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SUPPORTING INFORMATION

Microwave Assisted Synthesis of Tetracyclic 2, 5-Diketopiperazines on Soluble Polymer Support: A Structural Analogue of Tadalafil

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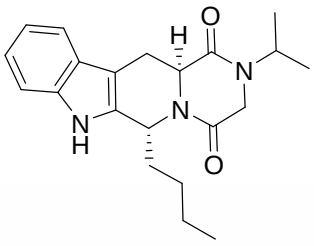
Table of contents

General Methods

Dichloromethane was distilled from calcium hydride before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated Kieselgel 60 F254 plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230-400 mesh). The microwave-assisted polymer-bound reactions described here were performed in CEM Discover Microwave System at a frequency of 2450 Hz (0–300 W) in open vessel system. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker DX-300 spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL TMS-HX 110 mass spectrometer. Optical rotations are reported as $[\alpha]^{20}_{D}$. PEG was purchased from SHOWA.

Crystal Data



7a trans

IC10636 in $P2_12_12_1$

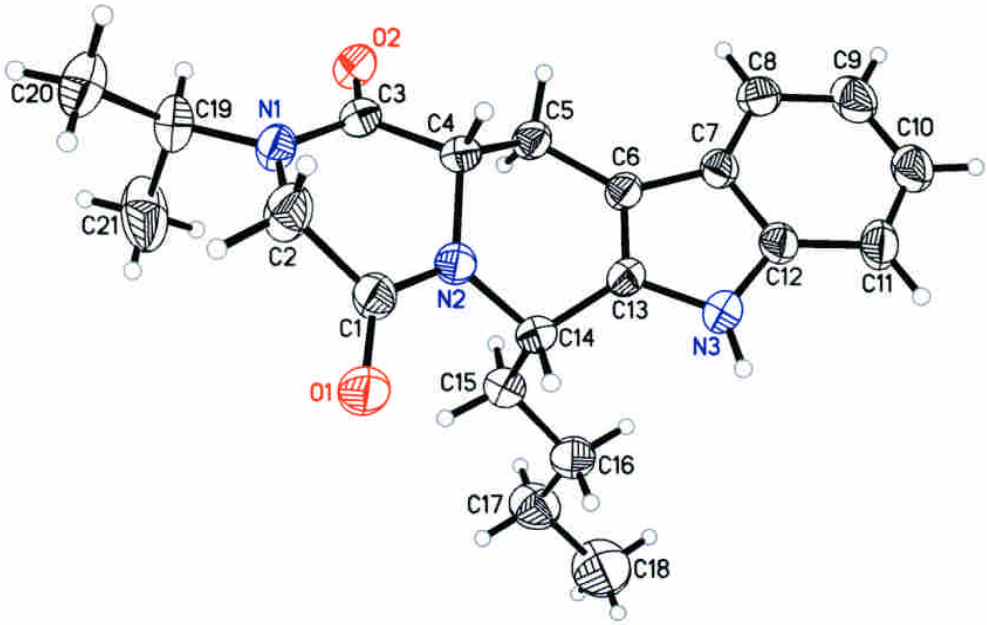


Table 1. Crystal data and structure refinement for ic10636.

Identification code	ic10636
Diffractometer used	Nonius KappaCCD
Empirical formula	$C_{22}H_{29}Cl_2N_3O_2$
Formula weight	438.38
Temperature	295(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.8353(2) Å alpha = 90° b = 14.8932(3) Å beta = 90° c = 18.6279(4) Å gamma = 90°
Volume, Z	2451.17(9) $Å^3$, 4
Density (calculated)	1.188 Mg/m^3
Absorption coefficient	0.286 mm^{-1}
F(000)	928
Crystal size	0.20 x 0.15 x 0.10 mm
θ range for data collection	1.75 to 27.48°
Limiting indices	$-11 \le h \le 11$, $-19 \le k \le 19$, $-23 \le l \le 24$
Reflections collected	15287
Independent reflections	5545 (R_{int} = 0.0349)
Completeness to θ = 27.48°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.929 and 0.914
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5545 / 0 / 282
Goodness-of-fit on F^2	1.690
Final R indices [I>2σ(I)]	R1 = 0.0997, wR2 = 0.2497
R indices (all data)	R1 = 0.1415, wR2 = 0.2664
Absolute structure parameter	0.1(2)
Extinction coefficient	0.086(10)
Largest diff. peak and hole	0.870 and -0.310 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for ic10636. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

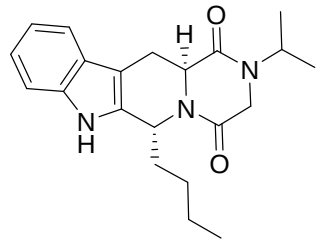
	x	y	z	U(eq)
O(1)	5553(4)	8244(2)	4364(2)	83(1)
O(2)	4378(3)	8233(2)	1619(1)	64(1)
N(1)	6152(3)	8310(2)	2503(2)	57(1)
N(2)	3940(3)	7812(2)	3476(2)	56(1)
N(3)	513(4)	6648(2)	4122(2)	61(1)
C(1)	5309(4)	8030(3)	3730(2)	60(1)
C(2)	6572(5)	7999(4)	3204(2)	76(1)
C(3)	4805(4)	8039(2)	2232(2)	49(1)
C(4)	3853(4)	7466(2)	2722(2)	47(1)
C(5)	2217(4)	7433(3)	2440(2)	56(1)
C(6)	1224(4)	7004(2)	3001(2)	50(1)
C(7)	-30(4)	6392(2)	2962(2)	55(1)
C(8)	-841(4)	5995(3)	2400(2)	68(1)
C(9)	-2029(5)	5415(3)	2583(3)	85(2)
C(10)	-2377(5)	5214(3)	3285(3)	82(1)
C(11)	-1584(5)	5586(3)	3858(3)	72(1)
C(12)	-424(4)	6189(2)	3675(2)	56(1)
C(13)	1509(4)	7139(3)	3701(2)	53(1)
C(14)	2656(5)	7783(3)	3984(2)	57(1)
C(15)	1976(5)	8720(3)	4057(2)	68(1)
C(16)	697(5)	8776(3)	4602(3)	77(1)
C(17)	170(7)	9748(4)	4730(3)	98(2)
C(18)	-1133(10)	9755(6)	5282(5)	151(3)
C(19)	7111(4)	8947(3)	2099(3)	70(1)
C(20)	8751(5)	8683(4)	2116(3)	90(2)
C(21)	6881(7)	9872(3)	2409(5)	131(3)
C(22)	407(9)	8179(6)	-414(4)	136(3)
Cl(1)	-636(8)	9060(4)	-410(5)	244(4)
Cl(2)	2176(13)	8191(11)	-801(7)	288(8)
Cl(1')	1166(8)	8059(4)	439(2)	177(3)
Cl(2')	1617(14)	8471(8)	-1102(5)	244(7)

Table 3. Bond lengths [Å] and angles [°] for ic10636.

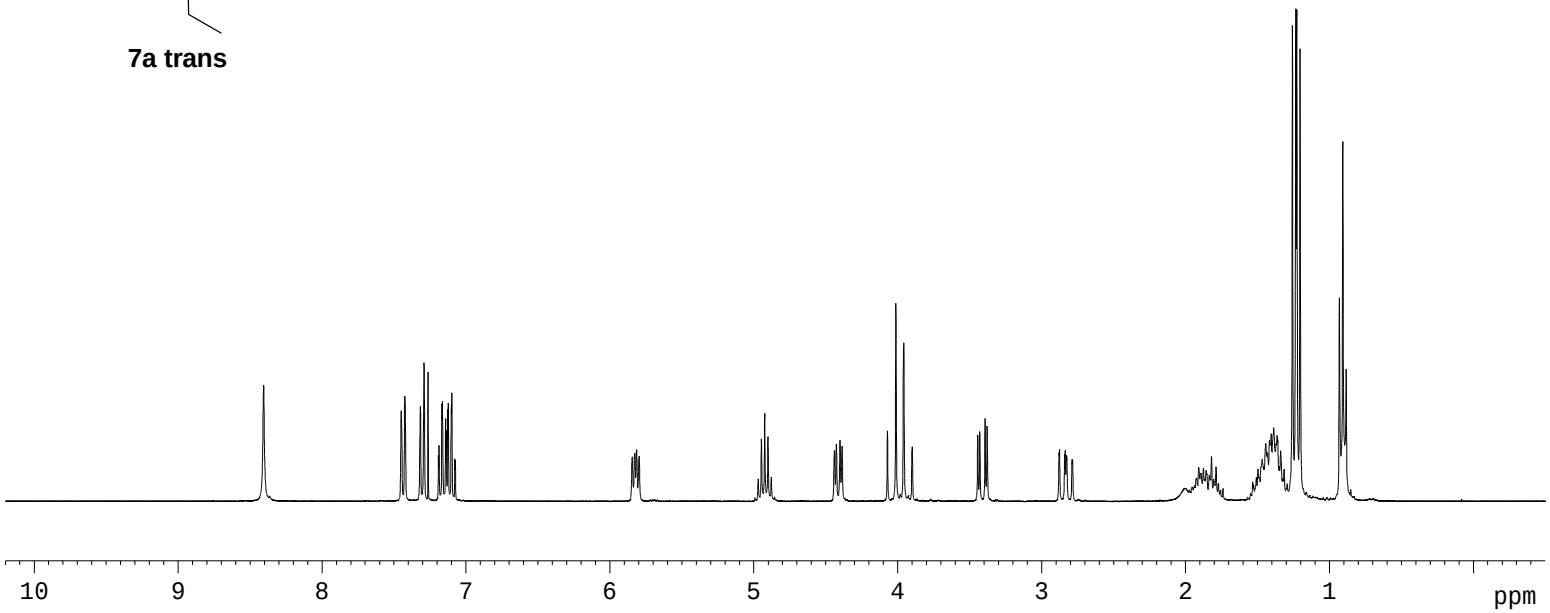
O(1)-C(1)	1.242(4)	O(2)-C(3)	1.236(4)
N(1)-C(3)	1.355(5)	N(1)-C(2)	1.434(5)
N(1)-C(19)	1.479(5)	N(2)-C(1)	1.339(5)
N(2)-C(14)	1.478(5)	N(2)-C(4)	1.498(5)
N(3)-C(12)	1.359(5)	N(3)-C(13)	1.388(5)
C(1)-C(2)	1.486(6)	C(3)-C(4)	1.505(5)
C(4)-C(5)	1.539(5)	C(5)-C(6)	1.506(5)
C(6)-C(13)	1.342(5)	C(6)-C(7)	1.436(5)
C(7)-C(8)	1.400(5)	C(7)-C(12)	1.405(5)
C(8)-C(9)	1.401(6)	C(9)-C(10)	1.376(7)
C(10)-C(11)	1.393(7)	C(11)-C(12)	1.405(6)
C(13)-C(14)	1.493(6)	C(14)-C(15)	1.525(6)
C(15)-C(16)	1.522(6)	C(16)-C(17)	1.539(7)
C(17)-C(18)	1.544(9)	C(19)-C(20)	1.502(6)
C(19)-C(21)	1.508(8)	C(22)-Cl(1)	1.603(11)
C(22)-Cl(2)	1.723(11)	C(22)-Cl(2')	1.725(11)
C(22)-Cl(1')	1.733(9)		

C(3)-N(1)-C(2)	118.2(3)	C(3)-N(1)-C(19)	120.3(3)
C(2)-N(1)-C(19)	121.5(3)	C(1)-N(2)-C(14)	118.2(3)
C(1)-N(2)-C(4)	117.5(3)	C(14)-N(2)-C(4)	123.5(3)
C(12)-N(3)-C(13)	107.7(3)	O(1)-C(1)-N(2)	123.8(4)
O(1)-C(1)-C(2)	120.3(4)	N(2)-C(1)-C(2)	116.0(3)
N(1)-C(2)-C(1)	113.3(3)	O(2)-C(3)-N(1)	122.9(3)
O(2)-C(3)-C(4)	121.5(3)	N(1)-C(3)-C(4)	115.6(3)
N(2)-C(4)-C(3)	110.2(3)	N(2)-C(4)-C(5)	112.2(3)
C(3)-C(4)-C(5)	109.7(3)	C(6)-C(5)-C(4)	109.0(3)
C(13)-C(6)-C(7)	106.8(3)	C(13)-C(6)-C(5)	120.0(3)
C(7)-C(6)-C(5)	133.1(3)	C(8)-C(7)-C(12)	119.2(4)
C(8)-C(7)-C(6)	134.5(4)	C(12)-C(7)-C(6)	106.2(3)
C(7)-C(8)-C(9)	117.6(4)	C(10)-C(9)-C(8)	122.2(5)
C(9)-C(10)-C(11)	122.0(4)	C(10)-C(11)-C(12)	115.8(4)
N(3)-C(12)-C(11)	128.0(4)	N(3)-C(12)-C(7)	108.7(3)
C(11)-C(12)-C(7)	123.2(4)	C(6)-C(13)-N(3)	110.6(3)
C(6)-C(13)-C(14)	124.6(3)	N(3)-C(13)-C(14)	124.7(3)
N(2)-C(14)-C(13)	108.2(3)	N(2)-C(14)-C(15)	109.4(3)
C(13)-C(14)-C(15)	110.6(3)	C(16)-C(15)-C(14)	113.7(4)
C(15)-C(16)-C(17)	112.3(4)	C(16)-C(17)-C(18)	109.6(5)
N(1)-C(19)-C(20)	112.0(4)	N(1)-C(19)-C(21)	108.3(4)
C(20)-C(19)-C(21)	111.2(4)	Cl(1)-C(22)-Cl(2)	120.9(9)
Cl(1)-C(22)-Cl(2')	98.7(8)	Cl(2)-C(22)-Cl(2')	28.7(8)
Cl(1)-C(22)-Cl(1')	107.7(5)	Cl(2)-C(22)-Cl(1')	91.9(7)
Cl(2')-C(22)-Cl(1')	117.8(6)		

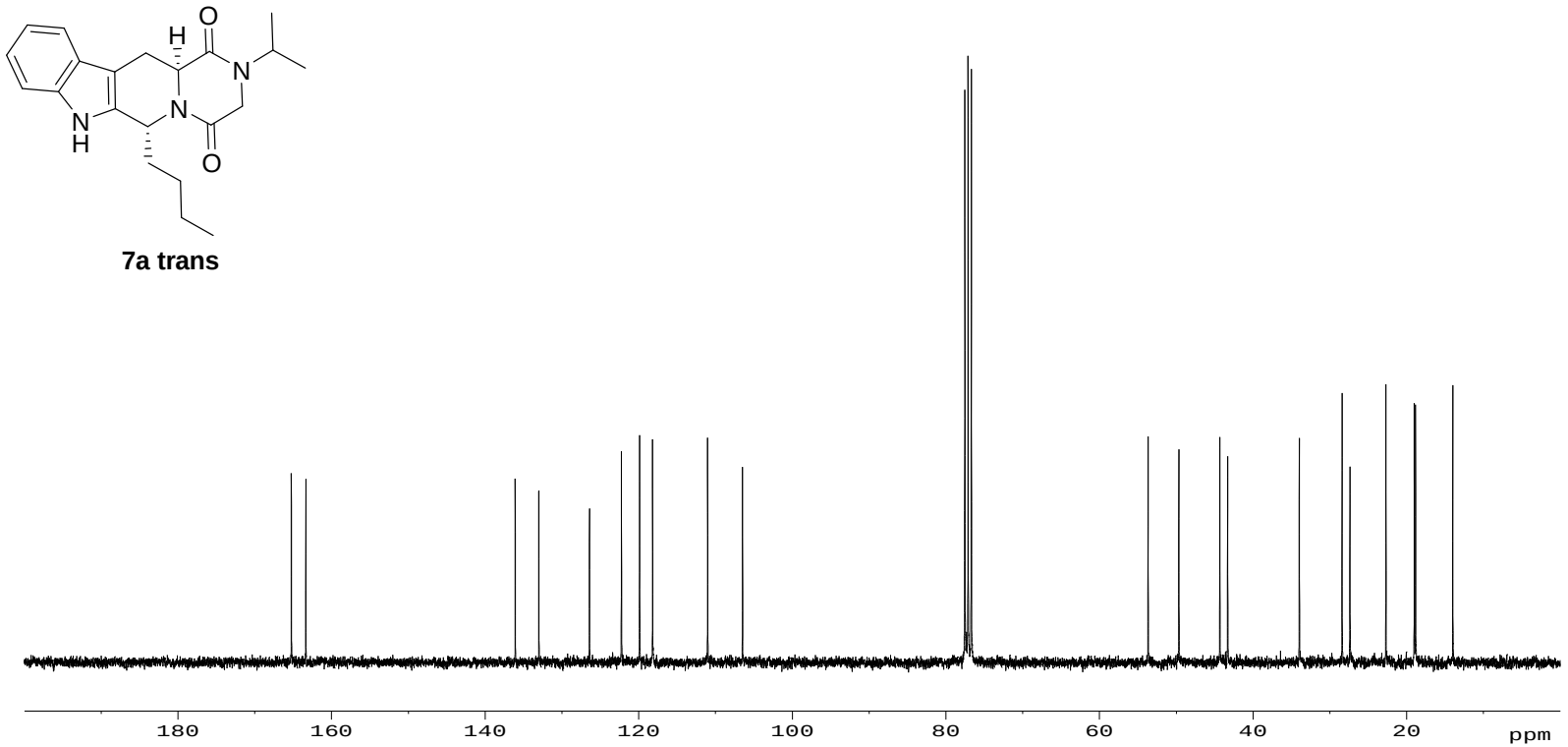
Symmetry transformations used to generate equivalent atoms:



7a trans

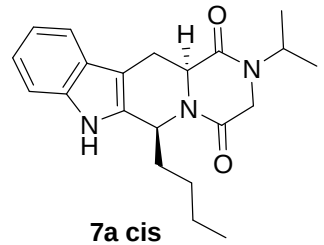


^{1}HNMR spectrum (300 MHz) of compound 7a (trans isomer) in $CDCl_3$

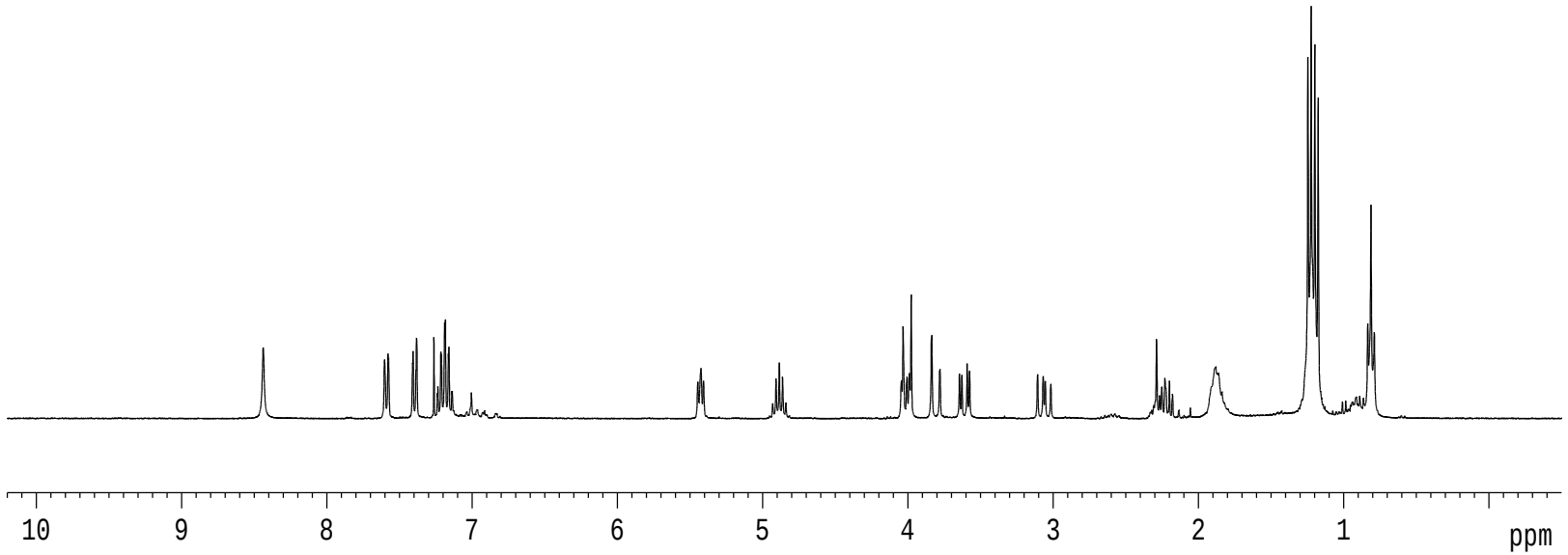


7a trans

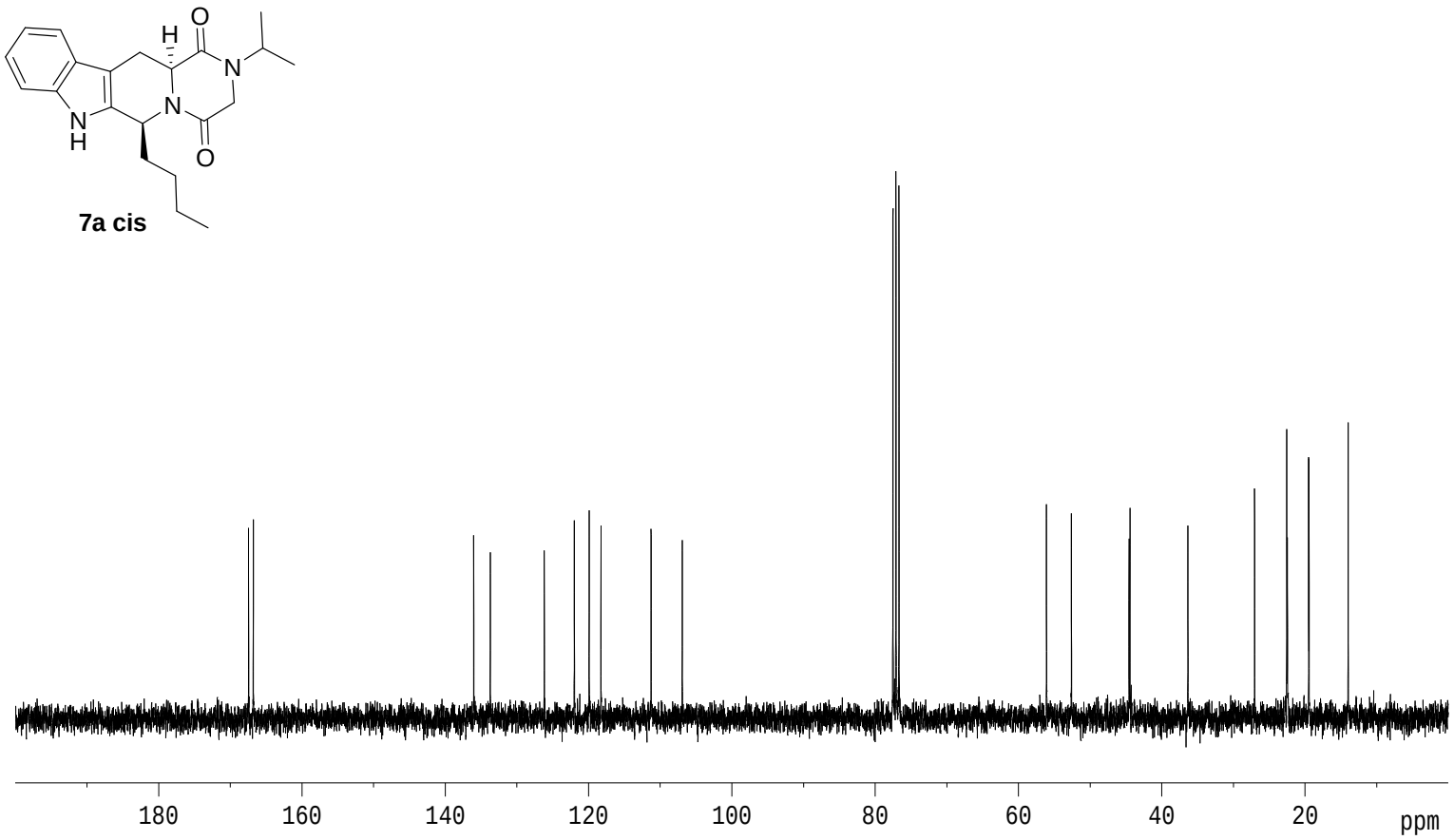
^{13}C NMR spectrum (75 MHz) of compound 7a (trans isomer) in $CDCl_3$



