Supporting Information

Bismuth(III)-catalyzed regioselective alkylation of tetrahydroquinolines and indolines towards the synthesis of bioactive core-biaryl oxindoles and CYP19 inhibitors

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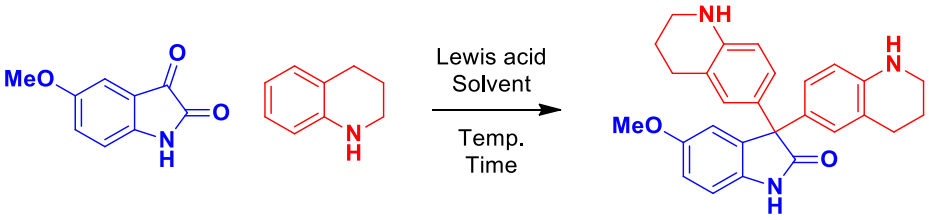
1. Optimization details:

For the optimization of reaction conditions, reactions are performed according to the general procedure (given below) on 0.06 mmol scale.

Procedure: Isatin derivative **1** (1 equiv, 0.3 mmol) was dissolved in DCE (0.25 M) solvent under N_2 atmosphere which was taken in an oven-dried sealed tube equipped with a magnetic stir bar at room temperature. A catalytic amount of $Bi(OTf)_3$ (10 mol %) was added to the reaction mixture followed by addition of tetrahydroquinoline derivative **2** (2.5 equiv, 0.6 mmol). The reaction was allowed to stir at 80 °C in a pre-heated aluminum block until the reaction completed. The reaction mixture was quenched with and diluted with EtOAc after completion of reaction (monitored by TLC). The reaction mixture was then passed through celite and evaporated. The evaporation residue was purified by column chromatography (200-400 mesh silica, basified by 5% Et_3N) to give the pure product **3**.

Table S1. Evaluation of all parameters of reaction.



1a 2a 3aa

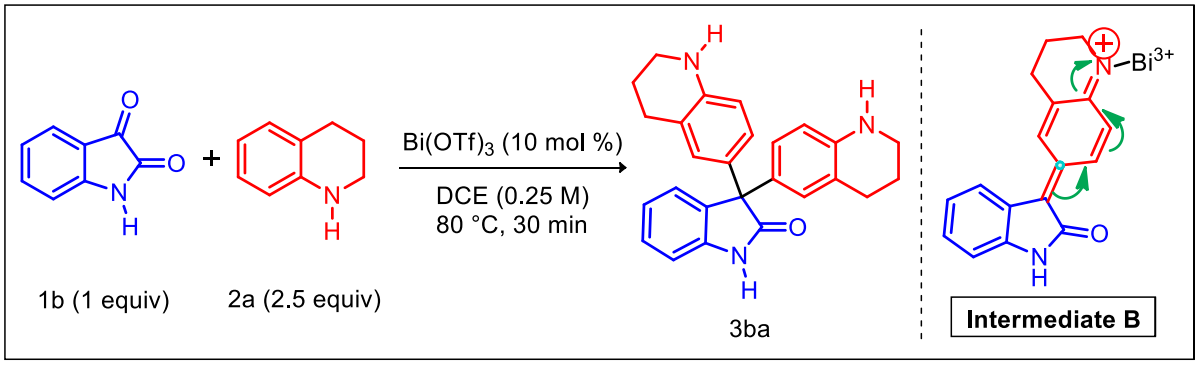
Sl no.	Methoxy isatin (equiv)	Tetrahydro quinoline (equiv)	Lewis Acid	Solvent (0.25 M)	Temp	Time	Yield of 3aa (%)[a,b]
Solvent Variation							
1.	1	2.5	$In(OTf)_3$ (0.1 equiv)	1,4-Dioxane	80 °C	6 h	59(55)
2.	1	2.5	$In(OTf)_3$ (0.1 equiv)	MeOH	80 °C	6 h	67
3.	1	2.5	$In(OTf)_3$ (0.1 equiv)	DMSO	80 °C	6 h	NR
4.	1	2.5	$In(OTf)_3$ (0.1 equiv)	DMF	80 °C	6 h	56
5.	1	2.5	$In(OTf)_3$ (0.1 equiv)	DCM	80 °C	6 h	64
6.	1	2.5	$In(OTf)_3$ (0.1 equiv)	DCE	80 °C	6 h	79

Lewis Acid Variation							
7.	1	2.5	$In(OTf)_3$ (0.1 equiv)	DCE	80 °C	6 h	79
8.	1	2.5	$ZnCl_2$ (0.1 equiv)	DCE	80 °C	6 h	58
9.	1	2.5	$AlCl_3$ (0.1 equiv)	DCE	80 °C	6 h	39
10.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	6 h	83 (75)[b]
Temp Variation							
11.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	rt	6 h	11
12.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	40 °C	6 h	49
13.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	60 °C	6 h	79 (73)[b]
14.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	6 h	83 (75)[b]
15.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	100 °C	6 h	48
16.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	120 °C	6 h	29
17.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	140 °C	6 h	NR
Time Variation							
18.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	4 h	47
19.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	6 h	83 (75)[b]
20.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	8 h	96 (92)[b]
21.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	10 h	82 (81)[b]
Coupling Partner Equiv Variation							
22.	1	2	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	8 h	68
23.	1	2.2	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	8 h	73
24.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	8 h	96 (92)[b]
25.	1	2.5	$Bi(OTf)_3$ (0.05 equiv)	DCE	80 °C	8 h	55
26.	1	2.8	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	8 h	75

27.	1	3	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	8 h	72
Mechanistic Study							
28.	1	2.5	$Bi(OTf)_3$ (0.1 equiv)	DCE	80 °C	8 h	96
29.	1	2.5	$Bi(OTf)_3$ (0.1 equiv) BHT (1 equiv)	DCE	80 °C	8 h	96
30.	1	2.5	$Bi(OTf)_3$ (0.1 equiv) TEMPO (1 equiv)	DCE	80 °C	8 h	78

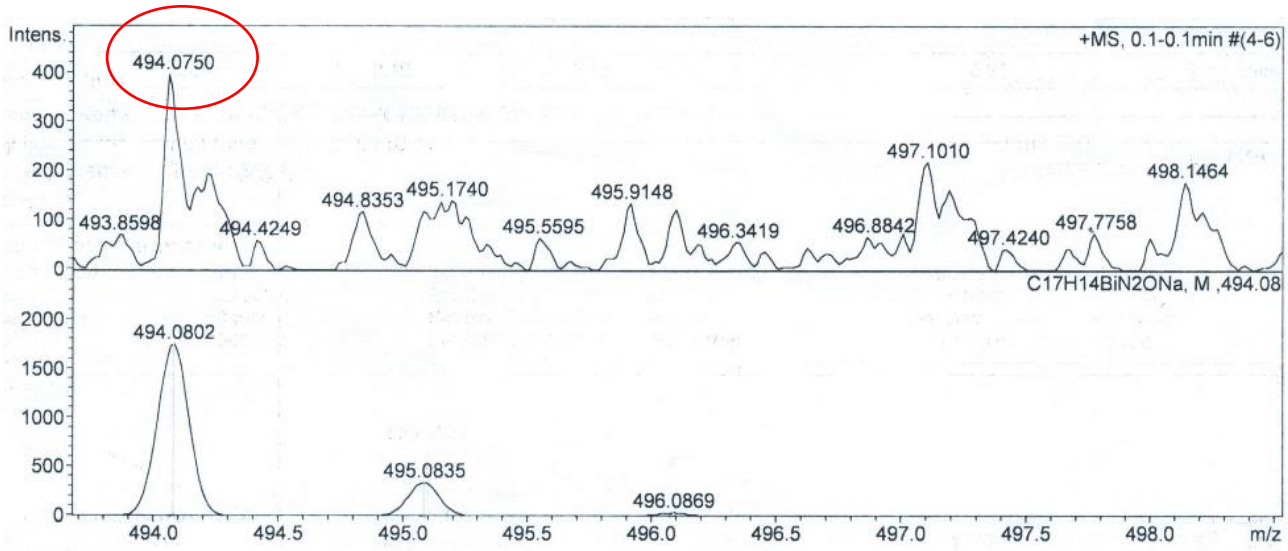
[a]Yield by NMR with 1,3,5-trimethoxy benzene as internal reference; [b]Isolated yield of **3aa**

2. Intermediate trapping:

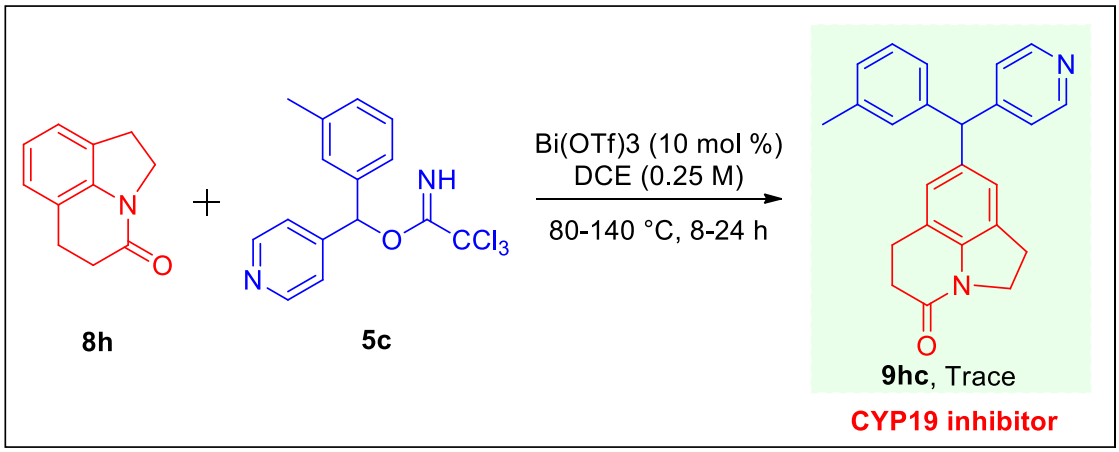


To a pre-dried sealed tube equipped with a magnetic stir bar under N_2, isatin **1b** (1 equiv, 0.01 mmol), tetrahydroquinoline **2a** (2.5 equiv, 0.03 mmol) were taken followed by addition of DCE (0.25 M) solvent. Then catalytic amount of $Bi(OTf)_3$ (10 mol %) was added to the reaction mixture. The reaction was allowed to stir at 80 °C in a pre-heated aluminum block for 30 minutes. After 30 min the reaction mixture was cooled to room temperature and quenched with EtOAc:Methanol (50:50) solvents. Then it is passed through a short celite pad and the solvent was evaporated under reduced pressure and the crude was submitted for HRMS in methanol.

Intermediate HRMS: HRMS (ESI) m/z: M+Na]$^{+}$ Calcd for $C_{17}H_{14}BiNaN_2O^{4+}$:494.0802, Found: 494.0750

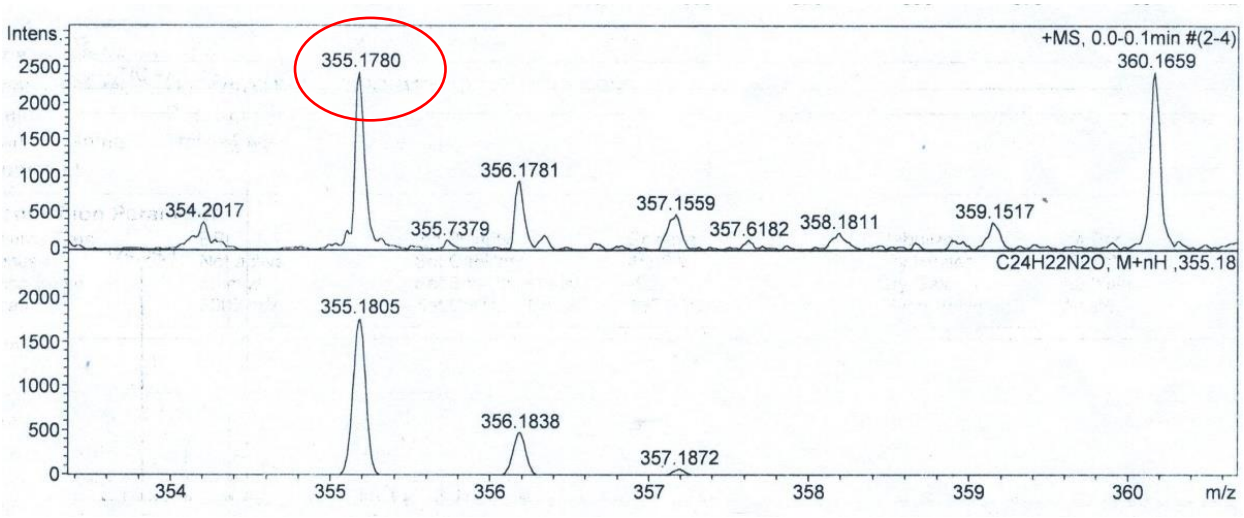


3. CYP-19 inhibitor reaction and its HRMS data:



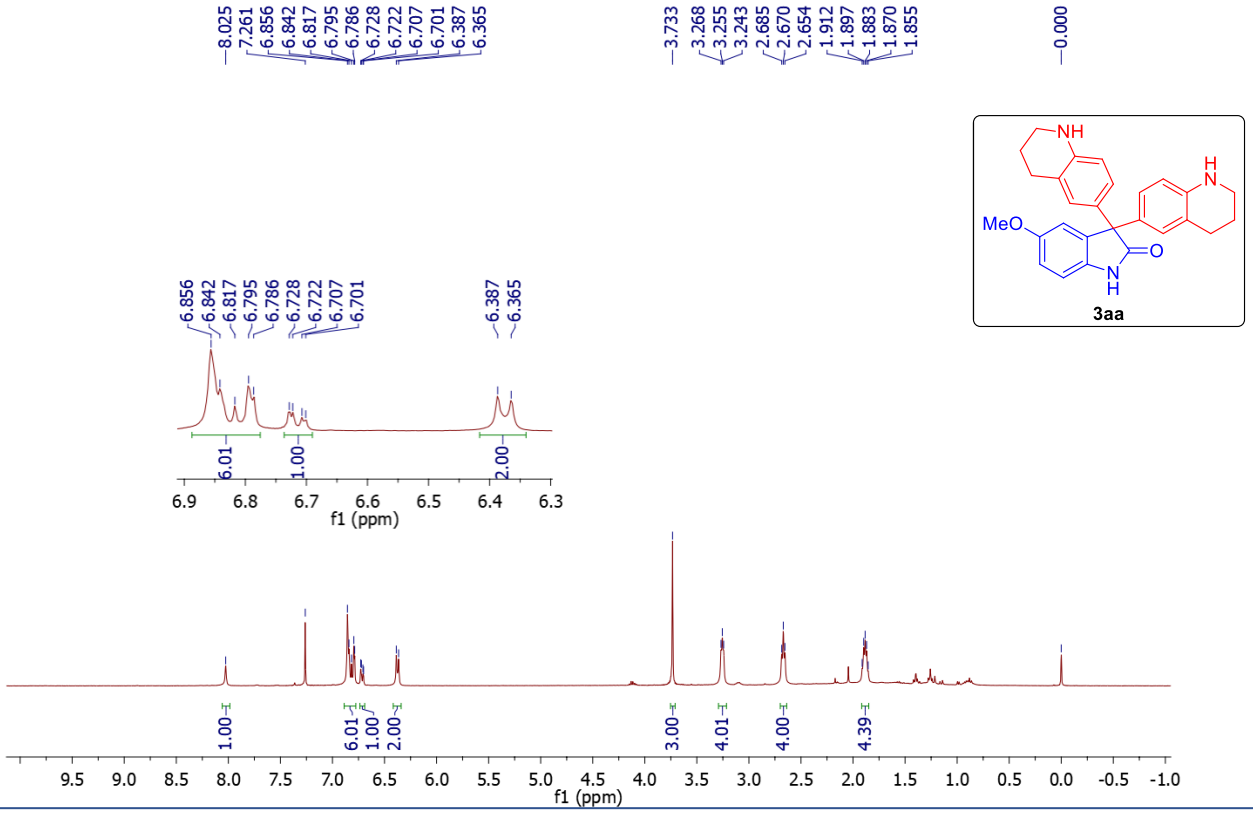
Tetrahydropyrroloquinolinone (**8h**, 24 mg, 0.14 mmol) was dissolved in DCE (0.25 M) under N_2 atmosphere in an oven-dried sealed tube equipped with a magnetic stir bar at room temperature. pyridin-4-yl(m-tolyl)methyl 2,2,2-trichloroacetimidate **5c** (1.5 equiv, 0.21 mmol) was added to the reaction mixture followed by addition of catalytic amount of $Bi(OTf)_3$ (10 mol %). The reaction mixture was allowed to stir at 80 °C in a pre-heated aluminum block for 8-24h. Then the reaction mixture was quenched and diluted with EtOAc and it was passed through celite and evaporated. The crude mixture was submitted for HRMS in methanol from which formation of 9**hc** was detected and it is formed in trace amount.

HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{23}N_2O$: 355.1805; Found: 355.1780.

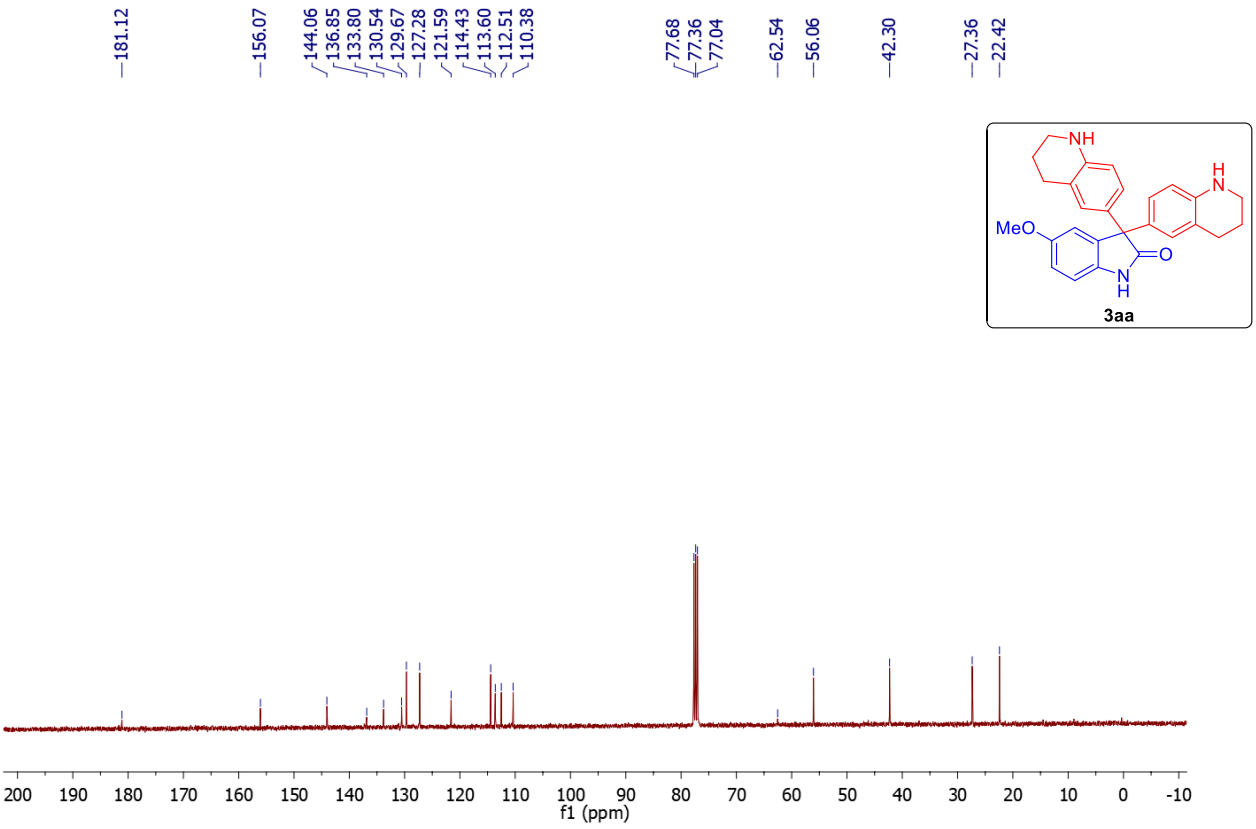


4. Copies of NMR spectra of the products and post-functionalized adducts:

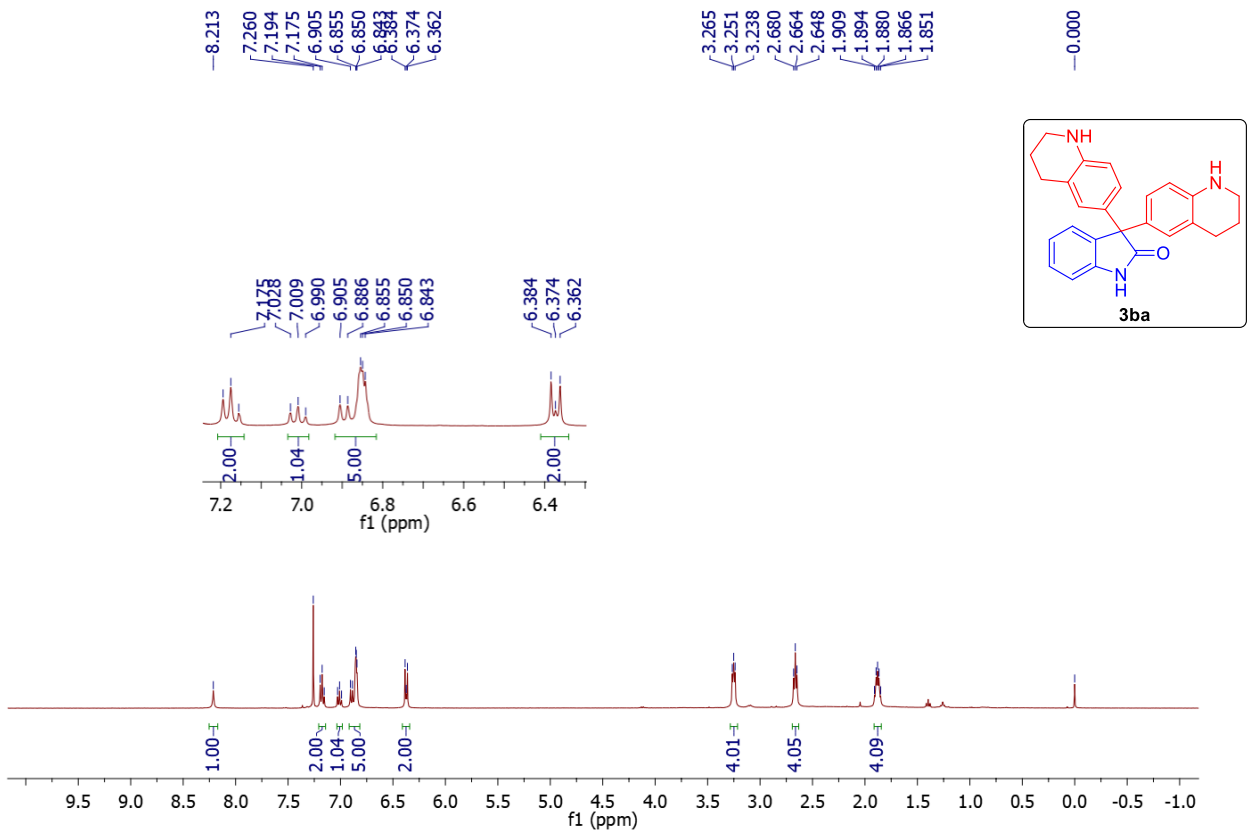
^{1}H NMR of 3aa (400 MHz, $CDCl_3$)



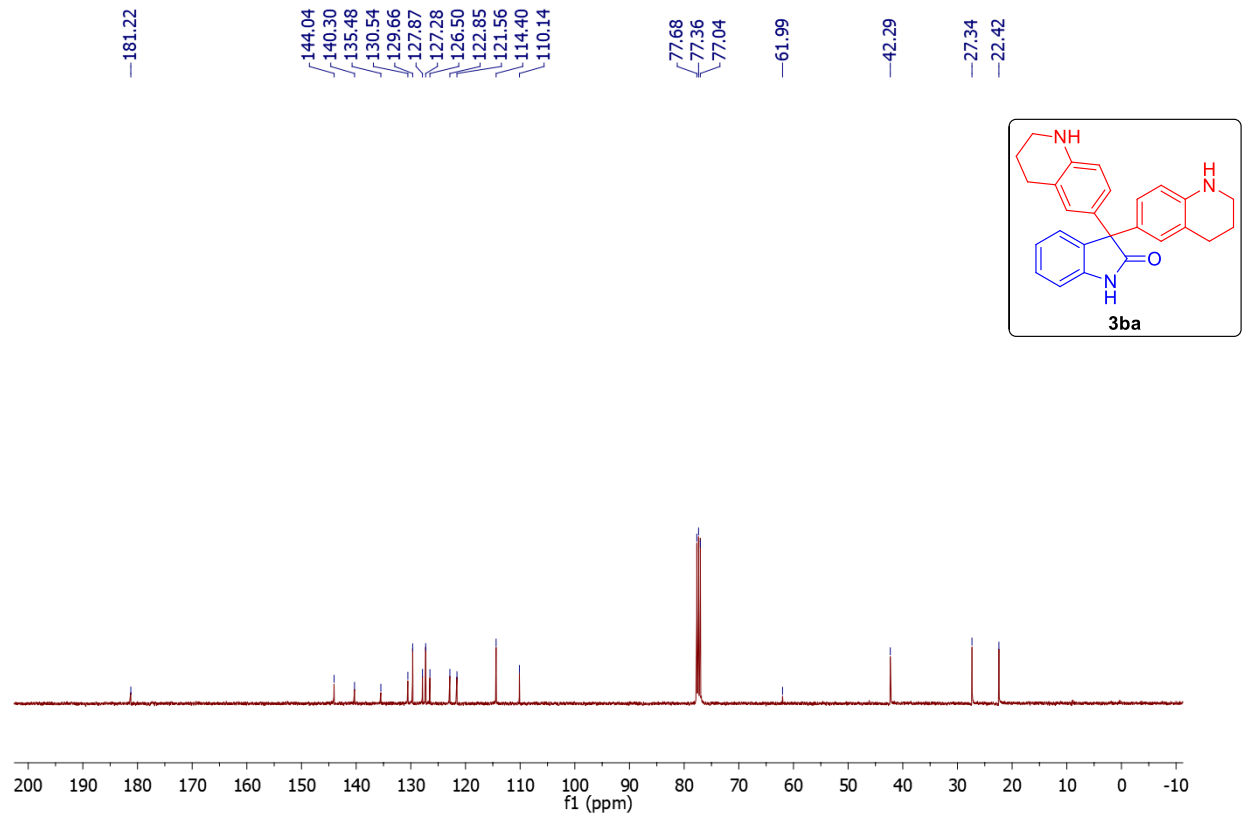
^{13}C NMR of 3aa (100 MHz, $CDCl_3$)



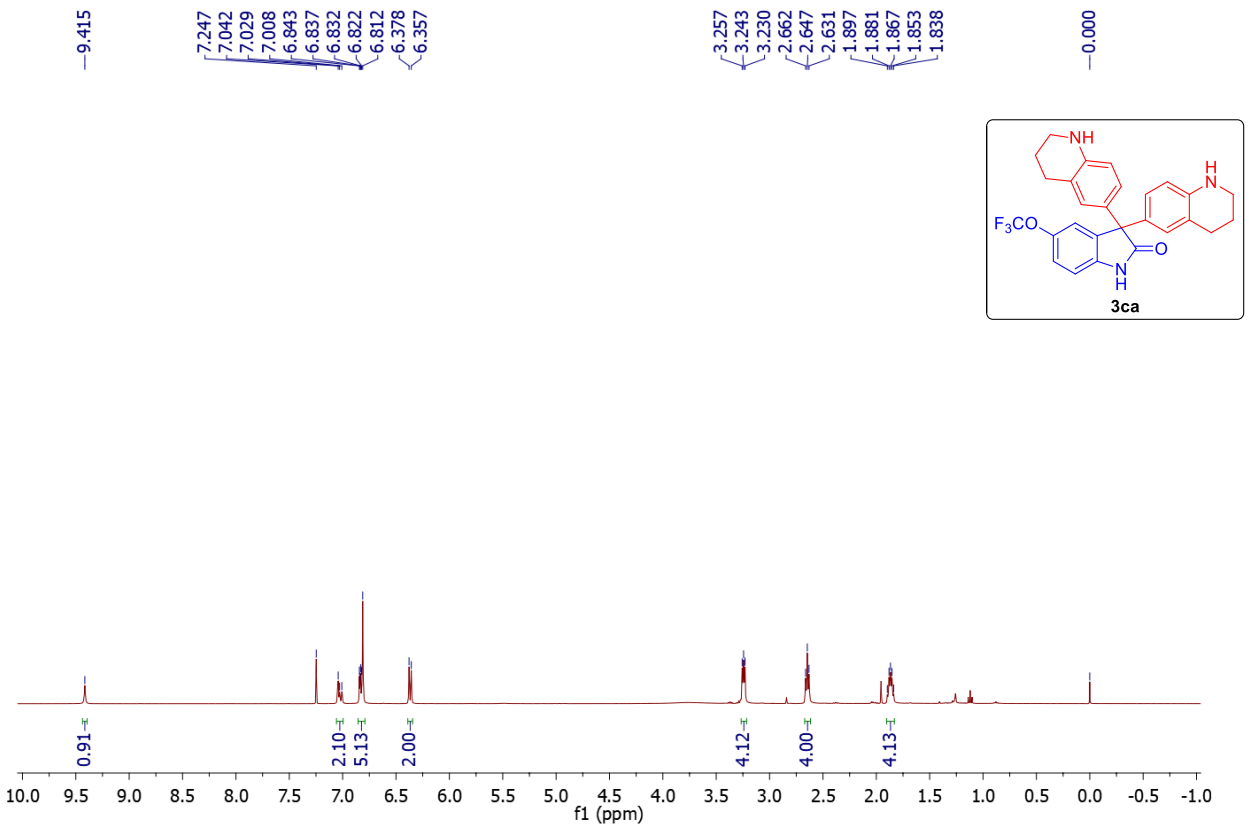
^{1}H NMR of 3ba (400 MHz, $CDCl_3$)



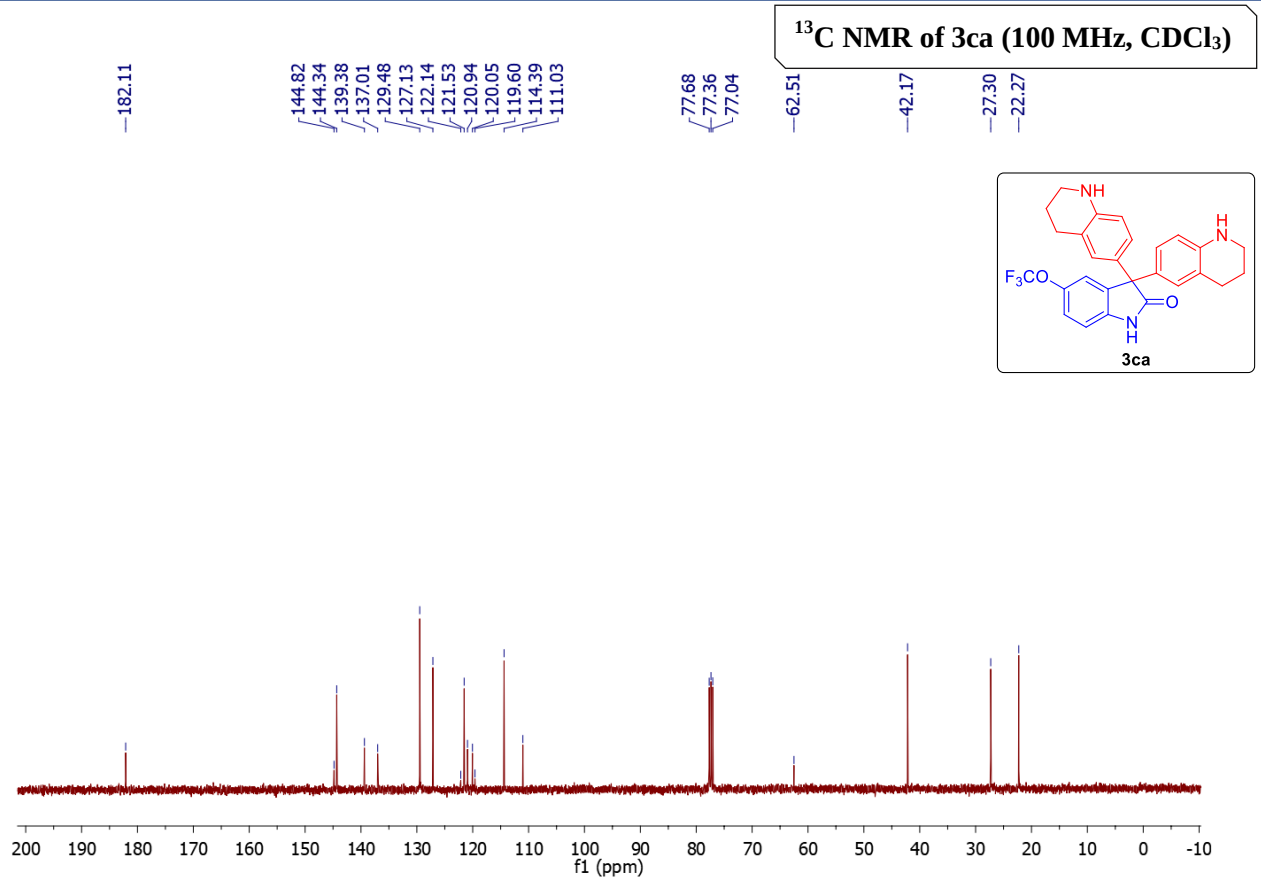
^{13}C NMR of 3ba (100 MHz, $CDCl_3$)



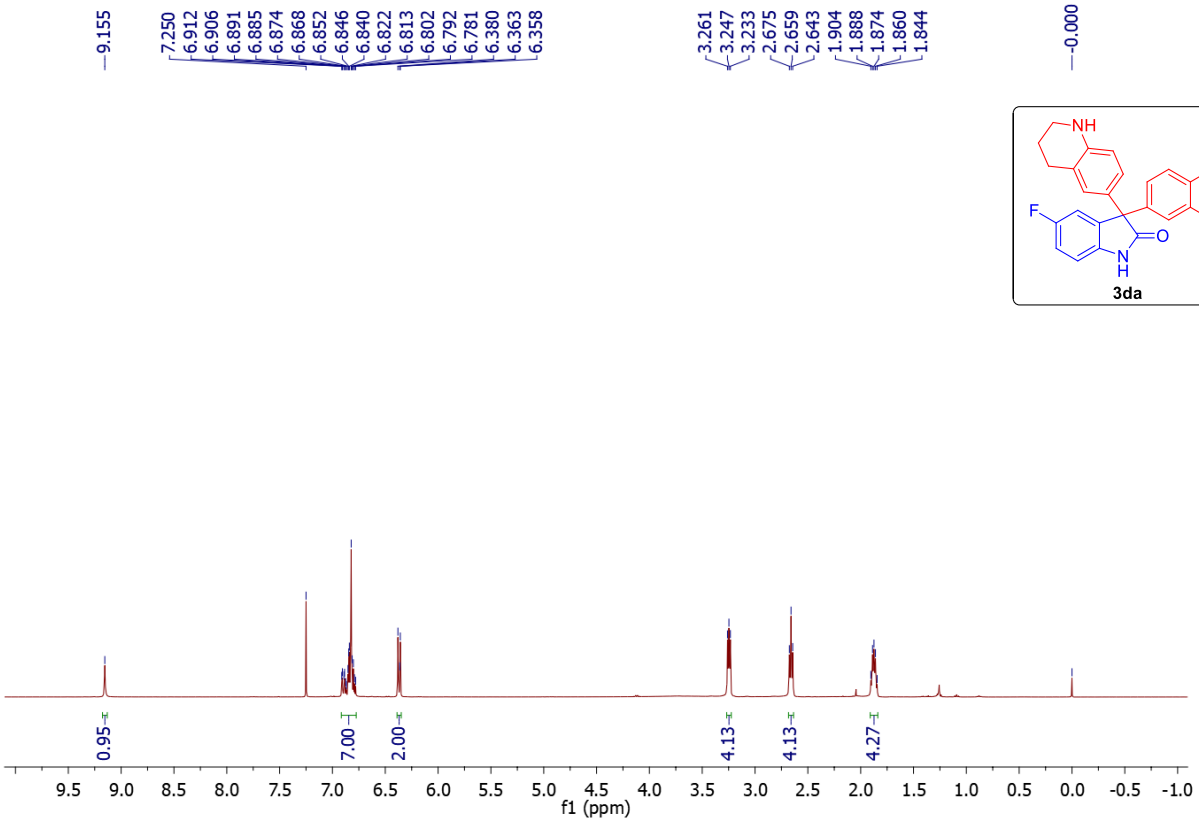
^{1}H NMR of 3ca (400 MHz, $CDCl_3$)



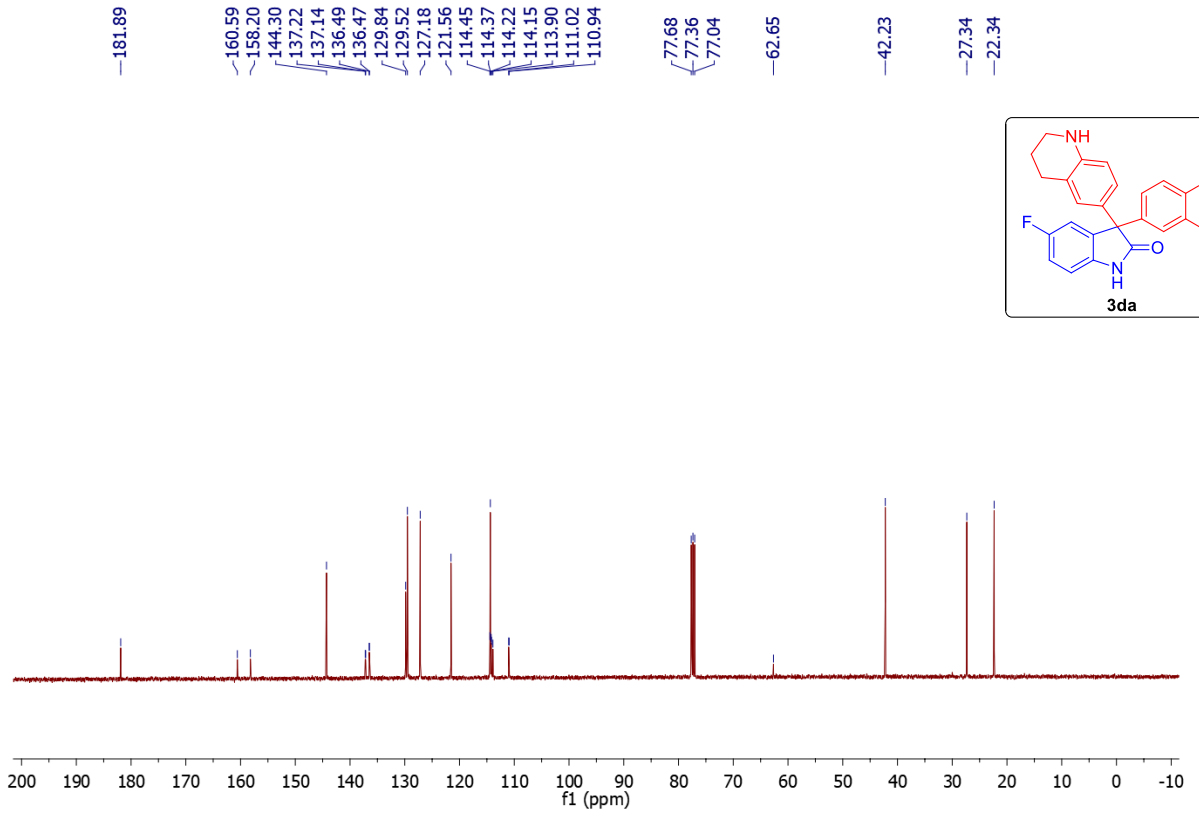
^{13}C NMR of 3ca (100 MHz, $CDCl_3$)



