Electronic Supporting Information

Catalyst-free anti-Markovnikov hydroamination and hydrothiolation of vinyl heteroarenes in aqueous medium: an improved process towards centhaquine

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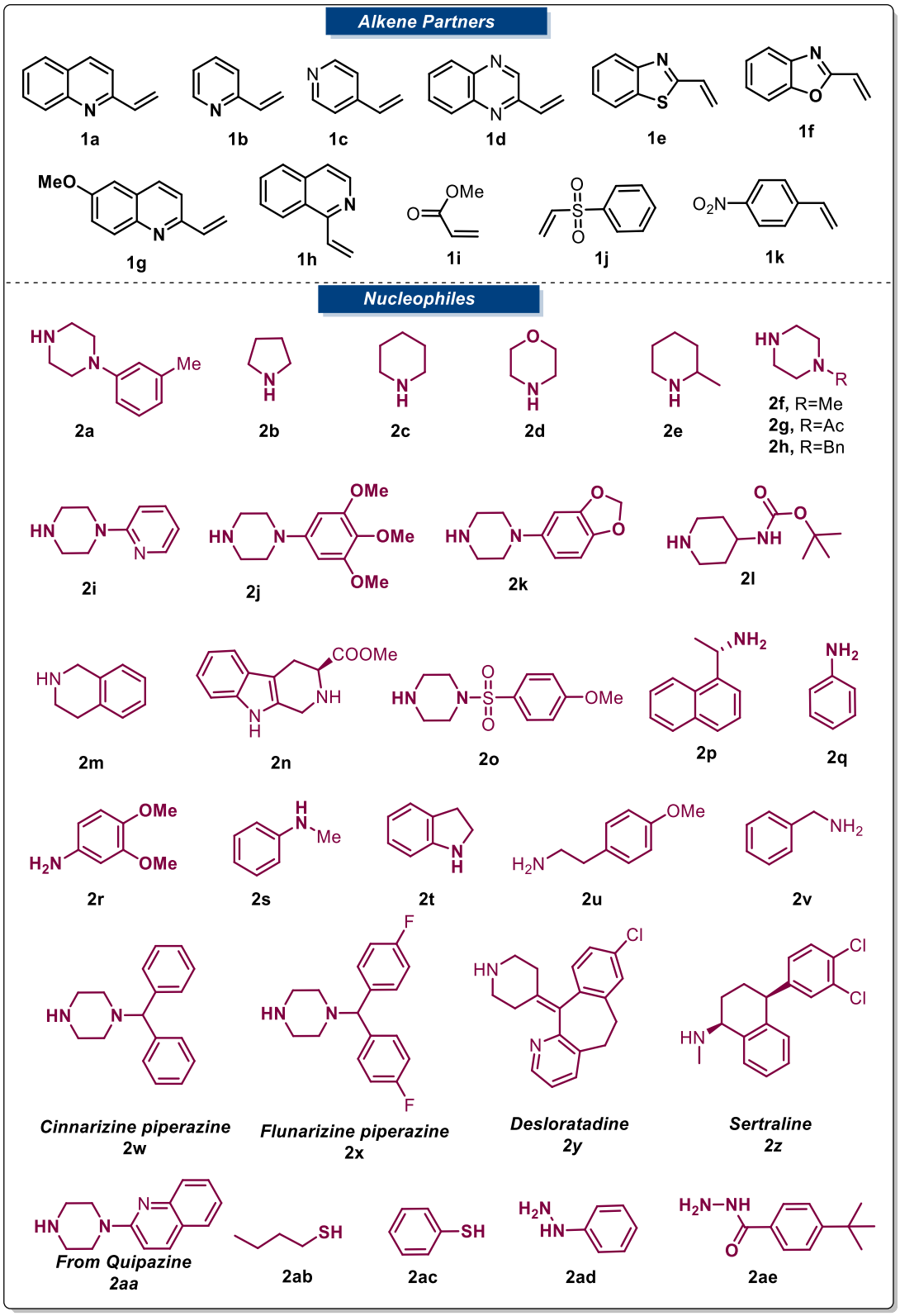
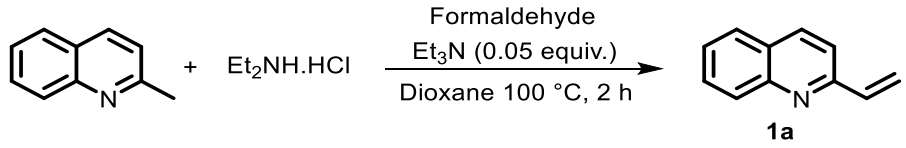
1. <u>General Information</u>. All the reagents and solvents were used as received from commercial sources without further purification. All air and moisture sensitive reactions were conducted under inert atmosphere of nitrogen. Reactions were monitored by thin-layer chromatography carried out on silica plates (Silica gel 60 F_{254}, Merck) using UV-light, iodine, ninhydrin and *p*-anisaldehyde for visualization. Column chromatography was carried out using silica gel (100-200 and 230-400 mesh) packed in glass columns. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent (300 and 75 MHz / 400 and 100 MHz, 500 and 125 MHz) at ambient temperature. The coupling constant *J* is given in Hz. The chemical shifts (δ) are reported in ppm on scale downfield from TMS and using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 ppm and C: δ = 77.00 ppm) or TMS (δ = 0.00) as internal standard and signal patterns are indicated as follows: *s* = singlet, *d* = doublet, dd = doublet of doublet, *ddd* = doublet of doublet of doublet, *dt* = doublet of triplet, *t* = triplet, *q* = quartet, *m* = multiplet. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Exactive ORBITRAP spectrometer using H_2O/MeOH mixed with 0.1% formic acid as mobile phase. Melting points were recorded on Stuart SMP30 melting point apparatus and are uncorrected.

2. Figure S1: list of alkene partners and nucleophiles

All the alkenes were prepared using reported literature.[1] Compounds (**2a**, **2j** and **2k**),[2] (**2w** and **2x**),[3] (**2aa)**[4] were prepared according to according to reported literature.



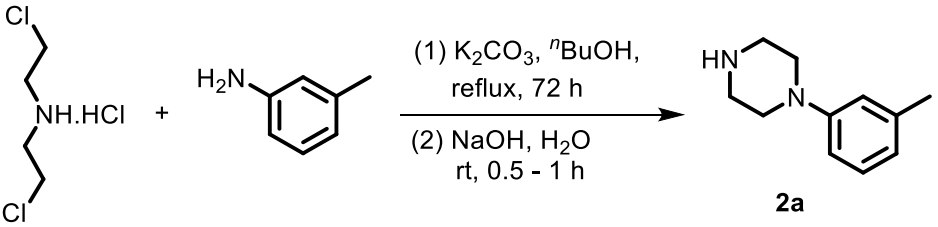
3. Procedure for the synthesis of 2-vinylquinoline (1a)



1a

In a 500 mL round bottom flask, Quinaldine (16.98 mL, 125.71 mmol), formaldehyde solution (12.17 mL, 163.42 mmol), diethylamine hydrochloride (17.91 g, 163.42 mmol), and trimethylamine (0.878 ml, 6.29 mmol) were taken in 1,4-dioxane (200 mL). The reaction mixture was heated at 100 ºC with stirring for 2 h. After completion, reaction mixture was cooled down to room temperature and dioxane was removed under reduced pressure. Water was added to the reaction mixture and organic layer was extracted with ethyl acetate. Organic layer was dried over sodium sulfate and solvent was removed under reduced pressure and the product was purified in 10% ethyl acetate/ Hexane to afford 1a as yellow oil with 75% yield (14.65 g); $\mathbf{R_f}$ = 0.5 (approximately in 10% ethyl acetate/hexane); **^{1}H NMR (400 MHz, $CDCl_3$):** ***δ*** 8.09 (dd, *J* = 17.4, 8.6 Hz, 2H), 7.82 – 7.74 (m, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.50 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.05 (dd, *J* = 17.7, 10.9 Hz, 1H), 6.28 (dd, *J* = 17.7, 0.8 Hz, 1H), 5.67 (dd, *J* = 10.9, 0.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** ***δ*** 156.2, 148.1, 138.1, 136.5, 129.8, 129.5, 127.6, 127.6, 126.5, 120.0, 118.5.

4. Procedure for the synthesis of m-tolylpiperazine (2a)

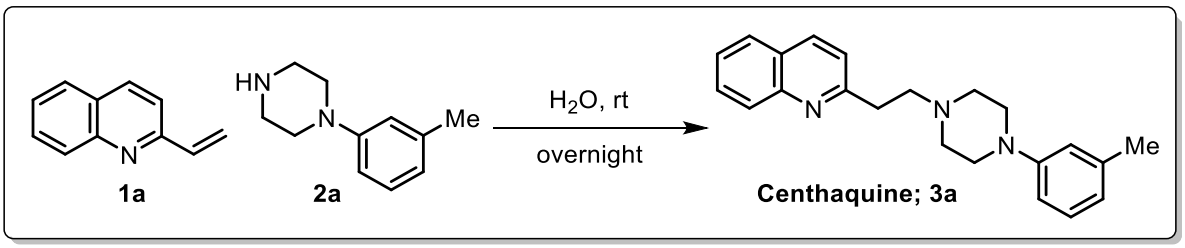


2a

Bis(2-chloroethyl)amine (20 g, 112.06 mmol) in ^{n}BuOH (90 mL) was added slowly to solution of substituted *m*-toluidine (11.04 mL, 101.97 mmol) in ^{n}BuOH (20 mL) and heated at reflux for 24 h. K_2CO_3 (30.97 g, 224.11 mmol) was added to the reaction mixture and again refluxed

for another 48 h. The hot mixture was filtered, and deep red liquor was evaporated under reduced pressure to afford m-tolylpiperazine hydrochloride. 150 mL water was added to m-tolylpiperazine hydrochloride, and the pH value was adjusted to 11–12 using aqueous solution of 40% NaOH. Compound was extracted using ethyl acetate (2 × 150 mL), and the combined extracts were washed with water (80 mL) and brine (80 mL) respectively. Organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. Product **2a** was purified using silica-gel column chromatography with 10% MeOH/DCM+2-3% Et_3N as off-white solid in 70% yield; $\mathbf{R_f}$ = 0.2 (approximately in 10% MeOH/DCM+2-3% Et_3N); **^{1}H NMR (300 MHz, $CDCl_3$):** ***δ*** 7.15 (td, *J* = 7.4, 1.1 Hz, 1H), 6.80 – 6.64 (m, 3H), 3.13 (dd, *J* = 6.2, 3.4 Hz, 4H), 3.03 (dd, *J* = 6.2, 3.4 Hz, 4H), 2.32 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** ***δ*** 152.0, 138.9, 129.1, 120.8, 117.2, 113.4, 50.7, 46.3, 21.9.

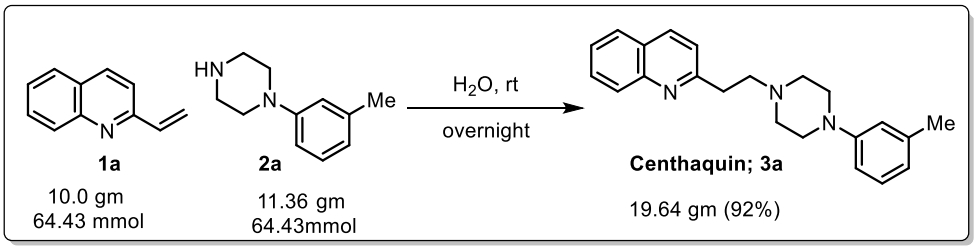
5. Gram-Scale Synthesis Of Centhaquine (*2-(2-(4-(m-tolyl)piperazin-1-yl)ethyl)quinoline) 3a*



In a 250 mL round bottom flask, 2-vinylquinoline **1a** (10.0 gm., 64.43 mmol) and *N*-(m-tolyl)piperazine **2a** (11.36 gm., 64.43mmol) were taken in triple distilled water (25 mL). The reaction mixture was stirred at room temperature for overnight. After completion, 25 mL water was added to the reaction mixture and organic layer was extracted using ethyl acetate (40 mL X 3). Organic layer was dried over anhydrous sodium sulphate and solvent was removed under high vacuum. 100 mL hexane was added into crude reaction mixture and heated than 1.0 gm charcoal was added. Heated reaction mixture was filtered using sintered glass funnel. Filtrate was kept at room temperature for 1-2 h to afford Centhaquine **3a** as an off-white crystalline

solid. **Yield:** 19.64 gm., 92%; **m.p:** 94-95 °C (Matched with US20150250782A1, 2015). **TLC specification:** R_f = = 0.4 (approximately); **Solvent system:** 100% Ethyl acetate using Merck silica gel 60 F254 pre-coated plates (0.25 mm); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.06 (dd, *J* = 8.1, 6.0 Hz, 2H), 7.78 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.51 – 7.12 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.17 – 7.12 (m, 1H), 6.76 – 6.73 (m, 2H), 6.69 – 6.67 (m, 1H), 3.24 – 3.16 (m, 6H), 2.96 – 2.91 (m, 2H), 2.75 – 2.72 (m, 4H), 2.31 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 161.0, 151.5, 148.1, 138.9, 136.4, 129.5, 129.0, 129.0, 127.6, 126.9, 126.0, 121.8, 120.7, 117.0, 113.3, 58.3, 53.3, 49.4, 36.8, 21.9; **HRMS (ESI)** *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{26}N_3$, 332.2127, found 332.2121.

6. GREEN METRICS CALCUALATIONS FOR OUR METHOD



1. NO OF STEPS: 1

2. PERCENTAGE YIELD: 92% yield

3. ATOM ECONOMY:

$$= \frac{\text{Molecular weight of Product [P]}}{\text{Molecular weight of Reactant [A+B]}} \text{ X } 100$$

$$= (331.4630 \text{ X } 100)/(155.2000 + 176.2630) = 33146.3/331.463 = 100\%$$

4. CARBON EFFICIENCY:

$$= \frac{\text{No. of mole of Product X No of carbon in Product}}{\text{No. of mole of Reactant (A+B) X No of carbon in Reactant (A+B)}} \text{ X } 100$$

$$= \frac{59.25 \text{ X } 22}{64.4 \text{ X } 11+64.4 \text{ X } 11} \text{ X } 100 \quad = \quad 92.05\%$$

5. REACTION MASS EFFICIENCY:

$$= \frac{\text{Mass of isolated Product}}{\text{Total mass of Reactant}} \text{ X } 100$$

$$= \quad 19.65/10 \text{ gm} + 11.36 \text{ gm} = 92\%$$

6. E FACTOR:

$$= \frac{\text{Mass of raw material - mass of product}}{\text{Mass of product}}$$

$$= \frac{(10.0 \text{ g} + 11.36 \text{ g}) - 19.65 \text{ g}}{19.65 \text{ g}} \quad = 0.08 \text{ (g/g)}$$

7. ATOM EFFICIENCY FACTOR (AEF):

$$= \frac{\text{Percentage yield X Atom economy}}{100}$$

$$= \quad 92 \text{ X } 100\backslash 100 = 92\%$$

8. OPTIMUM EFFICIENCY (OE):

$$= \frac{\text{Reaction Mass Efficiency}}{\text{Atom Efficiency}} \text{ X } 100$$

$$= \frac{92}{100} \text{ X } 100 = 92\%$$

9. PROCESS MASS INTENSITY (PMI):

$$= \frac{\text{Total mass used considering all solvents during reaction and work-up}}{\text{Mass of product}}$$

$$= \frac{10.0 \text{ g} + 11.36 \text{ g} + 49.91 \text{ g } (H_2O) + 451.32 \text{ g (EtOAc)}}{19.65 \text{ g}} = 26.59 \text{ (g/g)}$$

10. MASS INTENSITY (MI):

$$= \frac{\text{Total mass used in a process or process step (excluding water)}}{\text{Mass of product}}$$

$$= \frac{10 \text{ g} + 11.36 \text{ g}}{19.65 \text{ g}} = 1.08 \text{ (g/g)}$$

11. MASS PRODUCTIVITY (M.P):

$$= \frac{1}{\text{Mass Intensity}} \text{ X } 100$$

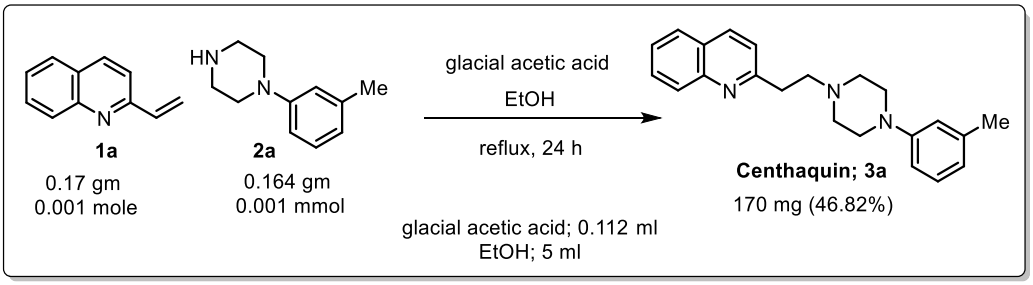
$$= \frac{1}{1.08} \text{ X } 100 = 92.59\%$$

12. WATER INTENSITY (WI):

$$= \frac{\text{Total mass of water used in the whole process}}{\text{Mass of product}}$$

$$= \frac{49.91\ \text{g}}{19.65\ \text{g}} = 2.54\ (\text{g/g})$$

7. GREEN METRICS CALCUALATIONS FOR PREVIOUS METHOD



1. NO OF STEPS: 1

2. PERCENTAGE YIELD: 46.82% yield (*Indian J. Chem.* **1989**, *28B*, 934-942)

3. ATOM ECONOMY:

$$= \frac{\text{Molecular weight of Product [P]}}{\text{Molecular weight of Reactant [A+B]}} \times 100$$

$$= (331.4630 \times 100)/(155.2000 + 176.2630) = 33146.3/331.463 = 100\%$$

4. CARBON EFFICIENCY:

$$= \frac{\text{No. of mole of Product X No of carbon in Product}}{\text{No. of mole of Reactant (A+B) X No of carbon in Reactant (A+B)}} \times 100$$

$$= \frac{0.512 \times 22}{1.10 \times 11 + 1.10 \times 11} \times 100 = 1126.4/24.2 = 46.54\%$$

5. REACTION MASS EFFICIENCY:

$$= \frac{\text{Mass of isolated Product}}{\text{Total mass of Reactant}} \text{ X } 100$$

= (170 mg X 100)/(170 mg + 193.07 mg) = 17000/363.07 = 46.82%

6. E FACTOR:

$$= \frac{\text{Mass of raw material - Mass of product}}{\text{Mass of product}}$$

$$= \frac{(0.170 \text{ g} + 0.193 \text{ g} + 0.118 \text{ g} + 3.95 \text{ g}) - 0.17 \text{ g}}{0.17 \text{ g}} = 25.06 \text{ (g/g)}$$

7. ATOM EFFICIENCY FACTOR (AEF):

$$= \frac{\text{Percentage yield X Atom economy}}{100}$$

= 46.82 X 100\100 = 46.82%

8. OPTIMUM EFFICIENCY (OE):

$$= \frac{\text{Reaction Mass Efficiency}}{\text{Atom Efficiency}} \text{ X } 100$$

= 46.82 X 100\100 = 46.82%

9. PROCESS MASS INTENSITY (PMI):

$$= \frac{\text{Total mass used considering all solvents during reaction and work-up}}{\text{Mass of product}}$$

$$= \frac{0.17\ g + 0.193\ g + 0.118\ g + 3.95\ g + 0.025\ g\ (NaOH) + 26.43\ g\ (EtOAc) + 5.0\ g\ (H_2O)}{0.17\ g}$$

$$= 211.09\ (g/g)$$

10. MASS INTENSITY (MI):

$$= \frac{\text{Total mass used in a process or process step (excluding water)}}{\text{Mass of Product}}$$

$$= (0.17\ g + 0.193\ g + 0.118\ g + 3.95\ g)\ /0.17\ g = 26.06\ (g/g)$$

11. MASS PRODUCTIVITY (M.P):

$$= \frac{1}{\text{Mass Intensity}} \times 100$$

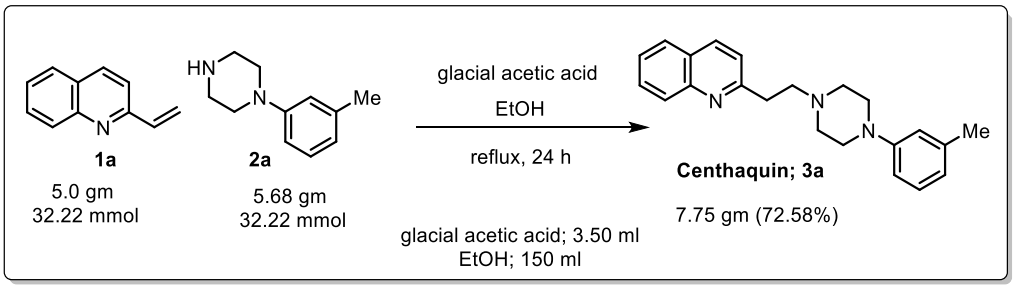
$$= \frac{1}{26.06} \times 100 = 3.83\%$$

12. WATER INTENSITY (WI):

$$= \frac{\text{Total mass of water used in the whole process}}{\text{Mass of product}}$$

$$= \frac{5.0\ g}{0.17\ g} = 29.41\ (g/g)$$

8. GREEN METRICS CALCUALATIONS FOR PREVIOUS METHOD



1. NO OF STEPS: 1

2. PERCENTAGE YIELD: 72.58 % yield (**Patent No: US20150250782A1**)

3. ATOM ECONOMY:

$$= \frac{\text{Molecular weight of Product [P]}}{\text{Molecular weight of Reactant [A+B]}} \text{ X } 100$$

$$= (331.4630 \text{ X } 100)/(155.2000 + 176.2630) = 33146.3/331.463 = 100\%$$

4. CARBON EFFICIENCY:

$$= \frac{\text{No. of mole of Product X No of carbon in Product}}{\text{No. of mole of Reactant (A+B) X No of carbon in Reactant (A+B)}} \text{ X } 100$$

$$= \frac{23.38 \text{ X } 22}{32.22 \text{ X } 11 + 32.22 \text{ X } 11} \text{ X } 100 = 51436/708.84 = 72.56\%$$

5. REACTION MASS EFFICIENCY:

$$= \frac{\text{Mass of isolated Product}}{\text{Total mass of Reactant}} \text{ X } 100$$

$$= (7.75 \text{ g X } 100)/(5.0 \text{ g} + 5.68 \text{ g}) = 72.56\%$$

6. E FACTOR:

$$= \frac{\text{Mass of raw material - Mass of product}}{\text{Mass of product}}$$

$$= \frac{(5.0\text{ g} + 5.68\text{ g} + 3.68\text{ g} + 118.35\text{ g}) - 7.75\text{ g}}{7.75\text{ g}} = 16.12\text{ (g/g)}$$

7. ATOM EFFICIENCY FACTOR (AEF):

$$= \frac{\text{Percentage yield X Atom economy}}{100}$$

$$= 72.5\text{ X }100\backslash100 = 72.5\%$$

8. OPTIMUM EFFICIENCY (OE):

$$= \frac{\text{Reaction Mass Efficiency}}{\text{Atom Efficiency}}\text{ X }100$$

$$= \frac{72.56}{100}\text{ X }100 = 72.56\%$$

9. PROCESS MASS INTENSITY (PMI):

$$= \frac{\text{Total mass used considering all solvents during reaction and work-up}}{\text{Mass of product}}$$

$$= \frac{5.0\text{ g} + 5.68\text{ g} + 3.68\text{ g} + 118.35\text{ g} + 0.6\text{ g (NaOH)} + 451\text{ g (EtOAc)} + 118\text{ g } (H_2O)}{7.75\text{ g}}$$

$$= 90.62\text{ (g/g)}$$

10. MASS INTENSITY (MI):

$$= \frac{\text{Total mass used in a process or process step (excluding water)}}{\text{Mass of Product}}$$

$$= \quad (5.0\ g + 5.68\ g + 3.68\ g + 118.35\ g)\ /7.75\ g \quad = \quad 17.12\ (g/g)$$

11. MASS PRODUCTIVITY (M.P):

$$= \quad \frac{1}{\text{Mass Intensity}} \quad X \quad 100$$

$$= \quad \frac{1}{17.12} \quad X\ 100 \quad = \quad 5.84\%$$

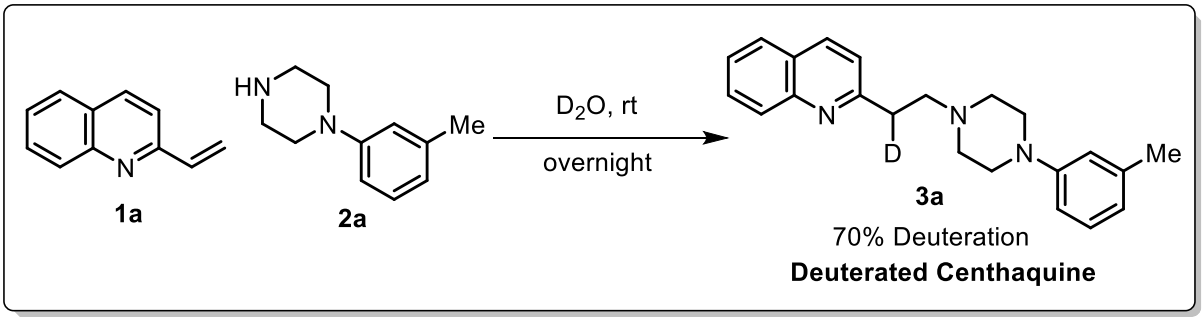
12. WATER INTENSITY (WI):

$$= \frac{\text{Total mass of water used in the whole process}}{\text{Mass of product}}$$

$$= \quad \frac{150.32\ g}{7.75\ g} \quad = 19.39\ (g/g)$$

9. Control experiments

(a) Synthesis of Centhaquine (*2-(2-(4-(m-tolyl)piperazin-1-yl)ethyl)quinoline) in D_2O*



In a 10 mL round bottom flask, 2-vinylquinoline **1a** (100 mg, 0.644 mmol) and *N*-(m-tolyl)piperazine (113 mg, 0.644 mmol) were taken in D_2O (1.0 mL). The reaction mixture was stirred at room temperature for overnight. After completion, 10 mL ethyl acetate was added to the reaction mixture and dried over anhydrous sodium sulphate and solvent was removed under high vacuum. Product was purified *via* basic alumina column chromatography in 20% ethyl acetate/hexane (193 mg, 90%). **TLC specification:** $\boldsymbol{R_f}$ = = 0.4 (approximately); **Solvent system:** 100% Ethyl acetate using Merck silica gel 60 F254 pre-coated plates (0.25 mm); **^{1}H NMR (400 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 8.06 (dd, *J* = 11.6, 8.4 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.51 – 7.48 (m, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.76 – 6.74 (m, 2H), 6.71 (d, *J* = 7.2 Hz, 1H), 3.23 – 3.21 (m, 5.3H), 2.94 – 2.92 (m, 2H), 2.75 – 2.73 (m, 4H), 2.32 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)**: $\boldsymbol{\delta}$ 161.0, 151.5, 148.1, 138.9, 136.4, 129.6, 129.1, 129.0, 127.7, 126.9, 126.0, 121.8, 120.8, 117.1, 113.3, 58.3, 58.2, 53.3, 49.4, 36.8, 21.9; **^{2}H NMR (61 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 3.22 (s, 0.7D); **HRMS (ESI)** *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{25}DN_3$, 333.2189, found 333.2191.

Figure S2: ESI-MS spectra of deuterated Centhaquine **D_1-3a**

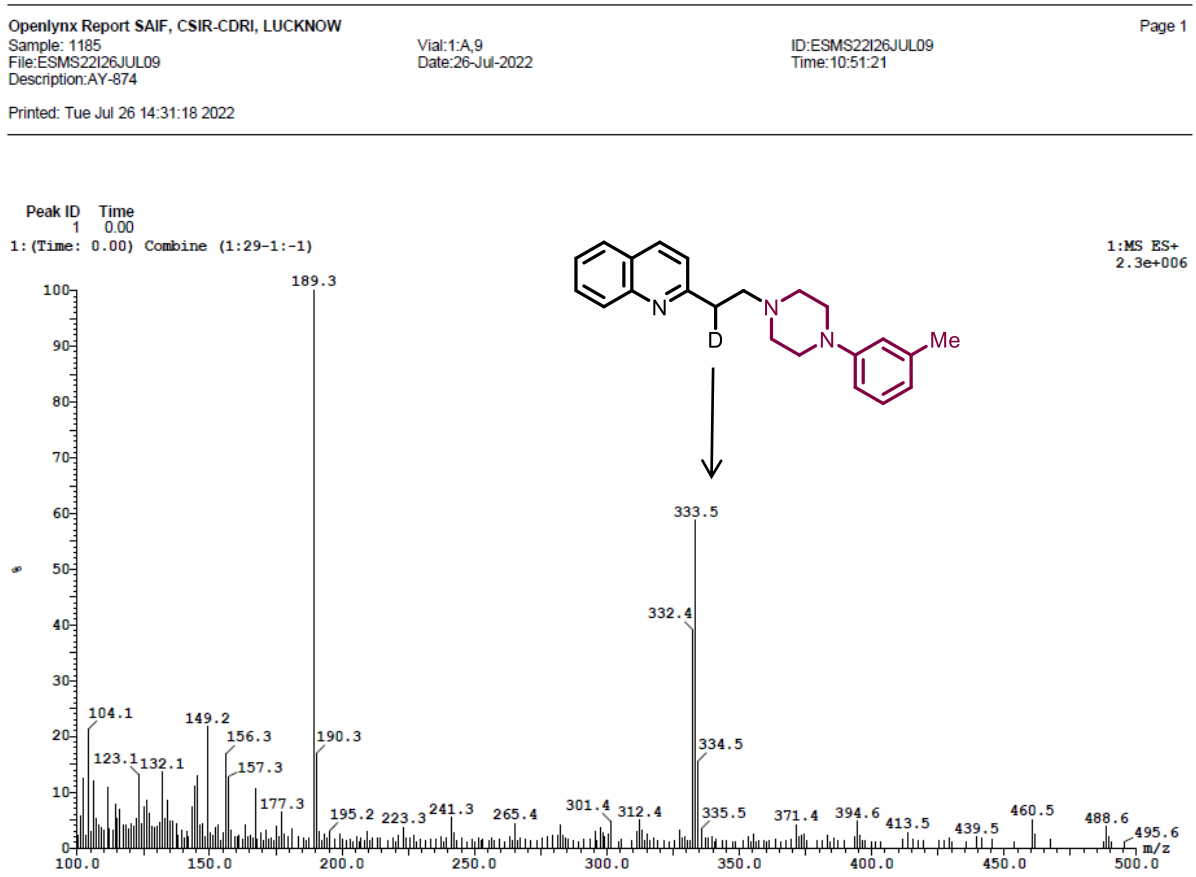
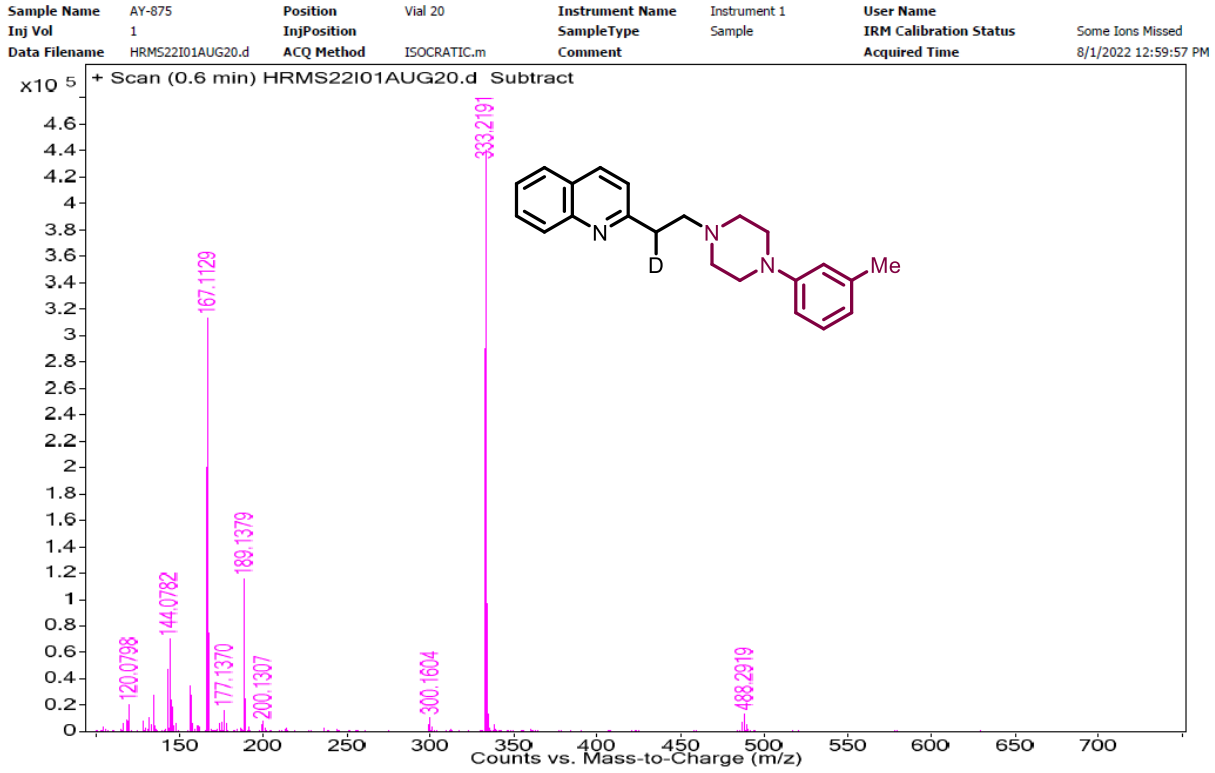
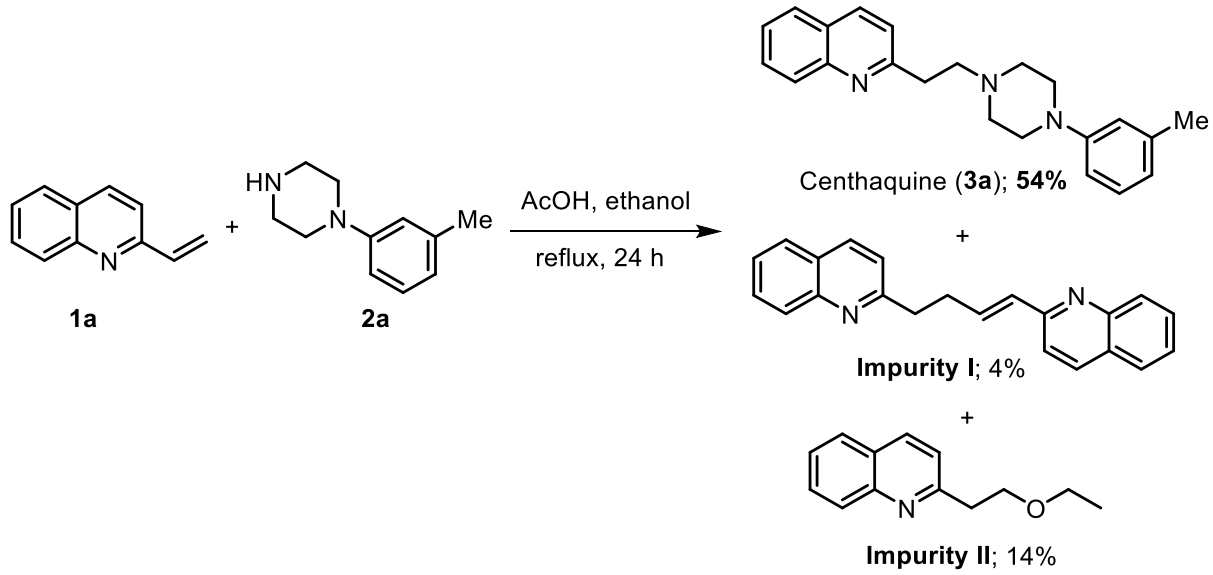


Figure S3: HRMS spectra of deuterated Centhaquine **D_1-3a**



(b) Synthesis of Centhaquine via known process (Gulati's method)



In a 50 mL round bottom flask, 2-vinylquinoline **1a** (1.0 g, 6.44 mmol) and *N*-(m-tolyl)piperazine (1.13 g, 6.44 mmol) and acetic acid (12.88 mmol) were taken in 15.0 ml ethanol and reaction mixture was refluxed for 24 hour. After that, the solvent was removed under high vacuum and ethyl acetate (20 ml) was added to the reaction mixture and basified using 1N NaOH solution. Organic layer was extracted using ethyl acetate and dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure and **impurity I** was purified via silica-gel column chromatography in 25-30% ethyl acetate/hexane (60 mg, 3%); **TLC specification:** $\boldsymbol{R_f}$ = = 0.25 approximately in 10% ethyl acetate/hexane; **Impurity I:** ^{1}**H NMR (300 MHz, CDCl$_3$):** $\boldsymbol{\delta}$ 8.11-8.03 (m, Hz, 4H), 7.79-7.74 (m, 2H), 7.71-7.65 (m, 3H), 7.52-7.45 (m, 2H), 7.37 (d, *J* = 9.0 Hz, 1H), 5.86 (d, *J* = 1.0 Hz, 1H), 5.51 (d, *J* = 1.0 Hz, 1H), 3.38 – 3.26 (m, 4H); ^{13}**C NMR (75 MHz, CDCl$_3$)**: $\boldsymbol{\delta}$ 162.6, 158.2, 148.3, 148.0, 147.9, 136.3, 136.1, 129.9, 129.5, 129.4, 129.0, 127.6, 127.5, 127.3, 126.9, 126.3, 125.8, 121.8, 118.9, 117.1, 38.4, 34.0; **HRMS (ESI)** *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{19}N_2$, 311.1548, found 311.1549.

Impurity II was purified via silica-gel column chromatography in 35% ethyl acetate/hexane (182 mg, 14%); **TLC specification:** $\boldsymbol{R_f}$ = = 0.2 approximately in 10% ethyl acetate/hexane;

Impurity II: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08-8.03 (m, 2H), 7.78 (dd, *J* = 8.4, 1.2, 1H), 7.70-7.66 (m, 1 H), 7.50-7.46 (m, 1 H), 7.38 (d, *J* = 8.4, 1H), 3.89 (t, *J* = 6.8, 1H), 3.53 (q, *J* = 6.8, 1H), 3.26 (t, *J* = 6.8, 1H), 1.86 (t, *J* = 7.2, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.2, 148.0, 136.3, 129.5, 128.9, 127.6, 127.0, 126.0, 122.1, 70.0, 66.4, 39.67, 15.3; **HRMS (ESI)** *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{16}NO$, 202.1232, found 202.2489.

Figure S4: ESI-MS spectra of impurity **I**

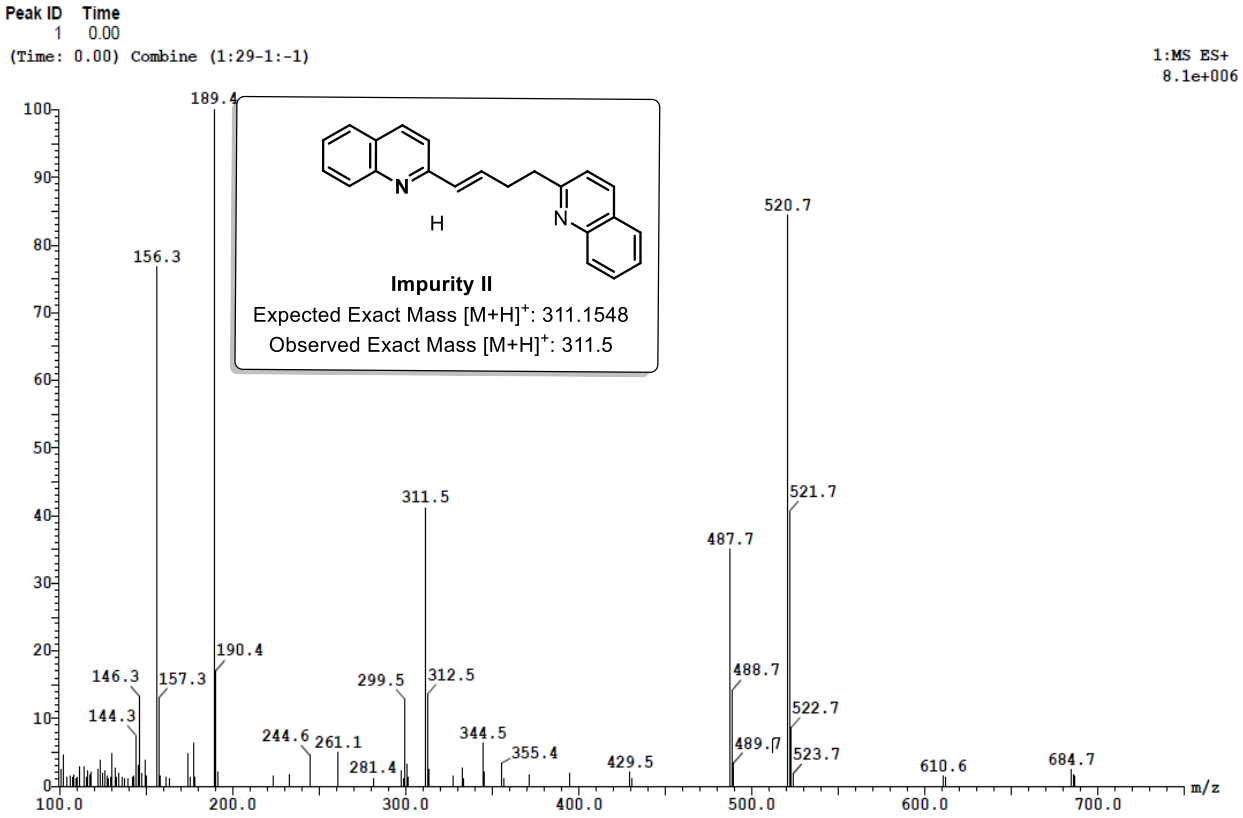
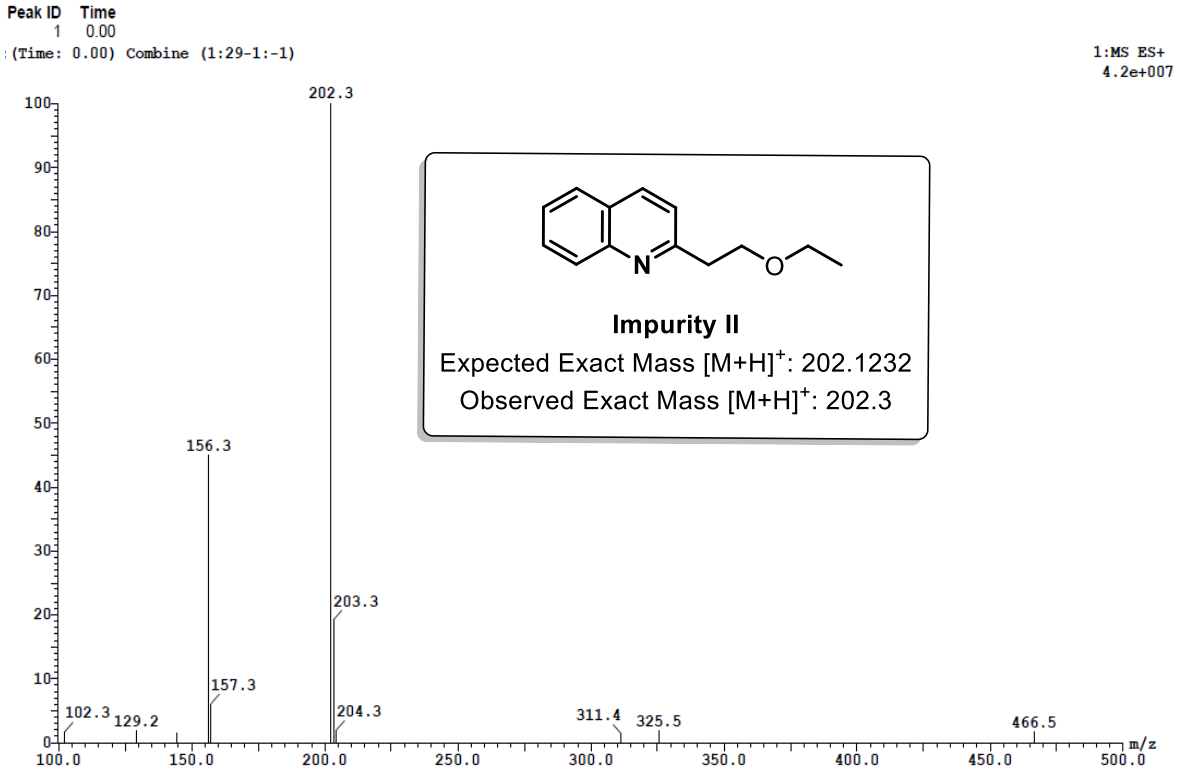
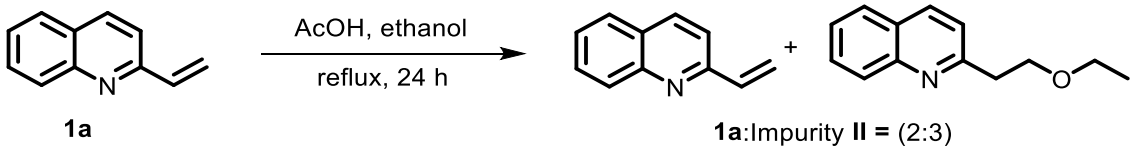


Figure S5: ESI-MS spectra of impurity **II**



(c) Reaction in absence of m-tolylpiperazine



In a 50 mL round bottom flask, 2-vinylquinoline 1a (1.0 g, 6.44 mmol) and *N*-(m-tolyl)piperazine (1.13 g, 6.44 mmol) and acetic acid (12.88 mmol) were taken in 15.0 ml ethanol and reaction mixture was refluxed for 24 hour. After that, the solvent was removed under high vacuum and ethyl acetate (20 ml) was added to the reaction mixture and basified using 1N NaOH solution. Organic layer was extracted using ethyl acetate and dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure to afford the mixture of 2-vinylquinoline (**1a**) and Impurity **II** in 2:3 ratio.

Figure S6: ESI-MS spectra of crude reaction mixture after 24 h

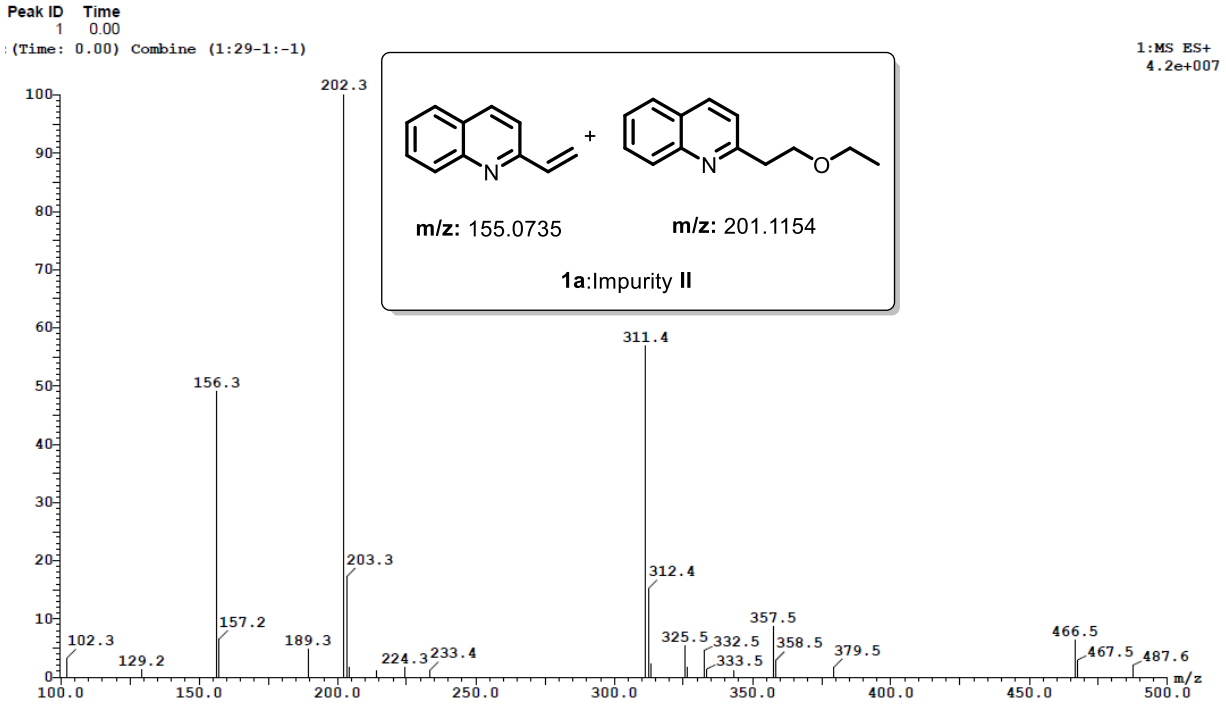
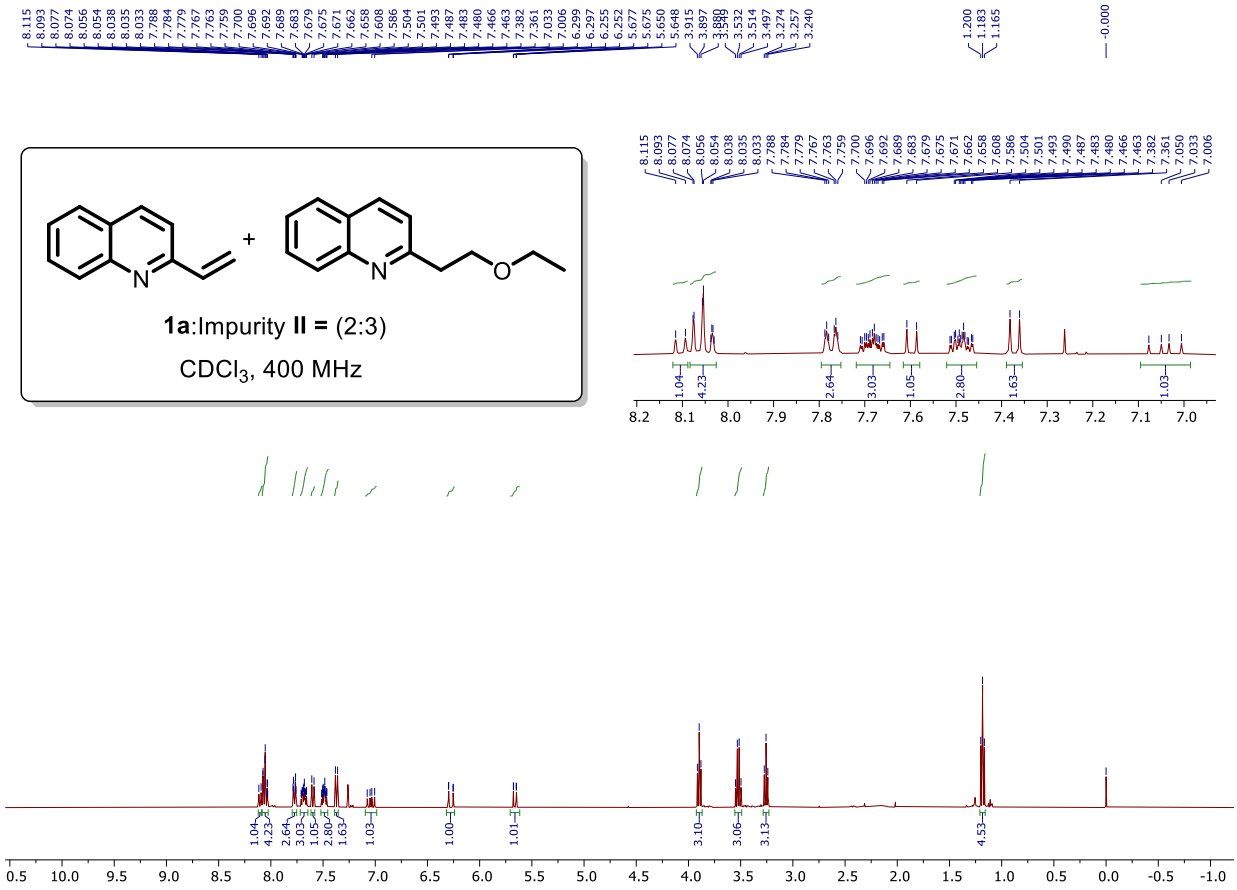
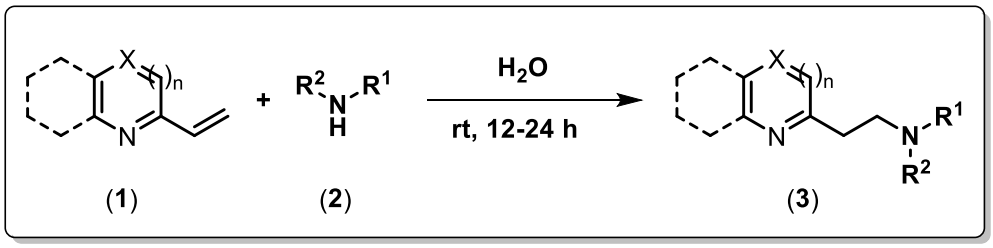


Figure S7: ^{1}H NMR of reaction mixture after 24 h



10. Experimental procedures and spectral data

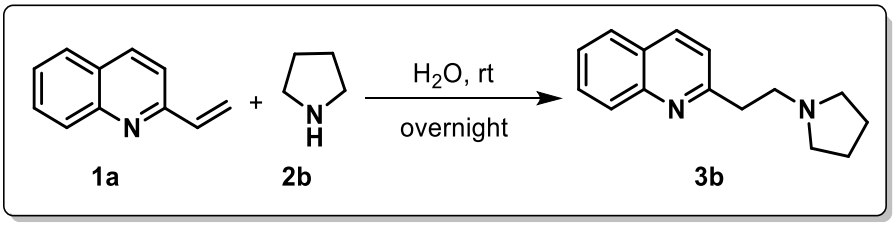
10a: General procedure for aza-michael-type addition



Vinyl *N*-heterocycles (**1**) (100 mg, 0.628 mmol) and alkyl/aryl amine (**2**) (0.628 mmol) was taken in 10 mL round bottom flask in 1.0 mL triple distilled water and stirred at room temperature. On completion of the reaction (based on TLC), the reaction mixture was diluted with 20 mL water and organic layer was extracted using ethyl acetate (15 mL X 2), and the combined organic layer was dried over anhydrous sodium sulfate, followed by evaporation of the solvent *in vacuo*. The crude was purified by silica gel and basic alumina column chromatography to afford the desired product **3.**

Spectral data

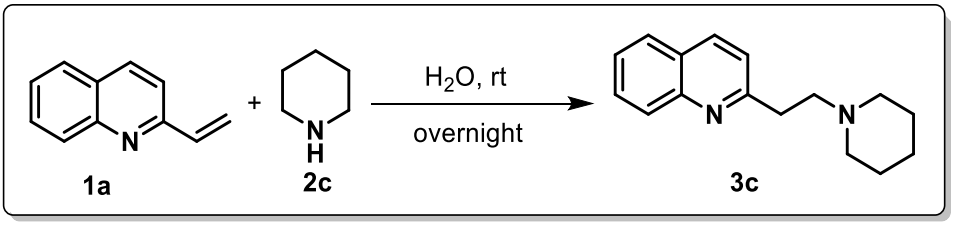
2-(2-(Pyrrolidin-1-yl)ethyl)quinoline (3b)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), pyrrolidine **2b** 26 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (20% MeOH/DCM) to yield **3b** as light yellow oil (136 mg, 93%); $\boldsymbol{R_f}$ = 0.1 (5% MeOH/EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 8.06 (t, *J* = 8.1 Hz, 2H), 7.78 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.51 – 7.46 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 3.25 – 3.19 (m, 2H), 3.00 – 2.95 (m, 2H), 2.65 – 2.61 (m, 4H), 1.83 – 1.79 (m, 4H); **^{13}C NMR (75**

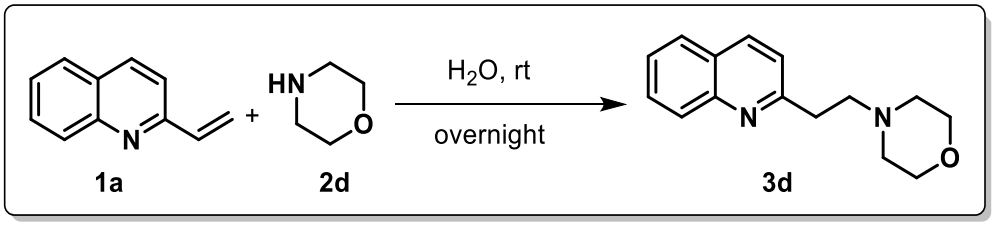
MHz, $CDCl_3$): δ 159.4, 147.9, 136.7, 129.6, 128.9, 127.7, 127.0, 126.1, 121.9, 54.9, 53.7, 36.7, 23.5; **HRMS (ESI) m/z:** [M+H]+ calcd. for $C_{15}H_{19}N_2$ 227.1548, found 227.1548.

2-(2-(Piperidin-1-yl)ethyl)quinolone (3c)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), piperidine **2c** (54.8 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (20% EtOAc in hexane) to yield **3c** as light brown oil (135 mg, 87%); $\boldsymbol{R_f}$ = 0.1 (10% MeOH/EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$): δ** 8.05 (dd, *J* = 8.4, 2.7 Hz, 2H), 7.76 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.50 – 7.45 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 3.21 – 3.16 (m, 2H), 2.85 – 2.80 (m, 2H), 2.53 – 2.49 (m, 4H), 1.62 (dt, *J* = 10.9, 5.6 Hz, 4H), 1.49 – 1.41 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$): δ** 161.4, 148.0, 136.3, 129.4, 129.0, 127.6, 126.9, 125.7, 121.8, 59.1, 54.6, 36.8, 26.1, 24.5; **HRMS (ESI) m/z:** [M+H]+ calcd. for $C_{16}H_{21}N_2$ 241.1705, found 241.1704.

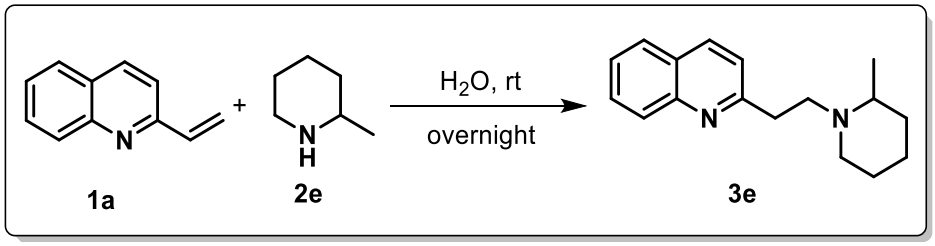
4-(2-(Quinolin-2-yl)ethyl)morpholine (3d)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), morpholine **2d** (56 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (5% MeOH/EtOAc) to yield **3d** as dark brown oil (144 mg, 92%); $\boldsymbol{R_f}$ = 0.1

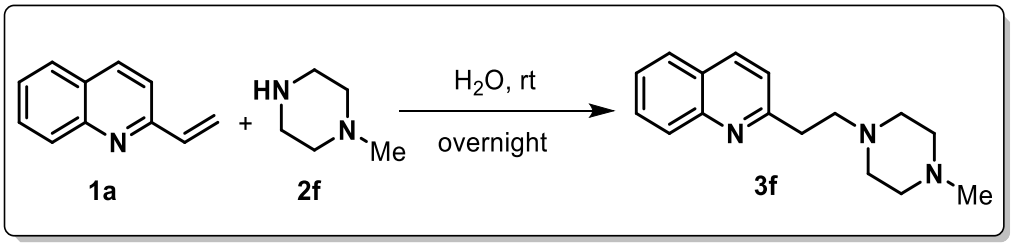
(100% EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$): δ** 8.08 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.79 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.53 – 7.47 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 3.78 – 3.75 (m, 4H), 3.25 – 3.20 (m, 2H), 2.99 – 2.94 (m, 2H), 2.67 – 2.64 (m, 4H); **^{13}C NMR (75 MHz, $CDCl_3$): δ** 160.4, 148.0, 136.6, 129.6, 128.9, 127.7, 127.0, 126.1, 121.8, 66.7, 58.3, 53.6, 36.0; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{15}H_{19}N_2O$ 243.1497, found 243.1491.

2-(2-(2-Methylpiperidin-1-yl)ethyl)quinolone (3e)



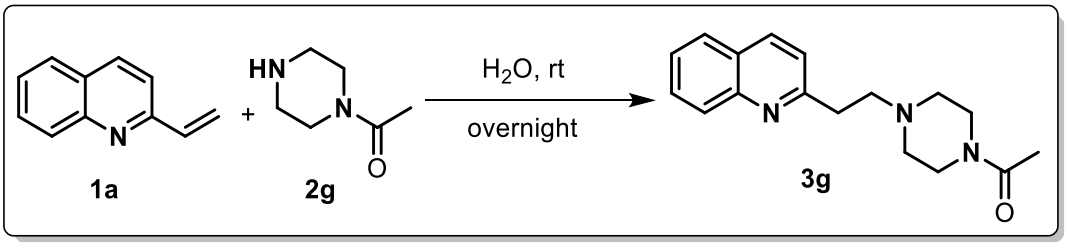
According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), 2-methylpiperidine **2e** (64 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (10% EtOAc in hexane) to yield **3e** as light yellow oil (144 mg, 88%); R_f = 0.2 (5% MeOH/EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$): δ** 8.06 (d, *J* = 4.8 Hz, 1H), 8.03 (d, *J* = 4.8 Hz, 1H), 7.77 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.50 – 7.45 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 3.16 – 311 (m, 3H), 3.05 – 2.96 (m, 2H), 2.45 – 2.34 (m, 2H), 1.70 – 1.56 (m, 3H), 1.35 – 1.26 (m, 3H), 1.14 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$): δ** 161.7, 148.1, 136.3, 129.47, 129.0, 127.6, 126.9, 125.9, 121.8, 55.5, 54.1, 52.5, 34.9, 34.8, 26.4, 24.3, 19.5; **HRMS (ESI) m/z:** [M+H]+ calcd. for $C_{17}H_{23}N_2$ 255.1861, found 255.1860.