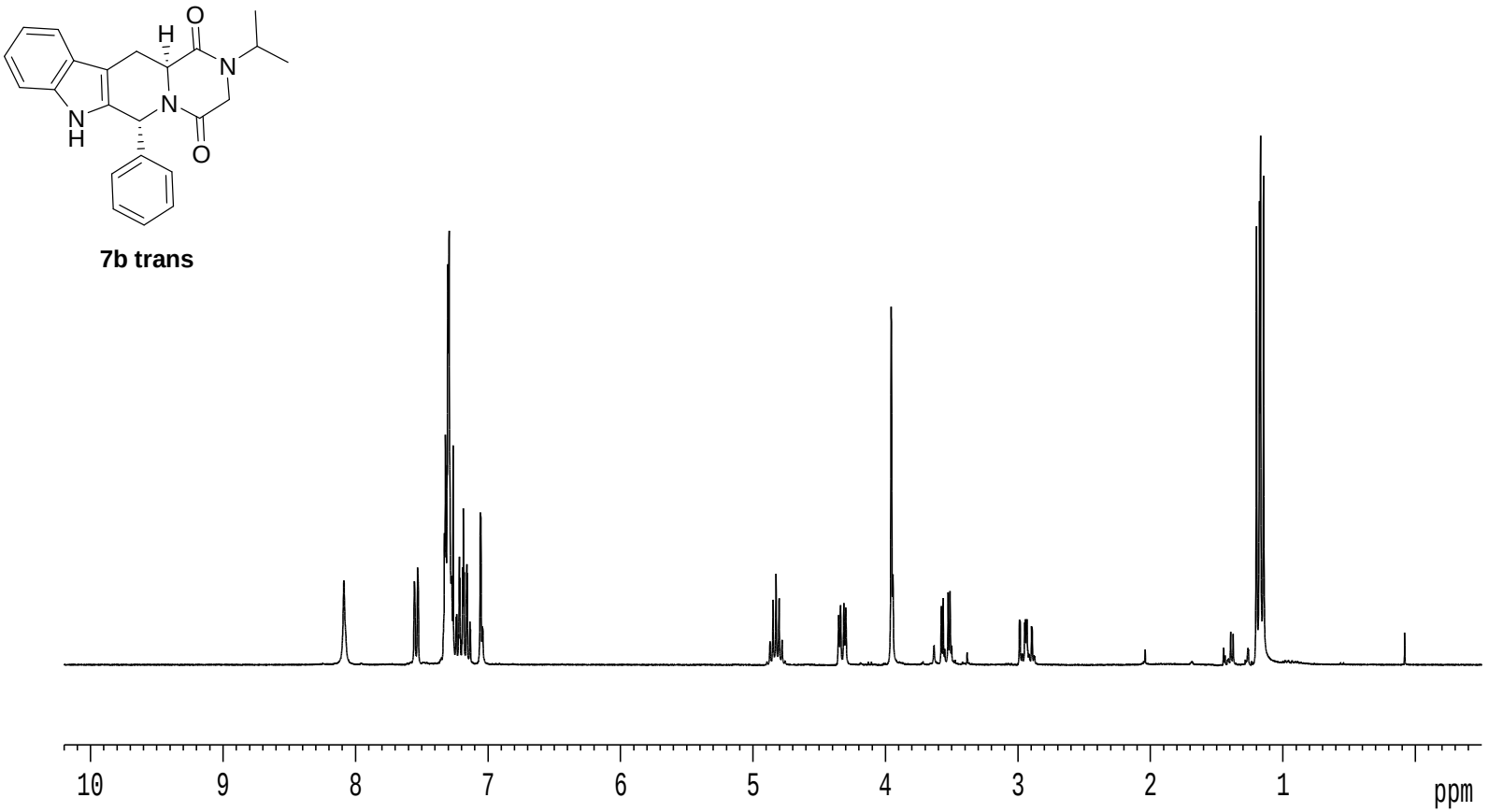
7a cis



^{1}HNMR spectrum (300 MHz) of compound 7a (cis isomer) in $CDCl_3$

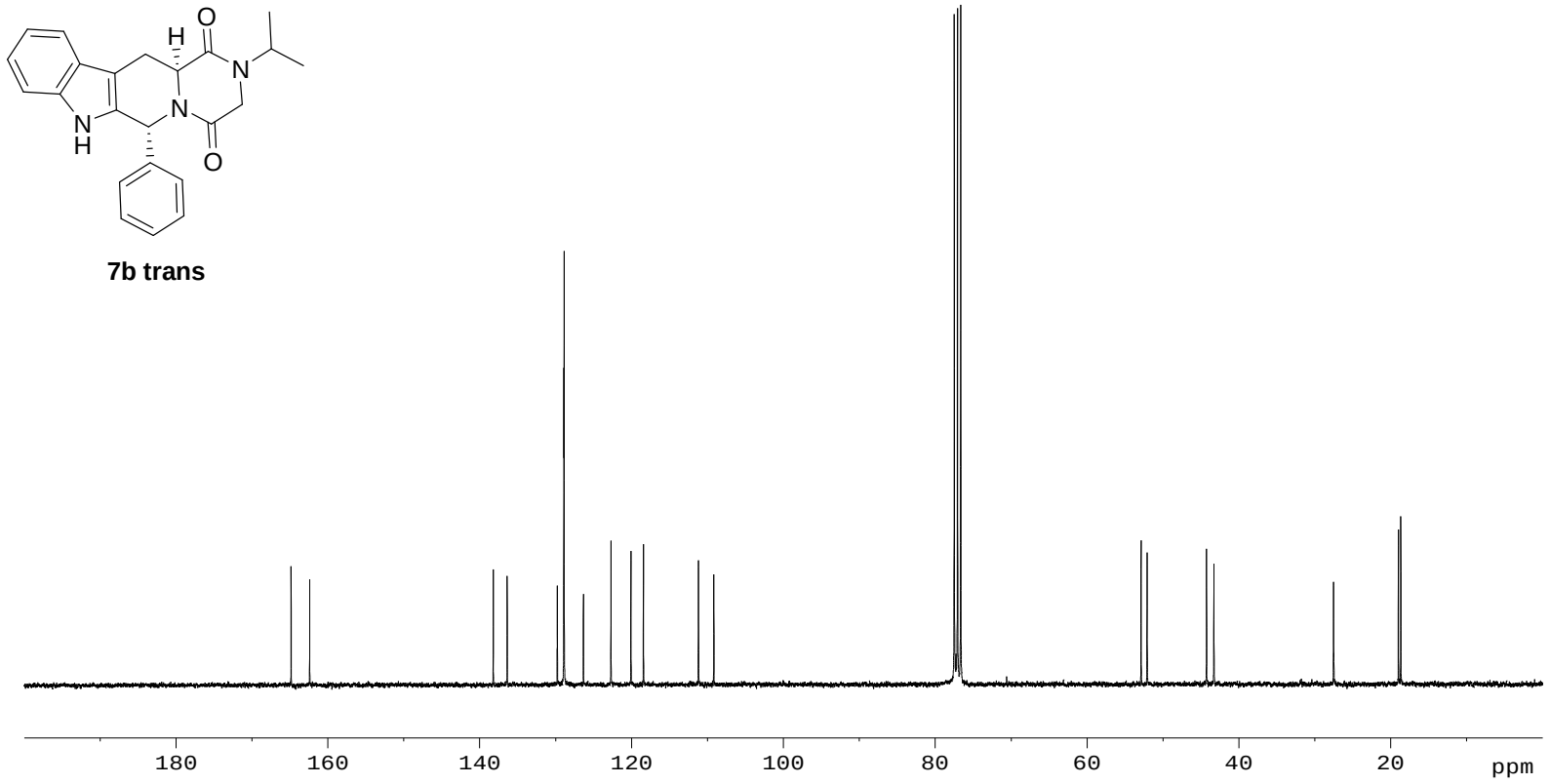


^{13}C NMR spectrum (75 MHz) of compound 7a (cis isomer) in $CDCl_3$

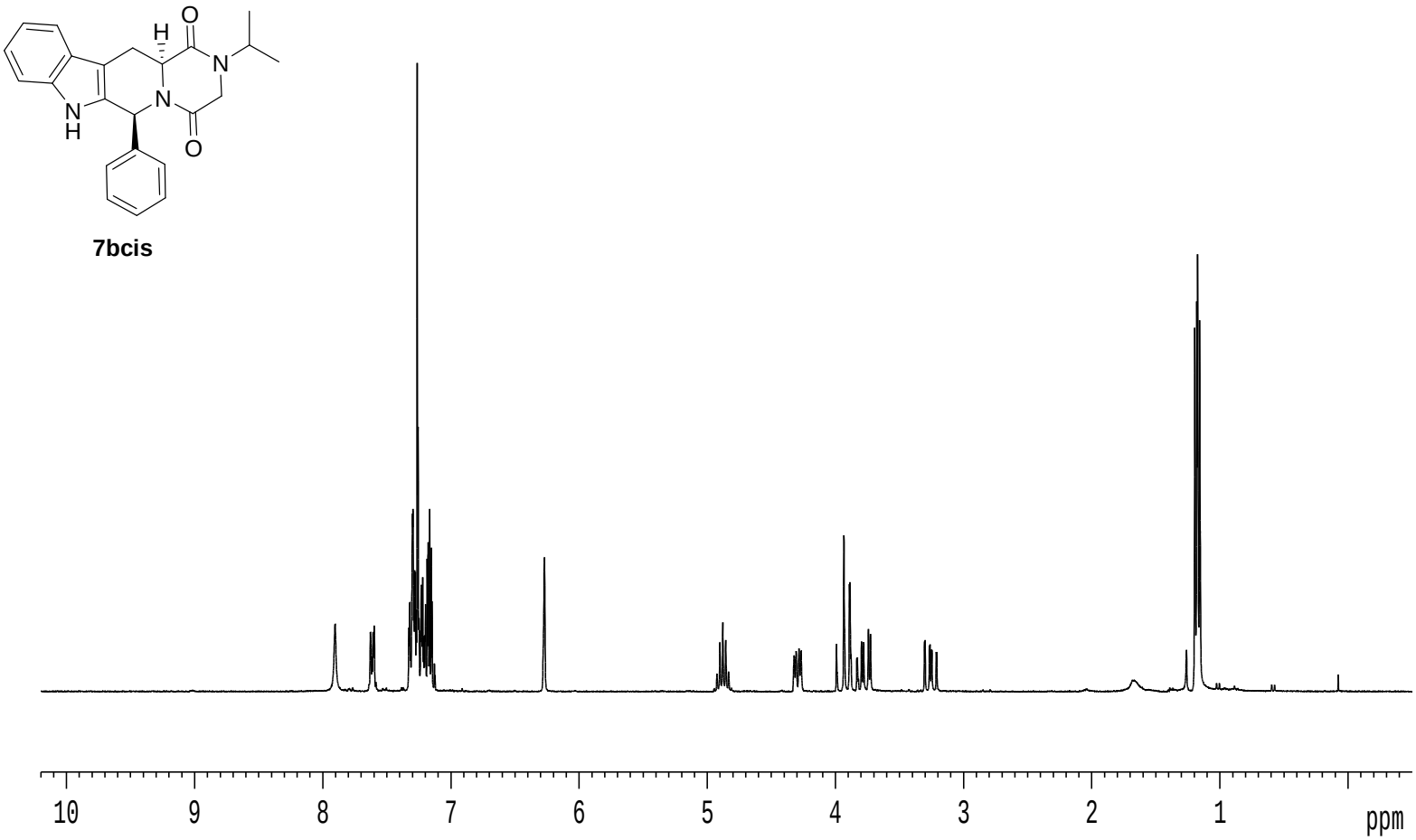


7b trans

^{1}HNMR spectrum (300 MHz) of compound 7b (trans isomer) in $CDCl_3$

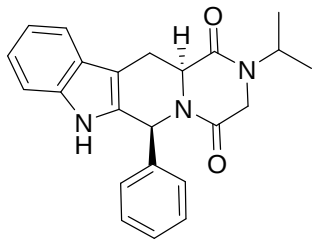


^{13}C NMR spectrum (75 MHz) of compound 7b (trans isomer) in $CDCl_3$



7bcis

^{1}HNMR spectrum (300 MHz) of compound 7b (cis isomer) in $CDCl_3$



7bcis

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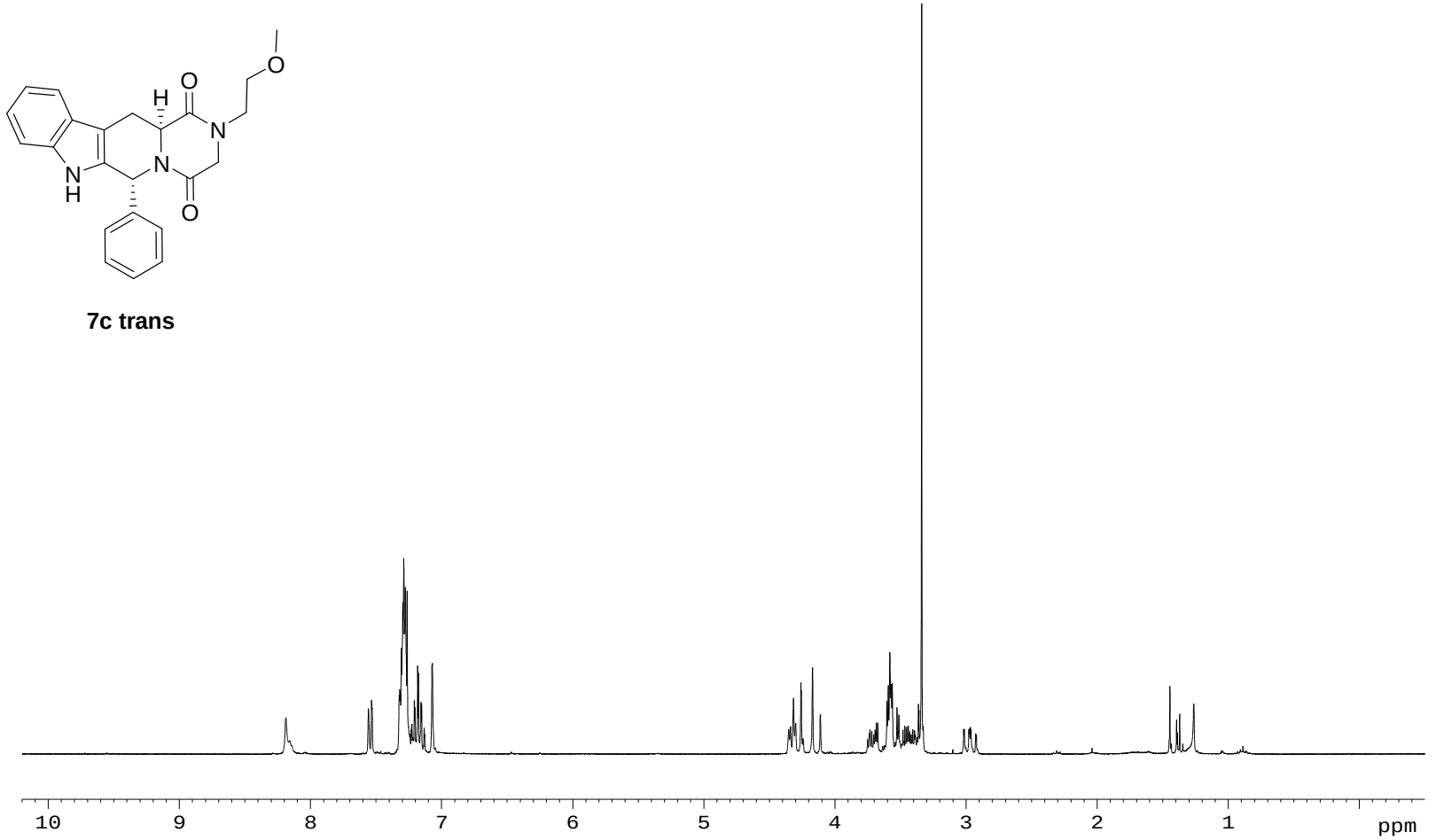
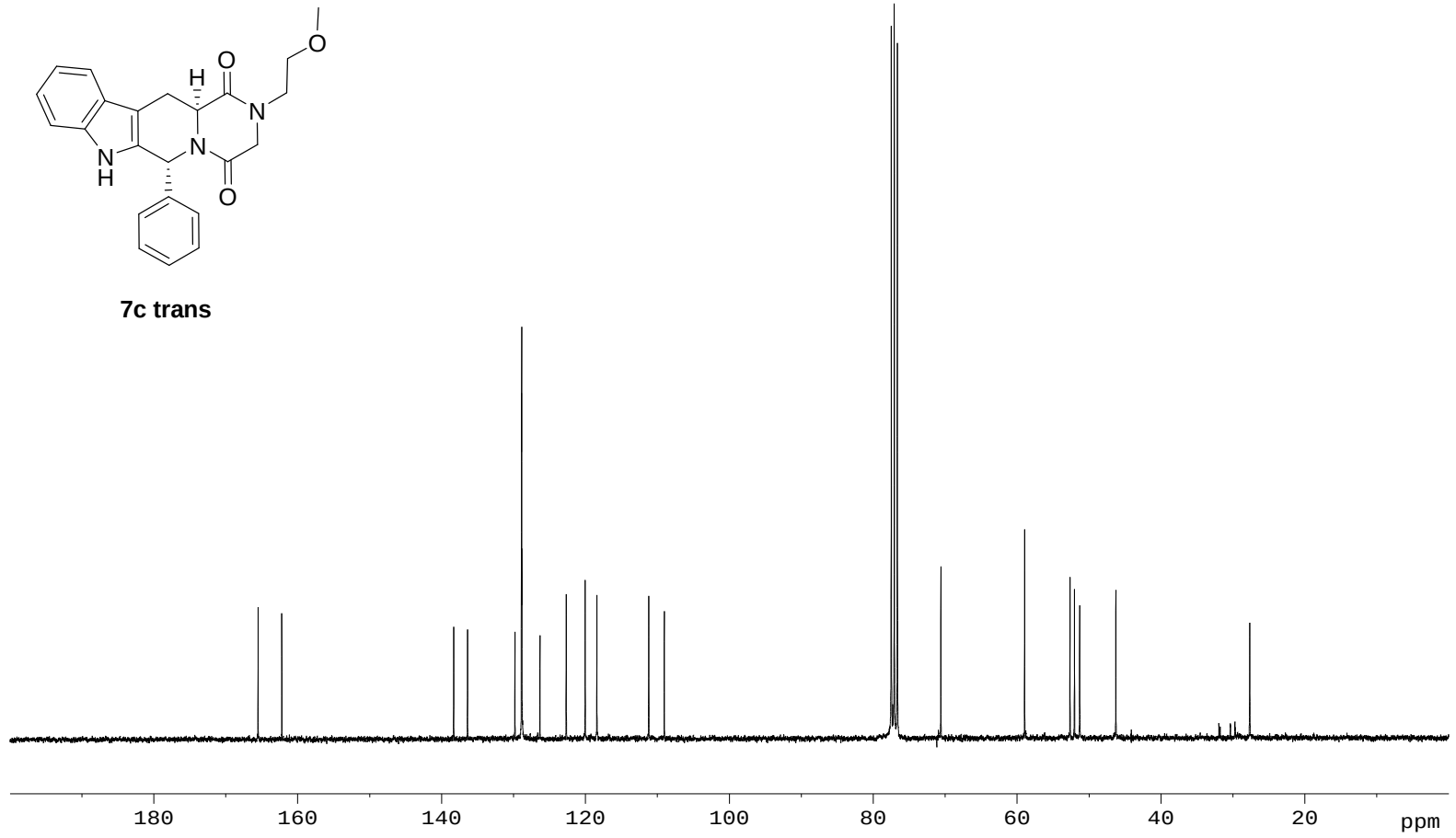


7c trans

^{1}HNMR spectrum (300 MHz) of compound 7c (trans isomer) in $CDCl_3$



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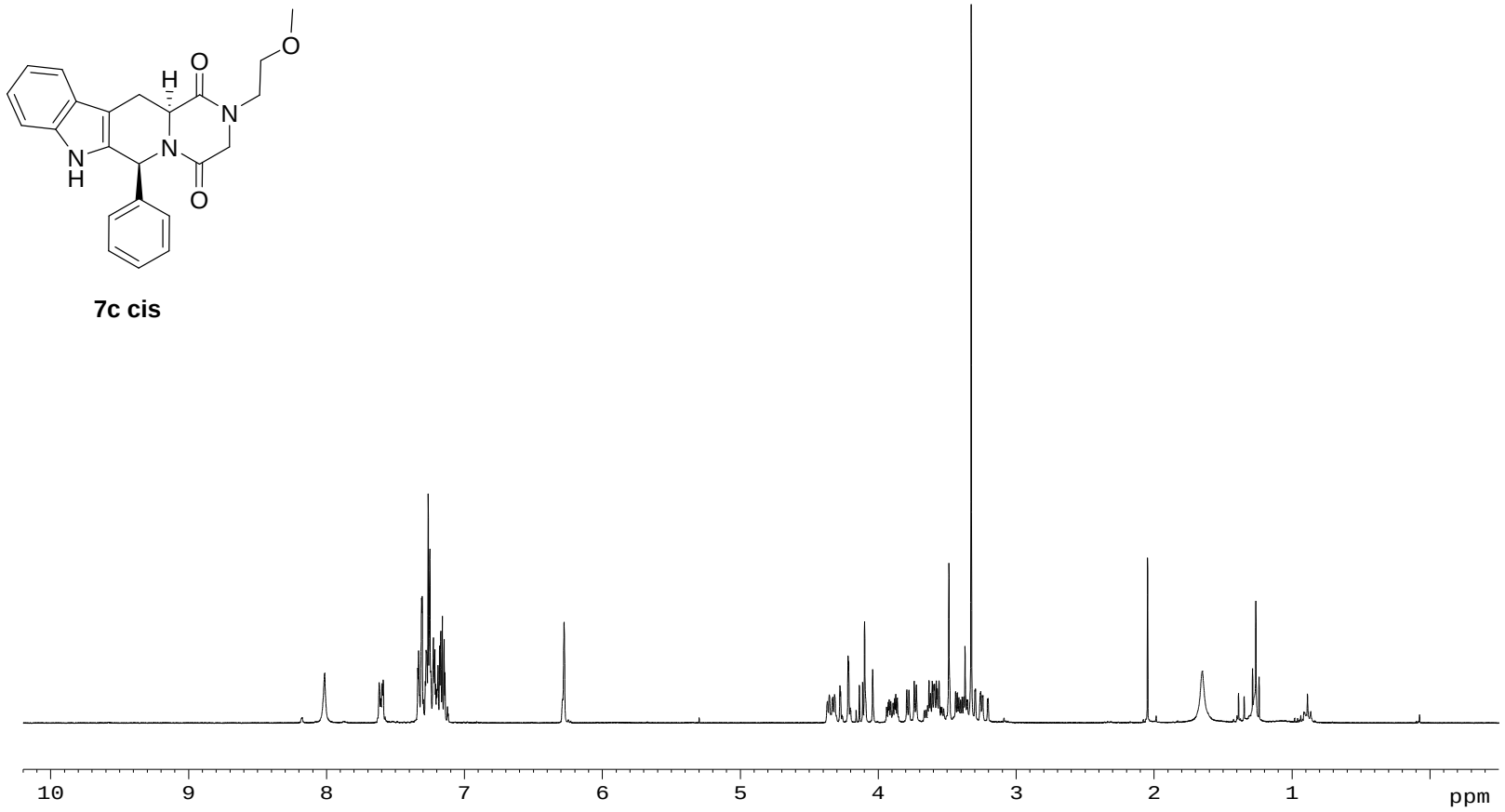
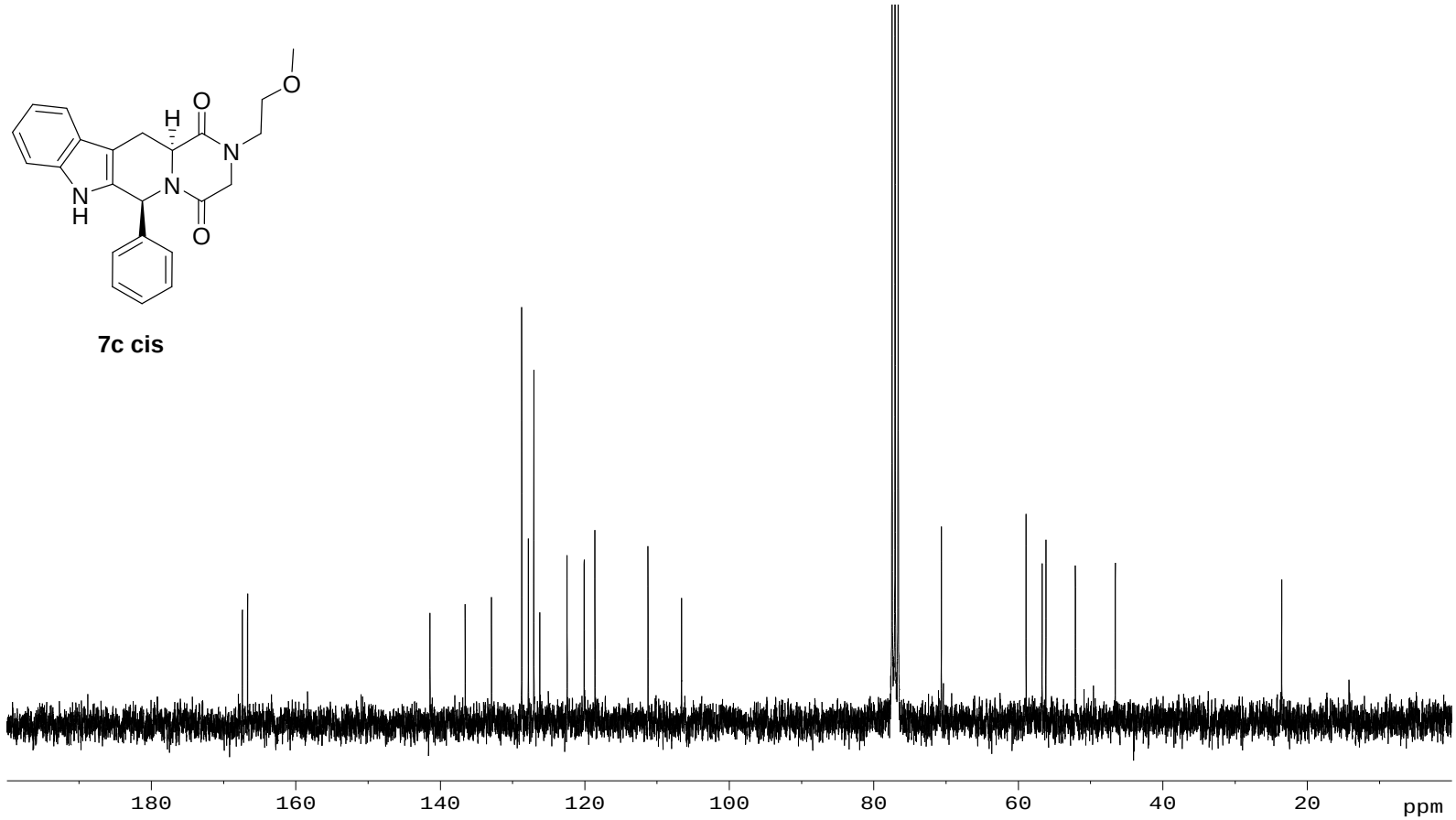
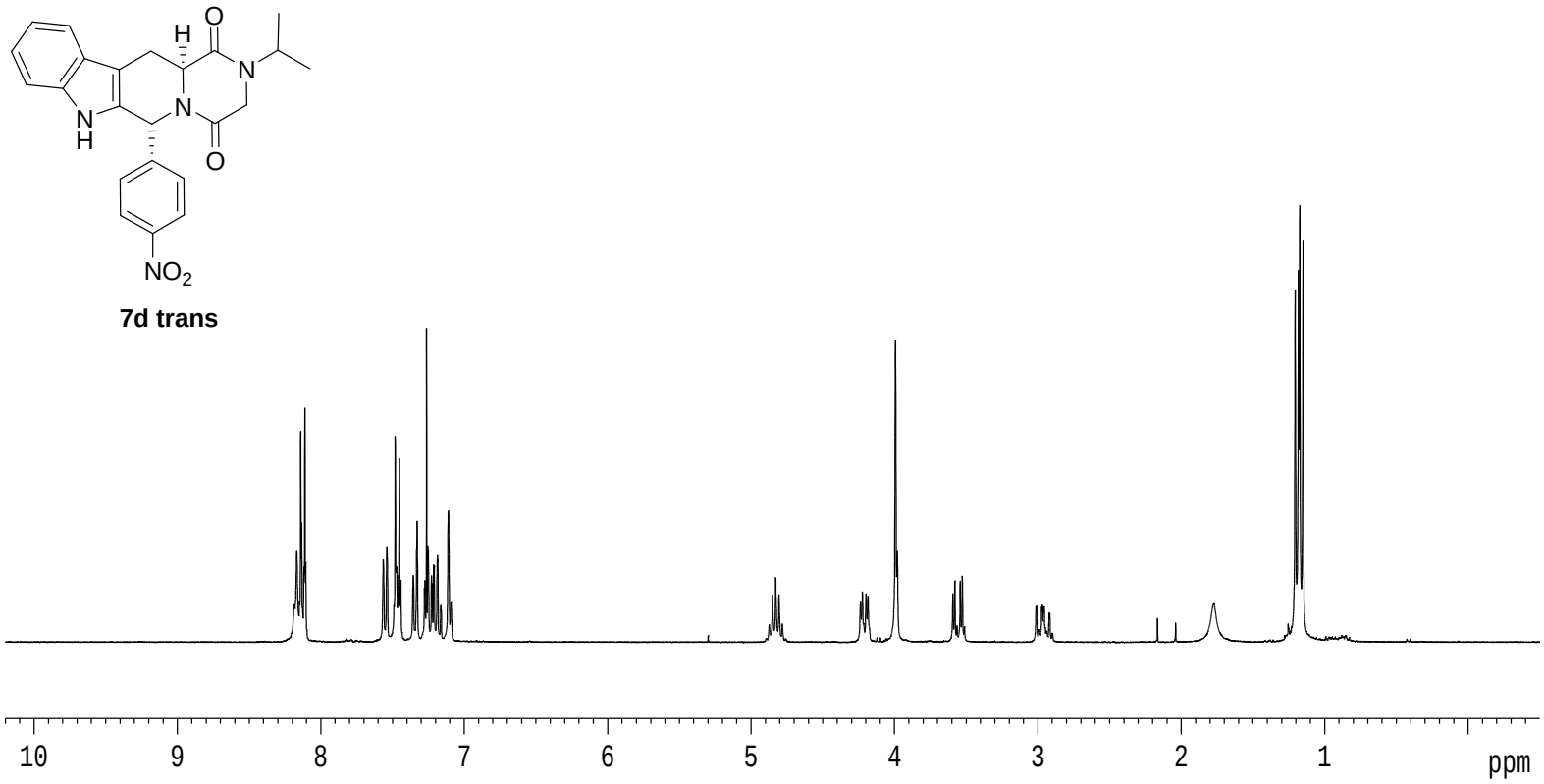


