Supporting Information

Enantioselective Synthesis of 3-(*N*-Indolyl)quinolines Containing Axial and Central Chiralities

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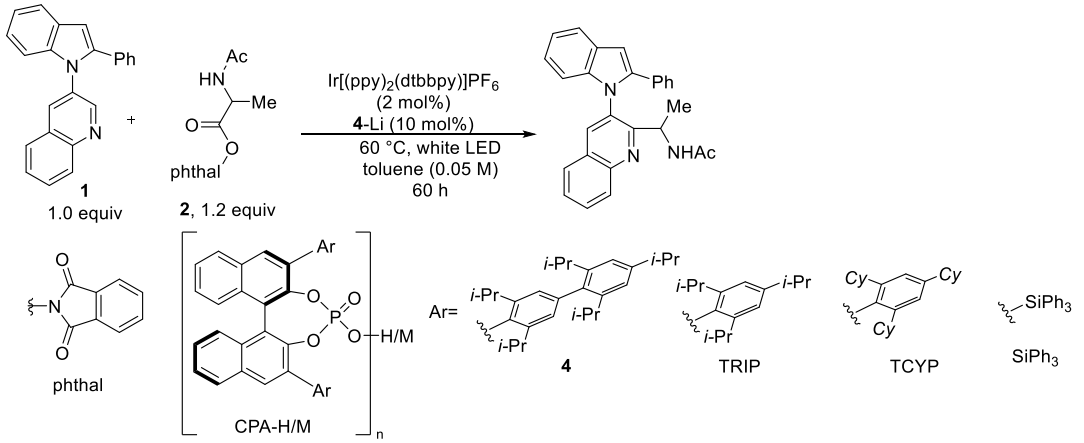
General information

NMR spectra were recorded using Bruker AVANCE-III (400 MHz for ^{1}H, 100 MHz for ^{13}C) and JEOL ECZ400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) spectrometer. Chemical shifts are reported in ppm using TMS or the residual solvent peak as a reference. ESI mass analyses were performed on Bruker micrOTOF mass spectrometer. Enantiomeric excesses were determined by HPLC analysis using chiral columns [4.6 mm x 250 mm, DAICEL CHIRALPAK IA-3, CHIRALPAK IB, CHIRALPAK ID, and CHIRALPAK IF-3 with hexane, 2-propanol (IPA), and ethanol as eluent. Emission spectra were recorded on a FP-6500 (JASCO Co., Ltd.). Cyclic Voltammetry was performed on VersaSTAT 4 (AMETEL Co., Ltd.). Visible light irradiation was performed with white LEDs (7.3W). Solvents were distilled according to the usual procedures and stored over molecular sieves.

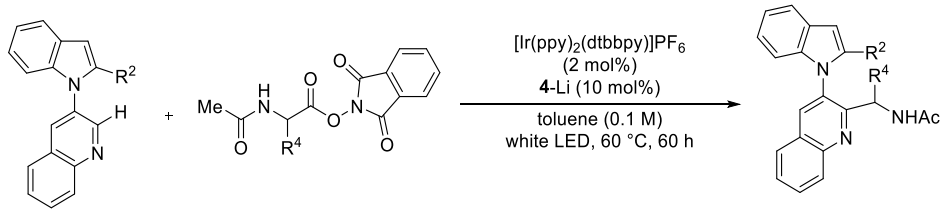
1. Screening of reaction conditions



entry	deviation from the standard conditions	yield (%)	dr	ee (%)
1	None	92	20:1	96
2	TRIP-H instead of **4**-Li	42	20:1	87
3	TRIP-Li instead of **4**-Li	91	20:1	90
4	TRIP-Na instead of **4**-Li	<10	–	–
5	TRIP-K instead of **4**-Li	trace	–	–
6	TRIP-Mg instead of **4**-Li	21	12:1	20
7	TRIP-Ca instead of **4**-Li	37	12:1	34
8	TCYP-Li	30	11:1	69
9	$SiPh_3$-Li	92	8:1	21
10	Ir[(dFCF$_3$ppy)$_2$(dtbbby)]PF$_6$ instead of Ir[(ppy)$_2$(dtbbby)]PF$_6$	88	19:1	88
11	4CzIPN instead of Ir[(ppy)$_2$(dtbbby)]PF$_6$	65	14:1	84
12	room temperature	<5	–	–
13	no Ir or no CPA-Li or light	0	–	–

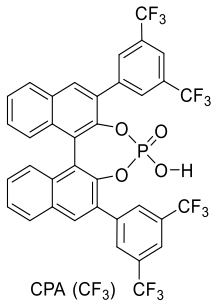
The combination of lithium phosphate and Ir[(bpy)2(dtbbpy)]PF_6 is crucial for achieving the high chemo-, regio-, and stereoselectivities because indole moiety is sensitive to oxidation conditions and has nucleophilic C2-carbon. For instance, the crude reaction mixture was contaminated with some byproducts when Ir[($dFCF_3ppy)_2$(dtbbby)]PF_6 ($E_{1/2}$red (*Ir(III)/Ir(II) = +1.21 V vs SCE) or 4CzIPN ($E_{1/2}$red (*PC/PC) = +1.43 V vs SCE) was used rather than Ir[$(bpy)_2$(dtbbpy)]PF_6 ($E_{1/2}$red (*Ir(III)/Ir(II) = +0.95 V vs SCE).[1] When TRIP-Mg and TRIP-Ca was used instead of TRIP-Li, over 95% of conversion was observed, and the crude reaction mixture was messy, which afforded the desired product in low yield and with low stereoselectivity. The regioselective Minisci-type addition reaction of heteroarenes is not always easy; mixtures of C2- and C4-substituted products were often obtained when quinoline was used as the substrate. Phipps and co-workers explored the effect of acid and solvent.[2,3] In our investigation, C4-adduct was also detected.

2. General procedure for **4**-Li-catalyzed radical addition reaction

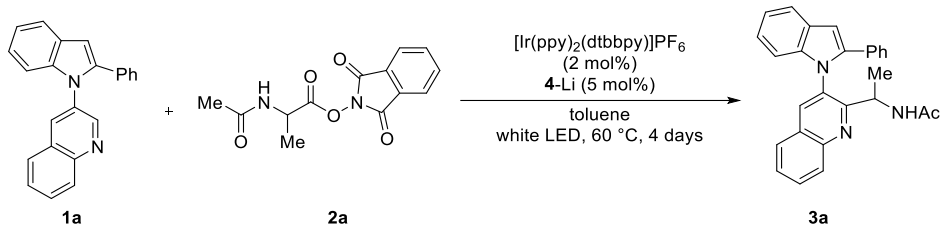


Sequentially, 3-arylquinoline (0.05 mmol), phthalimide ester (0.06 mmol), Ir[$(ppy)_2$(dtbbpy)]PF_6 (2 mol%), **4**-Li (10 mol%) and toluene (0.5 mL) were added to a 20 mL test tube containing a stirrer bar. The mixture was subjected to freeze-pump-thaw process (3 cycles), and back-filled with N_2. The mixture was irradiated with white LED at 60 ºC for 60 h. After being exposed to air, the reaction mixture was concentrated and purified by preparative TLC on SiO_2 (hexane: benzene: ethyl acetate = 40 : 20 : 40) to give the corresponding adduct.

Racemic product was prepared by using a 1:1 mixture of (*R*)- and (*S*)-CPA (CF_3).



3. 1 g scale reaction

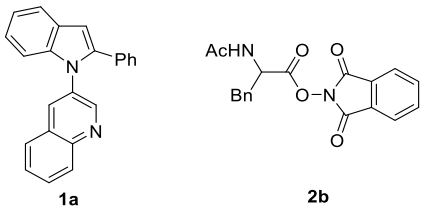


1a **2a** **3a**

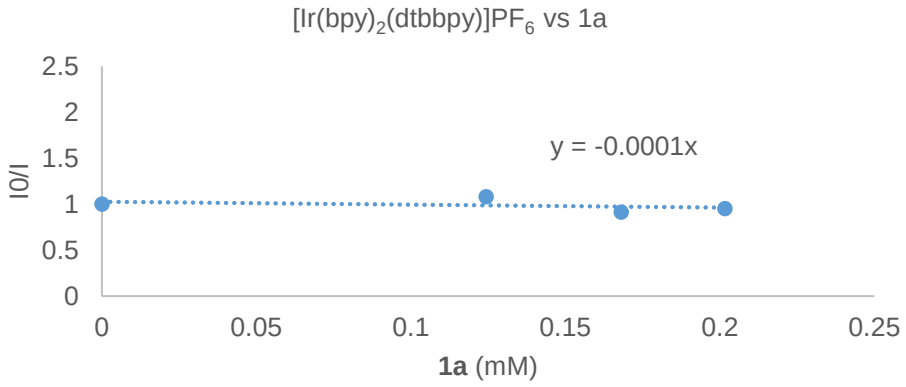
A mixture of quinoline **1a** (1.024 g, 3.19 mmol), redox-active ester **2a** (1.05 g, 3.81 mmol), $Ir[(ppy_2)(dtbppy_3)]PF_6$ (2 mol%), and CPA-Li (5 mol%) in toluene (64 mL) was subjected to freeze-pump-thaw process, and filled back with N_2 (3 cycles). The reaction mixture was stirred at 60 ºC for 4 days under white LEDs irradiation conditions (7 W x3), and concentrated under reduced pressure. The following purification by silica gel column chromatography on SiO_2 (hexane : ethyl acetate = 3 : 1 – 1 : 1, including 5% toluene) gave the corresponding adduct **3a** in 84 % yield (1.09 g, 2.68 mmol) as a white solid.

4. Quenching experiments

Stern-Volmer quenching experiments: Stern-Volmer quenching experiments were conducted on a FP-6500 (JASCO Co., Ltd.). All solutions were deaerated with N_2 bubbling prior to each measurement. The emission from $Ir(ppy)_2(dtbbpy)PF_6$ was recorded at 525 nm upon excitation at 420 nm.



1a **2b**



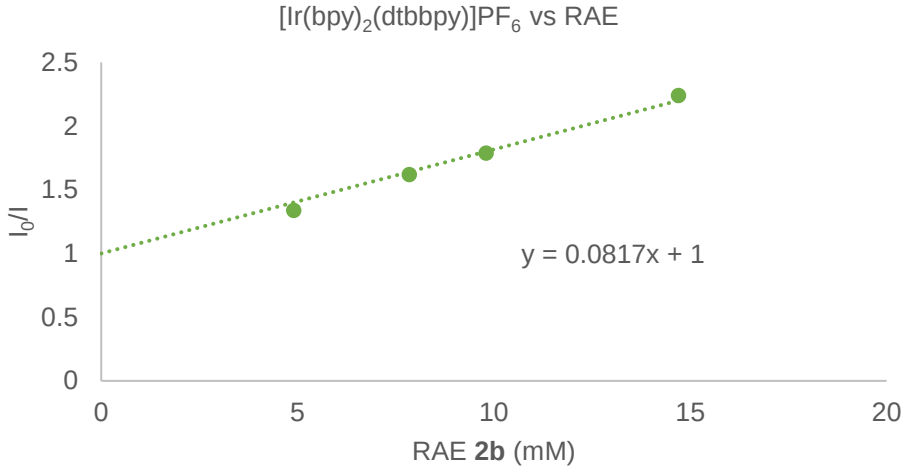
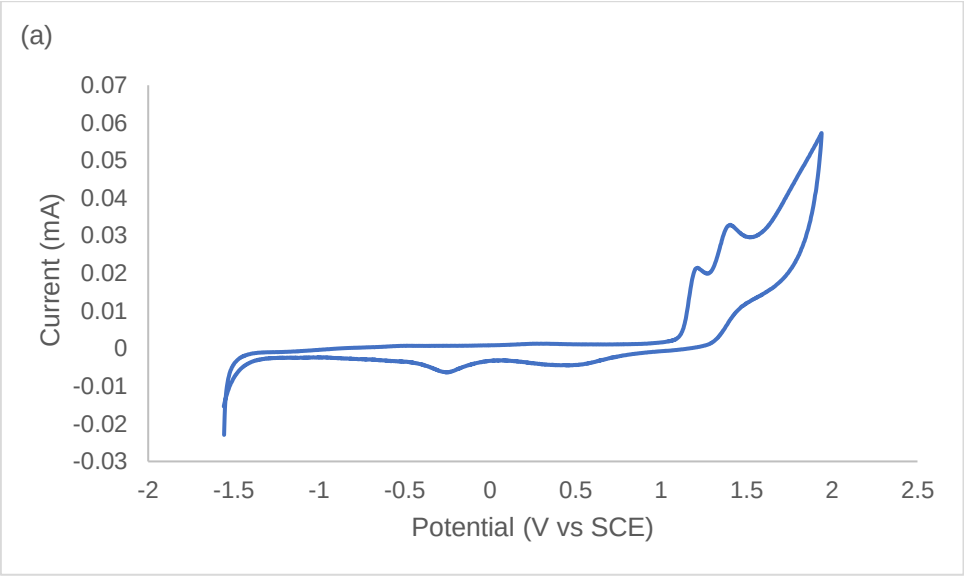
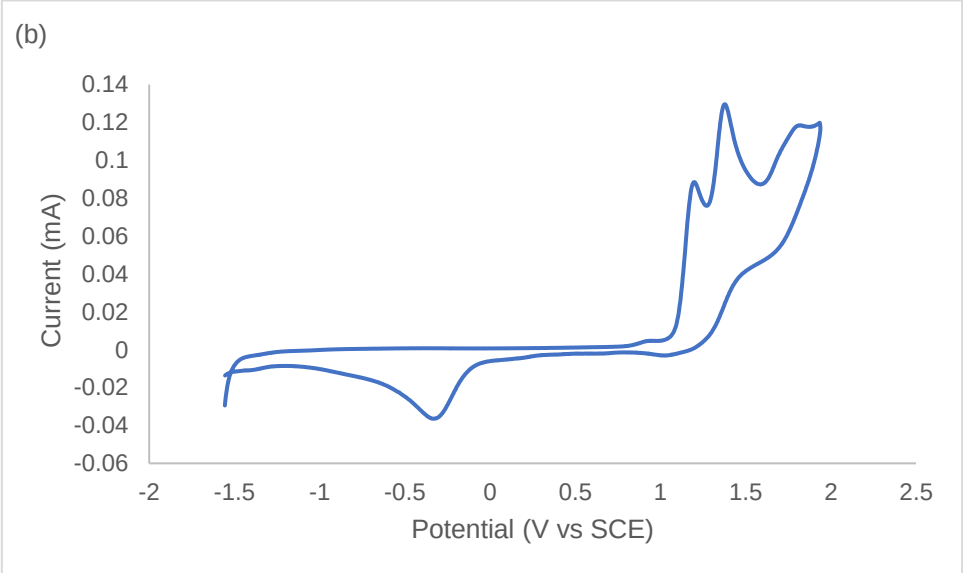


Figure S1. Stern-Volmer quenching plots of (a) $Ir(ppy)_2(dtbbpy)PF_6$ quenched with varying concentration of **1a** (blue) and **2b** (green).

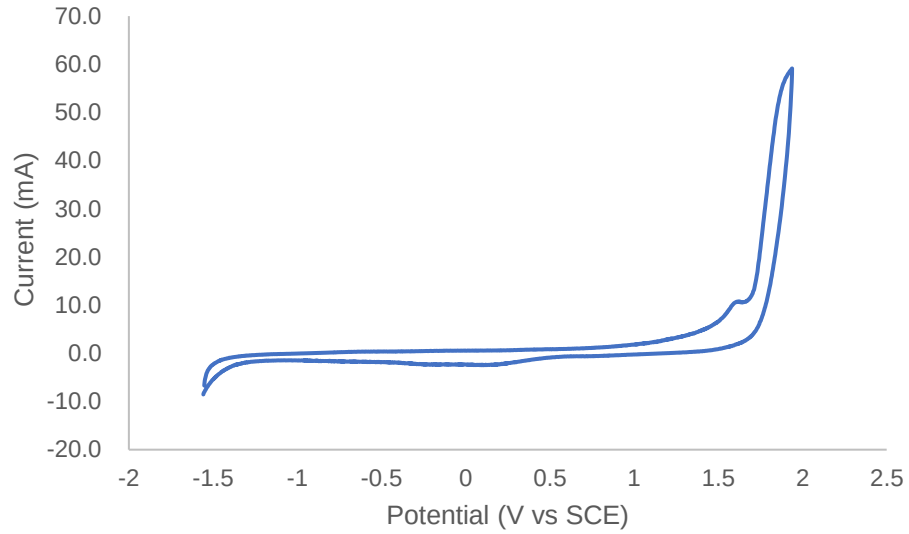
5. Cyclic voltammetry

Cyclic voltammetry: CV measurement were performed on an VersaSTAT 4 (AMETEL Co., Ltd.). The voltametric cell consisted of a $Ag/AgNO_3$ reference electrode, a platinum counter and working electrode. The measurements were carried out under N_2 using a sample solution of a concentration of 1.0 mM in MeCN containing tetrabutylammonium hexafluorophosphate as a supporting electrolyte (0.1 mM). The scan rate was 100 $mV \cdot s^{-1}$. The obtained potentials were calibrated to the saturated calomel electrode (SCE) scale with ferrocene/ferrocenium ion couple.

