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Supporting Information

A simple synthetic entryway into new families of NHC-gold-amido complexes and their *in vitro* antitumor activity

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Abstract: A simple synthetic pathway to Au-NHC amido complexes is described. Syntheses and isolation of [Au(NHC)(NR^1R^2)] complexes, bearing various NHC ligands and NH-containing heterocycles under mild conditions are reported. The *in vitro* anticancer activity of these gold-complexes was investigated on three human cancer cell lines. A number of these show comparable or even better antiproliferative activity than cisplatin. Noteworthy is the non-toxicity of most of the complexes on normal cells.

Table of Contents

Optimization of reaction conditions

Scheme S1. Optimization of reaction conditions on model reaction of [Au(IPr)Cl] with 5,6-dimethyl-1*H*-benzimidazole.

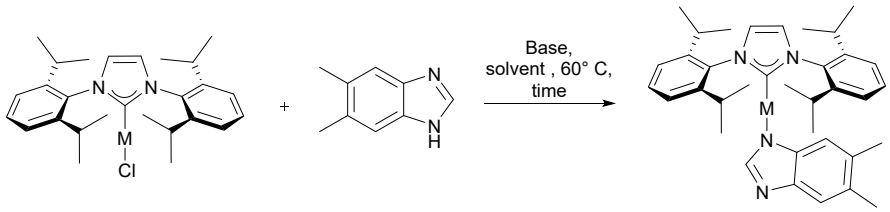


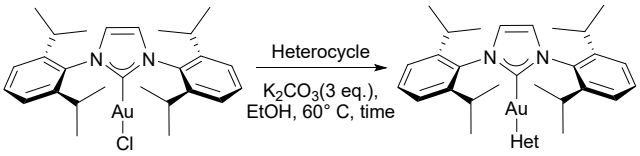
Table S1. The effect of different weak bases and solvents on the model reaction.

Entry/ Metal	Solvent	Base	Time	Conversion[a]
1/Au	Acetone	K_2CO_3 (3 eq.)	16h	100%
2/Au	Acetone	K_2CO_3 (3 eq.)	5h	100%
3/Au	Acetone	K_2CO_3 (3 eq.)	30min	71%
4/Au	EtOH	K_2CO_3 (3 eq.)	16h	100%
5/Au	EtOH	K_2CO_3 (3 eq.)	5h	100%
6/Au	**EtOH**	**K_2CO_3 (3 eq.)**	**30min**	**100%**
7/Au	Acetone	NaOAc (3 eq.)	24h	40%
8/Au	EtOH	NaOAc (3 eq.)	1h	82%
9/Au	EtOH	NaOAc (3 eq.)	24h	82%
10/Au	Acetone	Et_3N (3 eq.)	24h	66%
11/Au	EtOH	Et_3N (3 eq.)	1h	35%
12/Au	EtOH	Et_3N (3 eq.)	24h	35%
13Cu	EtOH	K_2CO_3 (3 eq.)	24h	NR
14/Cu	Acetone	K_2CO_3 (3 eq.)	24h	NR

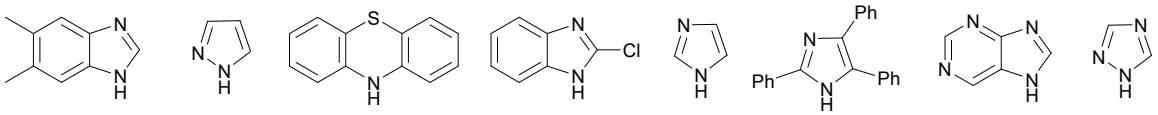
[a] Conversion was determined by NMR; NR=no reaction.

Scope of heterocyclic compounds

Scheme S2. Model reaction used for the scope of heterocyclic compounds.



Heterocycles under examination



1 **2** **3** **4** **5** **6** **7** **8**

Table S2. Scope of heterocyclic compounds.

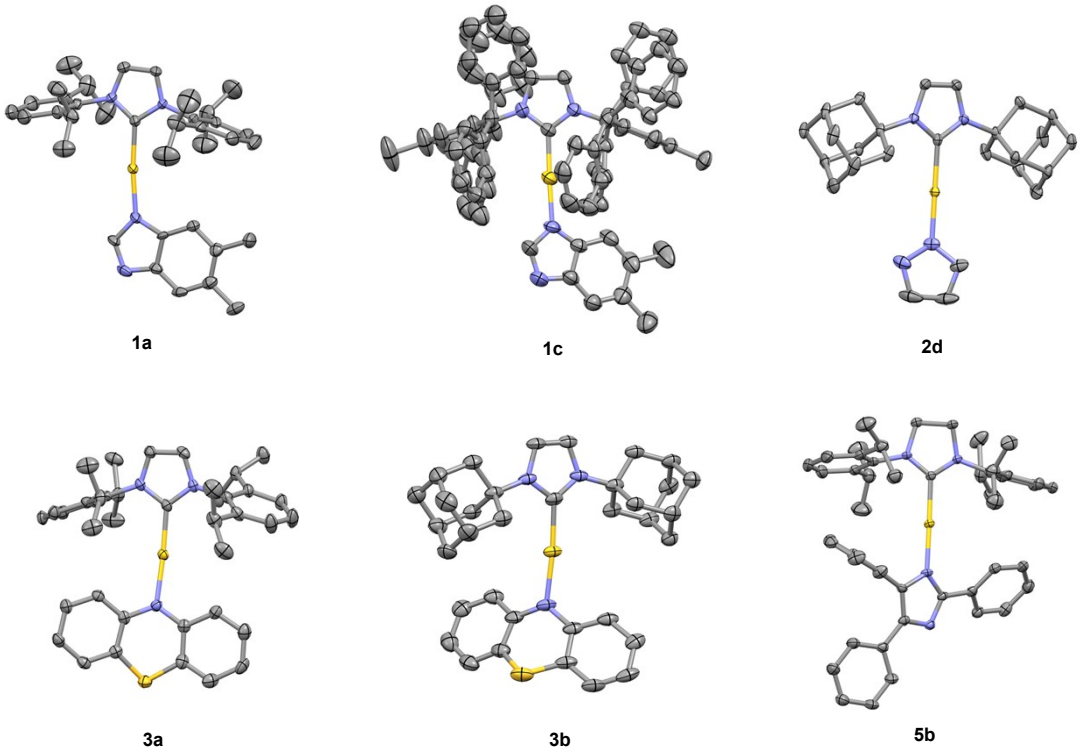
Heterocycle	pK_a	Time (h)	Conversion (%)
1 (5,6-dimethyl-1*H*-benzo[d]imidazole)	16.4 (for 1H-benzo[d]imidazole)	0.5	100
2 (1*H*-pyrazole)	19.8	0.5	100
3 (10*H*-phenothiazine)	23	0.5	100[a]
4 (2-chloro-1*H*-benzo[d]imidazole)	16.4 (for 1H-benzo[d]imidazole)	0.5	100
5 (1*H*-imidazole)	14.4	0.5	100
6 (2,4,5-triphenyl-1*H*-imidazole)	11.7 (predicted)	0.5	100
7 (7*H*-purine)	8.9	0.5	Unidentified mixture of compounds
		24	Ratio didn't changed
8 (1*H*-1,2,4-triazole)	10.3	0.5	Mixture of two compounds, which couldn't be separated
		24	

Reaction conditions: 1 eq. of [Au(IPr)Cl] (50 mg), 1 eq. of heterocycle, 3 eq. of K_2CO_3, 0,5 mL of EtOH; [a]inert atmosphere is required.

X-ray Crystallography

Crystals that were of suitable quality for single crystal X-ray diffraction analysis were obtained in all cases by slow vapor diffusion of the antisolvent (pentane) into saturated solutions of the complexes (in acetone or dichloromethane) at 4 °C. 2120383-2120388 **1a**, **1c**, **2d**, **3a**, **3b** and **5b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

FigureS3. X-ray molecular structures of complexes **1a**, **1c**, **2d**, **3a**, **3b** and **5b** are presented, showing thermal displacement ellipsoids at the 50% probability level and hydrogen atoms omitted for clarity.



Complex **1a** was obtained by slow vapor diffusion of the antisolvent (pentane) into saturated solutions of the complexes in DCM: CCDC number 2120383:

Empirical formula	$C_{73}H_{92}Au_2Cl_2N_8$
Formula weight	1546.39
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.2796(2)
b/Å	18.0093(2)
c/Å	28.1639(4)
α/°	90
β/°	99.6310(10)
γ/°	90
Volume/Å^3	7140.71(16)
Z	4
ρ_{calc}g/cm^3	1.438
μ/mm^{-1}	8.643
F(000)	3112.0
Crystal size/mm$_3$	0.099 × 0.048 × 0.032
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.85 to 147.694
Index ranges	-17 ≤ h ≤ 16, -22 ≤ k ≤ 21, -35 ≤ l ≤ 34
Reflections collected	65277
Independent reflections	14224 [R_{int} = 0.1044, R_{sigma} = 0.0770]
Data/restraints/parameters	14224/84/786
Goodness-of-fit on F^2	1.022
Final R indexes [I>=2σ (I)]	R_1 = 0.0529, wR_2 = 0.1236
Final R indexes [all data]	R_1 = 0.0819, wR_2 = 0.1403
Largest diff. peak/hole / e Å^{-3}	3.67/-2.15

Complex **1c** was obtained by slow vapor diffusion of the antisolvent (pentane) into saturated solutions of the complexes in DCM: CCDC number 2120384:

Empirical formula	$C_{78}H_{65}AuN_4$
Formula weight	1255.31
Temperature/K	100(2)
Crystal system	triclinic
Space group	P-1
a/Å	11.0142(2)
b/Å	13.9263(3)
c/Å	21.1975(5)
α/°	88.846(2)
β/°	83.837(2)
γ/°	86.417(2)
Volume/Å^3	3226.02(12)
Z	2
ρ_{calc}g/cm^3	1.292
μ/mm^{-1}	4.628
F(000)	1280.0
Crystal size/mm^3	0.02 × 0.012 × 0.01
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.36 to 147.694
Index ranges	-13 ≤ h ≤ 13, -17 ≤ k ≤ 15, -26 ≤ l ≤ 26
Reflections collected	60247
Independent reflections	12847 [R_{int} = 0.0694, R_{sigma} = 0.0552]
Data/restraints/parameters	12847/532/830
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0495, wR_2 = 0.1200
Final R indexes [all data]	R_1 = 0.0628, wR_2 = 0.1276
Largest diff. peak/hole / e Å^{-3}	2.37/-1.52

Complex **2d** was obtained by slow vapor diffusion of the antisolvent (pentane) into saturated solutions of the complexes in DCM: CCDC number 2120385:

Empirical formula	$C_{26}H_{35}AuN_4$
Formula weight	600.54
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	Pbcn
a/Å	20.70080(10)
b/Å	12.45040(10)
c/Å	27.2297(2)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	7018.00(8)
Z	12
ρ_{calc}g/cm^3	1.705
μ/mm^{-1}	11.961
F(000)	3576.0
Crystal size/mm^3	0.177 × 0.095 × 0.056
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	6.492 to 147.778
Index ranges	-25 ≤ h ≤ 25, -15 ≤ k ≤ 15, -27 ≤ l ≤ 33
Reflections collected	49241
Independent reflections	7066 [R_{int} = 0.0398, R_{sigma} = 0.0212]
Data/restraints/parameters	7066/0/421
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0194, wR_2 = 0.0447
Final R indexes [all data]	R_1 = 0.0236, wR_2 = 0.0462
Largest diff. peak/hole / e Å^{-3}	0.73/-0.75

Complex **3a** was obtained by slow vapor diffusion of the antisolvent (pentane) into saturated solutions of the complexes in Acetone: CCDC number 2120386:

Empirical formula	$C_{39}H_{44}AuN_3S$
Formula weight	783.80
Temperature/K	100.0(1)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	16.8713(2)
b/Å	39.1909(3)
c/Å	11.13870(10)

α/°	90
β/°	108.4560(10)
γ/°	90
Volume/Å^3	6986.12(12)
Z	8
ρ_{calc}g/cm^3	1.490
μ/mm-1	8.694
F(000)	3152.0
Crystal size/mm^3	0.112 × 0.047 × 0.032
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	5.966 to 133.196
Index ranges	-19 ≤ h ≤ 20, -46 ≤ k ≤ 46, -13 ≤ l ≤ 13
Reflections collected	48938
Independent reflections	12243 [R_{int} = 0.0470, R_{sigma} = 0.0405]
Data/restraints/parameters	12243/0/809
Goodness-of-fit on F^2	1.007
Final R indexes [I>=2σ (I)]	R_1 = 0.0288, wR_2 = 0.0626
Final R indexes [all data]	R_1 = 0.0409, wR_2 = 0.0677
Largest diff. peak/hole / e Å^{-3}	2.85/-1.49

Complex **3b** was obtained by slow vapor diffusion of the antisolvent (pentane) into saturated solutions of the complexes in DCM: CCDC number 2120387:

Empirical formula	$C_{35}H_{40}AuN_3S$
Formula weight	731.73
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	Pbca
a/Å	11.07582(15)
b/Å	18.5823(2)
c/Å	28.4054(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	5846.22(14)
Z	8
ρ_{calc}g/cm^3	1.663
μ/mm^{-1}	10.340
F(000)	2928.0
Crystal size/mm^3	0.132 × 0.097 × 0.077
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	6.224 to 147.732
Index ranges	-13 ≤ h ≤ 12, -22 ≤ k ≤ 23, -34 ≤ l ≤ 34
Reflections collected	28502
Independent reflections	5832 [R_{int} = 0.0548, R_{sigma} = 0.0423]
Data/restraints/parameters	5832/0/361
Goodness-of-fit on F^2	1.014
Final R indexes [I>=2σ (I)]	R_1 = 0.0384, wR_2 = 0.0980
Final R indexes [all data]	R_1 = 0.0499, wR_2 = 0.1069
Largest diff. peak/hole / e Å^{-3}	2.64/-0.81

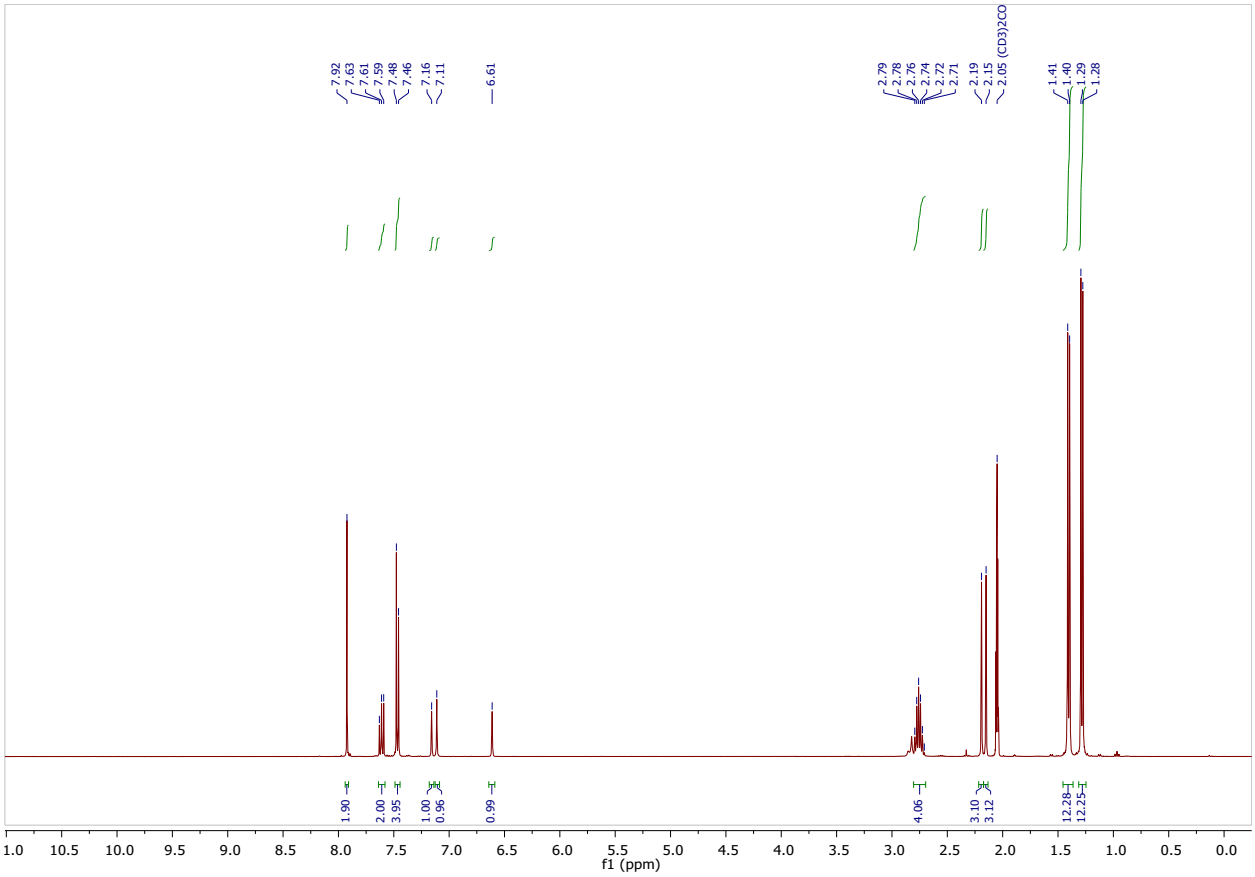
Complex **5b** was obtained by slow vapor diffusion of the antisolvent (pentane) into saturated solutions of the complexes in DCM: CCDC number 2120388:

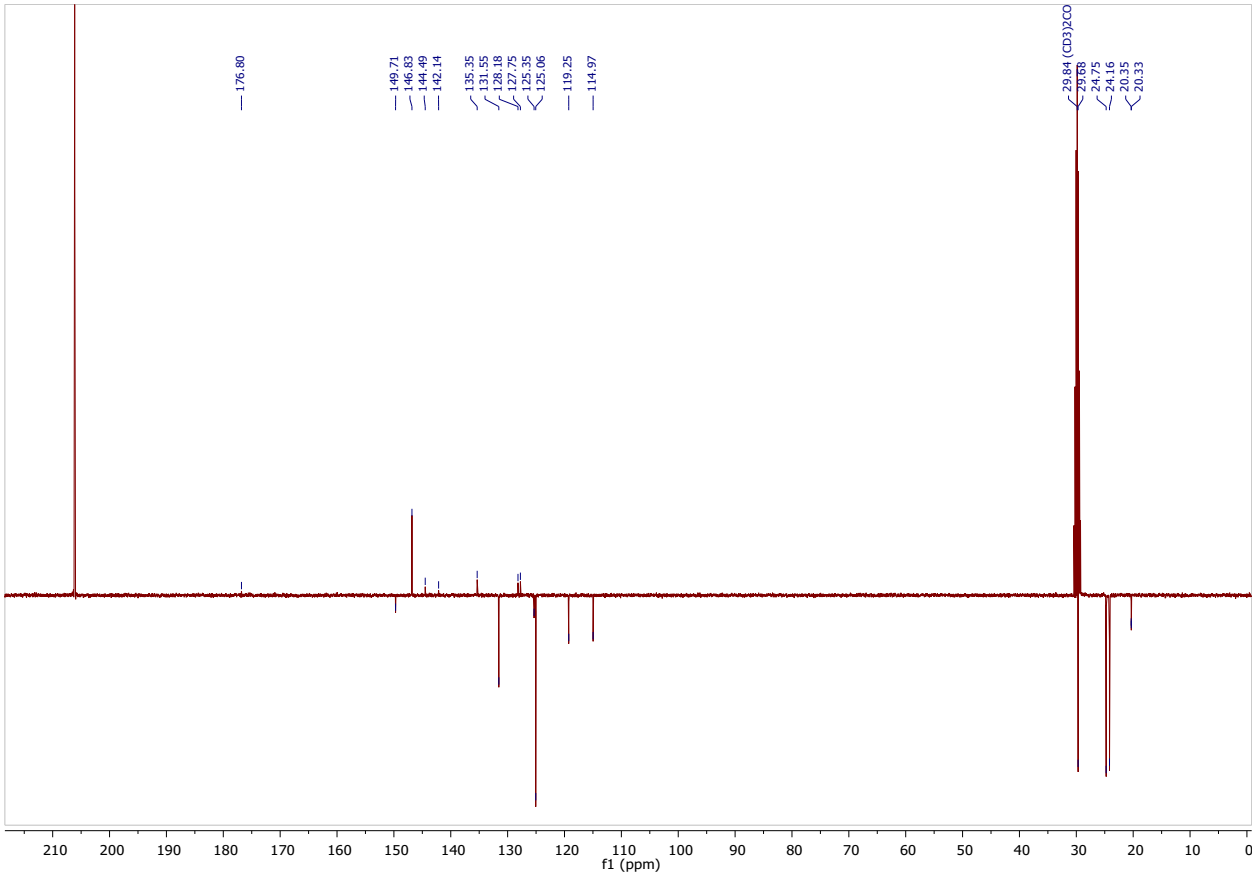
Empirical formula	$C_{48}H_{53}AuN_4$
Formula weight	882.91
Temperature/K	100.0(1)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	17.73610(10)
b/Å	18.81190(10)
c/Å	25.19810(10)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	8407.34(7)
Z	8
ρ_{calc}g/cm^3	1.395
μ/mm^{-1}	6.846
F(000)	3584.0
Crystal size/mm3	0.243 × 0.129 × 0.109

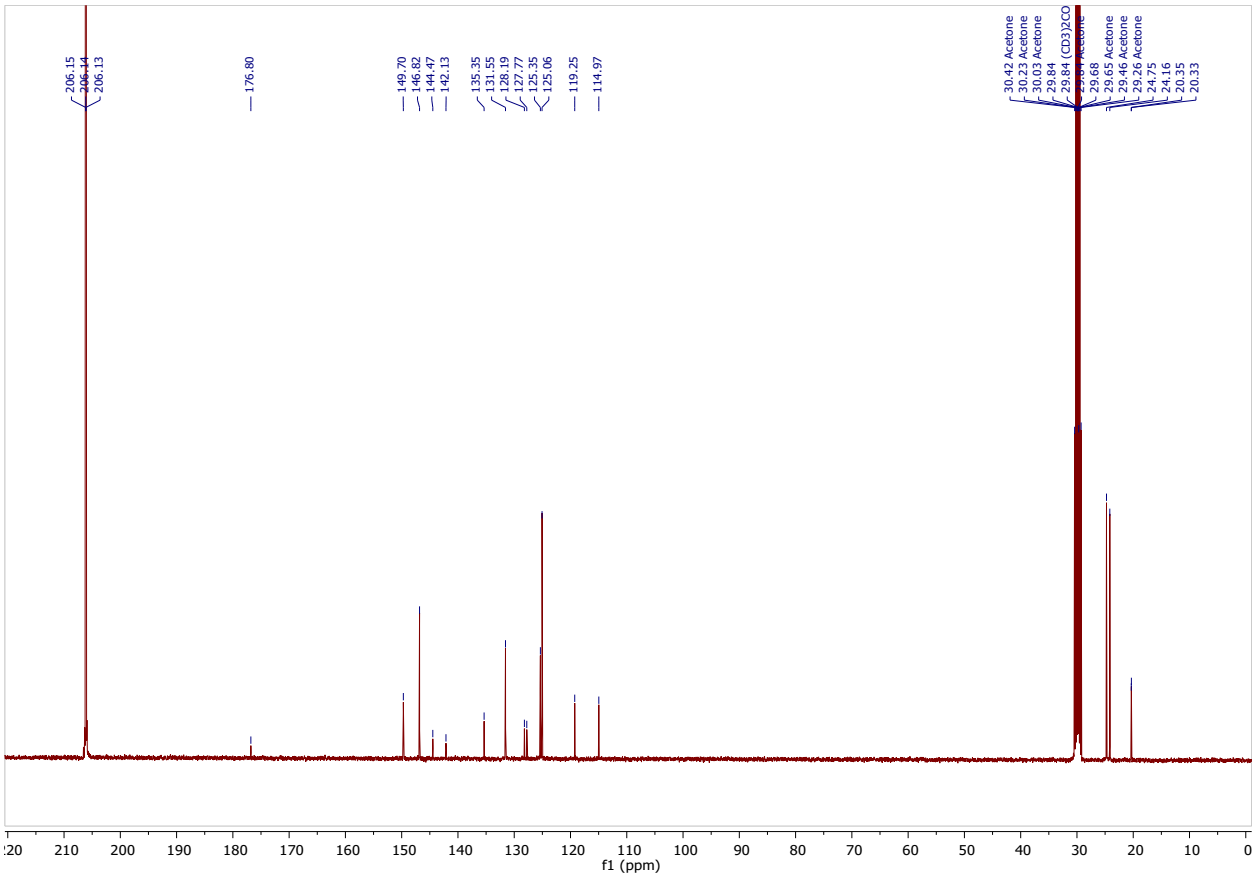
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	5.862 to 148.132
Index ranges	-20 ≤ h ≤ 21, -23 ≤ k ≤ 23, -31 ≤ l ≤ 31
Reflections collected	159999
Independent reflections	16900 [R_{int} = 0.0589, R_{sigma} = 0.0291]
Data/restraints/parameters	16900/0/972
Goodness-of-fit on F^2	1.031
Final R indexes [I>=2σ (I)]	R_1 = 0.0220, wR_2 = 0.0521
Final R indexes [all data]	R_1 = 0.0238, wR_2 = 0.0529
Largest diff. peak/hole / e $Å^{-3}$	0.89/-0.73
Flack parameter	0.291(5)