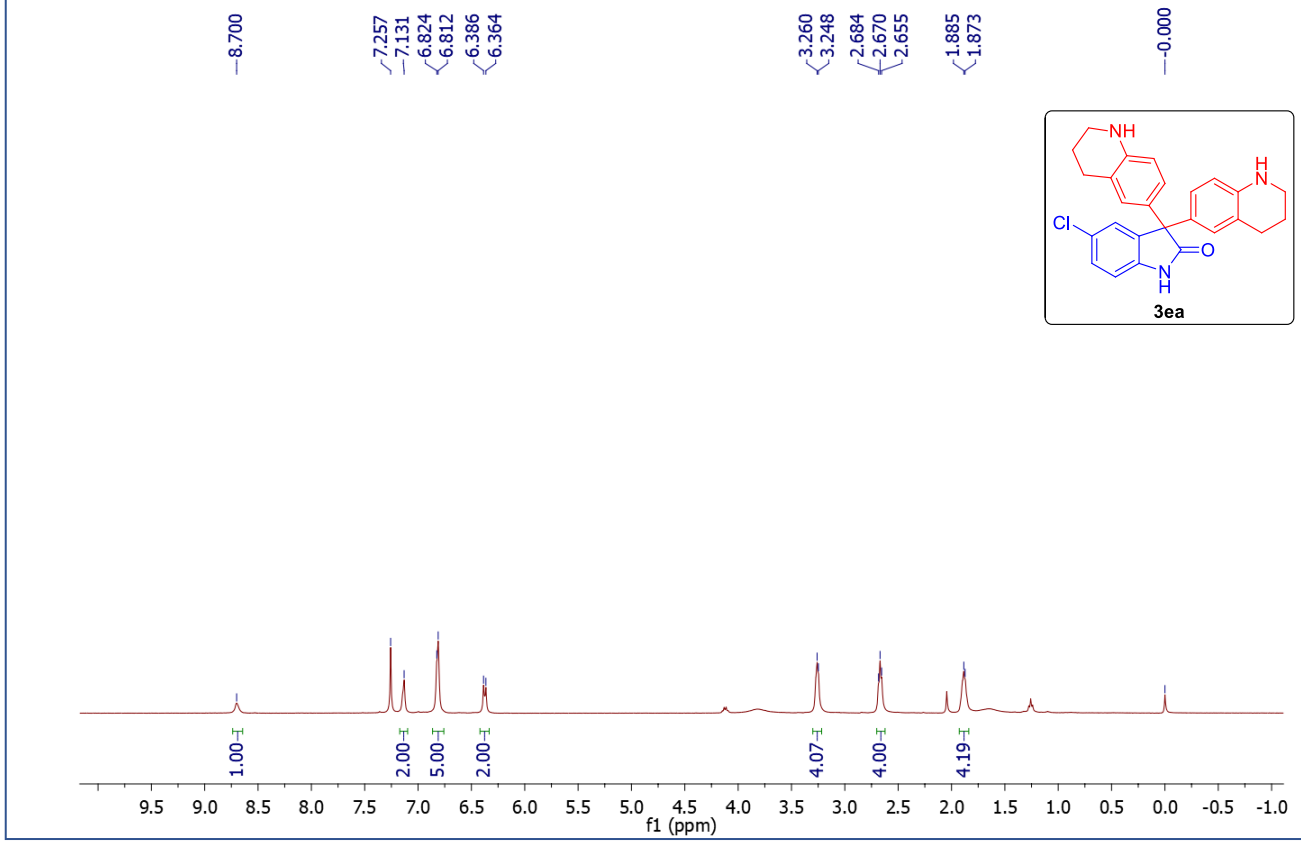
^{1}H NMR of 3da (400 MHz, $CDCl_3$)



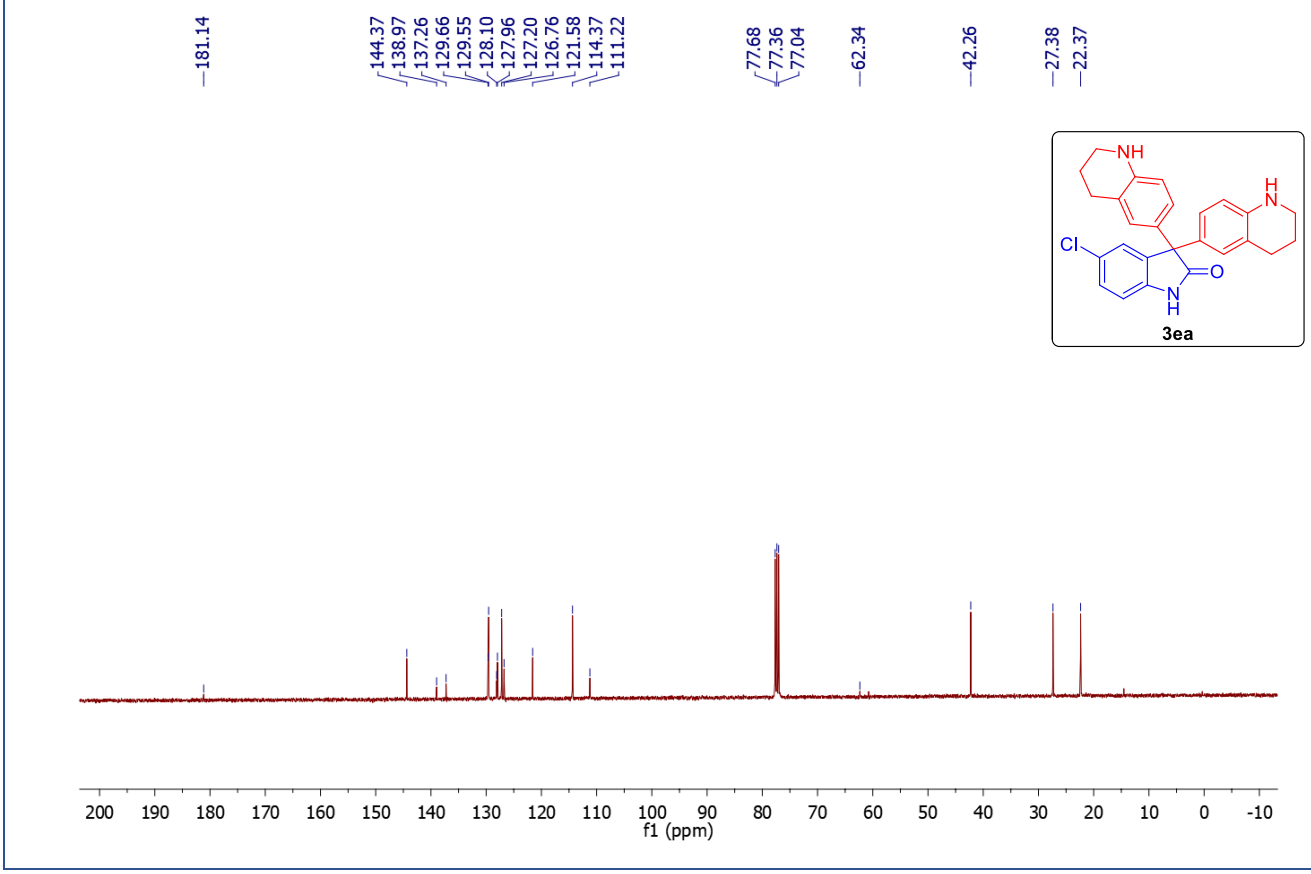
^{13}C NMR of 3da (100 MHz, $CDCl_3$)



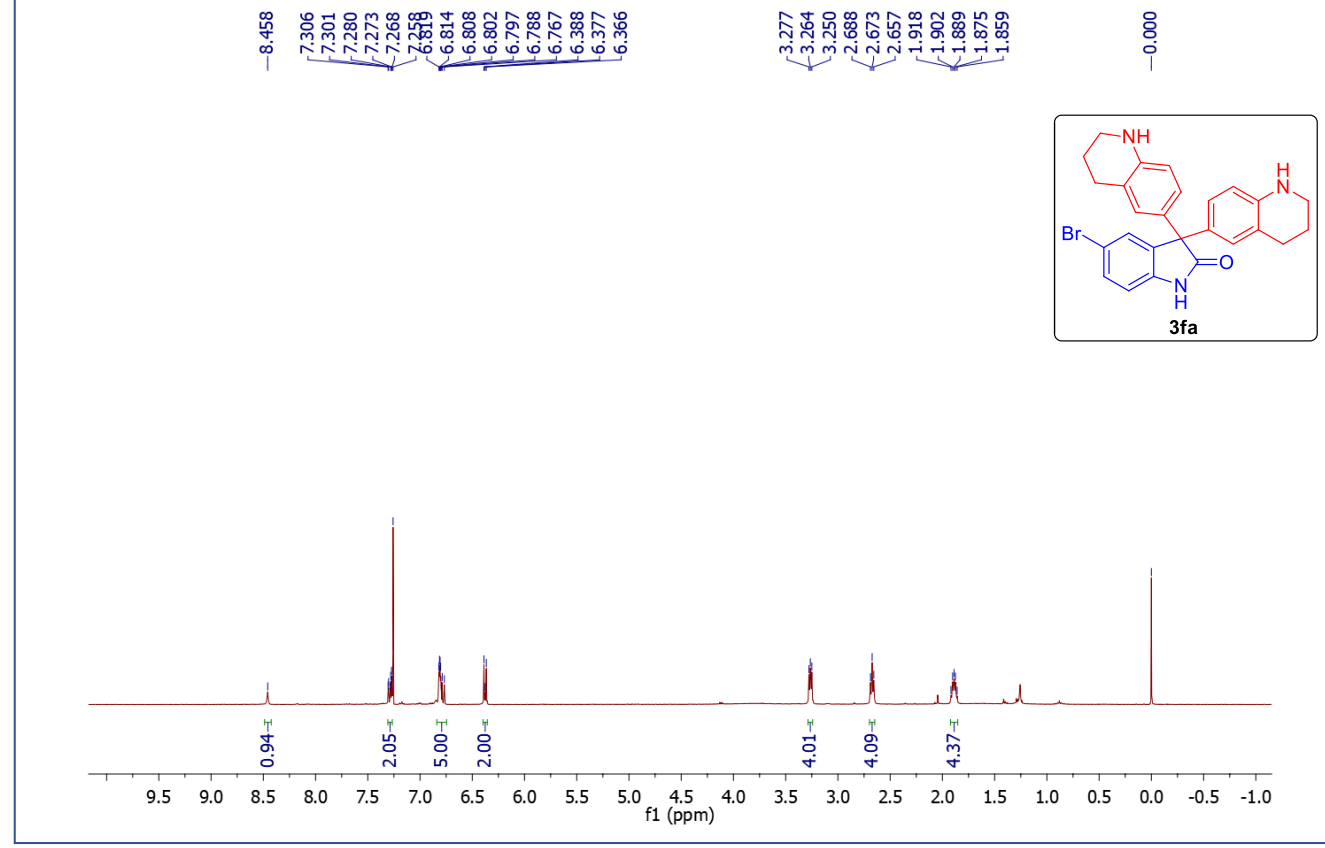
^{1}H NMR of 3ea (400 MHz, $CDCl_3$)



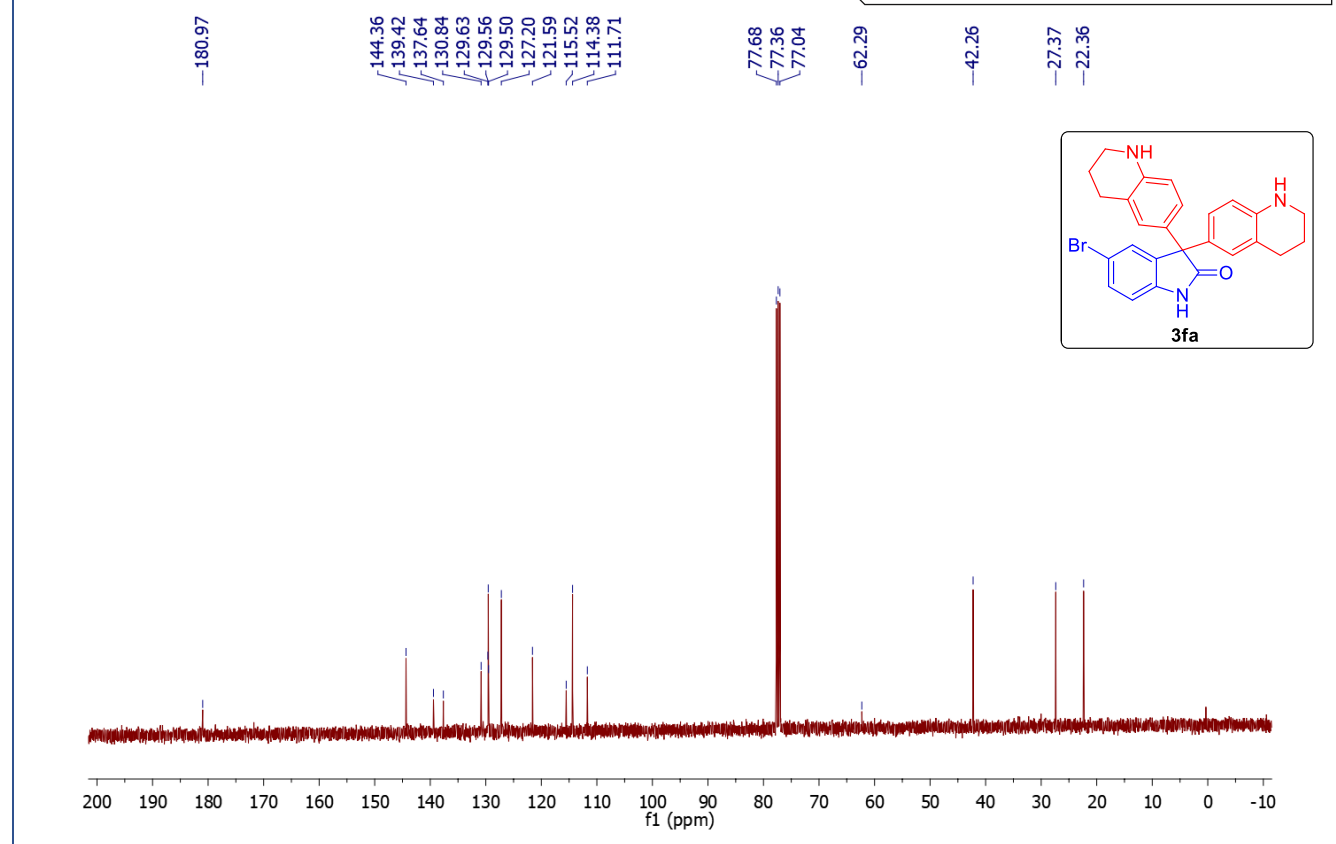
^{13}C NMR of 3ea (100 MHz, $CDCl_3$)



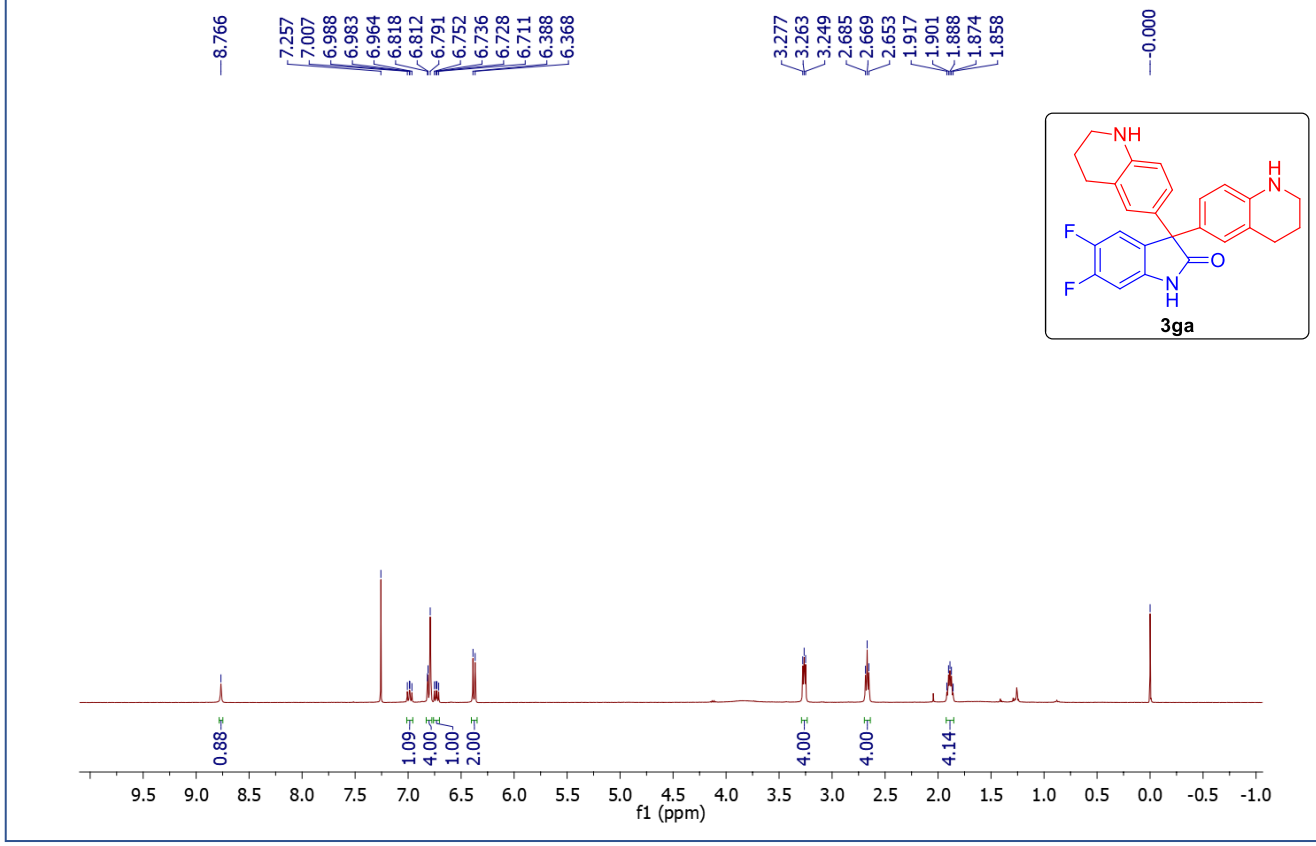
^{1}H NMR of 3fa (400 MHz, $CDCl_3$)



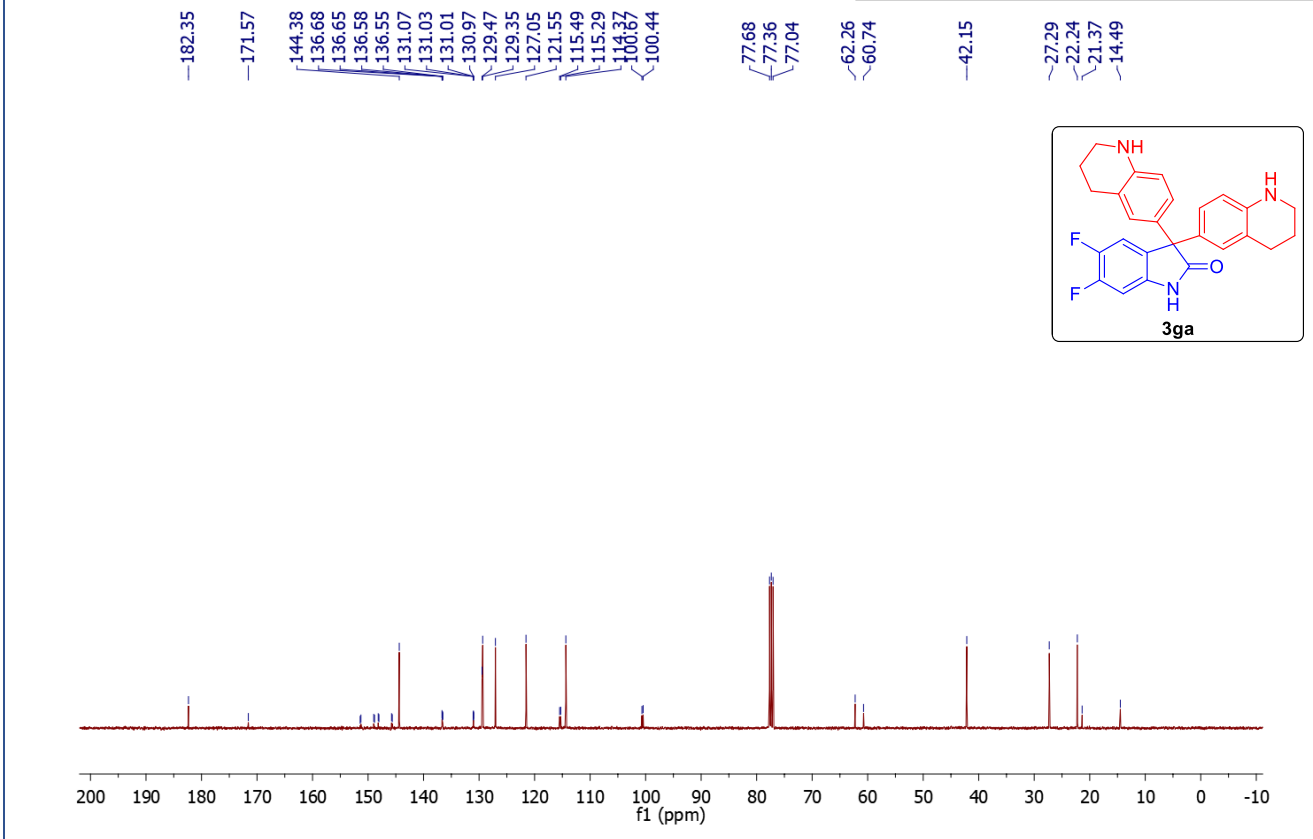
^{13}C NMR of 3fa (100 MHz, $CDCl_3$)



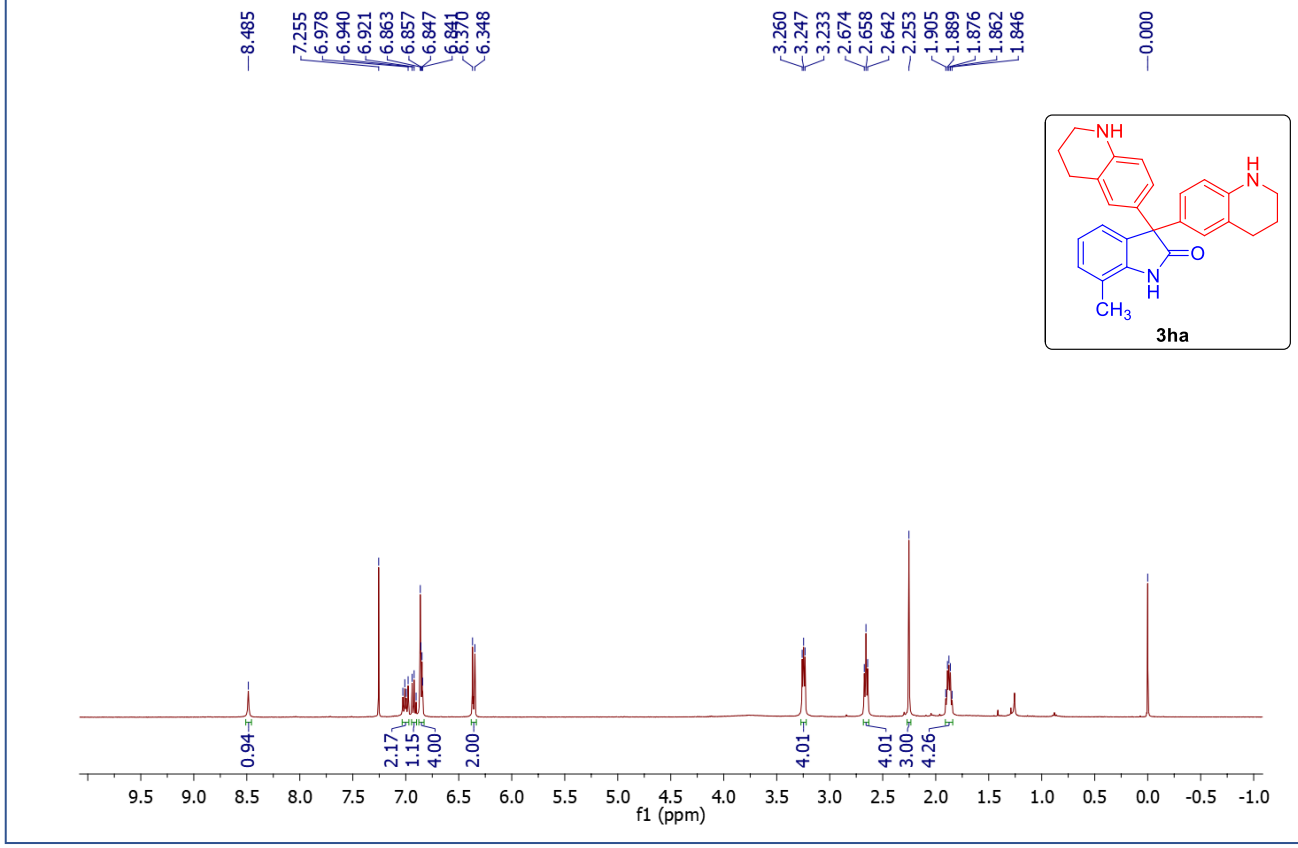
^{1}H NMR of 3ga (400 MHz, $CDCl_3$)



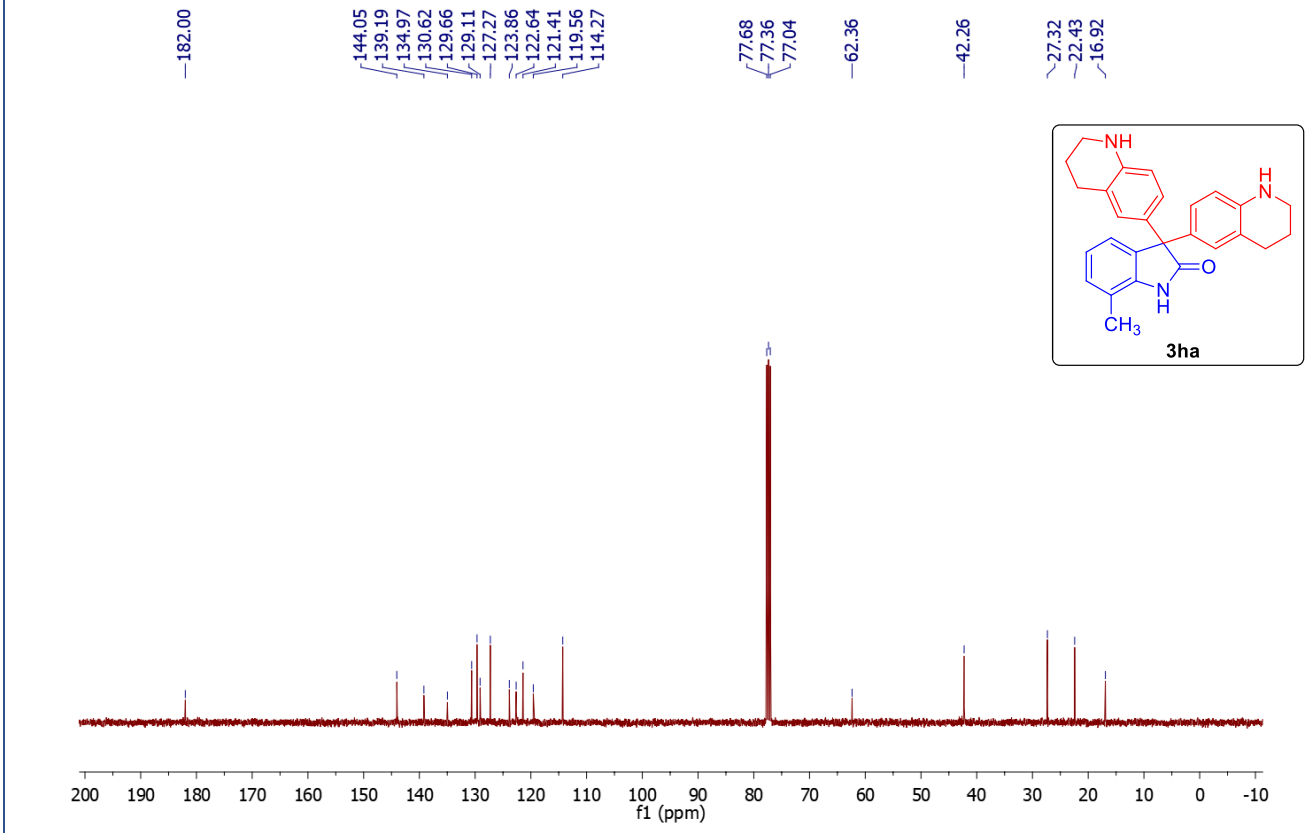
^{13}C NMR of 3ga (100 MHz, $CDCl_3$)



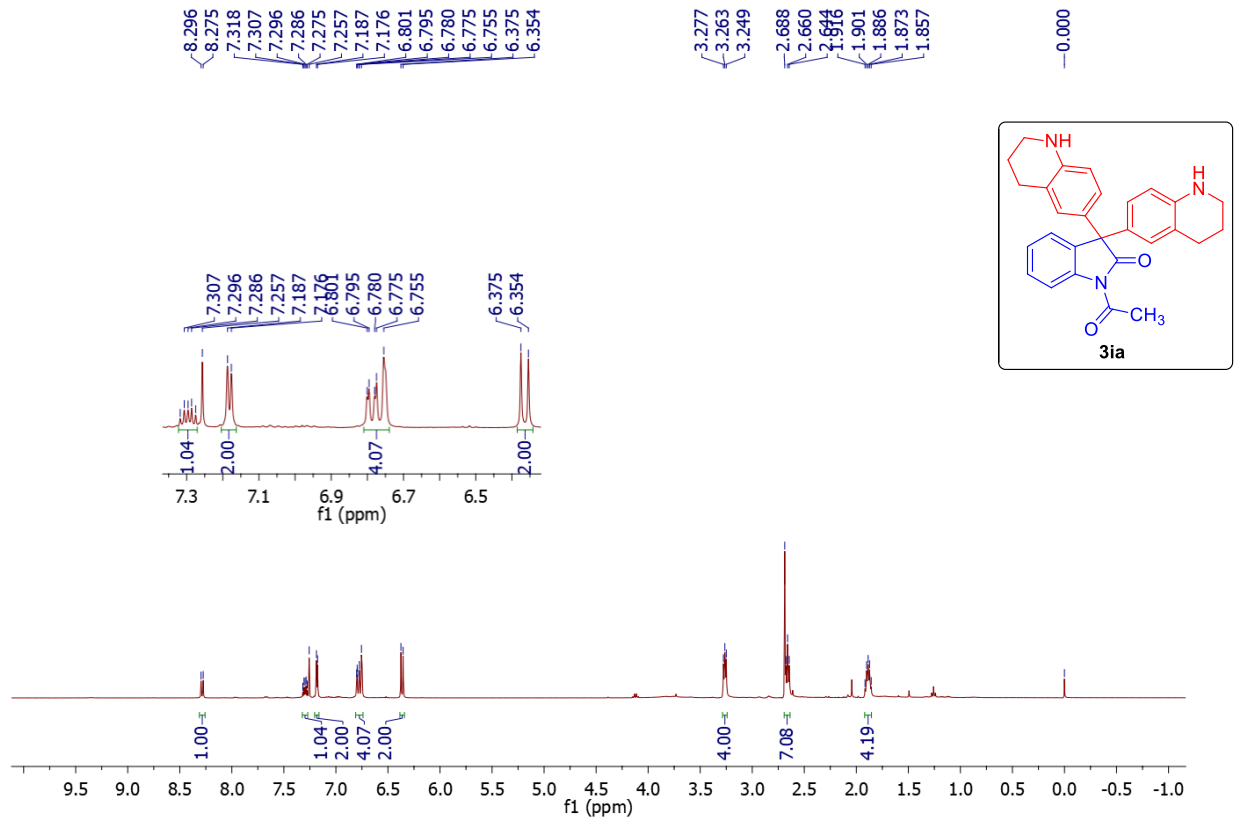
^{1}H NMR of 3ha (400 MHz, $CDCl_3$)



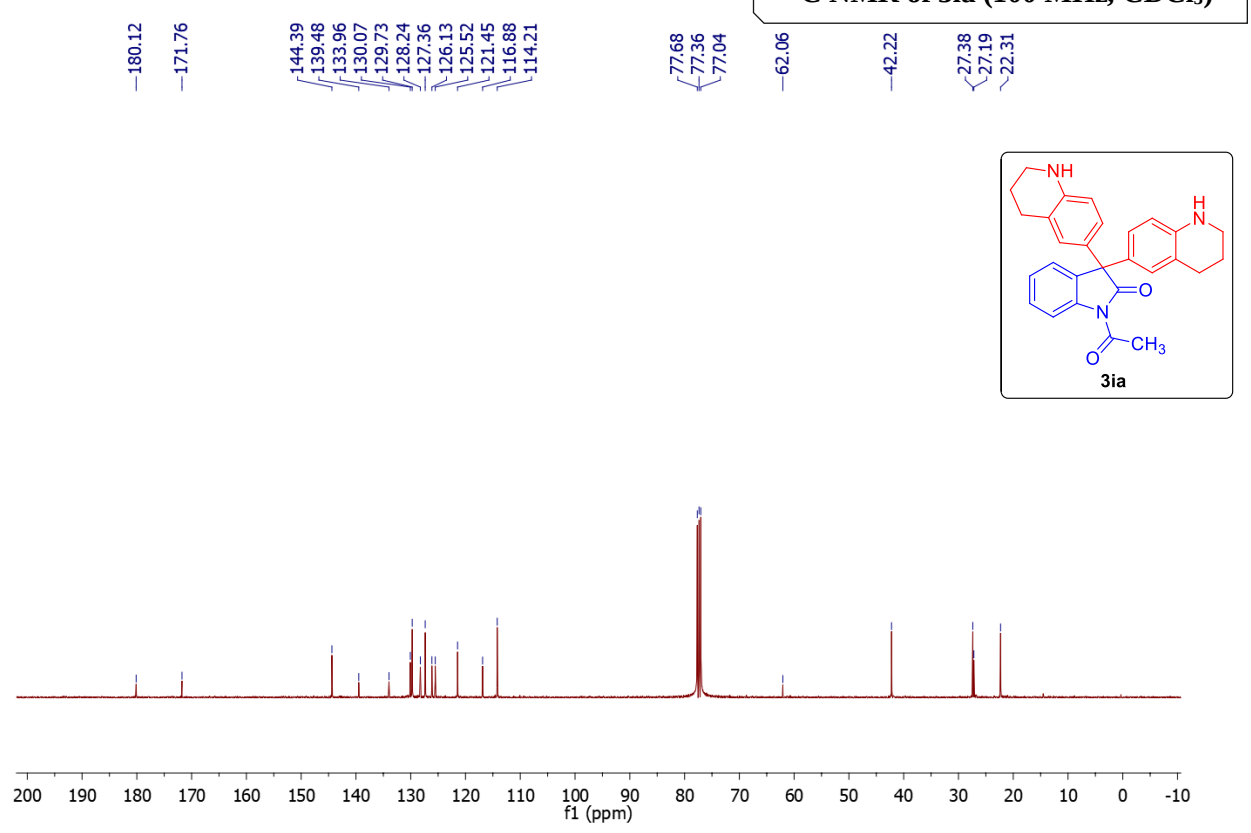
^{13}C NMR of 3ha (100 MHz, $CDCl_3$)



^{1}H NMR of 3ia (400 MHz, $CDCl_3$)



^{13}C NMR of 3ia (100 MHz, $CDCl_3$)



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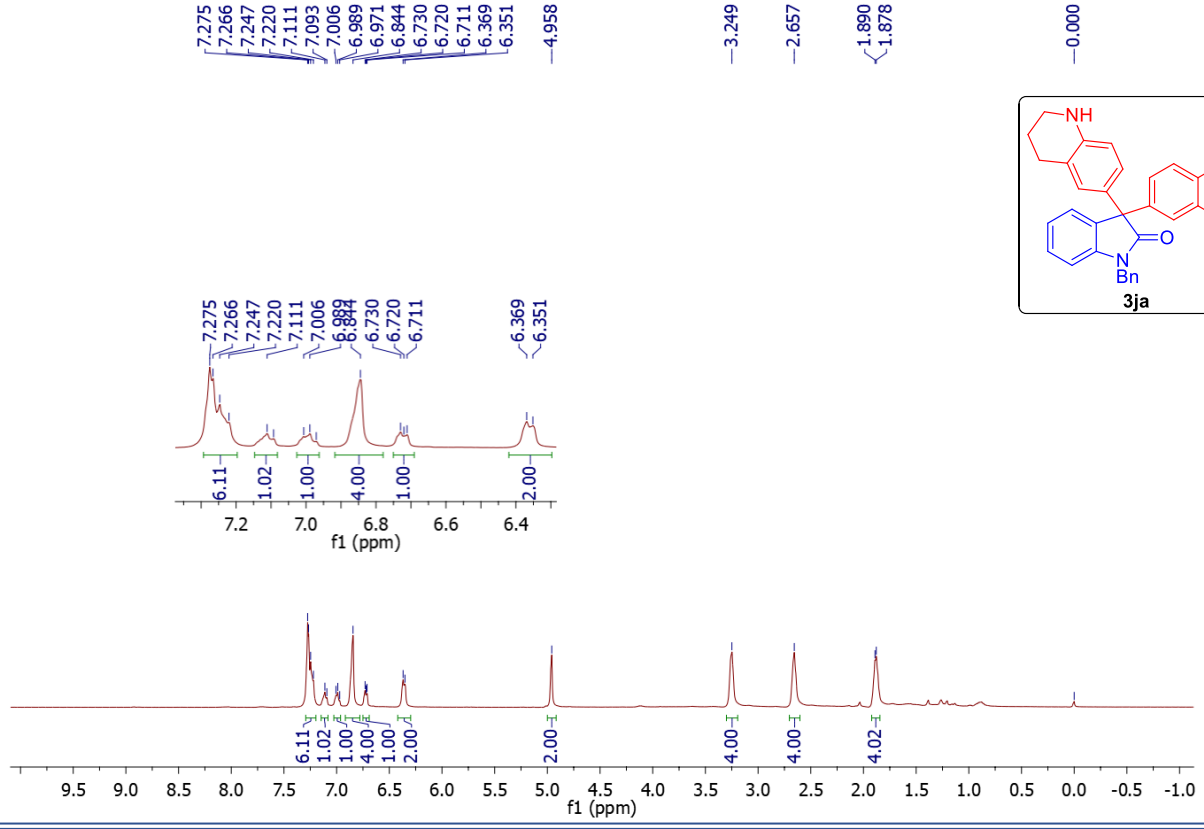