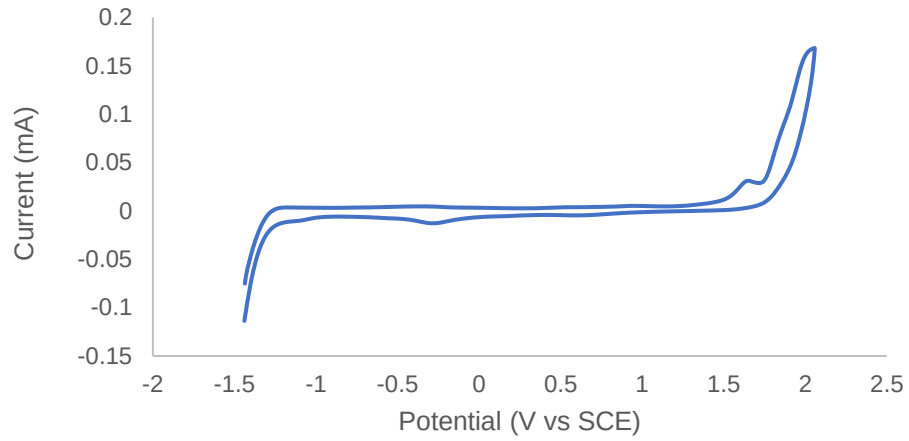




(c)


70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
-10.0
-20.0
Current (mA)
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
2.5
Potential (V vs SCE)

(d)


0.2
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
Current (mA)
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
2.5
Potential (V vs SCE)

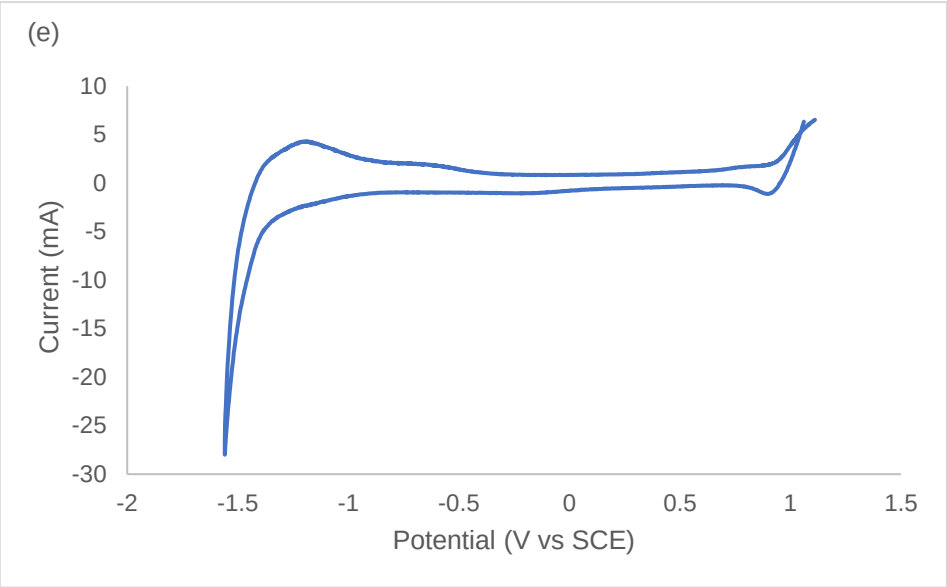
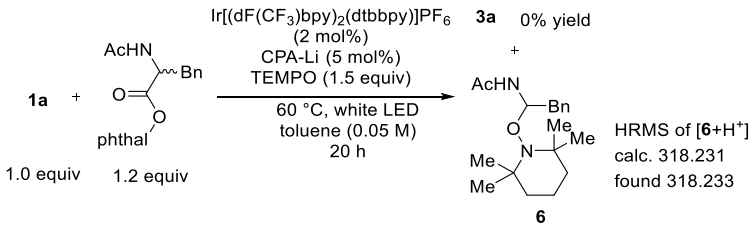


Figure S2. (a) **1a** (b) **1a** and TRIP-Li (c) **2b** (d) **2b** and TRIP-Li (e) TRIP-Li

6. Radical-Trapping experiment



Sequentially, **1a** (0.05 mmol), redox-active ester (0.06 mmol), Ir[(dF(CF_3)ppy_2)(dtbbpy)]PF_6 (2 mol%), CPA-Li (5 mol%), TEMPO (1.5 equiv) and toluene (0.5 mL) were added to a 20 mL test tube containing a stirrer bar. The mixture was subjected to freeze-pump-thaw process (3 cycles), and back-filled with N_2. The mixture was irradiated with white LED at room temperature for 40 h. After exposing to air and the reaction mixture was concentrated. The corresponding product **3a** was not observed in the crude reaction mixture, and [**6**+H^+] was detected by ESI-MS.

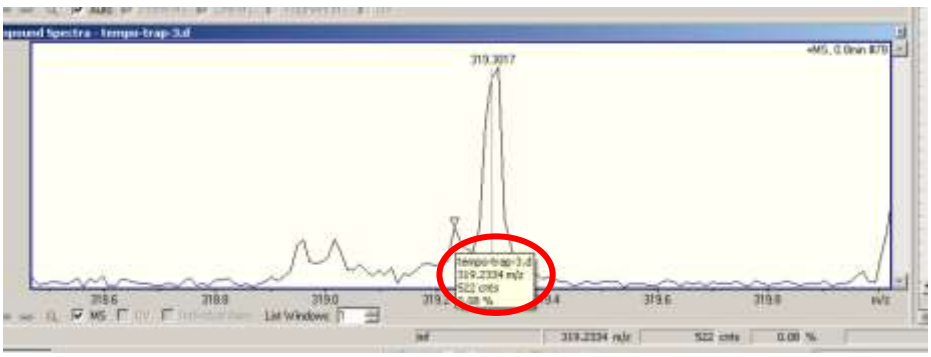
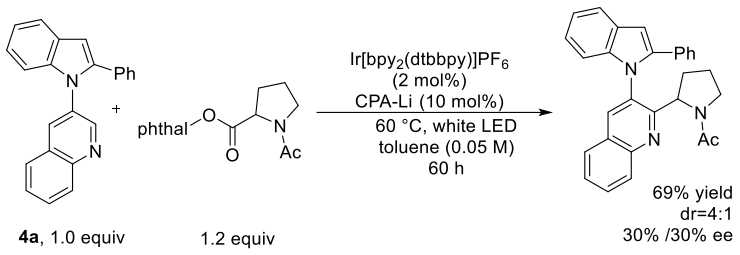


Figure S3. MS spectrum of **6**.

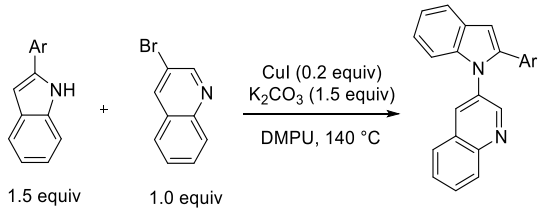
7. Minisci reaction with proline-derived redox active ester



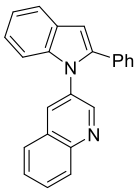
The reaction was conducted by following the general procedure described above. The diastereoselectivity was determined by ^{1}H NMR spectrum analysis, and ee was determined by HPLC using DAICEL® CHIRAL IA3 (hexane/2-propanol=95/5)

8. Synthesis of substrates

Redox-active esters were prepared according to the literature procedure[4]. 3-(*N*-indolyl)quinolines were prepared by the following procedure.

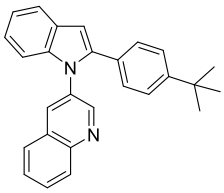


In a 20 mL two-neck flask under N_2 atmosphere, 2-arylindole (1.5 equiv), 3-bromoquinoline (1.0 equiv) K_2CO_3 (1.5 equiv) and CuI (0.2 equiv) were dissolved in *N*,*N*'-dimethylpropyleneurea (DMPU, 0.5 M), and stirred for 14 h at 140 ºC. The reaction mixture was cooled to rt, filtered through a pad of celite and washed with EtOAc. To the obtained brown residue was added 5% NH_3 aq. and extracted with ethyl acetate (x3). The organic layer was washed with brine and dried over Na_2SO_4, filtrated and evaporated. The residue was purified by column chromatography on SiO_2 (hexane : ethyl acetate = 95 : 5 – 90 : 10) to afford 3-(*N*-indolyl)quinoline.



1a

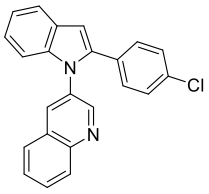
39% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (1H, s), 8.16–8.11 (2H, m), 7.82–7.72 (3H, m), 7.63–7.60 (1H, m), 7.33–7.21 (8H), 6.89 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 146.6, 140.8, 139.0, 133.1, 132.2, 131.8, 129.8, 129.5, 129.1, 128.6, 128.5, 127.8, 127.5, 122.9, 121.3, 120.9, 110.1, 104.7; HRMS (ESI) Calcd for $C_{23}H_{16}N_2$ ([M+Na]$^+$) 343.121. Found 343.1223.



1b

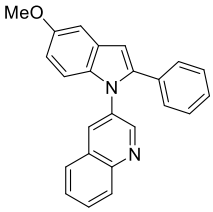
47% yield, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (1H, d, *J*= 2.3 Hz), 8.16–8.14 (2H, m), 7.83 (1H, d, *J*= 8.2 Hz), 7.77 (1H, d, *J*= 7.5 Hz), 7.71 (1H, d, 8.2 Hz), 7.61 (1H, dd, *J*= 7.2, 7.5 Hz), 7.30–7.19 (4H, m), 6.85 (1H, s), 1.23 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 150.4, 146.6, 140.9, 139.1, 133.1, 132.4, 129.9, 129.6, 128.9, 128.7, 127.9, 127.5, 125.6, 122.7,

121.3, 120.8, 110.1, 104.5, 34.6, 31.2; HRMS (ESI) Calcd for $C_{27}H_{24}N_2$ ([M+H]$^+$) 538.2858. Found 538.2849



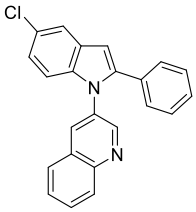
1c

70% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (1H, s), 8.14 (1H, d, *J*= 2.2 Hz), 8.04 (1H, s), 7.77–7.68 (3H, m), 7.59–7.55 (1H, m), 7.28–7.26 (5H, m), 6.84 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.7, 139.5, 139.2, 133.9, 133.2, 132, 130.4, 130.2, 130.1, 129.6, 129.5, 128.9, 128.6, 127.9, 127.8, 127.7, 123.3, 121.6, 121.1, 110.3, 105.2, 77.5, 77.2, 76.9; HRMS (ESI) Calcd for $C_{23}H_{15}ClN_2$ ([M+H]$^+$) 354.0924. Found 354.0927



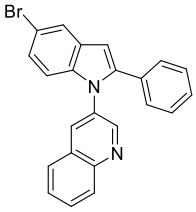
1d

39% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (1H, d, *J*= 2.2 Hz), 8.01 (1H, d, *J*= 8.4 Hz), 8.12 (1H, d, *J*= 2.2 Hz), 7.73–7.67 (2H, m), 7.54 –7.51 (1H, m), 7.24 –7.14 (6H, m), 6.84 (1H, dd, *J*= 2.4, 8.9 Hz), 6.77 (1H, s), 3.84 (3H, s);^{13}C NMR (100 MHz, CDCl3) δ 155.4, 150.2, 146.6, 141.4, 134.4, 132.9, 132.4, 132, 129.9, 129.6, 129.2, 129.1, 128.6, 127.9, 127.9, 127.8, 127.6, 113, 111.1, 104.7, 102.6, 55.9; HRMS (ESI) Calcd for $C_{24}H_{18}N_2O_1$ ([M+H]$^+$) 373.1497. Found 373.1481.



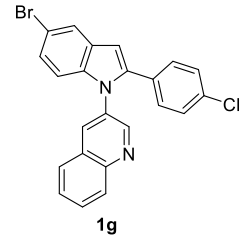
1e

7% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (1H, d, *J*= 2.3 Hz), 8.16 (1H, d, *J*= 8.7 Hz), 8.08–8.05 (1H, m), 7.81–7.75 (2H, m), 7.68–7.65 (1H, m), 7.61 (1H, d, *J*= 7.5 Hz), 7.27–7.13 (m), 6.80 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 146.8, 142.2, 137.5, 133.2, 131.8, 131.4, 130.2, 129.7, 129.6, 129.1, 128.7, 128.2, 127.9, 127.8, 127.7, 126.9, 123.1, 120.3, 111.3, 104.2, 55.9; $C_{23}H_{15}ClN_2$; HRMS (ESI) Calcd for $C_{23}H_{15}ClN_2$ ([M+Na]$^+$) 377.0828. Found 377.0839



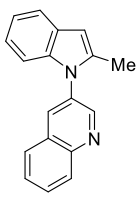
1f

58% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (1H, d, *J*= 2.3 Hz), 8.14 (1H, d, *J*= 8.4 Hz), 8.06 (1H, m), 7.82–7.74 (3H, m), 7.60 (1H, dd, *J*= 7.0, 7.4 Hz), 7.27–7.11 (7H, m), 6.79 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 146.7, 142, 137.7, 133.1, 131.7, 131.3, 130.2, 130.1, 129.5 (2C), 129.1 (2C), 128.6, 128.1, 127.8, 127.7, 127.7, 125.6, 123.3, 114.4, 111.6, 103.9; HRMS (ESI) Calcd for $C_{23}H_{15}BrN_2$ ([M+H]$^+$) 399.0497. Found 399.0490



1g

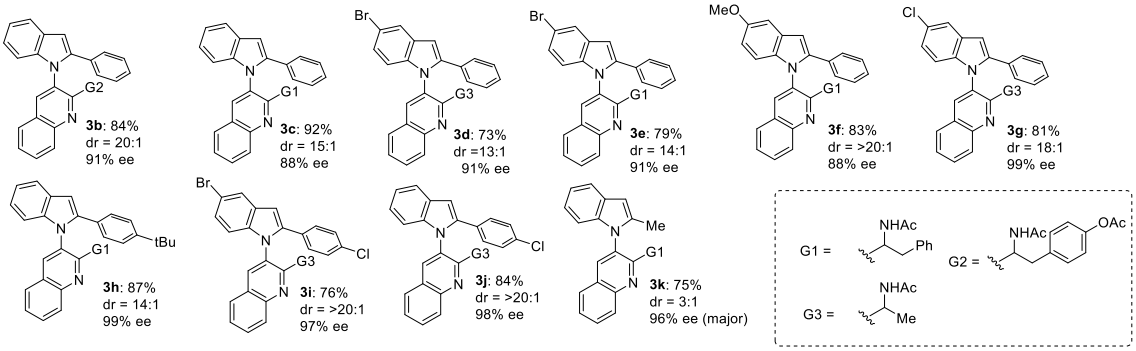
38 % yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (1H, d, *J*= 2.3 Hz), 8.16 (1H, d, *J*= 8.7 Hz), 8.08 (1H, d, *J*= 2.3 Hz), 7.84–7.78 (3H, m), 7.66–7.62 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.7, 139.5, 139.2, 133.9, 133.2, 132.0, 130.4, 130.2, 130.1, 129.6, 128.9, 128.6, 127.9, 127.8, 127.7, 123.3, 121.6, 121.1, 110.3, 105.2; $C_{23}H_{15}BrClN_2$ 432.0029. Found 432.00.30



1g

68% yield. white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (1H, d, *J*= 2.4 Hz), 8.23 (1H, d, *J*= 8.4 Hz), 8.17, (1H, d, *J*= 2.2 Hz), 7.89 (1H, d, *J*= 8.0 Hz), 7.82 (1H, dd, *J*= 8.4, 8.3 Hz), 7.66 (1H, dd, *J*= 7.1, 7.0 Hz), 7.60 (1H, d, *J*= 7.0 Hz), 7.11 (1H, d, *J*= 4.6 Hz), 7.17–7.11 (3H, m), 6.49 (1H, s), 2.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 147.1, 138.3, 137, 133.7, 131.5, 130.1, 129.5, 128.5, 127.9, 127.8, 127.6, 121.6, 120.6, 119.9, 109.6, 102.5, 13.4; HRMS (ESI) Calcd for $C_{18}H_{14}N_2$ ([M+Na]$^+$) 281.1055. Found 281.1019.

9. Chemical data of products



3a: 92% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.38 (1H, s), 8.11 (1H, d, *J*= 8.2 Hz), 7.91 (1H, d, *J*= 8.2 Hz), 7.81 (1H, m), 7.91 (1H, d, *J*= 7.3 Hz), 7.82 (1H, m), 7.20–7.13 (5H, m), 6.79 (1H, d, *J*= 8.2 Hz), 6.89 (1H, s), 6.85 (1H, *J*= 6.4 Hz), 4.81 (1H, m), 1.83 (3H, s), 0.91 (3H, d, *J*= 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 160.1, 146.8, 141, 139.6, 137.2, 134.2, 131.7, 130.6, 129.8, 129, 128.9, 128.5, 128.2, 127.7, 127.6, 127.4, 127.3, 123.5, 122.7, 121, 121, 109.9, 104.4; HRMS (ESI) Calcd for $C_{27}H_{23}N_3O$ ([M+H]$^+$) 406.5059. Found 406.5059. $[\alpha]_D^{23}$ 394.5 (c 2.4, $CHCl_3$) dr=20:1; HPLC ID, hexane/IPA = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, 79.2 min (major enantiomer), 97.6 min (minor enantiomer).

3b: 84 % yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.26 (1H, s), 7.99 (1H, d, *J*= 8.4 Hz), 7.84 (1H, d, *J*= 8.4 Hz), 7.84 (1H, d, *J*= 8.1 Hz), 7.74 (1H, d, *J*= 7.5, 7.4 Hz), 7.59 (1H, d, *J*= 7.6, 7.5 Hz), 7.16–7.14 (2H, m), 7.08–7.04 (4H, m), 6.87 (1H, dd, *J*= 7.9, 7.8 Hz), 6.77–6.73 (3H, m), 6.56 (1H, dd, *J*= 8.8, 2.4 Hz), 6.36 (1H, d, *J*= 7.2 Hz), 6.32 (1H, d, *J*= 8.8 Hz), 6.07 (1H, d, *J*= 7.6 Hz), 4.91–4.86 (1H, m), 2.59 (3H, s), 2.80, (1H, dd, *J*= 13.0, 8.2 Hz), 2.58 (1H, dd, *J*= 13.0, 5.3 Hz), 1.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 158.3, 154.9, 146.7, 141.3, 136.5, 136.2, 134.8, 131.9, 131.0, 130.4, 129.6, 129.3, 129.0, 128.9, 128.8, 128.7, 128.5, 128.2, 127.8, 127.7, 127.4, 127.4, 127.2; HRMS (ESI) Calcd for $C_{35}H_{30}N_3O_3$ ([M+H]$^+$) 540.2287. Found 540.2250. $[\alpha]_D^{23}$ 378.8 (c 2.0, $CHCl_3$), dr=15:1; HPLC IF-3, hexane/IPA = 9:1, flow rate = 1.0 mL/min, λ = 254 nm, 36.2 min (major enantiomer of major diastereomer), 43.9 min (minor enantiomer of major diastereomer). 50.7 min (minor diastereomer).

3c: 92% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.36 (s, 1H), 8.06 (1H, d, *J*= 8.4 Hz),7.92 (1H, d, *J*= 8.0 Hz),7.81 (1H, m), 7.68 (2H, dd, *J*= 8.3, 8.1 Hz), 7.25–7.22 (3H, m), 7.26–7.19 (5H, m), 7.05–6.90 (3H, m),

6.54 (1H, d, *J*= 8.1 Hz), 6.42 (2H, d, *J*= 7.1 Hz), 6.17 (1H, d, *J*= 7.6 Hz), 4.98 (1H, dd, *J*= 7.6, 5.1 Hz), 2.84 (1H, dd, *J*= 13.0, 6.1 Hz), 2.64 (1H, dd, *J*= 13.0, 7.6 Hz), 1.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 158.3, 146.8, 140.8, 139.4, 136.5, 136.4, 131.9, 130.8, 130.5, 129.6, 129.3, 129.1, 129.0, 128.4, 128.2, 127.8, 127.5, 127.3, 126.1, 122.9, 121.1, 120.9, 120.7, 110.1, 104.6, 77.4, 77.3, 77.1, 76.7, 51.4, 41.6, 23.4; HRMS (ESI) Calcd for $C_{33}H_{28}N_3O$ ([M+H]+) 482.2232. Found 482.2221. $[\alpha]_D^{23}$ 336.1 (c 2.4, $CHCl_3$), dr=13:1; HPLC ID, hexane/IPA = 9:1, flow rate = 1.0 mL/min, λ = 254 nm, 15.0 min (major enantiomer), 17.2 min (minor enantiomer).

