Supporting Information

From Imide to Lactam Metallo-Pyridocarbazoles: Distinct Scaffolds for the Design of Selective Protein Kinase Inhibitors

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Content

A) Screening of 1-3 (racemic) and (R_{Ru})-21 Against Human Protein Kinase Panel

Millipore KinaseProfiler: Remaining kinase activities in percent at a single concentration of **1** (100 nM), **2** (100 nM), **3** (30 nM), and (R_{Ru})-**21** (100 nM) at 10 μM ATP. Measurements were performed in duplicate and the average taken. Activities below 20% are highlighted in yellow; n.d. = not determined.

	3 @ 30 nM	**1** @ 100 nM	**2** @ 100 nM	(R_{Ru})-**21** @ 100nM
Abl(h)	95	102	107	95
Abl (H396P) (h)	100	99	98	n.d.
Abl (M351T)(h)	100	100	98	n.d.
Abl (Q252H) (h)	91	98	96	n.d.
Abl(T315I)(h)	108	110	108	n.d.
Abl(Y253F)(h)	104	108	96	n.d.
ACK1(h)	35	10	25	43
ALK(h)	61	37	81	108
ALK4(h)	118	121	128	91
Arg(h)	102	88	98	87
ARK5(h)	89	31	56	95
ASK1(h)	109	104	108	119
Aurora-A(h)	112	119	118	55
Aurora-B(h)	n.d.	n.d.	n.d.	94
Axl(h)	86	92	72	78
Bmx(h)	97	94	99	51
BRK(h)	110	112	100	102
BrSK1(h)	97	99	86	109
BrSK2(h)	82	100	87	88
BTK(h)	77	59	79	44
BTK(R28H)(h)	125	110	109	n.d.
CaMKI(h)	104	100	113	104
CaMKIIβ(h)	65	36	70	106
CaMKIIγ(h)	14	6	64	97
CaMKIδ(h)	95	104	104	112
CaMKIIδ(h)	20	5	73	100
CaMKIV(h)	77	81	66	100
CDK1/cyclinB(h)	74	105	89	95
CDK2/cyclinA(h)	75	108	97	74
CDK2/cyclinE(h)	36	86	87	58
CDK3/cyclinE(h)	90	115	82	103
CDK5/p25(h)	51	96	54	74
CDK5/p35(h)	57	95	50	89
CDK6/cyclinD3(h)	n.d.	n.d.	n.d.	94
CDK7/cyclinH/MAT1(h)	109	113	99	102
CDK9/cyclin T1(h)	32	47	35	22
CHK1(h)	95	116	90	97
CHK2(h)	88	87	70	95
CHK2(I157T)(h)	91	91	68	n.d.
CHK2(R145W)(h)	94	94	68	n.d.
CK1γ1(h)	61	99	44	94
CK1γ2(h)	38	100	28	76

CK1γ3(h)	59	114	17	104
CK1δ(h)	33	100	14	99
CK2(h)	110	111	105	106
CK2α2(h)	115	109	109	110
CLK2(h)	4	26	1	50
CLK3(h)	105	100	86	100
cKit(h)	108	112	113	100
cKit(D816V)(h)	104	106	106	n.d.
cKit(D816H)(h)	42	84	69	n.d.
cKit(V560G)(h)	69	76	91	n.d.
cKit(V654A)(h)	67	93	101	n.d.
CSK(h)	118	110	121	99
c-RAF(h)	100	100	92	89
cSRC(h)	74	62	94	68
DAPK1(h)	55	70	69	102
DAPK2(h)	46	92	81	89
DCAMKL2(h)	95	105	104	0
DDR2(h)	93	96	86	116
DMPK(h)	115	110	113	99
DRAK1(h)	88	89	94	113
DYRK2(h)	89	108	42	112
eEF-2K(h)	106	110	106	110
EGFR(h)	115	119	113	91
EGFR(L858R)(h)	66	100	49	n.d.
EGFR(L861Q)(h)	97	101	84	n.d.
EGFR(T790M)(h)	54	92	26	n.d.
EGFR(T790M,L858R)(h)	19	56	6	n.d.
EphA1(h)	104	95	103	102
EphA2(h)	99	105	99	99
EphA3(h)	110	110	117	105
EphA4(h)	112	109	110	113
EphA5(h)	135	135	129	99
EphA7(h)	113	118	101	92
EphA8(h)	133	127	114	109
EphB2(h)	110	100	106	103
EphB1(h)	110	120	90	77
EphB3(h)	114	107	95	73
EphB4(h)	107	116	120	108
ErbB4(h)	106	120	103	95
FAK(h)	110	70	101	102
Fer(h)	88	92	83	72
Fes(h)	92	100	94	91
FGFR1(h)	101	119	105	56
FGFR1(V561M)(h)	107	84	117	n.d.
FGFR2(h)	95	112	127	94
FGFR2(N549H)(h)	80	97	102	n.d.
FGFR3(h)	94	96	96	105
FGFR4(h)	103	110	105	107
Fgr(h)	81	67	92	73
Flt1(h)	28	46	37	63
Flt3(D835Y)(h)	4	1	13	n.d.
Flt3(h)	18	10	27	29

Flt4(h)	41	23	36	32
Fms(h)	60	61	90	100
Fyn(h)	60	45	89	64
GCK(h)	90	73	57	73
GRK5(h)	106	100	107	113
GRK6(h)	100	109	94	121
GRK7(h)	98	100	46	93
GSK3α(h)	0	70	42	36
GSK3β(h)	7	86	59	61
Haspin(h)	27	12	7	69
Hck(h)	60	50	79	63
Hck(h), activated	n.d.	n.d.	n.d.	65
HIPK1(h)	14	82	12	84
HIPK2(h)	8	61	6	69
HIPK3(h)	13	82	6	100
IGF-1R(h)	85	83	96	92
IGF-1R(h), activated	102	100	105	92
IKKα(h)	109	113	109	97
IKKβ(h)	86	94	83	111
IR(h)	102	96	100	99
IR(h), activated	103	97	104	91
IRR(h)	66	96	37	86
IRAK1(h)	93	90	81	98
IRAK4(h)	72	72	25	40
Itk(h)	84	82	80	32
JAK2(h)	85	28	60	70
JAK3(h)	79	65	69	76
JNK1α1(h)	107	105	105	111
JNK2α2(h)	100	95	100	99
JNK3(h)	103	90	100	115
KDR(h)	73	67	47	86
Lck(h)	90	77	88	90
Lck(h), activated	n.d.	n.d.	n.d.	105
LIMK1(h)	95	99	71	95
LKB1(h)	103	102	102	108
LOK(h)	84	74	45	81
Lyn(h)	33	34	89	60
MAPK1(h)	100	115	98	105
MAPK2(h)	110	108	109	95
MAPKAP-K2(h)	110	107	105	106
MAPKAP-K3(h)	109	111	114	104
MEK1(h)	103	104	96	71
MARK1(h)	59	81	85	51
MELK(h)	29	43	6	70
Mer(h)	24	53	30	58
Met(h)	112	113	101	99
MINK(h)	68	57	52	41
MKK6(h)	114	114	121	94
MKK7β(h)	72	65	70	96
MLCK(h)	5	4	6	26
MLK1(h)	57	31	26	20
Mnk2(h)	92	93	89	98

MRCKα(h)	110	106	97	100
MRCKβ(h)	94	95	106	103
MSK1(h)	83	87	73	126
MSK2(h)	75	102	69	102
MSSK1(h)	105	107	106	117
MST1(h)	63	50	50	31
MST2(h)	52	43	20	26
MST3(h)	40	103	204	81
mTOR(h)	102	85	96	113
mTOR/FKBP12(h)	111	104	96	103
MuSK(h)	107	106	117	105
NEK2(h)	95	98	100	57
NEK3(h)	94	95	97	97
NEK6(h)	104	110	104	111
NEK7(h)	99	100	93	105
NEK11(h)	6	18	45	69
NLK(h)	97	94	87	43
p70S6K(h)	81	105	67	100
PAK2(h)	95	98	85	70
PAK3(h)	118	99	93	51
PAK4(h)	82	85	85	52
PAK5(h)	44	69	68	29
PAK6(h)	69	90	81	58
PAR-1Bα(h)	33	47	66	55
PASK(h)	39	117	15	103
PDGFRα(h)	107	98	110	106
PDGFRα(D842V)(h)	21	67	41	n.d.
PDGFRα(V561D)(h)	40	56	53	n.d.
PDGFRβ(h)	108	105	104	113
PDK1(h)	87	98	74	101
PhKγ2(h)	112	85	58	100
Pim-1(h)	1	6	2	20
Pim-2(h)	-1	27	8	84
Pim-3(h)	20	92	64	85
PKA(h)	83	96	74	83
PKBα(h)	90	101	84	116
PKBβ(h)	103	101	97	110
PKBγ(h)	83	110	93	95
PKCα(h)	109	111	101	96
PKCβI(h)	65	101	48	99
PKCβII(h)	89	89	97	100
PKCγ(h)	105	102	100	102
PKCδ(h)	98	101	95	94
PKCε(h)	88	96	87	100
PKCη(h)	89	113	108	108
PKCι(h)	98	87	100	98
PKCμ(h)	111	107	101	98
PKCθ(h)	32	87	52	111
PKCζ(h)	111	113	109	100
PKD2(h)	106	102	101	102
PKG1α(h)	30	50	3	88
PKG1β(h)	29	54	2	85

Plk1(h)	104	102	88	90
Plk3(h)	105	109	105	99
PRAK(h)	83	85	80	76
PRK2(h)	50	48	30	16
PrKX(h)	68	84	32	103
PTK5(h)	84	75	72	78
Pyk2(h)	79	76	51	95
Ret(h)	38	38	42	12
Ret (V804L)(h)	65	50	36	n.d.
Ret(V804M)(h)	43	19	21	n.d.
RIPK2(h)	92	93	86	85
ROCK-I(h)	103	111	105	75
ROCK-II(h)	102	86	64	61
Ron(h)	103	114	101	114
Ros(h)	107	102	97	105
Rse(h)	39	37	90	128
Rsk1(h)	14	80	9	21
Rsk2(h)	40	81	40	37
Rsk3(h)	30	97	41	28
Rsk4(h)	21	81	15	27
SAPK2a(h)	118	113	110	96
SAPK2a(T106M)(h)	110	108	104	n.d.
SAPK2b(h)	105	100	101	107
SAPK3(h)	120	112	93	102
SAPK4(h)	105	104	73	102
SGK(h)	86	96	84	102
SGK2(h)	100	108	91	103
SGK3(h)	96	108	93	107
SIK(h)	48	38	94	98
Snk(h)	103	108	92	111
Src(1-530)(h)	65	55	102	n.d.
Src(T341M)(h)	71	53	76	n.d.
SRPK1(h)	107	99	105	113
SRPK2(h)	122	107	104	102
STK33(h)	98	76	64	93
Syk(h)	99	105	90	67
TAK1(h)	110	111	106	93
TAO1(h)	92	101	43	84
TAO2(h)	82	96	72	92
TAO3(h)	83	102	49	80
TBK1(h)	79	88	67	99
Tec(h) activated	55	36	90	20
Tie2(h)	97	116	103	39
Tie2(R849W)(h)	103	87	87	n.d.
Tie2(Y897S)(h)	112	99	92	n.d.
TLK2(h)	114	108	108	103
TrkA(h)	22	5	5	4
TrkB(h)	54	9	16	2
TSSK1(h)	93	86	72	93
TSSK2(h)	97	102	96	110
Txk(h)	57	34	73	16
ULK2(h)	103	101	100	106

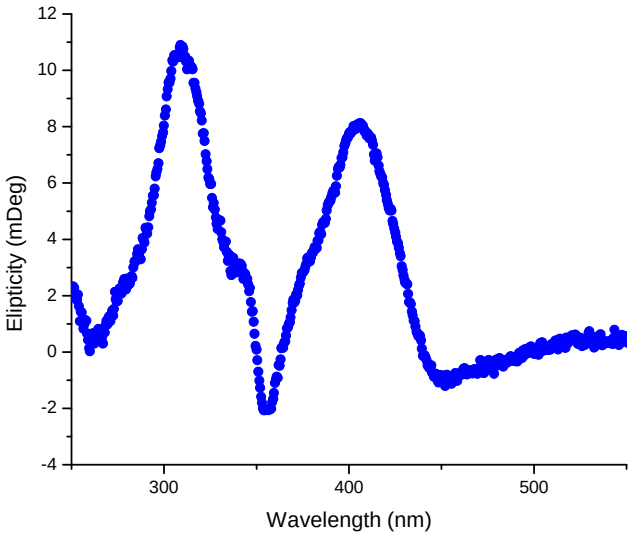
ULK3(h)	106	106	114	93
WNK2(h)	79	92	84	91
WNK3(h)	95	94	99	98
VRK2(h)	99	110	96	109
Yes(h)	71	75	102	68
ZAP-70(h)	129	122	130	111
ZIPK(h)	52	87	77	126

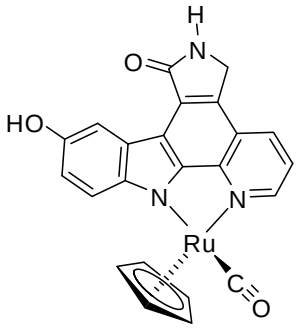
B) Assignment of the Absolute Configurations of (R_{Ru})-1, (S_{Ru})-1, (R_{Ru})-2, (S_{Ru})-2, (R_{Ru})-21, and (S_{Ru})-21

All compounds were measured at a concentration of 1 mM in DMSO. The CD-spectra of the pure enantiomers were compared with reference half sandwich compounds. See for example:

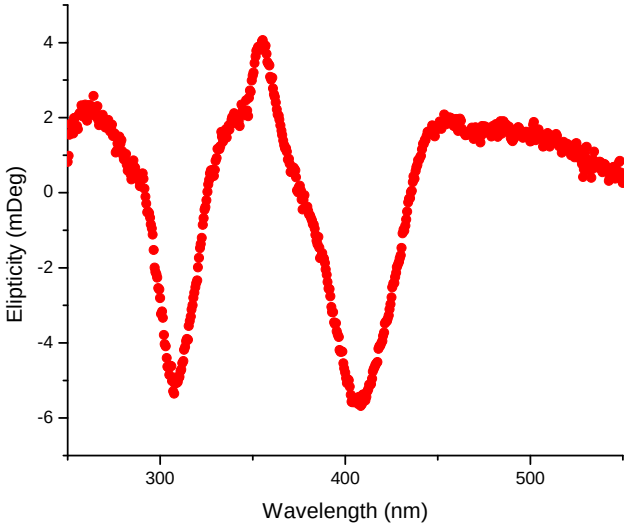
1.) J. É. Debreczeni, A. N. Bullock, G. E. Atilla, D. S. Williams, H. Bregman, S. Knapp, E. Meggers, *Angew. Chem. Int. Ed.* **2006**, *45*, 1580-1585.

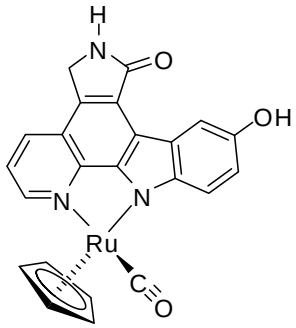
2.) G. E. Atilla, D. S. Williams, H. Bregman, N. Pagano, E. Meggers, *ChemBioChem* **2006**, 1443-1450.



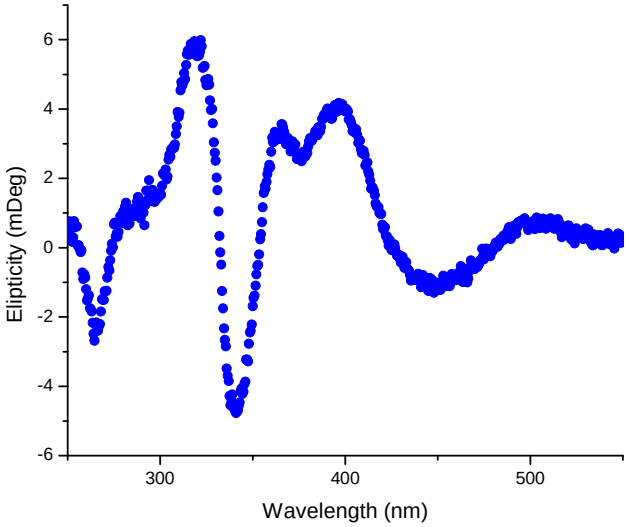


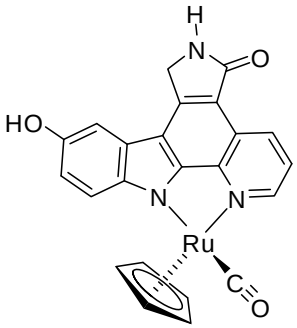
(R_{Ru})-**1**



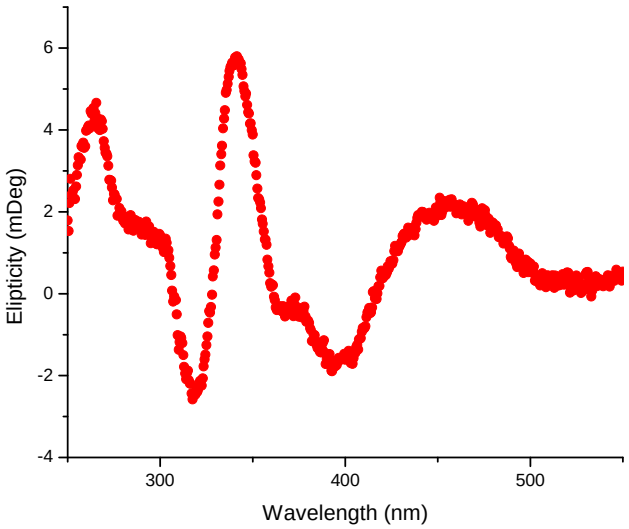


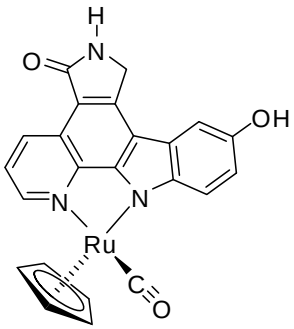
(S_{Ru})-**1**


Elipticity (mDeg)
Wavelength (nm)
6
4
2
0
-2
-4
-6
300
400
500

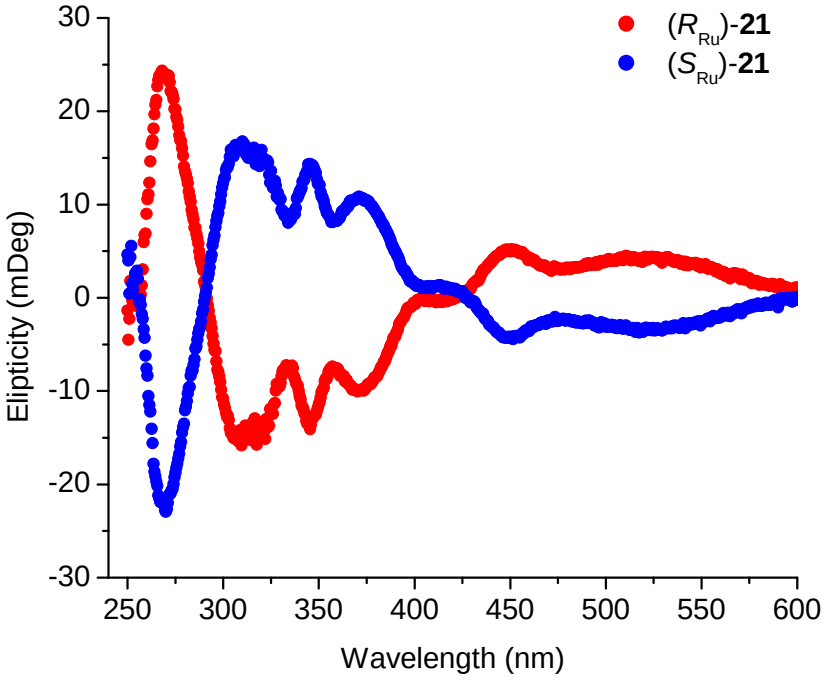

H
N
O
HO
N
N
Ru
C
O

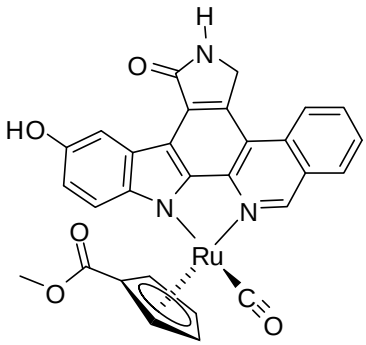
(R_{Ru})-**2**


Elipticity (mDeg)
Wavelength (nm)
6
4
2
0
-2
-4
300
400
500

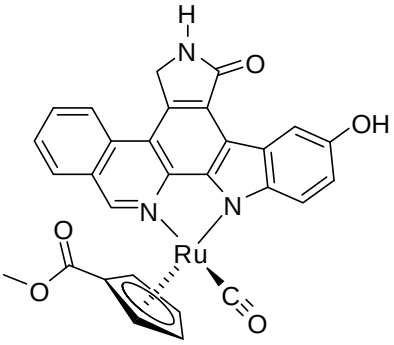

H
N
O
OH
N
N
Ru
C
O

(S_{Ru})-**2**


(R_Ru)-21
(S_Ru)-21
Elipticity (mDeg)
Wavelength (nm)
30
20
10
0
-10
-20
-30
250
300
350
400
450
500
550
600

