Supplementary Information for:

Cross-Bridged Cyclen or Cyclam Co(III) Complexes containing Cytotoxic Ligands as Hypoxia-Activated Prodrugs

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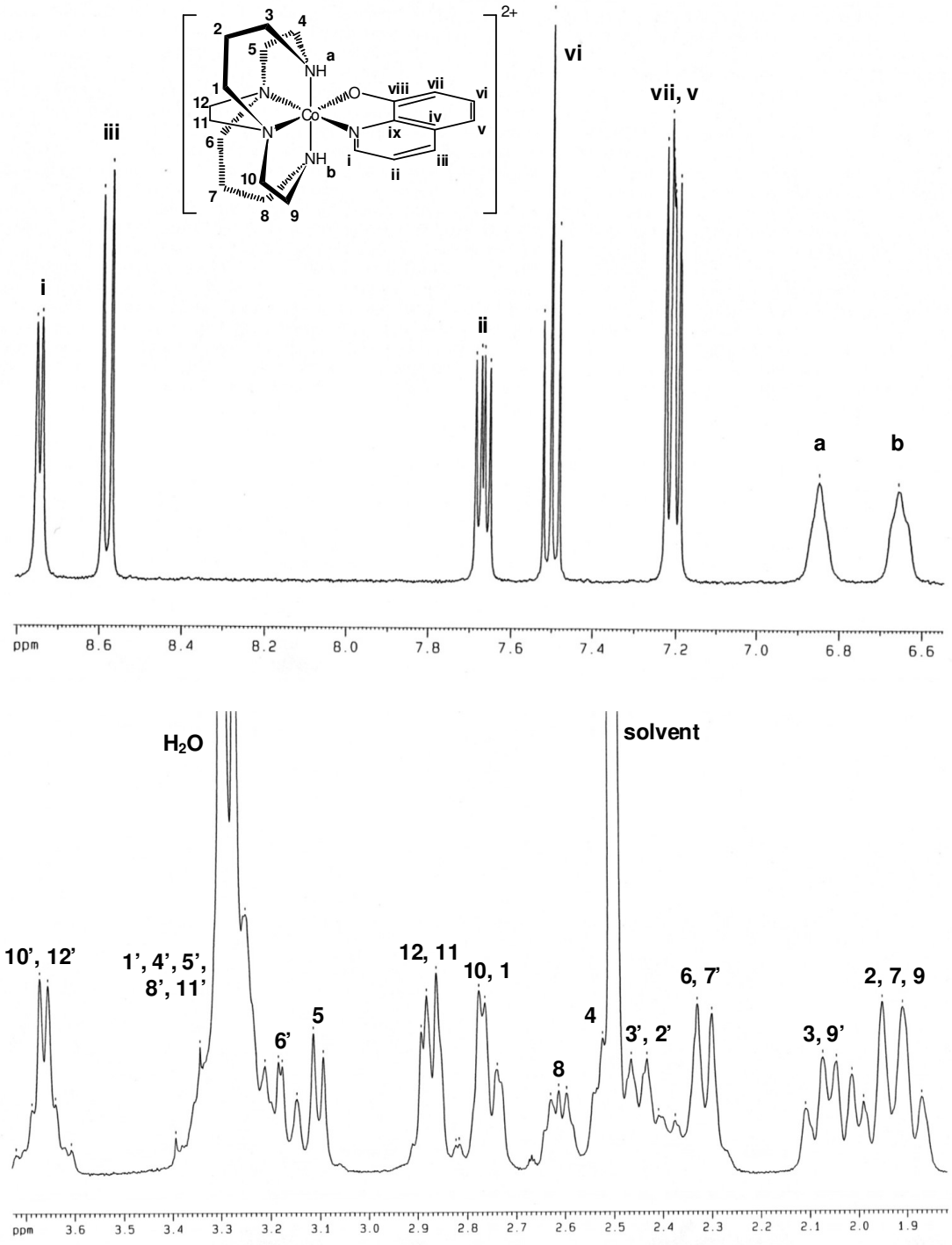
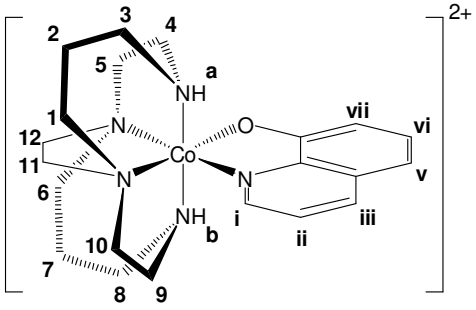


Figure S1. ^{1}H NMR spectrum of **21** (400 MHz, d_6-DMSO).

Table S1. ^{1}H NMR assignments for **21** (DMSO-d_6, 400 MHz)



δ (ppm)	Multiplicity and *J*(Hz)		Integral	Assignment
1.91	m		1	7
1.93	m		1	2
1.95	m		1	9
2.05	m		1	3
2.08	m		1	9’
2.33	m		2	6, 7’
2.43	m		1	2’
2.48	m		1	3’
2.53	m		1	4
2.61	m		1	8
2.74	m		1	1
2.78	m		1	10
2.87	m		1	11
2.88	m		1	12
3.11	m		1	5
3.18	m		1	6’
3.25	m		1	11’
3.26	m		3	4’, 5’, 8’
3.32	m		1	1’
3.67	m		2	10’,12’
6.65	bt		1	b
6.85	bt		1	a
7.20	m		1	v
7.22	m		1	vii
7.50	t	^{3}J 7.9	1	vi
7.68	dd	^{3}J 5.2 ^{3}J 8.3	1	ii
8.59	d	^{3}J 8.2	1	iii

	8.75	d	^{3}J 5.2	1	i

.

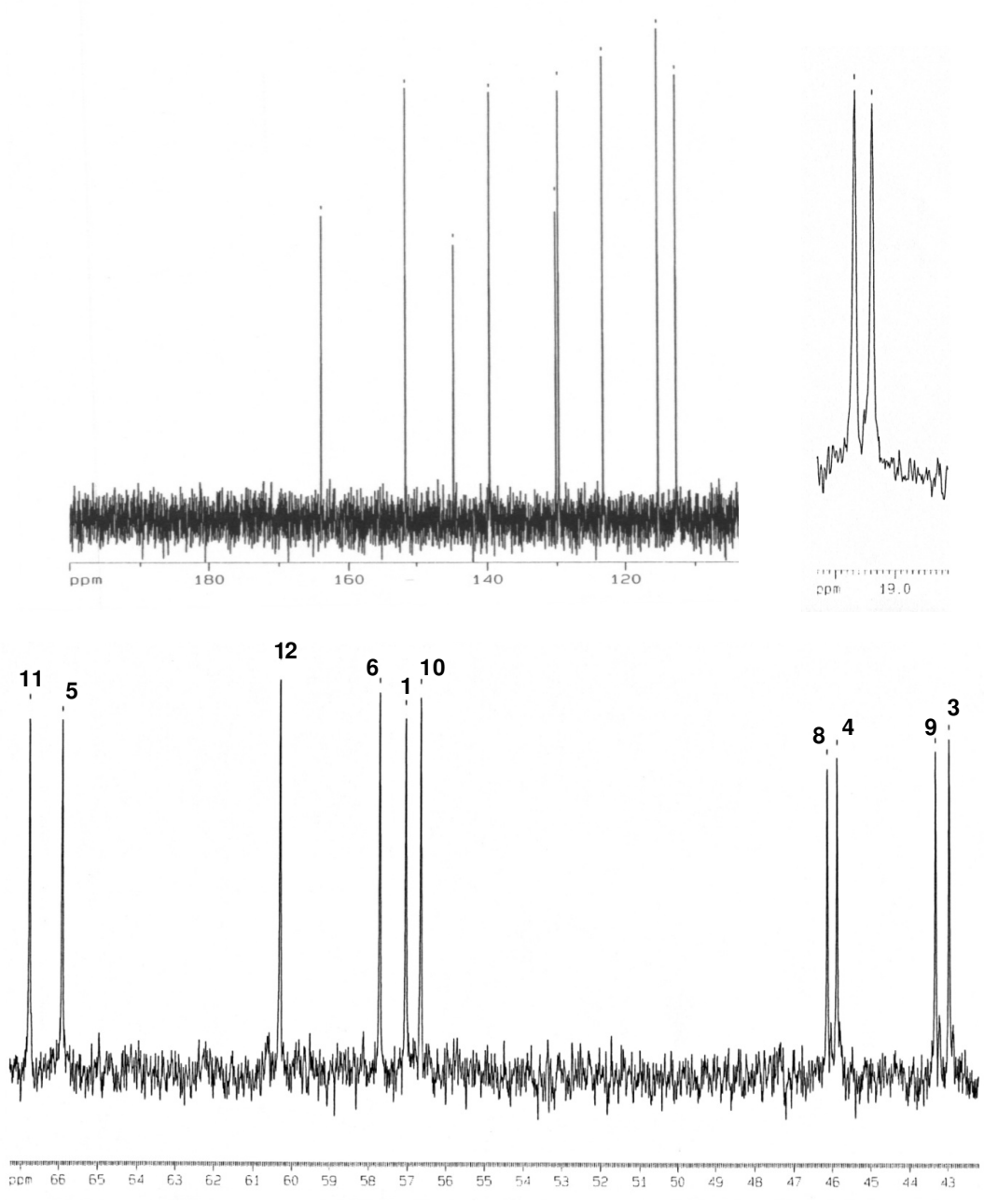
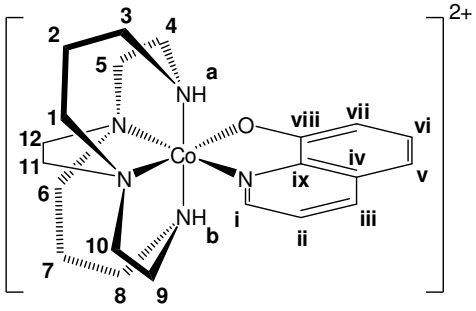
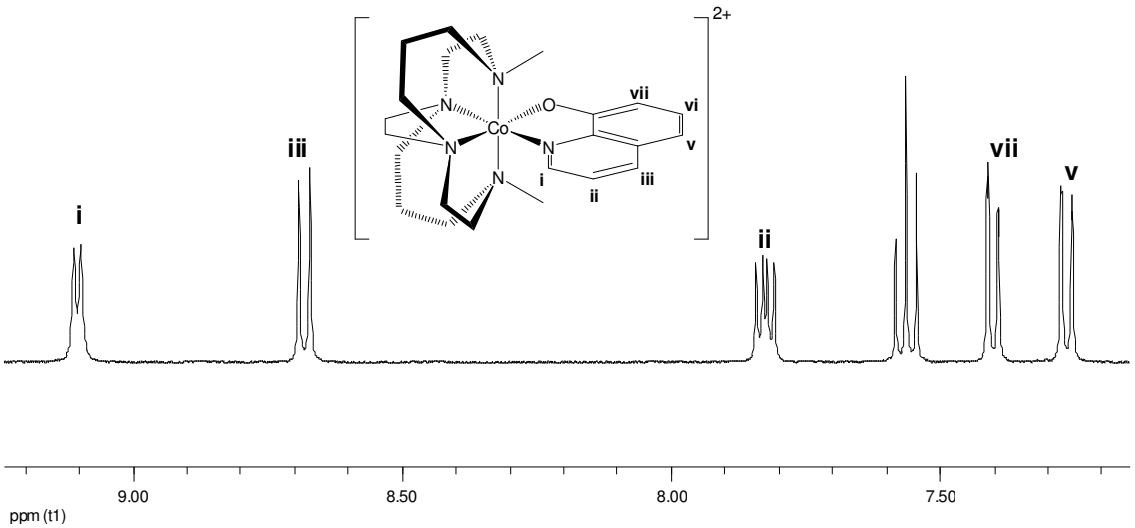


