856	2.918222	-0.766760
C	4.254591	0.165516	-1.644931	H	-1.981772	2.342809	-0.147571
H	5.334870	0.208210	-1.683206	C	-4.292545	-1.430942	0.110507
C	3.410030	-0.541371	-2.554136	C	-4.558042	-0.427374	1.057982
H	3.738444	-1.128459	-3.401095	H	-3.791808	-0.165700	1.781571
C	2.064407	0.425459	-0.934538	C	-5.793959	0.219503	1.080660
C	2.062875	-0.391289	-2.119425	H	-5.978199	0.995288	1.819781
H	1.186421	-0.827441	-2.579116	C	-6.794342	-0.131735	0.171078
C	1.149288	1.542646	1.583496	H	-7.757731	0.369634	0.193634
C	0.941660	0.731372	2.709153	C	-6.543311	-1.137326	-0.764145

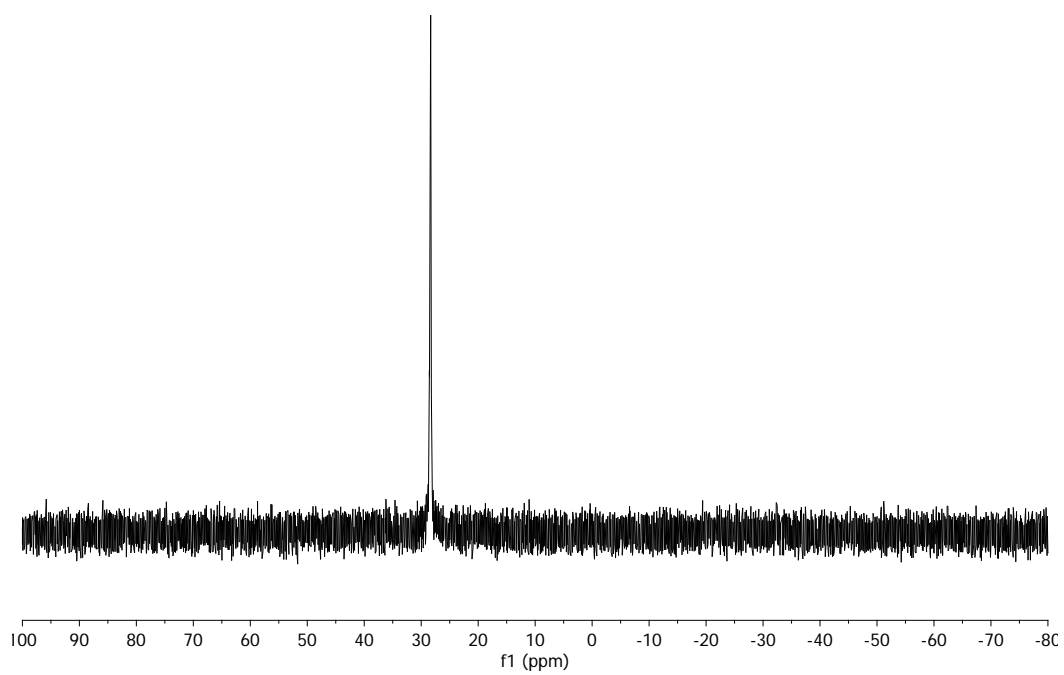
H	-7.312689	-1.422106	-1.477278	C	0.974123	1.390648	1.659186
C	-5.304038	-1.778693	-0.798896	C	0.633081	0.498460	2.686668
H	-5.110214	-2.552299	-1.535550	H	0.103063	-0.418917	2.448015
H	4.263233	-3.744992	-1.526861	C	0.953987	0.794625	4.012679
<b>4d</b>				H	0.679472	0.099081	4.800208
				C	1.610700	1.986238	4.324500
Charge: 0				H	1.854439	2.219146	5.356963
Multiplicity: 1				C	1.940320	2.886486	3.308351
				H	2.438662	3.821196	3.548491
Fe	3.263397	-1.233927	-0.476218	C	1.621368	2.593808	1.982023
C	2.658664	-3.223362	-0.383392	H	1.863203	3.308622	1.201303
H	2.016464	-3.700454	-1.111017	C	0.112607	2.546472	-0.874612
C	2.224813	-2.528529	0.783562	C	1.043404	3.335045	-1.566473
H	1.195081	-2.391410	1.083779	H	2.071676	3.001868	-1.666609
C	3.379024	-2.011992	1.447800	C	0.648168	4.545670	-2.139504
H	3.377961	-1.412816	2.347832	H	1.374343	5.148279	-2.677406
C	4.082786	-3.141529	-0.440656	C	-0.674084	4.977199	-2.025244
C	4.527995	-2.394595	0.691831	H	-0.979692	5.917882	-2.474064
H	5.553521	-2.134780	0.917535	C	-1.606502	4.192629	-1.342281
Au	-1.098268	-0.659184	-0.297698	H	-2.639385	4.518159	-1.261510
P	0.574126	0.953184	-0.082508	C	-1.219955	2.979417	-0.773790
S	-2.725897	-2.340927	-0.550638	H	-1.956174	2.362766	-0.264421
C	3.481102	0.826773	-0.418990	C	-4.239110	-1.535833	-0.127936
H	3.734402	1.388811	0.468706	H	4.712262	-3.547657	-1.221004
C	4.398998	0.274849	-1.357615	C	-6.029721	0.176414	0.525662
H	5.477340	0.338034	-1.298388	H	-6.196109	0.866350	-0.306830
C	3.652919	-0.421800	-2.356419	H	-6.530623	0.564110	1.415076
H	4.067127	-0.978637	-3.185990	C	-6.481278	-1.264774	0.173512
C	2.150076	0.473797	-0.837275	H	-7.332582	-1.244535	-0.515667
C	2.269905	-0.308537	-2.039159	H	-6.811851	-1.790560	1.081264
H	1.446040	-0.748048	-2.584610	S	-4.225879	0.022175	0.829842
				N	-5.381086	-2.016004	-0.415151

3.  $^1\text{H}$ ,  $^{31}\text{P}\{^1\text{H}\}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ ) spectra for the new compounds **2**, **3b-3e** and **3a-3e**

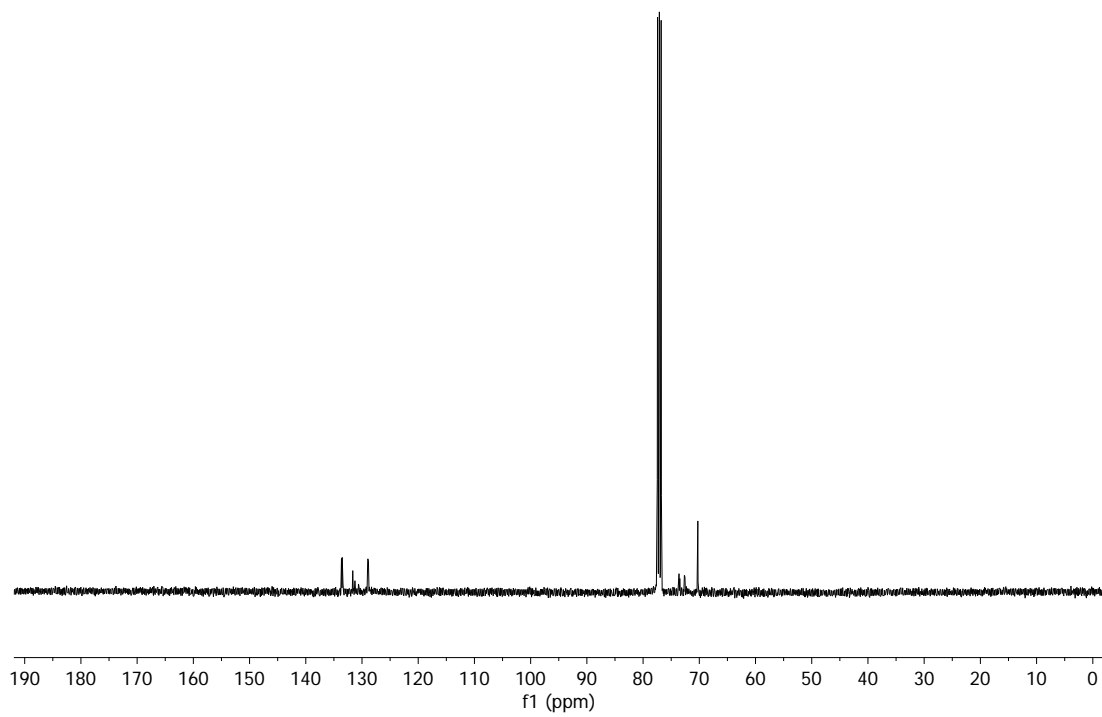


**Figure S4.**  $^1\text{H}$  NMR spectrum for compound **2** in  $\text{CDCl}_3$ .

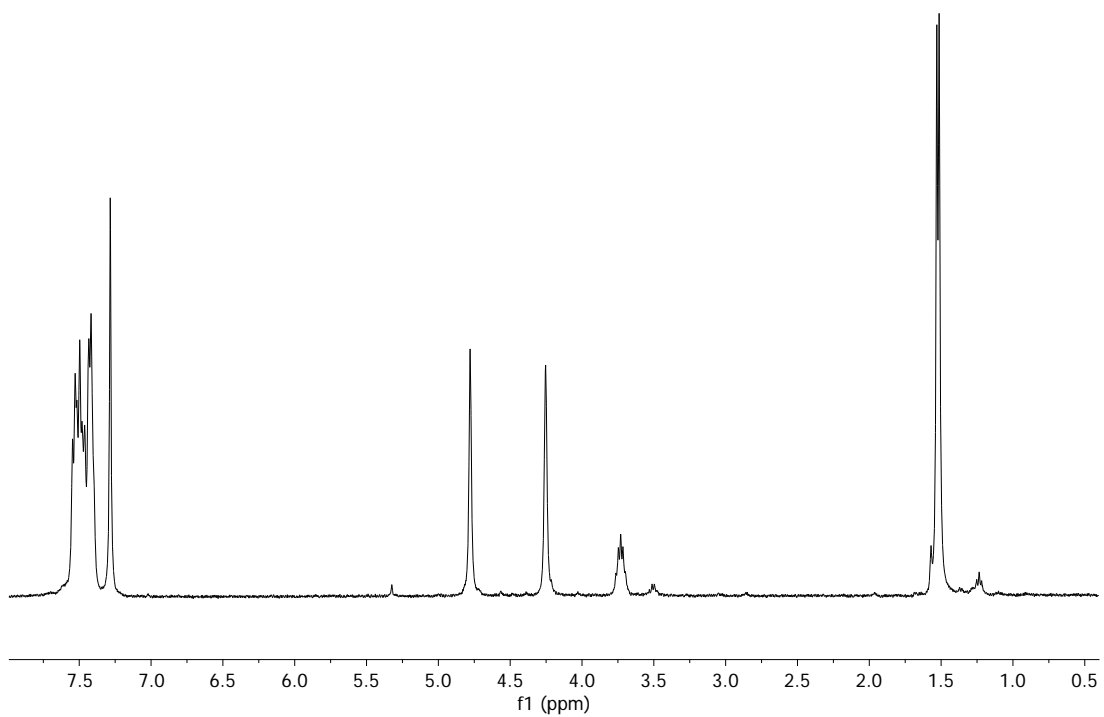




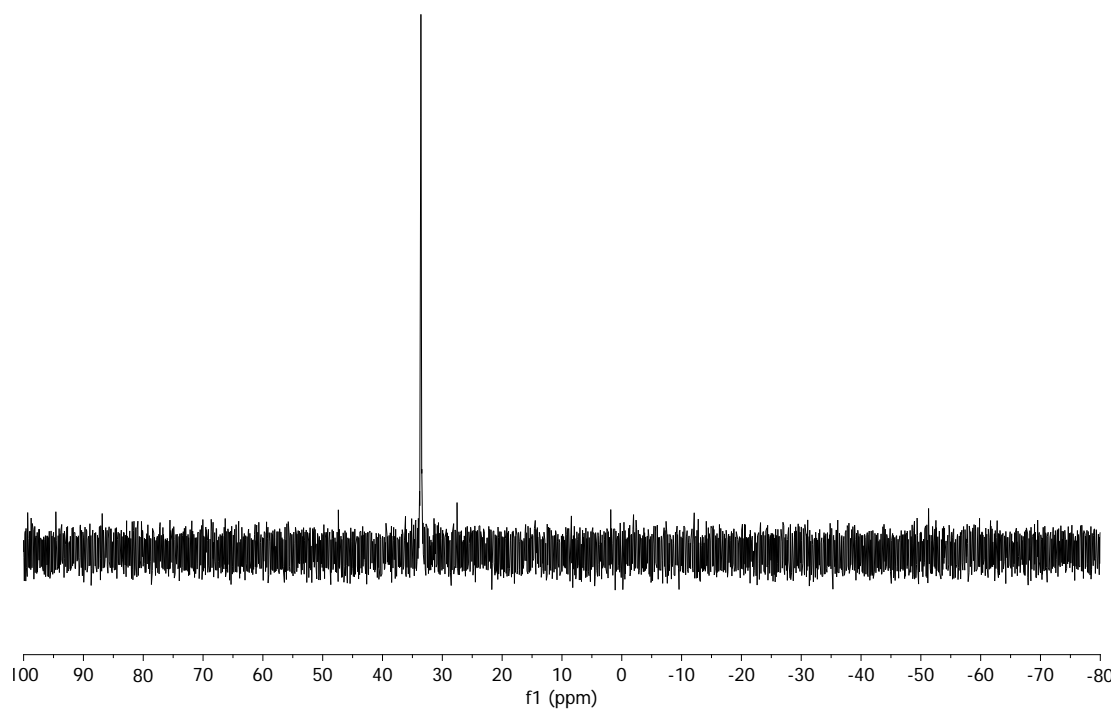
**Figure S5.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum for compound **2** in  $\text{CDCl}_3$ .



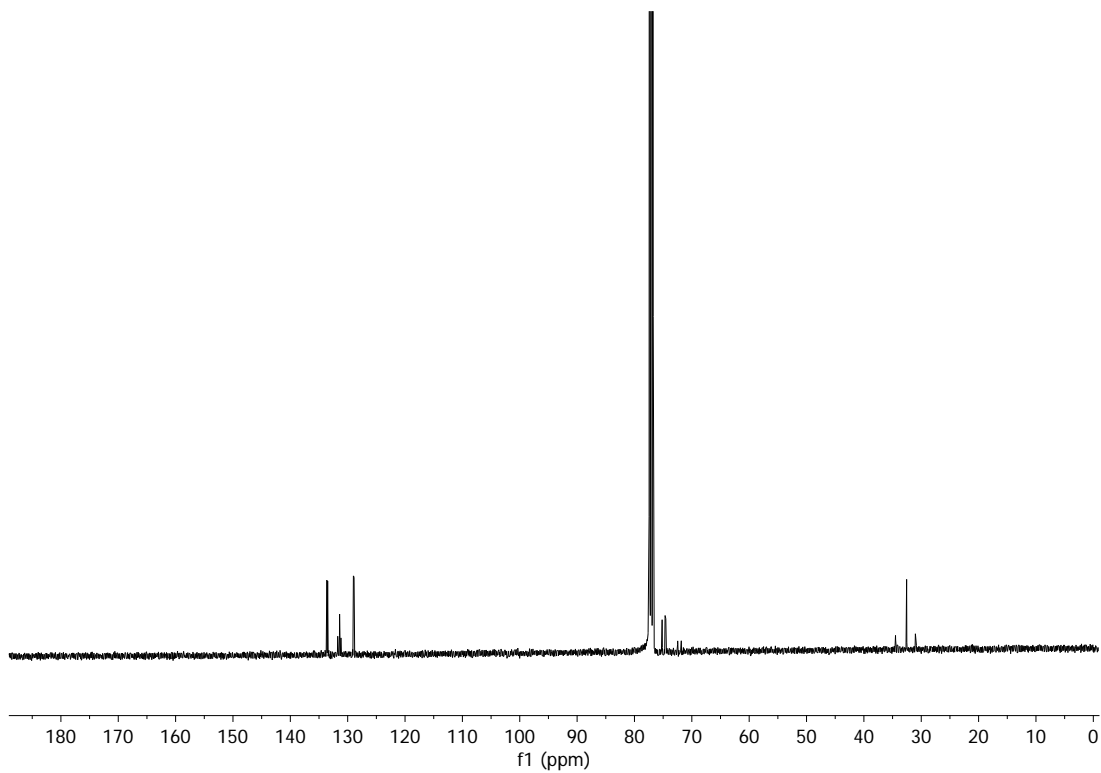
**Figure S6.**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum for compound **2** in  $\text{CDCl}_3$ .



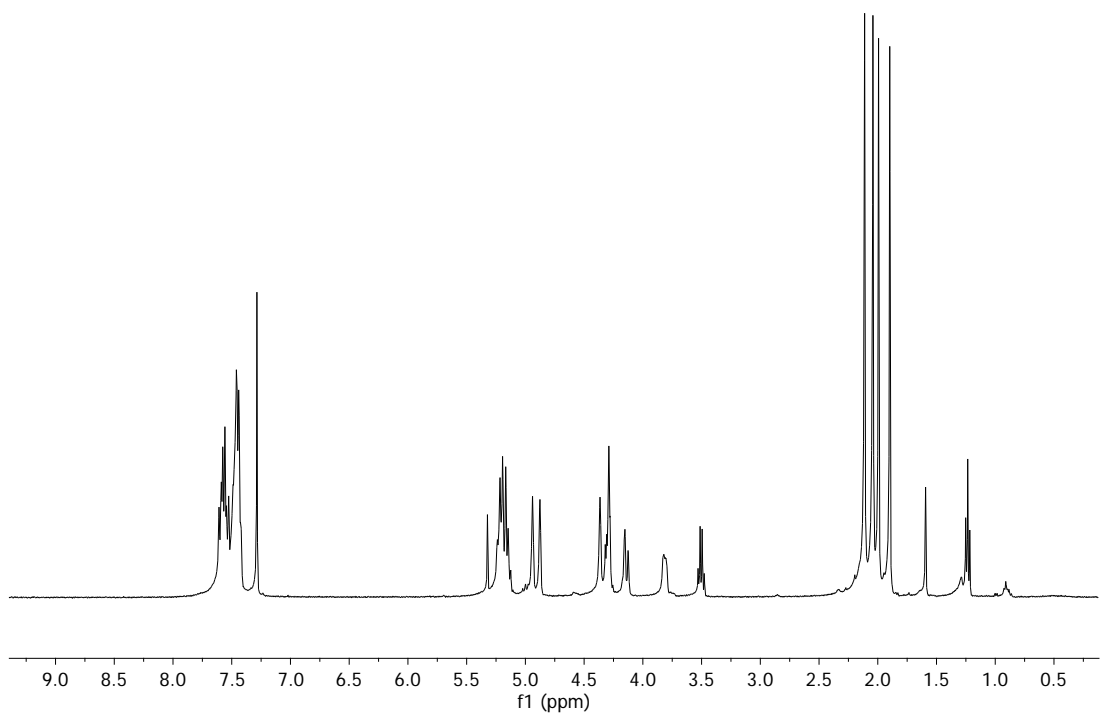
**Figure S7.**  $^1\text{H}$  NMR spectrum for compound **3b** in  $\text{CDCl}_3$ .



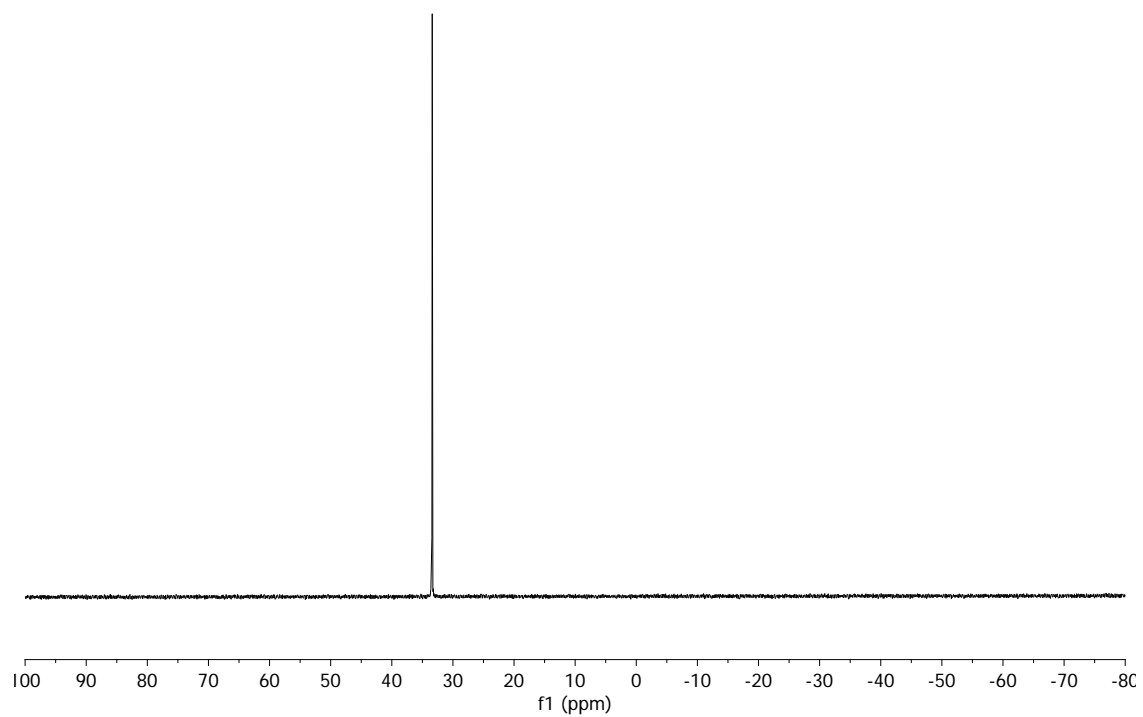
**Figure S8.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum for compound **3b** in  $\text{CDCl}_3$ .