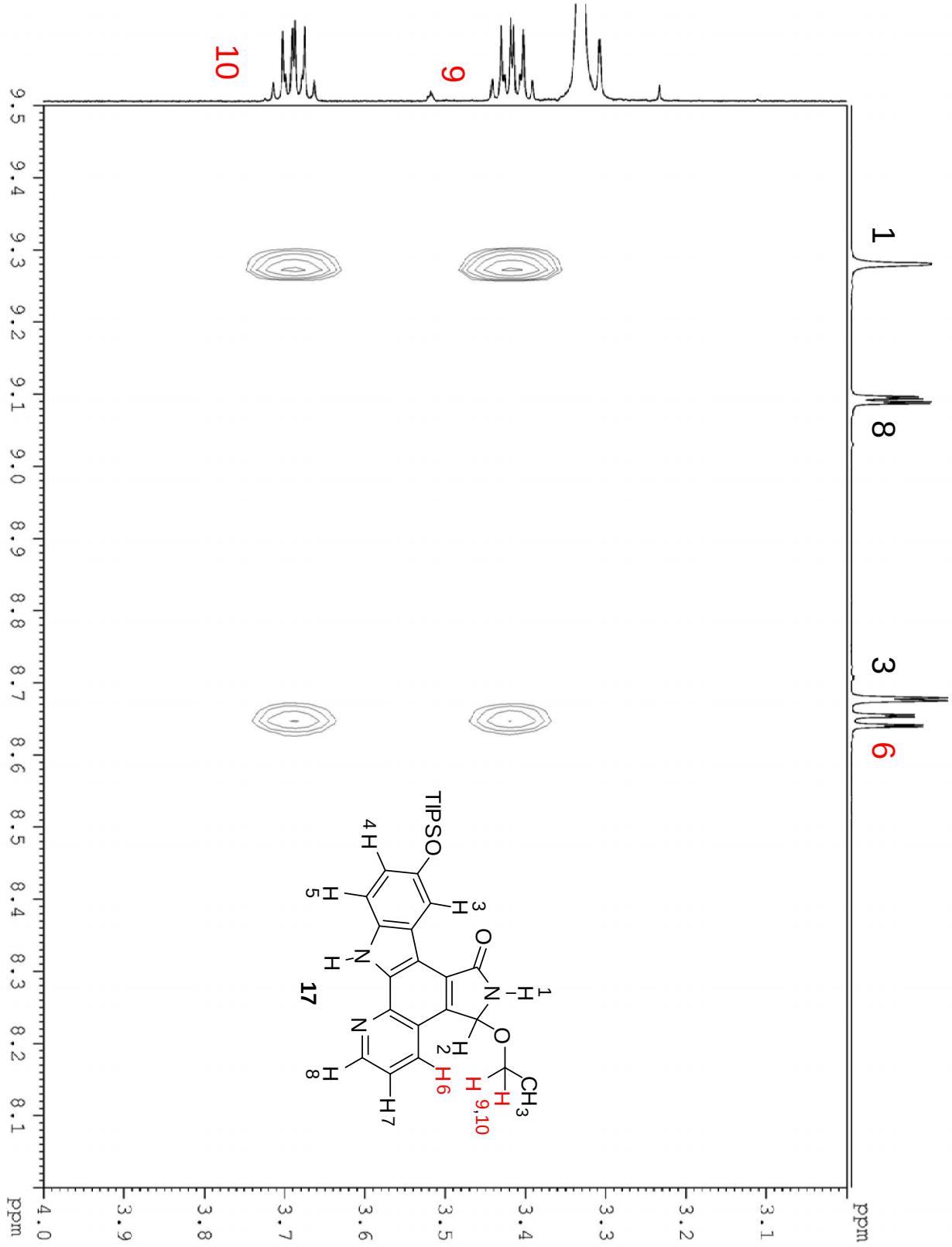

H
N
O
HO
N
N
Ru
O
O
C
O

(*R*$_{Ru}$)-**21**

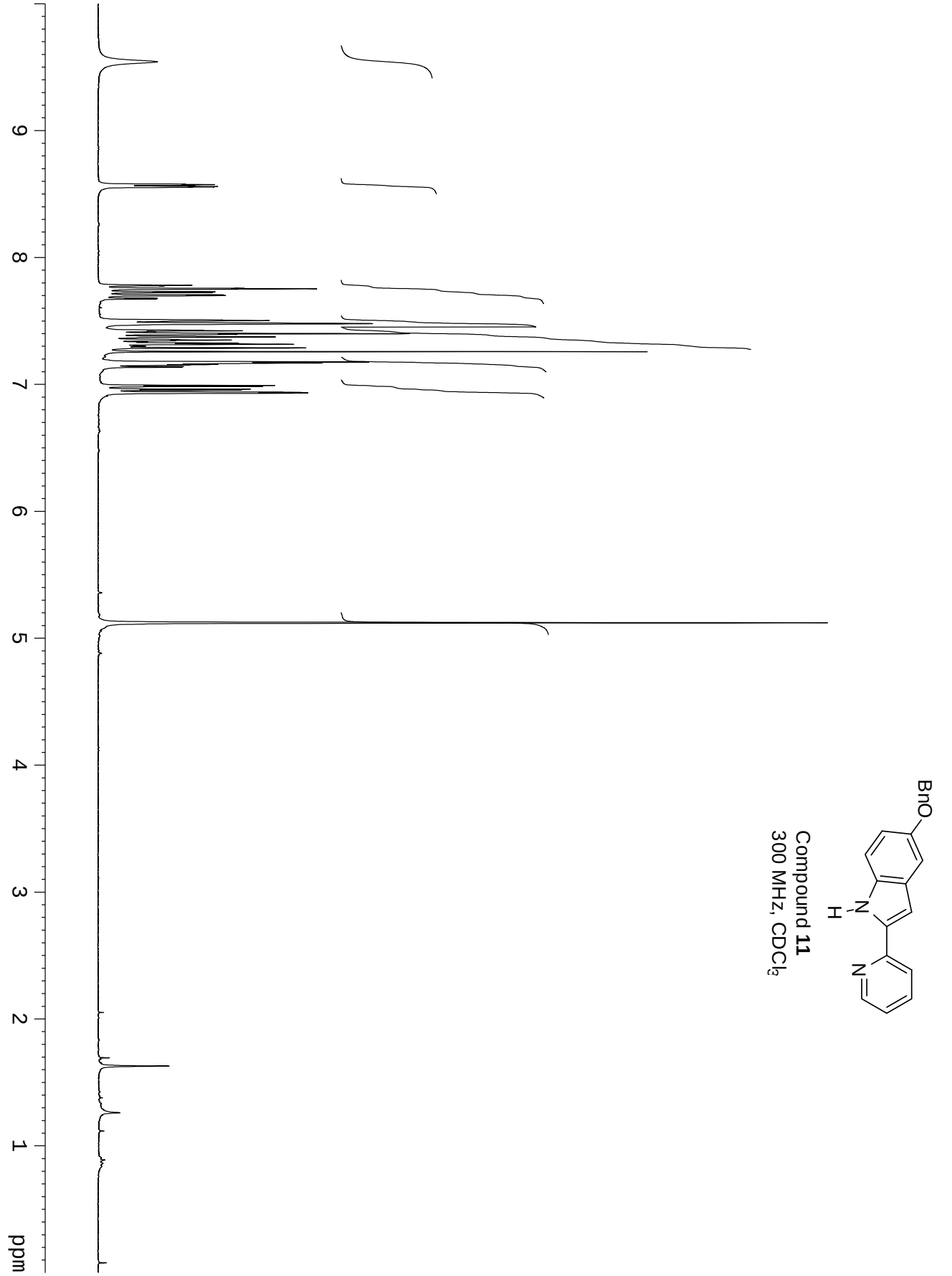

H
N
O
OH
N
N
Ru
O
O
C
O

(*S*$_{Ru}$)-**21**

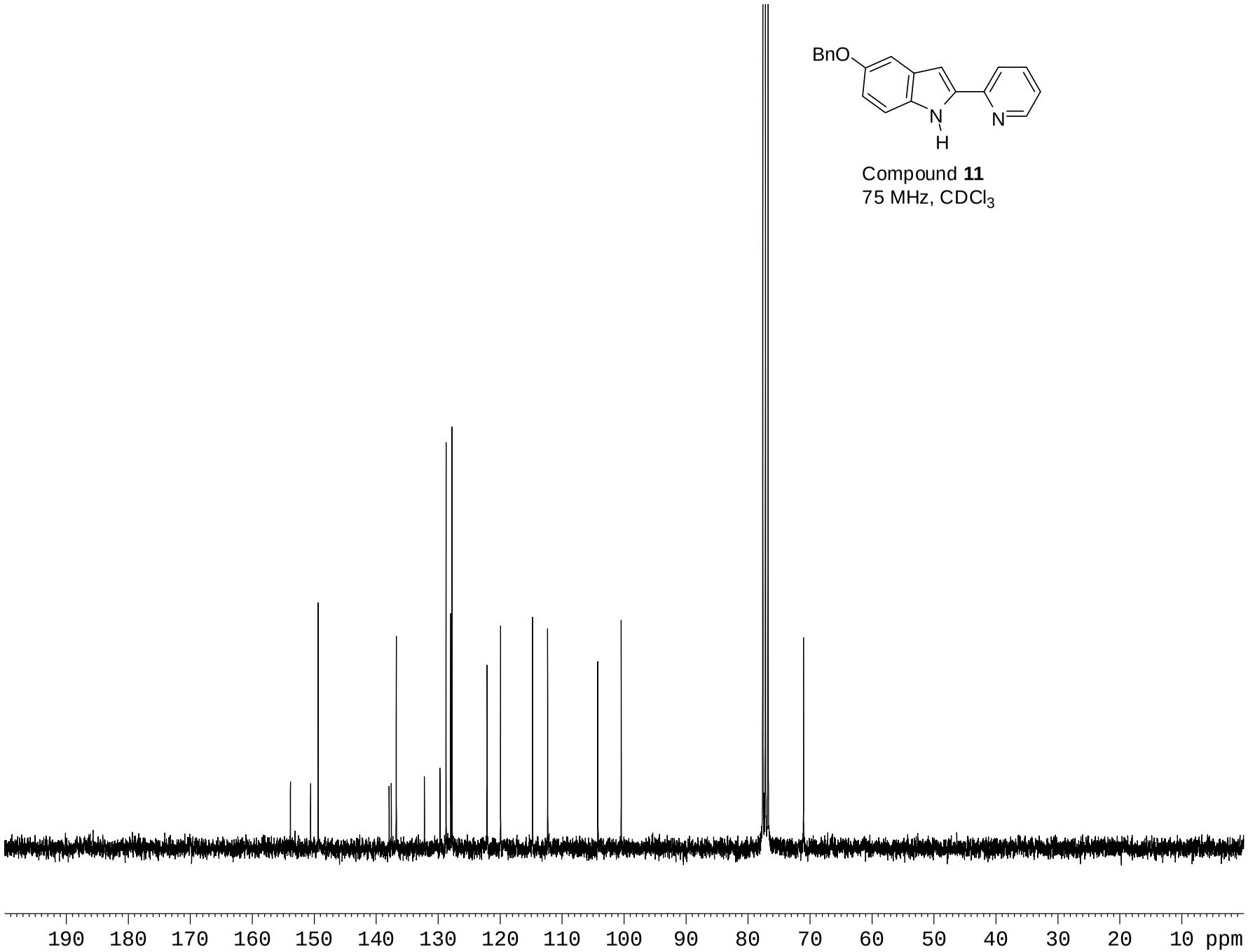
C) ROESY Analysis of Compound 17

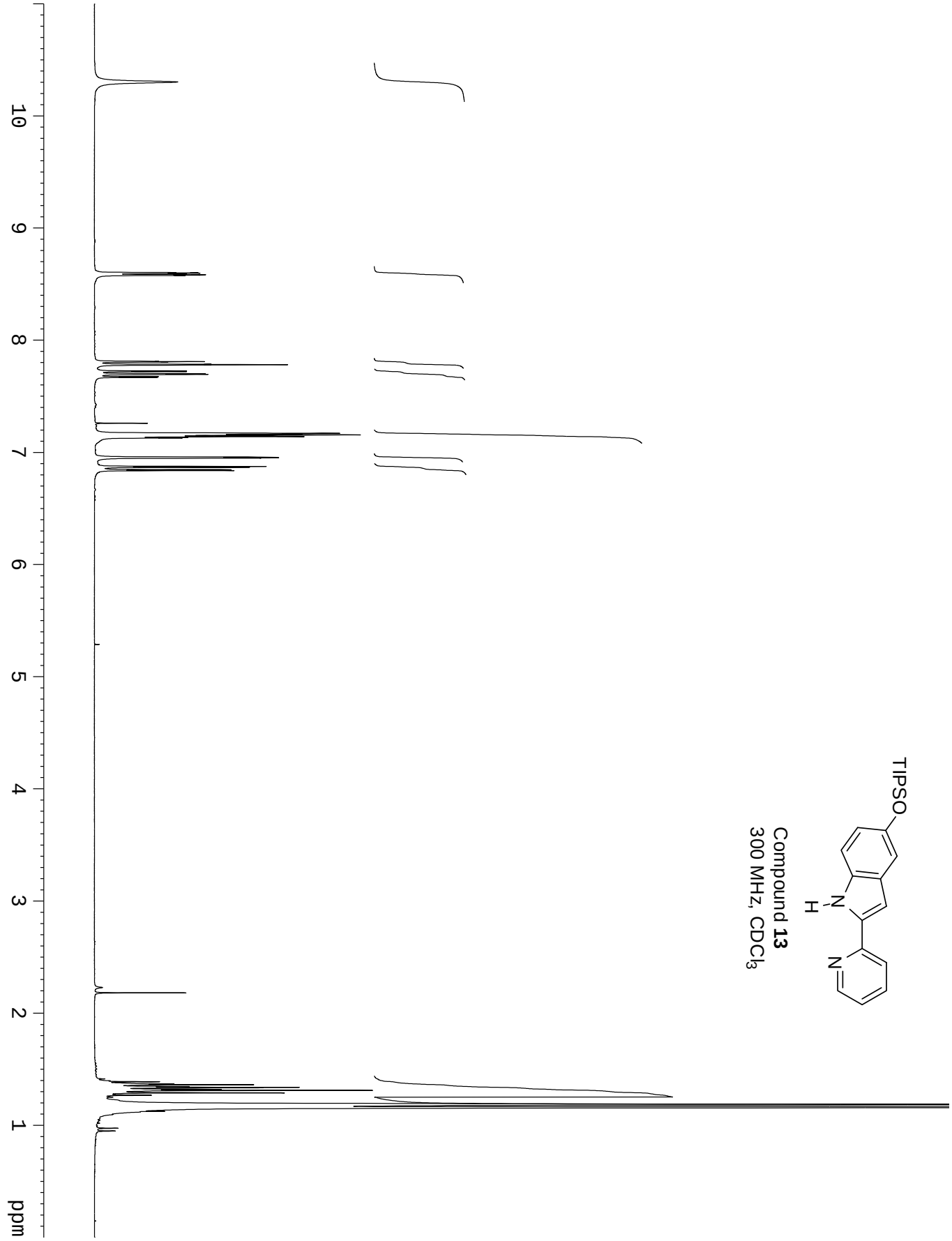


D) NMR Spectra

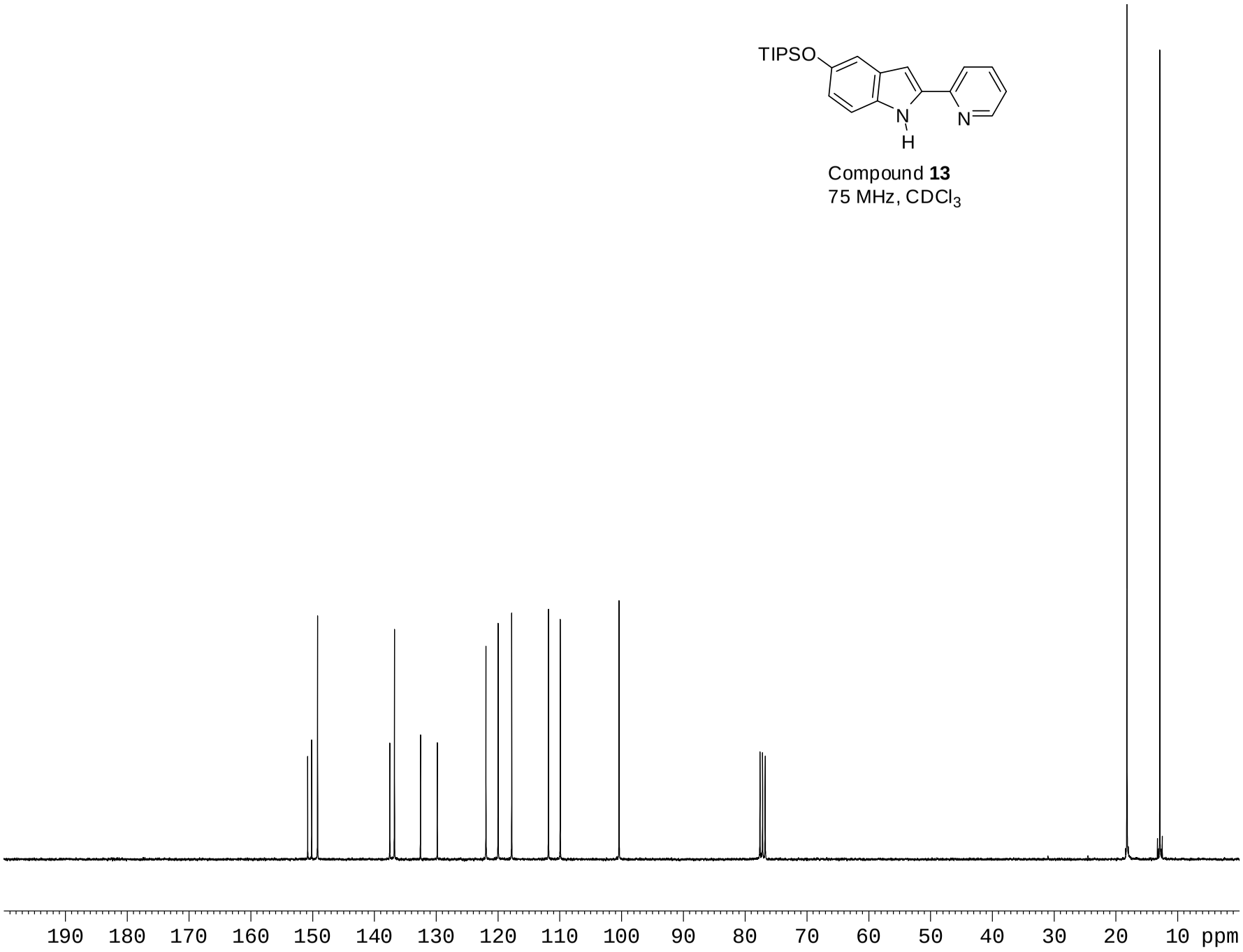


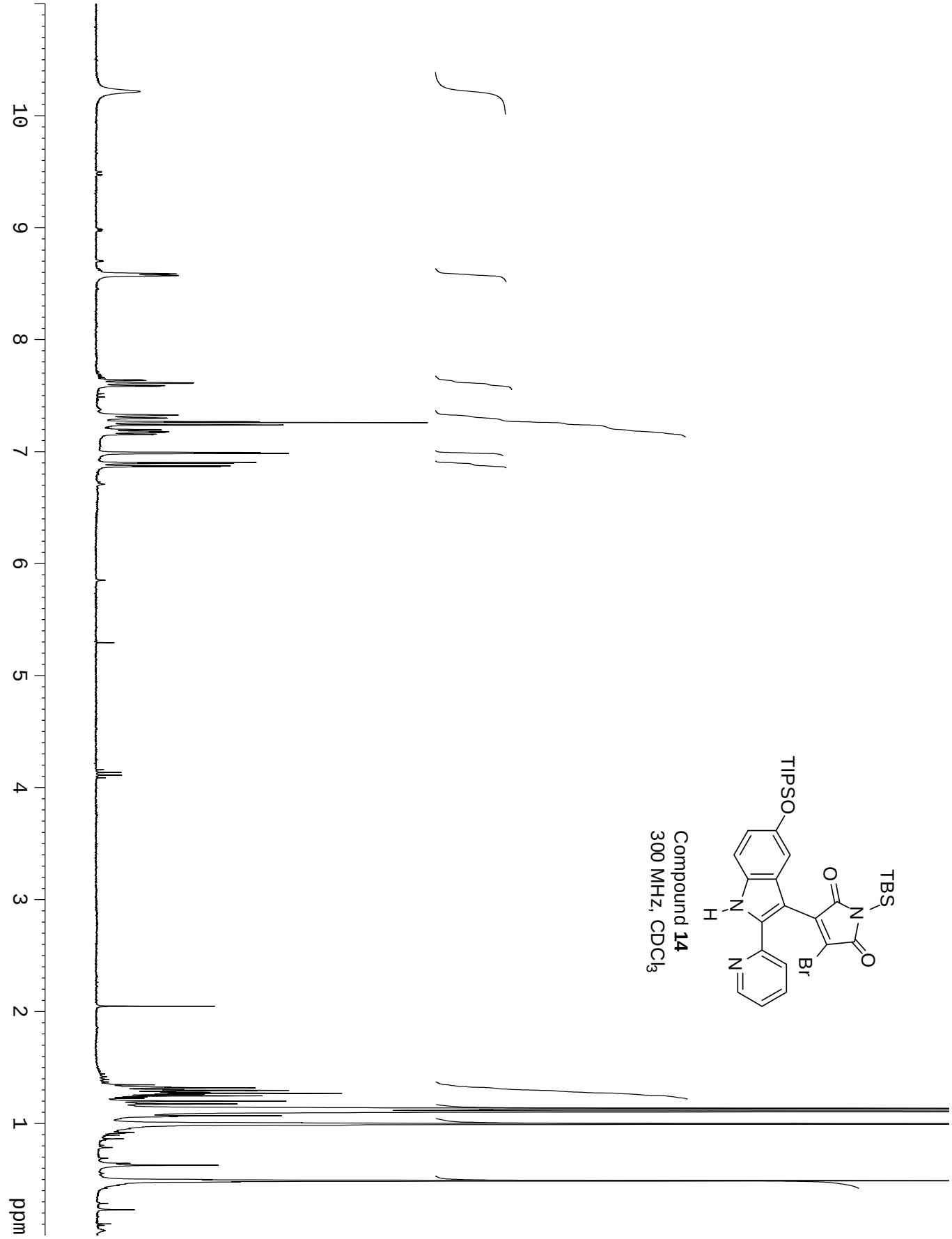