Figure S2. ^{13}C NMR spectrum of **21** (100 MHz, d_6-DMSO).

Table S2. ^{13}C NMR assignments for **21** (DMSO-d_6, 100 MHz).

	δ (ppm)	Assignment
	19.2	2
	19.4	7
	43.0	3
	43.3	9
	45.9	4
	46.2	8
	56.7	10
	57.1	1
	57.7	6
	60.3	12
	65.9	5
	66.8	11
	112.7	v
	115.3	vii
	123.3	iii
	129.8	vi
	130.2	iv
	139.7	ii
	144.8	ix
	151.7	i
	164.1	viii



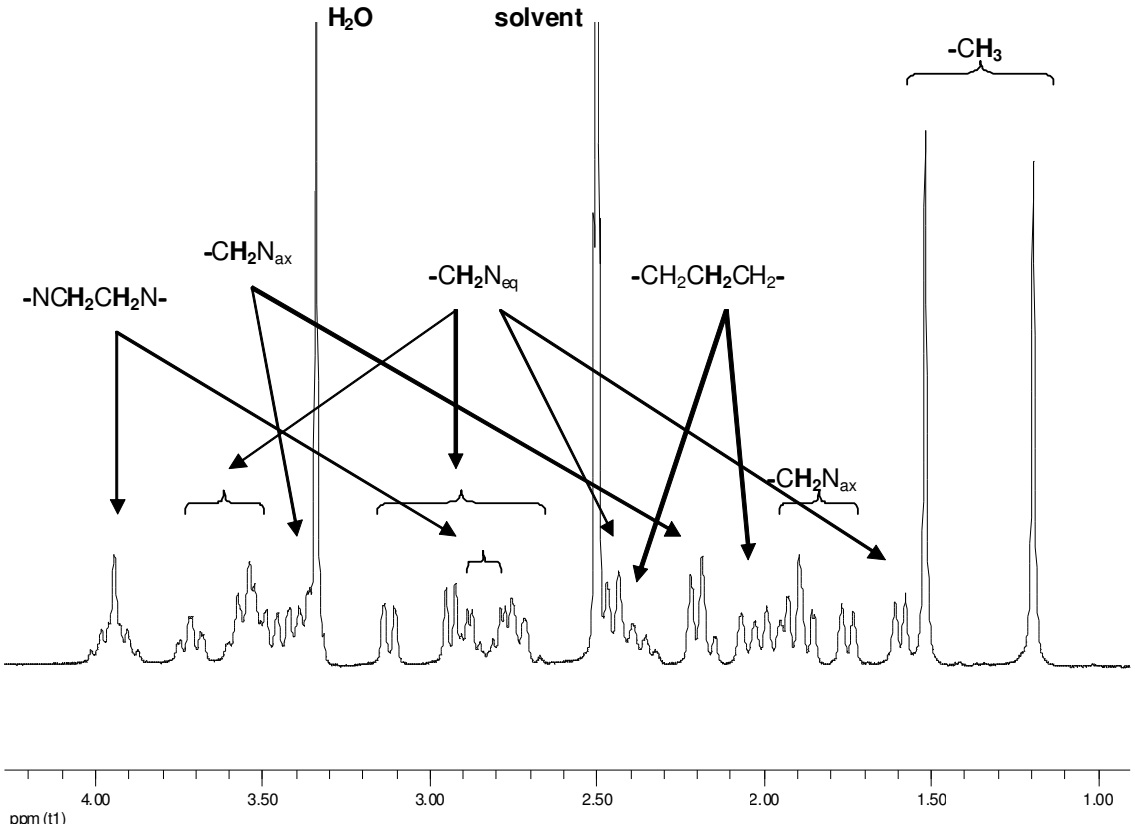
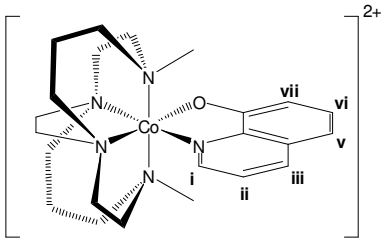


Figure S3. ^{1}H NMR spectrum of **22** (300 MHz, d_6-DMSO).

Table S3. ^{1}H NMR assignments for **22** (DMSO-d_6, 300 MHz).

	δ (ppm)	Multiplicity and *J*(Hz)		Integral	Assignment
	1.20	s		3	-NC**H**$_3$
	1.52	s		3	-NC**H**$_3$
	1.59	d	^{2}J 12.4	1	-N$_{eq}$C**H**$_2$-
	1.75	d	^{2}J 13.9	1	-N$_{ax}$C**H**$_2$-
	1.90	m		2	-N$_{ax}$C**H**$_2$-
	1.98	m		1	-C**H**$_2$-
	2.03	m		1	-C**H**$_2$-
	2.19	m		2	-N$_{ax}$C**H**$_2$-
	2.42 – 2.46	m		4	-C**H**$_2$- -N$_{eq}$C**H**$_2$-
	2.77	m		2	-N$_{eq}$C**H**$_2$- bridge
	2.89	m		1	bridge
	2.93	m		1	-N$_{eq}$C**H**$_2$-
	3.13	d	^{2}J 11.2	1	-N$_{eq}$C**H**$_2$-
	3.38 – 3.54	m		4	-N$_{ax}$C**H**$_2$- -N$_{eq}$C**H**$_2$-
	3.72	t	^{2}J 10.6	1	-N$_{eq}$C**H**$_2$-
	3.95	m		2	bridge
	7.26	dd	^{3}J = 8.1 ^{4}J = 0.8		v
	7.40	dd	^{3}J = 7.7 ^{4}J = 0.8		vii

7.56	t	$^3J = 7.8$		vi
7.83	dd	$^3J = 5.2$ $^3J = 8.2$		ii
8.68	d	$^3J = 8.2$		iii
9.10	d	$^3J = 5.2$		i