NMR Spectra

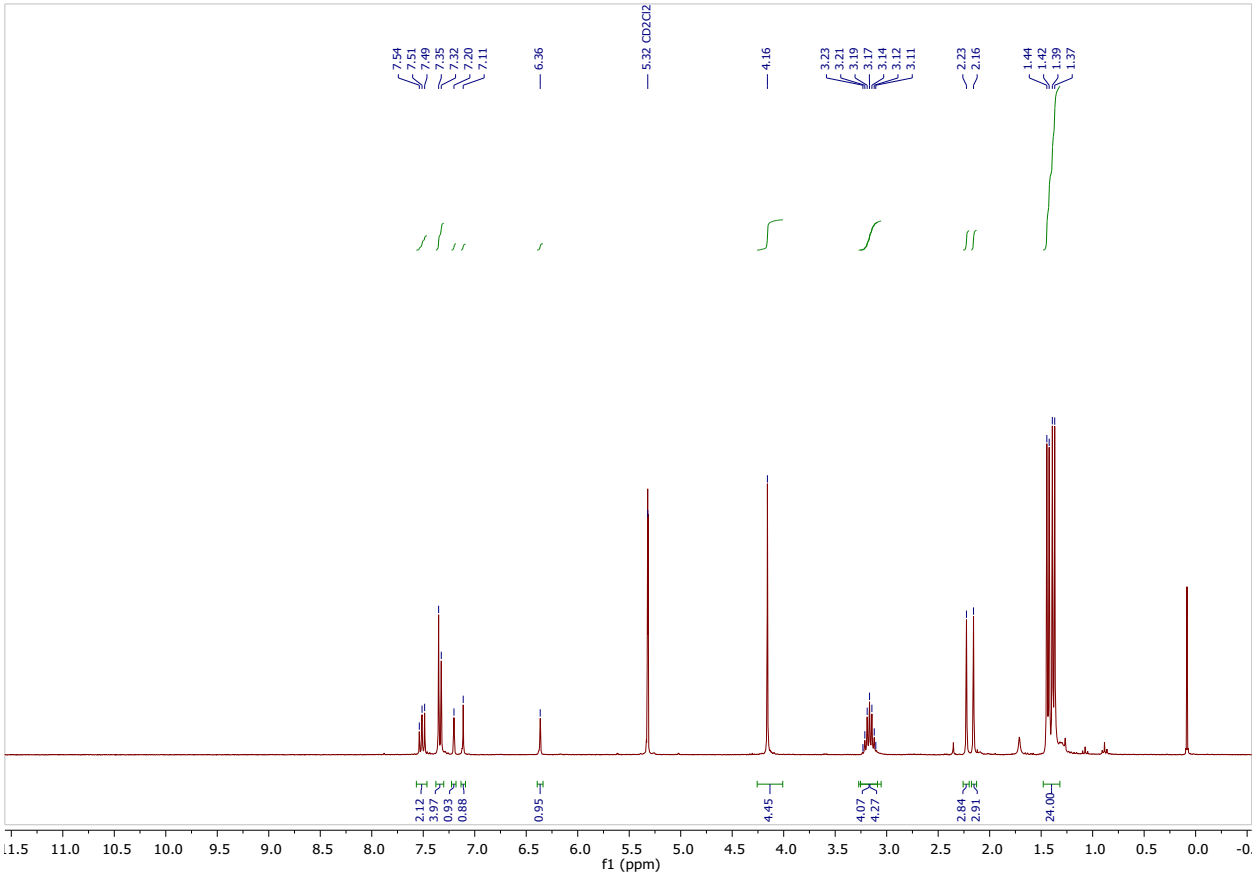
^{1}H NMR and ^{13}C {^{1}H} NMR for **[N,N'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)](5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)gold(I) 1a*:***

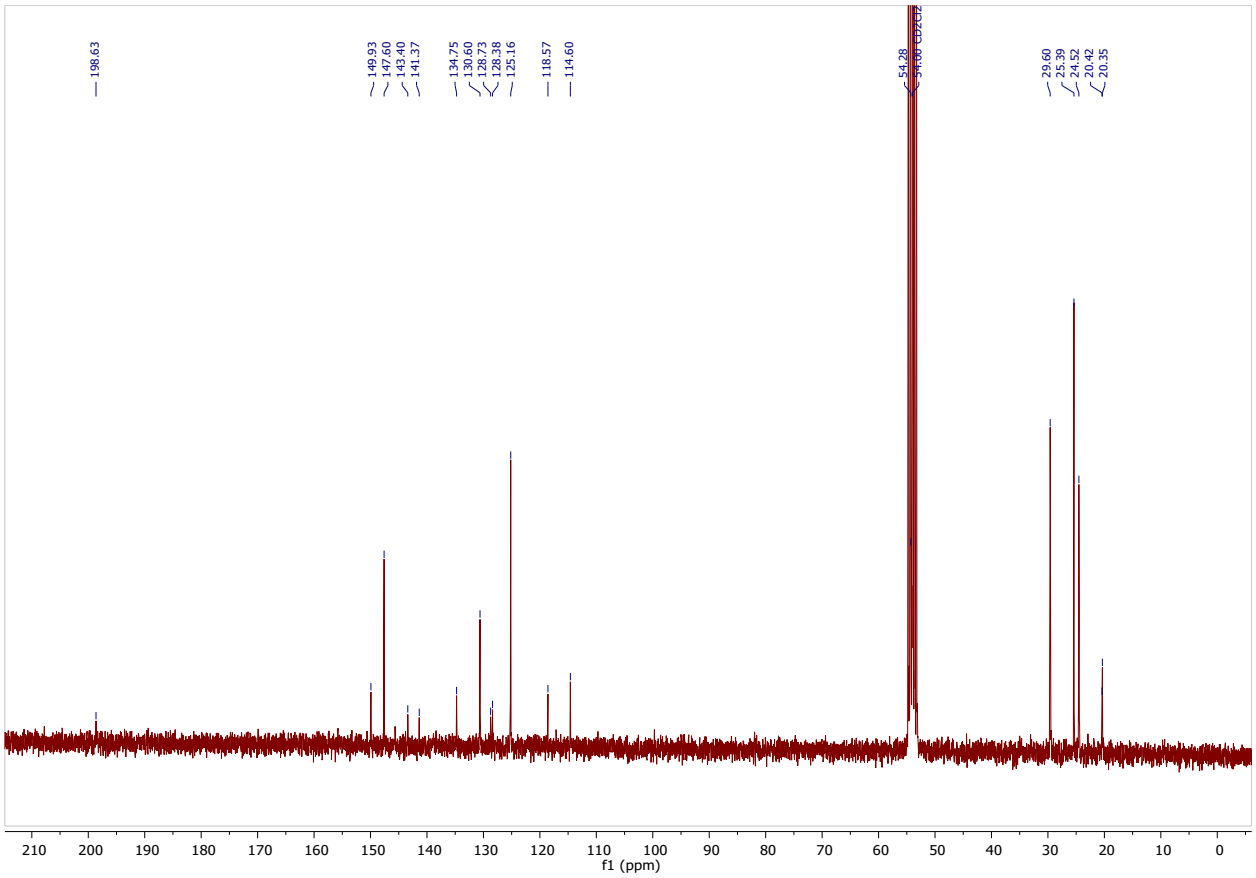




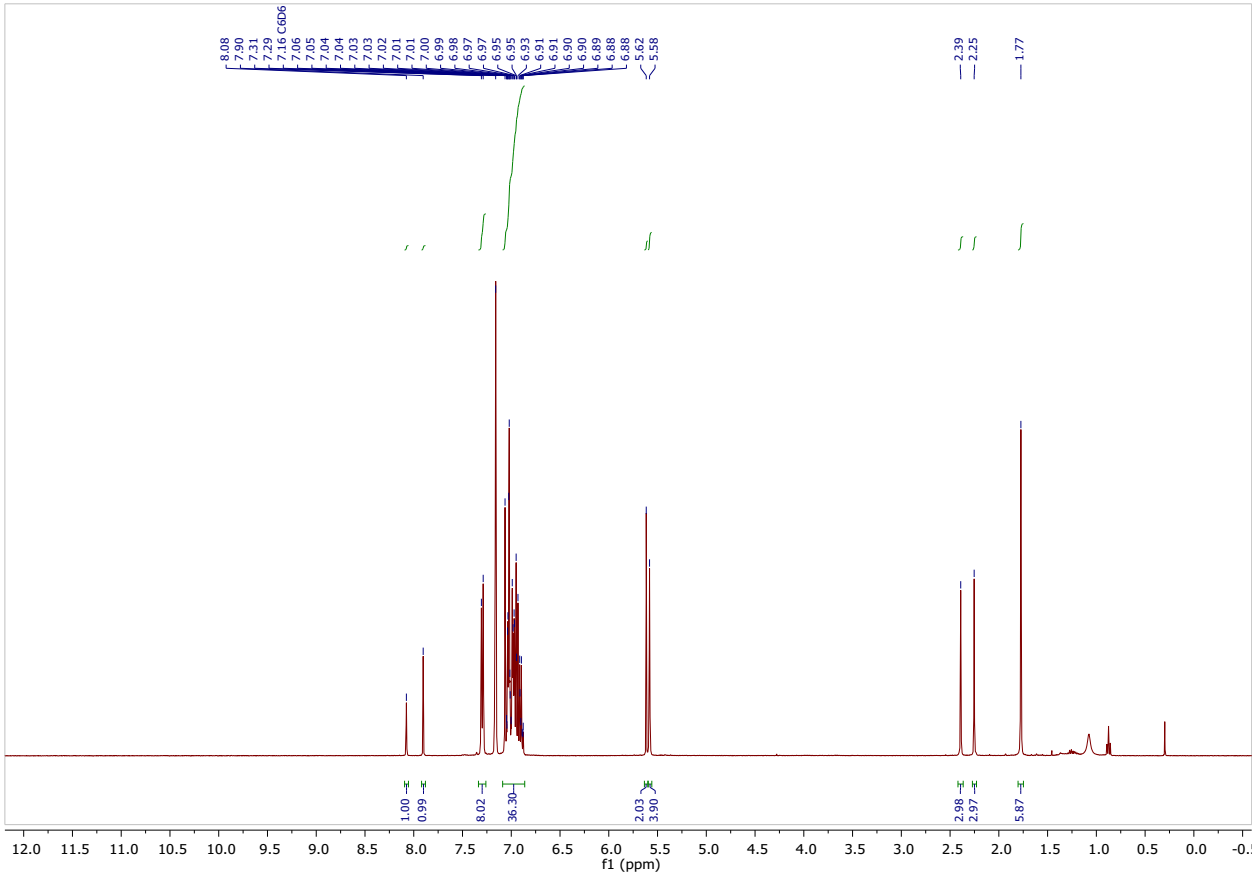


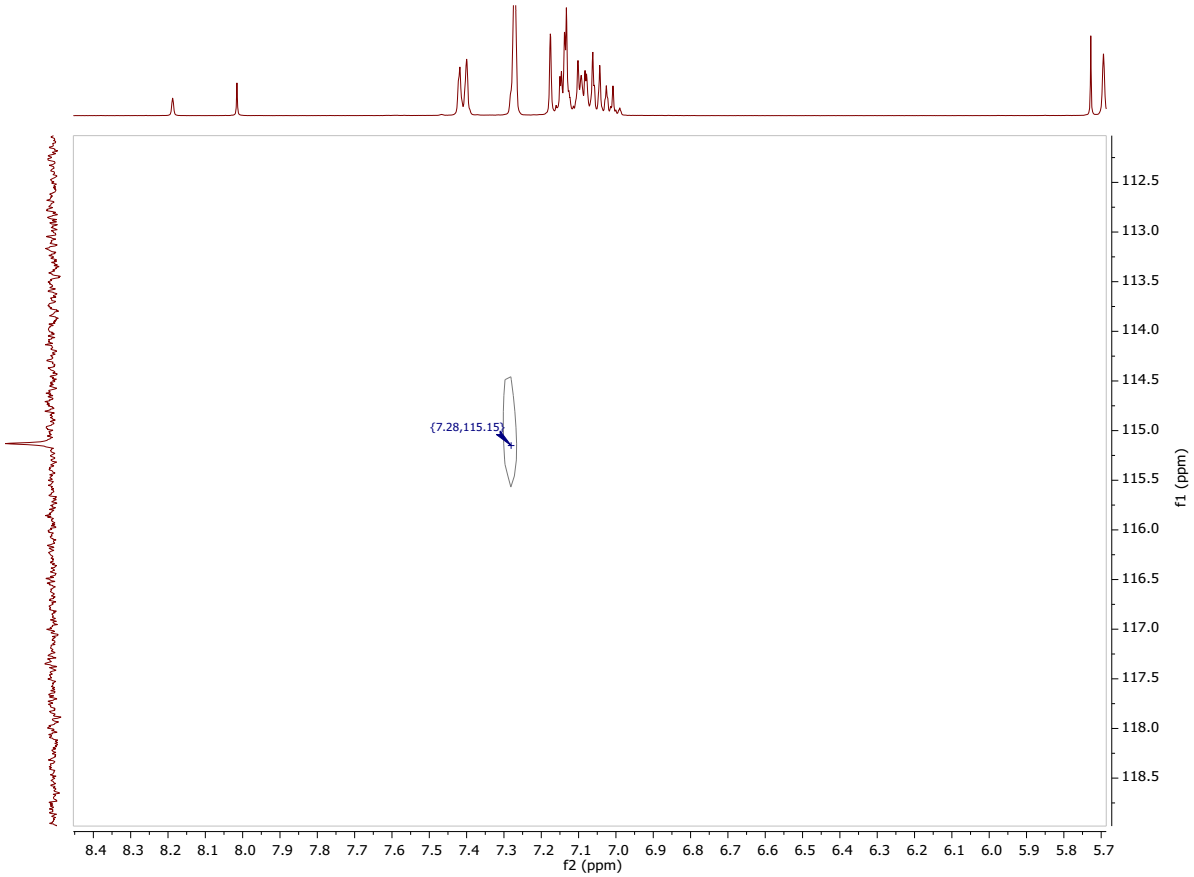
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [N,N'-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene)](5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)gold(I) 1b:**





***^{1}H NMR and ^{13}C {^{1}H} NMR for* [*N*,*N*-Bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene)](5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)gold(I) 1c*:**

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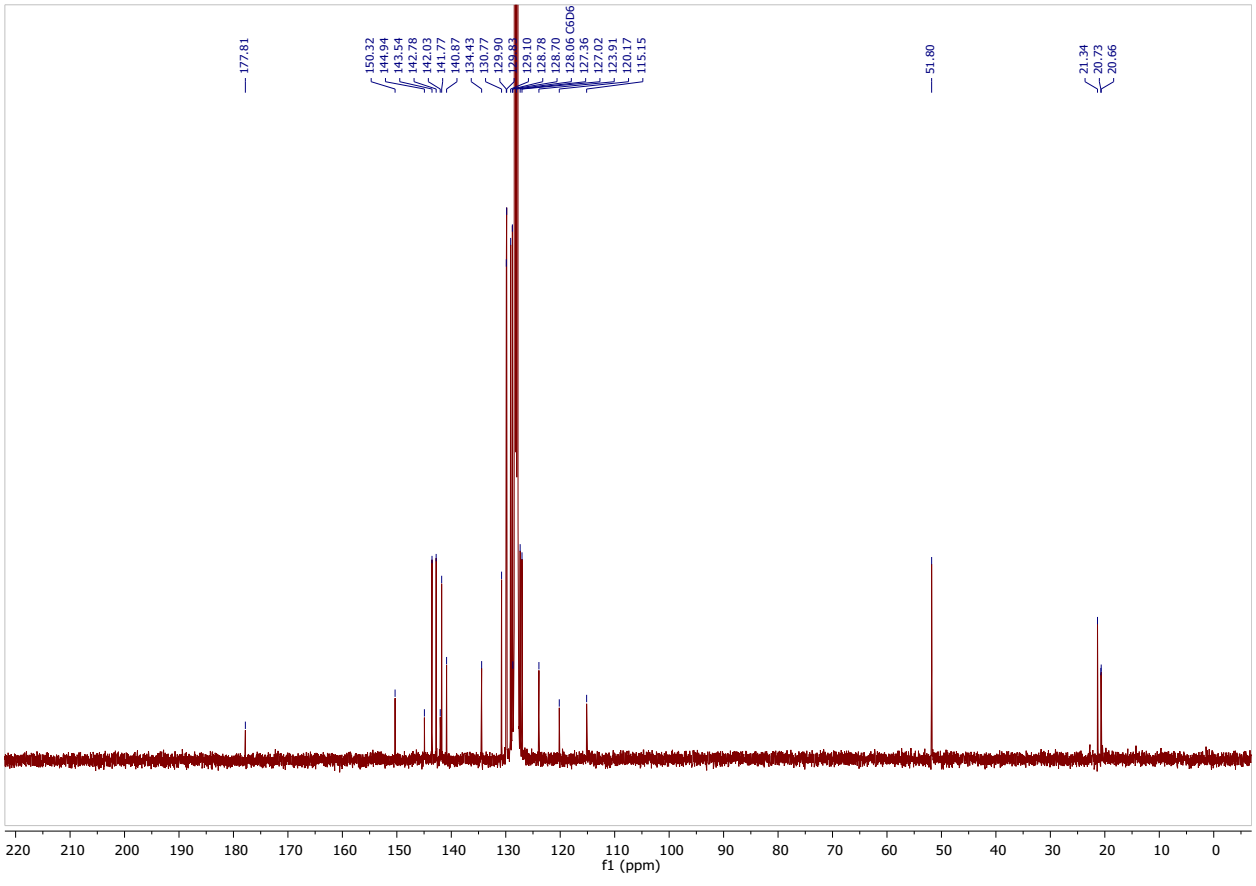
f2 (ppm)


177.81
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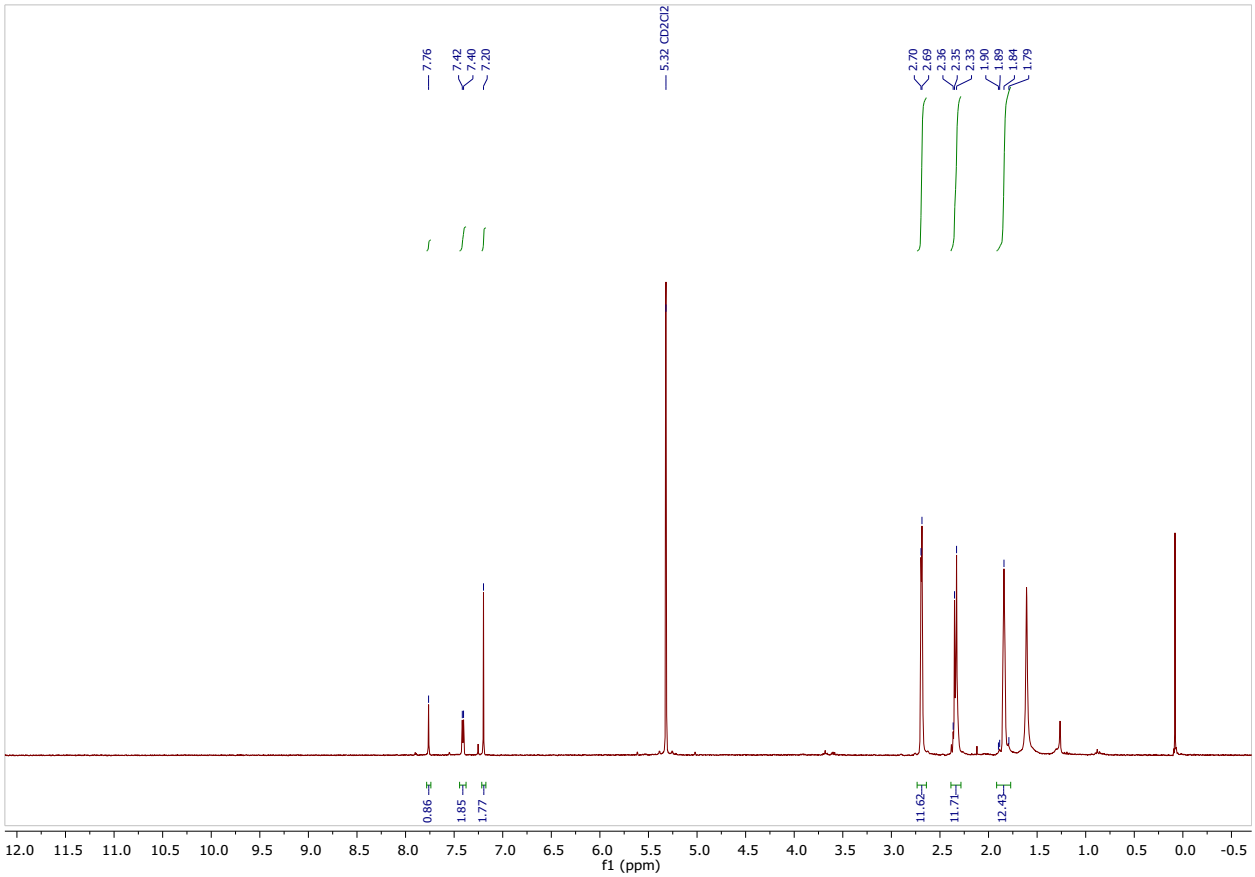
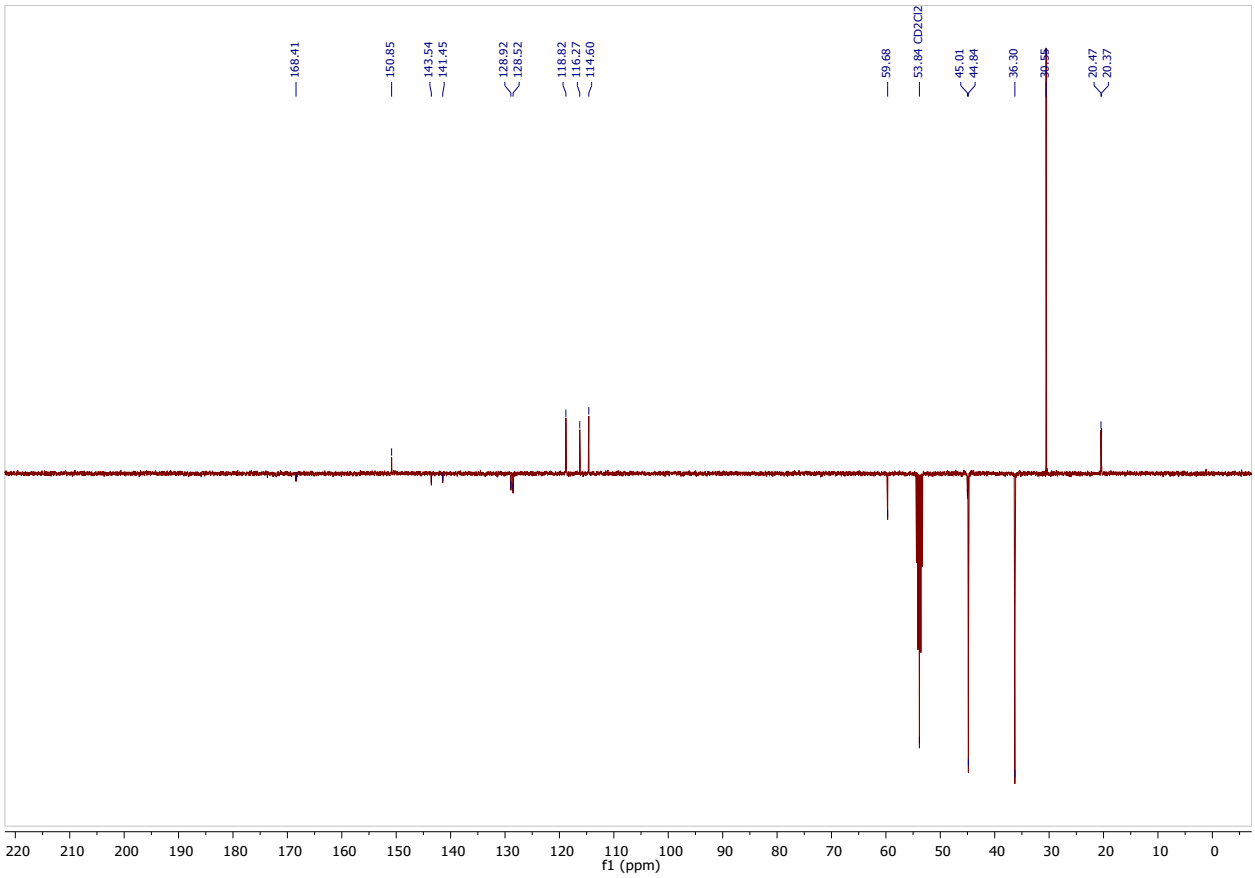
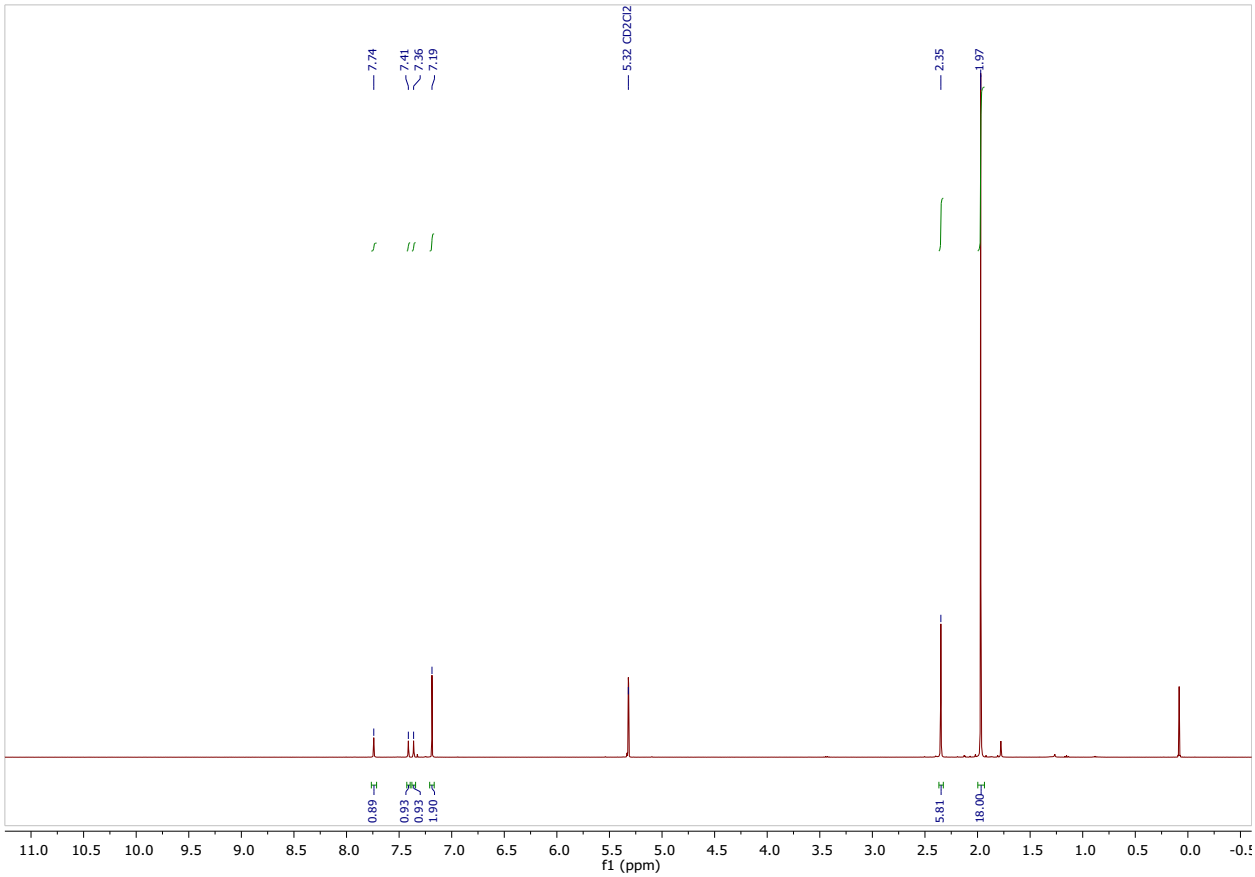
129.83
129.10
128.78
128.70
128.06 C6D6
127.36
127.02
123.91
120.17
115.15
51.80
21.34
20.73
20.66
f1 (ppm)