Compound **11**
75 MHz, $CDCl_3$



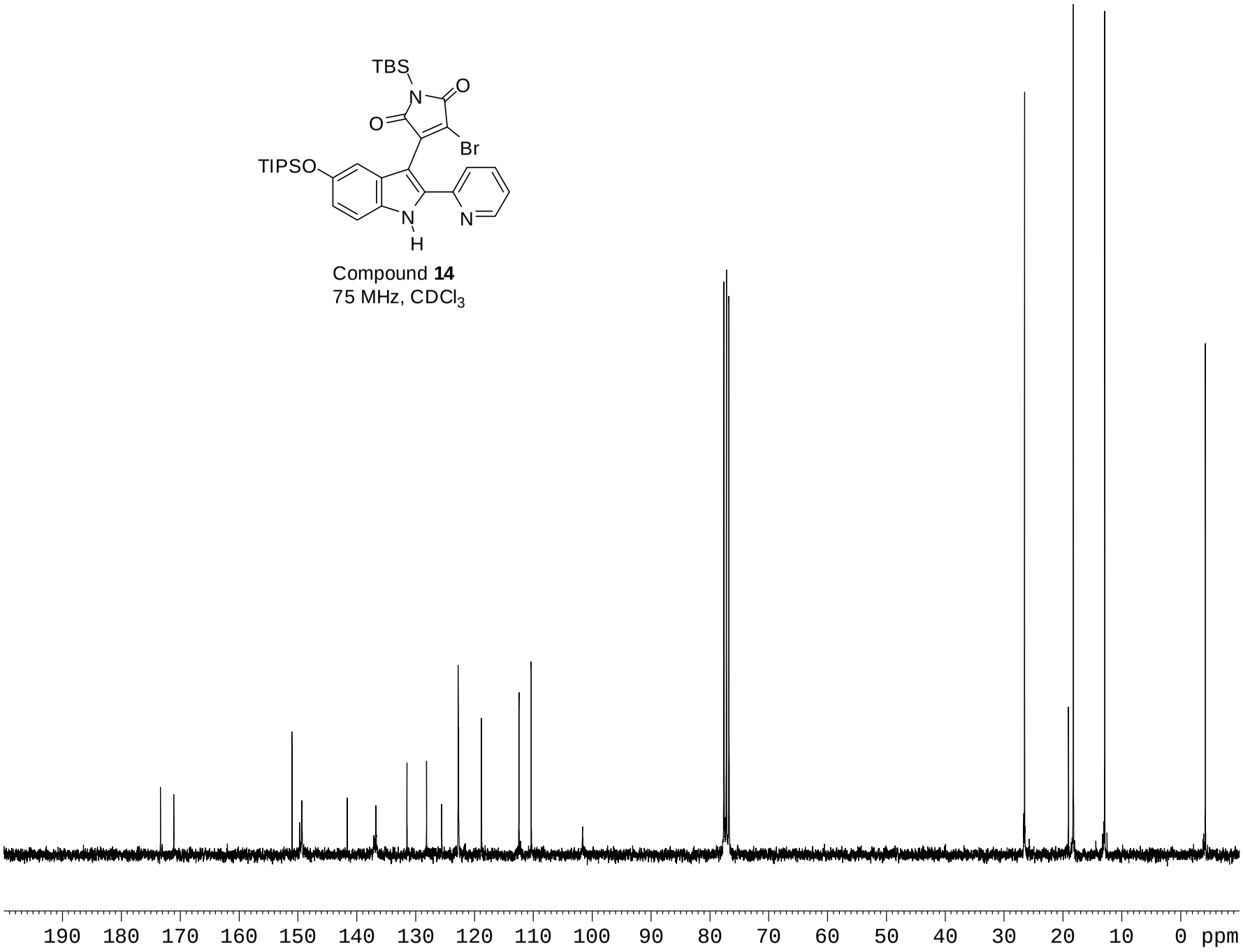

TIPSO
N
H
N
Compound **13**
300 MHz, $CDCl_3$
10
9
8
7
6
5
4
3
2
1
ppm

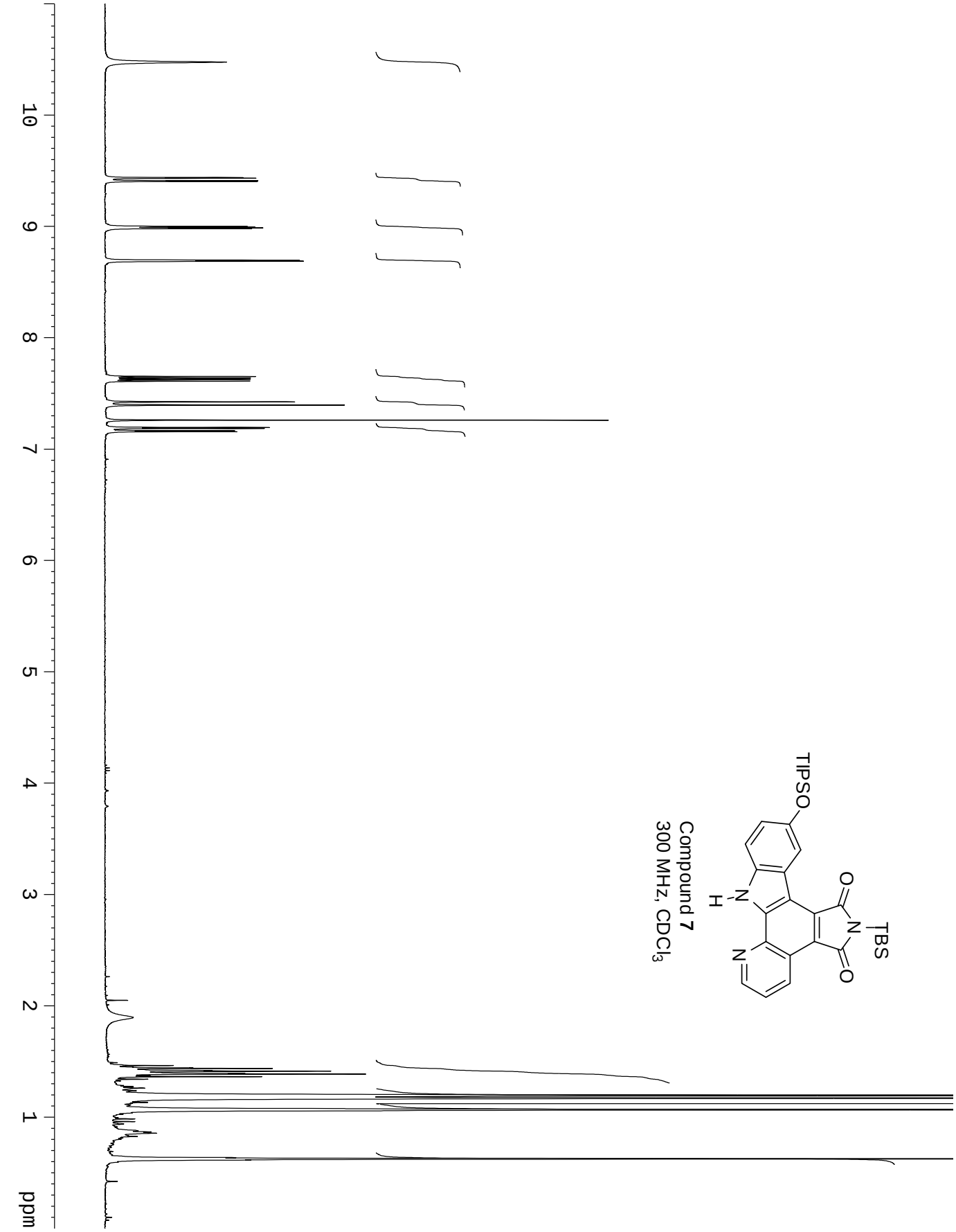
Compound **13**
75 MHz, $CDCl_3$



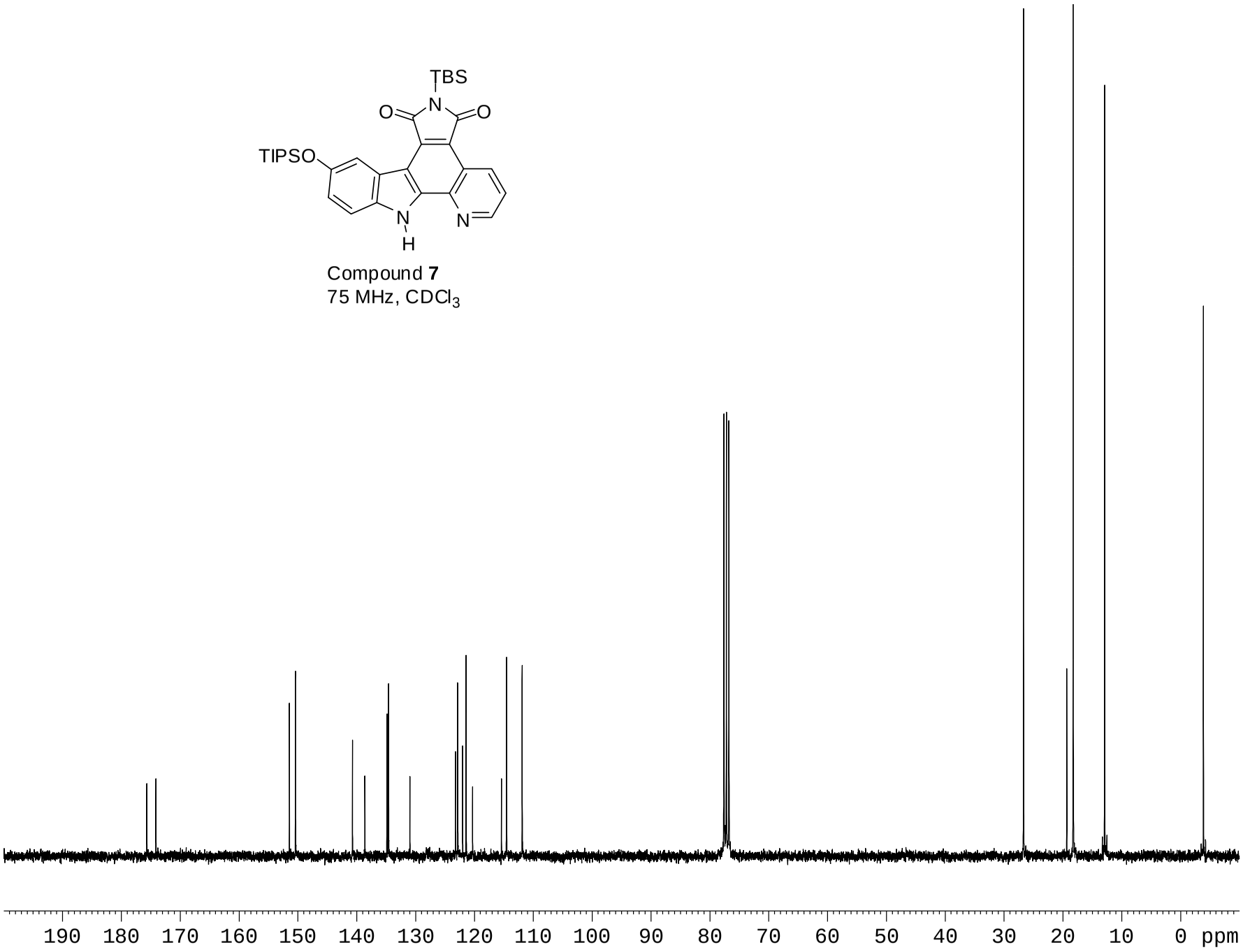

TIPSO
TBS
N
H
N
O
N
O
Br
N
Compound **14**
300 MHz, $CDCl_3$
10
9
8
7
6
5
4
3
2
1
ppm