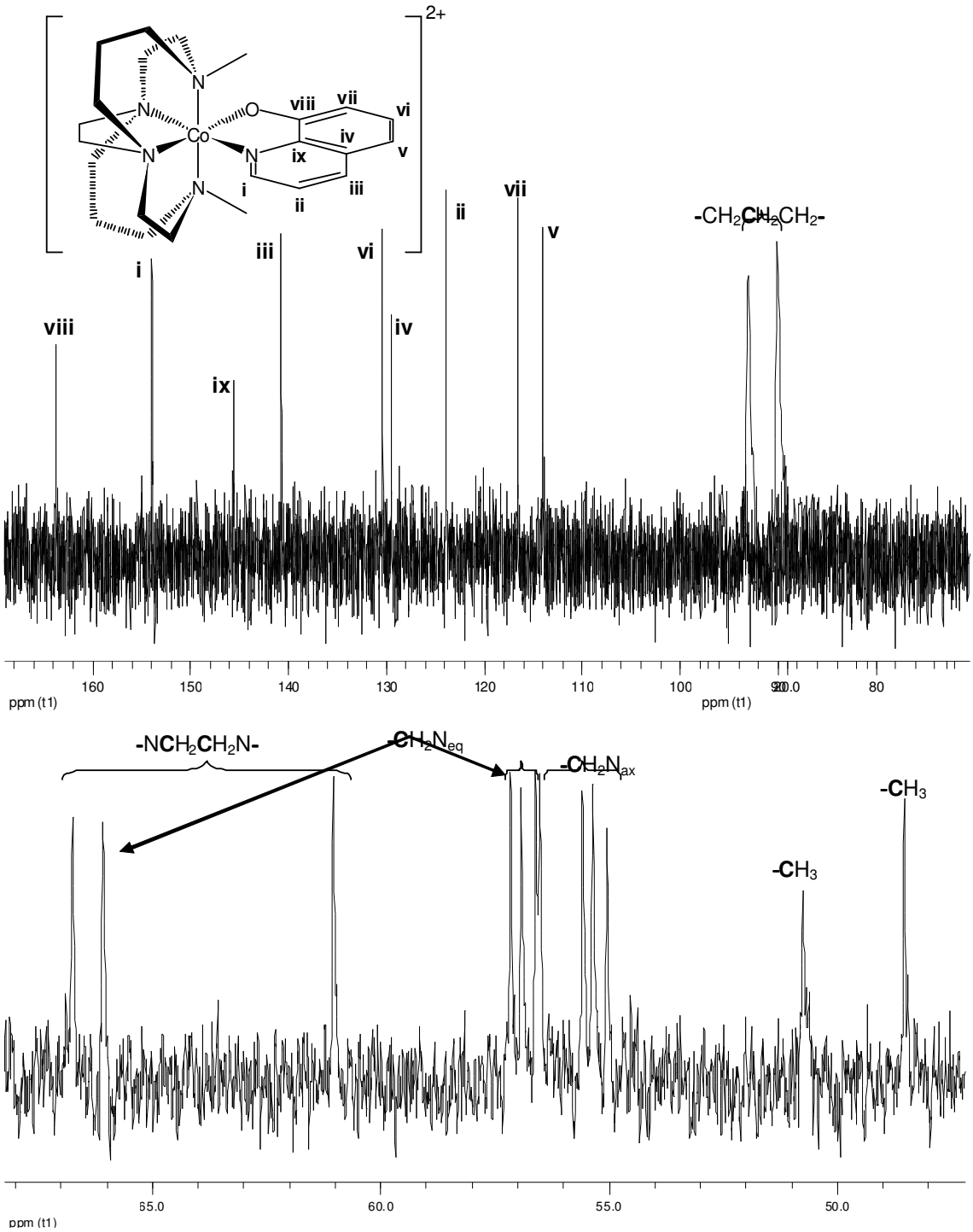
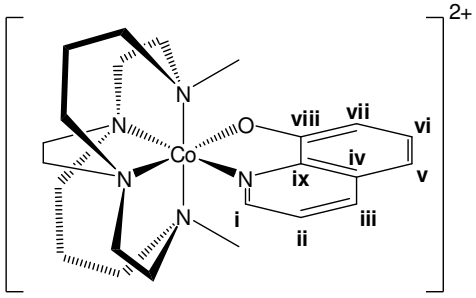


Figure S4. ^{13}C NMR spectrum of **22** (75 MHz, d_6-DMSO).

Table S4. ^{13}C NMR assignments for **22** (DMSO-d_6, 75 MHz).

	δ (ppm)	Assignment
	20.1, 20.5	-CH_2**C**H_2CH_2-
	48.5, 50.8	-N**C**H_3
	55.0, 55.4, 55.6, 56.6	-N_{ax}**C**H_2
	56.5, 56.9, 66.1, 66.7	-N_{eq}**C**H_2
	57.2, 61.0	-N**C**H_2CH_2N-
	114.0	v
	116.6	vii
	123.9	ii
	129.5	iv
	130.4	vi
	140.8	iii
	145.6	ix
	153.9	i
	163.7	viii

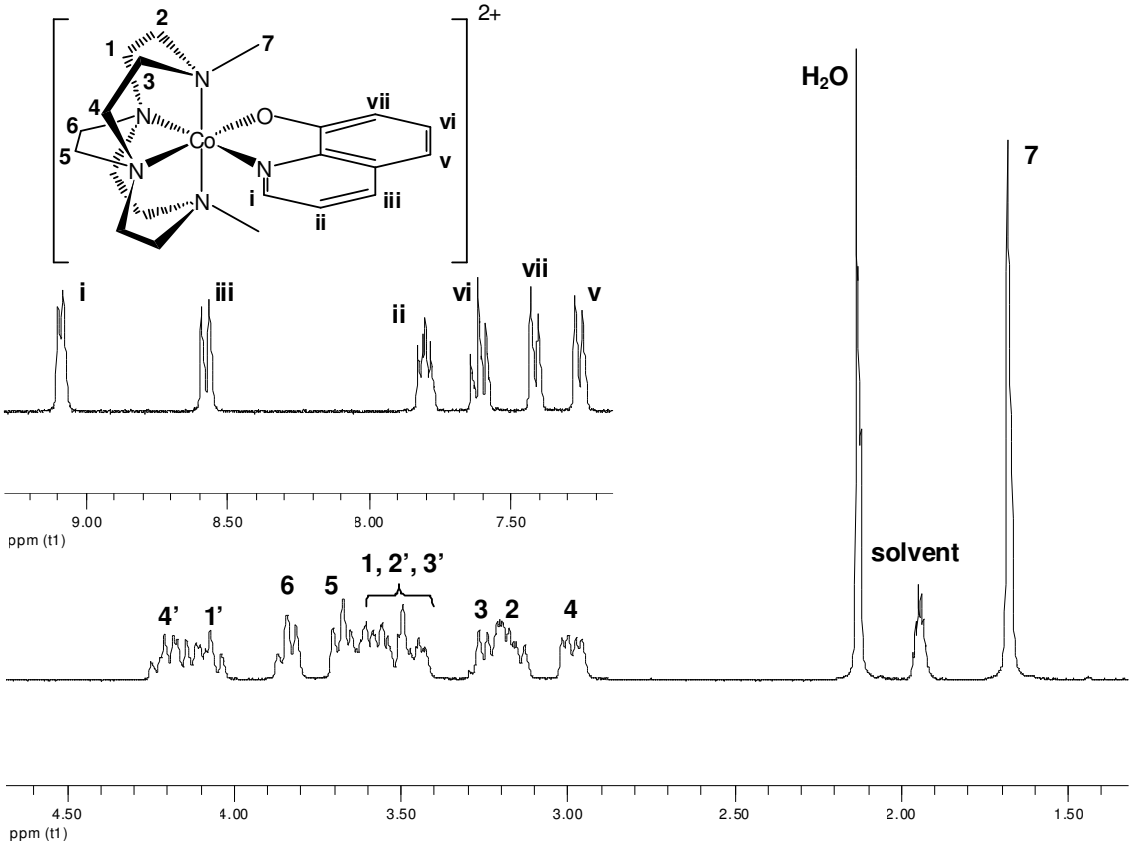
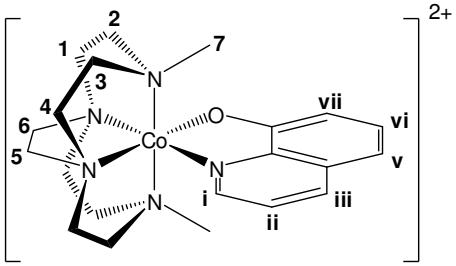


Figure S5. ^{1}H NMR spectrum of **16** (300 MHz, CD_3CN)**.**

Table S5. ^{1}H NMR assignments for **16** (CD_3CN, 300 MHz).

	δ (ppm)	Multiplicity and *J*(Hz)		Integral	Assignment
	1.67	s		6	7
	2.98	dd	^{2}J 12.3 ^{3}J 5.4	2	4
	3.18	m		2	2
	3.22	m		2	3
	3.46	m		2	1
	3.56	m		2	2’
	3.59	m		2	3’
	3.67	t	^{3}J 8.9	2	5
	3.83	t	^{3}J 8.3	2	6
	4.09	m		2	1’
	4.19	m		4	4’
	7.26	d	^{3}J 8.1	1	v
	7.41	d	^{3}J 8.1	1	vii
	7.61	t	^{3}J 8.1	1	vi
	7.80	dd	^{3}J 5.4 ^{3}J 8.1	1	ii
	8.58	d	^{3}J 8.1	1	iii
	9.08	d	^{3}J 5.1	1	i