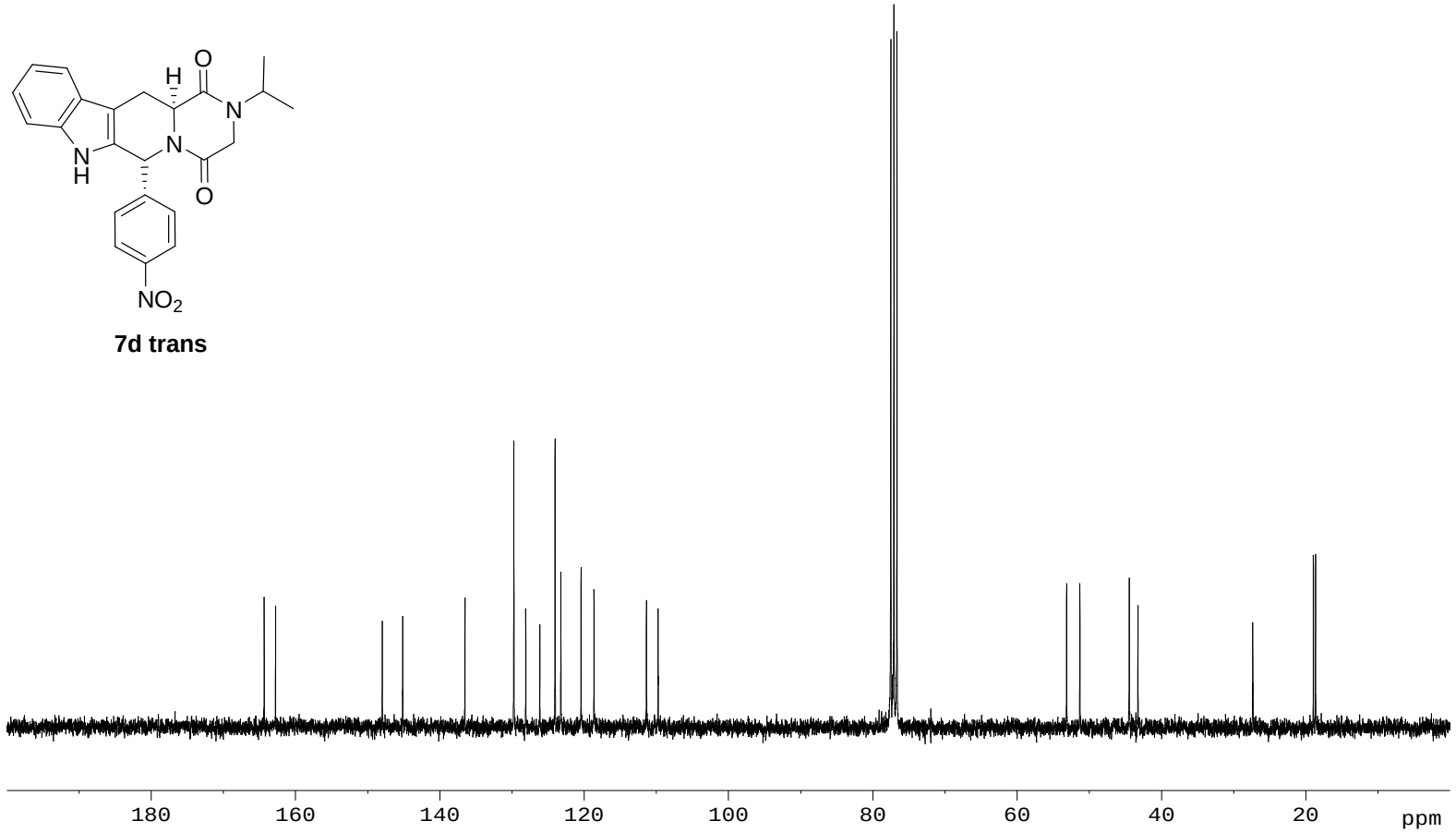
^{1}HNMR spectrum (300 MHz) of compound 7c (cis isomer) in $CDCl_3$



^{13}C NMR spectrum (75 MHz) of compound 7c (cis isomer) in $CDCl_3$

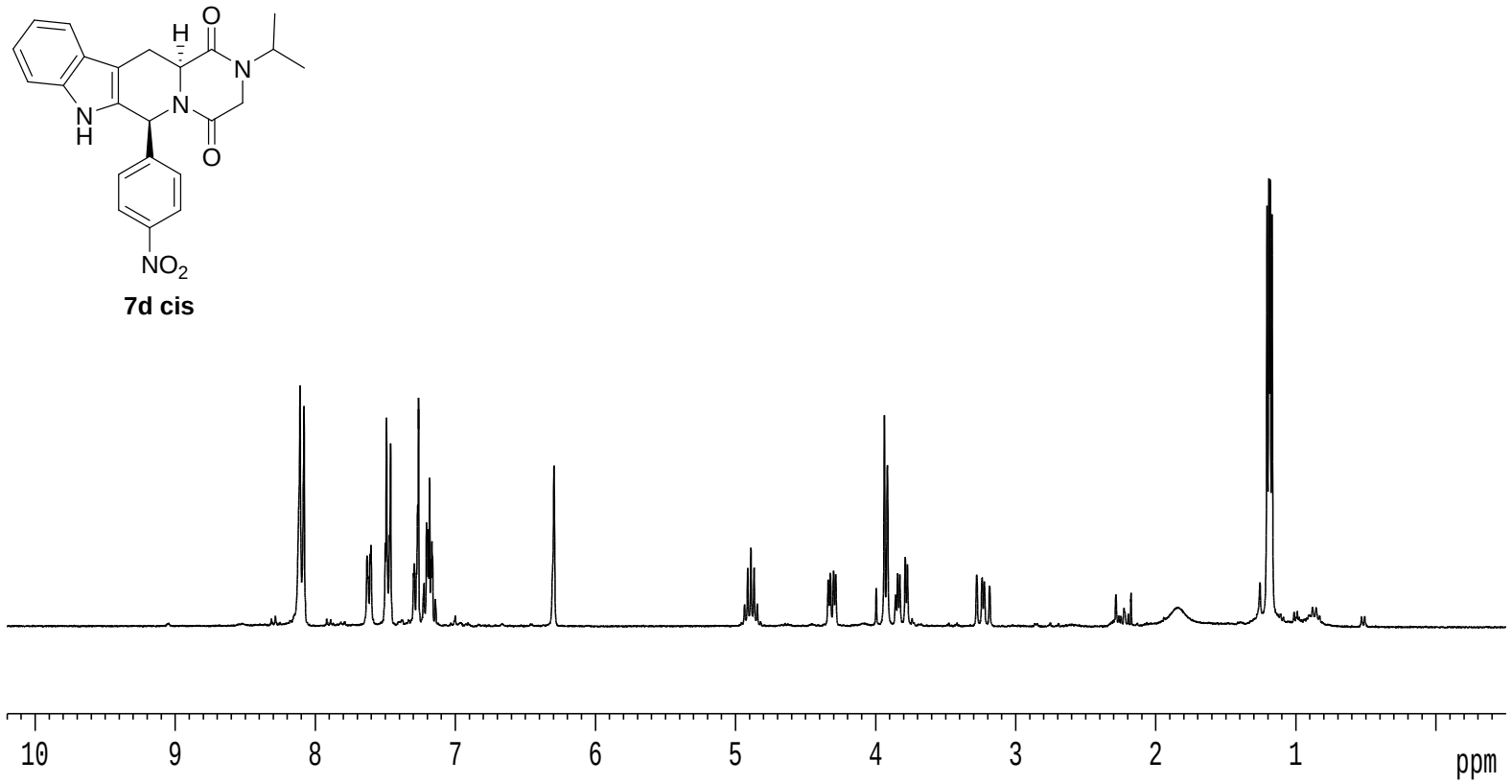


^{1}HNMR spectrum (300 MHz) of compound 7d (trans isomer) in $CDCl_3$



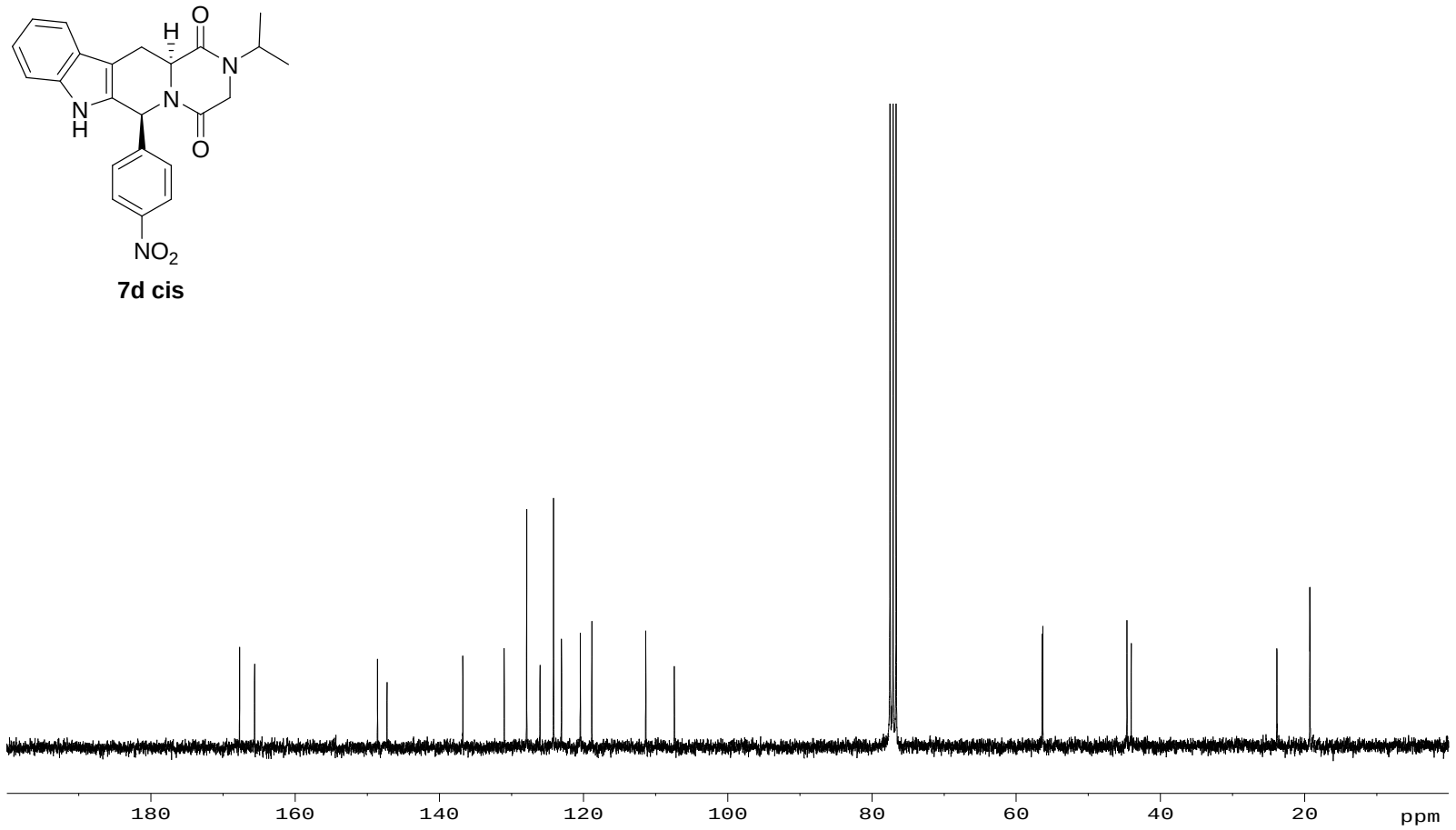
7d trans

^{13}C NMR spectrum (75 MHz) of compound 7d (trans isomer) in $CDCl_3$



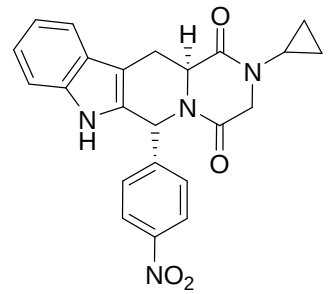
7d cis

^{1}HNMR spectrum (300 MHz) of compound 7d (cis isomer) in $CDCl_3$



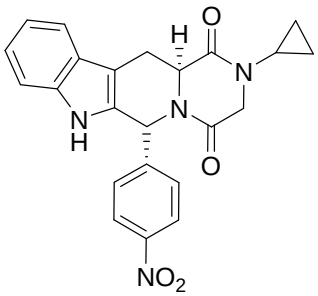
7d cis

^{13}C NMR spectrum (75 MHz) of compound 7d (cis isomer) in $CDCl_3$

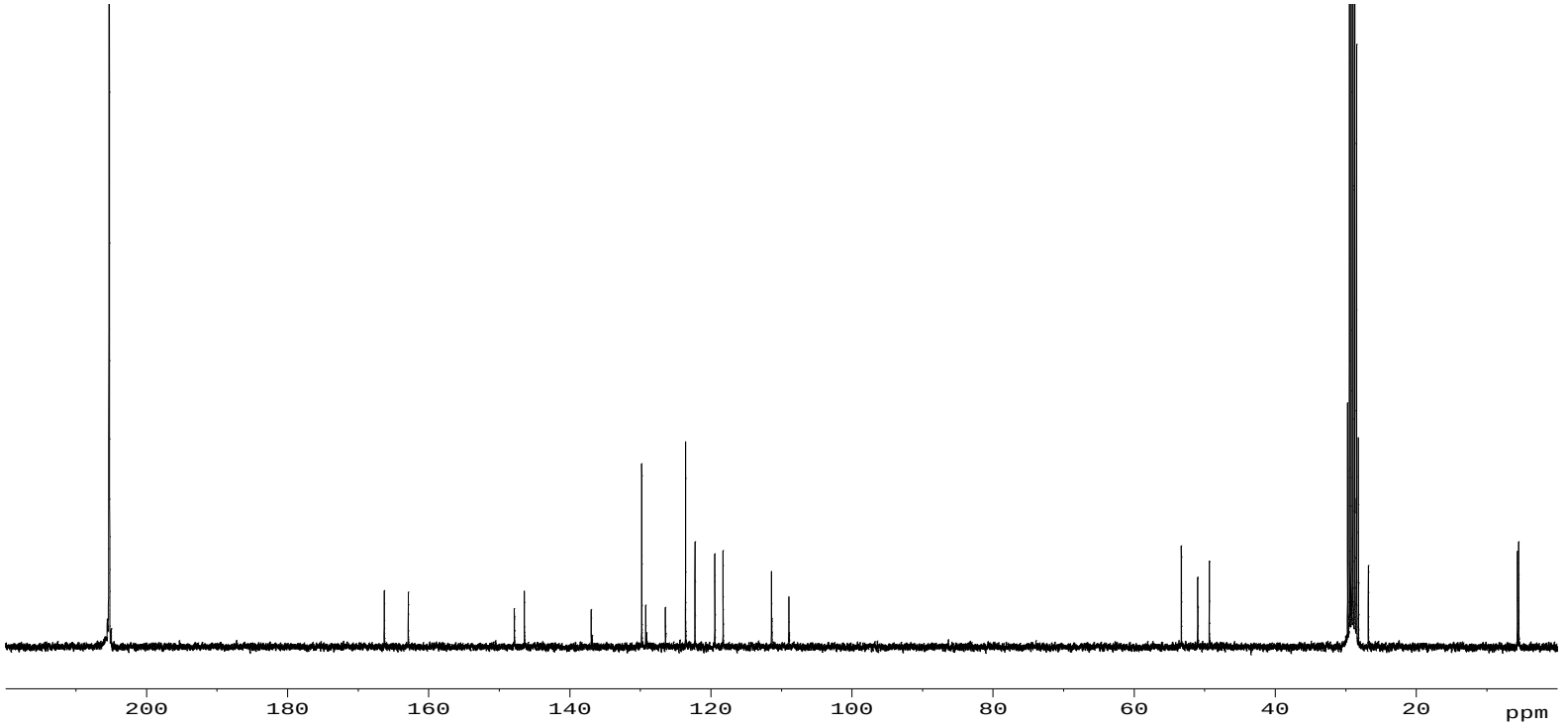


7e trans

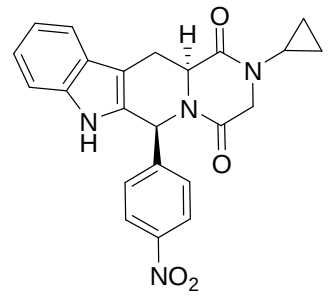
^{1}HNMR spectrum (300 MHz) of compound 7e (trans isomer) in $(CD_3)_2CO$