Compound **14**
75 MHz, $CDCl_3$

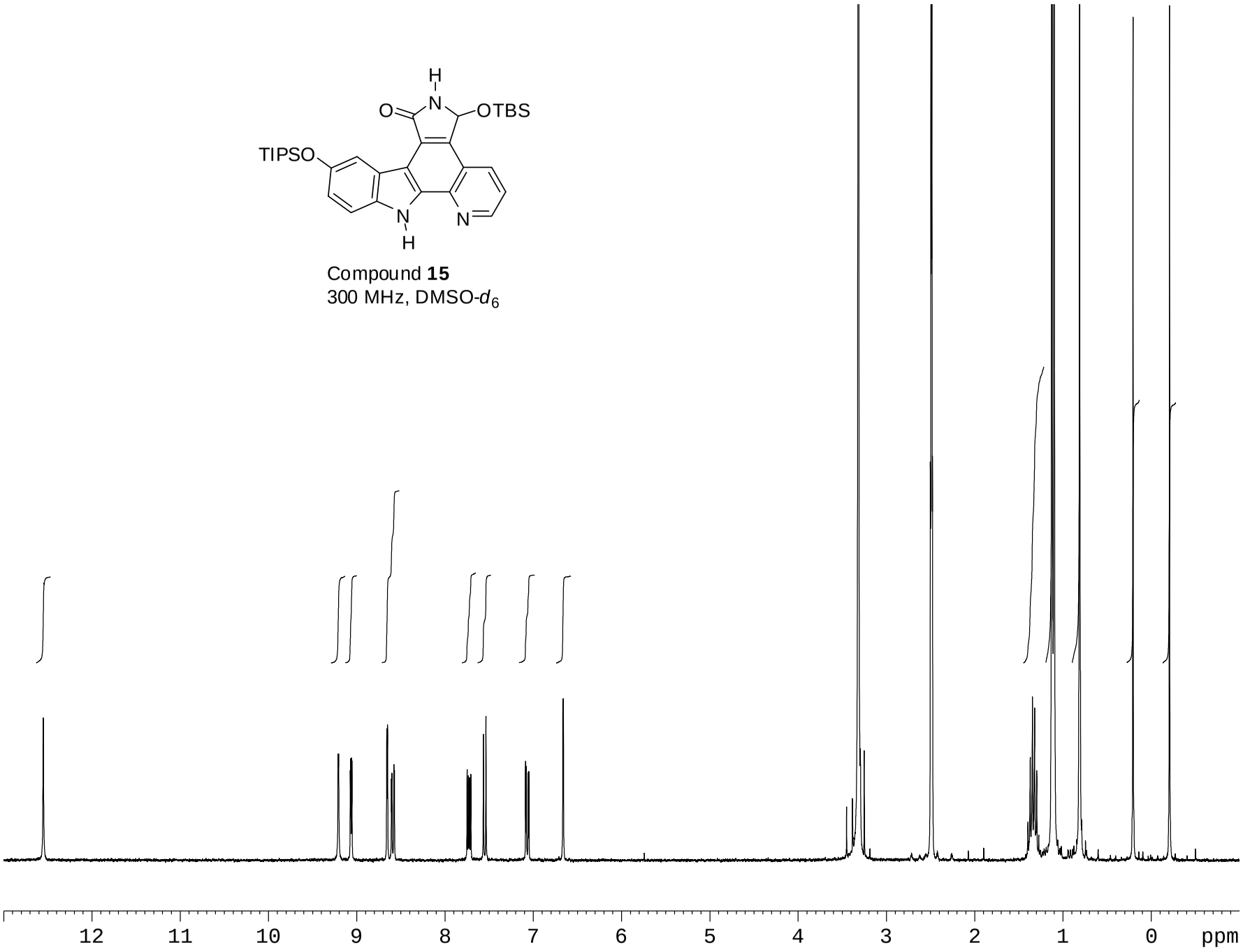



TIPSO
TBS
O
O
N
H
N
N
Compound 7
300 MHz, CDCl3
10
9
8
7
6
5
4
3
2
1
ppm

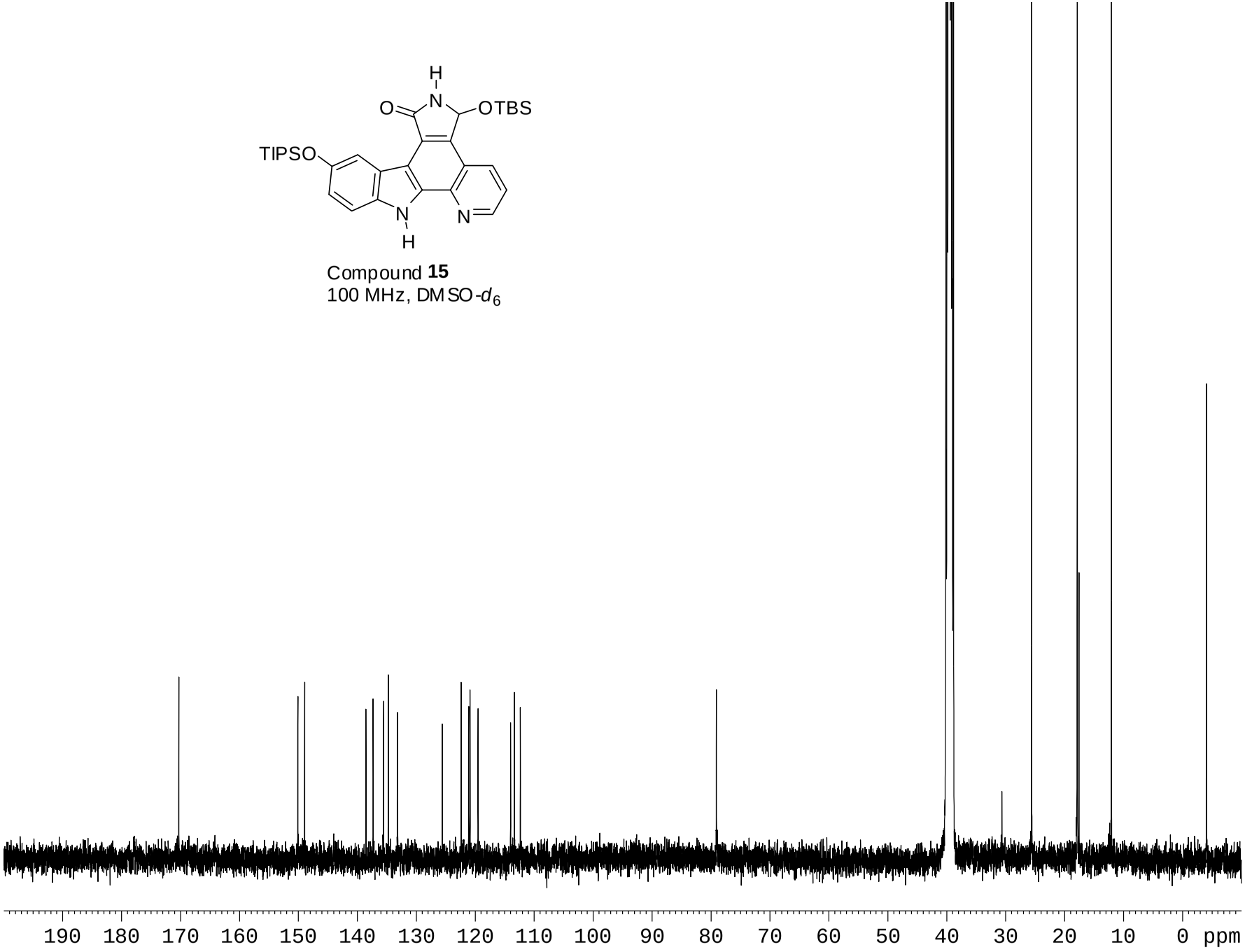
Compound **7**
75 MHz, $CDCl_3$



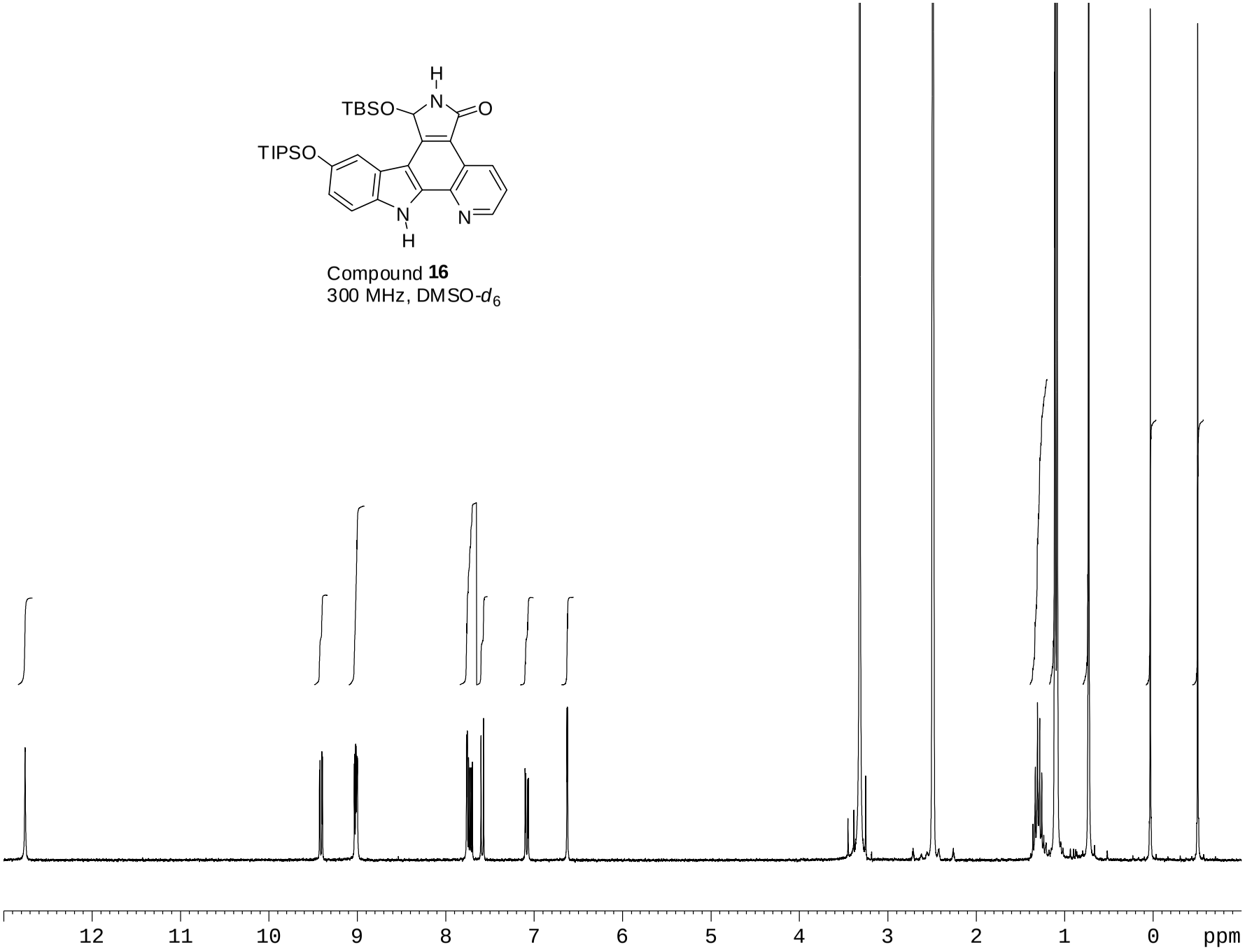
Compound **15**
300 MHz, DMSO-d_6



Compound **15**
100 MHz, DMSO-d_6

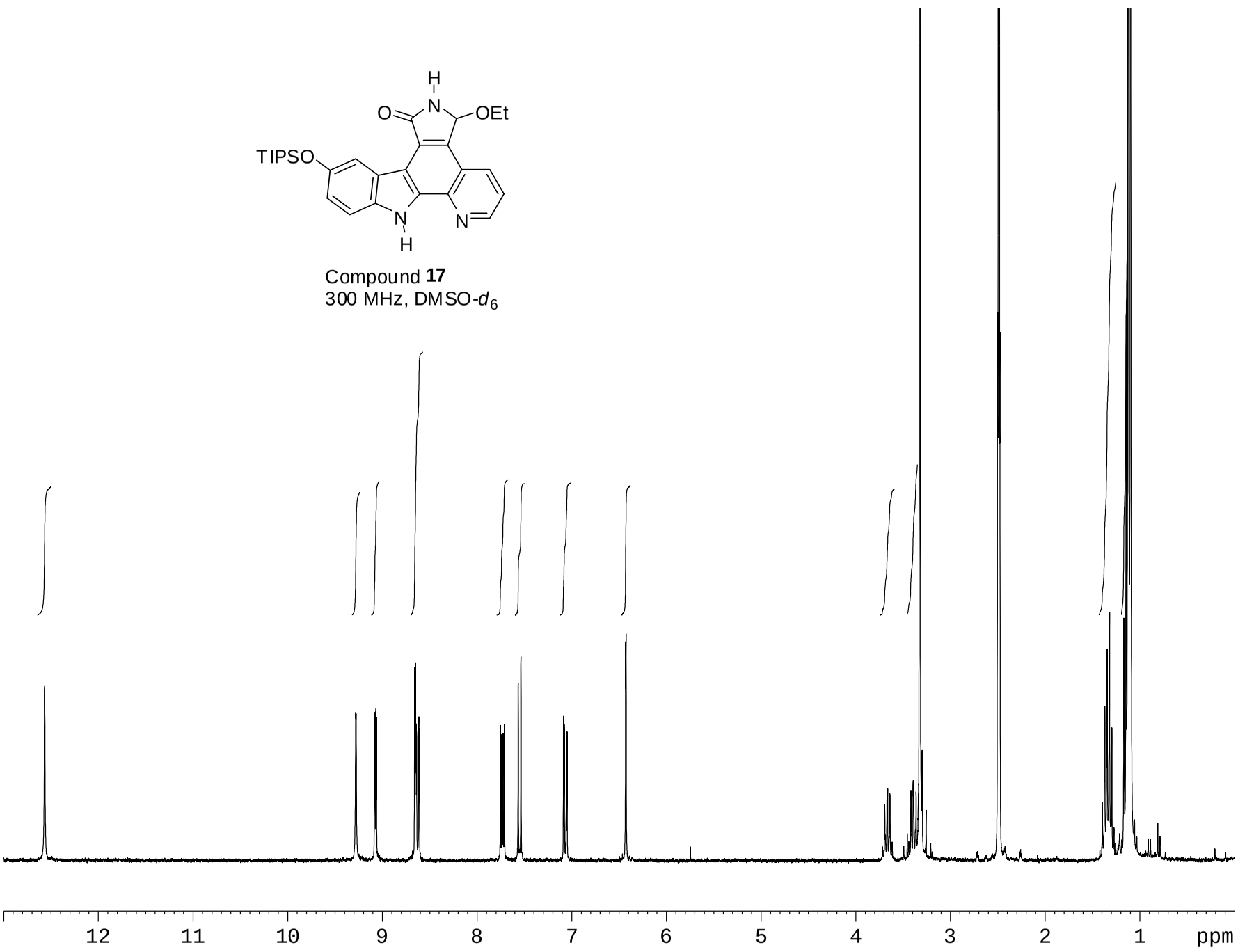


Compound **16**
300 MHz, DMSO-d_6

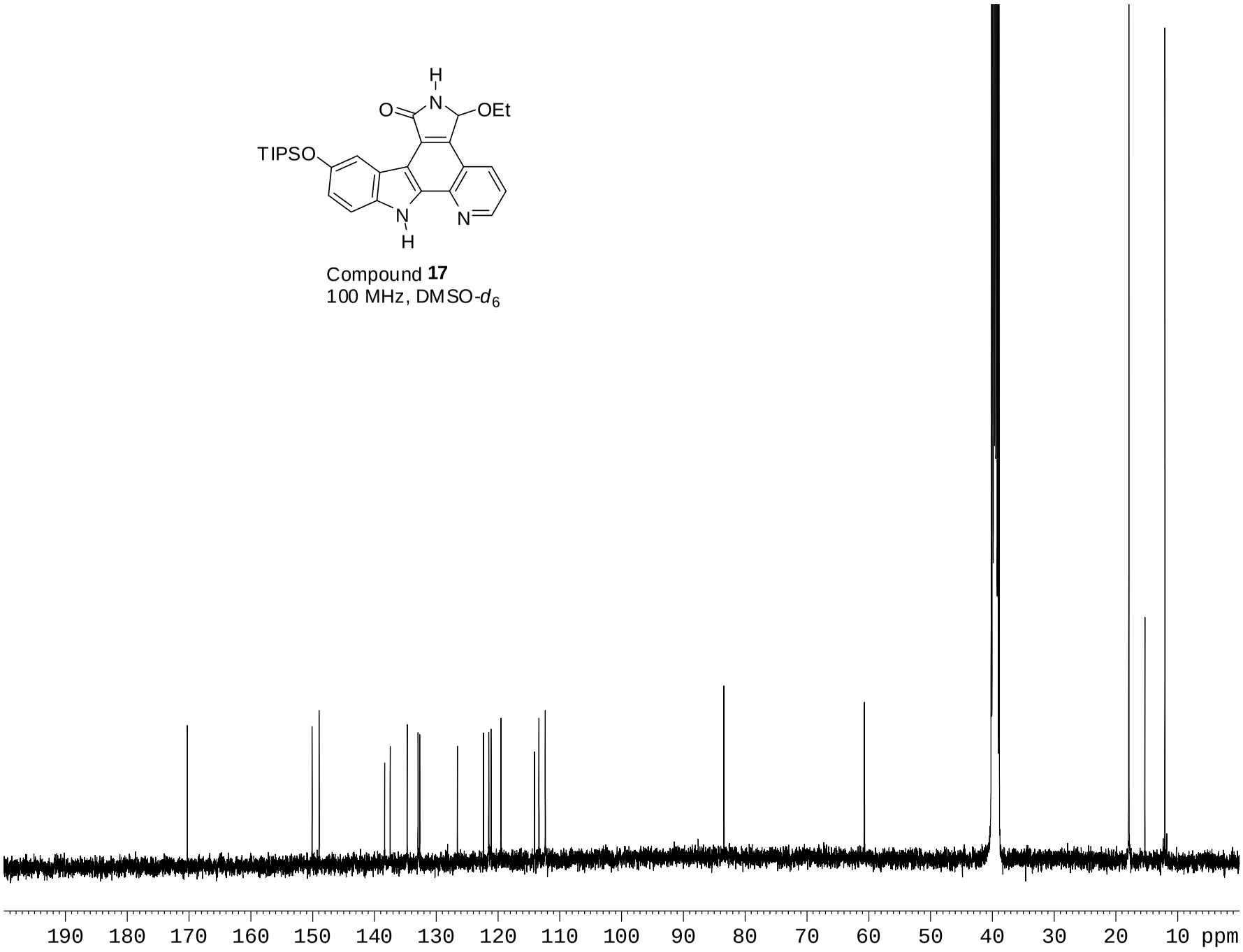


Compound **16**
100 MHz, DMSO-d_6
TIPSO
TBSO
H
N
H
N
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