2-(2-(4-Methylpiperazin-1-yl)ethyl)quinolone (3f)



According to general procedure by using *2-vinylquinoline* **1a** (100 mg, 0.644 mmol), *N*-methylpiperazine **2f** (64 mg, 0.644 mmol) were taken in H_2O (1.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (5% MeOH/EtOAc) to yield **3f** as light brown oil (153 mg, 93%); $\boldsymbol{R_f}$ = 0.1 (100% EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 8.05 (t, *J* = 8.4 Hz, 2H), 7.78 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.51 – 7.46 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 3.21 – 3.16 m, 2H), 2.91 – 2.86 (m, 2H), 2.63 (m, 4H), 2.49 (m, 4H), 2.30 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 161.1, 148.1, 136.4, 129.5, 129.0, 127.4, 126.9, 126.0, 121.8, 58.2, 55.2, 53.1, 46.1, 36.8; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{16}H_{22}N_3$ 256.1814, found 256.1814.

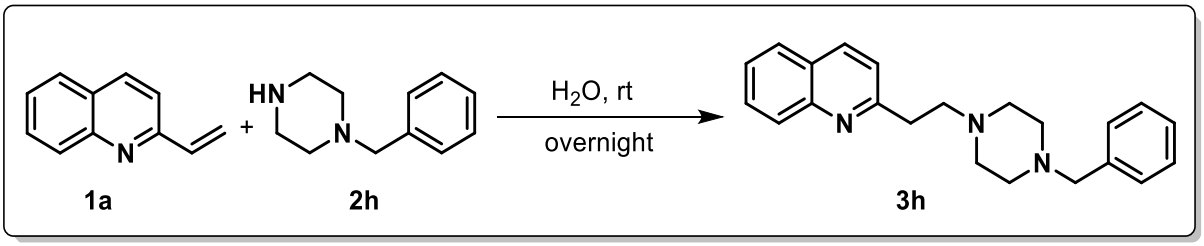
1-(4-(2-(Quinolin-2-yl)ethyl)piperazin-1-yl)ethan-1-one (3g)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), *N*-(piperazin-1-yl)ethan-1-one **2g** (82.6 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (25% EtOAc in hexane) to yield **3g** as light yellow oil (132 mg, 72%); $\boldsymbol{R_f}$ = 0.1 (100% EtOAc in hexane); **^{1}H NMR (300 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 8.07 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H),, 7.78 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.52 –

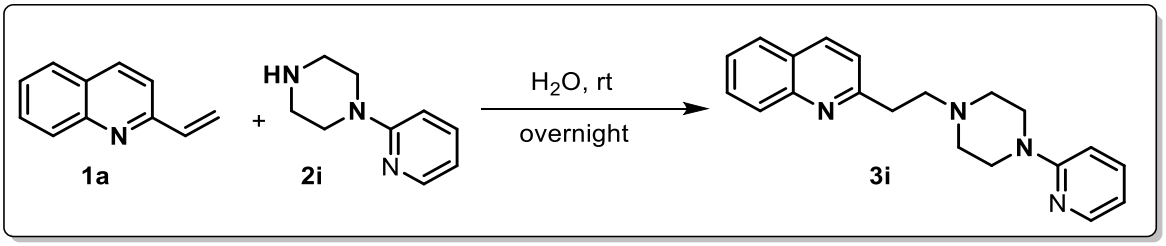
7.47 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 3.63 (t, *J* = 5.1 Hz, 2H), 3.46 (t, *J* = 5.1 Hz, 2H), 3.20 – 3.15 (m, 2H), 2.92 – 2.87 (m, 2H), 2.54 (dd, *J* = 10.2, 6.0 Hz, 4H), 2.08 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$): *δ*** 169.0, 160.7, 148.0, 136.4, 129.5, 128.9, 127.6, 126.9, 126.0, 121.7, 58.0, 53.3, 52.8, 46.4, 41.5, 36.6, 21.4; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{17}H_{22}N_3O$ 284.1763, found 284.1760.

2-(2-(4-Benzylpiperazin-1-yl)ethyl)quinolone (3h)



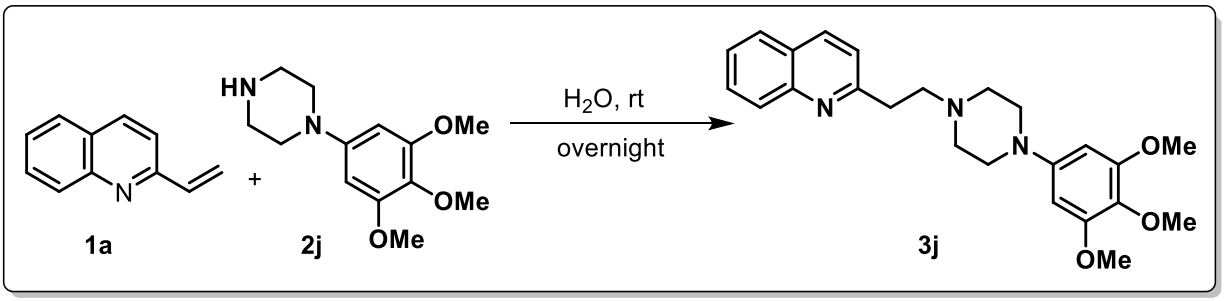
According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), N-benzylpiperazine **2h** (113.6 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (15% EtOAc in hexane) to yield **3h** as light yellow oil (170 mg, 79%); R_f = 0.2 (100% EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$): *δ*** 8.04 (t, *J* = 8.4 Hz, 2H), 7.77 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.50 – 7.46 (m, 1H), 7.33 – 7.29 (m, 5H), 7.28 – 7.23 (m, 1H), 3.52 (s, 2H), 3.19 – 3.15 (m, 2H), 2.89 – 2.85 (m, 2H), 2.61 (m, 4H), 2.52 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$): *δ*** 161.1, 148.0, 138.2, 136.39, 129.5, 129.4, 128.9, 128.3, 127.6, 127.2, 126.9, 125.9, 121.8, 63.2, 58.3, 53.2, 36.8; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{22}H_{26}N_3$ 332.2127, found 332.2112.

2-(2-(4-(Pyridin-2-yl)piperazin-1-yl)ethyl)quinolone (3i)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), 1-(pyridin-2-yl)piperazine **2i** (105.2 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (pure EtOAc) to yield **3i** as light brown oil (187 mg, 91%); $\boldsymbol{R_f}$ = 0.4 (100% EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$): δ** 8.20 – 8.81 (m, 1H), 8.07 – 8.03 (m, 2H), 7.77 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.50 – 7.43 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 6.64 – 6.59 (m, 2H), 3.57 (t, *J* = 5.1 Hz, 4H), 3.245 – 3.21 (m, 2H), 2.98 – 2.92 (m, 2H), 2.70 (t, *J* = 5.4 Hz, 4H); **^{13}C NMR (75 MHz, $CDCl_3$): δ** 160.8, 159.6, 148.0, 148.0, 137.5, 136.4, 129.5, 128.9, 127.6, 126.9, 125.9, 121.7, 113.4, 107.1, 58.2, 53.0, 45.2, 36.6; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{20}H_{23}N_4$ 319.1923, found 319.1823.

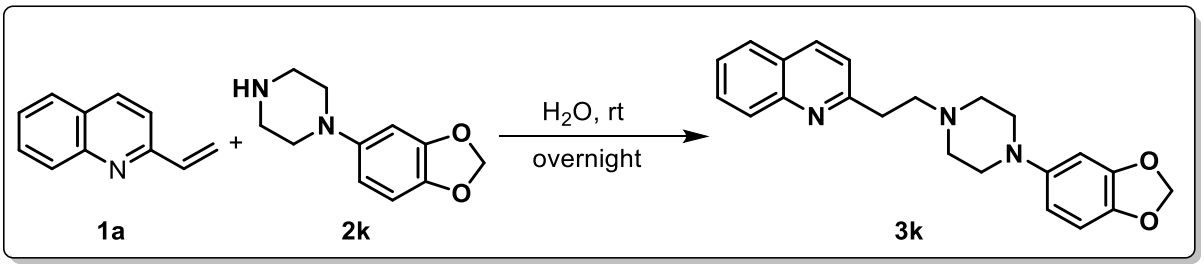
2-(2-(4-(3,4,5-Trimethoxyphenyl)piperazin-1-yl)ethyl)quinolone (3j)



According to general procedure by using 4-vinylquinoline **1a** (100 mg, 0.644 mmol), 1-(3,4,5-trimethoxyphenyl)piperazine **2j** (162.6 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (40% EtOAc in hexane) to yield **3j** as light yellow oil (206 mg, 78%);$\boldsymbol{R_f}$ = 0.6 (100% EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$): δ** 8.09 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.53 – 7.49 (m, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 6.18 (s, 2H), 3.85 (s, 6H), 3.80 (s, 3H), 3.28 – 3.24 (m, 2H), 3.22 – 3.19 (m, 4H), 3.03 – 3.00 (m, 2H), 2.81 (t, *J* = 4.8 Hz, 4H). **^{13}C NMR (100 MHz, $CDCl_3$): δ** 160.6, 153.7, 148.3, 148.0, 136.6, 132.4, 129.7, 128.9, 127.7, 127.0, 126.1, 121.8, 94.9, 61.1,

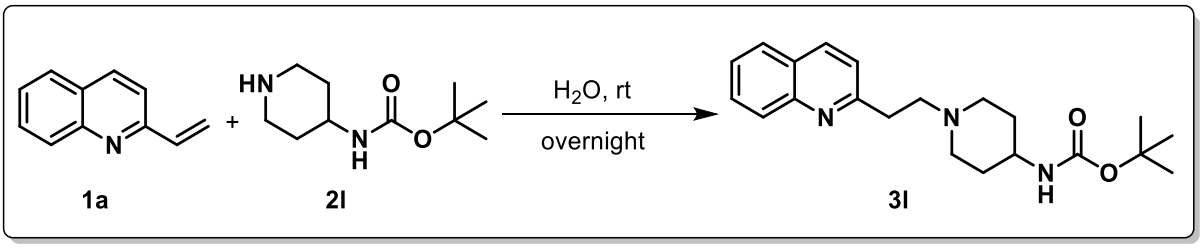
57.9, 56.2, 53.1, 50.0, 36.2; **HRMS (ESI) m/z:** $[M+H]^{+}$ calcd. for $C_{24}H_{30}N_3O_3$ 408.2287, found 408.2279.

2-(2-(4-(Benzo[d][1,3]dioxol-5-yl)piperazin-1-yl)ethyl)quinolone (3k)



According to general procedure by using *2-vinylquinoline* **1a** (100 mg, 0.644 mmol), 1-(benzo[d][1,3]dioxol-5-yl)piperazine **2k** (132.8 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (15% EtOAc in hexane) to yield **3k** as off-white solid (192 mg, 82%); **m.p:** 96-98 °C; R_f = 0.6 (100% EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$): δ** 8.08 – 8.04 (m, 2H), 7.78 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.51 – 7.47 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.37 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.89 (s, 2H), 3.24 – 3.20 (m, 2H), 3.12 – 3.09 (m, 4H), 2.96 – 2.92 (m, 2H), 2.74 – 2.72 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$): δ** 161.0, 148.3, 148.1, 147.6, 141.7, 136.4, 129.6, 129.0, 127.7, 126.9, 126.0, 121.8, 109.1, 108.3, 101.0, 100.0, 58.2, 53.3, 51.0, 36.8; **HRMS (ESI) m/z:** $[M+H]^{+}$ calcd. for $C_{22}H_{24}N_3O_2$ 362.1869, found 362.1860.

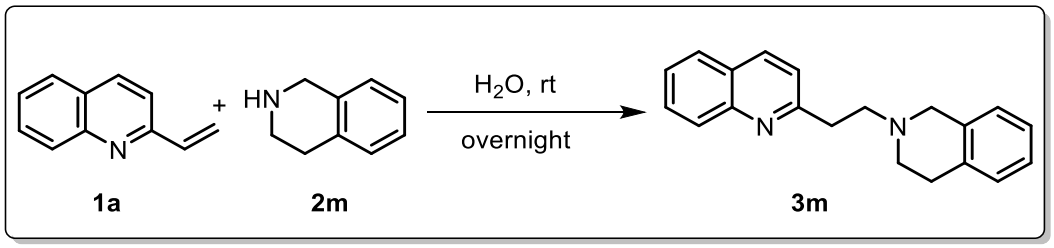
Tert-butyl (1-(2-(quinolin-2-yl)ethyl)piperidin-4-yl)carbamate (3l)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), *tert*-butyl piperidin-4-ylcarbamate **2l** (129 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at

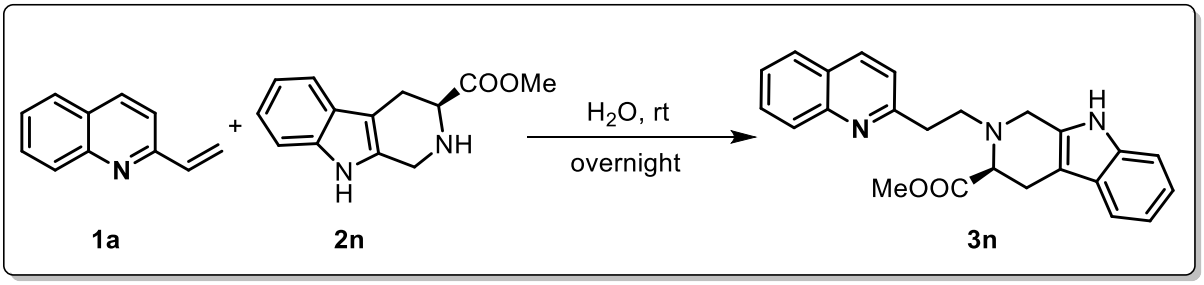
room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (20% EtOAc in hexane) to yield **3l** as white solid (150 mg, 65%); **m.p:** 98-100 °C; R_f = 0.2 (100% EtOAc); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.06 – 8.02 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.50 – 7.47 (m, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 4.45 (s, 1H), 3.48 (d, *J* = 1.5 Hz, 1H), 3.17 – 3.14 (m, 2H), 2.94 (d, *J* = 11.7 Hz, 2H), 2.87 – 2.84 (m, 2H), 2.23 – 2.19 (m, 2H), 1.95 (d, *J* = 11.5 Hz, 2H), 1.45 (s, 11H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 161.1, 148.1, 136.3, 129.5, 129.0, 127.6, 126.9, 125.9, 121.8, 79.4, 58.3, 52.4, 37.0, 32.8, 28.5; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{21}H_{30}N_3O_2$ 356.2338, found 356.2332.

2-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)ethyl)quinoline (3m)



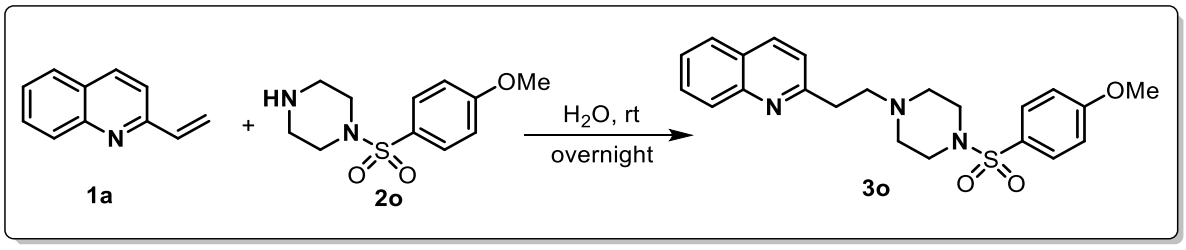
According to general procedure by using 4-vinylquinoline **1a** (100 mg, 0.644 mmol), 1,2,3,4-tetrahydroisoquinoline **2m** (85.8 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (20% EtOAc in hexane) to yield **3m** as light yellow crystalline solid (130 mg, 70%); **m.p:** 77-79 °C; R_f = 0.5 (100% EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.05 (dd, *J* = 9.0, 6.0 Hz, 2H), 7.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.49 – 7.44 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.13 – 7.08 (m, 3H), 7.06 – 7.01 (m, 1H), 3.76 (s, 2H), 3.31 – 3.26 (m, 2H), 3.06 – 3.01 (m, 2H), 2.93 – 2.90 (m, 2H), 2.86 – 2.82 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 161.0, 148.0, 136.4, 134.8, 134.4, 129.5, 128.9, 128.7, 127.6, 126.9, 126.7, 126.2, 125.9, 125.7, 121.8, 58.5, 56.1, 51.0, 37.1, 29.2; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{20}H_{21}N_2$ 289.1705, found 289.1702.

Methyl (S)-2-(2-(quinolin-2-yl)ethyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylate (3n)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), methyl (S)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole-3-carboxylate **2n** (148.4 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (80% EtOAc in hexane) to yield **3n** as light yellow solid (190 mg, 76%); **m.p:** 155-157 °C; $\boldsymbol{R_f}$ = 0.6 (100% EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 8.08 – 8.02 (m, 3H), 7.77 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.51 – 7.43 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.25 (m, 1H), 7.13 – 7.06 (m, 2H), 4.25 (d, *J* = 15.0 Hz, 1H), 4.04 – 3.95 (m, 2H), 3.59 (s, 3H), 3.35 – 3.19 (m, 4H), 3.15 – 3.04 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 173.5, 160.8, 147.9, 136.5, 136.3, 131.7, 129.6, 128.8, 127.7, 127.2, 127.0, 126.0, 121.9, 121.5, 119.4, 117.9, 110.9, 106.2, 60.4, 54.6, 51.6, 46.4, 38.0, 24.1; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{24}H_{24}N_3O_2$ 386.1869, found 386.1878.

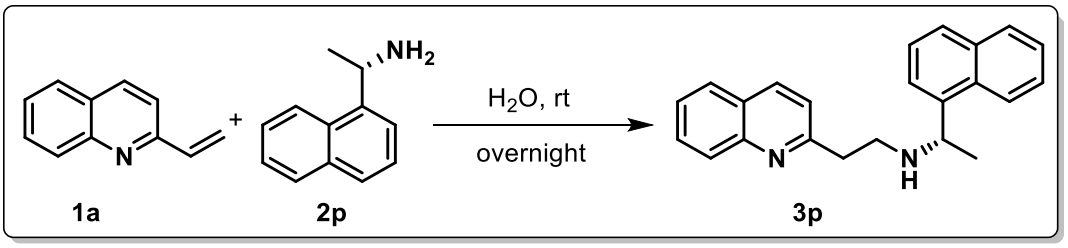
2-(2-(4-((4-Methoxyphenyl)sulfonyl)piperazin-1-yl)ethyl)quinoline (3o)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), 1-((4-methoxyphenyl)sulfonyl)piperazine **2o** (165 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by

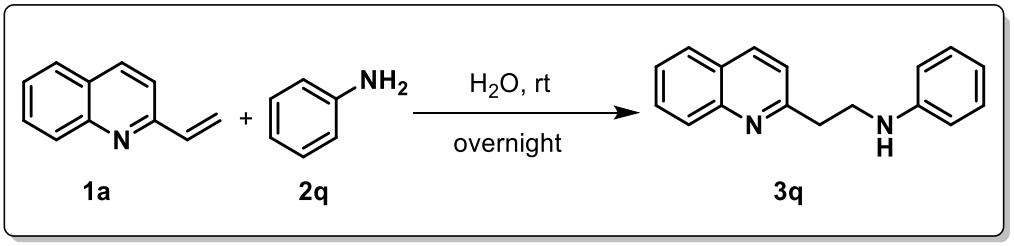
silica-gel column chromatography (5% MeOH/DCM) to yield **3o** as light brown solid (234 mg, 88%); **m.p:** 159-161 °C; R_f = 0.2 (100% EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.04 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.76 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.70 – 7.66 (m, 3H), 7.50 – 7.46 (m, 1H), 7.27 (d, *J* = 8.4, 1H), 6.99 – 6.97 (m, 2H), 3.86 (s, 3H), 3.12 – 3.08 (m, 2H), 3.03 (m, 4H), 2.89 – 2.85 (m, 2H), 2.68 – 2.63 (t, *J* = 4.8 Hz, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 163.2, 160.5, 148.0, 136.5, 130.0, 129.6, 128.9, 127.6, 127.2, 126.9, 126.0, 121.6, 114.3, 57.7, 55.7, 52.3, 46.2, 36.6; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{22}H_{26}N_3O_3S$ 412.1695, found 412.1692.

(S)-1-(naphthalen-1-yl)-N-(2-(quinolin-2-yl)ethyl)ethan-1-amine (3p)



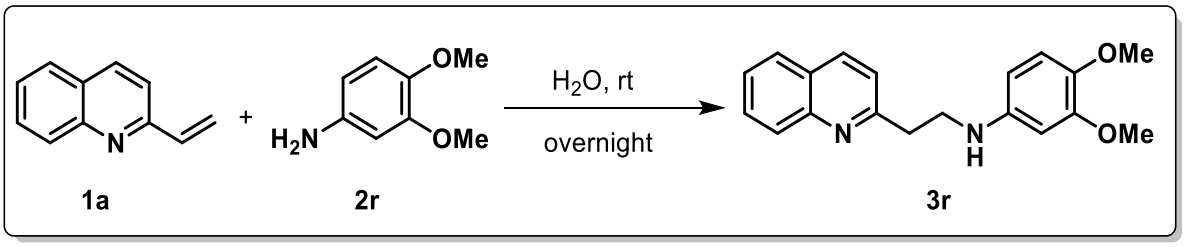
According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), (S)-1-(naphthalen-1-yl)ethan-1-amine **2p** (110.4 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (5% EtOAc in hexane) to yield **3p** as yellow oil (108 mg, 51%); R_f = 0.4 (100% EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.16 – 8.12 (m, 1H), 8.04 – 8.00 (m, 2H), 7.85 – 7.82 (m, 1H), 7.77 – 7.63 (m, 4H), 7.50 – 7.38 (m, 4H), 7.26 – 7.22 (m, 1H), 4.69 (q, *J* = 6.6 Hz, 1H), 3.21 – 3.16 (m, 2H), 3.11 – 3.06 (m, 2H), 1.49 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 161.1, 148.0, 141.2, 136.3, 134.1, 131.5, 129.5, 129.0, 127.6, 127.2, 126.9, 125.9, 125.8, 125.3, 123.1, 122.9, 121.9, 53.8, 47.2, 39.3, 23.7; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{23}H_{23}N_2$ 327.1861, found 327.1864.

N-(2-(quinolin-2-yl)ethyl)aniline (3q)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), aniline **2q** (66 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (12% EtOAc in hexane) to yield **3q** as off-white solid (116 mg, 72%); **m.p:** 70-72 °C; $\boldsymbol{R_f}$ = 0.3 (10% EtOAc in hexane); **^{1}H NMR (300 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 8.07 (d, *J* = 8.4 Hz, 2H), 7.78 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.53 – 7.47 (m, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.19 – 7.14 (m, 2H), 6.72 – 6.63 (m, 3H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.27 (t, *J* = 6.6 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 160.4, 148.3, 148.0, 136.6, 129.7, 129.4, 129.0, 127.7, 127.0, 126.1, 121.8, 117.5, 113.2, 43.4, 38.1; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{17}H_{17}N_2$ 249.1392, found 249.1390.

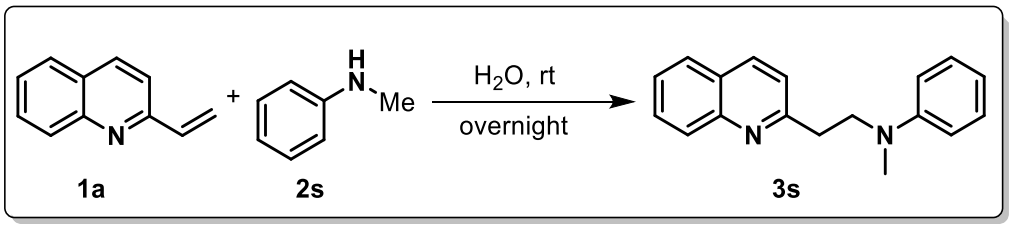
3,4-Dimethoxy-N-(2-(quinolin-2-yl)ethyl)aniline (3r)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), 3,4-dimethoxyaniline **2r** (98.8 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (50% EtOAc in hexane) to yield **3r** as dark brown oil (142 mg, 71%); $\boldsymbol{R_f}$ = 0.7 (100% EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 8.08 (dd, *J* = 8.1, 2.4 Hz, 2H), 7.79 (dd, *J* =

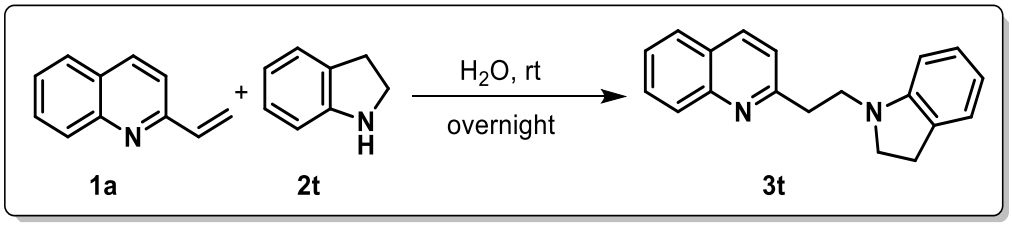
8.1, 1.2 Hz, 1H), 7.77 – 7.68 (m, 1H), 7.53 – 7.48 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.27 (d, *J* = 2.7, Hz, 2H), 6.20 (dd, *J* = 8.4, 2.4 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.27 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$): *δ*** 160.5, 150.2, 148.0, 143.3, 141.78, 136.7, 129.7, 129.0, 127.7, 127.0, 126.1, 121.8, 113.5, 104.1, 99.5, 56.9, 55.8, 44.4, 38.2; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{19}H_{21}N_2O_2$ 309.1603, found 309.1600.

N-methyl-N-(2-(quinolin-2-yl)ethyl)aniline (3s)



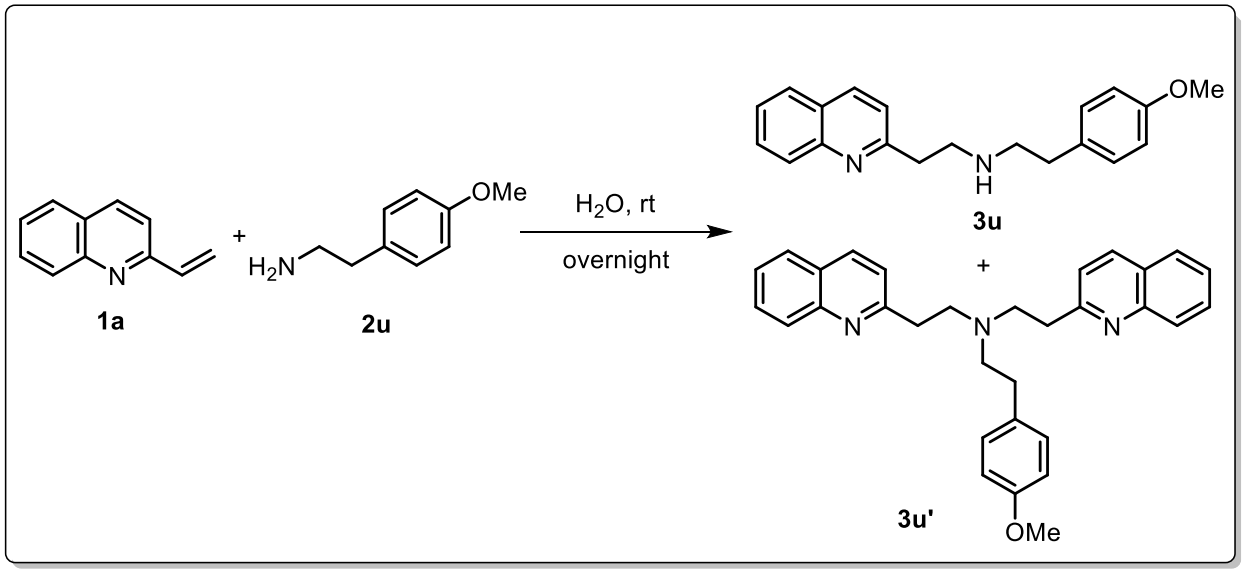
According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), *N*-methylaniline **2s** (69 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (10% EtOAc in hexane) to yield **3s** as light yellow oil (128 mg, 75%); $\boldsymbol{R_f}$ = 0.4 (10% EtOAc in hexane); **^{1}H NMR (300 MHz, $CDCl_3$): *δ*** 8.06 (t, *J* = 8.4 Hz, 2H), 7.77 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.52 – 7.46 (m, 1H), 7.27 – 7.22 (m, 3H), 6.80 – 6.76 (m, 2H), 6.73 – 6.68 (m, 1H), 3.91 – 3.80 (m, 2H), 3.25 – 3.20 (m, 2H), 2.90 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$): *δ*** 160.65, 149.01, 148.20, 136.45, 129.60, 129.38, 128.99, 127.69, 126.94, 126.02, 122.07, 116.44, 112.47, 77.58, 77.16, 76.74, 52.96, 38.59, 36.19; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{18}H_{19}N_2$ 263.1548, found 263.1552.

2-(2-(Indolin-1-yl)ethyl)quinolone (3t)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), indoline **2t** (76.8 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (10% EtOAc in hexane) to yield **3t** as light orange oil (134 mg, 76%); R_f = 0.5 (20% EtOAc in hexane); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.08 – 8.05 (m, 2H), 7.7 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.51 – 7.46 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.07 – 7.03 (m, 2H), 6.66 – 6.60 (m, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 3.64 – 3.59 (m, 2H), 3.42 (t, *J* = 8.4 Hz, 2H), 3.28 – 3.23 (m, 2H), 2.95 (t, *J* = 8.4 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 160.7, 152.3, 148.1, 136.5, 130.1, 129.6, 129.0, 127.7, 127.4, 127.0, 126.0, 124.5, 121.8, 117.6, 107.1, 53.2, 49.1, 36.7, 28.7; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{19}H_{19}N_2$ 275.1548, found 275.1544.

N-(4-methoxyphenethyl)-2-(quinolin-2-yl)ethan-1-amine (3u)

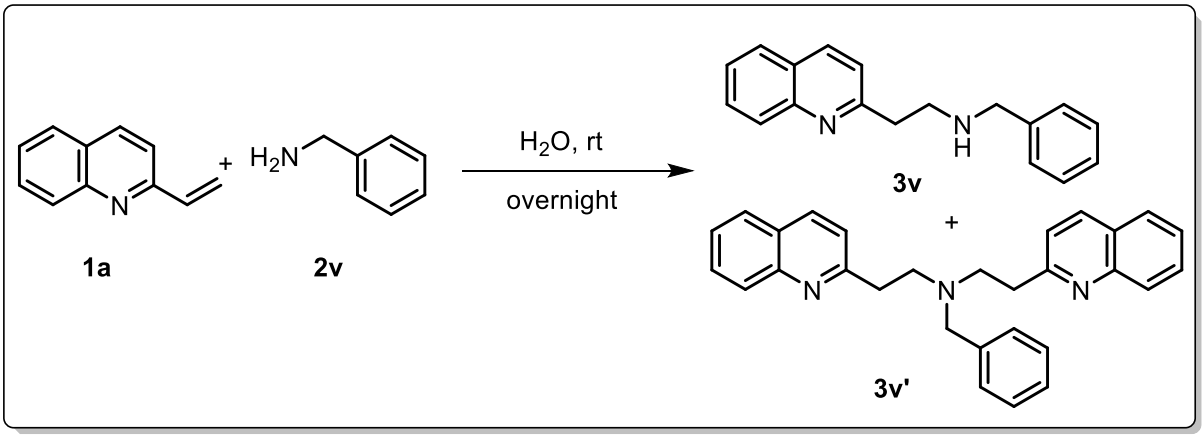


According to general procedure by using 4-vinylquinoline **1a** (100 mg, 0.644 mmol), 2-(4-methoxyphenyl)ethan-1-amine **2u** (97.4 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (30% EtOAc in hexane) to yield **3u** as light yellow oil (60 mg, 30%); R_f = 0.3 (100% EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.04 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 9.0 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.68 – 7.65 (m, 1H), 7.51 – 7.46 (m,

1H), 7.30 – 7.23 (m, 1H), 7.11 – 7.04 (m, 2H), 6.80 – 6.71 (m, 2H), 3.75 (s, 3H), 3.13 (t, *J* = 6.0 Hz, 4H), 2.90 (t, *J* = 6.0 Hz, 2H), 2.74 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR (75 MHz, $CDCl_3$): *δ*** 160.9, 158.1, 148.0, 136.4, 132.2, 129.7, 129.5, 129.1, 127.6, 126.9, 126.0, 121.8, 114.0, 55.4, 51.3, 49.2, 39.2, 35.4; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{20}H_{23}N_3O$ 307.1810, found 307.1808.

N-(4-methoxyphenethyl)-2-(quinolin-2-yl)-N-(2-(quinolin-2-yl)ethyl)ethan-1-amine (3u'): The title compound was prepared and purified by basic alumina column chromatography (30% EtOAc in hexane) to yield **3u'** as brown oil (150 mg, 50%); ***R*$_f$** = 0.4 (100% EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$): *δ*** 8.05 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H), 7.74 (d, *J* = 9.0 Hz, 2H), 7.69 – 7.64 (m, 2H), 7.50 – 7.45 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.02 – 6.97 (m, 2H), 6.75 – 6.70 (m, 2H), 3.75 (s, 3H), 3.12 (s, 8H), 2.86 – 2.81 (m, 2H), 2.71 – 2.66 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$): *δ*** 161.5, 157.9, 148.0, 136.1, 132.8, 129.8, 129.4, 129.0, 127.6, 126.9, 125.8, 122.1, 113.7, 56.2, 55.3, 53.8, 36.9, 33.0; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{31}H_{32}N_3O$ 462.2545, found 462.2558.

N-benzyl-2-(quinolin-2-yl)ethan-1-amine (3v)

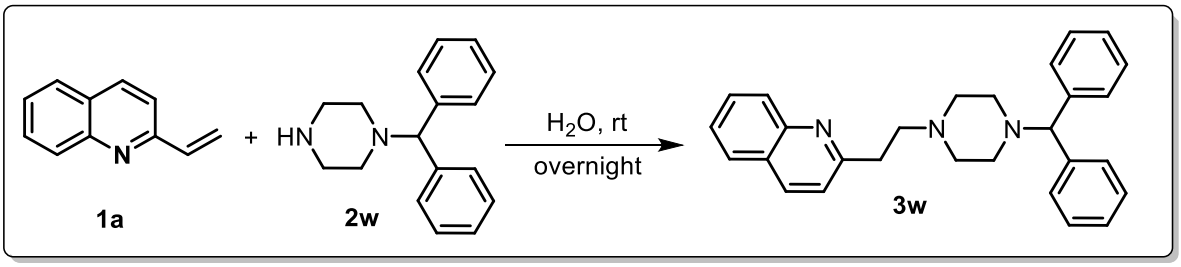


According to general procedure by using *4-vinylquinoline* **1a** (10 mg, 0.644 mmol), benzylamine **2v** (69 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina chromatography (35% EtOAc in hexane) to yield **3v** as brown oil (40 mg, 23%); ***R*$_f$** = 0.2 (100%

EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** ***δ*** 8.04 (t, *J* = 8.0 Hz, 2H), 7.77 (dd, *J* = 8.1 Hz, 1H), 7.68 – 7.66 (m, 1H), 7.50 – 7.46 (m, 1H), 7.33 – 7.27 (m, 5H), 7.26 – 7.21 (m, 1H), 3.85 (s, 2H), 3.22 – 3.19 (m, 2H), 3.16 – 3.13 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** ***δ*** 160.9, 148.0, 140.2, 136.4, 129.5, 129.0, 128.5, 128.3, 127.6, 127.1, 126.9, 126.0, 121.8, 53.9, 48.7, 39.1; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{20}H_{16}N_3O_2$ 263.1548, found 263.1539.

N-benzyl-2-(quinolin-2-yl)-N-(2-(quinolin-2-yl)ethyl)ethan-1-amine (3v'): The title compound was prepared and purified by basic alumina column chromatography (30% EtOAc in hexane) to yield **3v′** as brown oil (130 mg, 48%); ***R_f*** = 0.4 (100% EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** ***δ*** 8.00 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.72 (dd, *J* = 8.0, Hz, 2H), 7.68 – 7.64 (m, 2H), 7.49 – 7.45 (m, 2H), 7.25 – 7.12 (m, 5H), 7.07 (d, *J* = 8.0 Hz, 2H), 3.75 (s, 2H), 3.16 – 3.12 (m, 4H), 3.08 – 3.04 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$): δ** 161.4, 147.9, 139.6, 135.9, 129.4, 128.9, 129.0, 128.1, 127.6, 126.8, 126.8, 125.8, 122.0, 58.6, 53.7, 37.0; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{29}H_{28}N_3$ 418.2283, found 418.2284.

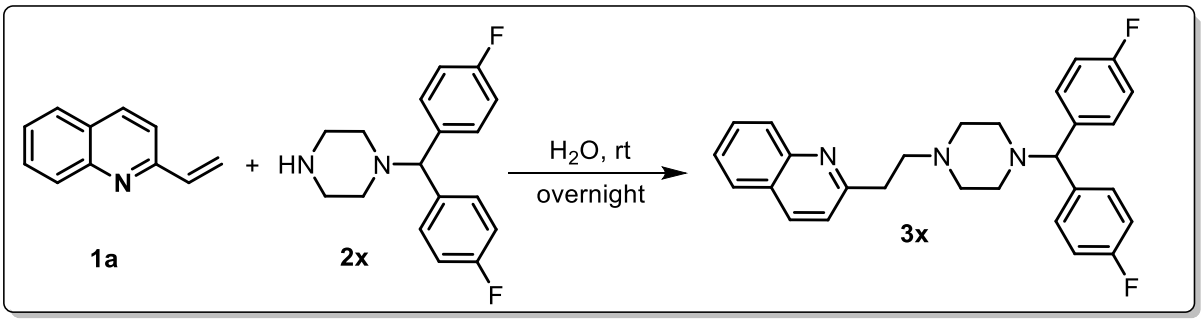
2-(2-(4-Benzhydrylpiperazin-1-yl)ethyl)quinoline (3w)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), 1-benzhydrylpiperazine **2w** (162 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica-gel column chromatography (3% MeOH/DCM) to yield **3w** as off-white solid (211 mg, 80%); **m.p:** 124-126 °C; ***R_f*** = 0.3 (100% EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** ***δ*** 8.04 (t, *J* = 8.0 Hz, 2H), 7.76 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.69 – 7.65 (m, 1H), 7.50 – 7.46 (m, 1H), 7.43 – 7.41 (m, 4H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.28 – 7.24 (m, 4H), 7.19 – 7.14 (m, 2H), 4.22 (s, 1H), 3.18 –

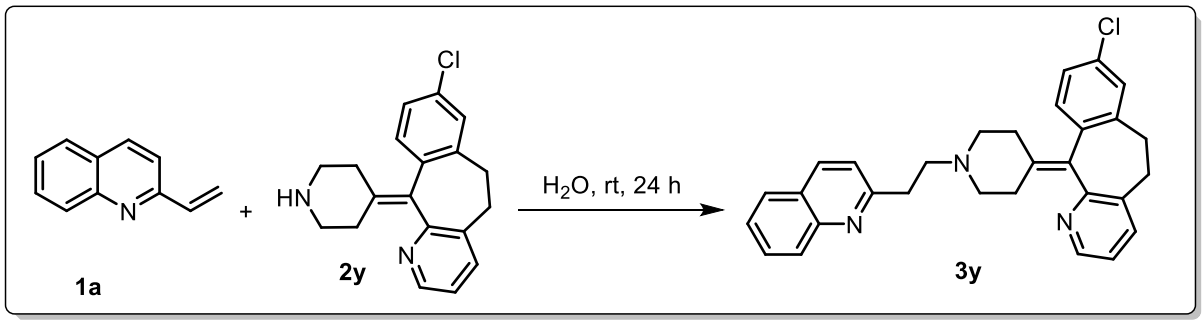
3.15 (m, 2H), 2.89 – 2.85 (m, 2H), 2.60 (m, 4H), 2.45 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** ***δ*** 161.2, 148.0, 142.9, 136.4, 129.5, 129.0, 128.6, 128.1, 127.6, 127.0, 126.9, 125.9, 121.8, 76.5, 58.3, 53.5, 52.1, 36.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{28}H_{30}N_3$ 408.2440, found 408.2436.

2-(2-(4-(Bis(4-fluorophenyl)methyl)piperazin-1-yl)ethyl)quinoline (3x)



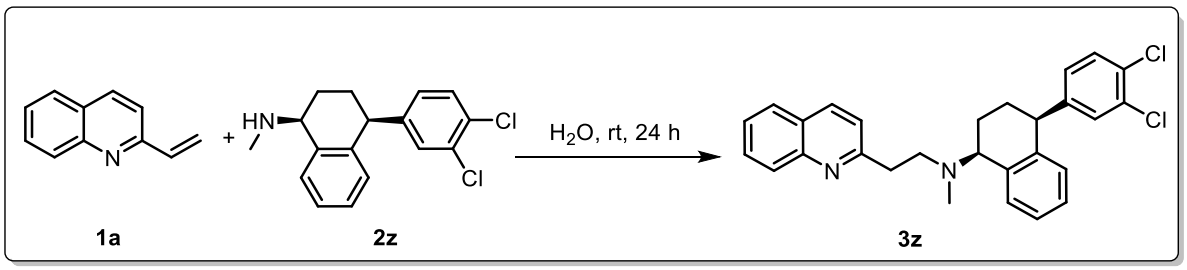
According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), 1-(bis(4-fluorophenyl)methyl)piperazine **2x** (185 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (3% MeOH/DCM) to yield **3x** as yellow oil (203 mg, 71%); ***R*$_f$** = 0.3 (100% EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** ***δ*** 8.04 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H),7.77 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.51 – 7.48 (m, 1H), 7.37 – 7.31 (m, 5H), 6.99 – 6.95 (m, 4H), 4.22 (s, 1H), 3.20 – 3.16 (m, 2H), 2.92 – 2.88 (m, 2H), 2.62 (m, 4H), 2.43 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** ***δ*** 162.0 (d, *J* = 244 Hz), 160.9, 138.4, 136.5, 129.6, 129.4, 129.4, 129.0, 127.7, 126.9, 126.0, 121.8, 115.6 (d, *J* = 21 Hz) , 74.7, 58.1, 53.5, 51.8, 36.7; **^{19}F NMR (377 MHz, $CDCl_3$):** ***δ*** -115.68 (s); **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{28}H_{38}F_2N_3$ 444.2251, found 444.2248.

8-chloro-11-(1-(2-(quinolin-2-yl)ethyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (3y)



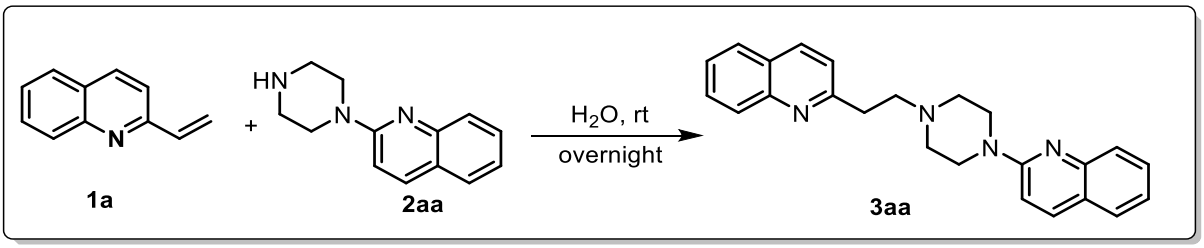
According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), Desloratadine **2y** (200 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for 24 h, the title compound was prepared and purified by silica-gel column chromatography (80% ethyl acetate/Hexane) to yield **3y** as yellow oil (170 mg, 56%); $\boldsymbol{R_f}$ = 0.4 (5% MeOH/Ethyl acetate); **^{1}H NMR (300 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 8.40 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.08 – 8.01 (m, 2H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.51 – 7.45 (m, 1H), 7.45 – 7.42 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.15 – 7.07 (m, 4H), 3.47 – 3.32 (m, 2H), 3.23 – 3.17 (m, 2H), 2.94 – 2.87 (m, 3H), 2.85 – 2.76 (m, 2H), 2.71 (m, 2H), 2.63 – 2.53 (m, 1H), 2.49 – 2.38 (m, 2H), 2.35 – 2.27 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 175.8, 159.5, 156.8, 147.8, 146.5, 139.6, 137.9, 137.5, 136.9, 136.4, 133.8, 133.7, 133.2, 130.6, 129.7, 129.1, 128.7, 127.7, 127.0, 126.3, 126.2, 122.6, 121.9, 56.6, 53.8, 34.8, 31.7, 31.5, 29.8, 22.1; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{30}H_{29}ClN_3$ 466.2050, found 466.2046.

(1S,4S)-4-(3,4-dichlorophenyl)-N-methyl-N-(2-(quinolin-2-yl)ethyl)-1,2,3,4-tetrahydronaphthalen-1-amine (3z)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), Sertraline **2z** (196 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for 24 h, the title compound was prepared and purified by silica-gel column chromatography (70% ethyl acetate/Hexane) to yield **3z** as yellow oil (212 mg, 71%); R_f = 0.4 (100% DCM); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.06 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.81 – 7.78 (m, 1H), 7.71 – 7.66 (m, 1H), 7.52 – 7.46 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.10 – 6.99 (m, 3H), 6.85 – 6.77 (m, 2H), 4.13 – 4.07 (m, 1H), 3.95 – 3.89 (m, 1H), 3.21 (t, *J* = 7.2 Hz, 2H), 3.04 – 2.92 (m, 2H), 2.34 (s, 3H), 2.18 – 2.07 (m, 1H), 1.99 – 1.98 (m, 1H), 1.72 – 1.61 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 161.6, 148.0, 147.7, 139.5, 138.1, 136.1, 132.2, 130.8, 130.2, 130.0, 129.9, 129.4, 128.9, 128.6, 128.3, 127.6, 126.9, 126.9, 126.8, 125.8, 122.0, 62.5, 53.8, 43.7, 38.3, 37.3, 30.1, 15.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{28}H_{27}Cl_2N_2$ 461.1551, found 461.1544.

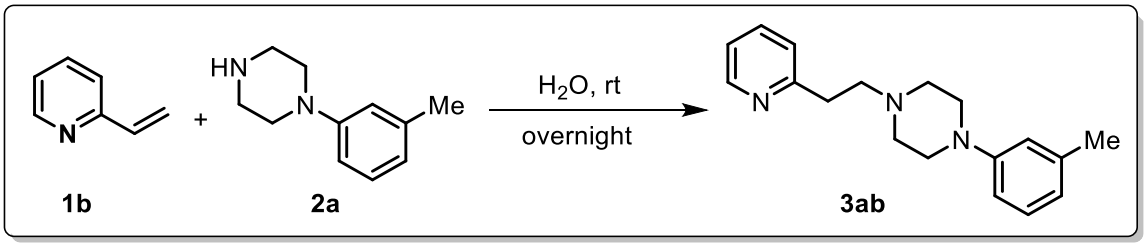
2-(4-(2-(Quinolin-2-yl)ethyl)piperazin-1-yl)quinoline (3aa)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol) Quipazine **2aa** (137 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica-gel column chromatography (5% MeOH/DCM) to yield **3aa** as off-white solid (188 mg, 79%); **m.p:** 119-121 °C; R_f = 0.1 (100% EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.06 (dd, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.79 – 7.77 (m, 1H), 7.72 – 7.67 (m, 2H), 7.59 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.26 – 7.20 (m, 1H), 6.97 (d, *J* = 9.2 Hz, 1H), 3.79 (t, *J* = 5.2 Hz, 4H), 3.27 – 3.23 (m, 2H), 2.99 – 2.95 (m, 2H), 2.73 (t, *J* = 5.2 Hz 4H); **^{13}C NMR (100**

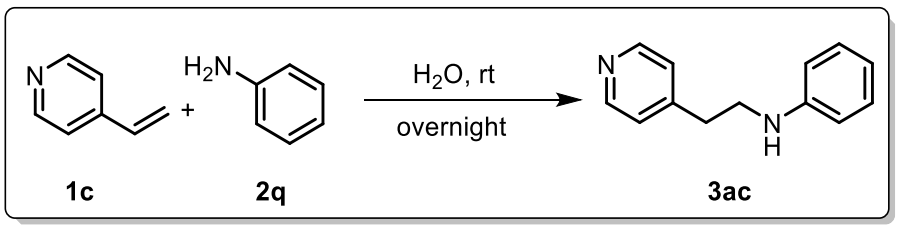
MHz, $CDCl_3$): δ 160.8, 157.5, 148.0, 148.0, 137.6, 136.4, 129.6, 129.6, 129.0, 127.7, 127.3, 126.9, 126.8, 126.0, 123.2, 122.5, 121.8, 109.7, 58.2, 53.2, 45.2, 36.7; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{24}H_{25}N_4$ 369.2079, found 369.2072.

1-(2-(Pyridin-2-yl)ethyl)-4-(m-tolyl)piperazine (3ab)



According to general procedure by using 2-vinylpyridine **1b** (100 mg, 0.951 mmol), N-(m-tolyl)piperazine **2a** (167.7 mg, 0.951 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (7% MeOH/EtOAc) to yield **3ab** as light yellow oil (220 mg, 82%); $\boldsymbol{R_f}$ = 0.4 (5% MeOH/EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$): δ** 8.54 – 8.52 (m, 1H), 7.60 (td, *J* = 7.7, 1.8 Hz, 1H), 7.22 (d, *J* = 9.0 Hz, 1H), 7.20 – 7.10 (m, 2 H) 6.76 – 6.73 (m, 2H), 6.69 (d, *J* = 9.0 Hz, 1H), 3.24 – 3.21 (m, 4H), 3.08 – 3.03 (m, 2H), 2.90 – 2.84 (m, 2H), 2.76 – 2.73 (m, 4H), 2.31 (s, 3H); **^{1}H NMR (100 MHz, $CDCl_3$): δ** 160.1, 151.4, 149.3, 138.9, 136.6, 136.6, 129.1, 123.4, 121.4, 120.8, 117.1, 113.4, 58.3, 53.2, 49.2, 35.5, 21.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{18}H_{24}N_3$ 282.1970, found 282.1996.

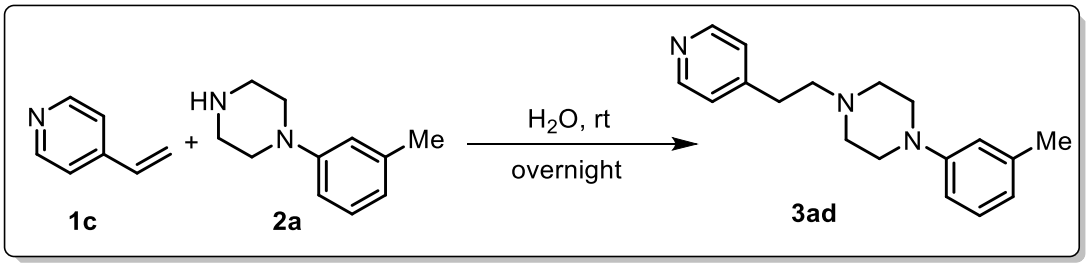
N-(2-(pyridin-4-yl)ethyl)aniline (3ac)



According to general procedure by using 4-vinylpyridine **1c** (100 mg, 0.951 mmol), aniline **2q** (88 mg, 0.951 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (60%

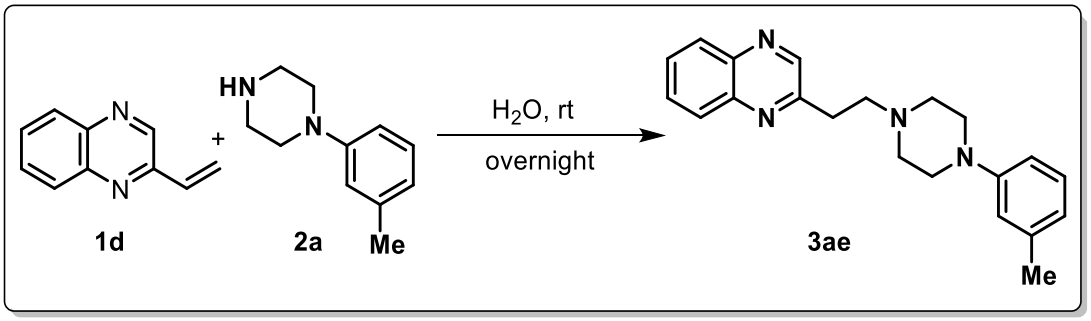
EtOAc/Hexane) to yield **3ac** as light yellow oil (144 mg, 76%); R_f = 0.4 (50% EtOAc/Hexane); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.53 (dd, *J* = 4.2, 1.5 Hz, 2H), 7.23 – 7.14 (m, 4H), 6.76 – 6.70 (m, 1H), 6.63 – 6.60 (m, 2H), 3.45 (t, *J* = 6.9 Hz, 2H), 2.92 (t, *J* = 6.9 Hz, 2H); **^{1}H NMR (125 MHz, $CDCl_3$):** δ 150.0, 148.6, 147.7, 129.5, 124.3, 118.0, 113.1, 44.2, 35.1; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{13}H_{15}N_2$ 199.1235, found 199.1232.

1-(2-(Pyridin-4-yl)ethyl)-4-(m-tolyl)piperazine (3ad)



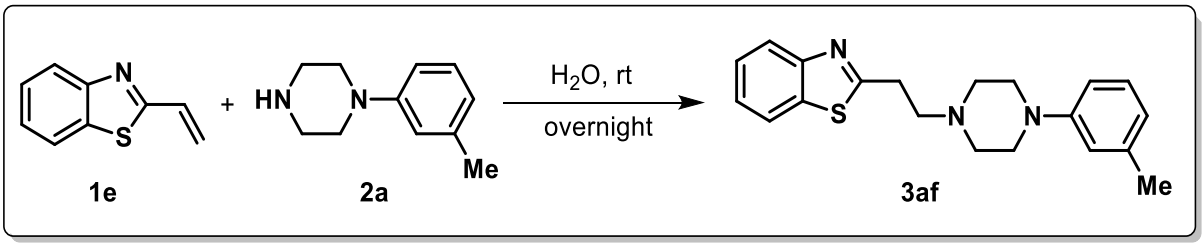
According to general procedure by using 4-vinylpyridine **1c** (100 mg, 0.951 mmol), N-(m-tolyl)piperazine **2a** (167.7 mg, 0.951 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (pure EtOAc) to yield **3ad** as light yellow solid (199 mg, 74%); **m.p:** 52-54 °C; R_f = 0.3 (100% EtOAc); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.50 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.18 – 7.13 (m, 3H), 6.76 – 6.73 (m, 2H), 6.69 (d, *J* = 7.2 Hz, 1H), 3.19 (t, *J* = 4.8 Hz, 4H), 2.86 – 2.81 (m, 2H), 2.70 – 2.64 (m, 6H), 2.32 (s, 3H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 151.4, 149.8, 149.5, 138.9, 129.1, 124.3, 120.8, 117.1, 113.3, 59.1, 53.3, 49.3, 33.0, 21.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{18}H_{24}N_3$ 282.1970, found 282.1958.

2-(2-(4-(m-tolyl)piperazin-1-yl)ethyl)quinoxaline (3ae)



According to general procedure by using *2-vinylquinoxaline* **1d** (100 mg, 0.64 mmol), N-(m-tolyl)piperazine **2a** (112.8 mg, 0.64 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel basic alumina (15% EtOAc in hexane) to yield **3ae** as light yellow oil (168 mg, 79%); **m.p:** 107-109 °C; R_f = 0.5 (100% EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.80 (s, 1H), 8.10 – 8.03 (m, 2H), 7.77 – 7.69 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.75 – 6.72 (m, 2H), 6.68 (d, *J* = 7.2 Hz, 1 H), 3.25 (t, *J* = 7.2 Hz, 2H), 3.22 – 3.18 (m, 4H), 2.97 – 2.94 (m, 2H), 2.74 – 2.71 (m, 4H), 2.31 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 155.9, 151.4, 146.1, 142.3, 141.4, 138.9, 130.1, 129.3, 129.2, 129.0, 129.0, 120.8, 117.1, 113.3, 57.6, 53.3, 49.4, 34.0, 21.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{21}H_{25}N_4$ 333.2079, found 333.2072.

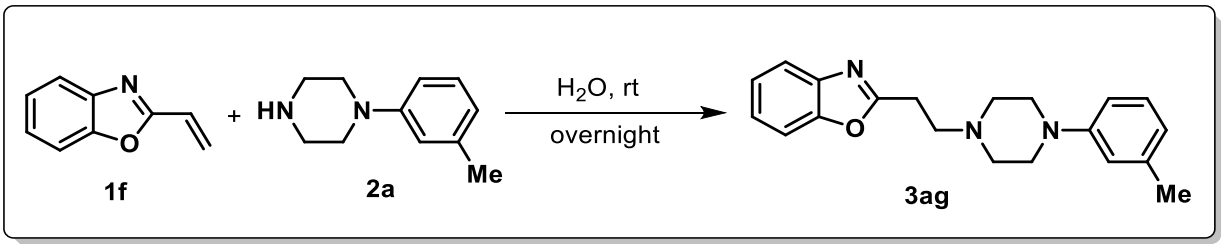
2-(2-(4-(m-tolyl)piperazin-1-yl)ethyl)benzo[d]thiazole (3af)



According to general procedure by using 2-vinylbenzo[d]thiazole **1e** (100 mg, 0.62 mmol), N-(m-tolyl)piperazine **2a** (109.2 mg, 0.62 mmol) were taken in H_2O (1.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (40% EtOAc in hexane) to yield **3af** as white solid (176 mg, 84%); **m.p:** 90-92 °C; R_f = 0.3 (20% EtOAc in hexane); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.43 (m, 1H), 7.36 – 7.33 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.76 – 6.74 (m, 2H), 6.68 (d, *J* = 7.5 Hz, 1H), 3.35 – 3.32 (m, 2H), 3.23 (t, *J* = 5.0 Hz, 4H), 2.94 – 2. 91 (m, 2H), 2.73 (t, *J* = 5.0 Hz, 4H), 2.32 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 170.1, 153.0, 151.5, 138.9, 135.6, 129.1, 126.0, 124.8, 122.6, 121.6, 120.8, 117.1, 113.4,

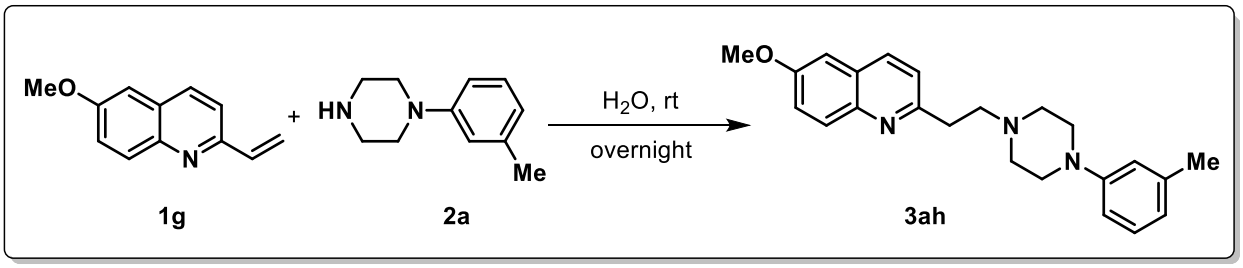
57.0, 53.2, 49.4, 32.1, 21.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{20}H_{24}N_3S$ 338.1691, found 338.1641.

2-(2-(4-(m-tolyl)piperazin-1-yl)ethyl)benzo[d]oxazole (3ag)



According to general procedure by using 2-vinylbenzo[d]oxazole **1f** (100 mg, 0.688 mmol), N-(m-tolyl)piperazine **2a** (121.4 mg, 0.688 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (15% EtOAc in hexane) to yield **3ag** as light yellow oil (180 mg, 81%); **m.p:** 107-109 °C; R_f = 0.4 (50% EtOAc in hexane); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.69 – 7.67 (m, 1H), 7.50 – 7.47 (m, 1H), 7.33 – 7.29 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.74 – 6.72 (m, 2H), 6.68 (d, *J* = 7.6 Hz, 1 H), 3.21 – 3.17 (m, 6H), 3.03 – 3.00 (m, 2H), 2.71 (t, *J* = 4.8 Hz, 4H), 2.31 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 165.7, 151.4, 150.9, 138.9, 129.1, 124.7, 124.3, 120.8, 119.7, 117.1, 113.34, 110.5, 55.2, 53.1, 49.3, 26.8, 21.89; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{20}H_{24}N_3O$ 322.1919, found 322.1903.