7e trans

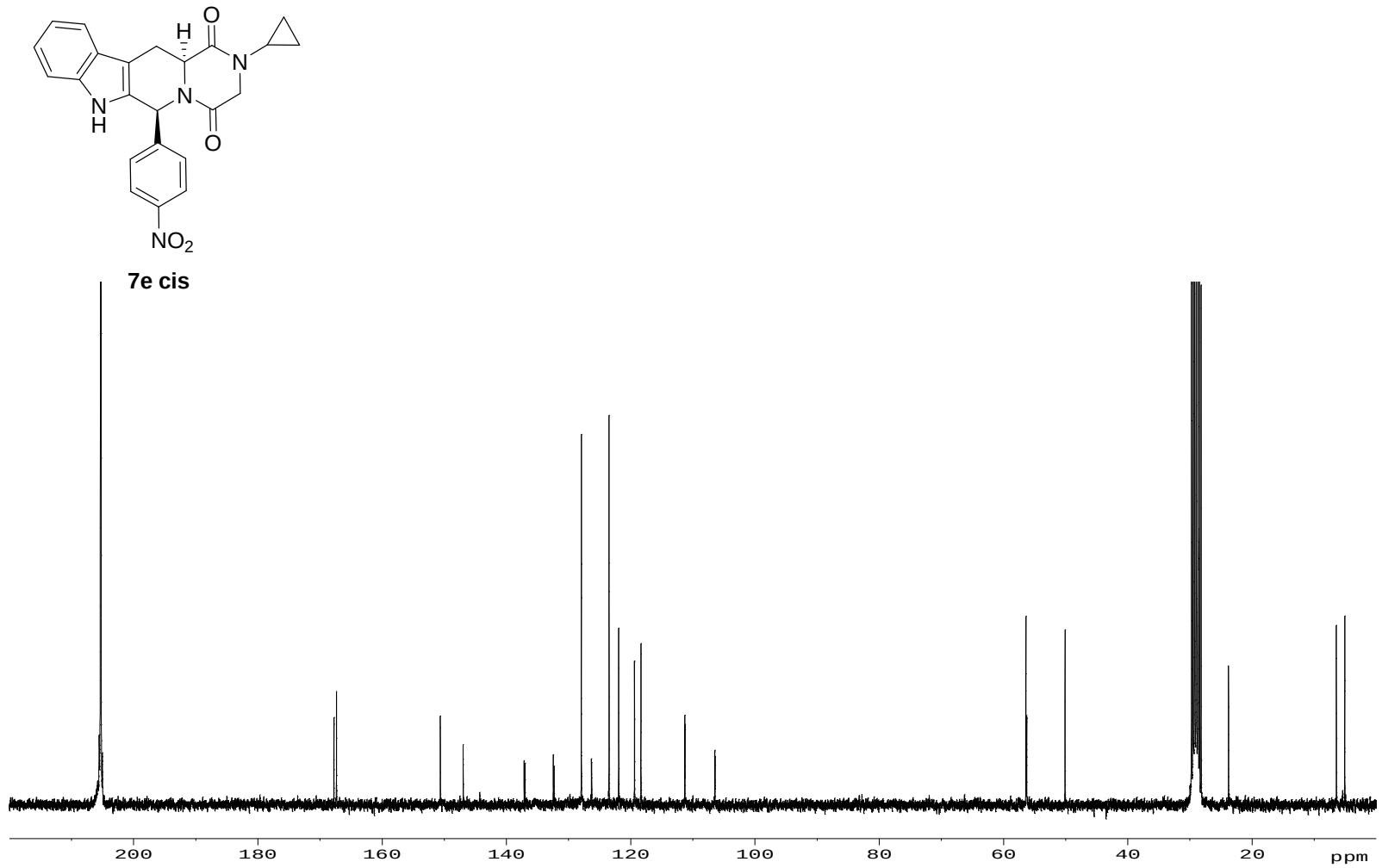


^{13}C NMR spectrum (75 MHz) of compound 7e (trans isomer) in $(CD_3)_2CO$

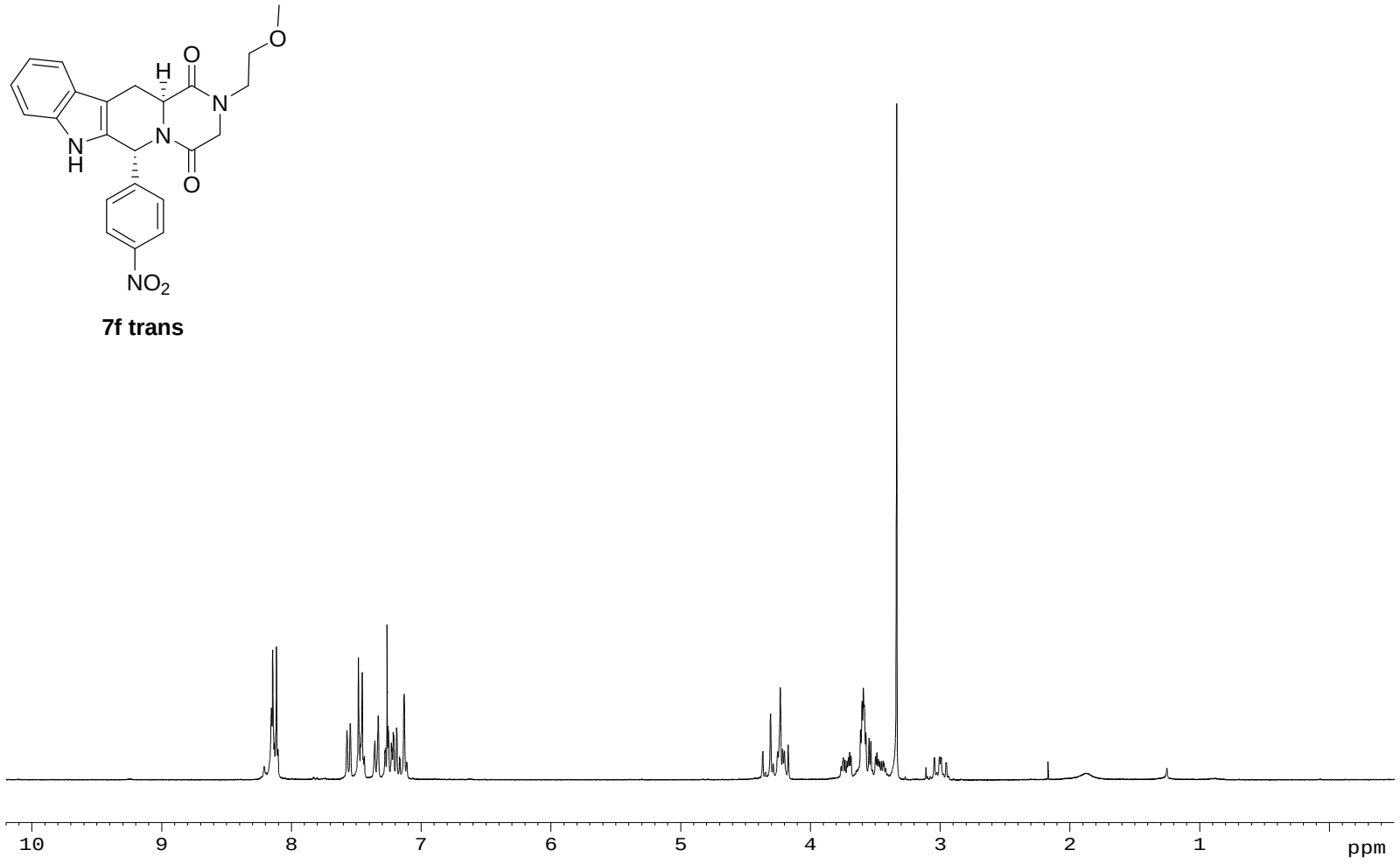


7e cis

^{1}HNMR spectrum (300 MHz) of compound 7e (cis isomer) in $(CD_3)_2CO$

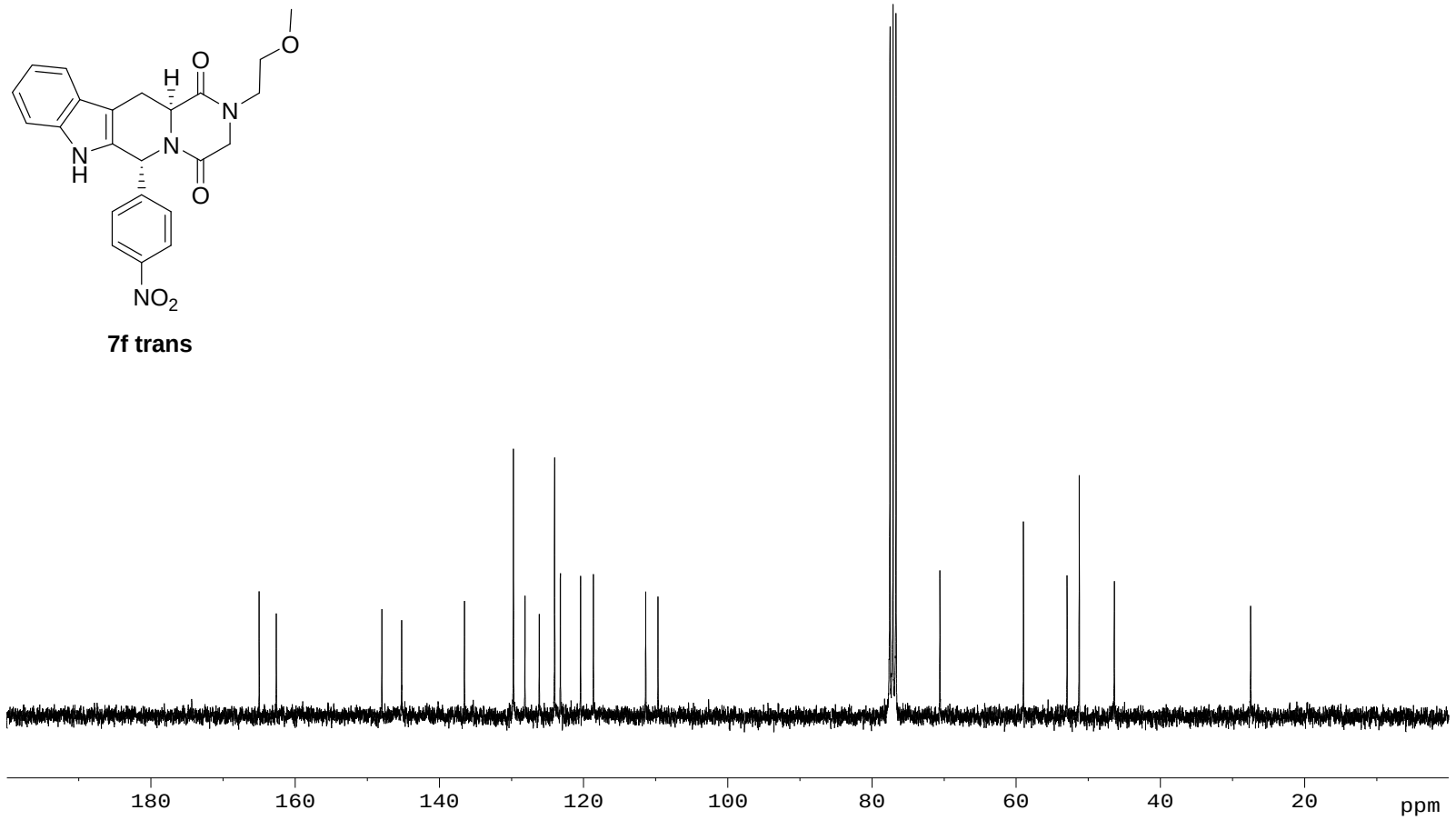


^{13}C NMR spectrum (75 MHz) of compound 7e (cis isomer) in $(CD_3)_2CO$



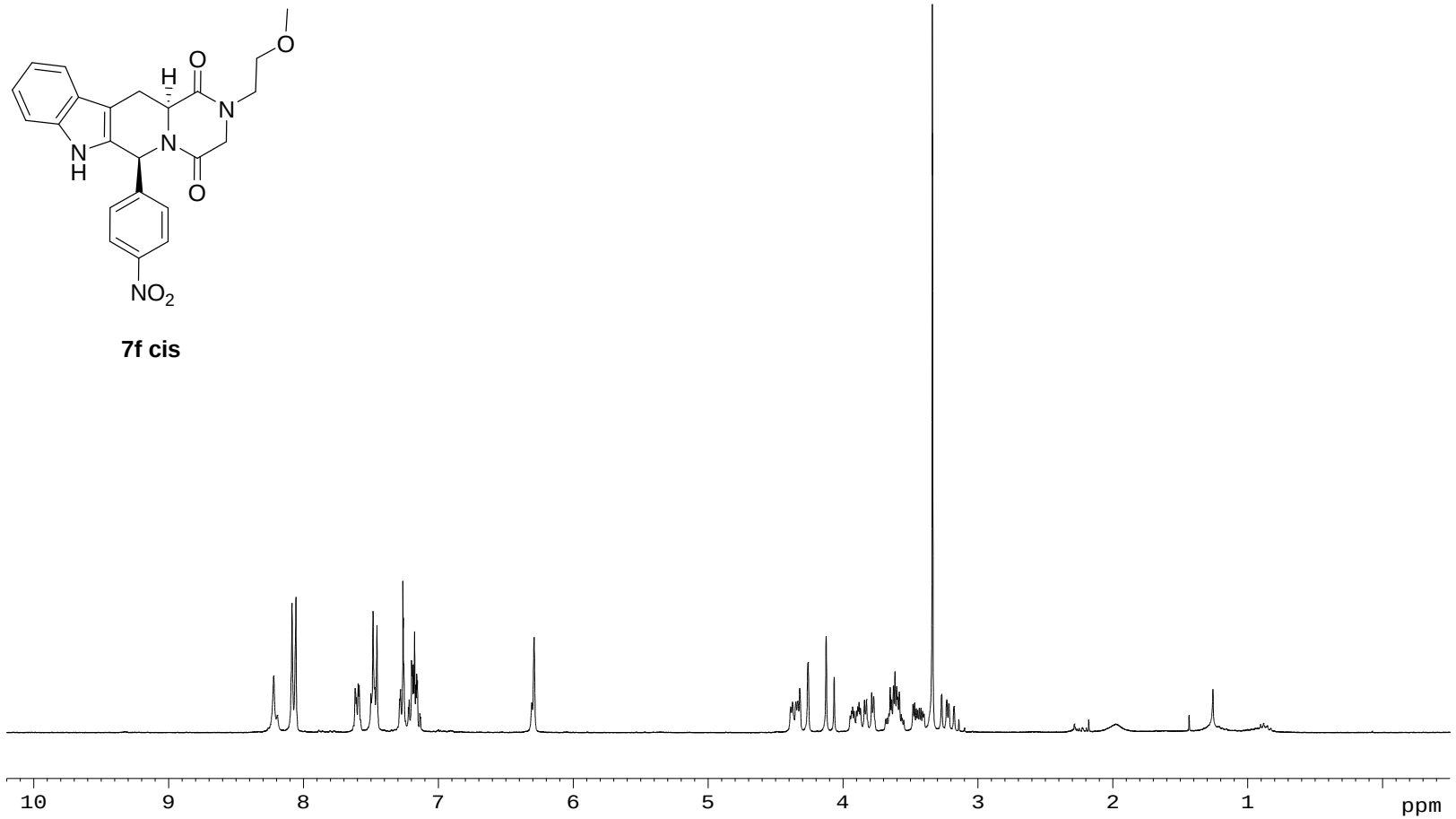
7f trans

^{1}HNMR spectrum (75 MHz) of compound 7f (trans isomer) in $CDCl_3$



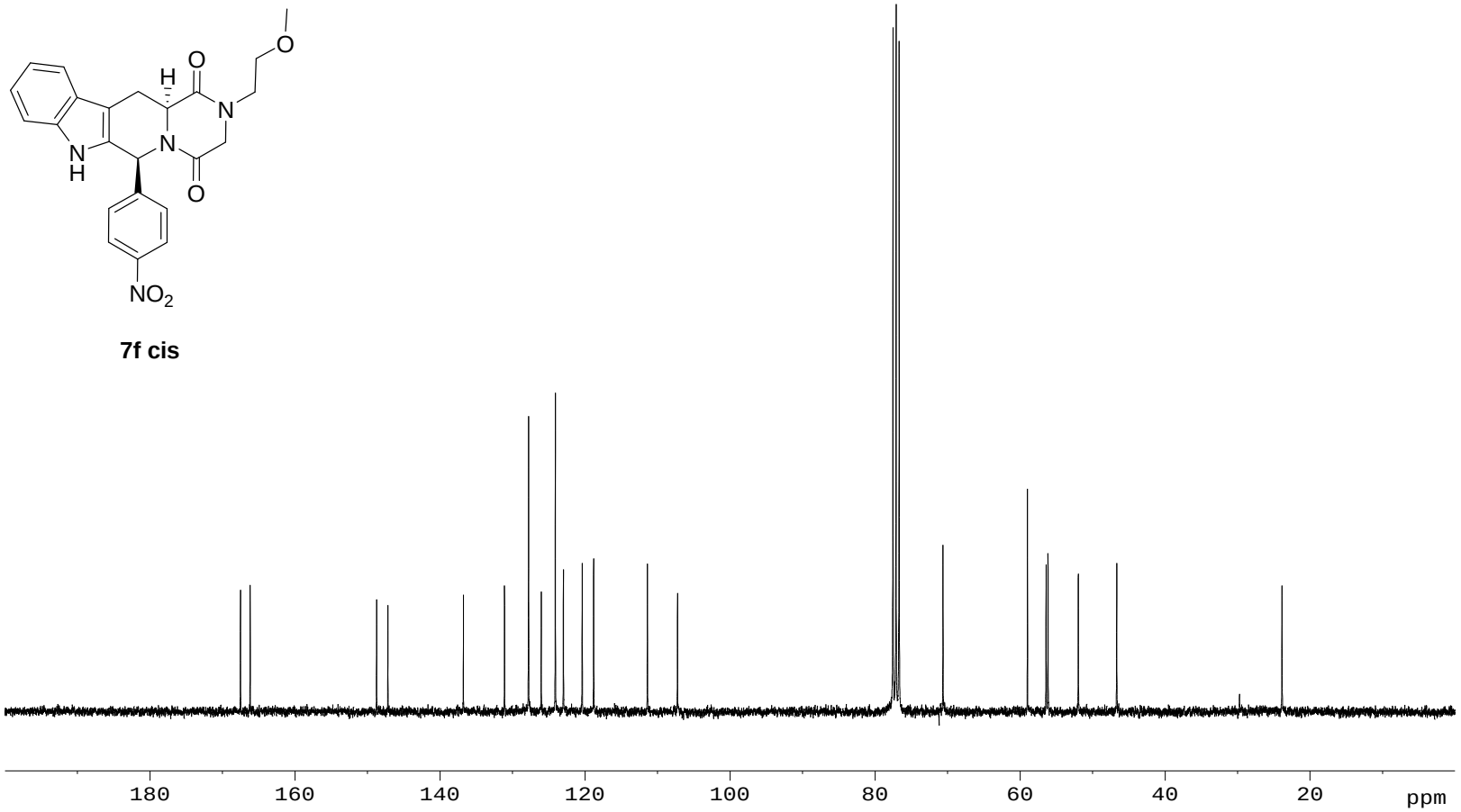
7f trans

^{13}C NMR spectrum (75 MHz) of compound 7f (trans isomer) in $CDCl_3$



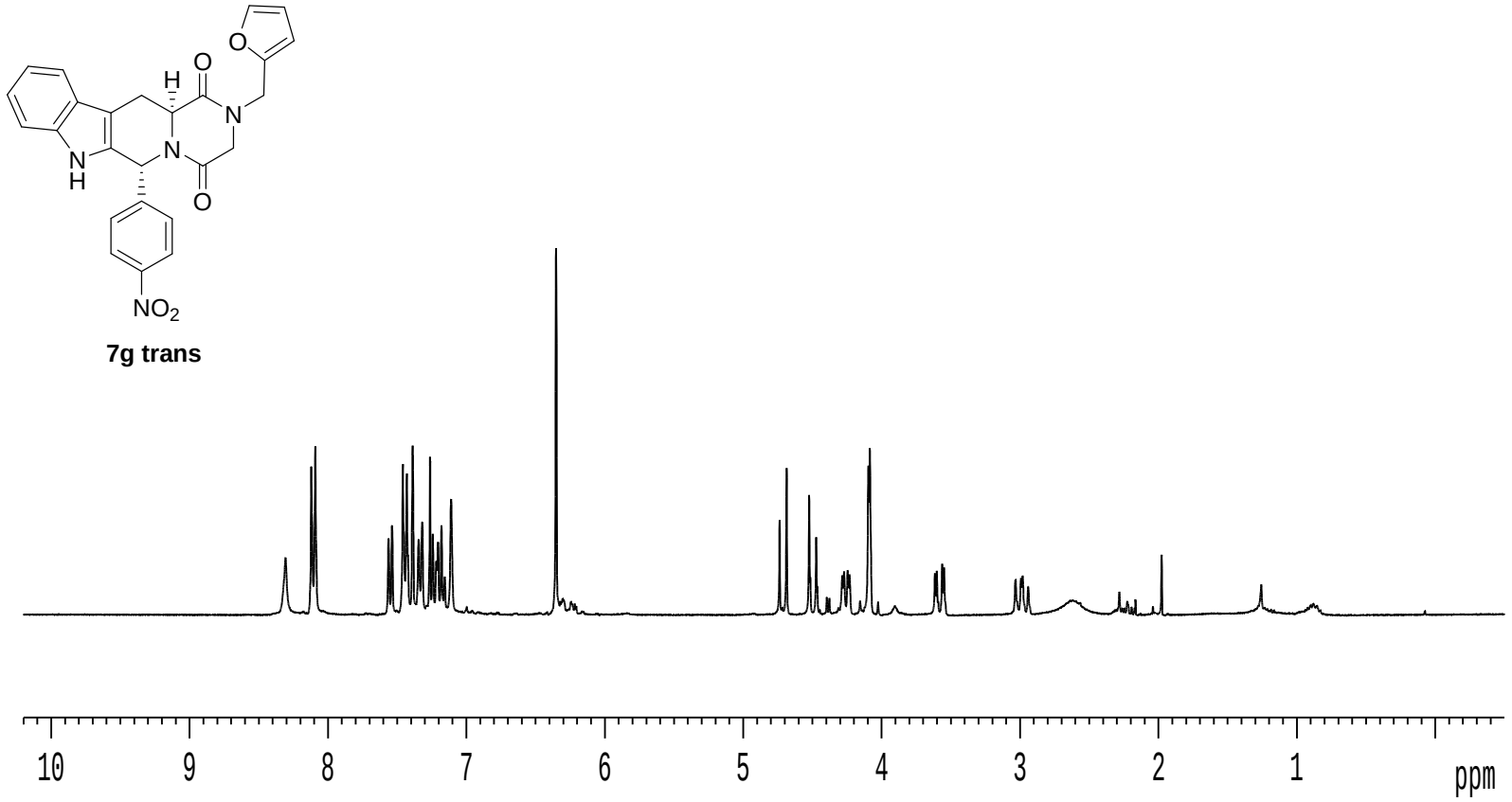
7f cis

^{1}HNMR spectrum (300 MHz) of compound 7f (cis isomer) in $CDCl_3$



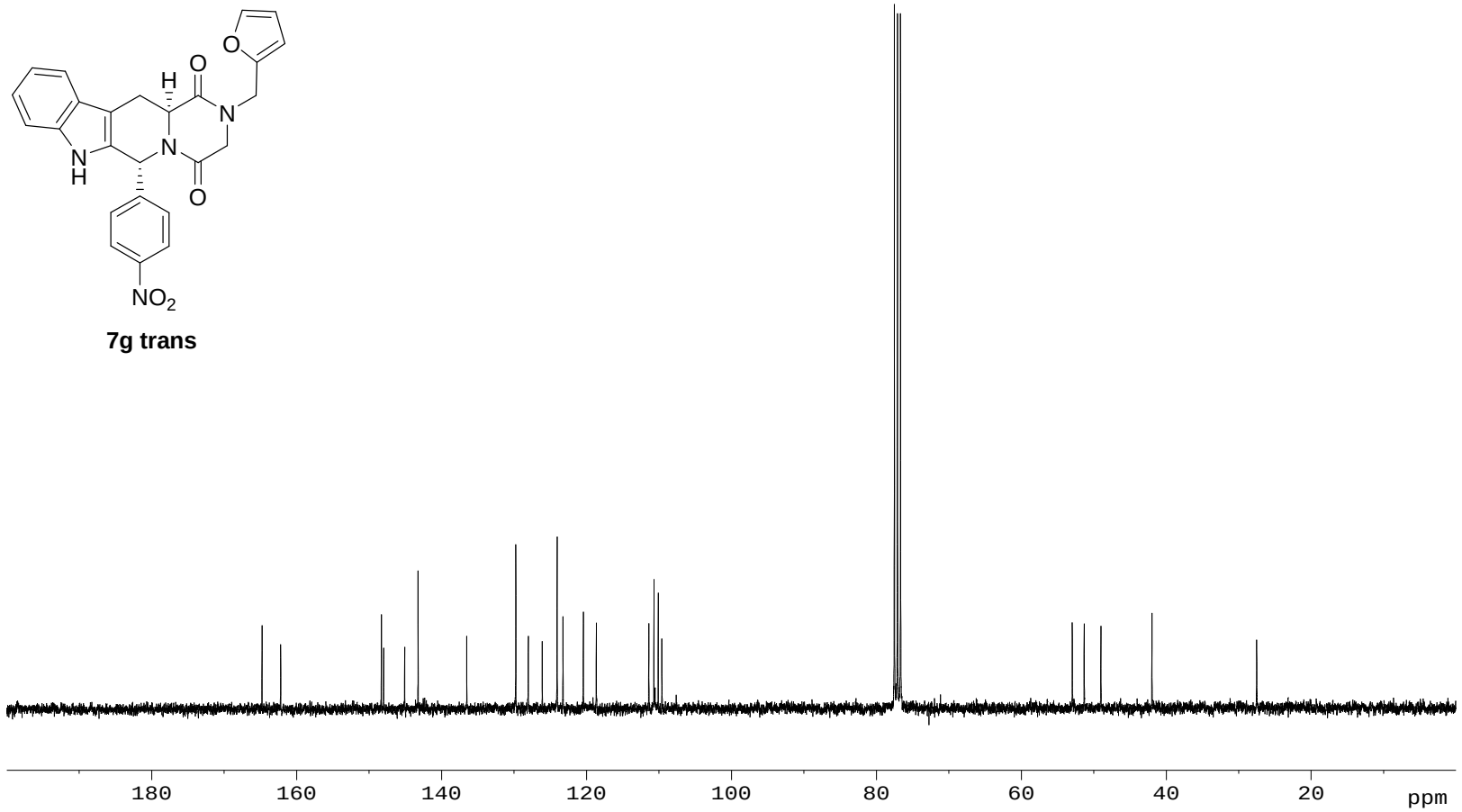
7f cis

^{13}C NMR spectrum (75 MHz) of compound 7f (cis isomer) in $CDCl_3$



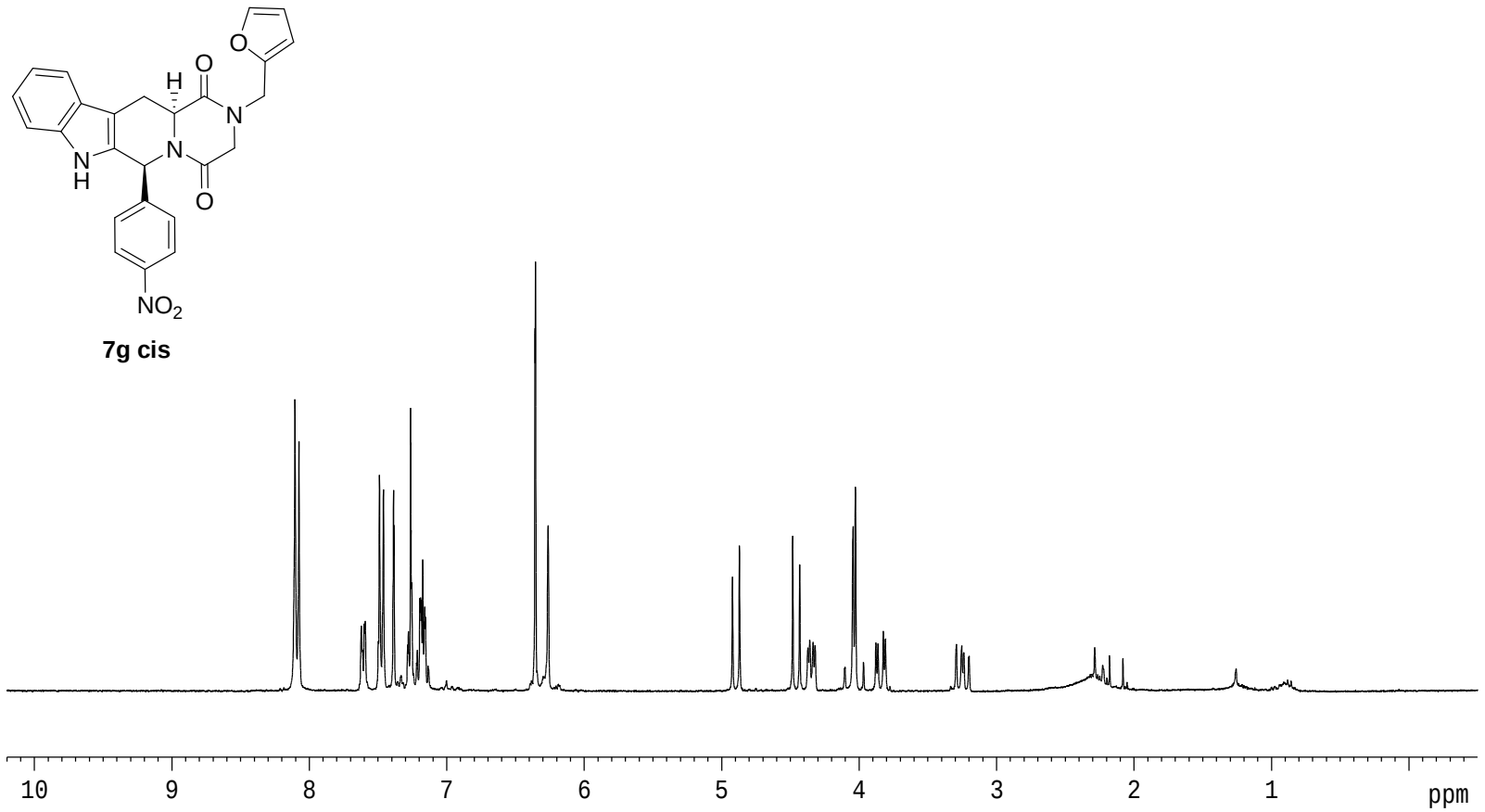