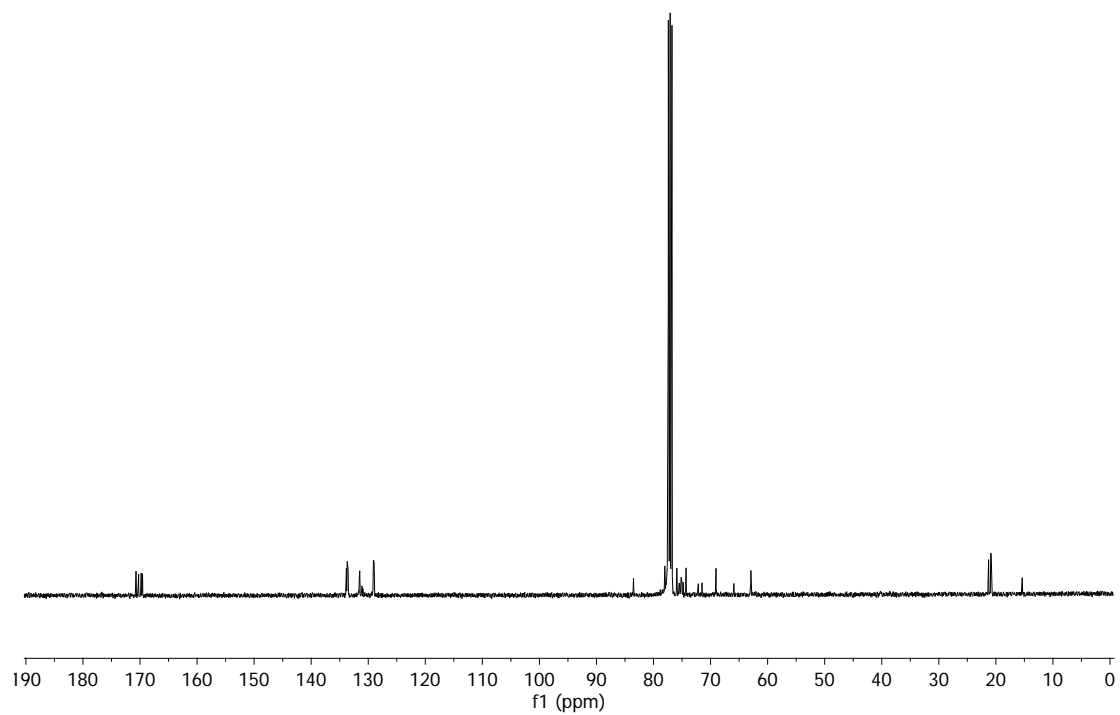
**Figure S9.**  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR spectrum for compound **3b** in  $\text{CDCl}_3$ .



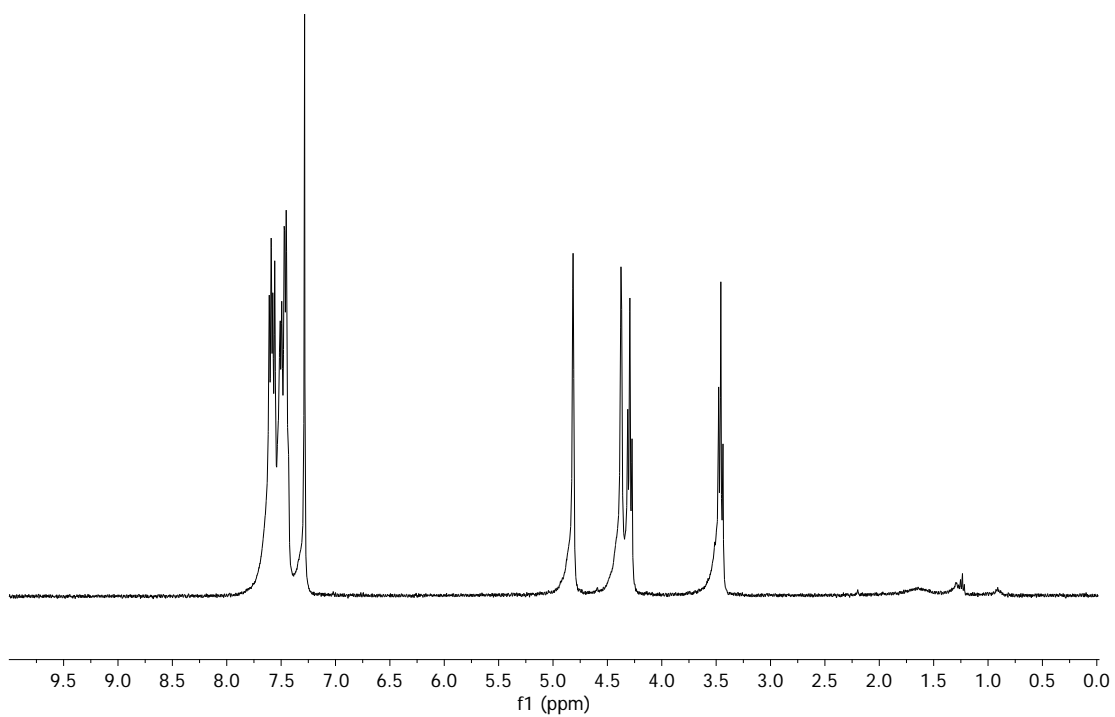
**Figure S10.**  $^1\text{H}$  NMR spectrum for compound **3c** in  $\text{CDCl}_3$ .



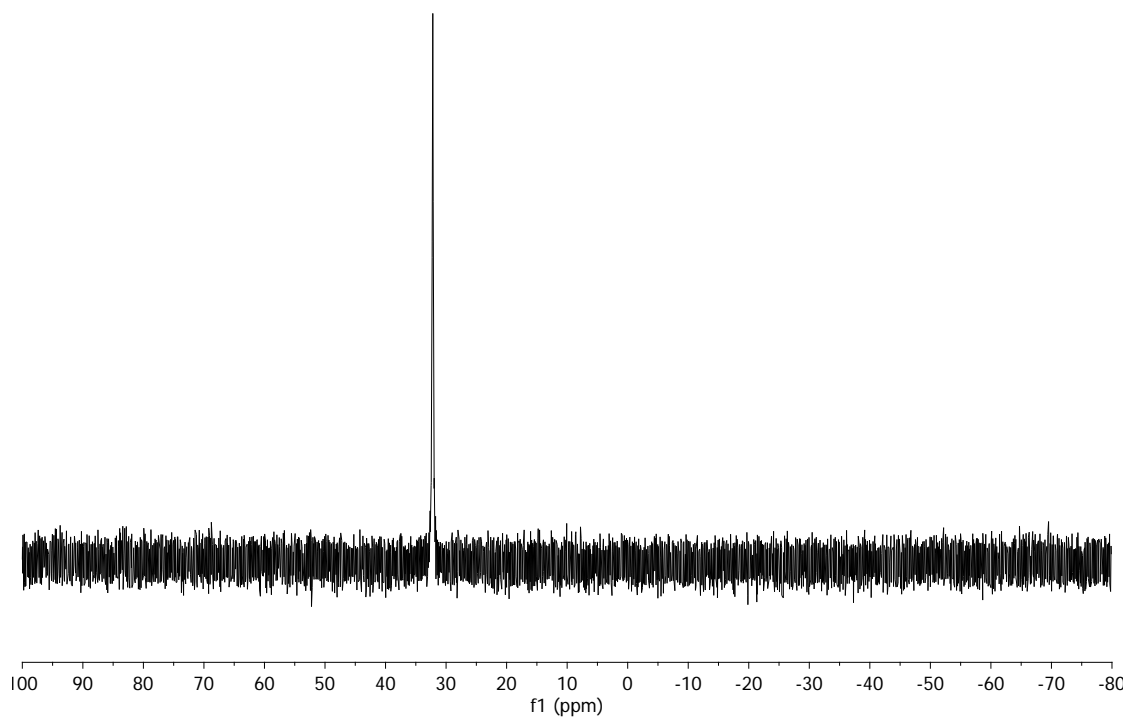
**Figure S11.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum for compound **3c** in  $\text{CDCl}_3$ .



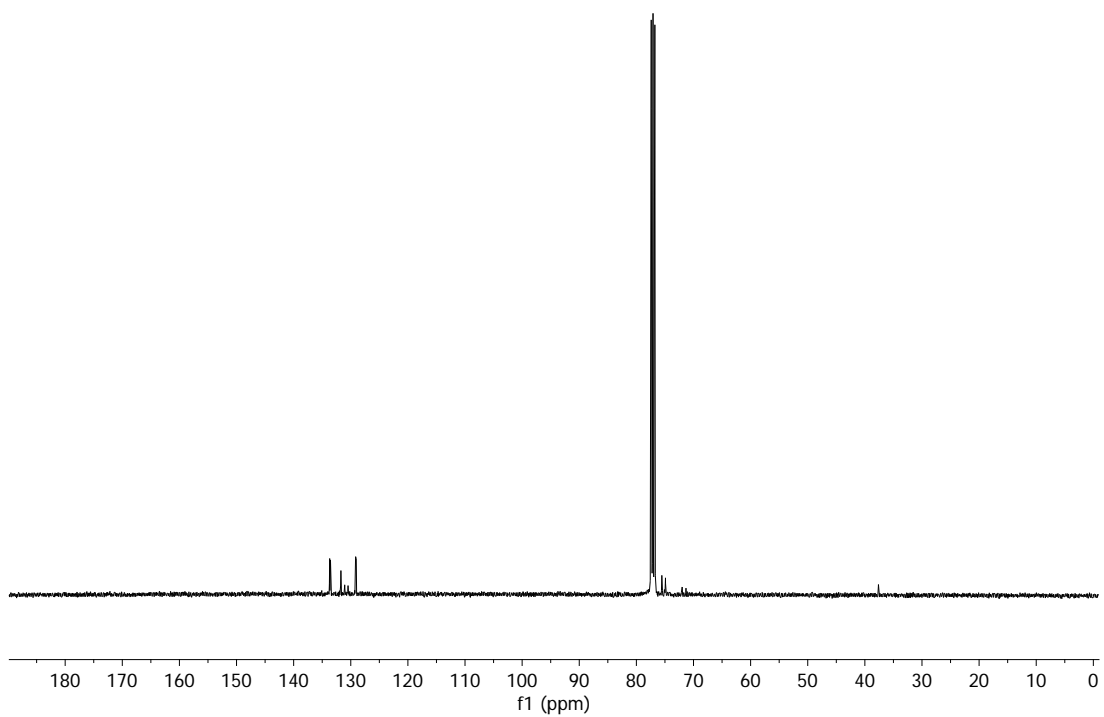
**Figure S12.**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum for compound **3c** in  $\text{CDCl}_3$ .



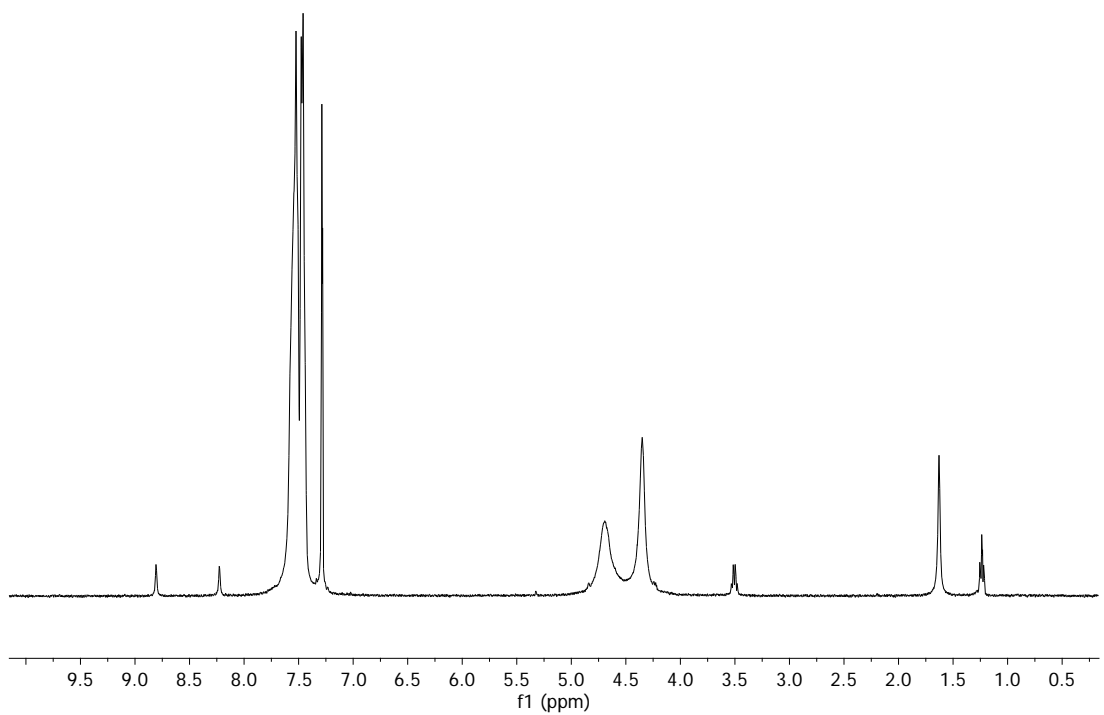
**Figure S13.**  $^1\text{H}$  NMR spectrum for compound **3d** in  $\text{CDCl}_3$ .



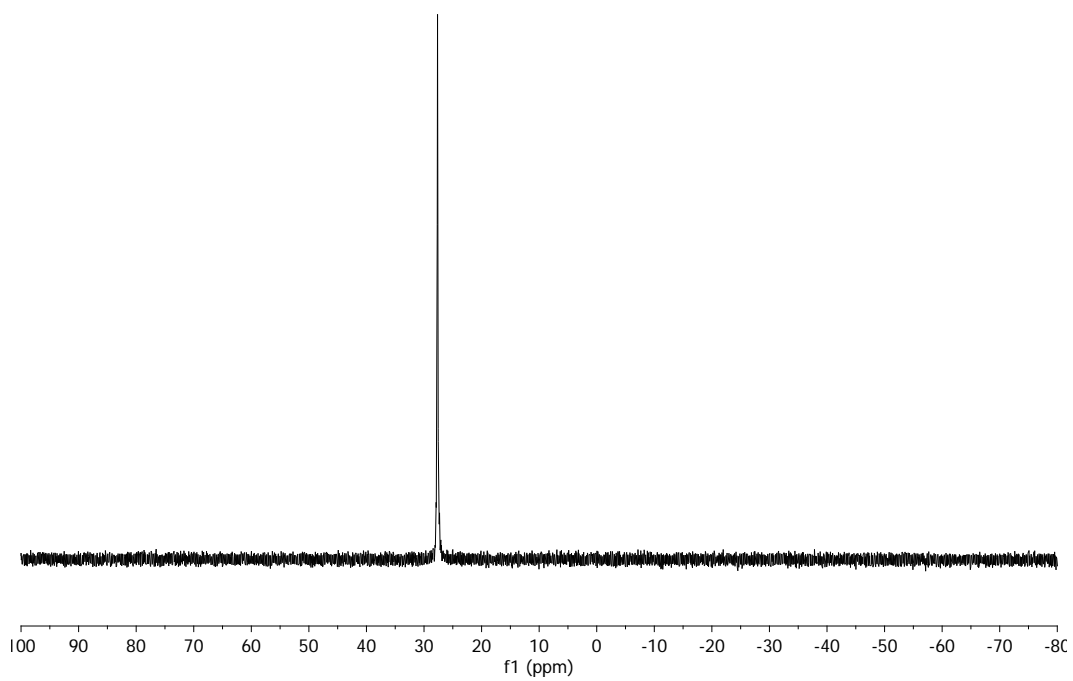
**Figure S14.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum for compound **3d** in  $\text{CDCl}_3$ .



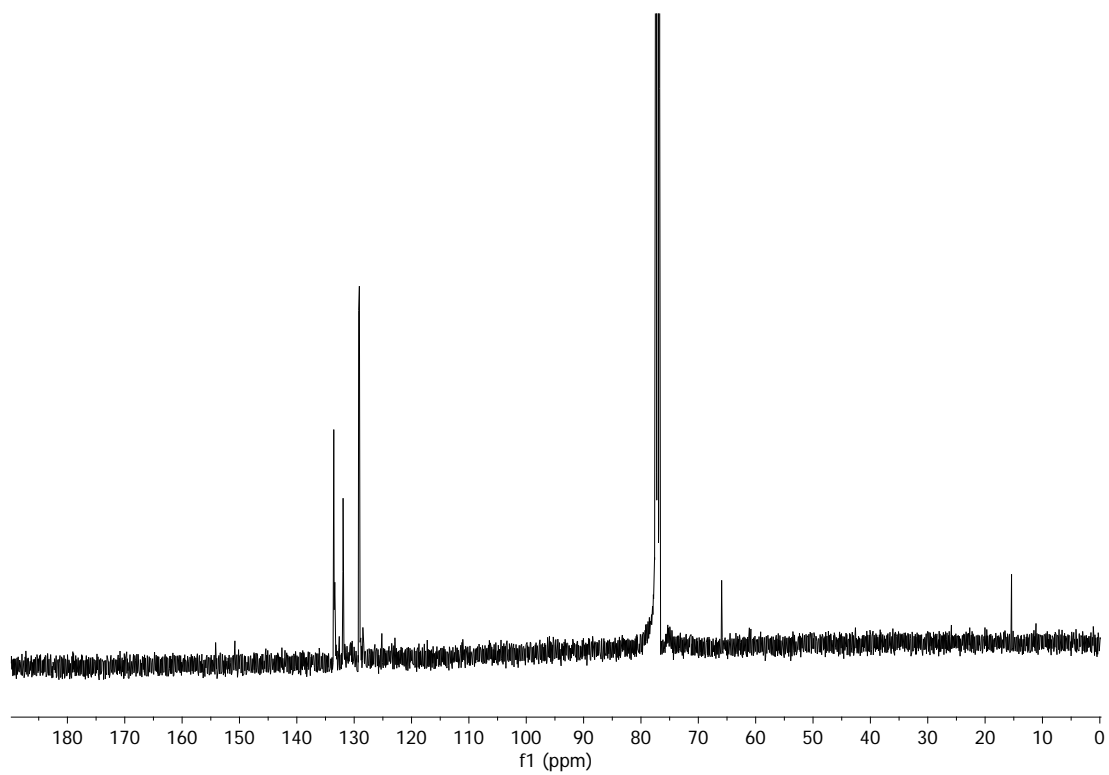
**Figure S15.**  $^{13}\text{C}$  { $^1\text{H}$ } NMR spectrum for compound **3d** in  $\text{CDCl}_3$ .



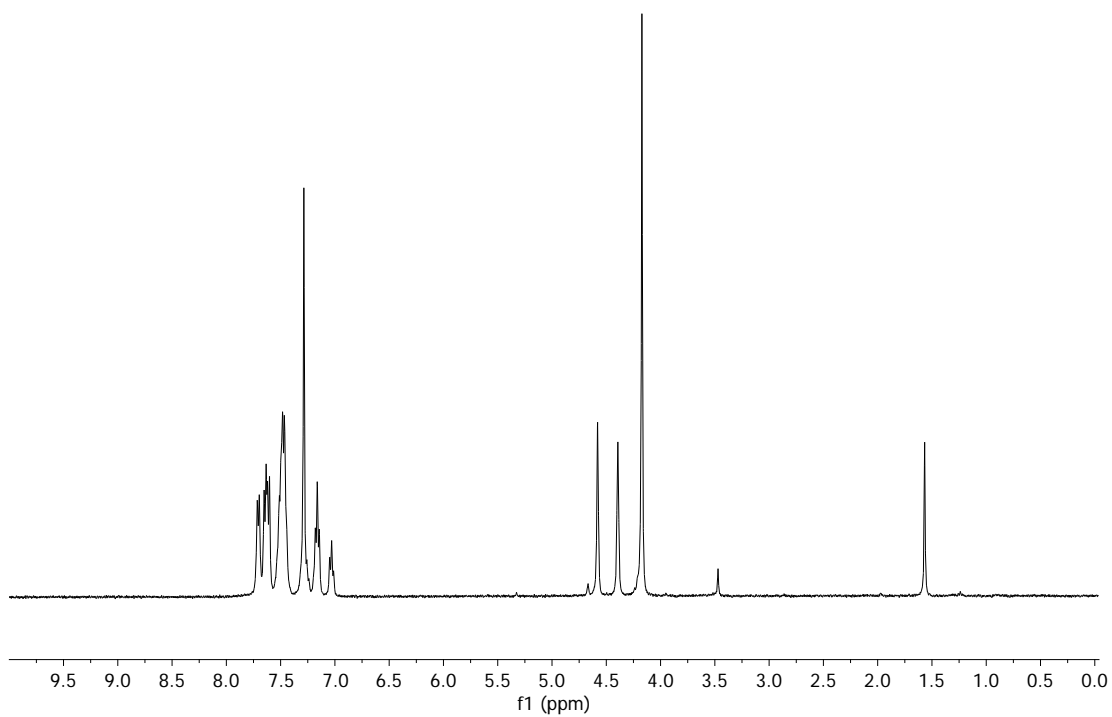
**Figure S16.**  $^1\text{H}$  NMR spectrum for compound **3e** in  $\text{CDCl}_3$ .