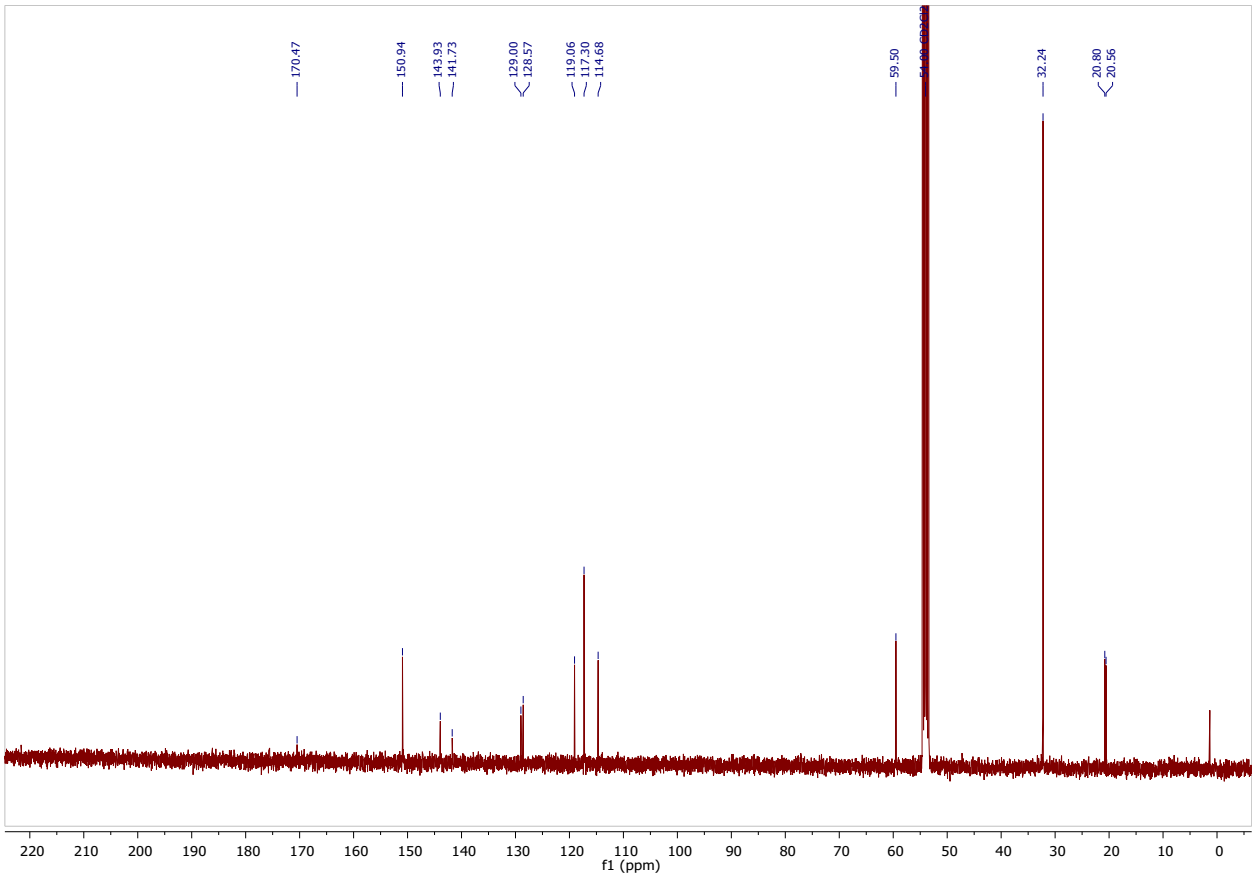
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [*N*,*N*-Bis(adamantyl)imidazol-2-ylidene](5,6-dimethyl-1*H*-benzo[d]imidazol-1-yl)gold(I) 1d:**



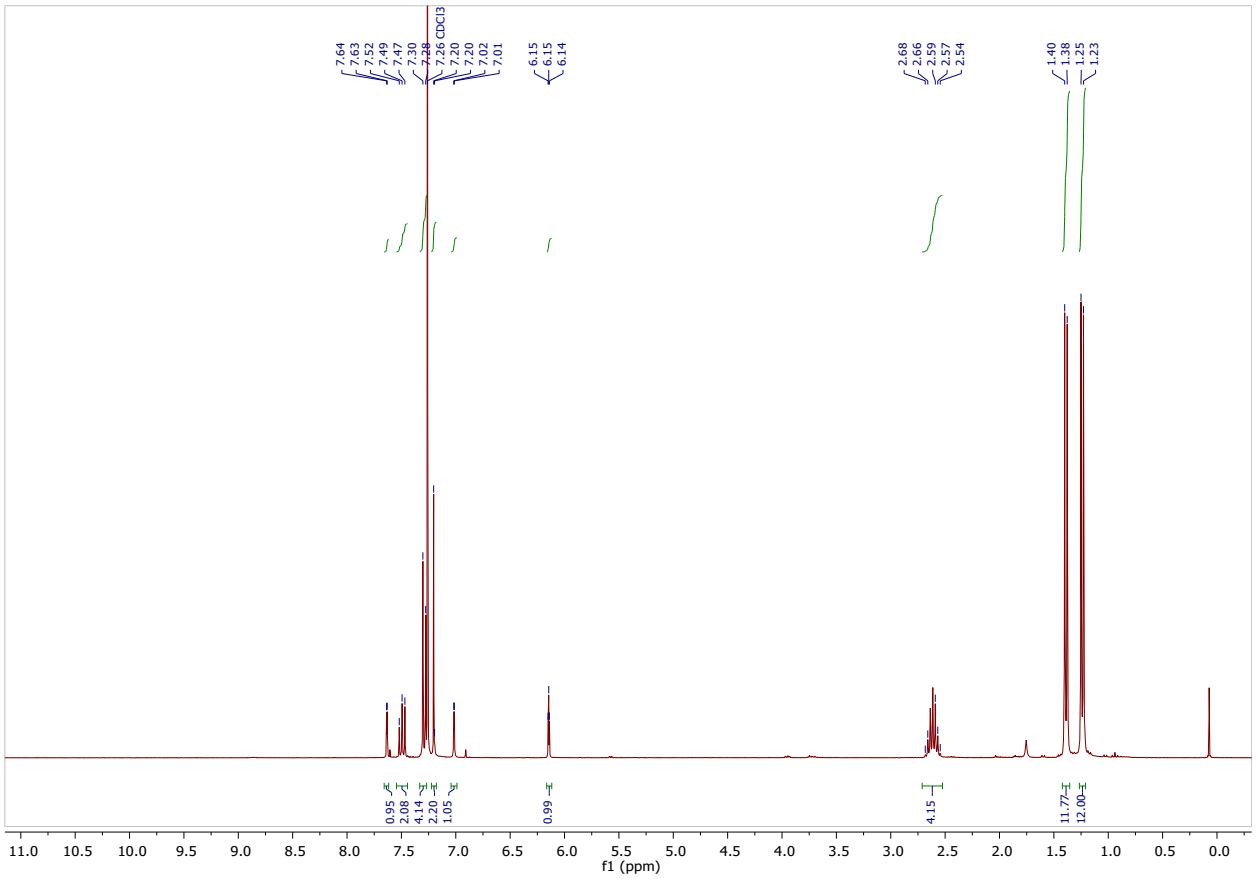


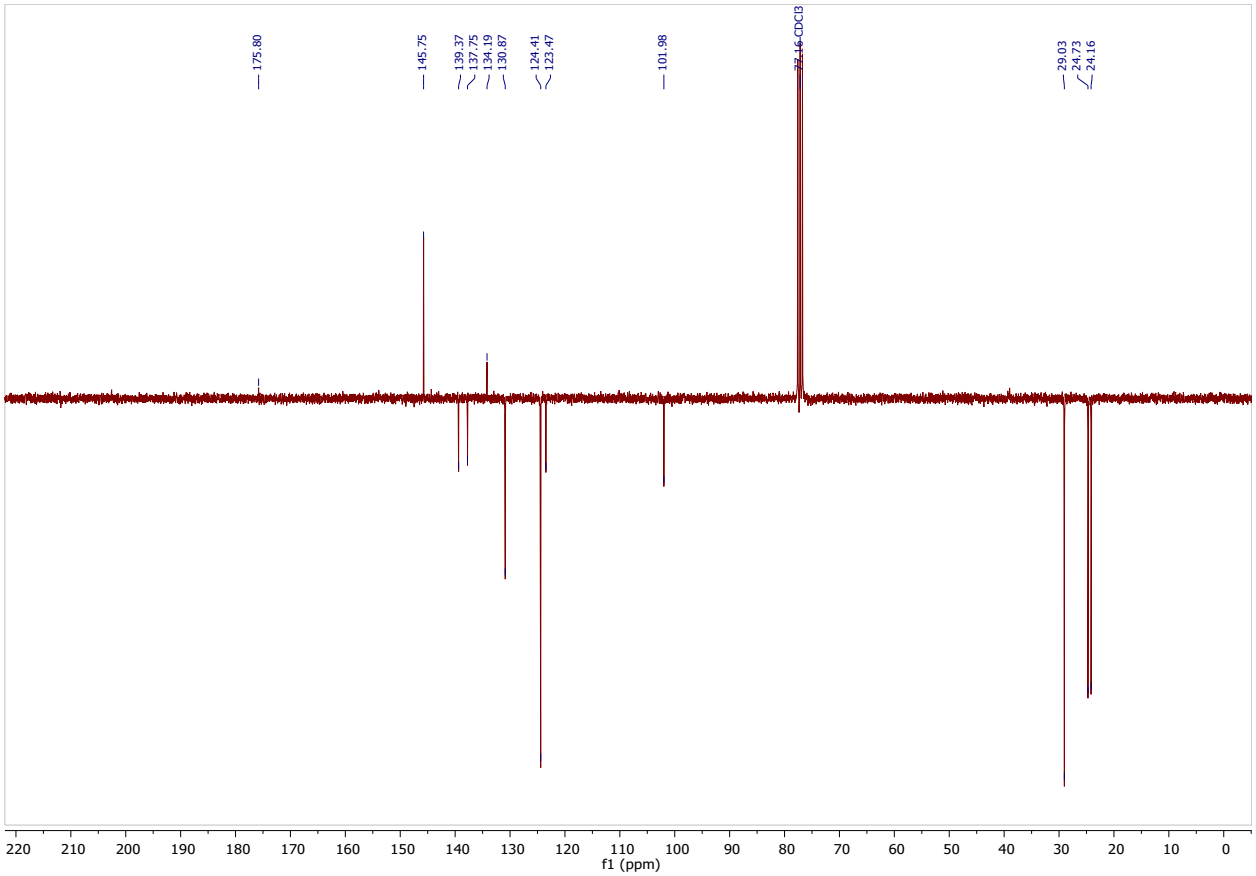
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [*N*,*N*-Bis(*tert*-butyl)imidazol-2-ylidene] (5,6-dimethyl-1*H*-benzo[d]imidazol-1-y)gold(I) 1e:**



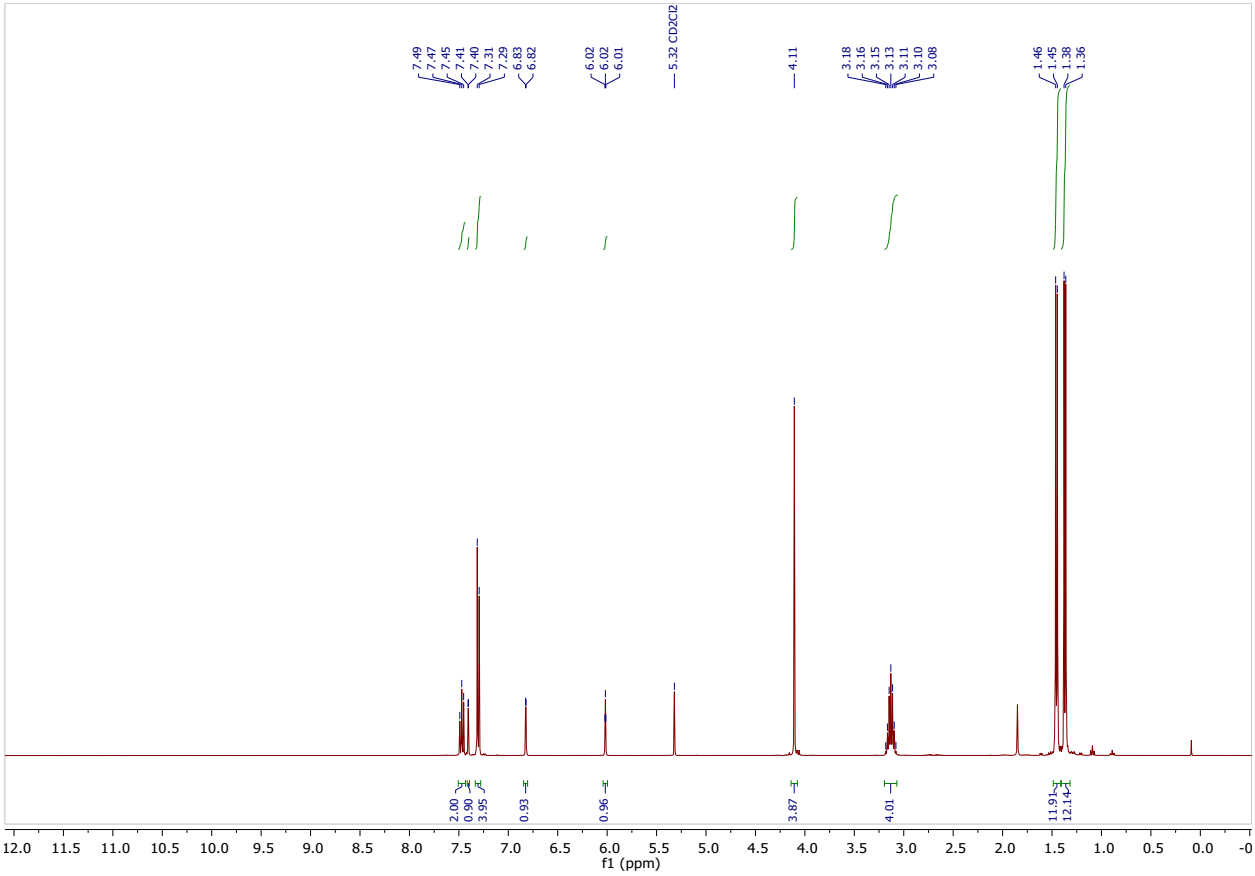


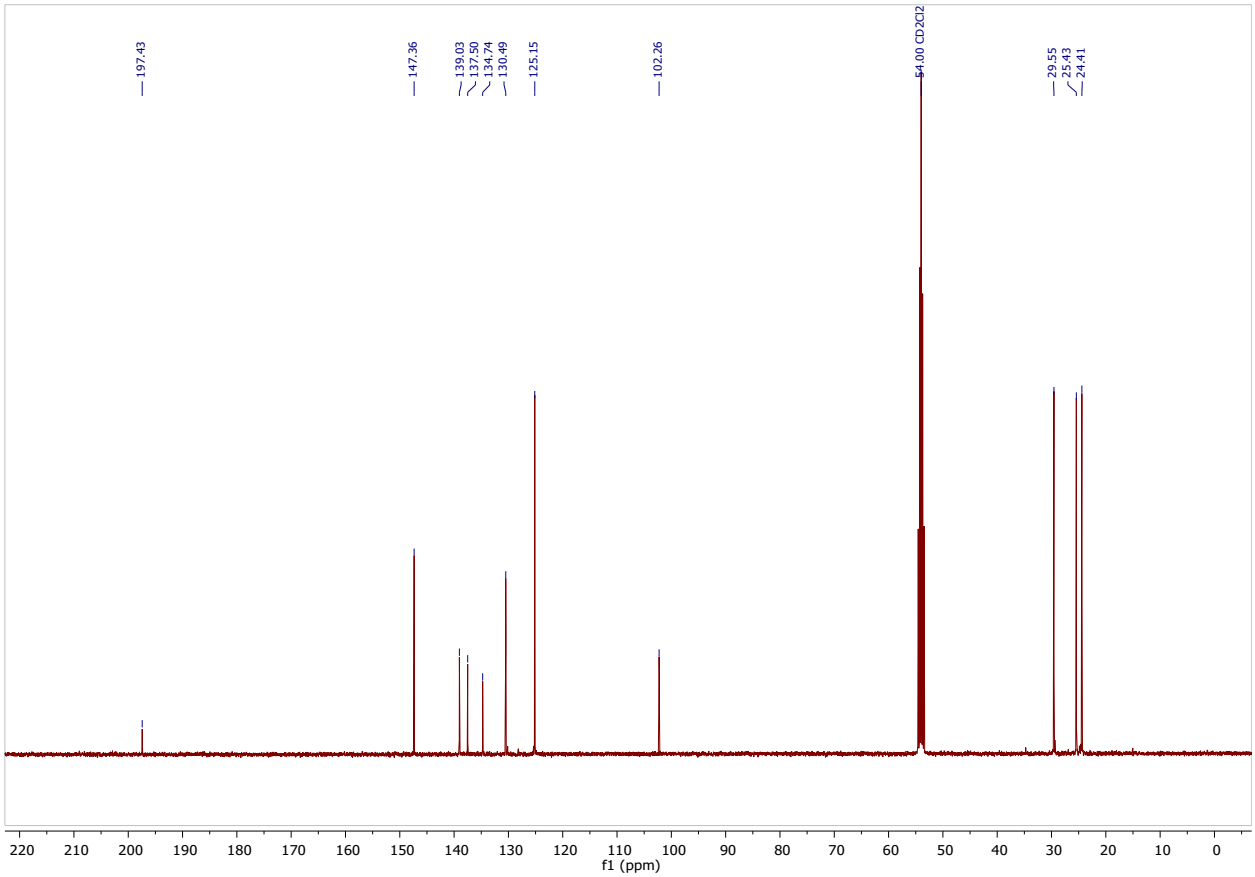
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [N,N'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)](1*H*-pyrazol-1-yl)gold(I) 2a:**

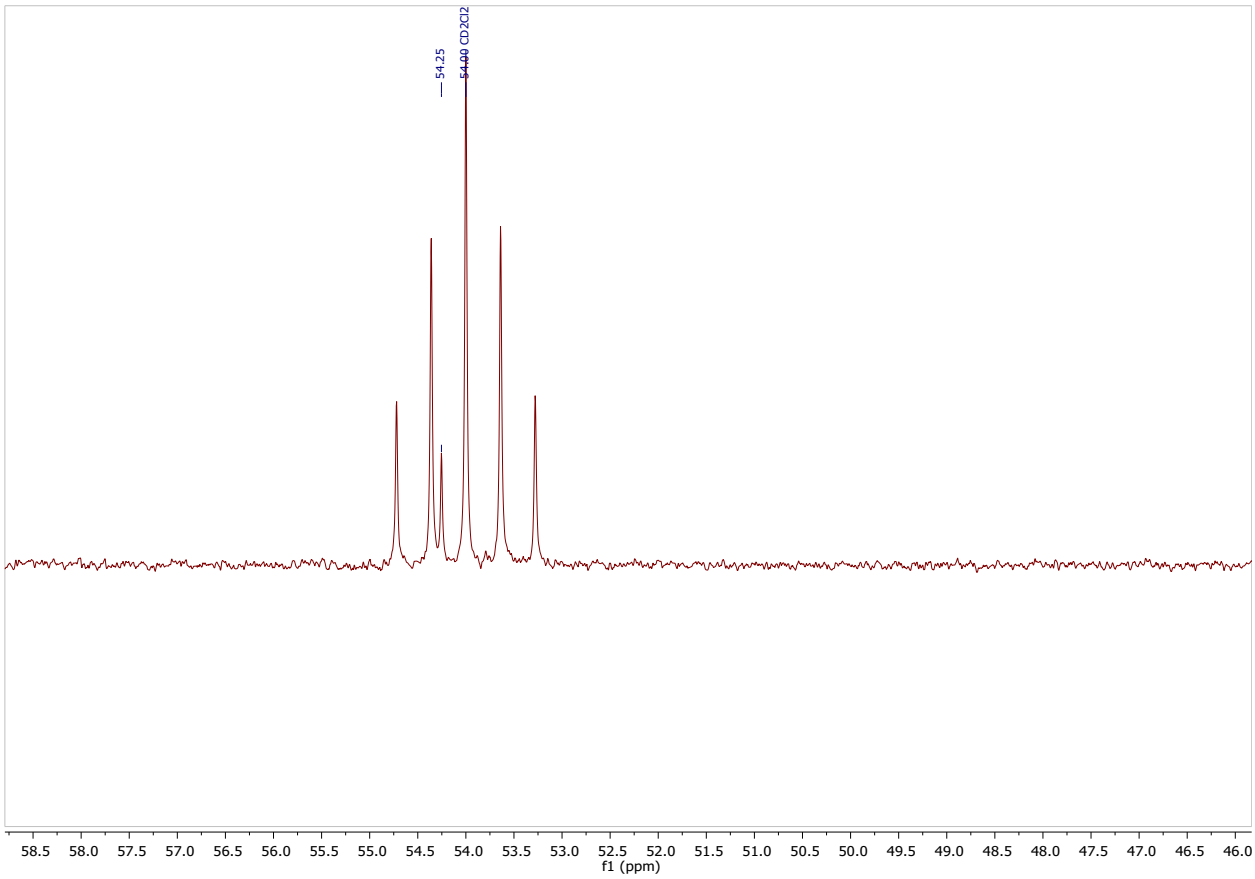




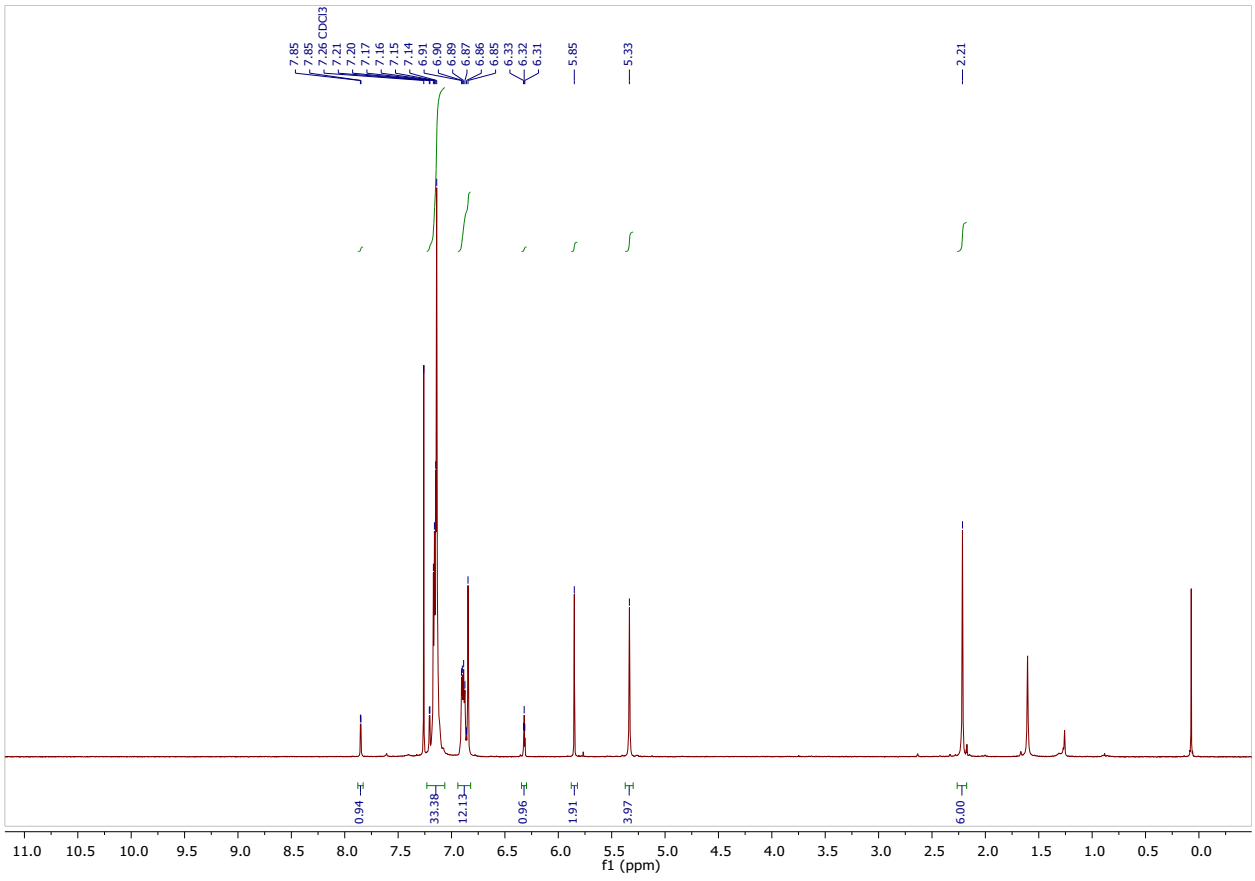
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [N,N'-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene)](1*H*-pyrazol-1-yl)gold(I) 2b:**