7g trans

^{1}HNMR spectrum (300 MHz) of compound 7g (trans isomer) in $CDCl_3$



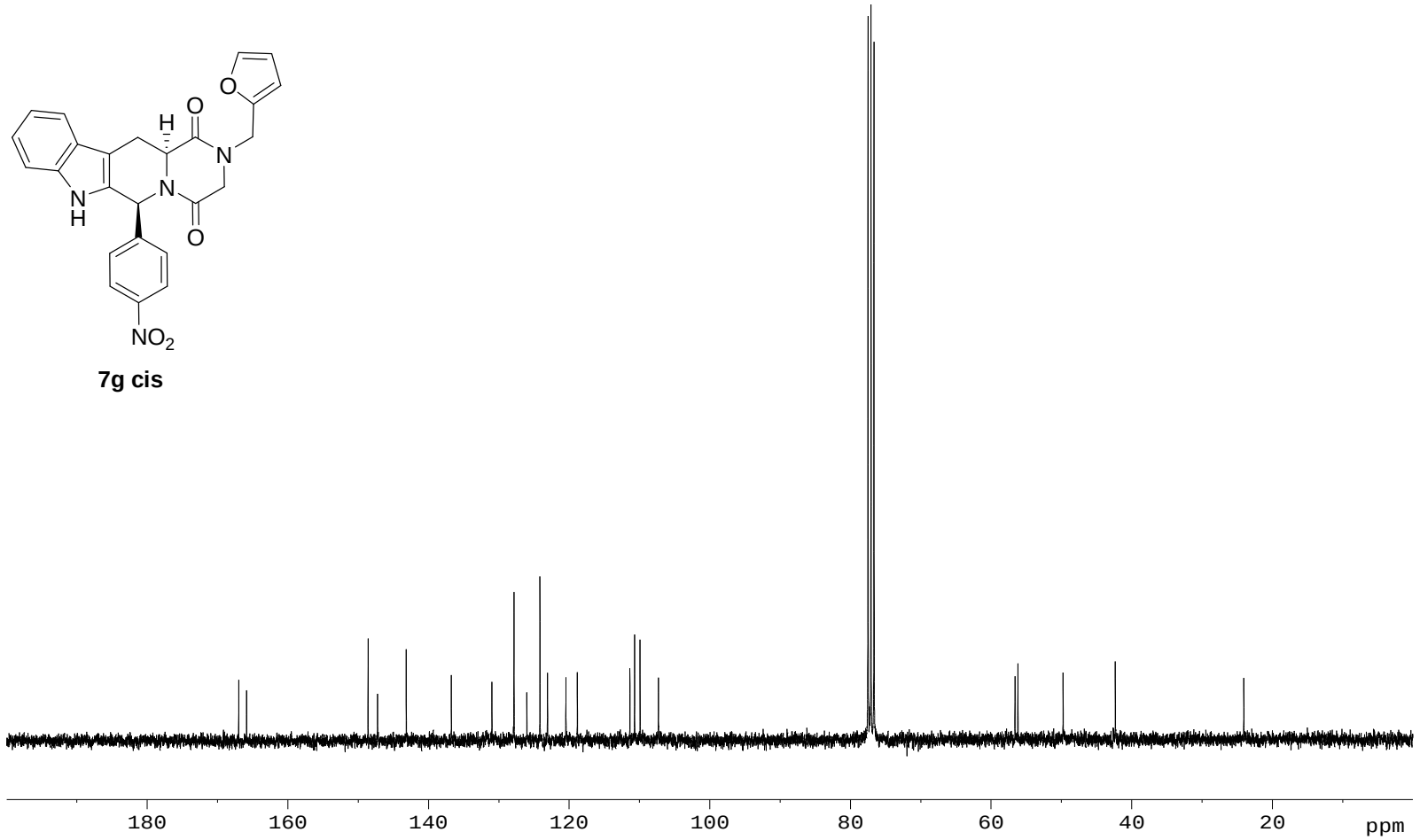
7g trans

^{13}C NMR spectrum (75 MHz) of compound 7g (trans isomer) in $CDCl_3$



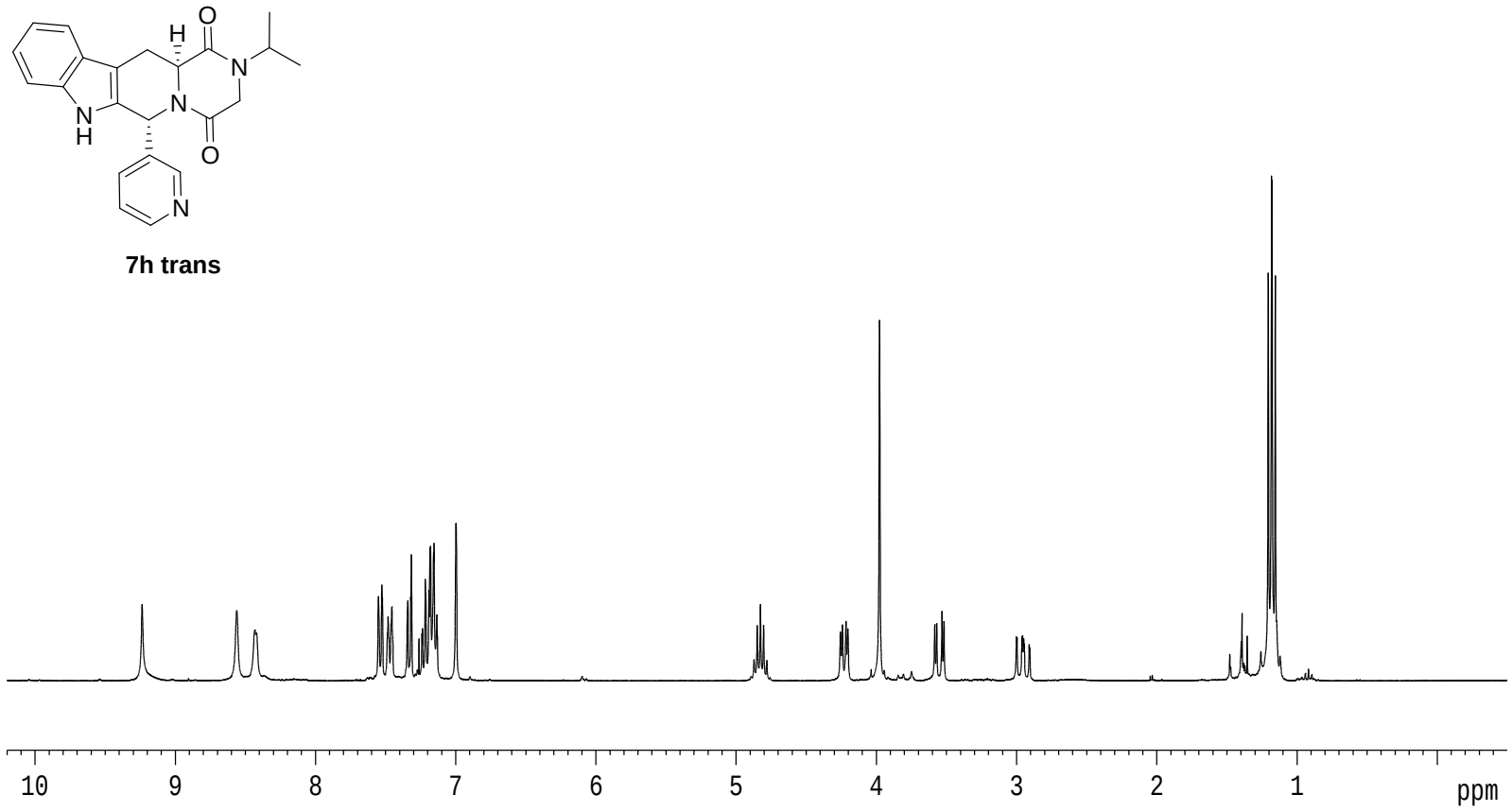
7g cis

^{1}HNMR spectrum (300 MHz) of compound 7g (cis isomer) in $CDCl_3$



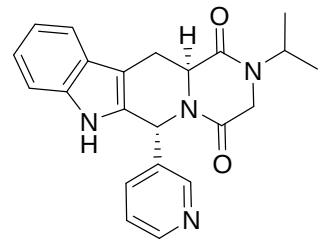
7g cis

^{13}C NMR spectrum (75 MHz) of compound 7g (cis isomer) in $CDCl_3$

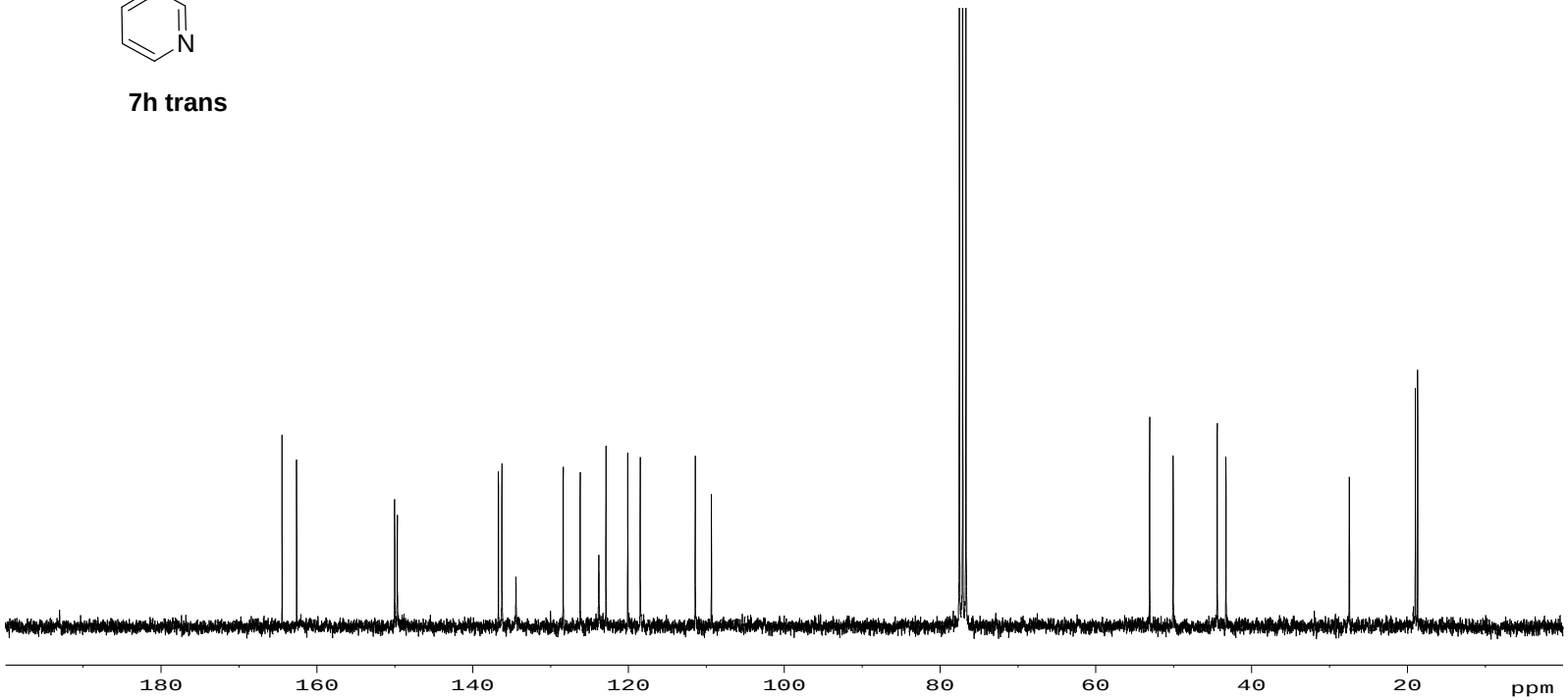


7h trans

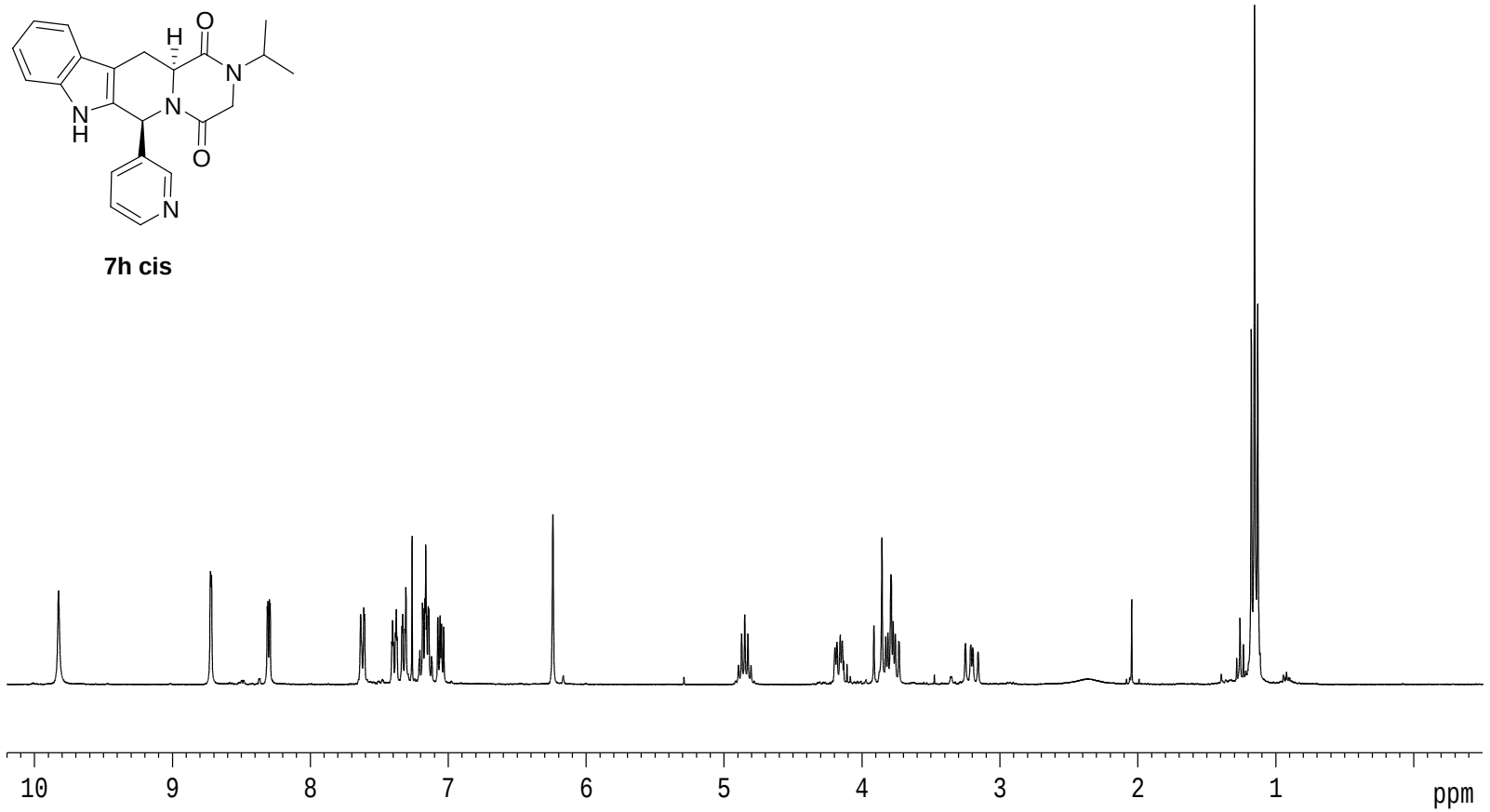
^{1}HNMR spectrum (300 MHz) of compound 7h (trans isomer) in $CDCl_3$



7h trans

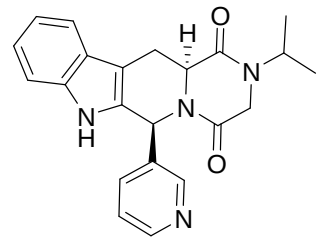


^{13}C NMR spectrum (75 MHz) of compound 7h (trans isomer) in $CDCl_3$

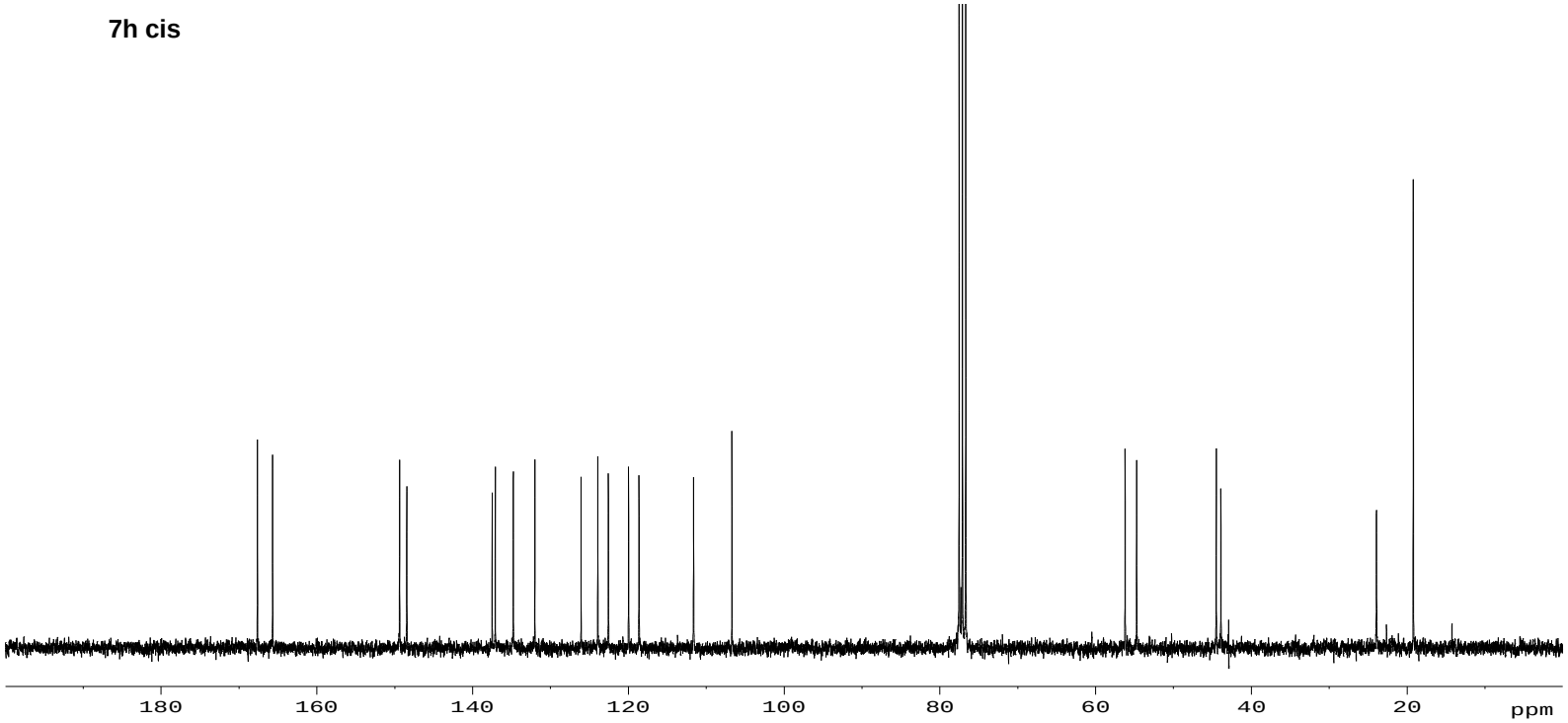


7h cis

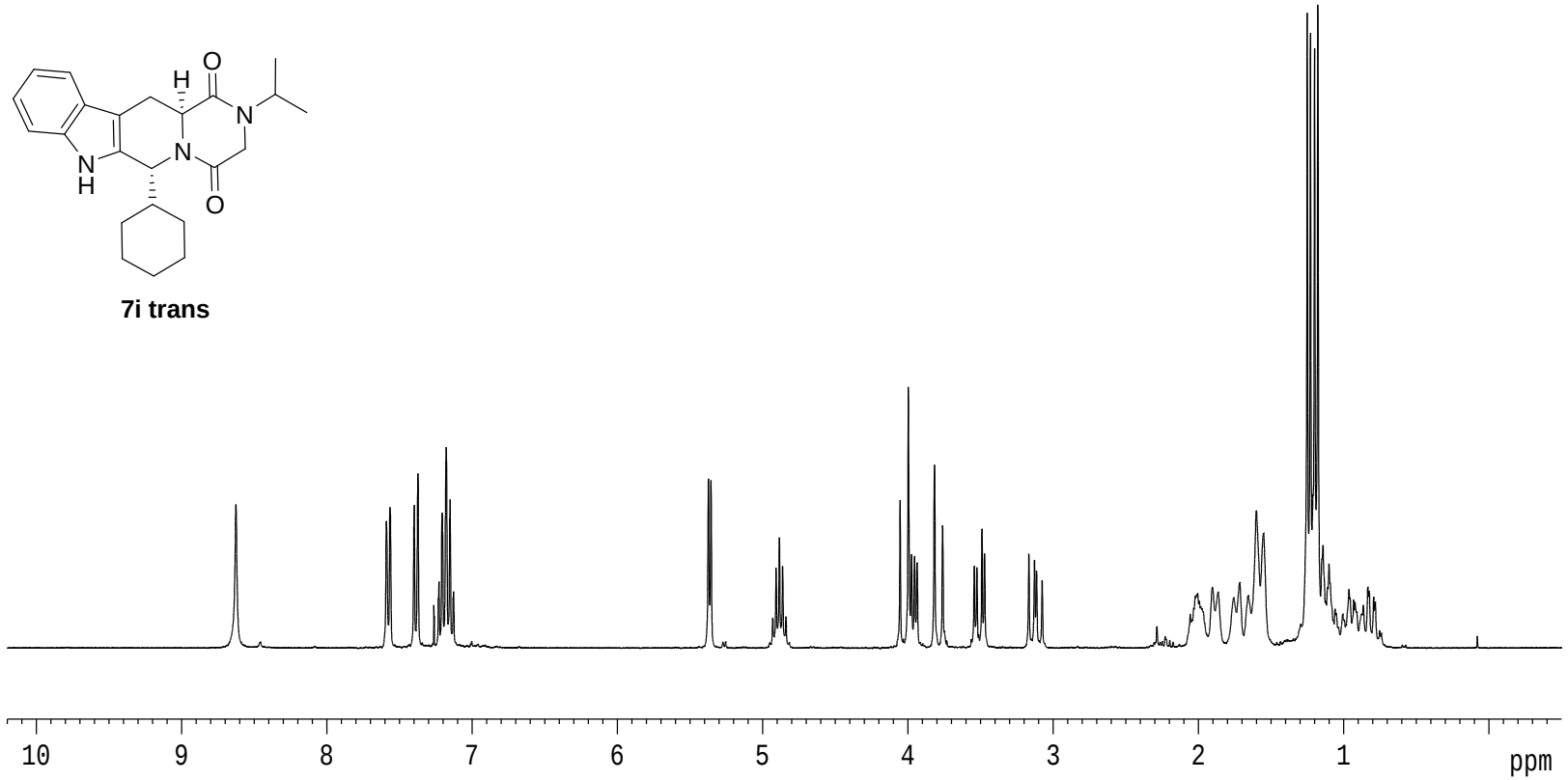
^{1}HNMR spectrum (300 MHz) of compound 7h (cis isomer) in $CDCl_3$