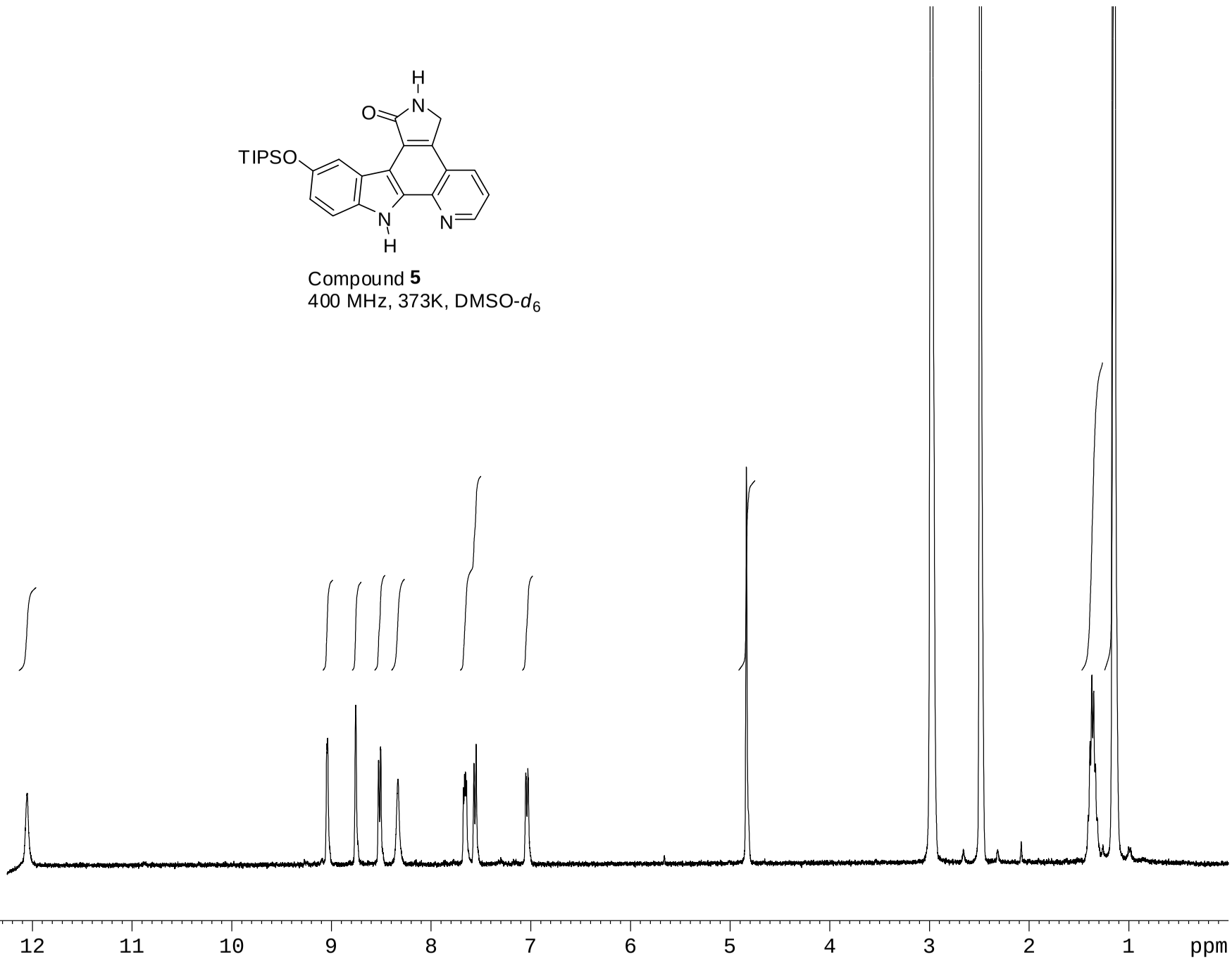
Compound **17**
300 MHz, DMSO-d_6



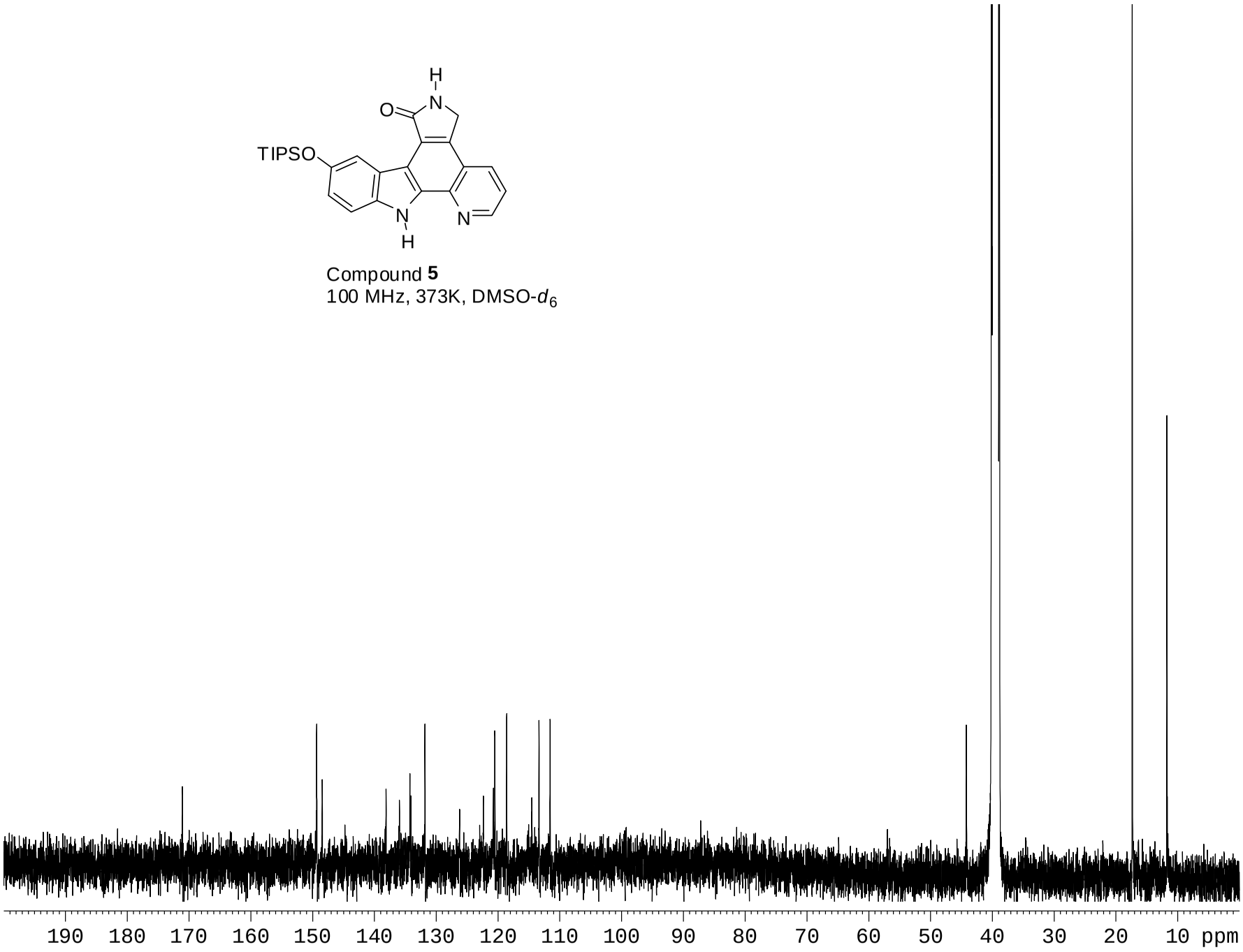
Compound **17**
100 MHz, DMSO-d_6



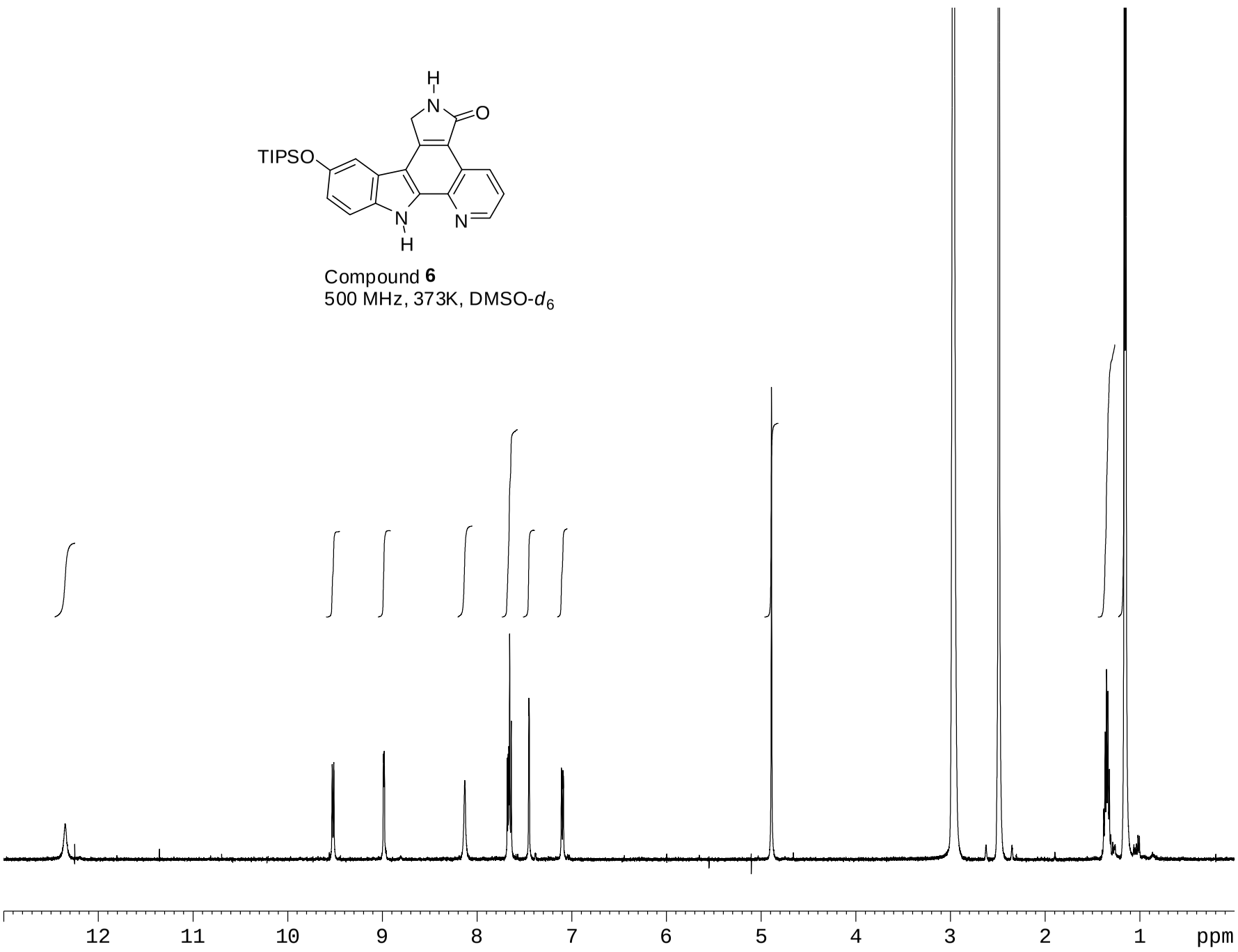
Compound **5**
400 MHz, 373K, DMSO-d_6

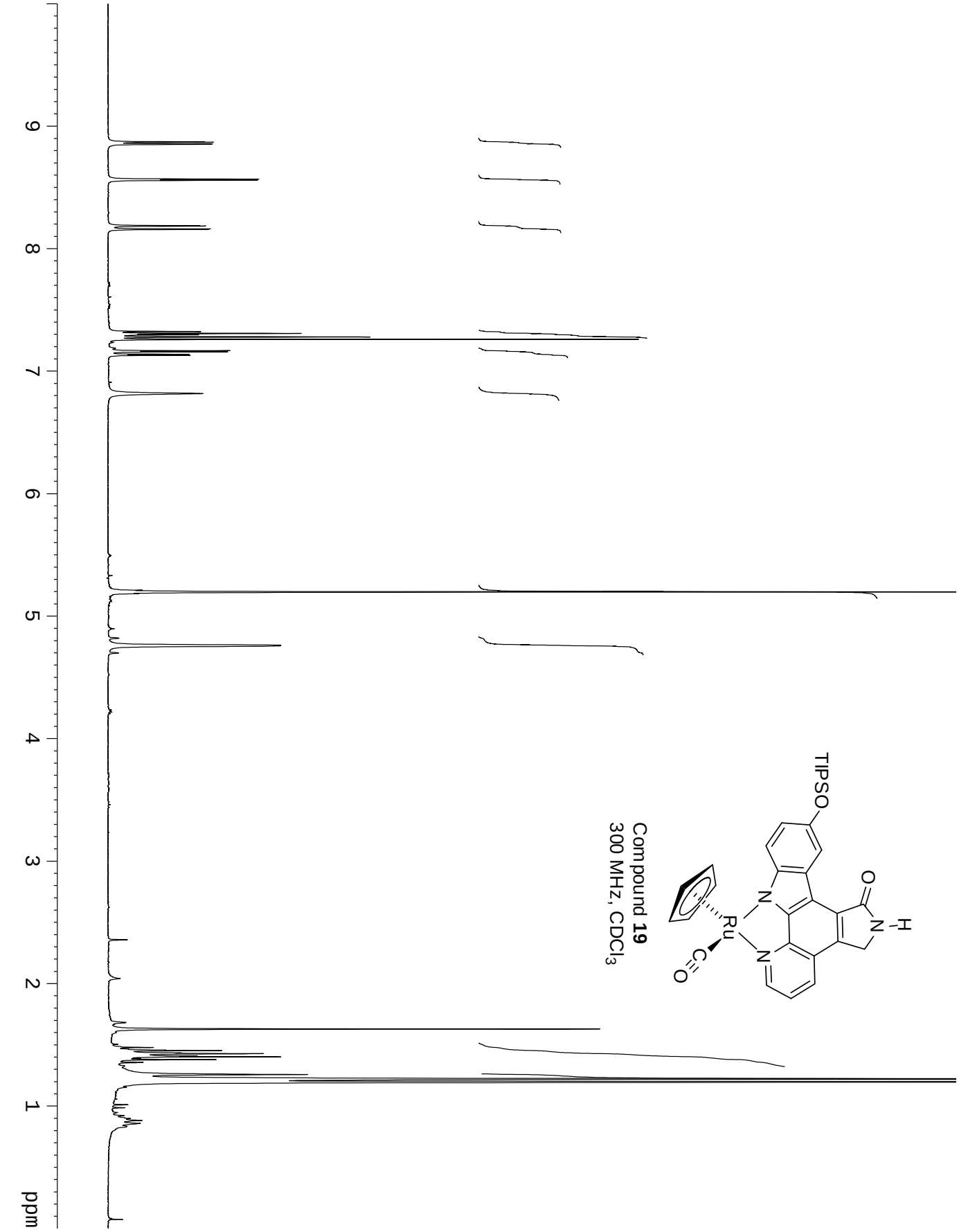


Compound **5**
100 MHz, 373K, DMSO-d_6

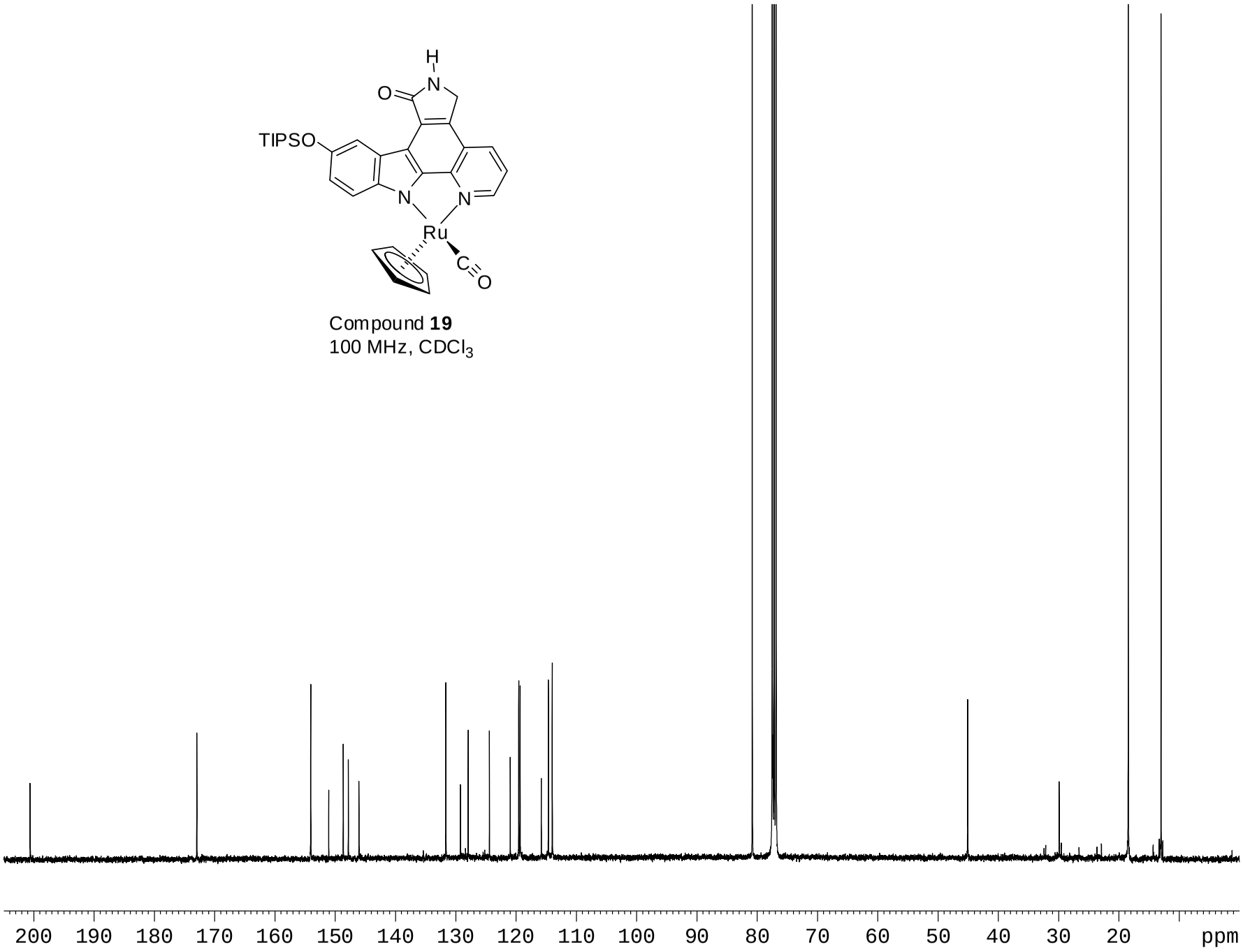


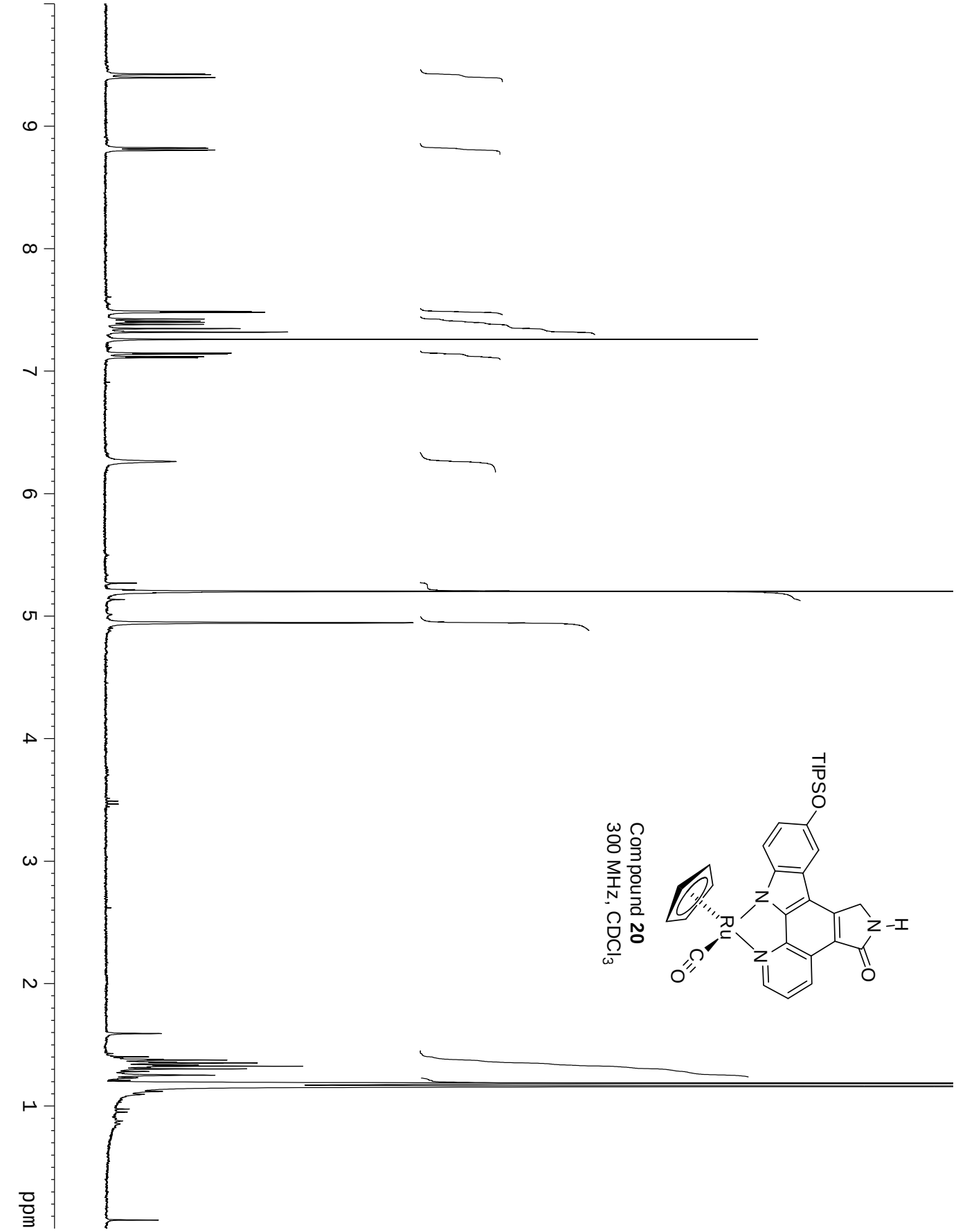
Compound **6**
500 MHz, 373K, DMSO-d_6



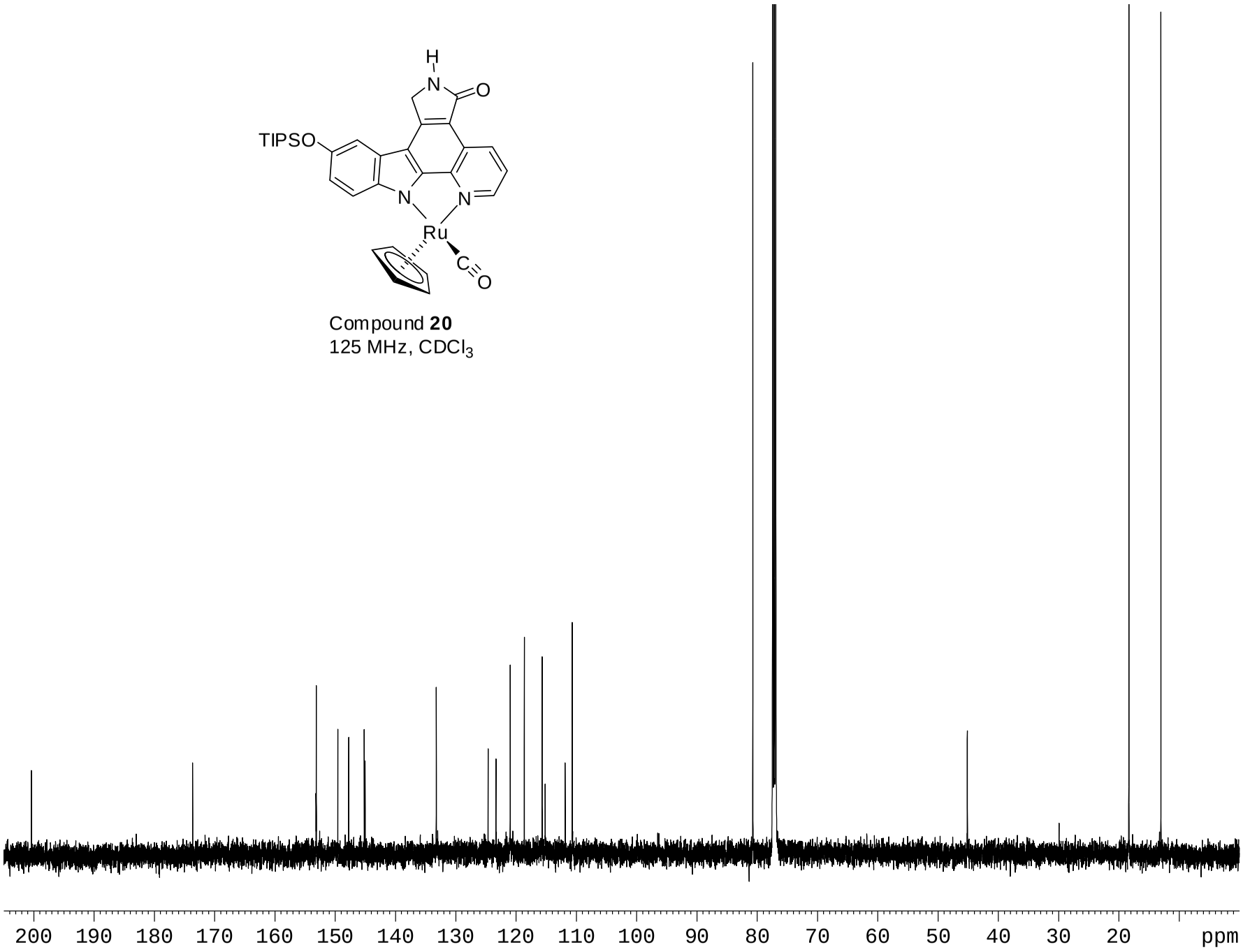

Compound **19**
300 MHz, $CDCl_3$
TIPSO
O
N
H
Ru
C
O
N
N
9
8
7
6
5
4
3
2
1
ppm