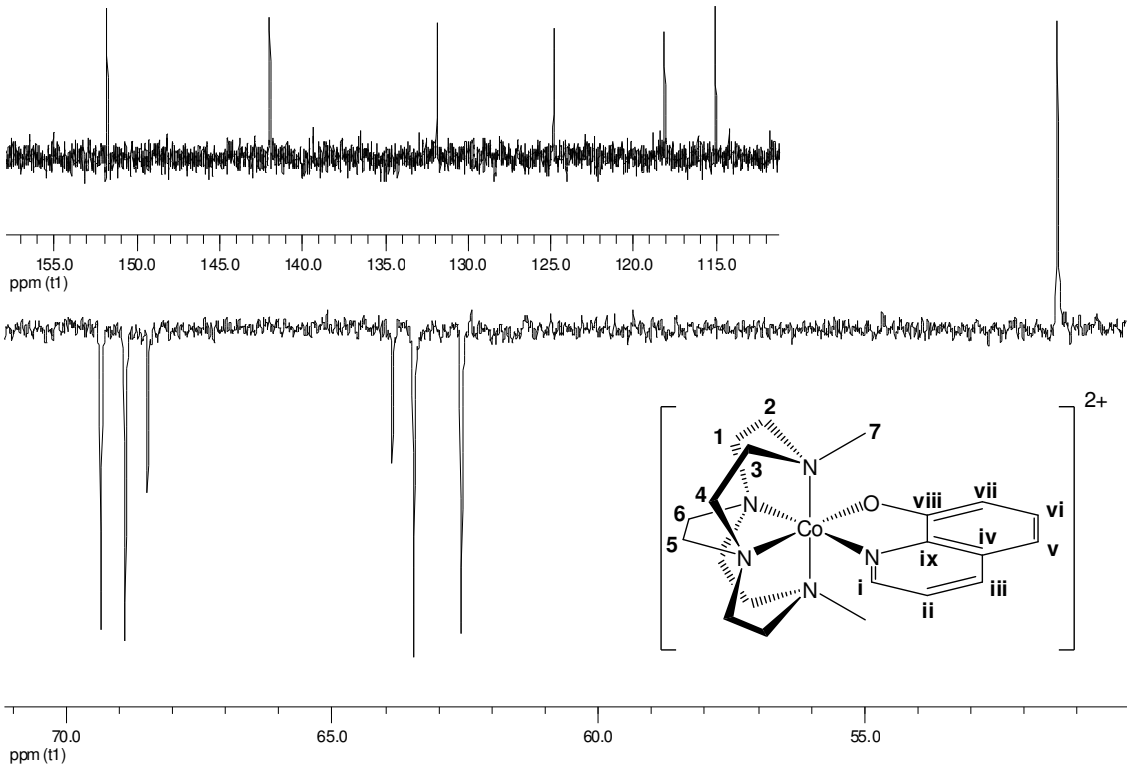
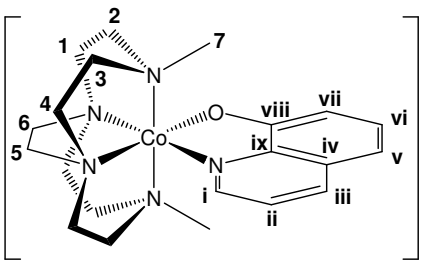

155.0
150.0
145.0
140.0
135.0
130.0
125.0
120.0
115.0
ppm (t1)
2+
1
2
3
4
5
6
7
N
O
Co
viii
vii
vi
v
iv
ix
i
ii
iii
70.0
65.0
60.0
55.0
ppm (t1)

Table S6. ^{13}C NMR assignments for **16** (CD_3CN, 75 MHz).

	δ (ppm)	Assignment
	51.4	7
	62.6	1
	63.5	4
	63.9	5
	68.5	6
	68.9	2
	69.3	3
	115.0	v
	118.1	vii
	124.8	ii
	131.6	iv
	131.9	vi
	142.0	iii
	145.9	ix
	151.8	i
	165.2	viii

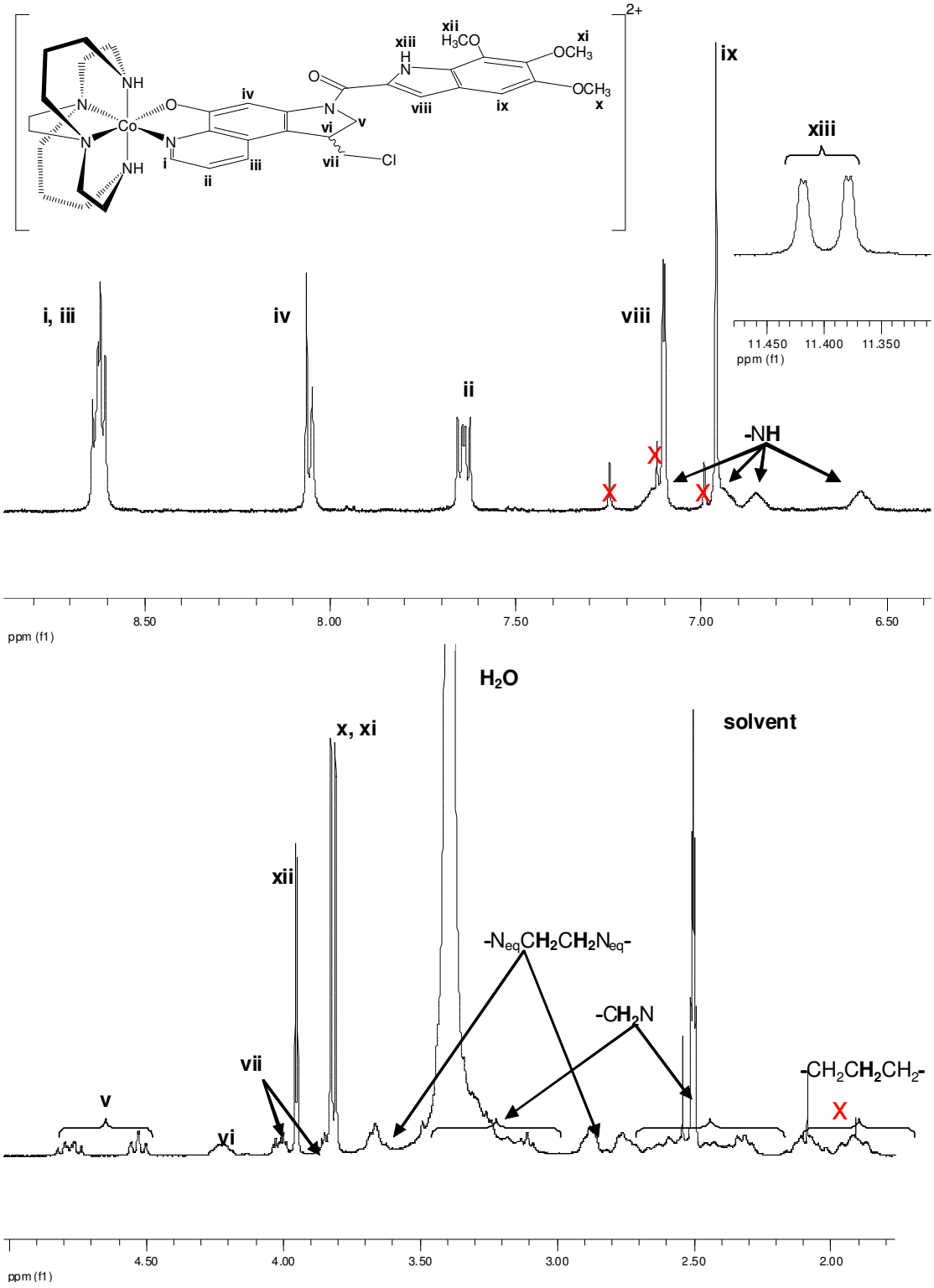
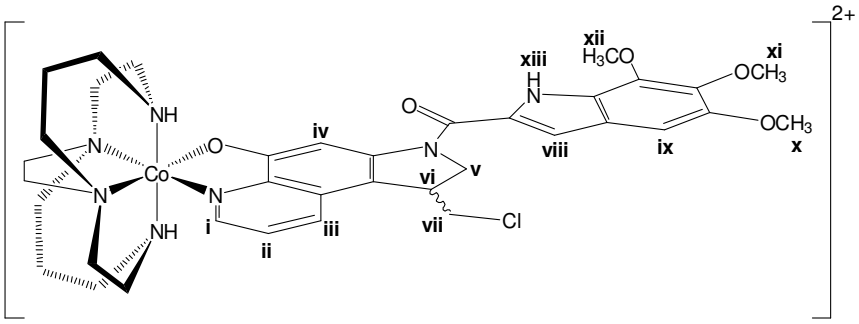


Figure S7. ^{1}H NMR spectrum of **9** (400 MHz, d_6-DMSO).

Table S7. ^{1}H NMR assignments for **9** (DMSO-d_6, 400 MHz).