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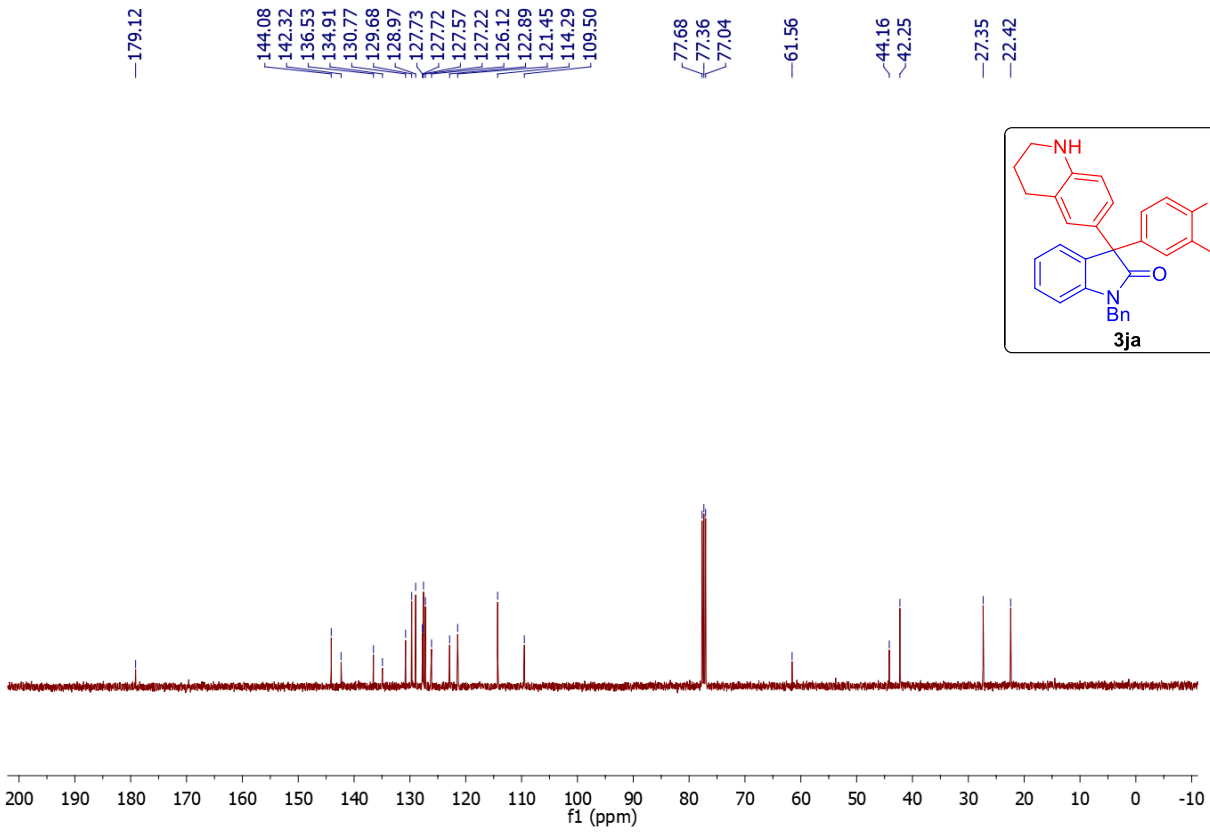
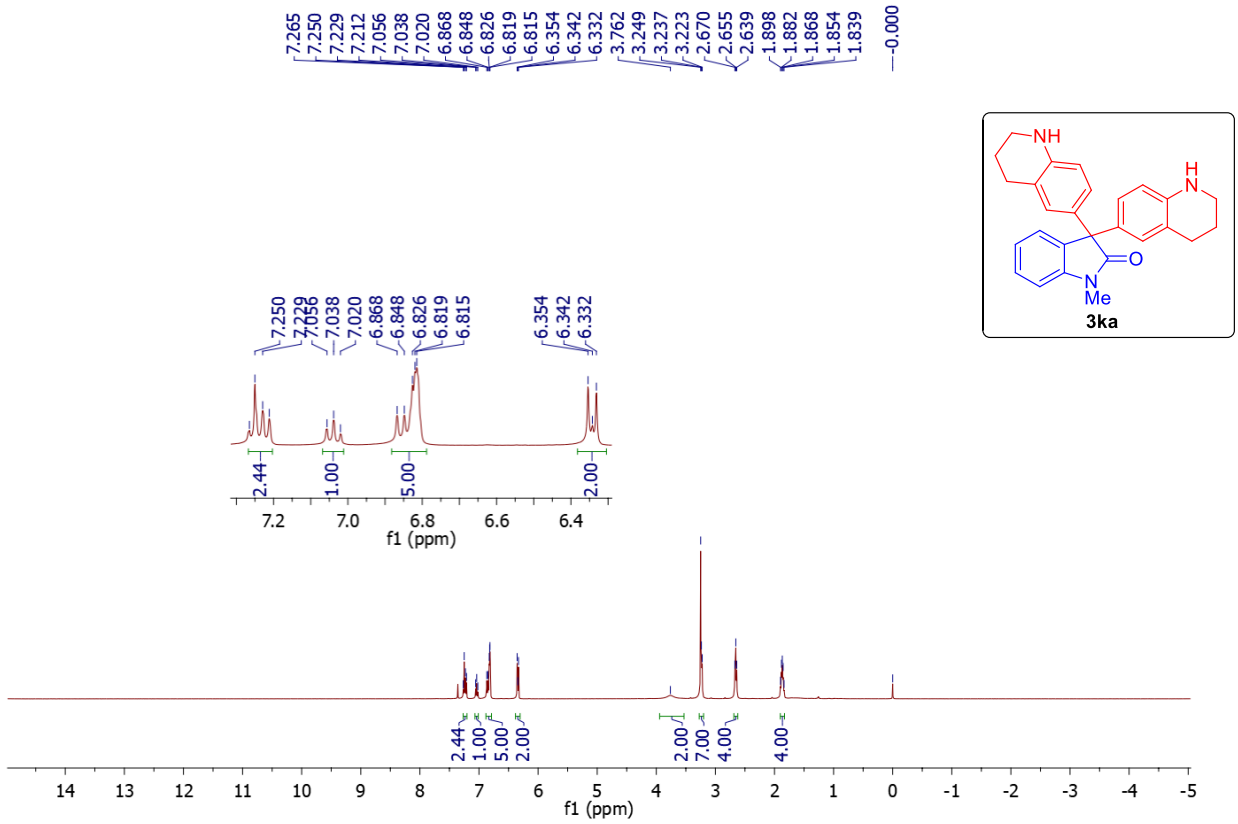
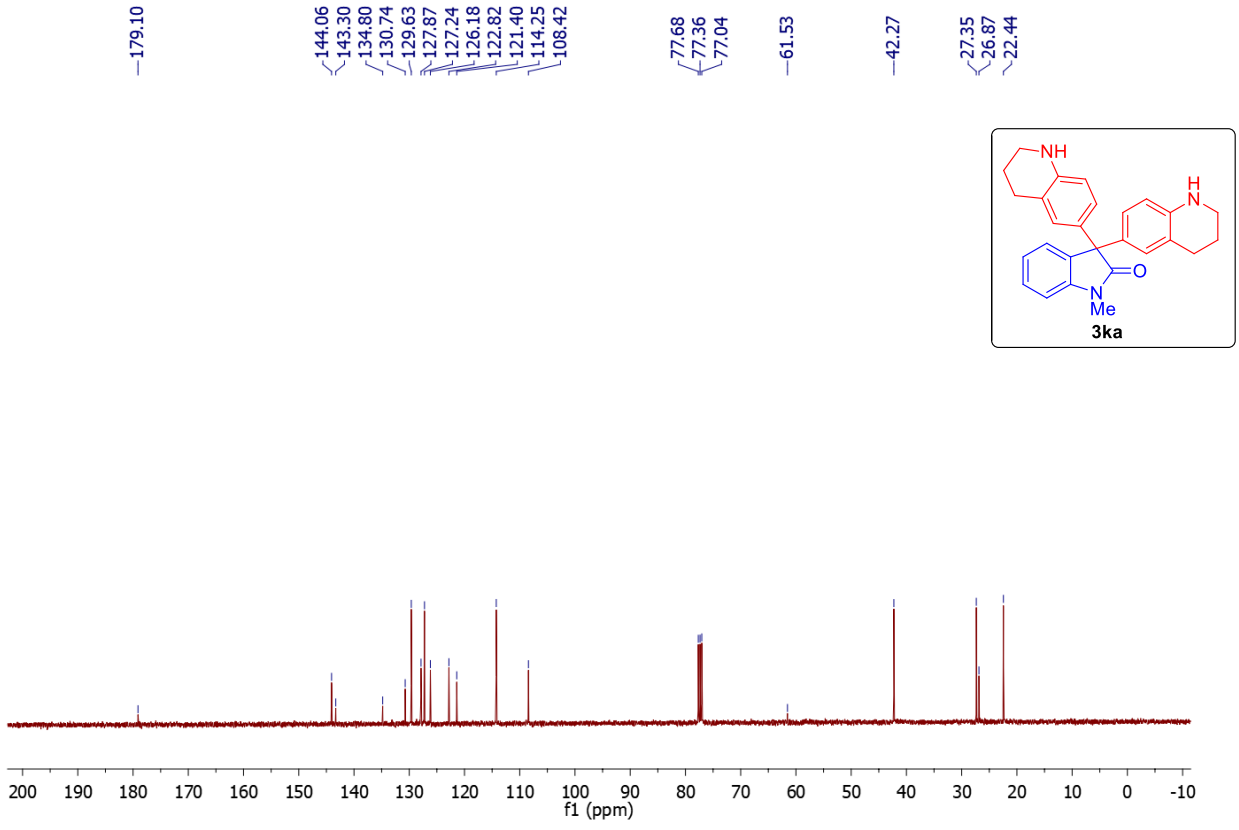


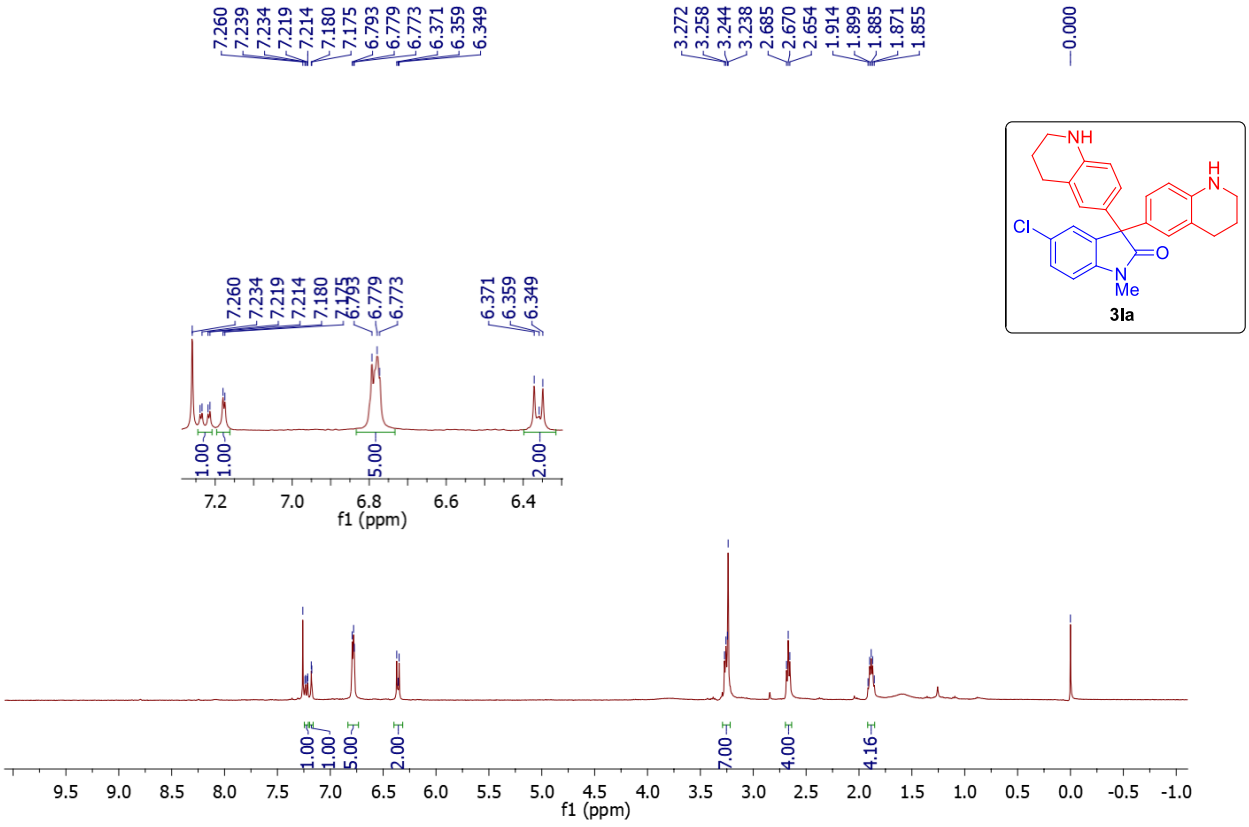
^{1}H NMR of 3ka (400 MHz, $CDCl_3$)



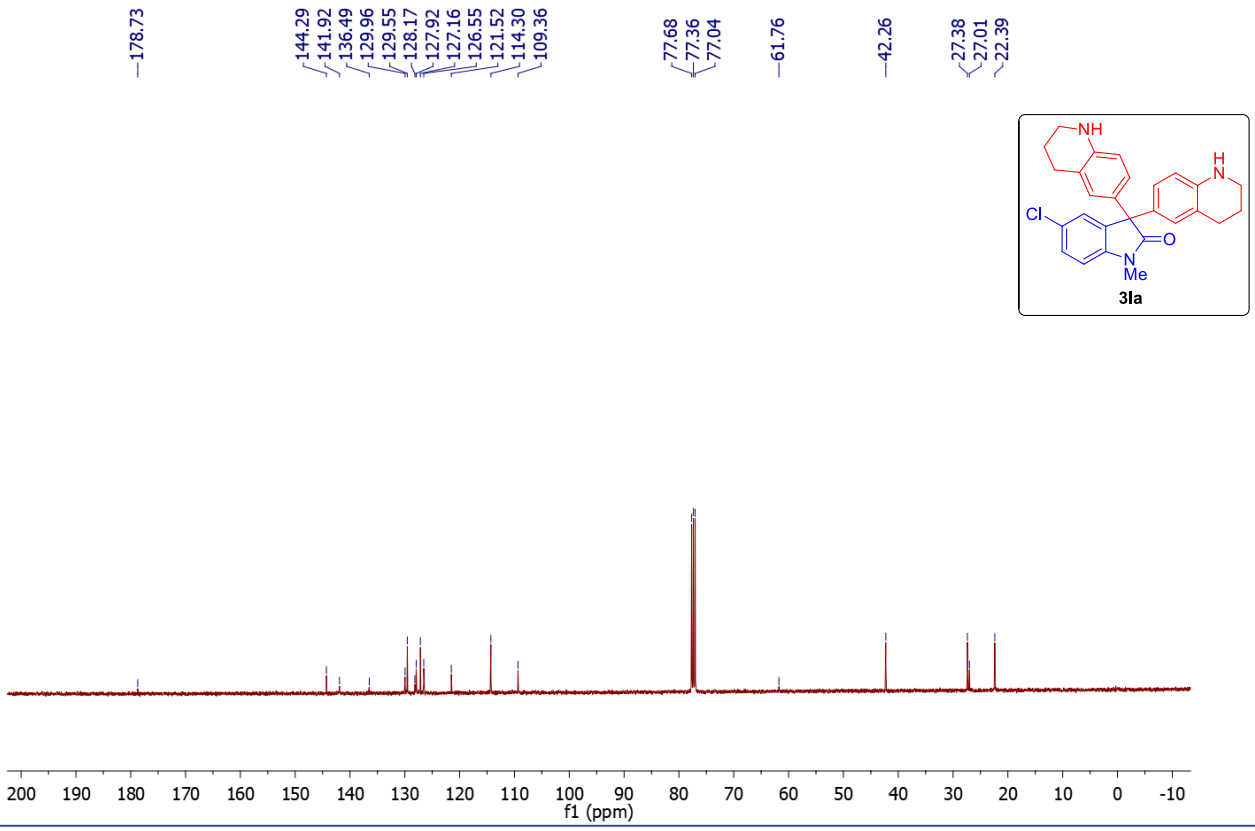
^{13}C NMR of 3ka (100 MHz, $CDCl_3$)



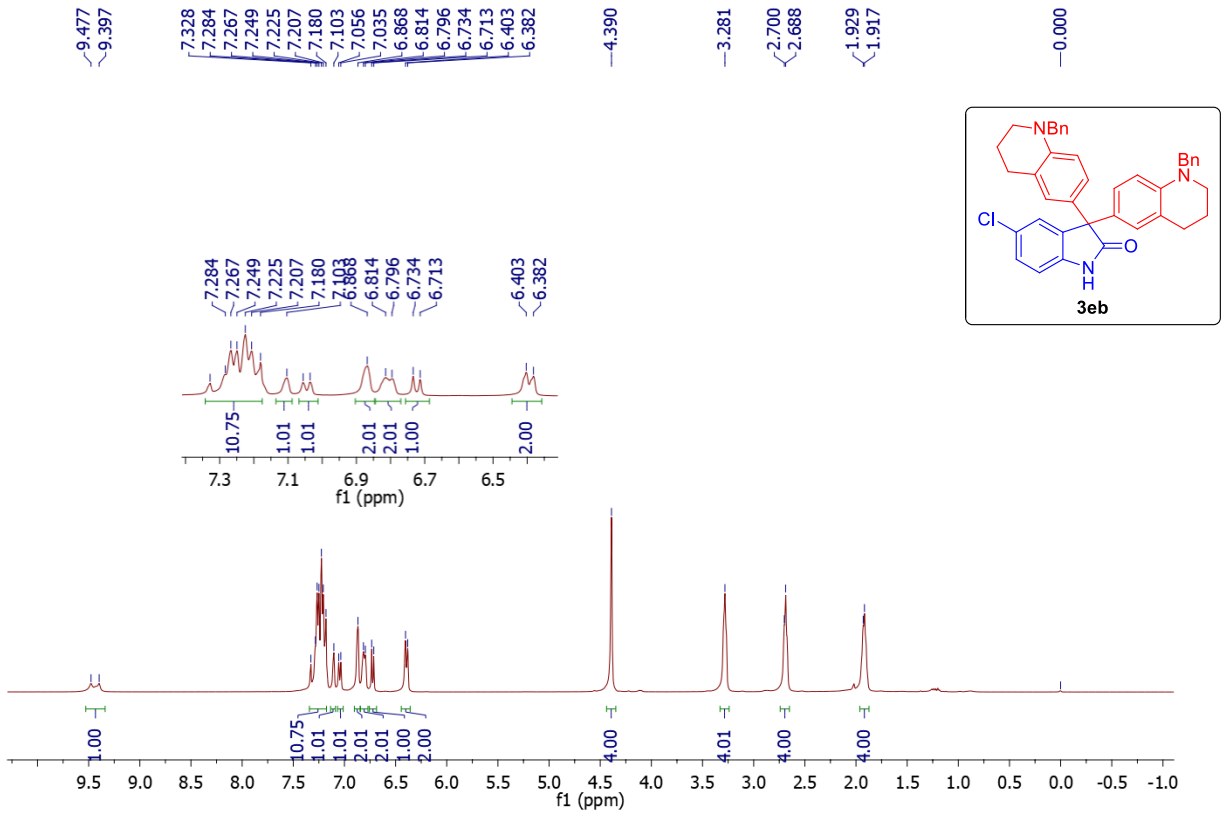
^{1}H NMR of 3la (400 MHz, $CDCl_3$)



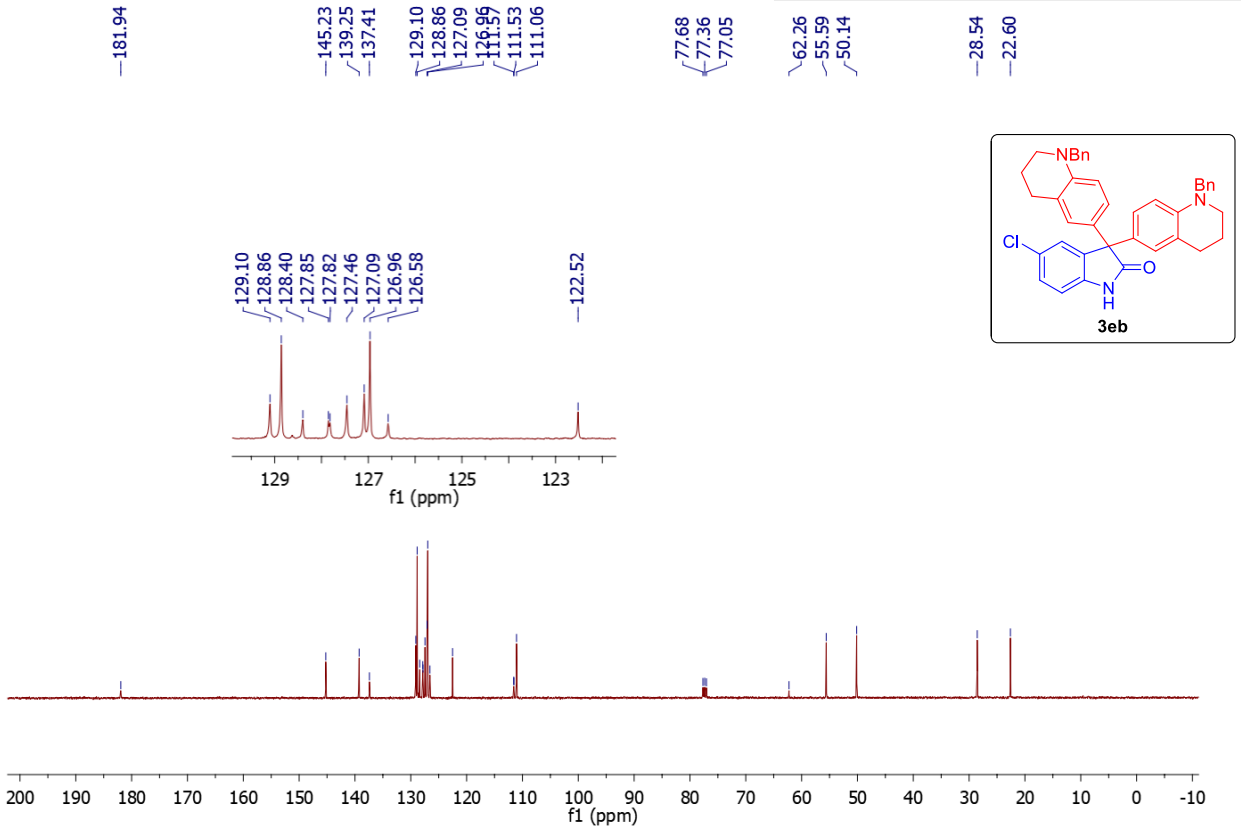
^{13}C NMR of 3la (100 MHz, $CDCl_3$)



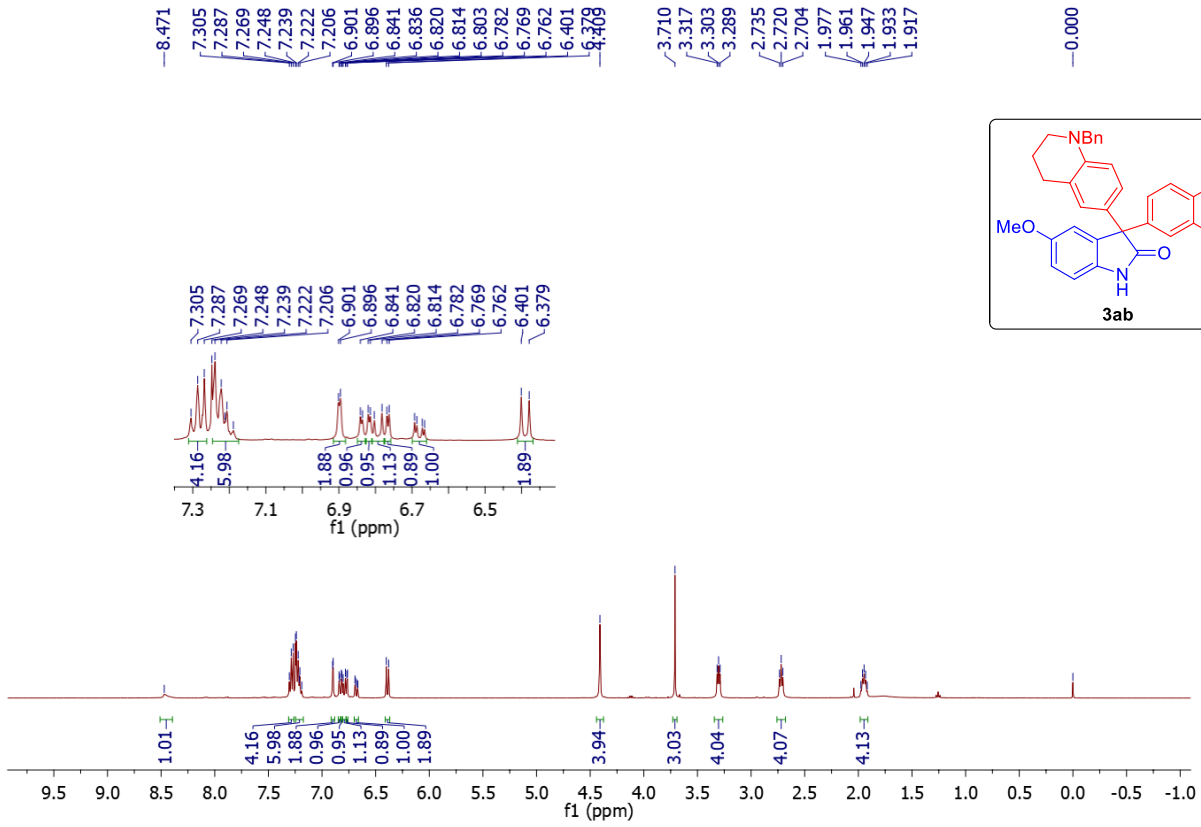
^{1}H NMR of 3eb (400 MHz, $CDCl_3$)



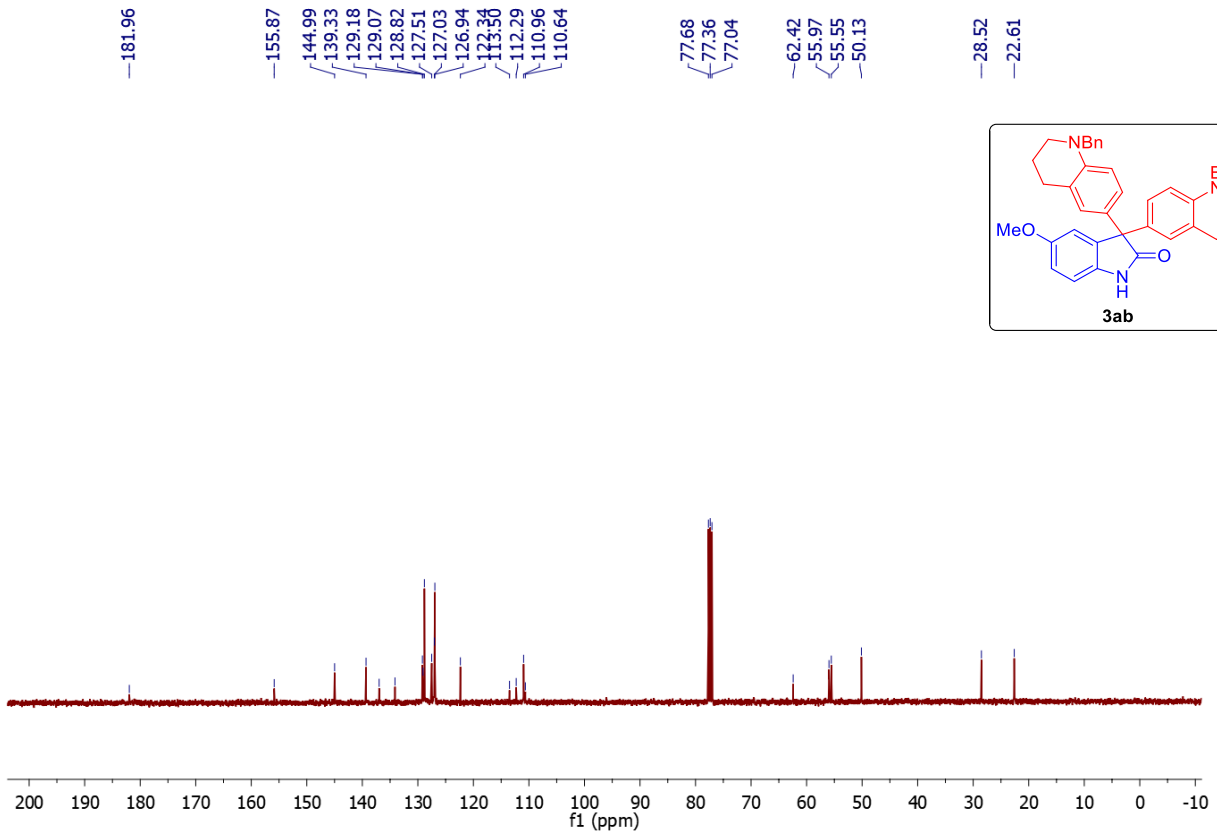
^{13}C NMR of 3eb (100 MHz, $CDCl_3$)



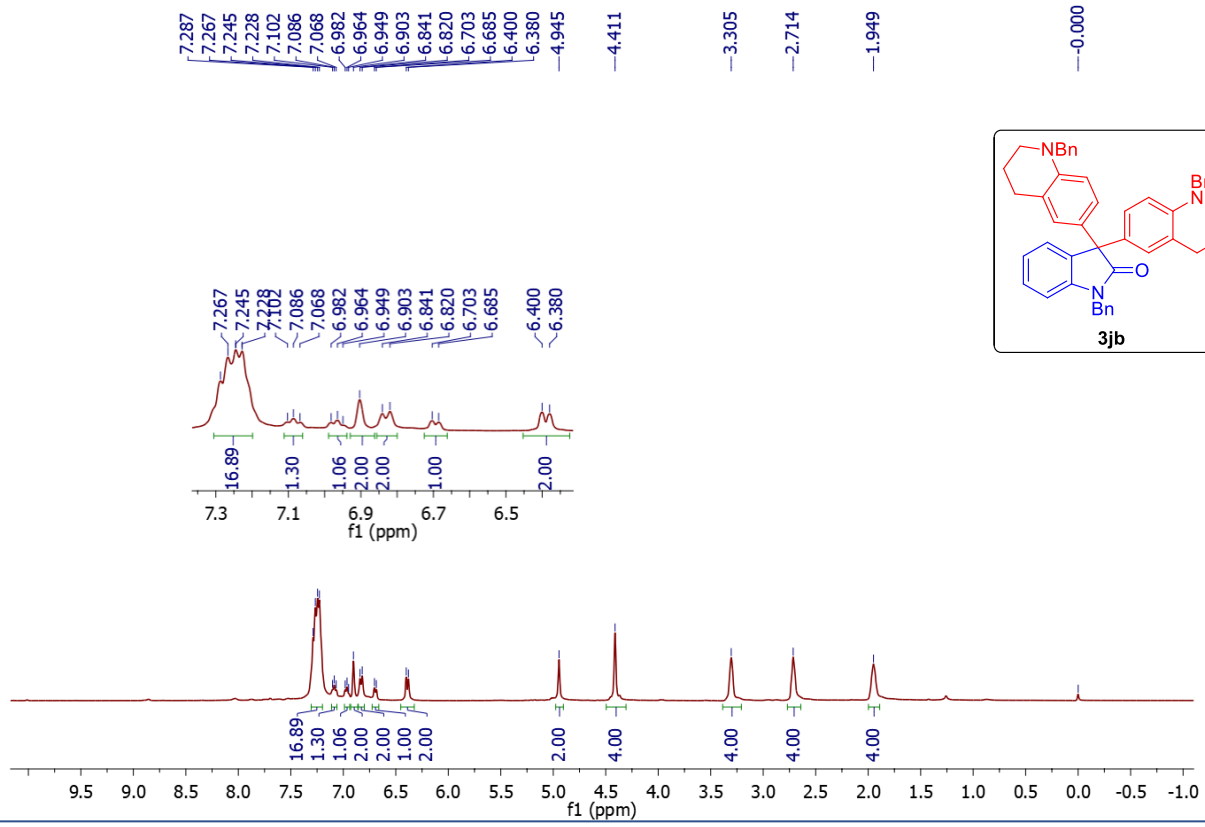
^{1}H NMR of 3ab (400 MHz, $CDCl_3$)



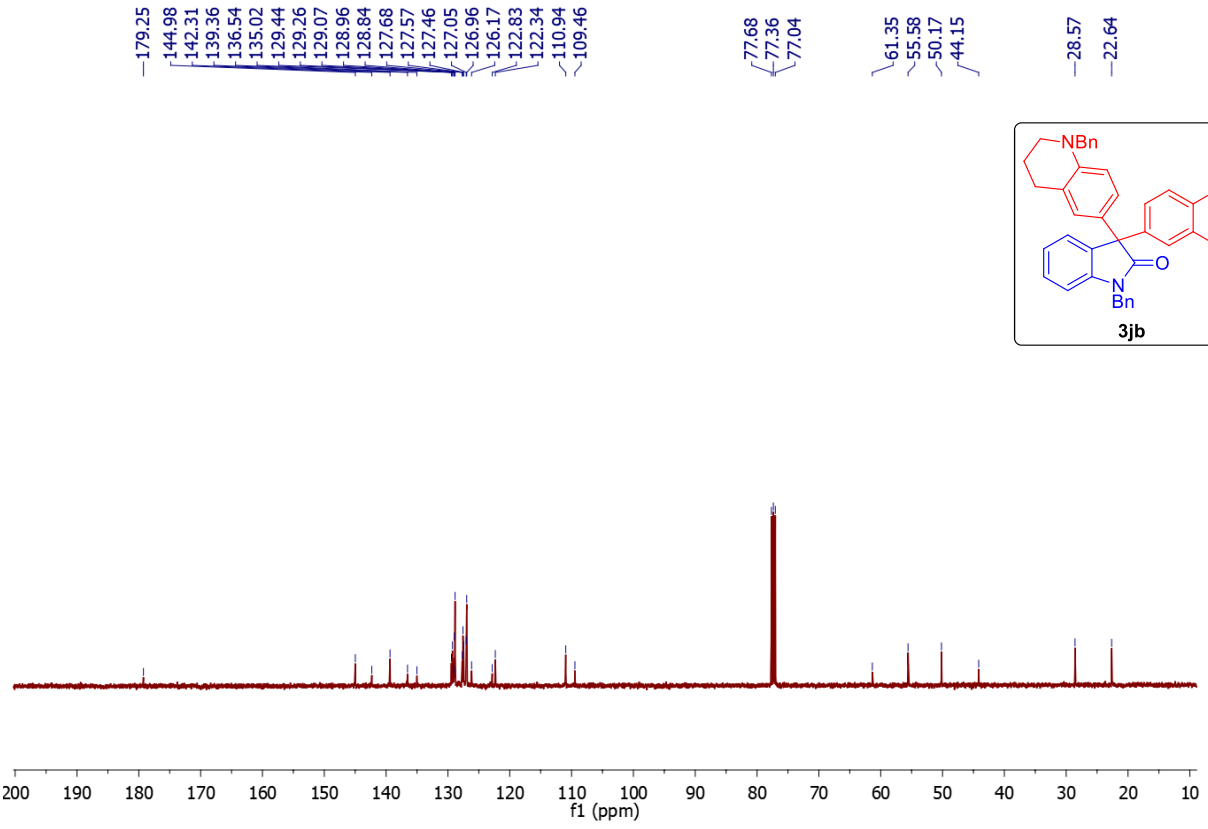
^{13}C NMR of 3ab (100 MHz, $CDCl_3$)



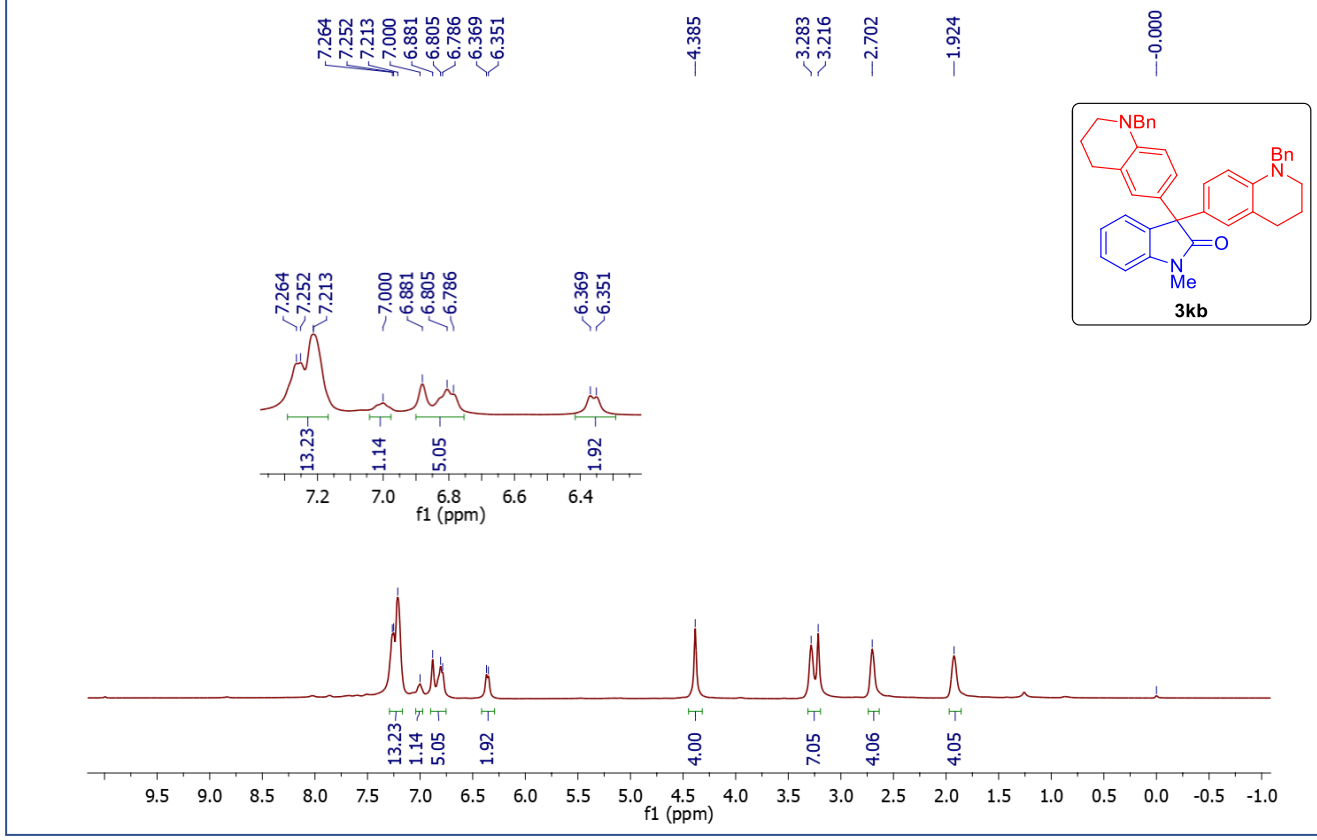
^{1}H NMR of 3jb (400 MHz, $CDCl_3$)



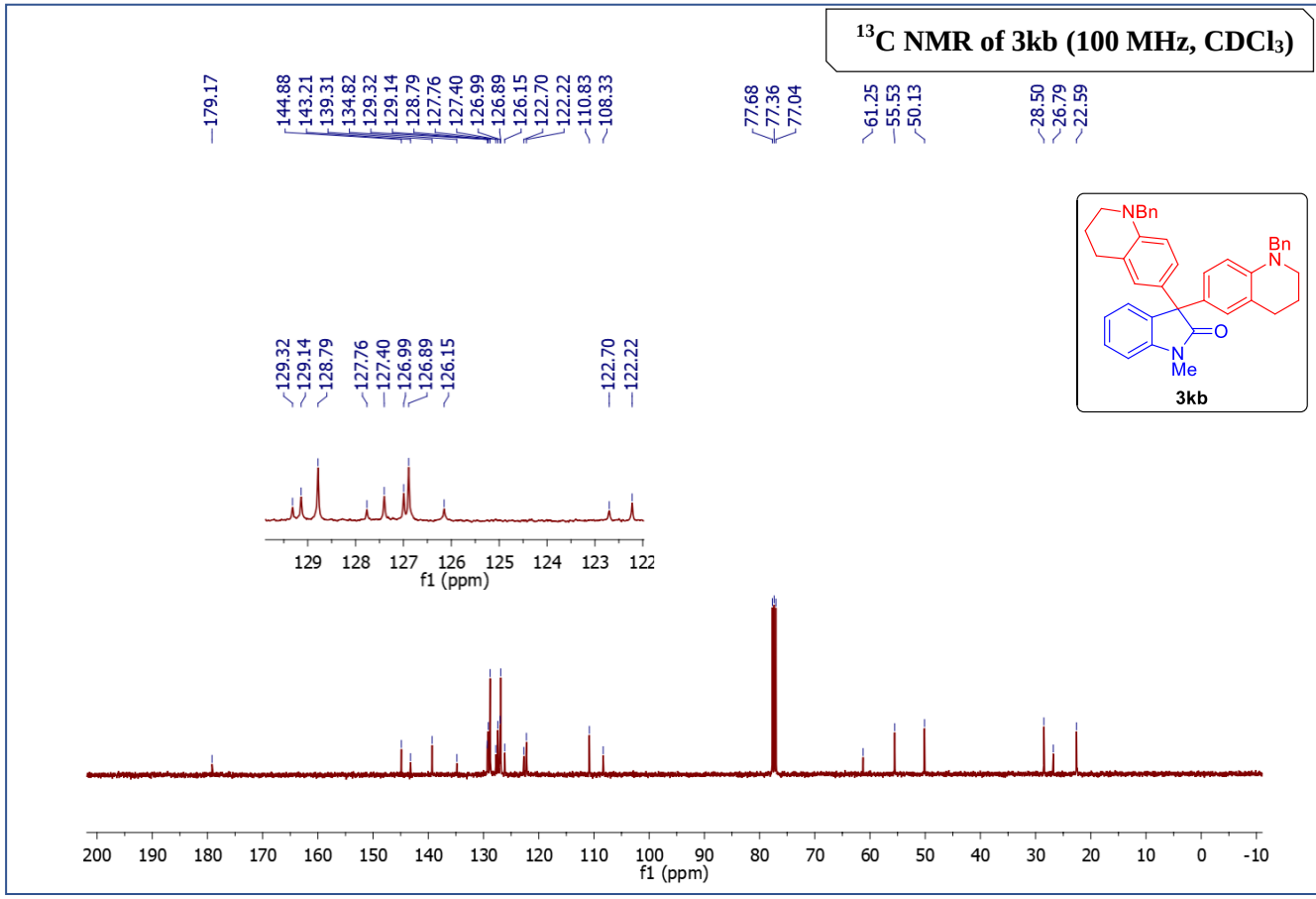
^{13}C NMR of 3jb (100 MHz, $CDCl_3$)