Compound **19**
100 MHz, $CDCl_3$

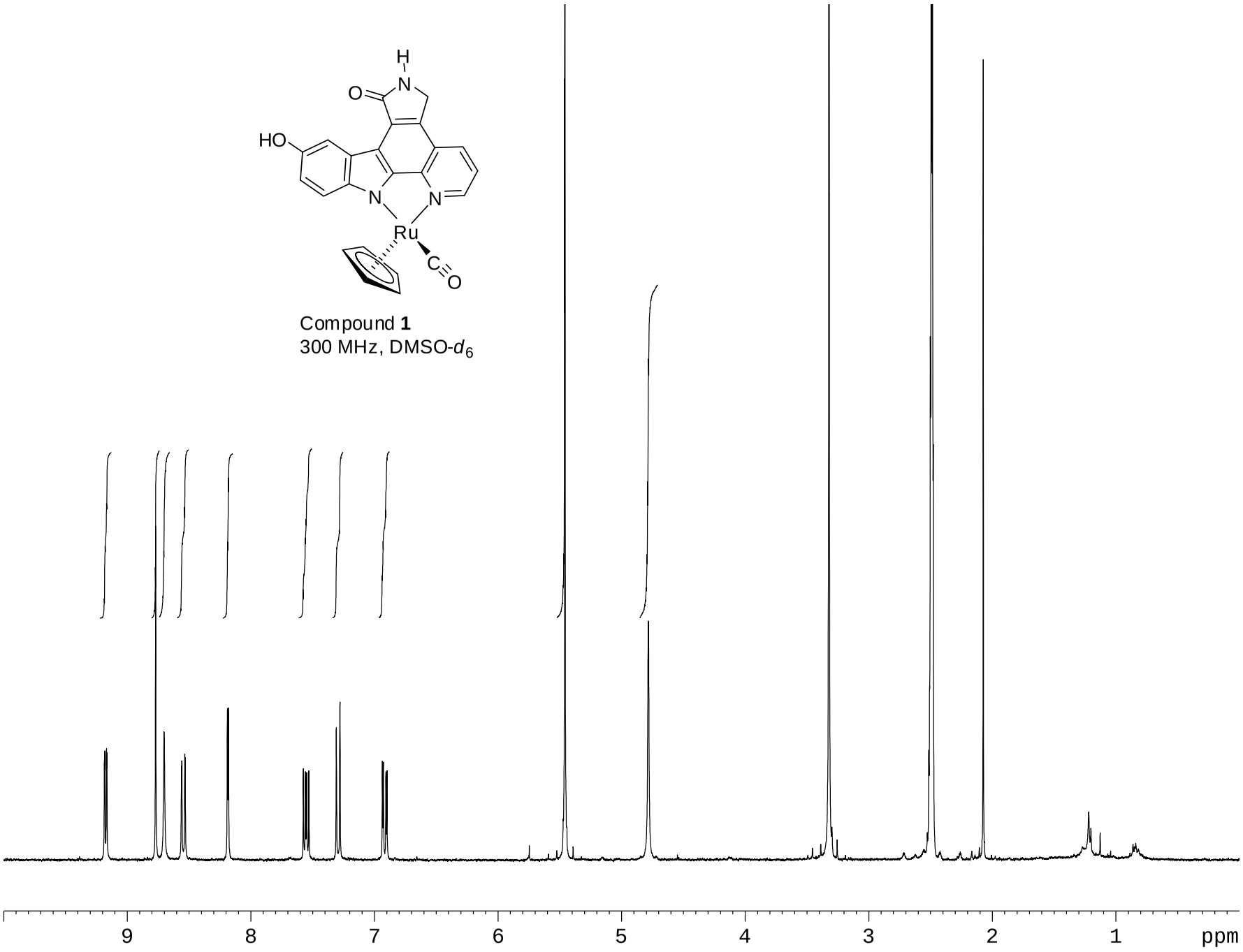



Compound **20**
300 MHz, $CDCl_3$
TIPSO
Ru
C
O
N
H
O
9
8
7
6
5
4
3
2
1
ppm

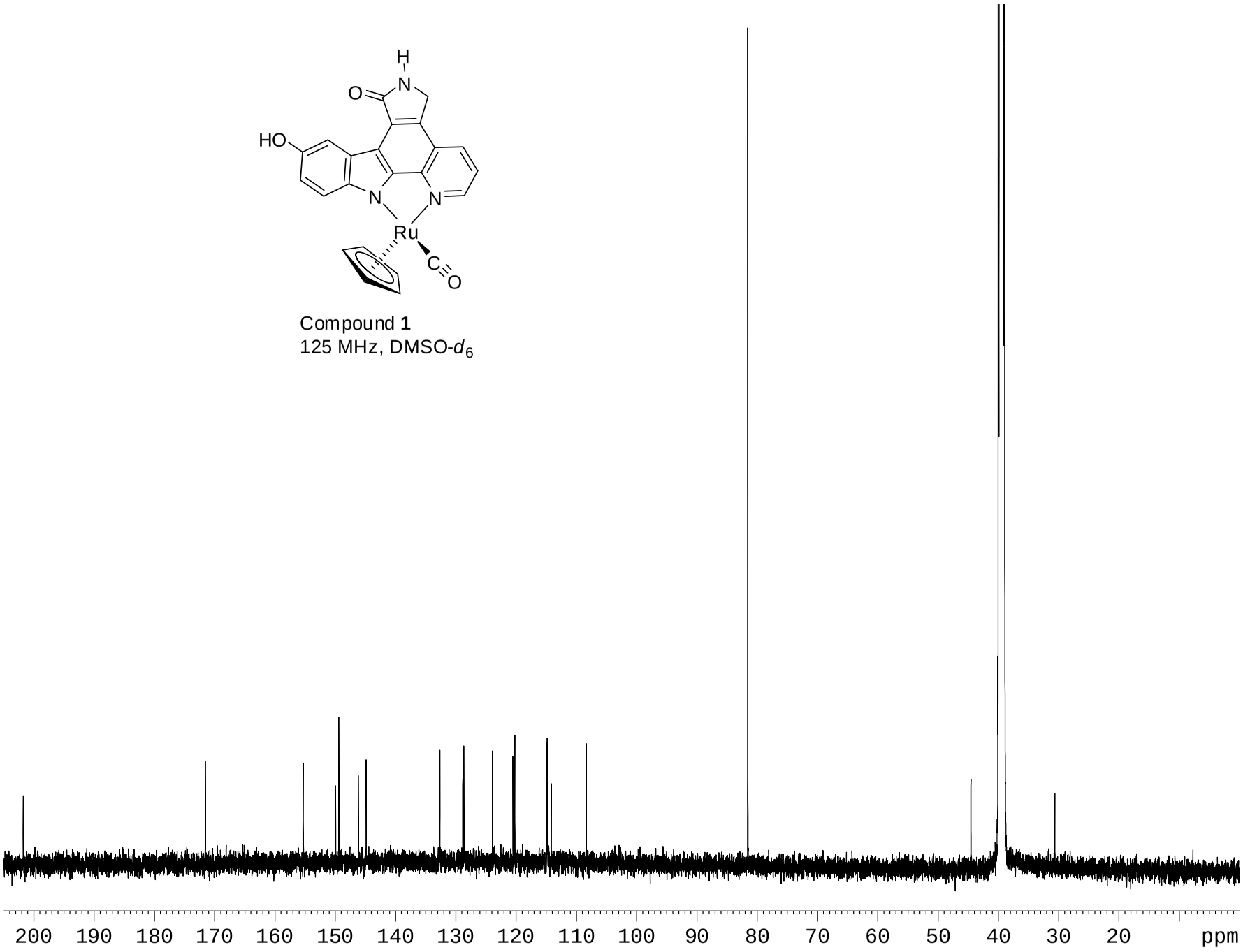
Compound **20**
125 MHz, $CDCl_3$



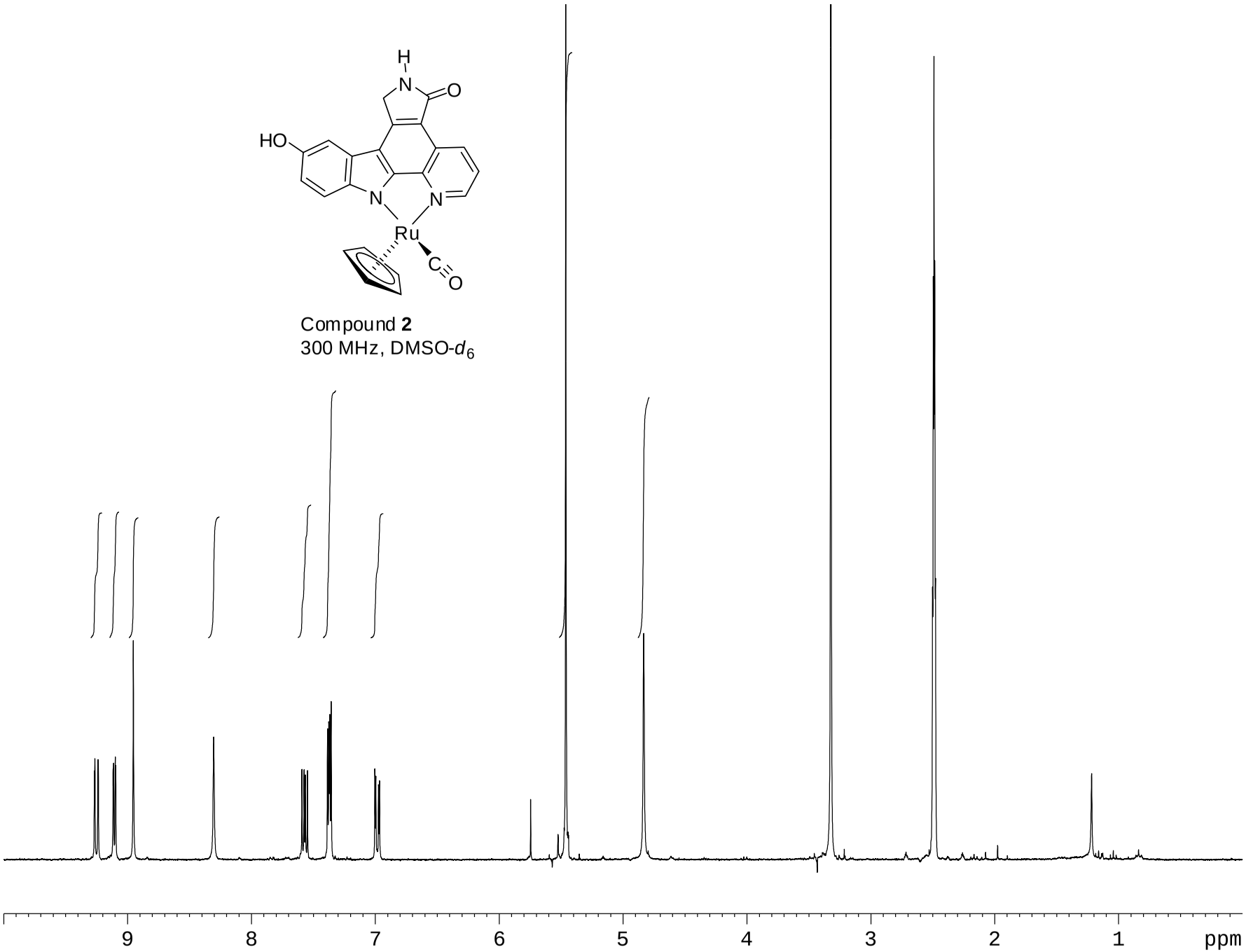
Compound **1**
300 MHz, DMSO-d_6



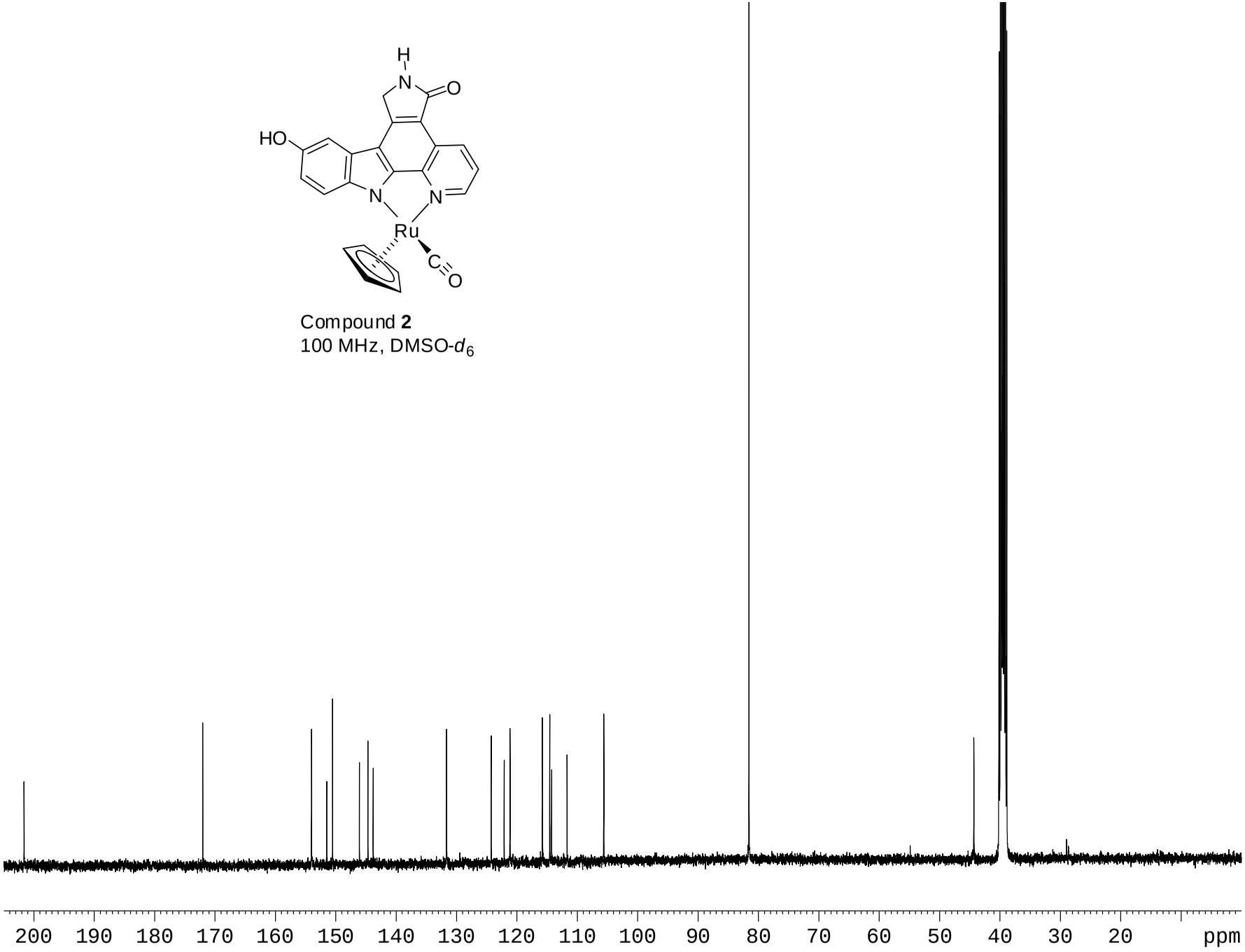
Compound **1**
125 MHz, DMSO-d_6

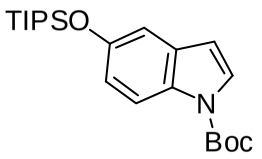


Compound **2**
300 MHz, DMSO-d_6

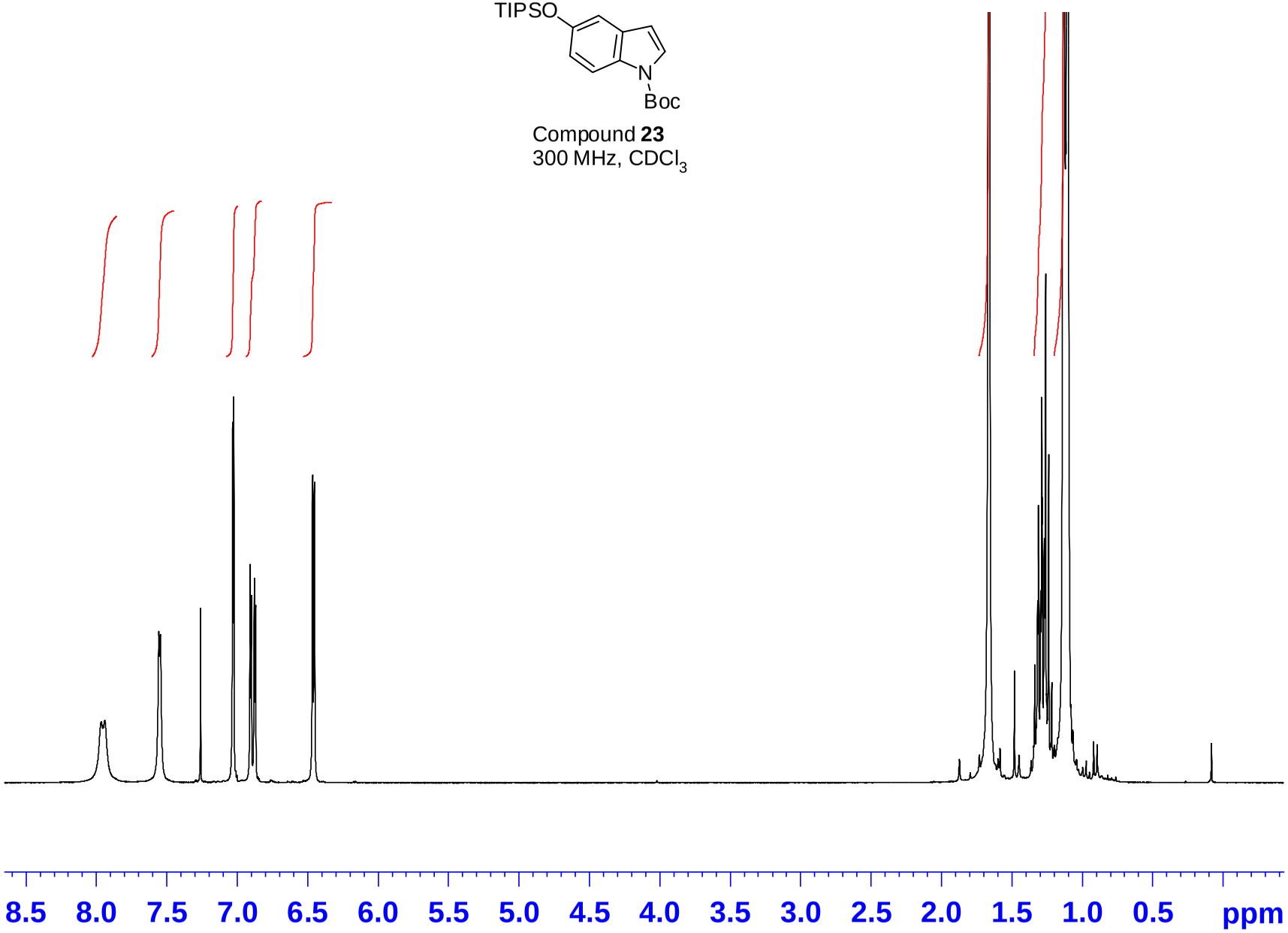


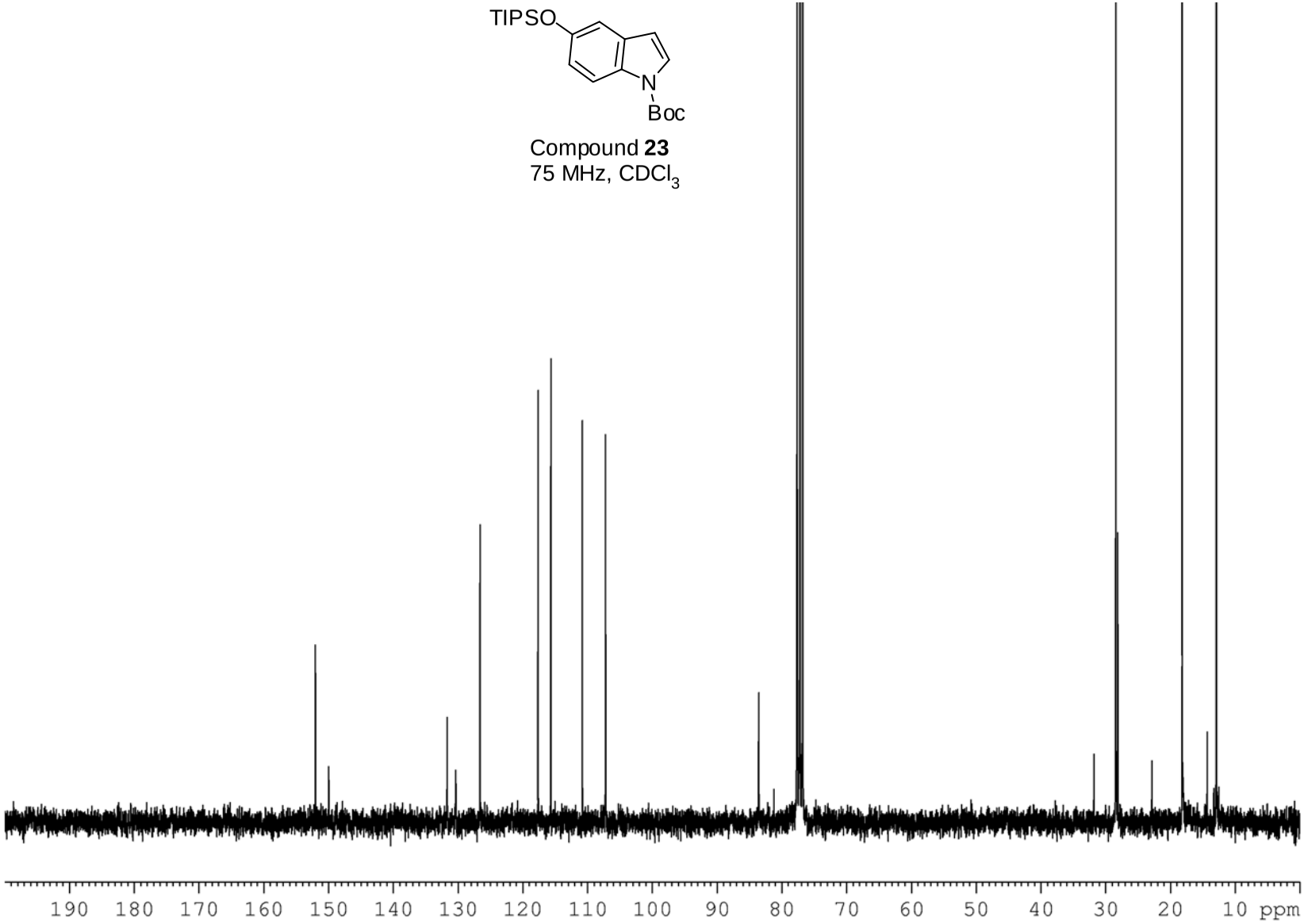
Compound **2**
100 MHz, DMSO-d_6