Ancillary Ligand Signals				Cytotoxin Signals			
δ(ppm)	Multiplicity and *J*(Hz)	Integral	Assignment	δ(ppm)	Multiplicity and *J*(Hz)	Integral	Assignment
1.92	m	4	–C**H**$_2$–	3.81	s	6	xi
2.10	m	4	–C**H**$_2$–	3.83	s	6	x
2.33	m	4	–C**H**$_2$N	3.86	m	2	vii
2.44	m	4	–C**H**$_2$N	3.95	s	3	xii
2.61	m	4	–C**H**$_2$N	3.96	s	3	xii
2.77	m	4	bridge	4.02	m	2	vii
3.11	m	2	–C**H**$_2$N	4.23	m	2	vi
3.18 – 3.49	m	16	–C**H**$_2$N	4.53	td	^{4}J 2.0 ^{2}J 11.2	2	v
3.67	m	6	bridge –C**H**$_2$N	4.78	m	2	v
6.57	bs	1	–N**H**	6.96	s	2	ix
6.85	bs	1	–N**H**	7.09	s	1	viii
6.94	bs	1	–N**H**	7.10	s	1	viii
7.13	bs	1	–N**H**	7.64	dd	^{3}J 5.2 ^{3}J 8.0	2	ii
				8.05	s	1	iv
				8.06	s	1	iv
				8.62	m	4	i, iii
				11.38	d	^{4}J 2.0	1	xiii
				11.42	d	^{4}J 1.6	1	xiii

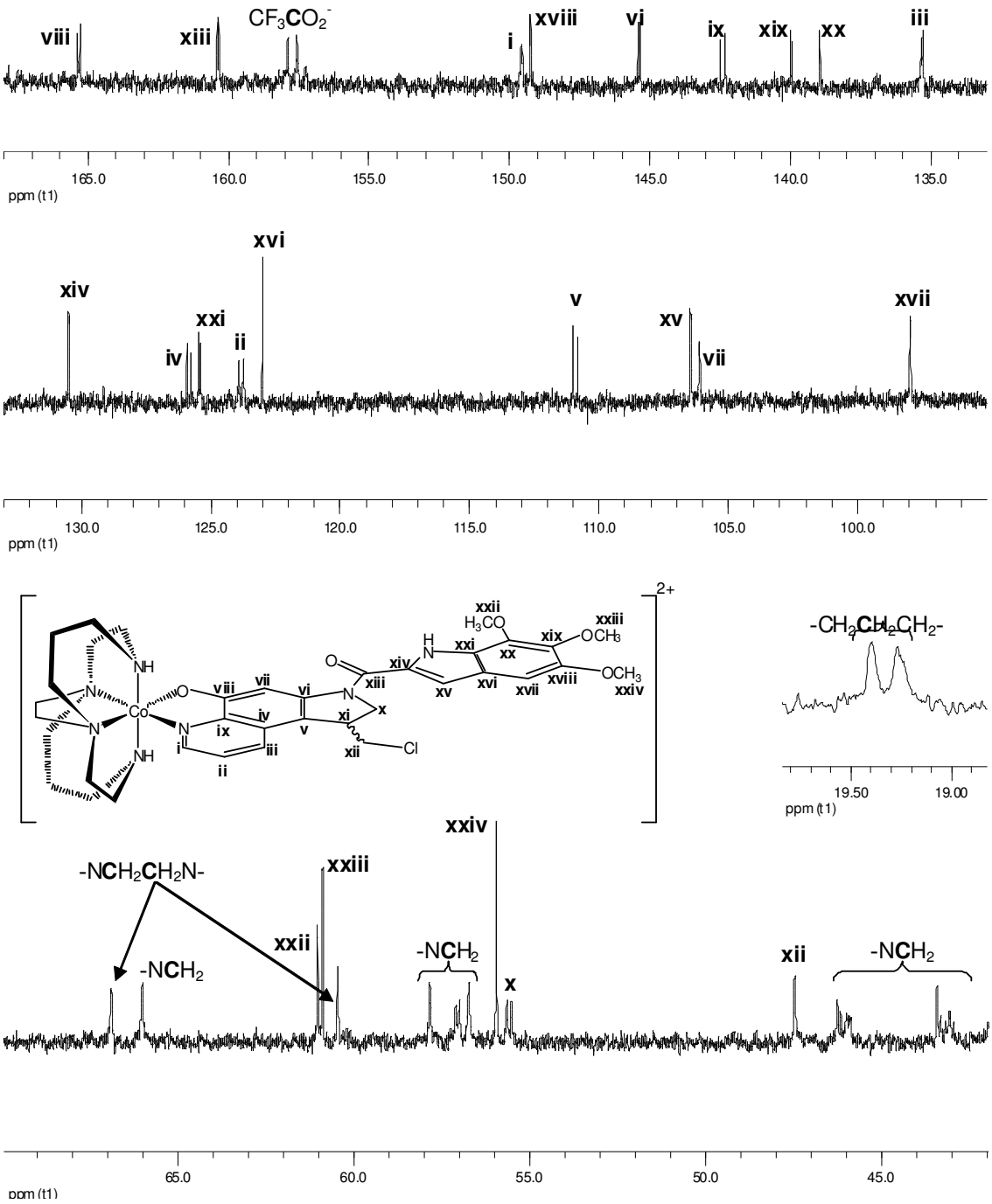
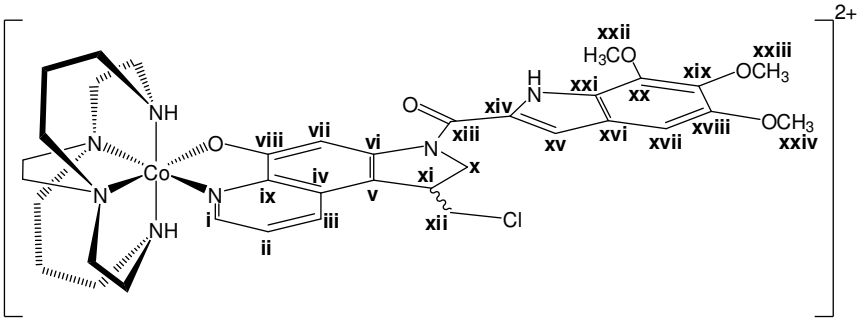

viii
xiii
CF3CO2-
i
xviii
vi
ix
xix
xx
iii
165.0
160.0
155.0
150.0
145.0
140.0
135.0
ppm (t1)
xiv
xvi
xxi
iv
ii
v
xv
vii
xvii
130.0
125.0
120.0
115.0
110.0
105.0
100.0
ppm (t1)
2+
-CH2CH2CH2-
19.50
19.00
ppm (t1)
-NCH2CH2N-
-NCH2
xxii
xxiii
xxiv
-NCH2
x
xii
-NCH2
65.0
60.0
55.0
50.0
45.0
ppm (t1)

Figure S8. ^{13}C NMR spectrum of **9** (100 MHz, d_6-DMSO).



δ (ppm)	Assignment	δ (ppm)	Assignment
19.3	-CH_2**C**H_2CH_2-	106.0/106.1	vii
19.4	-CH_2**C**H_2CH_2-	106.4/106.5	xv
40.1	xi	110.8/111.0	v
43.0	-**C**H_2N	123.0	xvi
43.3/43.4	-**C**H_2N	123.7/123.9	ii
45.8/45.9	-**C**H_2N	125.4/125.5	xxi
46.1/46.2	-**C**H_2N	125.8/125.9	iv
47.4	xii	130.5	xiv
55.5/55.6	x	135.2/135.3	iii
55.9	xxiv	138.9/139.0	xx
56.7	-**C**H_2N	139.9/140.0	xix
57.0/57.1	-**C**H_2N	142.3/142.5	ix
57.8	-**C**H_2N	145.3/145.4	vi
60.4	-N**C**H_2CH_2N-	149.2/149.3	xviii
60.9	xxiii	149.5/149.6	i
61.0	xxii	157.6/157.9 $^2J_{CF}$ = 32.3 Hz	CO of the TFA counter anion
66.0	-**C**H_2N	160.3/160.4	xiii
66.9	-N**C**H_2CH_2N-	165.3/165.4	viii
97.9/98.0	xvii		