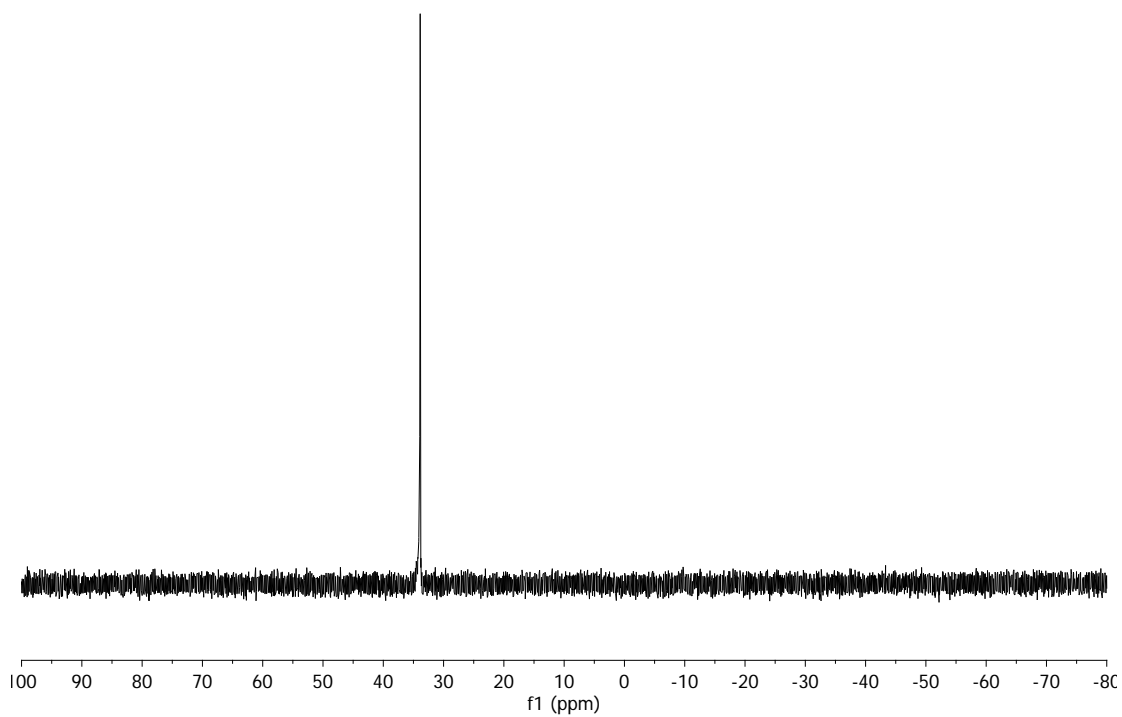
**Figure S17.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum for compound **3e** in  $\text{CDCl}_3$ .



**Figure S18.**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum for compound **3e** in  $\text{CDCl}_3$ .

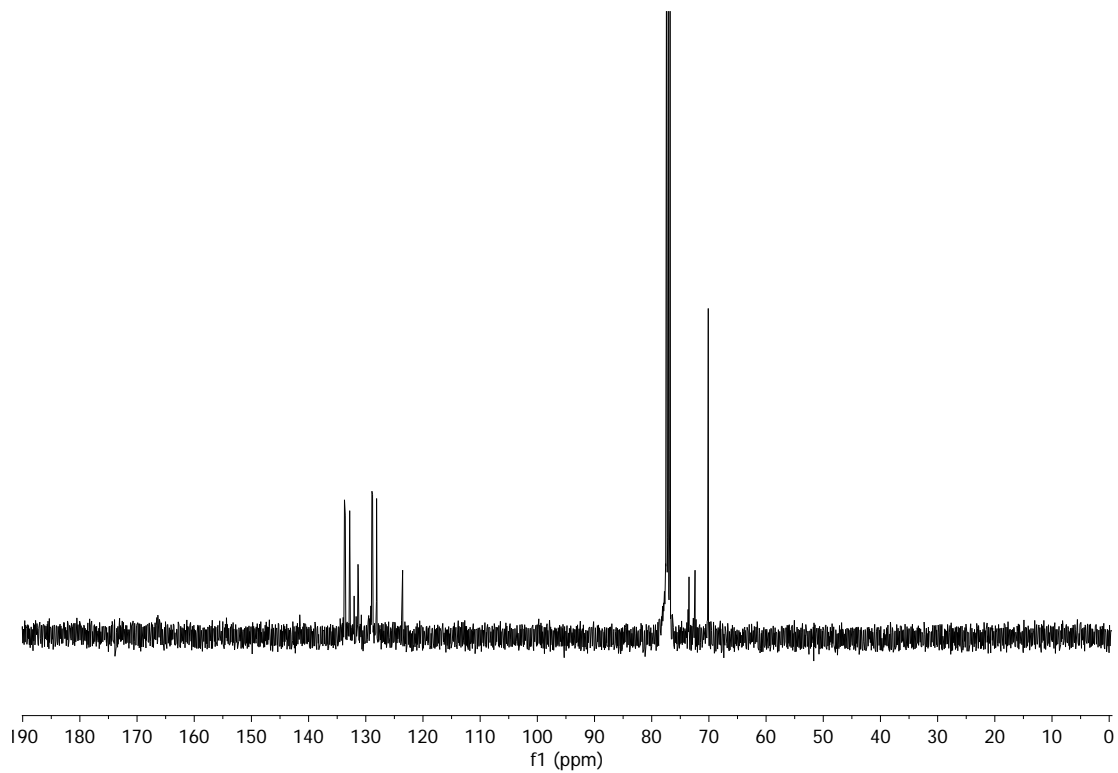


**Figure S19.**  $^1\text{H}$  NMR spectrum for compound **4a** in  $\text{CDCl}_3$ .

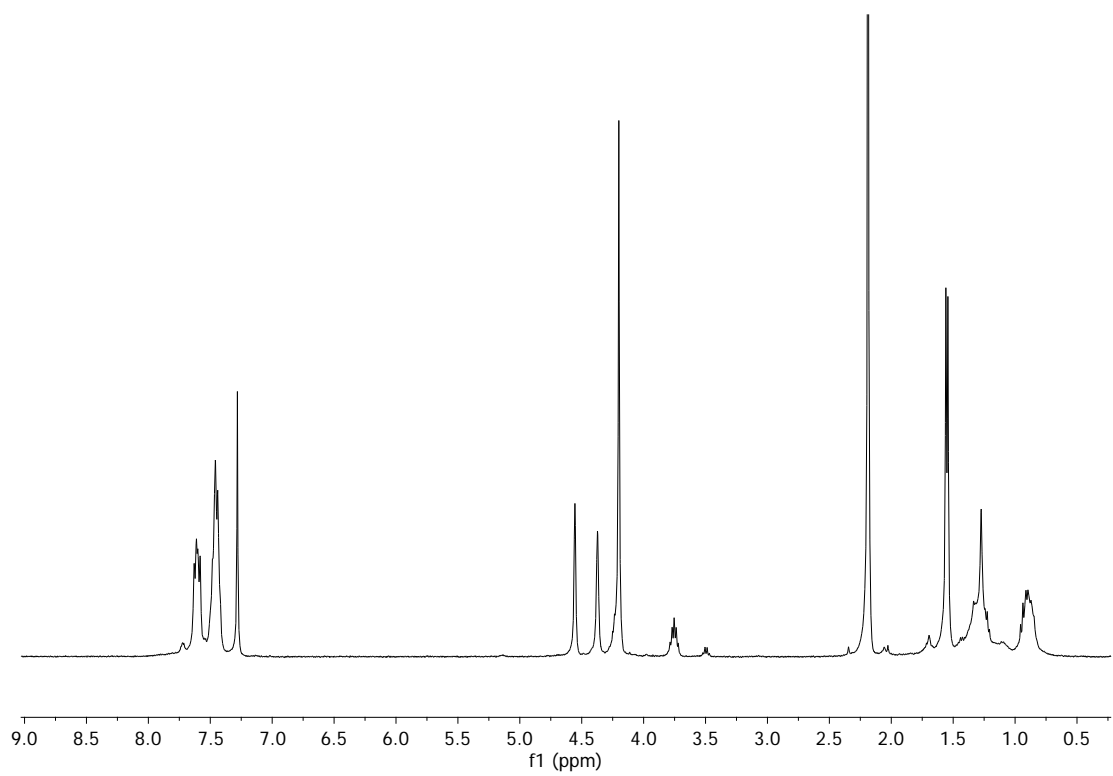


**Figure S20.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum for compound **4a** in  $\text{CDCl}_3$ .

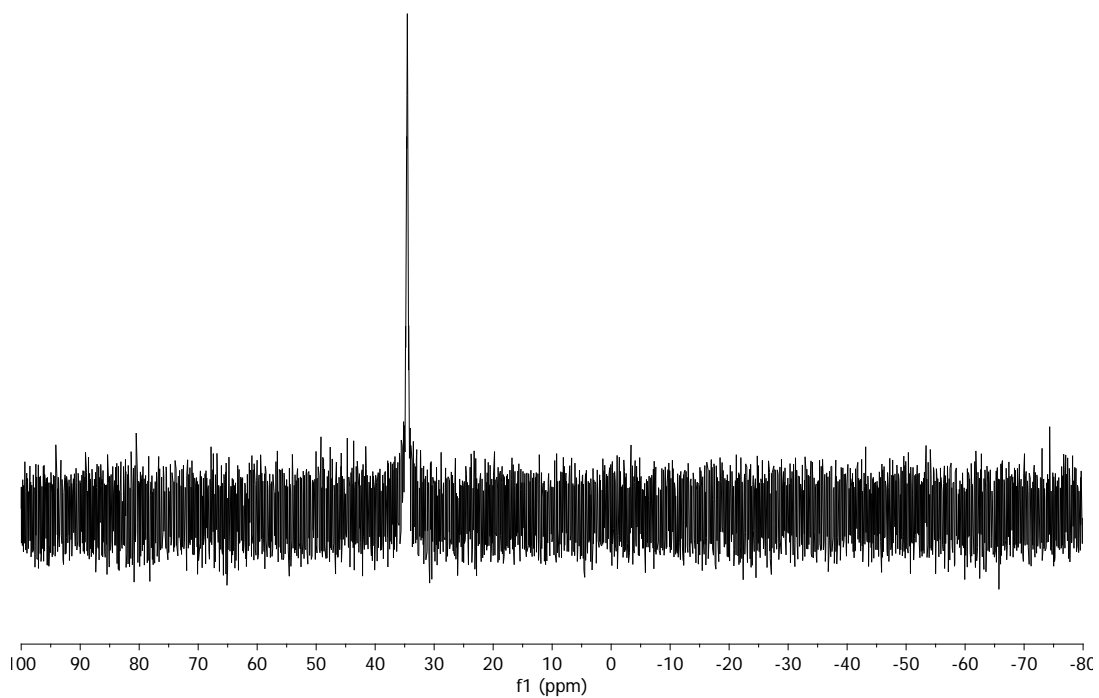




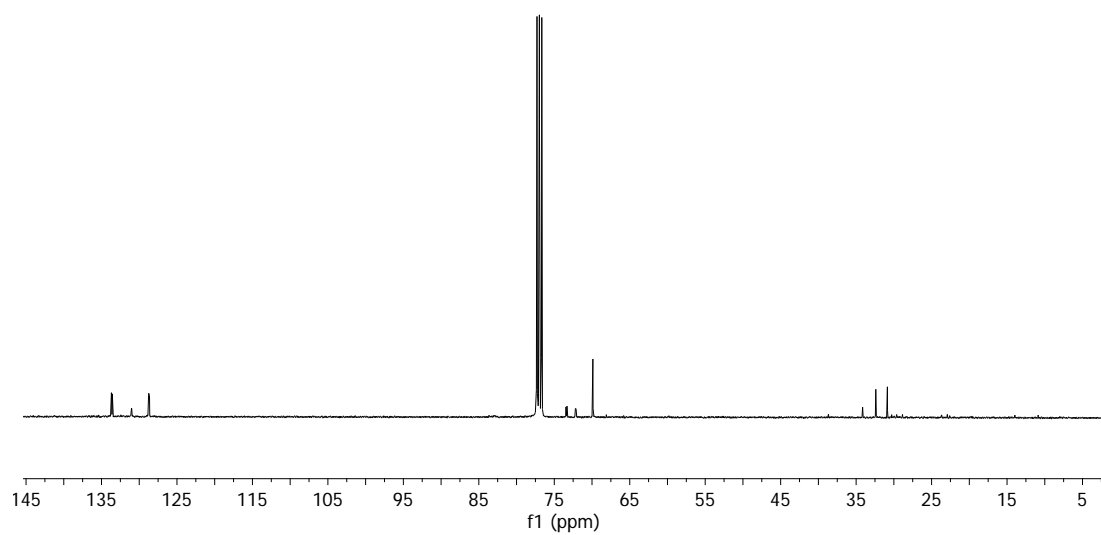
**Figure S21.**  $^{13}\text{C}$  { $^1\text{H}$ } NMR spectrum for compound **4a** in  $\text{CDCl}_3$ .



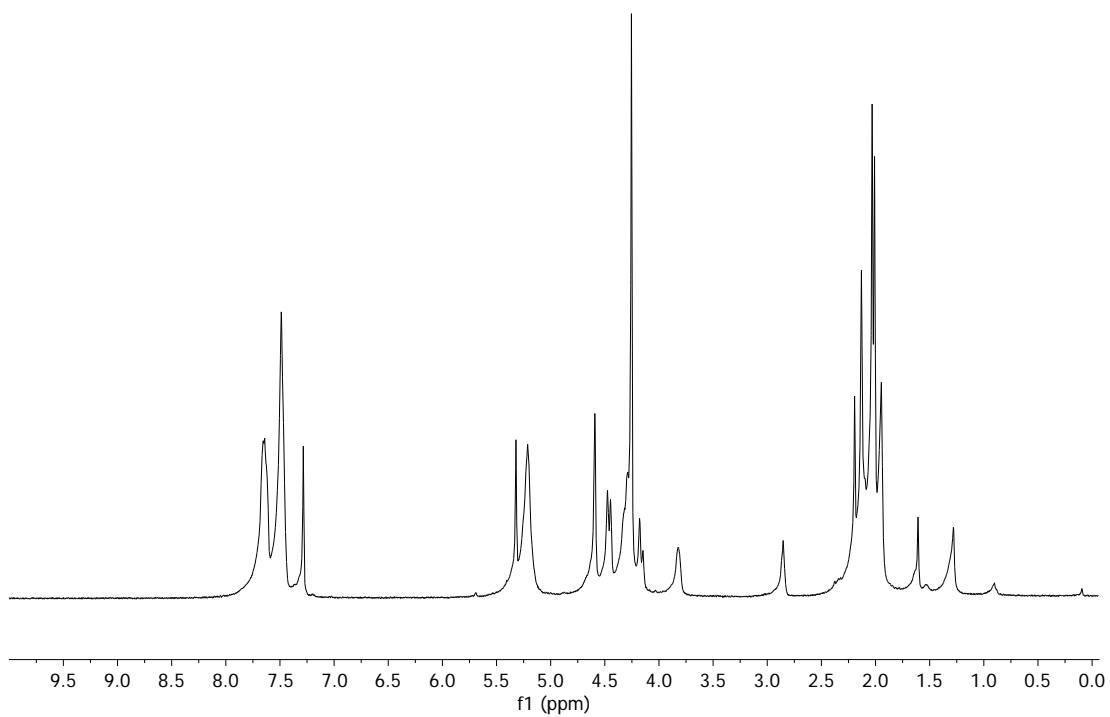
**Figure S22.**  $^1\text{H}$  NMR spectrum for compound **4b** in  $\text{CDCl}_3$ .



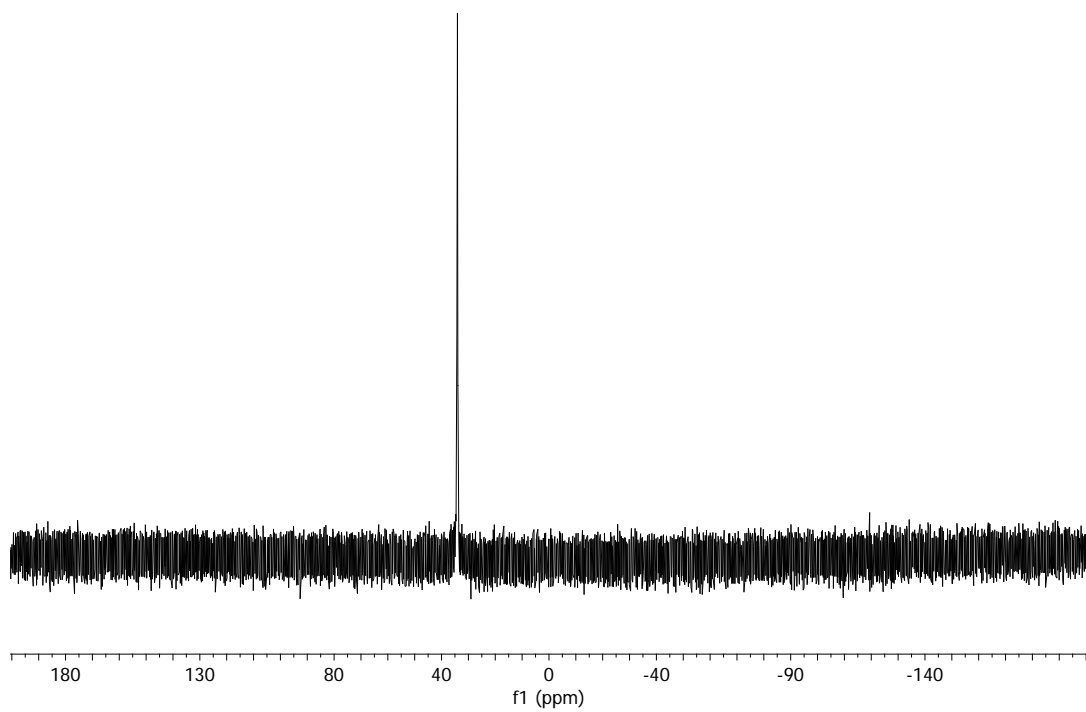
**Figure S23.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum for compound **4b** in  $\text{CDCl}_3$ .



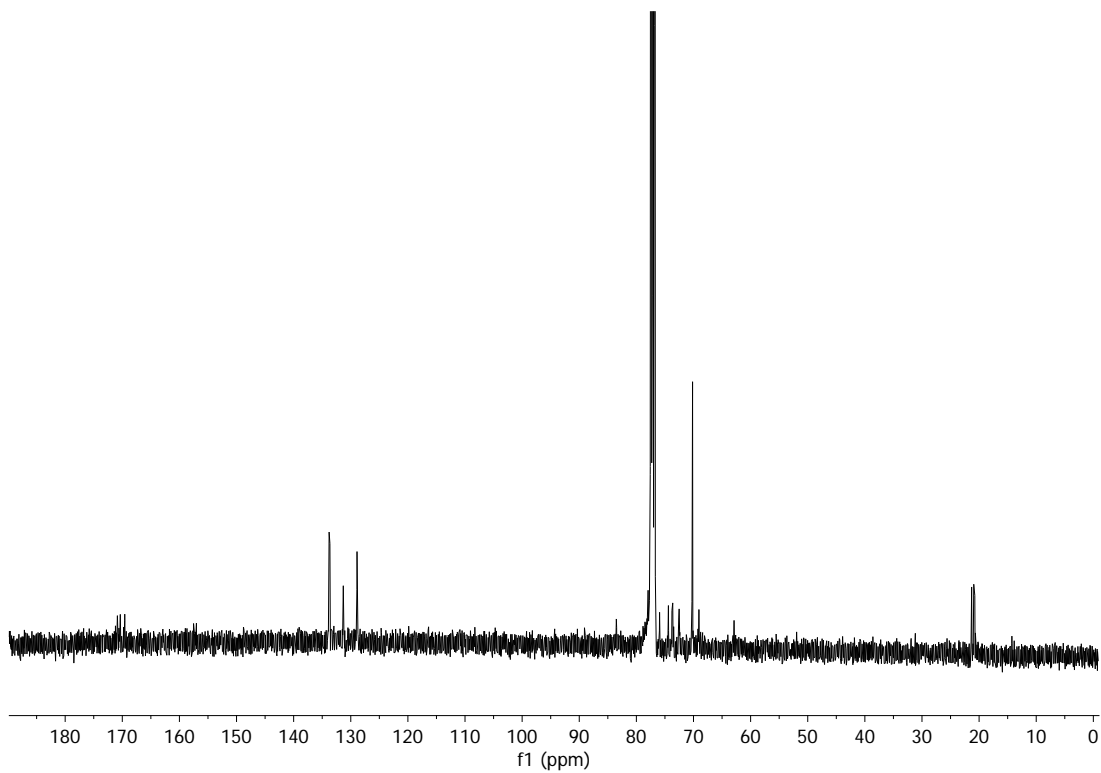
**Figure S24.**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum for compound **4b** in  $\text{CDCl}_3$ .