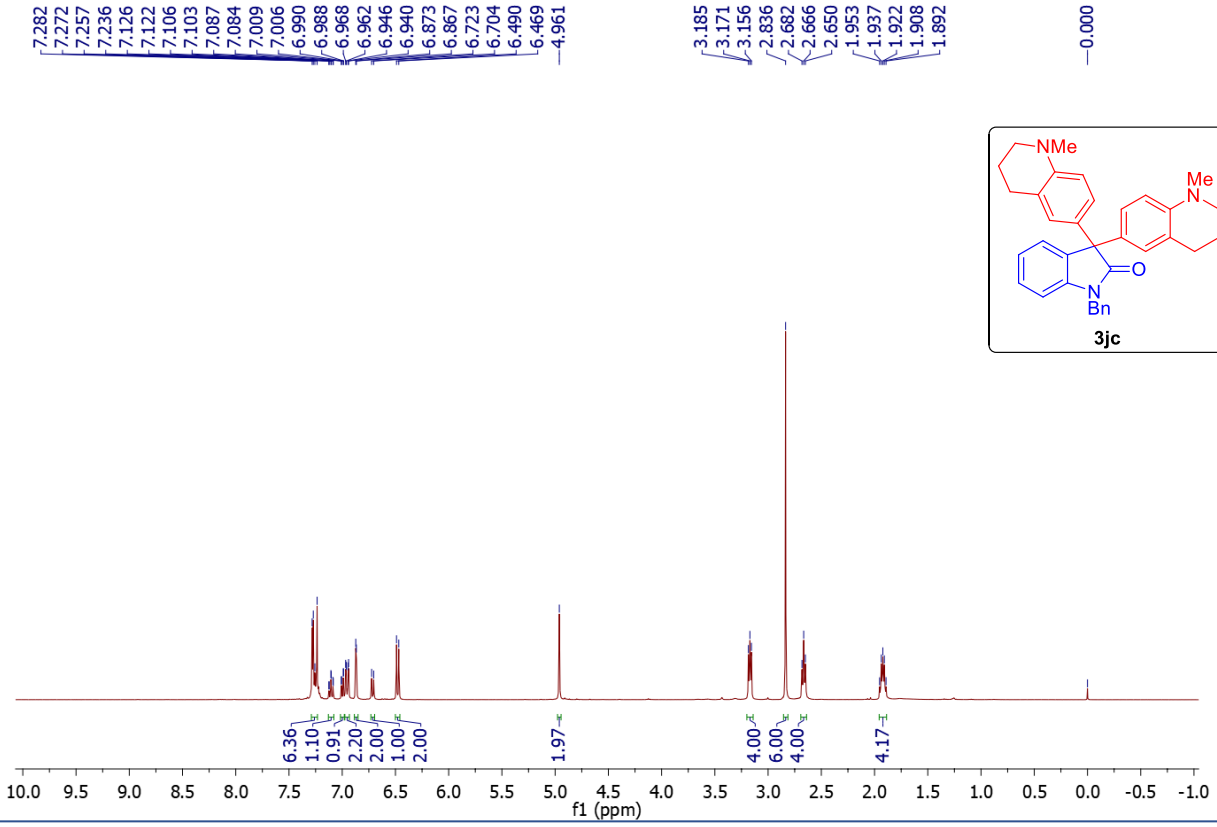
^{1}H NMR of 3kb (400 MHz, $CDCl_3$)



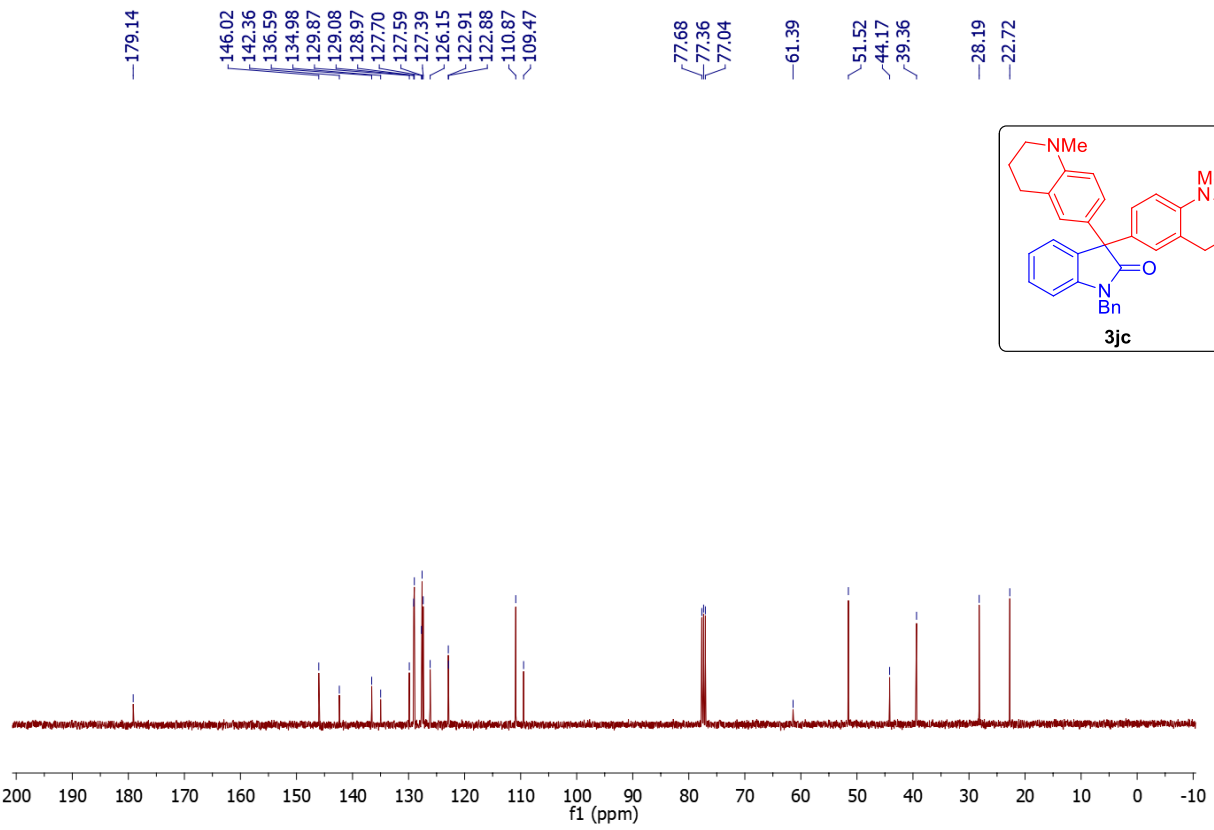
^{13}C NMR of 3kb (100 MHz, $CDCl_3$)



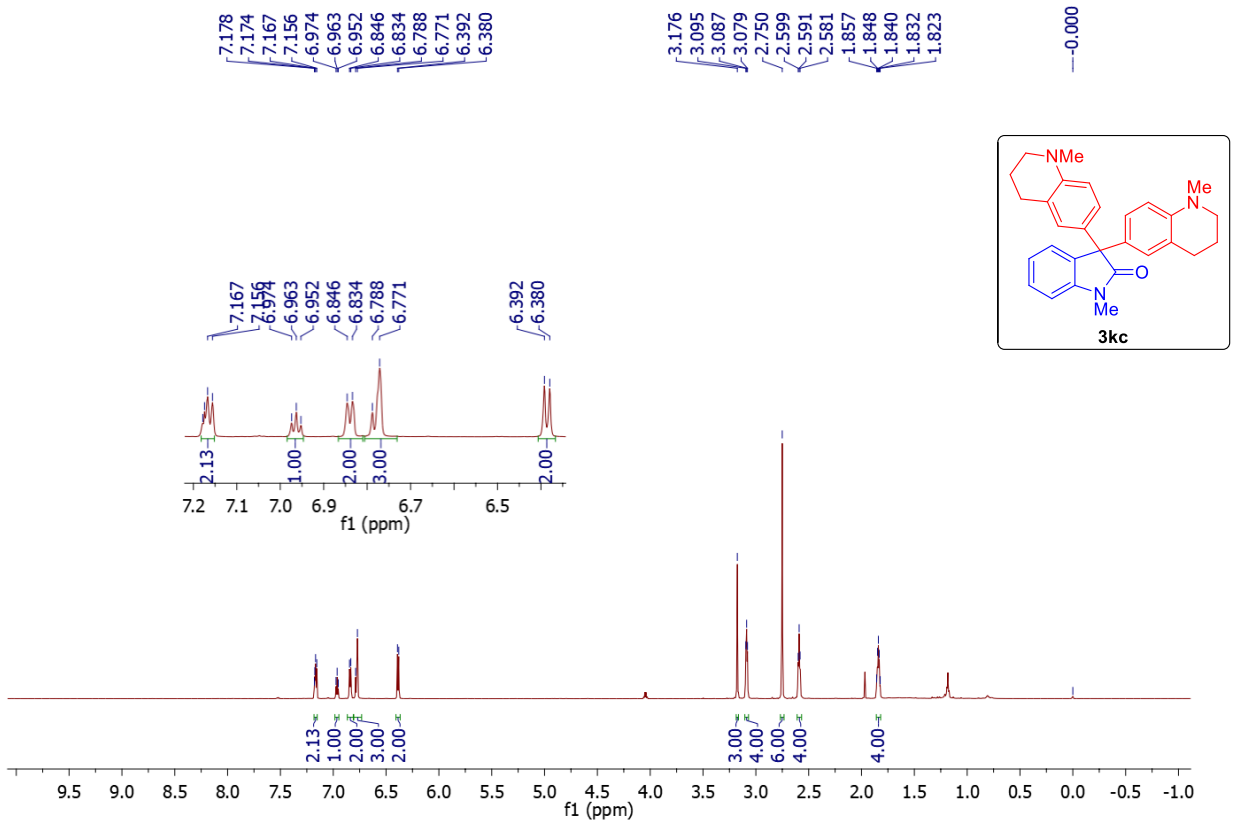
^{1}H NMR of 3jc (400 MHz, $CDCl_3$)



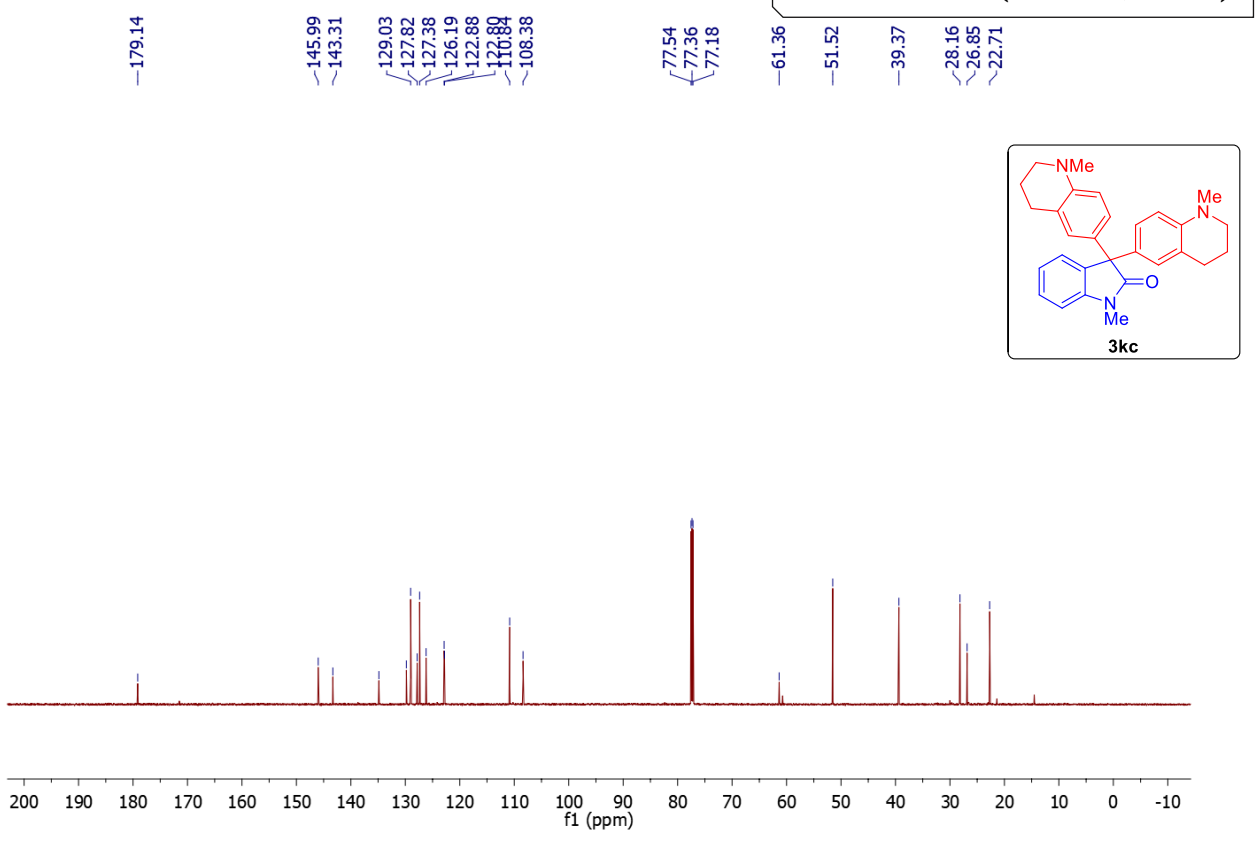
^{13}C NMR of 3jc (100 MHz, $CDCl_3$)



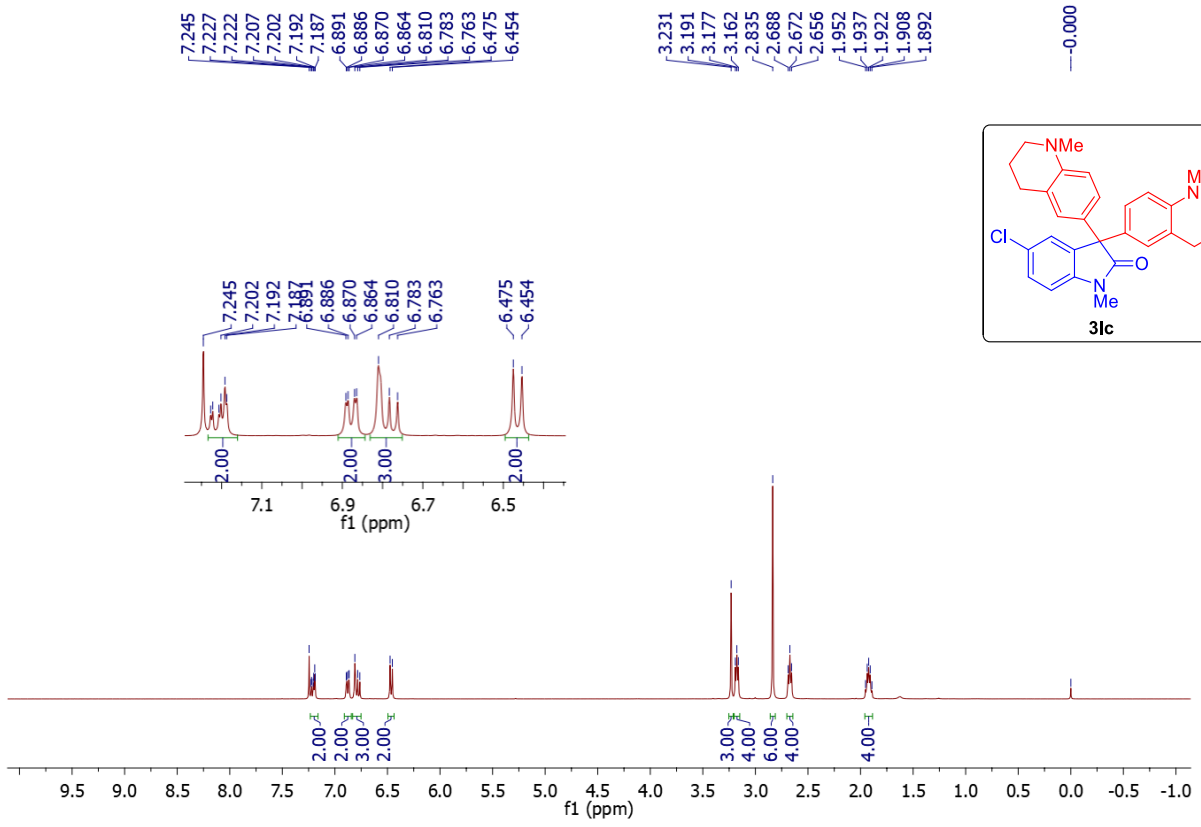
^{1}H NMR of 3kc (700 MHz, $CDCl_3$)



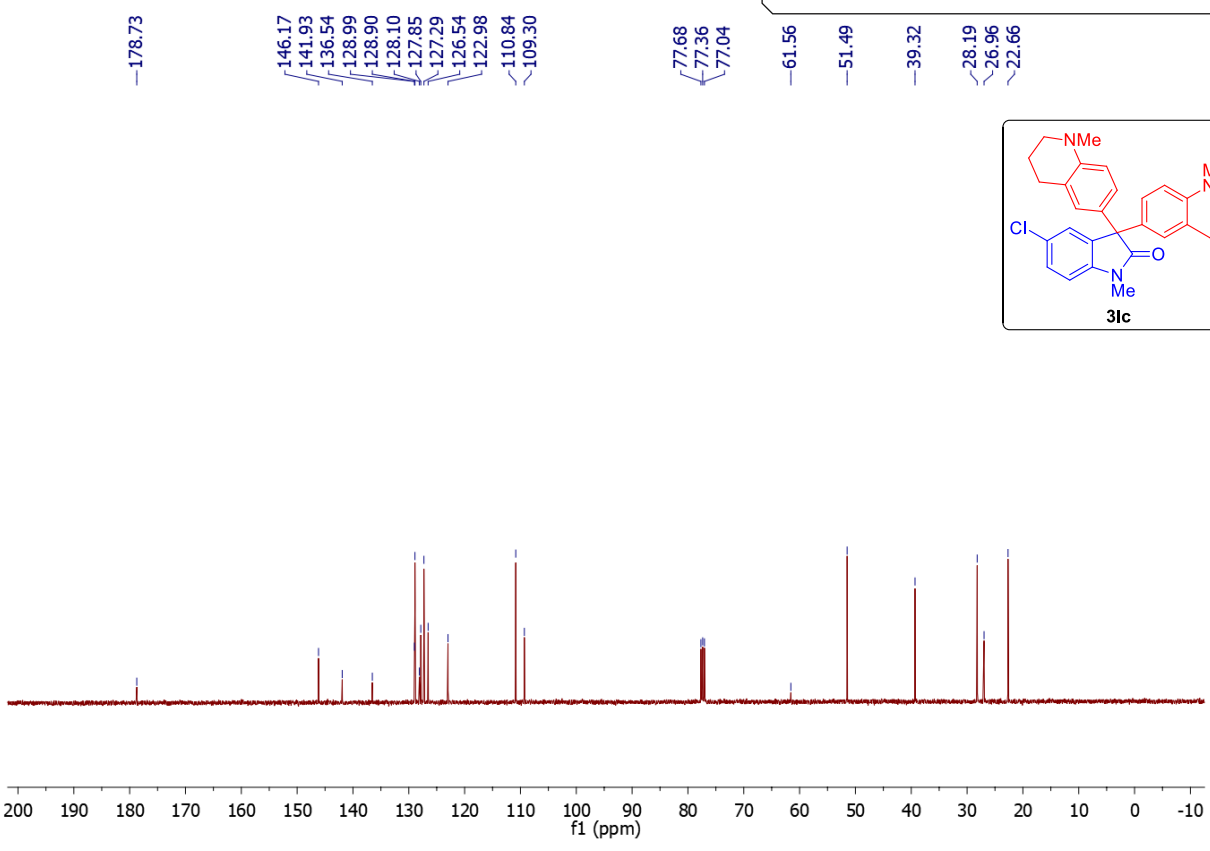
^{13}C NMR of 3kc (176 MHz, $CDCl_3$)



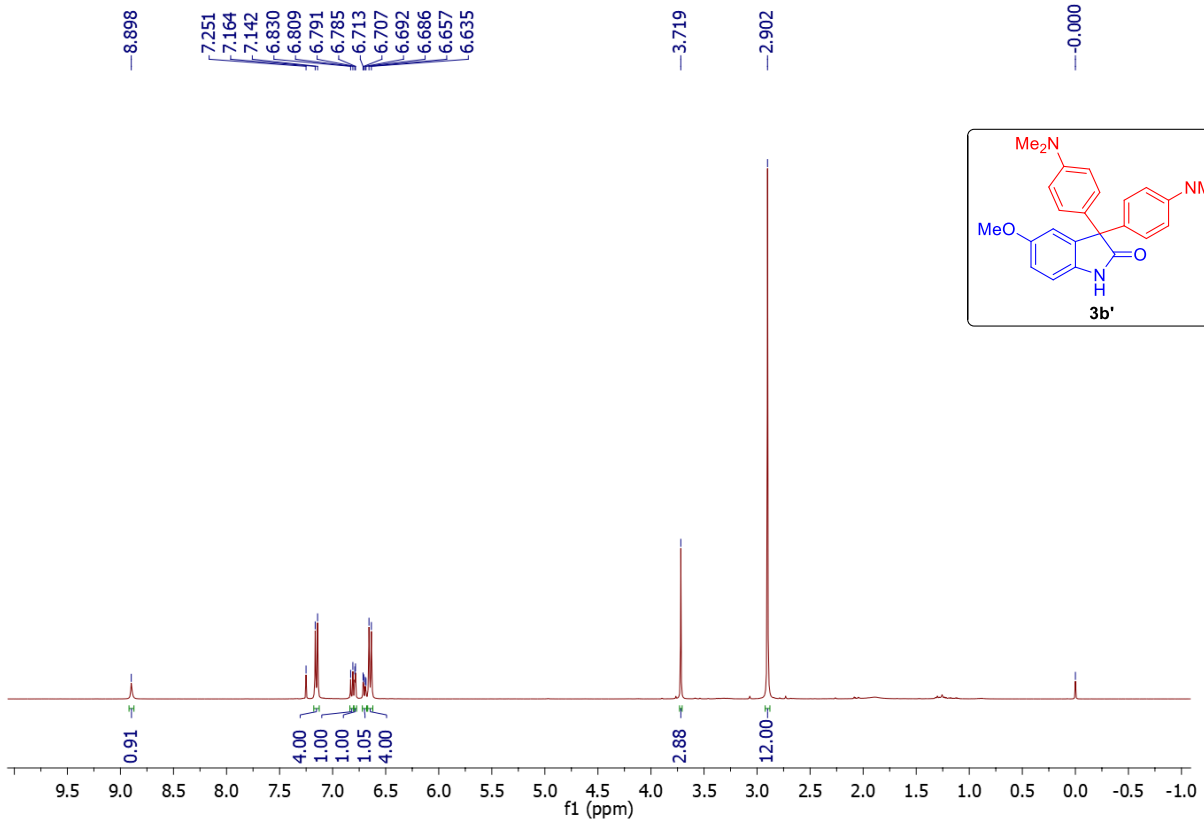
^{1}H NMR of 3lc (400 MHz, $CDCl_3$)



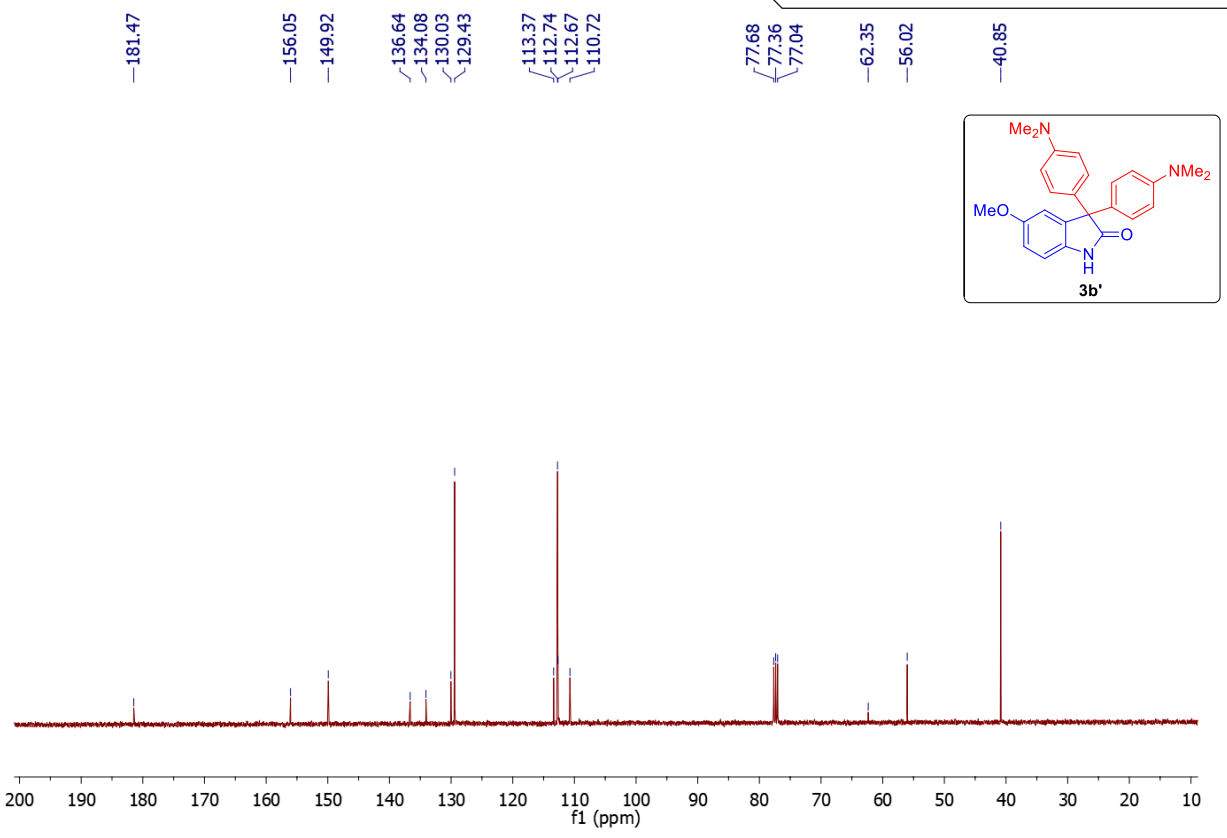
^{13}C NMR of 3lc (100 MHz, $CDCl_3$)



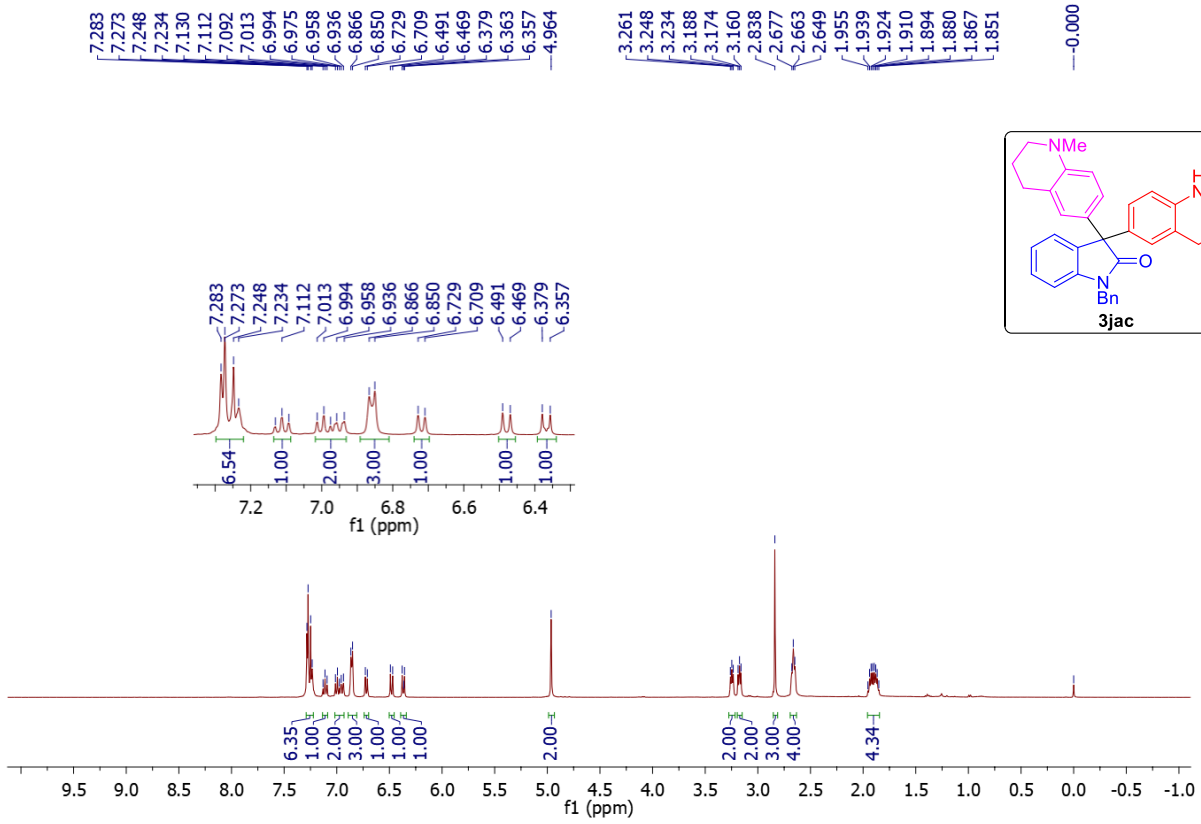
^{1}H NMR of 3b' (400 MHz, $CDCl_3$)



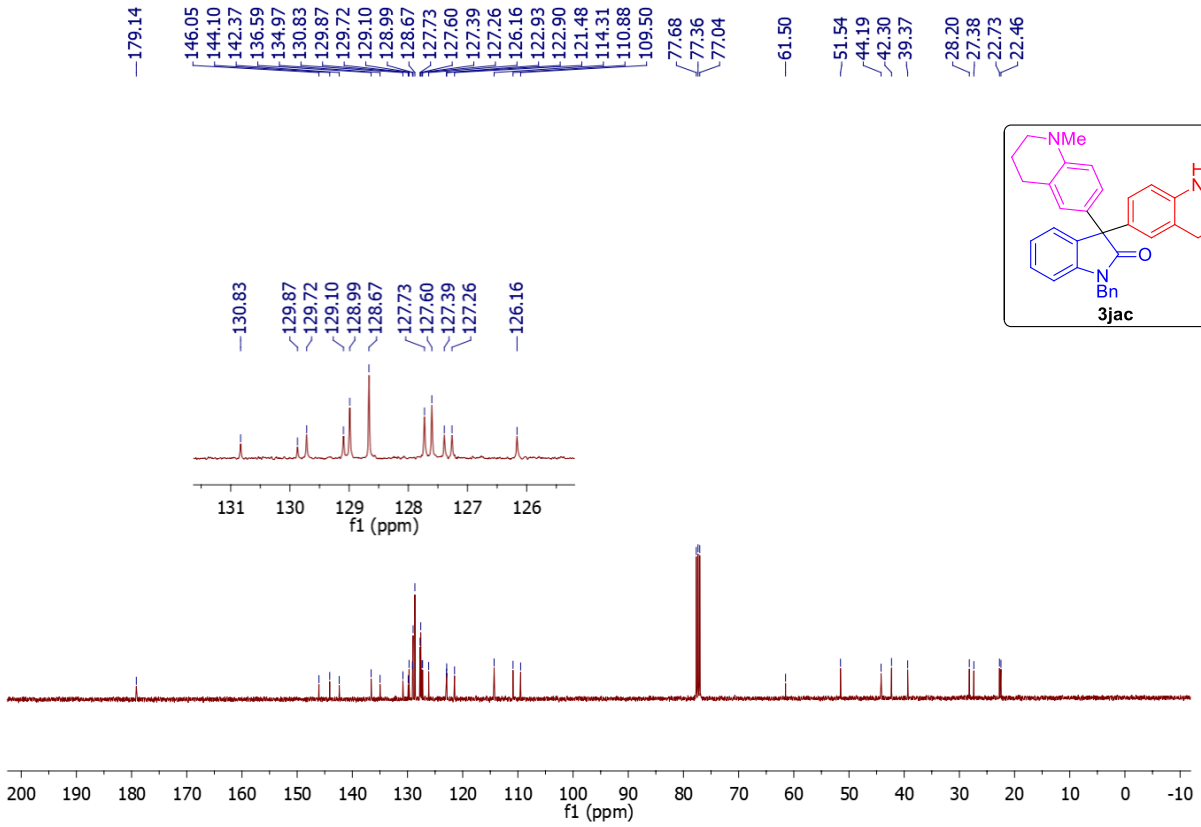
^{13}C NMR of 3b' (100 MHz, $CDCl_3$)



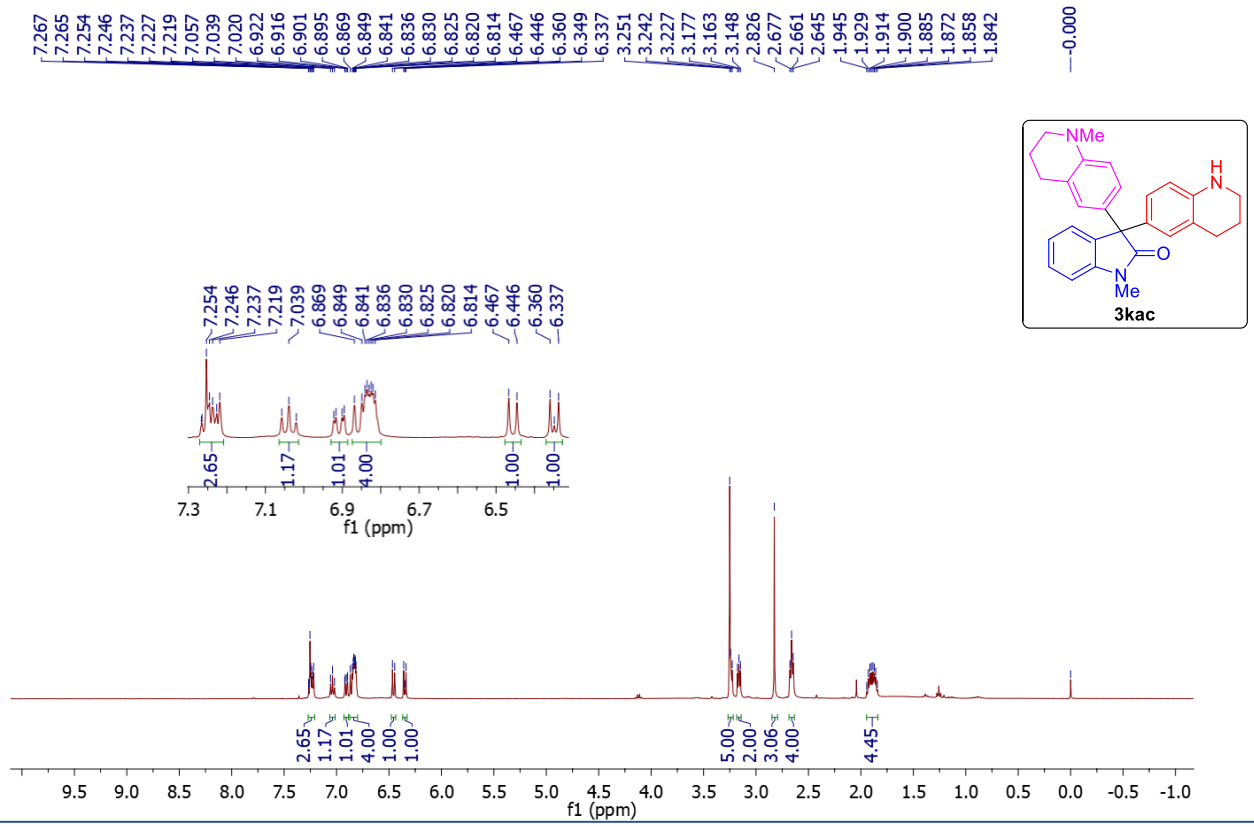
^{1}H NMR of 3jac (400 MHz, $CDCl_3$)



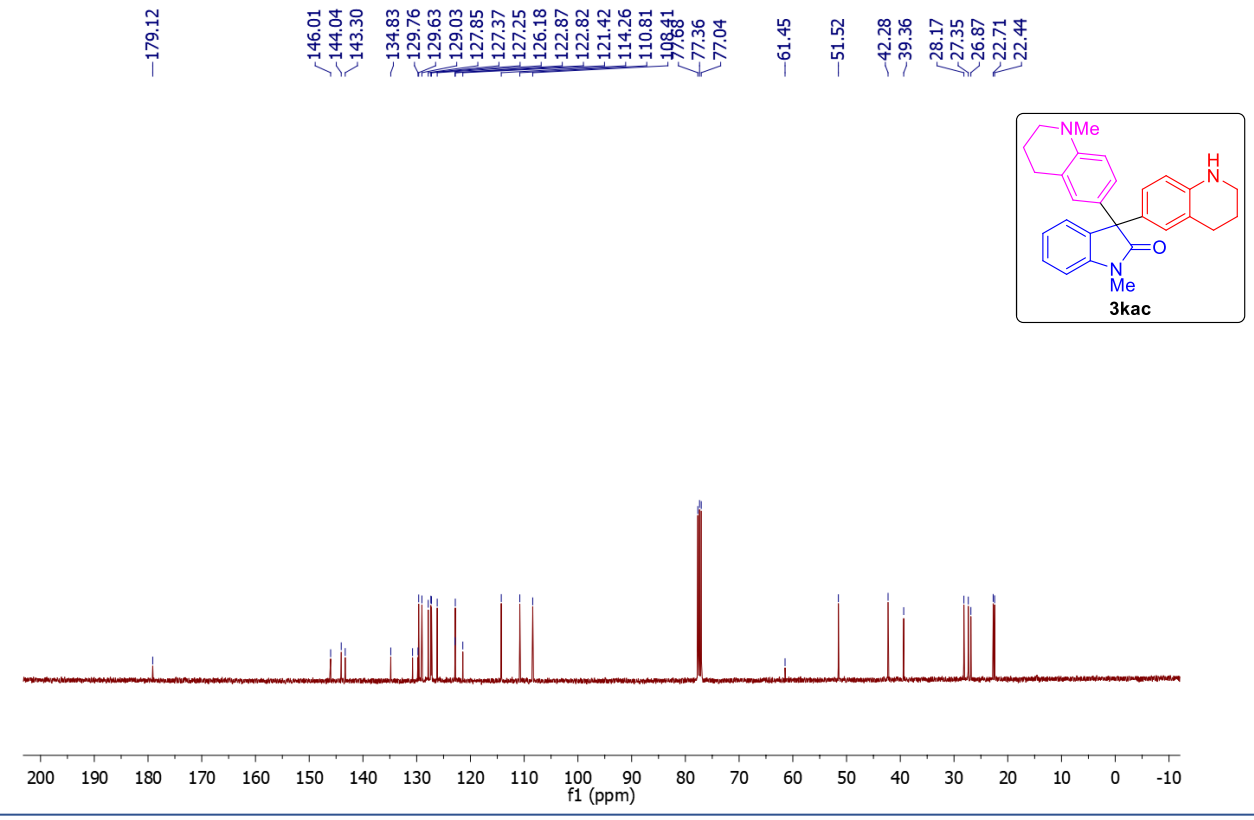
^{13}C NMR of 3jac (100 MHz, $CDCl_3$)