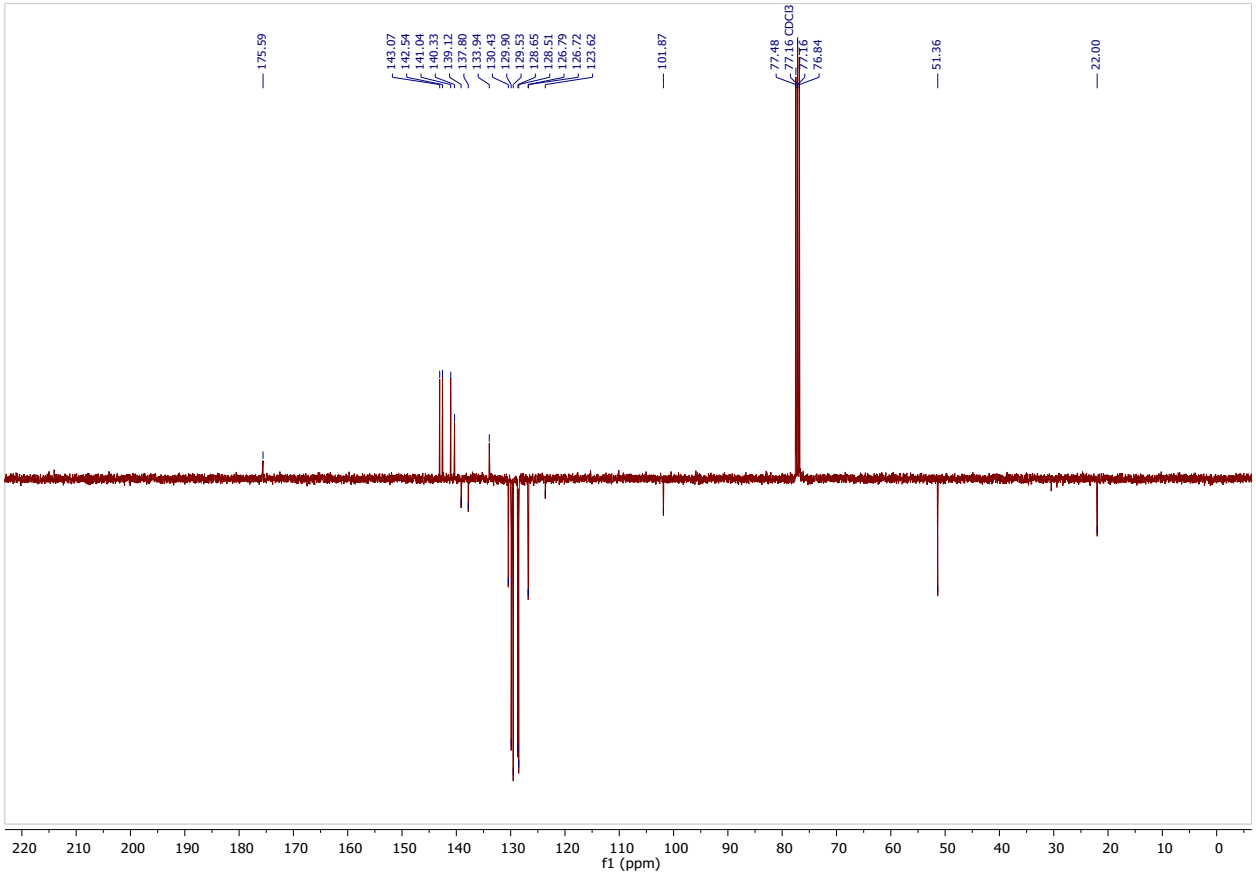




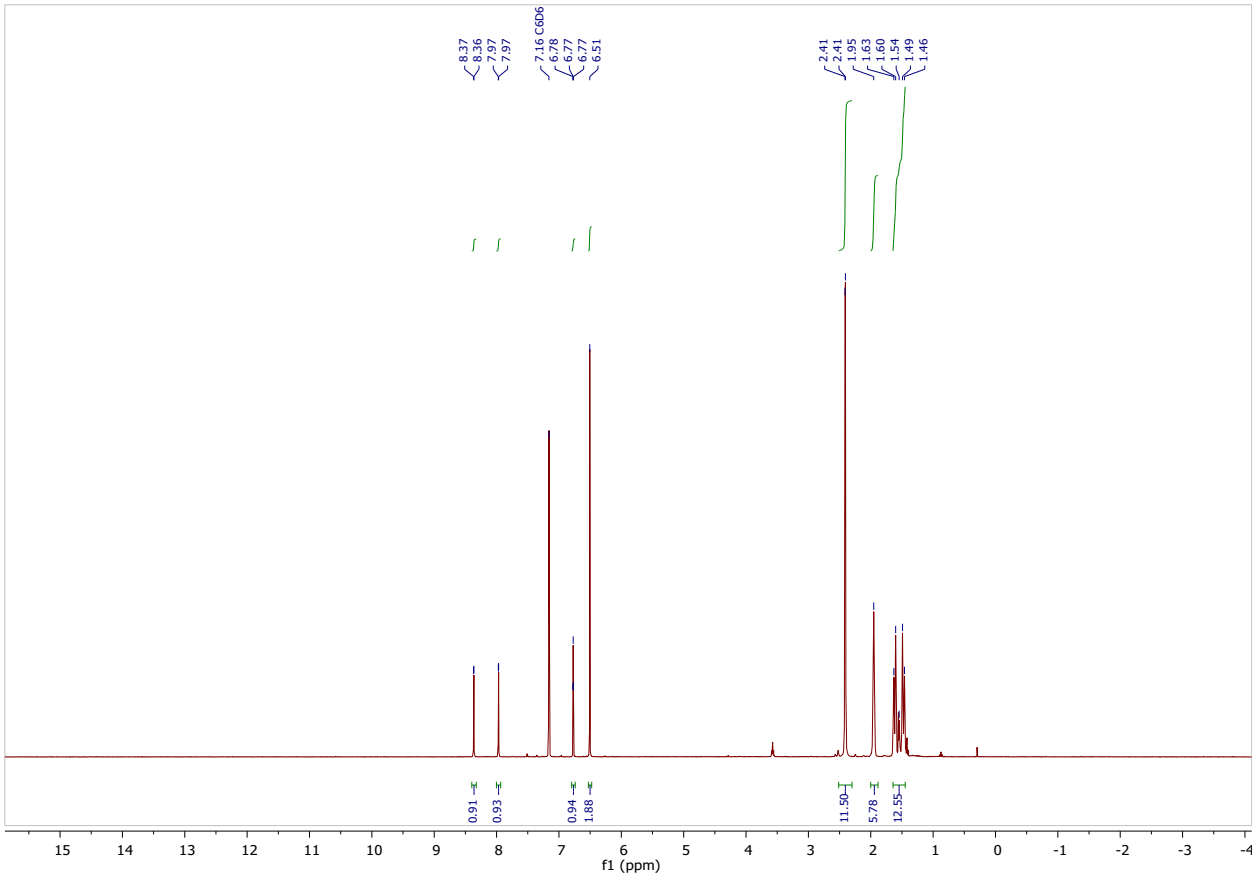


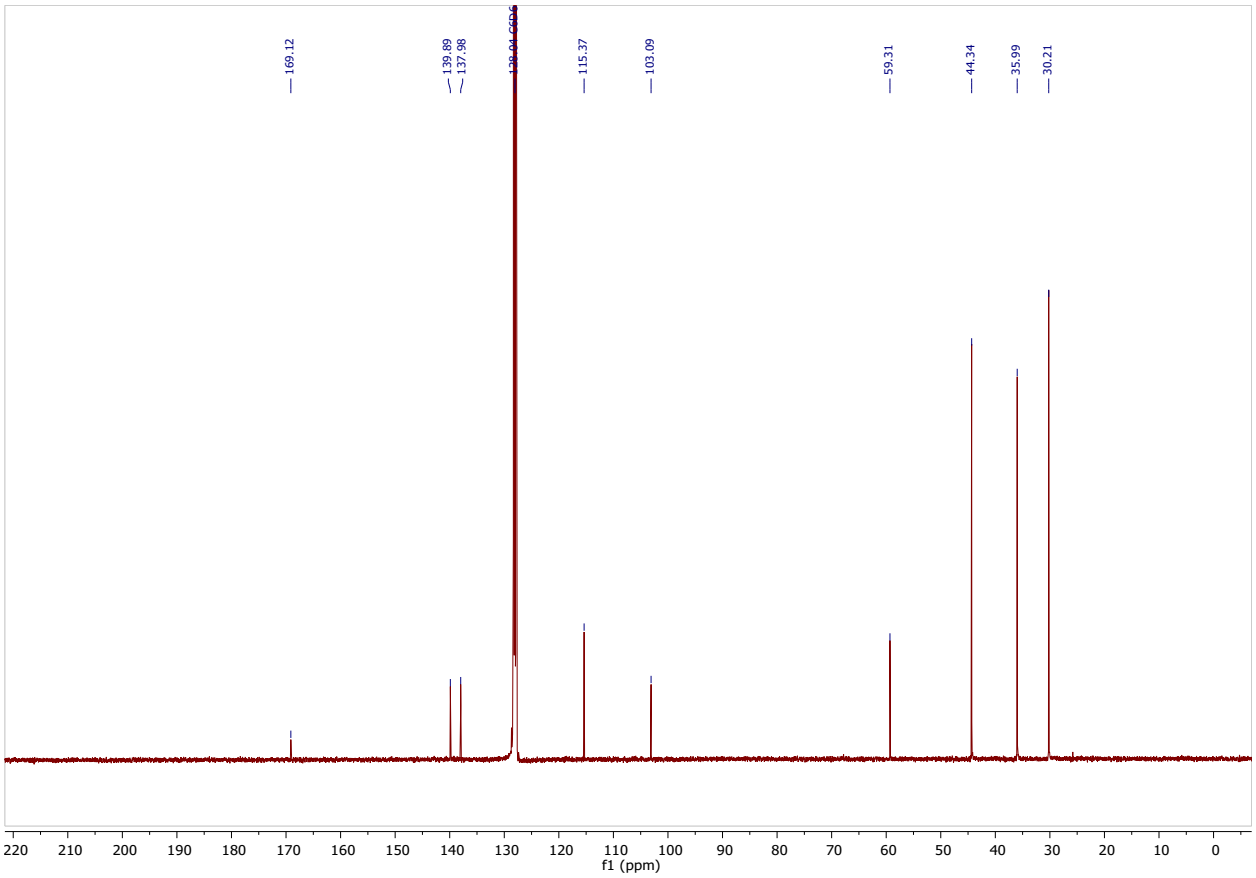
***[1]H NMR and [13]C {[1]H} NMR for* [*N*,*N*-Bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene](1*H*-pyrazol-1-yl)gold(I) 2c:**



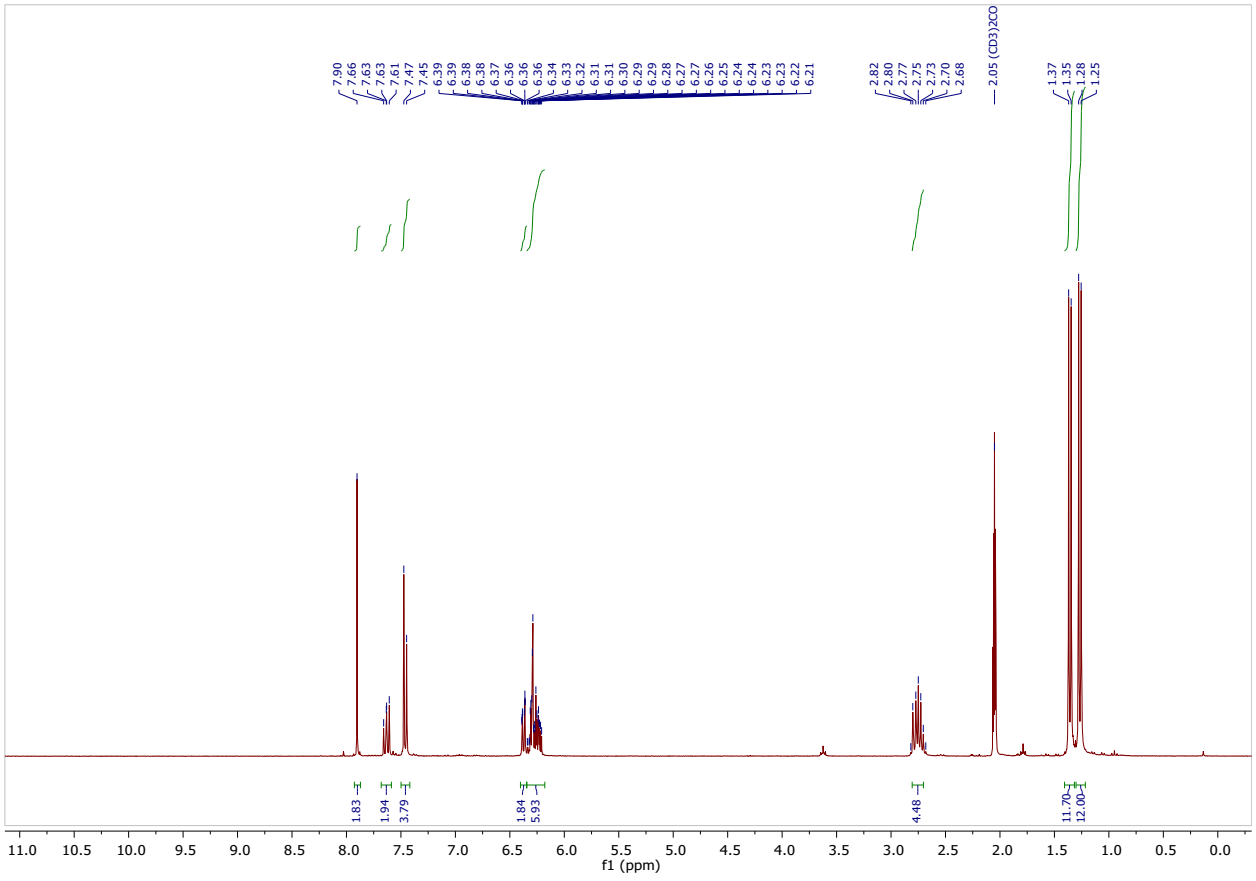


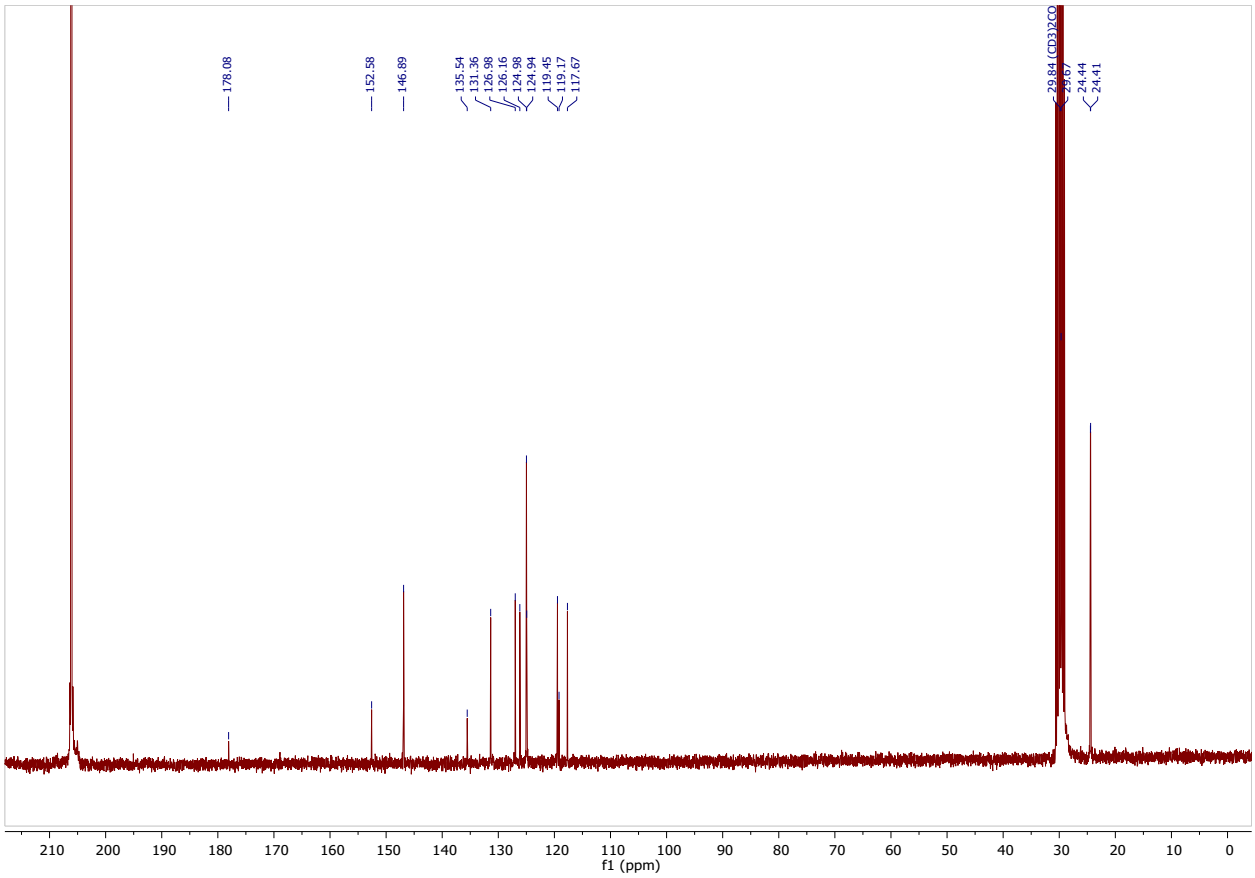
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [*N*,*N*-Bis(adamantyl)imidazol-2-ylidene][(1*H*-pyrazol-1-yl)gold(I) 2d:**

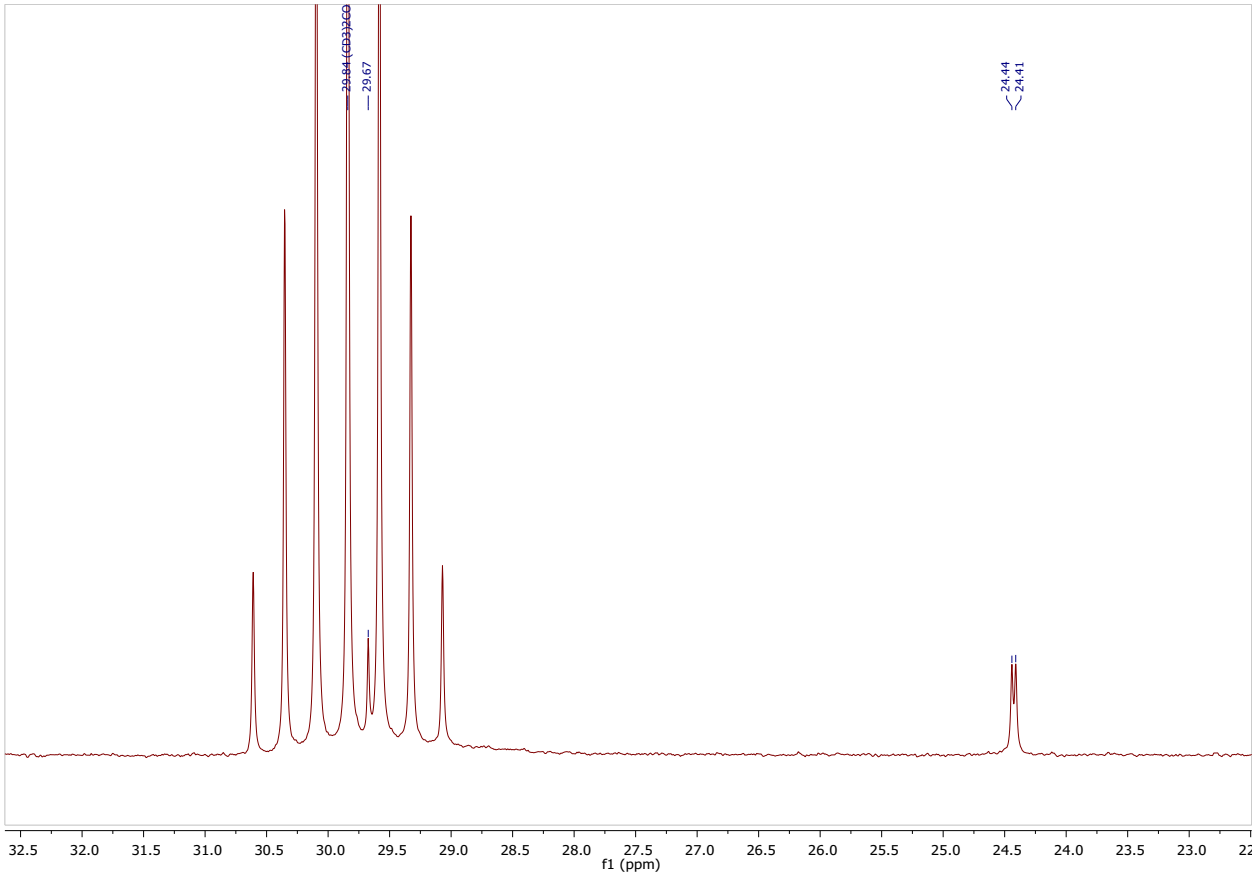




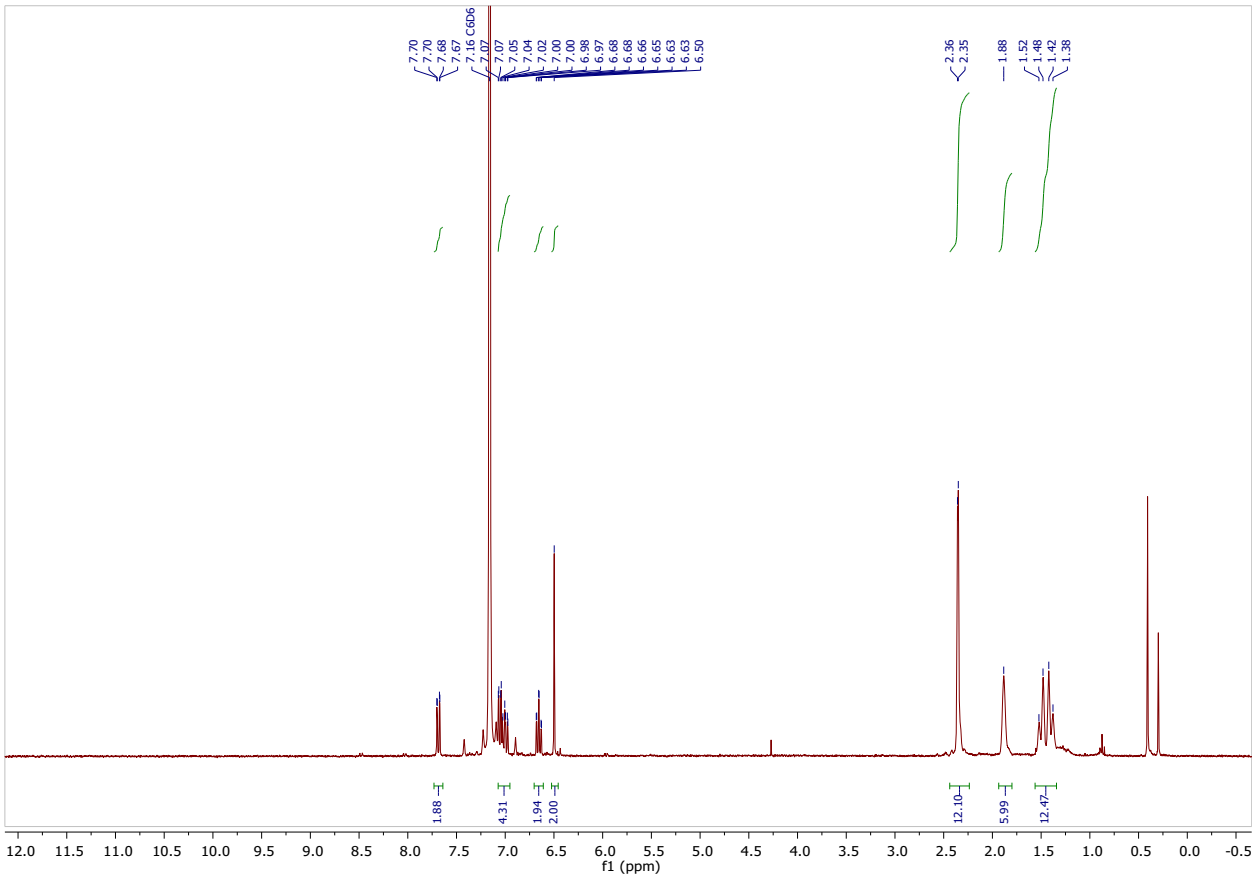
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [N,N'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)](10*H*-phenothiazin-10-yl)gold(I) 3a:**