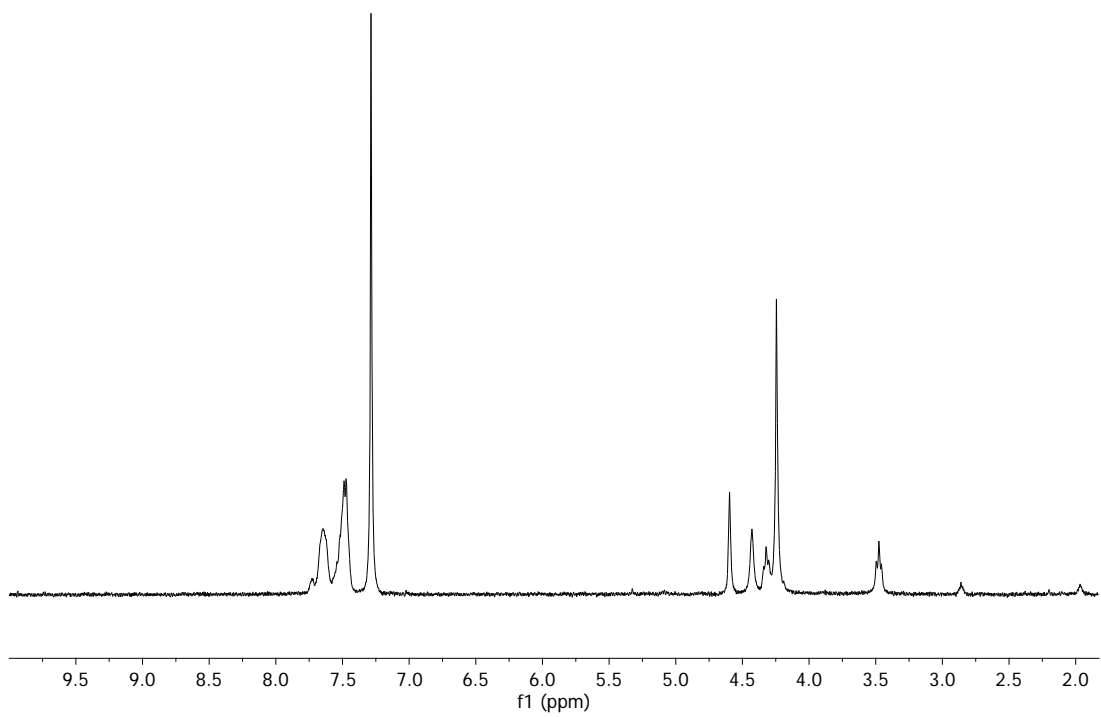
**Figure S25.**  $^1\text{H}$  NMR spectrum for compound **4c** in  $\text{CDCl}_3$ .



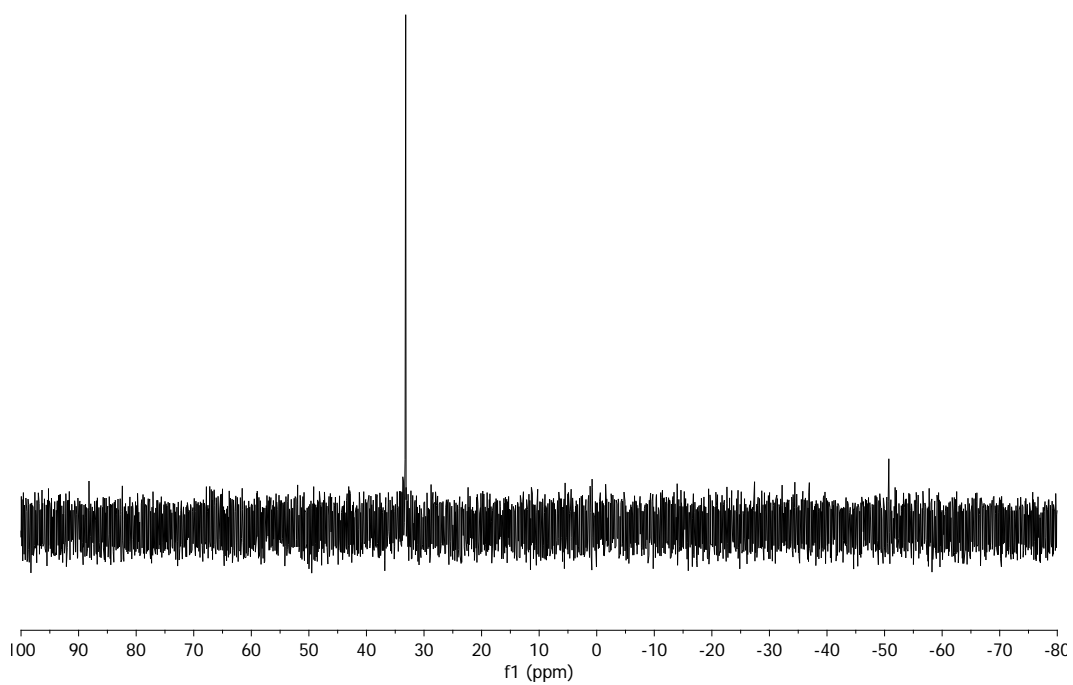
**Figure S26.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum for compound **4c** in  $\text{CDCl}_3$ .



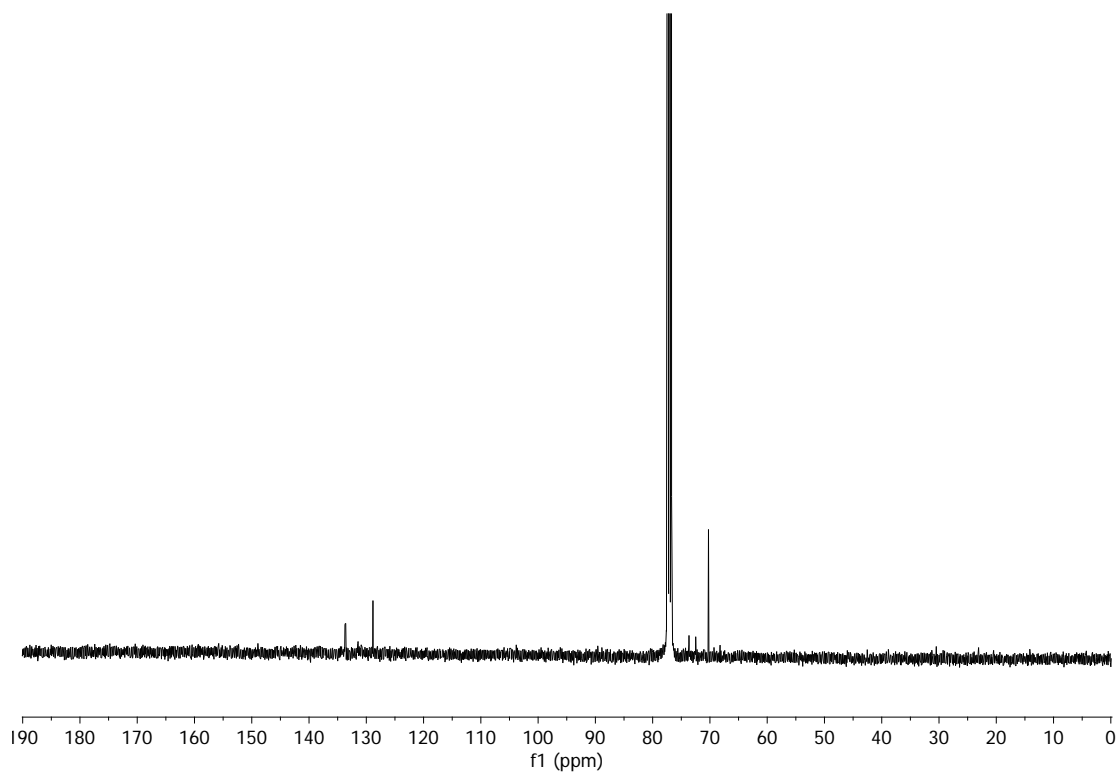
**Figure S27.**  $^{13}\text{C}$  { $^1\text{H}$ } NMR spectrum for compound **4c** in  $\text{CDCl}_3$ .



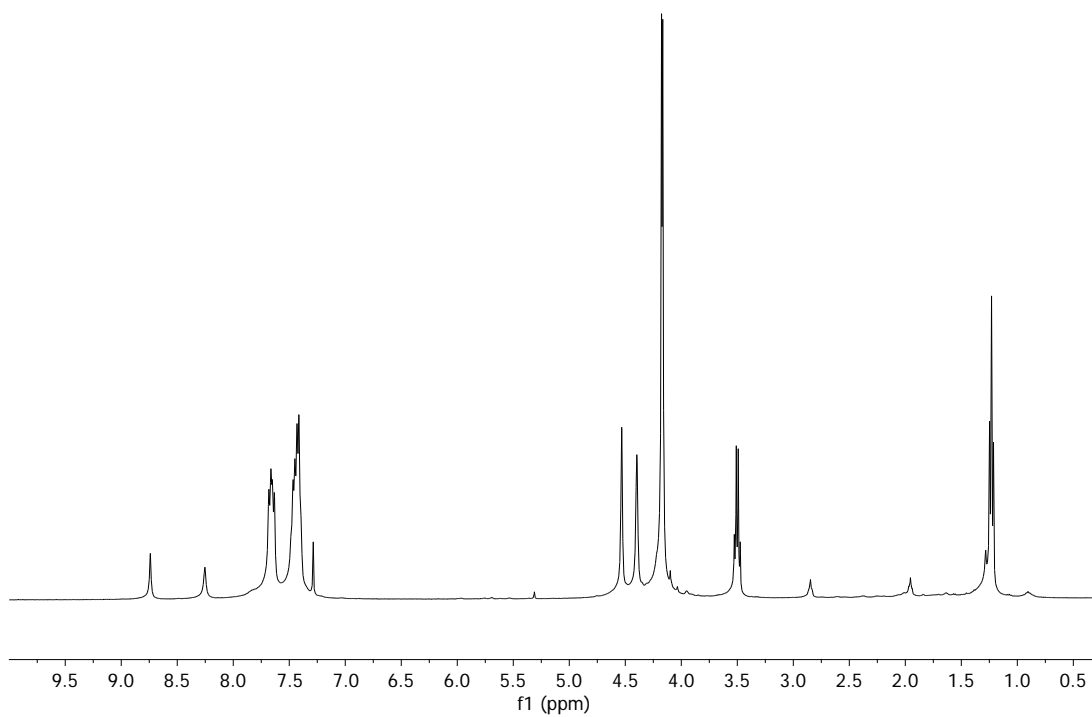
**Figure S28.**  $^1\text{H}$  NMR spectrum for compound **4d** in  $\text{CDCl}_3$ .



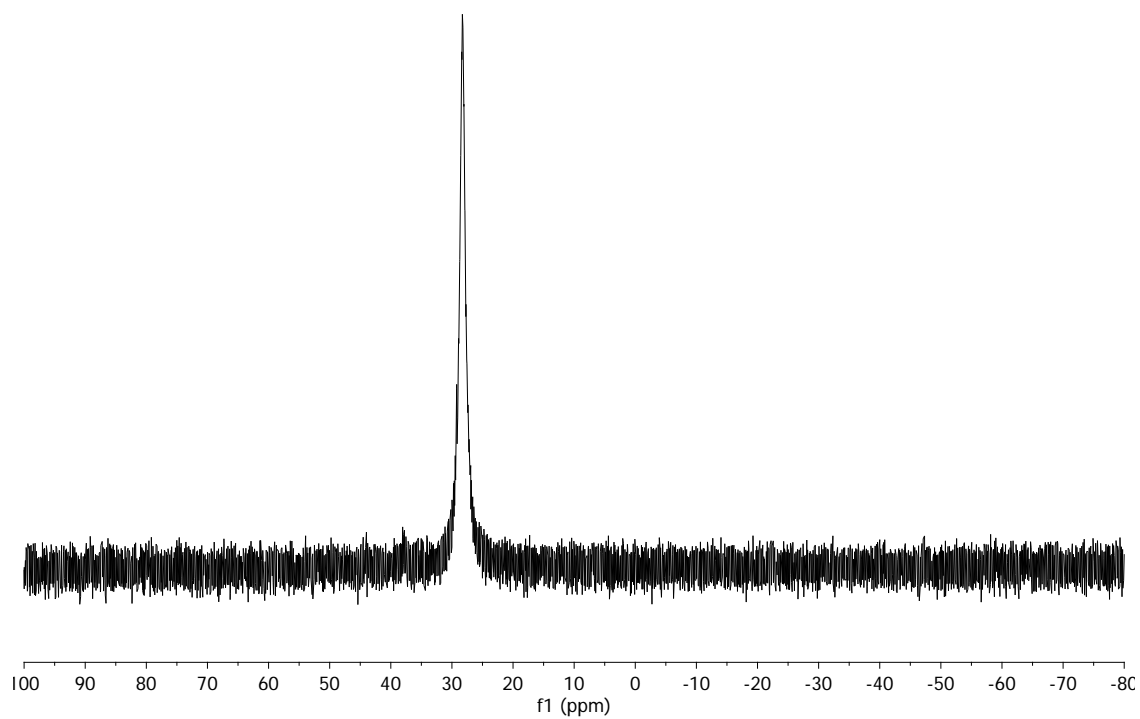
**Figure S29.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum for compound **4d** in  $\text{CDCl}_3$ .



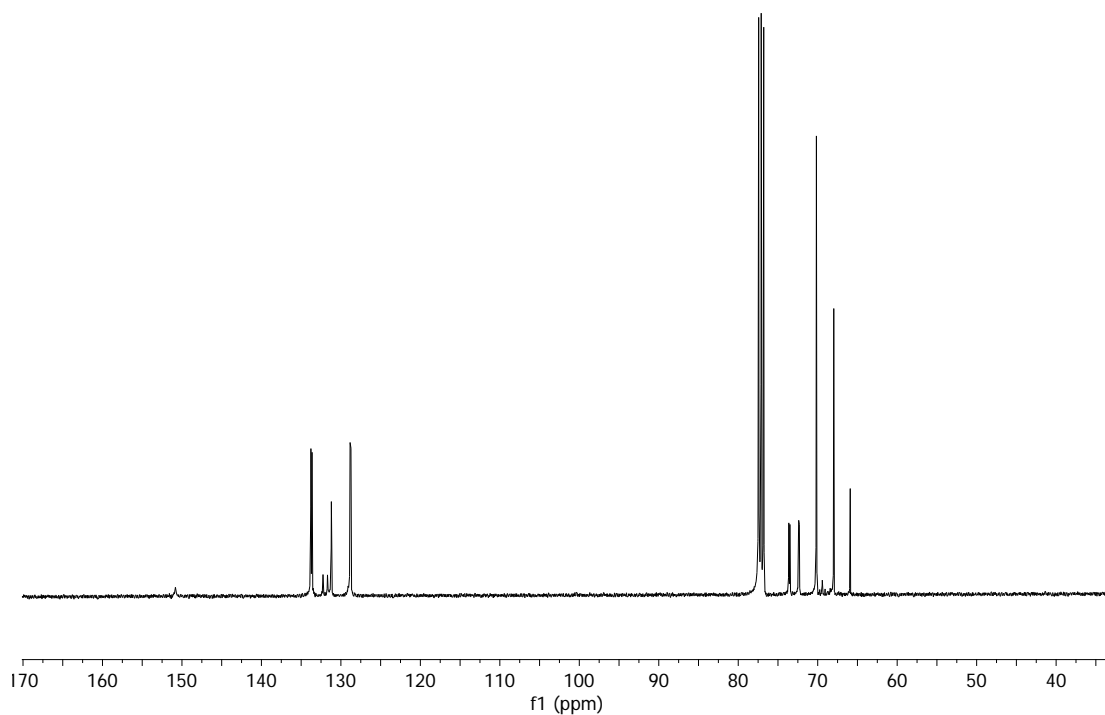
**Figure S30.**  $^{13}\text{C}\{^1\text{H}\}$  NMR spectrum for compound **4d** in  $\text{CDCl}_3$ .



**Figure S31.**  $^1\text{H}$  NMR spectrum for compound **4e** in  $\text{CDCl}_3$ .

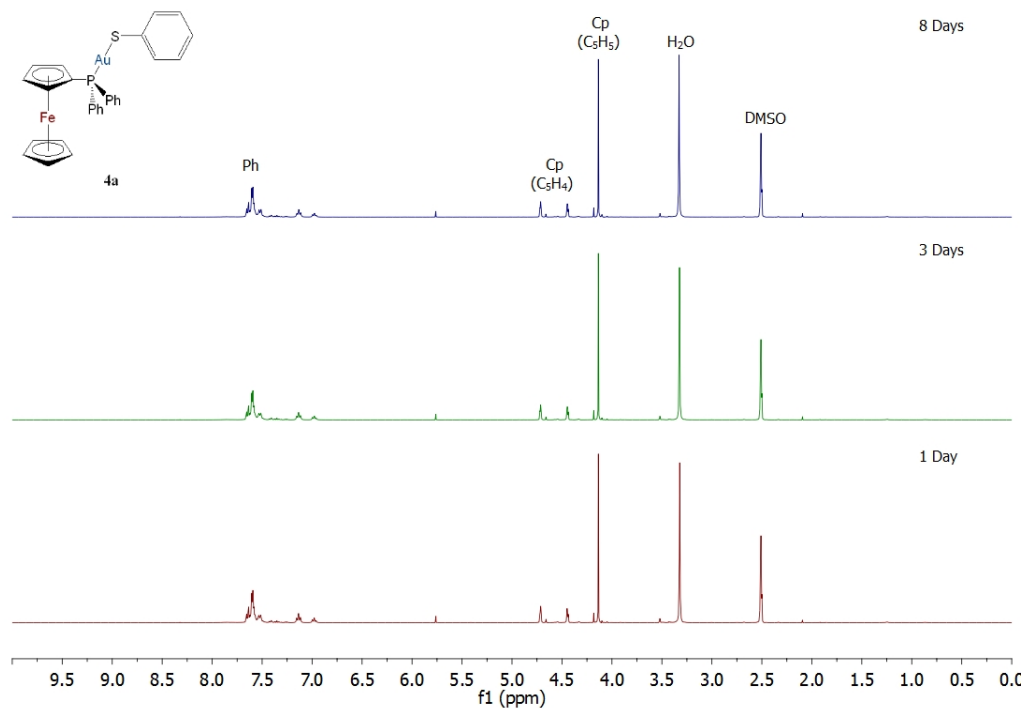


**Figure S32.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum for compound **4e** in  $\text{CDCl}_3$ .

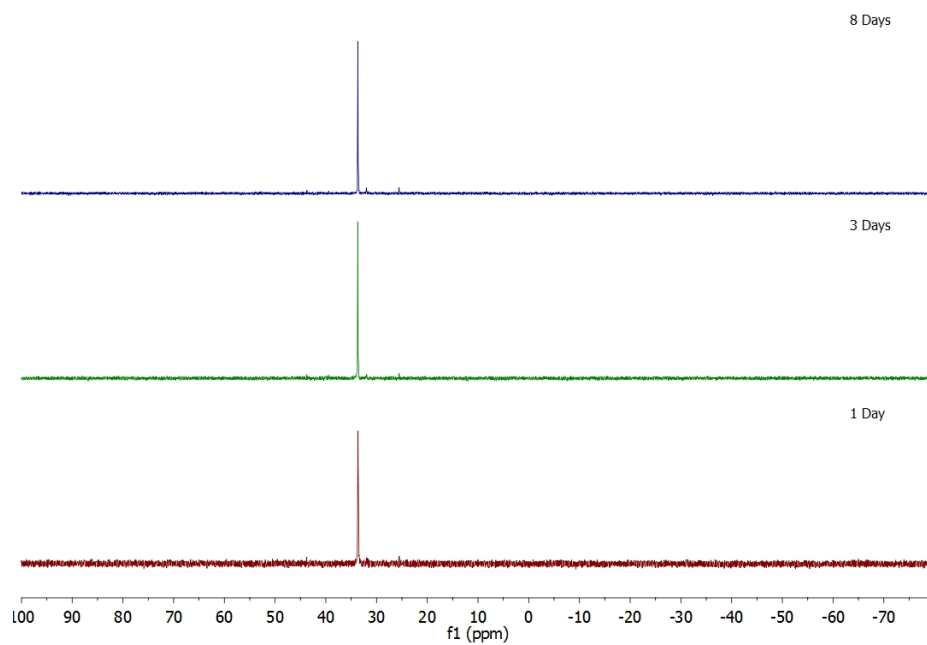


**Figure S33.**  $^{13}\text{C}$   $\{^1\text{H}\}$  NMR spectrum for compound **4e** in  $\text{CDCl}_3$ .

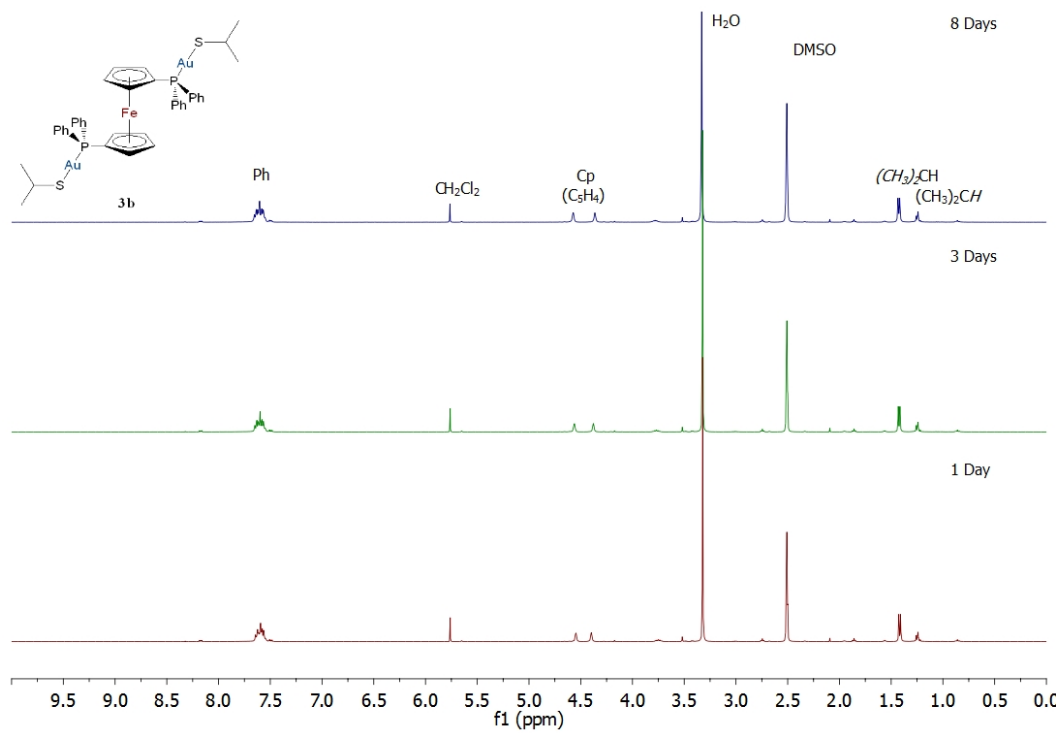
**4. Selected  $^1\text{H}$  and  $^{31}\text{P}\{^1\text{H}\}$  NMR spectra ( $\text{DMSO-d}_6$ ) overtime for complexes **4a**, **3b**, **3c** **4d** and **4e**.**