3d: 83% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.35 (1H, s), 8.11 (1H, d, *J*= 8.7 Hz), 7.92 (1H, d, *J*= 7.8 Hz), 7.85–7.80 (H, m), 7.66 (H, dd, *J*= 8.2, 7.8 Hz), 7.24–7.21 (H, m), 7.15–7.12 (H, m), 6.87–6.80 (2H, m), 6.83 (1H, s), 4.77 (1H, m), 1.83 (3H, s), 0.91 (3H, d, *J*= 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 159.9, 147.0, 142.3, 138.3, 137.2, 131.2, 130.9, 130.2, 129.4, 129.1, 129.0, 128.7, 128.4, 128.1, 127.8, 127.6, 127.4, 127.3, 125.5, 123.5, 114.3, 112, 111.5, 103.8, 46.3, 23.4; HRMS (ESI) Calcd for $C_{33}H_{26}N_3ONa$ ([M+Na]$^+$) 506.0844. Found 586.0849. $[\alpha]_D^{23}$ 338.8 (c 1.1, $CHCl_3$), dr=13:1; HPLC IB, hexane/IPA = 9:1, flow rate = 1.0 mL/min, λ = 254 nm, 11.2 min (minor enantiomer of major diastereomer), 12.3 min (minor enantiomer of minor diastereomer). 14.0 min (major enantiomer of major diastereomer), 15.5 min (major enantiomer of minor diastereomer).

3e: 79% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.31 (1H, s), 8.11 (1H, d, *J*= 8.2 Hz), 7.92 (1H, d, *J*= 12.3 Hz), 7.87–7.83 (1H, m), 7.79 (1H, s), 7.70–7.66 (m, 2H), 7.22–7.12 (4H, m), 7.01–6.93 (2H, m), 6.82–6.78 (1H, m), 6.42 (1H, d, *J*= 7.3 Hz), 6.23 (d, *J*= 8.6 Hz), 6.07 (1H, d, *J*= 7.8 Hz), 4.90–4.84 (1H, m), 2.86 (1H, dd, *J*= 12.8, 8.6 Hz), 2.74 (1H, dd, *J*= 12.8, 4.5 Hz), 1.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 158.2, 147, 142, 138.1, 136.4, 136.2, 131.3, 130.7, 130.5, 129.8, 129.1, 129, 128.3, 127.9, 127.8, 127.7, 127.2, 126.3, 125.7, 122.9, 113.9, 111.4, 103.7, 51.6, 41.9, 23.4; HRMS (ESI) Calcd for $C_{33}H_{26}BrN_3O$ ([M+H]$^+$) 560.1388. Found 560.1410. $[\alpha]_D^{23}$ 344.9 (c 1.5, $CHCl_3$), dr=14:1; HPLC IA-3, hexane/ethanol = 9:1, flow rate = 1.0 mL/min, λ = 254 nm, 11.2 min (minor enantiomer of major diastereomer), 14.0 min (major enantiomer of major diastereomer) 15.5 min (major enantiomer of minor diastereomer), 20.6 min (minor enantiomer of minor diastereomer).

3f: 83% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.26 (1H, s), 7.99, (1H, d, *J*= 8.4 Hz), 7.84 (1H, d, *J*= 8.1 Hz), 7.74 (1H, m), 7.58 (1H, t, *J*= 7.5 Hz), 7.60–7.04 (5H, m), 6.87, (1H, m), 6.75, (1H, m), 6.56 (1H, dd, *J*= 8.8, 2.4 Hz), 6.36, (1H, d, *J*= 7.2 Hz), 6.32, (1H, d, *J*= 8.8 Hz), 6.07, (1H, d, *J*= 7.6 Hz), 4.88 (1H, dd, *J*= 8.2, 5.5 Hz), 3.82 (3H, s), 2.79 (1H, dd, *J*= 12.9, 8.4 Hz), 2.57 (1H, dd, *J*= 12.9, 7.7 Hz), 1.63 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 146.7, 141.3, 136.4, 136.2, 134.7, 131.9, 131, 130.4, 129.6 (2C), 129.3, 129.0, 128.9, 128.8, 128.7, 128.5, 128.2, 127.7, 127.6, 127.4, 127.3, 127.2, 126.1, 113, 110.8, 104.3, 102.1, 55.9, 51.4, 41.5, 23.3. HRMS(ESI) Calcd for $C_{34}H_{30}N_3O_2Na$ ([M+Na]$^+$) 512.2338. Found 512.2350. $[\alpha]_D^{23}$ 369.1 (c 3.0, $CHCl_3$), dr=>20:1; HPLC IA-3, hexane/IPA = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, 28.1 min (major enantiomer of major diastereomer), 35.2 min (minor enantiomer of major diastereomer).

3g: 81% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.30 (1H, s), 8.12 (1H, d, *J*= 8.4 Hz), 7.93 (1H, d, *J*= 8.2 Hz), 7.84–7.80 (1H, m), 7.74 (d, 1H, *J*= 7.8 Hz), 7.67–7.63 (1H, m), 7.23–7.13 (5H, m), 6.97 (1H, d, *J*=

7.8 Hz), 6.91–6.89 (1H, m), 6.84 (1H, d, *J*= 8.2 Hz), 4.86–4.79 (1H, m), 1.84 (3H, s), 0.92 (3H, d, *J*= 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 158.2, 147.0, 142.1, 137.8, 136.4, 136.2, 131.4, 130.7, 130.5, 129.2, 129.1, 129,0 128.3, 127.9, 127.8, 127.7, 127.2, 126.3, 126.3, 123.1, 119.8, 111,0 103.8, 51.6, 41.9, 23.4; HRMS (ESI) Calcd for $C27_2ClN_3O$ ($[M+H]^+$) 439.1451. Found 139.1479. $[\alpha]_D^{23}$ 391.2 (c 3.8, $CHCl_3$), dr=18:1; HPLC IA-3, hexane/ethanol = 9:1, flow rate = 1.0 mL/min, λ = 254 nm, 10.9 min (major enantiomer of major diastereomer), 12.2 min (minor enantiomer of major diastereomer).

3h: 87% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.24, (1H, s), 8.06 (1H, d, *J*= 8.7 Hz), 7.85 (1H, d, *J*= 8.2 Hz), 7.78 (1H, m) 7.71 (1H, d, *J*= 7.3 Hz), 7.60 (1H, m), 7.37 (1H, d, *J*= 8.7 Hz), 7.19–7.11 (5H, m), 7.04–7.00 (2H, m), 6.92 (1H, s), 6.86 (1H, d, *J*= 7.8 Hz), 6.63 (1H, d, 7.8 Hz), 6.10 (1H, d, *J*= 8.2 Hz), 5.13 (1H, dd, *J*= 8.2, 5.5 Hz), 2.88 (1H, dd, *J*= 8.2, 7.3 Hz), 2.71 (1H, dd, *J*= 8.2, 7.3 Hz), 1.63, (3H, s), 1.18 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 158.5, 150.7, 140.9, 137.9, 137.2, 131.2, 130.4, 129.6, 129.3, 129.2, 128.5, 128.4, 128.1, 127.8, 127.7, 127.3, 126.1, 125.9, 125.6, 122.7, 121.2, 120.7, 110.6, 104.3, 50.8, 39.2, 34.5, 31.2, 23.0; HRMS (ESI) Calcd for $C_{37}H_{35}N_3O$ ($[M+H]^+$) 482.2232. Found 482.2258. $[\alpha]_D^{23}$ 316.5 (c 2.4, $CHCl_3$), dr=14:1; HPLC IF-3, hexane/IPA = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, 24.8 min (minor enantiomer of major diastereomer), 27.8 min (minor enantiomer of major diastereomer).

3i: 76 % yield, pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.35 (1H, s), 8.14 (1H, d, *J*= 8.3 Hz), 7.92 (1H, d, *J*= 8.3 Hz), 7.90–7.82 (2H, m) 7.71–7.64 (1H, m), 7.62 (1H, m), 7.22–7.09 (4H, m), 7.91–6.77 (3H, m), 4.76 (1H, m), 1.87, (3H, s), 0.92 (3H, d, *J*= 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 159.8, 147.1, 141.0, 138.3, 137.0, 134.1, 131.0 (2C), 130.3 (2C), 130.0, 129.7, 129.0, 128.6, 127.7 (2C), 127.2, 125.8, 123.6, 114.4, 111.5, 104.0, 46.0, 23.4, 22.7; HRMS (ESI) Calcd for $C_{33}H_{26}N_3OClBr$ ($[M+H]^+$) 594.0948. Found 594.0928. $[\alpha]_D^{23}$=421.1 (c=1.4,$CHCl_3$), dr=>20:1; HPLC IF-3 hexane/IPA = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, 18.4 min (major enantiomer of major diastereomer), 22.2 min (minor enantiomer of major diastereomer).

3j: 84% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.37, (1H, s), 8.12 (1H, d, *J*= 8.7 Hz), 7.92 (1H, d, *J*= 8.2 Hz), 7.85–7.81 (1H, m) 7.71 (1H, d, *J*= 7.3 Hz), 7.6–7.60 (1H, m), 7.25–7.09 (5H, m), 6.97 (1H, d, *J*= 7.8 Hz), 6.92 (1H, s), 6.85 (1H, d, *J*= 7.8 Hz), 6.63 (1H, d, 7.8 Hz), 6.10 (1H, d, *J*= 8.2 Hz), 5.13 (1H, dd, *J*= 8.2, 5.5 Hz), 2.88 (1H, dd, *J*= 8.2, 7.3 Hz), 2.71 (1H, dd, *J*= 8.2, 6.4 Hz), 1.63 (3H, s), 1.18 (3H, d, *J*= 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 160.1, 147, 139.8, 139.7, 137.2, 133.8, 130.8, 130.3, 129.6, 129, 128.5, 128.5, 127.8, 127.6, 127.4, 123, 121.3, 121.2, 110, 104.8, 46.2, 29.8, 23.5, 22.6; HRMS (ESI) Calcd for $C_{33}H_{26}N_3OCl$ ($[M+H]^+$) 516.1843. Found 516.18478. $[\alpha]_D^{23}$=361.3 (c=2.9, dr=>20:1); HPLC IA-3, hexane/IPA = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, 26.3 min (minor enantiomer of major diastereomer), 30.2 min (major enantiomer of major diastereomer).

3k: 71% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ 8.37 (1H, s), 8.12 (1H, d, *J*= 8.7 Hz), 7.92 (1H, d, *J*= 8.2 Hz), 7.85–7.81 (1H, m) 7.71 (1H, d, *J*= 7.3 Hz), 7.6–7.60 (1H, m), 7.25–7.09 (5H, m), 6.97 (1H, d, *J*= 7.8 Hz), 6.92 (1H, s), 6.85 (1H, d, *J*= 7.8 Hz), 6.63 (1H, d, 7.8 Hz), 6.10 (1H, d, *J*= 8.2 Hz), 5.13 (1H, dd, *J*= 8.2, 5.5 Hz), 2.88 (1H, dd, *J*= 8.2, 7.3 Hz), 2.71 (1H, dd, *J*= 8.2, 6.4 Hz), 1.63, (3H, s), 1.18 (3H, d, *J*= 6.1 Hz); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 168.0, 158.9, 146.2, 137.9, 136.9, 136.2, 135.8, 129.6, 128.8, 128.6, 128.3, 128.0, 127.7, 127.1, 127.0, 126.7, 126.5, 126.3, 125.3, 120.5, 119.3, 119.0, 108.5, 101.4, 50.0, 40.8, 22.3, 11.9; HRMS (ESI) Calcd for $C_{28}H_{26}N_3O$ ($[M+H]^+$) 420.2027. Found 420.20218, $[\alpha]_D^{23}$=193.3 (c=1.0, single diastereomer); HPLC IA-3, hexane/IPA = 95:5, flow rate = 1.0 mL/min, λ = 254 nm, 19.1 min (major enantiomer), 25.6 min (minor enantiomer).

10. X-ray Crystallographic analysis

Single crystal of **3a** for X-ray diffraction was obtained by vapor diffusion (dichloromethane/hexane). Data collection was performed on BL-17A beamline in KEK PF.

Table S1. Crystal data for **3a**.

Formula	$C_{55}H_{48}N_6O_{12}Cl_2$
Formula wight	895.89
Temperature	95.15 K
Radiation	Synchrotron (λ = 0.9000 Å)
Crystal system	Orthorhombic
Space group	$P2_12_12$
Cell length (Å)	a = 17.0150(13), b = 17.560(2), c = 7.712(2)
Cell angles	α = 90°, β = 90°, γ = 90°
Cell Volume (Å^3)	2304.2(7)
Z	2
Density (calculated) (Mg/m^3)	1.291 g·cm^{-3}
Absorption coefficient (mm^{-1})	0.354
F(000)	940
Crystal size (mm^3)	0.1 × 0.02 × 0.02
Theta range for data collection (°)	2.110 to 32.822
Index ranges	–20<=h<=20, –21<=k<=21, –9<=l<=9
Reflections collected	29161
Independent reflections	4204 [R(int) = 0.0418]
Completeness to theta = 32.684° (%)	99.6
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.459
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4204 / 0 / 299
Goodness-of-fit on F^2	1.067
Final R indices [I>2sigma(I)]	R_1 = 0.0347, wR_2 = 0.0925
R indices (all data)	R_1 = 0.0360, wR_2 = 0.0936
Absolute structure parameter	–0.011(11)
Extinction coefficient	n/a
Largest diff. peak and hole (e.Å^{-3})	0.139 and -0.389

11. References

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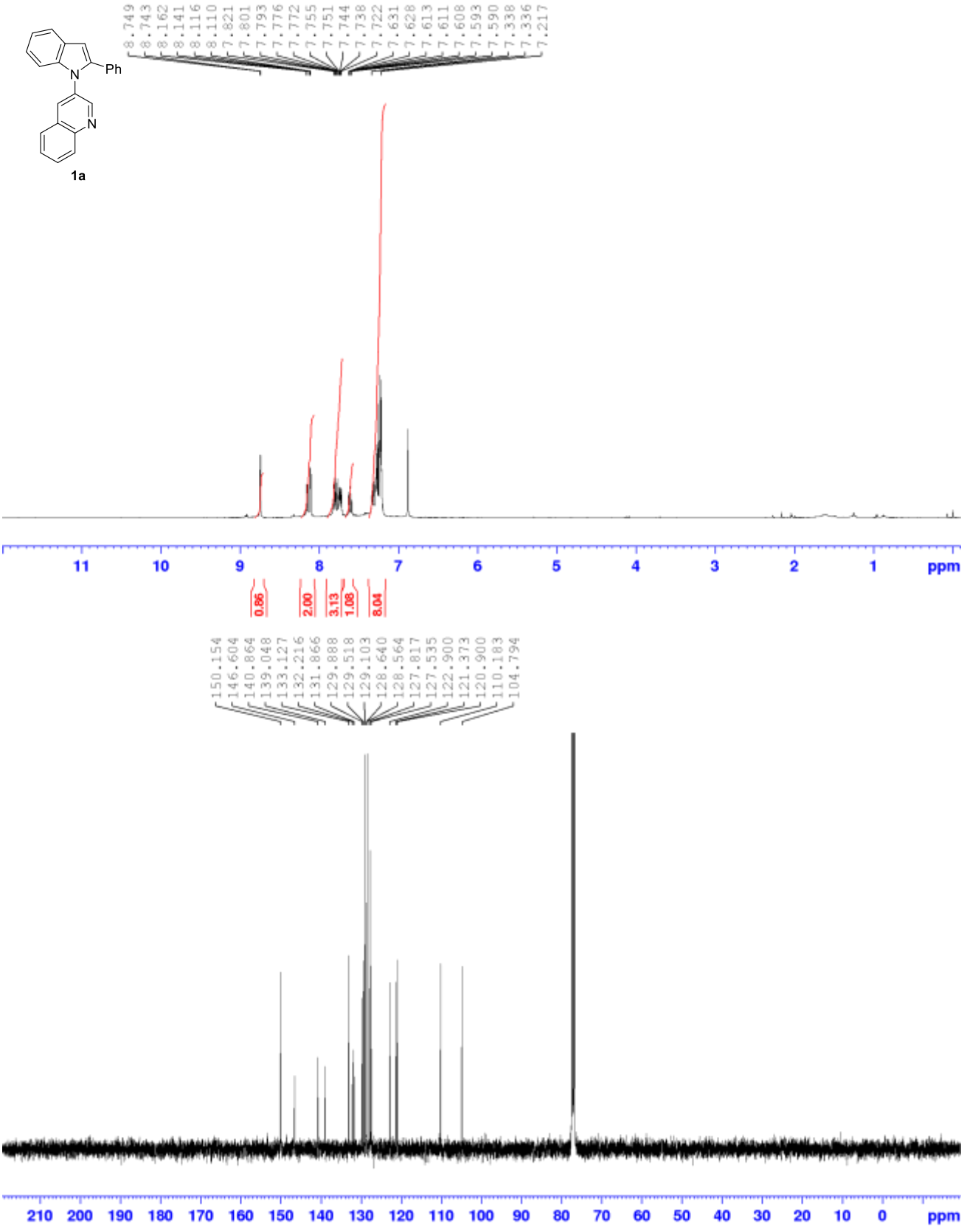
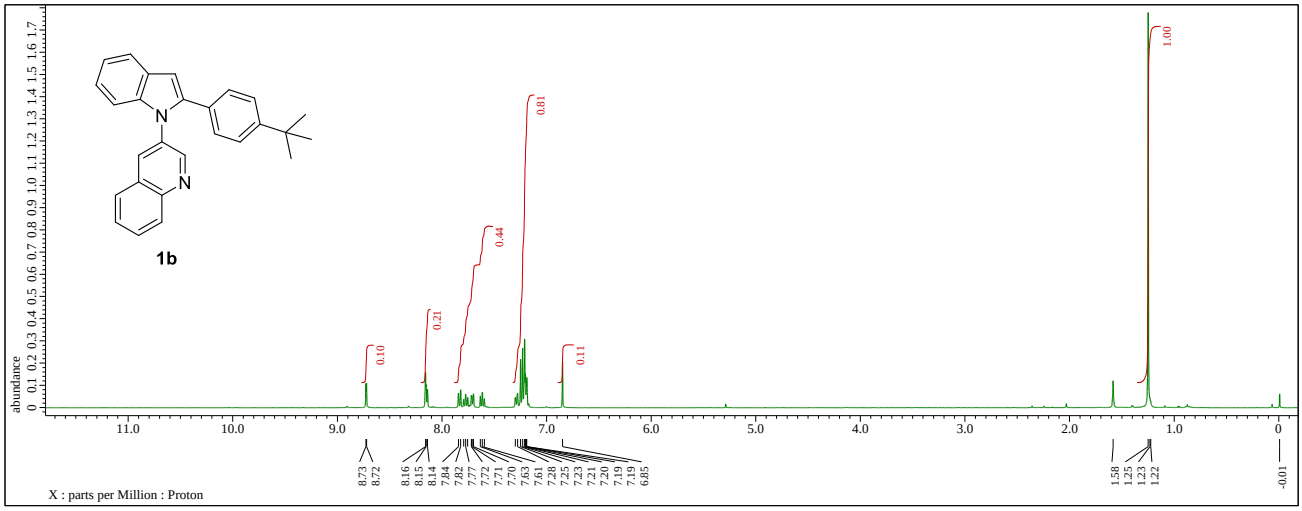
2. R. S. J. Proctor, H. J. Davis and R. J. Phipps, *Science*, 2018, **360**, 419.
3. R. J. Phipps and B. W. Hadrys, *Synlett,* 2021, **32**, 179.
4. N. G. Connelly and W. E. Geiger, *Chem. Rev.*, 1996, **96**, 877.