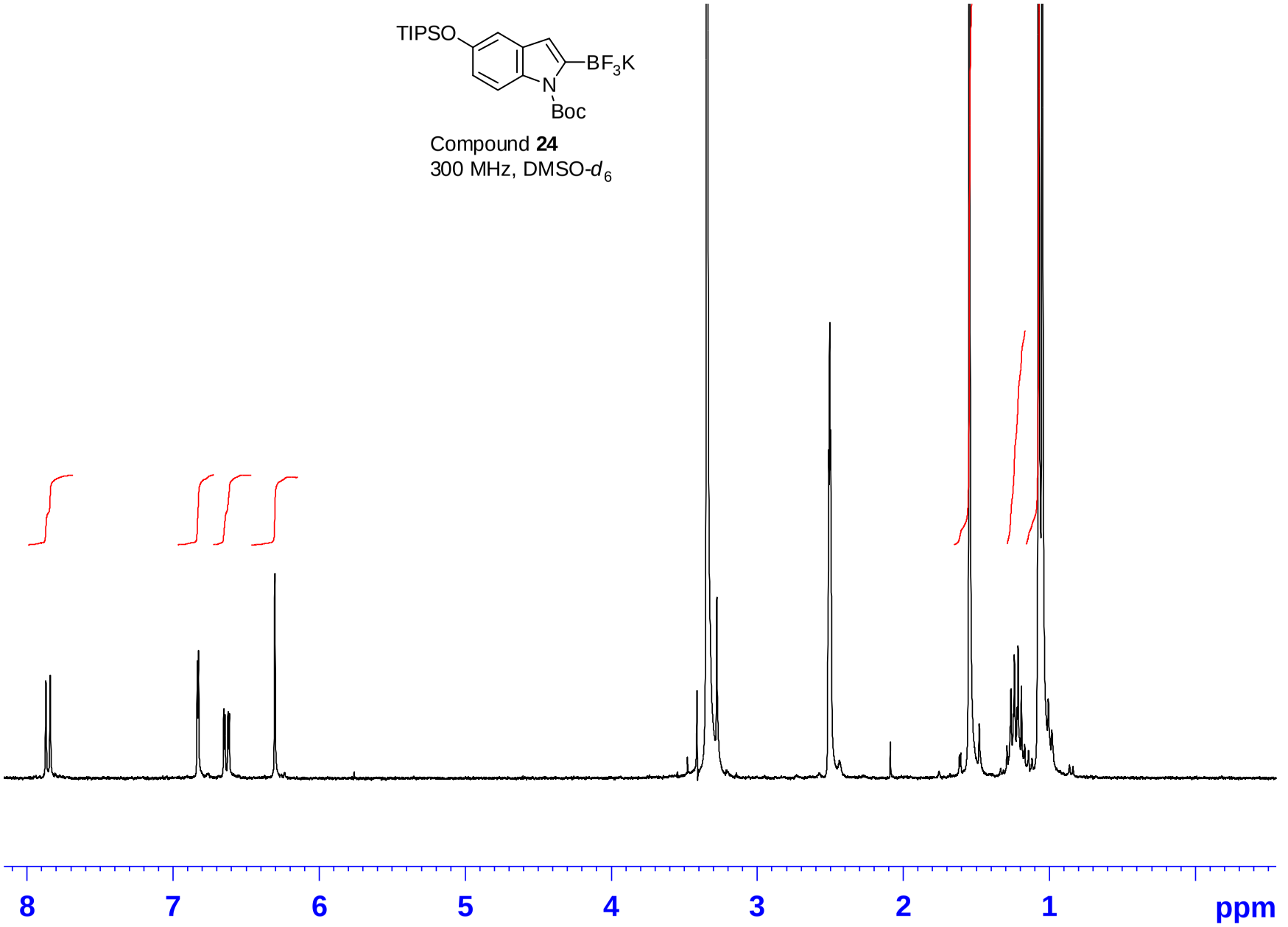
Compound **23**
300 MHz, $CDCl_3$



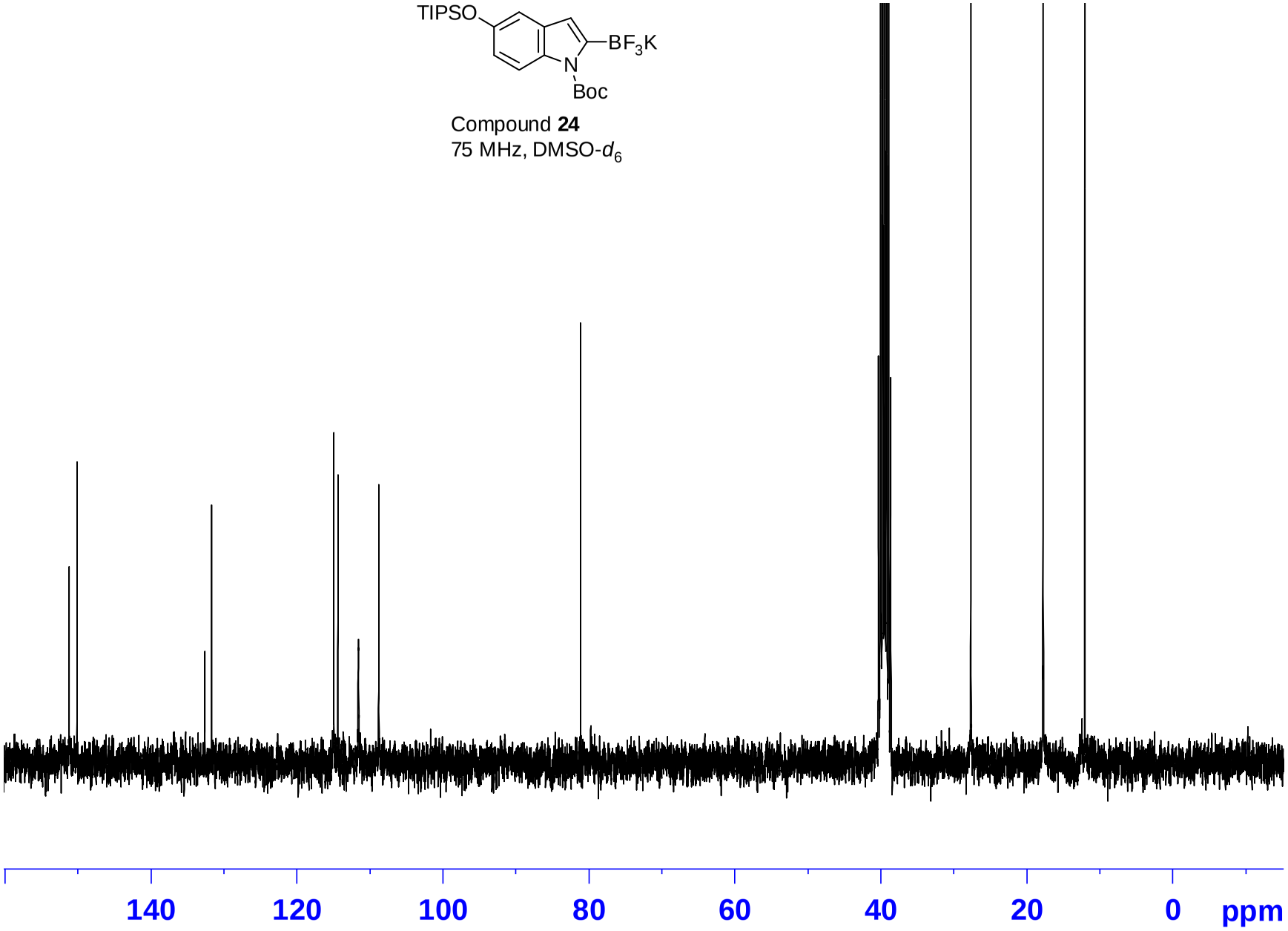


Compound **23**
75 MHz, $CDCl_3$

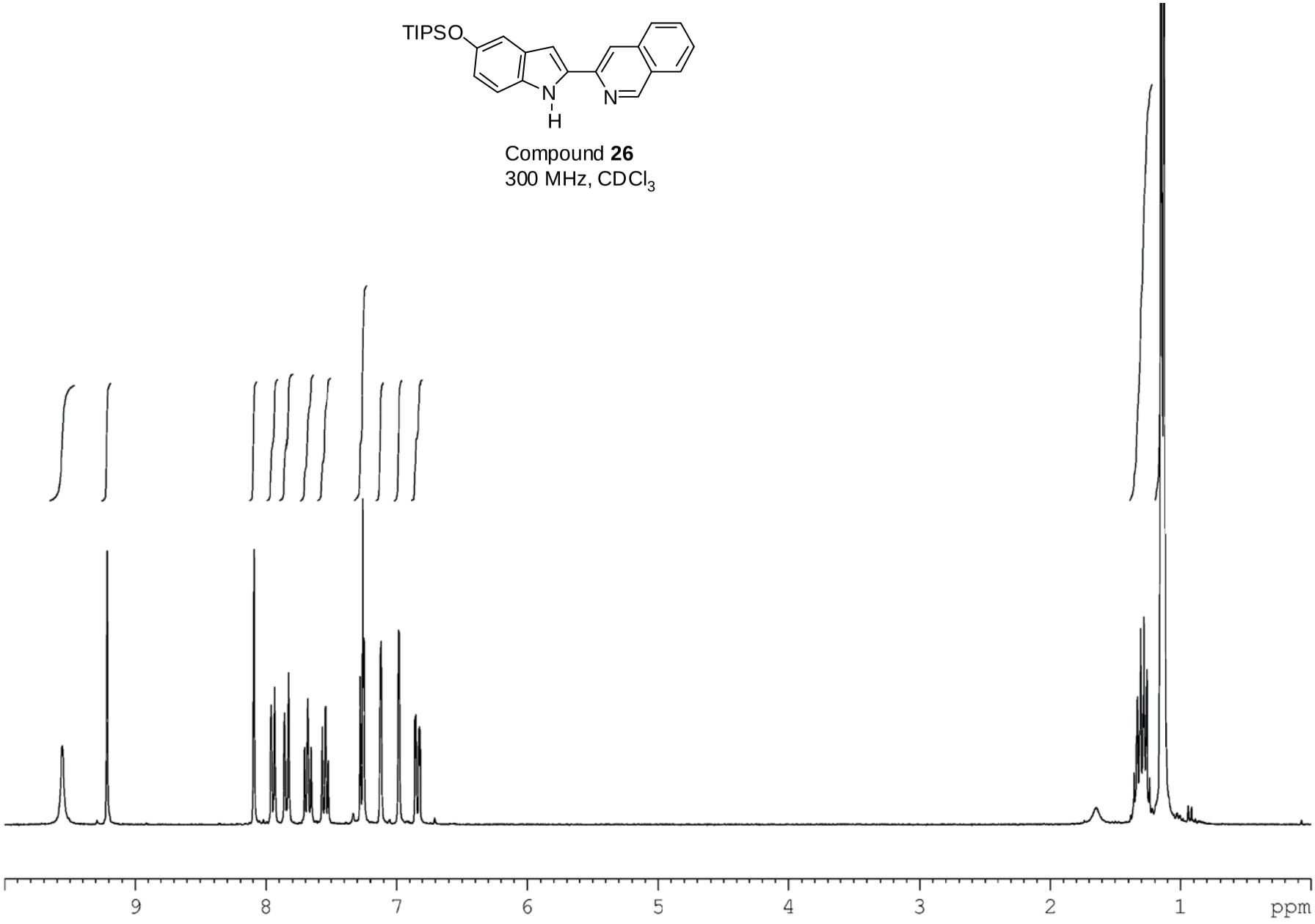
Compound **24**
300 MHz, DMSO-d_6

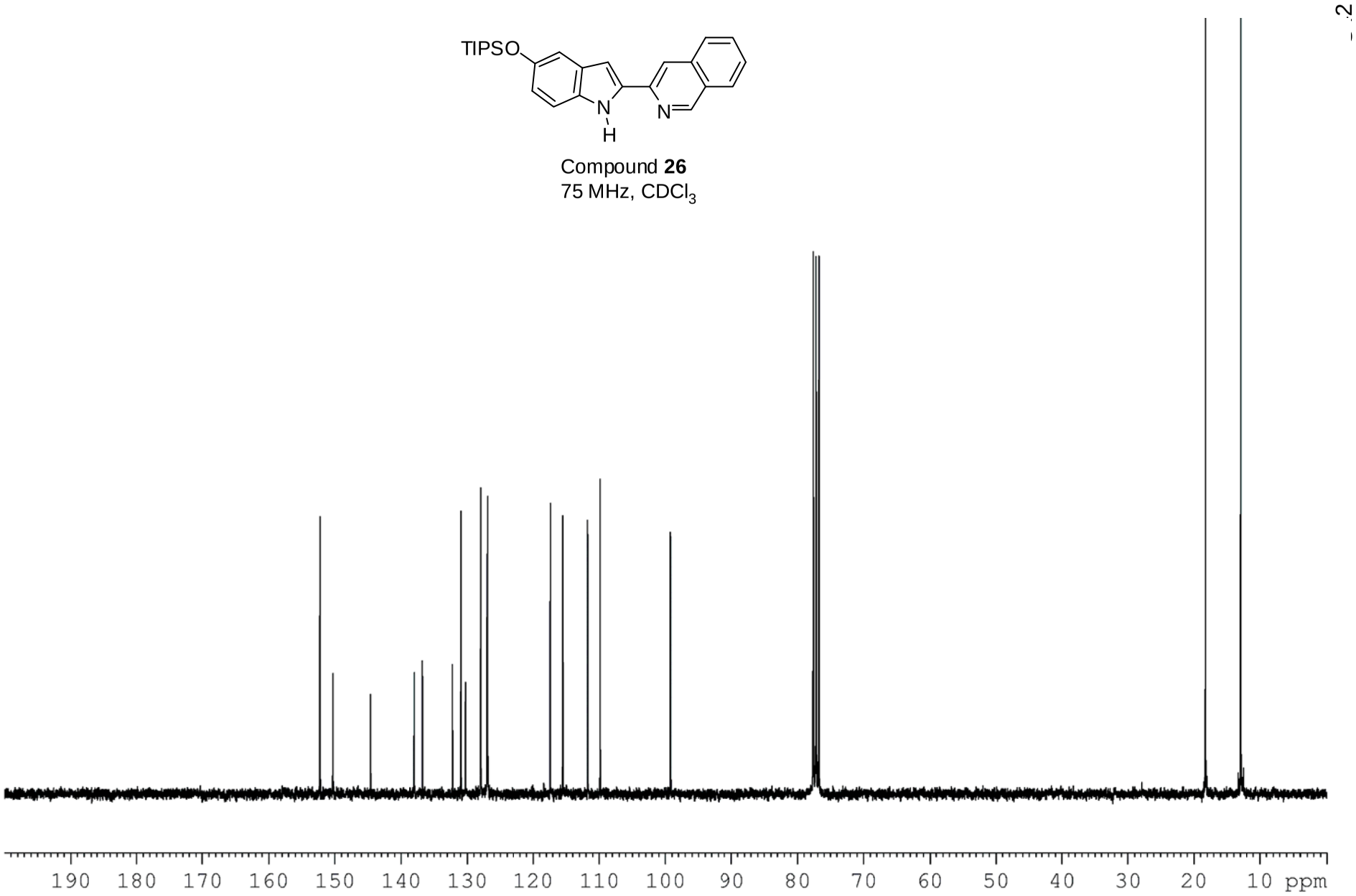


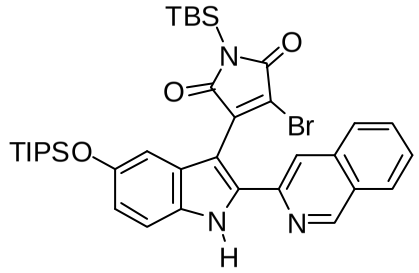
Compound **24**
75 MHz, DMSO-d_6



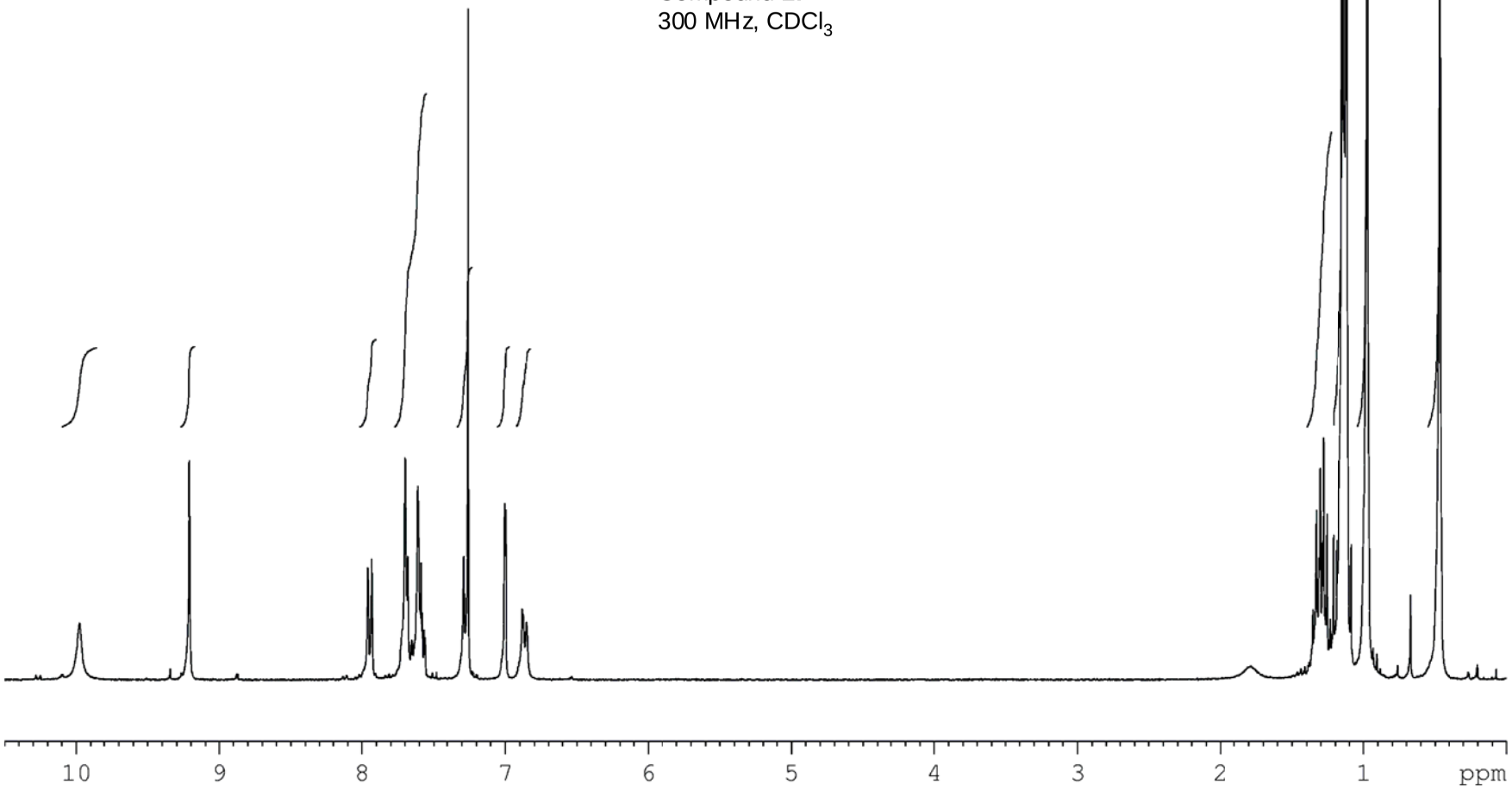
Compound **26**
300 MHz, $CDCl_3$



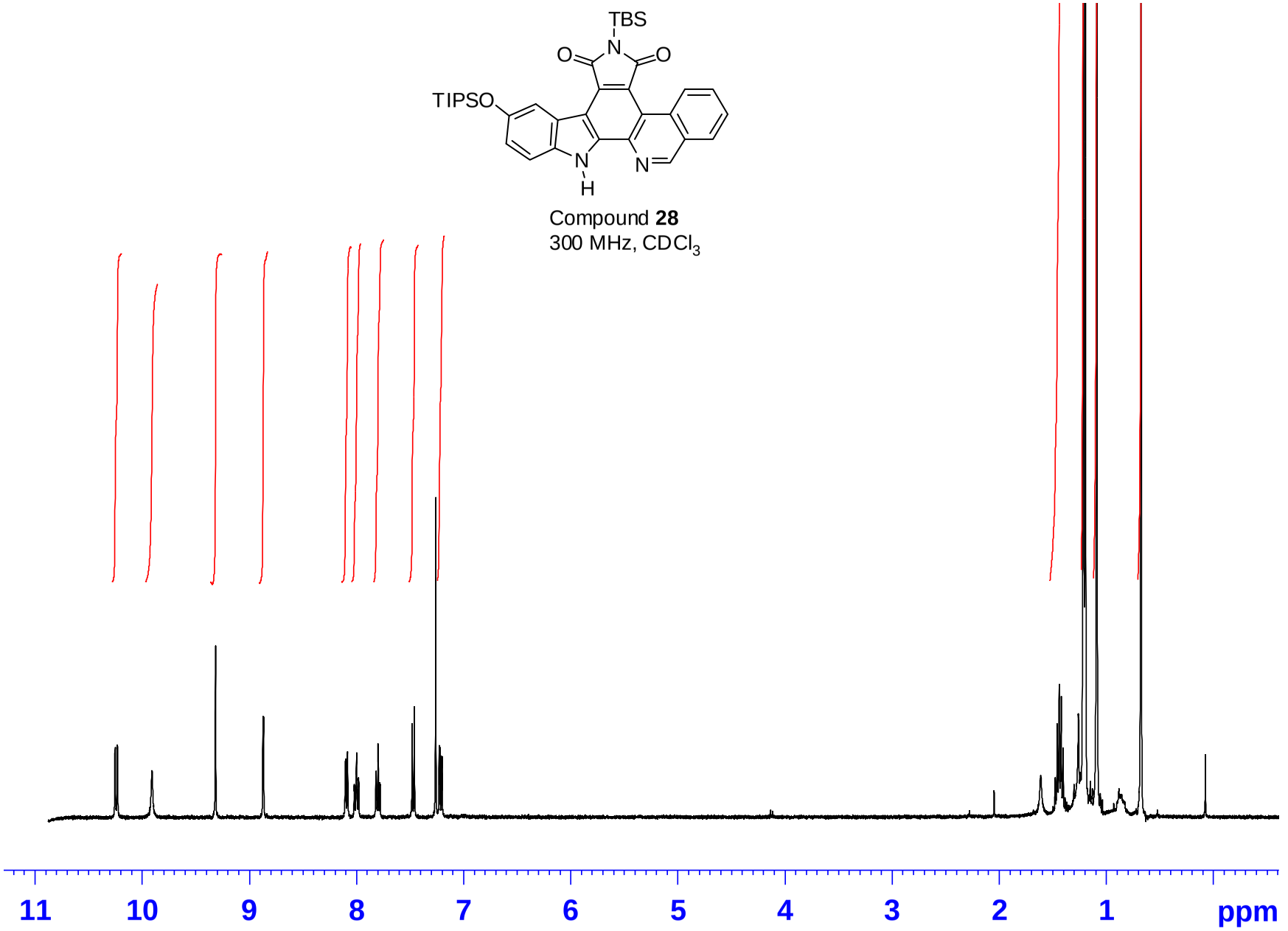

TIPSO
N
H
N
Compound **26**
75 MHz, $CDCl_3$
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