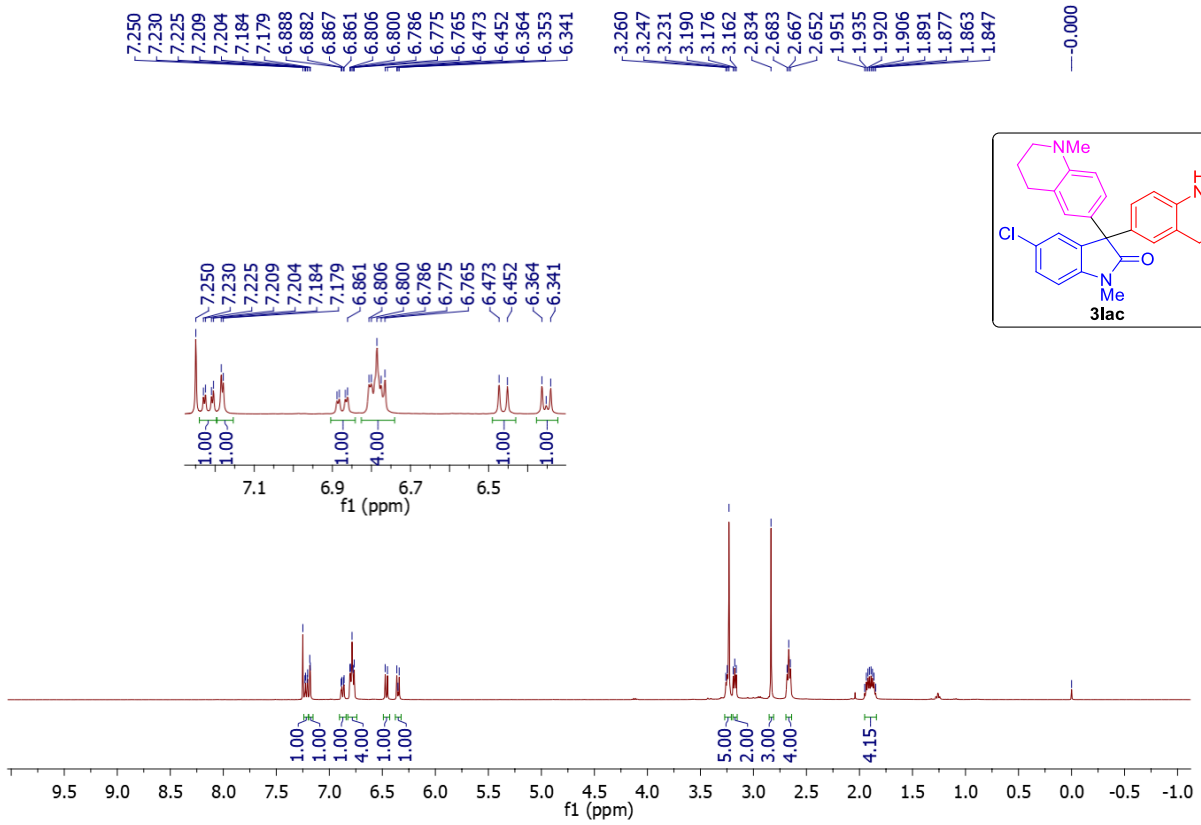
^{1}H NMR of 3kac (400 MHz, $CDCl_3$)



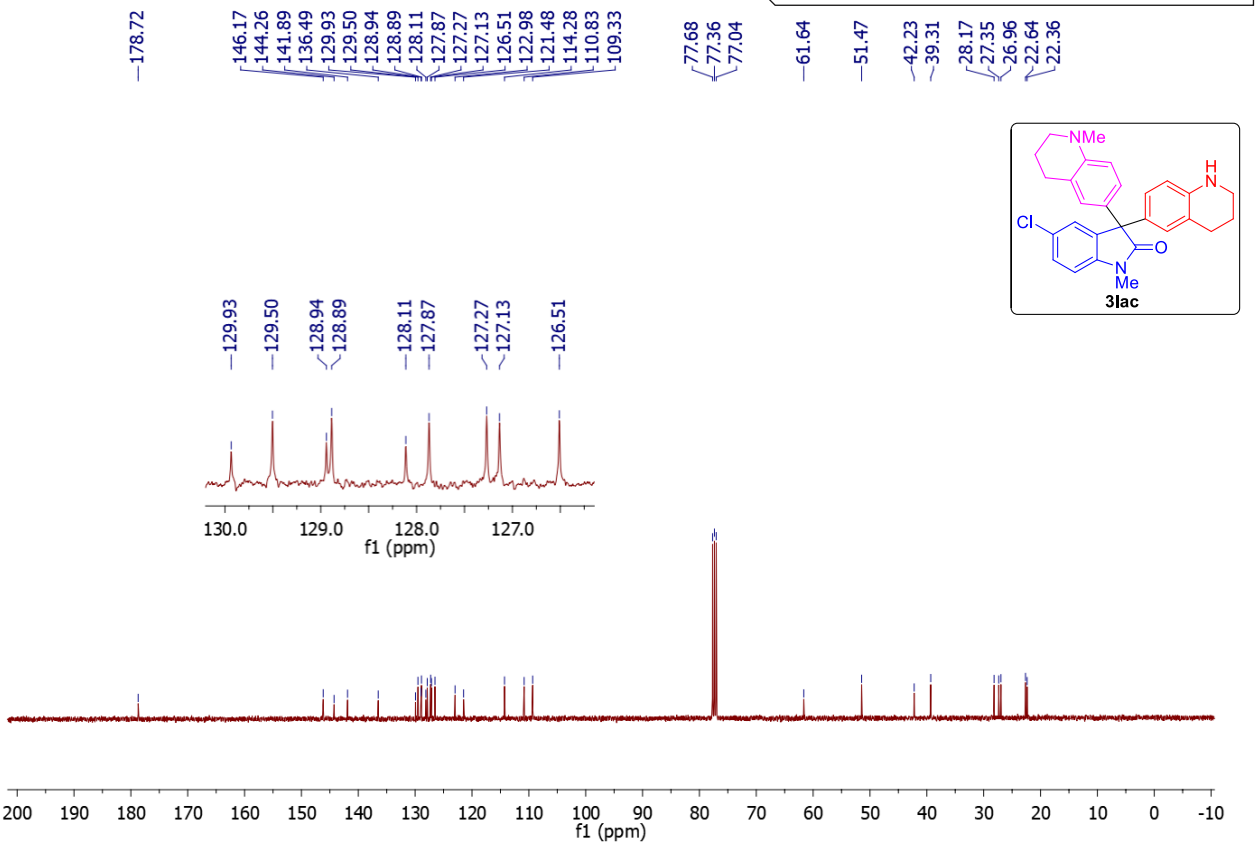
^{13}C NMR of 3kac (100 MHz, $CDCl_3$)



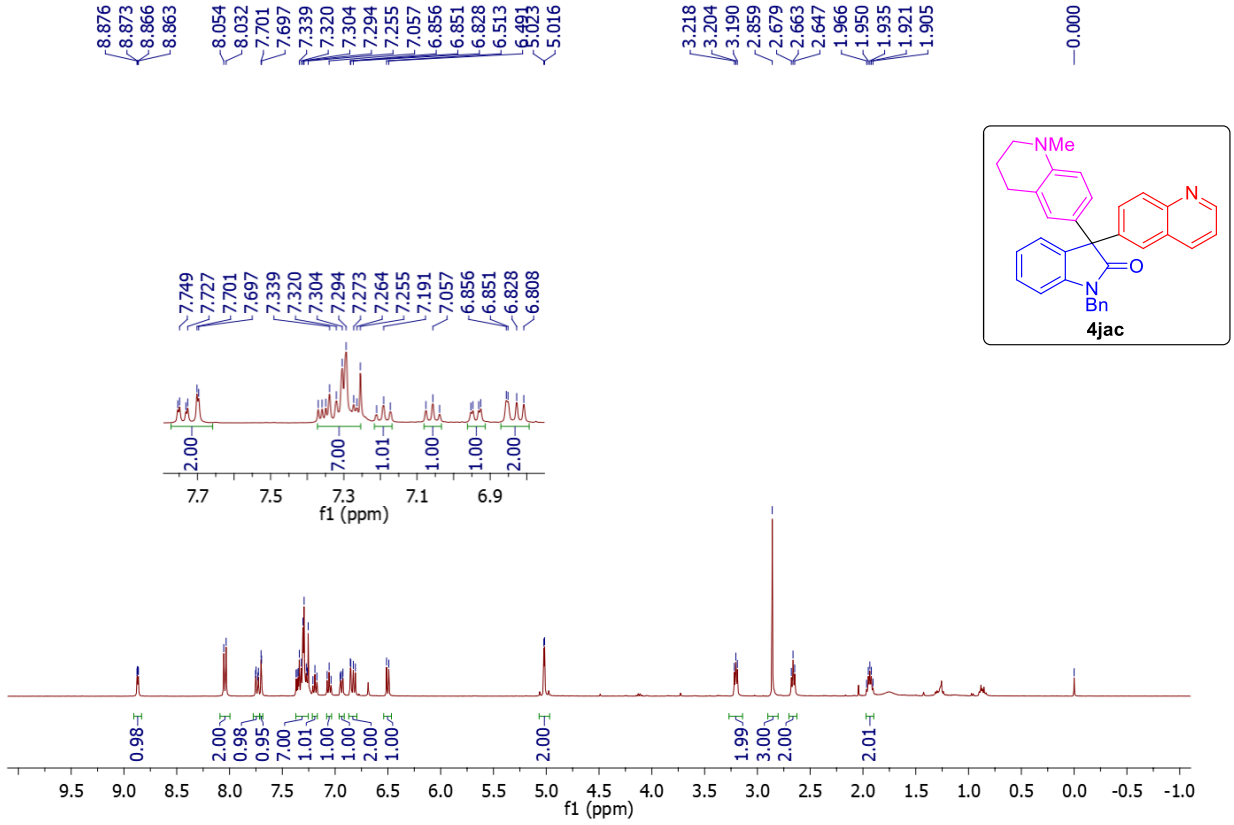
^{1}H NMR of 3lac (400 MHz, $CDCl_3$)



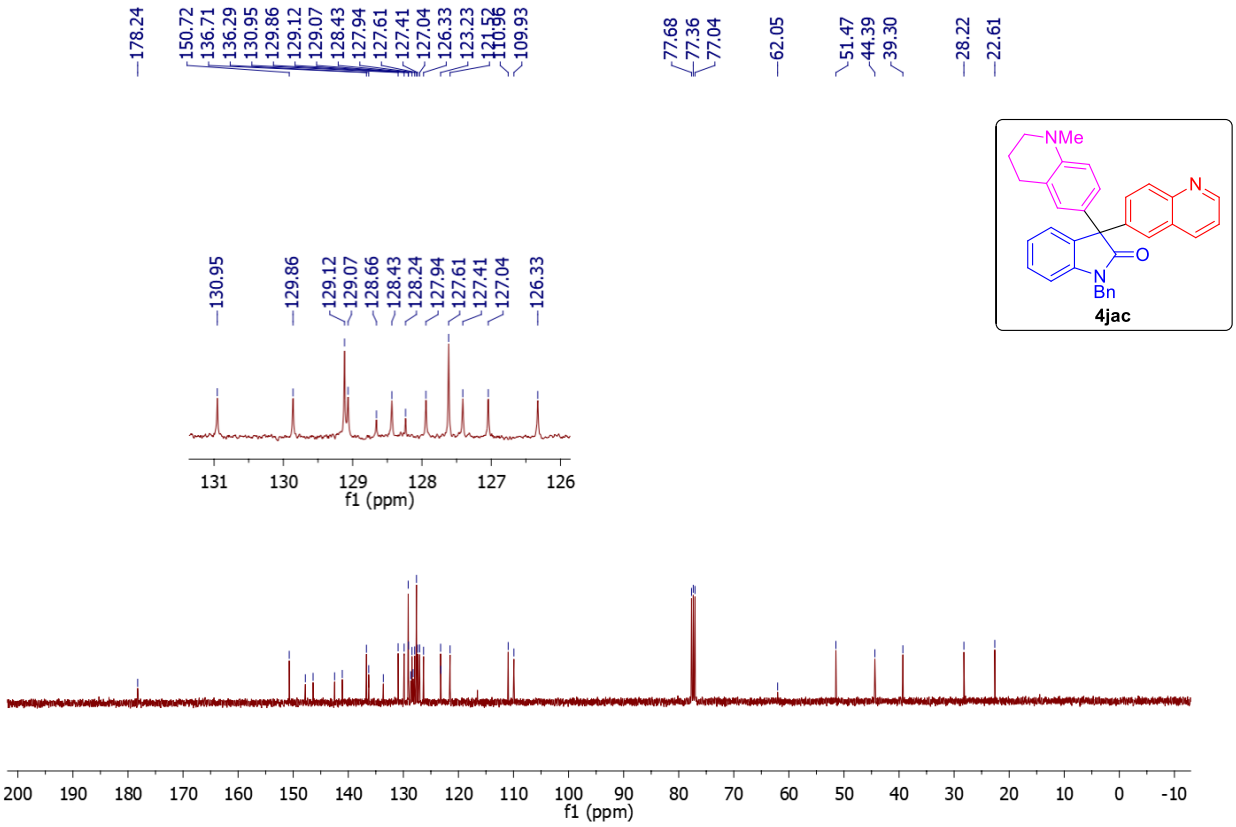
^{13}C NMR of 3lac (100 MHz, $CDCl_3$)



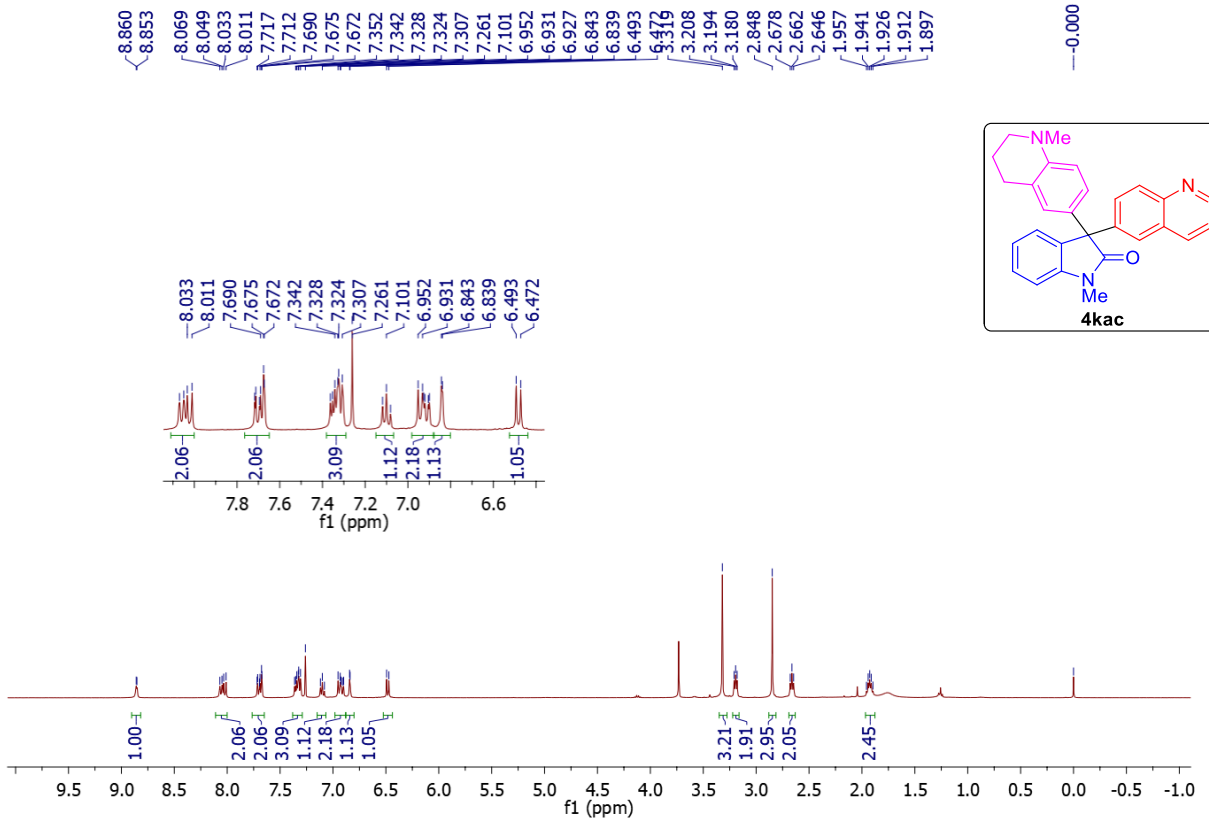
^{1}H NMR of 4jac (400 MHz, $CDCl_3$)



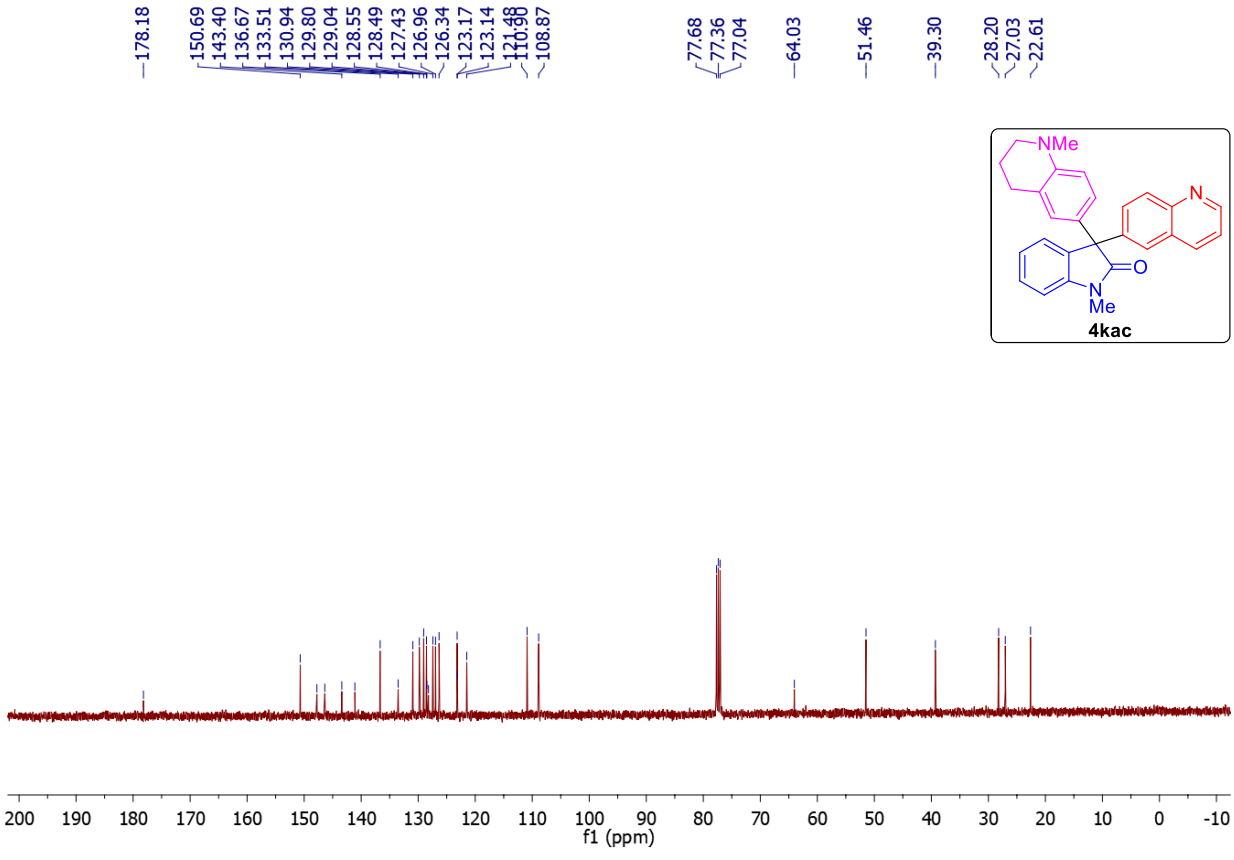
^{13}C NMR of 4jac (100 MHz, $CDCl_3$)



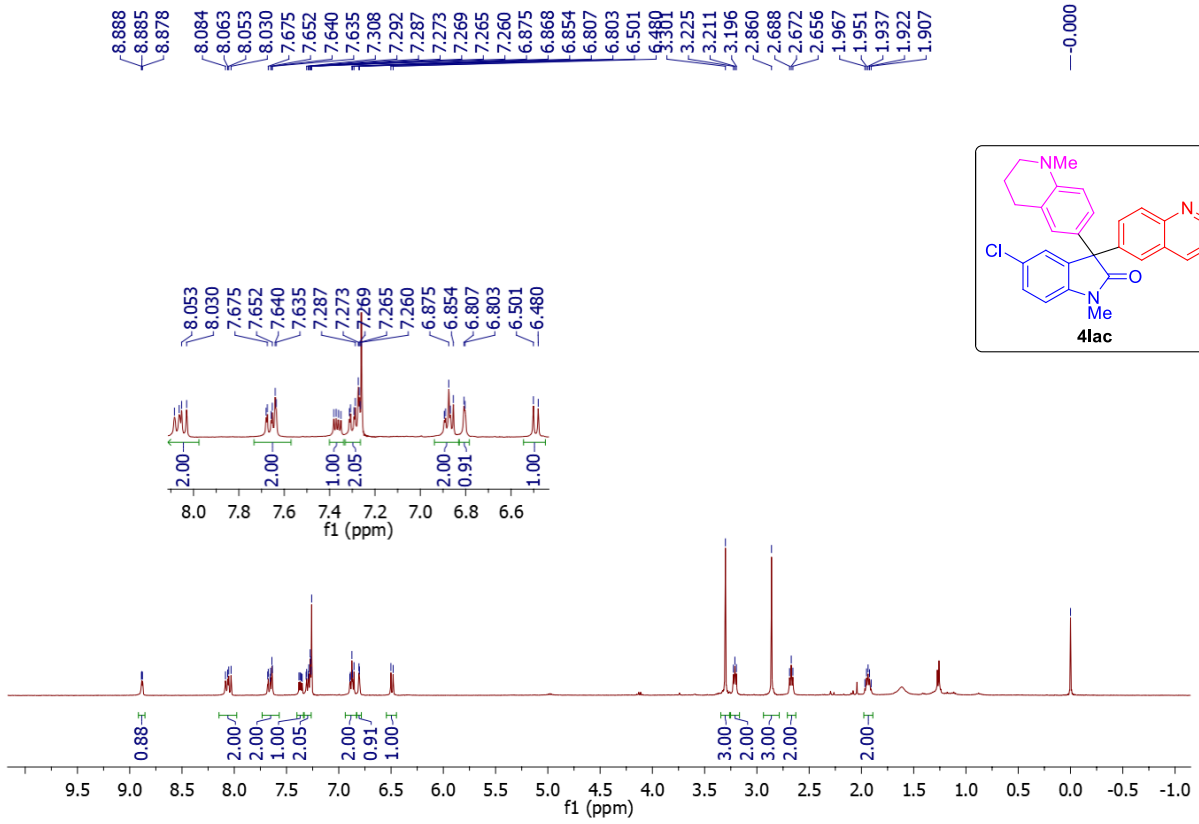
^{1}H NMR of 4kac (400 MHz,



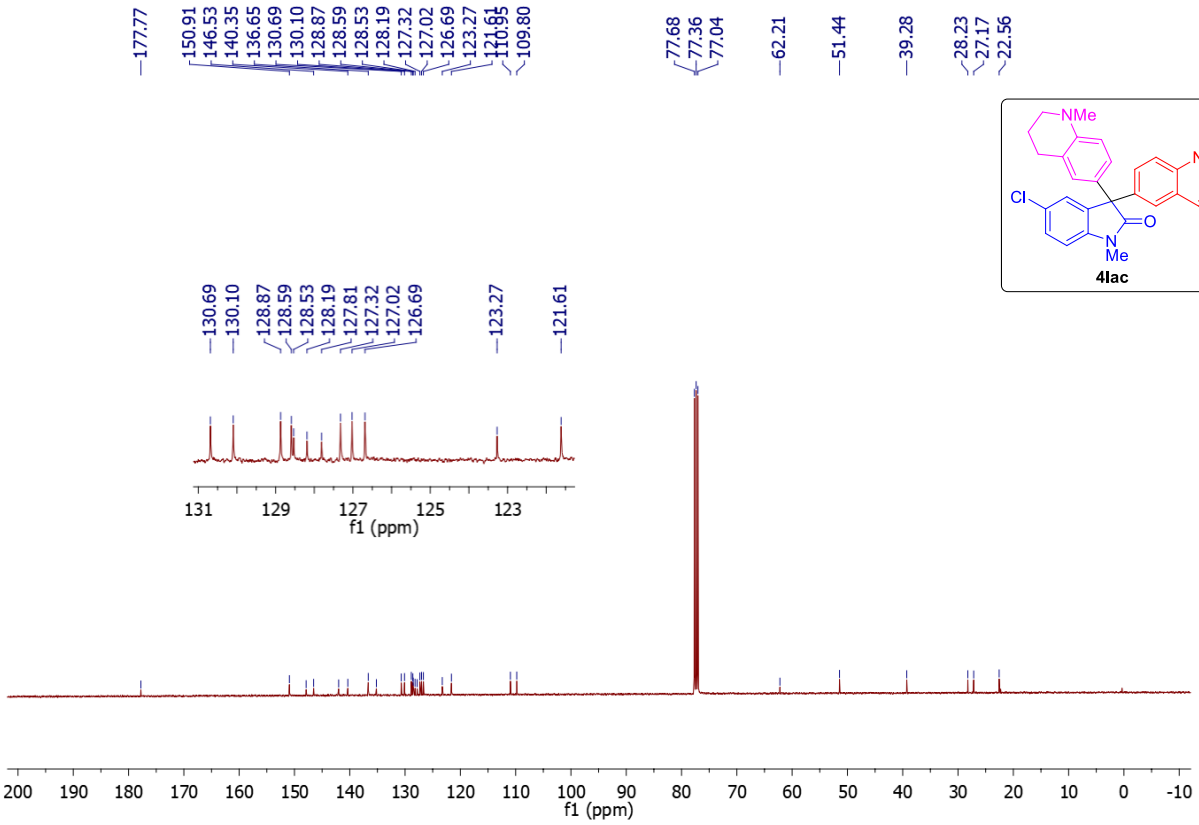
^{13}C NMR of 4kac (100 MHz,



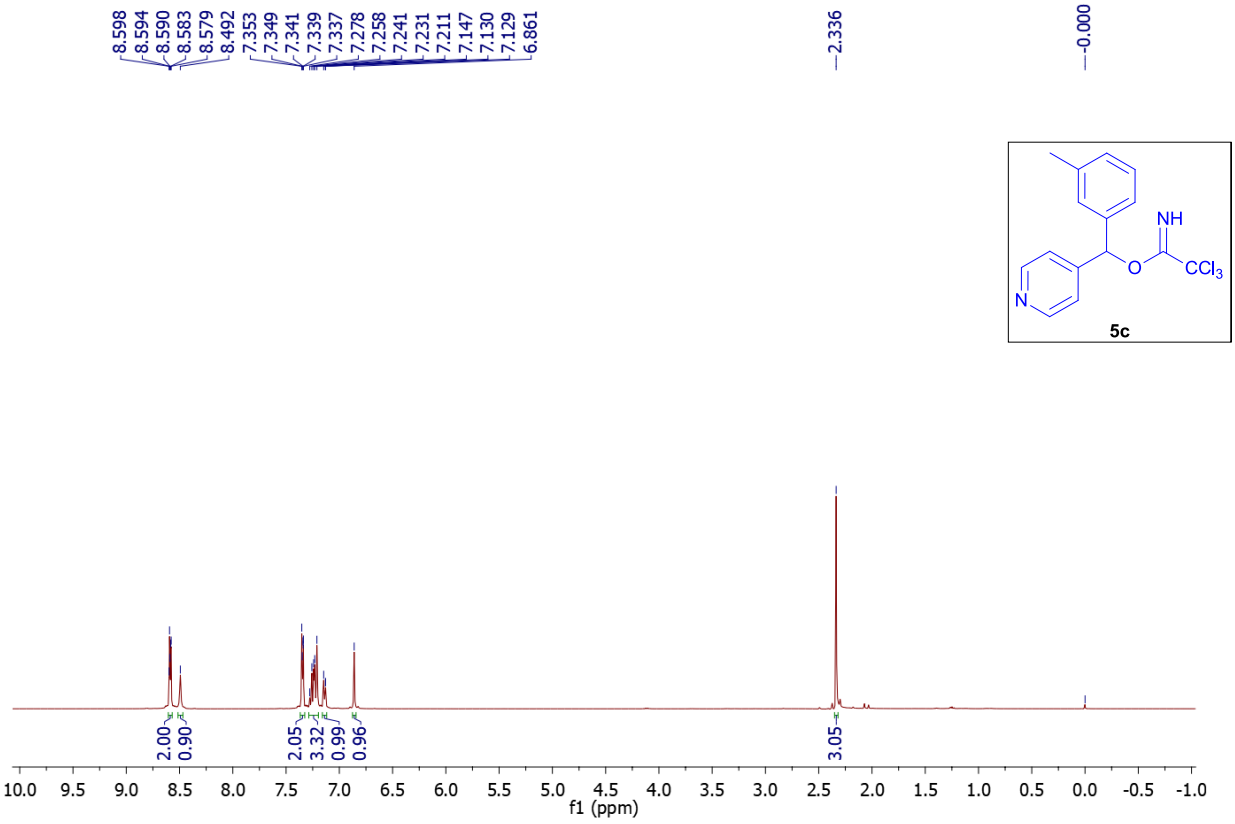
^{1}H NMR of 4lac (400 MHz, $CDCl_3$)



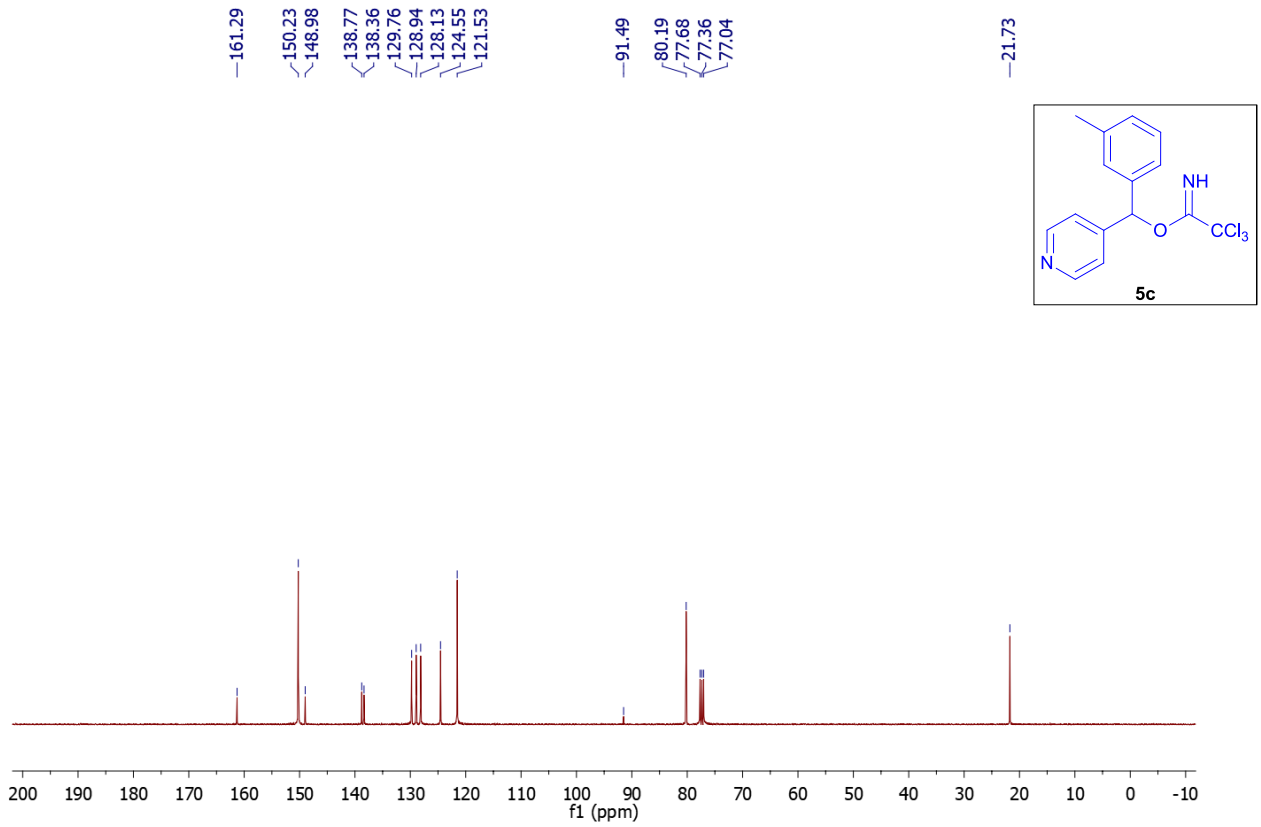
^{13}C NMR of 4lac (100 MHz, $CDCl_3$)



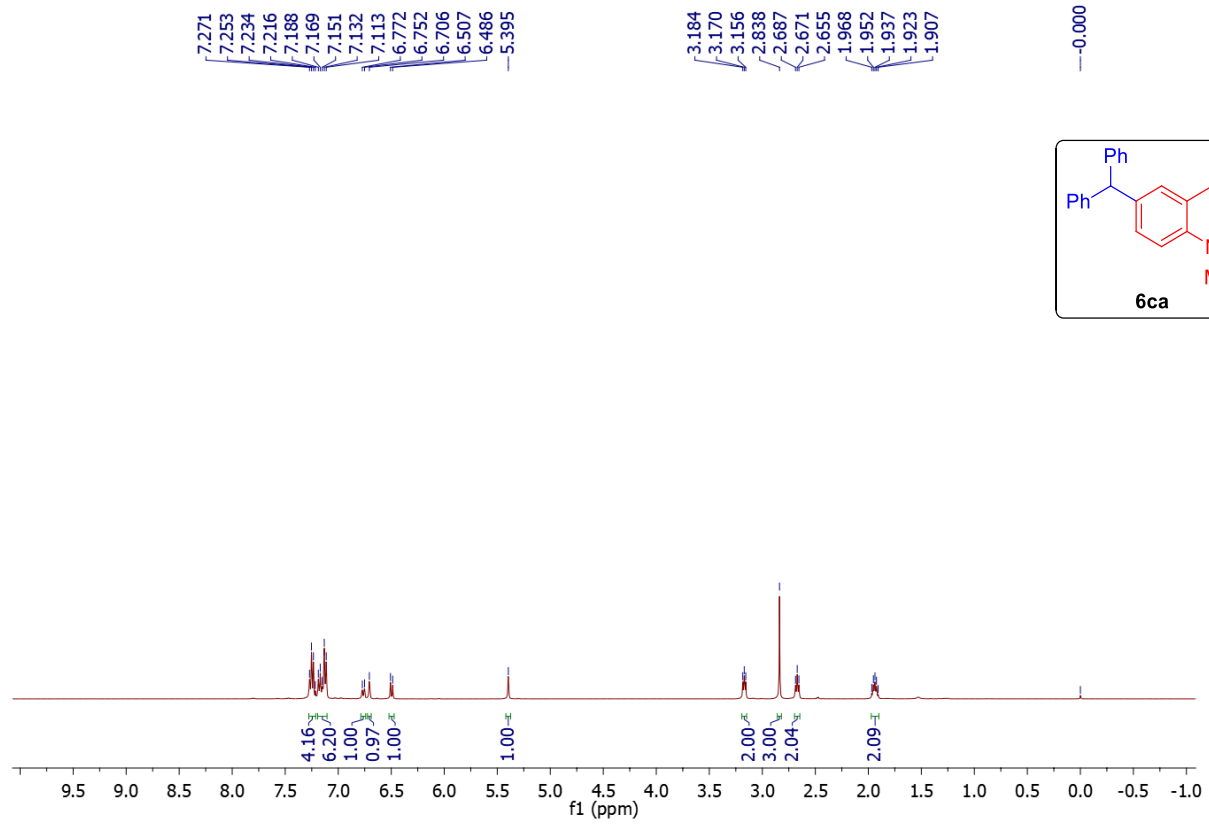
^{1}H NMR of 5c (400 MHz, $CDCl_3$)



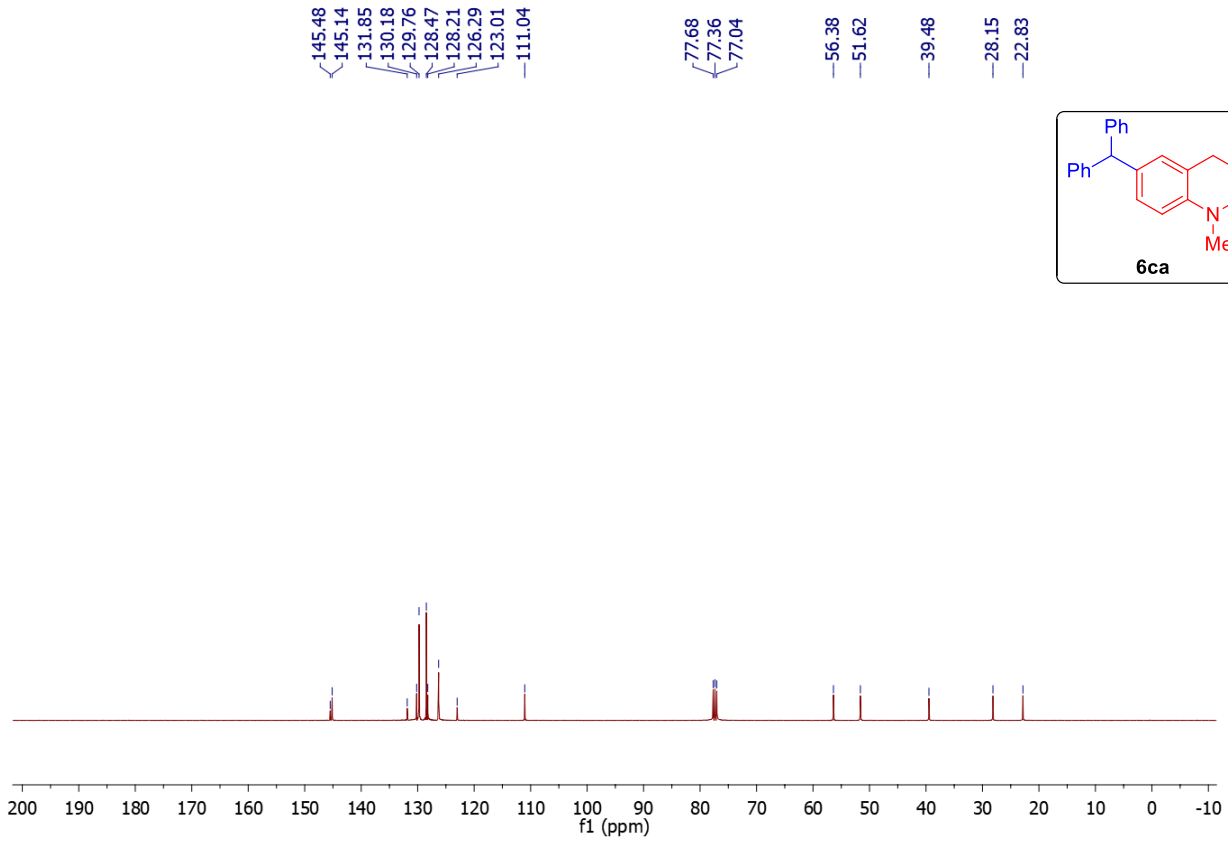
^{13}C NMR of 5c (100 MHz, $CDCl_3$)