12. ^{1}H and ^{13}C NMR spectra

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7.77
7.72
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7.70
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7.23
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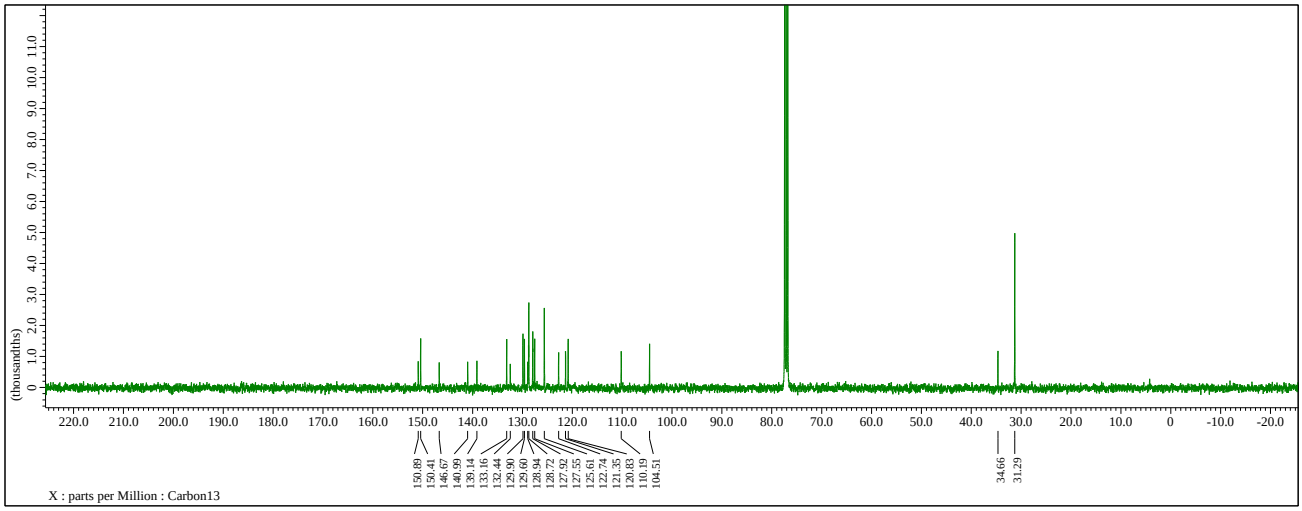
X : parts per Million : Proton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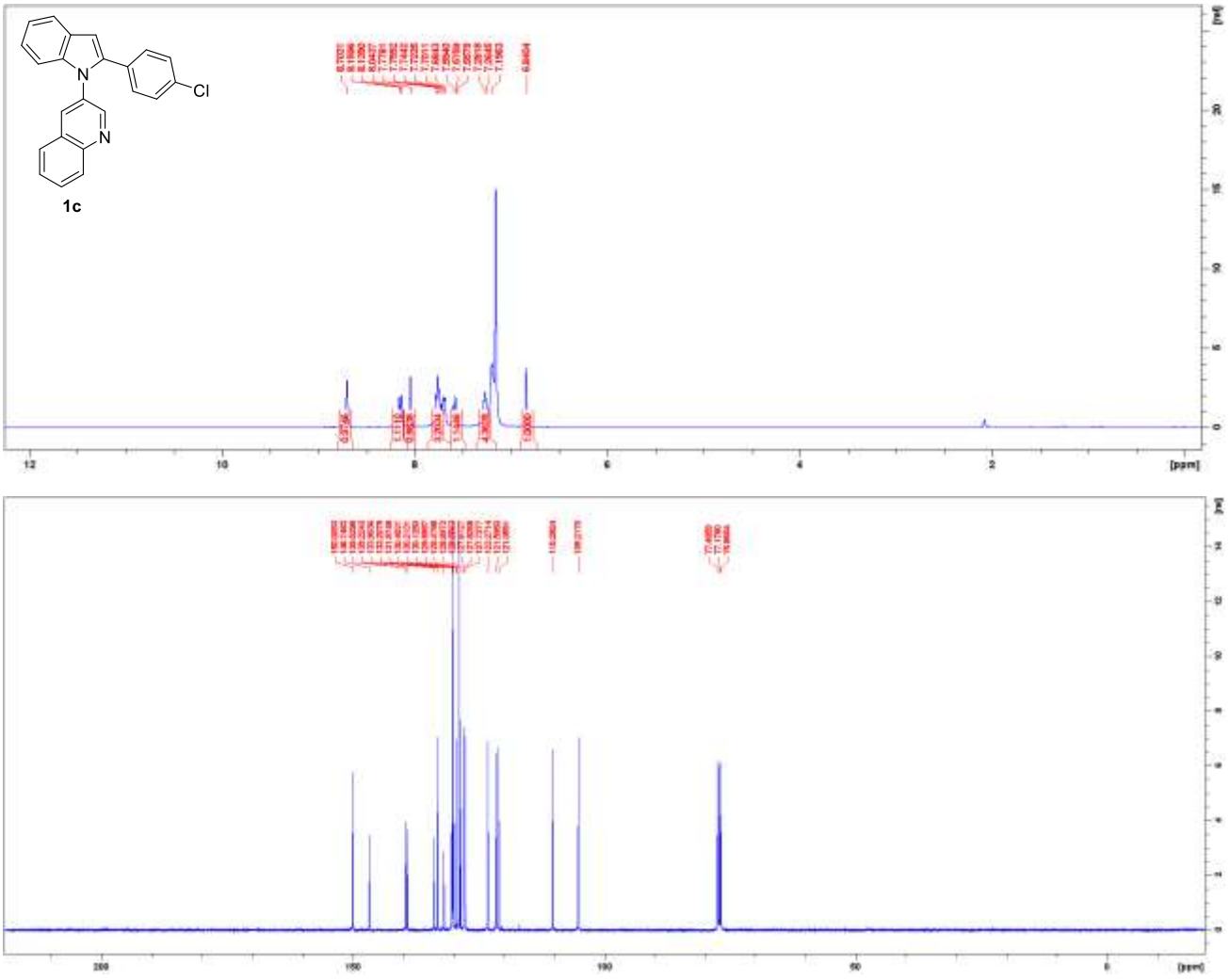
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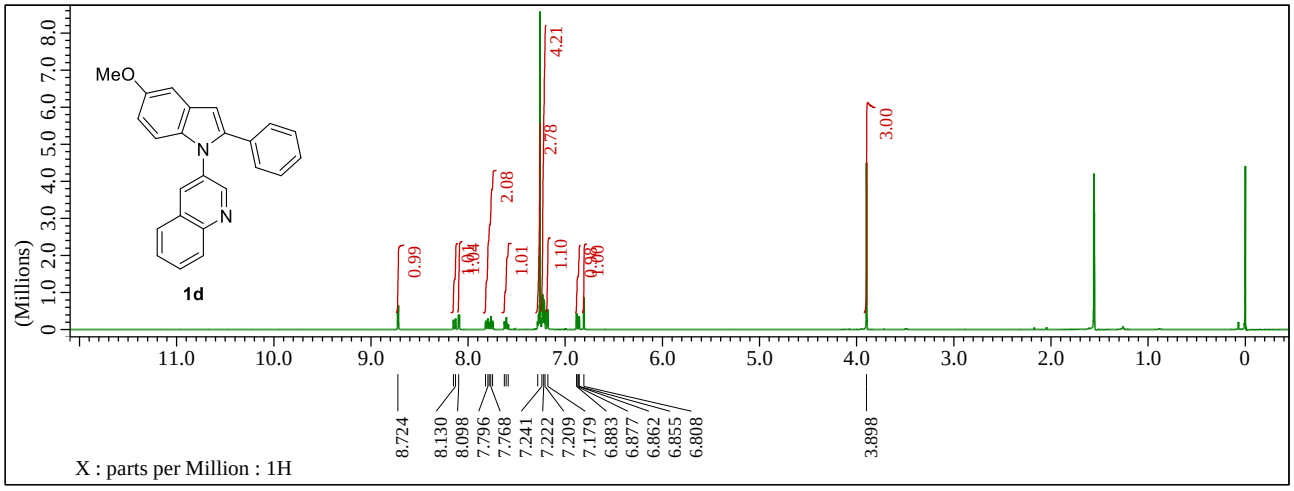
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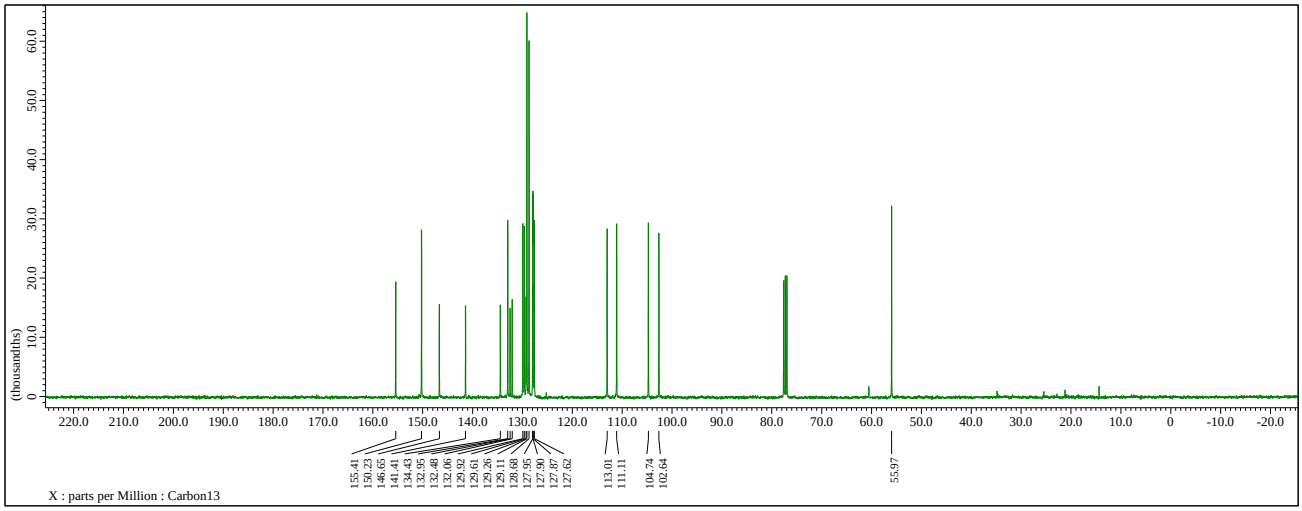
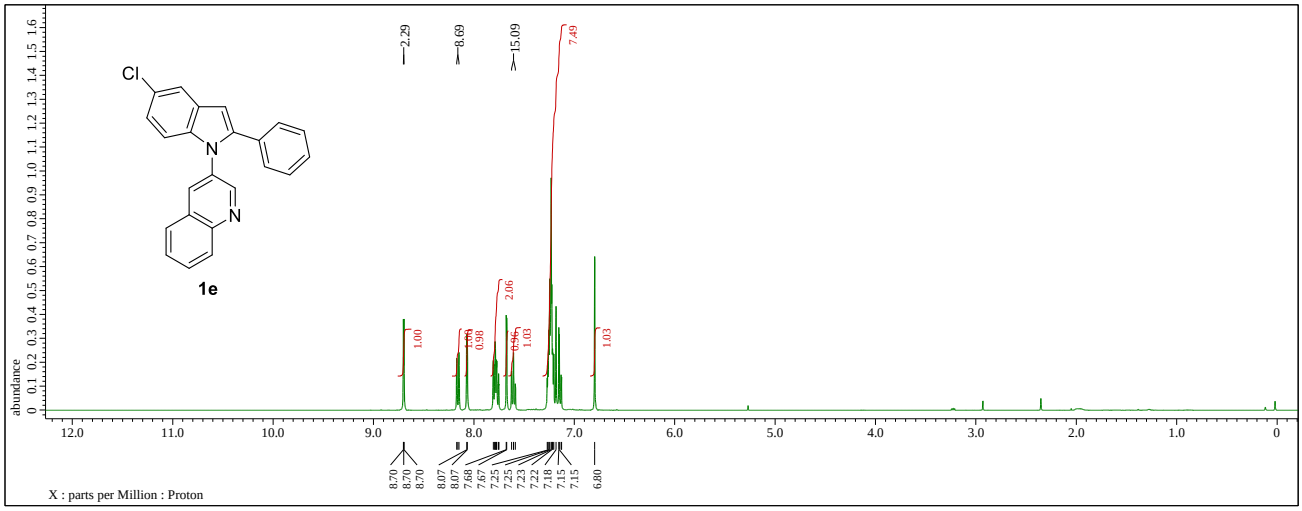
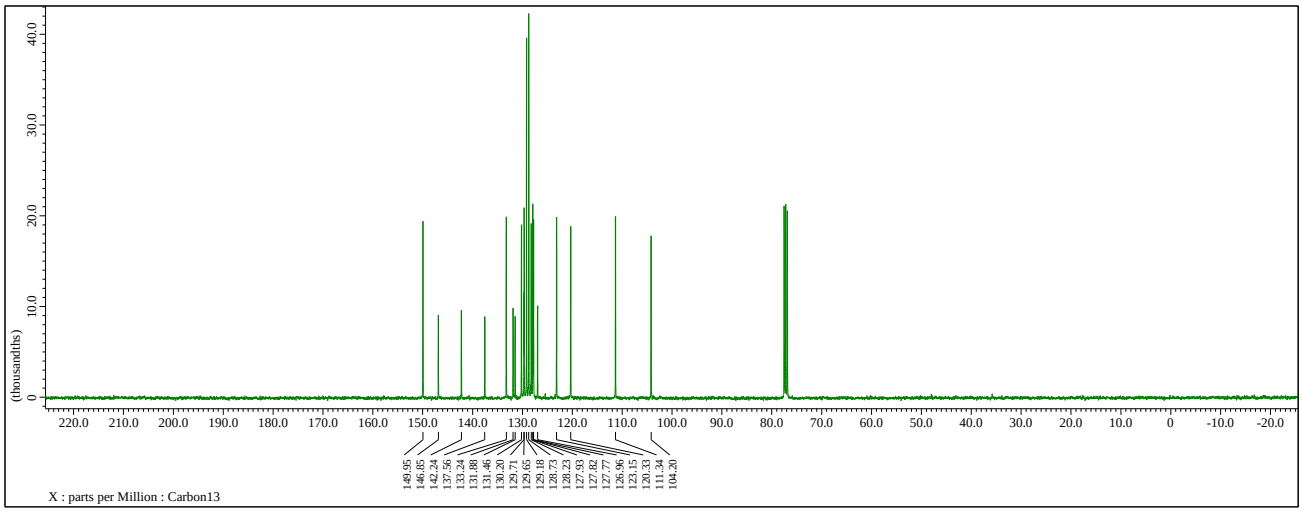
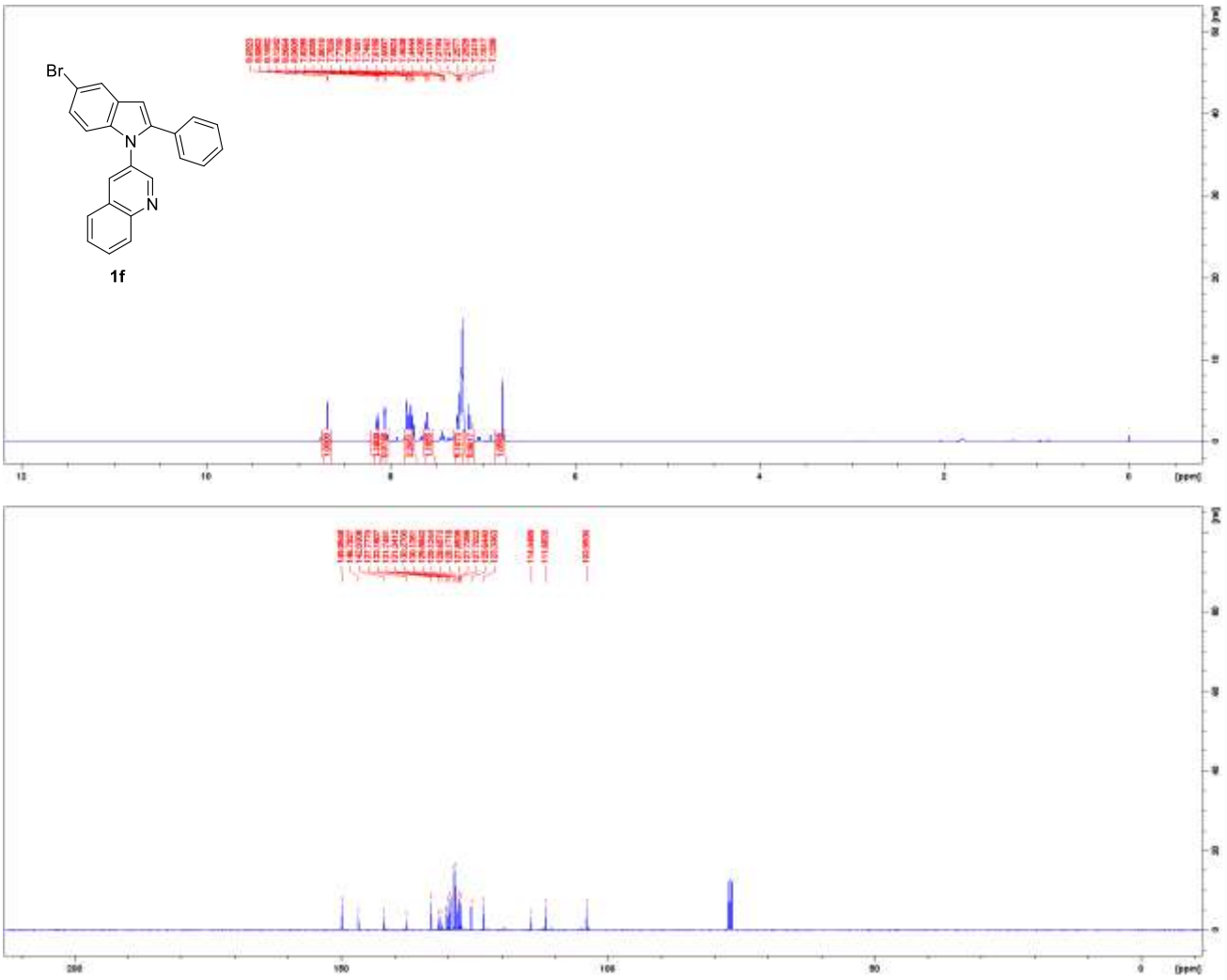
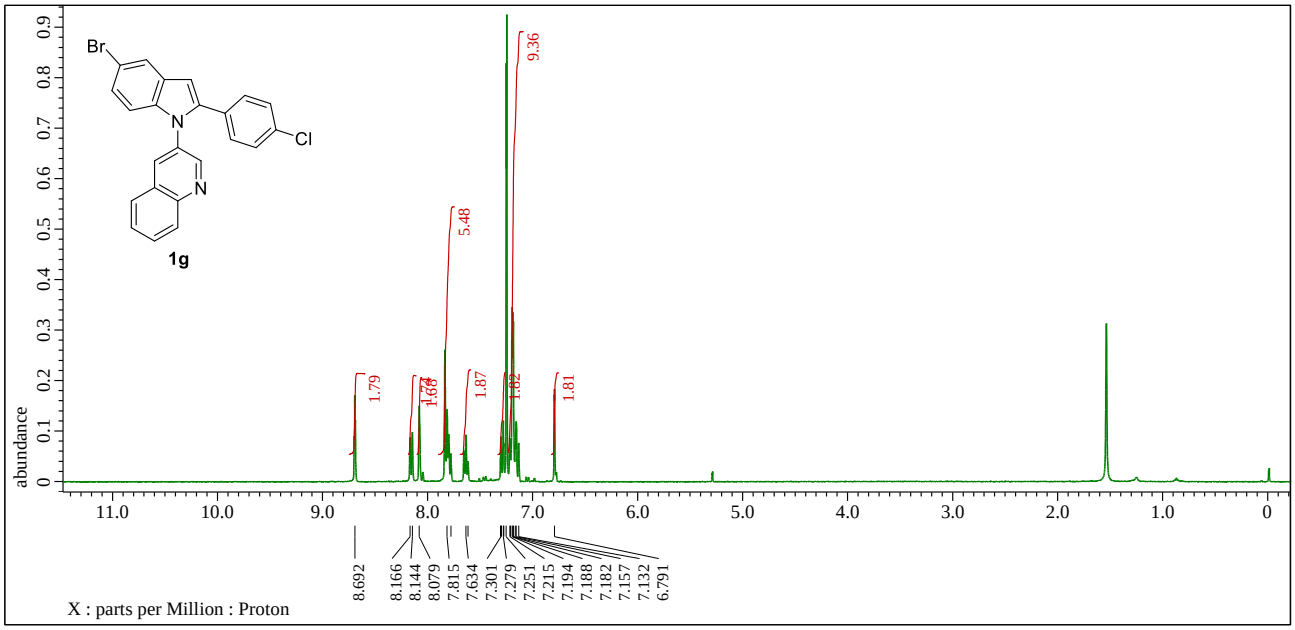
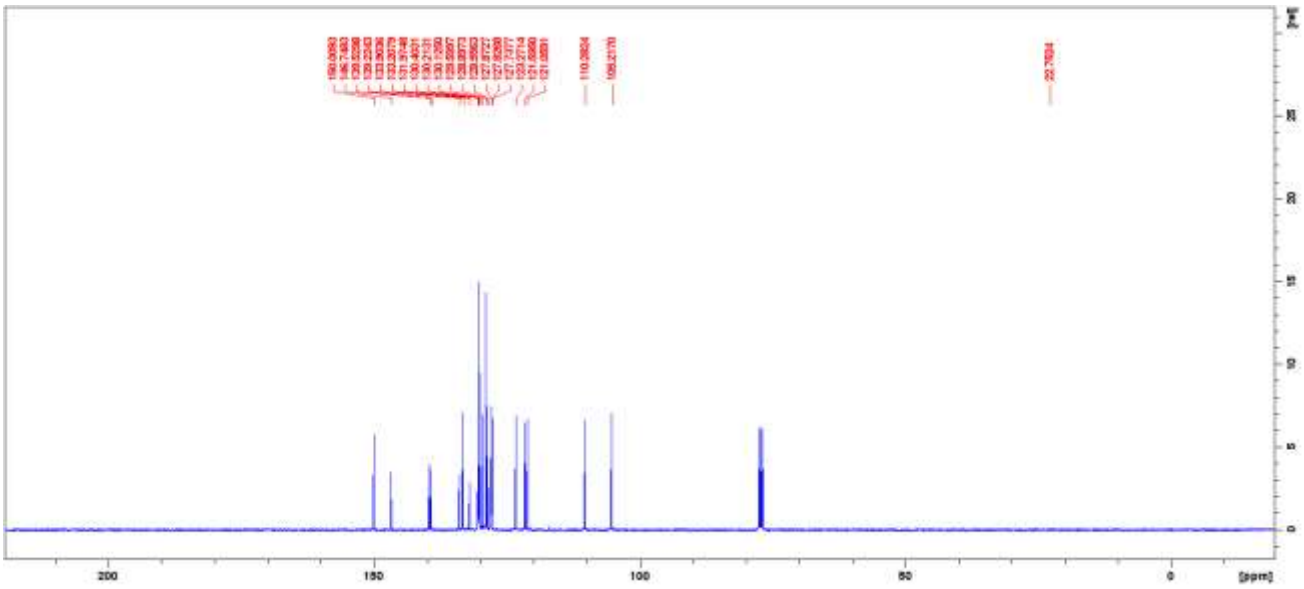