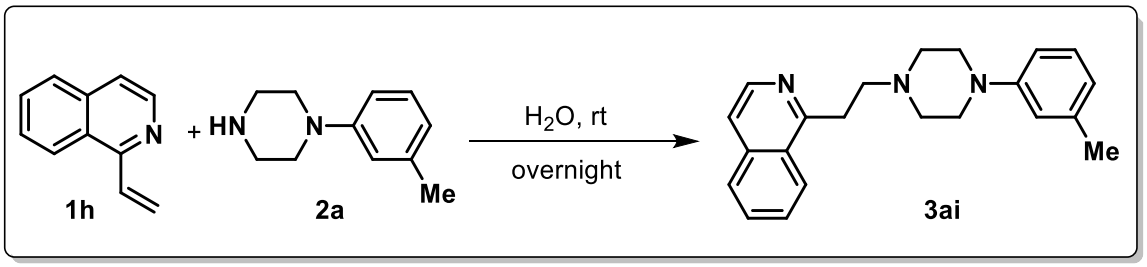
6-Methoxy-2-(2-(4-(m-tolyl)piperazin-1-yl)ethyl)quinolone (3ah)



According to general procedure by using *6-methoxy-2-vinylquinoline* **1g** (100 mg, 0.538 mmol), N-(m-tolyl)piperazine **2a** (95.2 mg, 0.538 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by

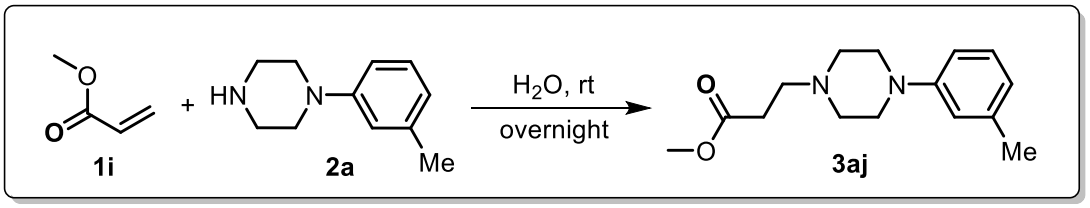
basic alumina column chromatography (15% EtOAc in hexane) to yield **3ah** as white solid (168 mg, 86%); **m.p:** 109-111 °C; R_f = 0.4 (50% EtOAc in hexane); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.95 (dd, *J* = 10.4, 1.6 Hz, 2H), 7.34 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 2.8 Hz, 1H), 6.76 – 6.74 (m, 2H), 6.68 (d, *J* = 7.6, Hz, 1H), 3.92 (s, 3H), 3.23 – 3.16 (m, 6H), 2.93 – 2.89 (m, 2H), 2.736 – 2.70 (t, *J* = 4.8 Hz, 1H), 2.31 (s, 3H).; **^{13}C NMR (100 MHz, $CDCl_3$):** δ 158.4, 157.4, 151.5, 144.1, 138.9, 135.3, 130.4, 129.1, 127.8, 122.1, 120.7, 117.0, 113.3, 105.3, 58.4, 55.6, 53.3, 49.4, 36.5, 21.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{23}H_{28}N_3O$ 362.2232, found 362.2213.

1-(2-(4-(m-tolyl)piperazin-1-yl)ethyl)isoquinoline (3ai)



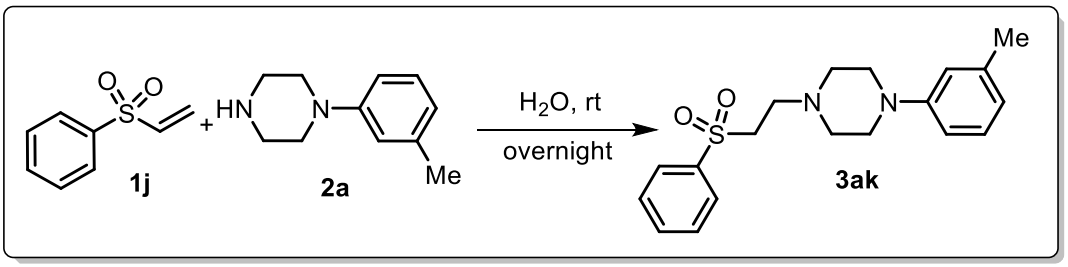
According to general procedure by using N-vinylisoquinoline **1h** (100 mg, 0.644 mmol), N-(m-tolyl)piperazine **2a** (113.6 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (15% EtOAc in hexane) to yield **3ai** as brown oil (162 mg, 76%); R_f = 0.6 (100% EtOAc); **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.44 (d, *J* = 5.5 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 7.0 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 5.5 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.77 – 6.75 (m, 2H), 6.69 (d, *J* = 7.0 Hz, 1H), 3.60 – 3.55 (m, 2H), 3.25 (t, *J* = 4.5 Hz, 4H), 3.02 – 2.99 (m, 2H), 2.80 – 2.78 (m, 4H), 2.32 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$): δ** 160.2, 151.5, 142.0, 138.9, 136.4, 130.0, 129.1, 127.6, 127.3, 127.3, 125.3, 120.8, 119.6, 117.1, 113.3, 57.9, 53.5, 49.4, 32.8, 21.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{22}H_{26}N_3$ 332.2127, 332.2125.

Methyl 3-(4-(m-tolyl)piperazin-1-yl)propanoate (3aj)



According to general procedure by using methyl acrylate **1i** (100 mg, 1.16 mmol), *N*-(m-tolyl)piperazine **2a** (204 mg, 1.16 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica-gel column chromatography (60% EtOAc in hexane) to yield **3aj** as light yellow oil (214 mg, 70%); $\boldsymbol{R_f}$ = 0.3 (60% EtOAc/Hexane); **^{1}H NMR (400 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 7.14 (t, *J* = 7.6 Hz, 1H), 6.74 – 6.71 (m, 2H), 6.68 (d, *J* = 7.2 Hz, 1H), 3.69 (s, 3H), 3.19 – 3.16 (m, 4H), 2.76 (t, *J* = 7.2 Hz, 2H), 2.62 (t, *J* = 4.8 Hz, 4H) 2.55 (t, *J* = 7.6 Hz, 2H), 2.31 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 173.0, 151.4, 138.9, 129.0, 120.8, 117.1, 113.3, 53.7, 53.1, 51.8, 49.3, 32.2, 21.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{15}H_{23}N_2O_2$ 263.1760, found 263.1742.

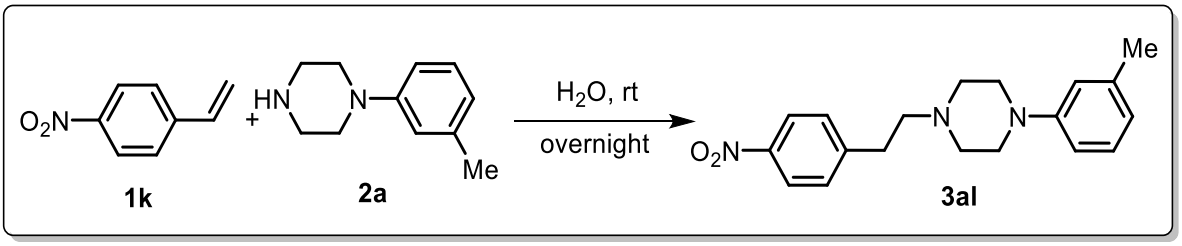
1-(2-(Phenylsulfonyl)ethyl)-4-(m-tolyl)piperazine (3ak)



According to general procedure by using (vinylsulfonyl)benzene **1j** (100 mg, 0.594 mmol), *N*-(m-tolyl)piperazine **2a** (104 mg, 0.594 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica-gel column chromatography (45% EtOAc in hexane) to yield **3ak** as white solid (181 mg, 88%); **m.p:** 88-90 °C; $\boldsymbol{R_f}$ = 0.2 (50% EtOAc/Hexane); **^{1}H NMR (400 MHz, $CDCl_3$):** $\boldsymbol{\delta}$ 7.94 (d, *J* = 7.6 Hz, 2H), 7.66 – 7.63 (m, 1H), 7.58 – 7.54 (m, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.68 – 6.66 (m, 3H), 3.34 (t, *J* = 7.2 Hz, 2H), 3.02 (m, 4H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.51 (m, 4H), 2.30 (s, 3H); **^{13}C**

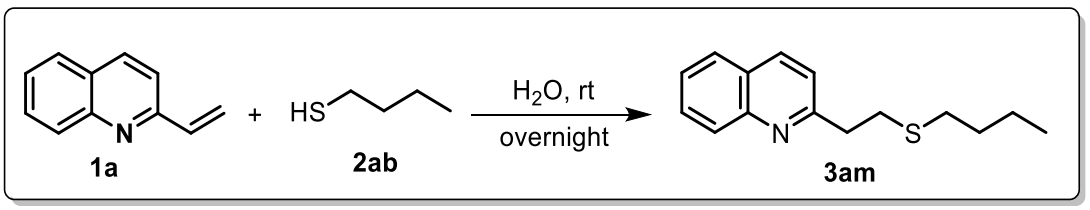
NMR (100 MHz, $CDCl_3$): ***δ*** 151.2, 139.9, 138.9, 133.8, 129.3, 129.1, 128.2, 120.9, 117.1, 113.3, 53.7, 52.9, 51.5, 49.1, 21.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{19}H_{25}N_2O_2S$ 345.1637, found 345.1624.

1-(4-Nitrophenethyl)-4-(m-tolyl)piperazine (3al)



According to general procedure by using 1-nitro-4-vinylbenzene **1k** (100 mg, 0.670 mmol), *N*-(m-tolyl)piperazine **2a** (118 mg, 0.670 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica-gel column chromatography (45% EtOAc in hexane) to yield **3al** as yellow solid (138 mg, 63%); **m.p:** 109-111 °C; $\mathbf{R_f}$ = 0.2 (50% EtOAc/Hexane); **^{1}H NMR (400 MHz, $CDCl_3$):** ***δ*** 8.15 (d, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.75 – 7.73 (m, 2H), 6.69 (d, *J* = 6.8 Hz, 1H), 3.21 (m, 4H), 2.96 – 2.93 (m, 2H), 2.68 (m, 6H), 2.32 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** ***δ*** 151.4, 148.4, 146.7, 138.9, 129.7, 129.1, 123.8, 120.9, 117.1, 113.4, 59.5, 53.3, 49.4, 33.6, 21.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{19}H_{24}N_3O_2$ 326.1869, found 326.1859.

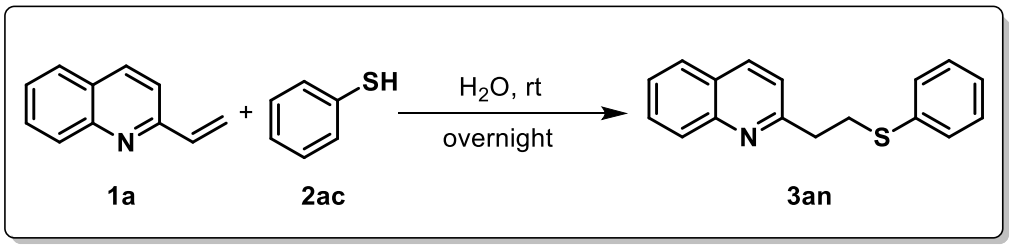
2-(2-(Butylthio)ethyl)quinoline (3am)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), butane-1-thiol **2ab** (58 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica-gel column

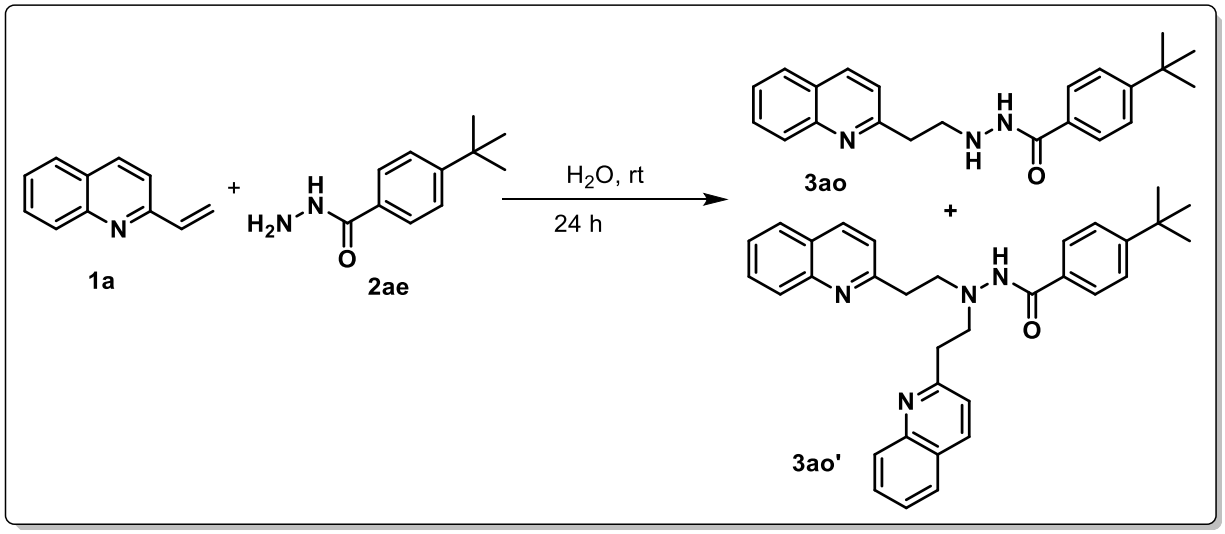
chromatography (15% EtOAc in hexane) to yield **3am** as light yellow oil (108 mg, 68%); R_f = 0.3 (10% EtOAc/Hexane); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.09 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.52 – 7.48 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 3.28 – 3.24 (m, 2H), 3.05 – 3.01 (m, 2H), 2.57 (t, *J* = 7.2 Hz , 2H), 1.62 – 1.54 (m, 2H), 1.44 – 1.34 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 160.9, 148.1, 136.5, 129.6, 129.0, 127.7, 126.1, 121.7, 39.5, 32.2, 31.9, 31.8, 22.1, 13.8; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{15}H_{20}NS$ 246.1316, found 246.1312.

2-(2-(Phenylthio)ethyl)quinolone (3an)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), benzenethiol **2ac** (71 mg, 0.644 mmol) were taken in H_2O (1.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by silica gel column chromatography (5% EtOAc in hexane) to yield **3an** as light yellow oil (144 mg, 84%); R_f = 0.5 (10% EtOAc in hexane); **^{1}H NMR (300 MHz, $CDCl_3$):** δ 8.04 (dd, *J* = 8.1, 2.1 Hz, 2H), 7.77 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.51 – 7.46 (m, 1H), 7.40 – 7.37 (m, 2H), 7.29 – 7.25 (m, 3H), 7.19 – 7.16 (m, 1H), 3.48 – 3.43 (m, 2H), 3.32 – 3.26 (m, 2H); **^{13}C NMR (75 MHz, $CDCl_3$):** δ 160.3, 148.1, 136.4, 136.4, 129.6, 129.6, 129.0, 127.6, 127.0, 126.2, 126.1, 121.7, 38.7, 33.2; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{17}H_{16}NS$ 266.1003, found 266.0997.

4-(Tert-butyl)-N'-(2-(quinolin-2-yl)ethyl)benzohydrazide (3ao)



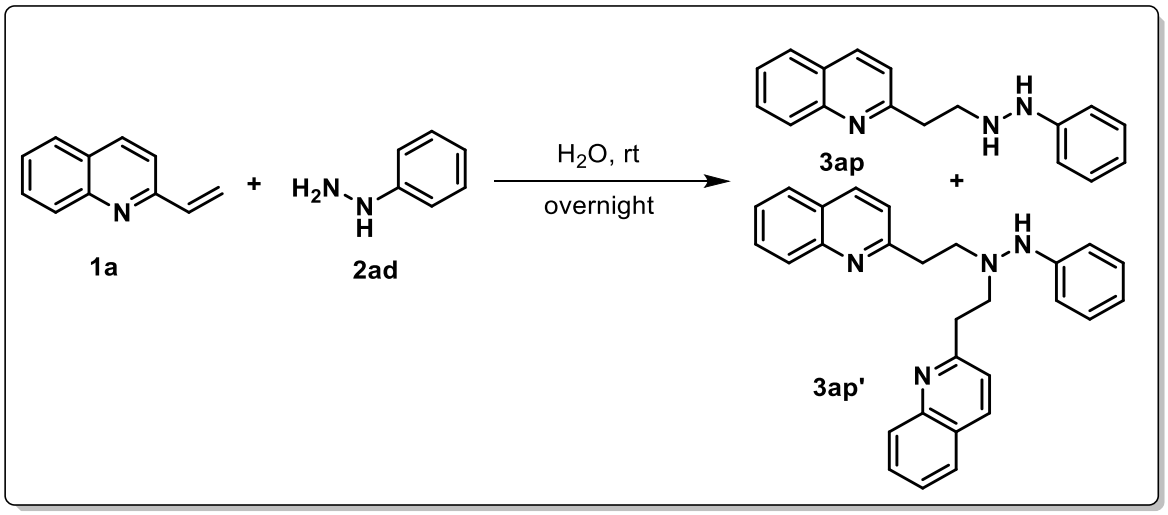
According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), *tert*-butyl piperidin-4-ylcarbamate **2ae** (124 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for 24 h, the title compound was prepared and purified by basic alumina column chromatography (30% EtOAc in hexane) to yield **3ao** as light yellow oil (34 mg, 30%); R_f = 0.7 (100% EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$): δ** 8.10 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.79 – 7.77 (m, 1H), 7.71 – 7.65 (m, 3H), 7.52 – 7.50 (m, 1H), 7.42 – 7.35 (m, 3H), 3.47 (t, *J* = 7.8 Hz, 2H), 3.25 (t, *J* = 6.4 Hz, 2H), 1.32 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$): δ** 167.0, 161.1, 154.9, 147.8, 136.3, 130.6, 129.4, 128.7, 127.6, 126.9, 125.8, 125.3, 122.0, 56.4, 36.9, 34.9, 31.2; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{22}H_{26}N_3O$ 348.2076, found 348.2077 (**50% conversion**).

4-(Tert-butyl)-N',N'-bis(2-(quinolin-2-yl)ethyl)benzohydrazide (3ao')

the title compound was prepared and purified by basic alumina column chromatography (70% EtOAc in hexane) to yield **3ao'** as lignt yellow oil (67 mg, 41%); R_f = 0.4 (100% EtOAc);**^{1}H NMR (400 MHz, $CDCl_3$): δ** 7.96 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.69 – 7.63 (m, 4H), 7.52 – 7.44 (m, 4H), 7.26 – 7.22 (m, 4H), 3.56 (t, *J* = 6.8 Hz, 4H), 3.24 (t, *J* = 6.8 Hz, 4H), 1.29 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$): δ** 166.9, 160.6, 155.3, 147.9, 136.7, 130.1,

129.6, 128.9, 127.7, 126.8, 126.1, 125.6, 121.7, 51.1, 37.6, 35.0, 31.2; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{33}H_{35}N_4O$ 503.2811, found 503.2806.

2-(2-(2-Phenylhydrazineyl)ethyl)quinolone (3ap)



According to general procedure by using 2-vinylquinoline **1a** (100 mg, 0.644 mmol), *tert*-butyl piperidin-4-ylcarbamate **2ad** (70 mg, 0.644 mmol) were taken in H_2O (2.0 mL) and stirred at room temperature for overnight, the title compound was prepared and purified by basic alumina column chromatography (60% EtOAc in hexane) to yield **3ap** as light yellow oil (26 mg, 31%); R_f = 0.7 (70% EtOAc/hexane); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.10 – 8.06 (m, 2H), 7.79 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.66 – 7.63 (m, 2H), 7.52 – 7.50 (m, 1H), 7.48 – 7.41 (m, 3H), 7.37 (d, *J* = 8.4 Hz, 1H), 4.61 (t, *J* = 7.2 Hz, 2H), 3.61 (t, *J* = 7.2 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 160.2, 152.2, 136.6, 130.6, 129.7, 129.1, 129.0, 127.7, 126.2, 122.3, 122.1, 68.7, 37.2; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{17}H_{18}N_3$ 264.1501, found 264.1496 (**50% conversion**).

2,2'-((2-Phenylhydrazine-1,1-diyl)bis(ethane-2,1-diyl))diquinoline (3ap')

The title compound was prepared and purified by basic alumina column chromatography (100% EtOAc) to yield **3ap'** as light yellow oil (64 mg, 48%); R_f = 0.4 (70% EtOAc/hexane); **1H NMR (400 MHz, $CDCl_3$):** δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J*

= 8.0 Hz, 2H), 7.70 – 7.66 (m, 2H), 7.51 – 7.47 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.02 – 6.98 (m, 2H), 6.69 – 6.65 (m, 1H), 6.61 (dd, *J* = 8.8, 1.2 Hz, 2H), 3.30 – 3.27 (m, 4H), 3.21 – 3.18 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$):** ***δ*** 161.1, 149.0, 148.0, 136.0, 129.5, 129.0, 128.9, 127.6, 126.9, 125.9, 122.3, 118.7, 113.1, , 58.2, 36.9; **HRMS (ESI) m/z:** $[M+H]^+$ calcd. for $C_{28}H_{27}N_4$ 419.2236, found 419.2229.