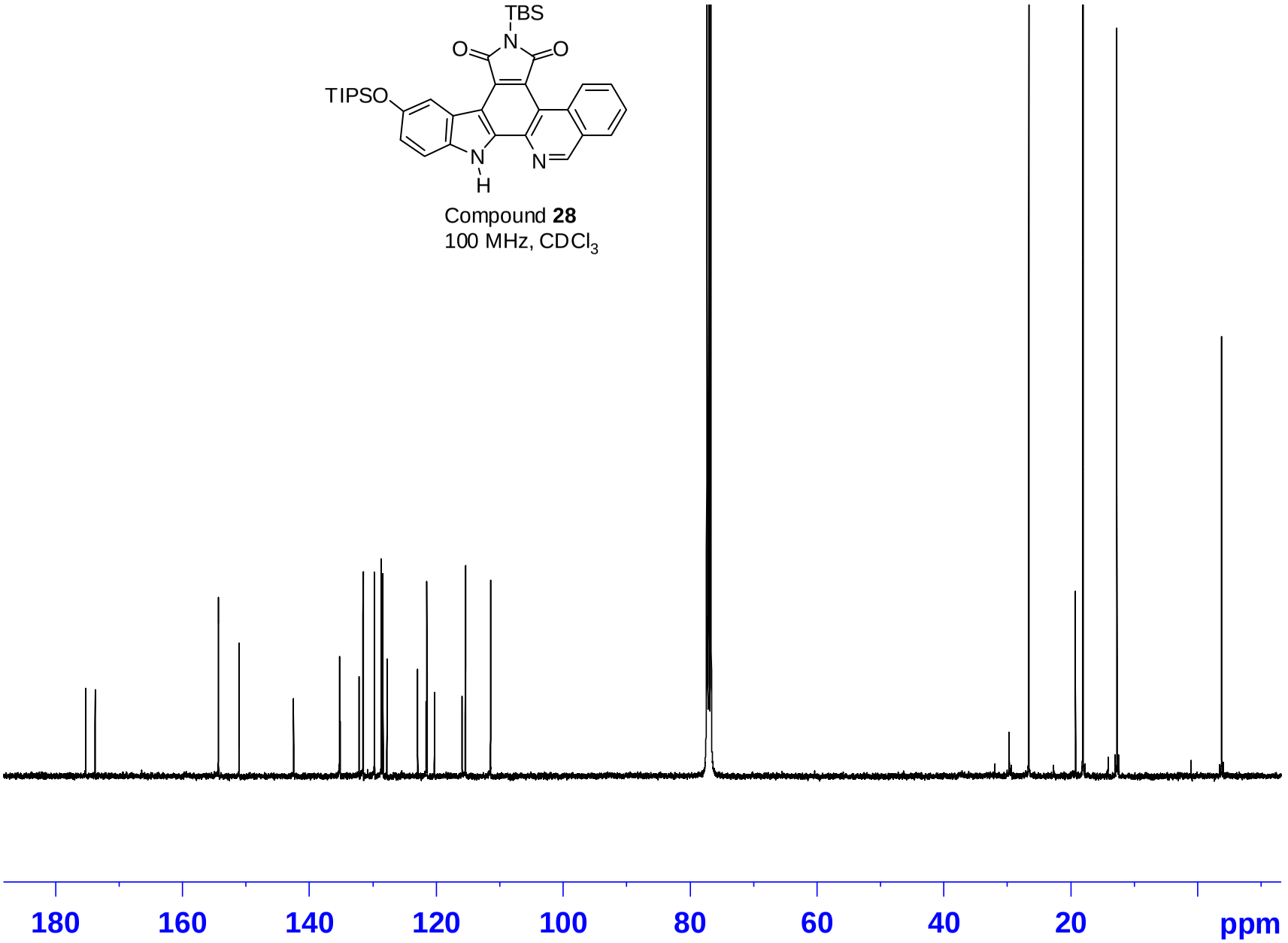
Compound **27**
300 MHz, $CDCl_3$

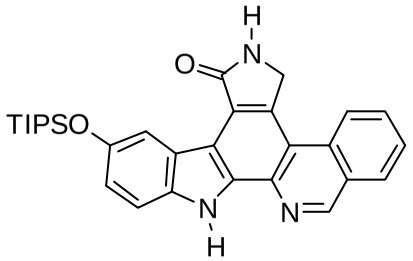


Compound **28**
300 MHz, $CDCl_3$

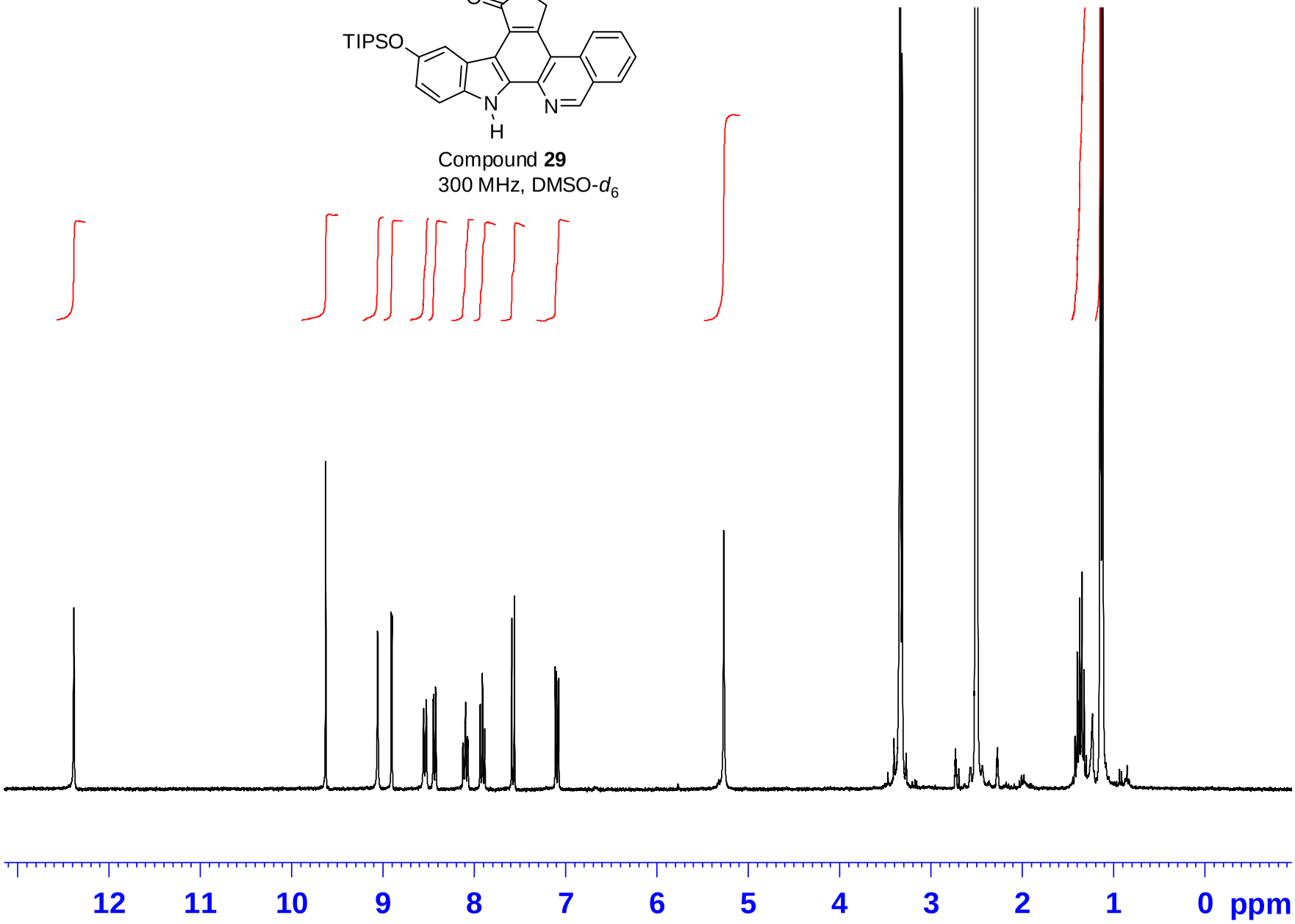


Compound **28**
100 MHz, $CDCl_3$

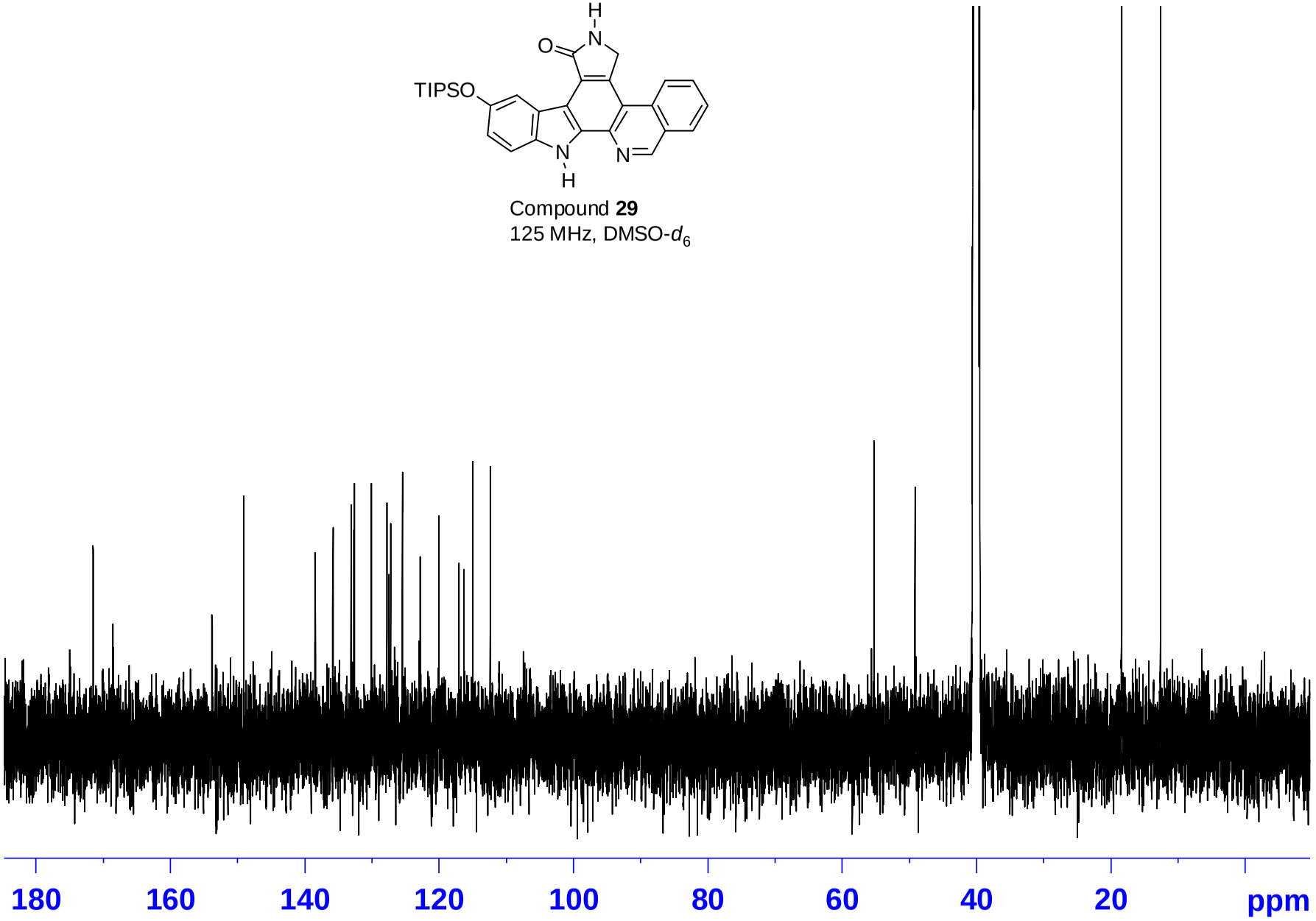


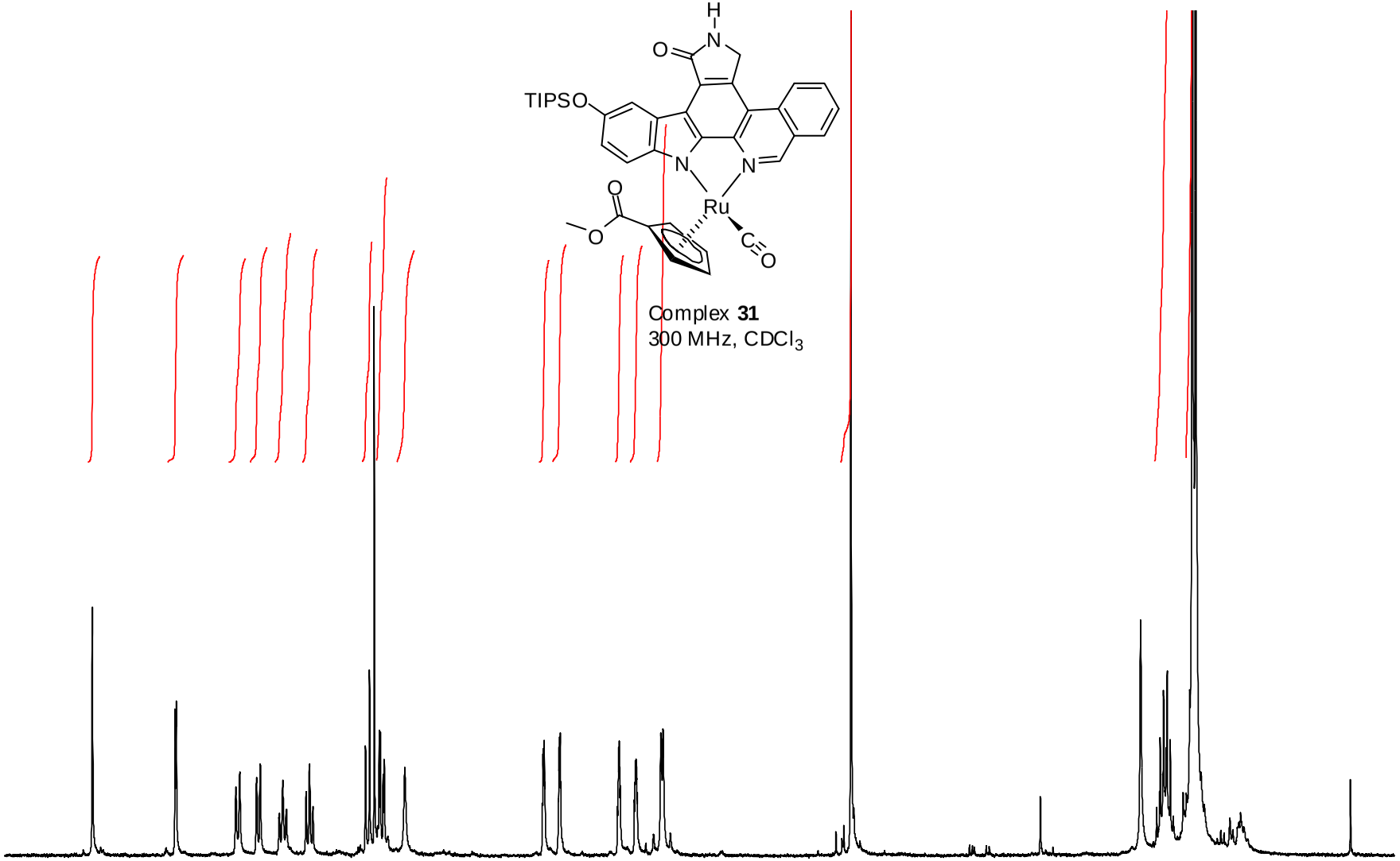


Compound **29**
300 MHz, DMSO-d_6

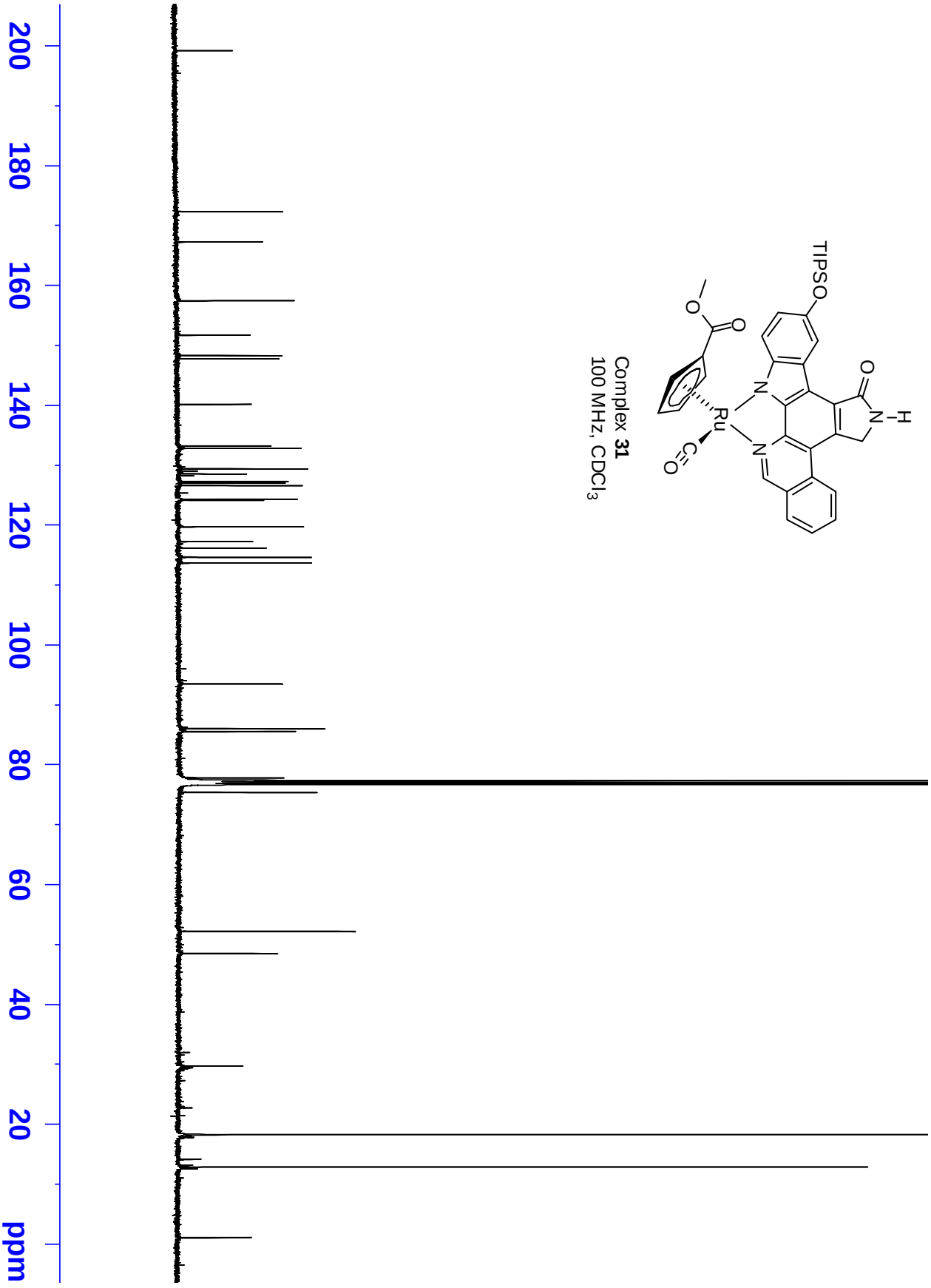


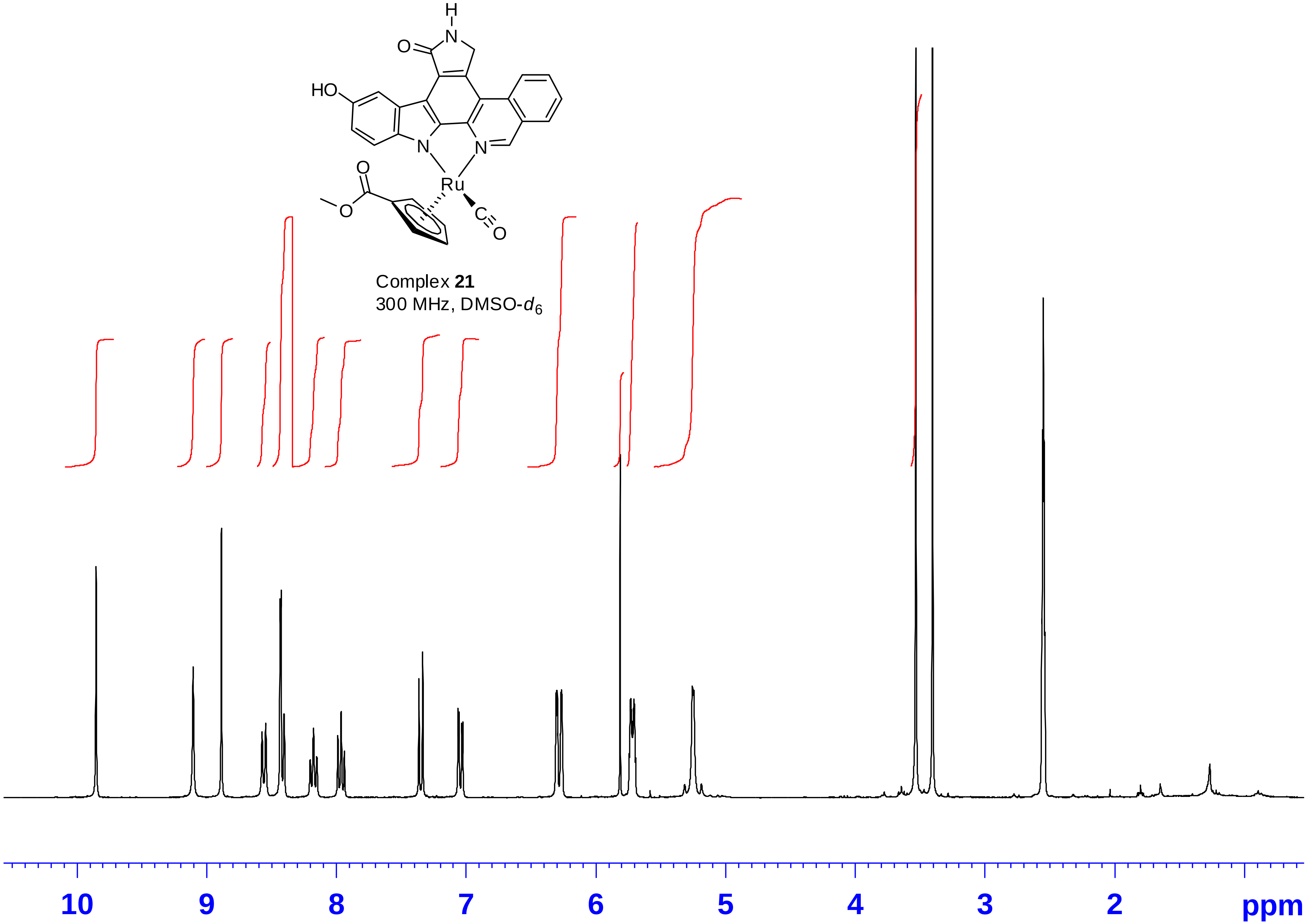
Compound **29**
125 MHz, DMSO-d_6





Complex **31**
300 MHz, $CDCl_3$


200
180
160
140
120
100
80
60
40
20
ppm
Complex 31
100 MHz, CDCl3
TIPSO
O
O
N
H
Ru
N
N
O
O
C
O



Complex **21**
300 MHz, DMSO-d_6

Complex **21**
100 MHz, DMSO-d_6