(thousandths)
0 10.0 20.0 30.0 40.0 50.0 60.0
220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0
155.41
150.23
146.65
141.41
134.42
132.95
132.46
132.06
130.92
129.62
129.26
129.11
128.68
127.95
127.90
127.87
127.62
113.01
111.11
104.74
102.64
55.97
X : parts per Million : Carbon13

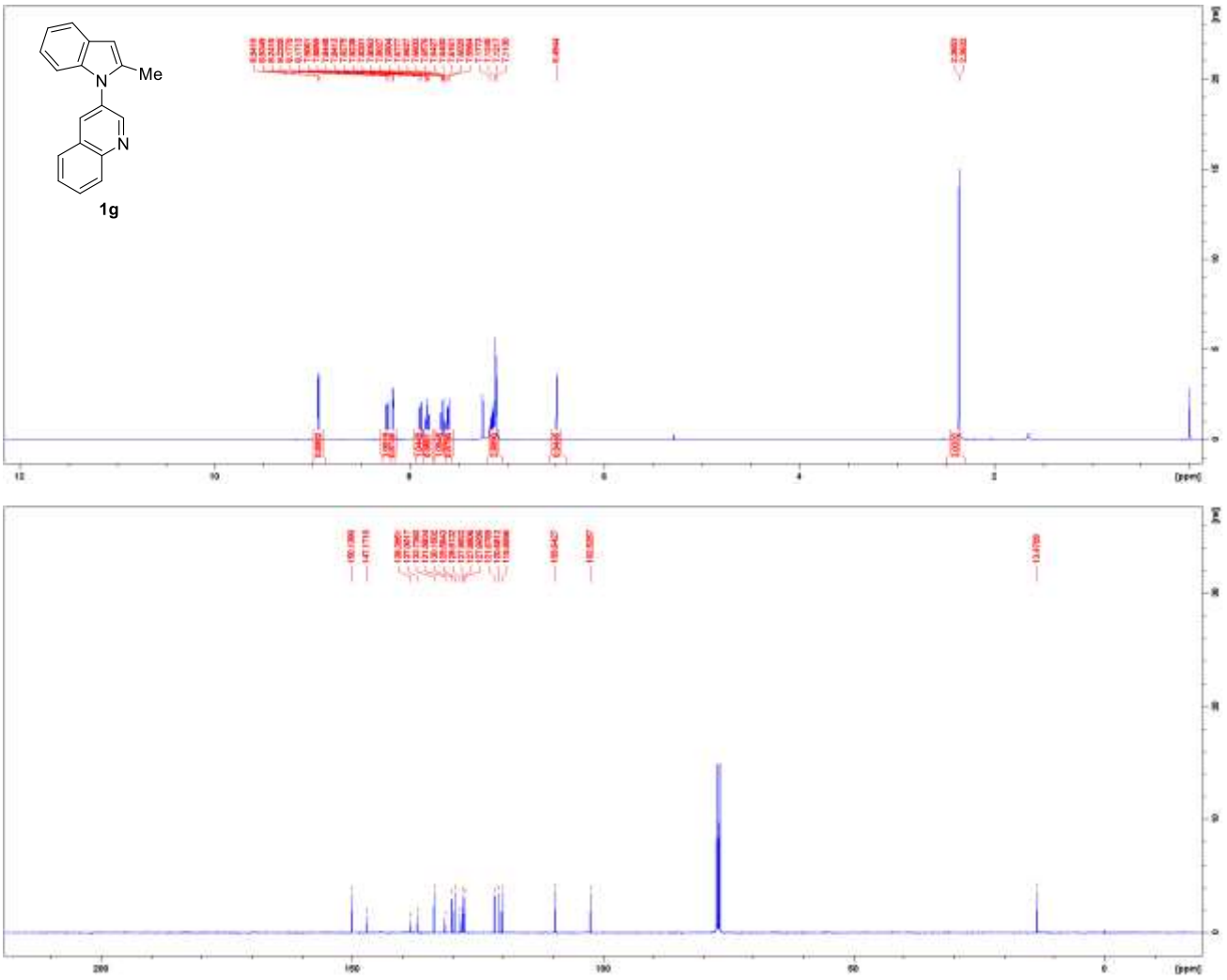

Cl
N
N
1e
2.29
8.69
15.09
7.49
2.06
1.00
1.03
1.03
abundance
X : parts per Million : Proton


(thousandths)
X : parts per Million : Carbon13

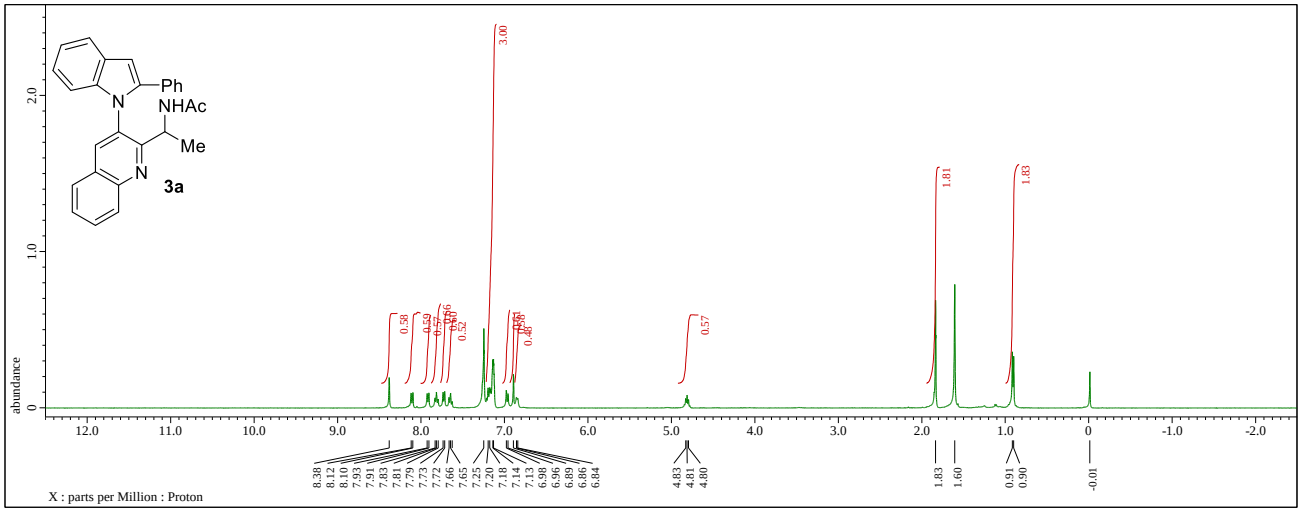

Br
N
N
1f

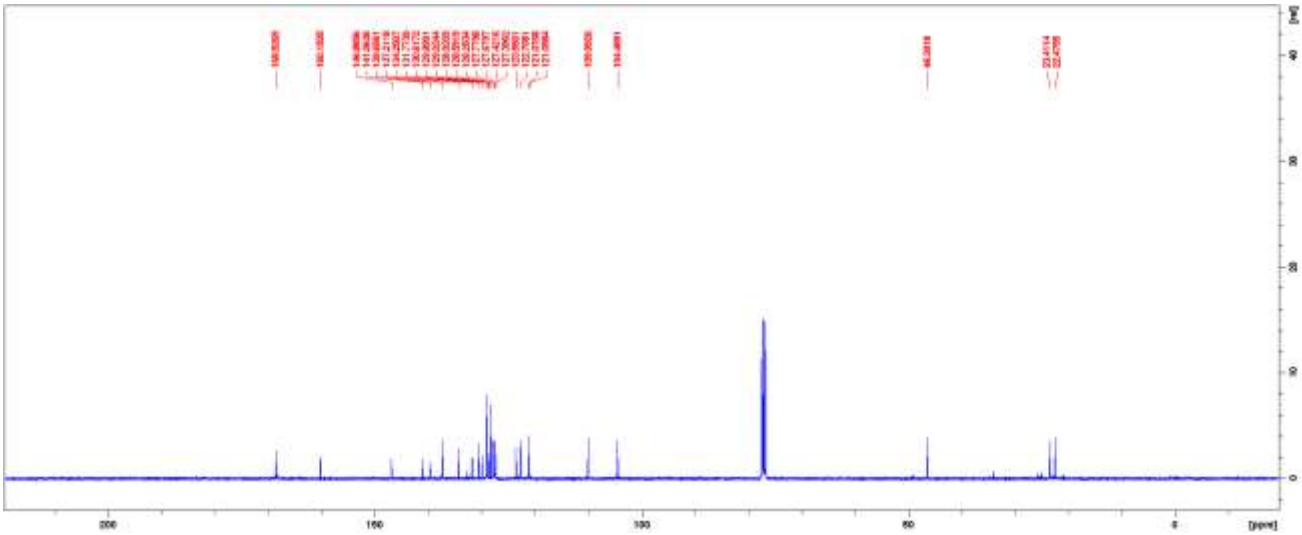

Br
N
Cl
N
1g
abundance
9.36
5.48
1.79
1.87
1.81
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
8.692
8.166
8.144
8.079
7.815
7.634
7.301
7.279
7.251
7.215
7.194
7.188
7.182
7.157
7.132
6.791
X : parts per Million : Proton


200
150
100
50
0
[ppm]