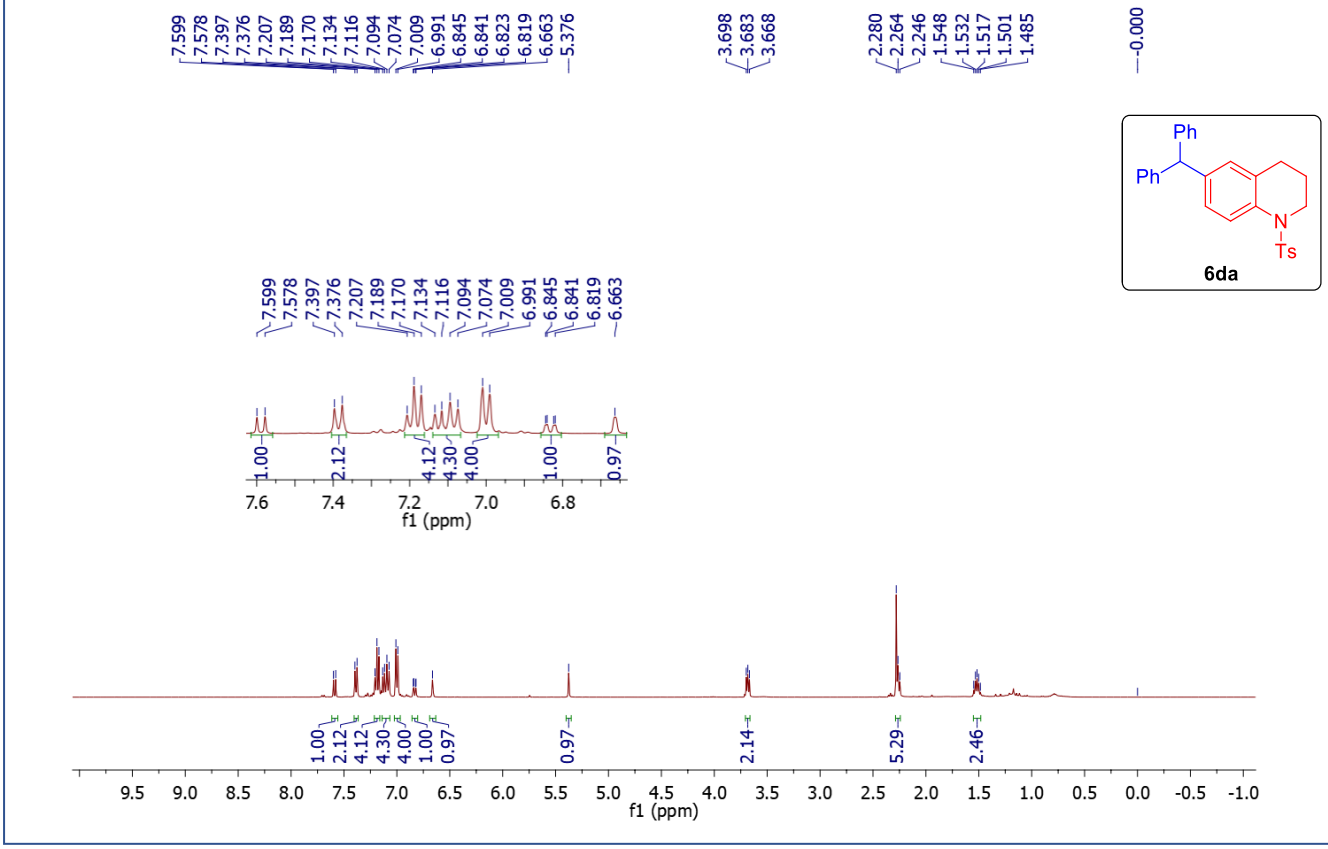
^{1}H NMR of 6ca (400 MHz, $CDCl_3$)



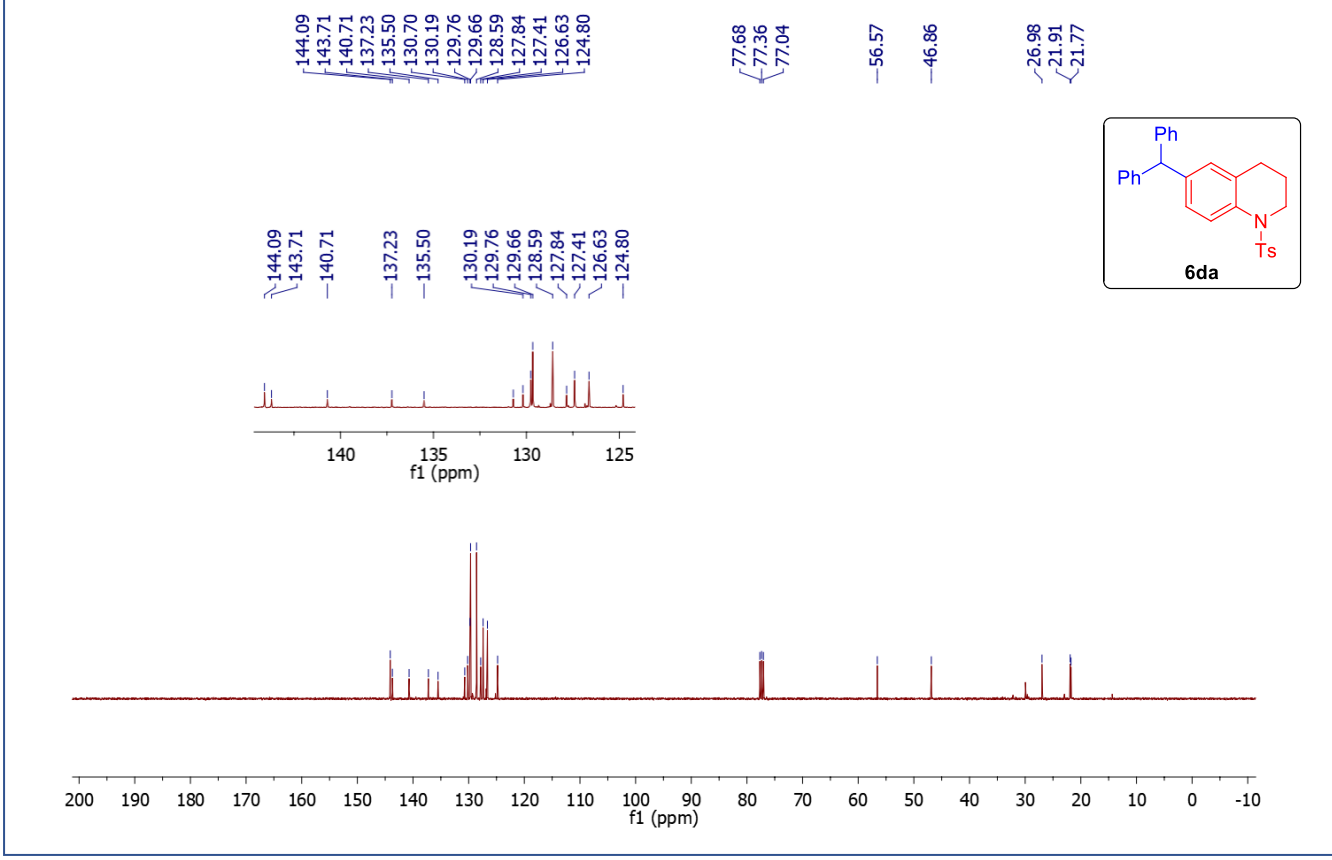
^{13}C NMR of 6ca (100 MHz, $CDCl_3$)



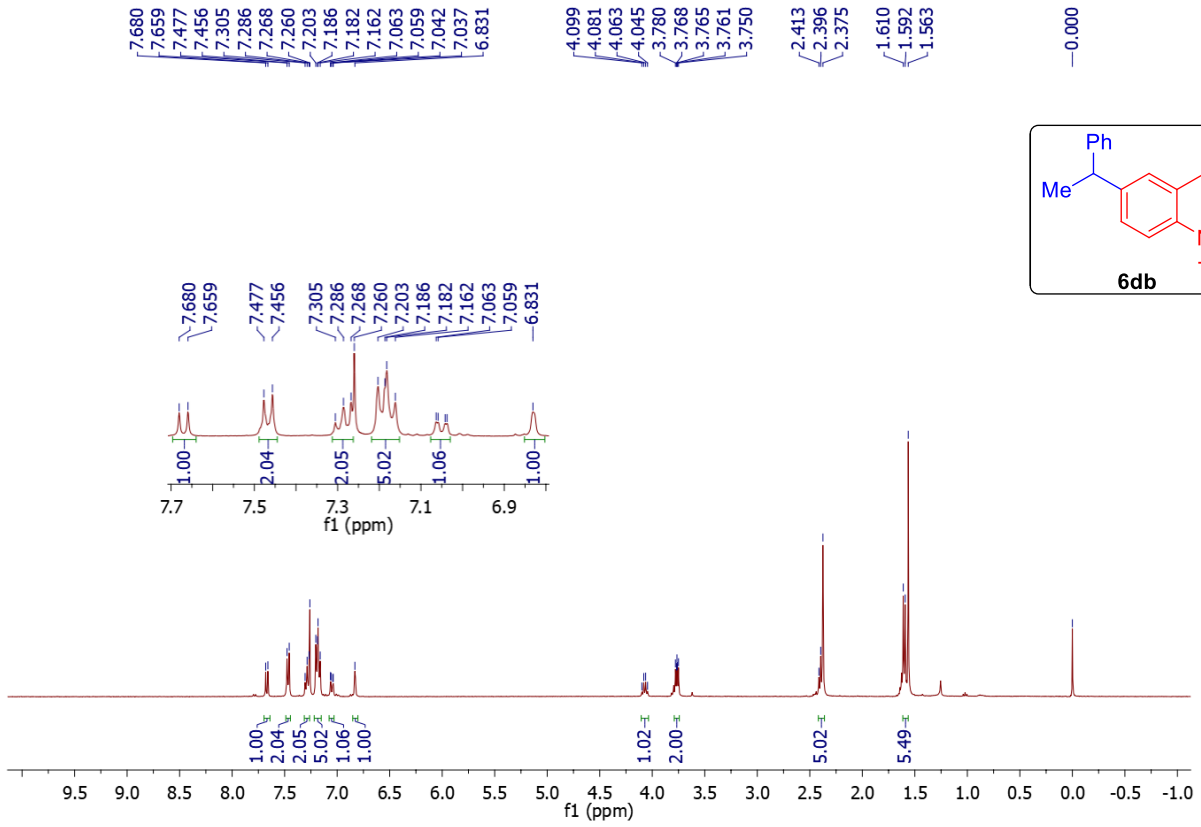
^{1}H NMR of 6da (400 MHz, $CDCl_3$)



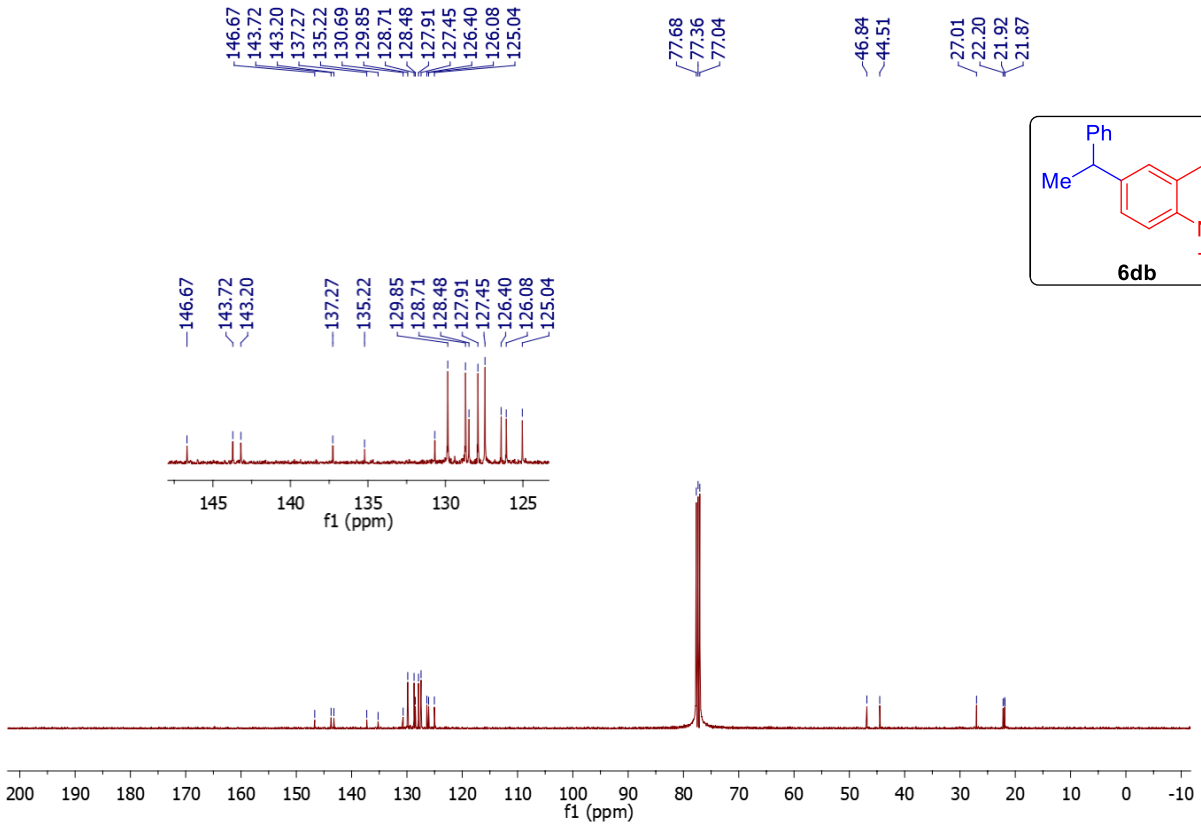
^{13}C NMR of 6da (100 MHz, $CDCl_3$)



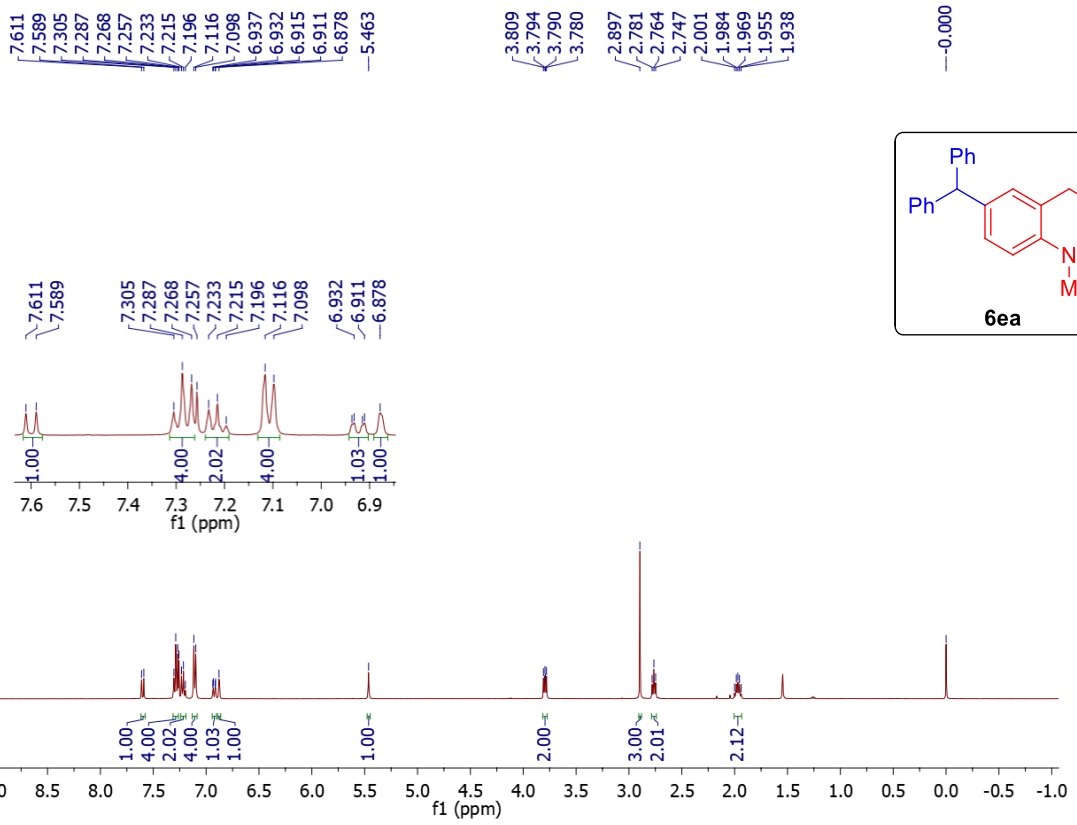
^{1}H NMR of 6db (400 MHz, $CDCl_3$)



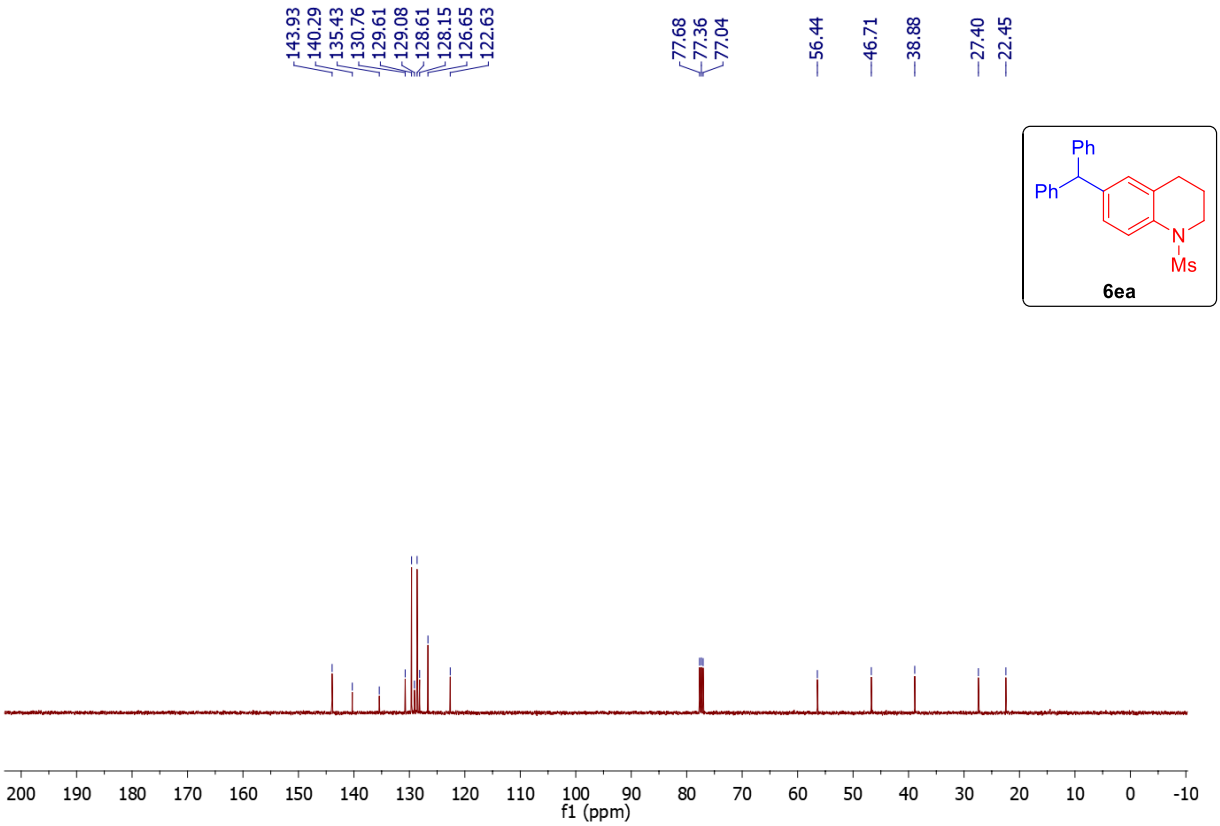
^{13}C NMR of 6db (100 MHz, $CDCl_3$)



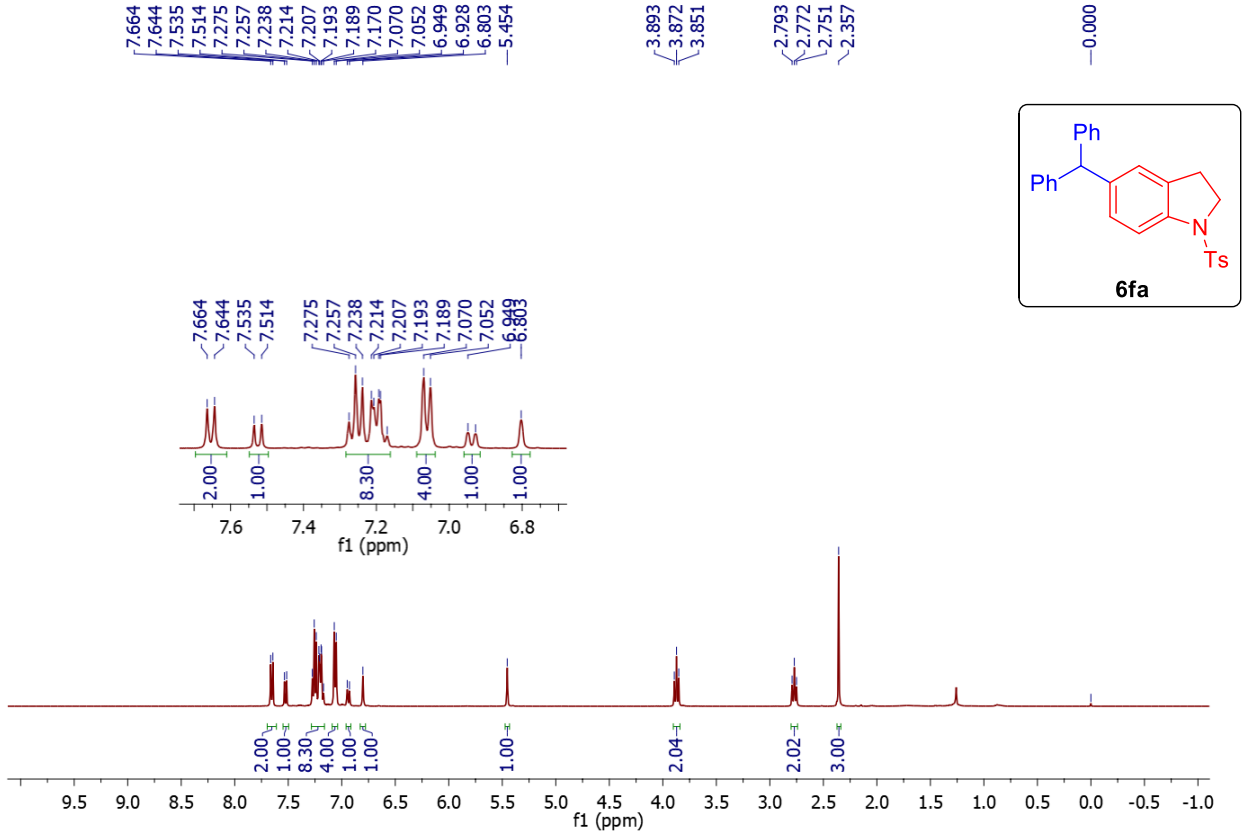
^{1}H NMR of 6ea (400 MHz, $CDCl_3$)



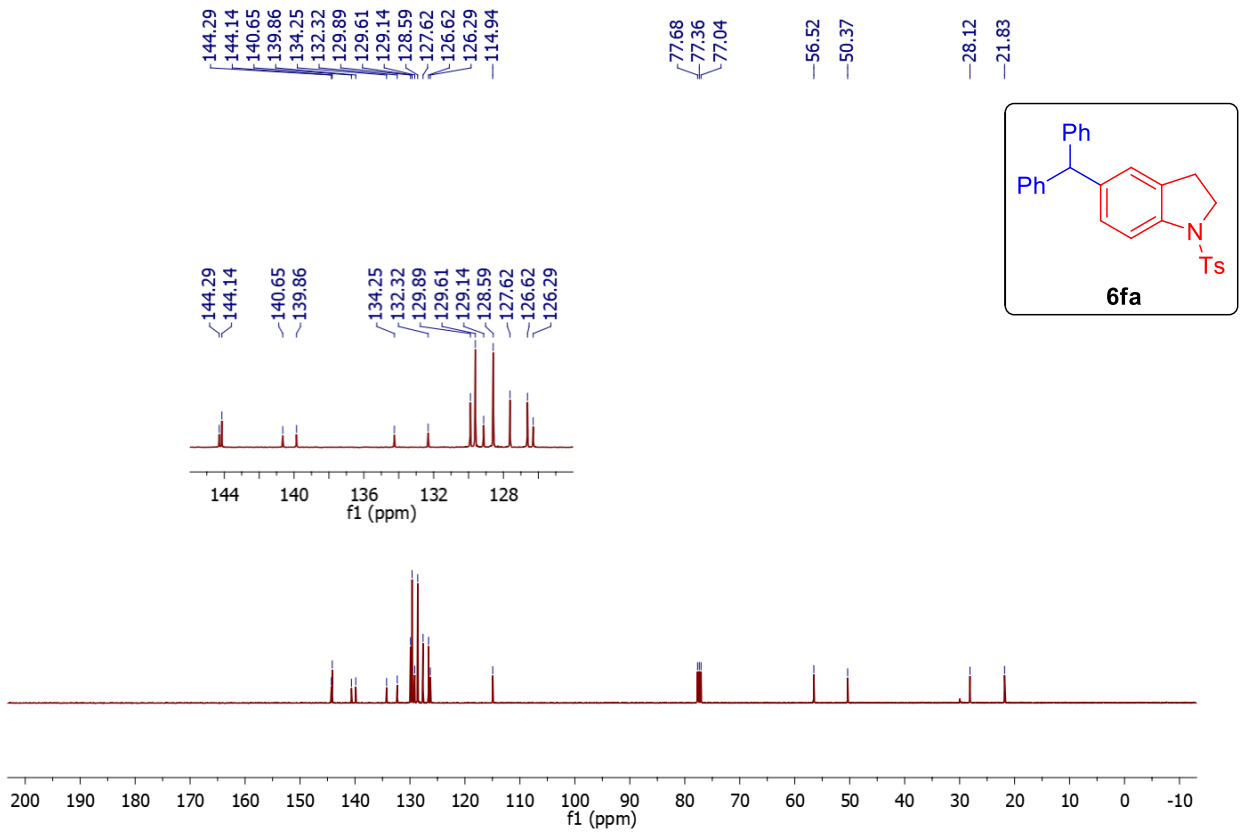
^{13}C NMR of 6ea (100 MHz, $CDCl_3$)



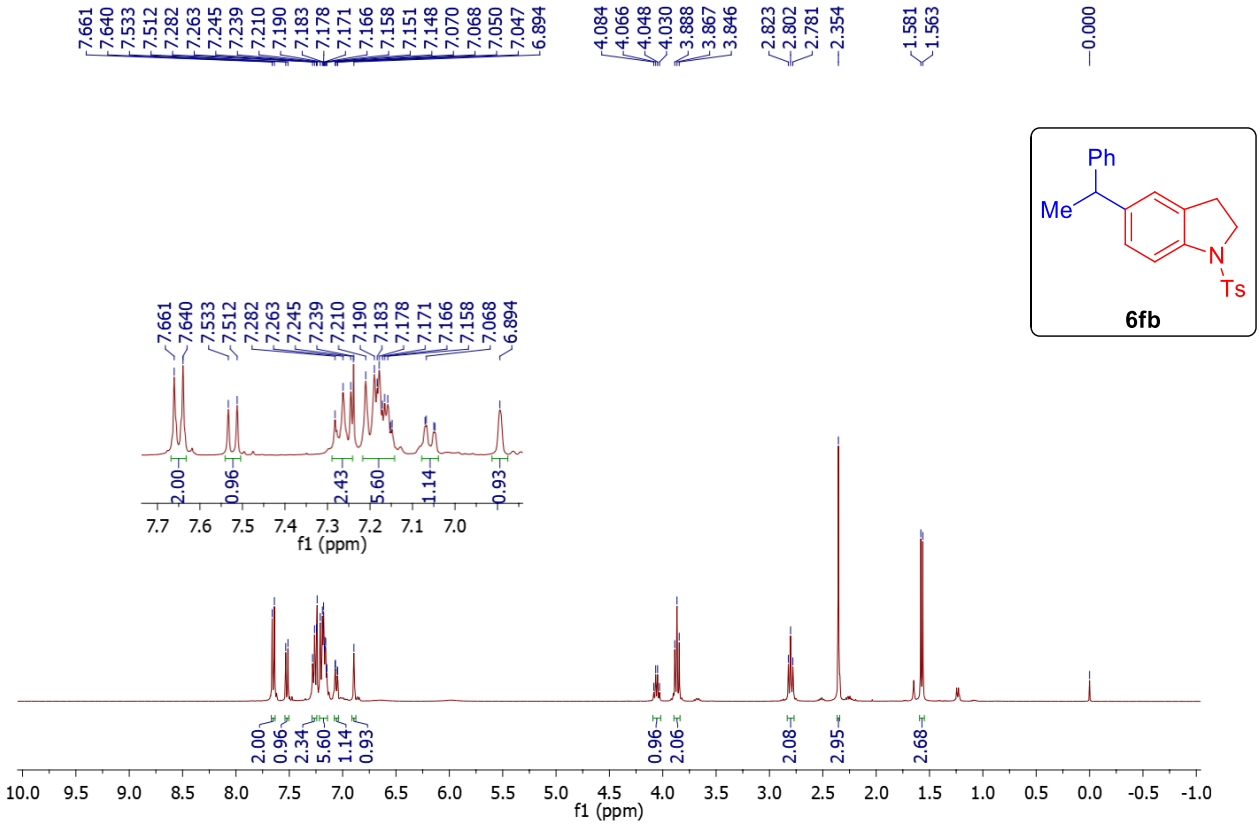
^{1}H NMR of 6fa (400 MHz, $CDCl_3$)



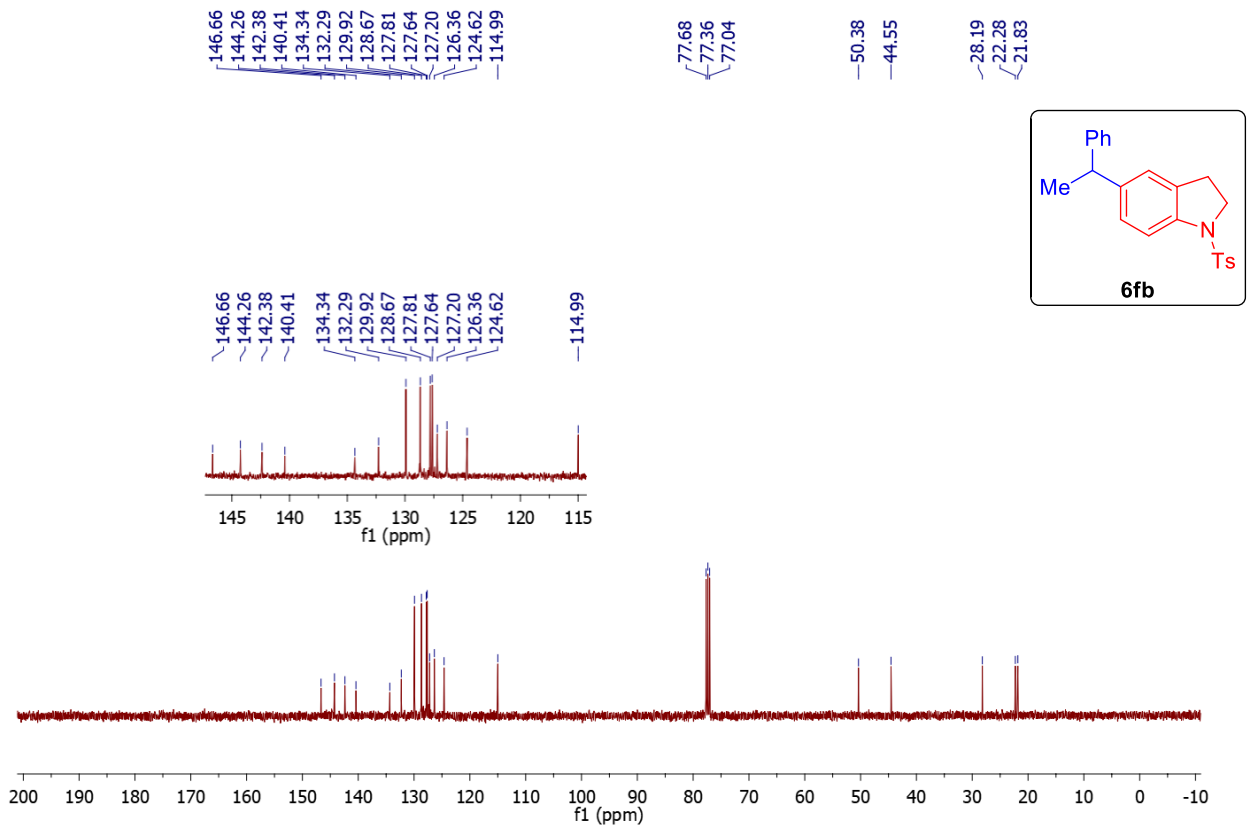
^{13}C NMR of 6fa (100 MHz, $CDCl_3$)



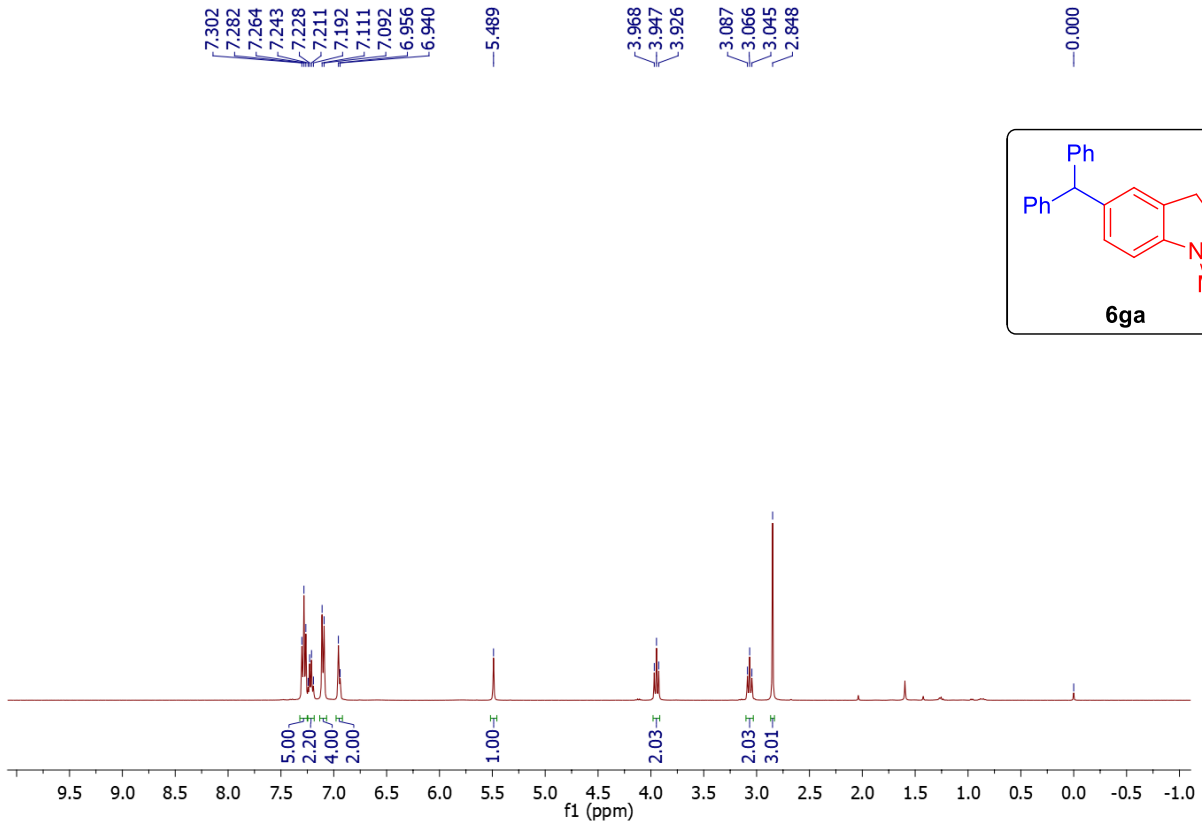
^{1}H NMR of 6fb (400 MHz, $CDCl_3$)



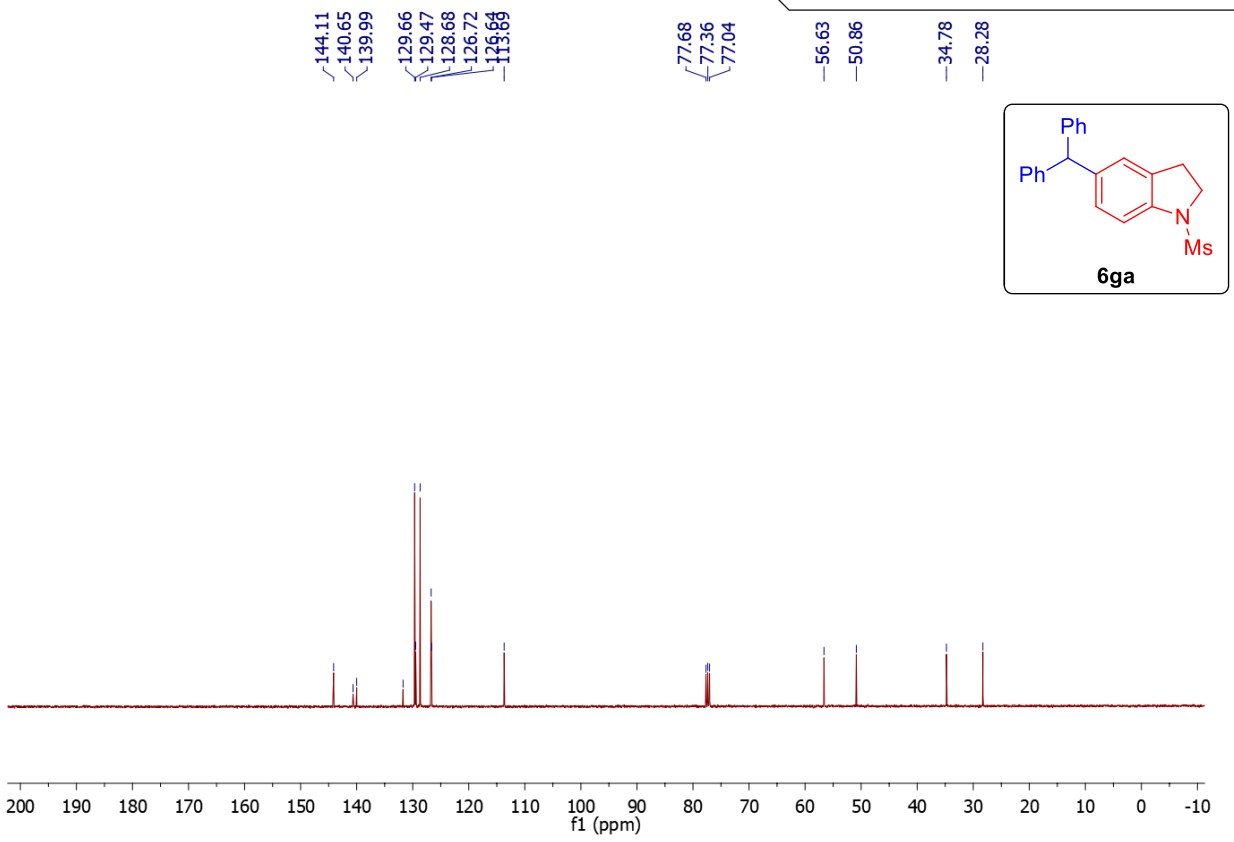
^{13}C NMR of 6fb (100 MHz, $CDCl_3$)