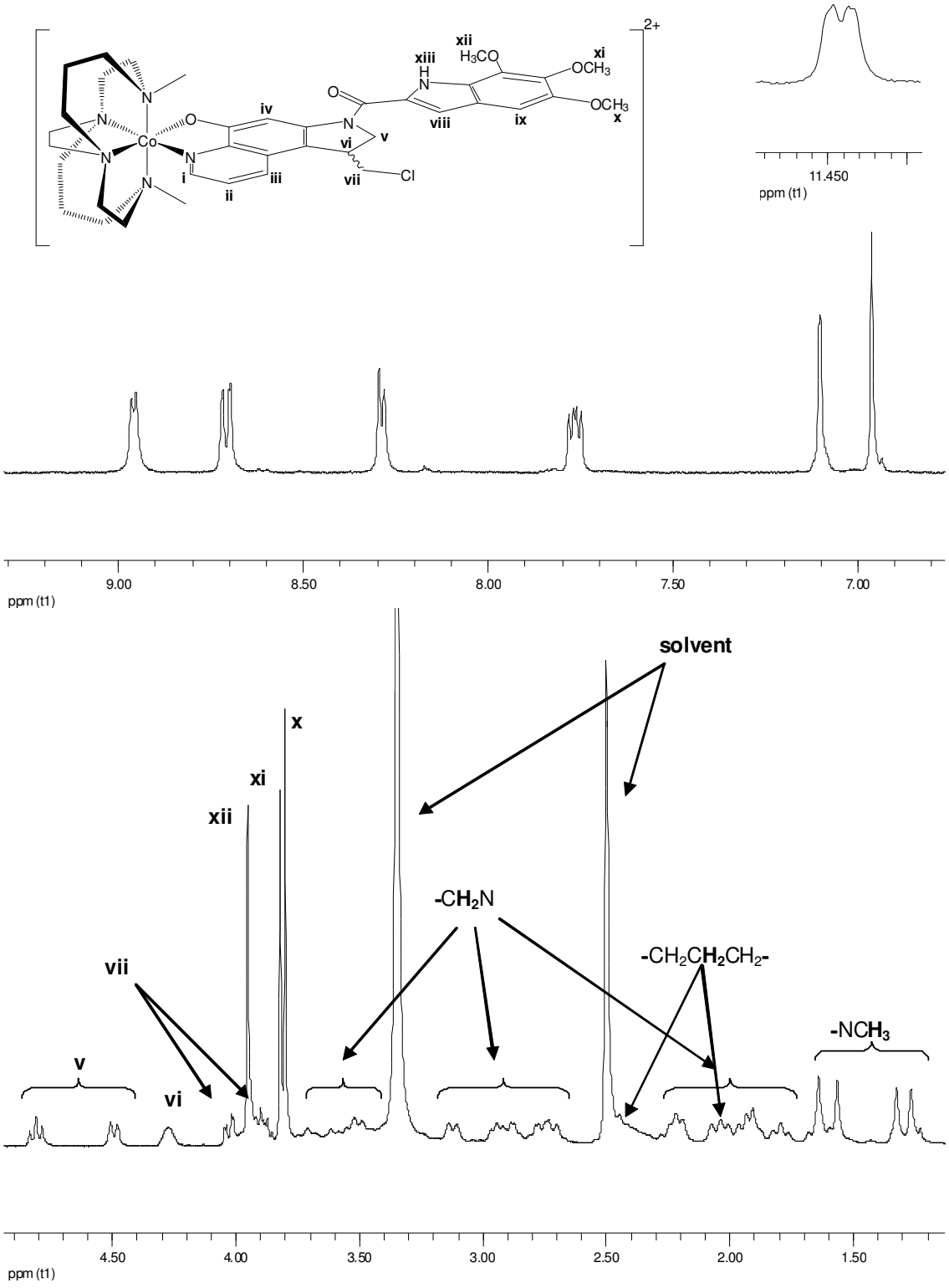
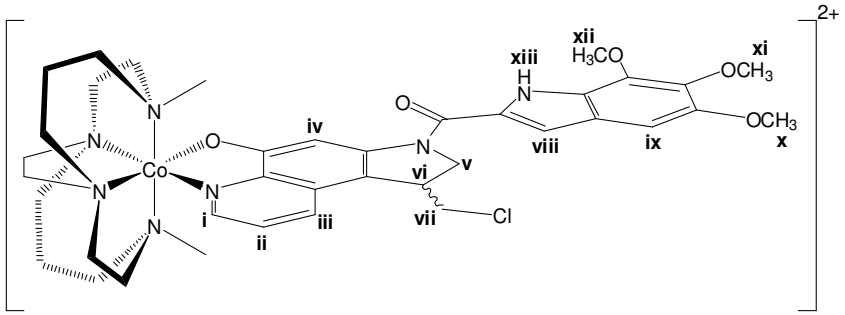
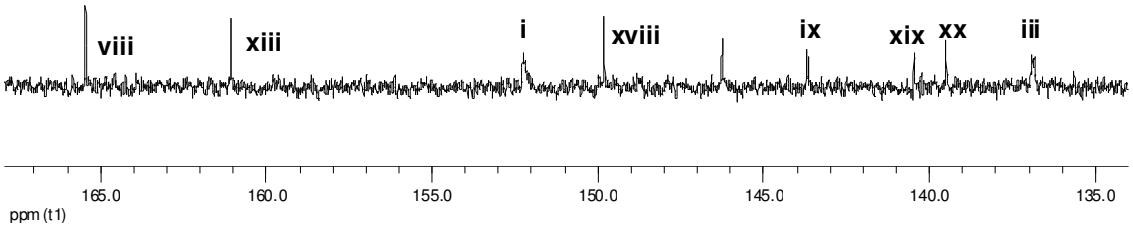


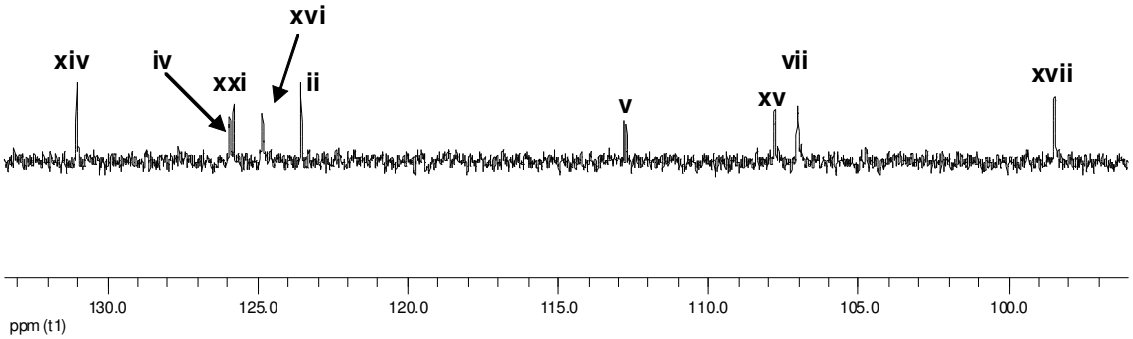
Figure S9. ^{1}H NMR spectrum of **10** (400 MHz, d_6-DMSO).

Table S9. ^{1}H NMR assignments for **10** (DMSO-d_6, 400 MHz).



Ancillary Ligand Signals				Cytotoxin Signals			
δ(ppm)	Multiplicity and *J*(Hz)	Integral	Assignment	δ(ppm)	Multiplicity and *J*(Hz)	Integral	Assignment
1.27	s	3	-NC**H**$_3$	3.80	s	6	x
1.33	s	3	-NC**H**$_3$	3.82	s	6	xi
1.57	s	3	-NC**H**$_3$	3.90	m	2	vii
1.64	s	3	-NC**H**$_3$	3.95	s	6	xii
1.80	m	3	-C**H**$_2$N	4.02	m	2	vii
1.93	m	6	-C**H**$_2$N	4.27	m	2	vi
2.04	m	4	-C**H**$_2$N	4.50	d ^{2}J 10.8	2	v
2.22	m	5	-C**H**$_2$N	4.81	t ^{3}J 9.2	2	v
2.45	m	6	-C**H**$_2$N	6.96	s	2	ix
2.73	m	6	-C**H**$_2$N	7.10	s	2	viii
2.92	m	5	-C**H**$_2$N	7.77	dd ^{3}J 5.2 ^{3}J 8.0	2	ii
3.13	m	3	-C**H**$_2$N	8.28 8.29	s	2	iv
3.52	m	5	-C**H**$_2$N	8.71	d ^{3}J 8.4	2	iii
3.60	m	2	-C**H**$_2$N	8.96	d ^{3}J 4.8	2	i
3.71	m	3	-C**H**$_2$N	11.44 11.45	s	2	xiii


viii
xiii
i
xviii
ix
xix
xx
iii
165.0
160.0
155.0
150.0
145.0
140.0
135.0
ppm (t1)


xiv
iv
xxi
xvi
ii
v
vii
xv
xvii
130.0
125.0
120.0
115.0
110.0
105.0
100.0
ppm (t1)