**Figure S34.**  $^1\text{H}$  NMR spectrum in  $\text{DMSO-d}^6$  of **4a** over time.

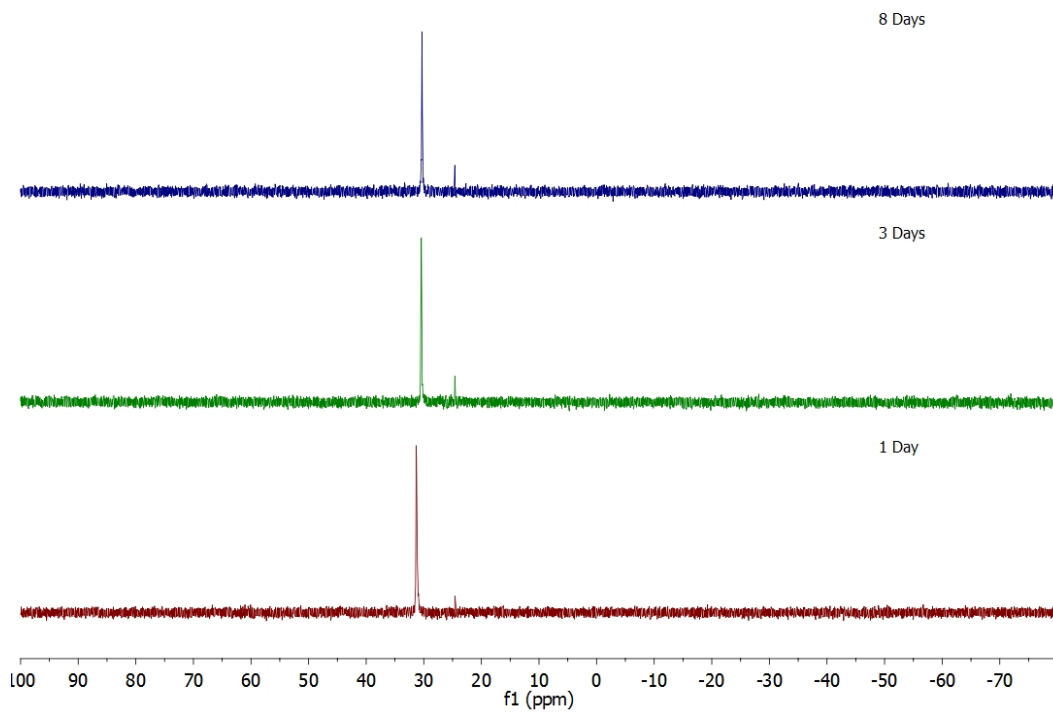


**Figure S35.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum in  $\text{DMSO-d}^6$  of **4a** over time.

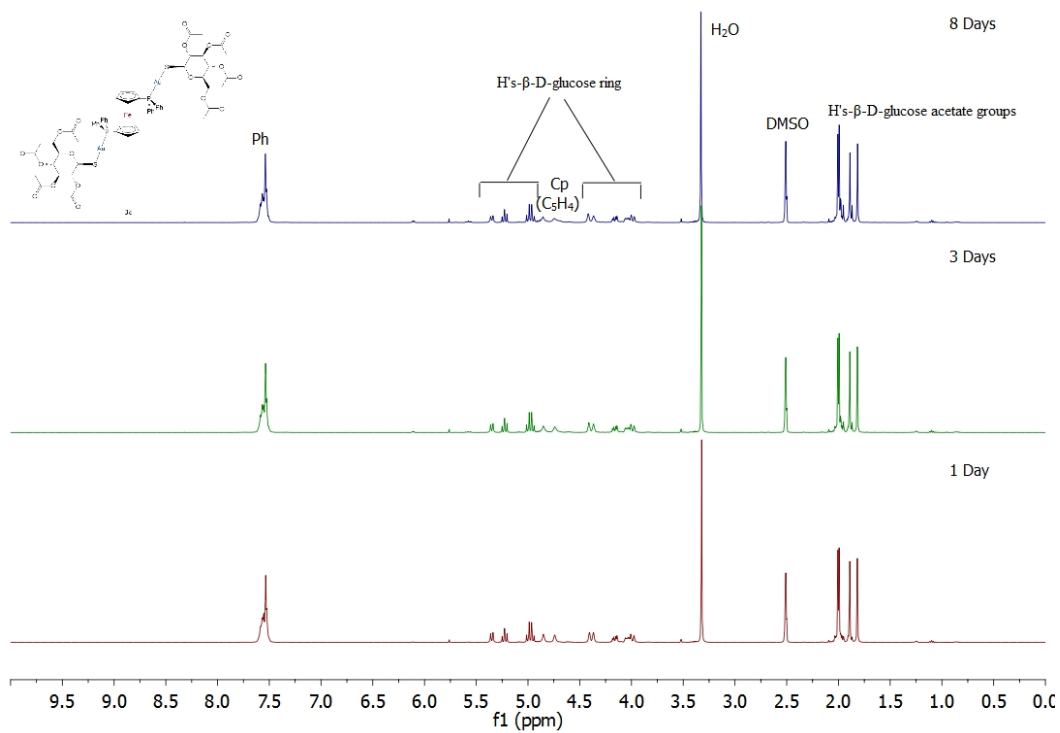


**Figure S36.**  $^1\text{H}$  NMR spectrum in  $\text{DMSO-d}^6$  of **3b** over time.

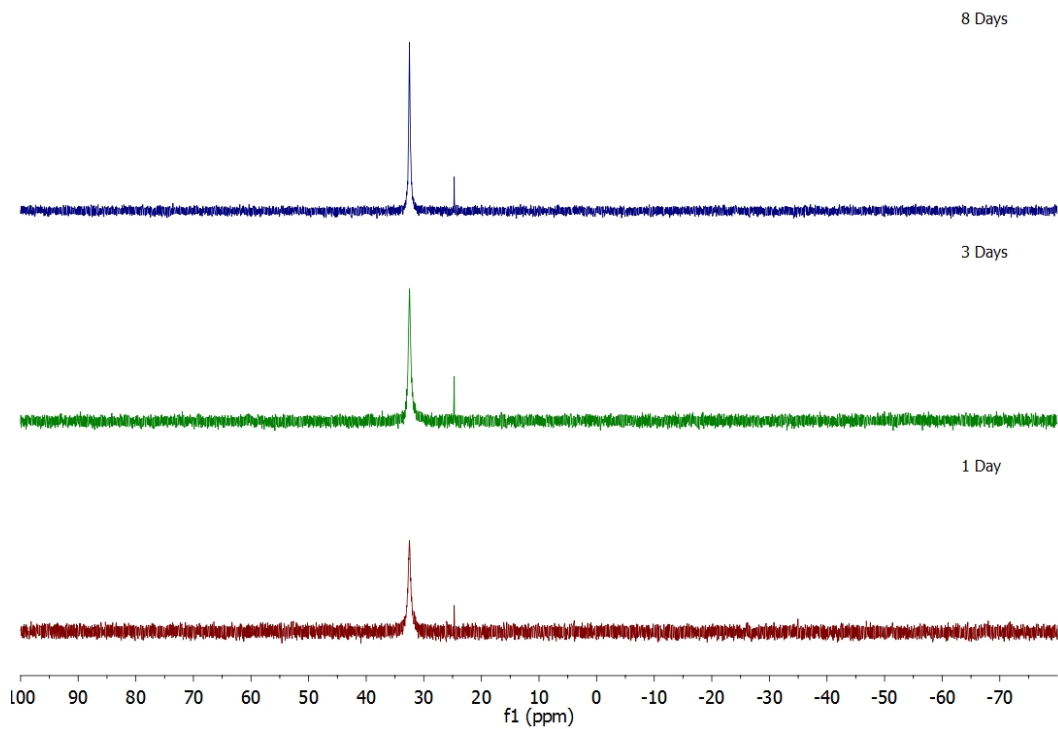




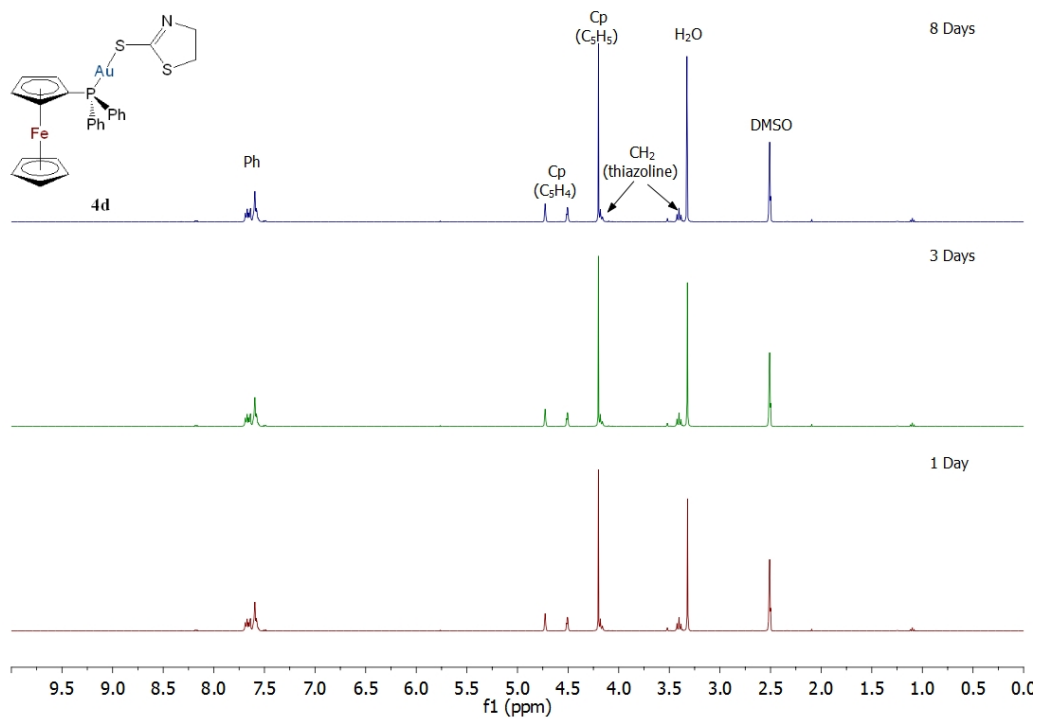
**Figure S37.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum in  $\text{DMSO-d}_6$  of **3b** over time.



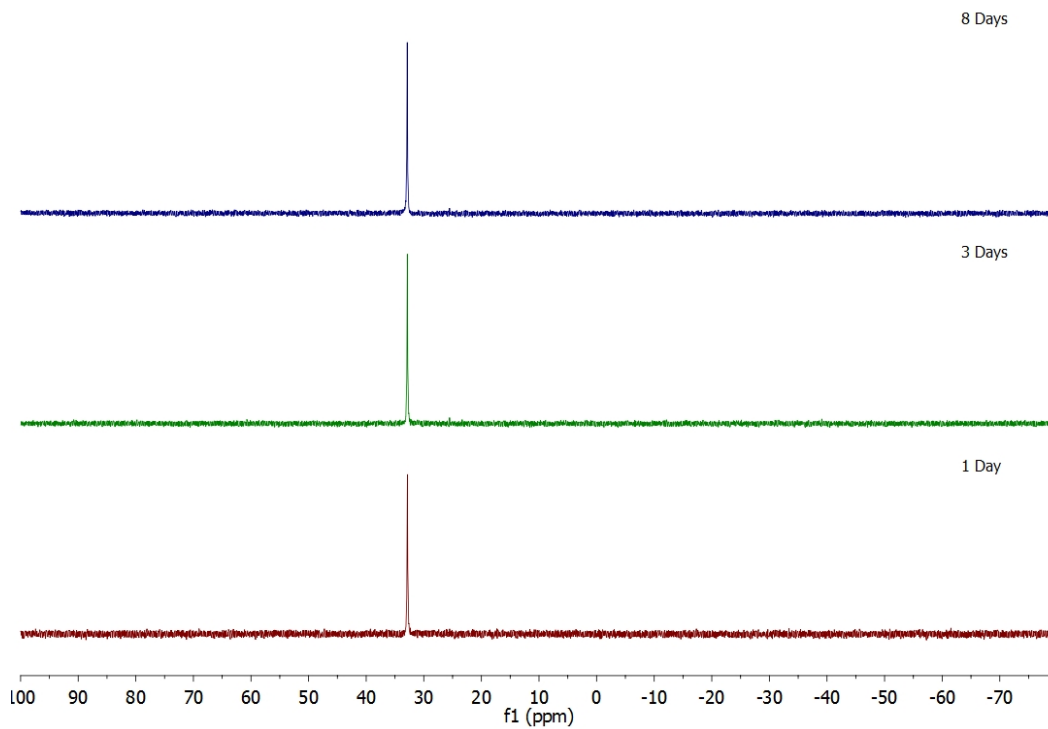
**Figure S38.**  $^1\text{H}$  NMR spectrum in  $\text{DMSO-d}_6$  of **3c** over time.



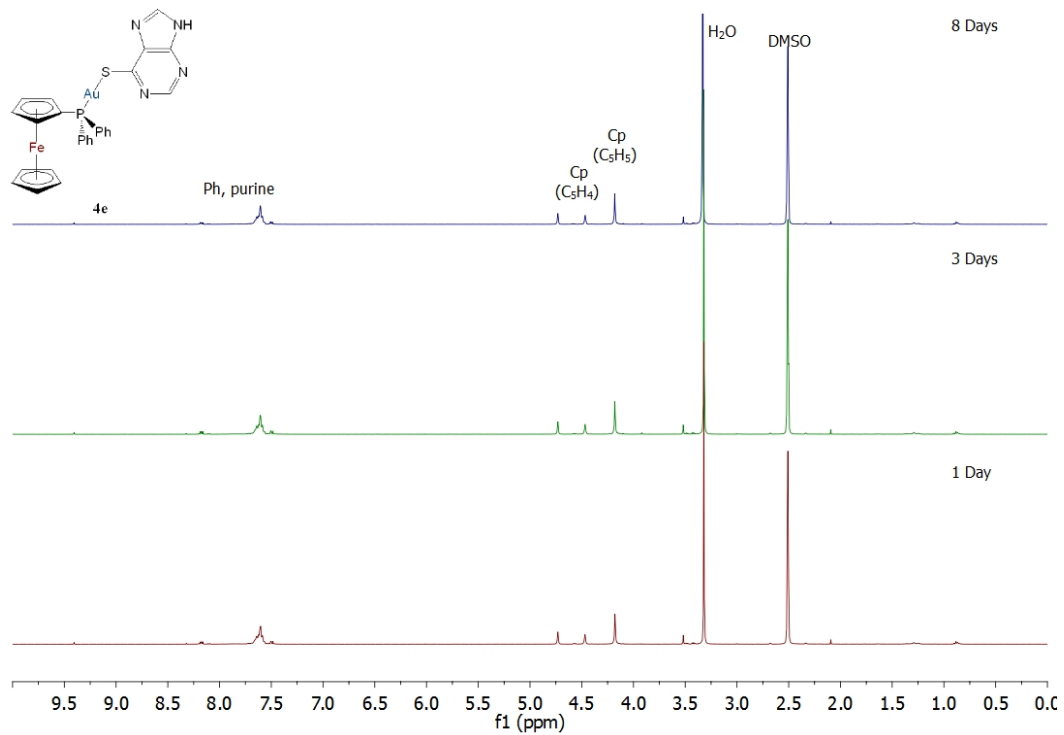
**Figure S39.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum in  $\text{DMSO-d}_6$  of **3c** over time.



**Figure S40.**  $^1\text{H}$  NMR spectrum in  $\text{DMSO-d}_6$  of **4d** over time.



**Figure S41.**  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum in  $\text{DMSO-d}_6$  of **4d** over time.



**Figure S42.**  $^1\text{H}$  NMR spectrum in  $\text{DMSO-d}_6$  of **4e** over time.

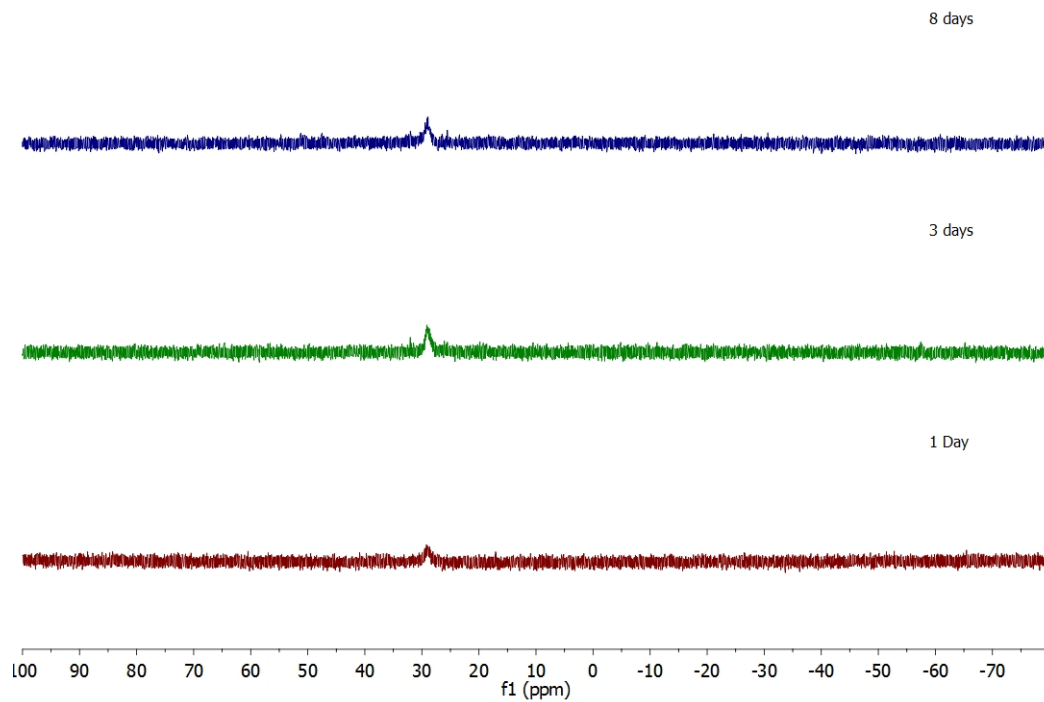
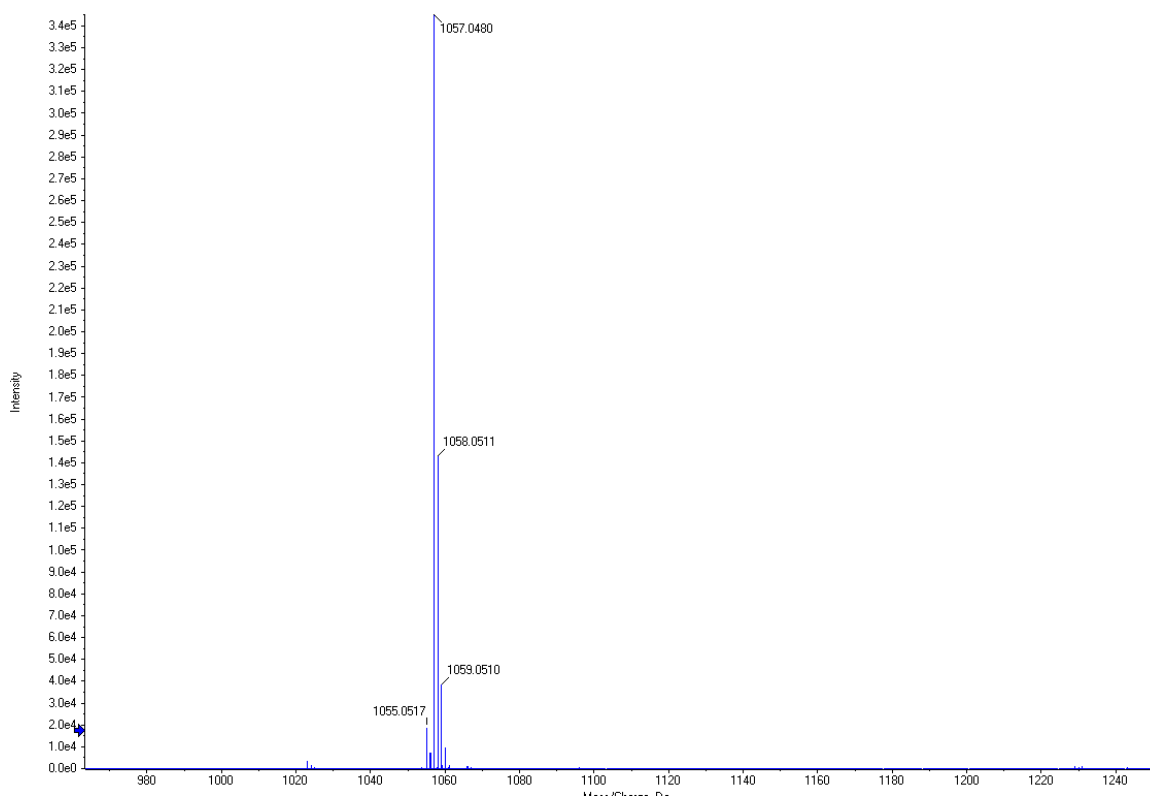
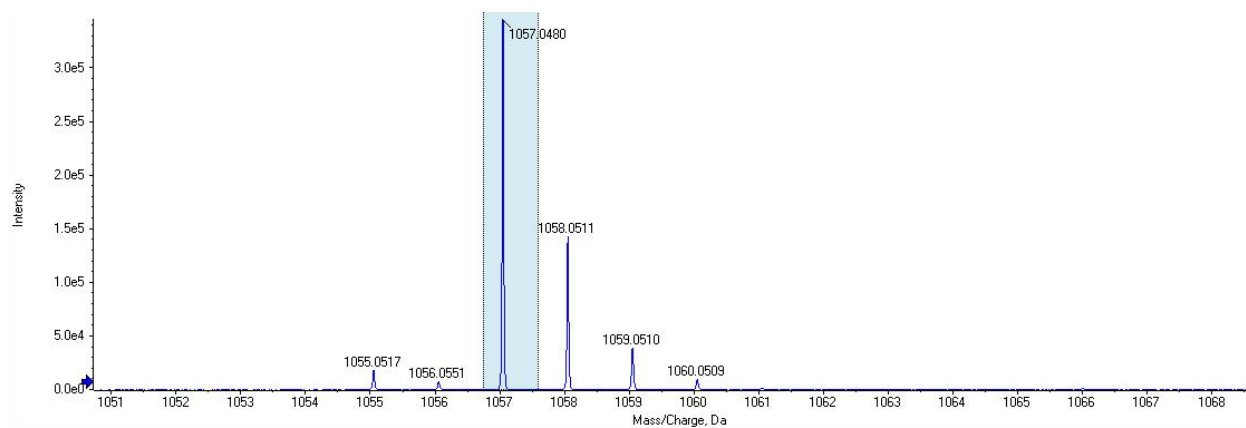


Figure S43.  $^{31}\text{P}\{^1\text{H}\}$  NMR spectrum in  $\text{DMSO-d}_6$  of **4e** over time.