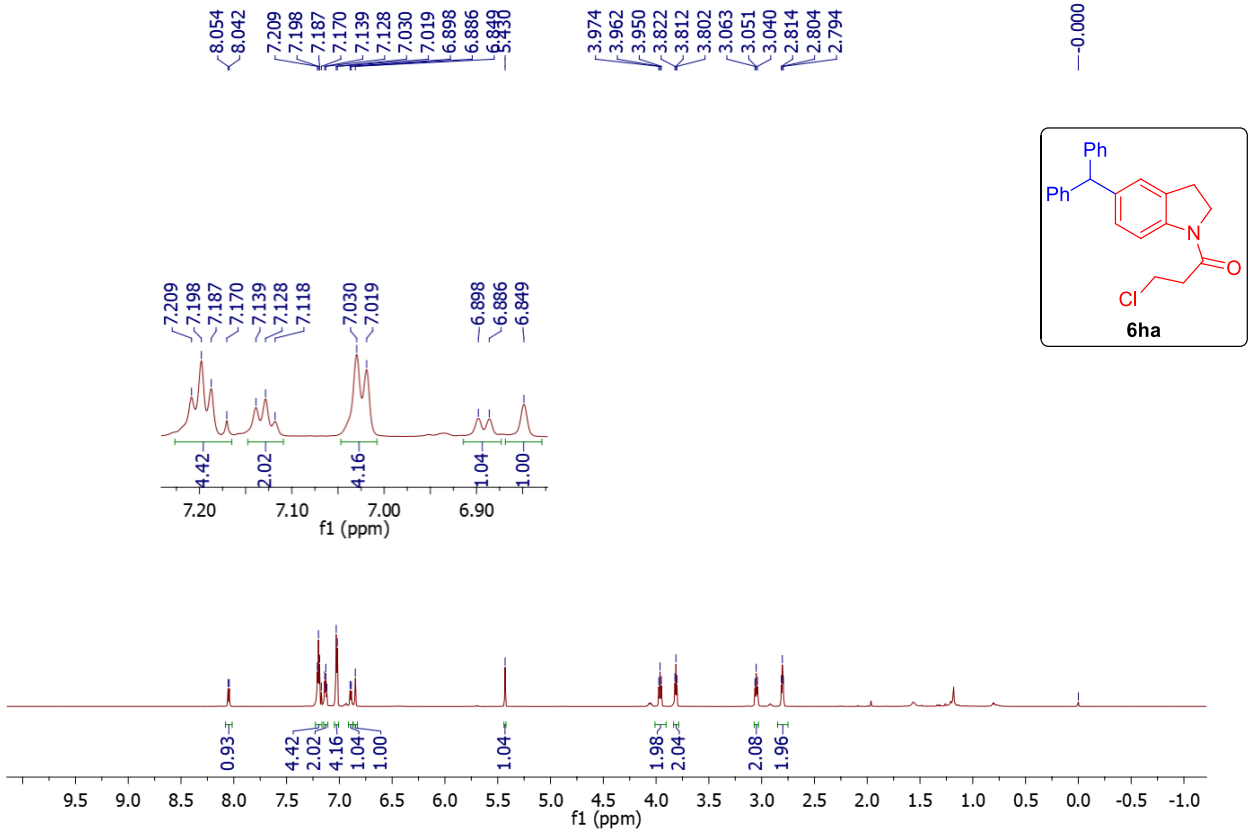
^{1}H NMR of 6ga (400 MHz, $CDCl_3$)



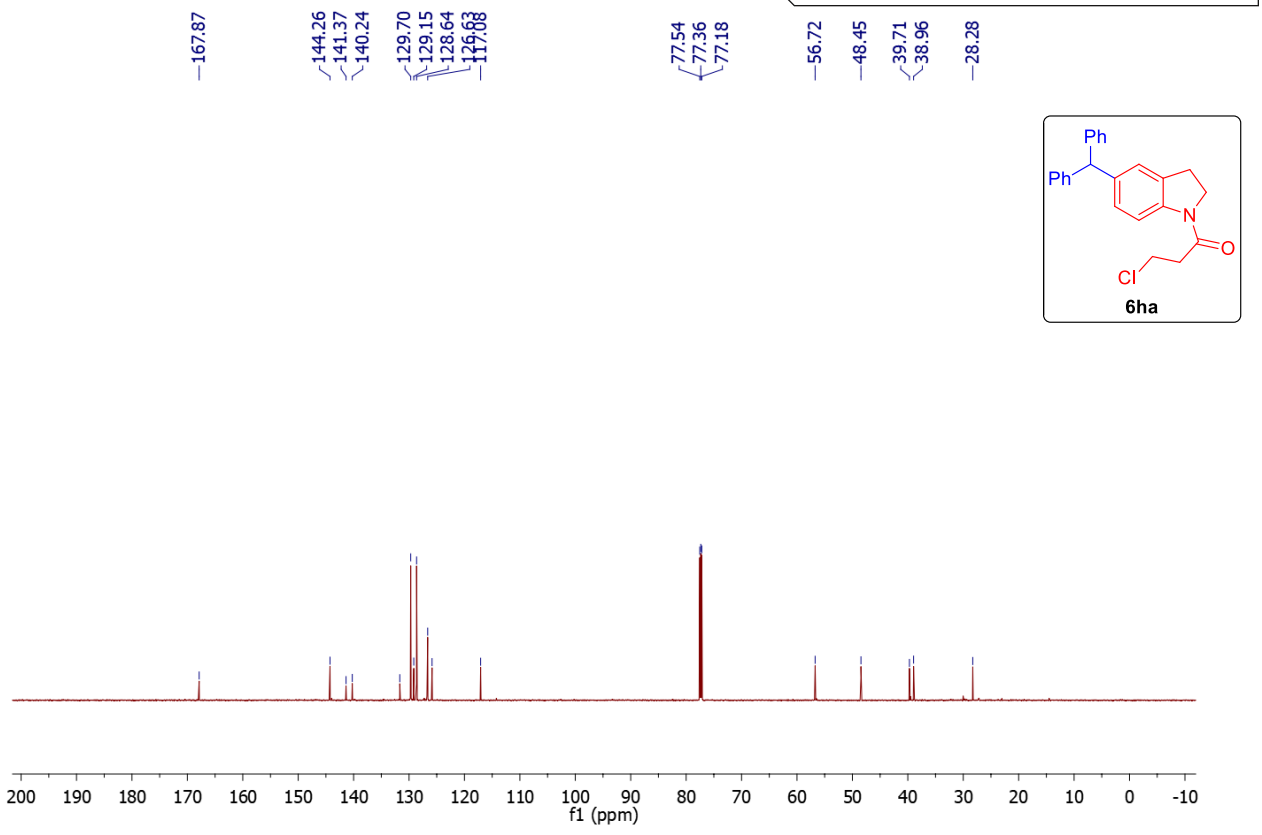
^{13}C NMR of 6ga (100 MHz, $CDCl_3$)



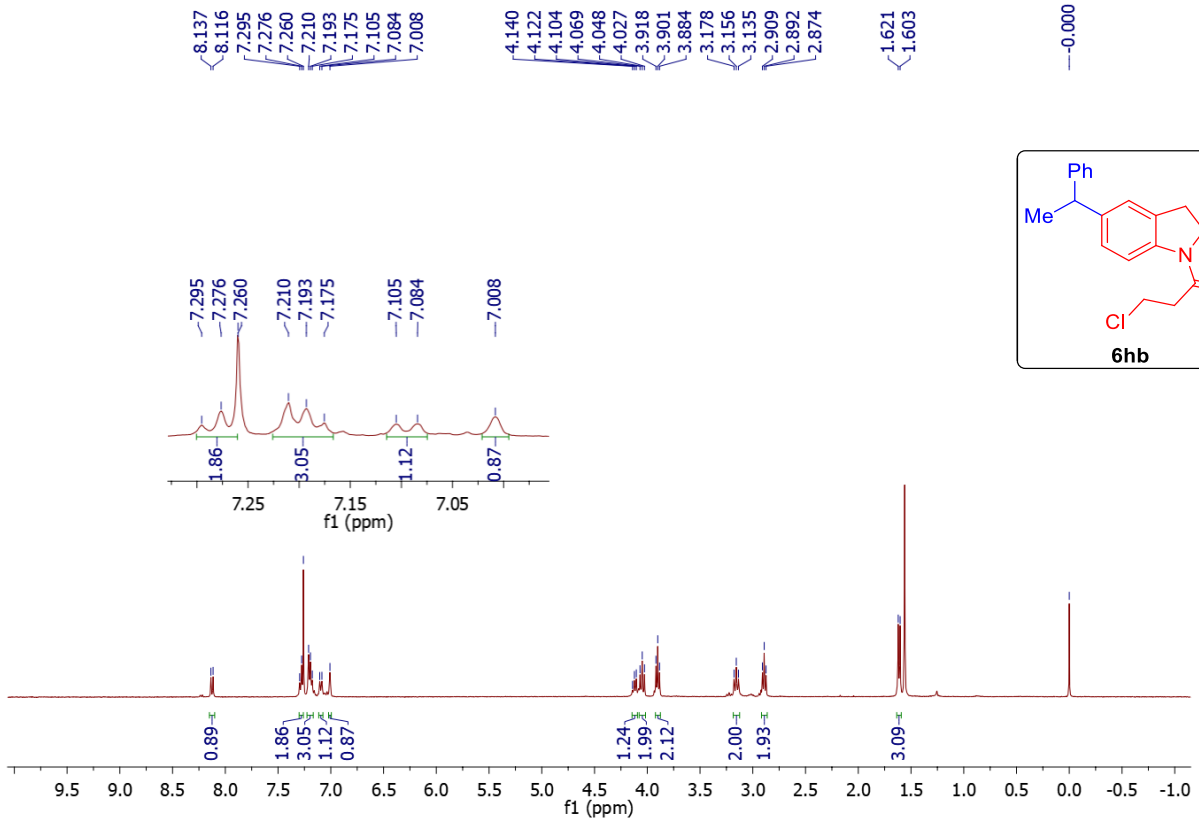
^{1}H NMR of 6ha (700 MHz, $CDCl_3$)



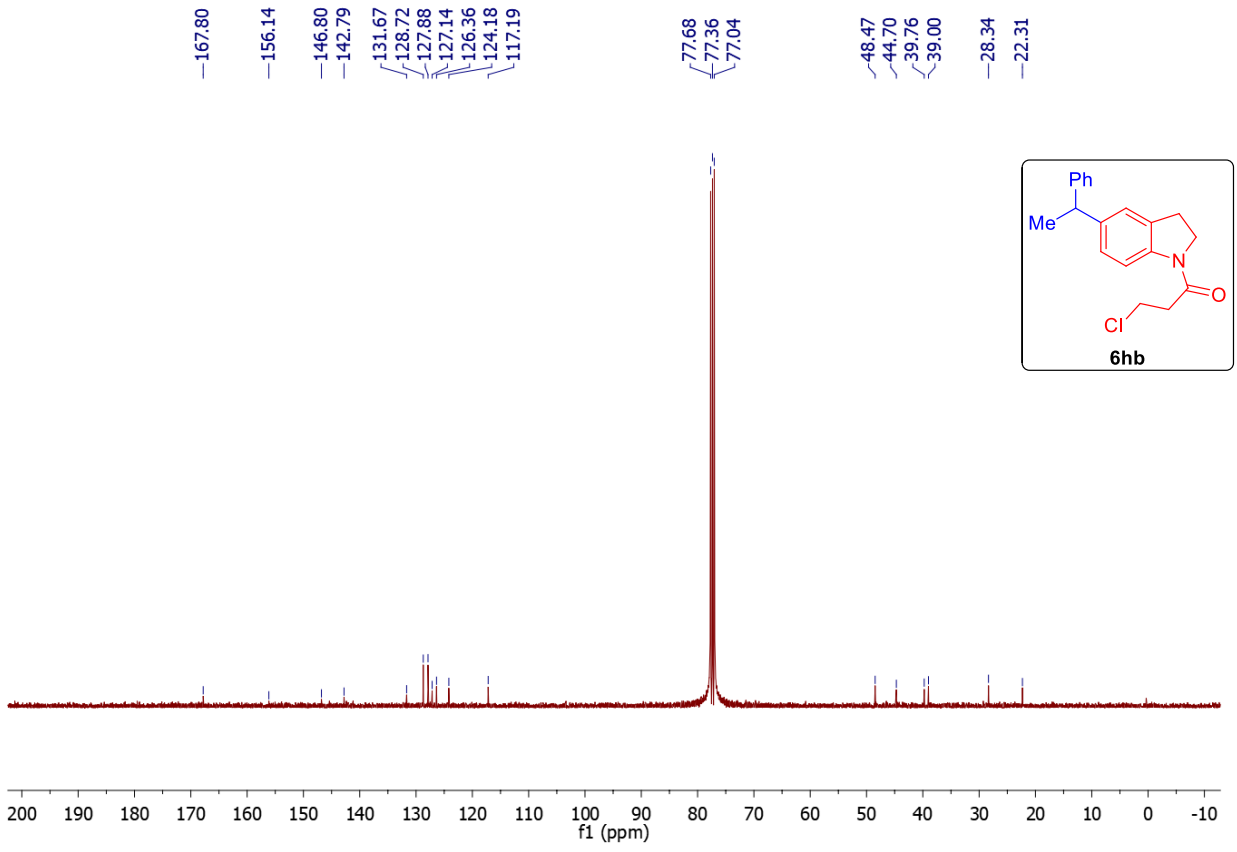
^{13}C NMR of 6ha (176 MHz, $CDCl_3$)



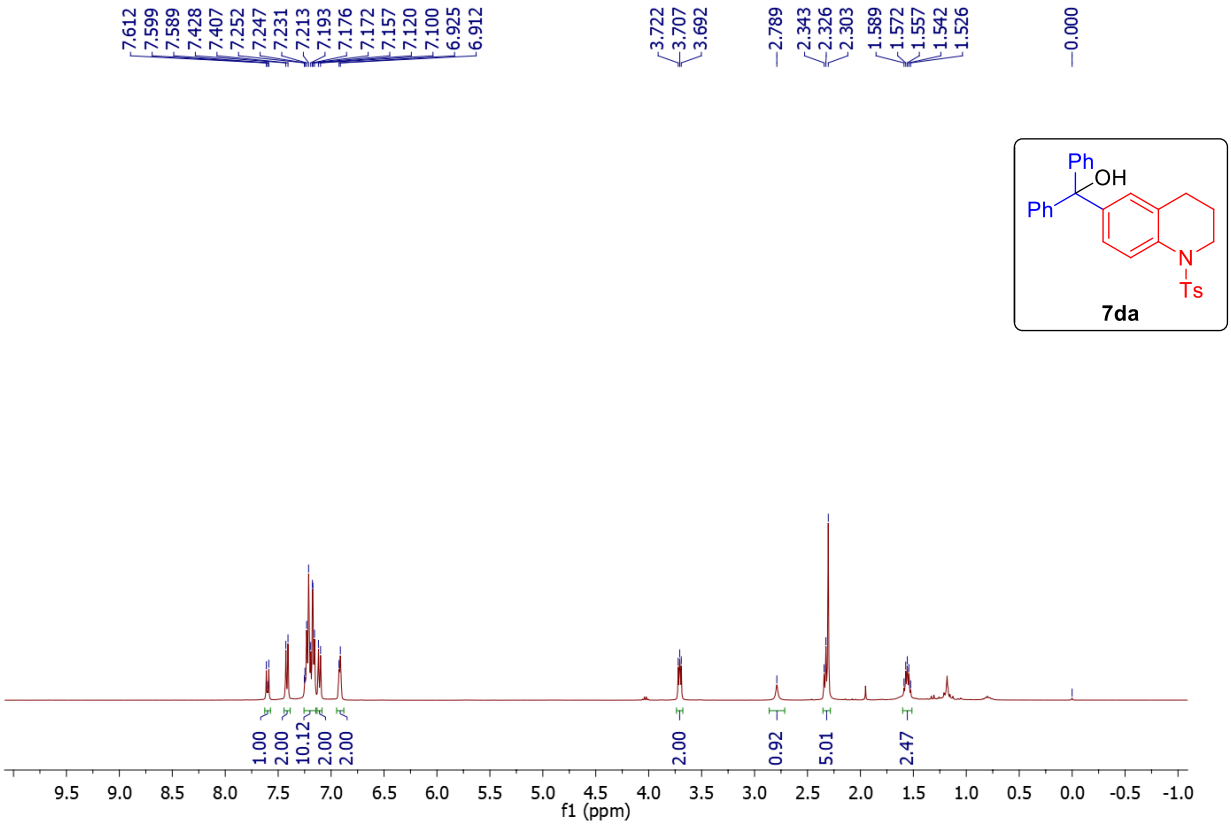
^{1}H NMR of 6hb (400 MHz, $CDCl_3$)



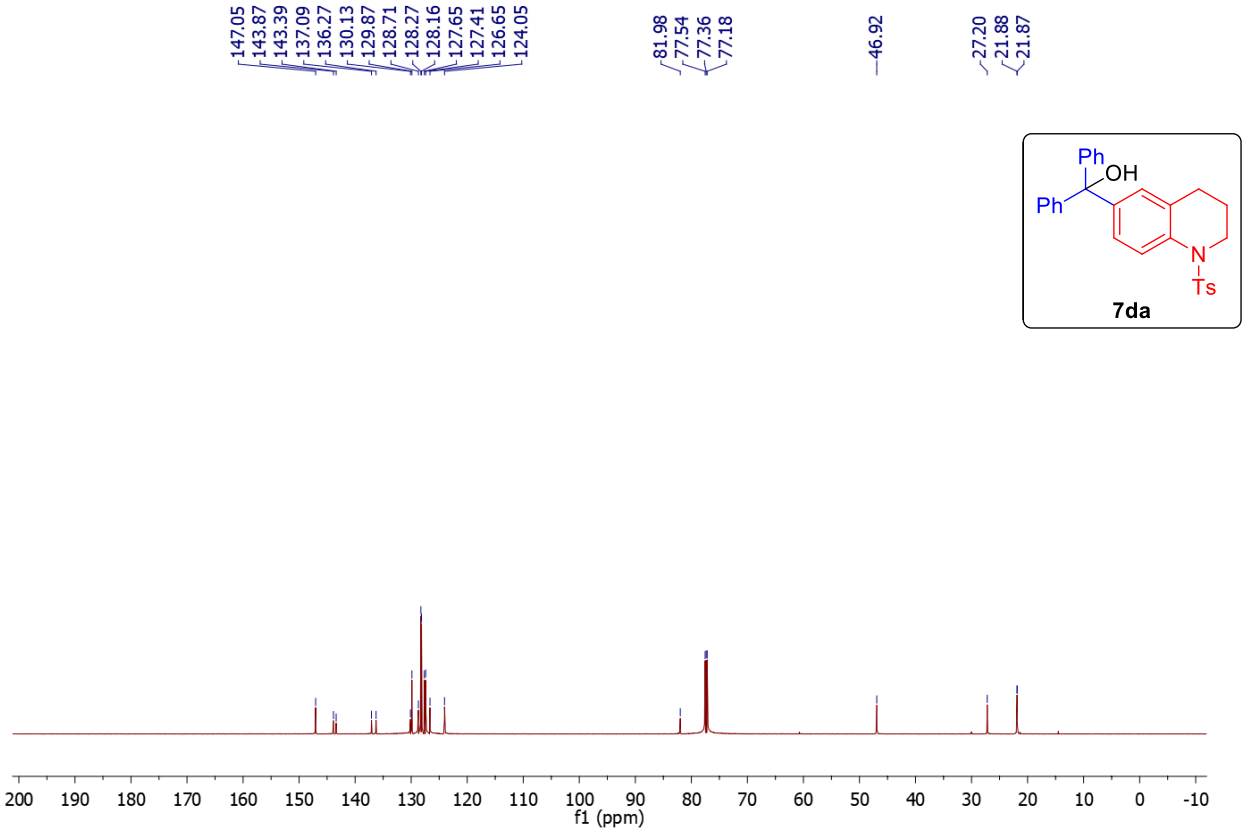
^{13}C NMR of 6hb (100 MHz, $CDCl_3$)



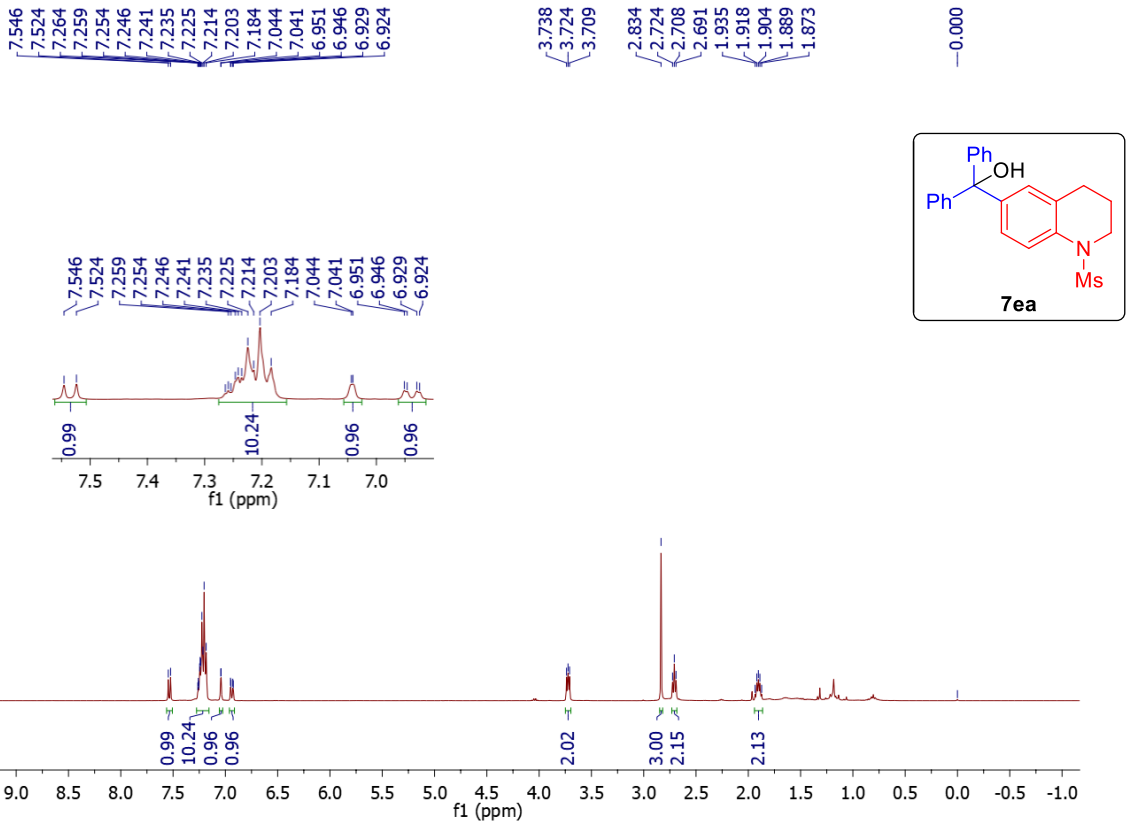
^{1}H NMR of 7da (400 MHz, $CDCl_3$)



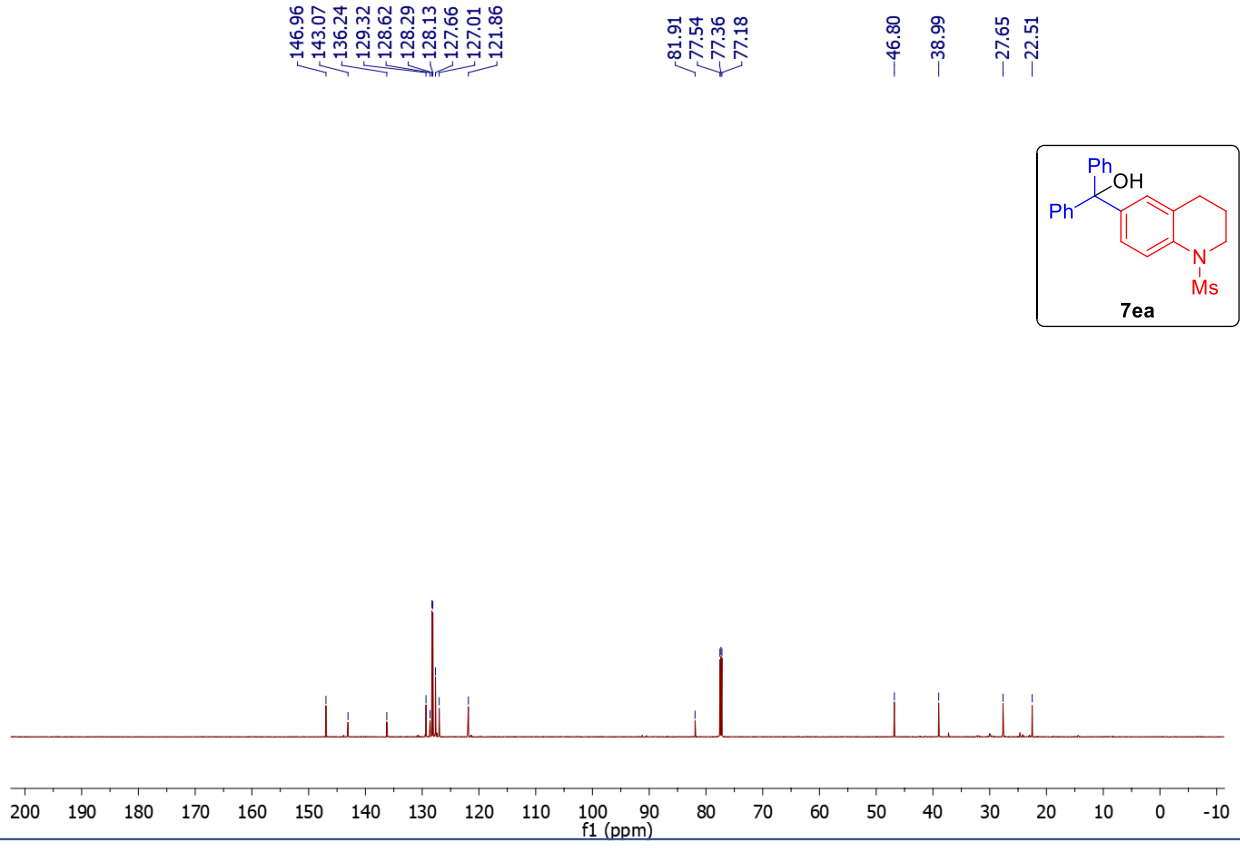
^{13}C NMR of 7da (176 MHz, $CDCl_3$)



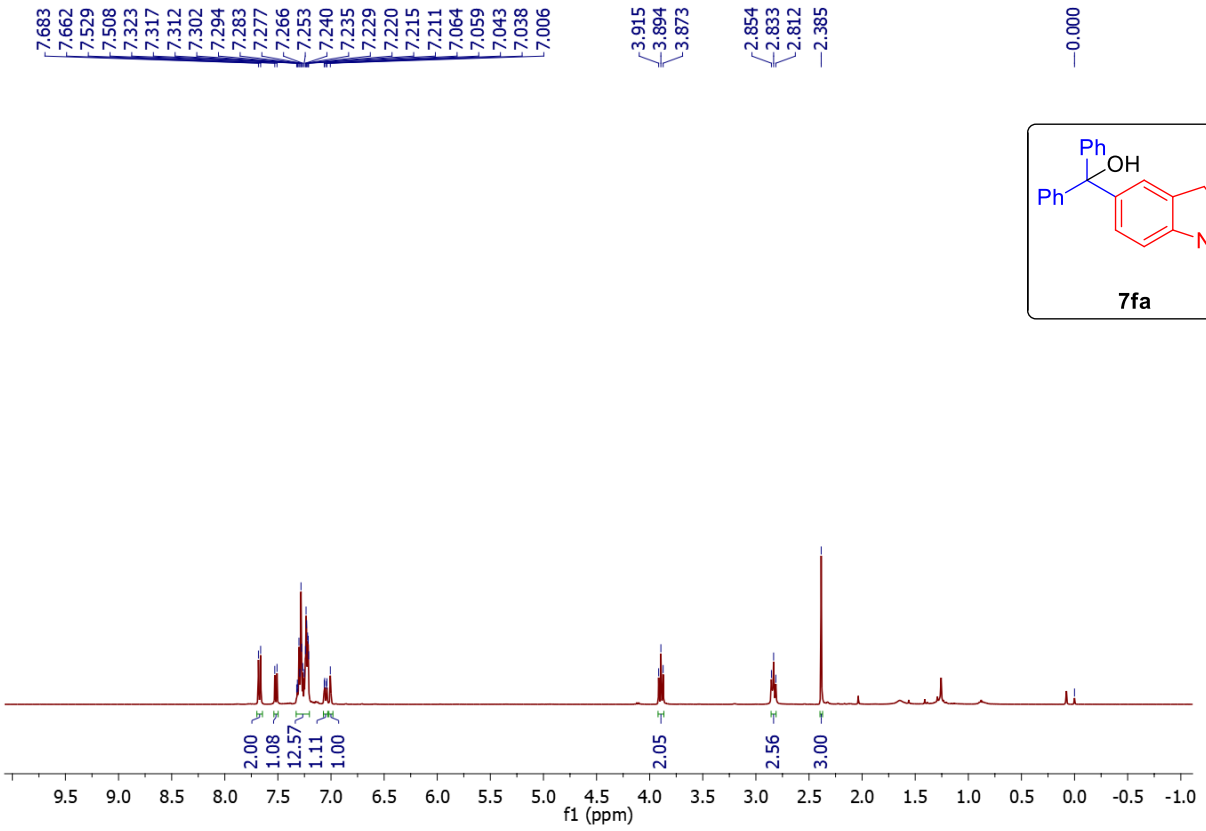
^{1}H NMR of 7ea (400 MHz, $CDCl_3$)



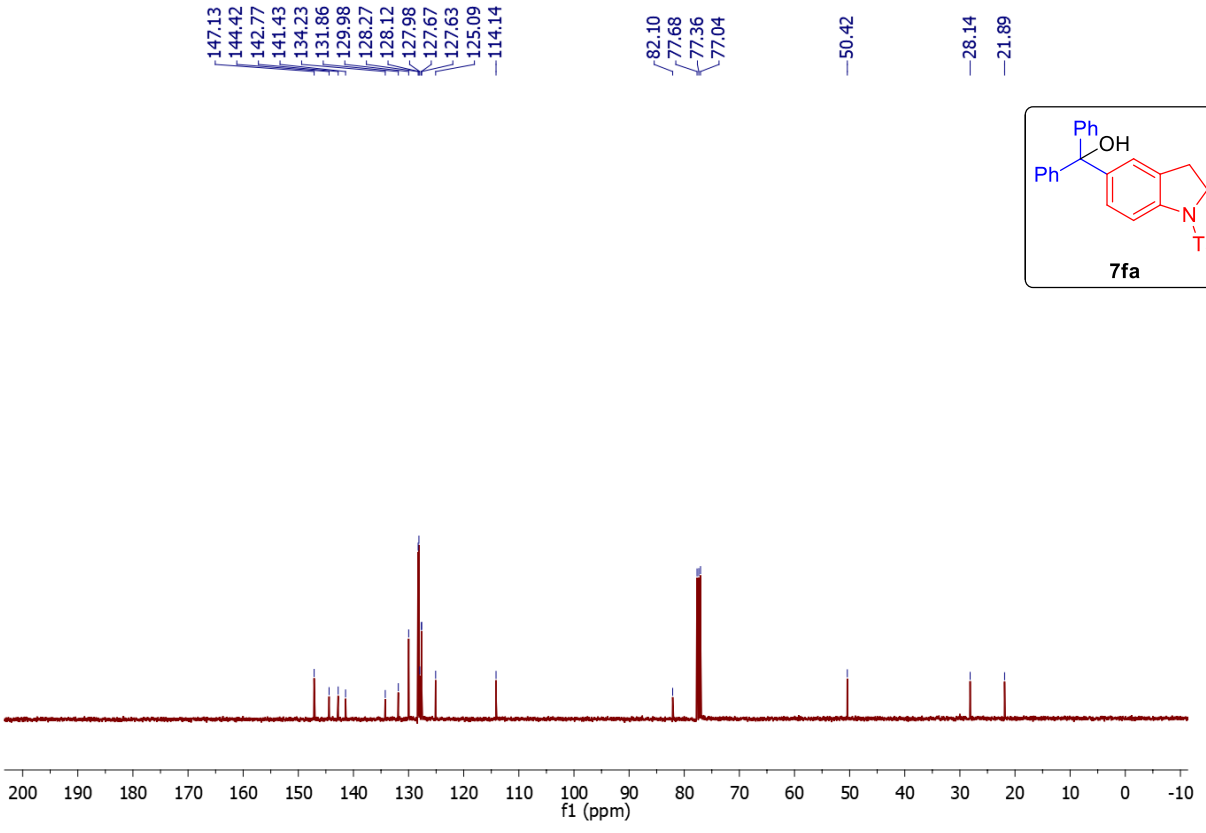
^{13}C NMR of 7ea (176 MHz, $CDCl_3$)



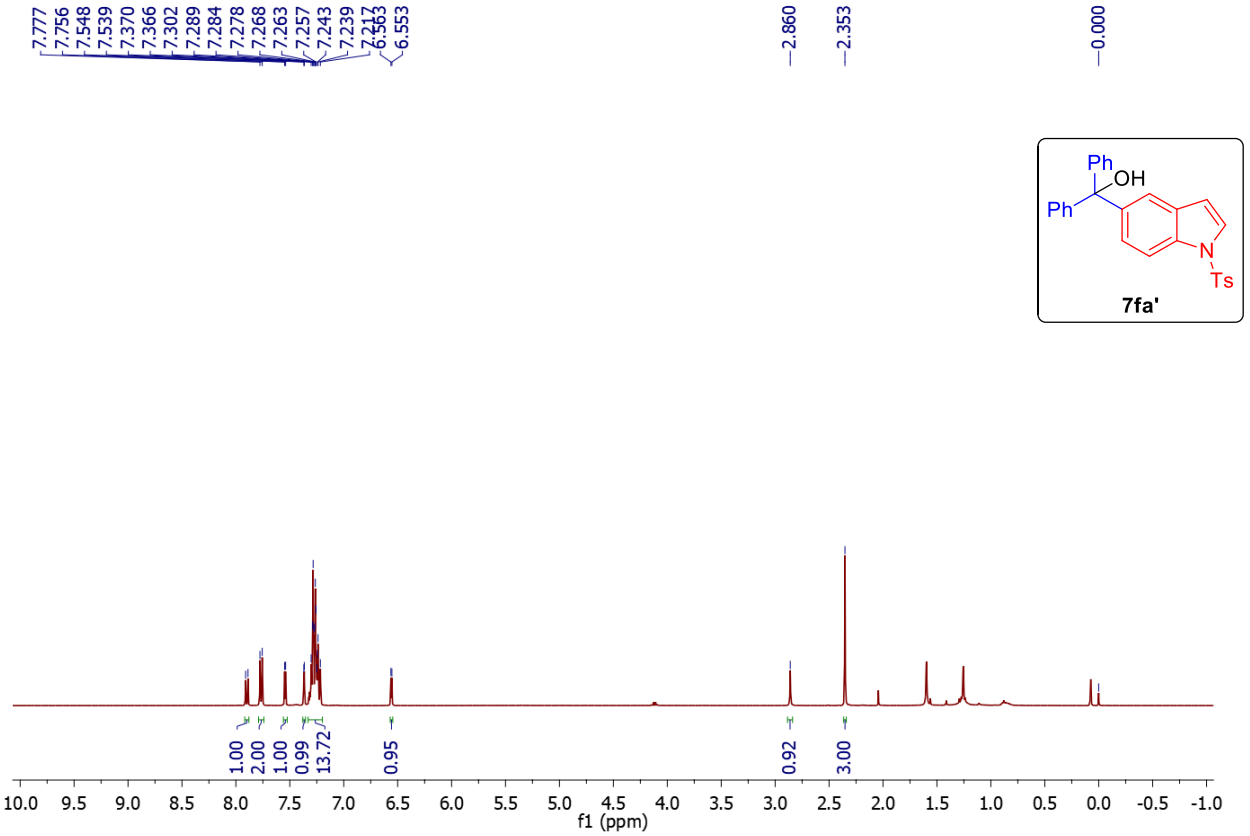
^{1}H NMR of 7fa (400 MHz, $CDCl_3$)



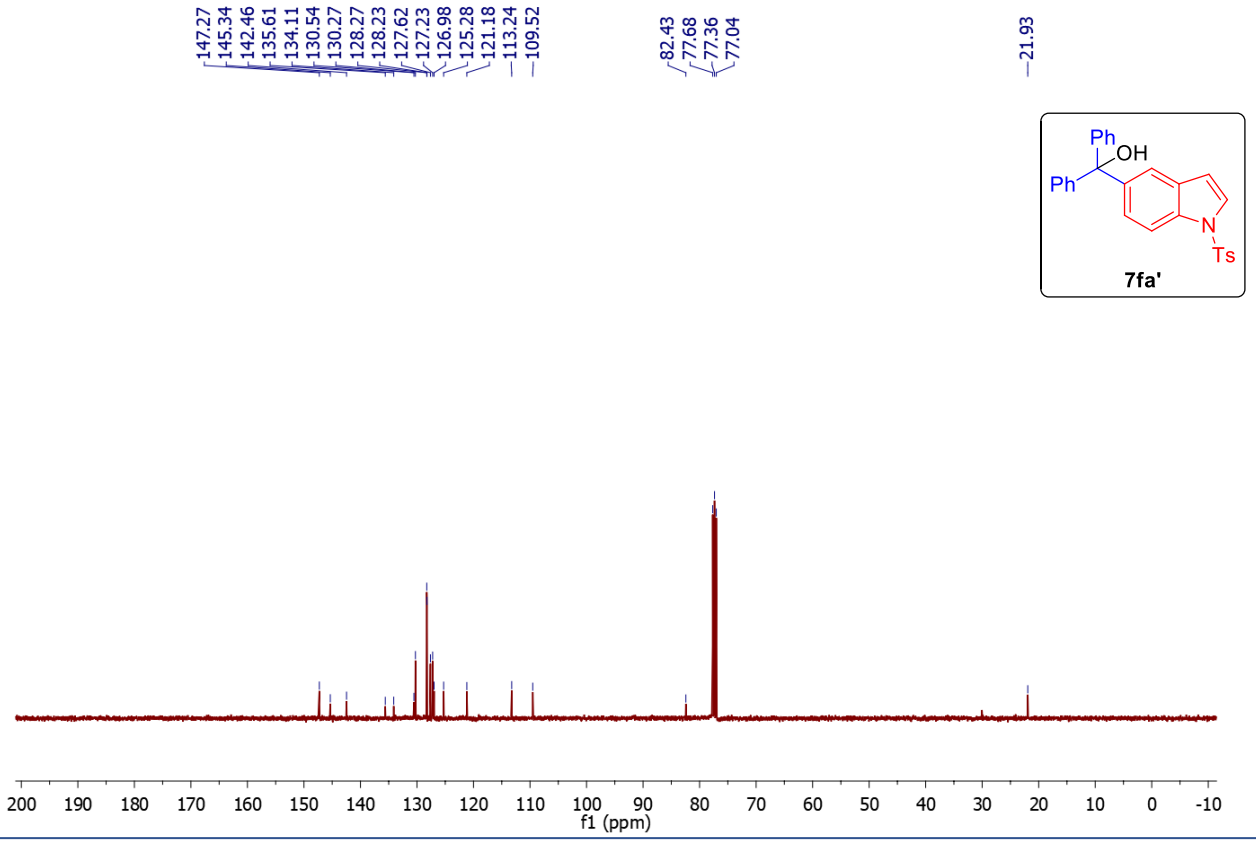
^{13}C NMR of 7fa (100 MHz, $CDCl_3$)



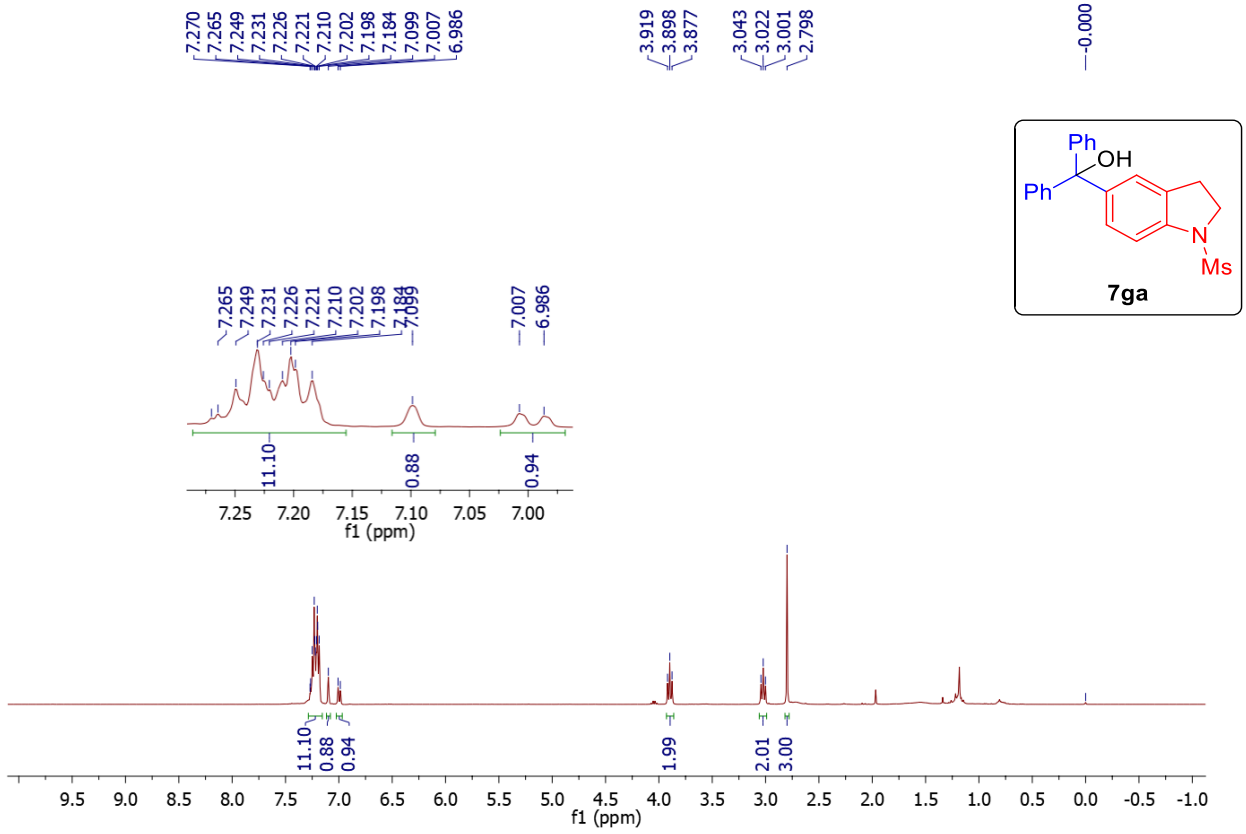
^{1}H NMR of 7fa' (400 MHz, $CDCl_3$)