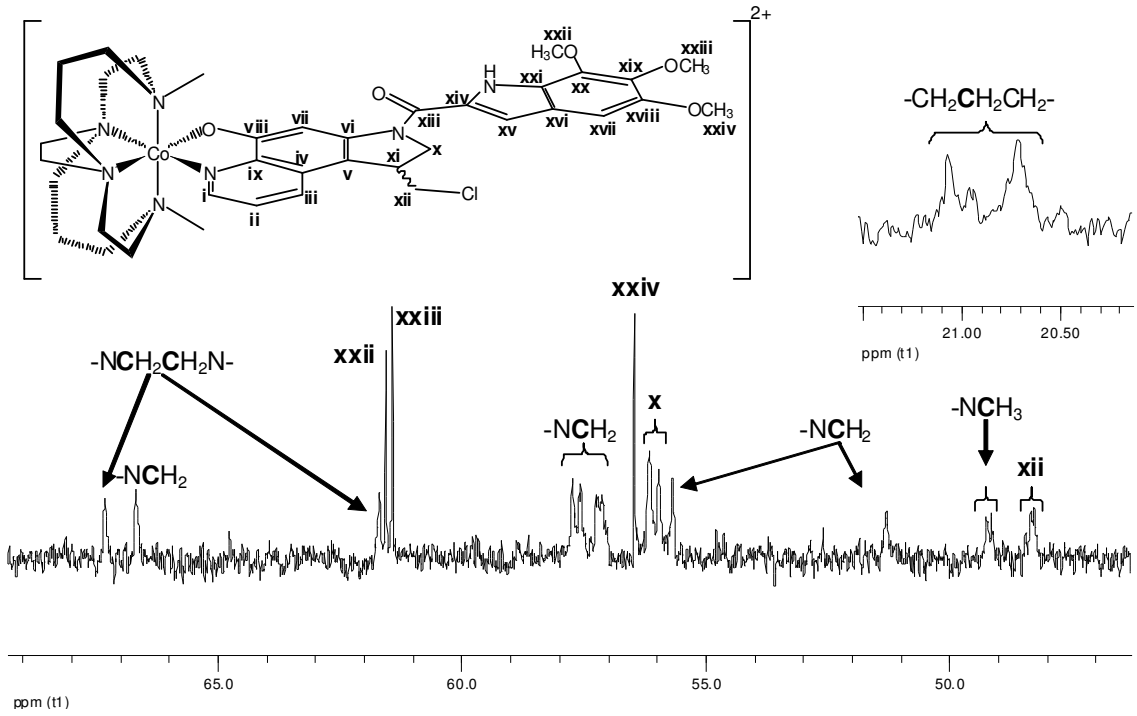
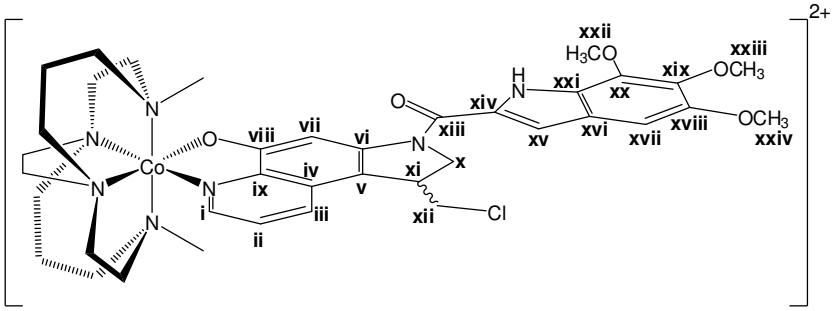
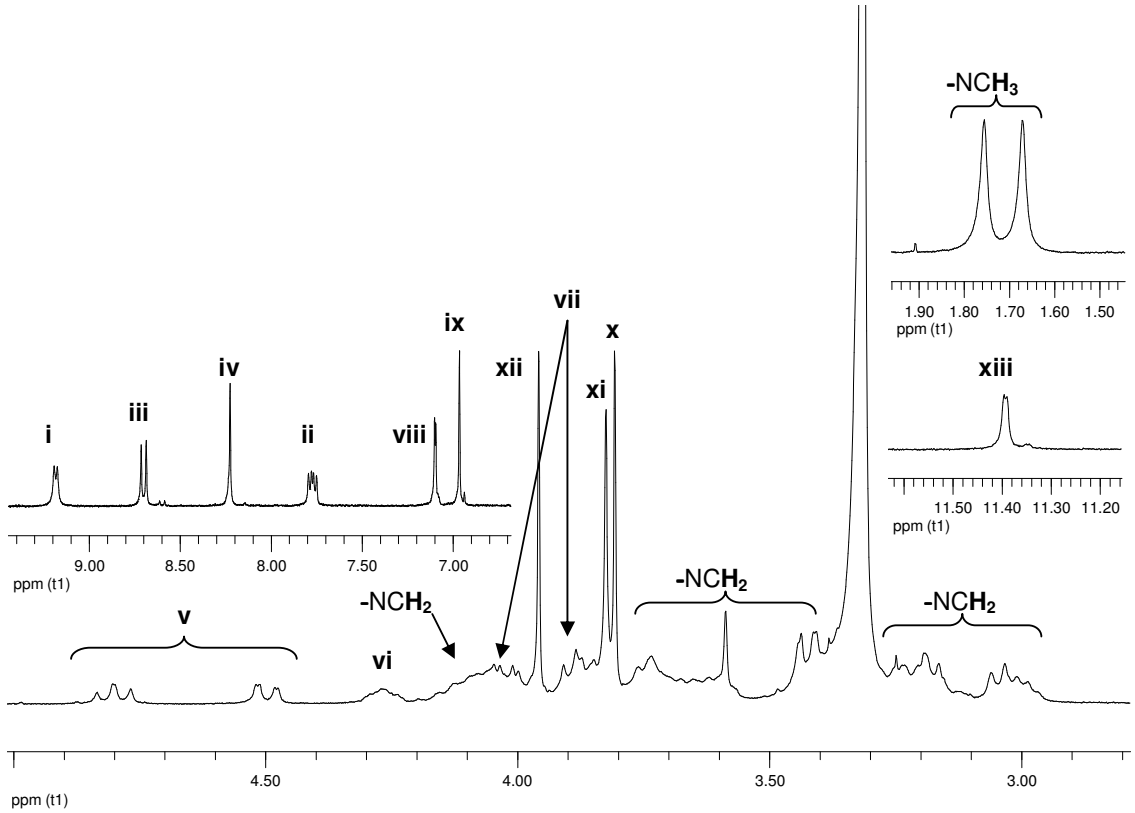

2+
xxii
H3CO
xxiii
xix
OCH3
xxi
xx
xiv
xviii
OCH3
xxiv
xv
xvi
xvii
xiii
viii
vii
vi
iv
xi
x
ix
v
i
iii
ii
xii
Cl
-CH2CH2CH2-
21.00
20.50
ppm (t1)
xxiv
xxiii
xxii
-NCH2CH2N-
-NCH2
x
-NCH2
-NCH2
-NCH3
xii
65.0
60.0
55.0
50.0
ppm (t1)

Figure S10. ^{13}C NMR spectrum of **10** (75 MHz, d_6-DMSO).

Table S10. ^{13}C NMR assignments for **10** (DMSO-d_6, 100 MHz).



δ (ppm)	Assignment	δ (ppm)	Assignment
20.1	-CH_2**C**H_2CH_2-	97.9	xvii
20.5	-CH_2**C**H_2CH_2-	106.5	vii
40.1	xi	107.2	xv
47.7/47.8	xii	112.1/112.2	v
48.6/48.7	-N**C**H_3	123.0	xvi
50.7	-N**C**H_3	124.3	ii
55.4/55.6	x	125.2	xxi
55.9	xxiv	125.3	iv
56.4	-N**C**H_2	130.4	xiv
56.5	-N**C**H_2	136.2/136.3	iii
56.6	-N**C**H_2	138.9	xx
56.7	-N**C**H_2	139.9	xix
57.0	-N**C**H_2	143.0/143.1	ix
57.2	-N**C**H_2	145.7	vi
60.8	xxiii	149.2	xviii
61.0	xxii	151.6/151.7	i
61.1	-N**C**H_2CH_2N-	160.5	xiii
66.1	-N**C**H_2	164.9	viii
66.7	-N**C**H_2CH_2N-		



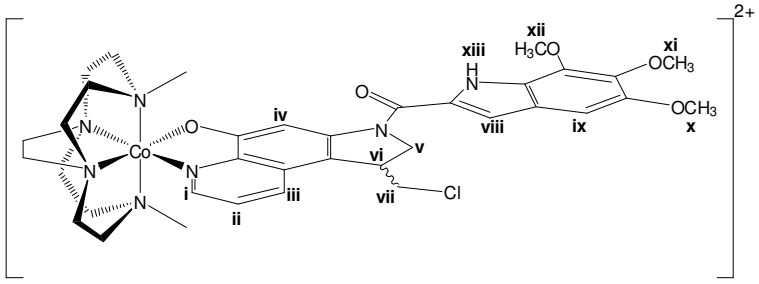
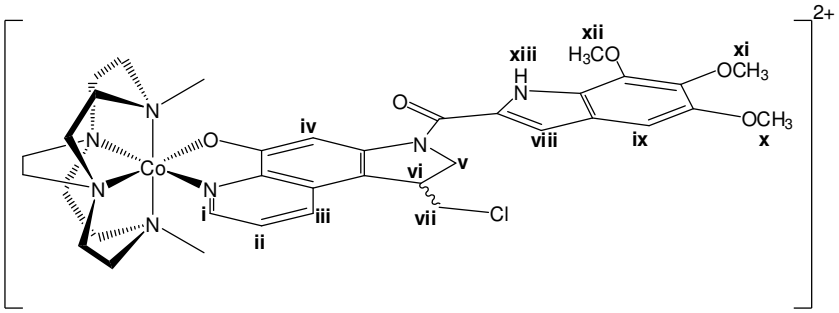


Figure S11. ^{1}H NMR spectrum of **8** (300 MHz, d_6-DMSO).

Table S11. ^{1}H NMR assignments for **8** (DMSO-d_6, 300 MHz)



Ancillary Ligand Signals				Cytotoxin Signals			
δ(ppm)	Multiplicity and *J*(Hz)	Integral	Assignment	δ(ppm)	Multiplicity and *J*(Hz)	Integral	Assignment
1.67	s	3	-C**H**$_3$	3.81	s	3	x
1.76	s	3	-C**H**$_3$	3.83	s	3	xi
3.01	m	1	-C**H**$_2$N	3.96	m	5	vii, xii
3.05	m	2	-C**H**$_2$N	4.27	bt	1	vi
3.24	m	3	-C**H**$_2$N	4.50	dd ^{3}J 1.8 ^{2}J 11.1	1	v
3.43	m	2	-C**H**$_2$N	4.80	t ^{2}J 10.8	1	v
3.59 – 3.68	m	5	-C**H**$_2$N	6.97	s	1	ix
3.85 – 3.91	m	2	-C**H**$_2$N	7.10	d ^{4}J 2.1	1	viii
4.00 – 4.16	m	5	-C**H**$_2$N	7.77	dd ^{3}J 4.8 ^{3}J 8.4	1	ii
				8.23	s	1	iv
				8.71	d ^{3}J 8.4	1	iii
				9.19	d ^{3}J 5.1	1	i
				11.39	bs	1	xiii