7. Copies of ^{1}H, ^{13}C NMR

Figure S8: ^{1}H NMR of impurity **I**

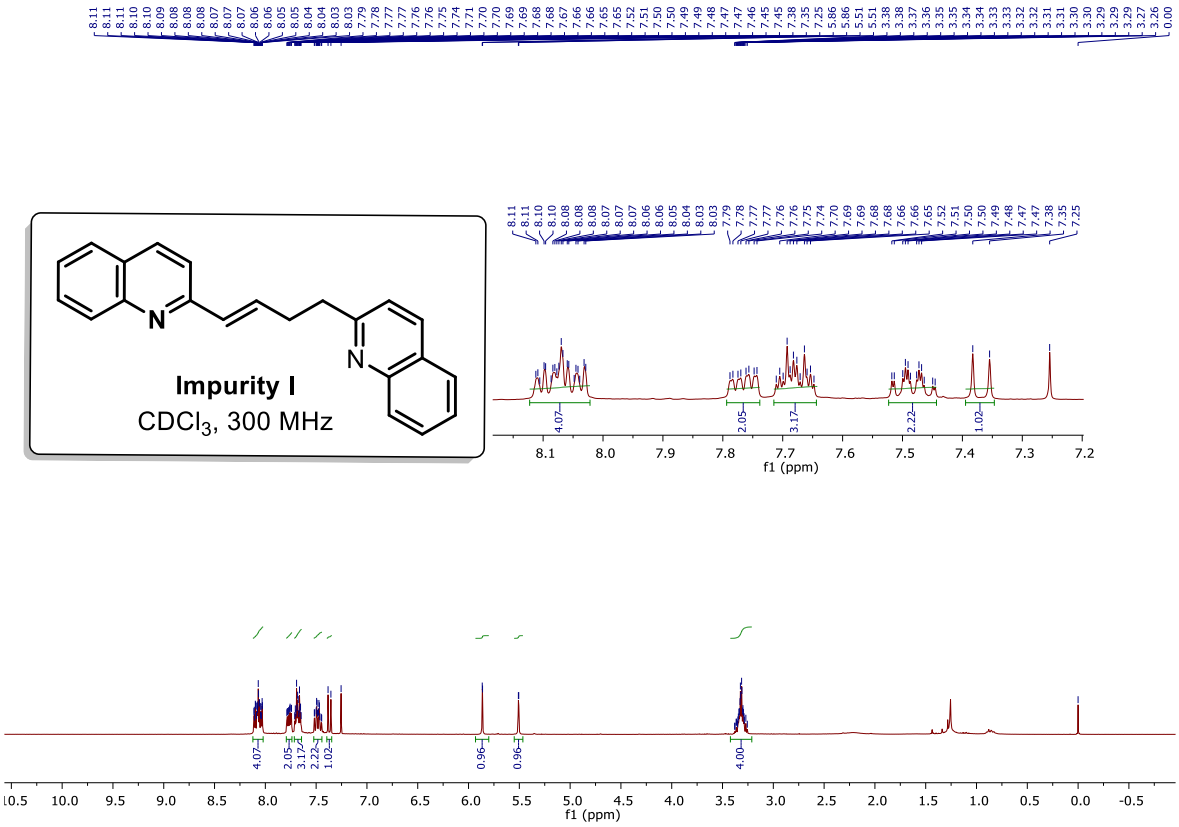


Figure S9: ^{13}C NMR of impurity **I**

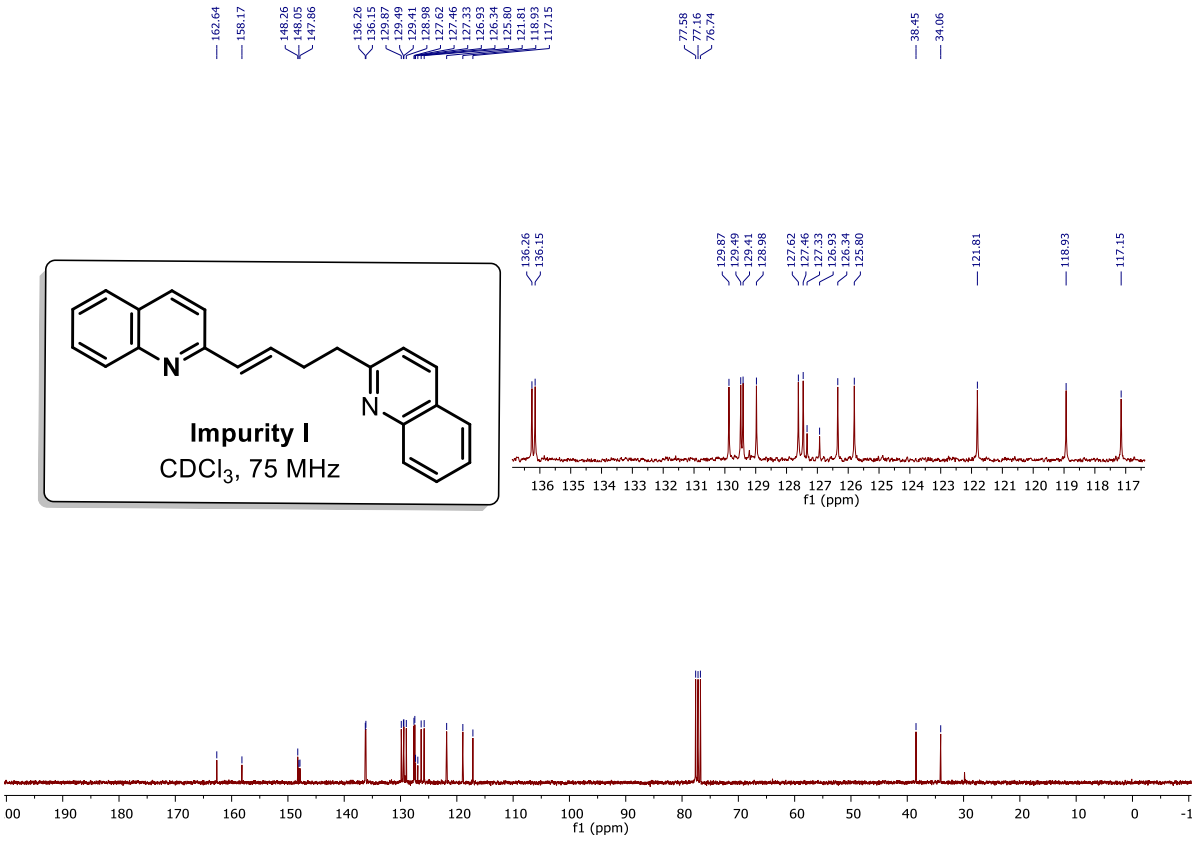


Figure S10: ^{1}H NMR of impurity **II**

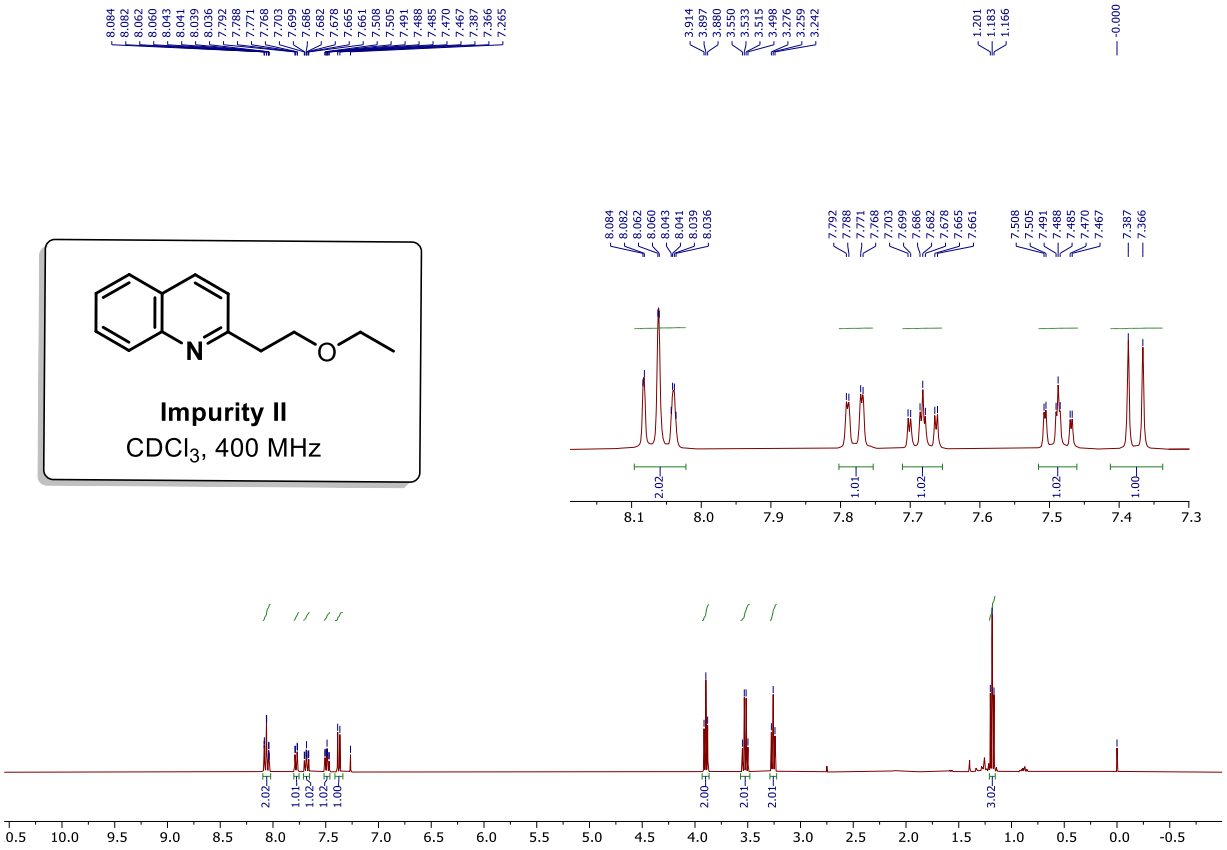


Figure S11: ^{13}C NMR of impurity **II**

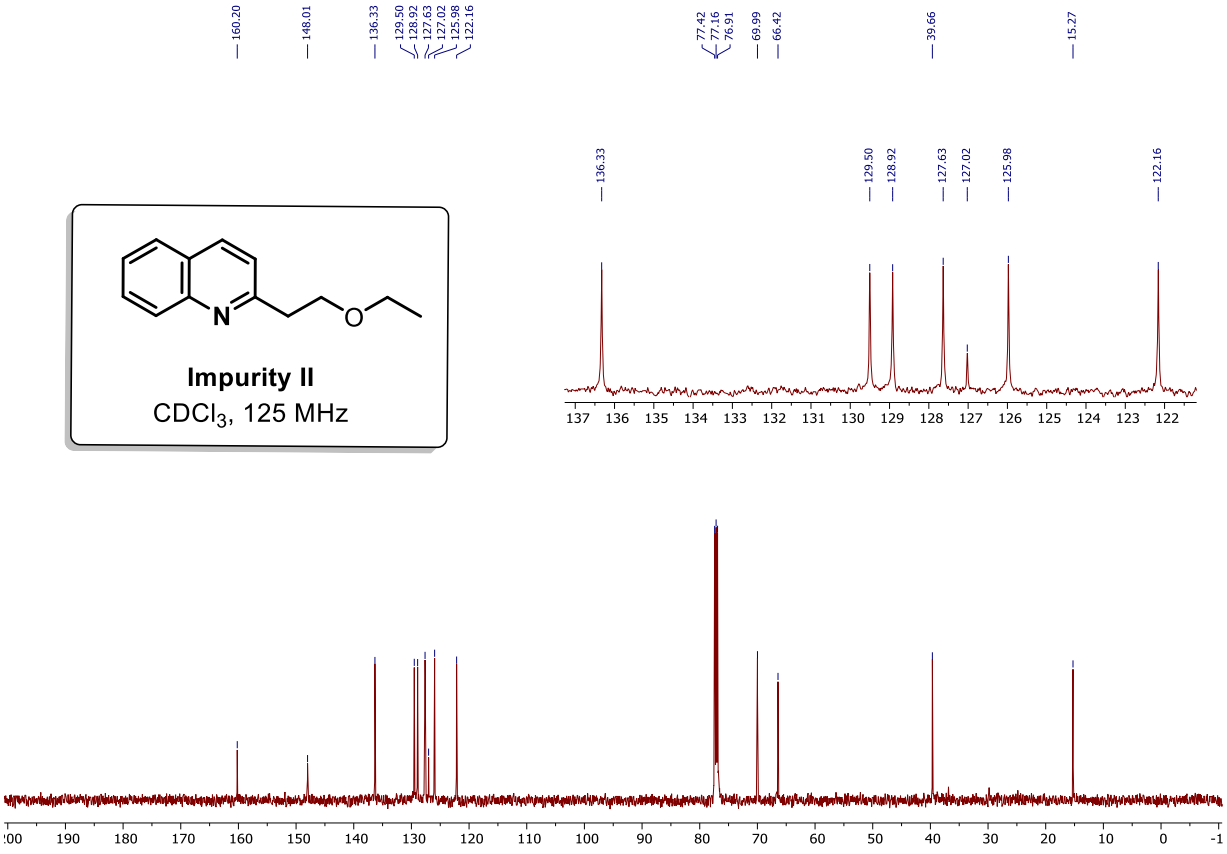


Figure S12: ^{1}H NMR of 2-vinylquinoline **(1a)**

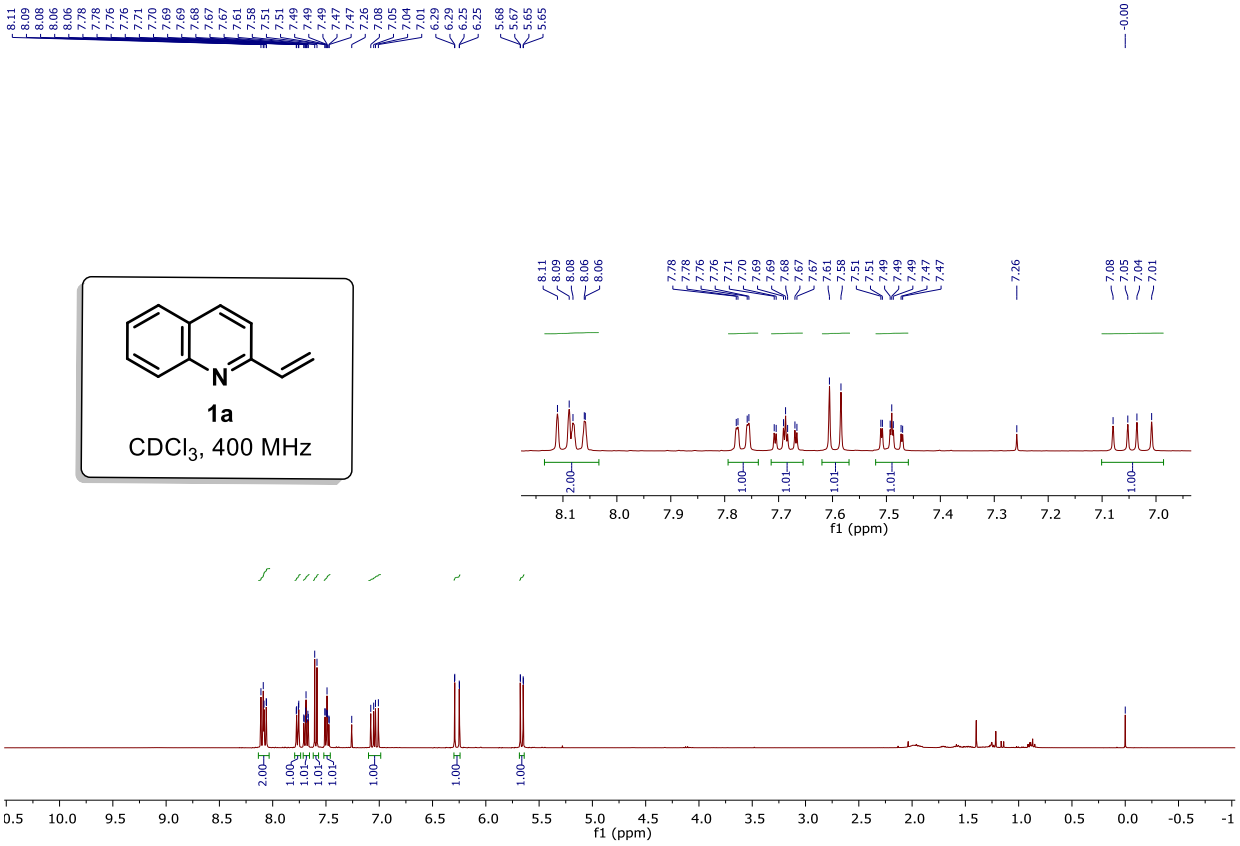


Figure S13: ^{13}C NMR of 2-vinylquinoline **(1a)**

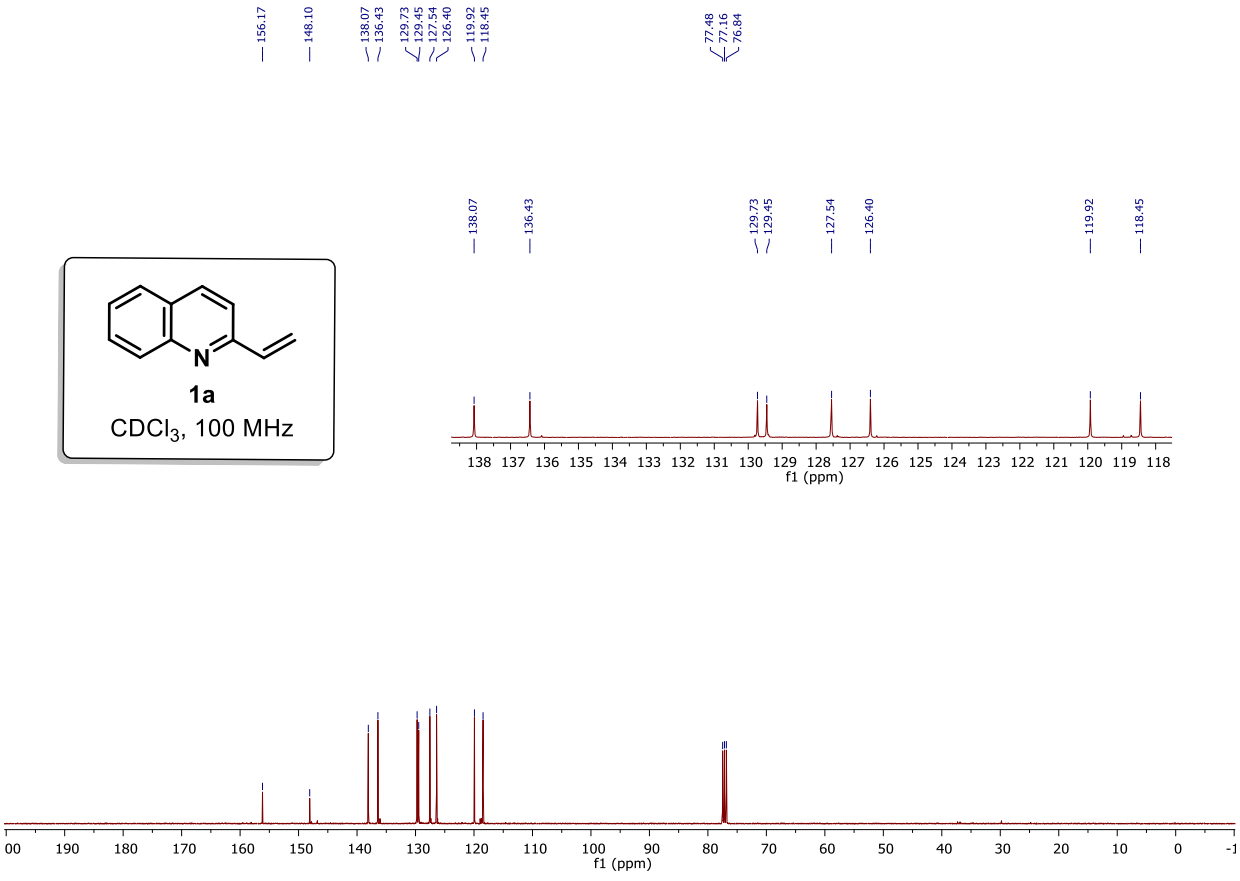


Figure S14: ^{1}H NMR of *m*-tolylpiperazine **(2a)**

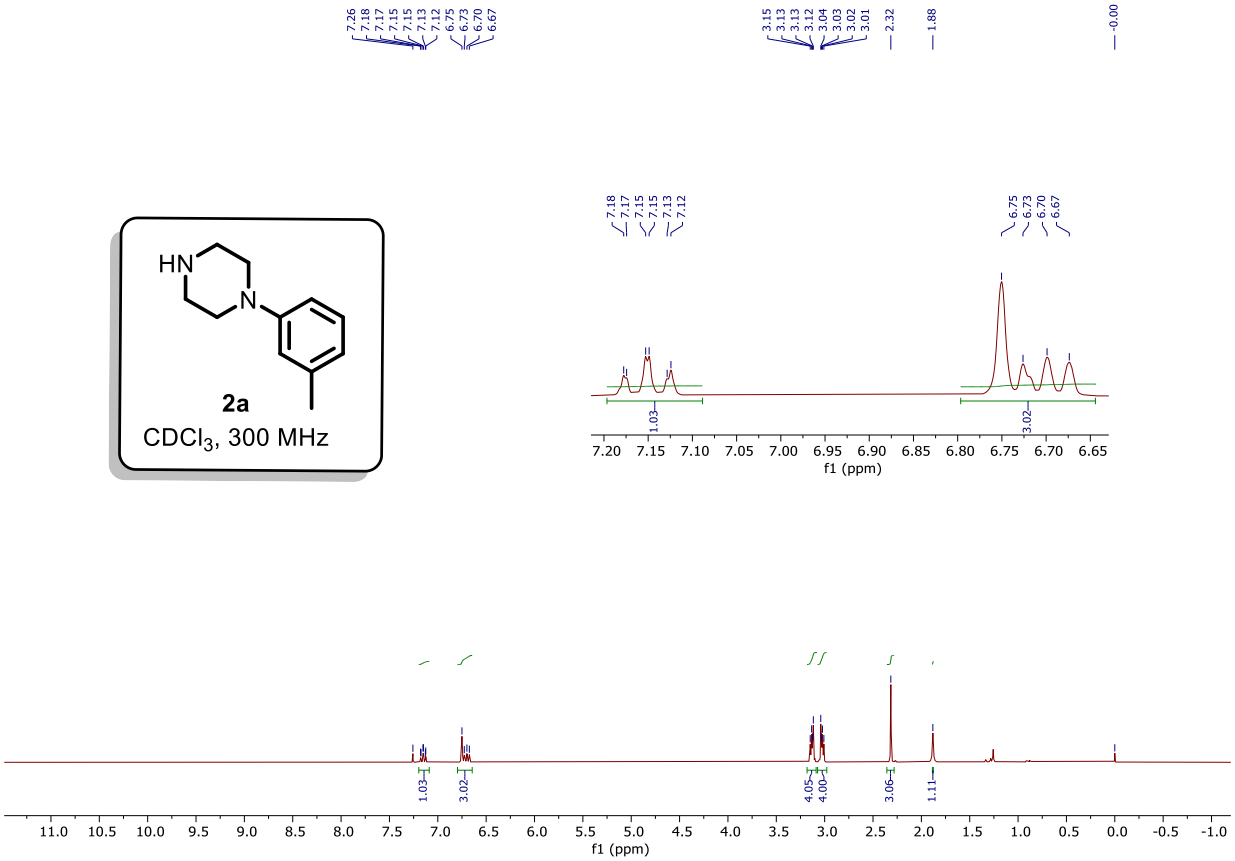


Figure S15: ^{13}C NMR of *m*-tolylpiperazine **(2a)**

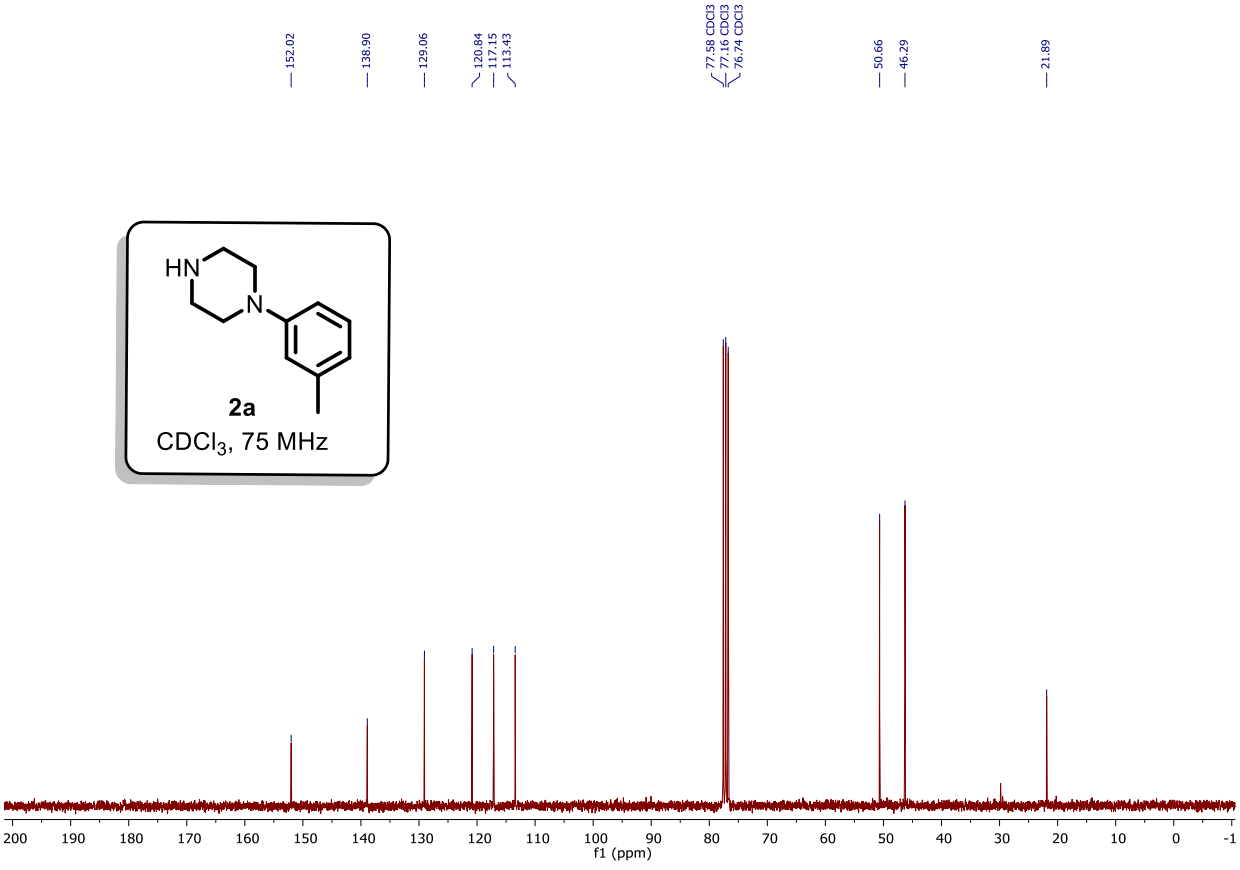


Figure S16: ^{1}H NMR of **Centhaquine 3a**

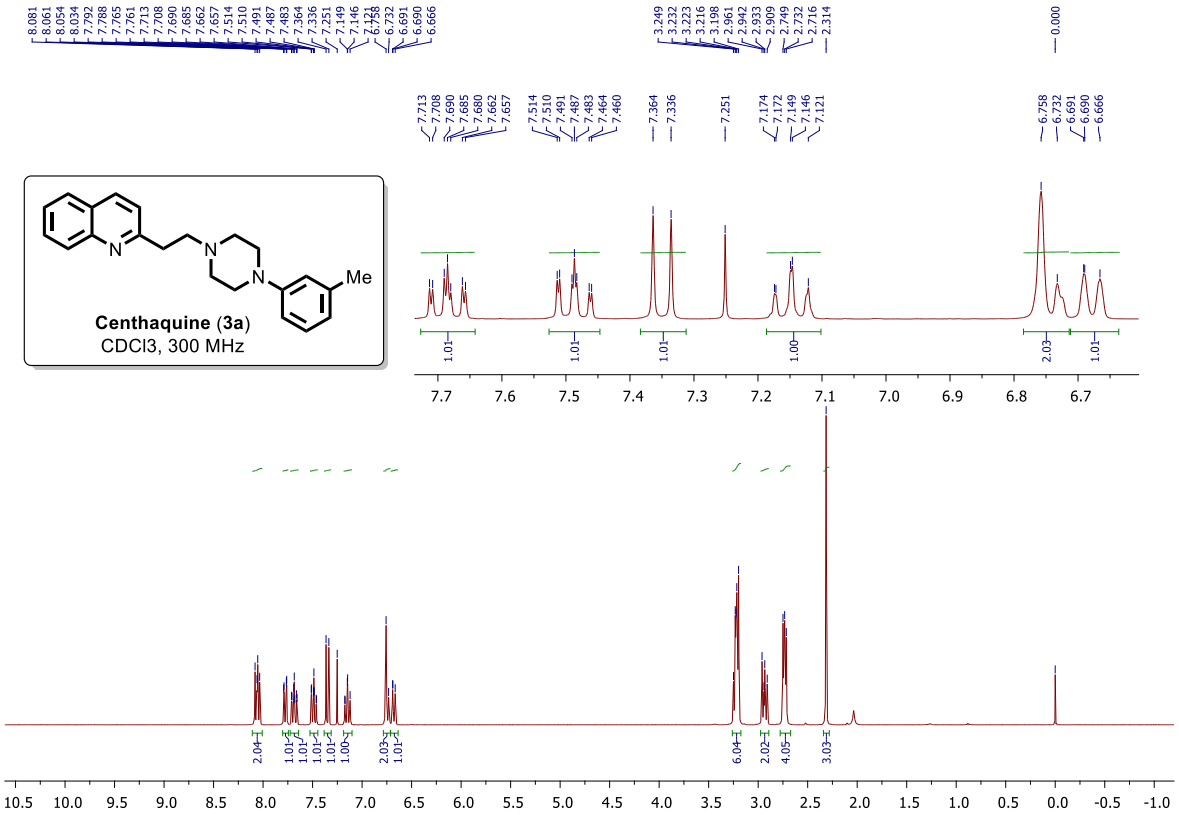


Figure S17: ^{13}C NMR of compound **Centhaquine 3a**

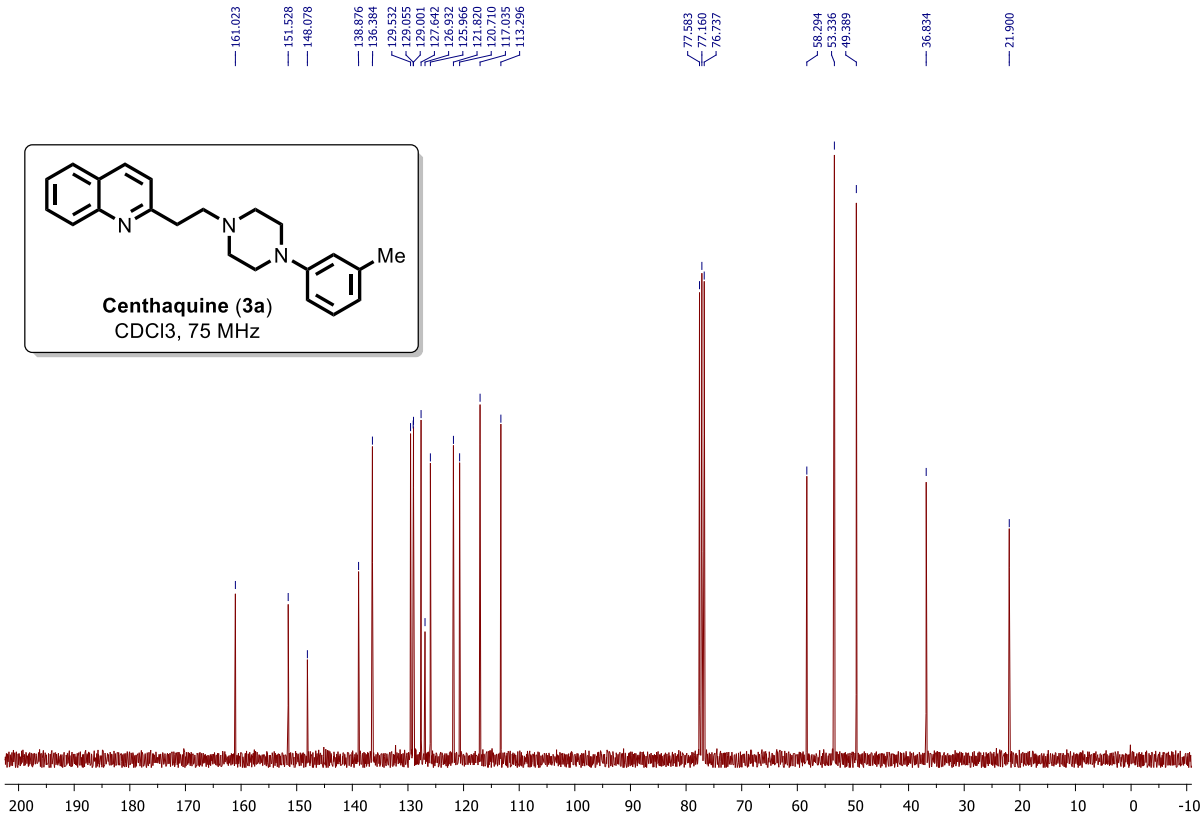


Figure S18: ^{1}H NMR of **deuterated Centhaquine D$_1$-3a**

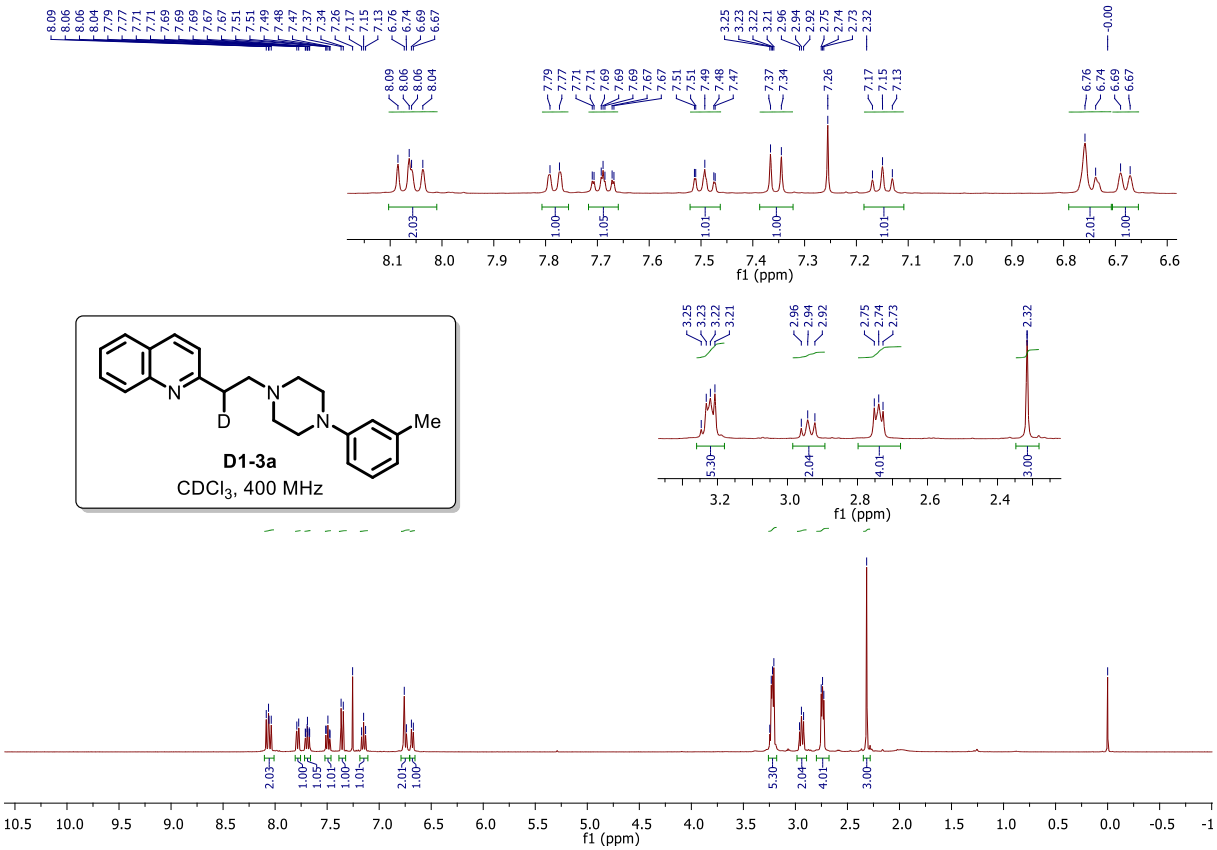


Figure S19: ^{13}C NMR of **deuterated Centhaquine D$_1$-3a**

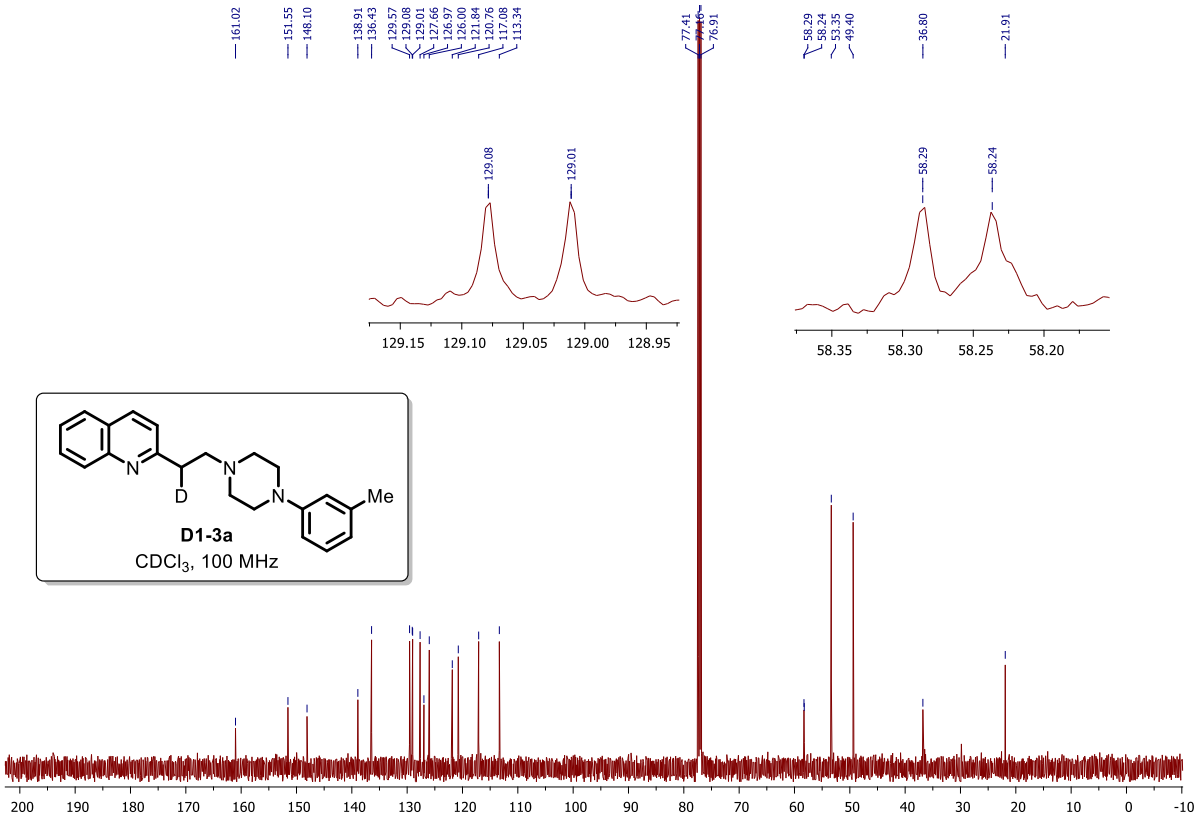


Figure S20: ^{2}H NMR of **deuterated Centhaquine D$_1$-3a**

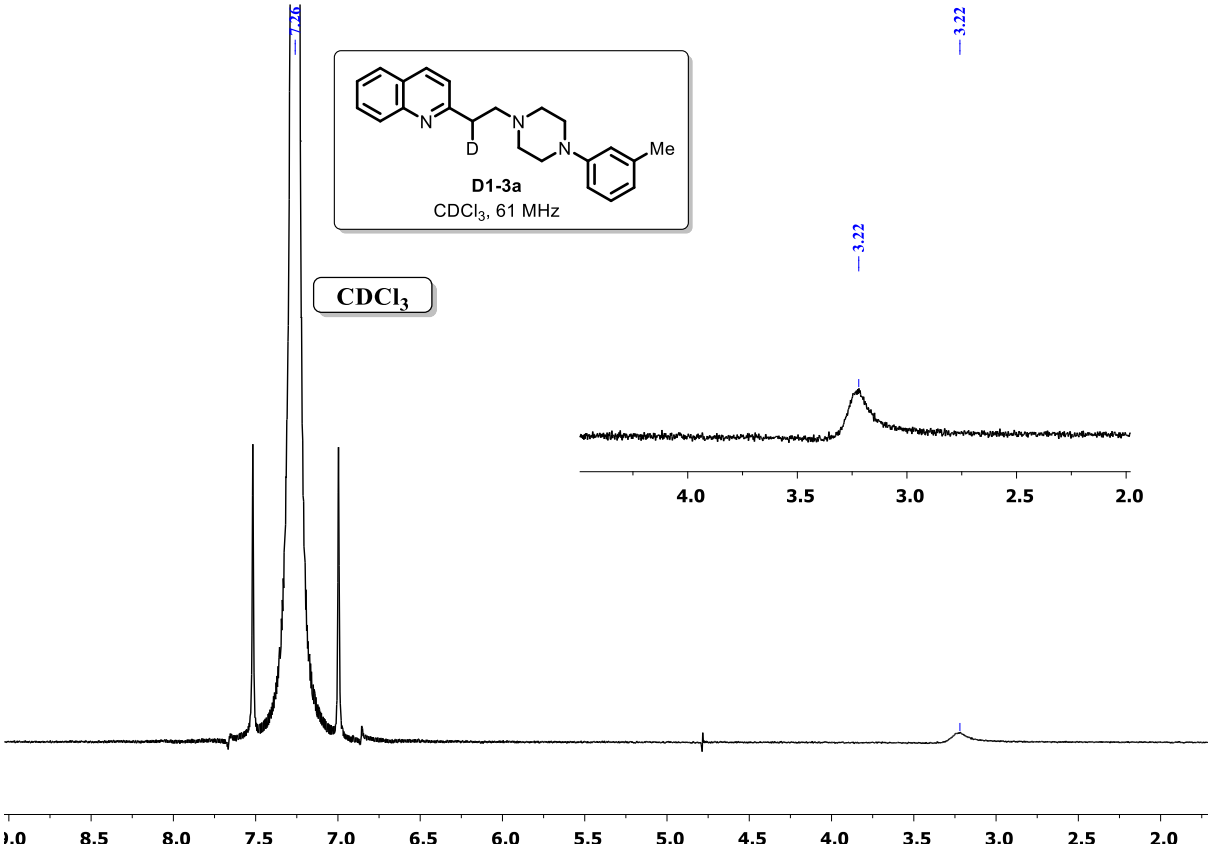


Figure S21: ^{1}H NMR of compound **3b**

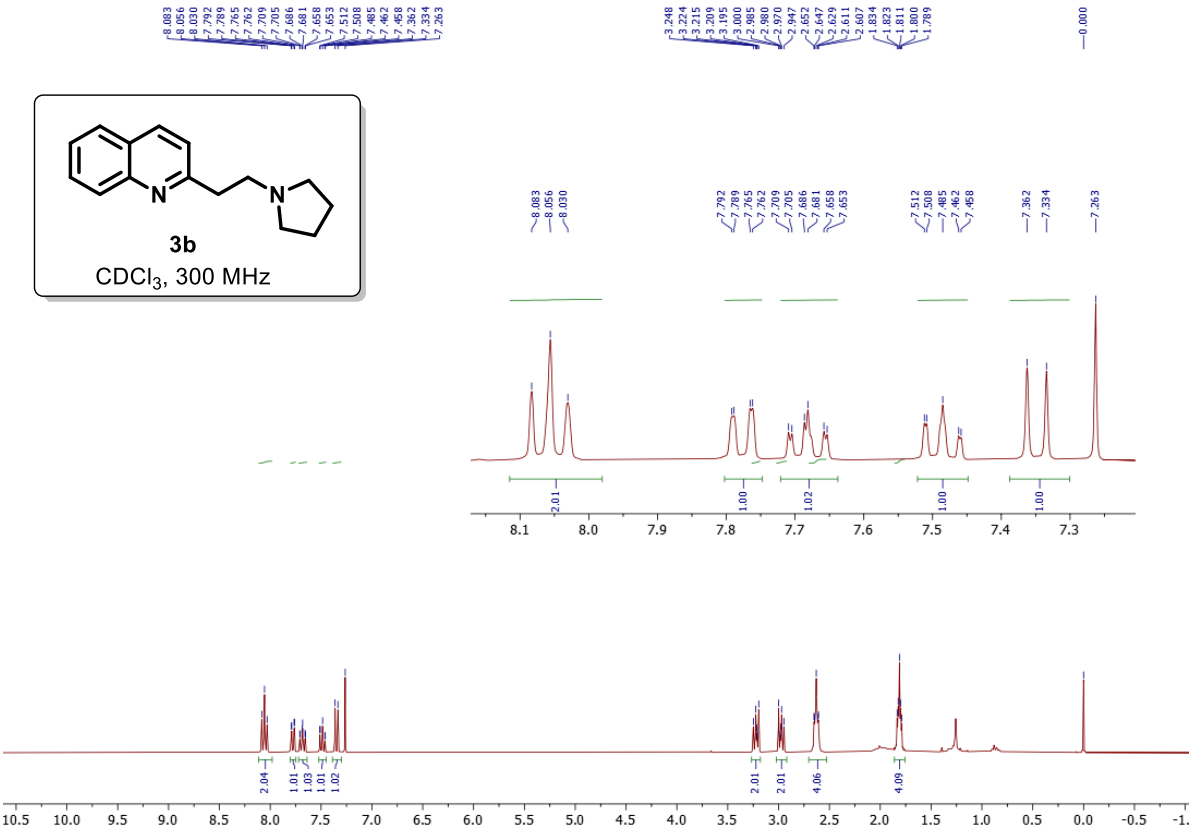


Figure S22: ^{13}C NMR of compound **3b**

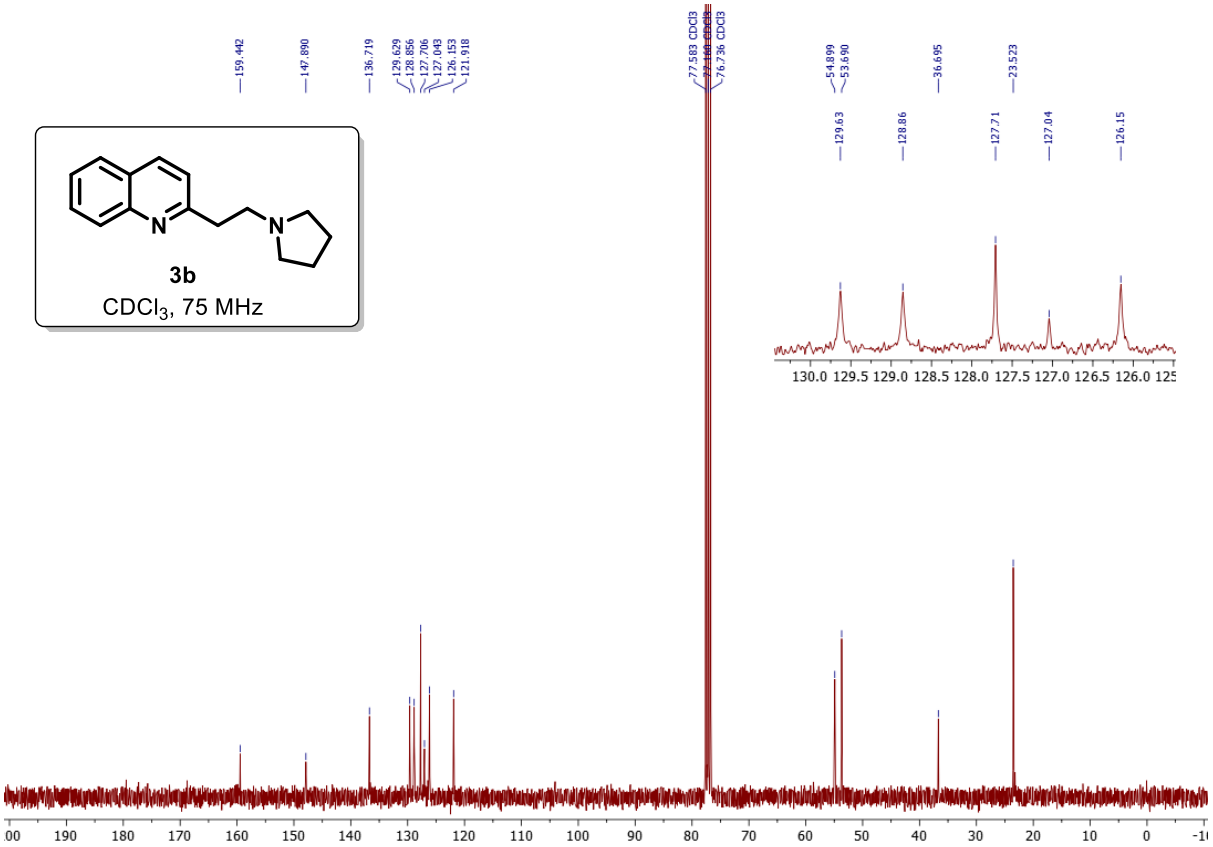


Figure S23: ^{1}H NMR of compound **3c**

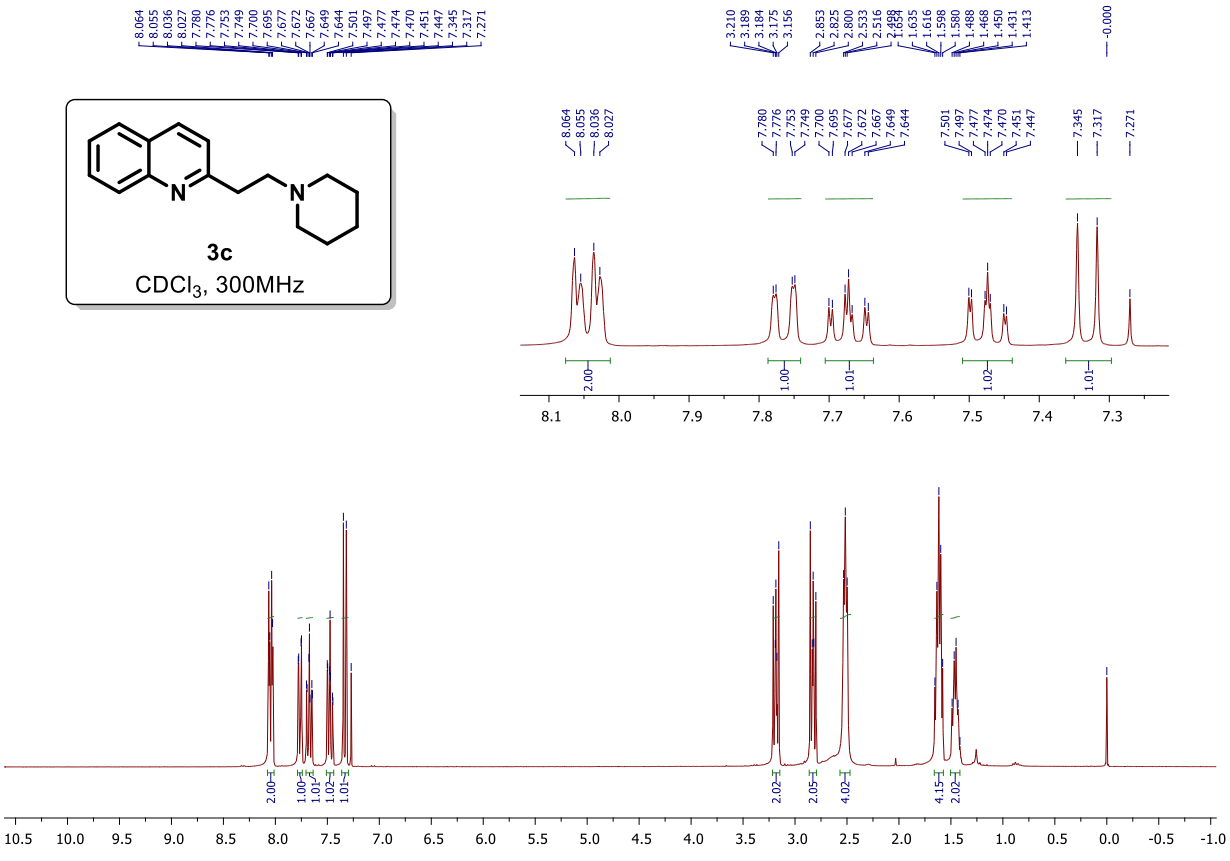


Figure S24: ^{13}C NMR of compound **3c**

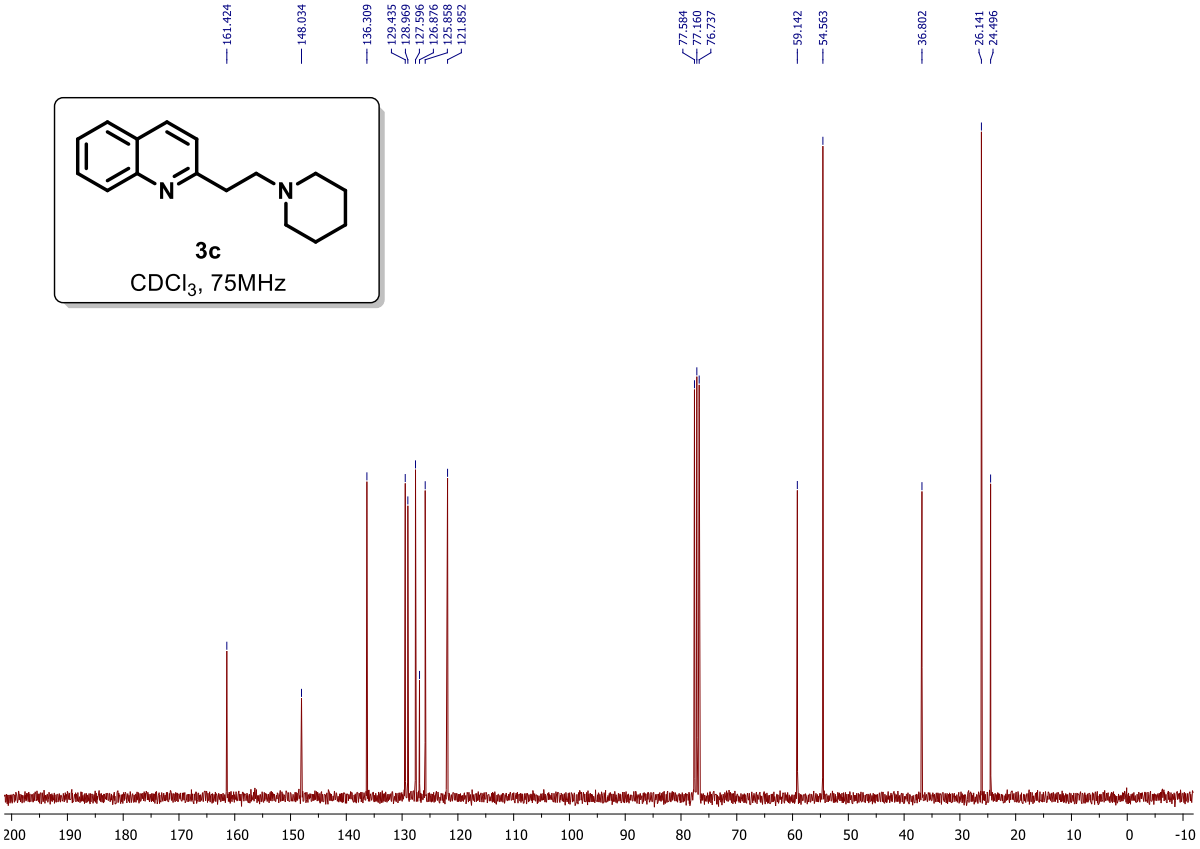


Figure S25: ^{1}H NMR of compound **3d**

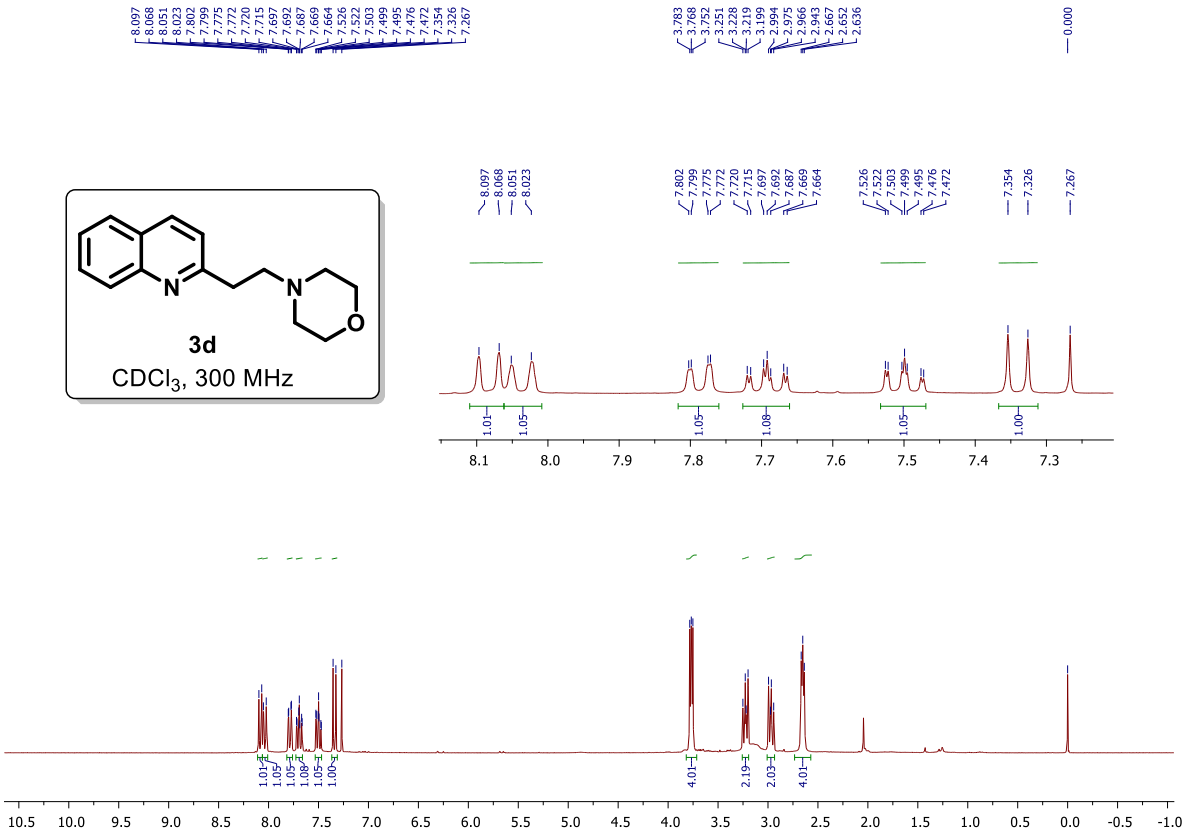


Figure S26: ^{13}C NMR of compound **3d**

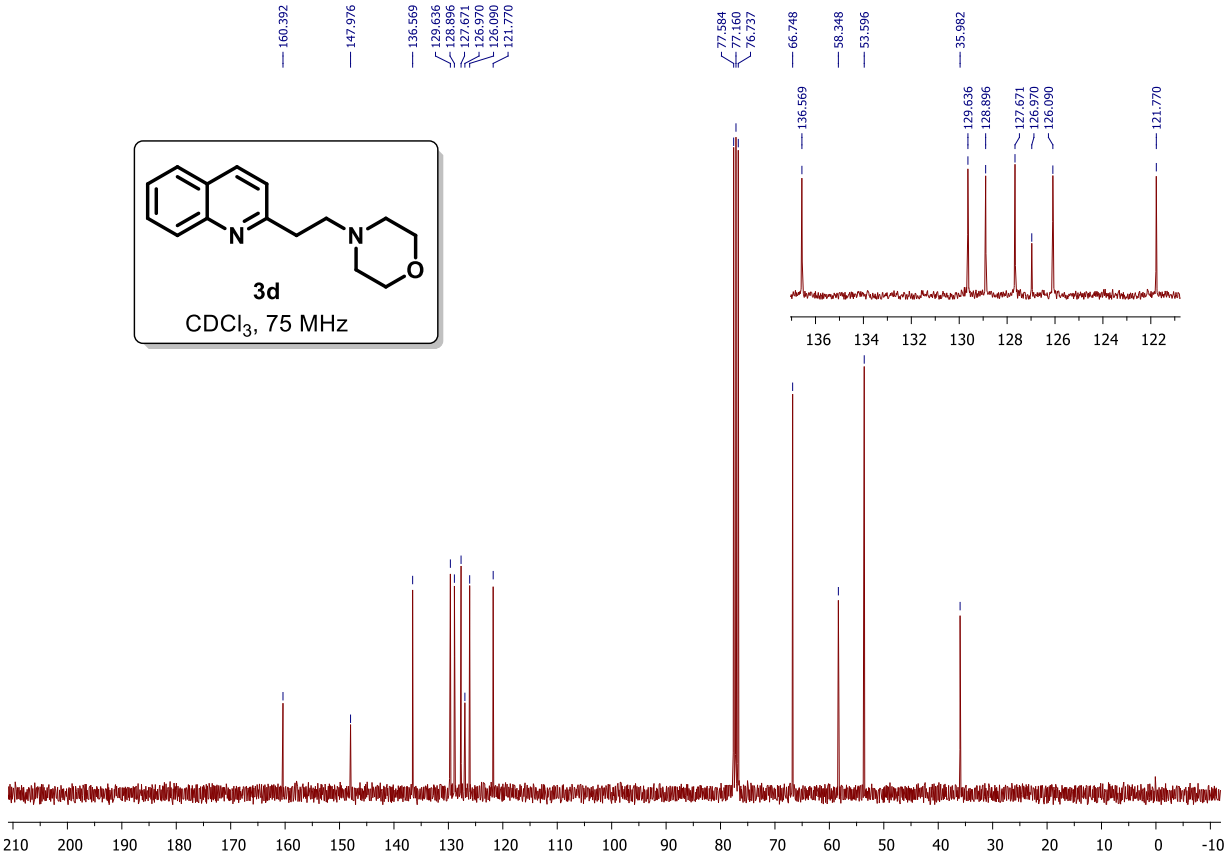


Figure S27: ^{1}H NMR of compound **3e**