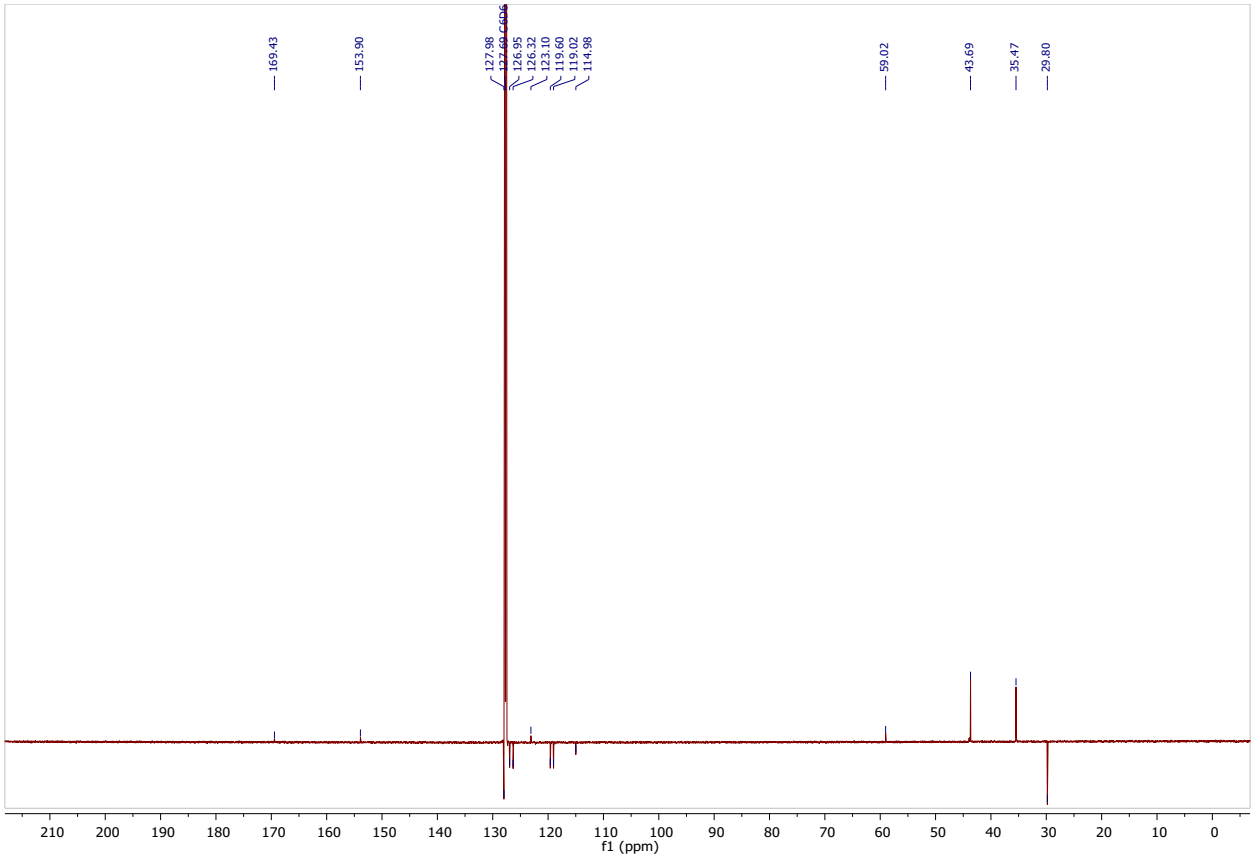


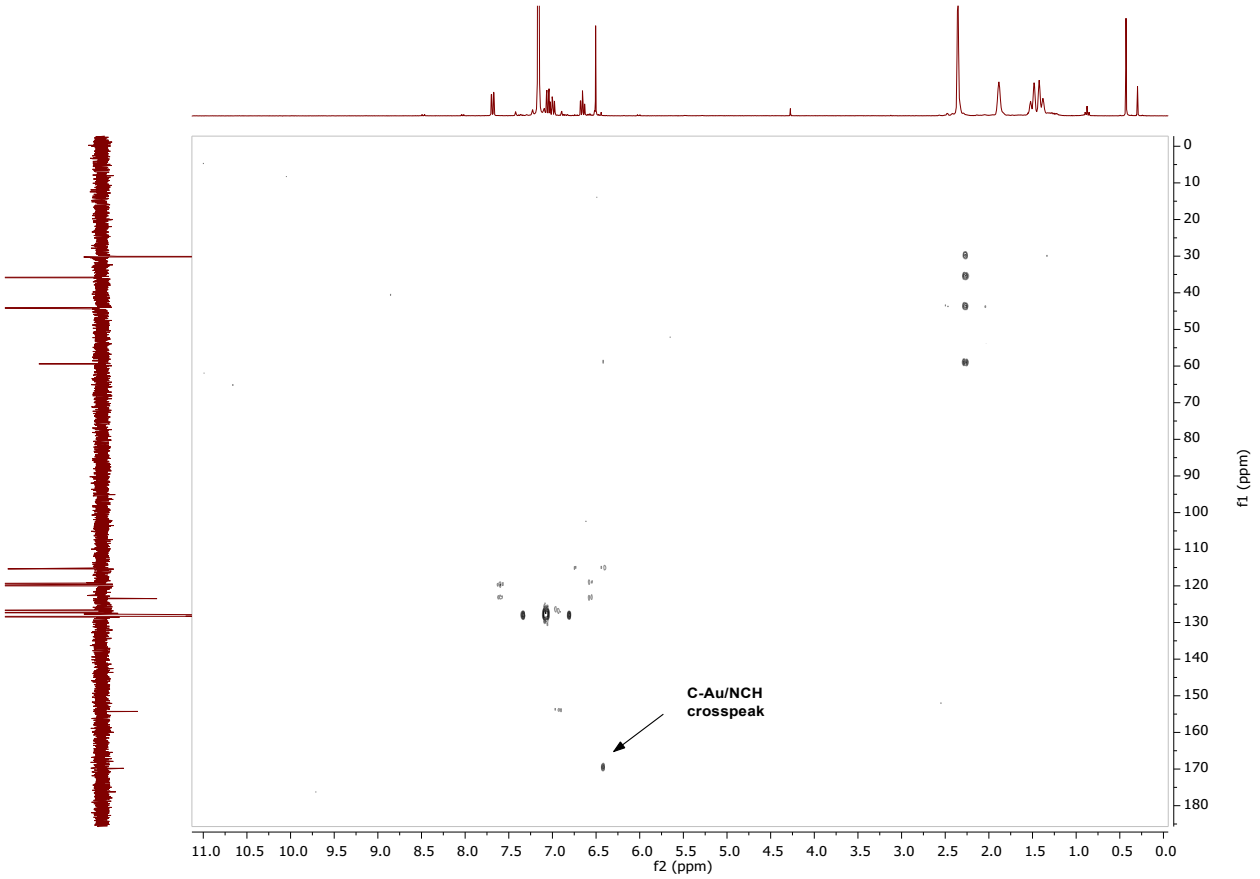

178.08
152.58
146.89
135.54
131.36
126.98
126.16
124.98
124.94
119.45
119.17
117.67
29.84 (CD3)2CO
29.67
24.44
24.41
f1 (ppm)


29.84 (CD3)2CO
29.67
24.44
24.41
f1 (ppm)

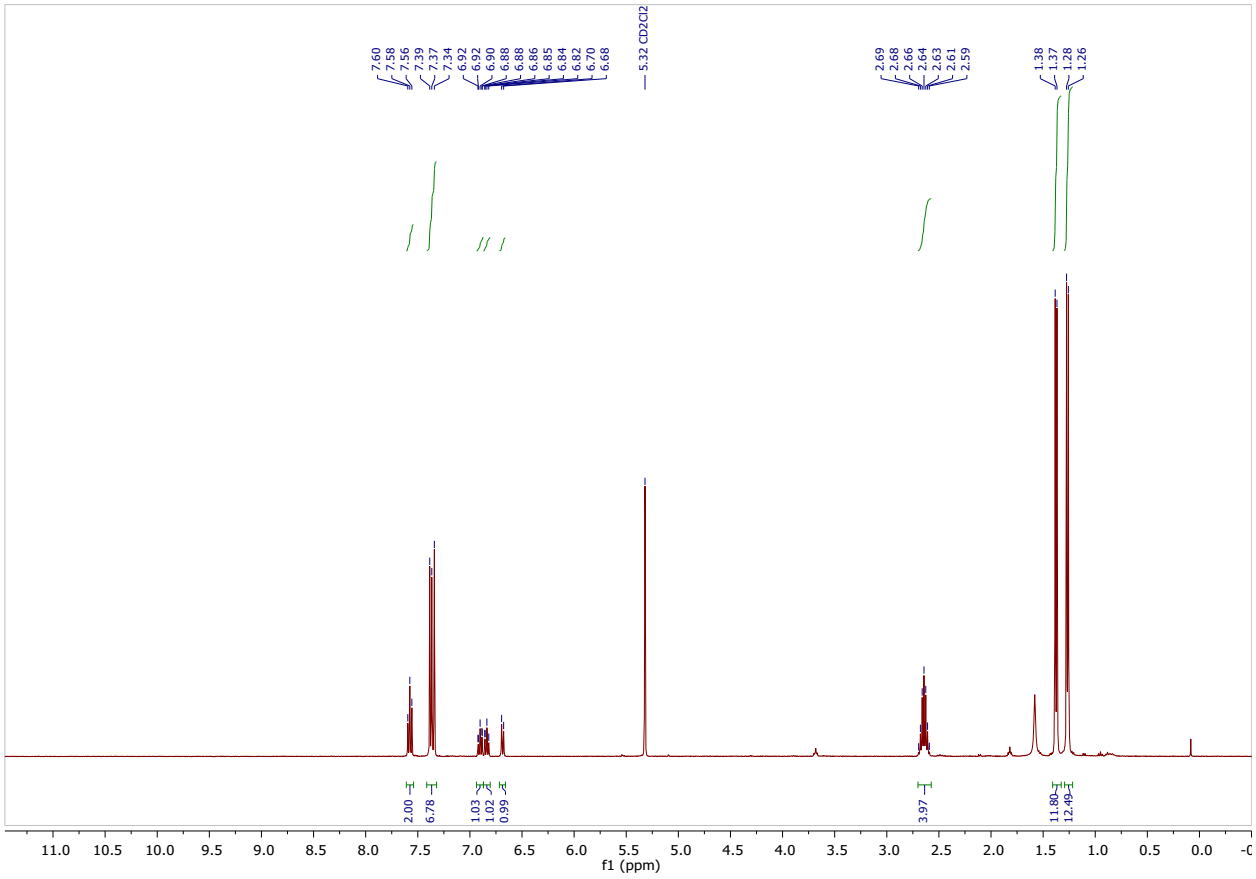
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [*N*,*N*-Bis(adamantyl)imidazol-2-ylidene](10*H*-phenothiazin-10-yl)gold(I) 3b:**

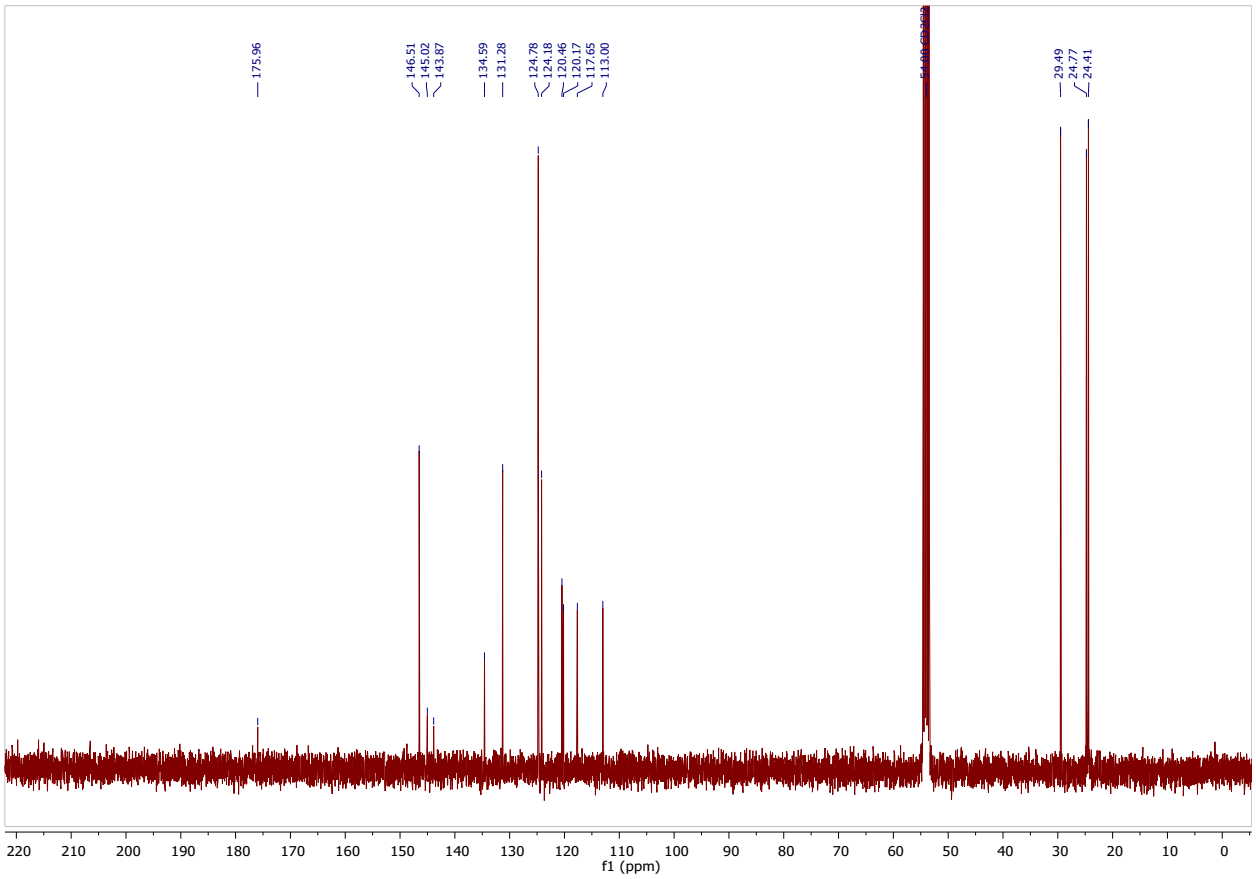




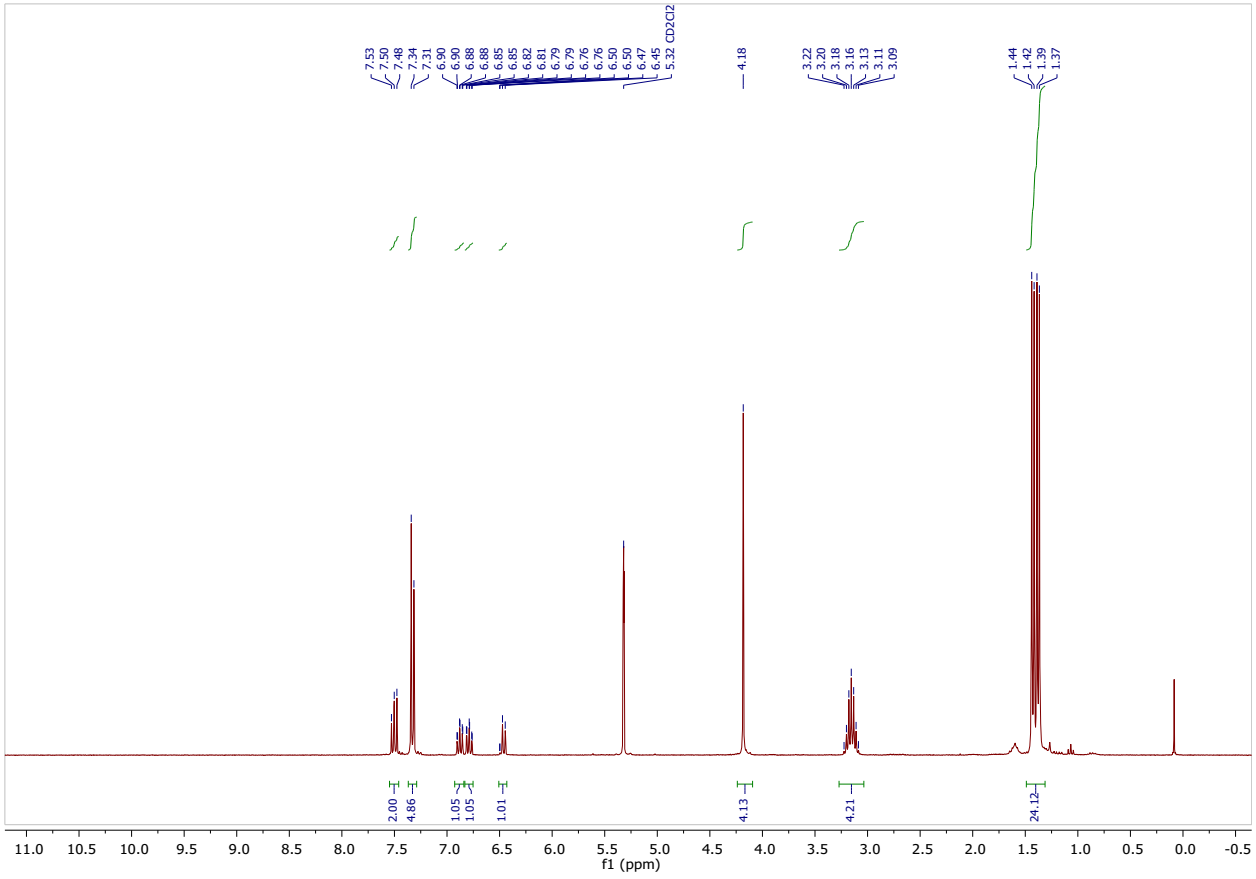


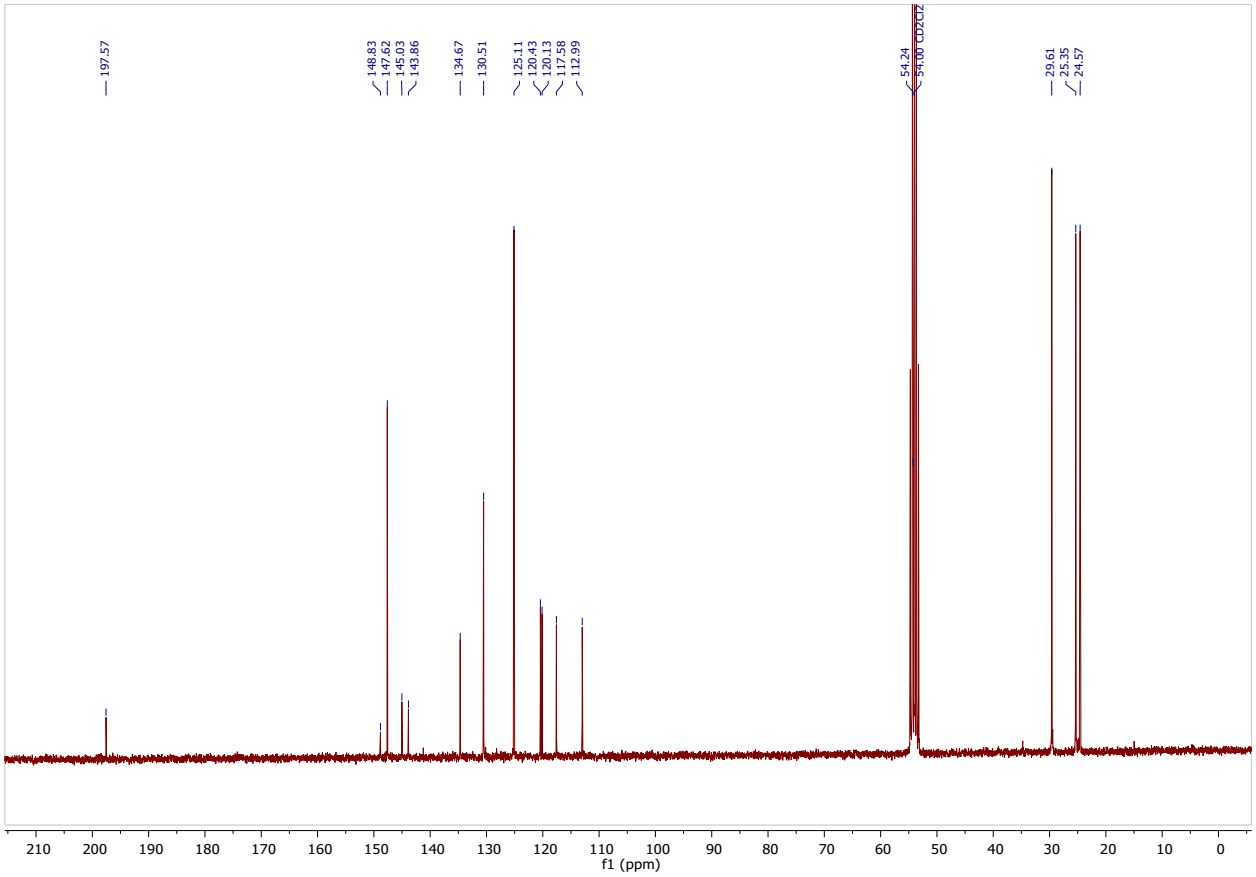
^{1}H NMR and ^{13}C {^{1}H} NMR for **[N,N'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)](2-chloro-1H-benzo[d]imidazol-1-yl)gold(I) 4a:**