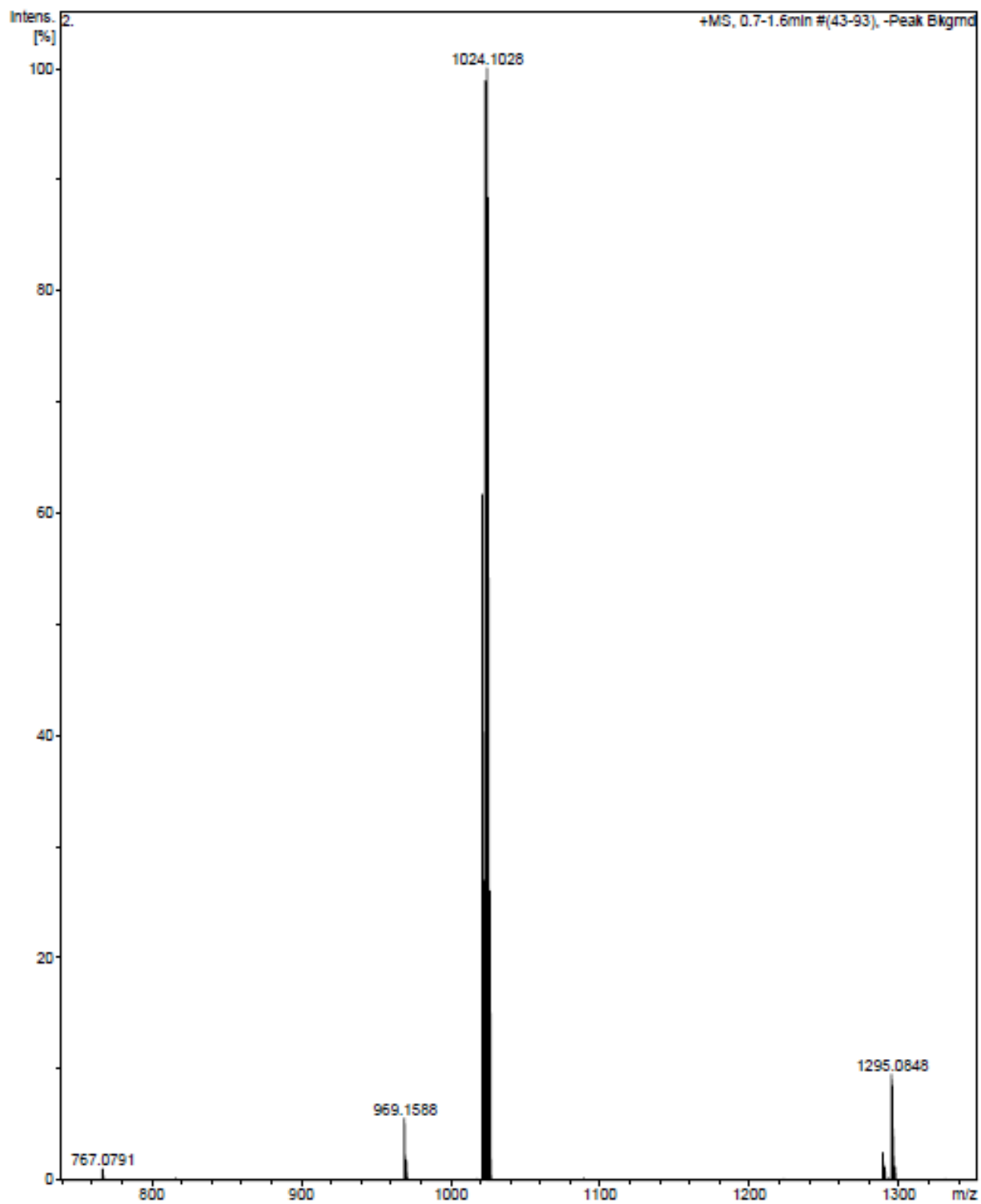
## 5. ESI Mass spectra of compounds 3a-e and 4a-e in $\text{CH}_2\text{Cl}_2$ .



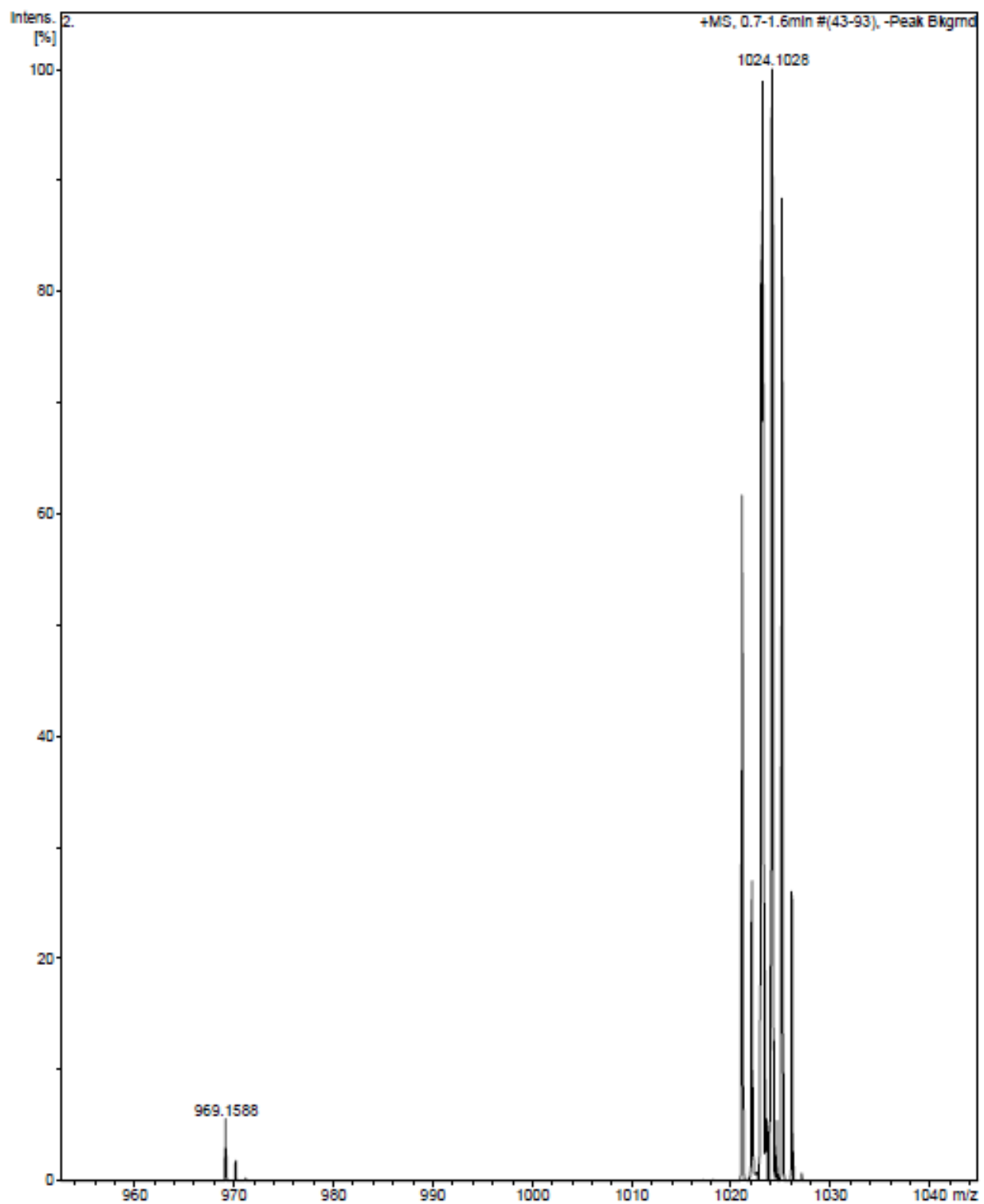
**Figure S44.** Mass spectrum of compound **3a**.



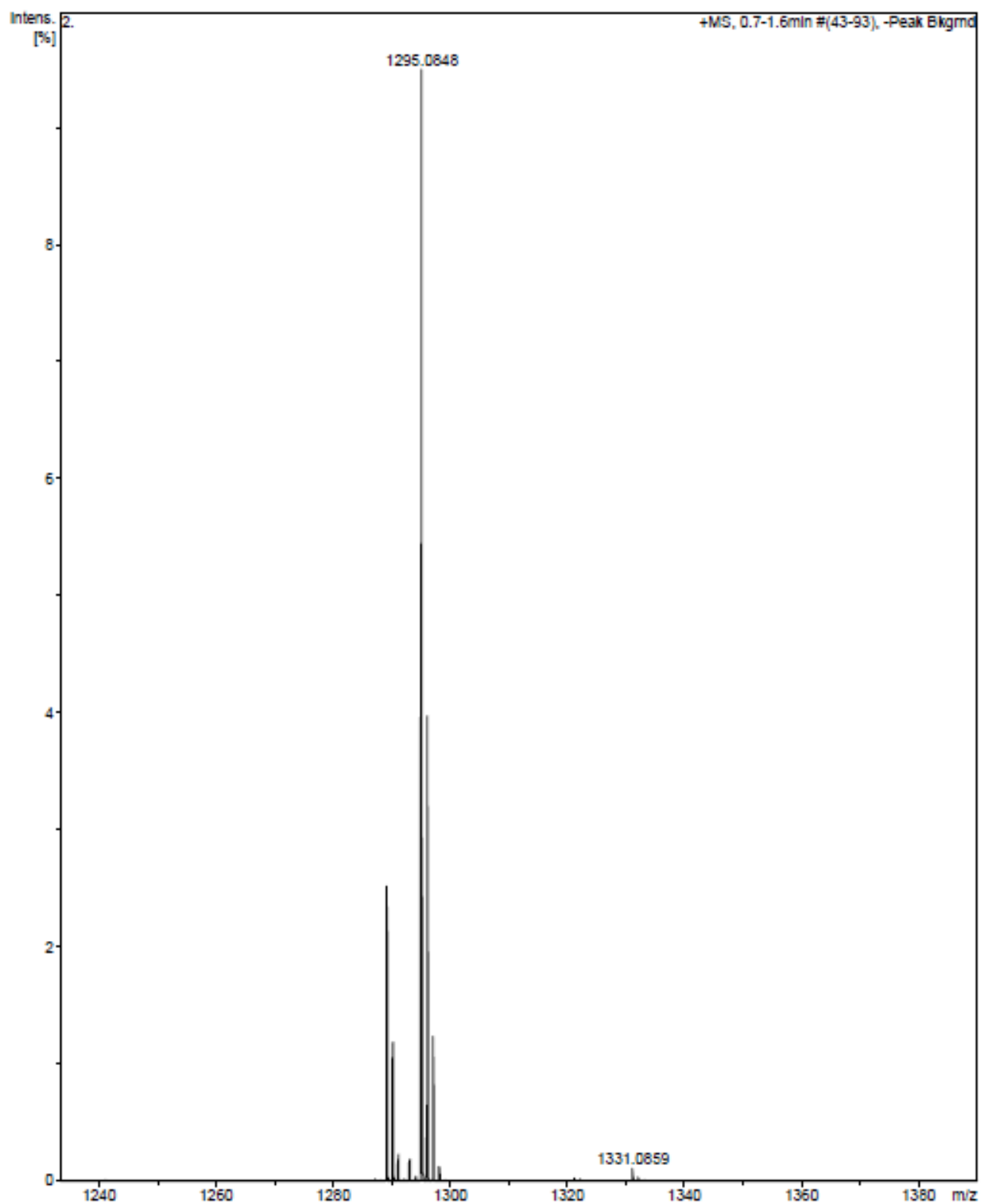
**Figure S45.** Isotopic distribution of compound **3a** for  $[M - SR]^+$ ,  $m/z = 1057.05$  (1%).