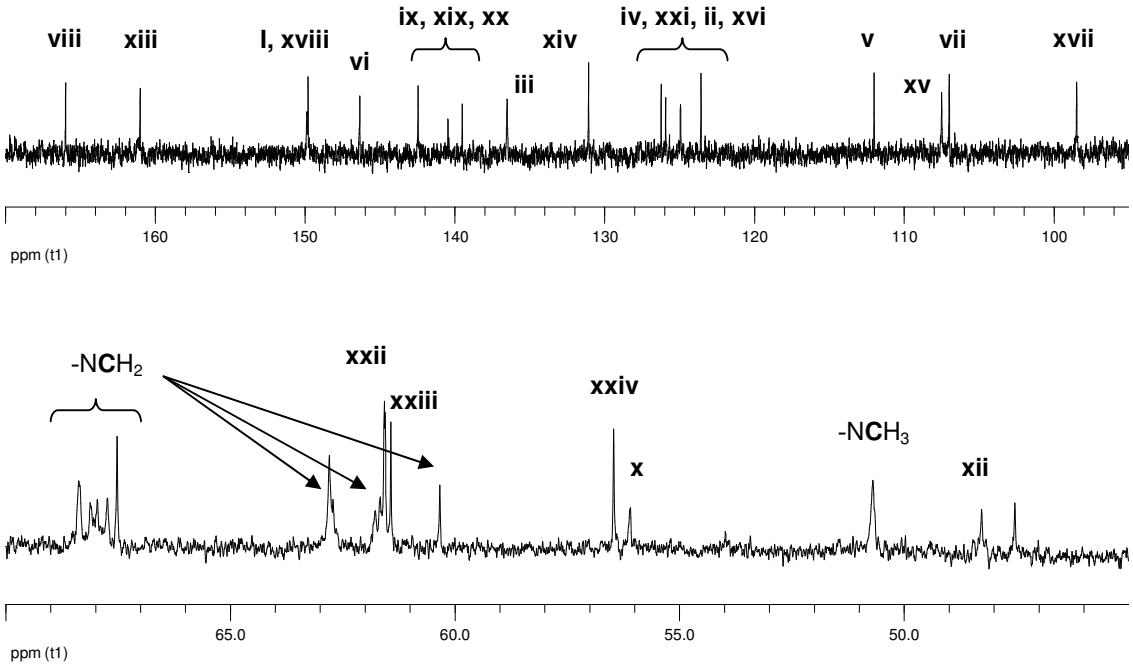
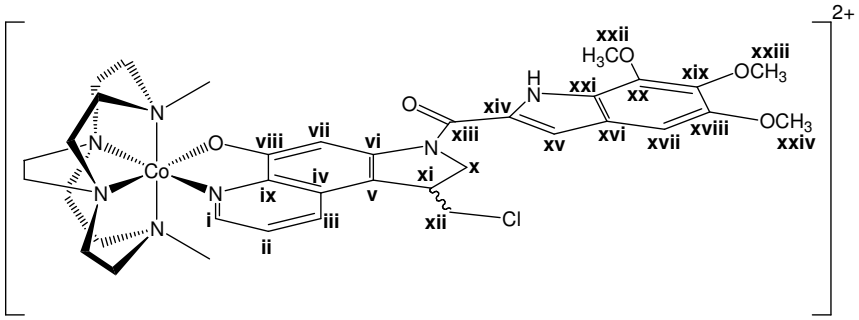


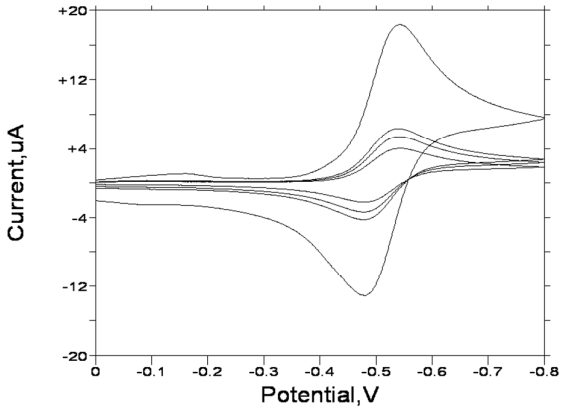
Figure S12. ^{13}**C** NMR spectrum of **8** (75 MHz, d_6-DMSO).

Table S12. ^{13}C NMR assignments for **8** (DMSO-d_6, 75 MHz).

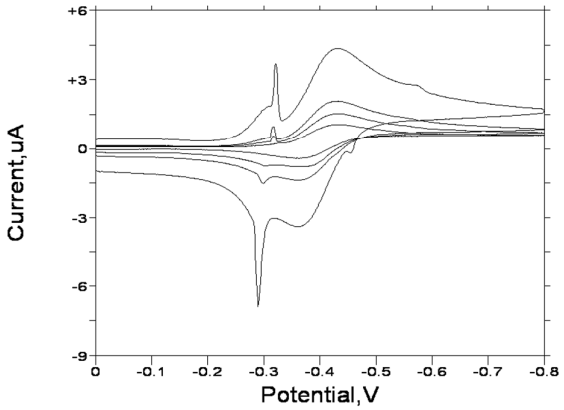


δ (ppm)	Assignment	δ (ppm)	Assignment
40.5	xi	107.0	vii
48.3	xii	107.5	xv
50.7	–N**C**H_3	112.0	v
56.1	x	123.6	xvi
56.5	xxiv	124.9	ii
60.3	–N**C**H_2	125.9	xxi
61.4	xxiii	126.2	iv
61.6	xxii	131.1	xiv
61.7	–N**C**H_2	136.5	iii
61.8	–N**C**H_2	139.5	xx
62.8	–N**C**H_2	140.5	xix
67.5	–N**C**H_2	142.5	ix
67.7	–N**C**H_2	146.4	vi
68.0	–N**C**H_2	149.8	xviii
68.1	–N**C**H_2	149.9	i
68.4	–N**C**H_2	161.0	xiii
98.5	xvii	166.0	viii

(A) **21**



(B) **16**



(C) **15**

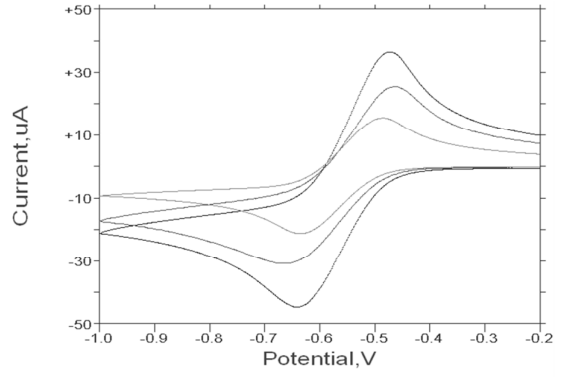


Figure S13. Cyclic voltammograms of **21** (A), **16** (B) and **15** (C) at different scan rates. Potentials were measured against an Ag/AgCl reference electrode in an 0.1 mol L^{-1} $NaNO_3$ electrolyte solution; scan rates (A), (B) 20, 50, 100 and 500 mV sec^{-1}; scan rates (C) 50, 100 and 300 mV sec^{-1}**;** spikes in the CV in B are an instrument artefact.

Table S13. Crystal data and structure refinement for **21, 16** and **14a**

	21	**16**	**14a**
Empirical formula	$C_{21}H_{32}Cl_2CoN_5O_9$	$C_{21}H_{32}Cl_2CoN_5O1_{0.5}$	$C1_5H_{30}CoF_9N_4O_{11}S_3$
Formula weight	628.35	652.35	768.54
Temperature / K	90(2)	83(2)	83(2)
Wavelength / Å	0.71073	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	P 21 21 21	P2/c	P21/c
A / Å	a = 10.1242(2)	a = 15.1203(2)	a = 9.6800(2)
B / Å	b = 12.8813(2)	b = 11.6196(1)	b = 13.0346(2)
C / Å	c = 19.6988(3)	c = 15.3173(1)	c = 22.5653(2)
a / deg	90	90	90
b / deg	90	97.984(1)	94.003(1)
g / deg	90	90	90
Volume / $Å^3$	2568.98(8)	2665.04(5)	2840.23(8)
Z	4	4	4
Density (calculated) / mg m^{-3}	1.625	1.626	1.797
Absorption coefficient / mm^{-1}	0.937	0.911	0.943
F(000)	1304	1352	1568
Crystal size / mm^3	0.34 x 0.18 x 0.16	0.22 x 0.18 x 0.10	0.32 x 0.30 x 0.26
Theta range for data collection / deg	1.89 to 25.20	1.36 to 26.70	1.81 to 26.36
Index ranges	-12<=h<=12, 0<=k<=15, 0<=l<=23	-19<=h<=18, 0<=k<=14, 0<=l<=18	-12<=h<=12, 0<=k<=16, 0<=l<=28
Reflections collected	14203	15923	16965
Independent reflections	4625 [R(int) = 0.0213]	5422 [R(int) = 0.0287]	5767 [R(int) = 0.0174]
Completeness to theta = 25.20°	99.8 %	96.0 %	99.5 %
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.8645 and 0.7412	0.9152 and 0.7995	0.8136 and 0.6710
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	4625 / 0 / 343	5422 / 0 / 355	5767 / 0 / 404
Goodness-of-fit on F^2	1.046	1.059	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0276, wR2 = 0.0721	R1 = 0.0507, wR2 = 0.1069	R1 = 0.0488, wR2 = 0.1289
R indices (all data)	R1 = 0.0295, wR2 = 0.0732	R1 = 0.0657, wR2 = 0.1150	R1 = 0.0534, wR2 = 0.1332
Absolute structure parameter	0.010(12)		
Largest diff. peak and hole / e $Å^{-3}$	0.692 and -0.394	1.313 and -0.854	1.615 and -0.585