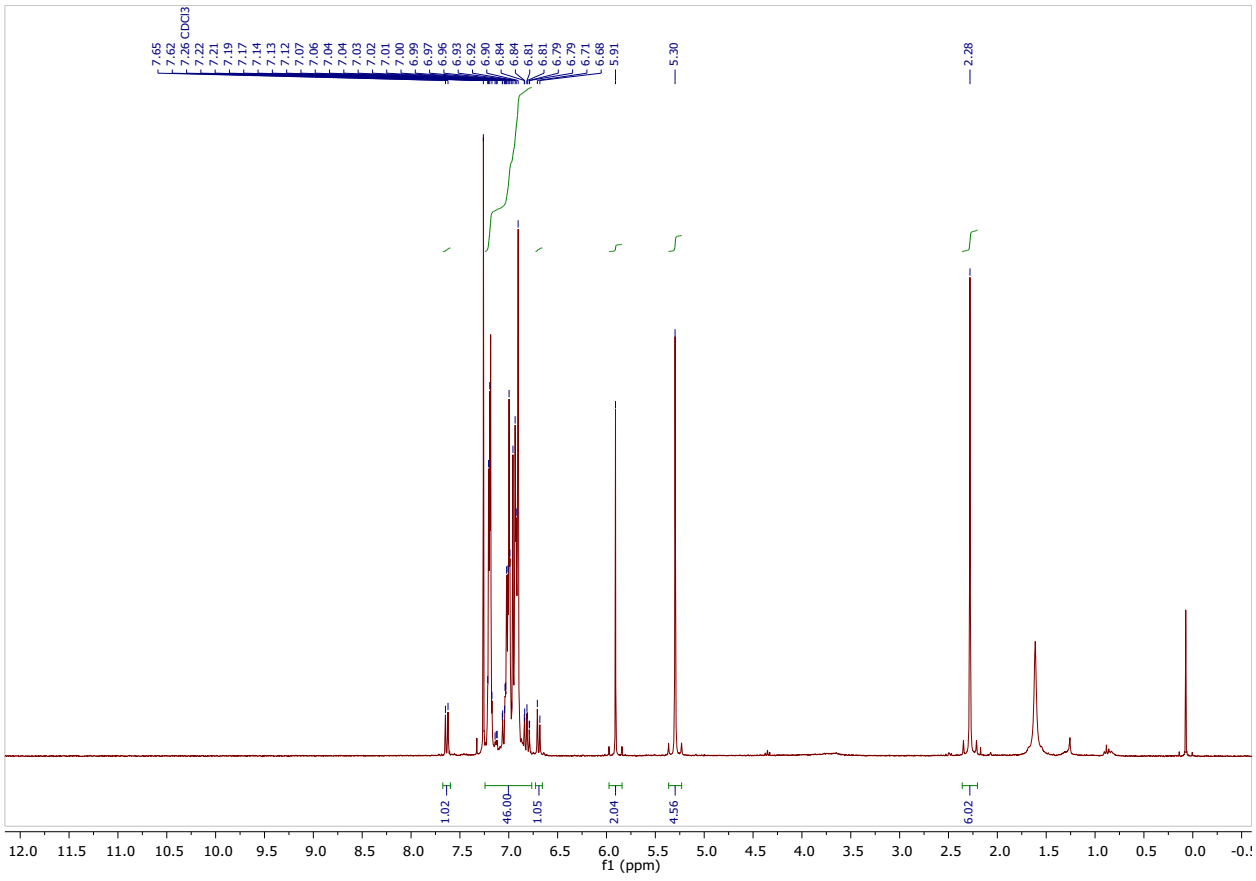


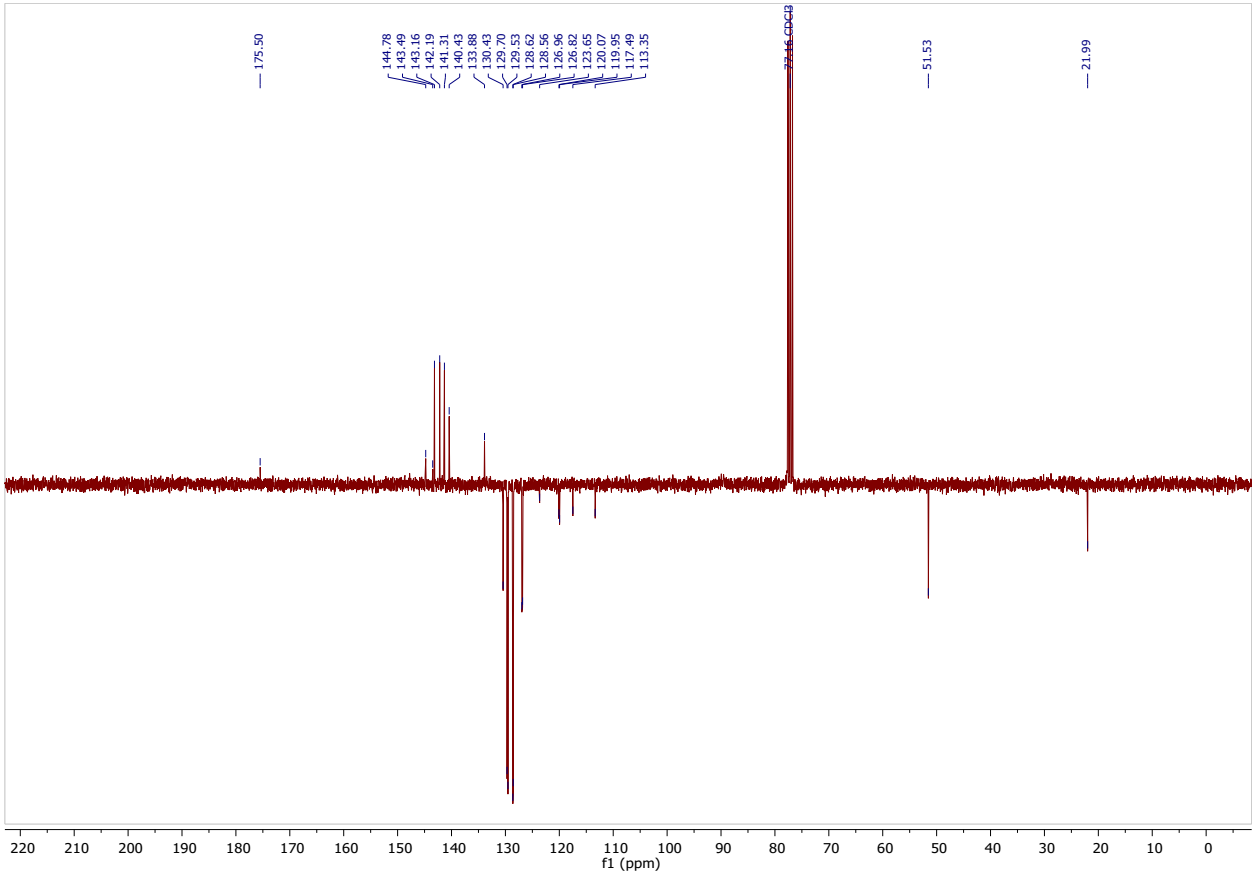
^{1}H NMR and ^{13}C {^{1}H} NMR for **[N,N'-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene)](2-chloro-1H-benzo[d]imidazol-1-yl)gold(I) 4b:**



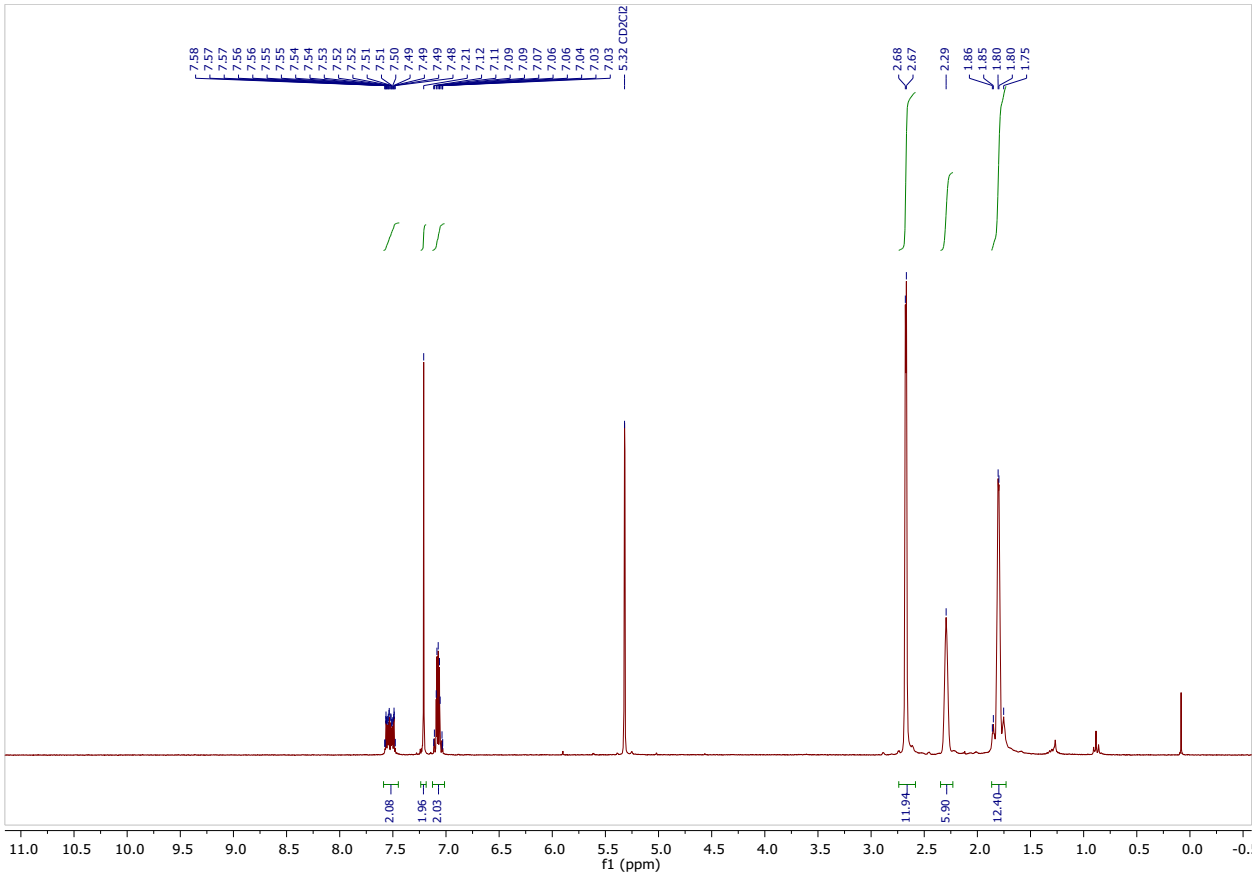


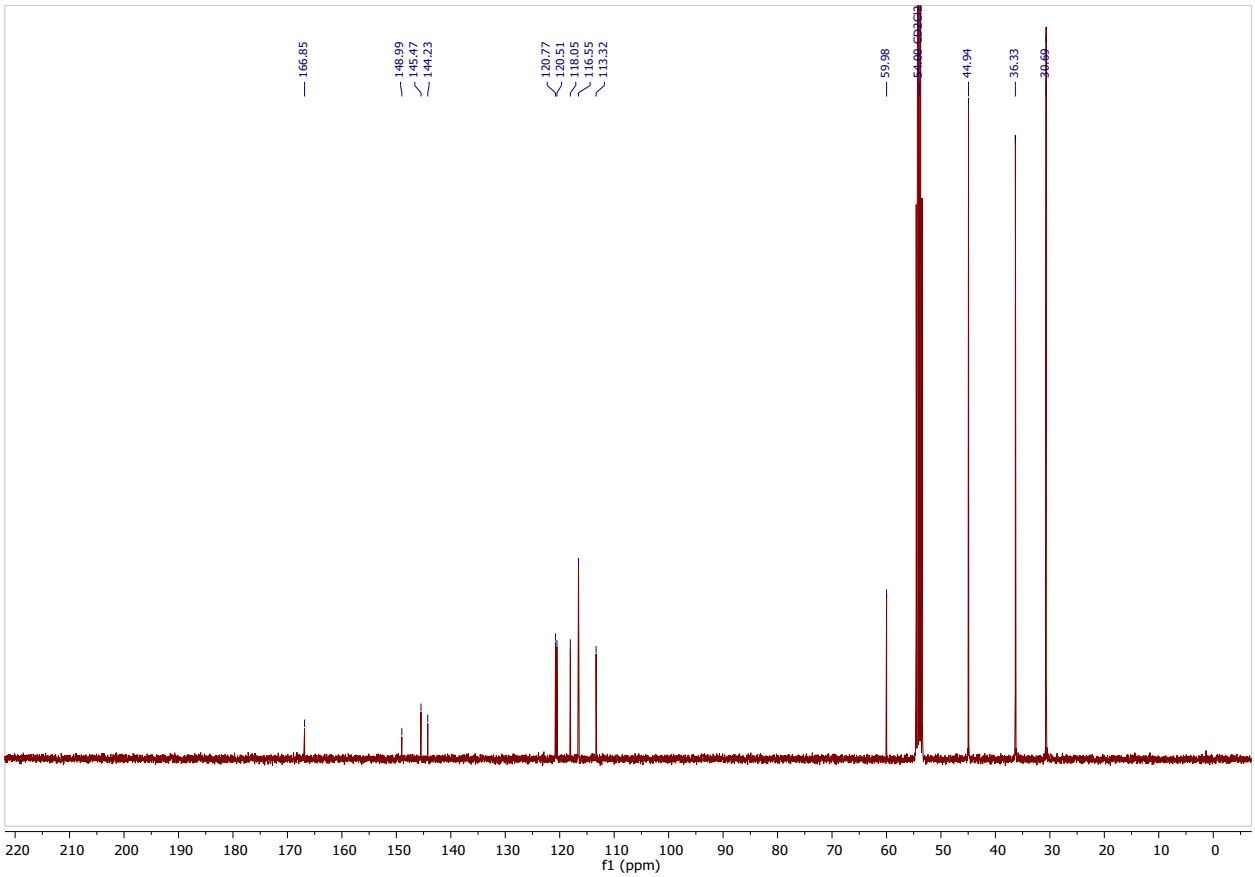
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [*N*,*N*-Bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene](2-chloro-1H-benzo[d]imidazol-1-yl)gold(I) 4c:**



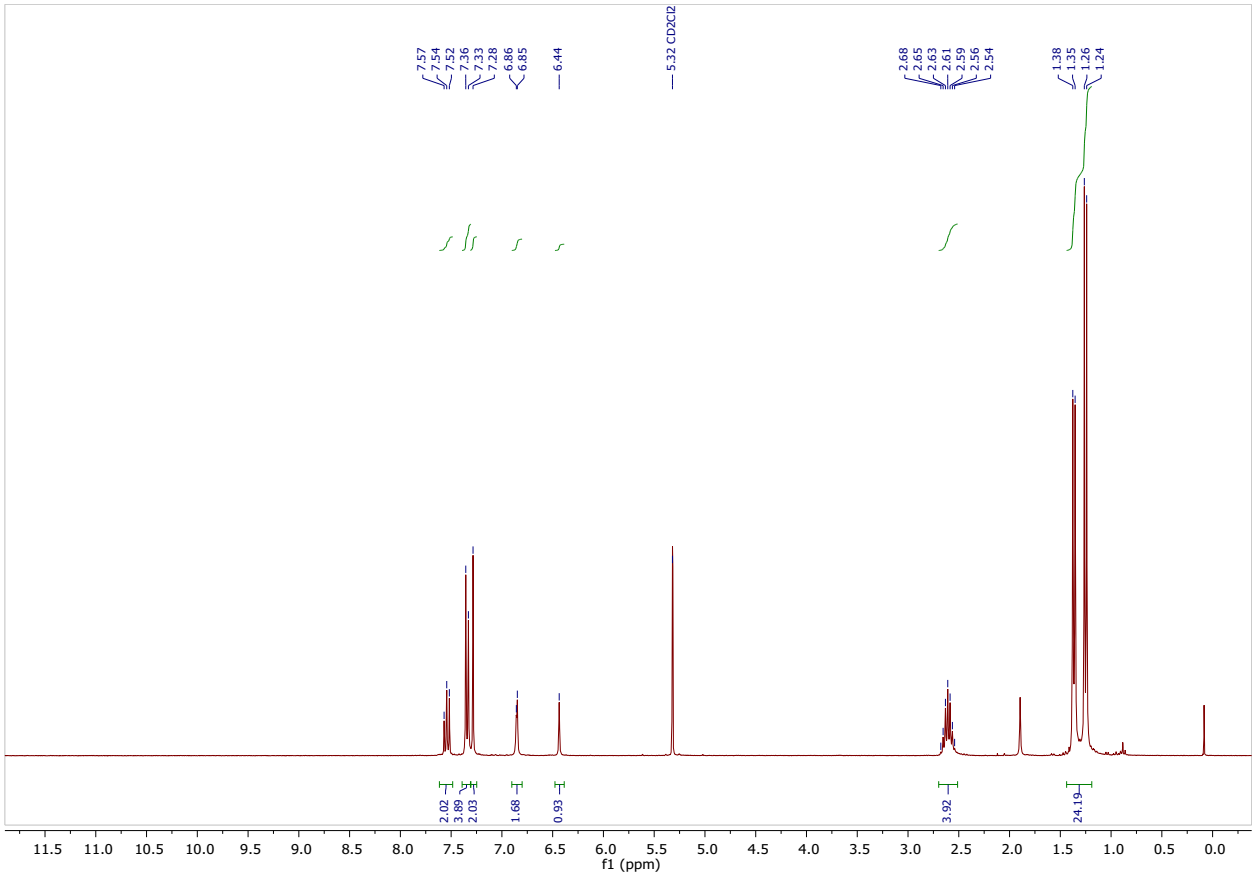


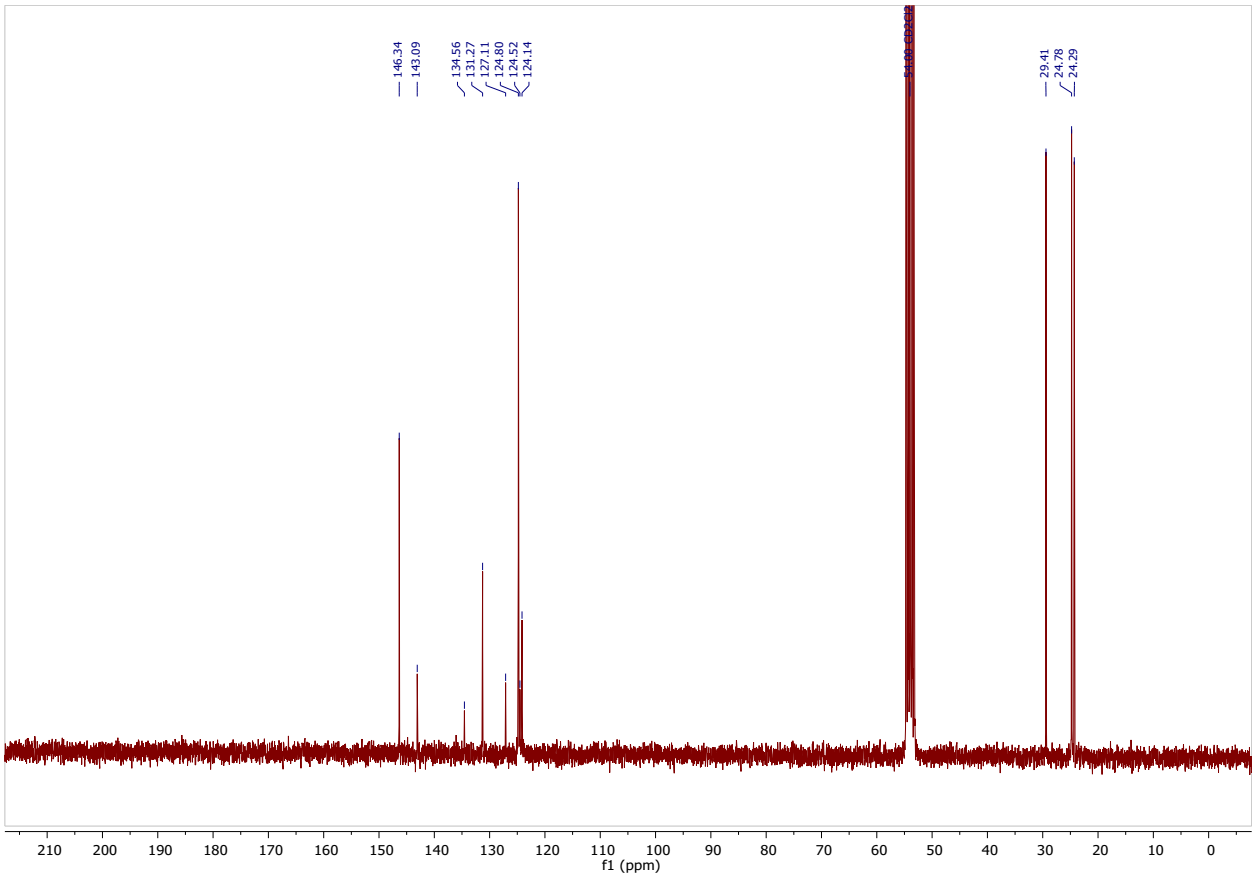
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [*N*,*N*-Bis(adamantyl)imidazol-2-ylidene](2-chloro-1H-benzo[d]imidazol-1-yl)gold(I) 4d:**



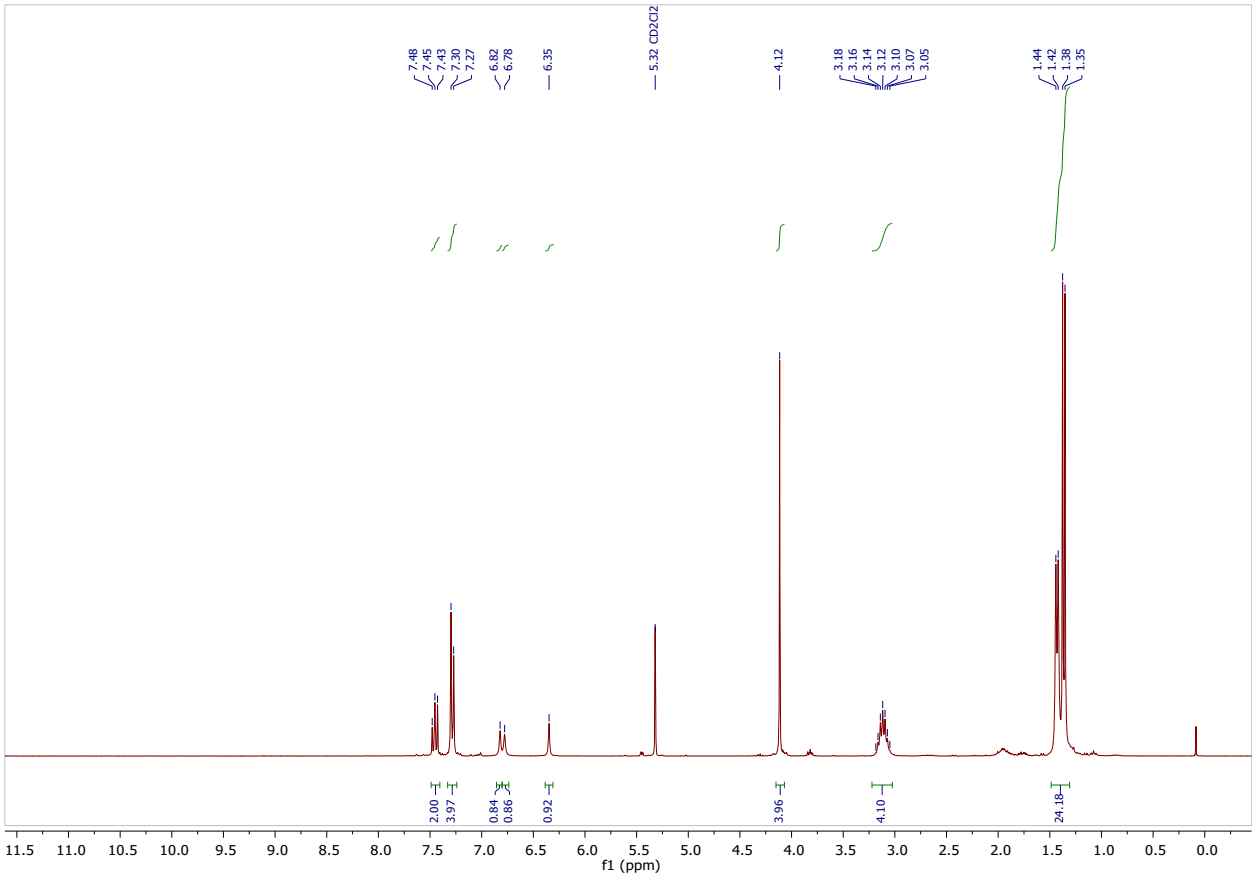


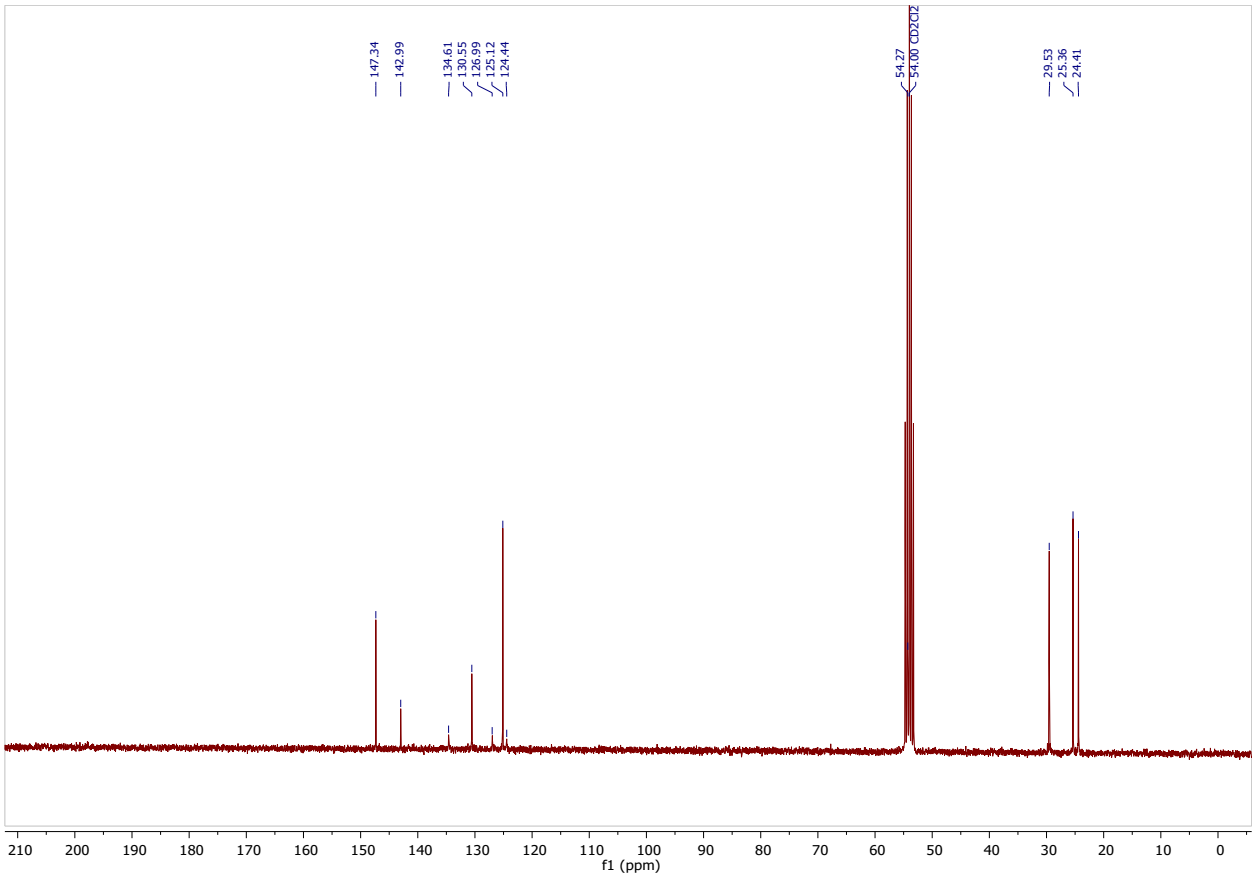
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [N,N'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)](1H-imidazol-1-yl))gold(I) 5a:**