**Figure S46.** Mass spectrum of compound **3b**.

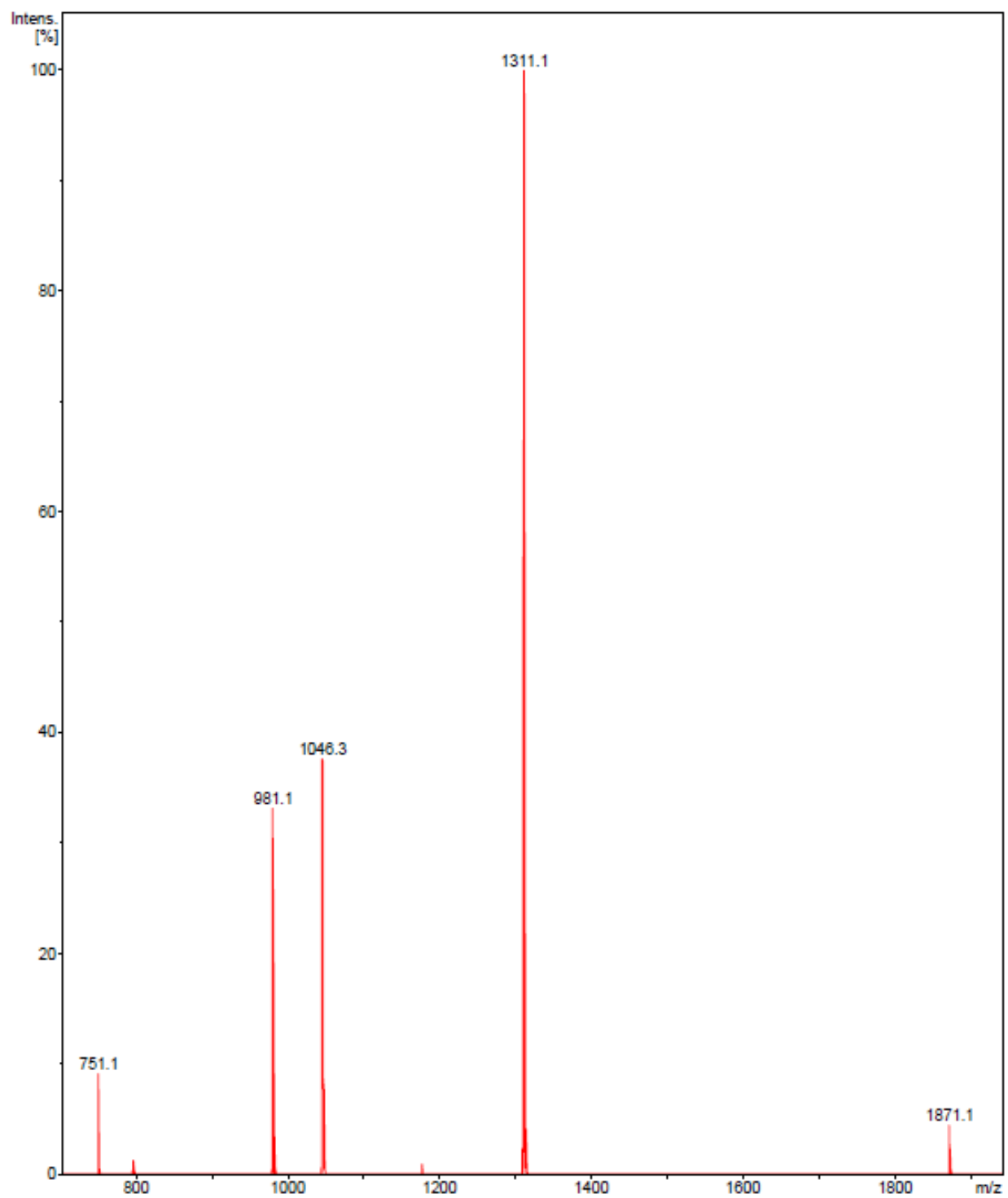


**Figure S47.** Isotopic distribution of compound **3b** for  $[M - SR]^+$ ,  $m/z = 1024.05$  (100%).

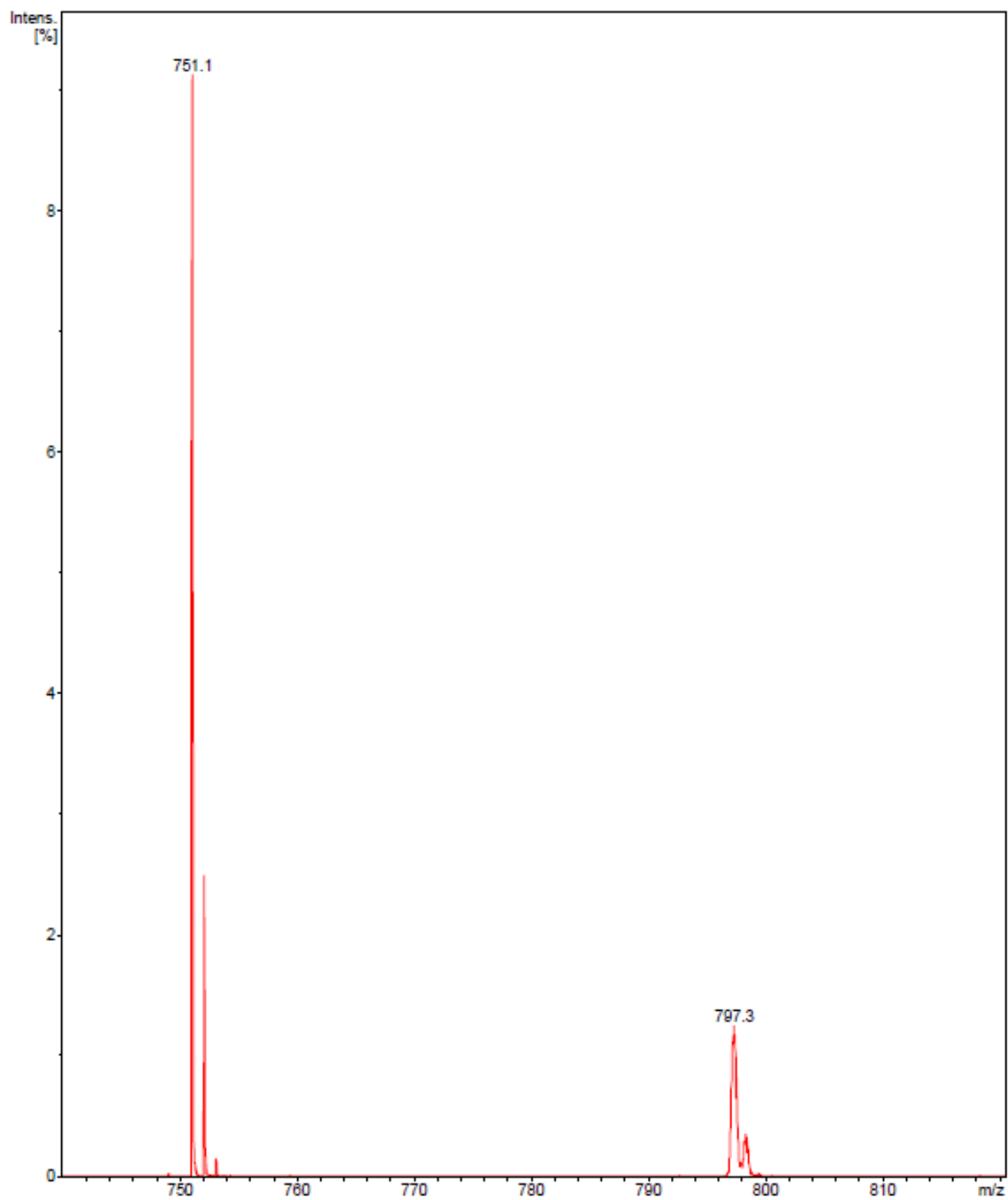


**Figure S48.** Isotopic distribution of compound **3b** for  $[M + Au]^+$ ,  $m/z = 1295.08$  (10%)

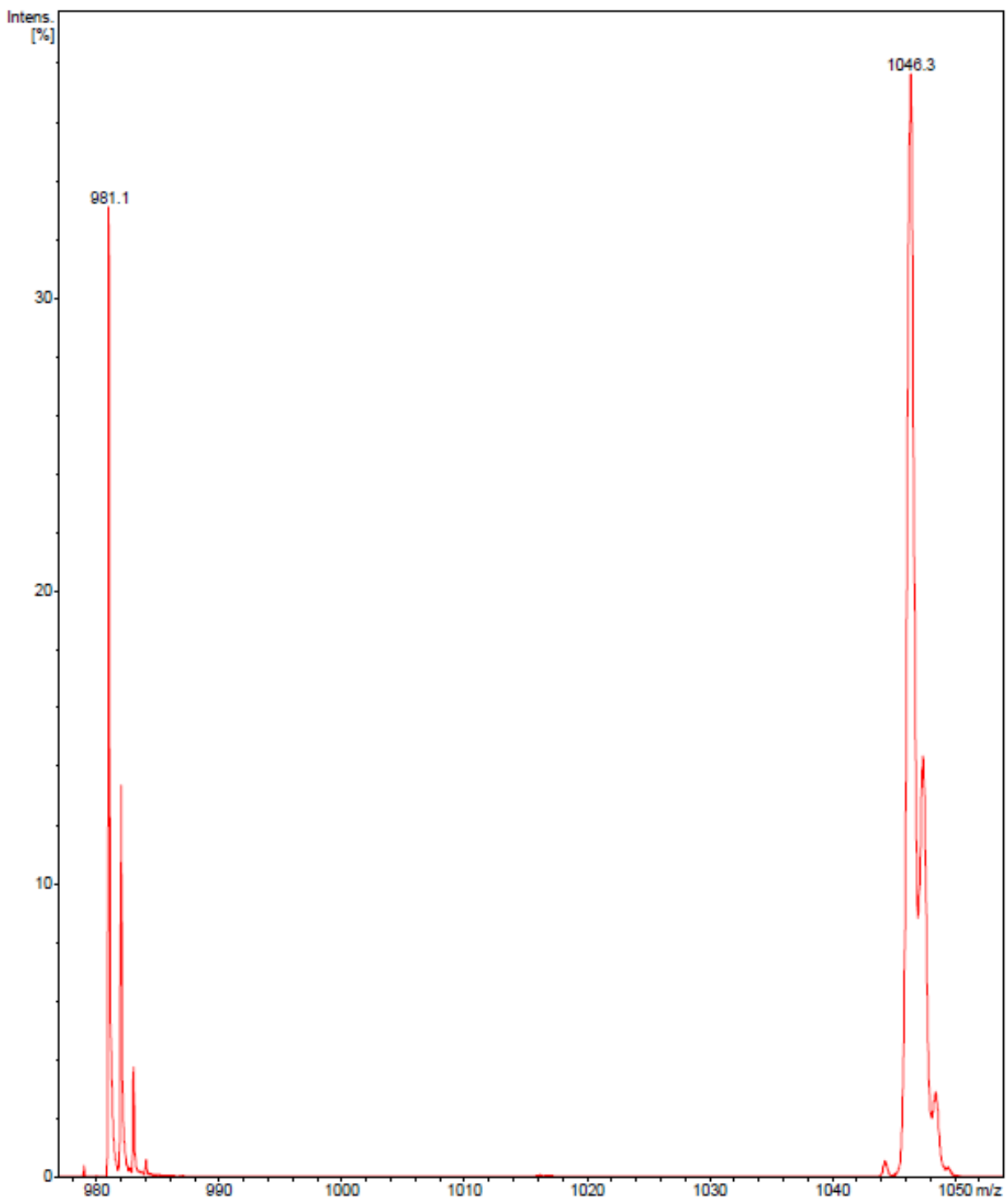




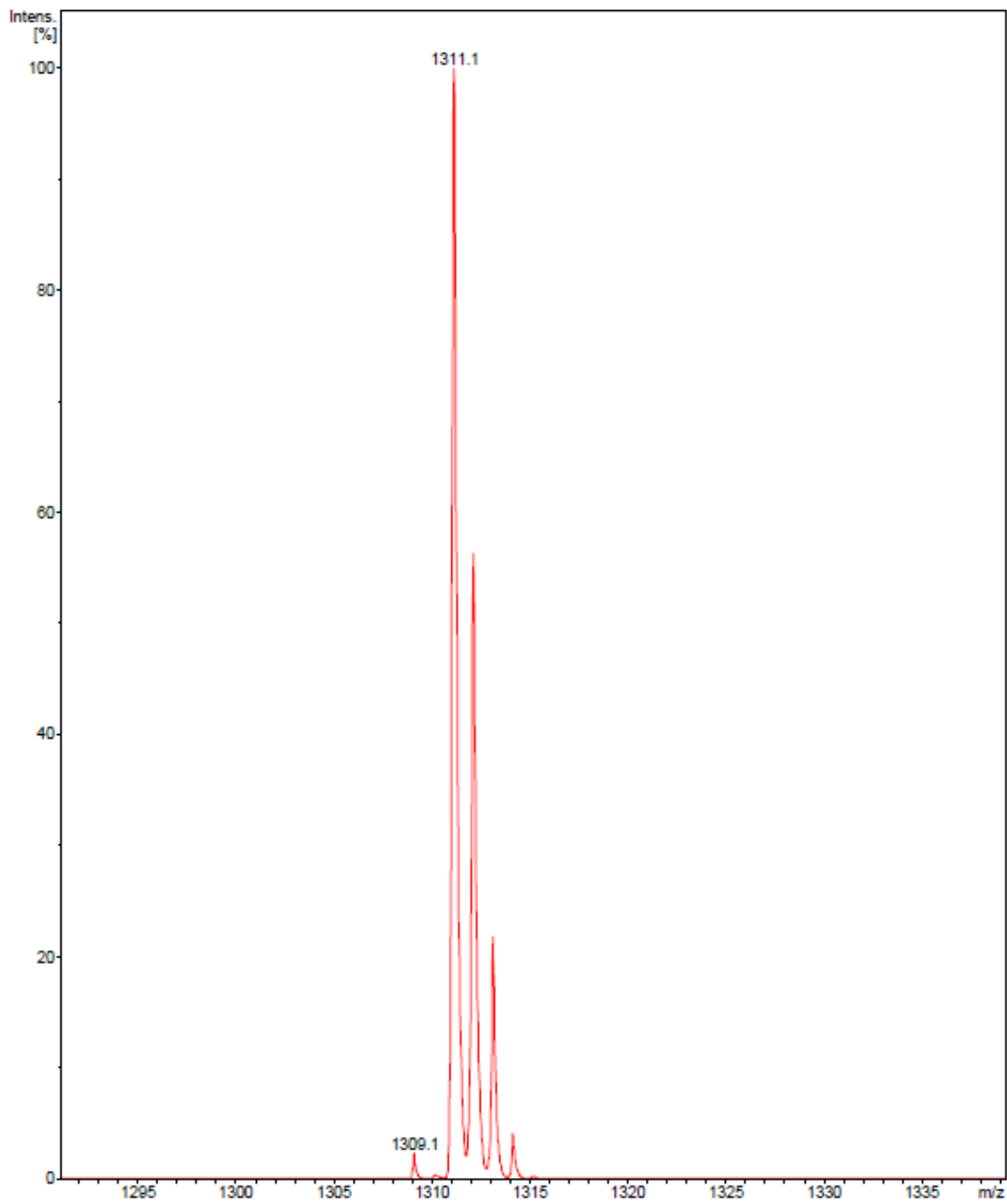
**Figure S49.** Mass spectrum of compound **3c**.



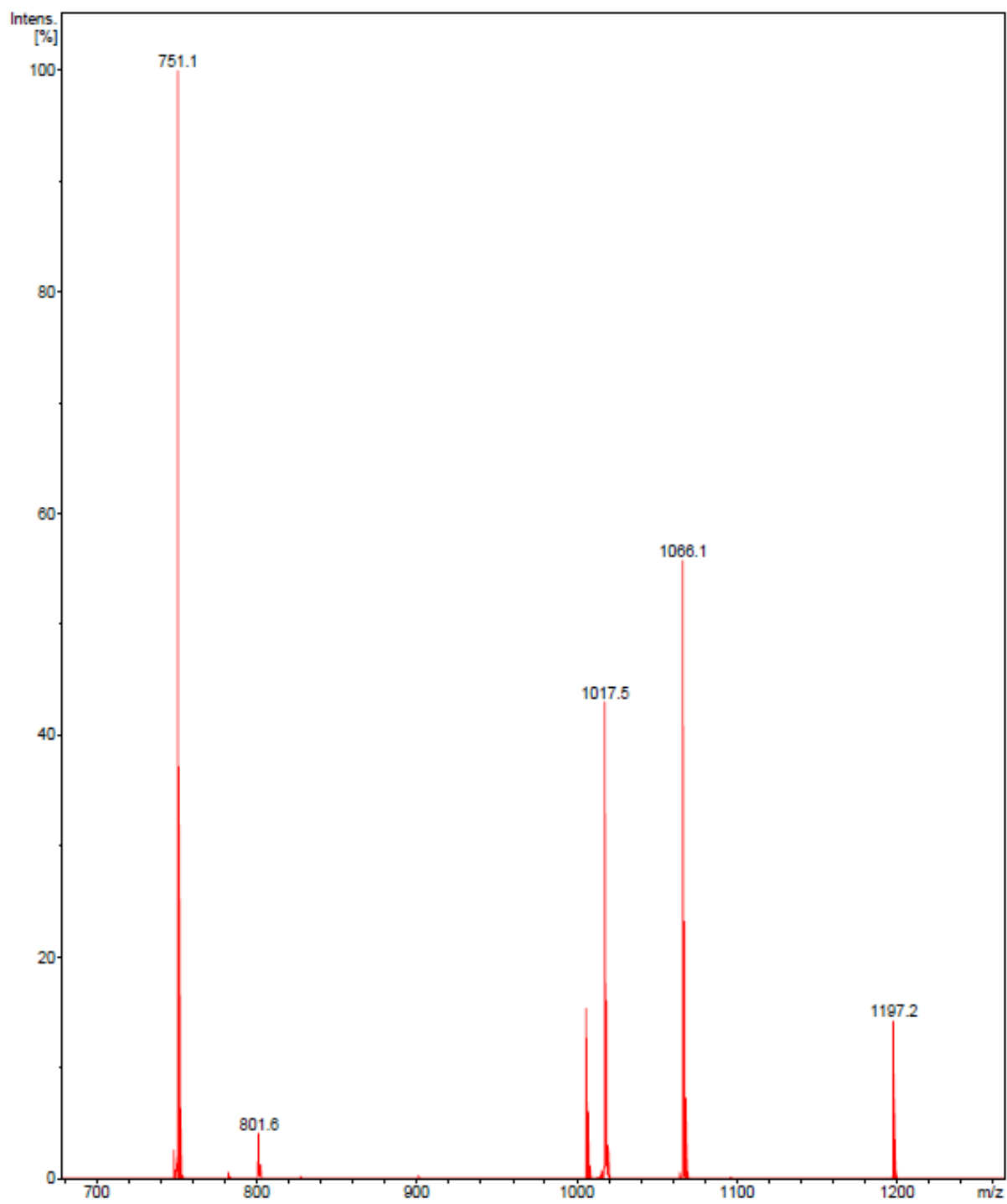
**Figure S50.** Isotopic distribution of compound **3c** for [DPPF + Au]<sup>+</sup>, m/z =751.10 (10%).



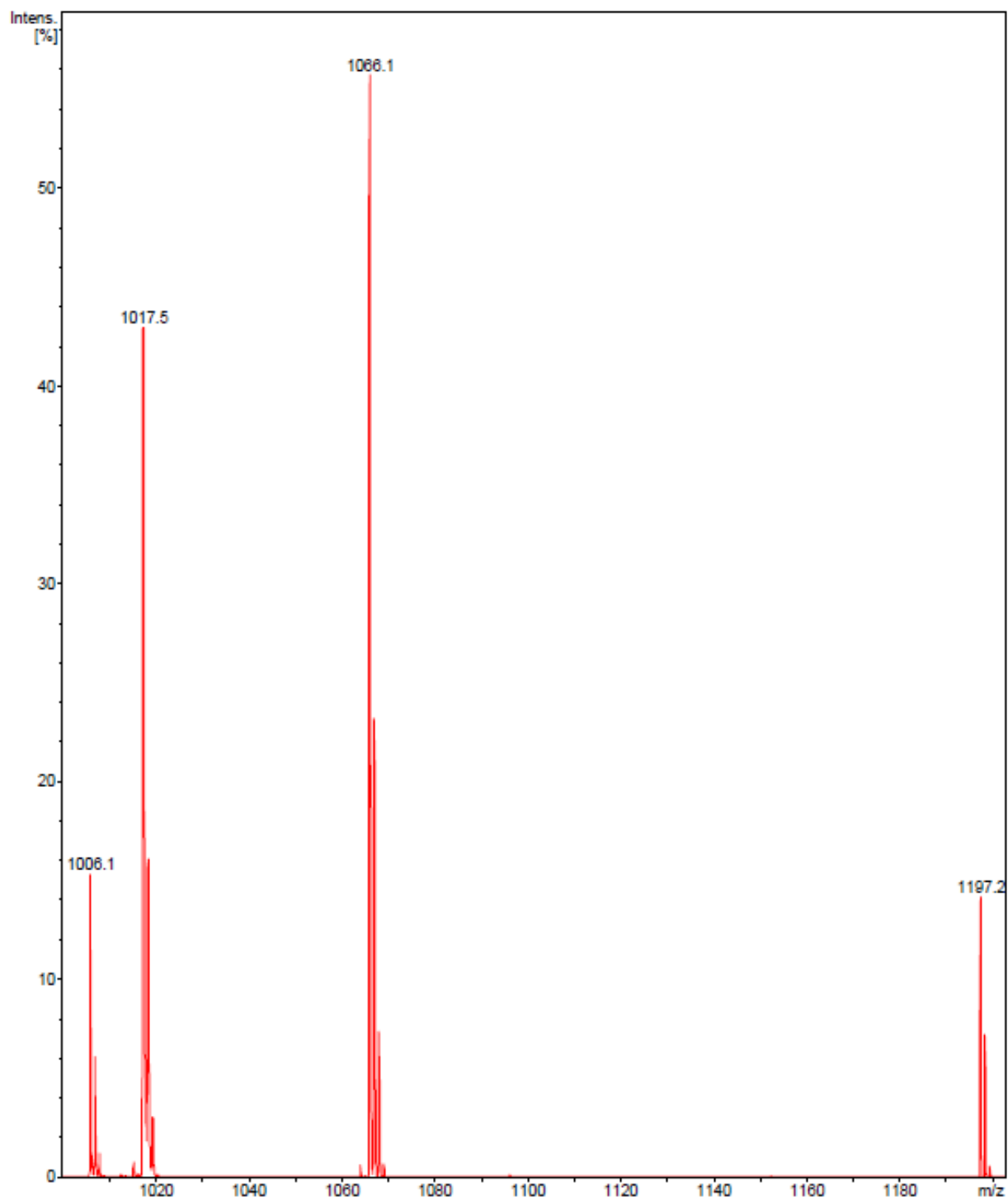
**Figure S51.** Isotopic distribution of compound **3c** for [DPPF + 2Au]<sup>2+</sup>, m/z = 981.10 (35%) .



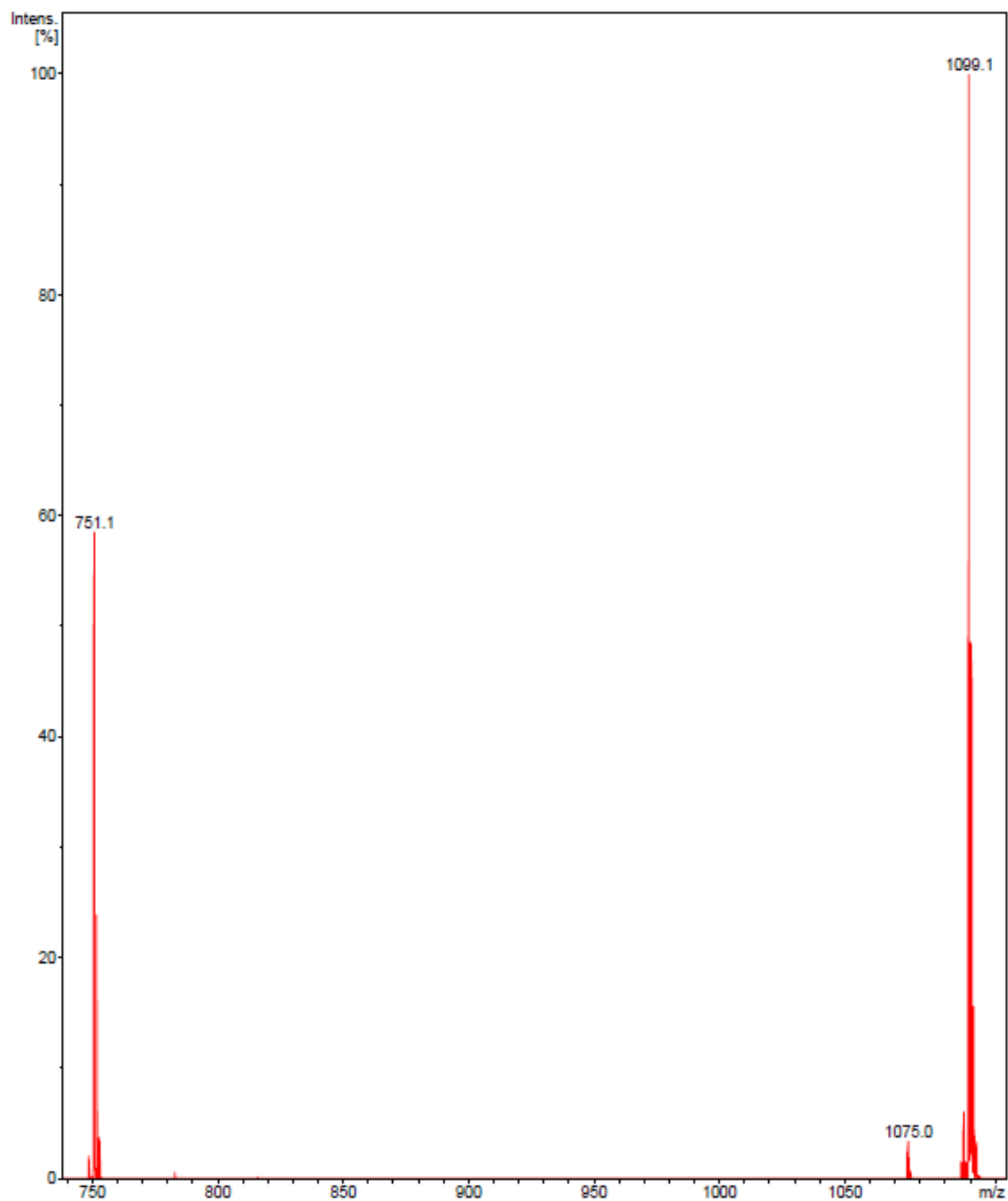
**Figure S52.** Isotopic distribution of compound **3c** for  $[M - SR]^+$ ,  $m/z = 1311.10$  (100%)



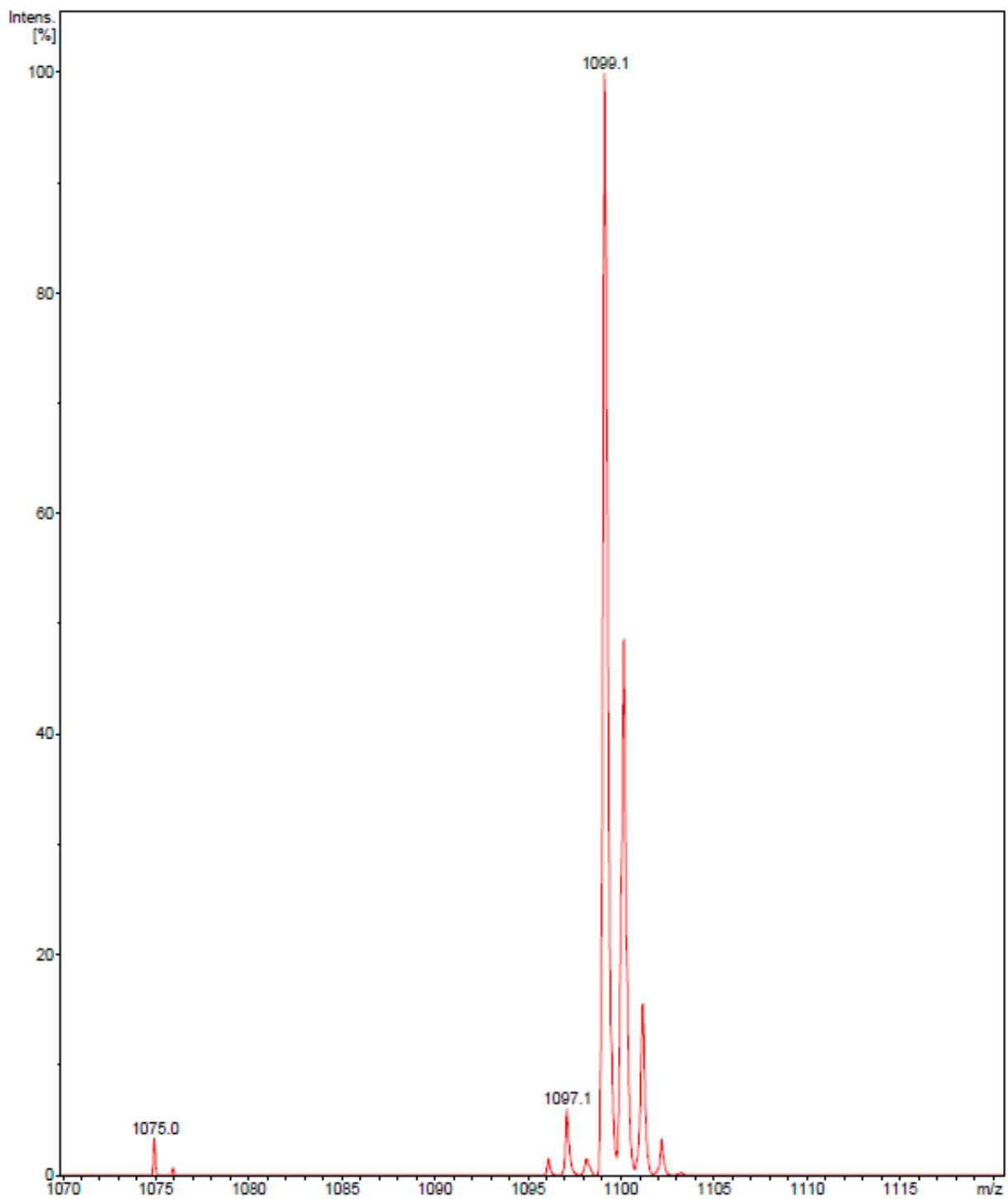
**Figure S53.** Mass spectrum of compound **3d**.