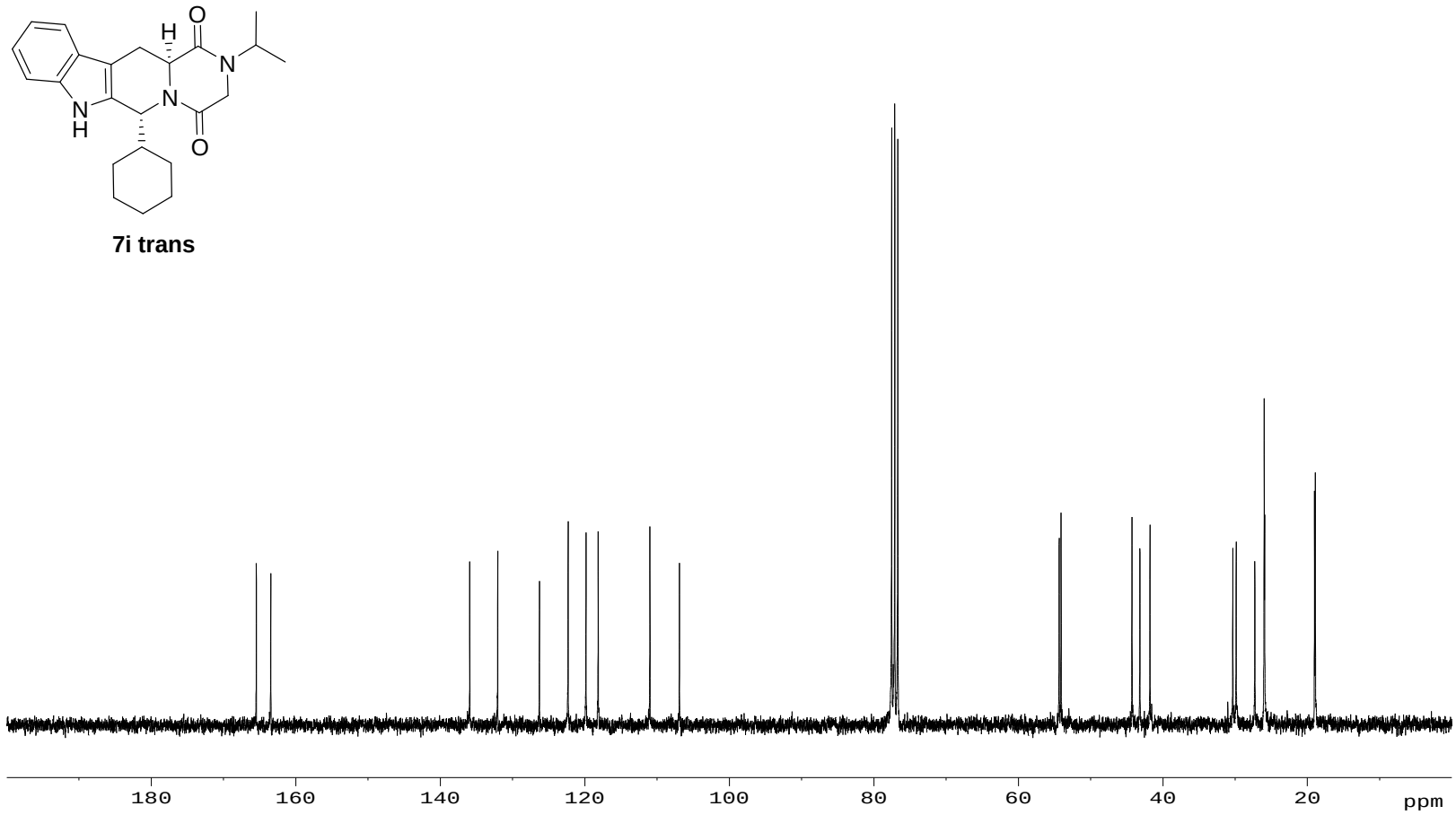
7h cis



^{13}C NMR spectrum (75 MHz) of compound 7h (cis isomer) in $CDCl_3$

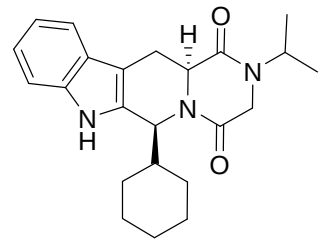


^{1}HNMR spectrum (300 MHz) of compound 7i (trans isomer) in $CDCl_3$



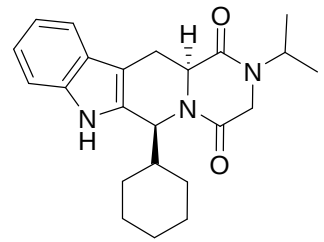
7i trans

^{13}C NMR spectrum (75 MHz) of compound 7i (trans isomer) in $CDCl_3$

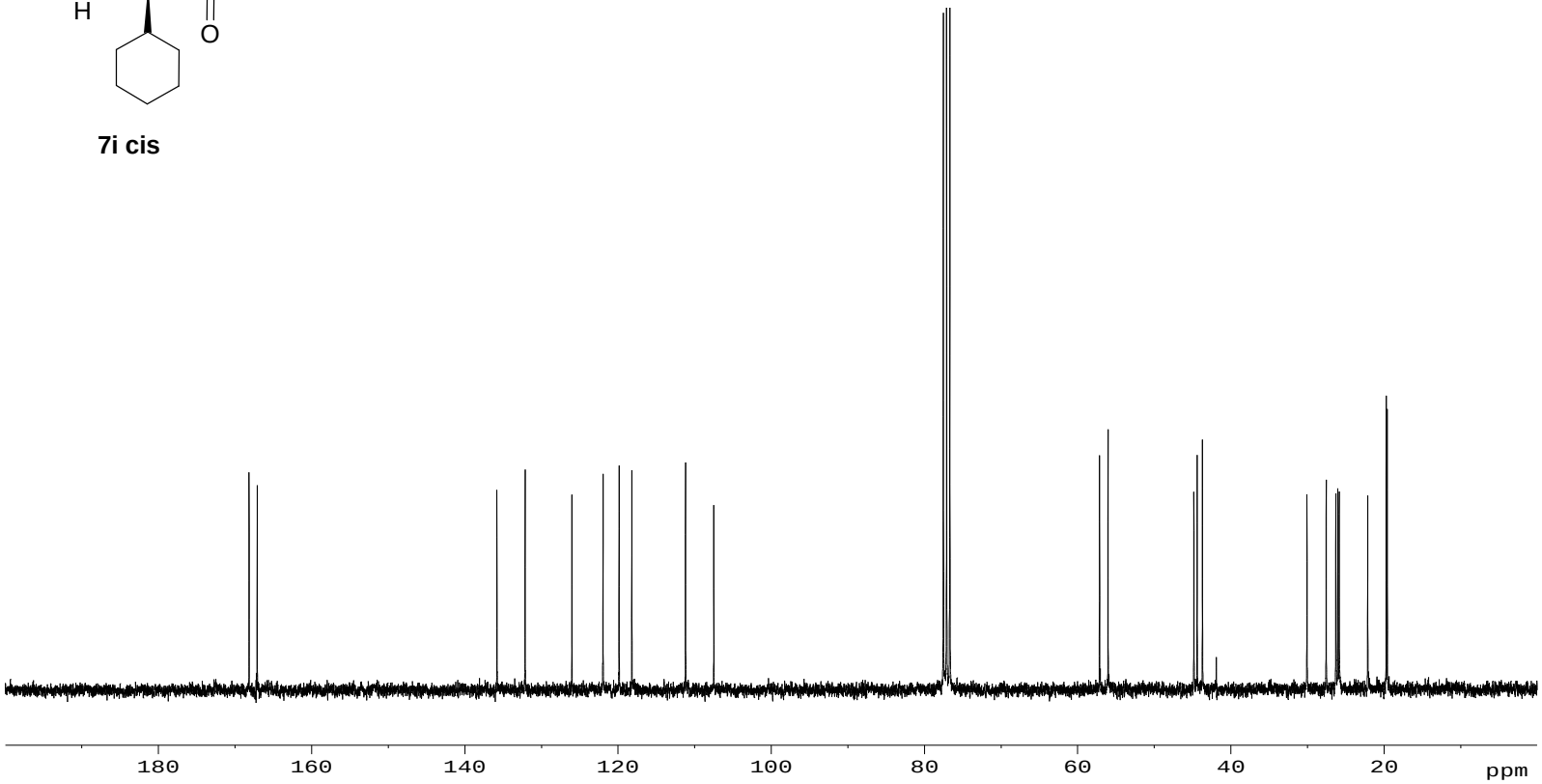


7i cis

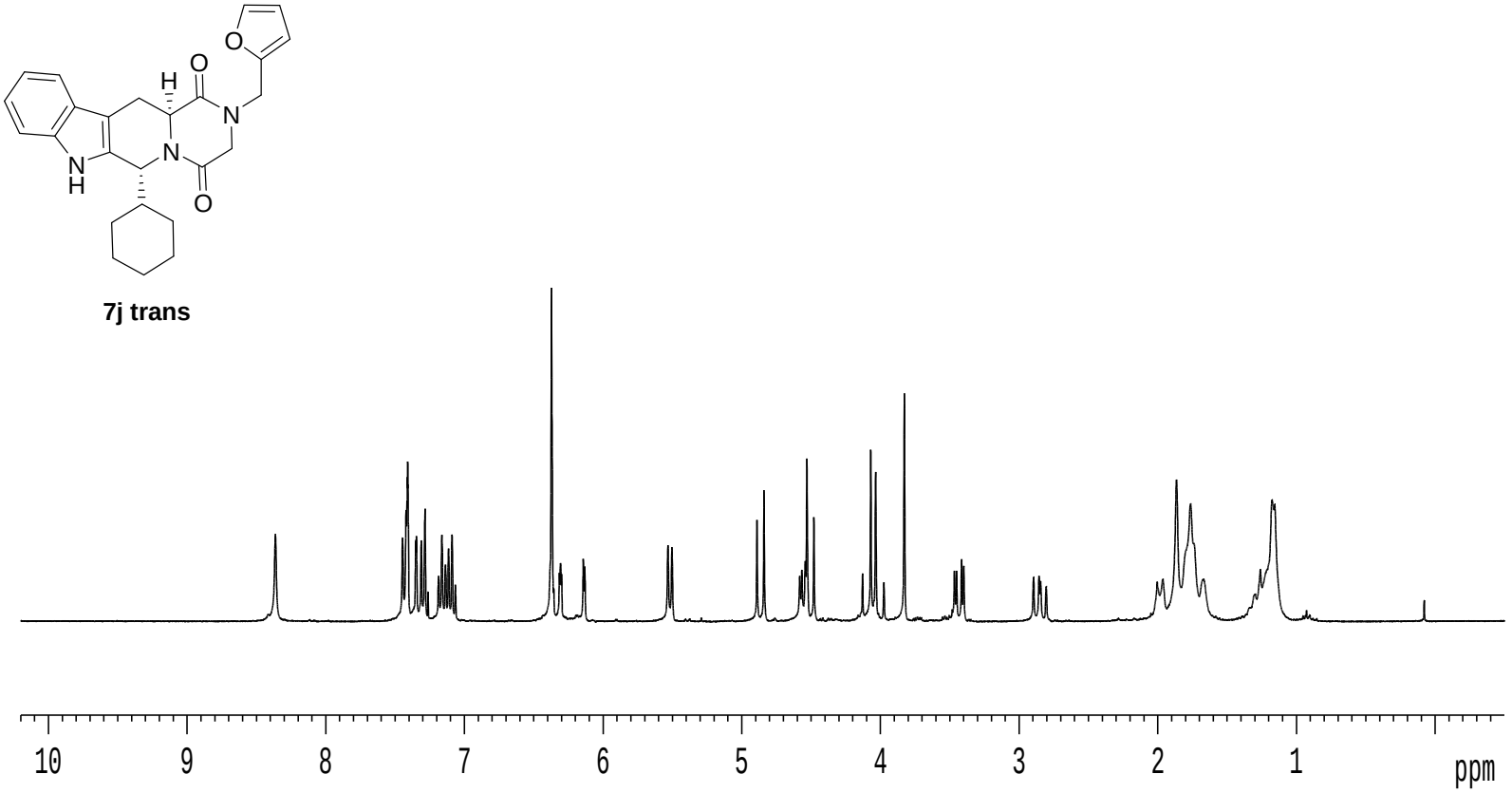
^{1}HNMR spectrum (300 MHz) of compound 7i (cis isomer) in $CDCl_3$



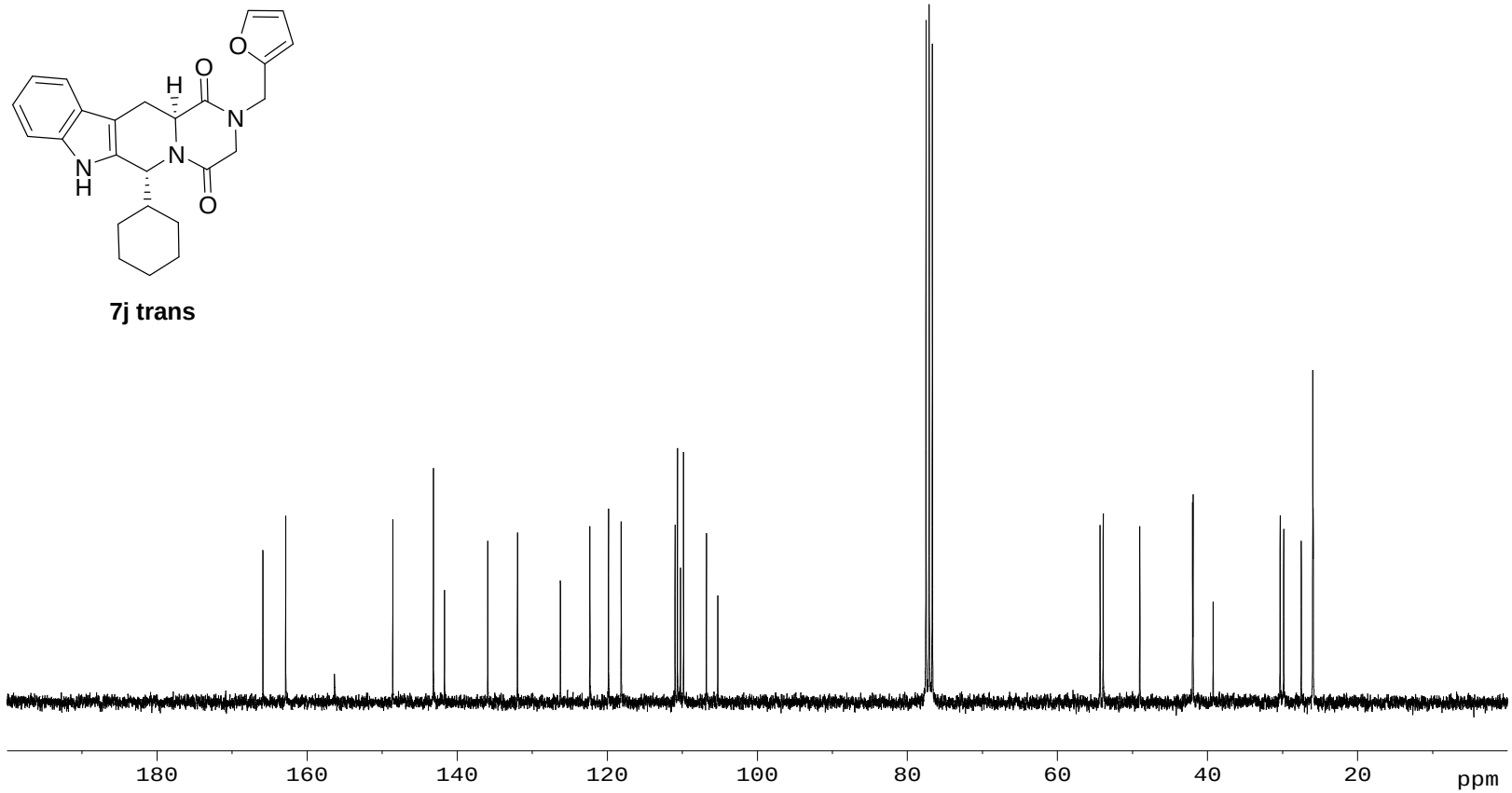
7i cis



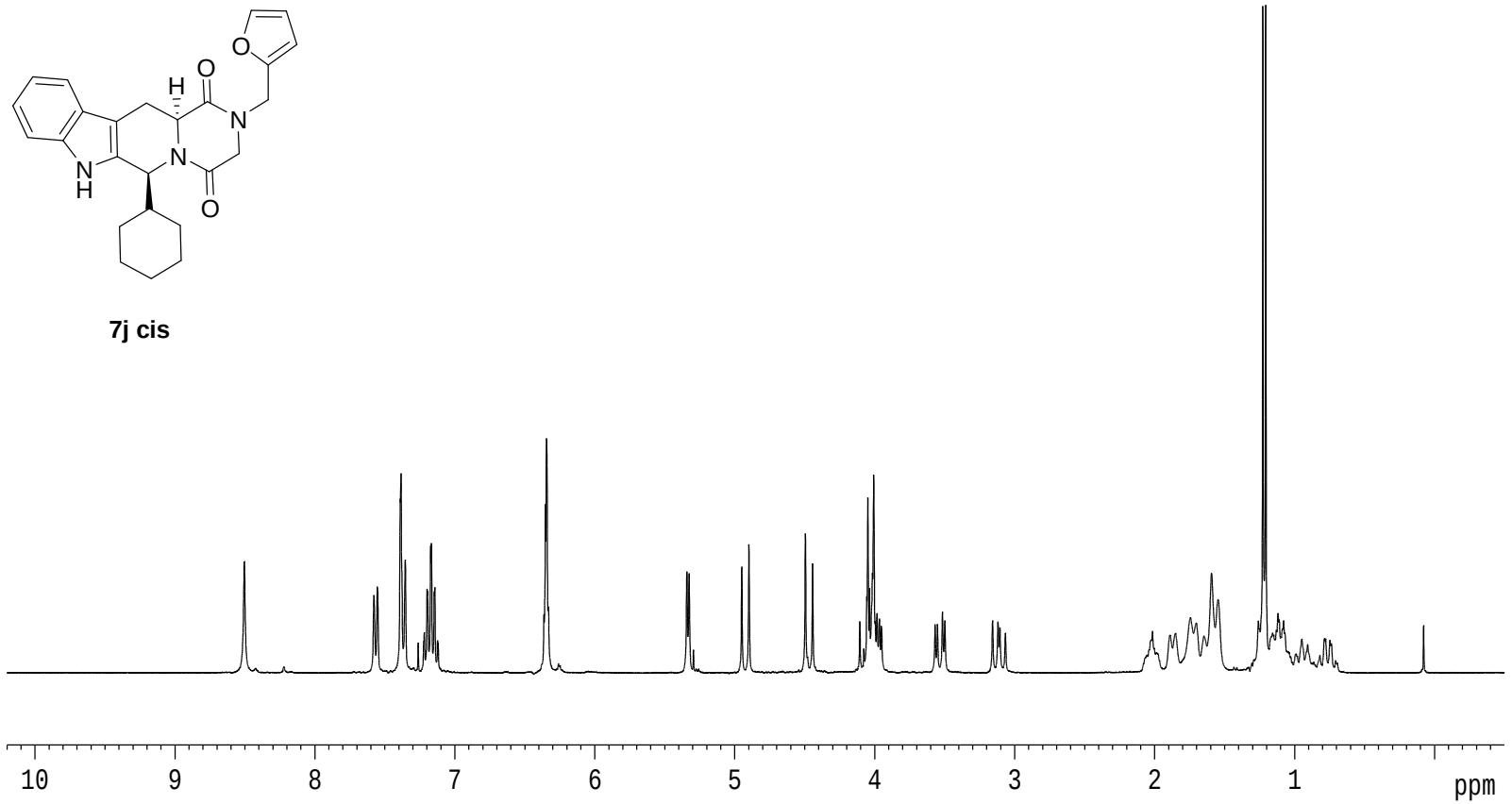
^{13}C NMR spectrum (75 MHz) of compound 7i (cis isomer) in $CDCl_3$