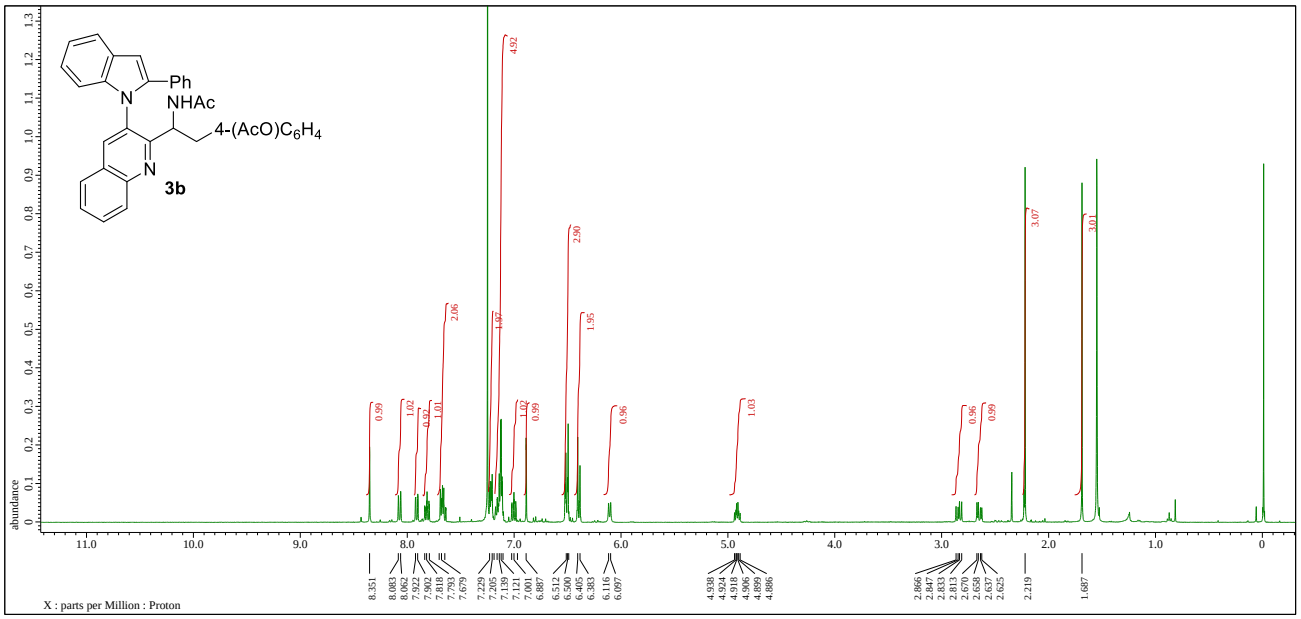

Me
N
N
1g

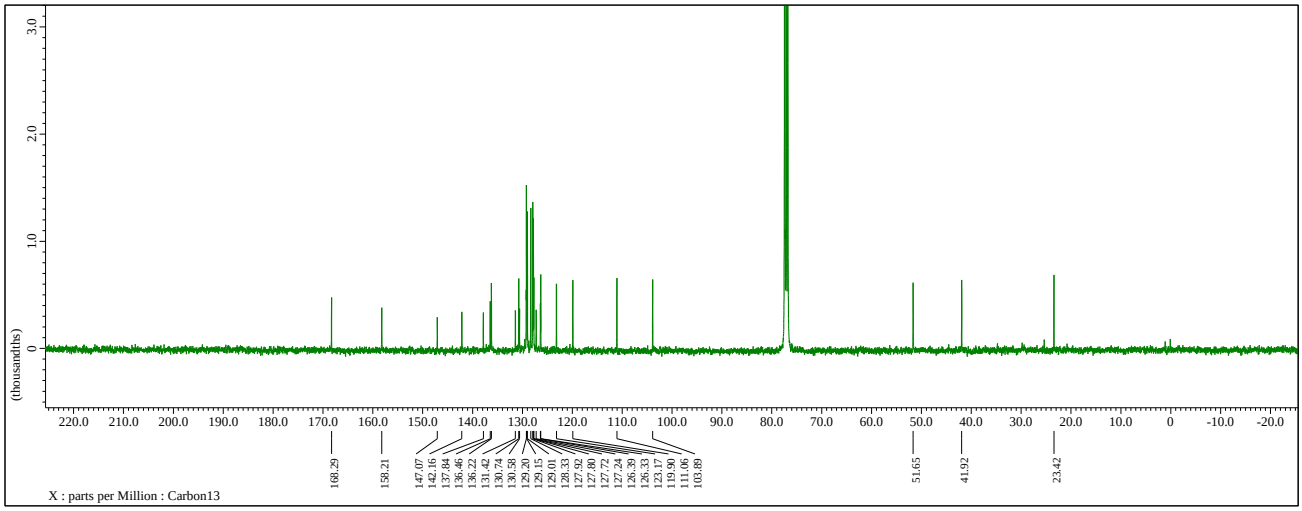
3a



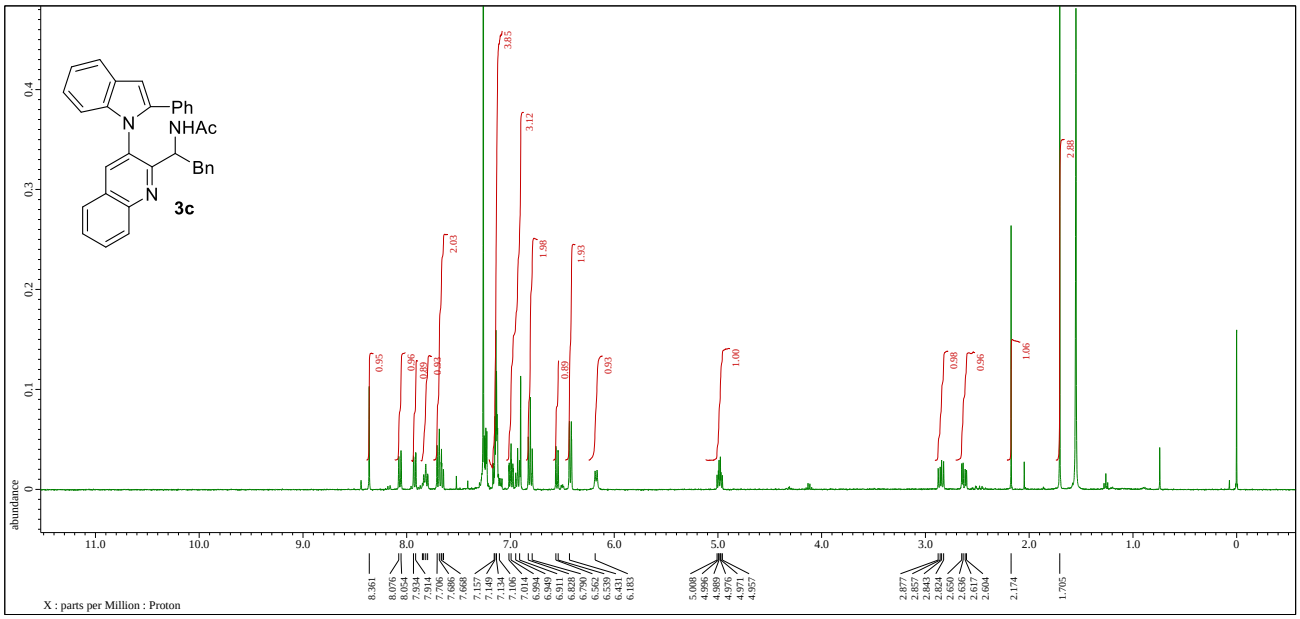


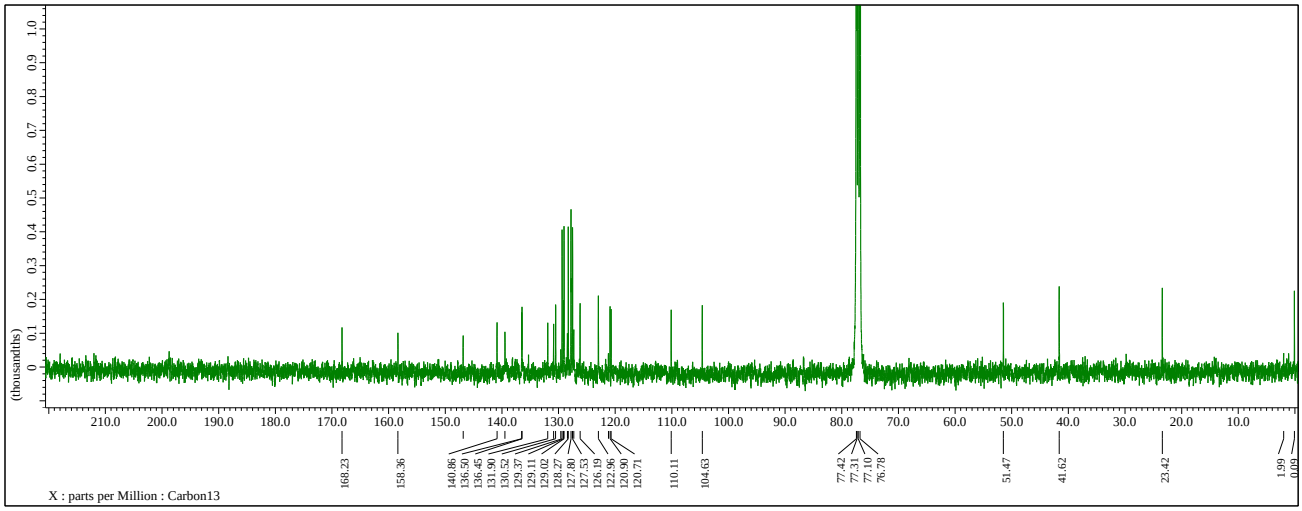
3b


Ph
NHAc
4-(AcO)C6H4
N
N
3b
abundance
X : parts per Million : Proton

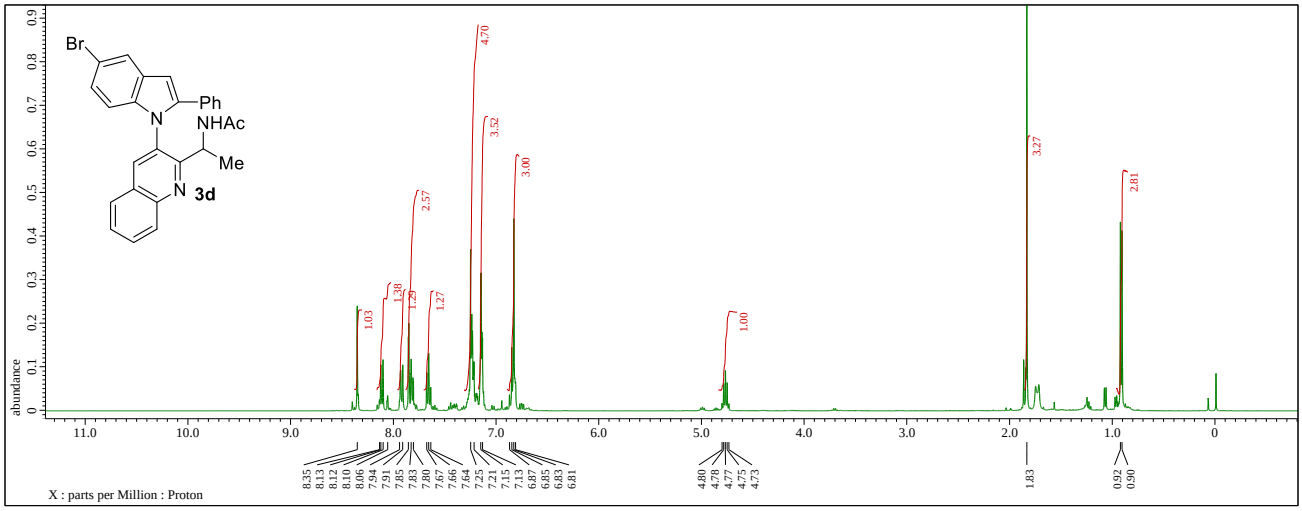

(thousandths)
X : parts per Million : Carbon13

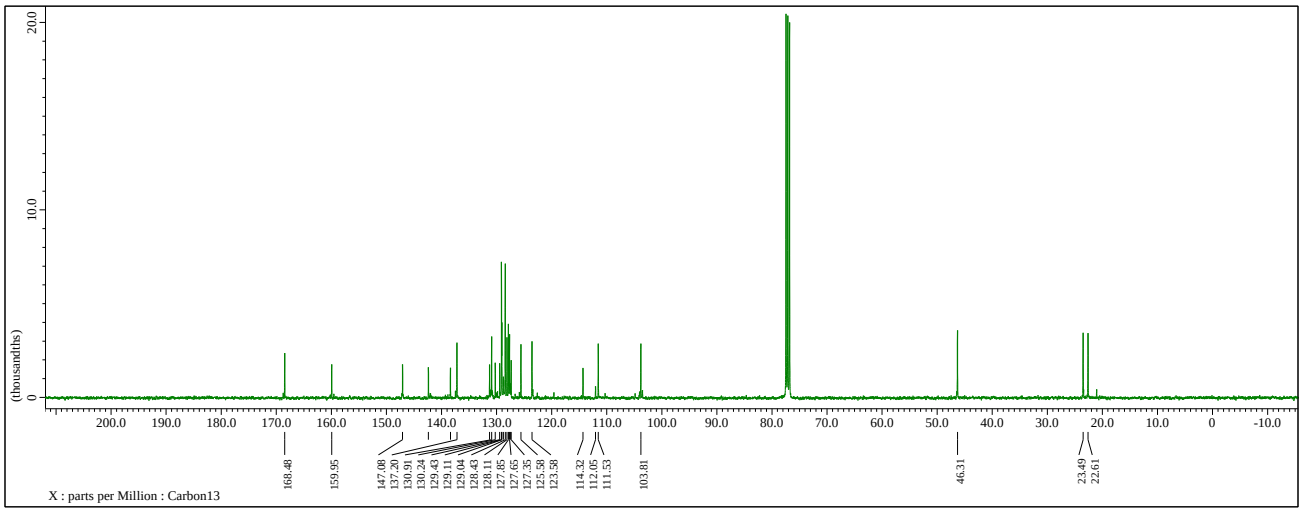
3c


Ph
NHAc
Bn
3c
abundance
X : parts per Million : Proton

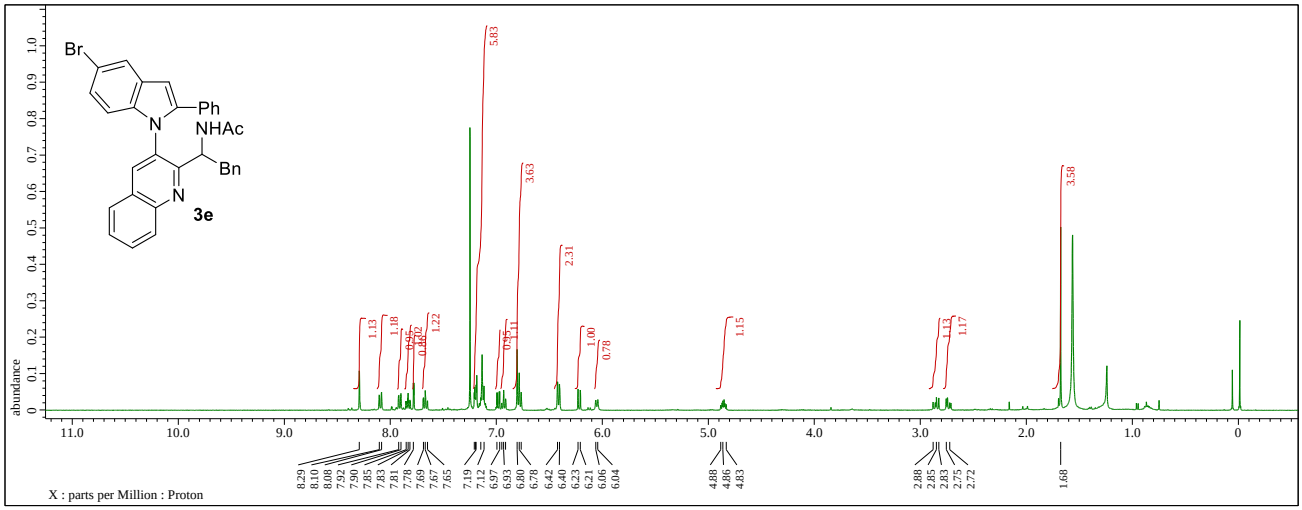

(thousandths)
X : parts per Million : Carbon13

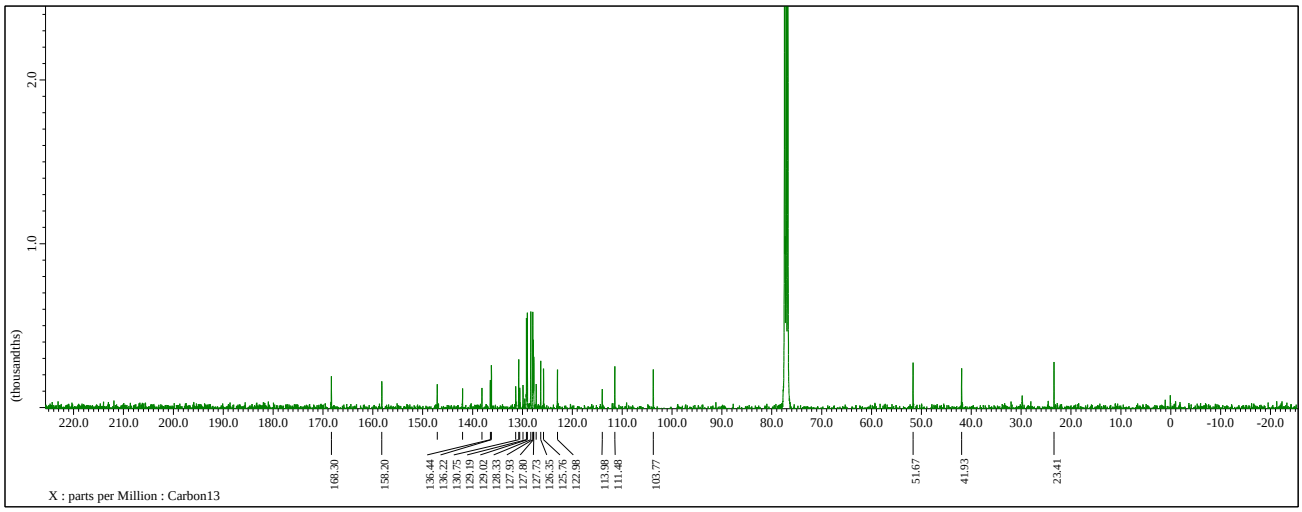
3d


Br
Ph
NHAc
Me
N
N
3d
abundance
X : parts per Million : Proton

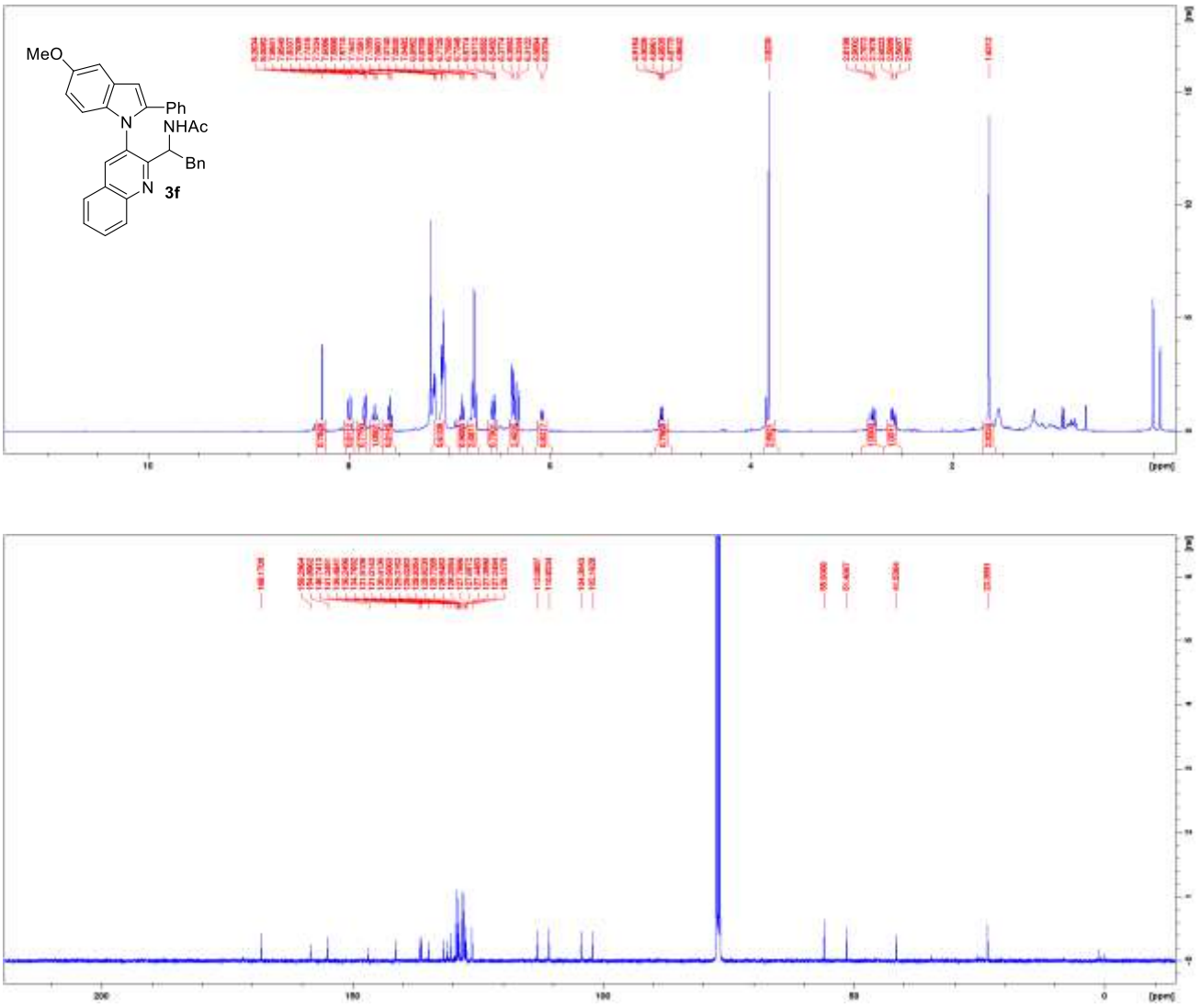

(thousandths)
X : parts per Million : Carbon13

3e

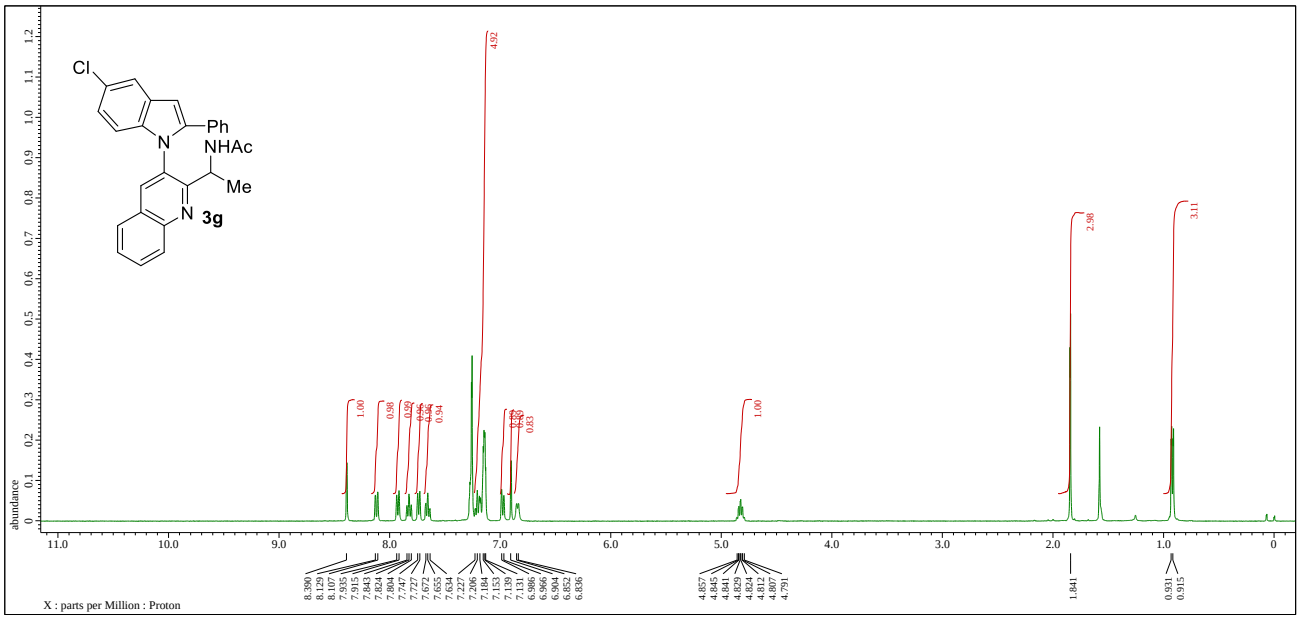

Br
Ph
NHAc
Bn
N
N
3e
abundance
X : parts per Million : Proton

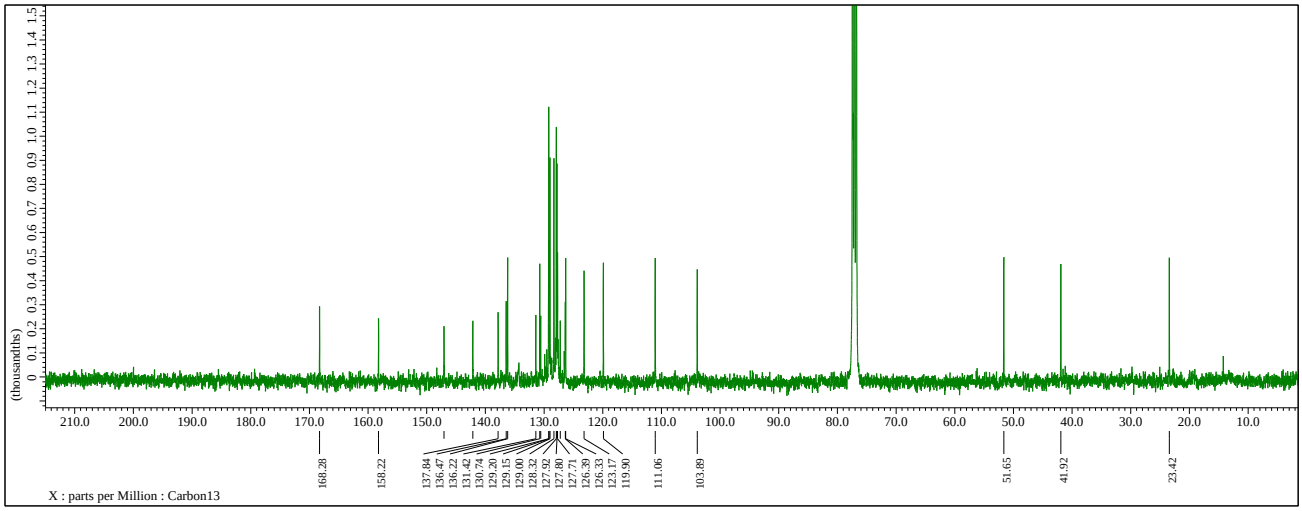

(thousandths)
X : parts per Million : Carbon13

3f

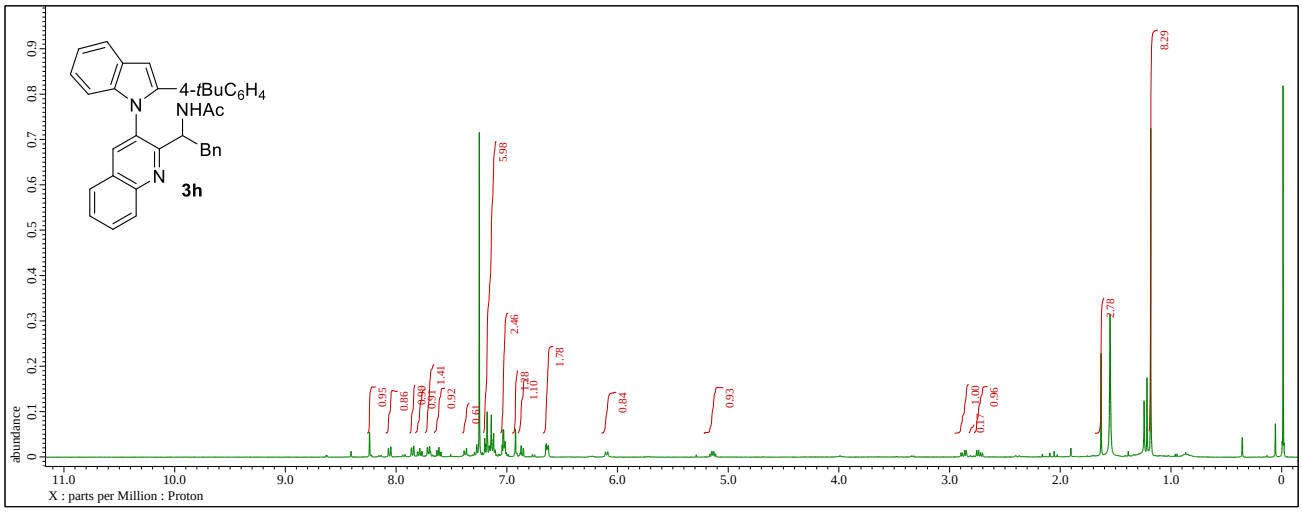


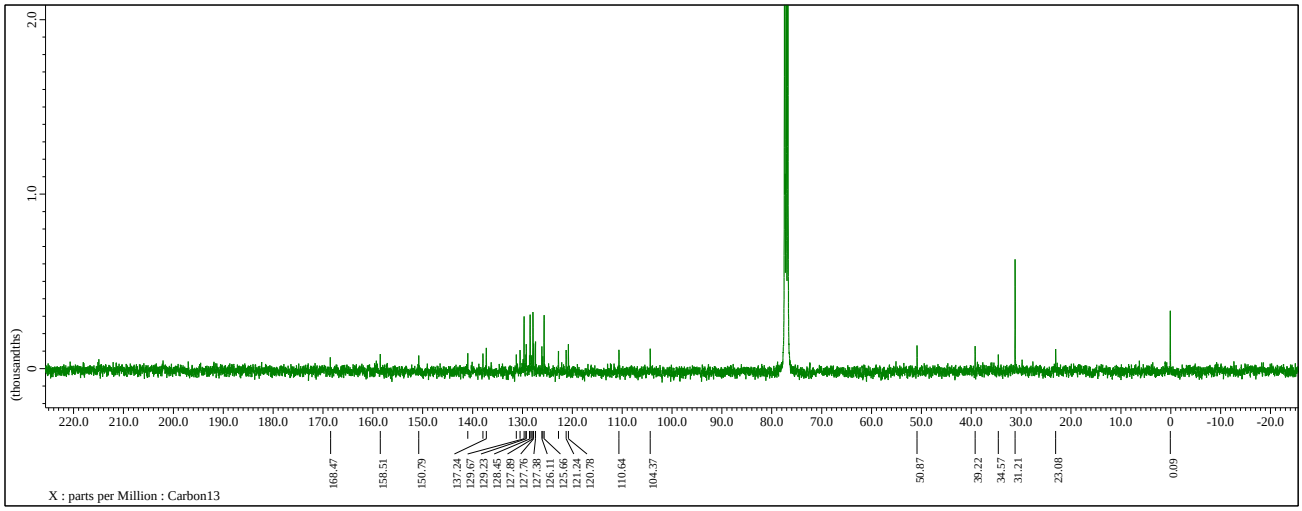
3g


Cl
Ph
NHAc
Me
N
N
3g
abundance
X : parts per Million : Proton

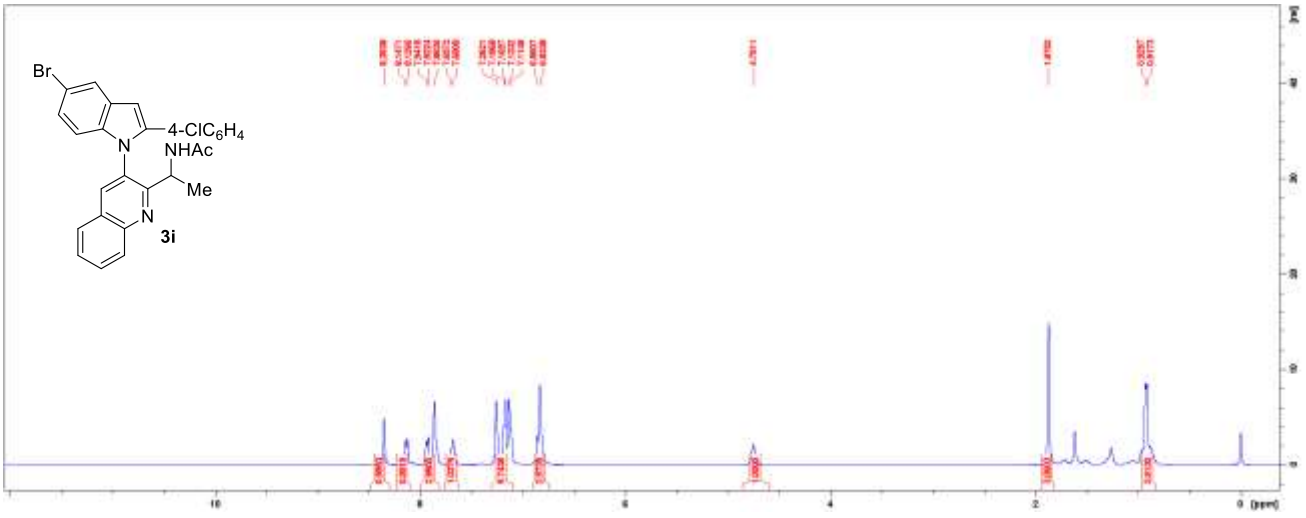

(thousandths)