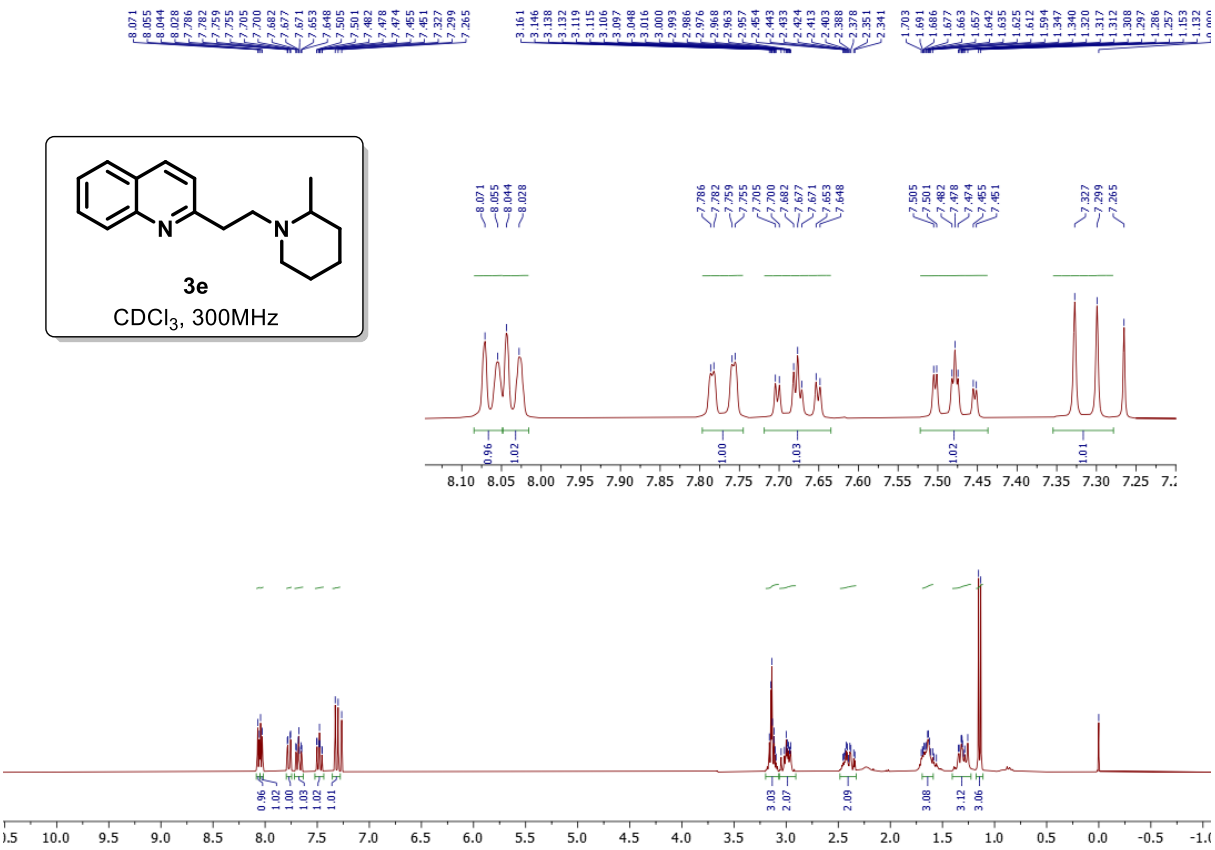


Figure S28: ^{13}C NMR of compound **3e**

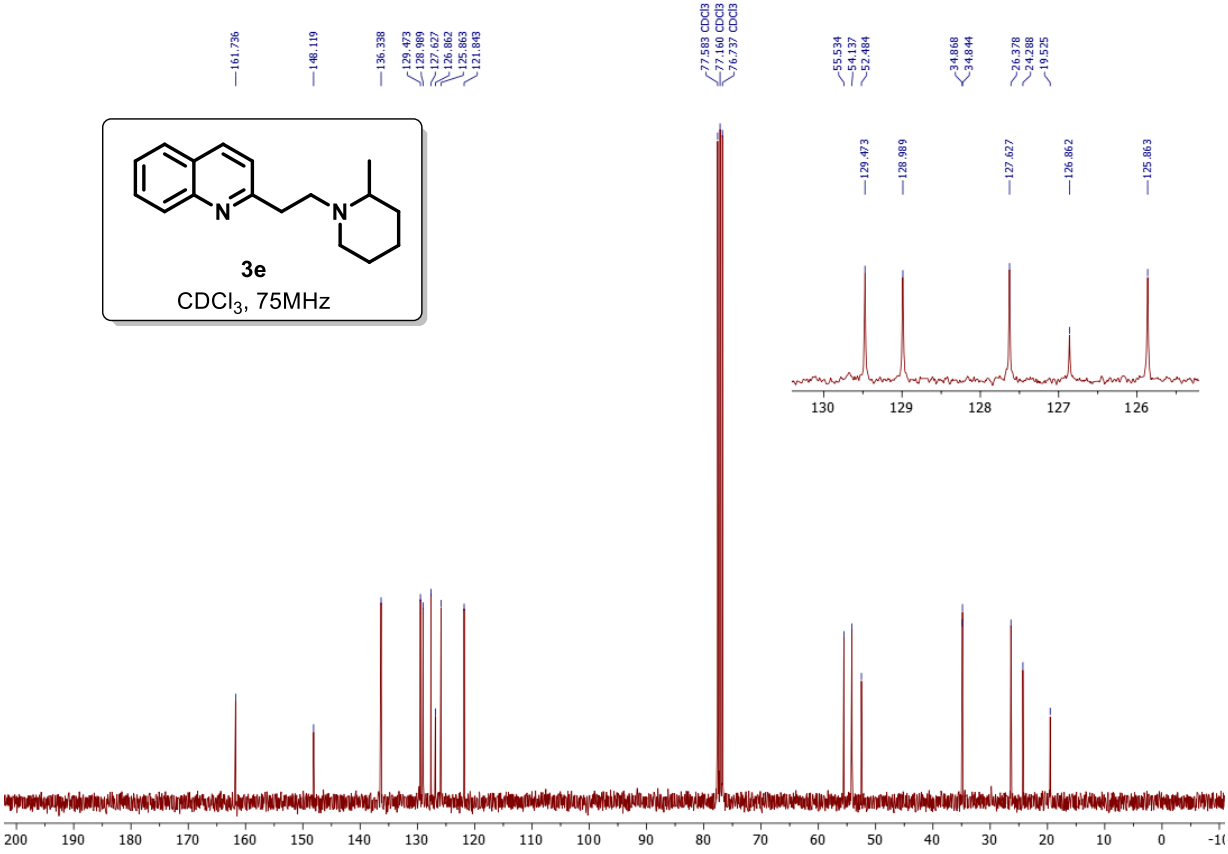


Figure S29: ^{1}H NMR of compound **3f**

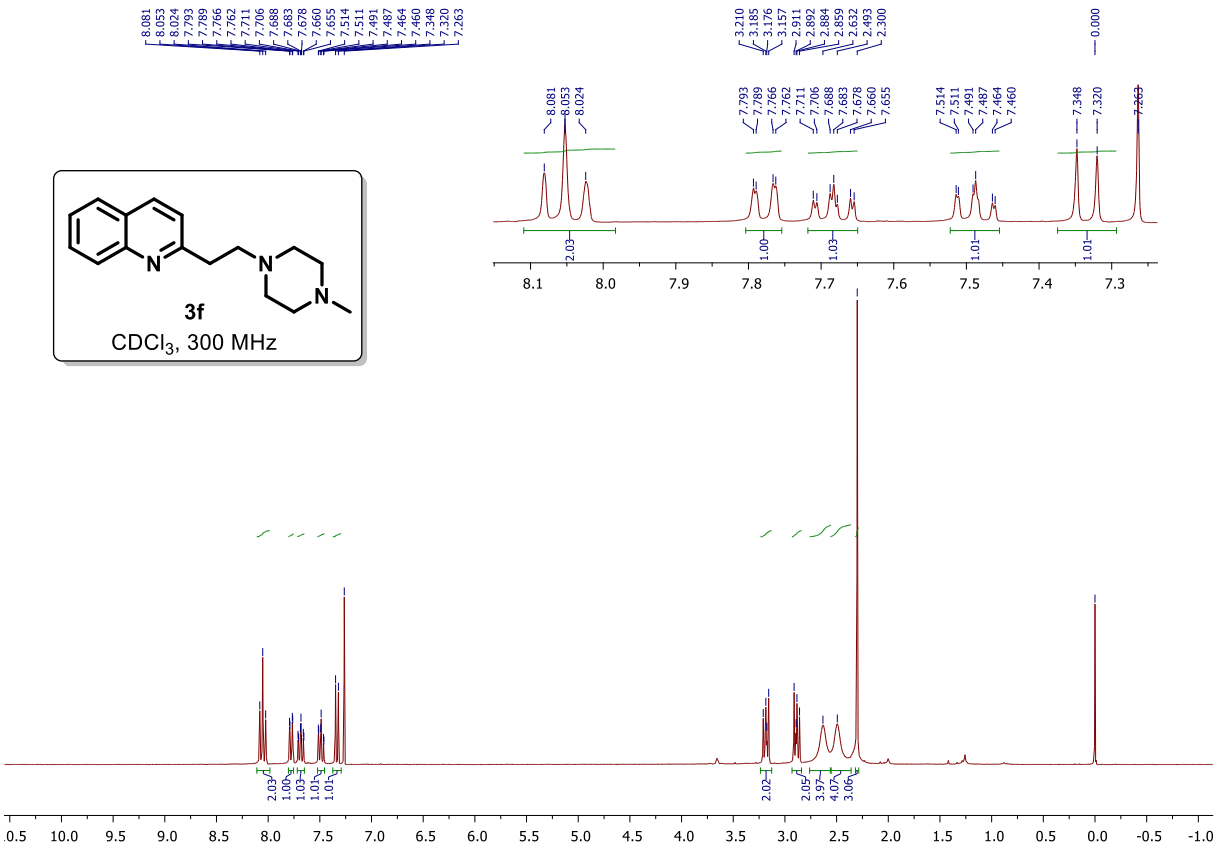


Figure S30: ^{13}C NMR of compound **3f**

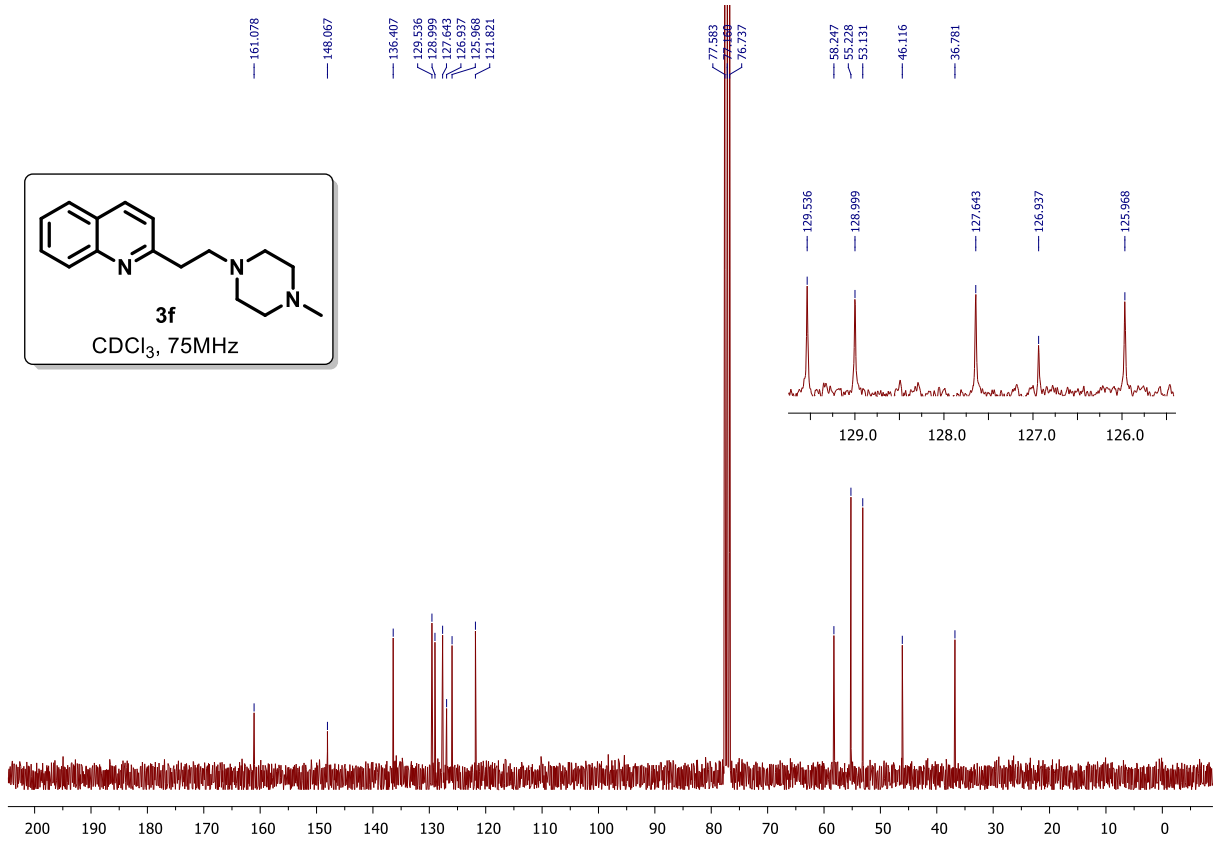


Figure S31: ^{1}H NMR of compound **3g**

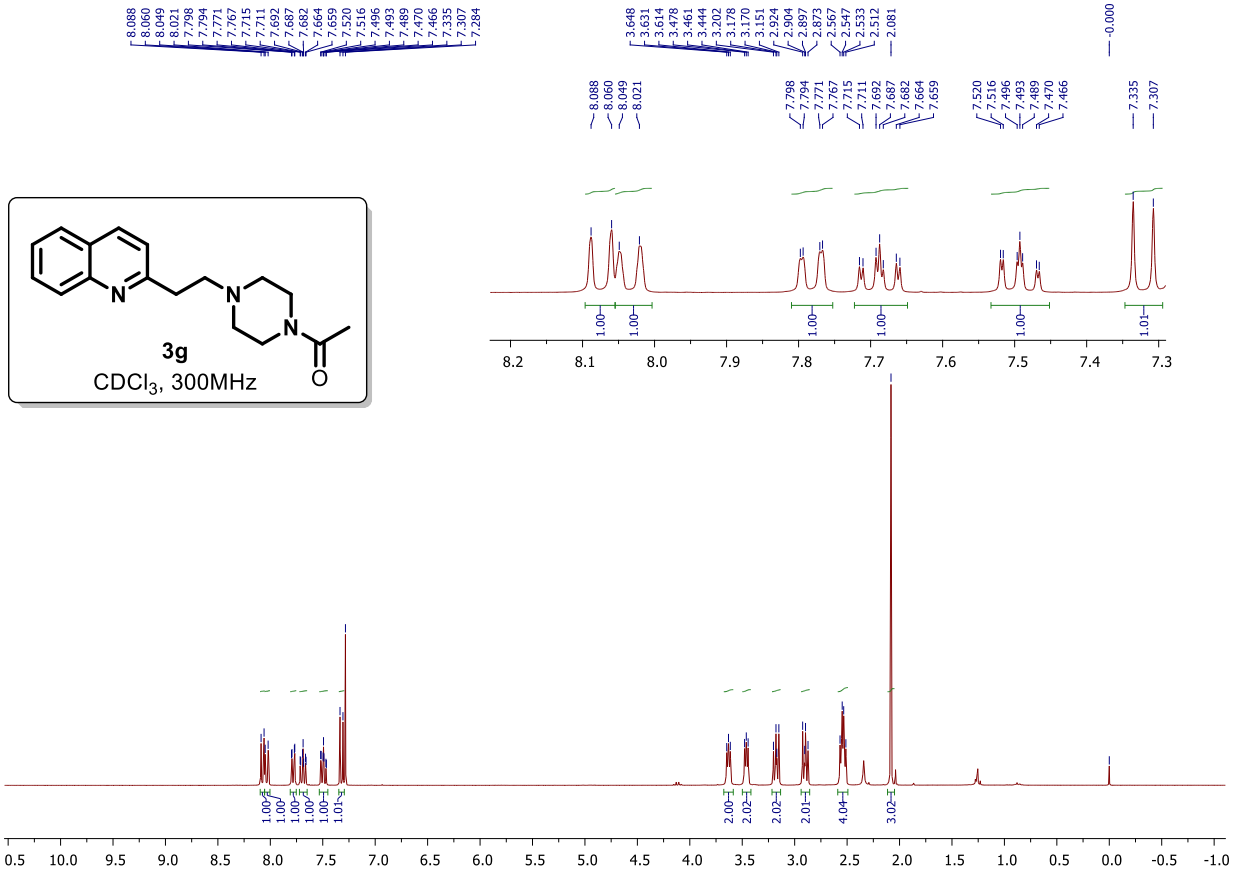


Figure S32: ^{13}C NMR of compound **3g**

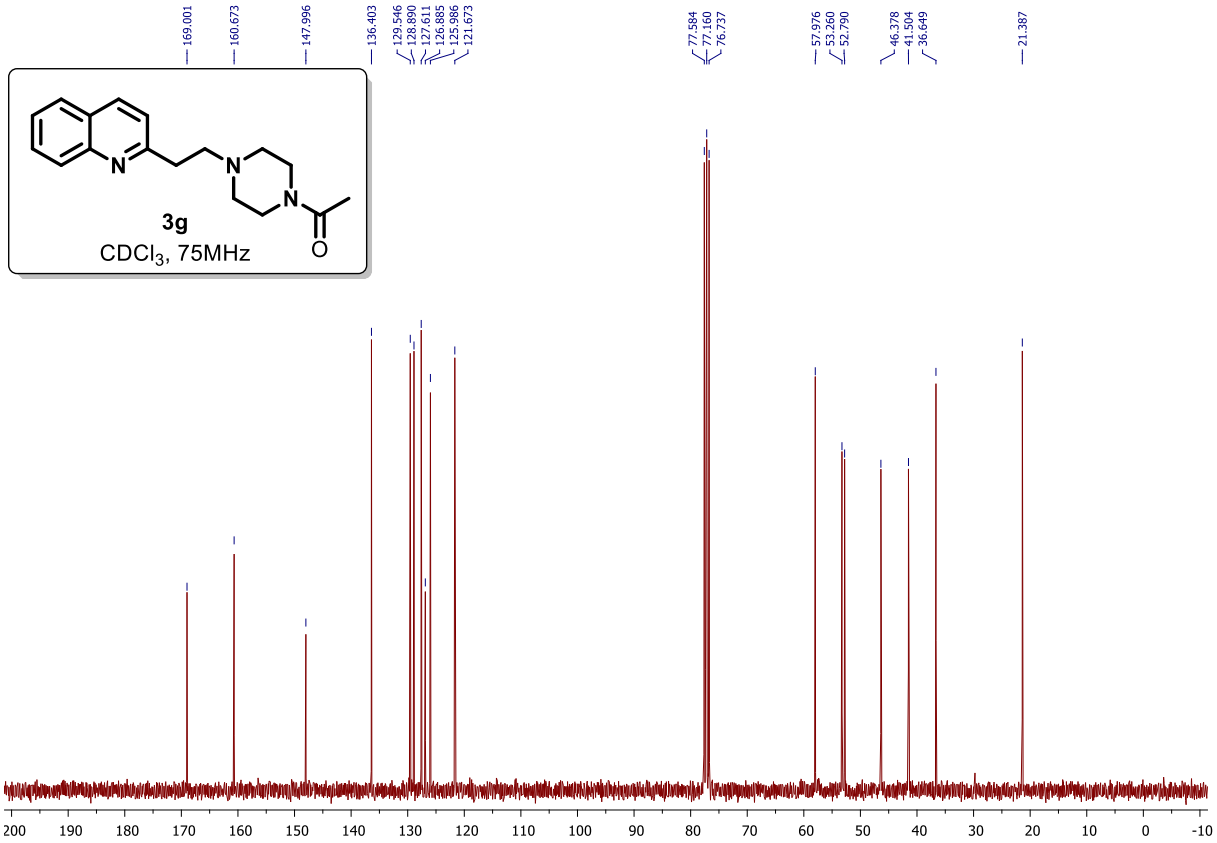


Figure S33: ^{1}H NMR of compound **3h**

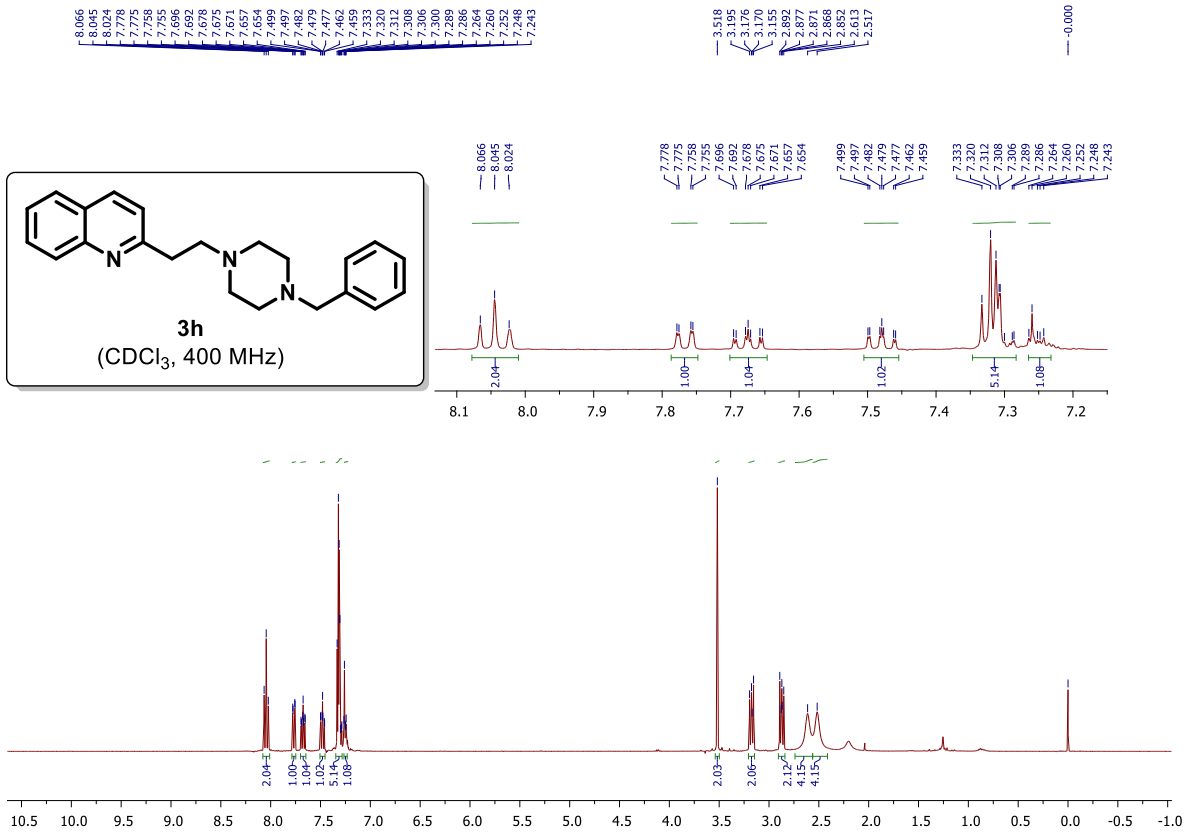


Figure S34: ^{13}C NMR of compound **3h**

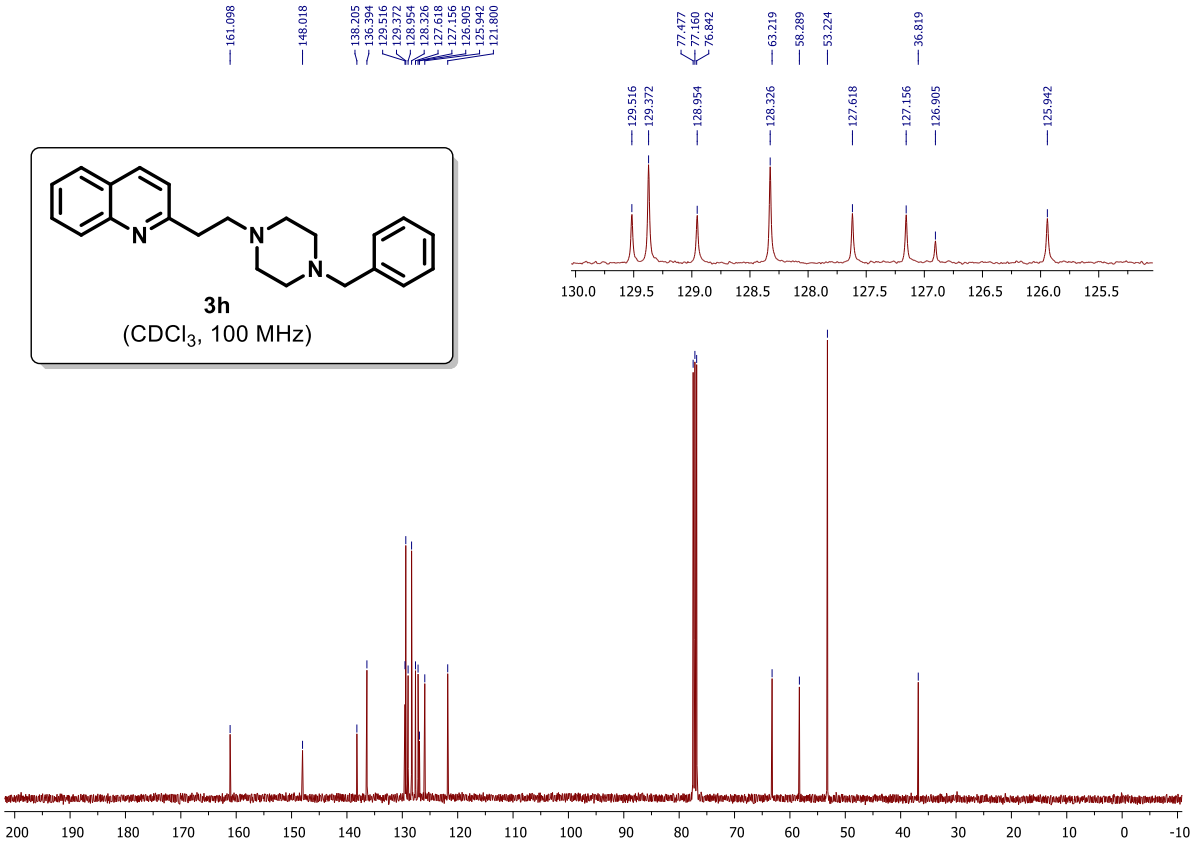


Figure S35: ^{1}H NMR of compound **3i**

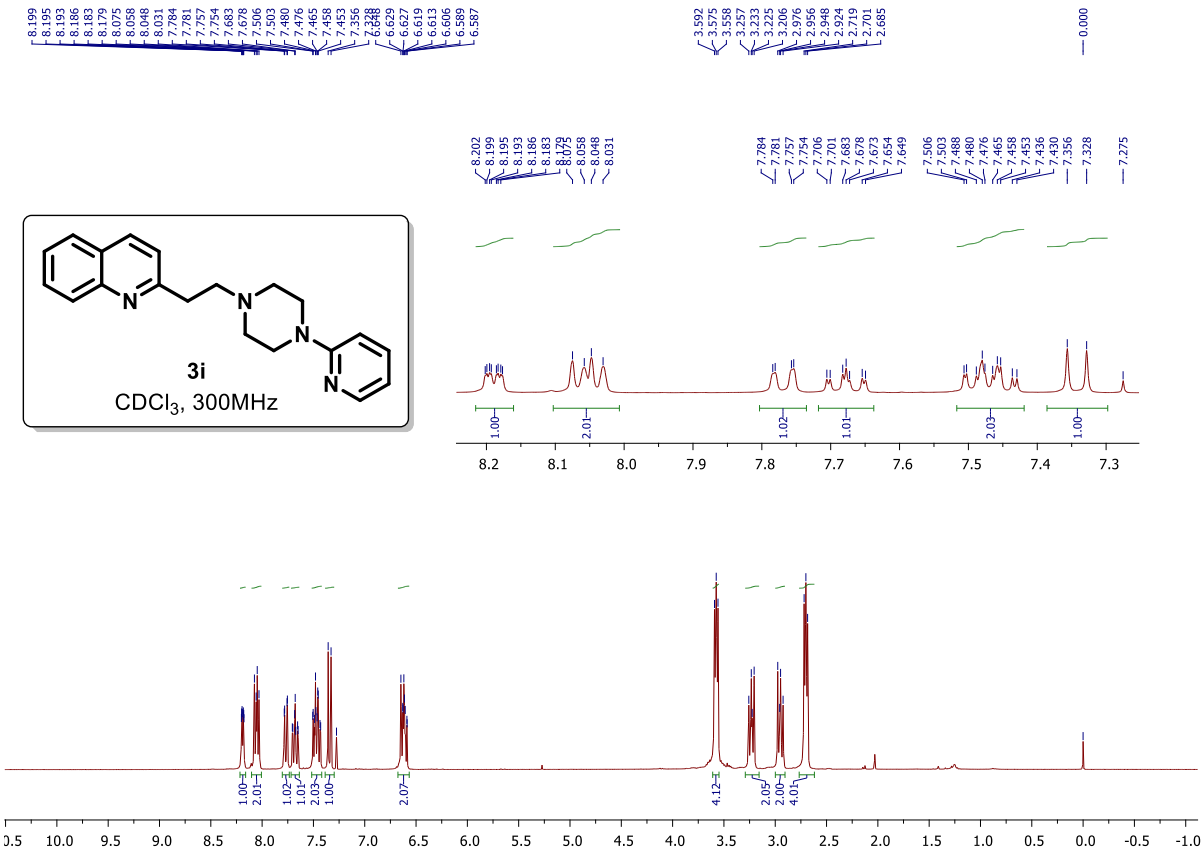


Figure S36: ^{13}C NMR of compound **3i**

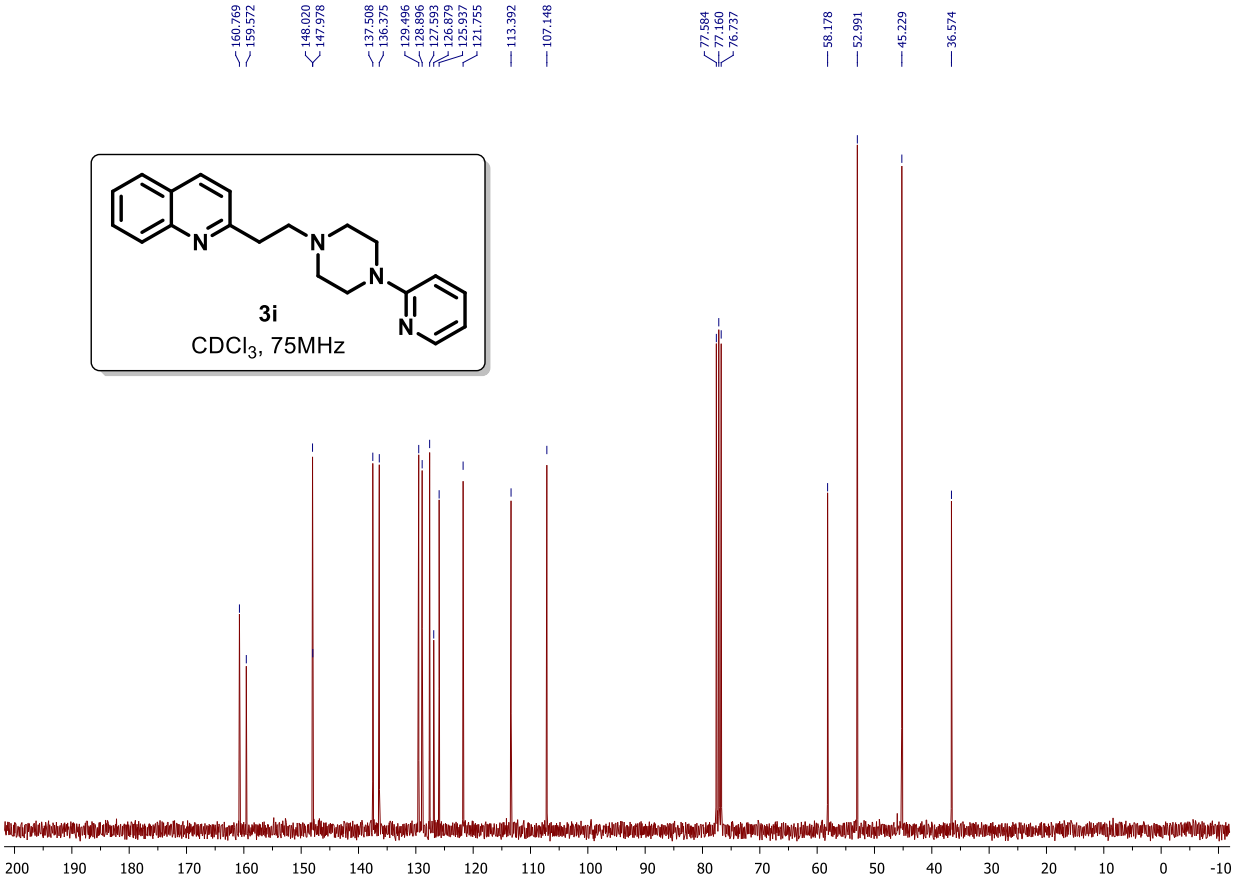


Figure S37: ^{1}H NMR of compound **3j**

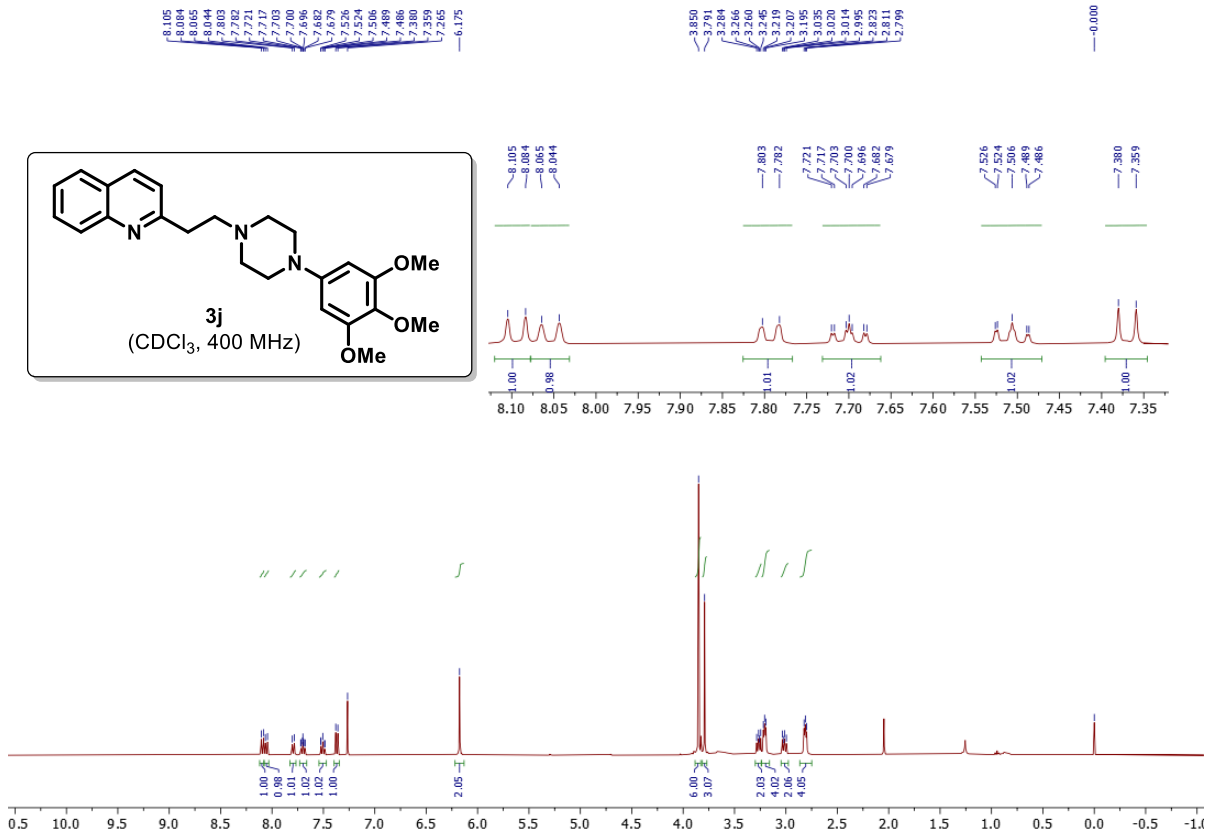


Figure S38: ^{13}C NMR of compound **3j**

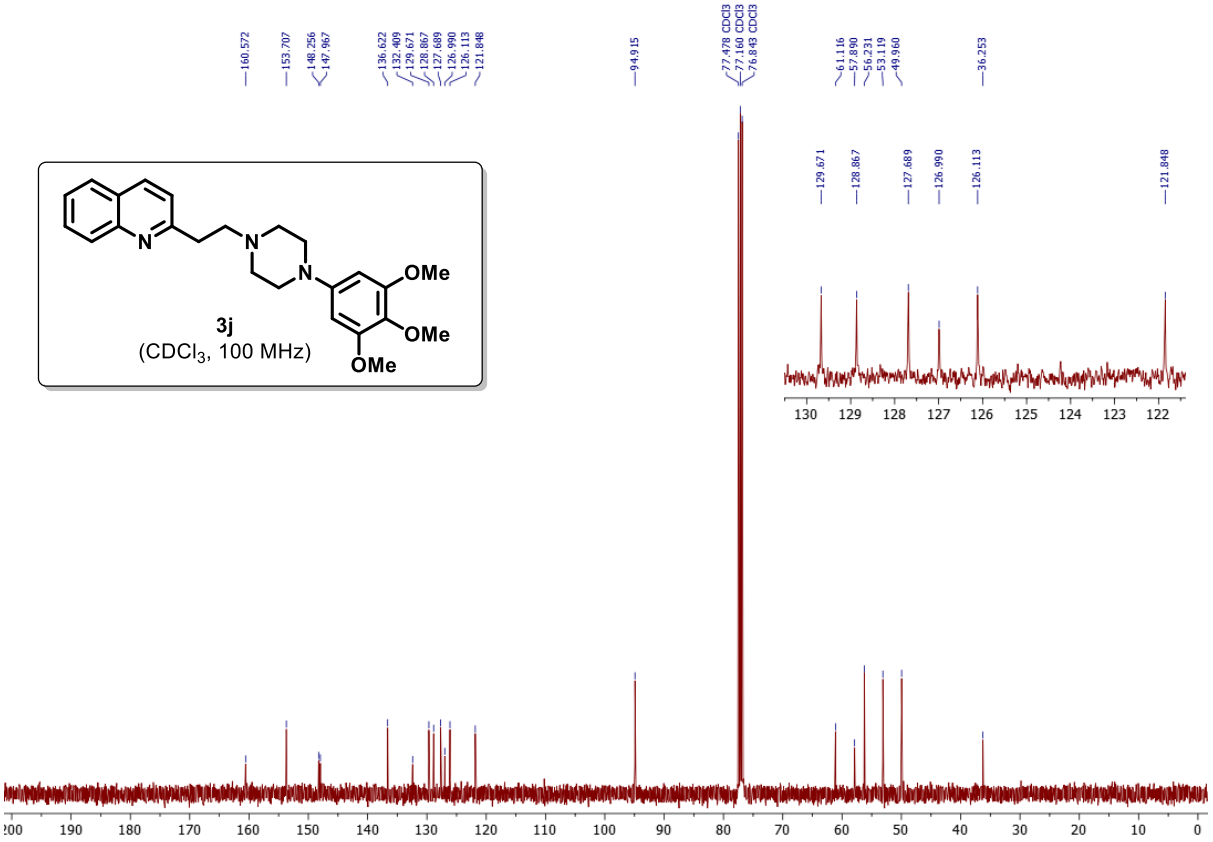


Figure S39: ^{1}H NMR of compound **3k**

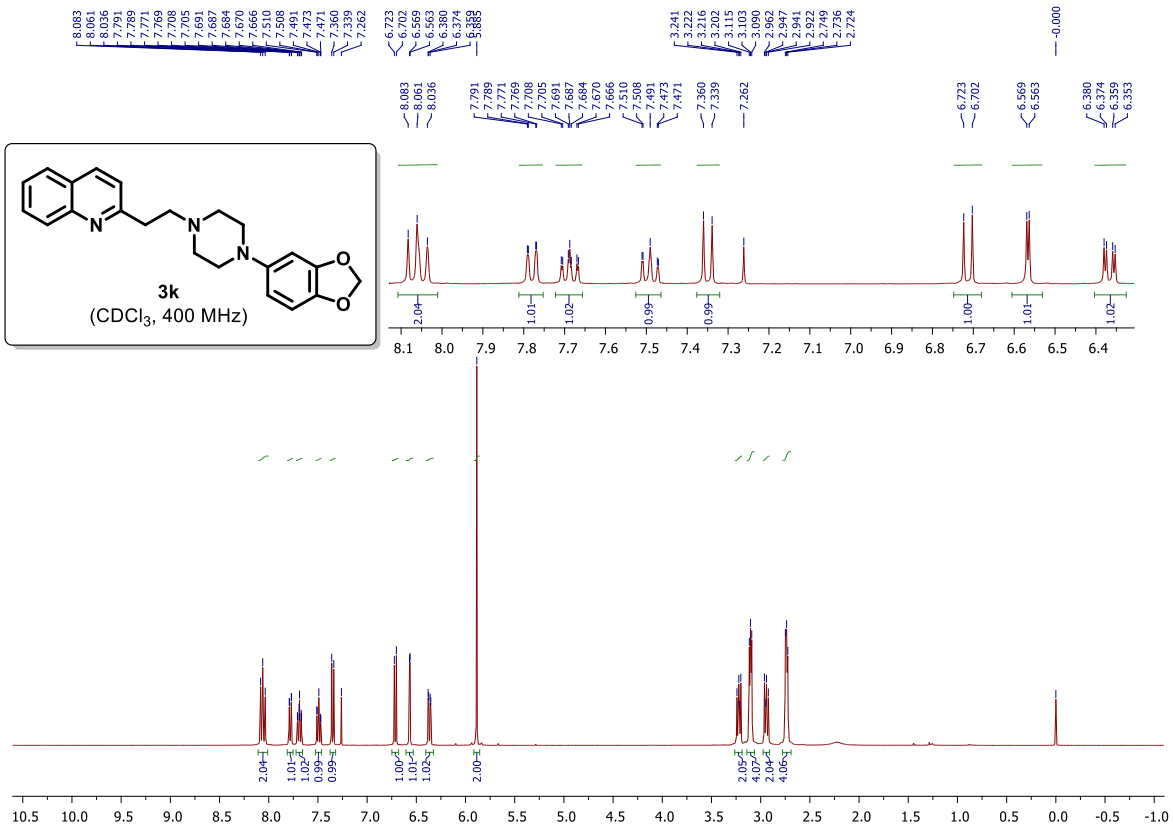


Figure S40: ^{13}C NMR of compound **3k**

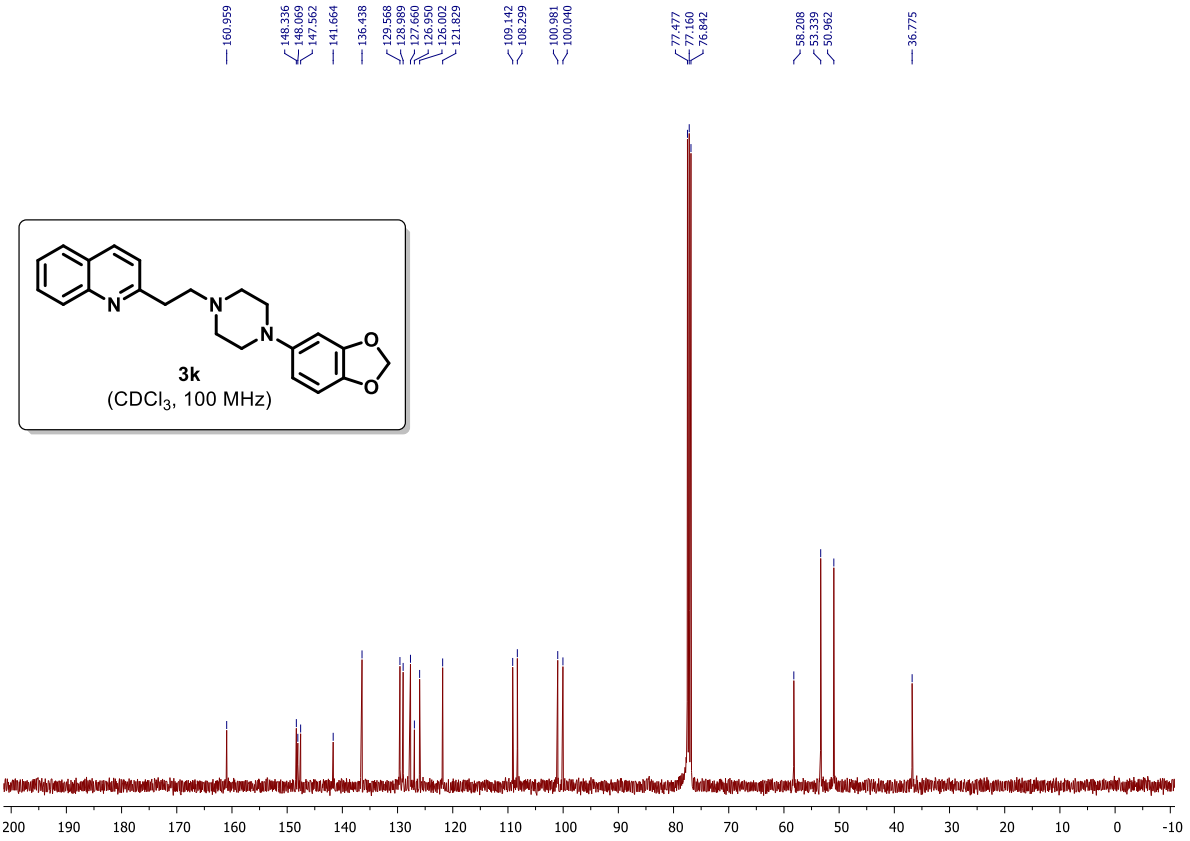


Figure S41: ^{1}H NMR of compound **3l**

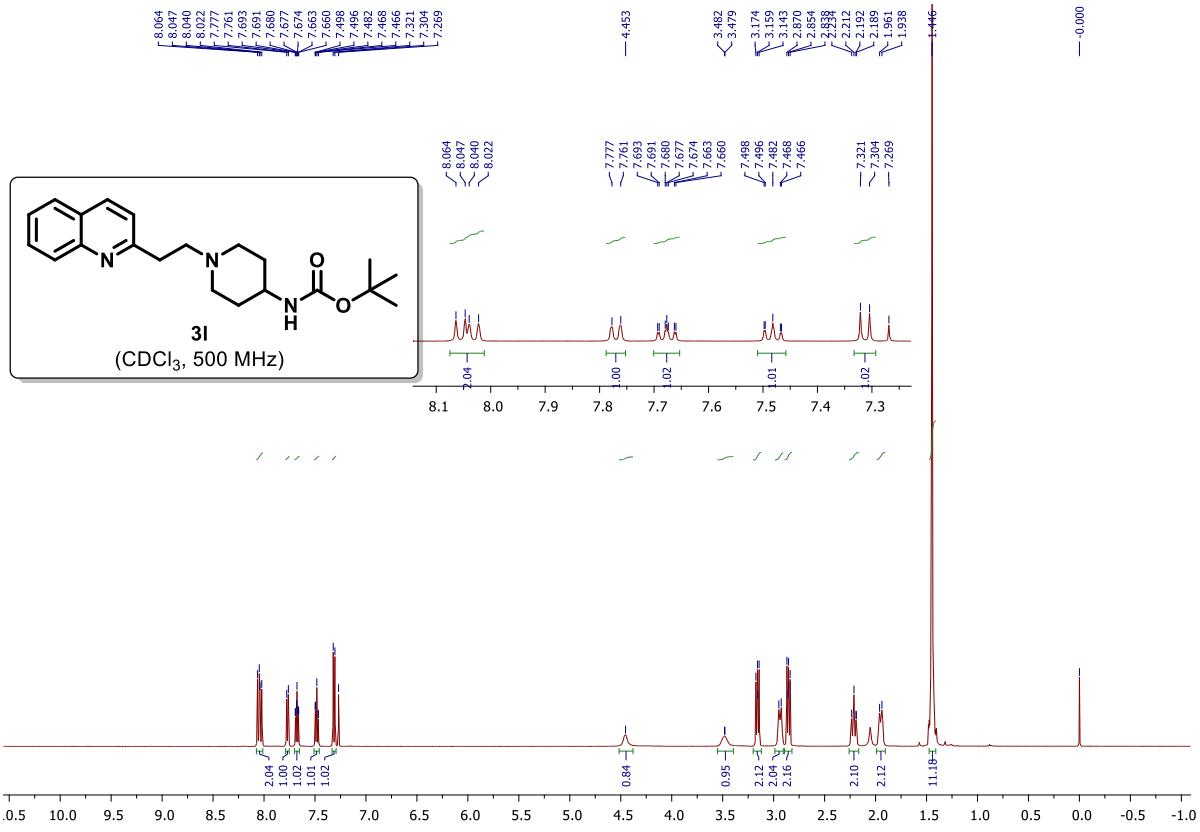


Figure S42: ^{13}C NMR of compound **3l**

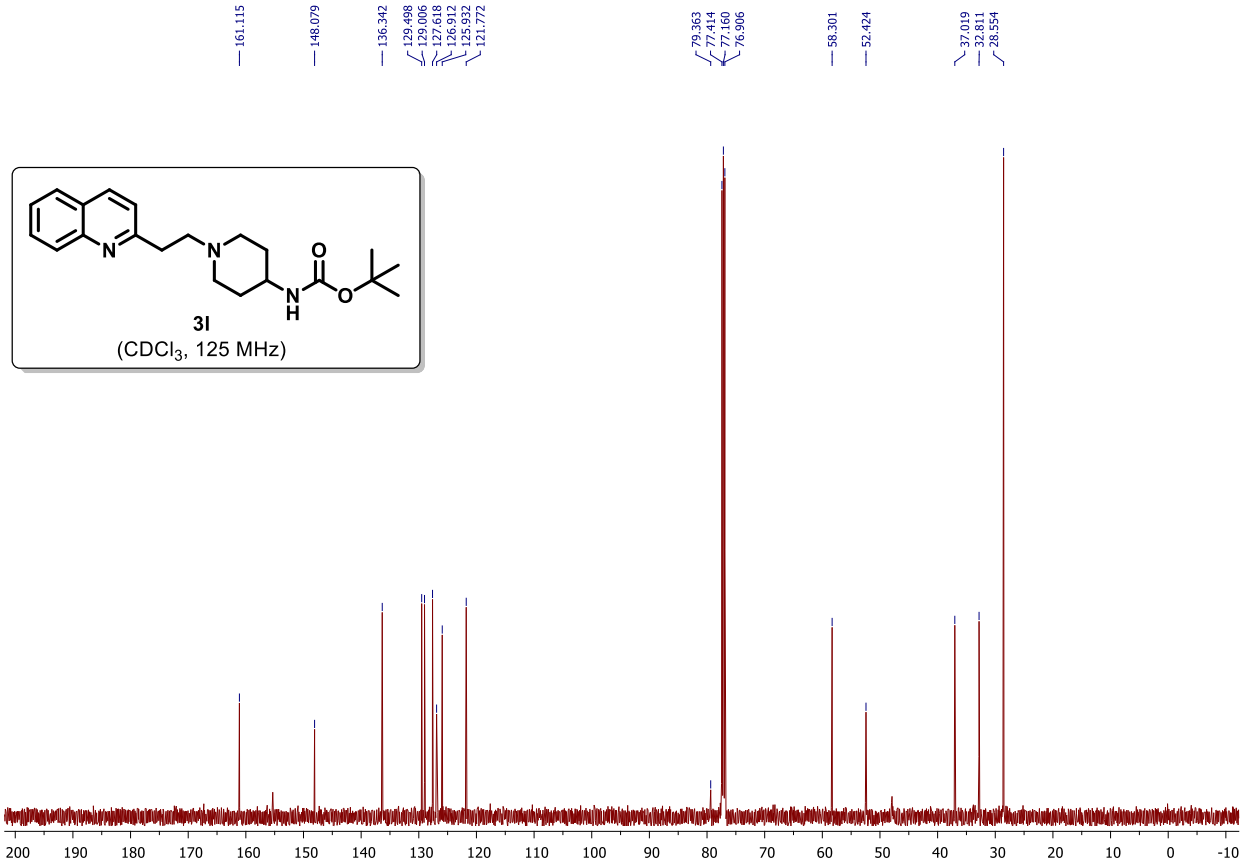


Figure S43: ^{1}H NMR of compound **3m**

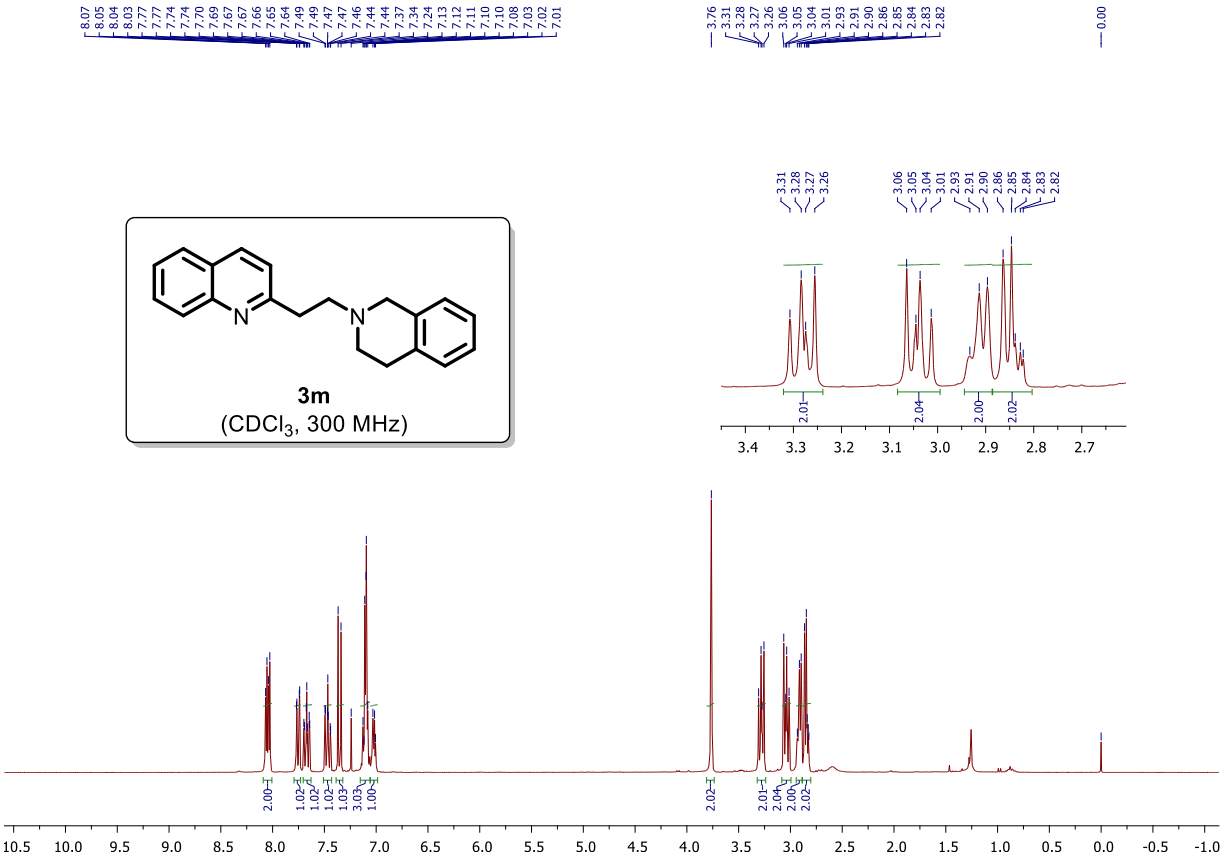


Figure S44: ^{13}C NMR of compound **3m**

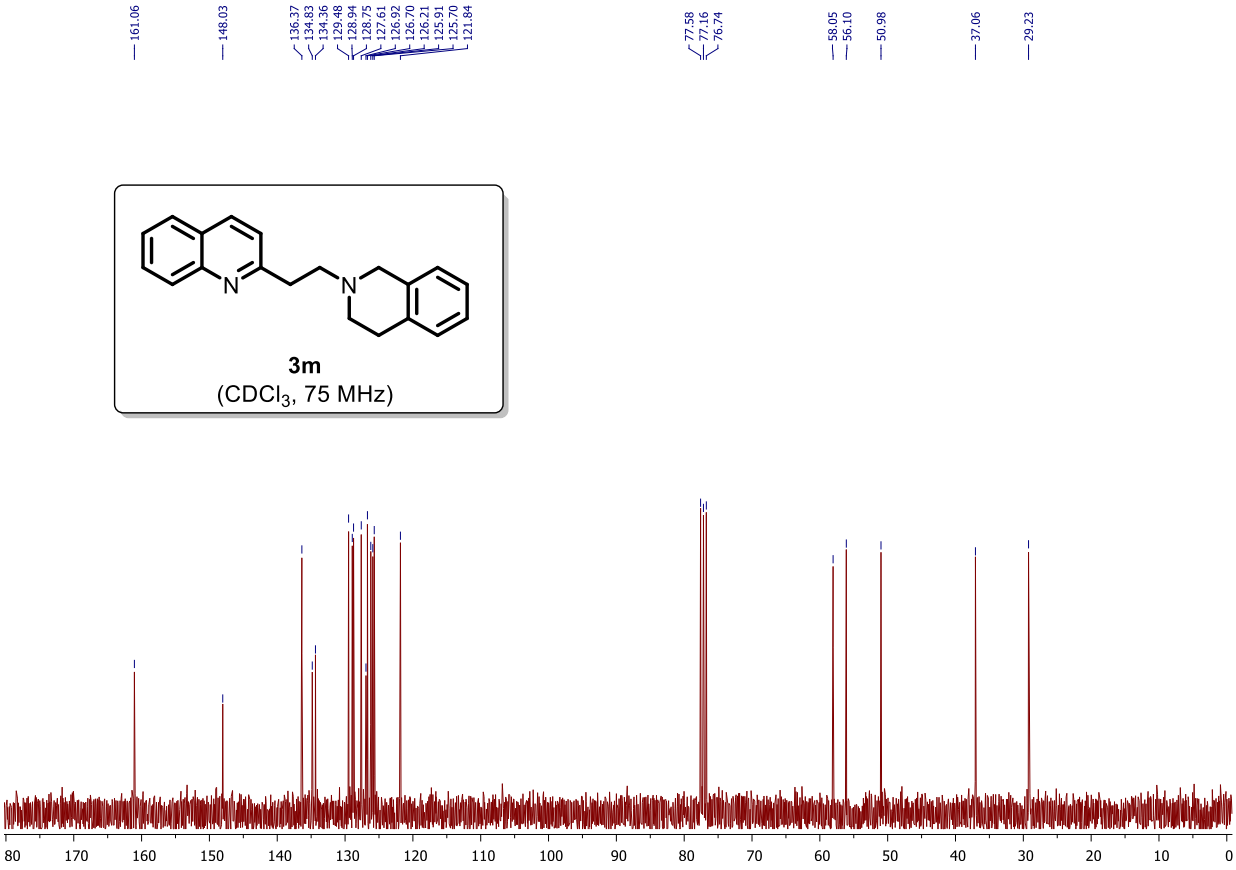


Figure S45: ^{1}H NMR of compound **3n**

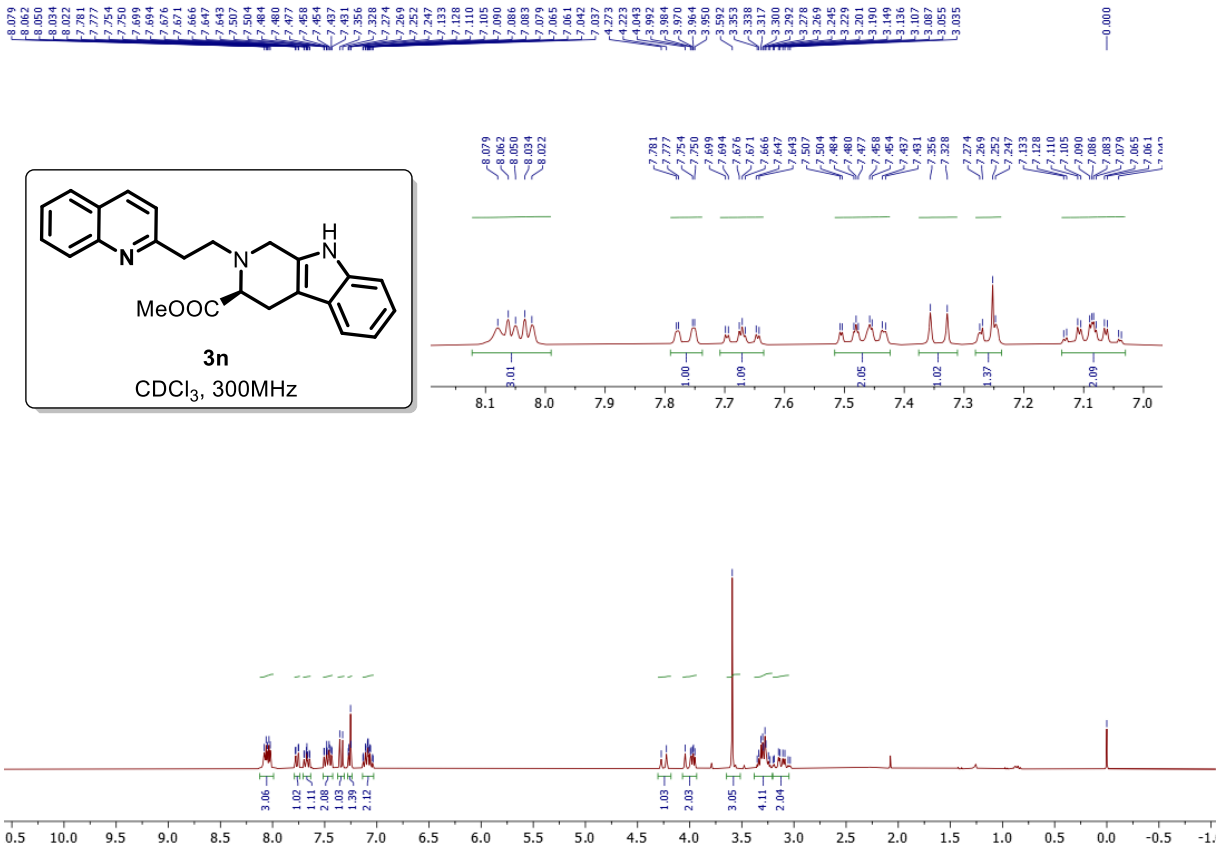


Figure S46: ^{13}C NMR of compound **3n**

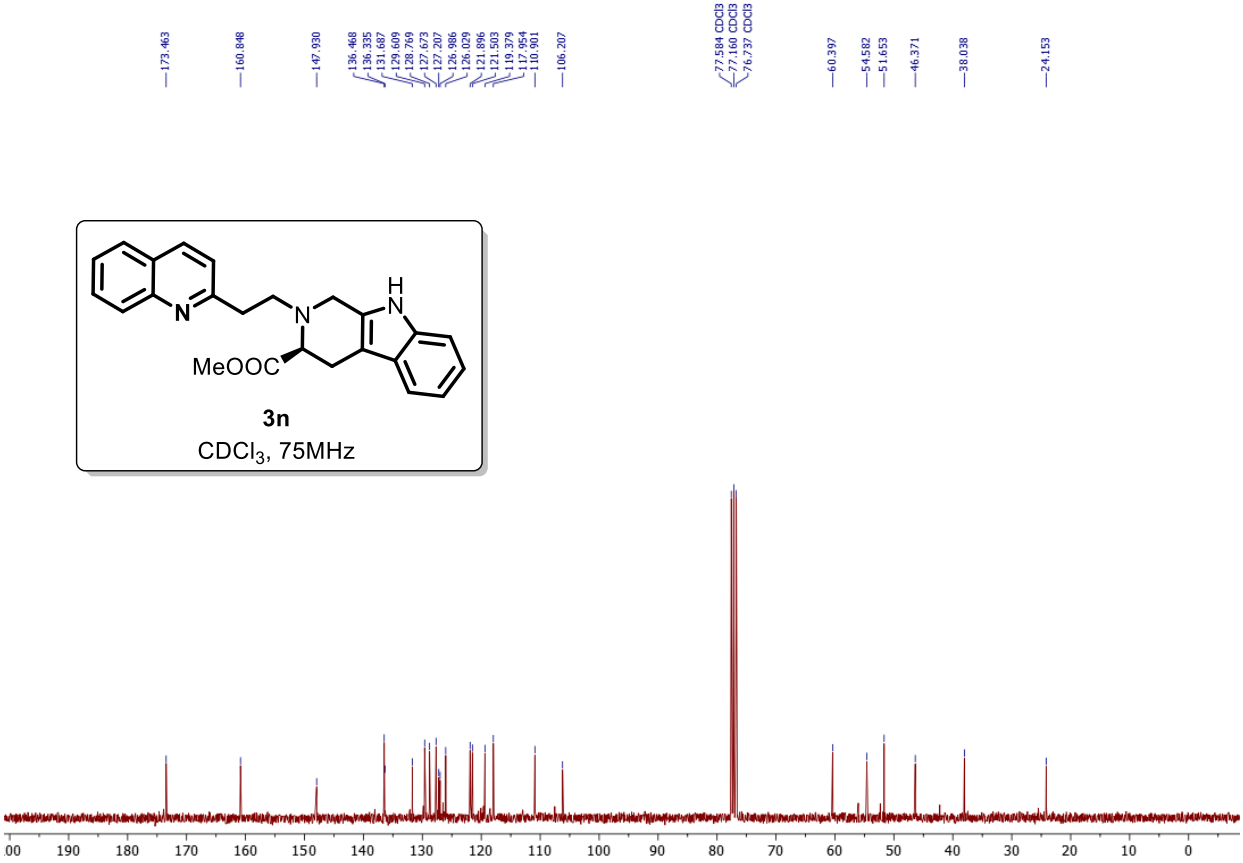


Figure S47: ^{1}H NMR of compound **3o**

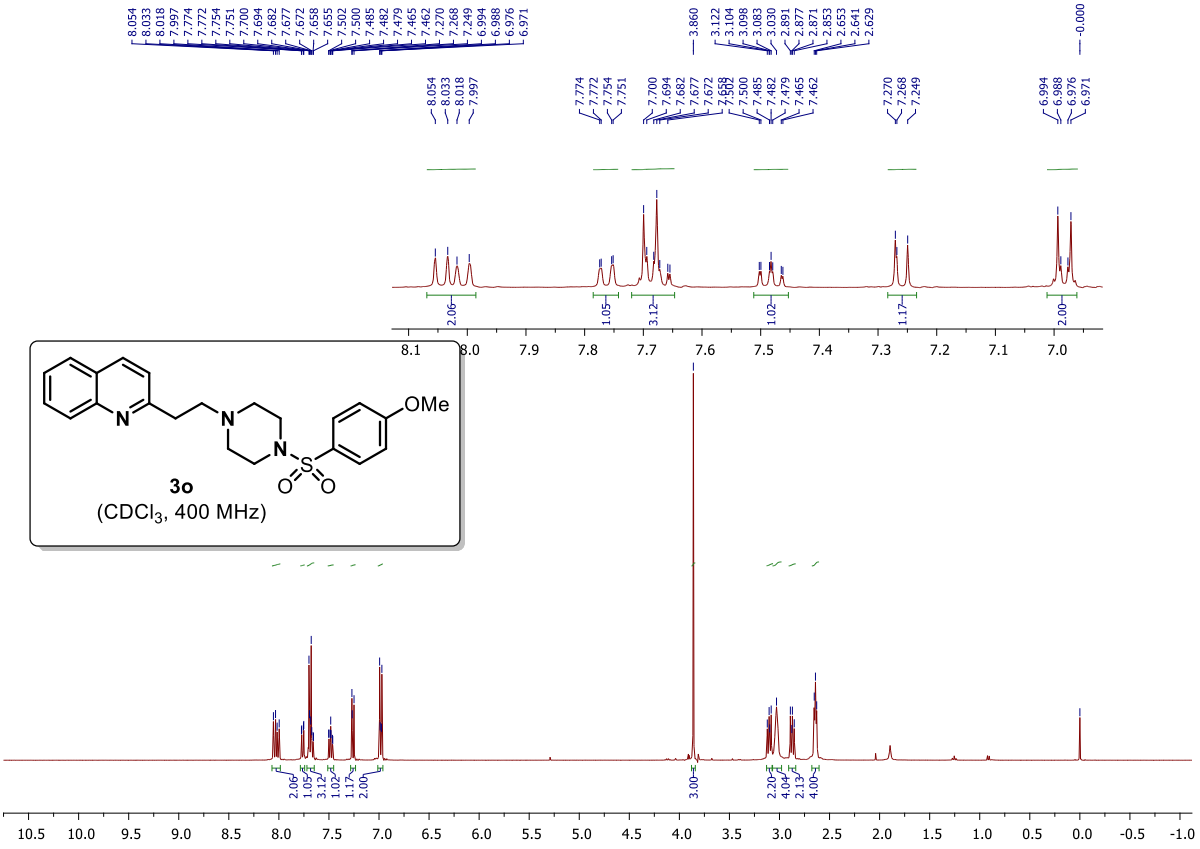


Figure S48: ^{13}C NMR of compound **3o**

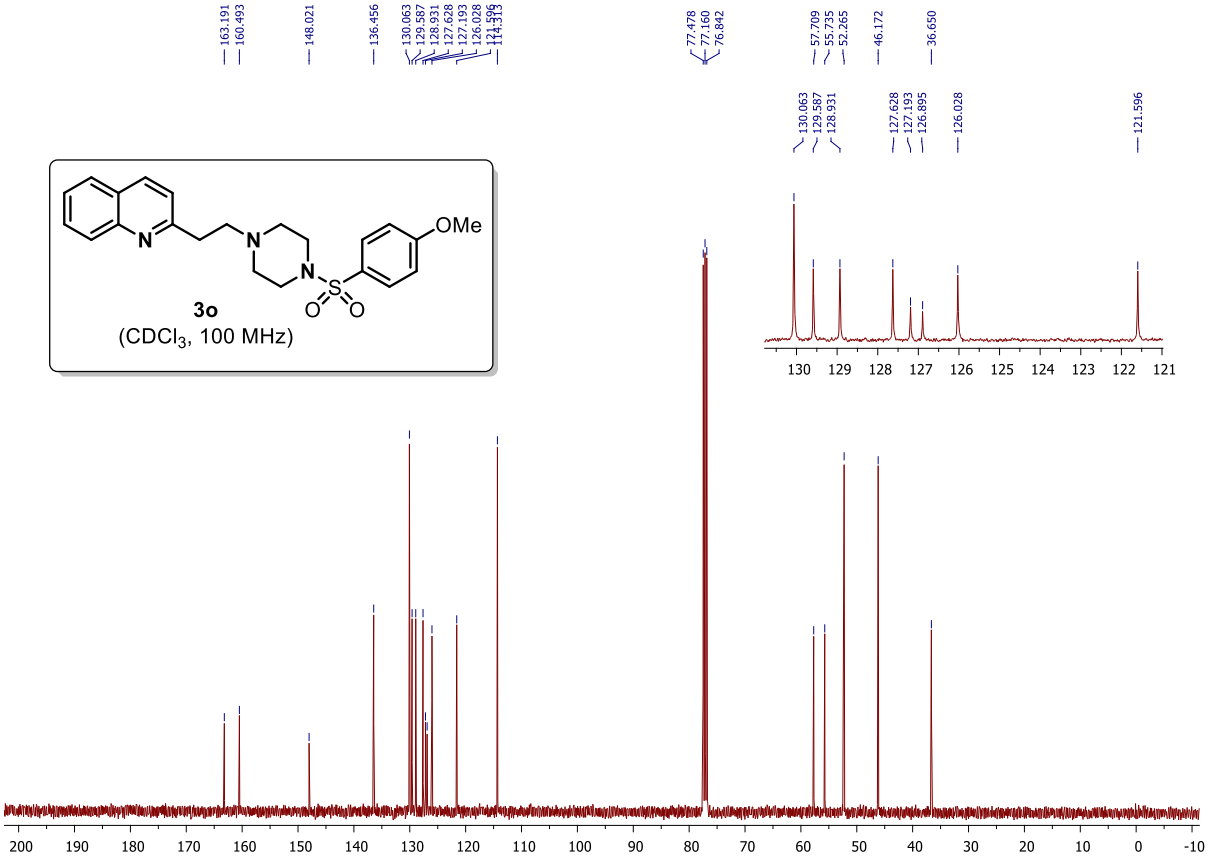