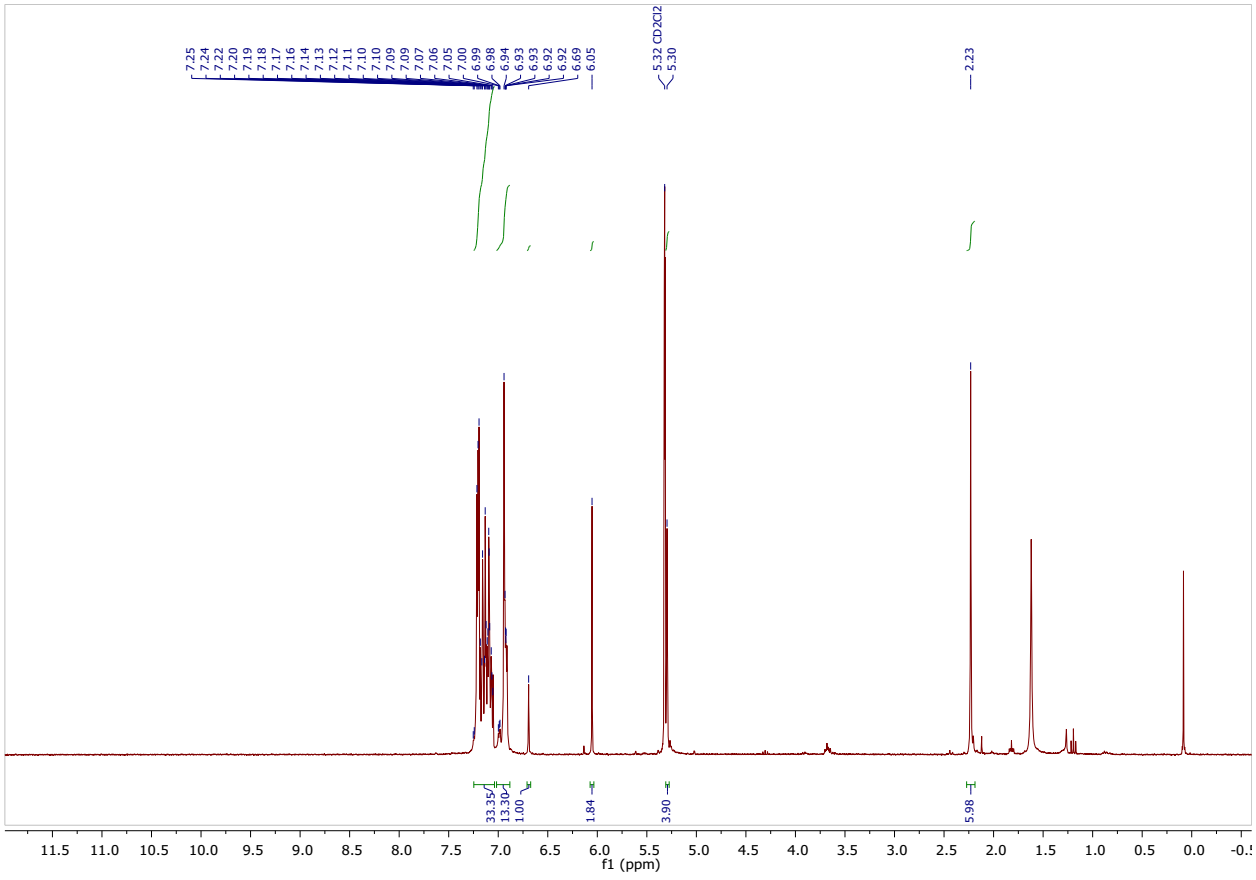


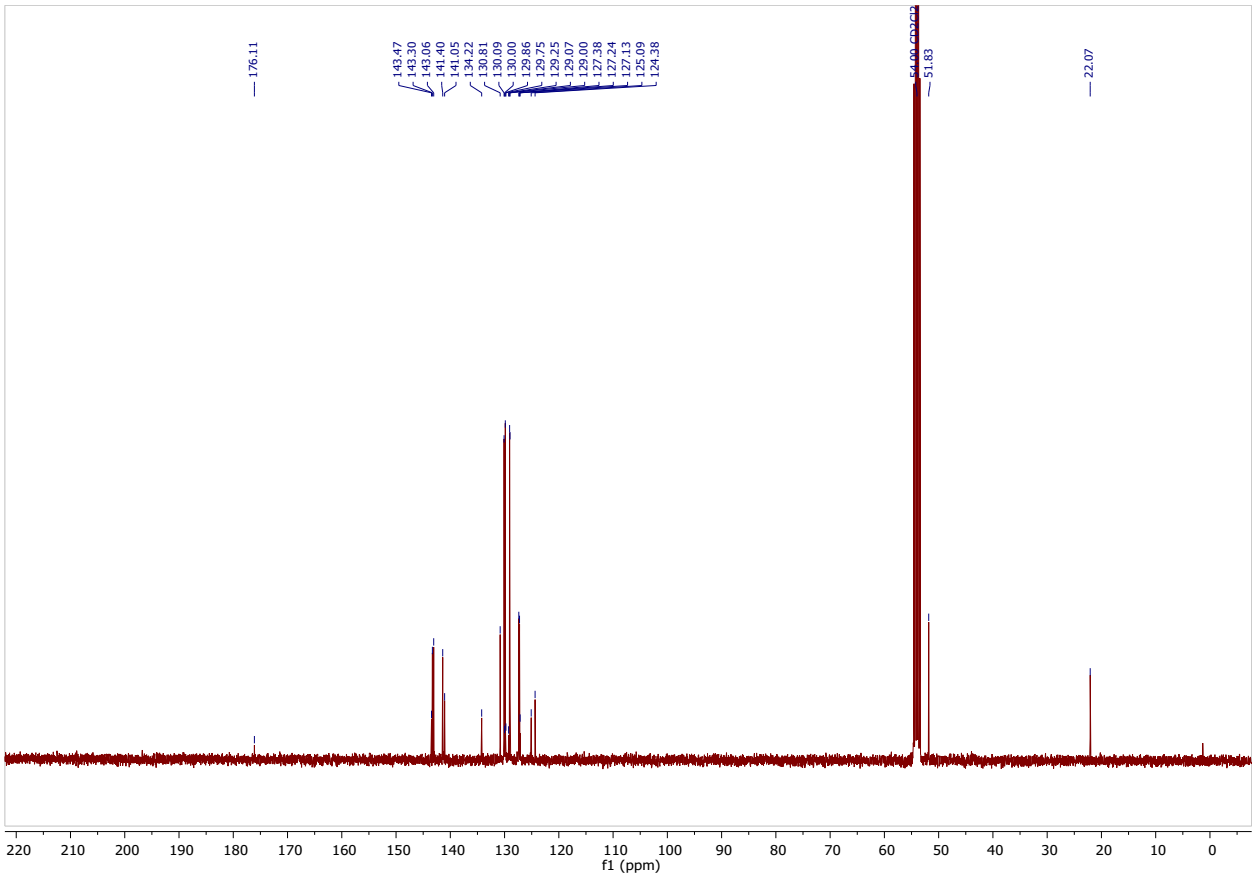
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [N,N'-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene)](1H-imidazol-1-yl))gold(I) 5b:**



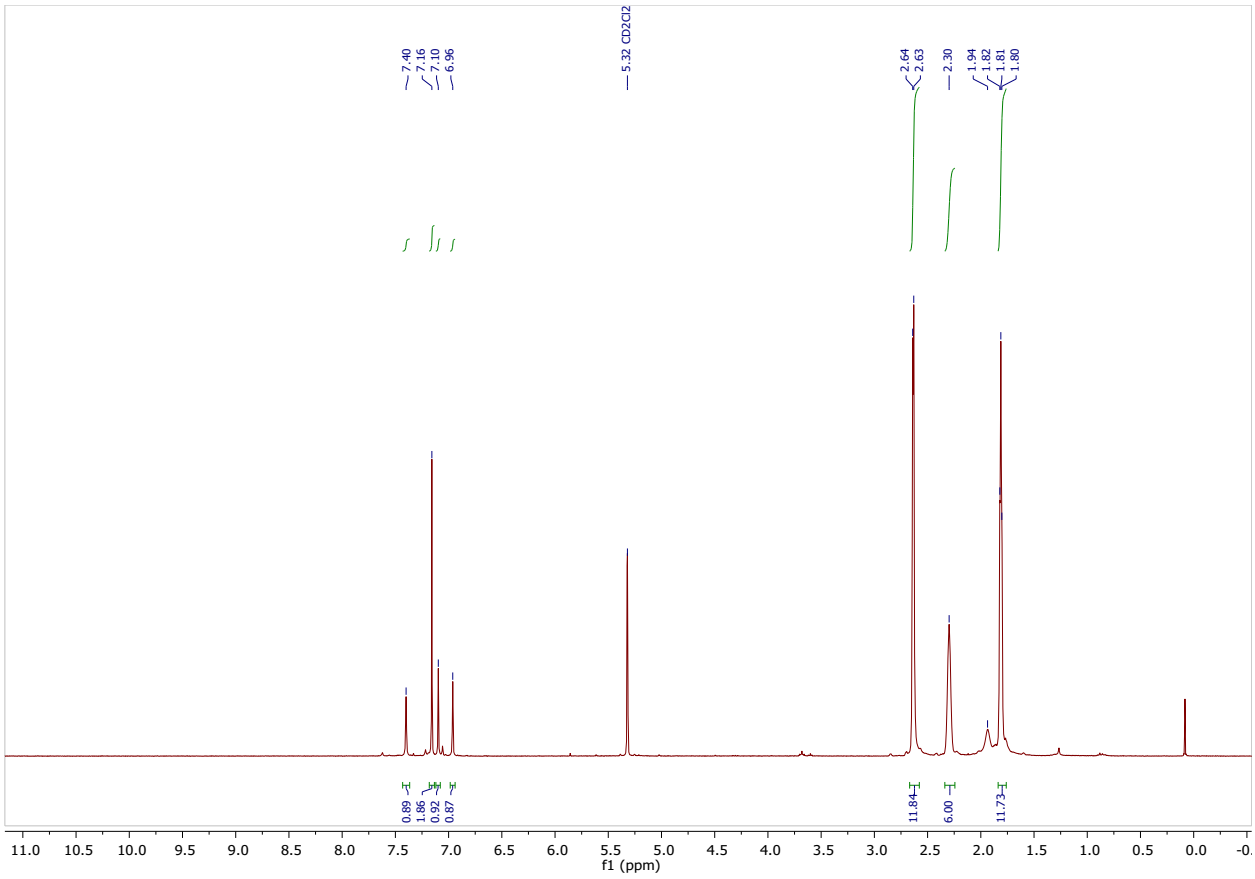


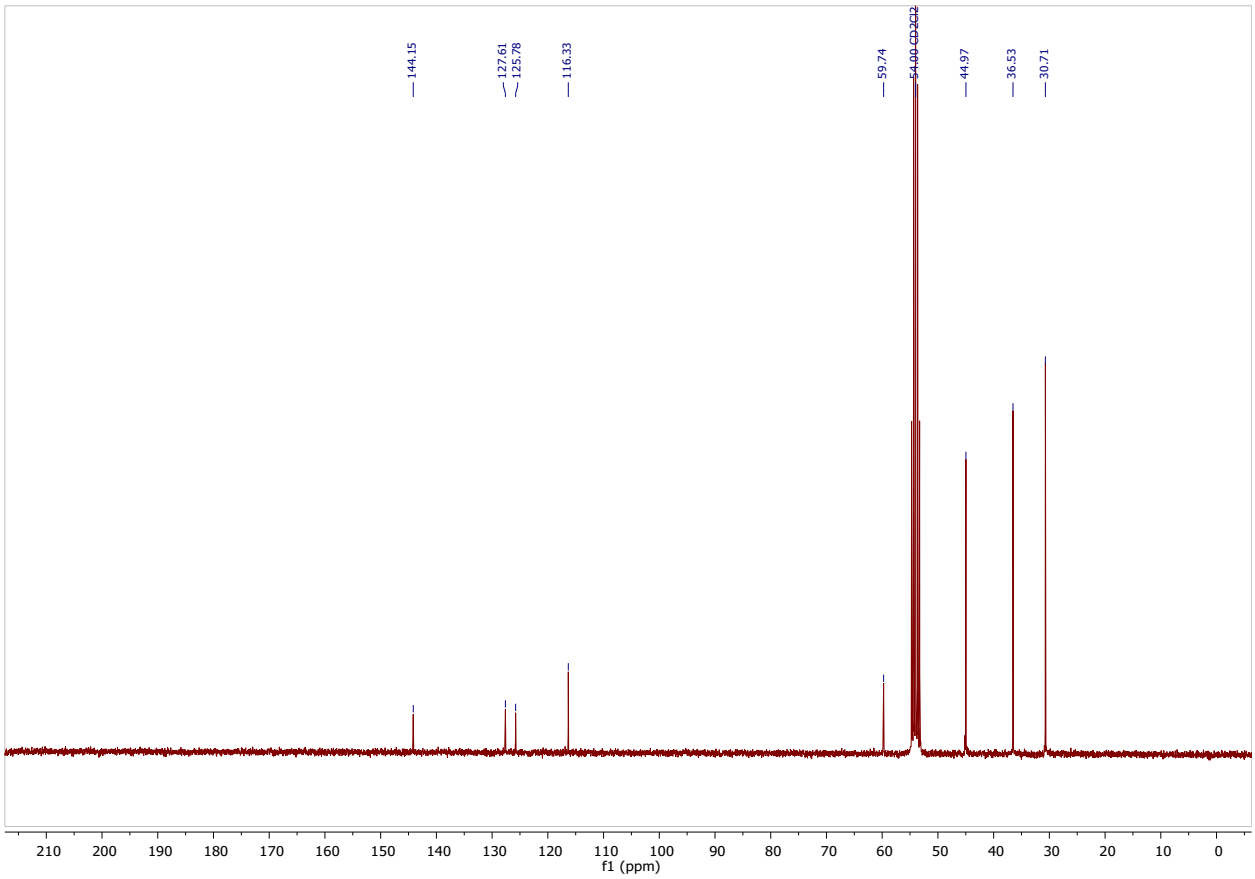
^{1}H NMR and ^{13}C {^{1}H} NMR for **[*N*,*N*-Bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene](1H-pyrazol-1-yl)gold(I) 5c:**



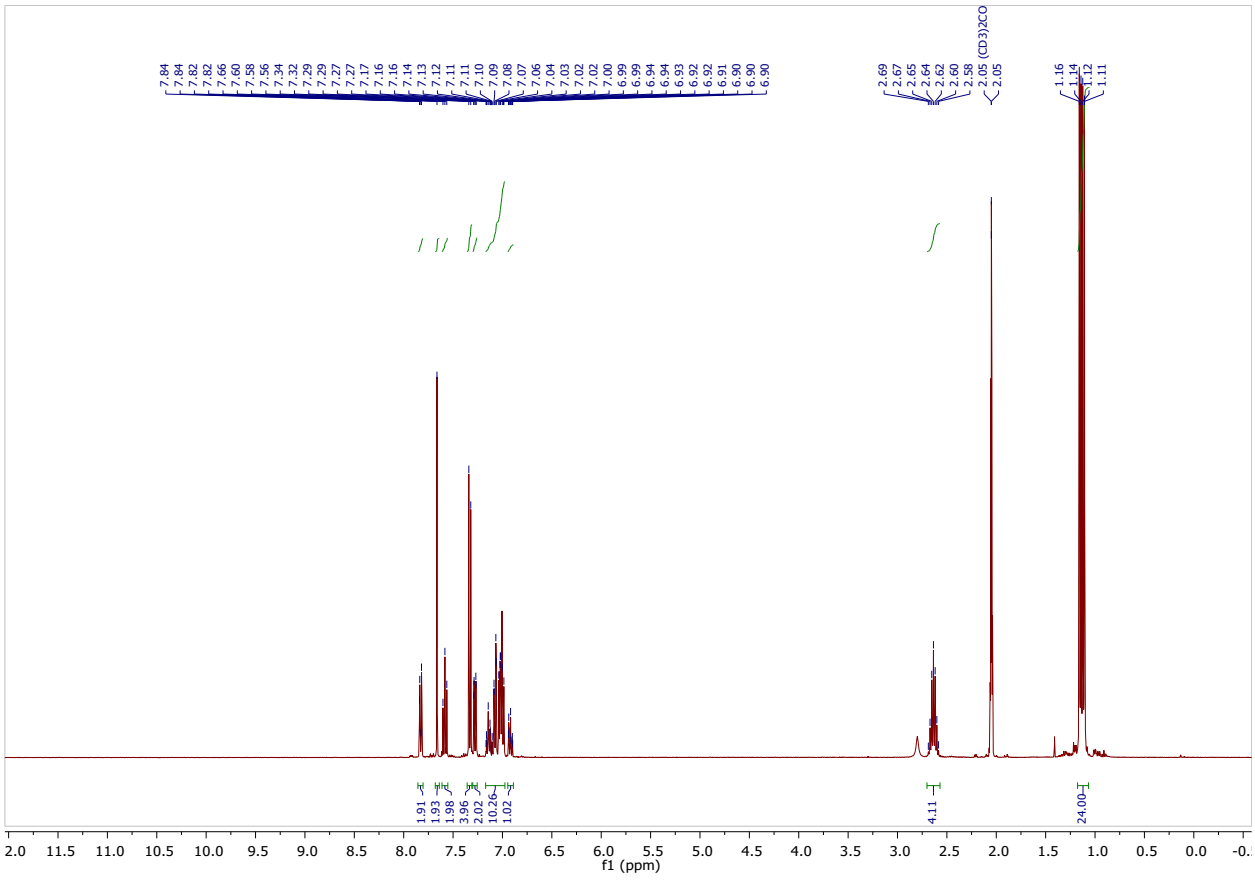


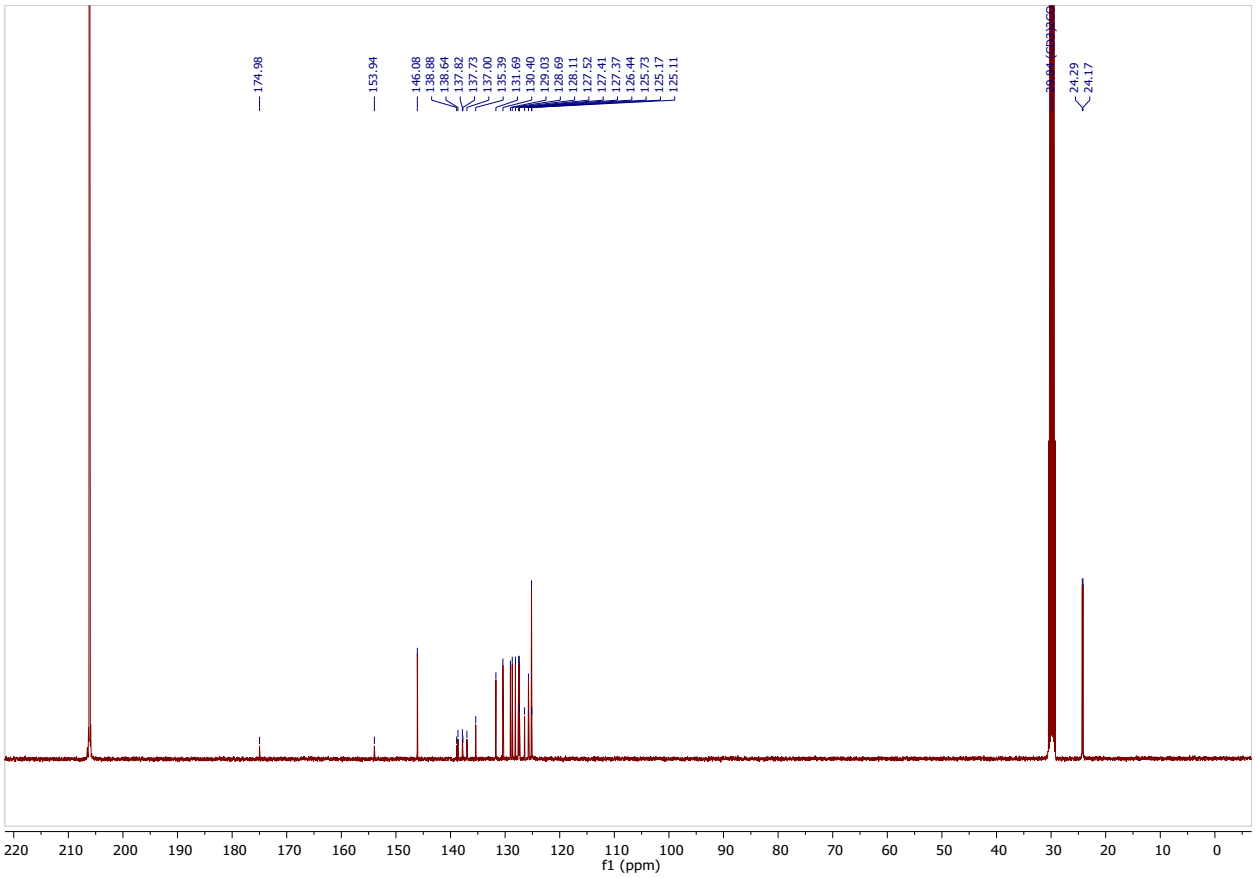
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [*N*,*N*-Bis(adamantyl)imidazol-2-ylidene](1H-imidazol-1-yl)gold(I) 5d:**