X : parts per Million : Carbon13

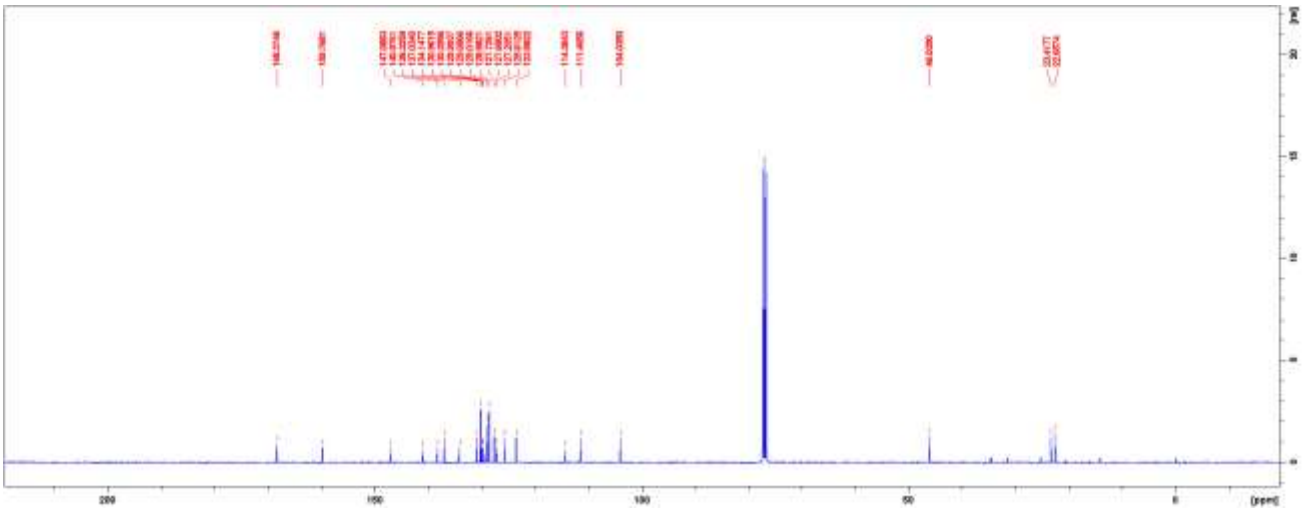
3h


4-tBuC6H4
NHAc
Bn
3h
abundance
X : parts per Million : Proton

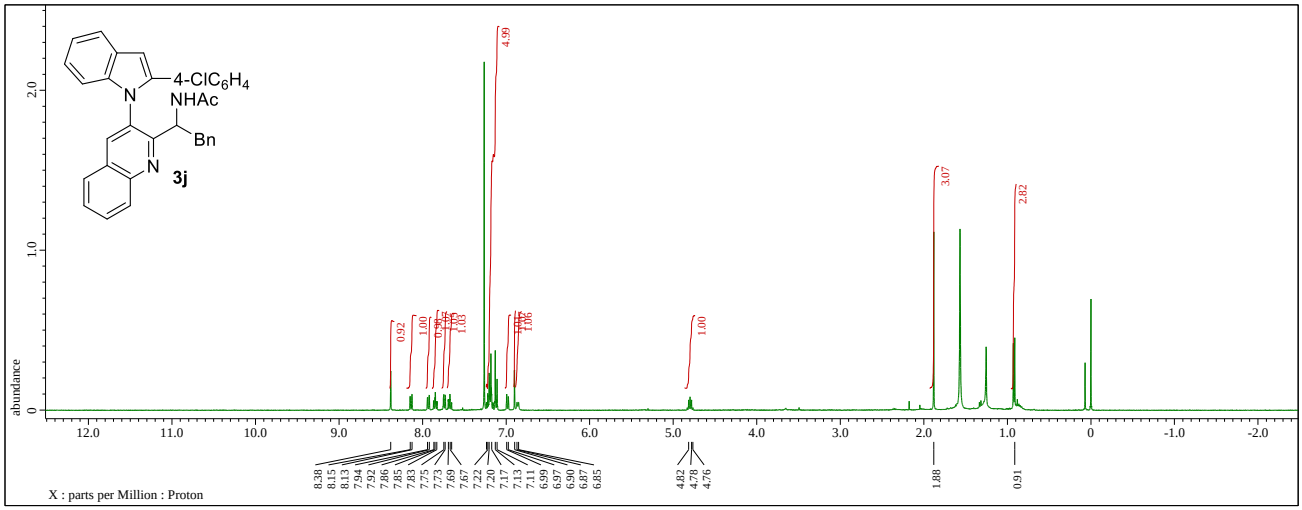

(thousandths)
X : parts per Million : Carbon13

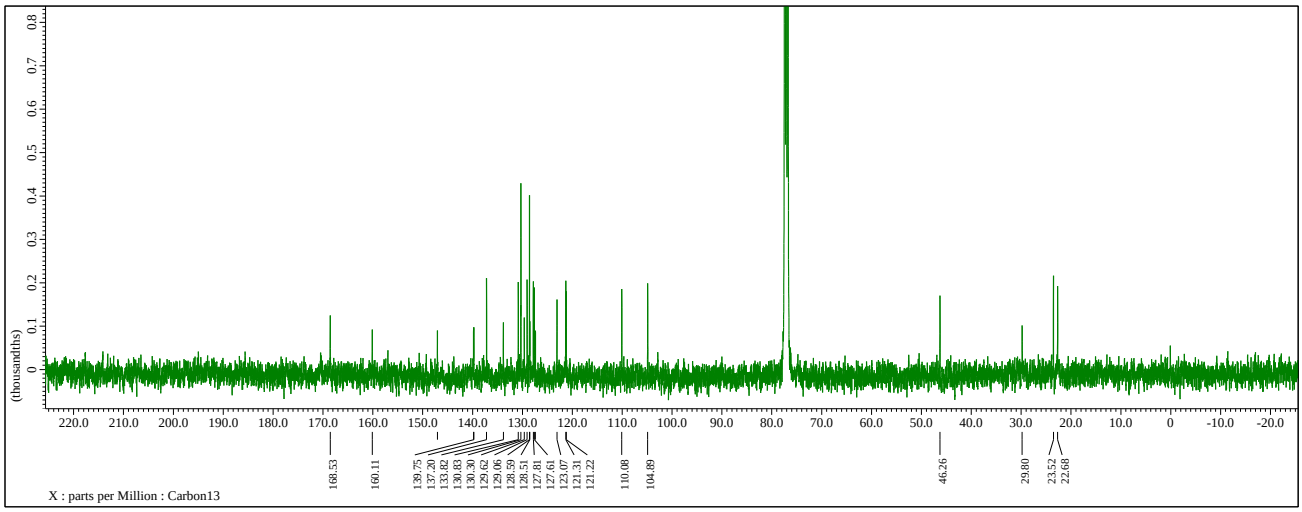
3i



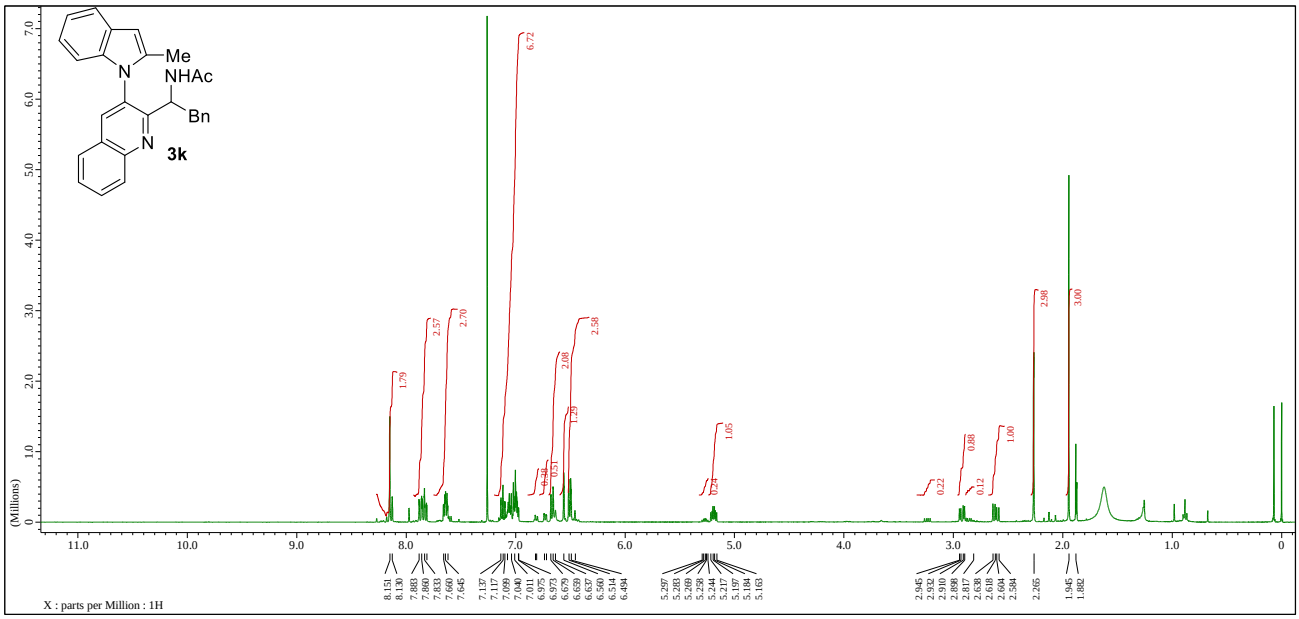


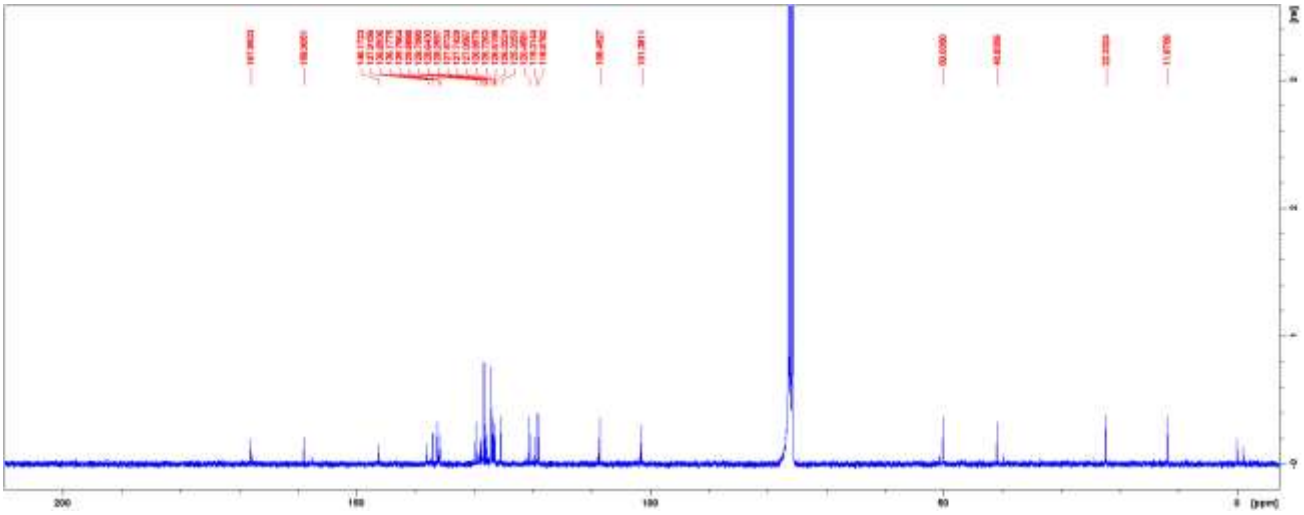
3j


4-ClC6H4
NHAc
Bn
N
N
3j
abundance
X : parts per Million : Proton


(thousandths)
X : parts per Million : Carbon13

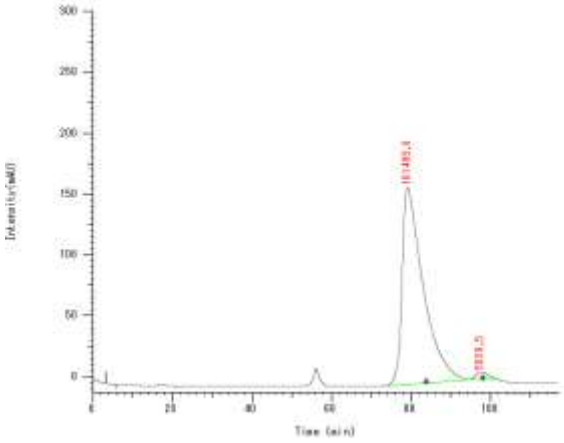
3k





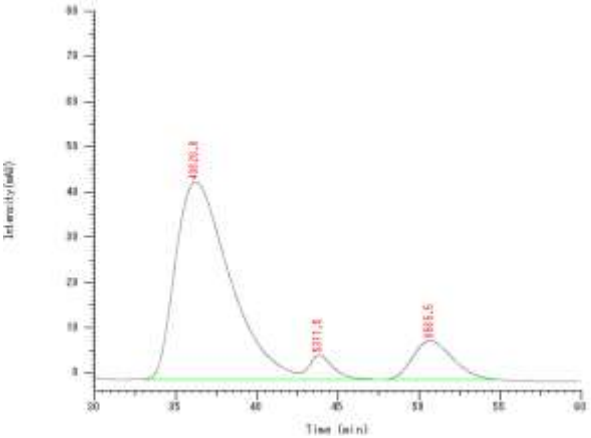
13. HPLC chart

1_**3a**



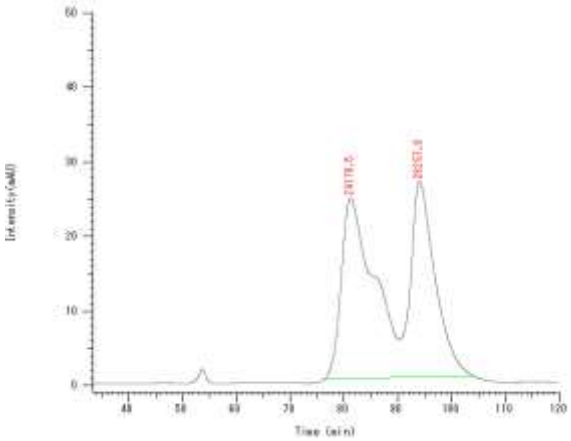
RT	area	%
79.2	59372480	97.935
97.6	1251683	2.065

2_**3b**

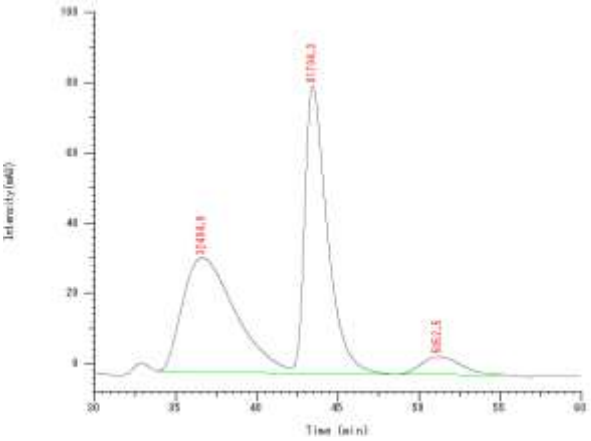


RT	area	%
36.2	10169721.7	83.751
43.9	509593.2	4.197
50.7	1463495.3	12.052

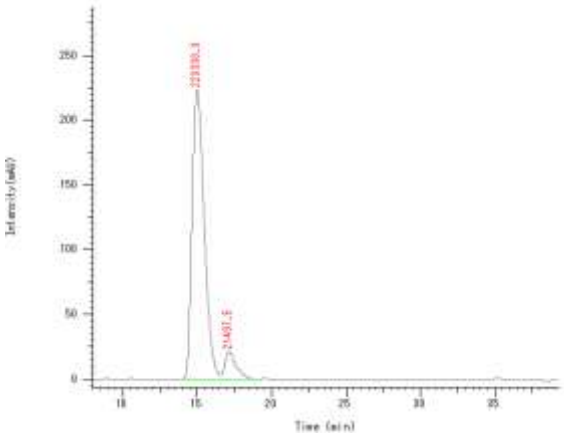
rac-**3a**



rac-**3b**

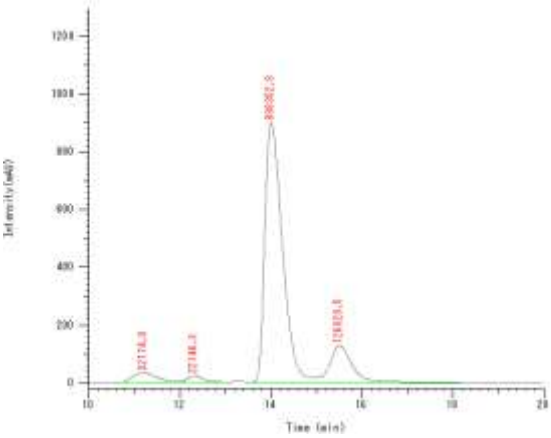


3_**3c**



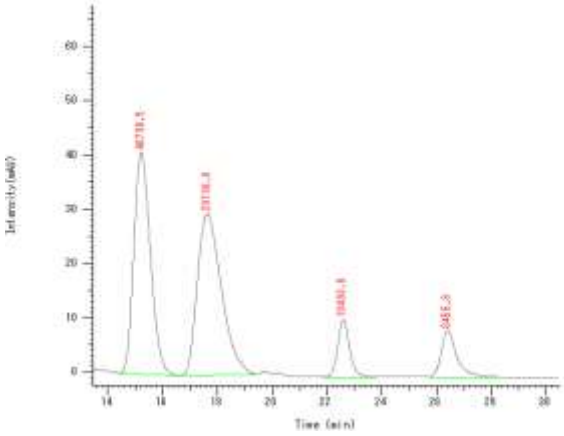
RT	area	%
15	12665588	91.78
17.2	1134338	8.22

4_**3d**

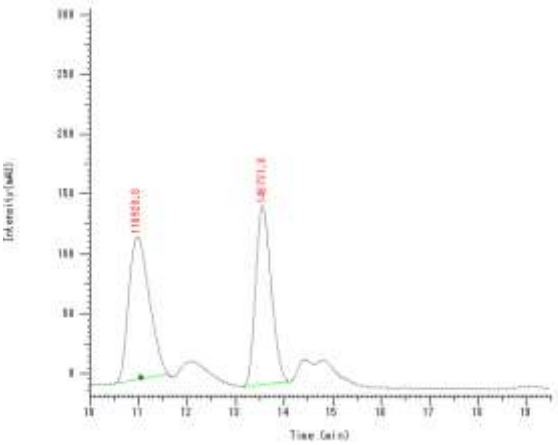


RT	area	%
11.2	1150301.2	3.838
12.3	494722.9	1.651
14	24015875.9	80.139