^{1}HNMR spectrum (300 MHz) of compound 7j (trans isomer) in $CDCl_3$

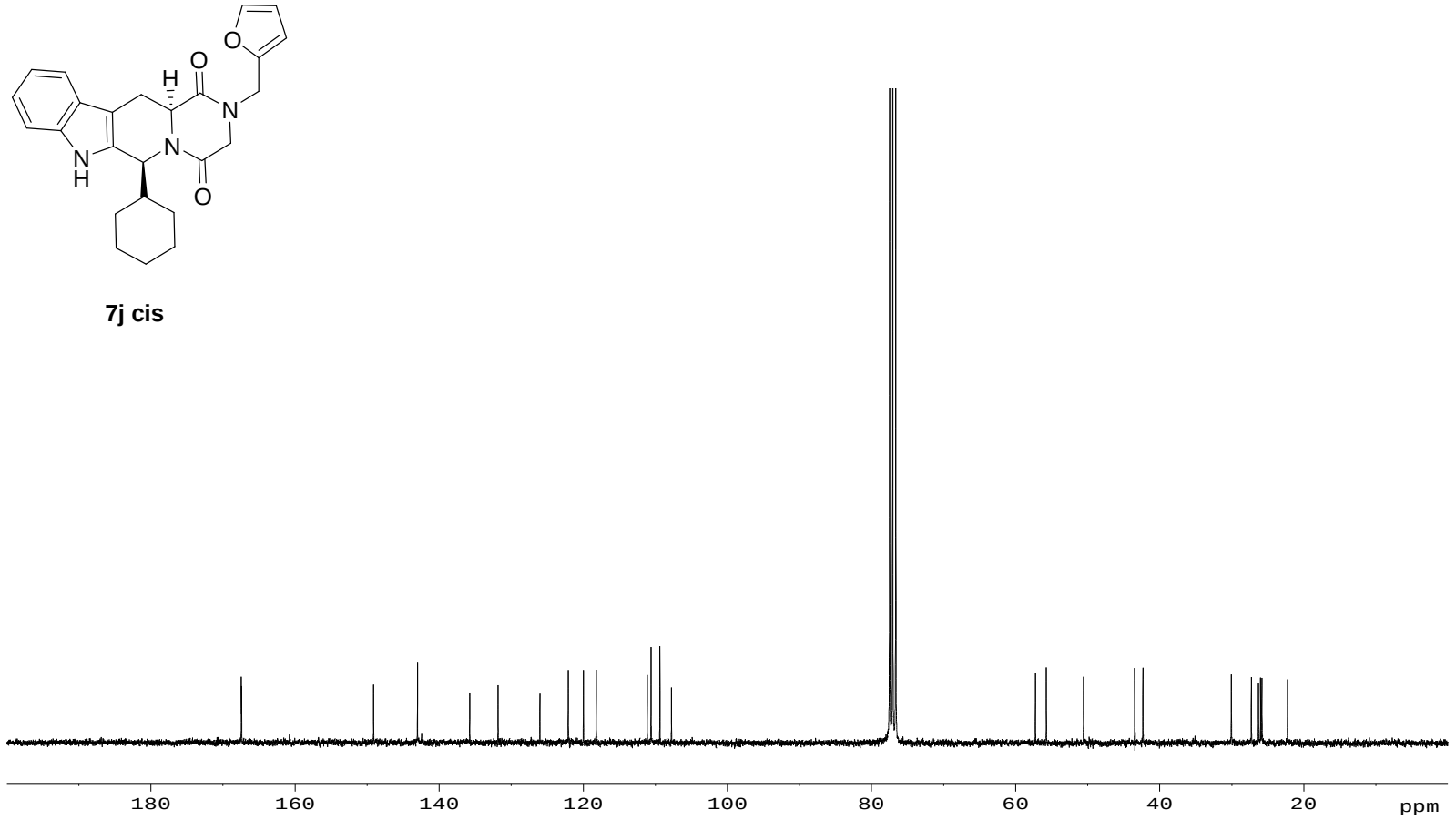


^{13}C NMR spectrum (75 MHz) of compound 7j (trans isomer) in $CDCl_3$



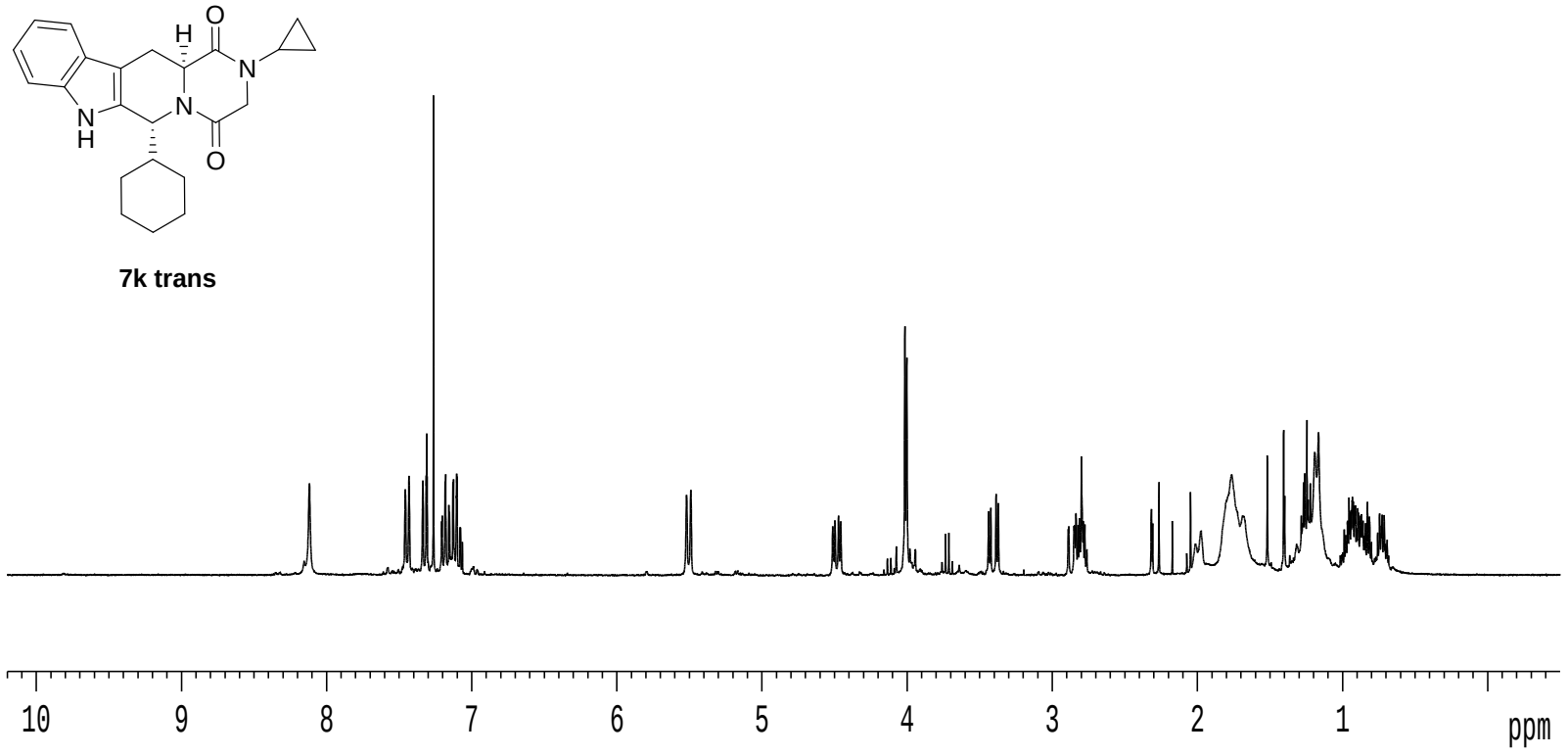
7j cis

^{1}HNMR spectrum (300 MHz) of compound 7j (cis isomer) in $CDCl_3$



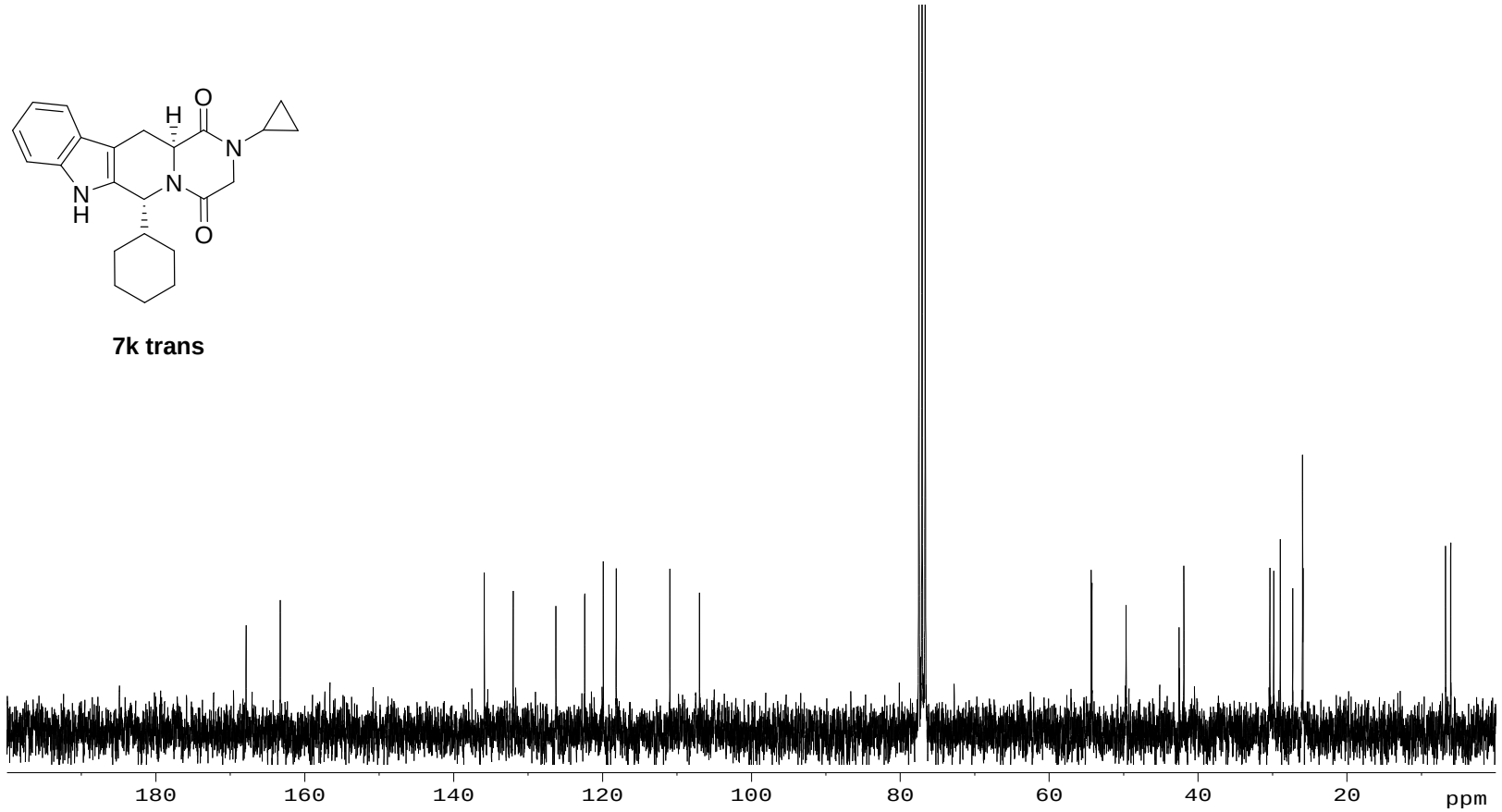
7j cis

^{13}C NMR spectrum (75 MHz) of compound 7j (cis isomer) in $CDCl_3$



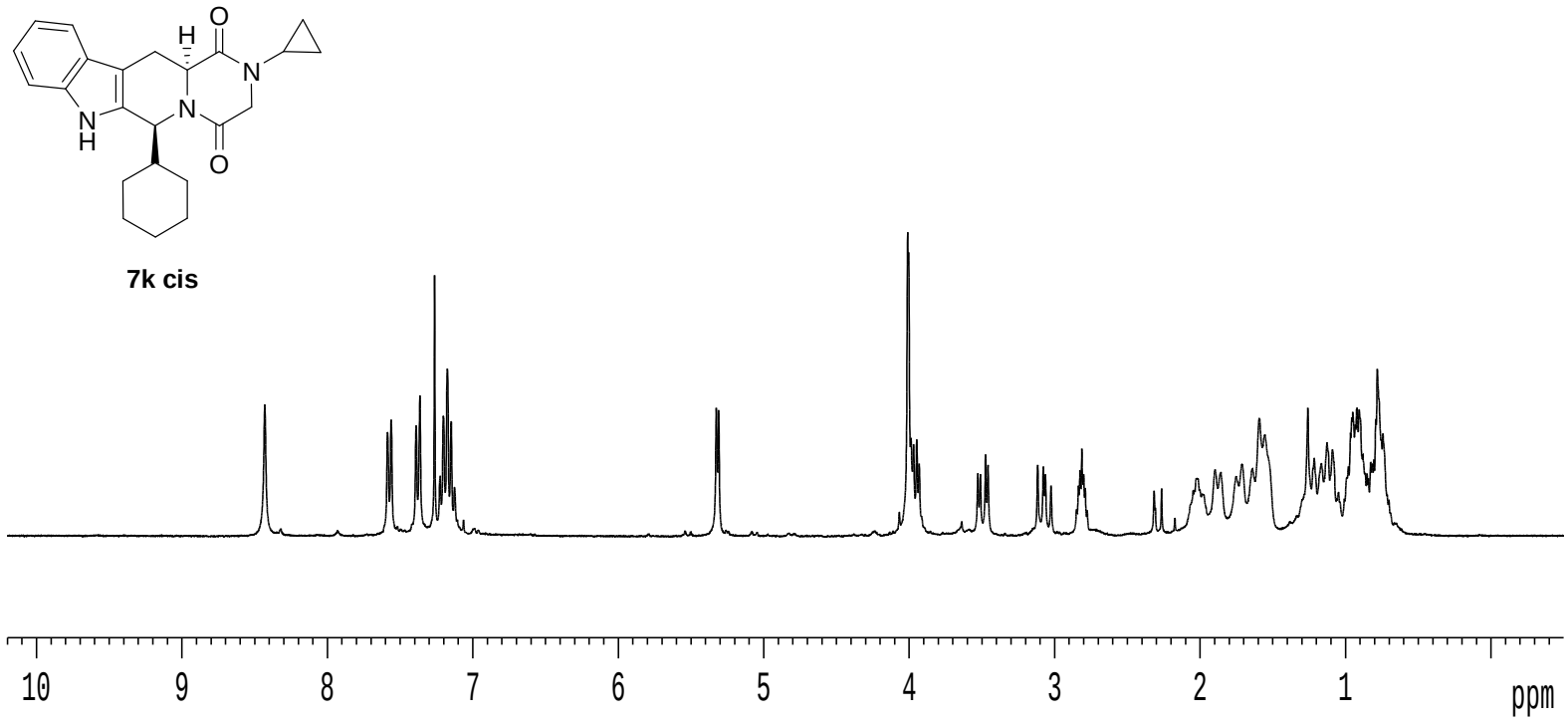
7k trans

^{1}HNMR spectrum (300 MHz) of compound 7k (trans isomer) in $CDCl_3$

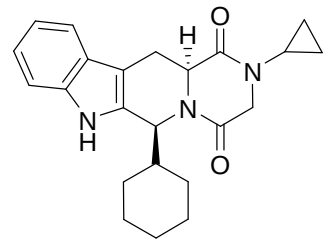


7k trans

^{13}C NMR spectrum (75 MHz) of compound 7k (trans isomer) in $CDCl_3$

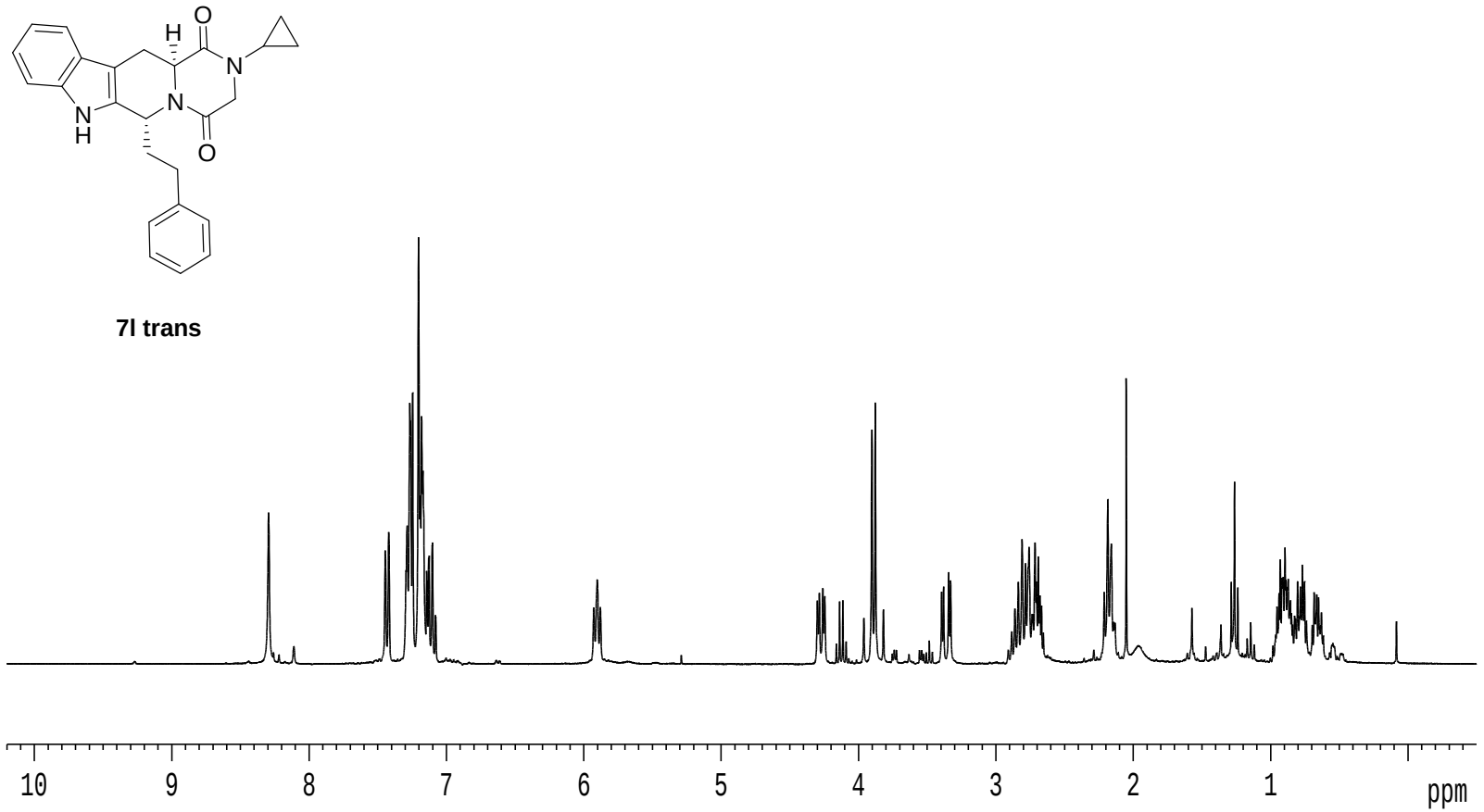


^{1}HNMR spectrum (300 MHz) of compound 7k (cis isomer) in $CDCl_3$

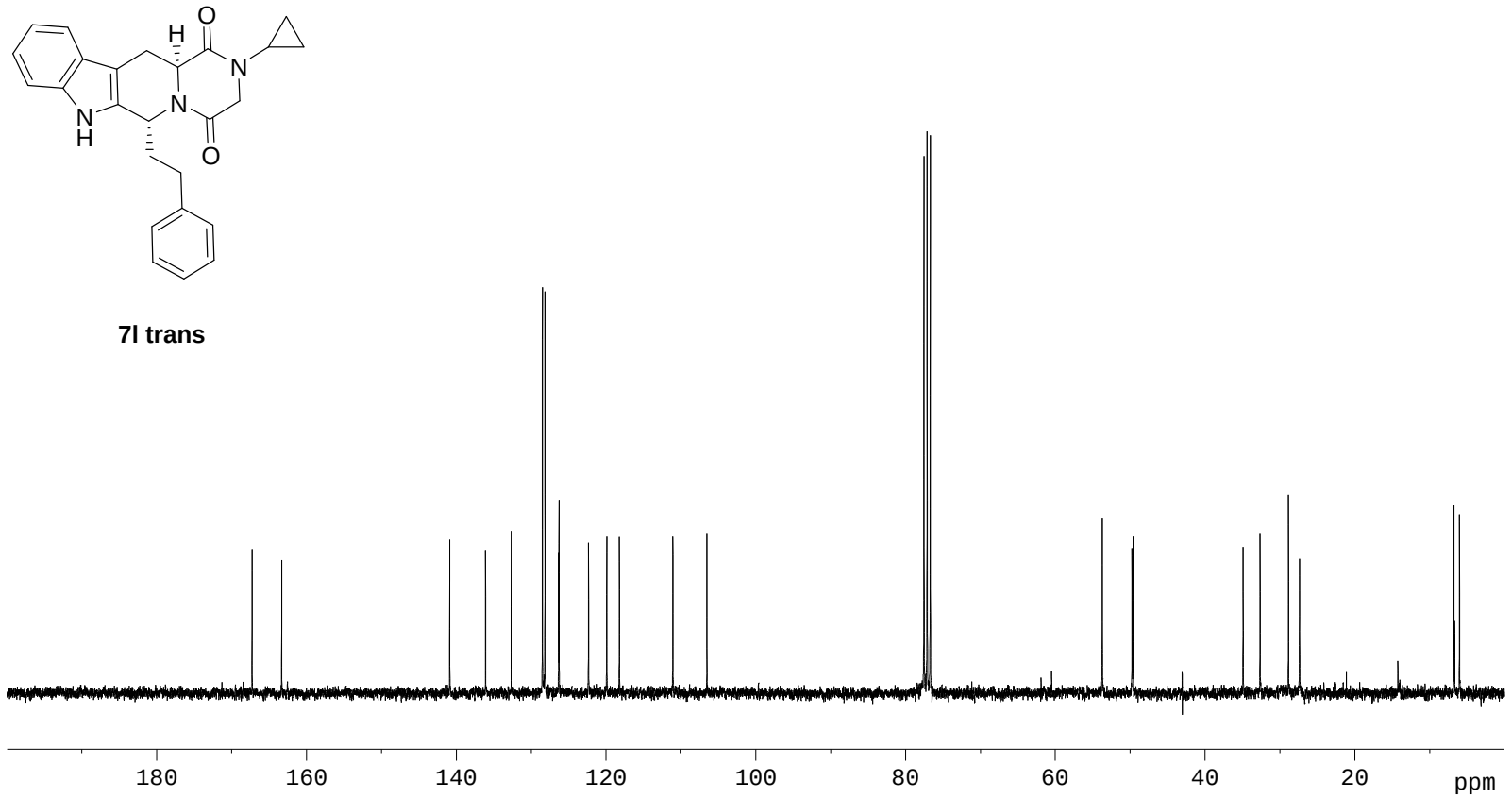


7k cis

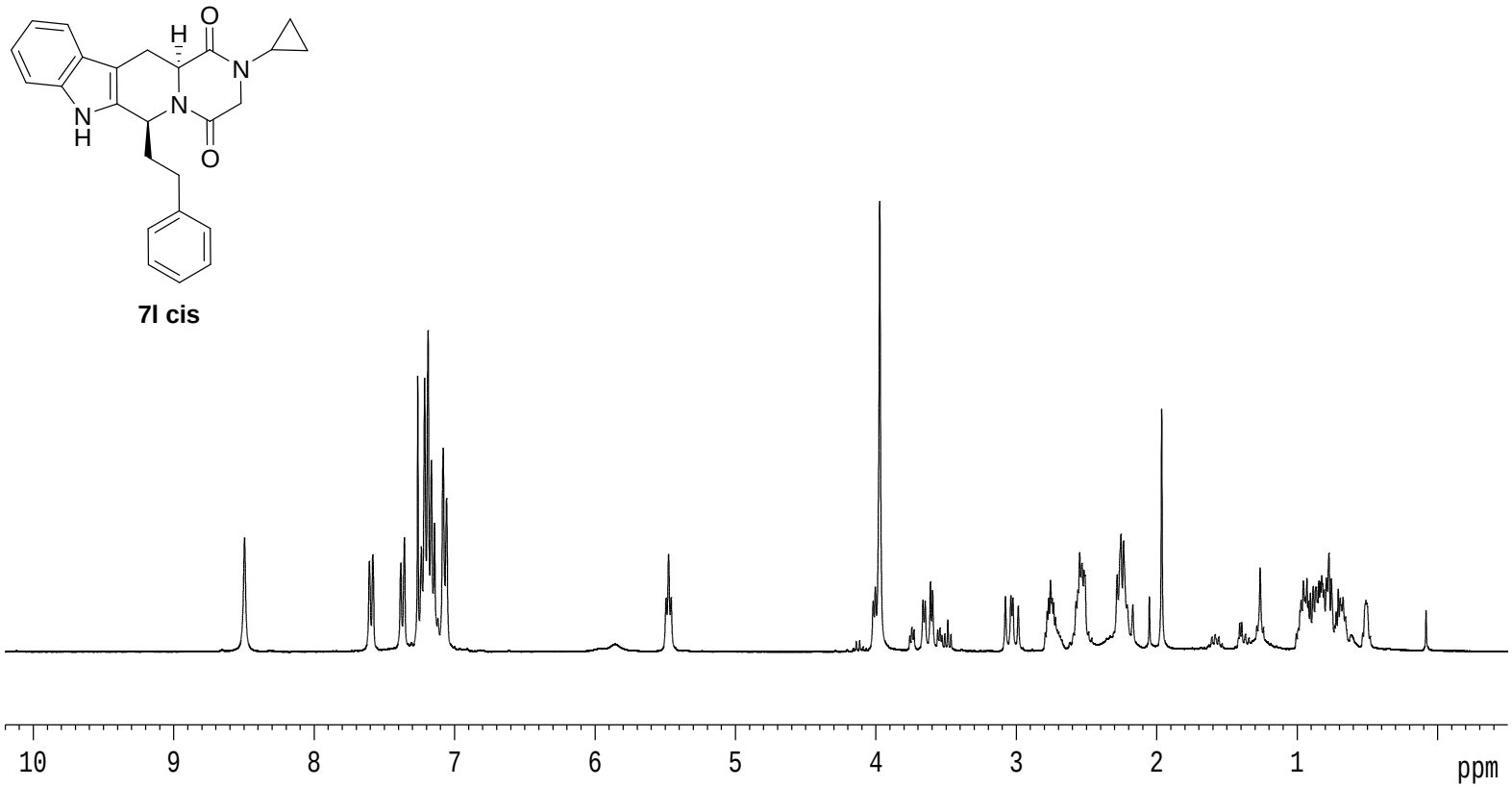
^{13}C NMR spectrum (75 MHz) of compound 7k (cis isomer) in $CDCl_3$



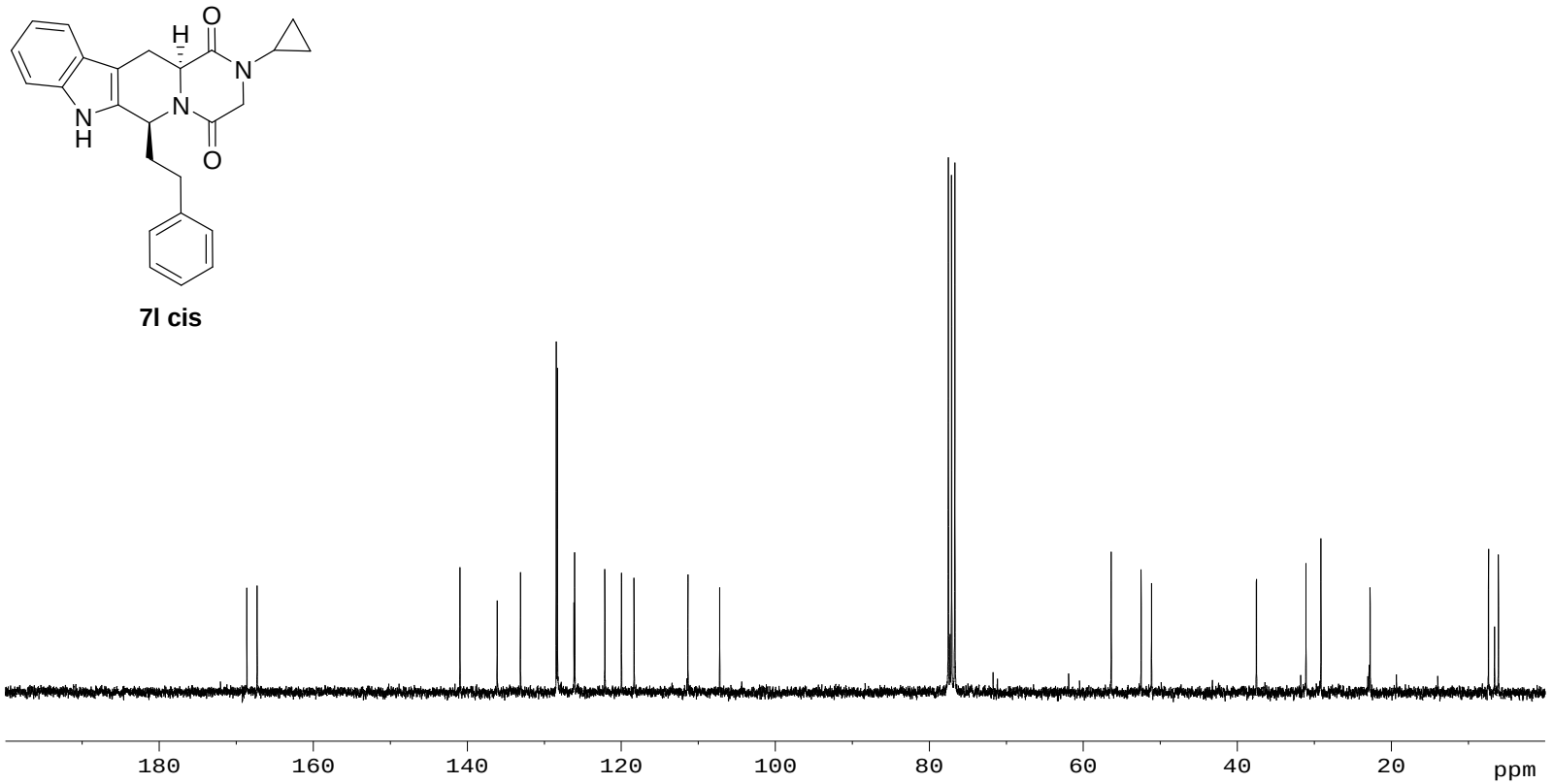
^{1}HNMR spectrum (300 MHz) of compound 7l (trans isomer) in $CDCl_3$