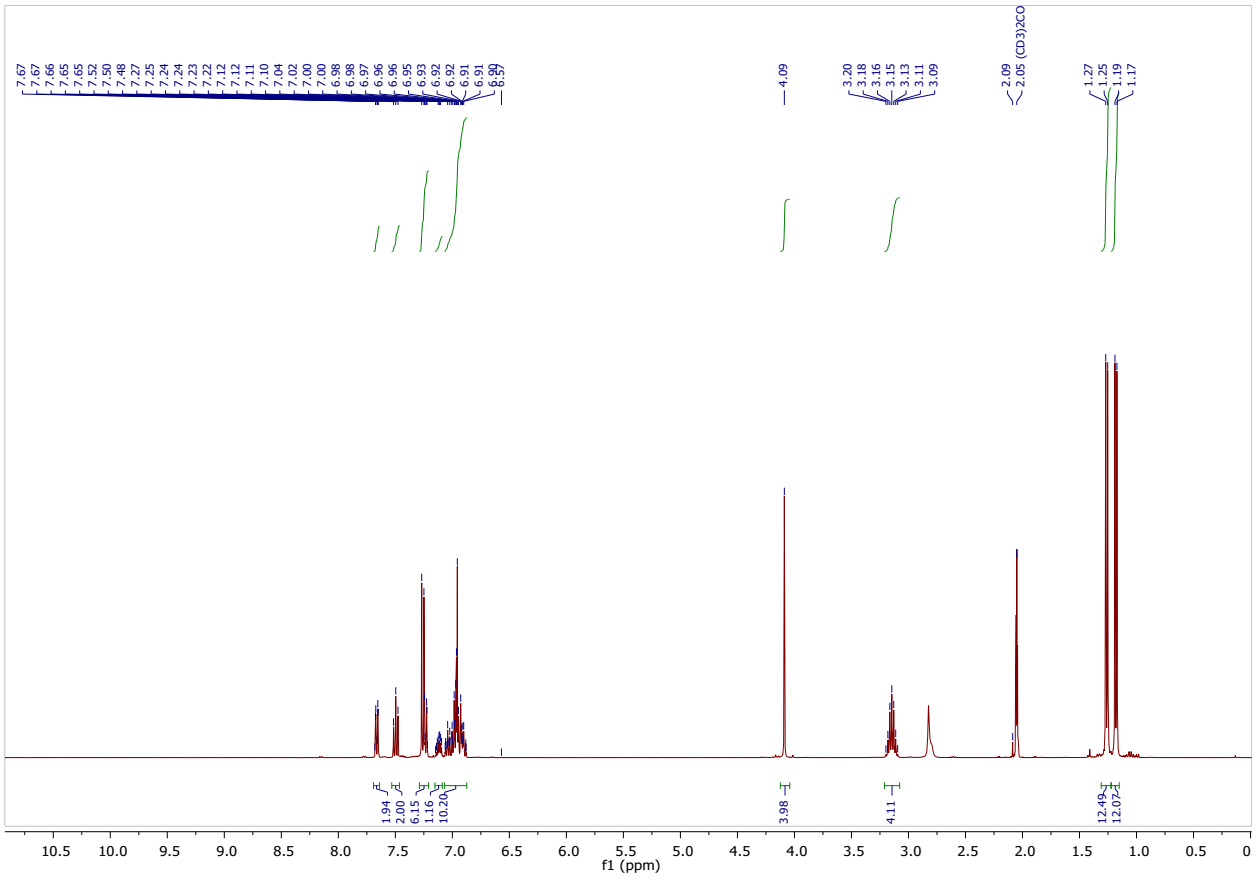


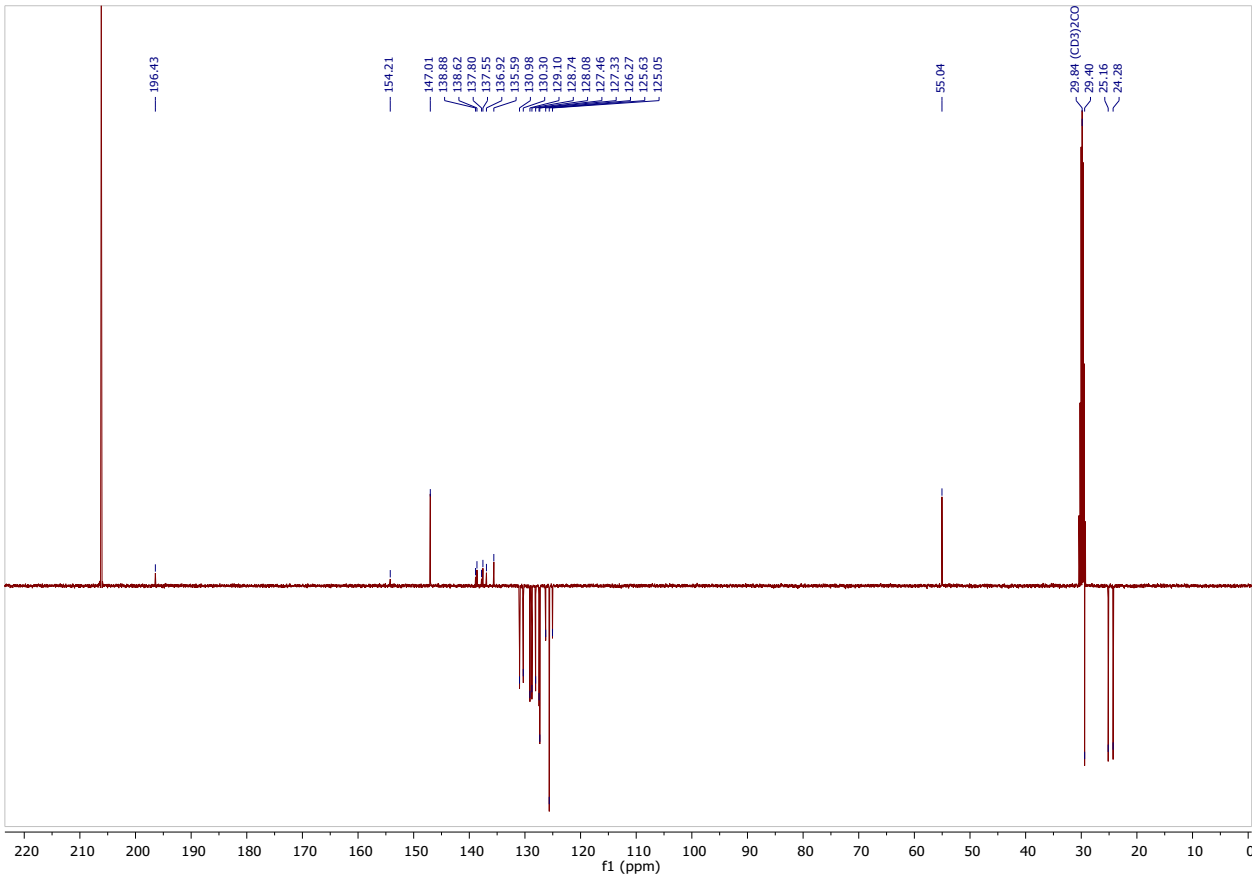
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [N,N'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)](2,4,5-triphenyl-1H-imidazol-1-yl)gold(I)] 6a:**



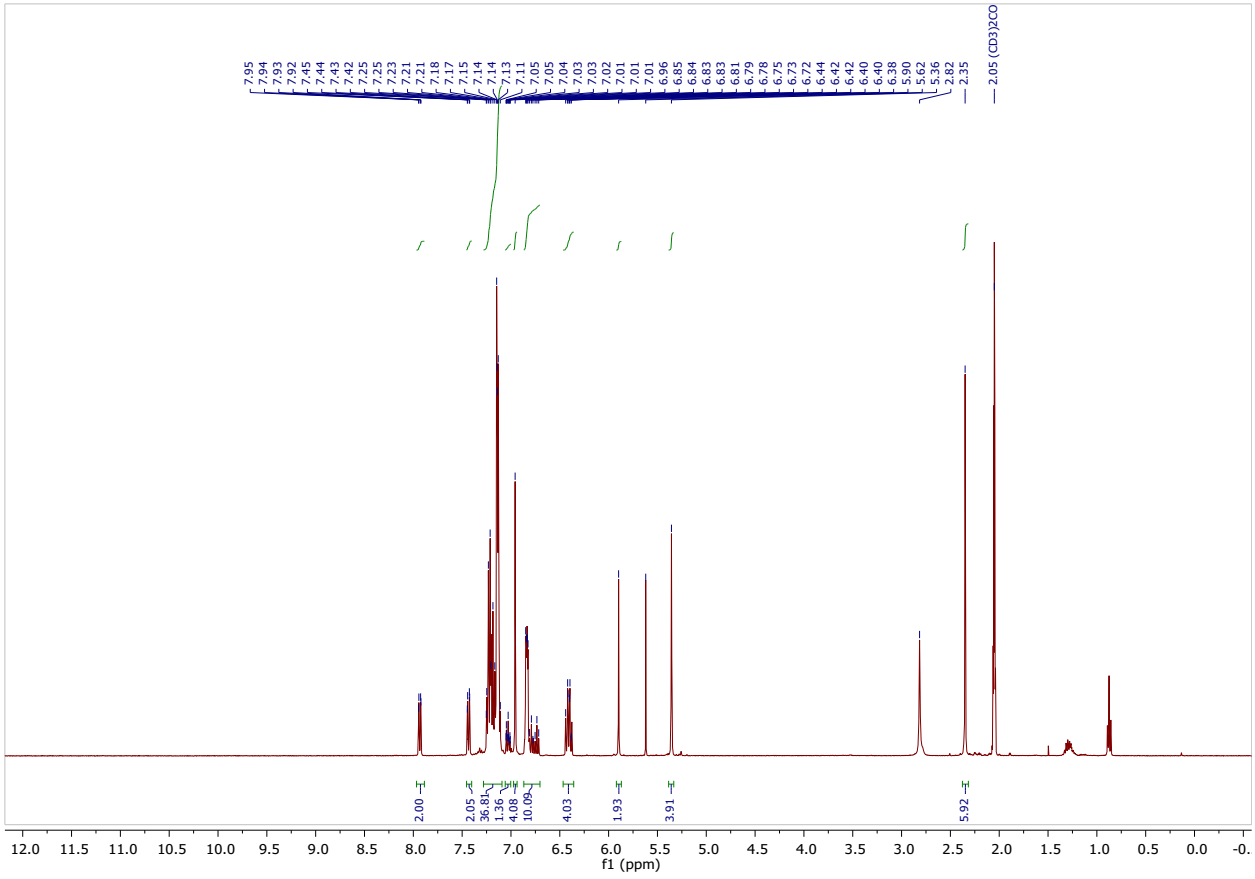


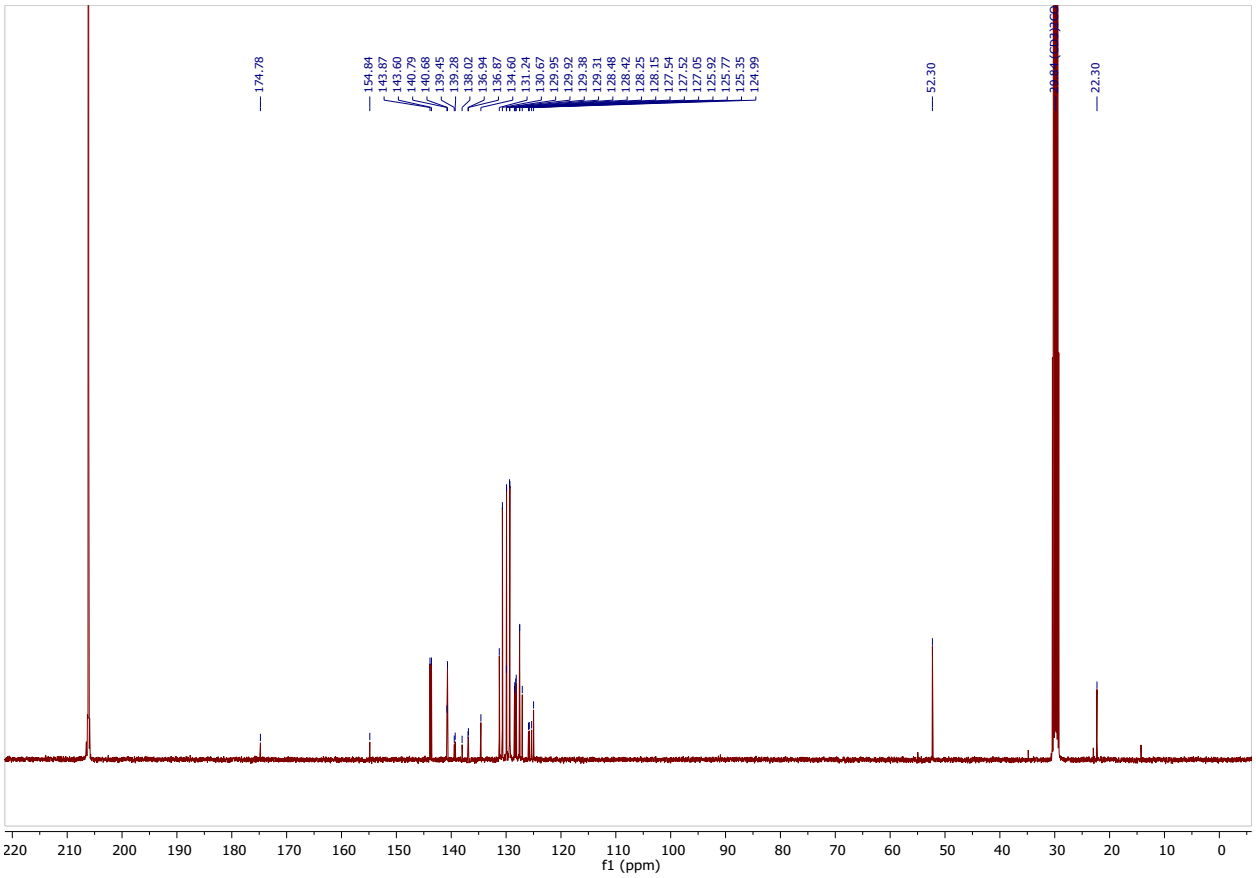
^{1}H NMR and ^{13}C {^{1}H} NMR for **[N,N'-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene)](2,4,5-triphenyl-1H-imidazol-1-yl)gold(I) 6b:**



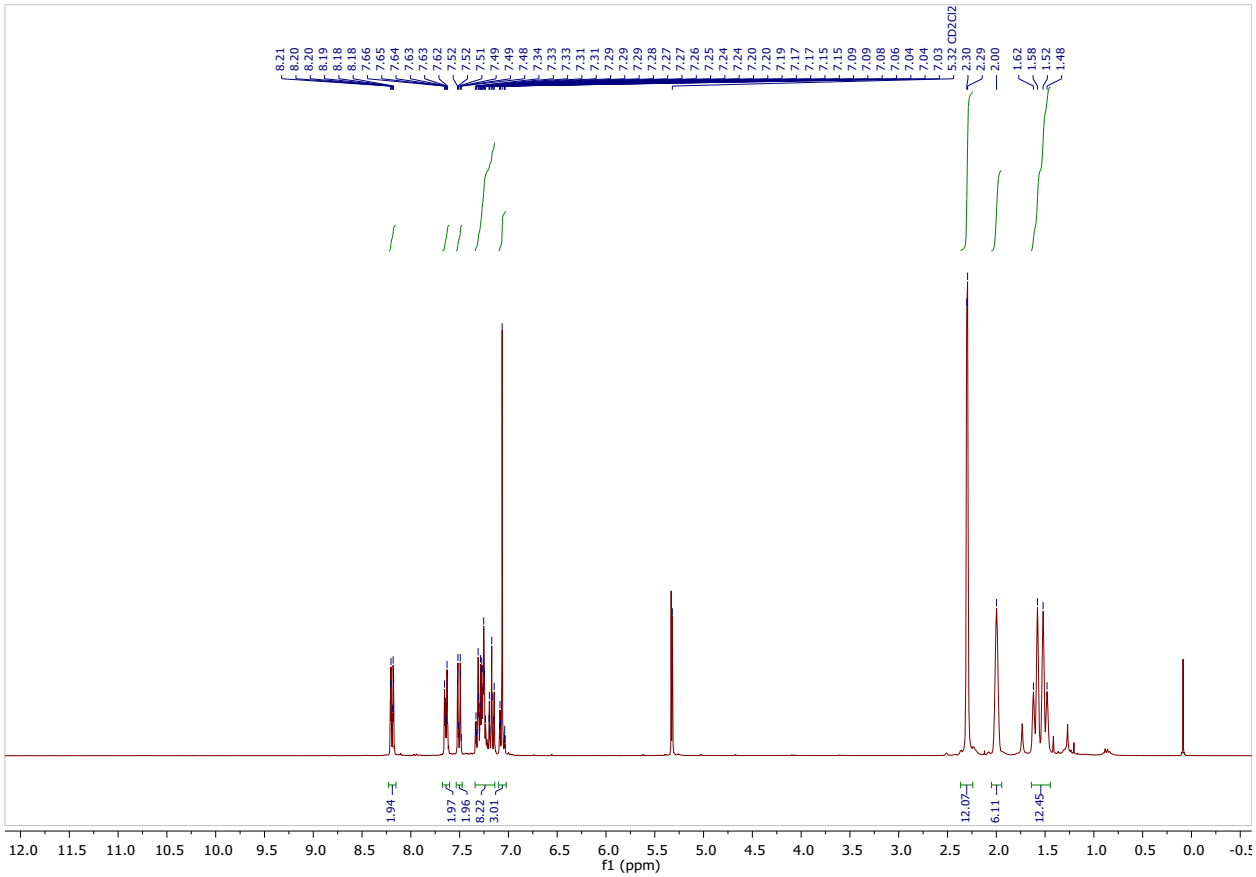


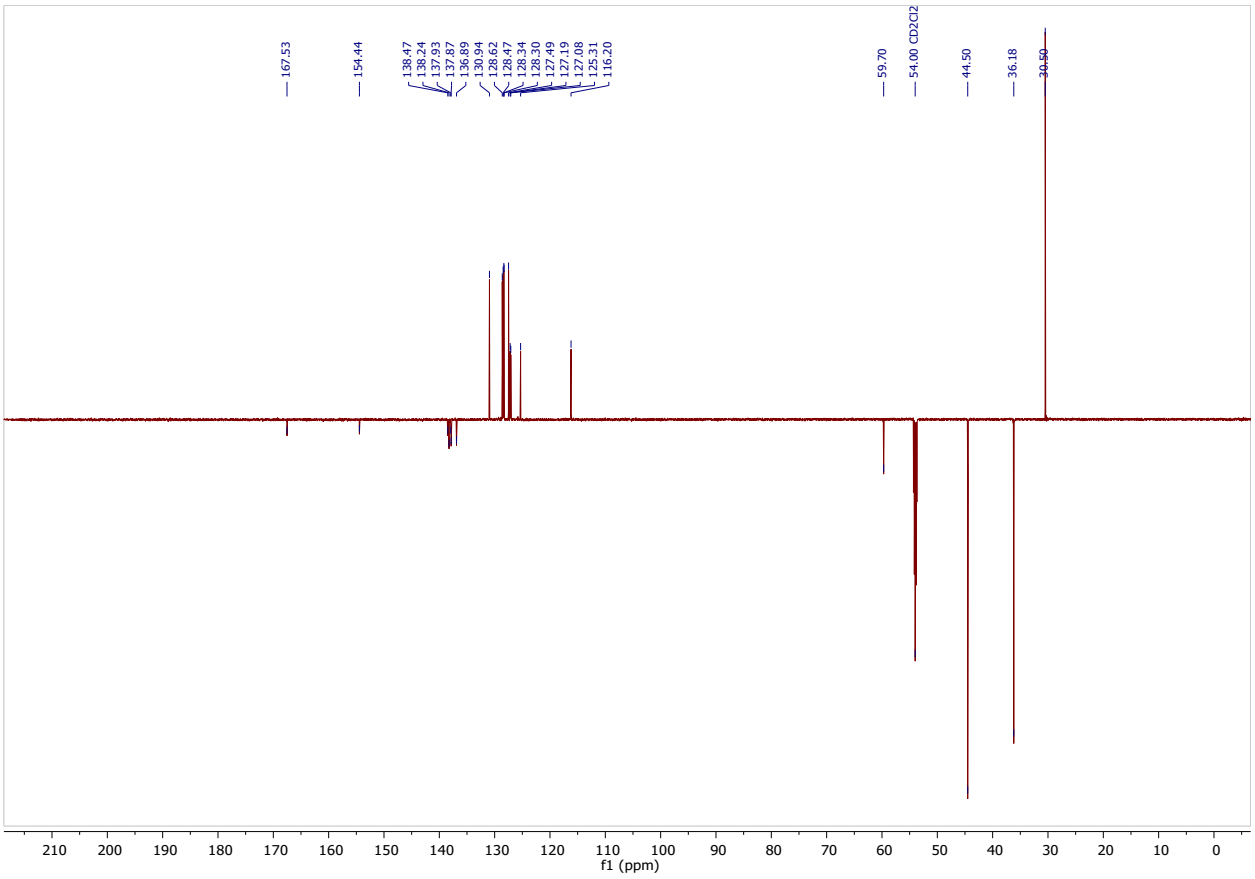
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [*N*,*N*-Bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene](2,4,5-triphenyl-1H-imidazol-1-yl)gold(I) 6c:**





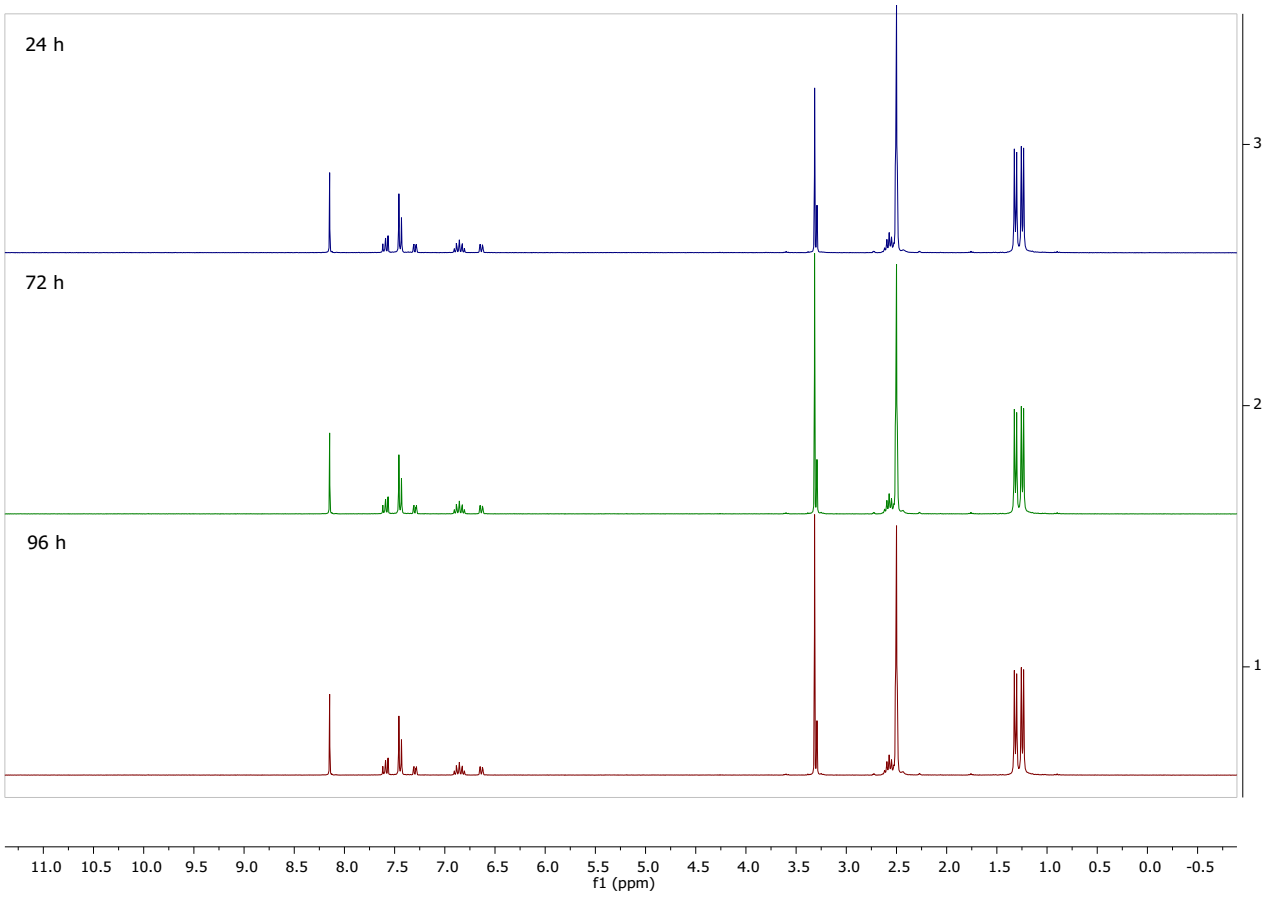
***^{1}H NMR and ^{13}C {^{1}H} NMR for* [*N*,*N*-Bis(adamantyl)imidazol-2-ylidene](2,4,5-triphenyl-1H-imidazol-1-yl)gold(I) 6d:**




167.53
154.44
138.47
138.24
137.93
137.87
136.89
130.94
128.62
128.47
128.34
128.30
127.49
127.19
127.08
125.31
116.20
59.70
54.00 CD2Cl2
44.50
36.18
30.60
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Stability of the complex 4a in DMSO-d_6/D_2O (3:1)

^{1}H NMR in DMSO-d_6/D_2O for **[N,N'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)](2-chloro-1H-benzo[d]imidazol-1-yl)gold(I) 4a after 24, 72 and 96 hours:**



^{1}H NMR spectra were recorded at the same concentration as the stock solution prepared for biological tests (10 mM).