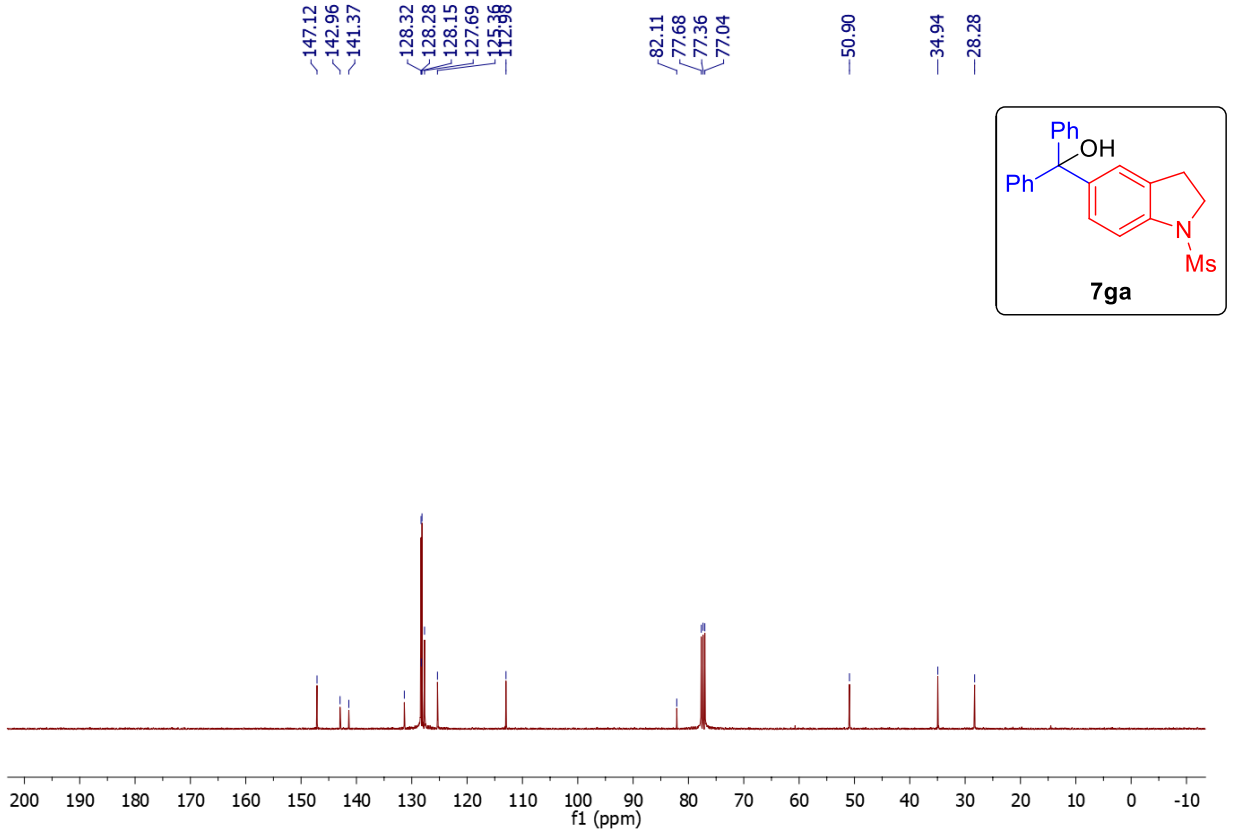
^{13}C NMR of 7fa' (100 MHz, $CDCl_3$)



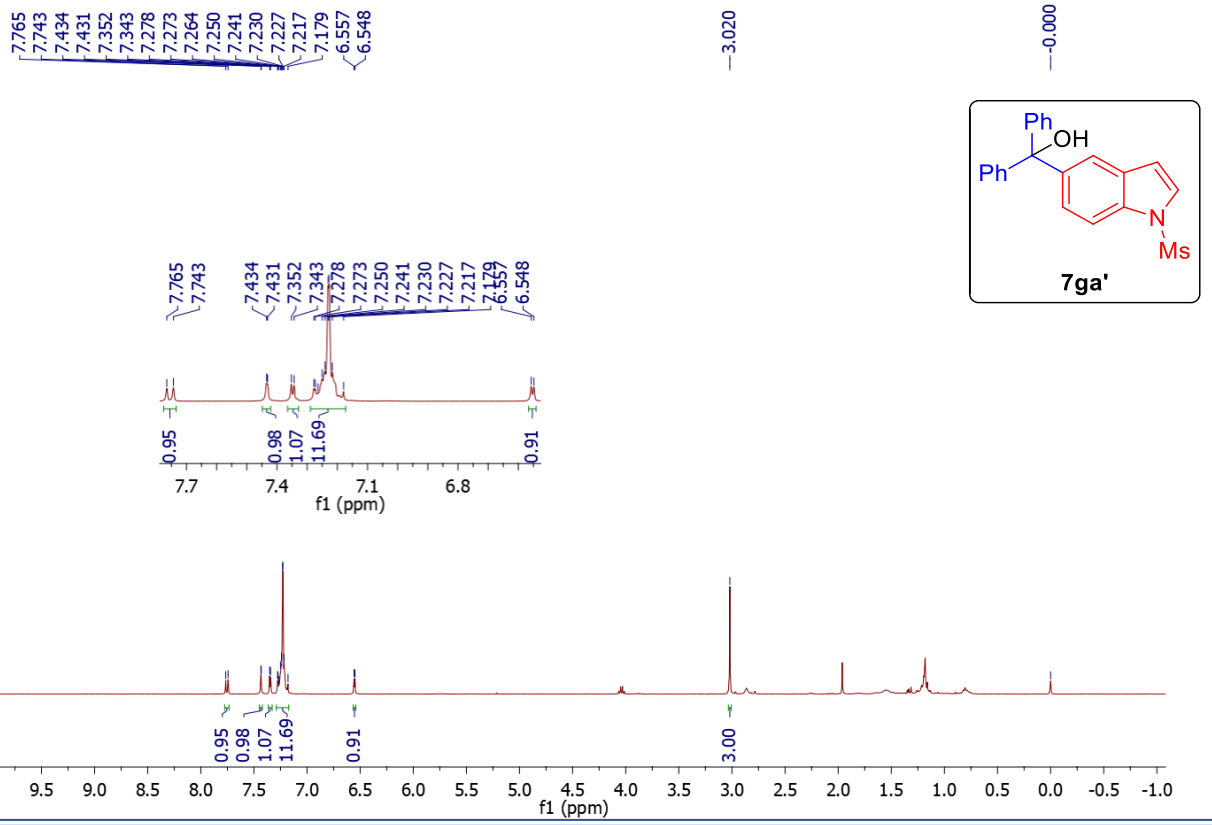
^{1}H NMR of 7ga (400 MHz, $CDCl_3$)



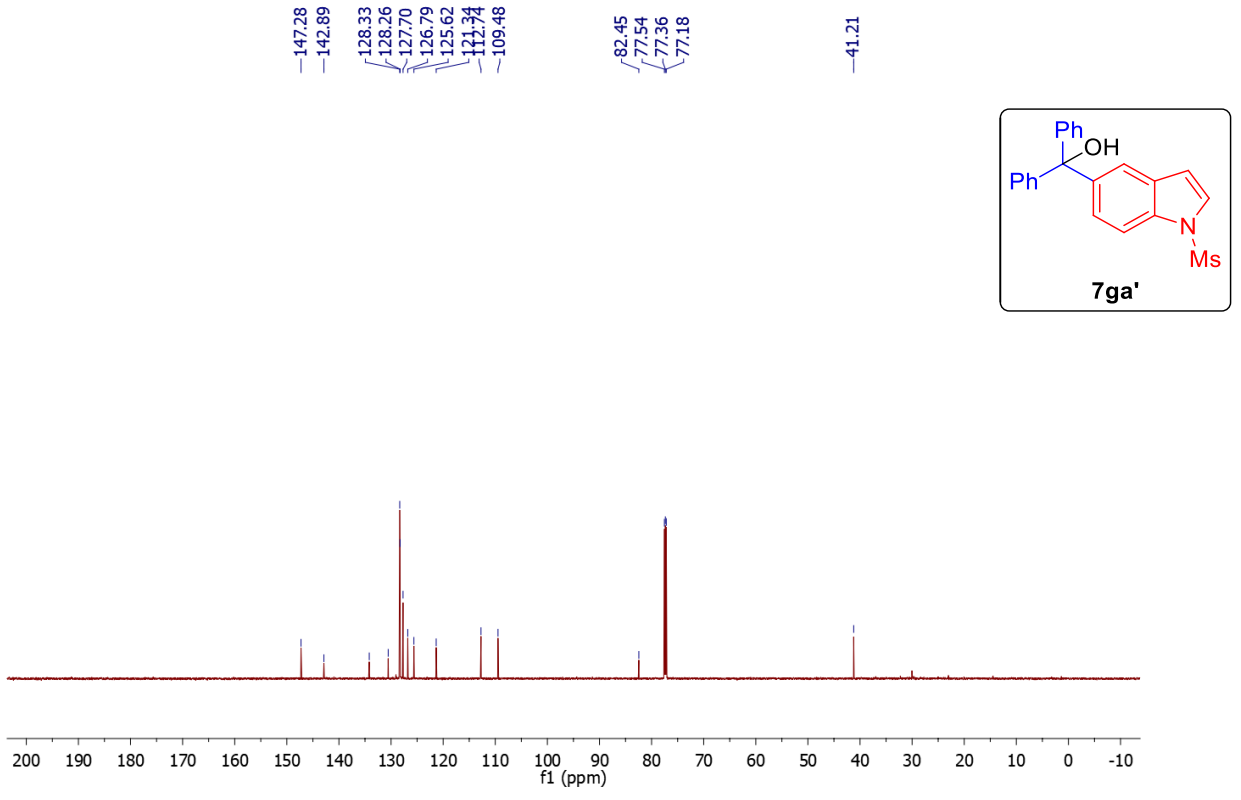
^{13}C NMR of 7ga (100 MHz, $CDCl_3$)



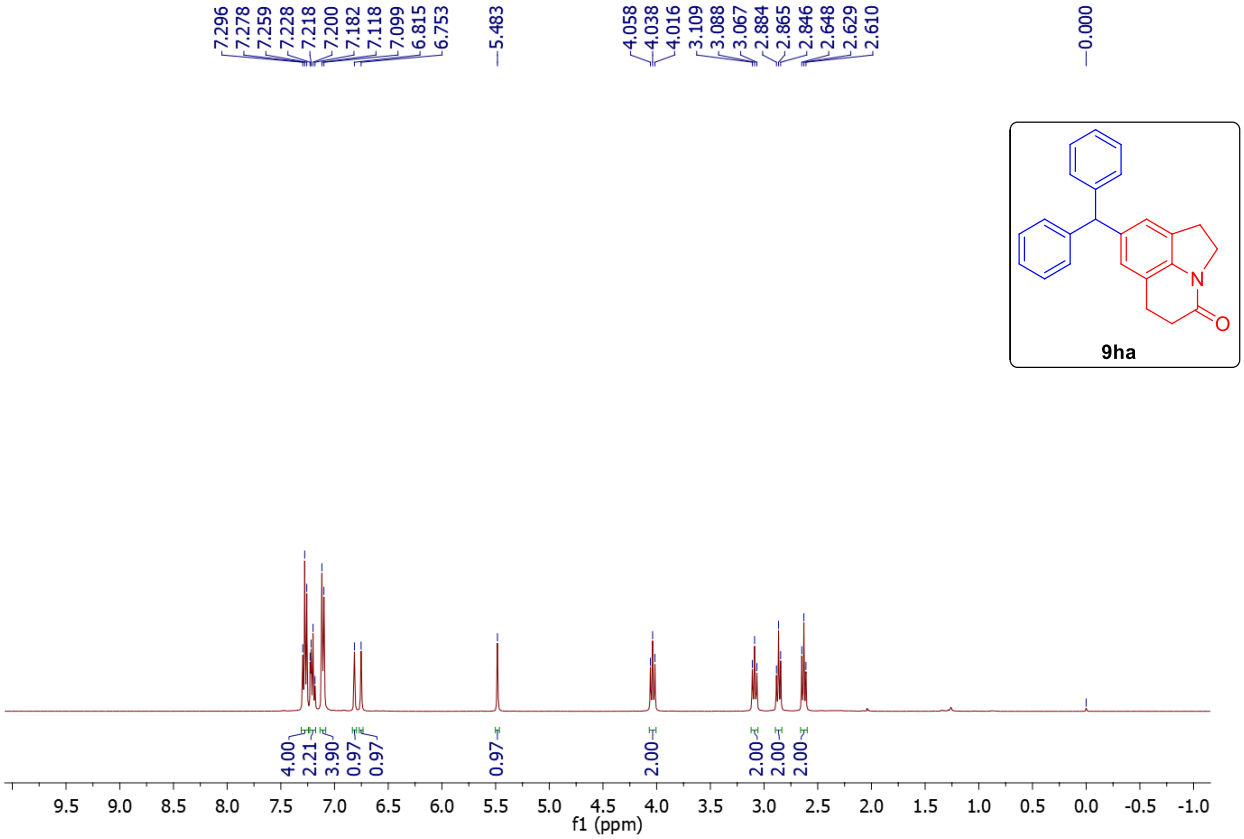
^{1}H NMR of 7ga' (400 MHz, $CDCl_3$)



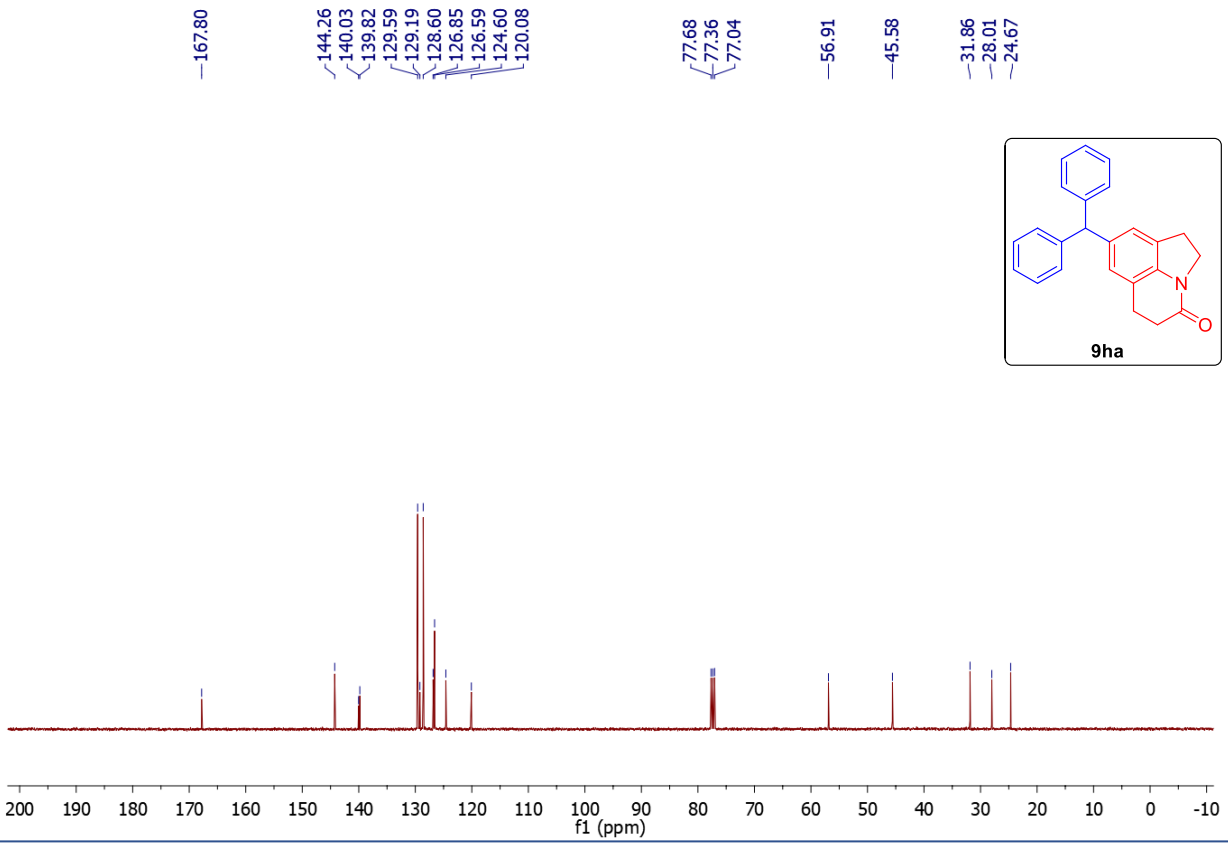
^{13}C NMR of 7ga' (176 MHz, $CDCl_3$)



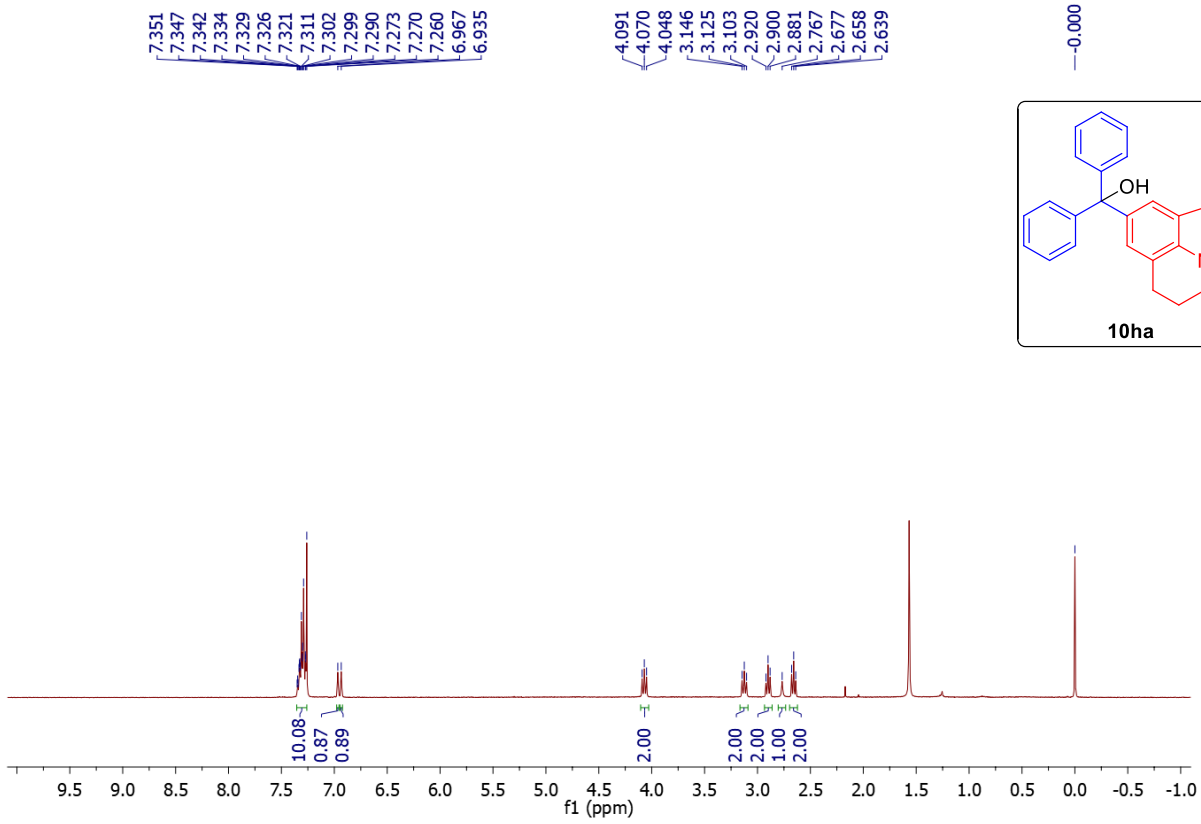
^{1}H NMR of 9ha (400 MHz, $CDCl_3$)



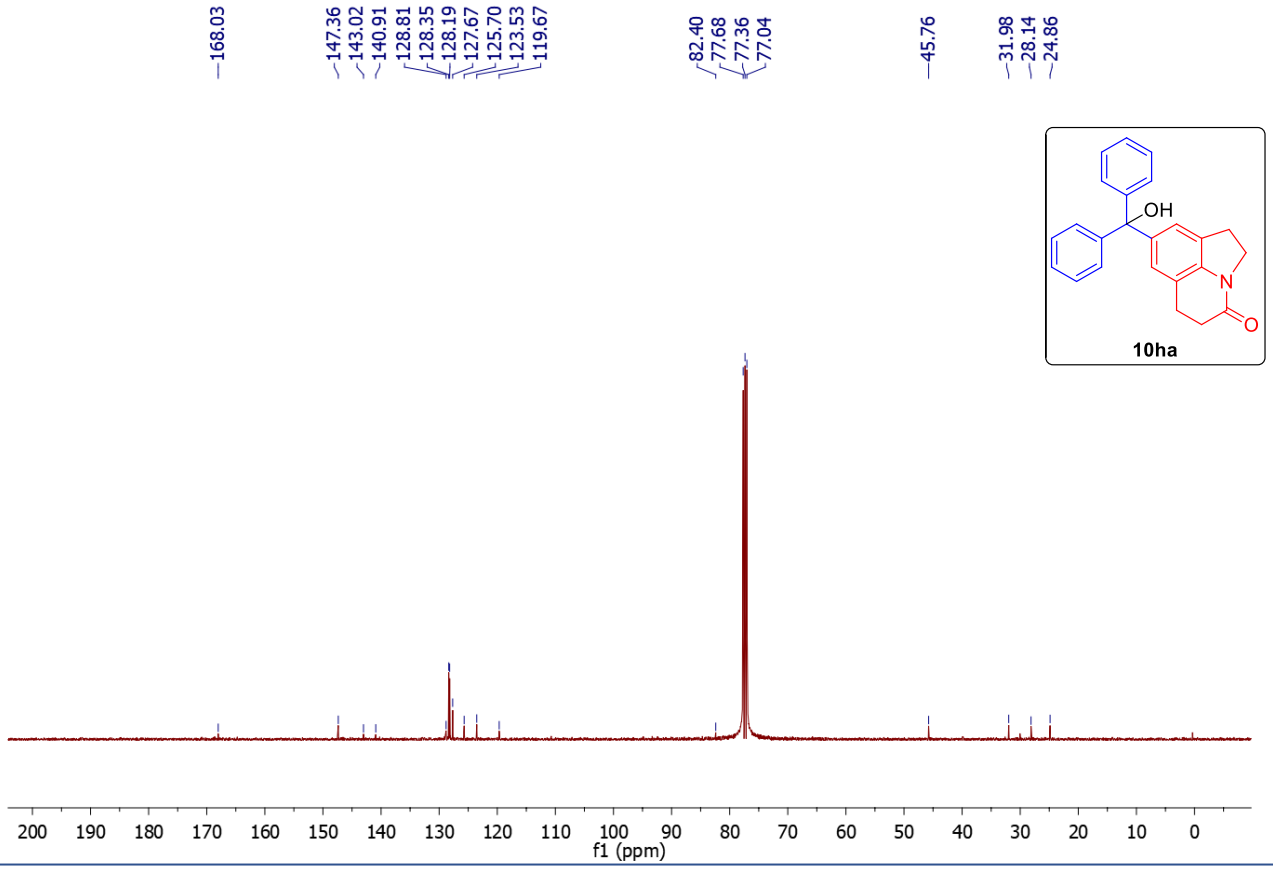
^{13}C NMR of 9ha (100 MHz, $CDCl_3$)



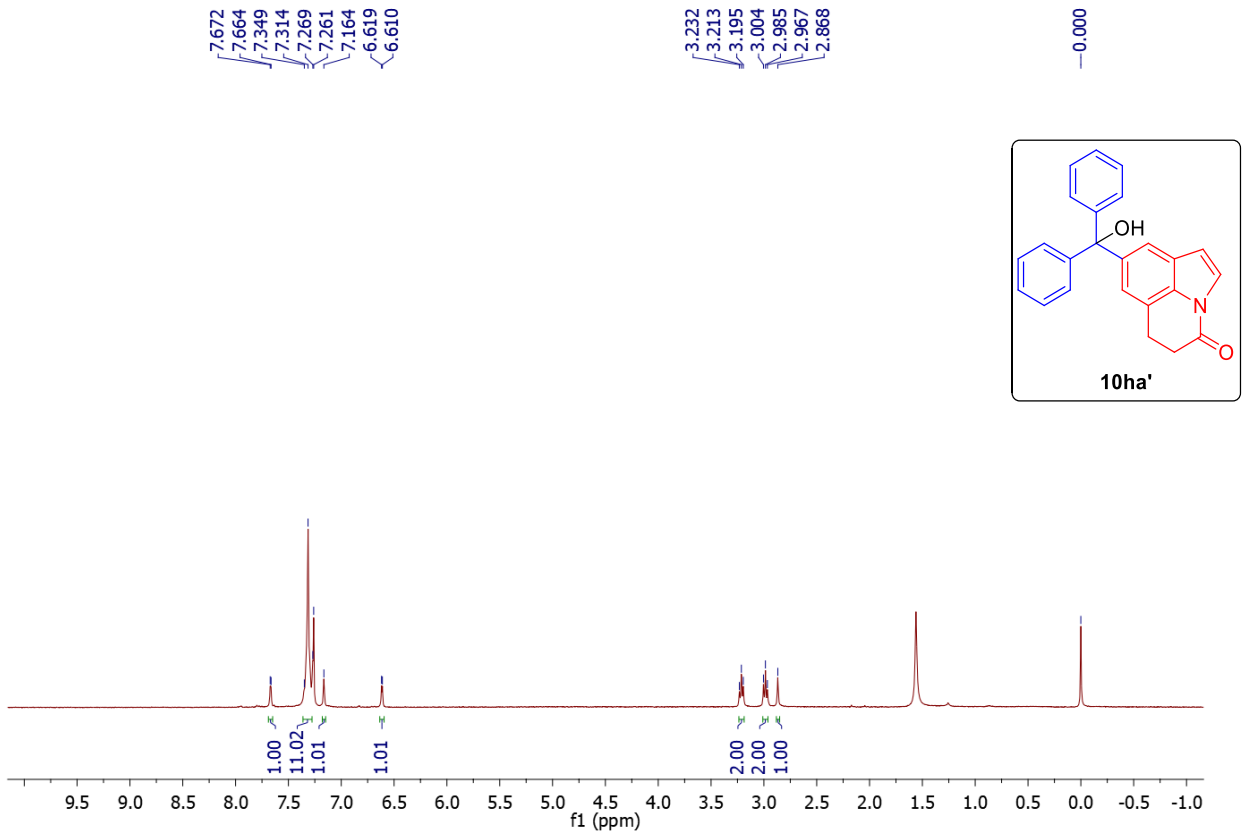
^{1}H NMR of 10ha (400 MHz, $CDCl_3$)



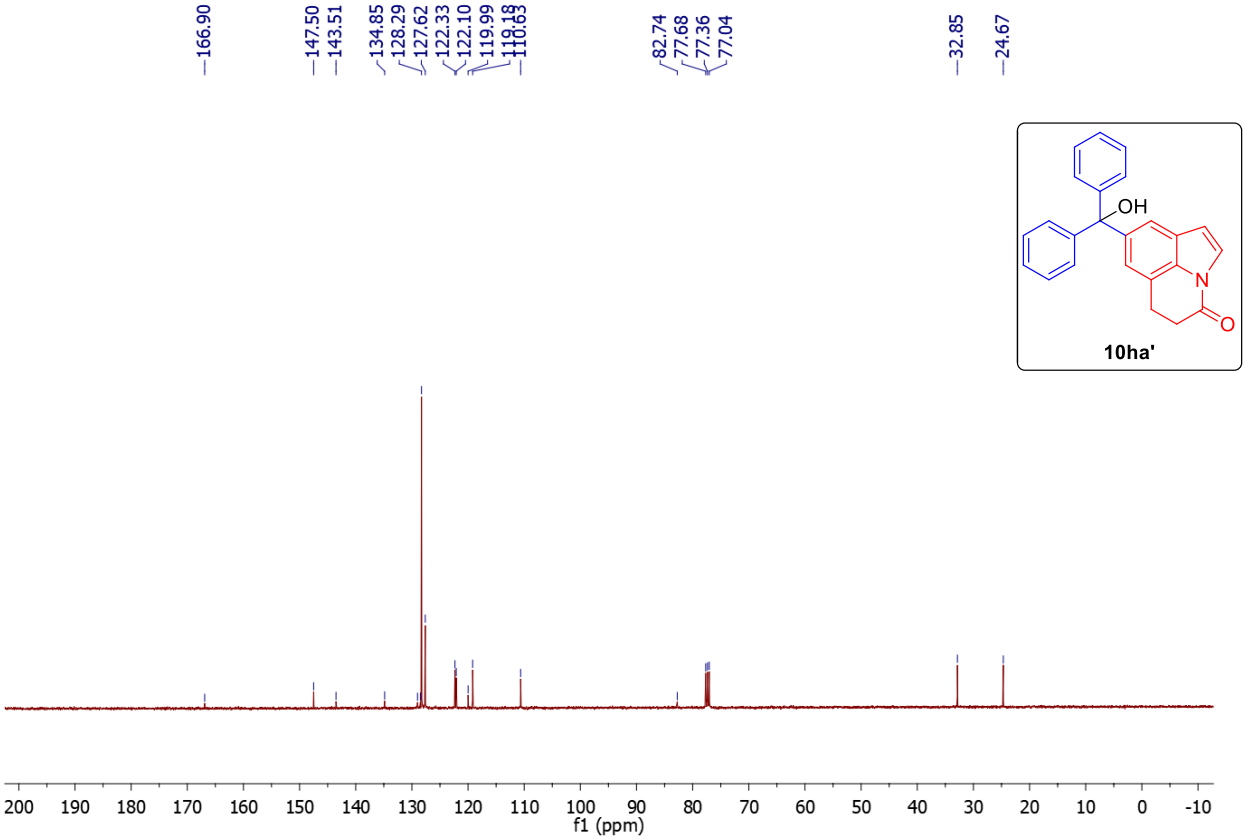
^{13}C NMR of 10ha (100 MHz, $CDCl_3$)



^{1}H NMR of 10ha' (400 MHz, $CDCl_3$)

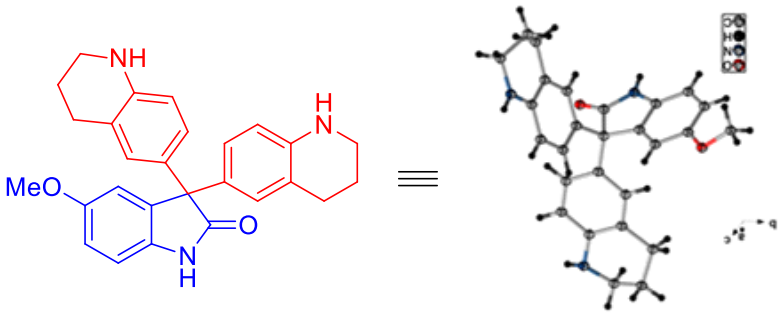


^{13}C NMR of 10ha' (100 MHz, $CDCl_3$)



5. X-ray data:

(a) X-ray data of 5-methoxy-3,3-bis(1,2,3,4-tetrahydroquinolin-6-yl)indolin-2-one (3aa):



3aa CCDC **2041963**

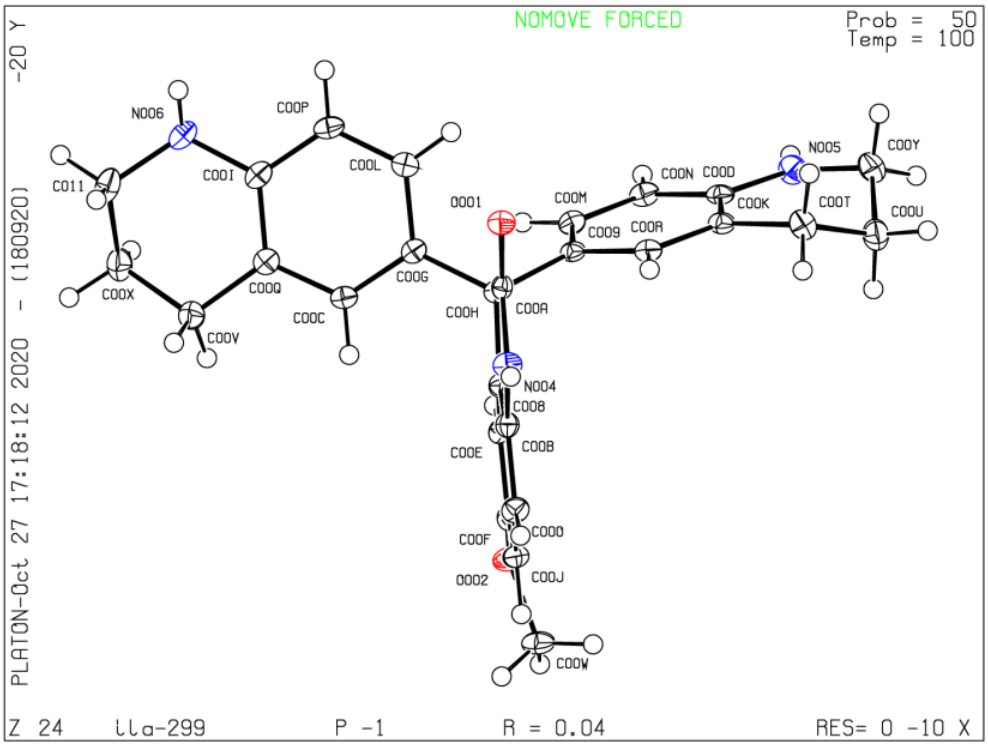
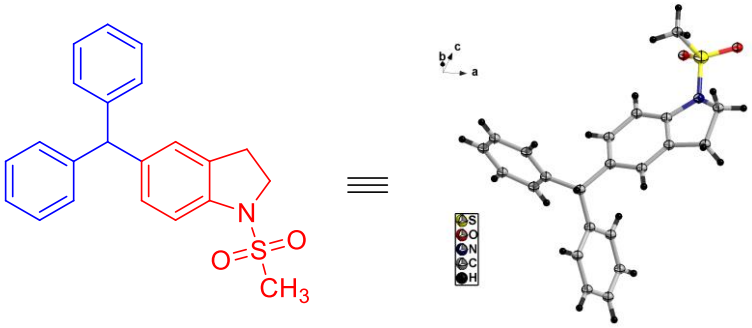


Table S2. Crystal data and structure refinement for 5-methoxy-3,3-bis(1,2,3,4-tetrahydroquinolin-6-yl)indolin-2-one **(3aa):**

	ila-299
Crystal data	
Chemical formula	$2(C_{27}H_{27}N_3O_2)$
M_r	851.03
Crystal system, space group	Triclinic, *P*
Temperature (K)	100

a, *b*, *c* (Å)	9.8262 (2), 10.2492 (2), 14.6317 (3)
α, β, γ (°)	95.916 (2), 102.954 (2), 111.833 (2)
V (Å^3)	1304.44 (5)
Z	1
Radiation type	Cu *K*α
μ (mm^{-1})	0.55
Crystal size (mm)	0.13 × 0.12 × 0.1
Data collection	
Diffractometer	SuperNova, Dual, Cu at home/near, Pilatus 200K
Absorption correction	Multi-scan *CrysAlis PRO* 1.171.40.63a (Rigaku Oxford Diffraction, 2019) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.892, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	19586, 4776, 4531
R_{int}	0.025
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.602
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.036, 0.091, 1.03
No. of reflections	4776
No. of parameters	290
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.25, −0.21

(b) X-ray data of 5-benzhydryl-1-(methylsulfonyl)indoline (6ga):



6ga CCDC **2041964**

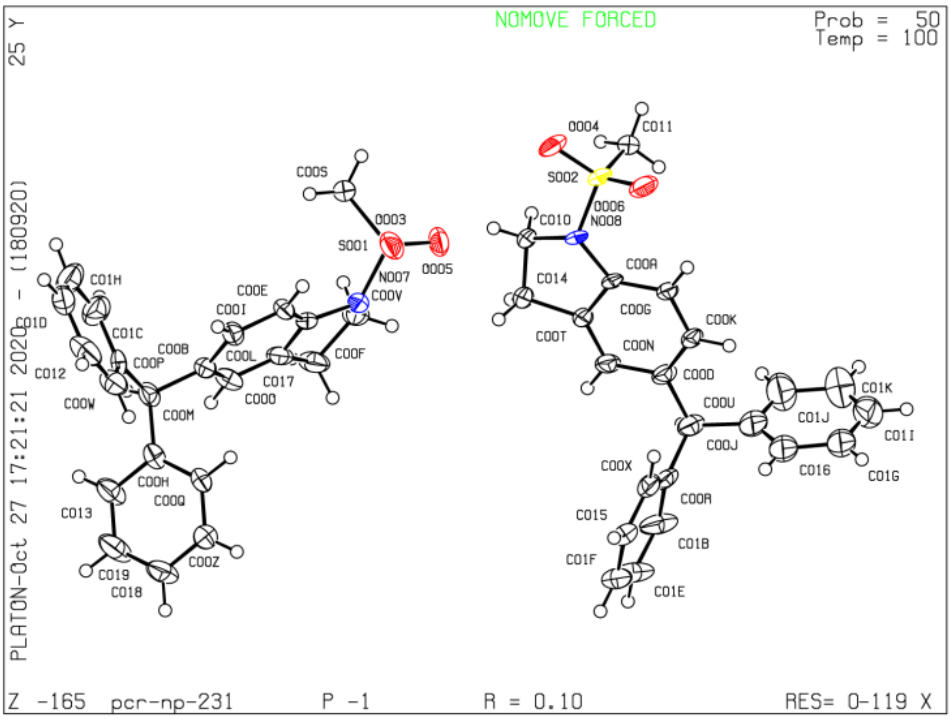


Table S3. Crystal data and structure refinement for 5-benzhydryl-1-(methylsulfonyl)indoline **(6ga):**

	pcr-np-231
Crystal data	
Chemical formula	$2(C_{22}H_{21}NO_2S)$
M_r	827.98
Crystal system, space group	Triclinic, *P*
Temperature (K)	100
a, *b*, *c* (Å)	11.5475 (3), 11.5869 (3), 16.7480 (3)
α, β, γ (°)	86.787 (2), 70.290 (2), 89.647 (2)
V (Å^3)	2106.08 (9)
Z	2
Radiation type	Cu *K*α
μ (mm^{-1})	1.60
Crystal size (mm)	0.13 × 0.12 × 0.1
Data collection	
Diffractometer	SuperNova, Dual, Cu at home/near, Pilatus 200K

Absorption correction	Multi-scan *CrysAlis PRO* 1.171.40.63a (Rigaku Oxford Diffraction, 2019) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.
T_{min}, T_{max}	0.403, 1.000
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	28843, 7581, 6925
R_{int}	0.114
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.602
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.100, 0.269, 1.03
No. of reflections	7581
No. of parameters	471
No. of restraints	36
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.93, −0.82