15.5	4307038.8	14.372

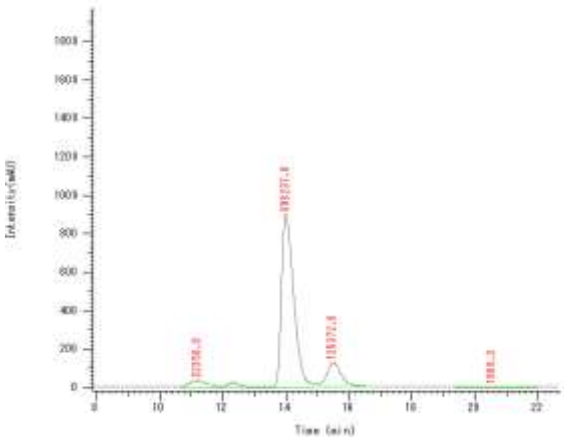
rac-**3c**



rac-**3d**

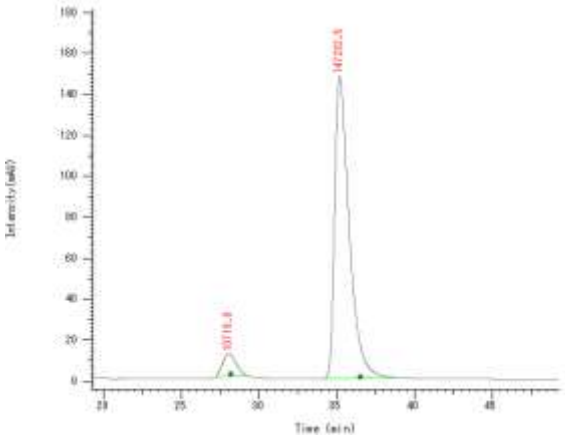


5_**3e**



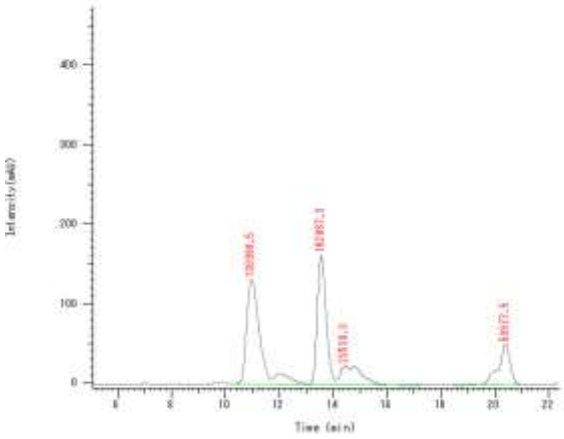
RT	area	%
11.2	1166898	3.955
14	23999837	81.35
15.5	4182947	14.178
20.6	152445.2	0.517

6_**3f**

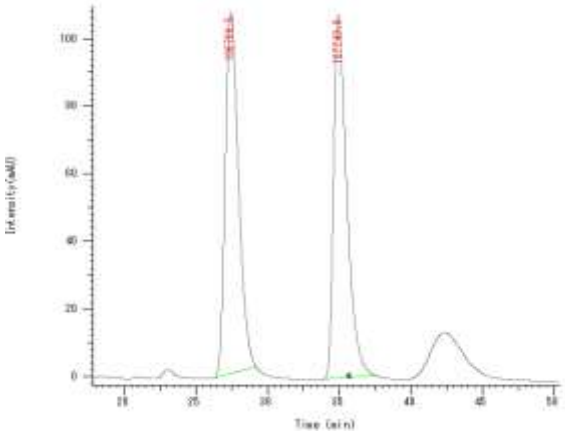


RT	area	%
28.1	605042.3	6.151
35.2	9535785	93.849

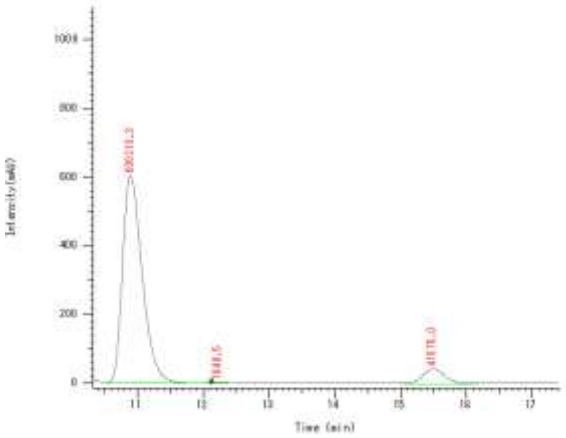
rac-**3e**



rac-**3f**

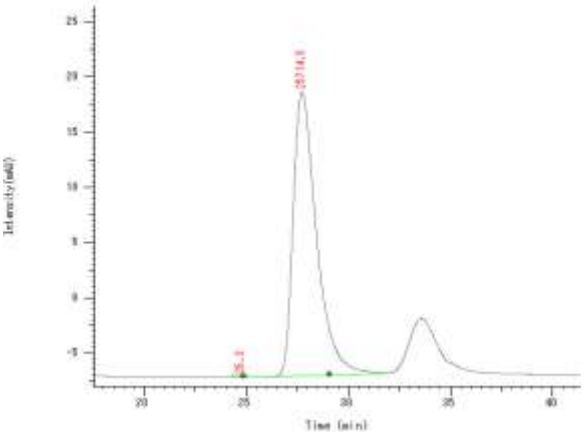


7_**3g**



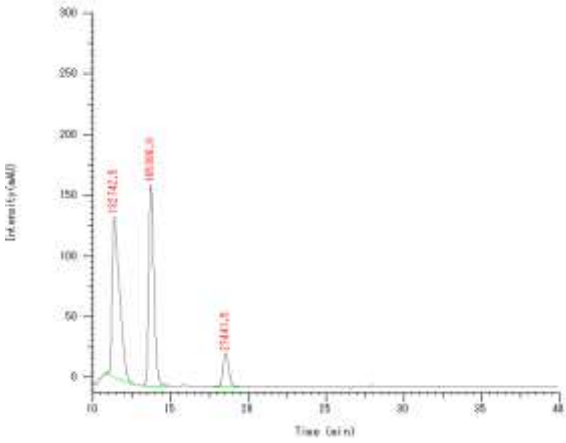
RT	area	%
10.9	12426416	92.966
12.2	24616.3	0.184
15.5	915561.7	6.85

8_**3h**

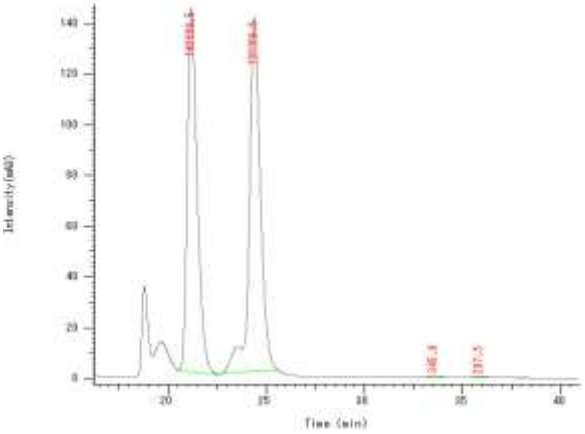


RT	area	%
24.8	2531.8	0.124
27.8	2040524	99.876

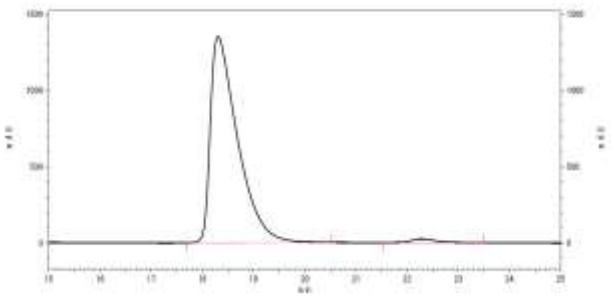
rac-**3g**



rac-**3h**

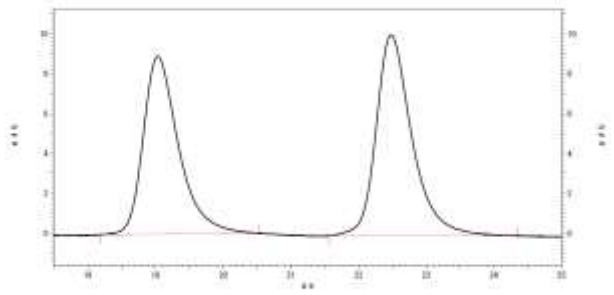


9_**3i**

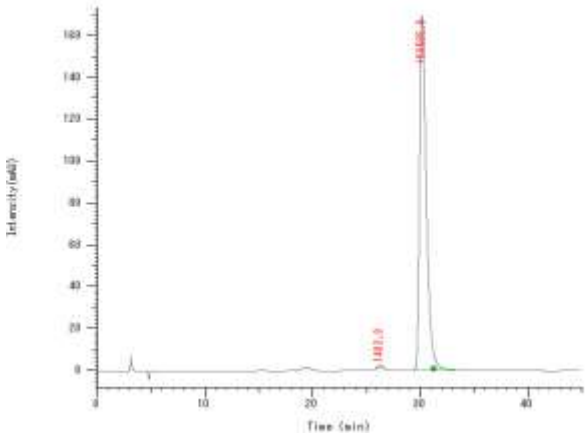


RT	area	%
18.3	199392193	98.31
22.2	3417969	1.68

rac-**3i**

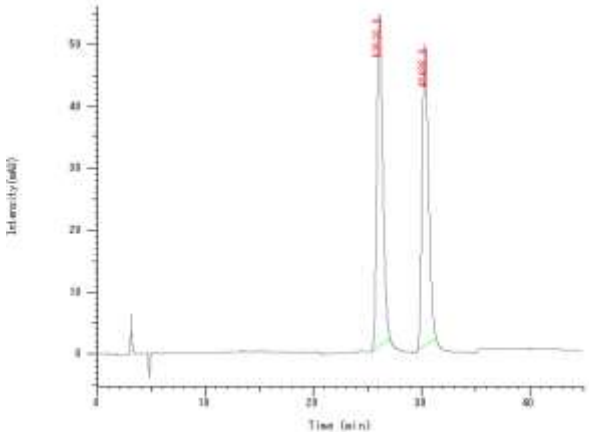


10_**3j**

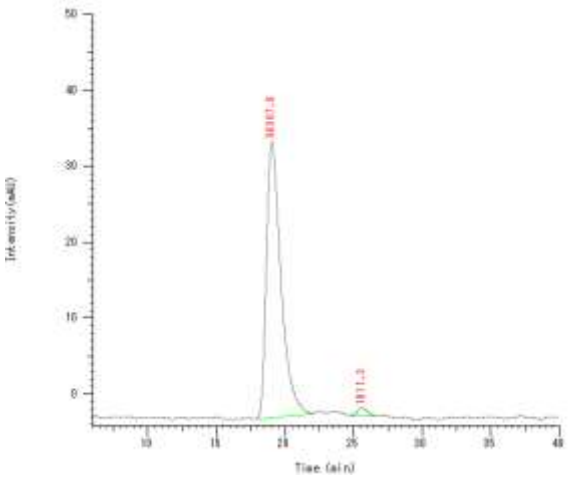


RT	area	%
26.3	36080.3	0.49
30.2	7331461	99.51

rac-**3j**



11_**3k**



RT	area	%
19.1	2666632	98.088
25.6	51969.7	1.912

rac-**3k**