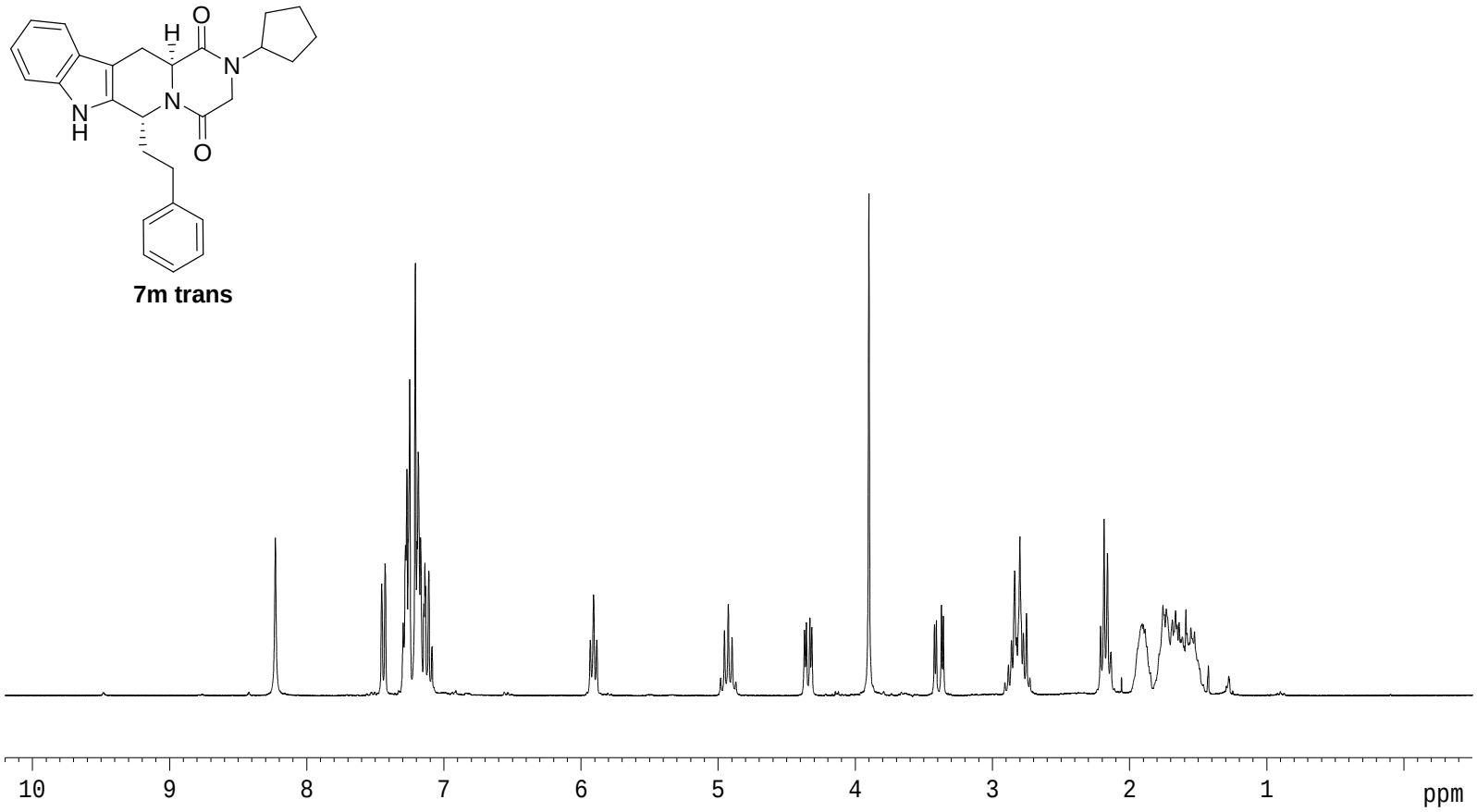
^{13}C NMR spectrum (75 MHz) of compound 7l (trans isomer) in $CDCl_3$



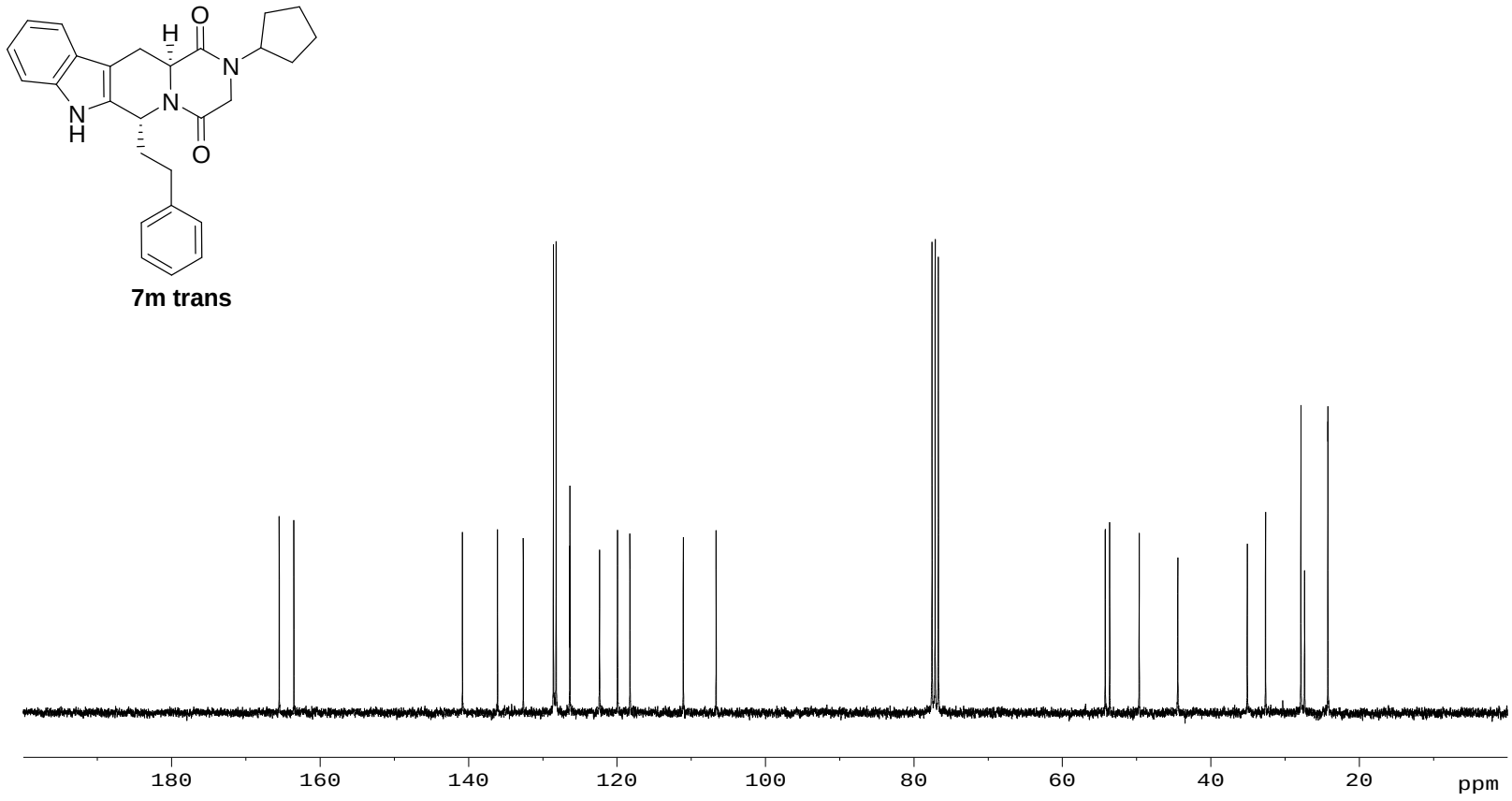
^{1}HNMR spectrum (300 MHz) of compound 7l (cis isomer) in $CDCl_3$



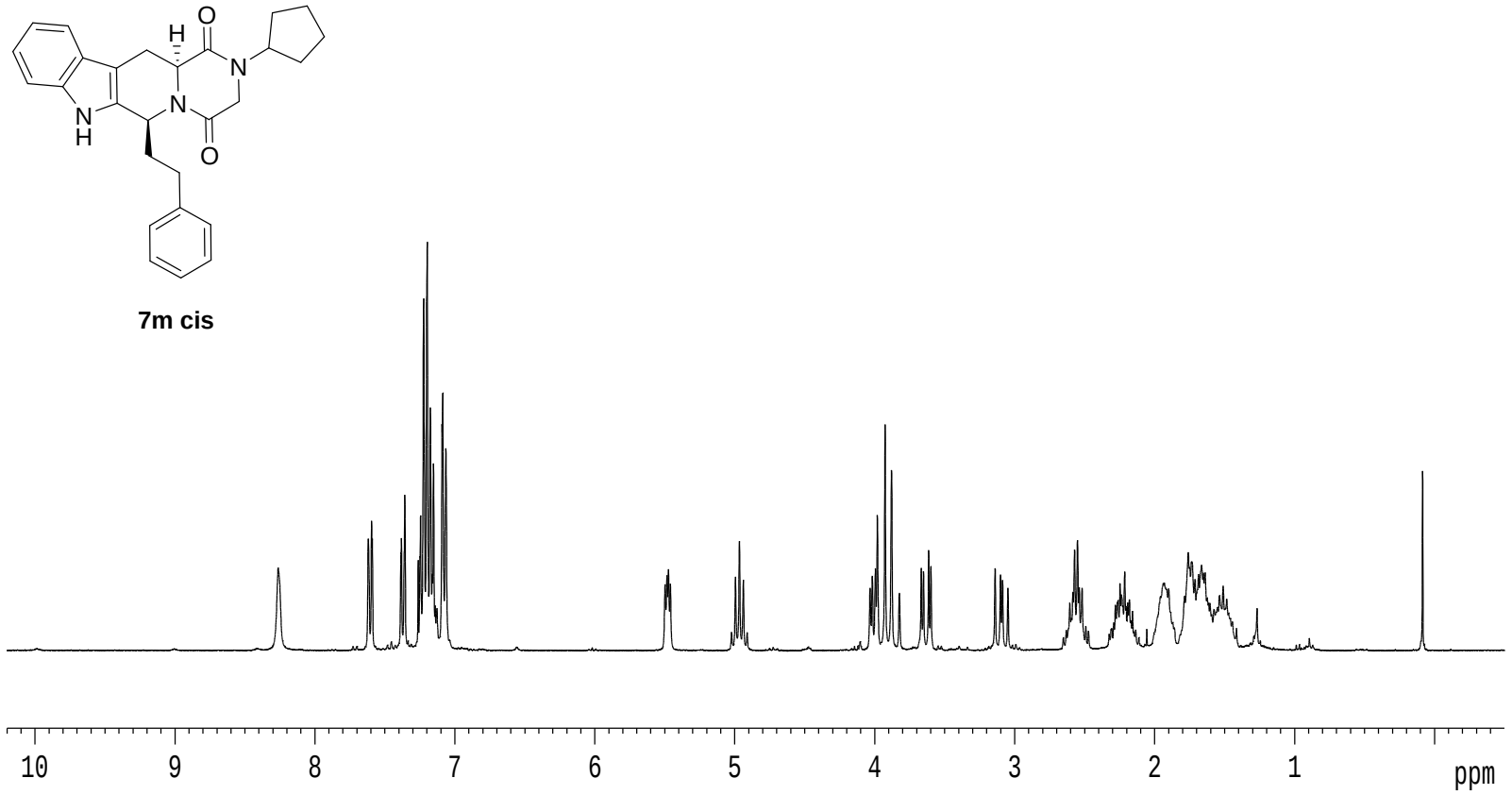
^{13}C NMR spectrum (75 MHz) of compound 7l (cis isomer) in $CDCl_3$



^{1}HNMR spectrum (300 MHz) of compound 7m (trans isomer) in $CDCl_3$

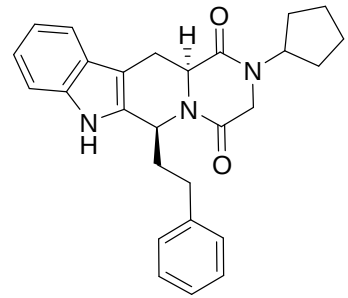


^{13}C NMR spectrum (75 MHz) of compound 7m (trans isomer) in $CDCl_3$

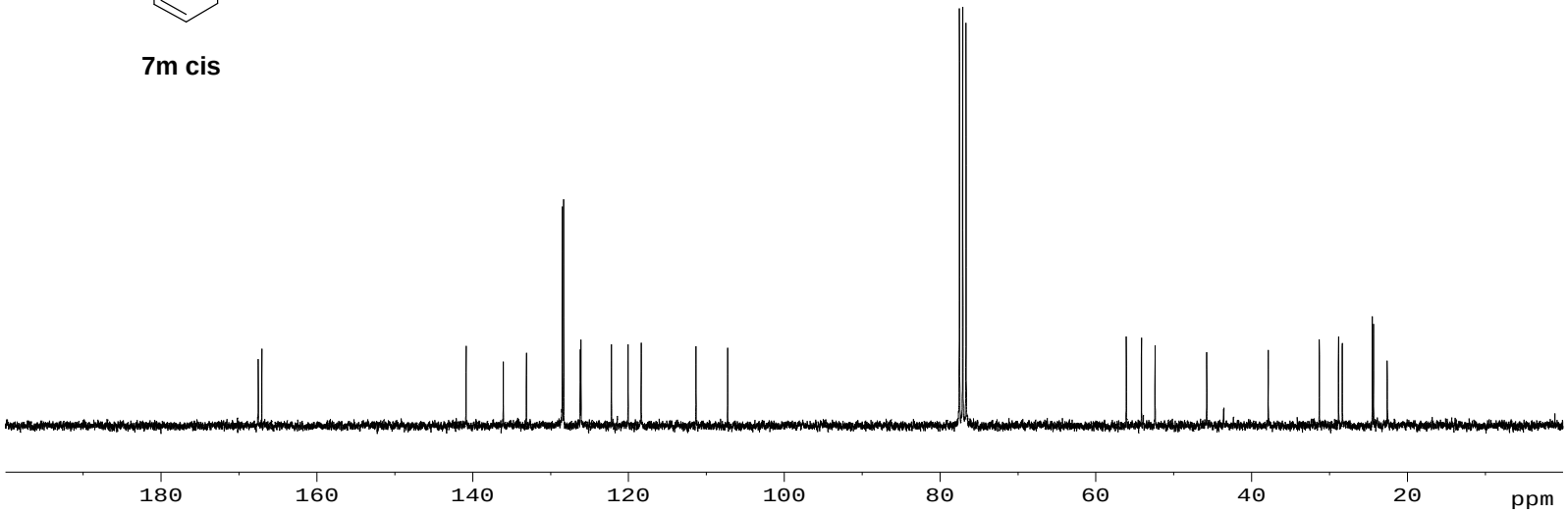


7m cis

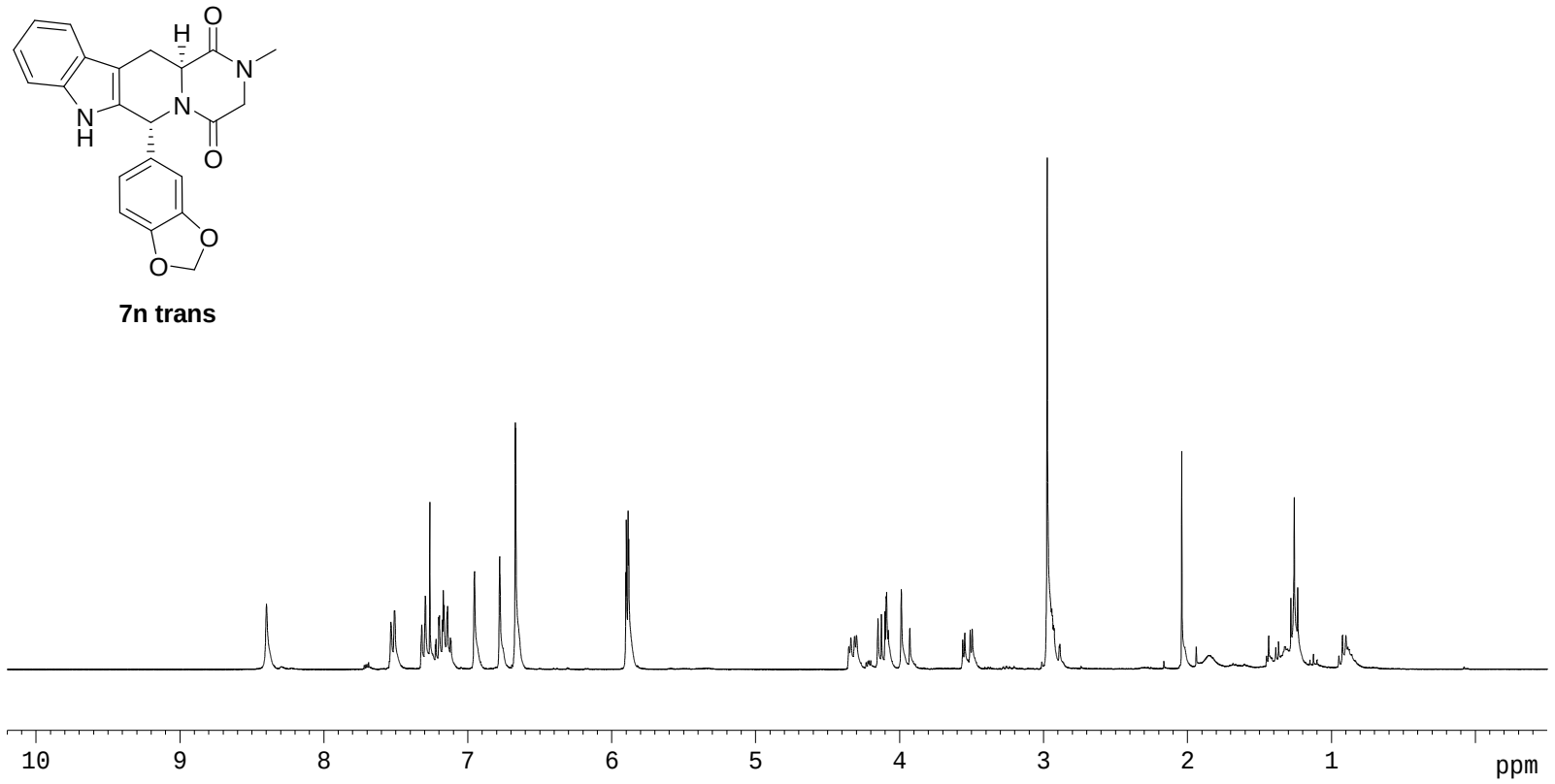
^{1}HNMR spectrum (300 MHz) of compound 7m (cis isomer) in $CDCl_3$



7m cis

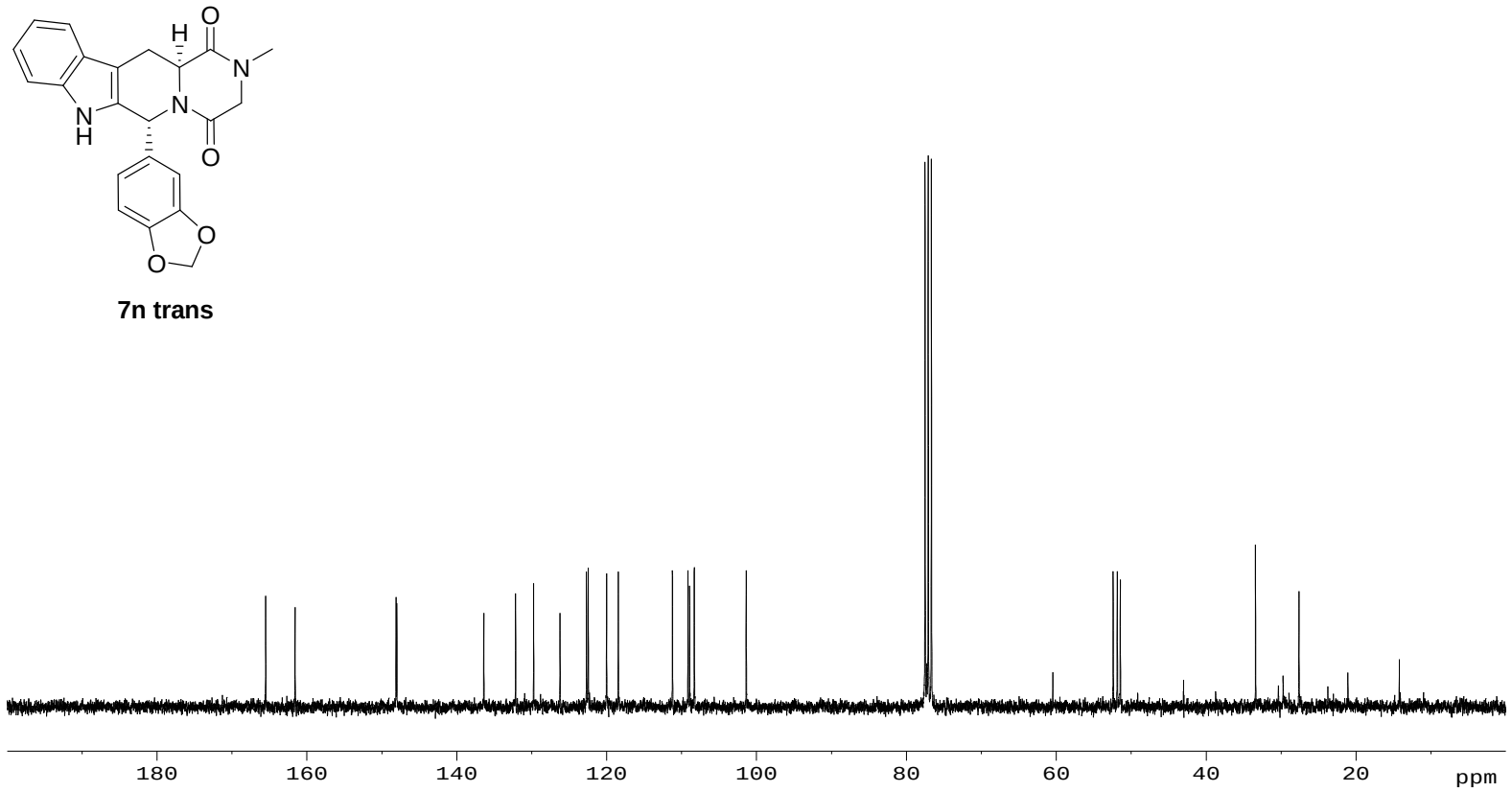


^{13}C NMR spectrum (75 MHz) of compound 7m (cis isomer) in $CDCl_3$



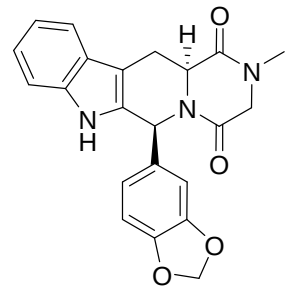
7n trans

^{1}HNMR spectrum (300 MHz) of compound 7n (trans isomer) in $CDCl_3$

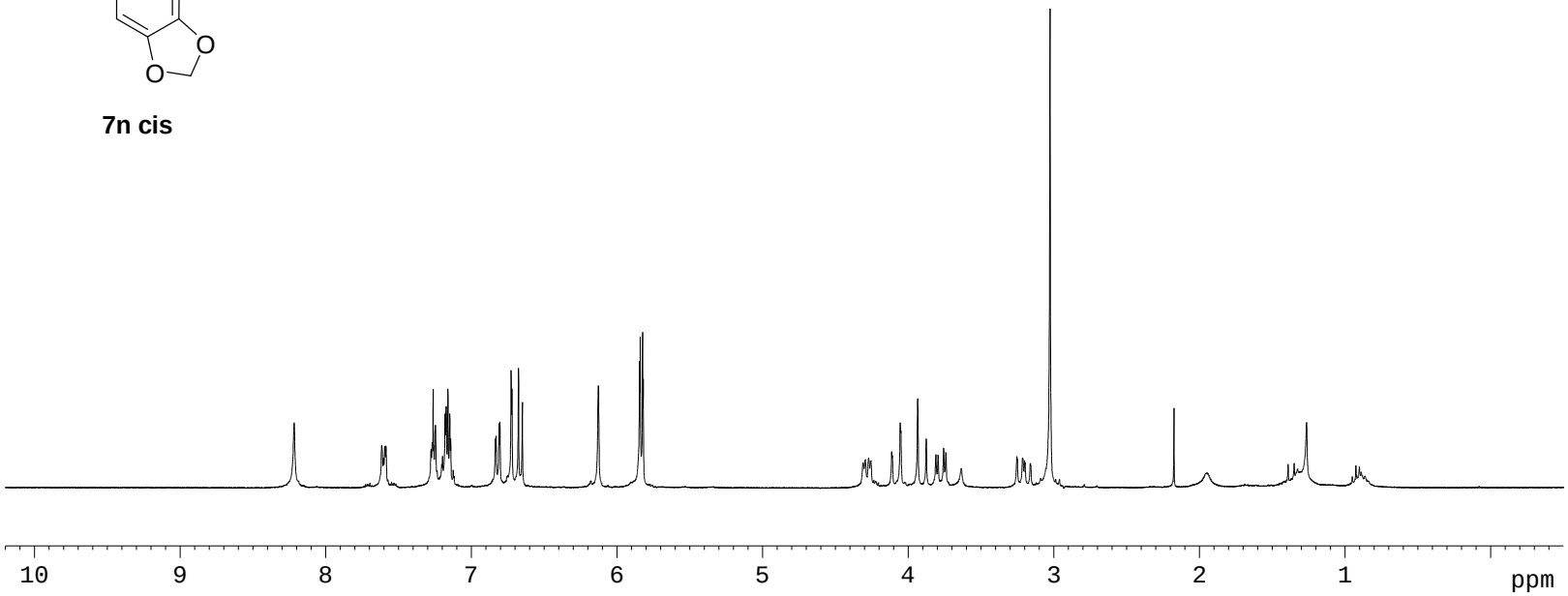


7n trans

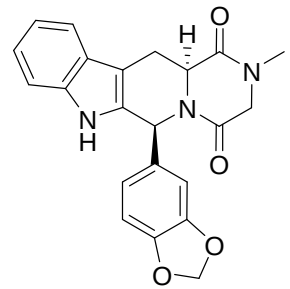
^{13}C NMR spectrum (75 MHz) of compound 7o (trans isomer) in $CDCl_3$



7n cis



^{1}HNMR spectrum (300 MHz) of compound 7o (cis isomer) in $CDCl_3$



7n cis

^{13}C NMR spectrum (75 MHz) of compound 7o (cis isomer) in $CDCl_3$