**Figure S54.** Isotopic distribution of compound **3d** for  $[M - SR]^+$ ,  $m/z = 1066.10$  (57%).

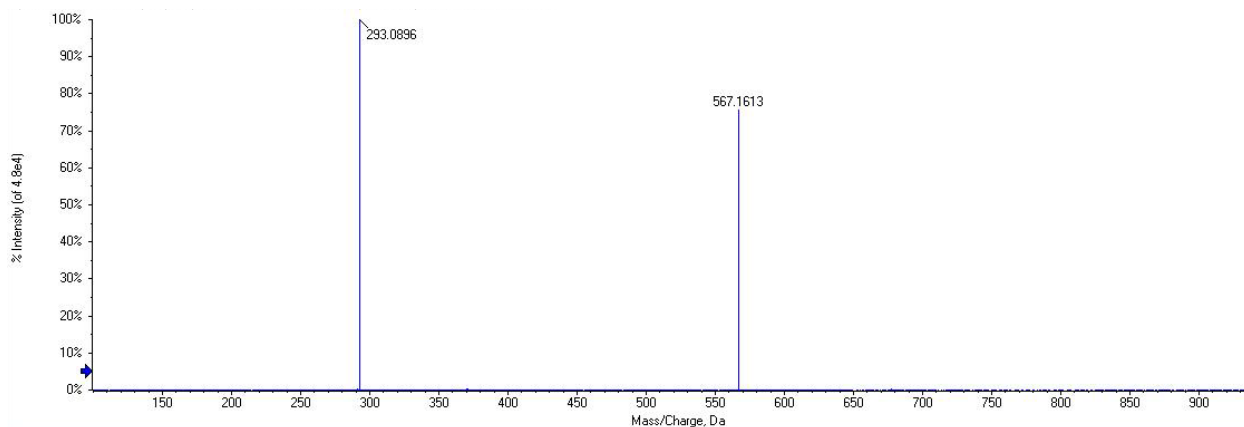


**Figure S55.** Mass spectrum of compound **3e**.

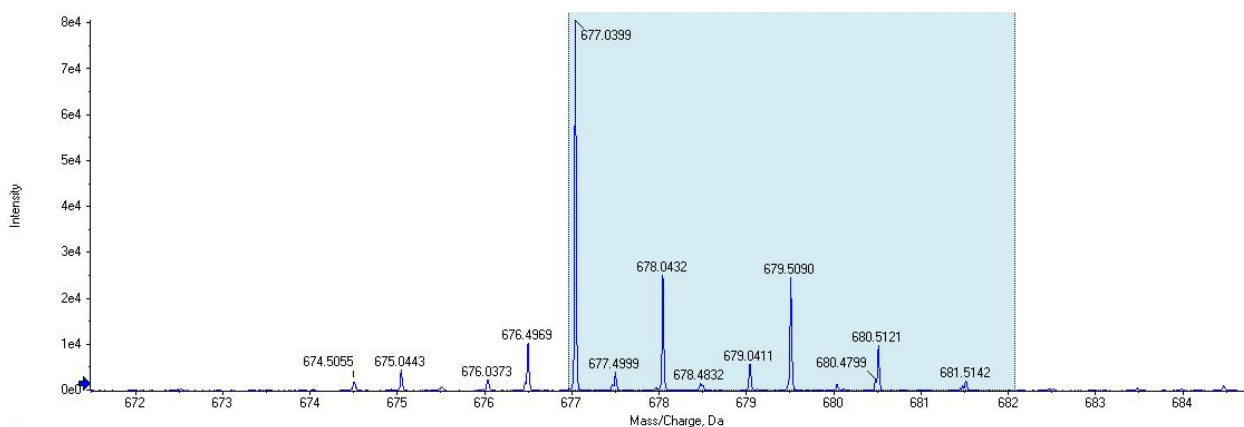


**Figure S56.** Isotopic distribution of compound **3e** for  $[M - SR]^+$ ,  $m/z = 1099.10$  (100%).

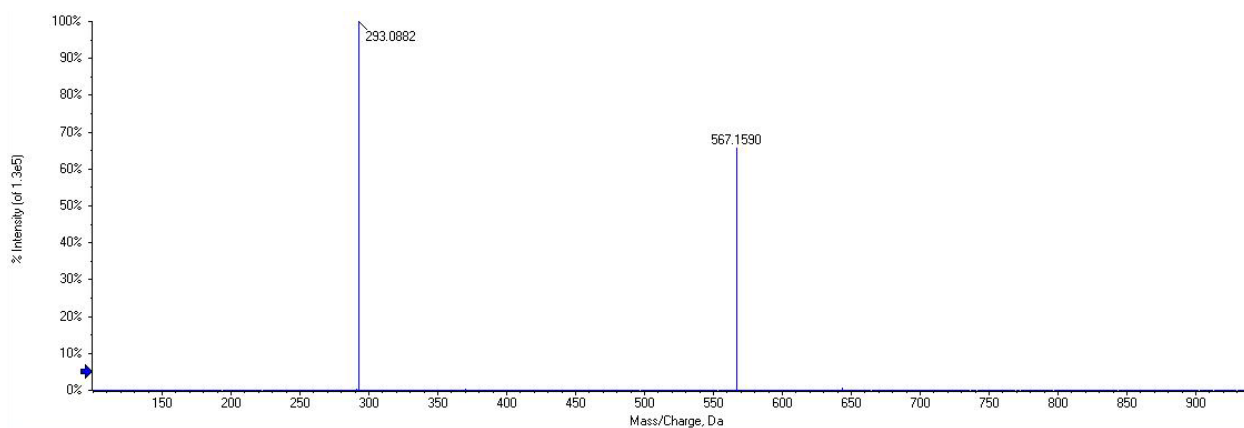




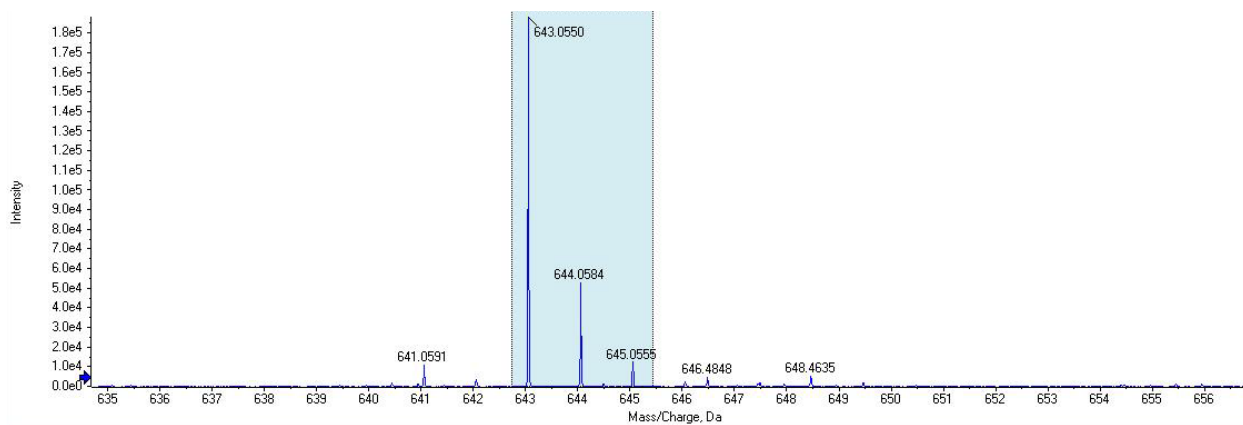
**Figure S57.** Mass spectrum of compound **4a**.



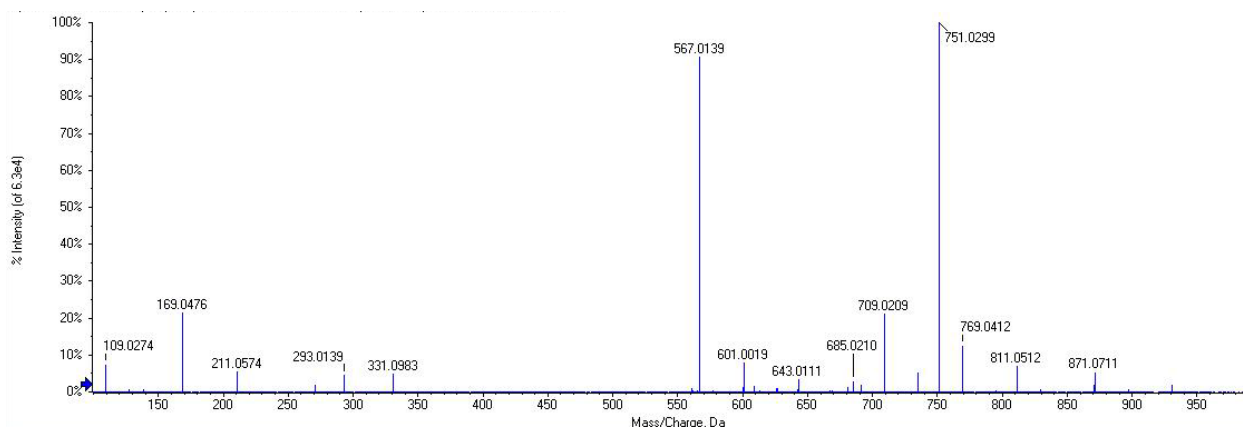
**Figure S58.** Isotopic distribution of compound **4a** for  $[M + H]^+$ ,  $m/z = 677.04$  (0.1%).



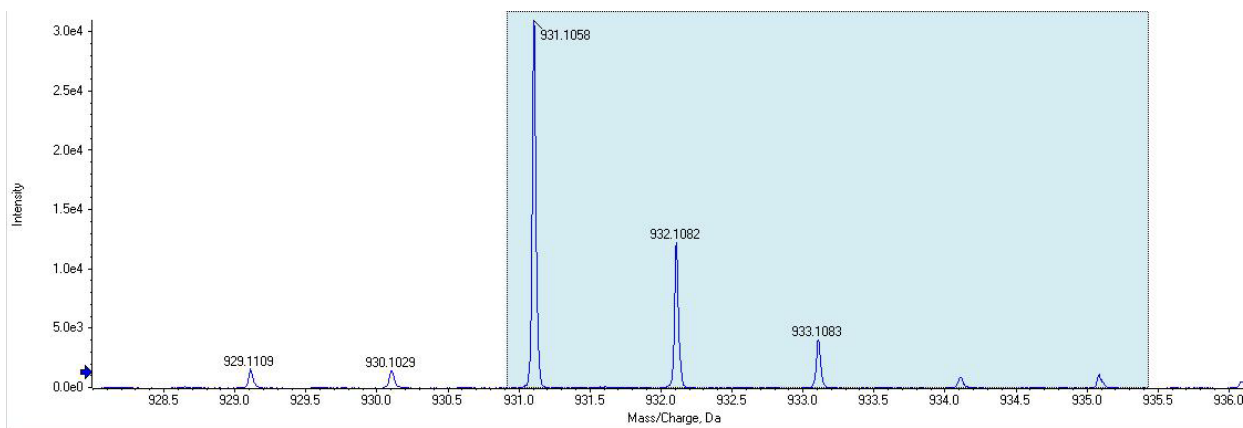
**Figure S59.** Mass spectrum of compound **4b**.



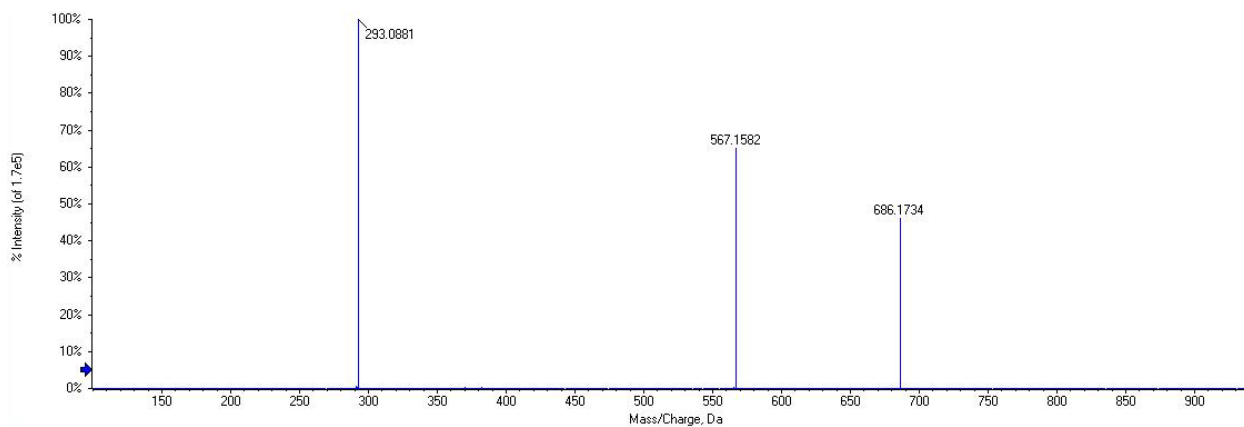
**Figure S60.** Isotopic distribution of compound **4b** for  $[M + H]^+$   $m/z = 643.05$  (0.5%).



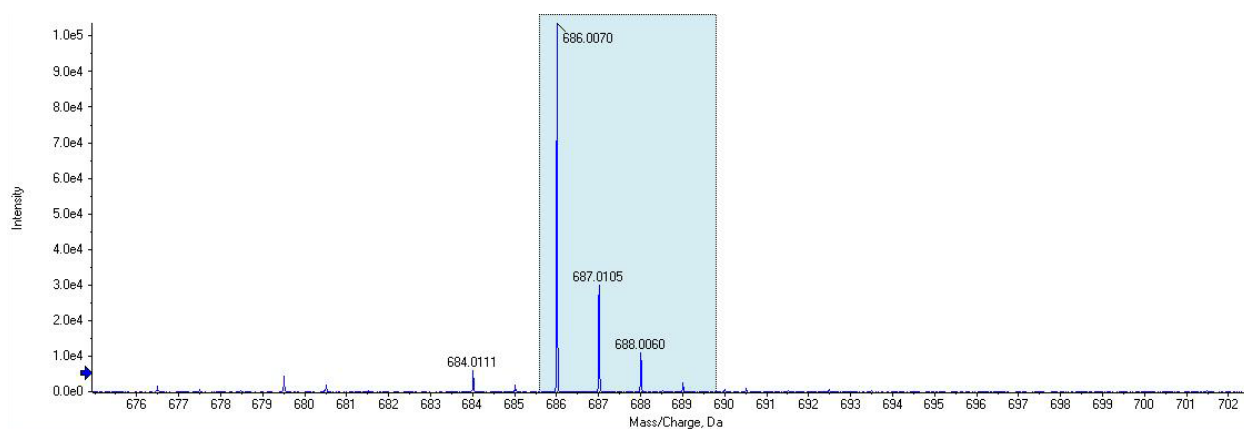
**Figure S60.** Mass spectrum of compound **4c**.



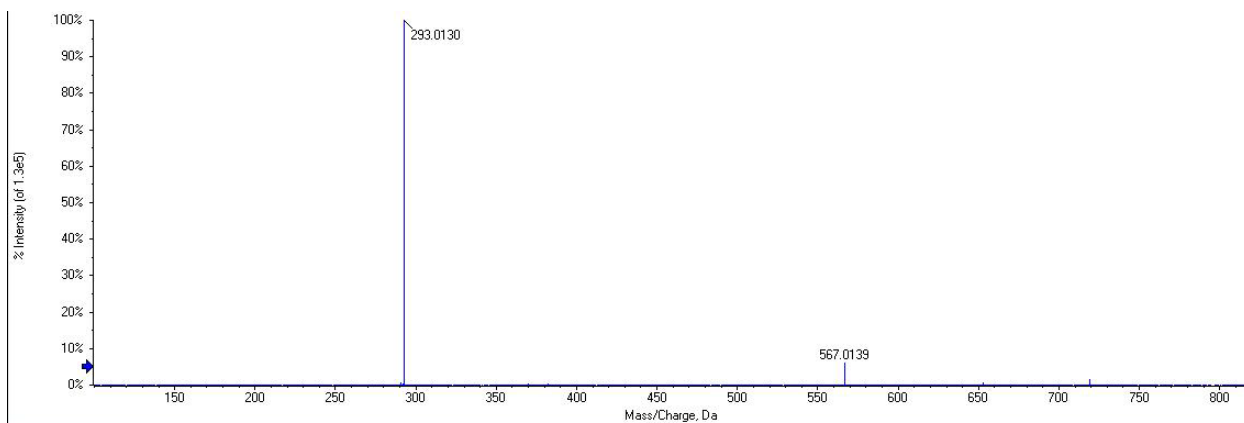
**Figure S61.** Isotopic distribution of compound **4c** for  $[M + H]^+$   $m/z = 931.10$  (2%).



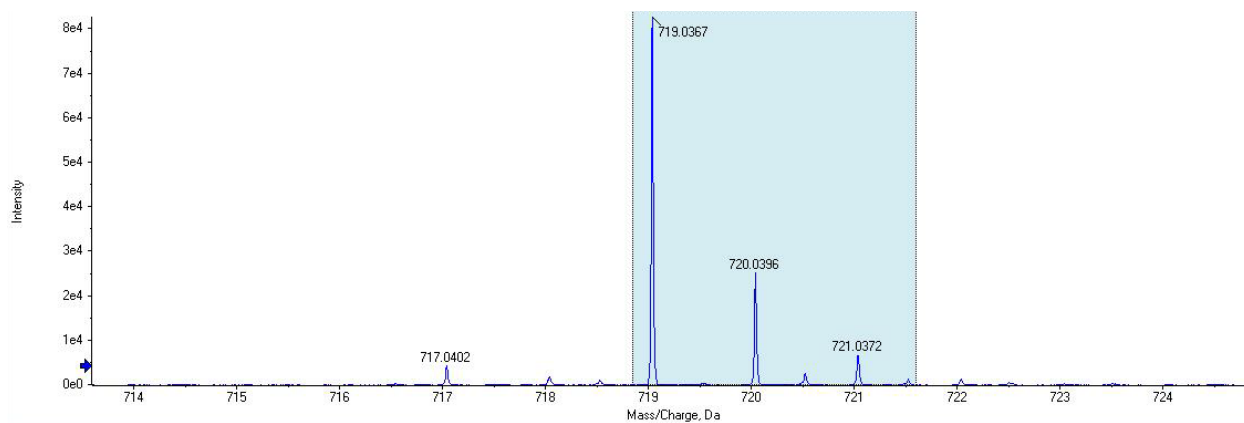
**Figure S62.** Mass spectrum of compound **4d**.



**Figure S63.** Isotopic distribution of compound **4d** for  $[M + H]^+$   $m/z = 686.17$  (50%).



**Figure S64.** Mass spectrum of compound **4e**.



**Figure S65.** Isotopic distribution of compound **4e** for  $[M + H]^+$   $m/z = 719.03$  (2%).