Figure S49: ^{1}H NMR of compound **3p**

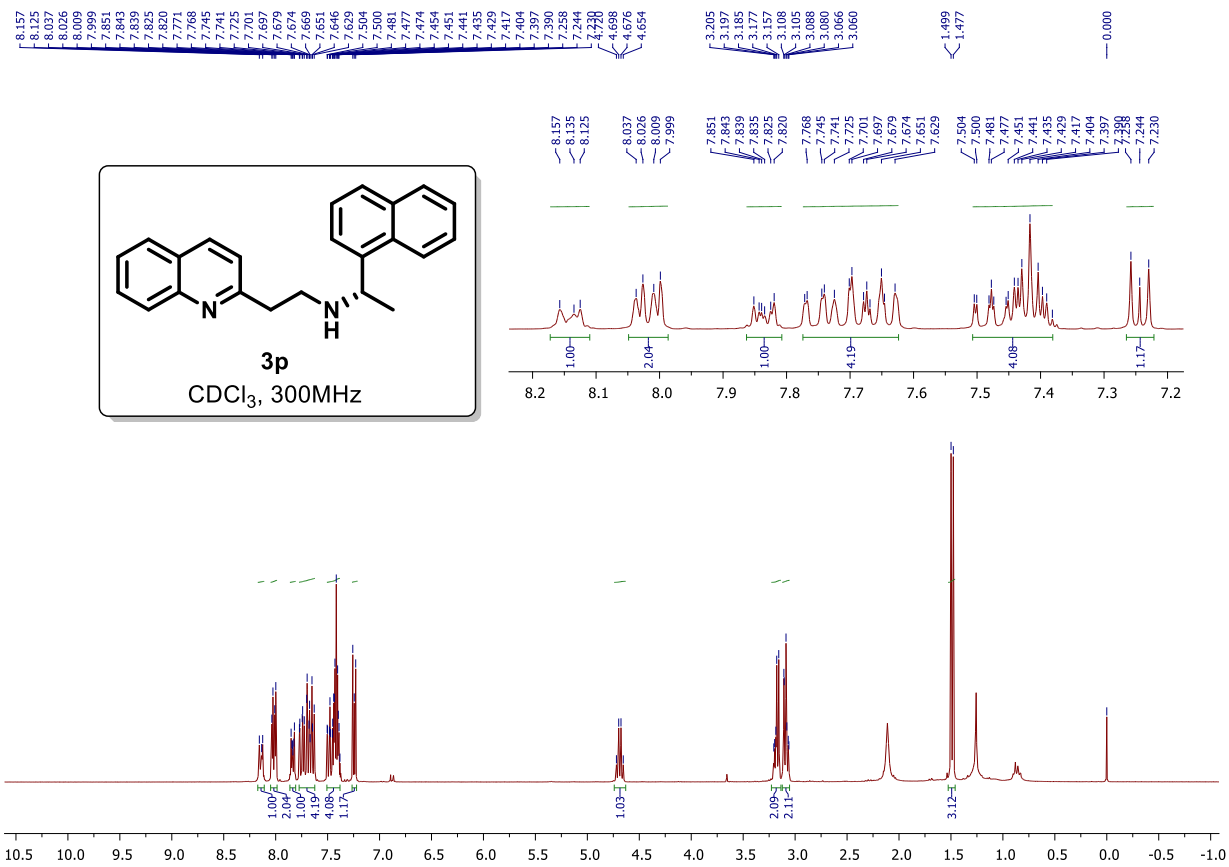


Figure S50: ^{13}C NMR of compound **3p**

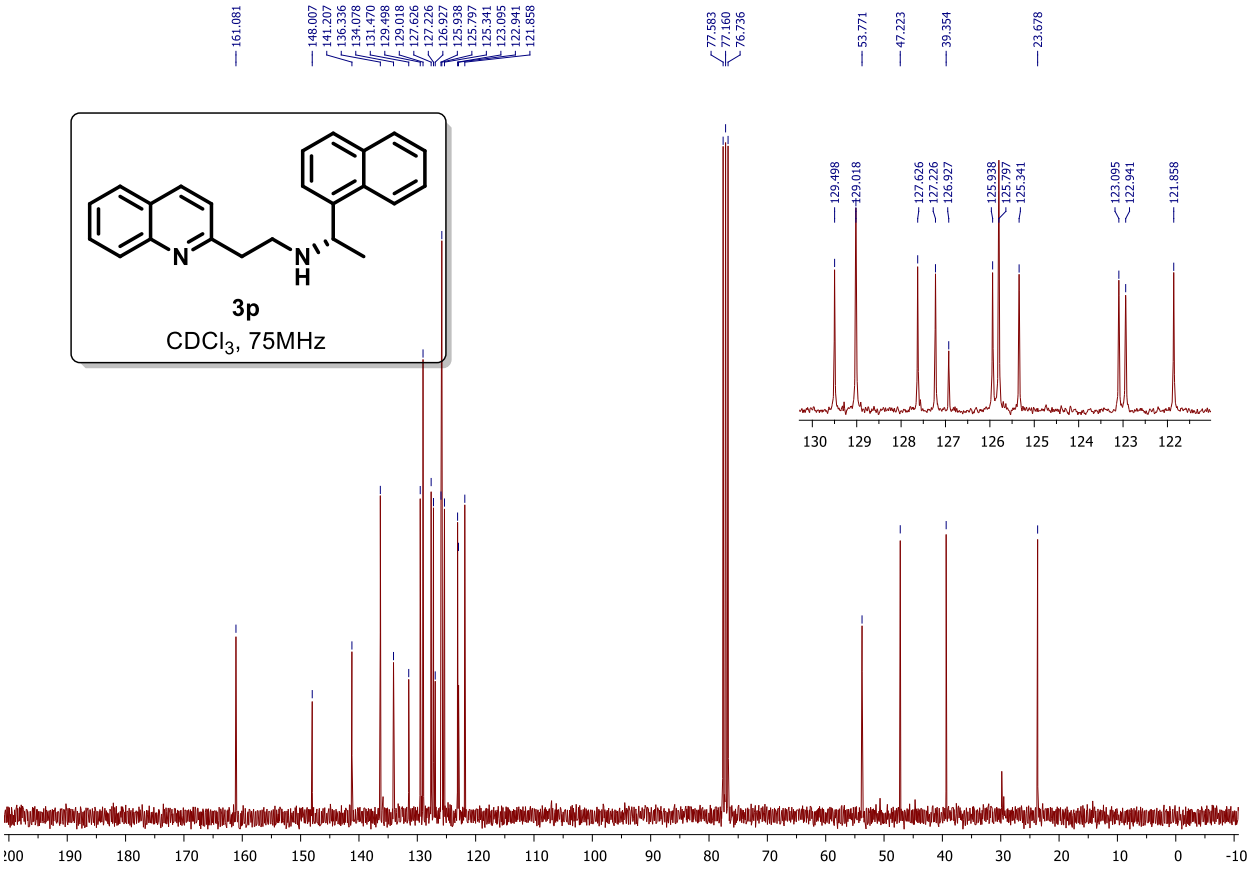


Figure S51: ^{1}H NMR of compound **3q**

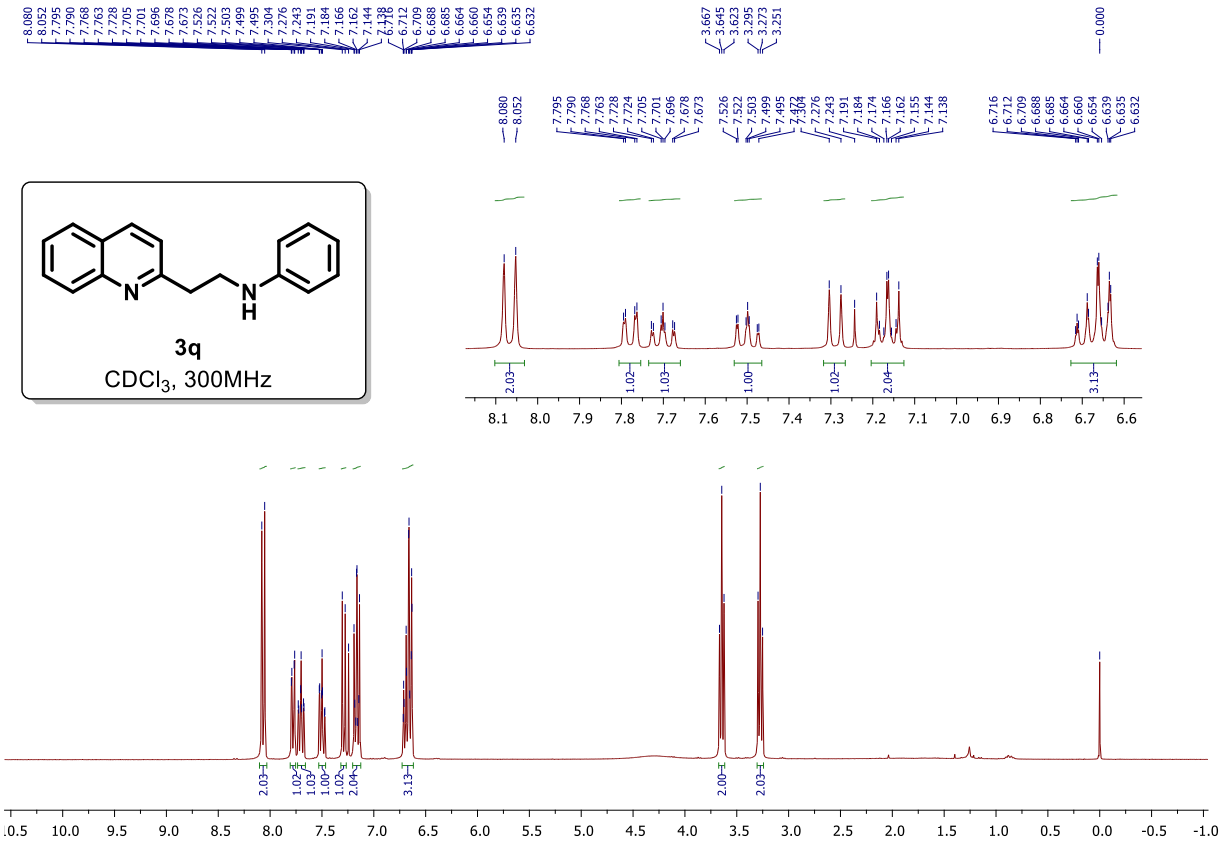


Figure S52: ^{13}C NMR of compound **3q**

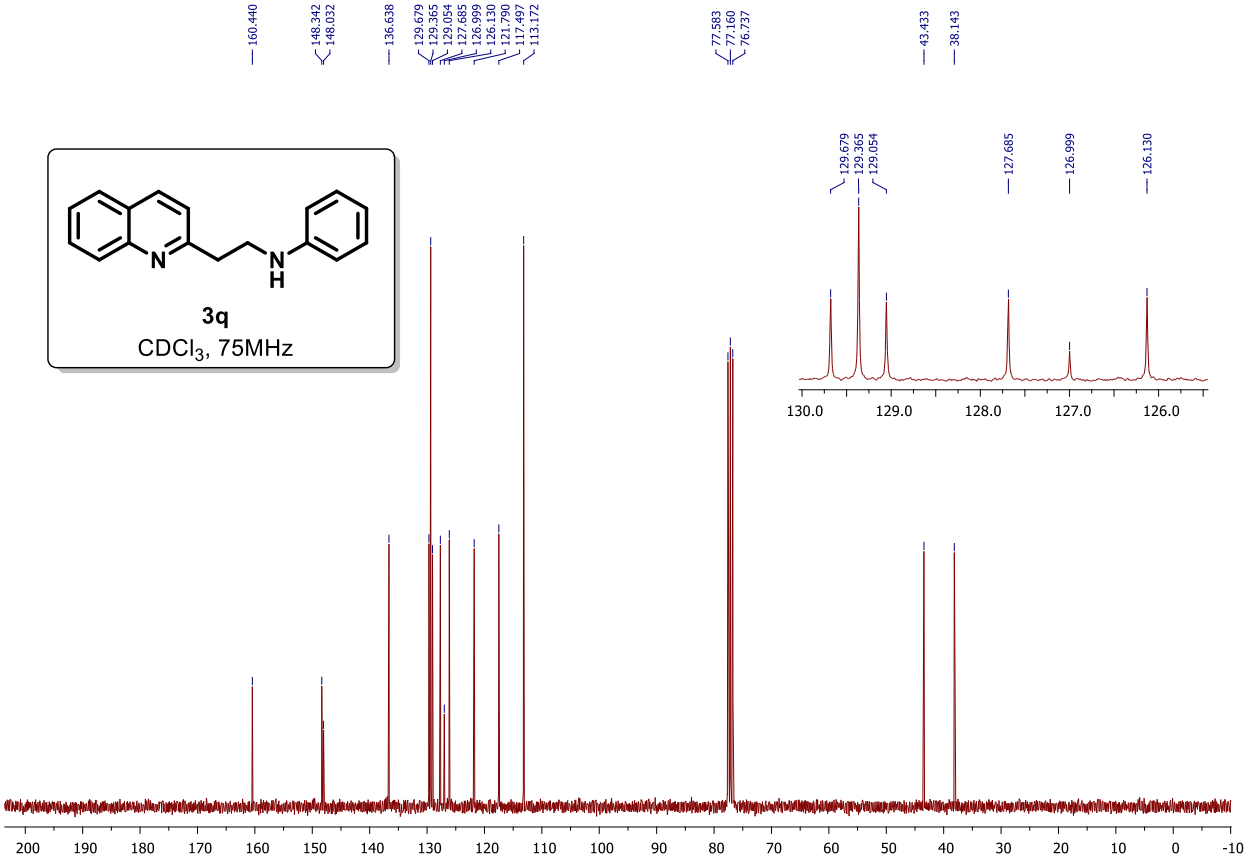


Figure S53: ^{1}H NMR of compound **3r**

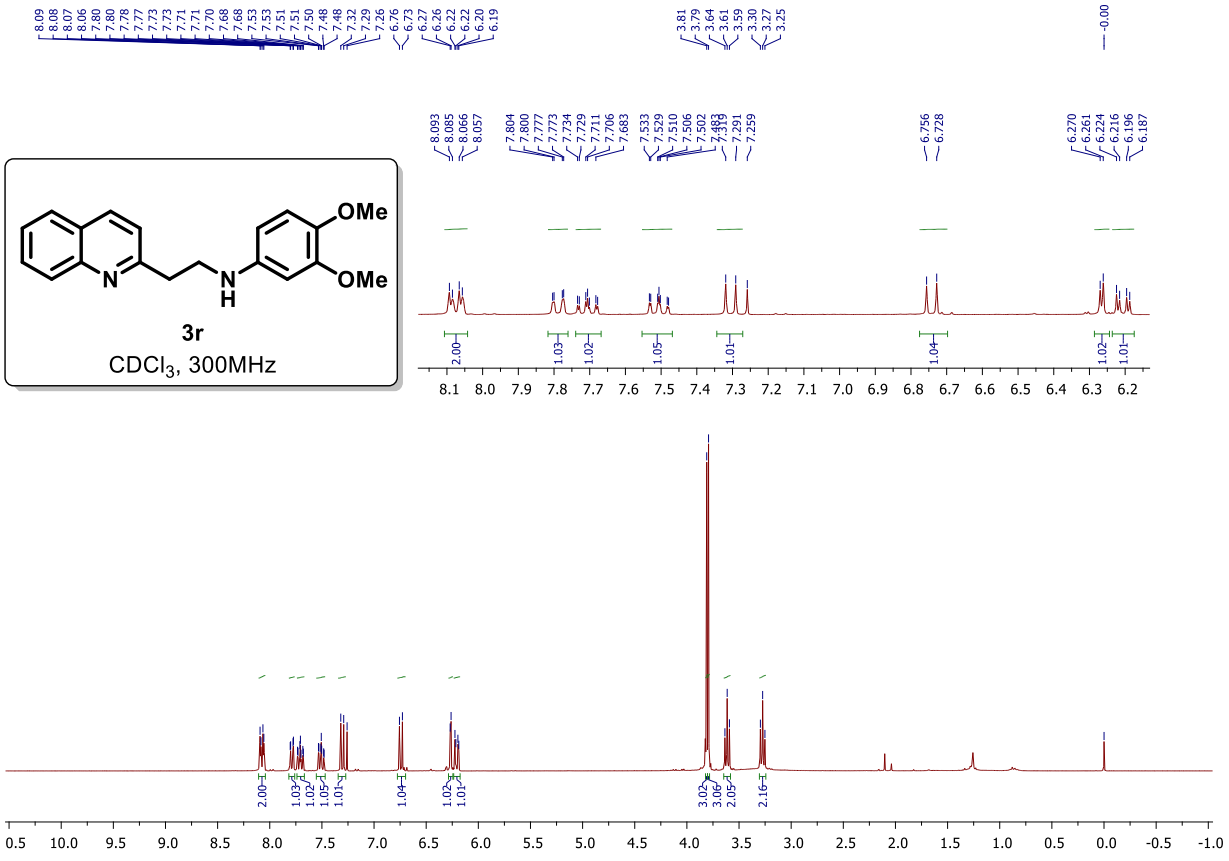


Figure S54: ^{13}C NMR of compound **3r**

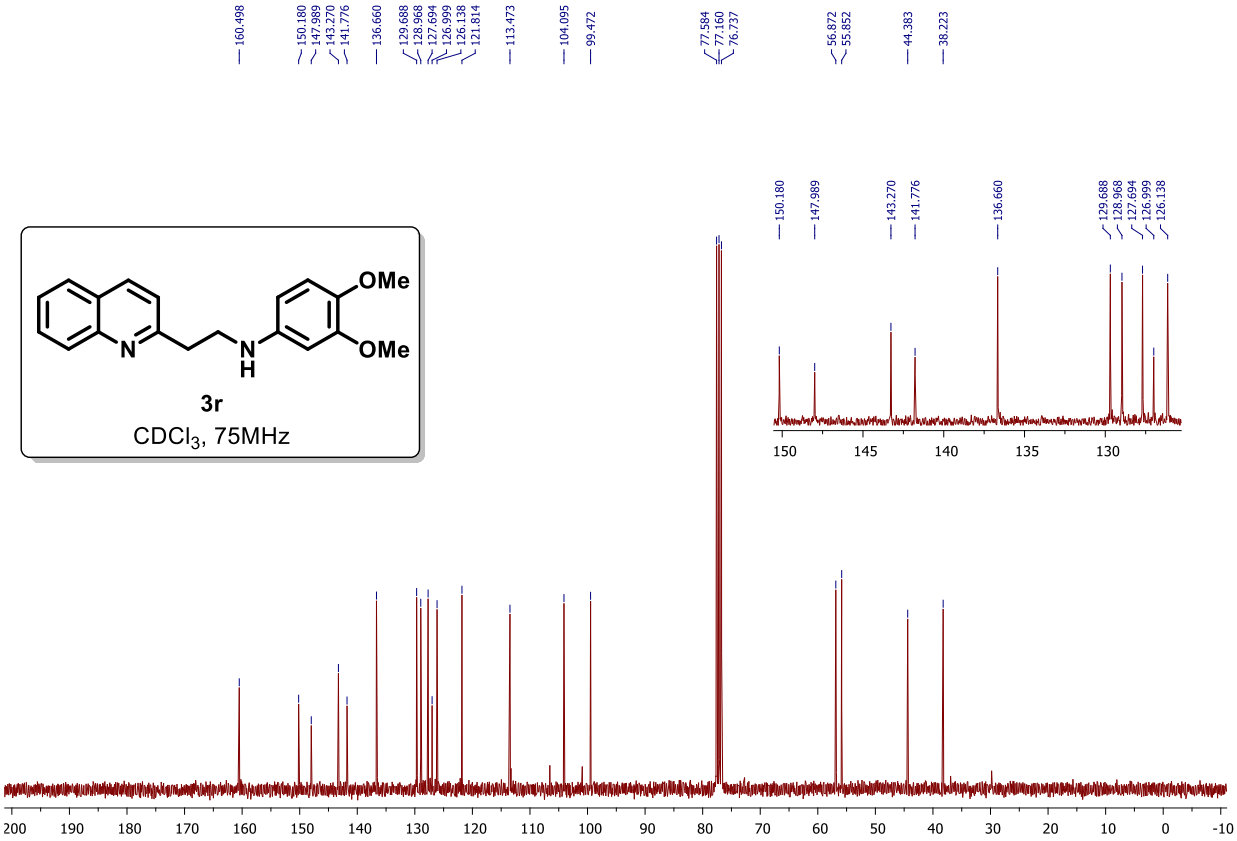


Figure S55: ^{1}H NMR of compound **3s**

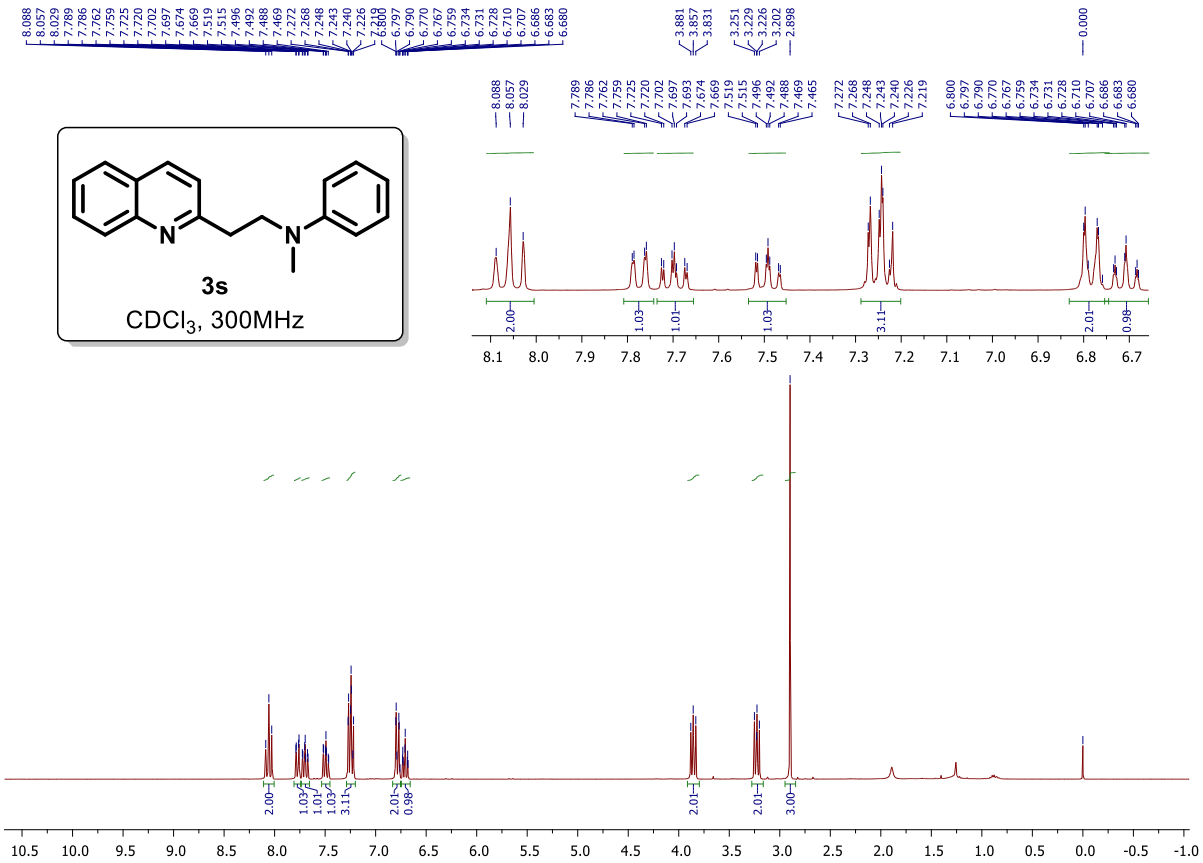


Figure S56: ^{13}C NMR of compound **3s**

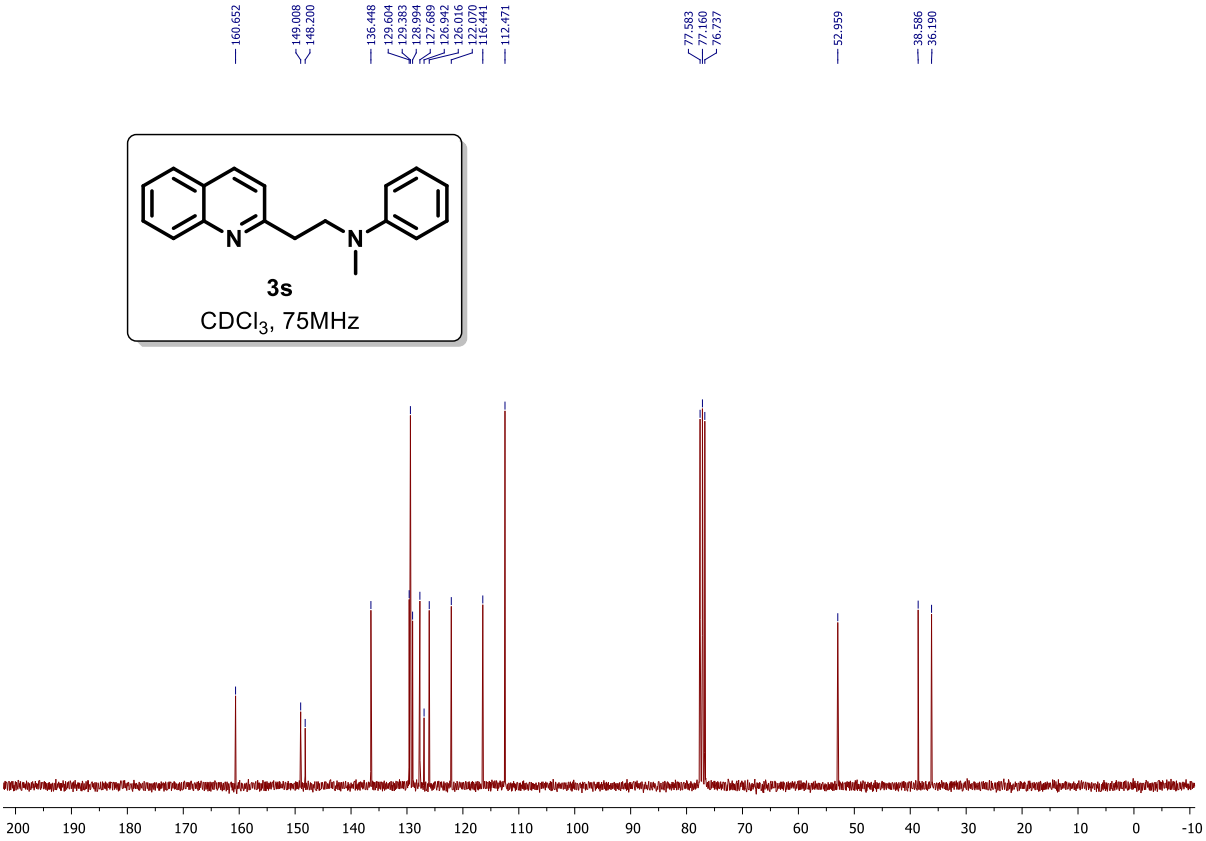


Figure S57: ^{1}H NMR of compound **3t**

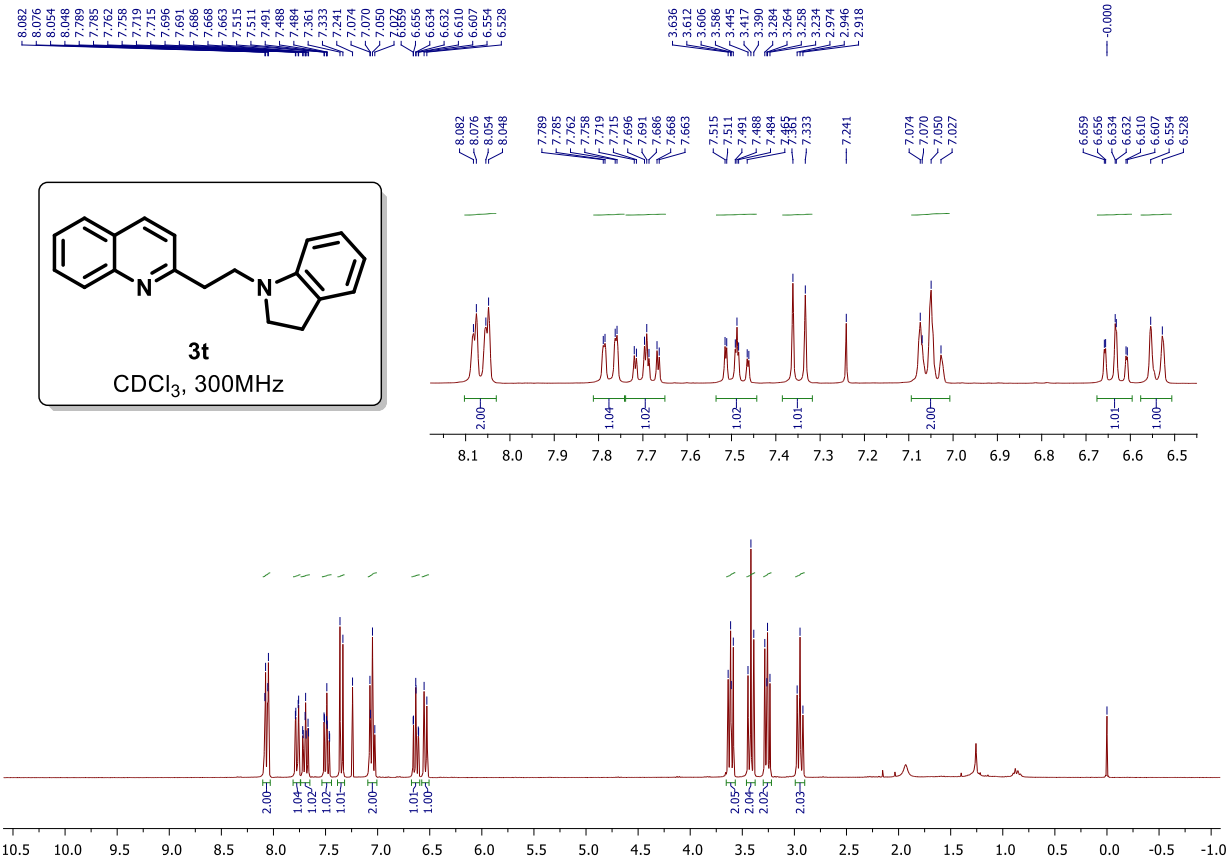


Figure S58: ^{13}C NMR of compound **3t**

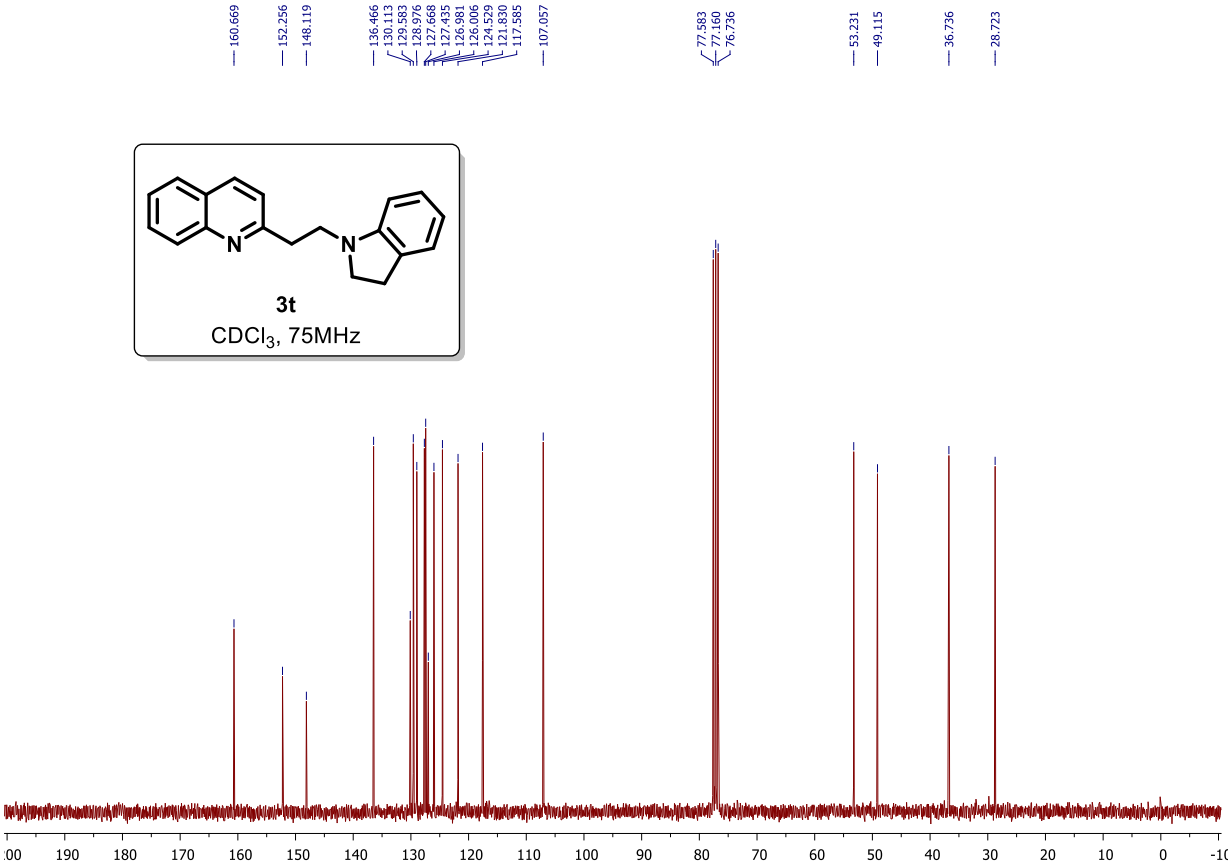


Figure S59: ^{1}H NMR of compound **3u**

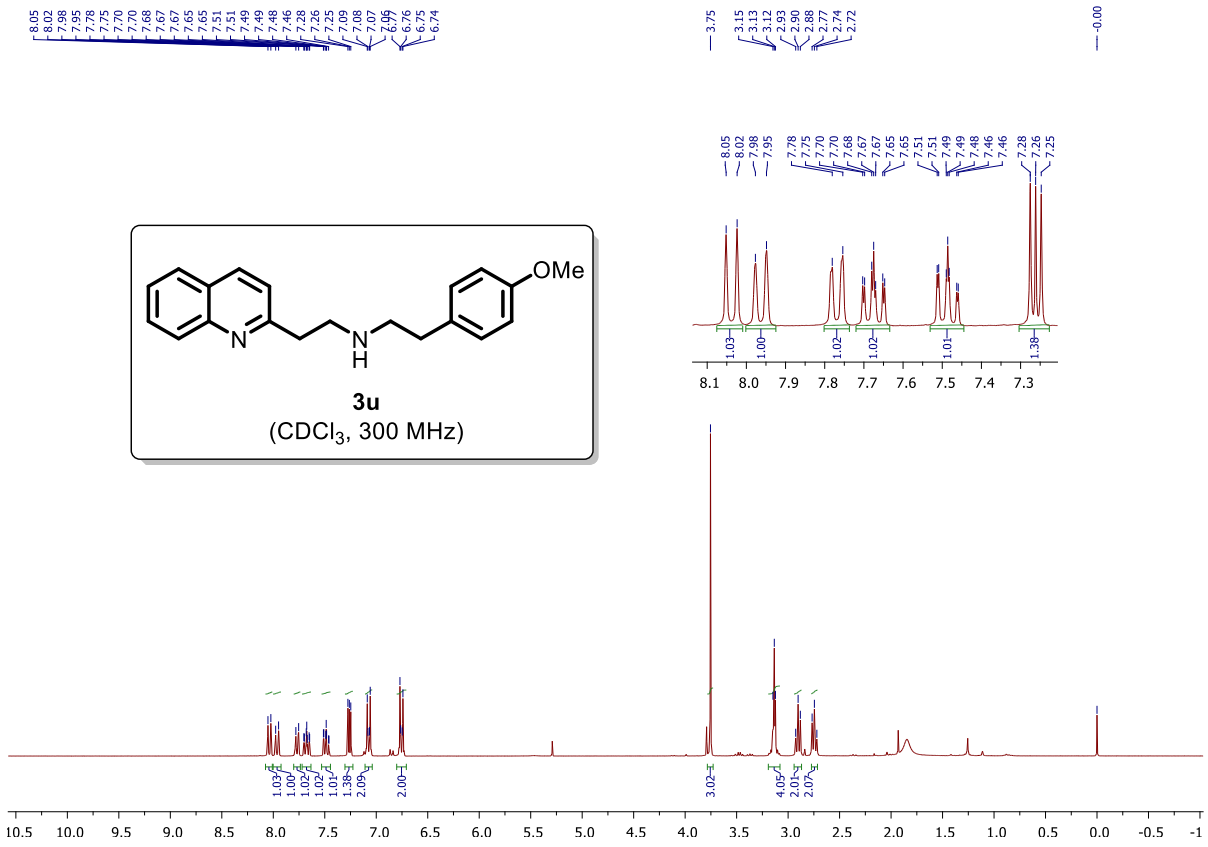


Figure S60: ^{13}C NMR of compound **3u**

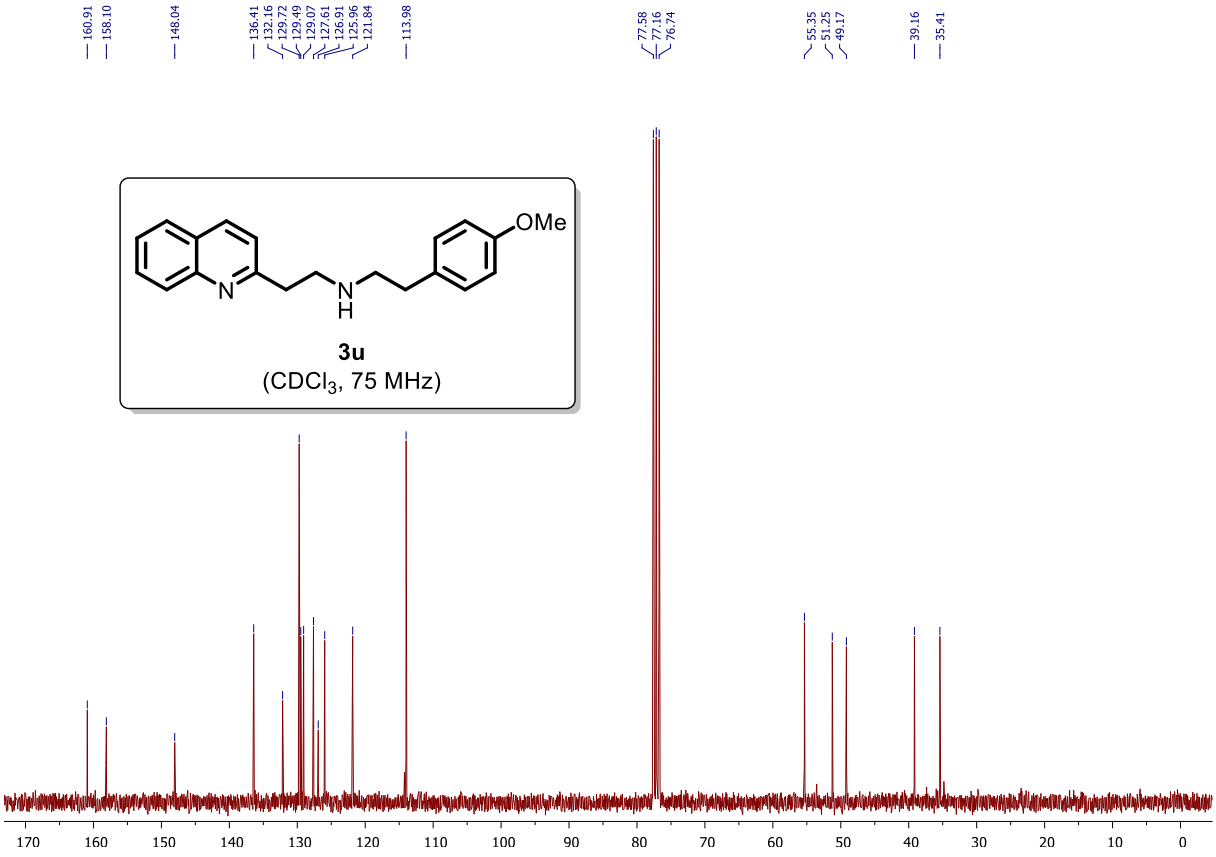


Figure S61: ^{1}H NMR of compound **3u'**

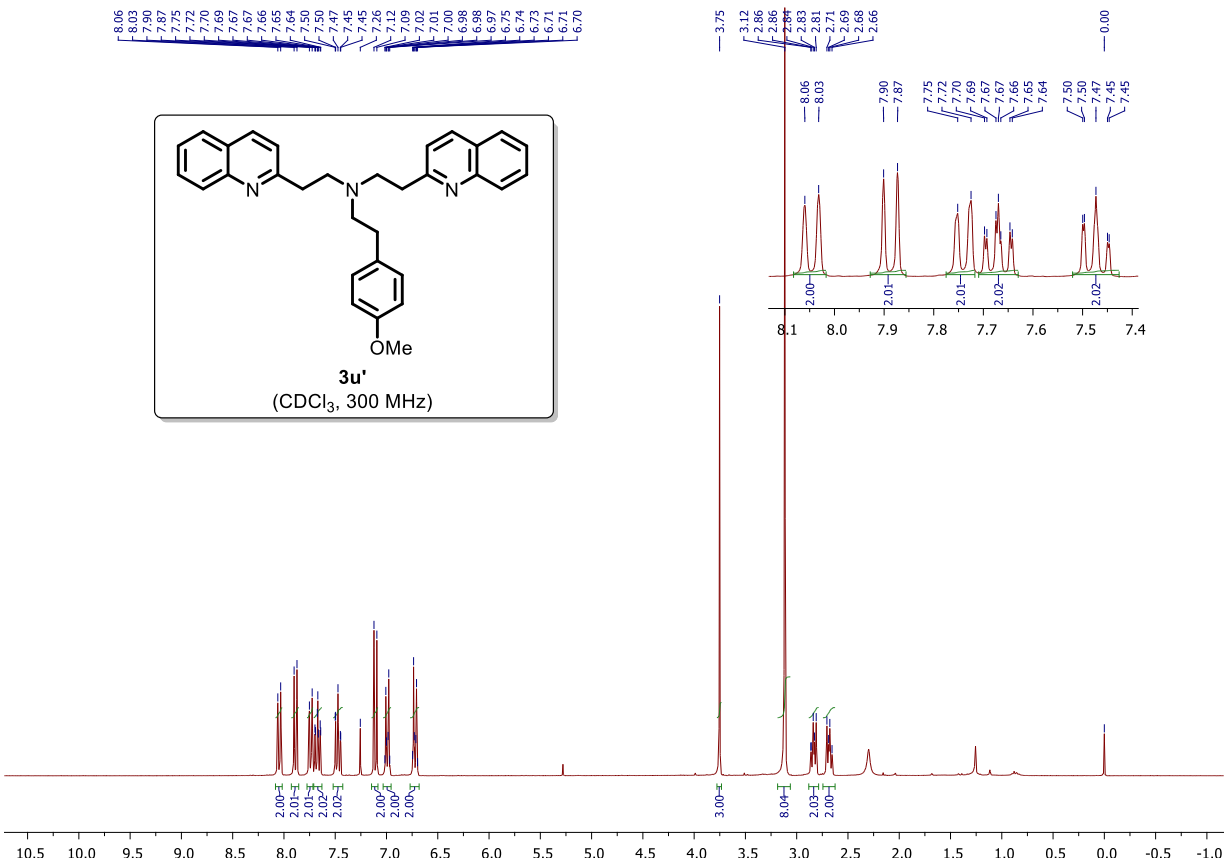


Figure S62: ^{13}C NMR of compound **3u'**

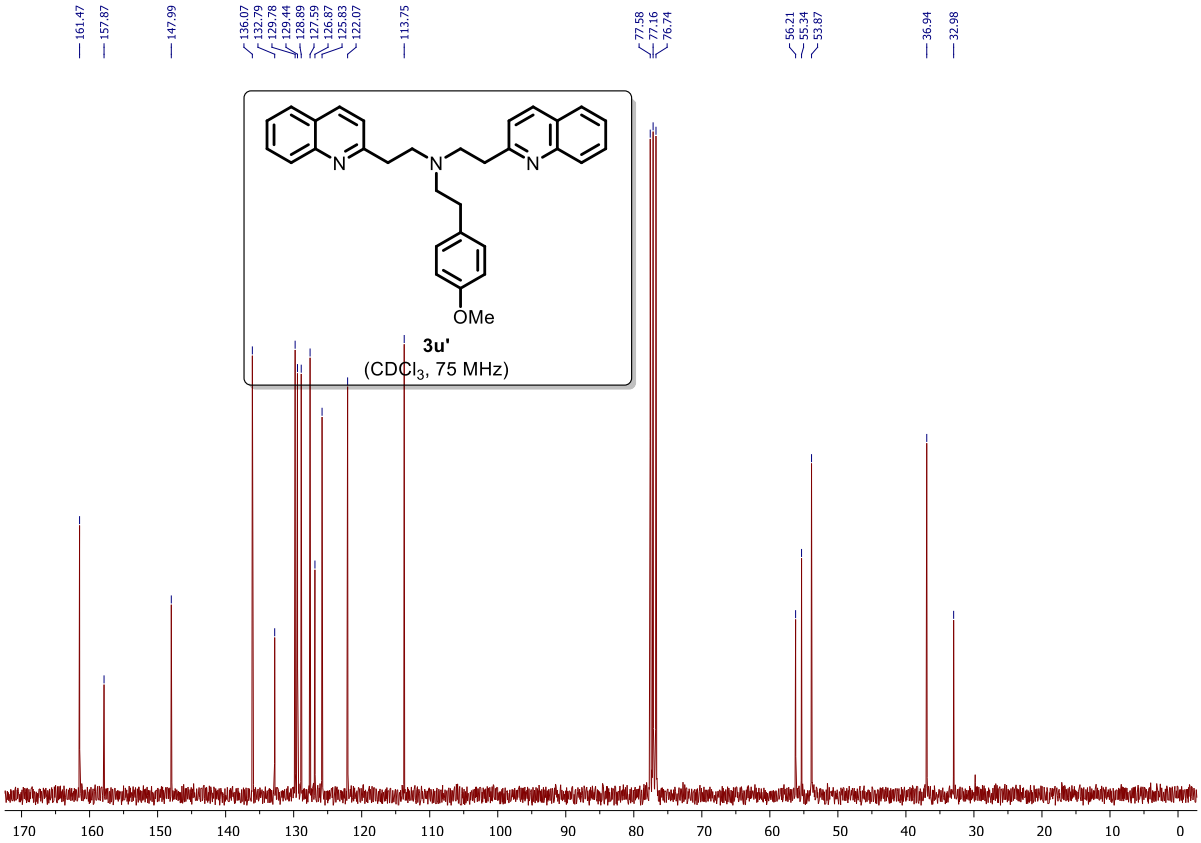


Figure S63: ^{1}H NMR of compound **3v**

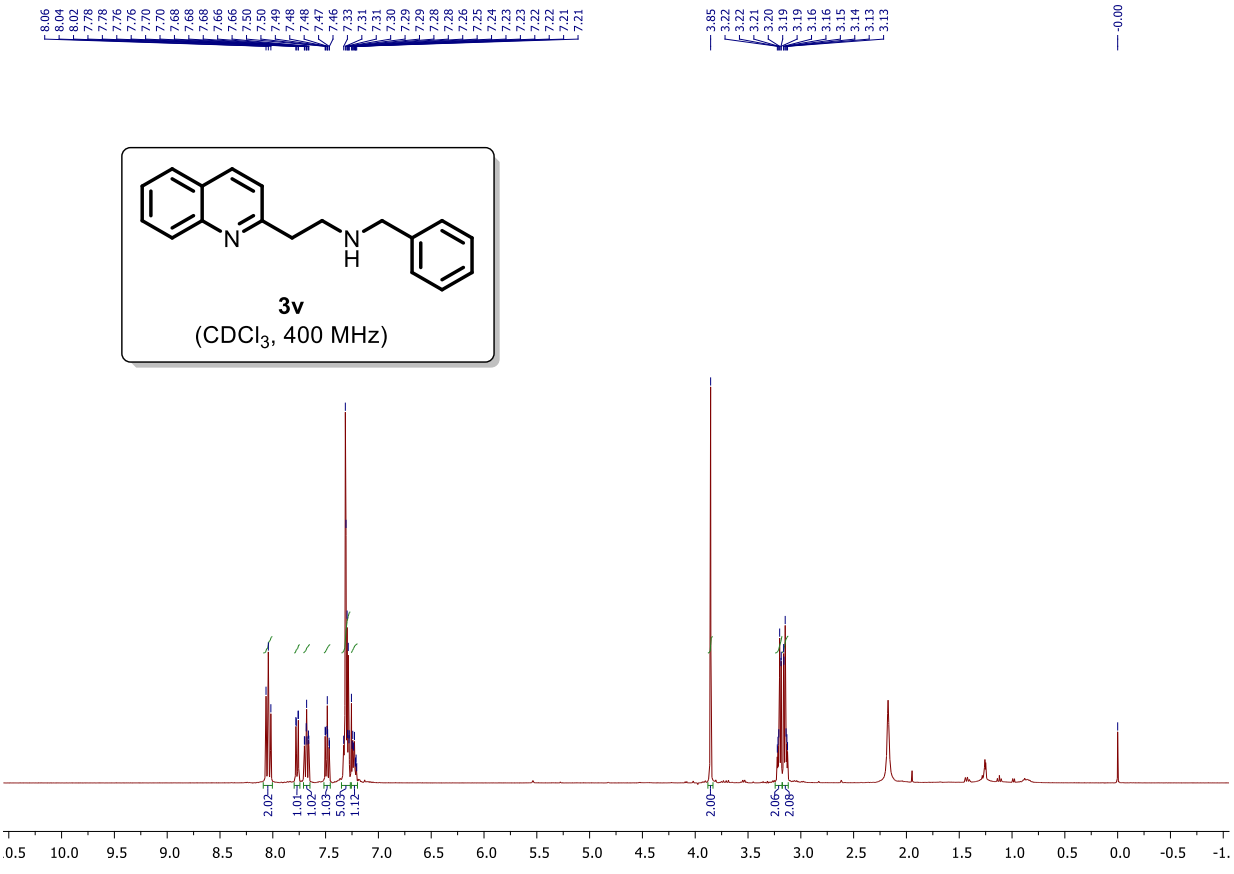


Figure S64: ^{13}C NMR of compound **3v**

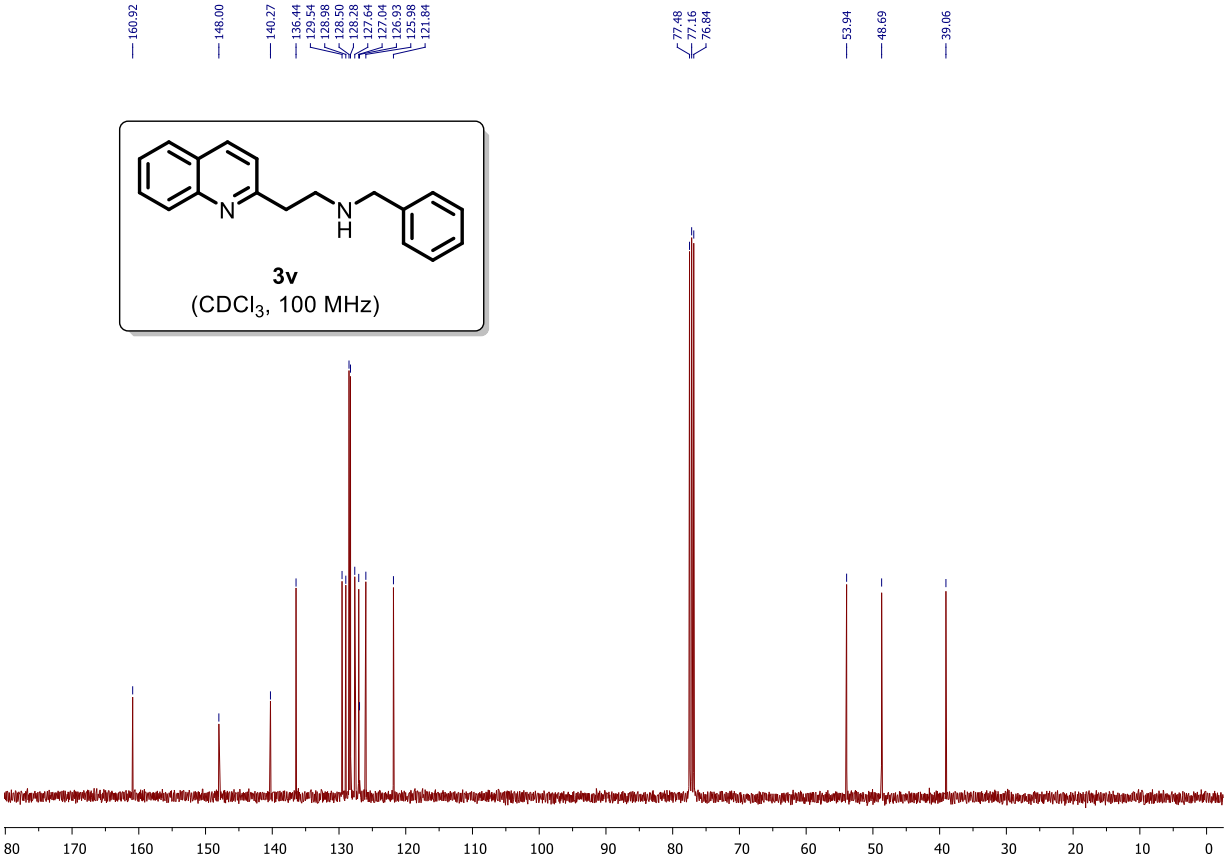


Figure S65: ^{1}H NMR of compound **3v'**

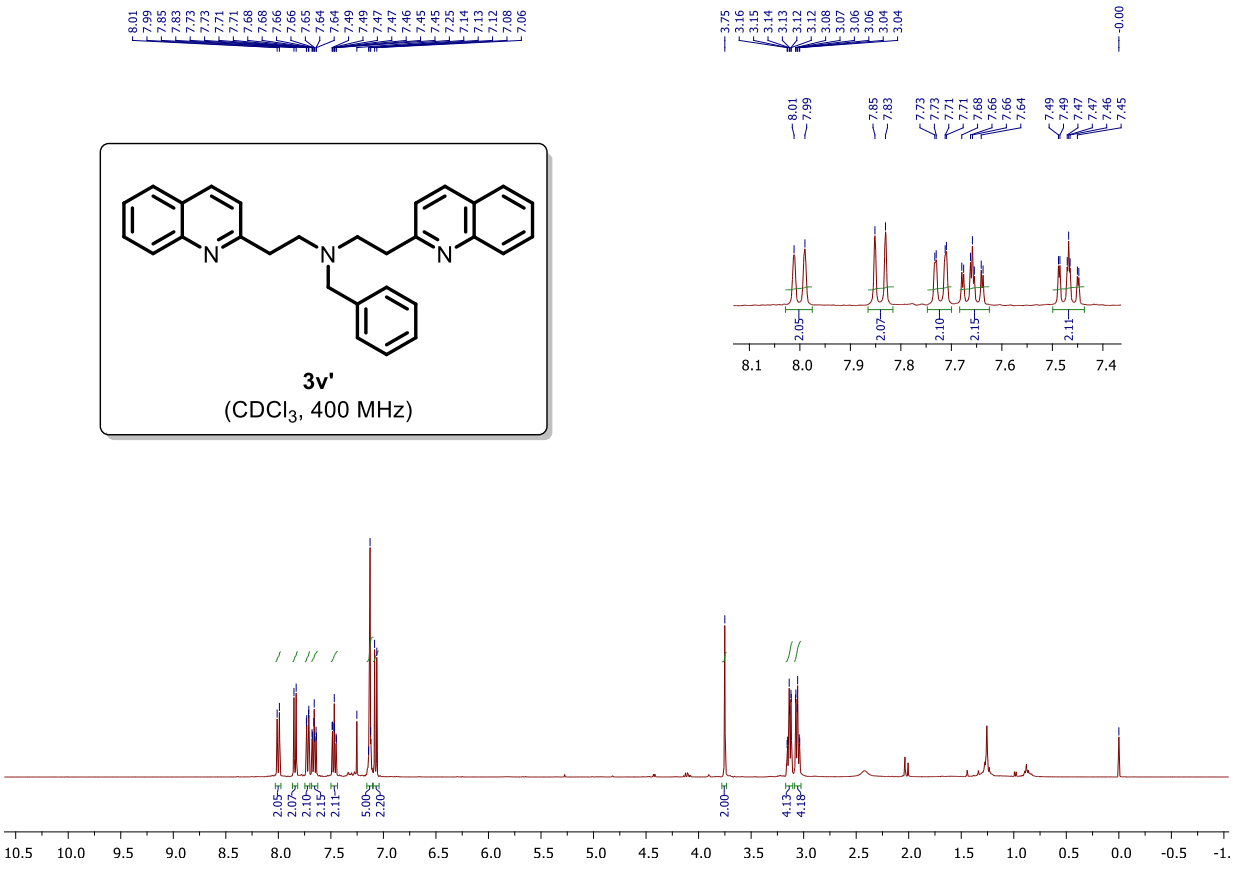


Figure S66: ^{13}C NMR of compound **3v'**

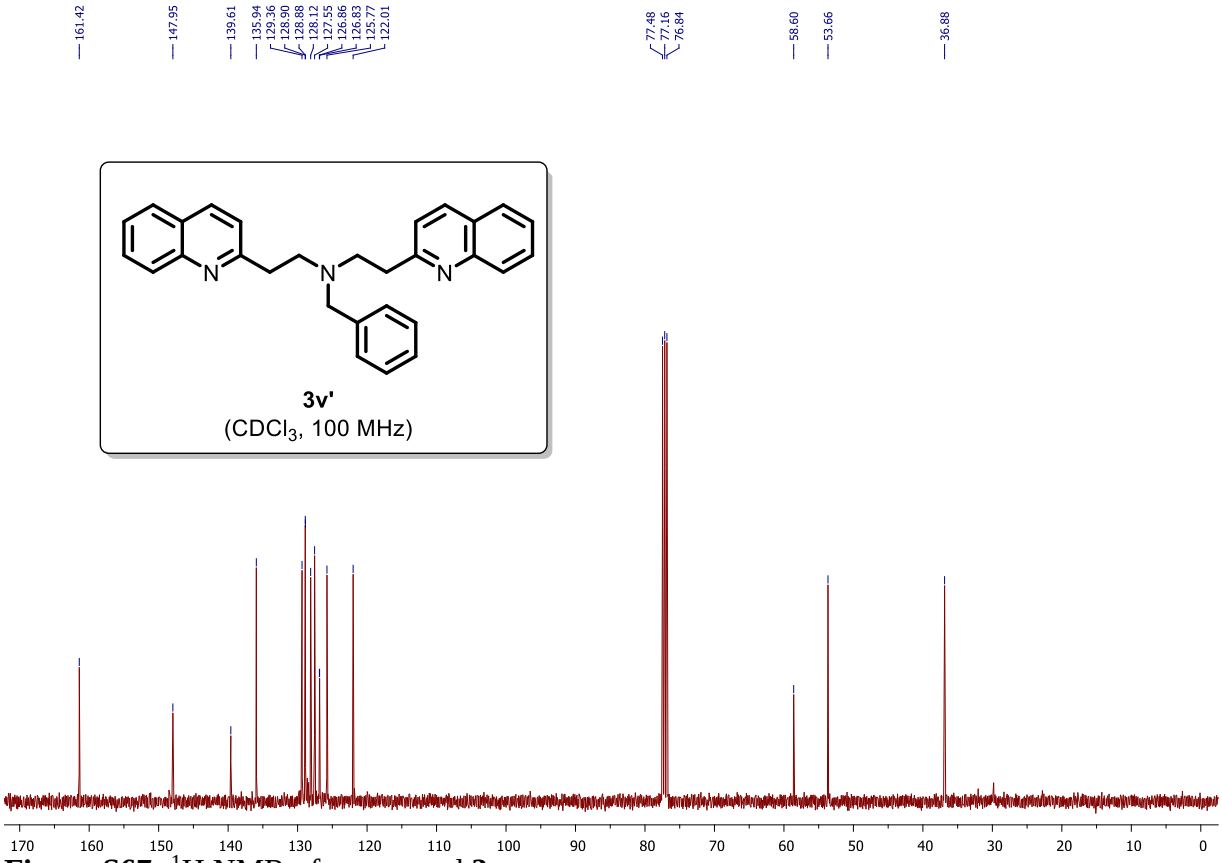


Figure S67: ^{1}H NMR of compound **3w**

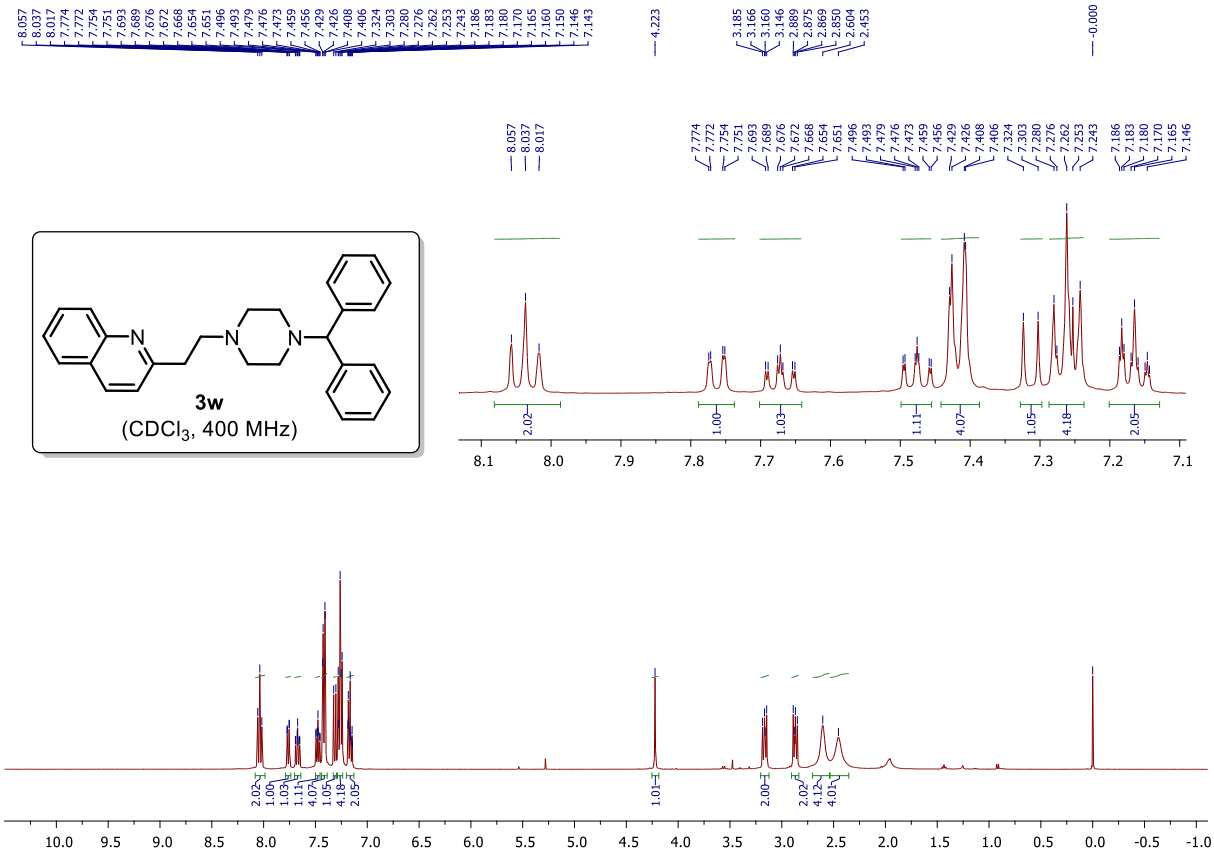


Figure S68: ^{13}C NMR of compound **3w**

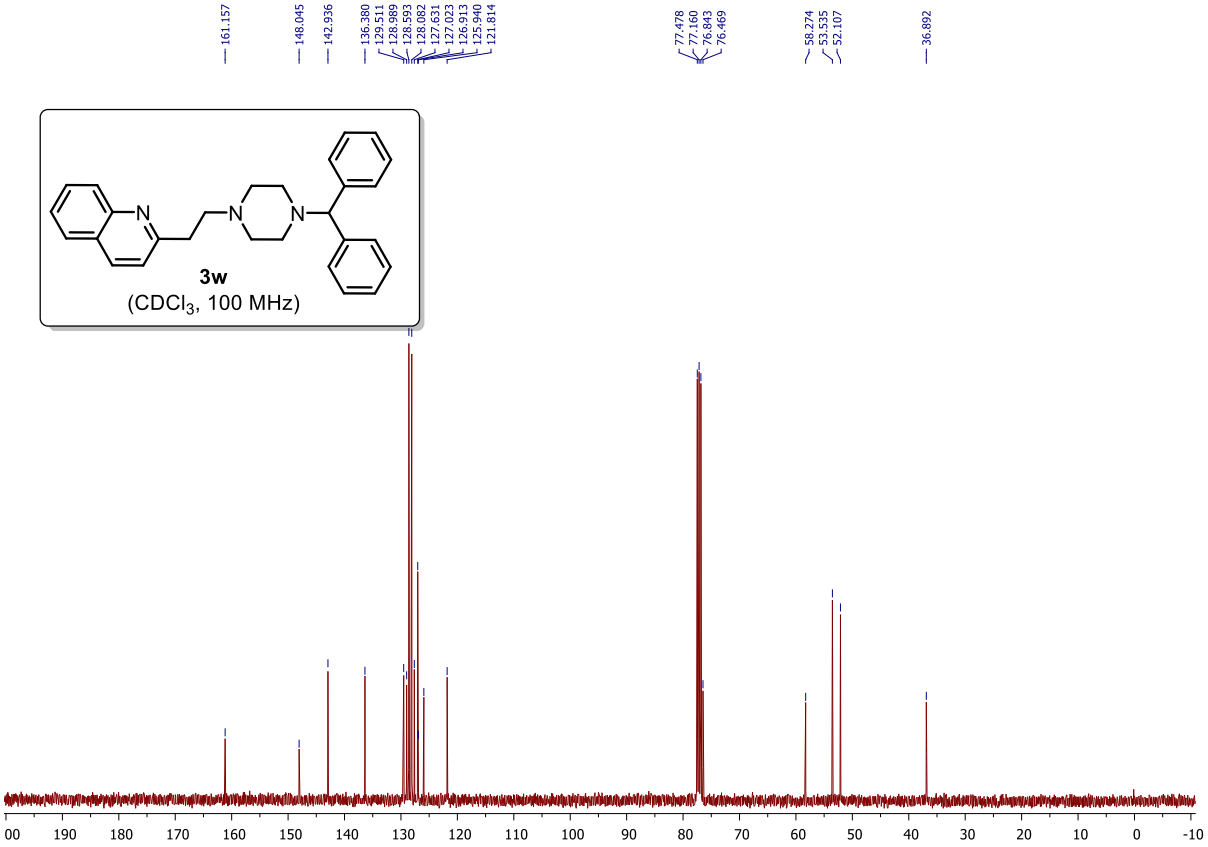


Figure S69: ^{1}H NMR of compound **3x**

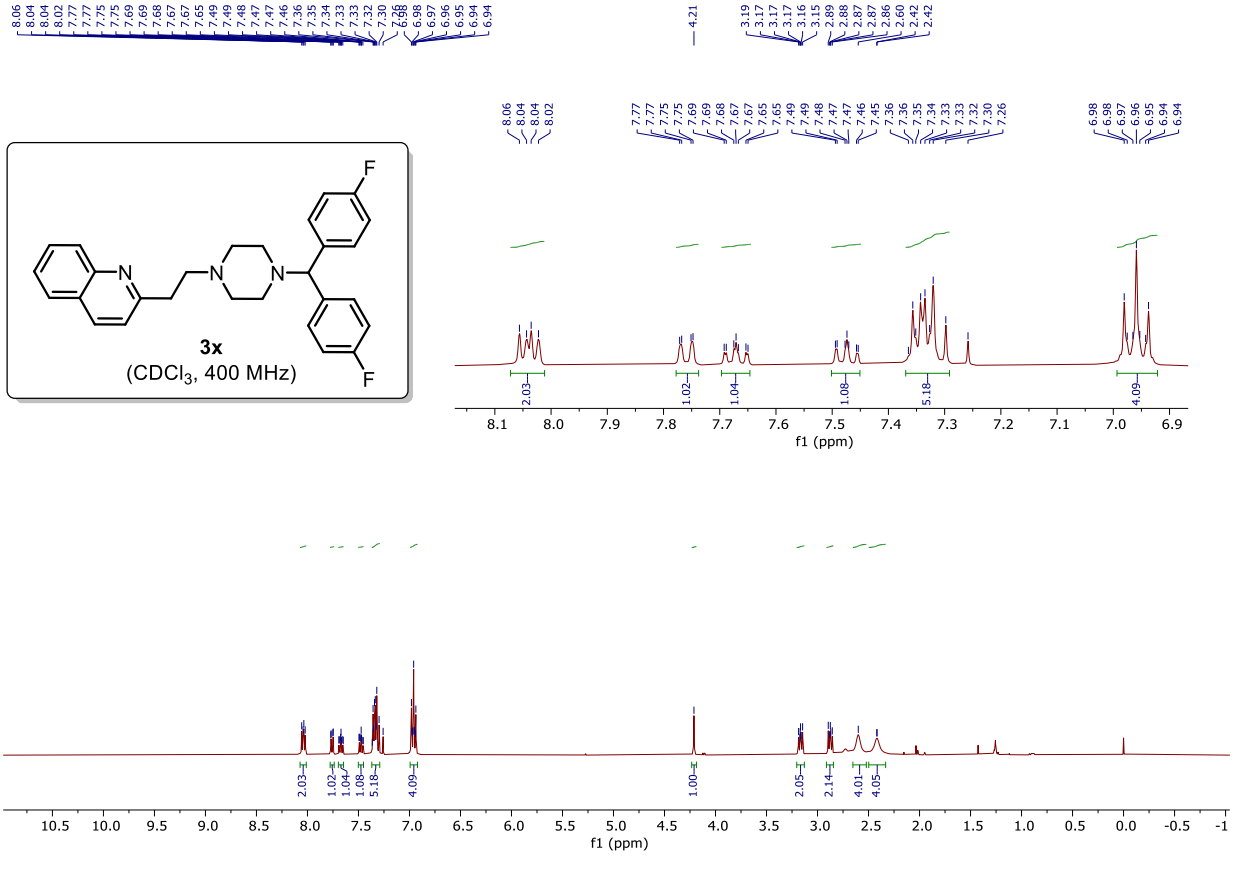


Figure S70: ^{13}C NMR of compound **3x**

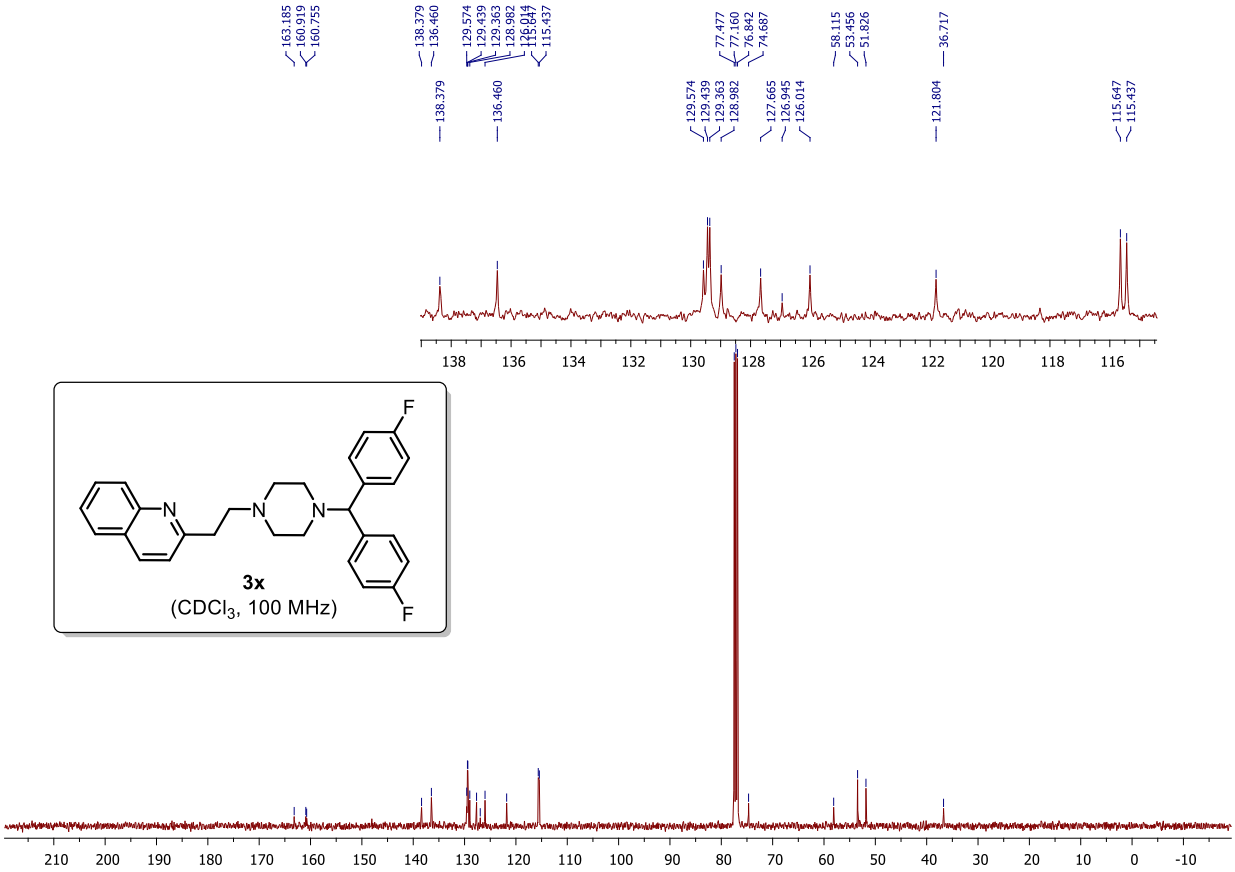


Figure S71: ^{19}F NMR of compound **3x**

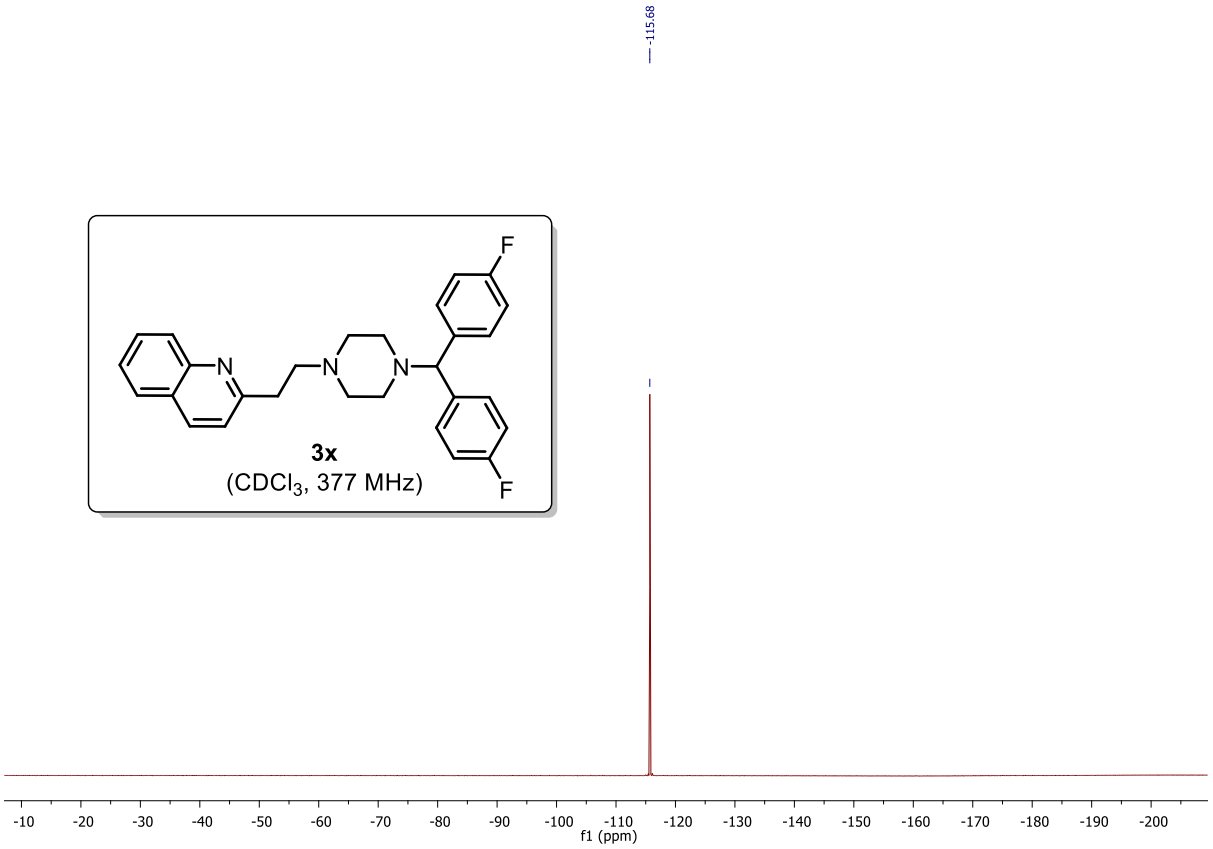


Figure S72: ^{1}H NMR of compound **3y**

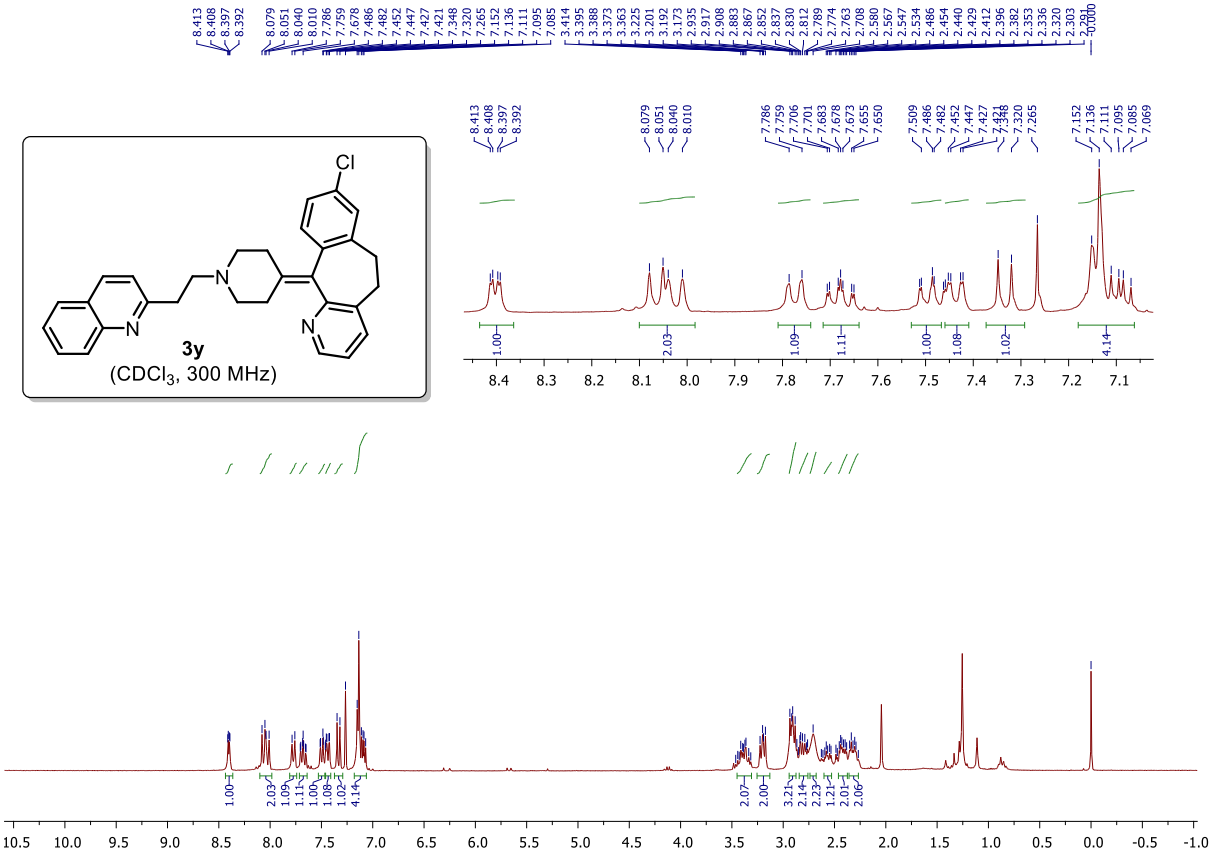


Figure S73: ^{13}C NMR of compound **3y**

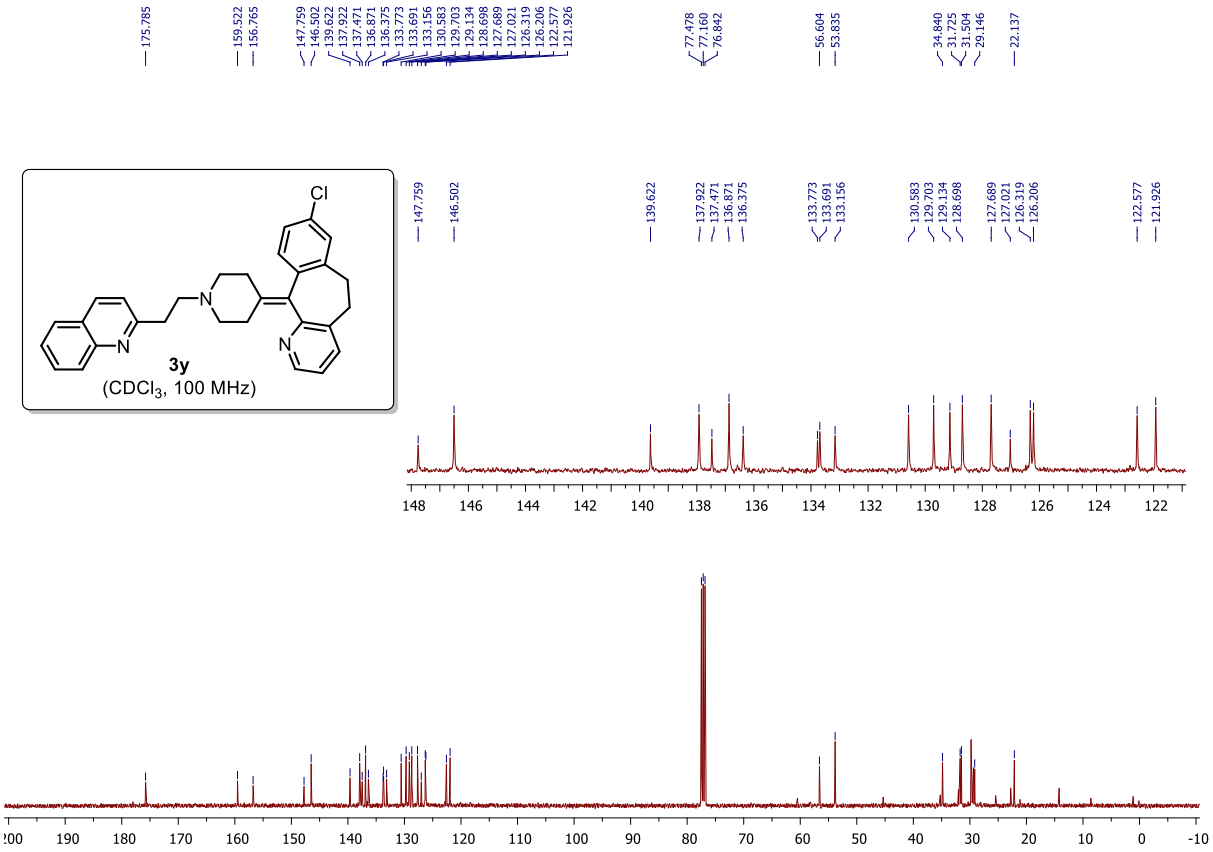


Figure S74: ^{1}H NMR of compound **3z**

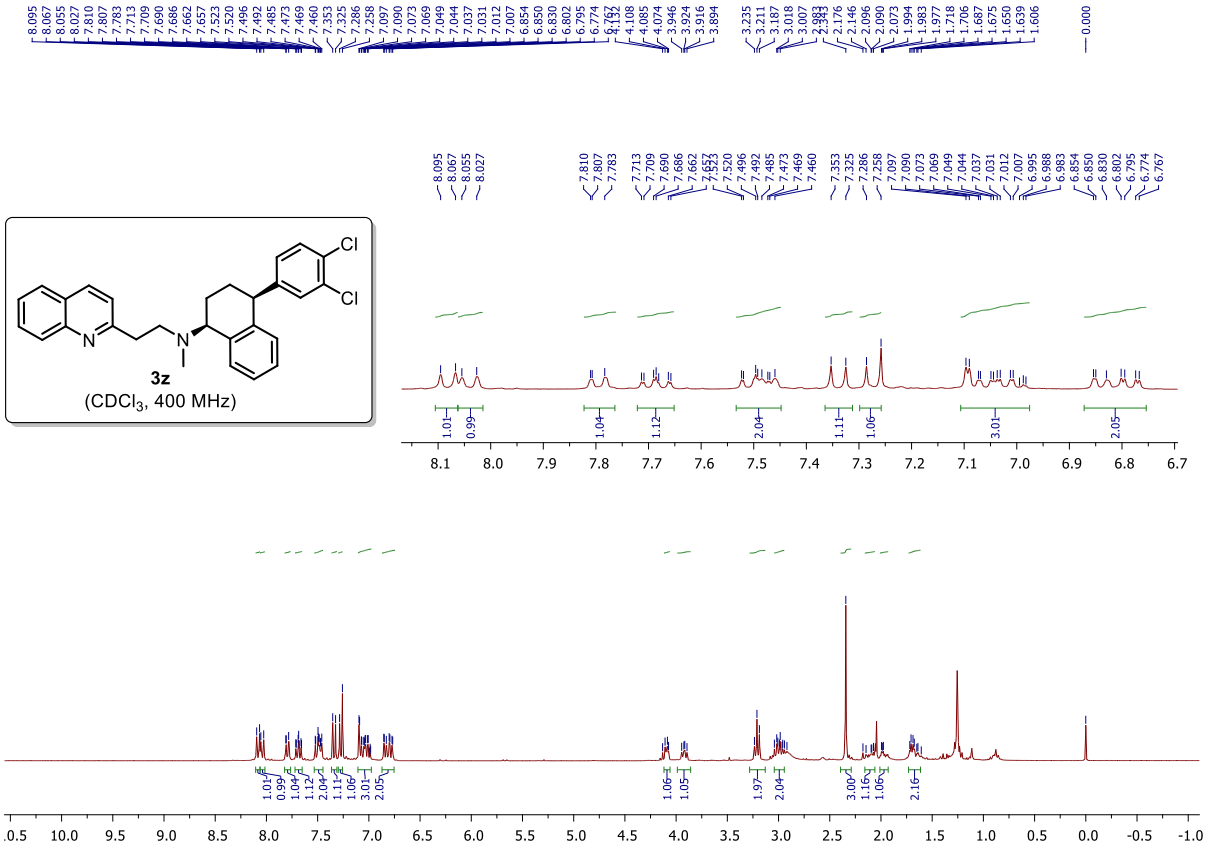


Figure S75: ^{13}C NMR of compound **3z**

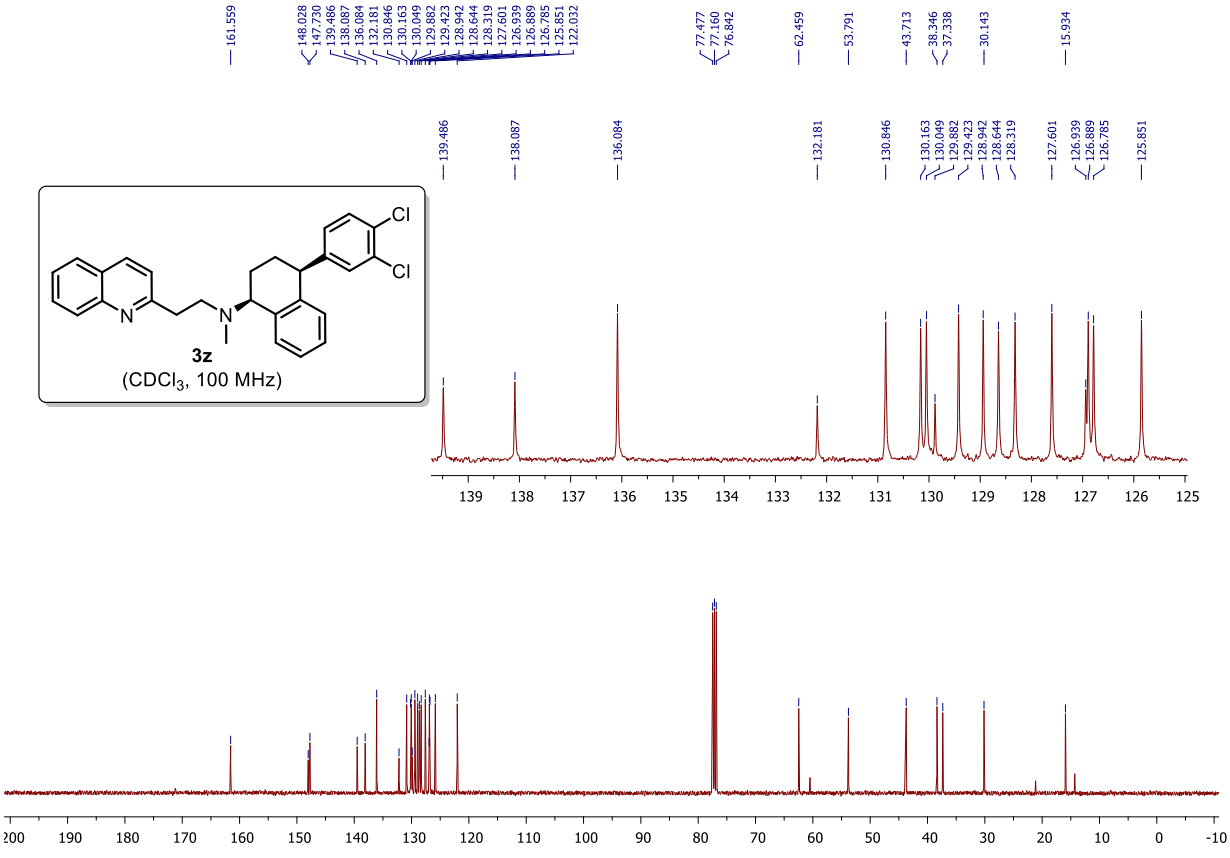


Figure S76: ^{1}H NMR of compound **3aa**

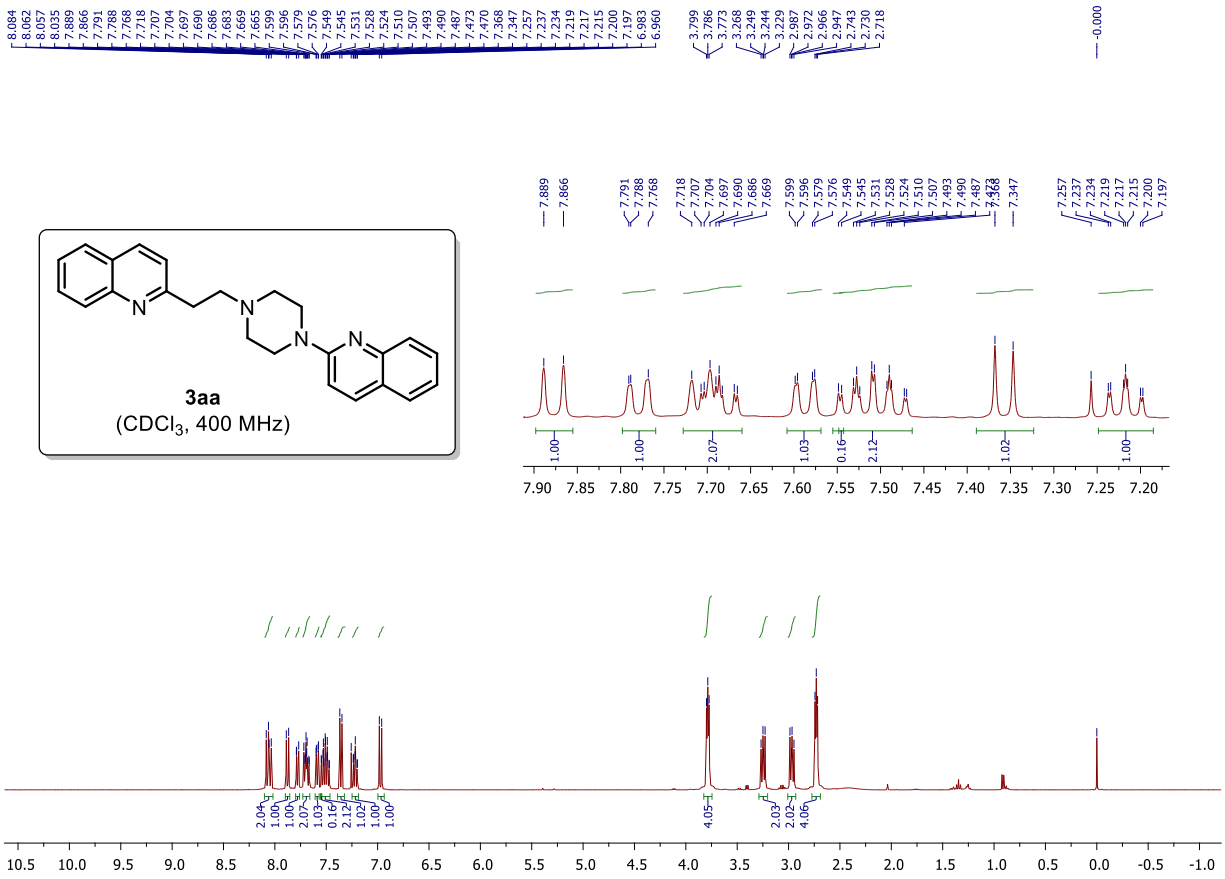


Figure S77: ^{13}C NMR of compound **3aa**

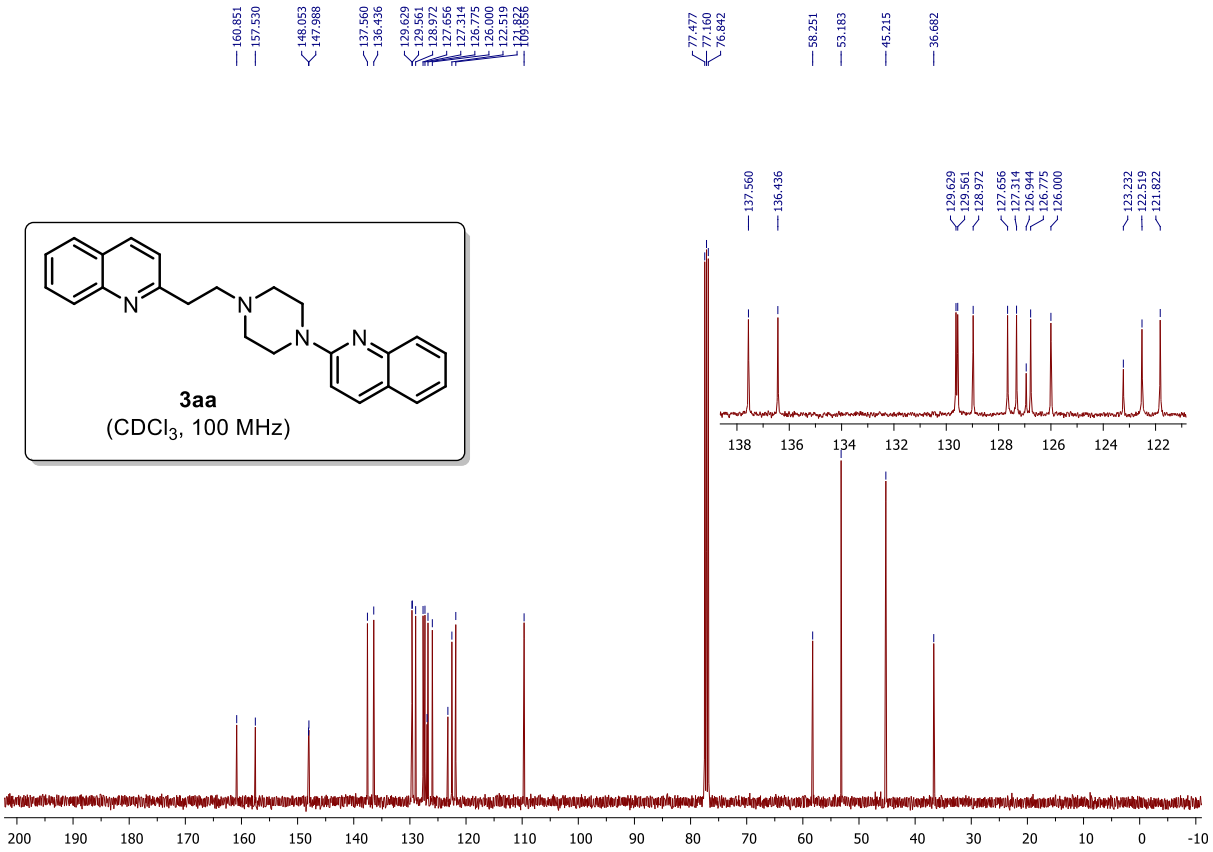


Figure S78: ^{1}H NMR of compound **3ab**

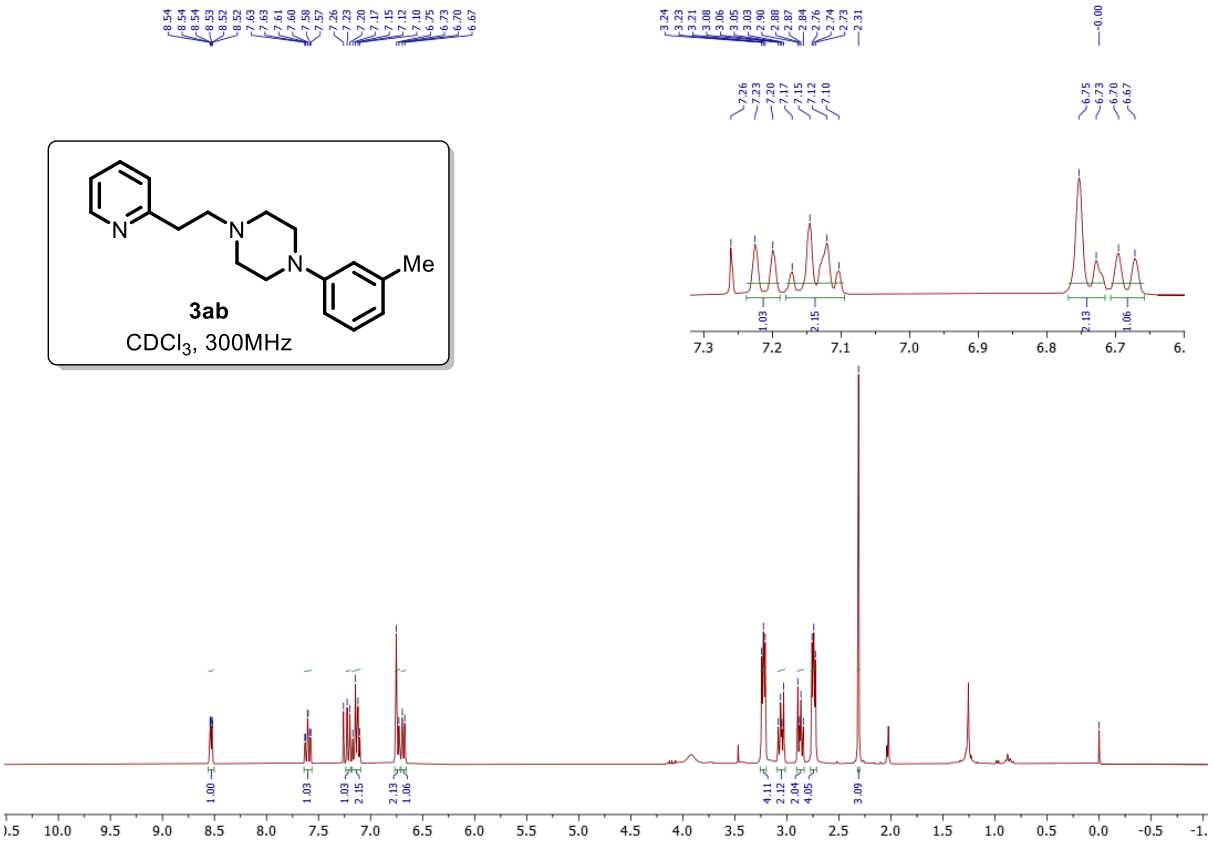


Figure S79: ^{13}C NMR of compound **3ab**

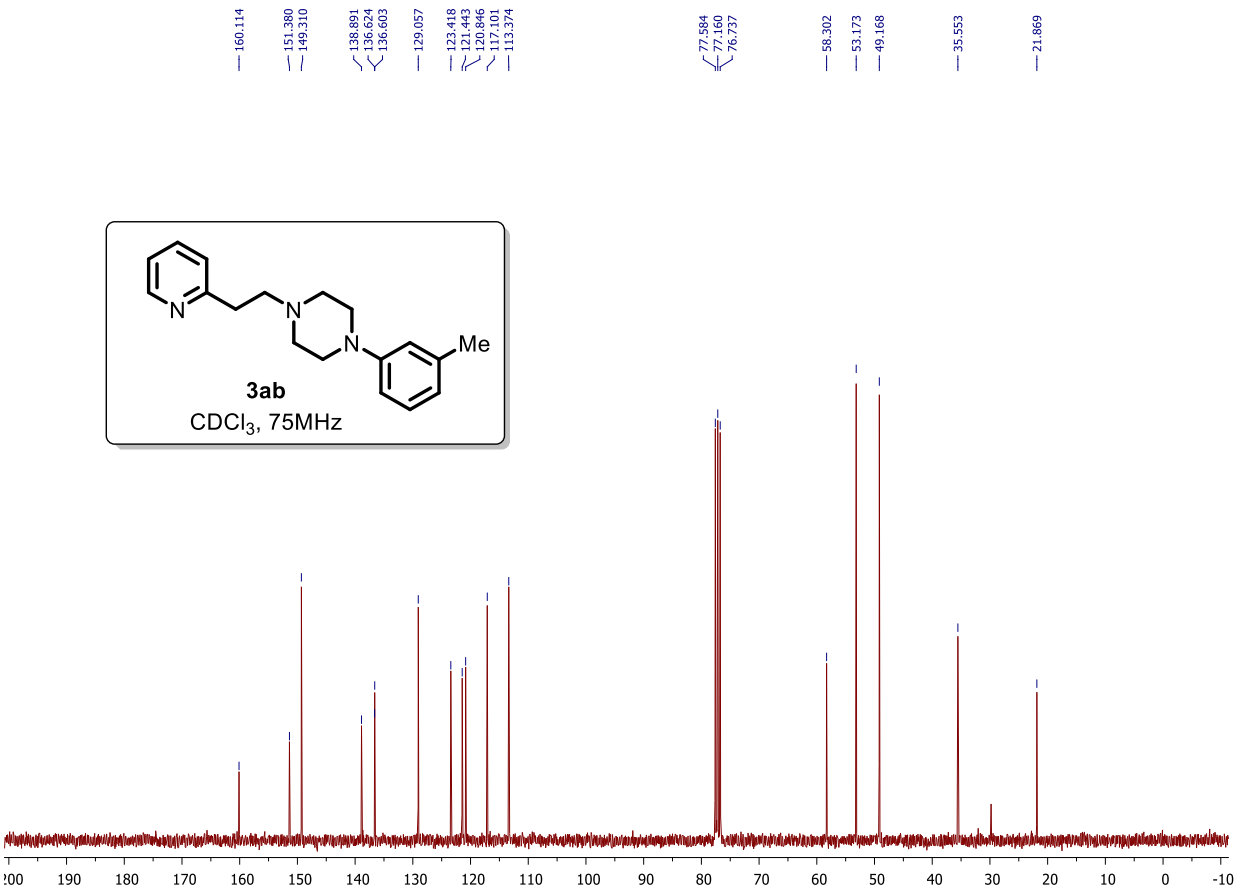


Figure S80: ^{1}H NMR of compound **3ac**

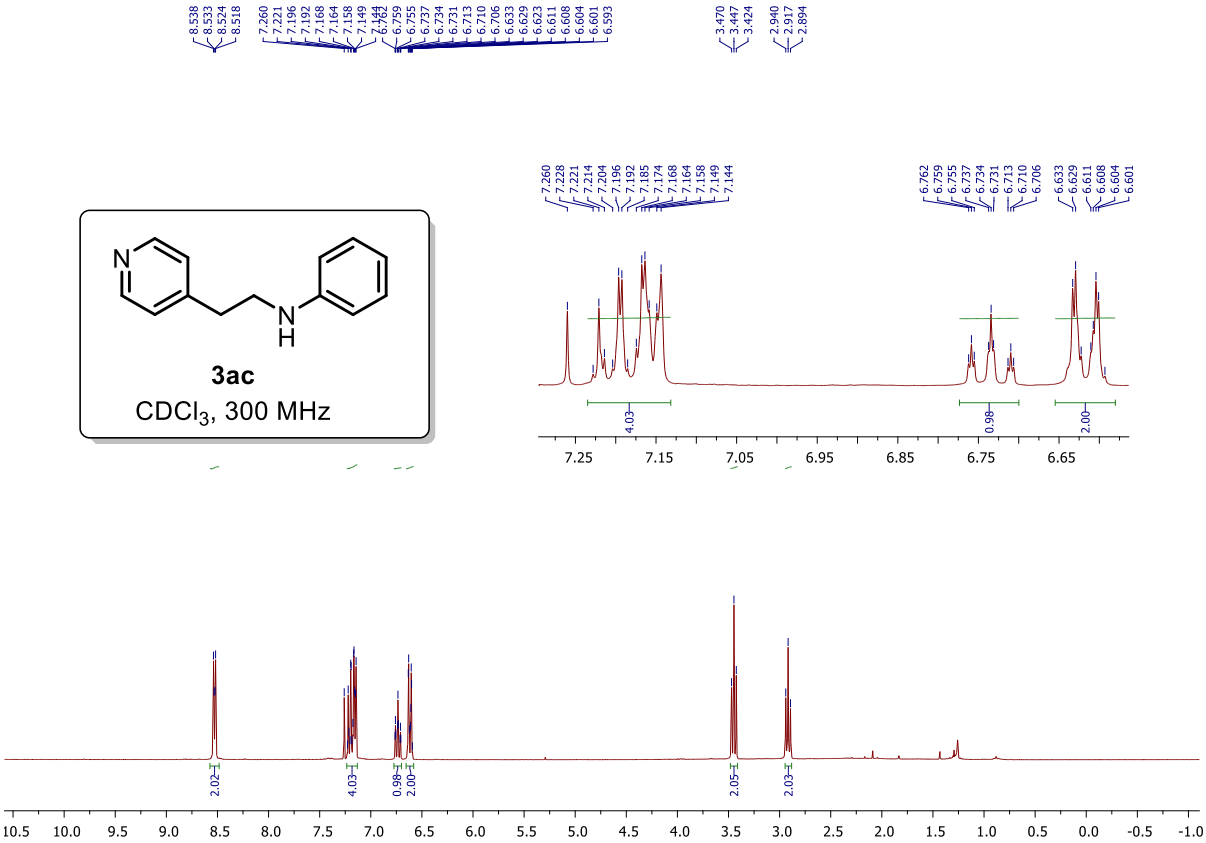


Figure S81: ^{13}C NMR of compound **3ac**

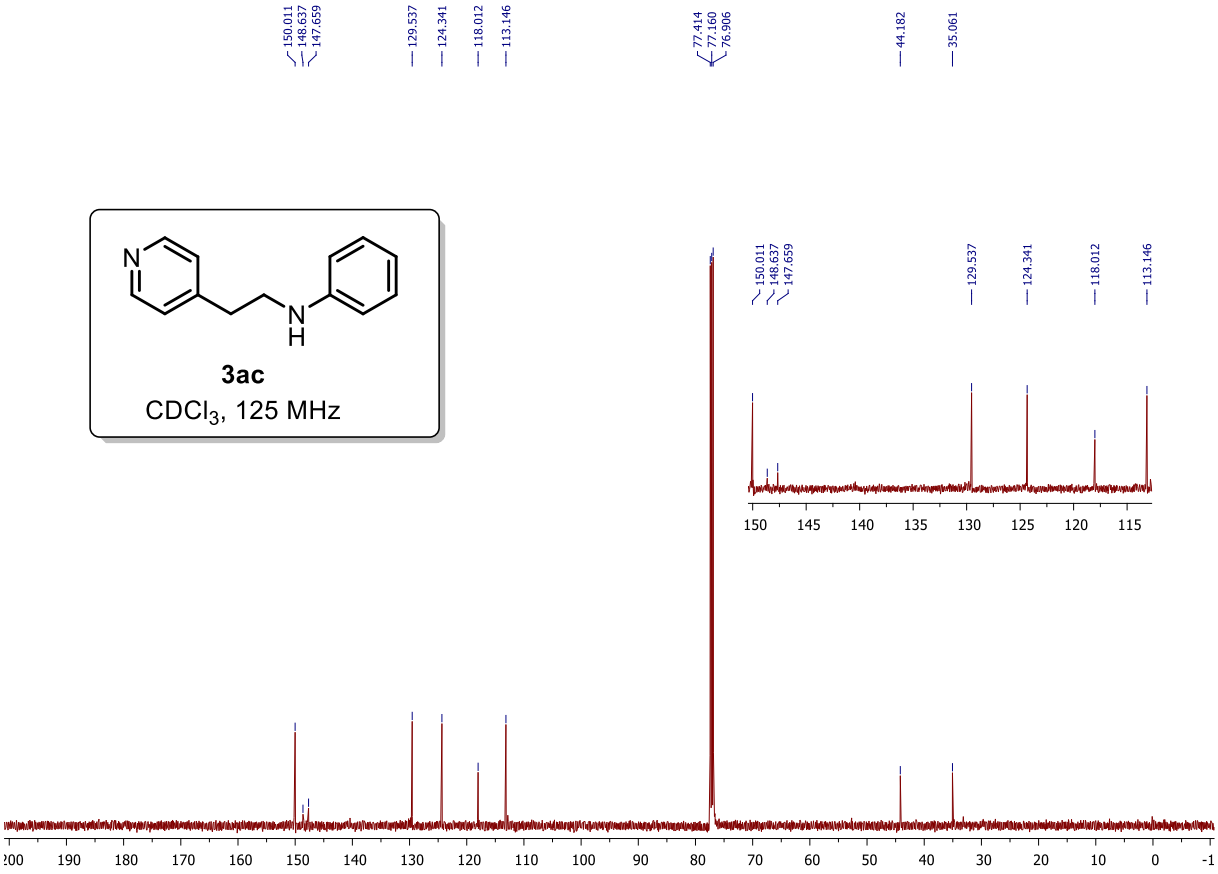


Figure S82: ^{1}H NMR of compound **3ad**

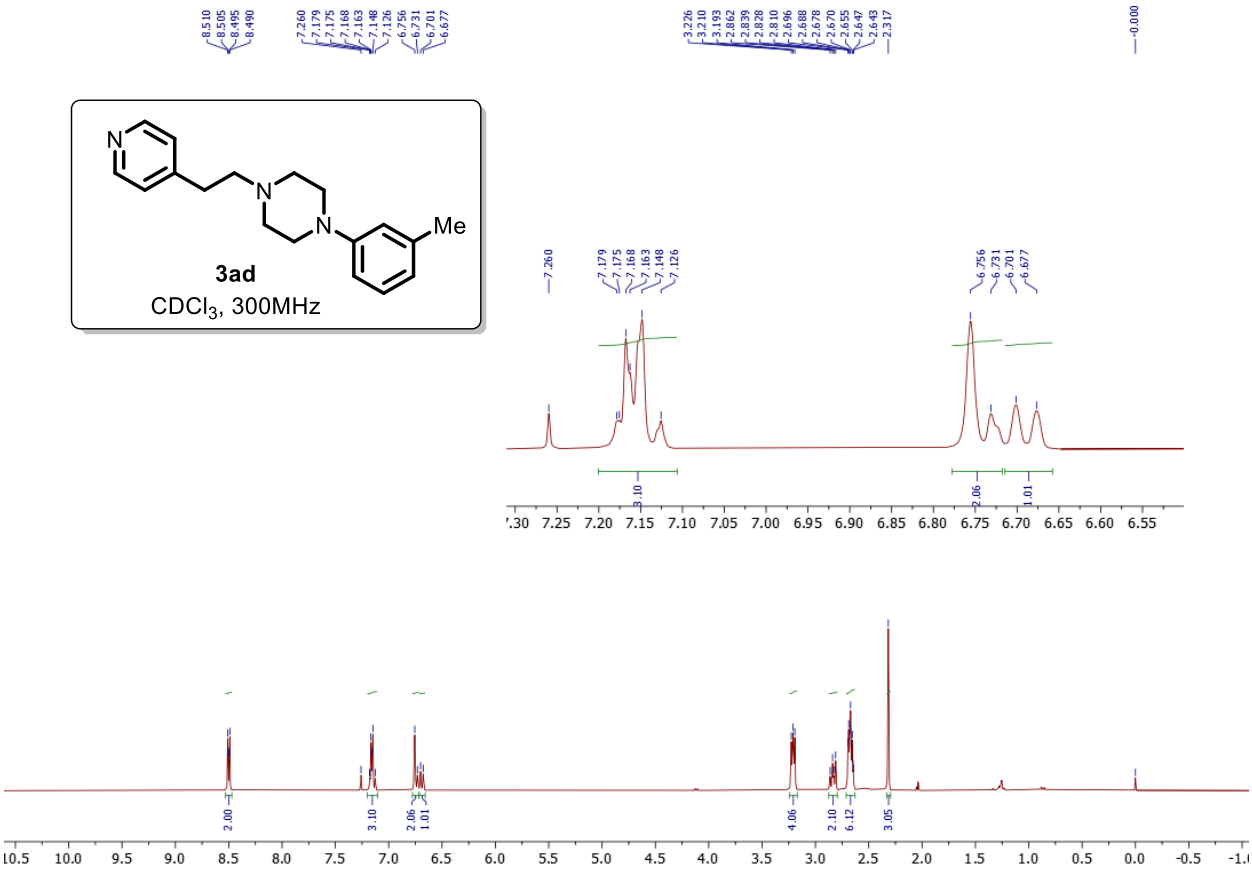


Figure S83: ^{13}C NMR of compound **3ad**

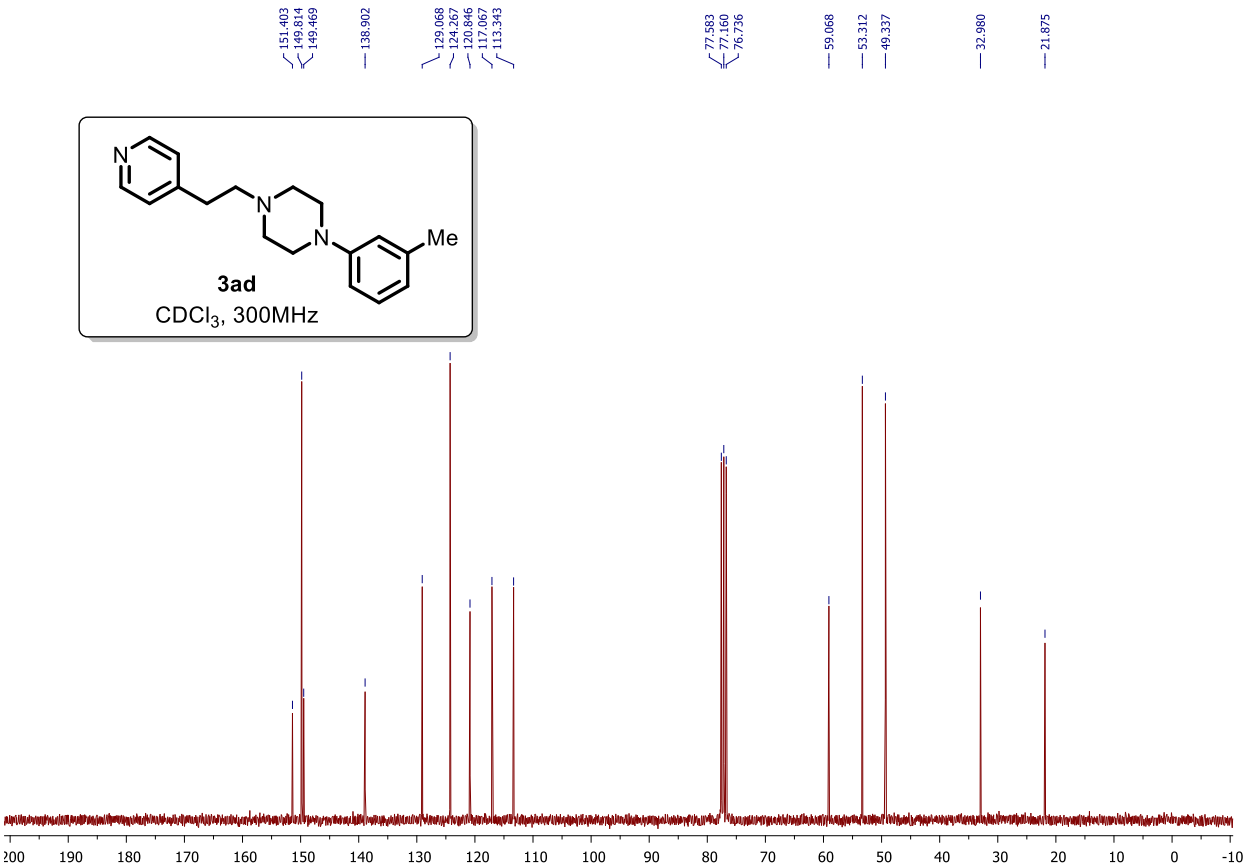


Figure S84: ^{1}H NMR of compound **3ae**

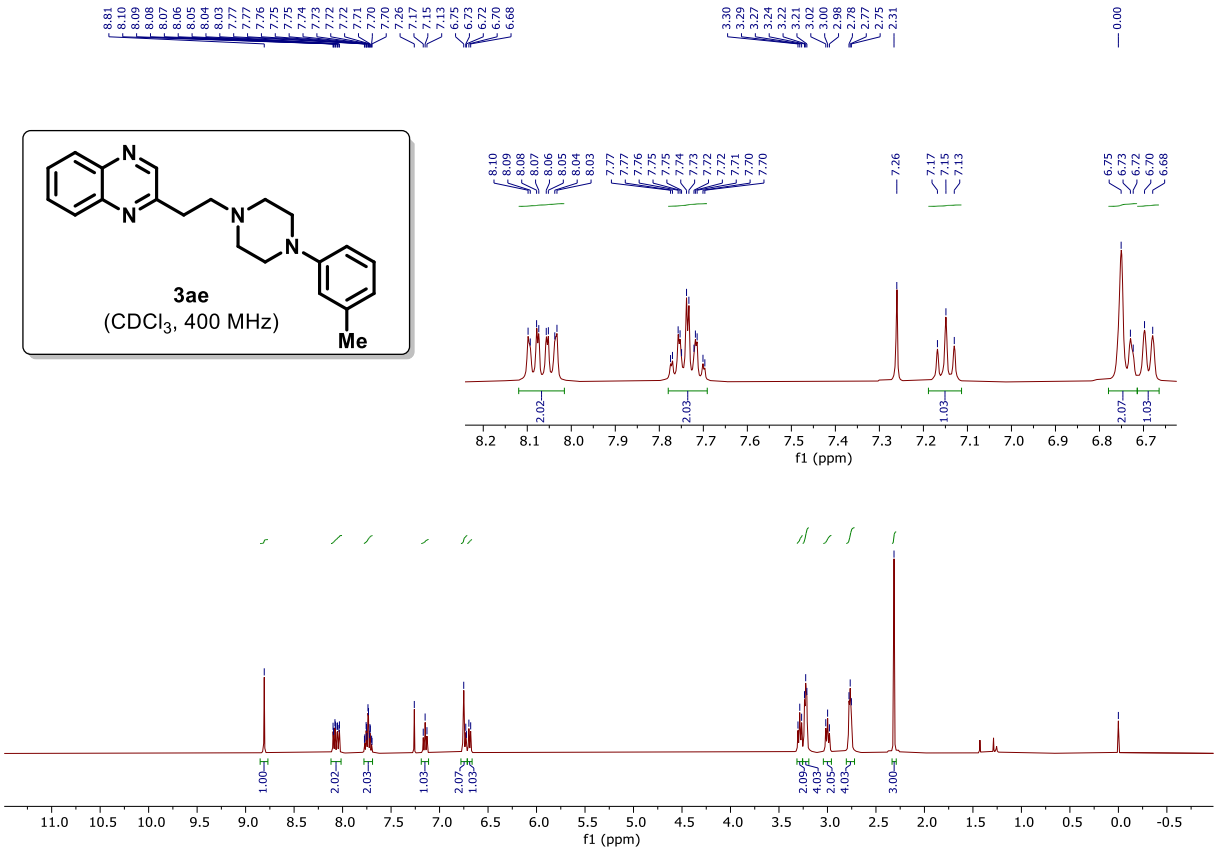


Figure S85: ^{13}C NMR of compound **3ae**

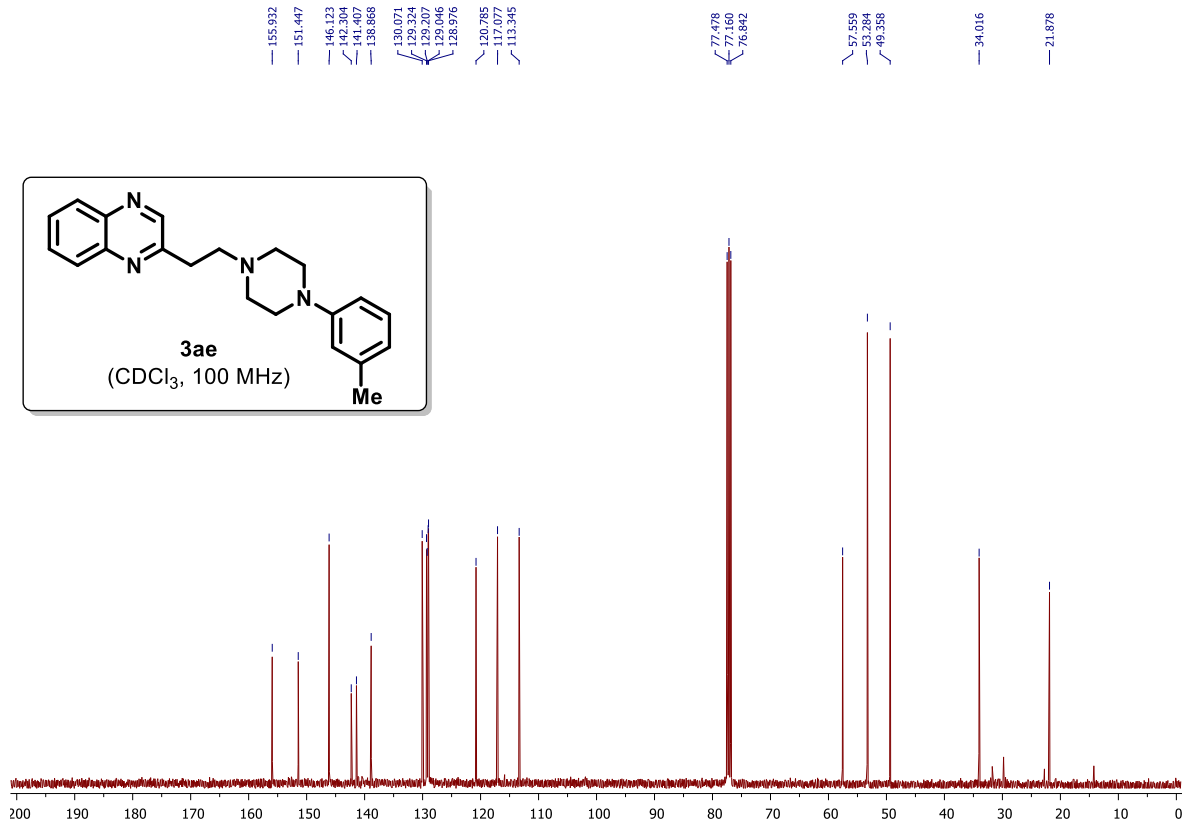


Figure S86: ^{1}H NMR of compound **3af**

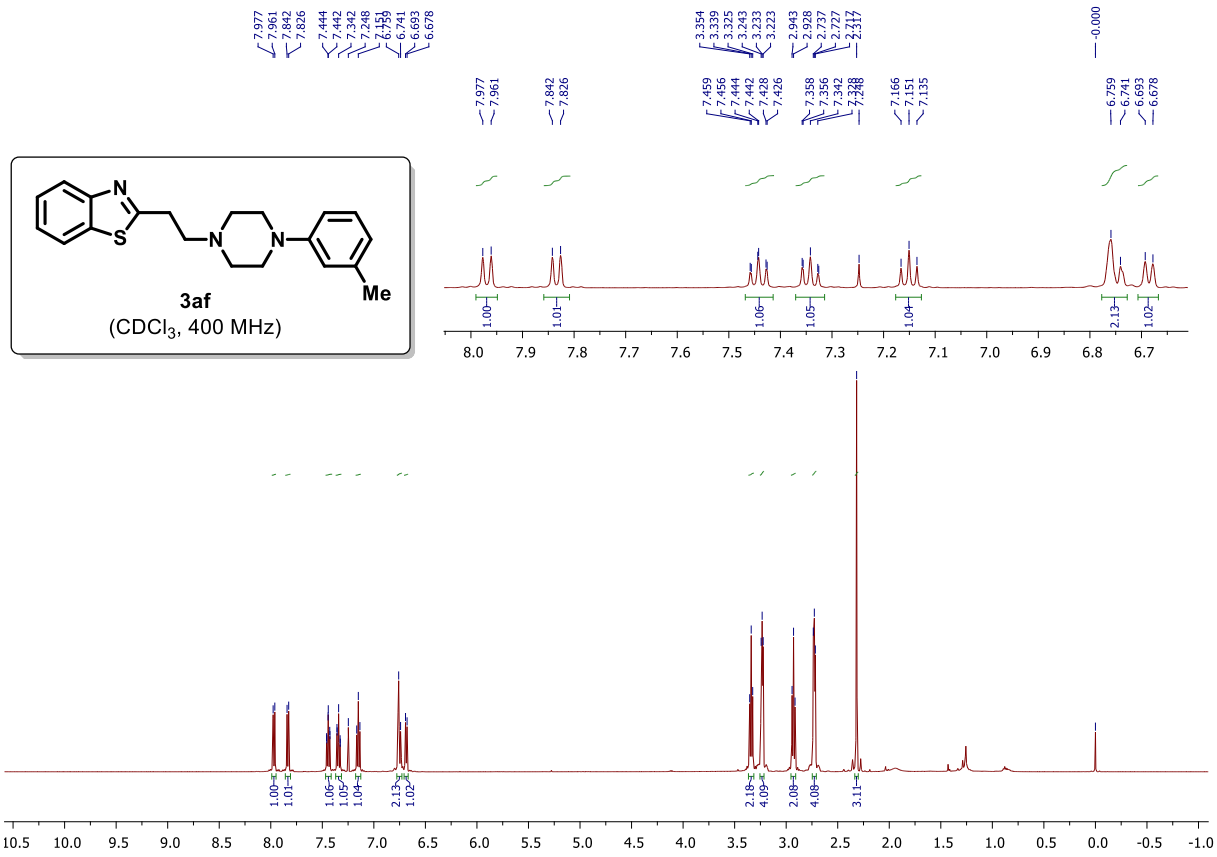


Figure S87: ^{13}C NMR of compound **3af**

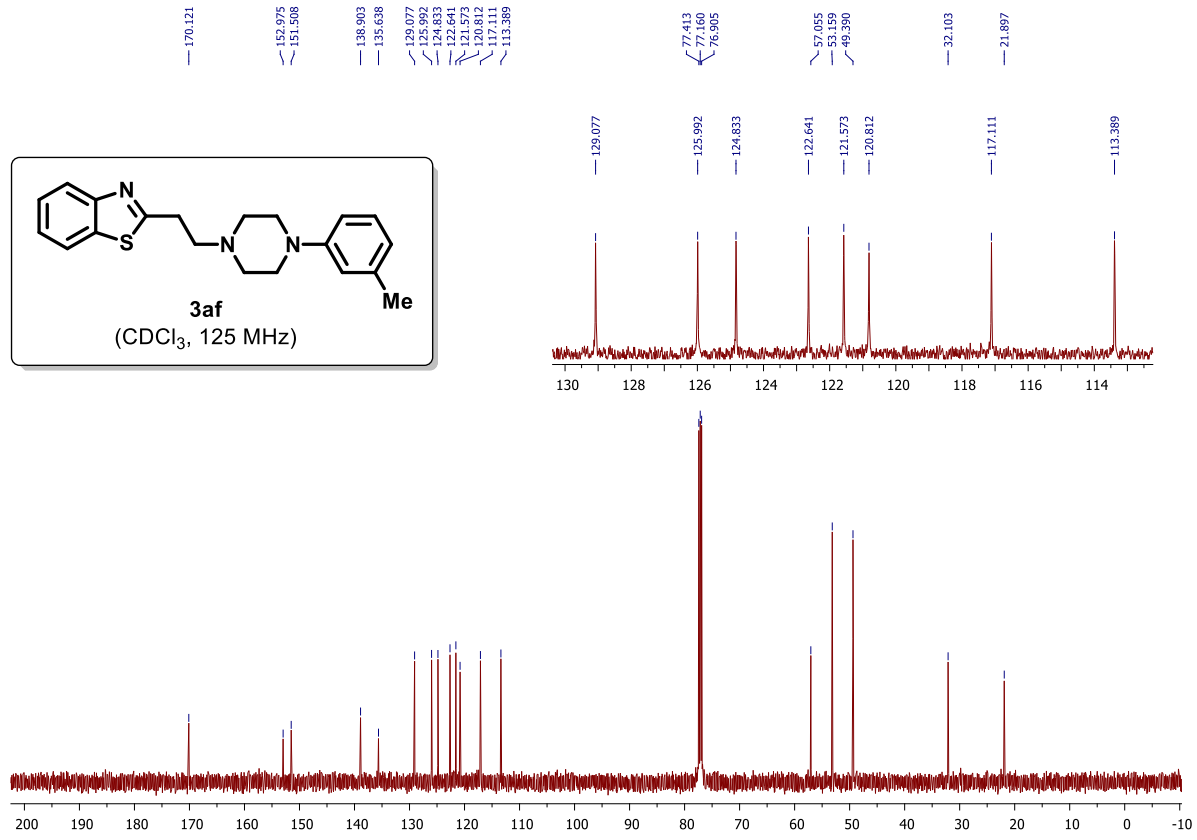


Figure S88: ^{1}H NMR of compound **3ag**

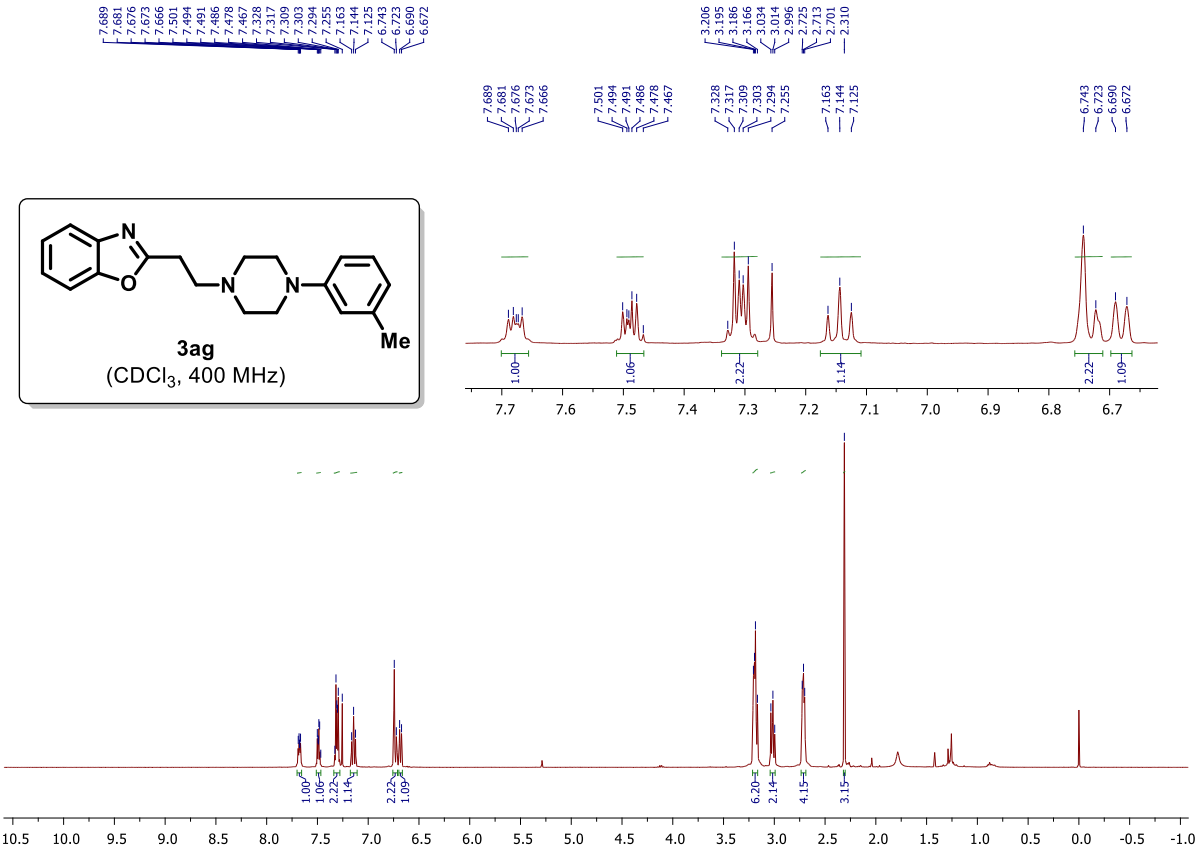


Figure S89: ^{13}C NMR of compound **3ag**

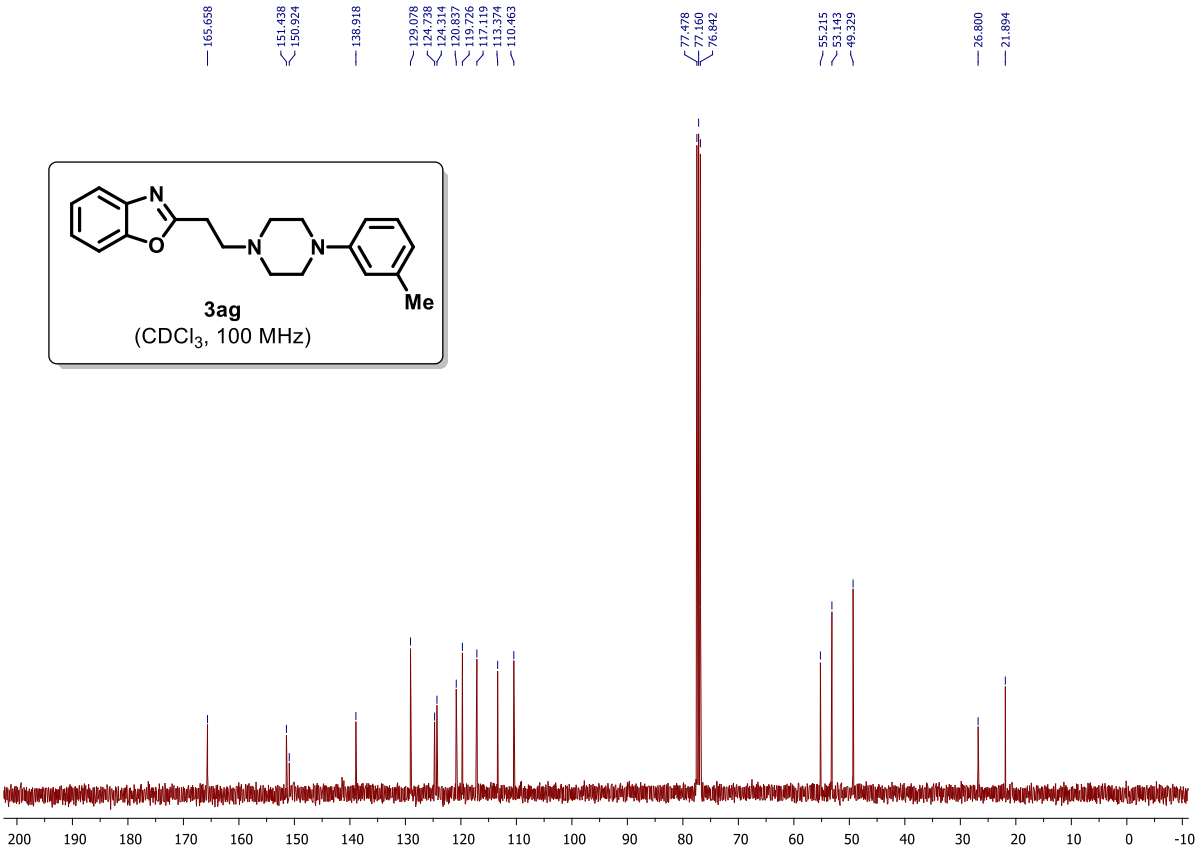


Figure S90: ^{1}H NMR of compound **3ah**

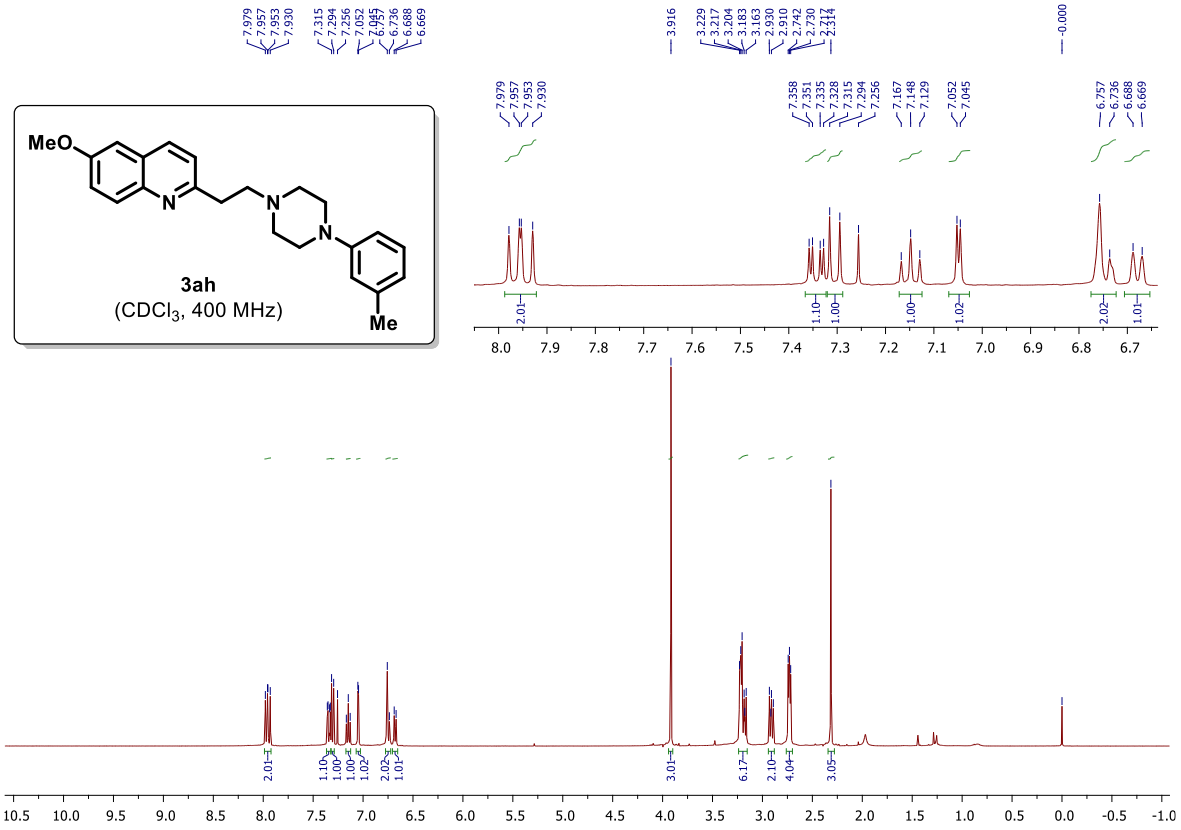


Figure S91: ^{13}C NMR of compound **3ah**

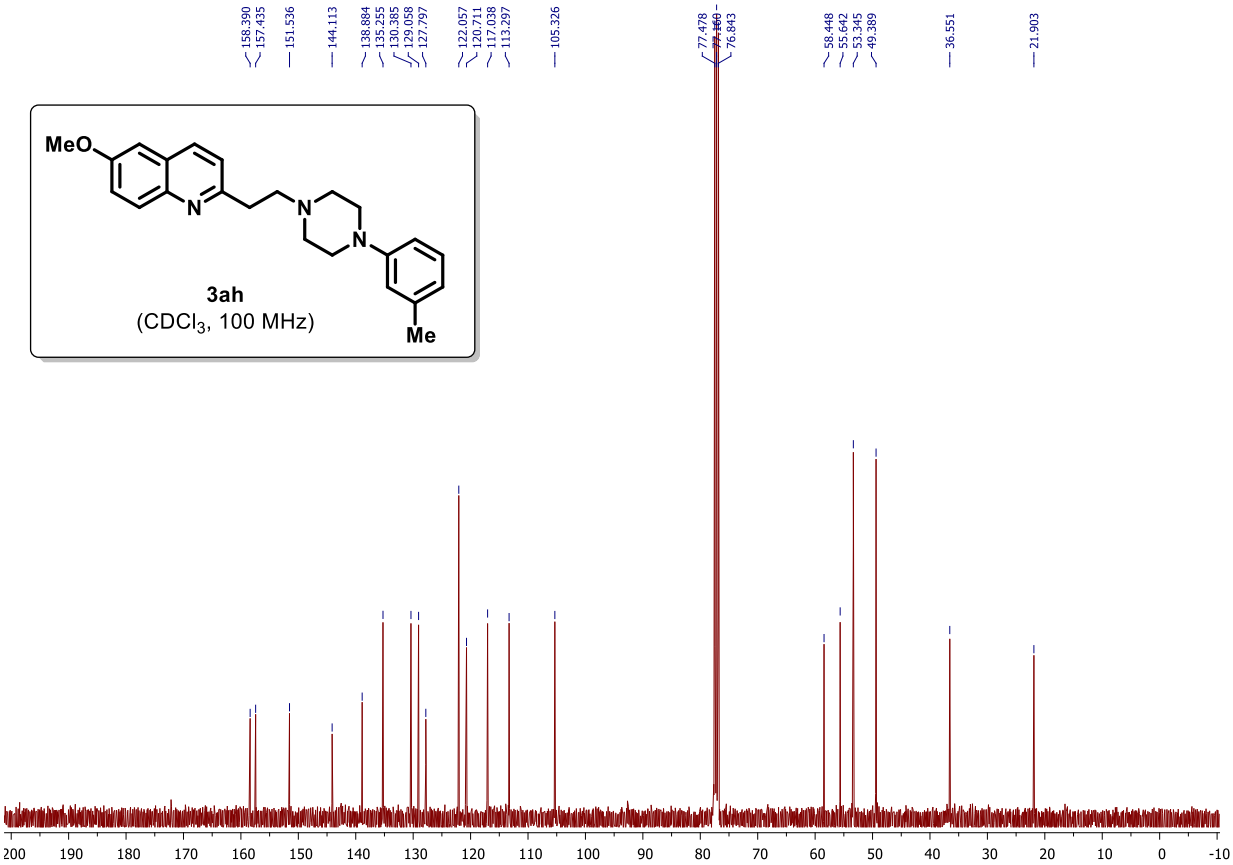


Figure S92: ^{1}H NMR of compound **3ai**

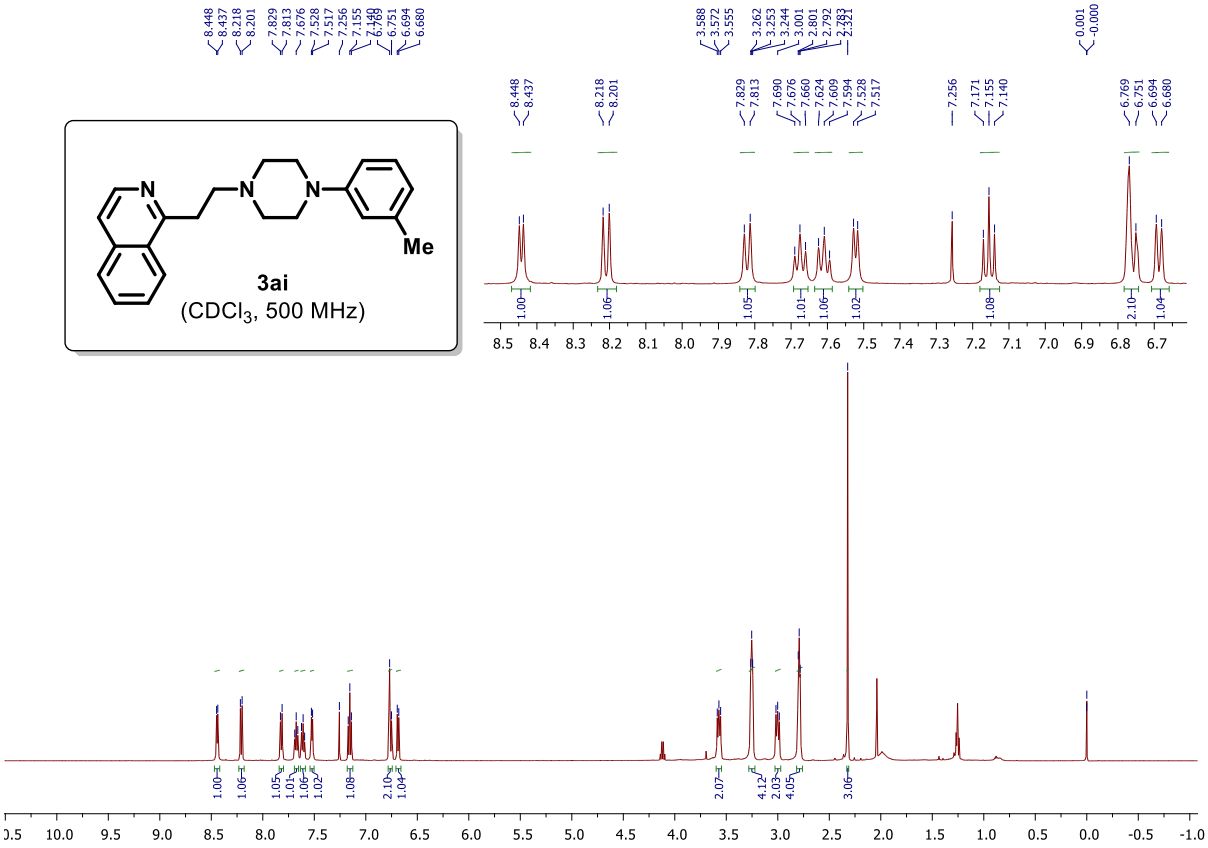


Figure S93: ^{13}C NMR of compound **3ai**

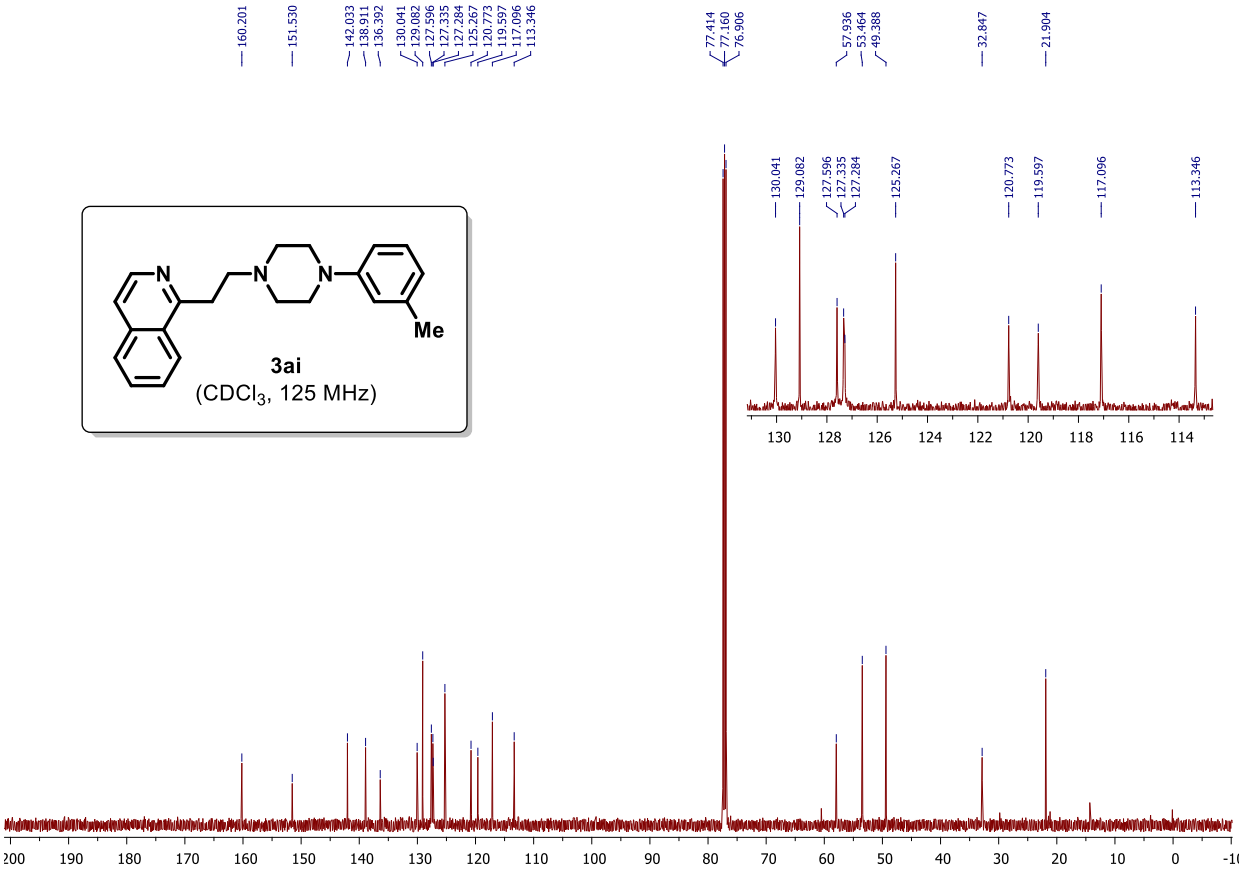


Figure S94: ^{1}H NMR of compound **3aj**

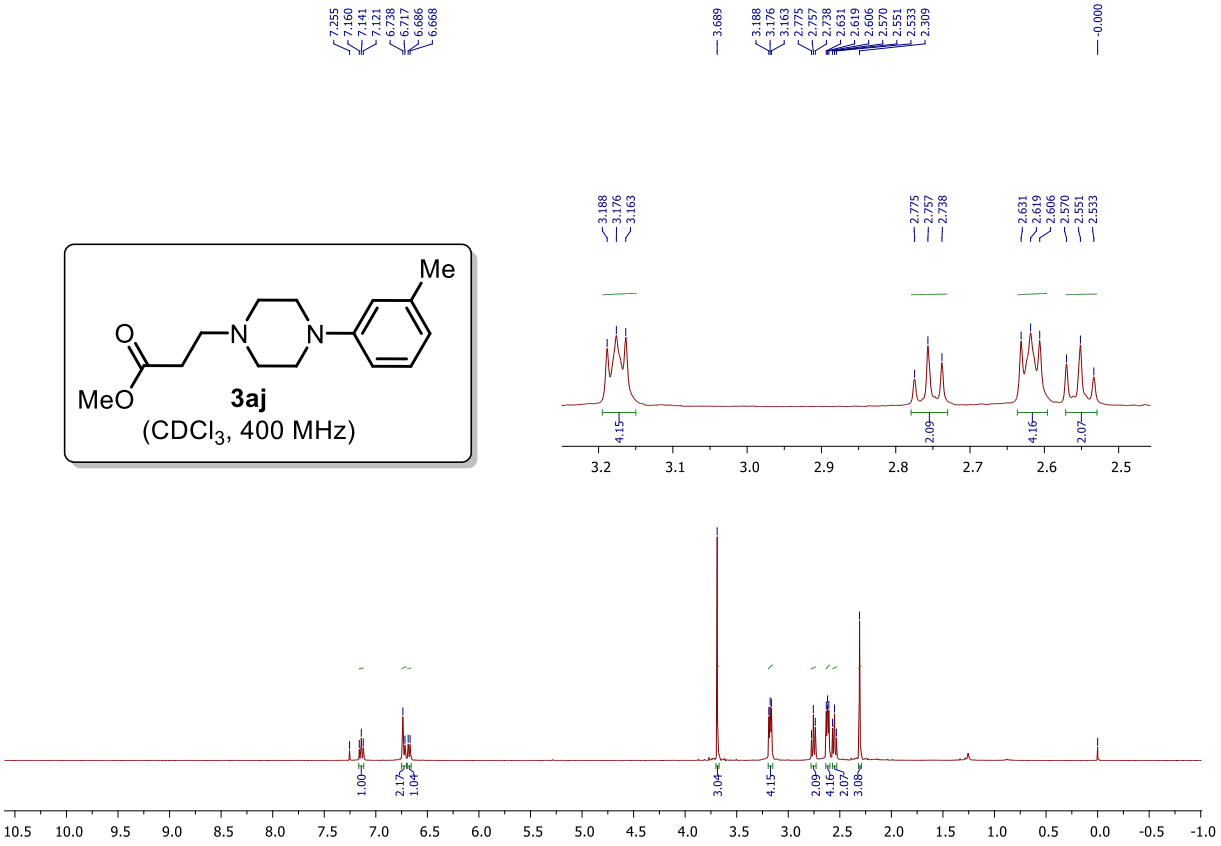


Figure S95: ^{13}C NMR of compound **3aj**

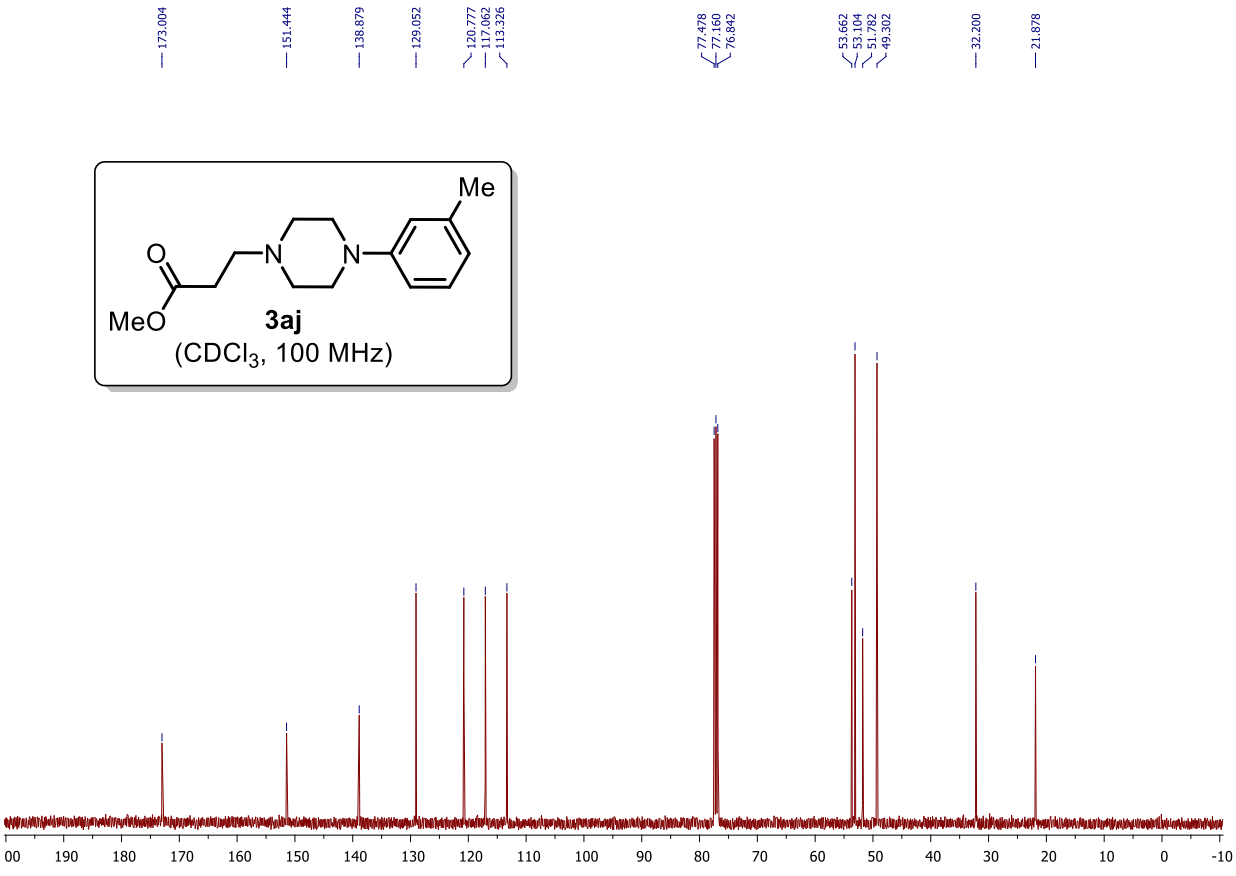


Figure S96: ^{1}H NMR of compound **3ak**

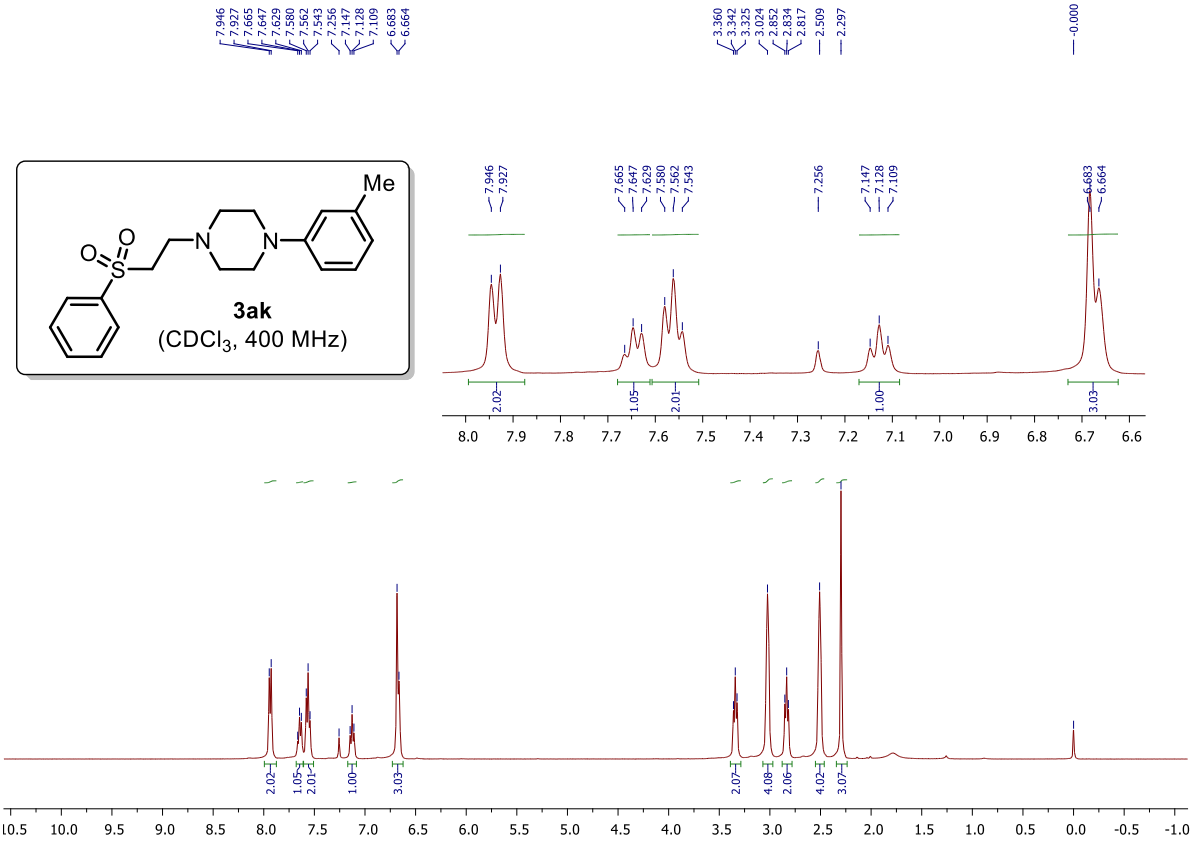


Figure S97: ^{13}C NMR of compound **3ak**

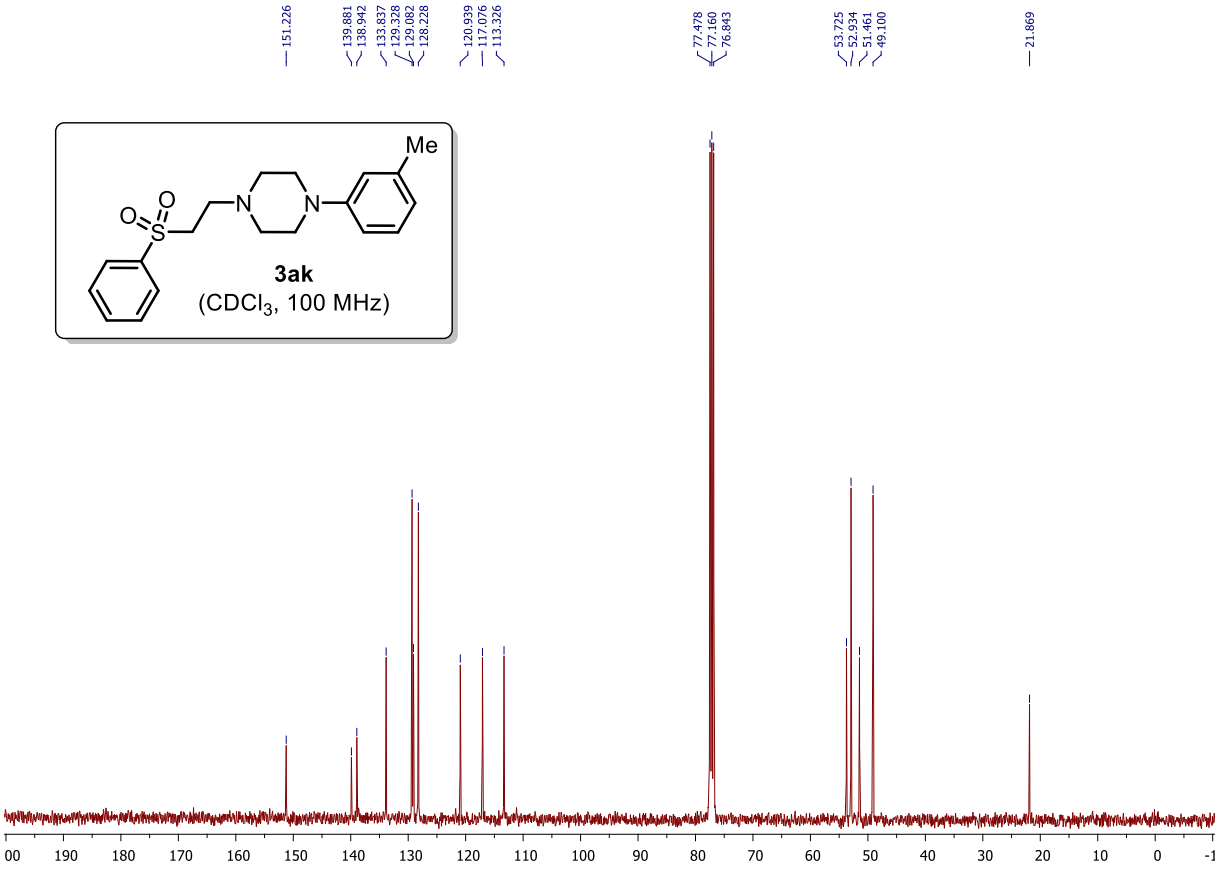


Figure S98: ^{1}H NMR of compound **3al**

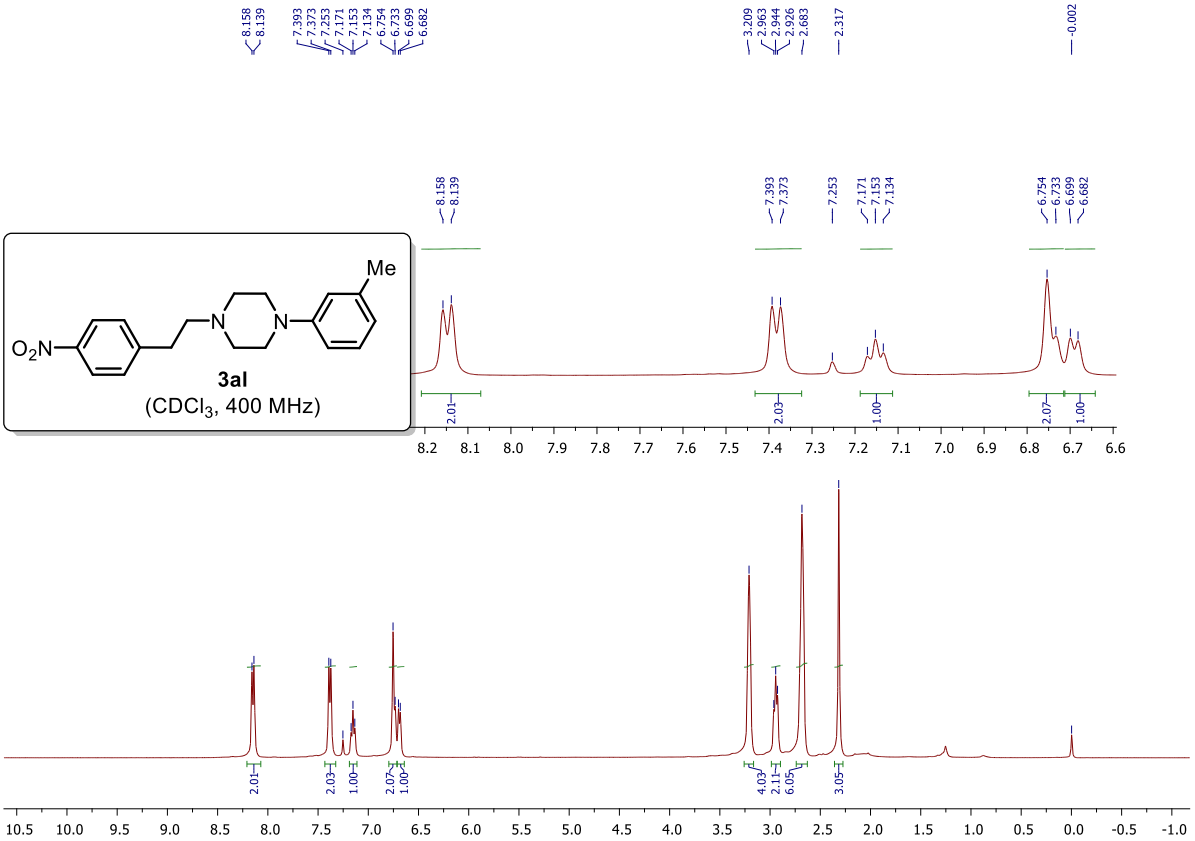


Figure S99: ^{13}C NMR of compound **3al**

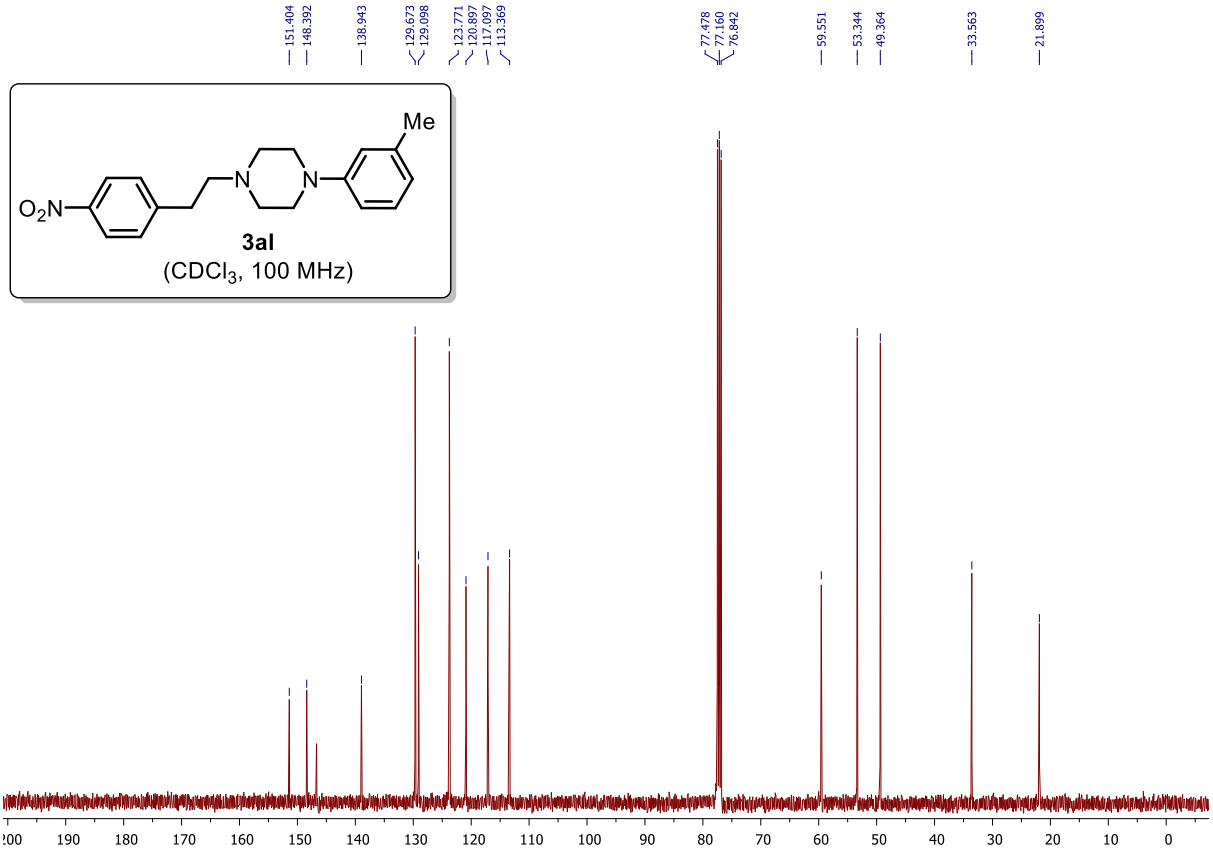


Figure S100: ^{1}H NMR of compound **3am**

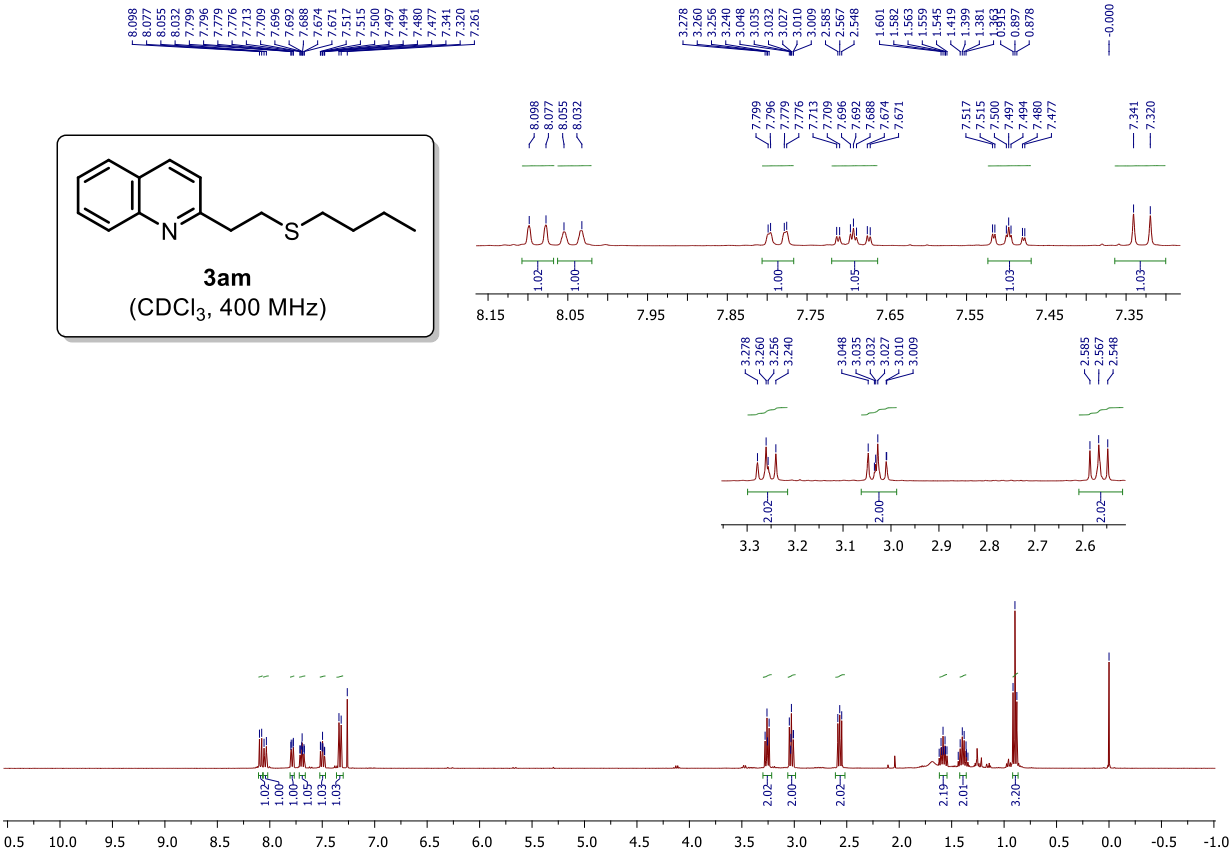


Figure S101: ^{13}C NMR of compound **3am**

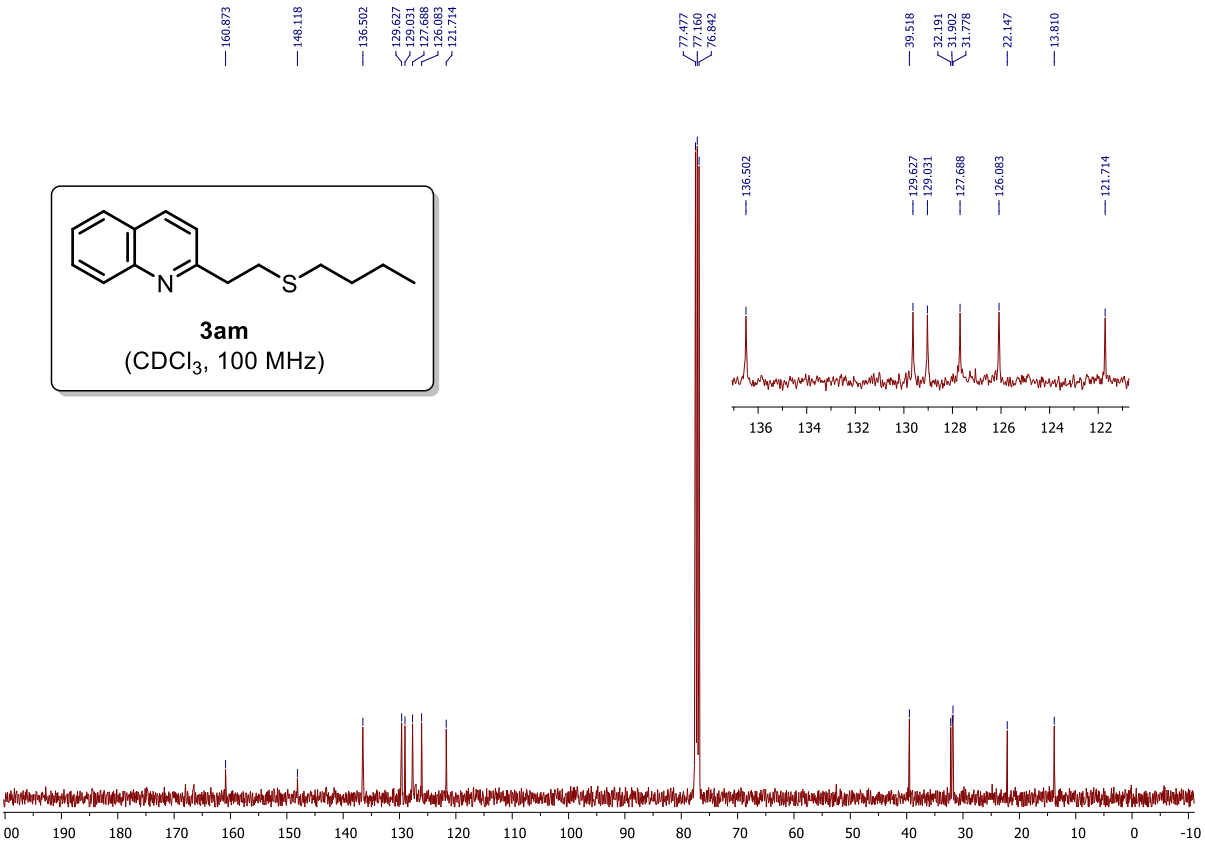


Figure S102: ^{1}H NMR of compound **3an**

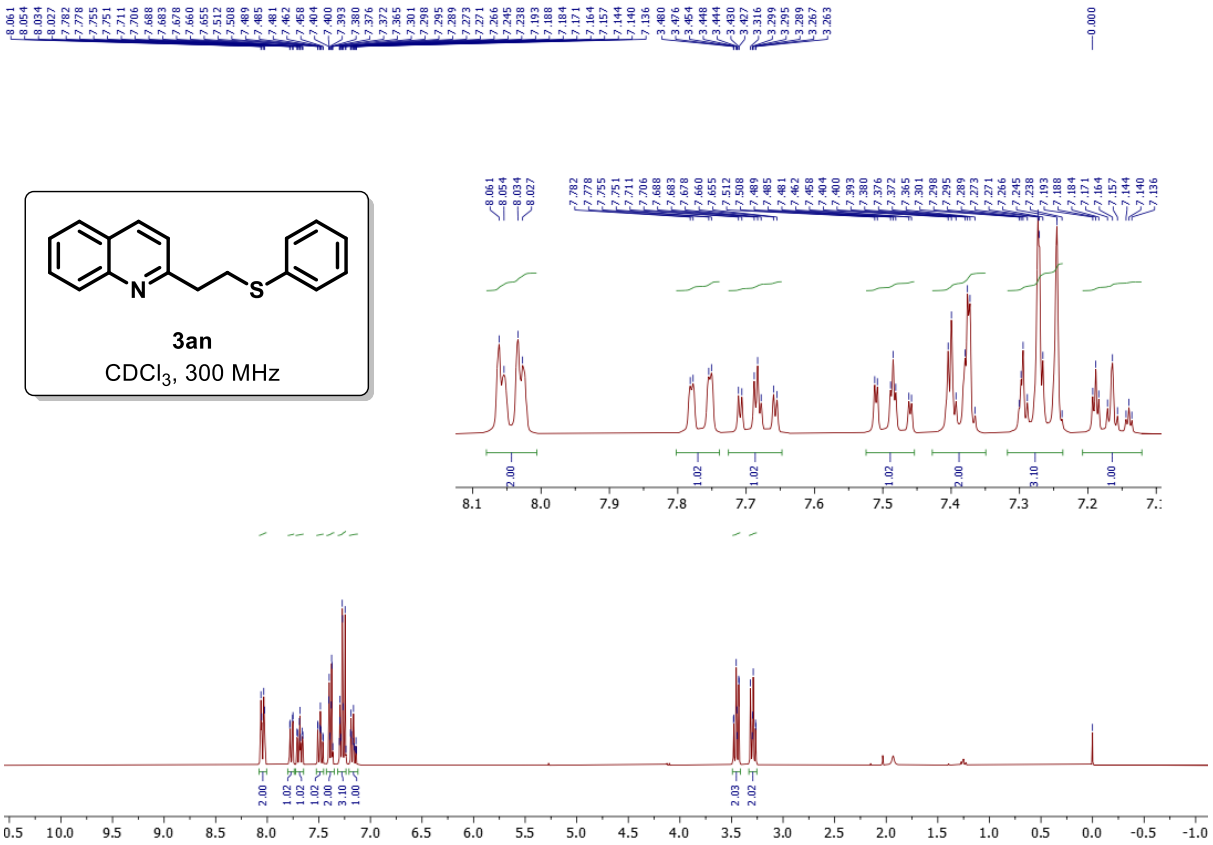


Figure S103: ^{13}C NMR of compound **3an**

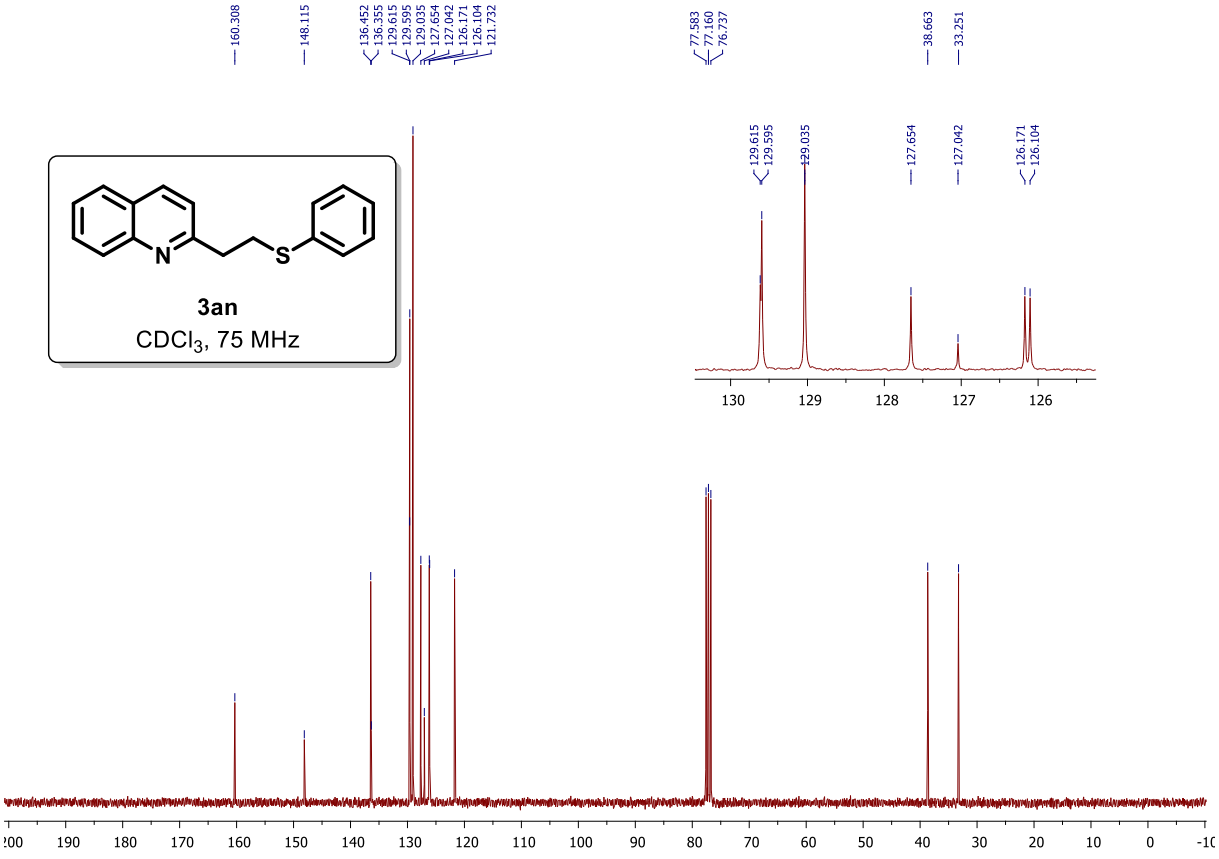


Figure S104: ^{1}H NMR of compound **3ao**

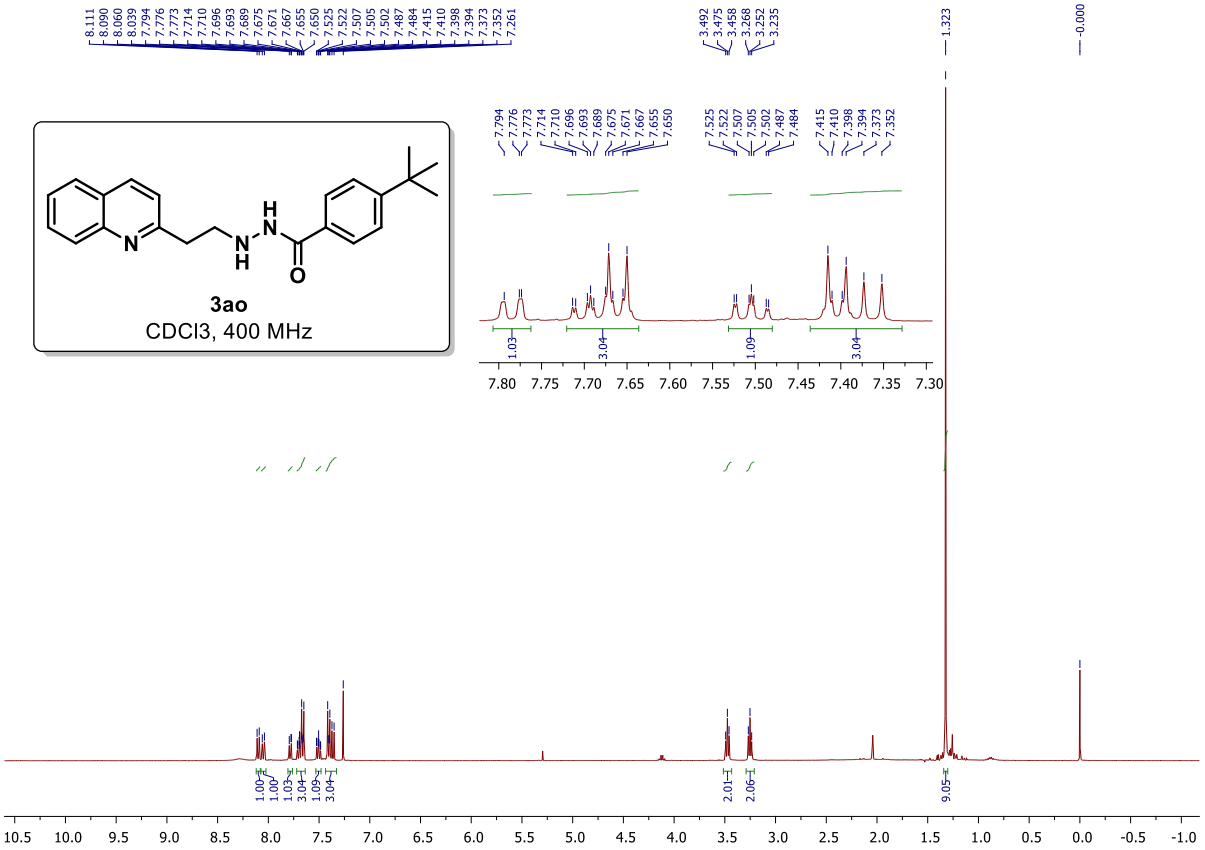


Figure S105: ^{13}C NMR of compound **3ao**

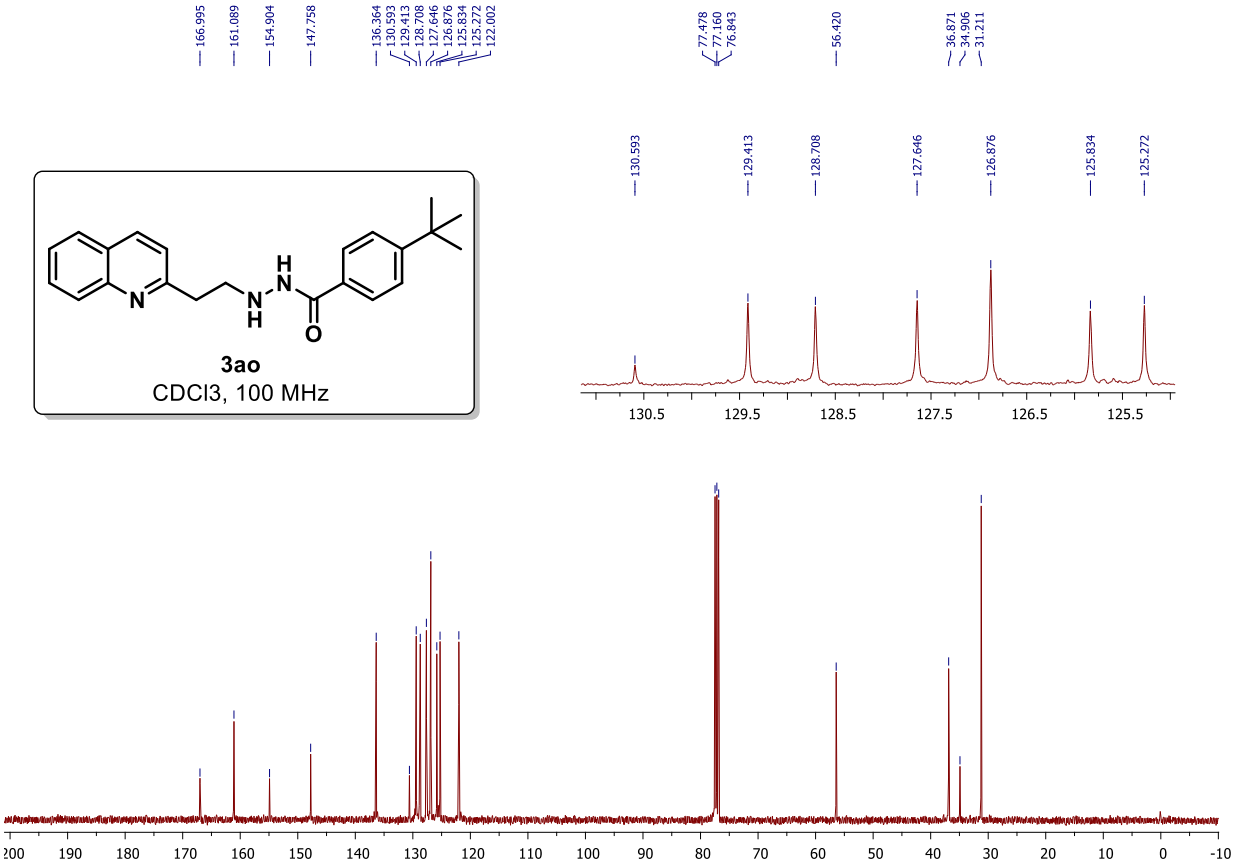


Figure S106: ^{1}H NMR of compound **3ao'**

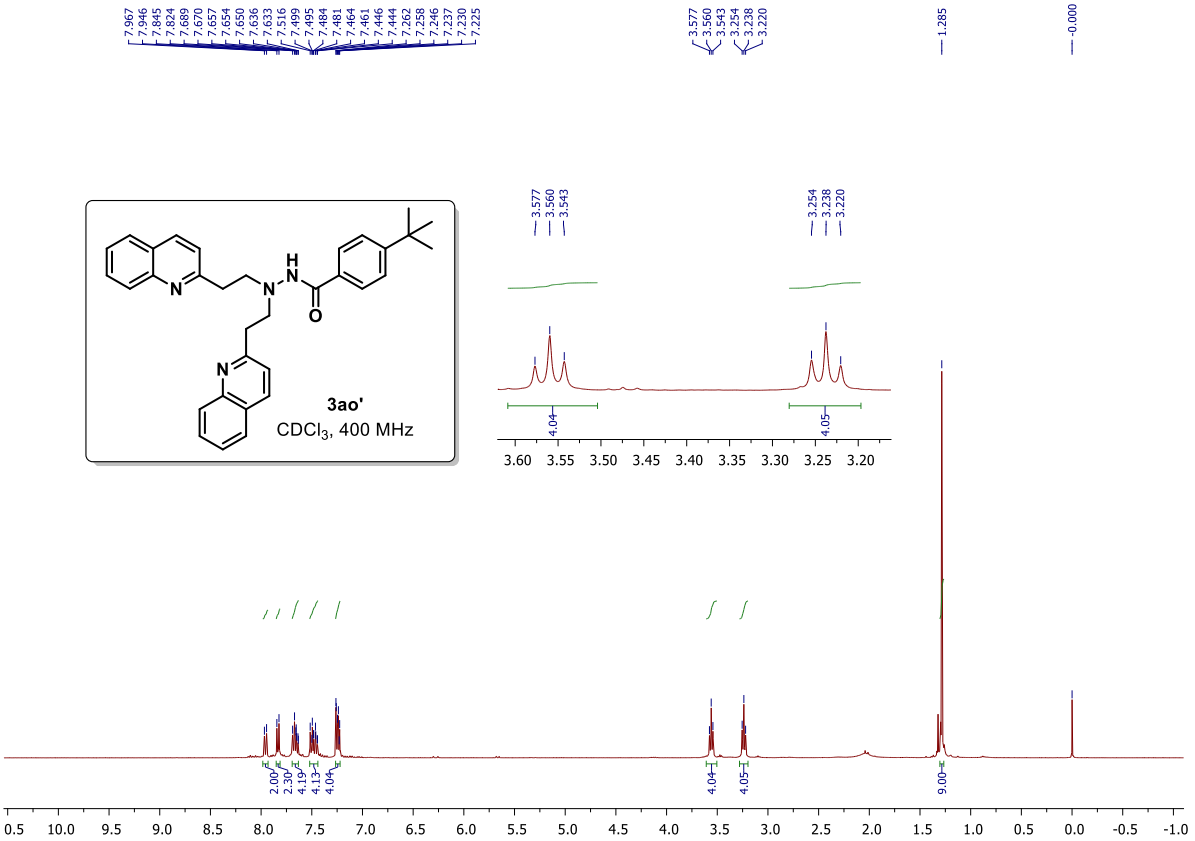


Figure S107: ^{13}C NMR of compound **3ao'**

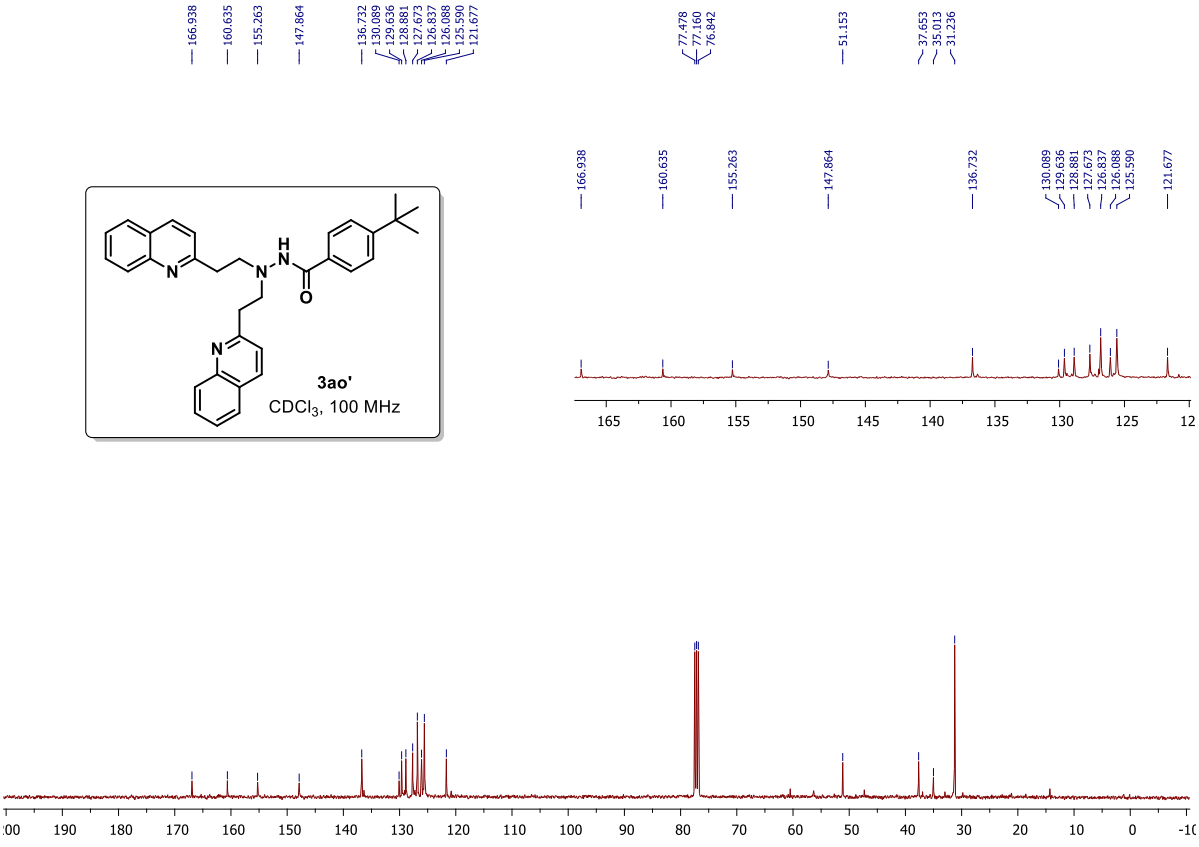


Figure S108: ^{1}H NMR of compound **3ap**

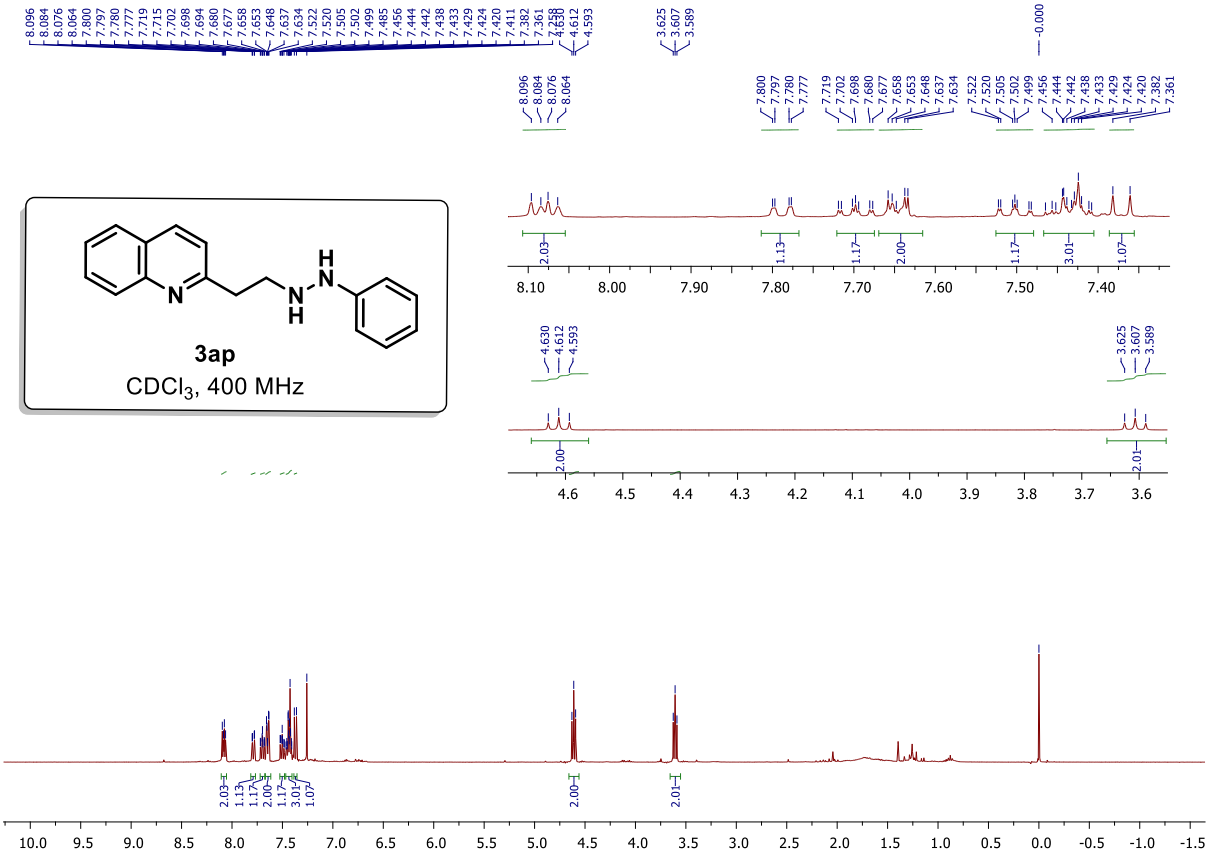


Figure S109: ^{13}C NMR of compound **3ap**

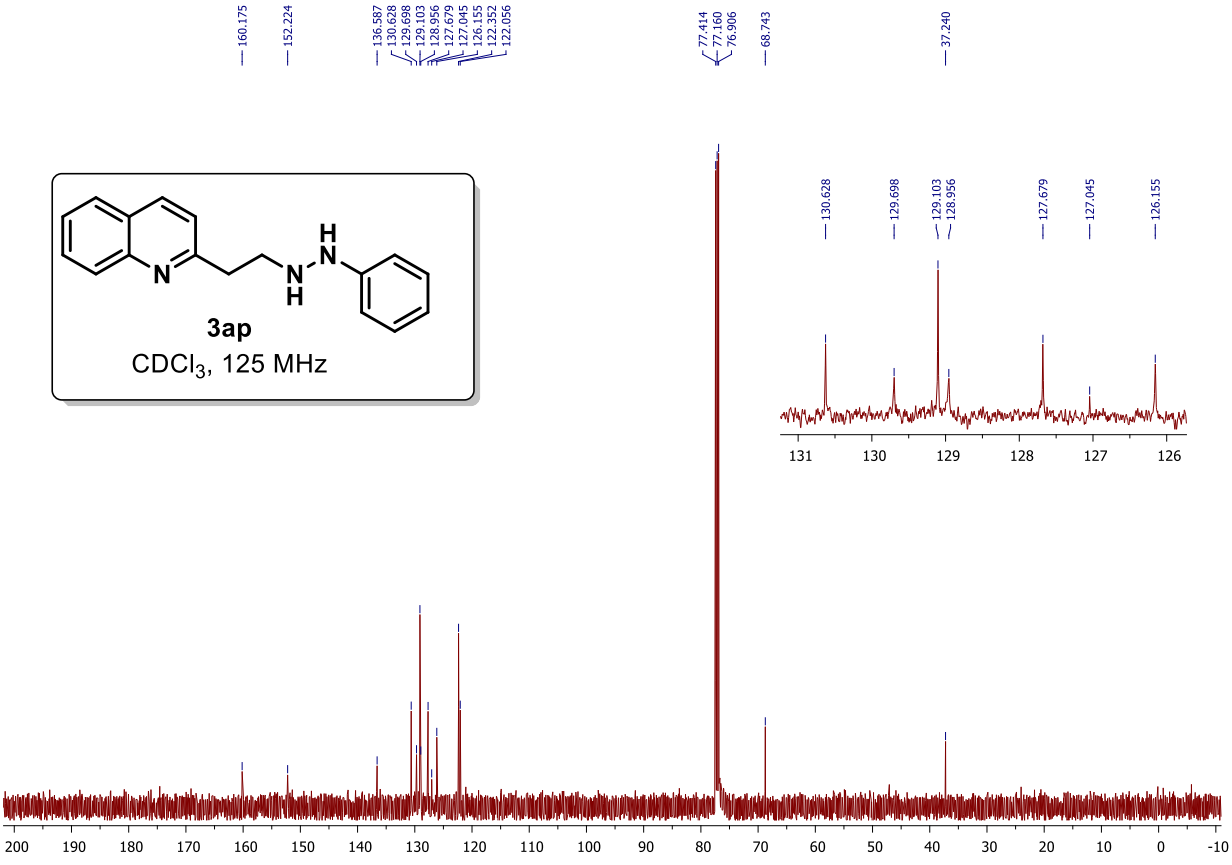


Figure S110: ^{1}H NMR of compound **3ap'**

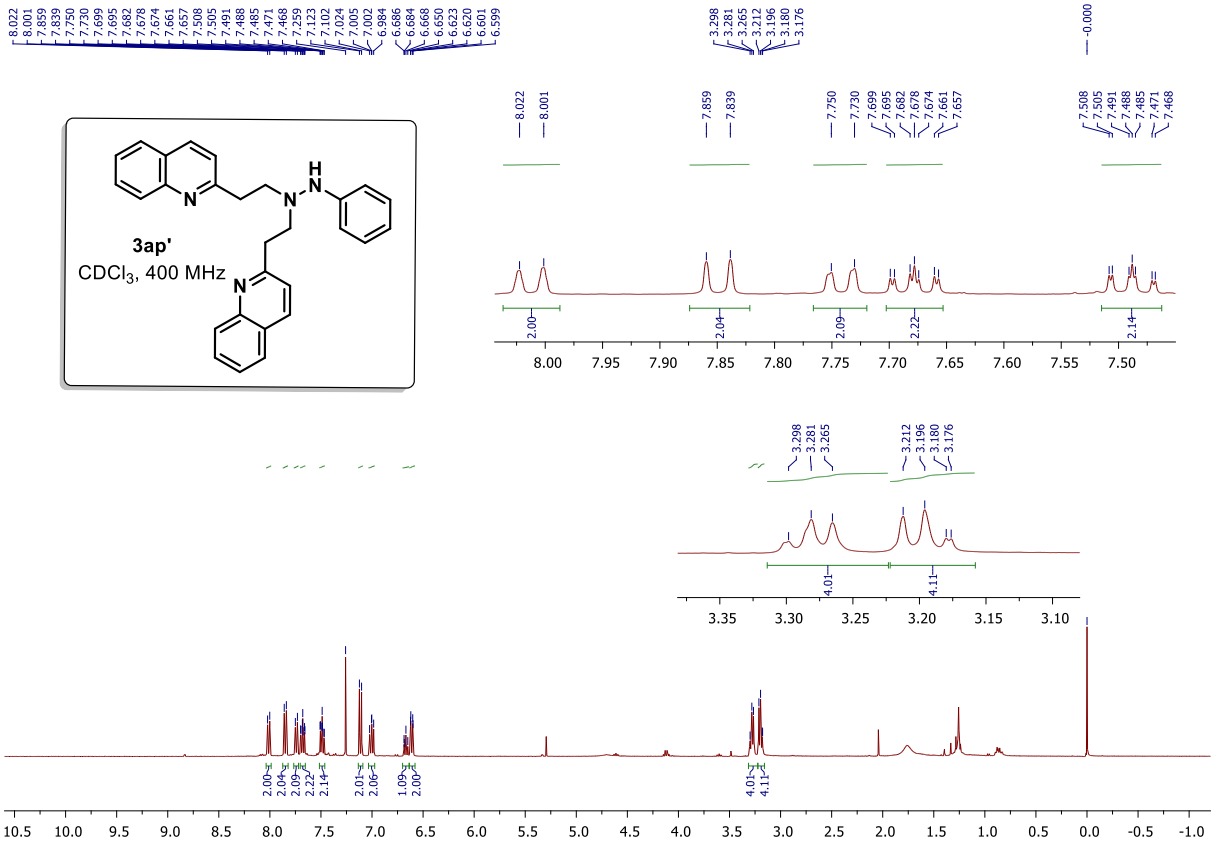
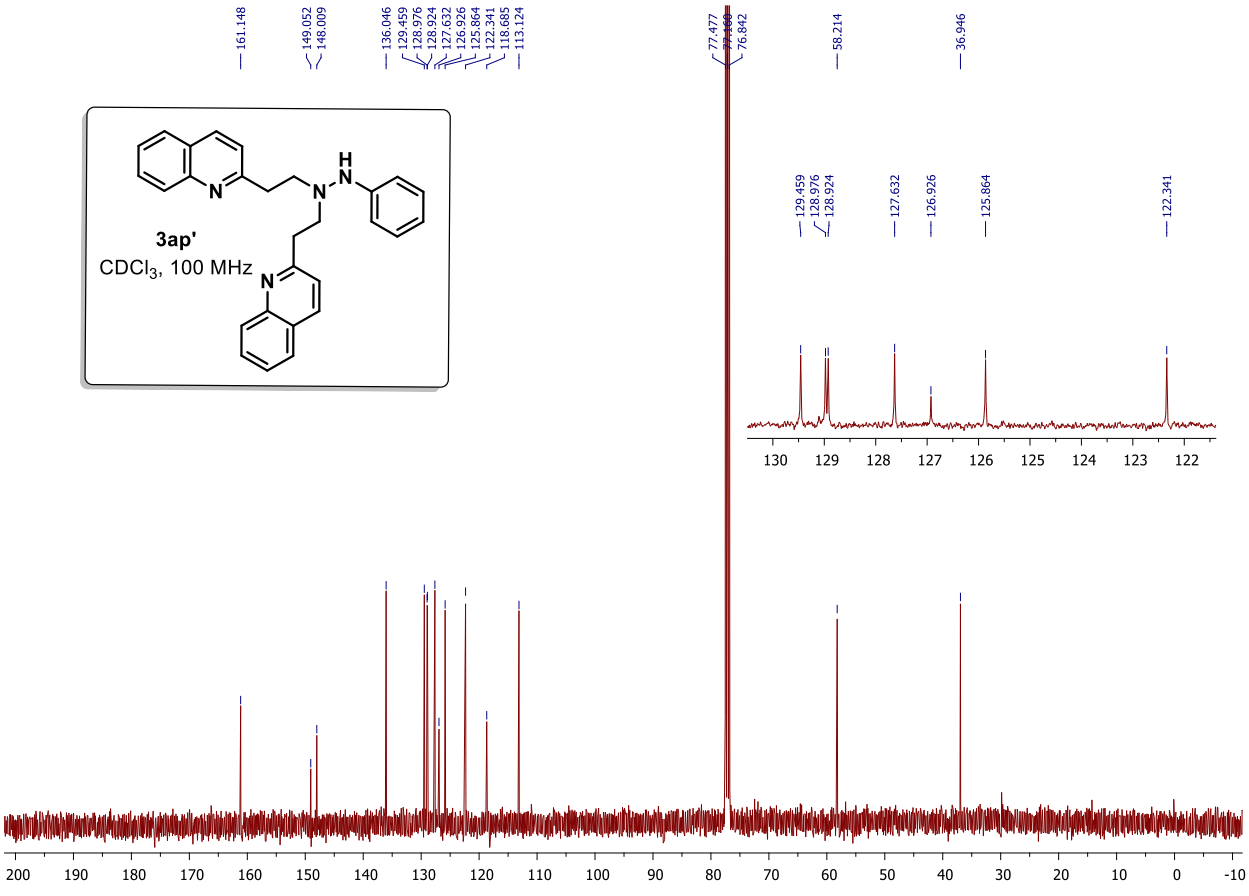


Figure S111: ^{13}C NMR of compound **3ap'**



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