Supporting Information

Facile access to C-substituted piperazin-2-ones and mianserin derivative enabled by chemoselective carbene insertion and cyclization cascade

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1. General Information:

All the reactions were performed using oven-dried Schlenk tubes and monitored by Merck silica gel 60 F_{254} precoated plates (0.25 mm) visualizing under UV light (254 nm) or I_2 staining. Temperature mentioned for any reaction is corresponding to the oil bath temperature. Column chromatography was performed using silica gel 60-120 Å or 100-200 Å mesh of Merck Company.

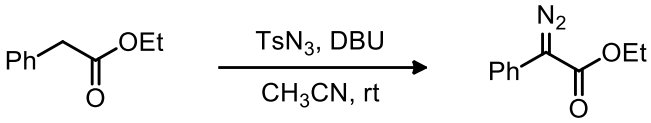
^1H, ^{13}C, and ^{19}F nuclear magnetic resonance spectra were recorded on Bruker Advance III 400 MHz spectrometer at 25 °C. NMRs of the products were measured in $CDCl_3$. The chemical shifts in ^1H NMR and $^{13}C\{1H\}$ NMR spectra are reported in parts per million (ppm) and are referenced to the residual solvent signal as the internal standard; ^1H NMR spectra ($CDCl_3$: δ 7.26 ppm or TMS: δ 0.00 ppm) and ^{13}C ($CDCl_3$: δ 77.16). The coupling constant (*J*) was reported in Hertz (Hz). Splitting patterns are denoted as "s" for singlet; "d" for doublet; "t" for triplet; "q" for quartet; "sext" for sextet; "sept" for septet; "m" for multiplet, "br" for broad; "dt" for doublet of triplets; "td" for triplet of doublets. ESI-HRMS were recorded on AGILENT 6520 Q-TOF spectrometer. The melting point was recorded on STUART SMP10 digital melting point apparatus. IR spectra were recorded on Bruker FT-IR Spectrometer ALPHA II.

All commercially available chemicals were used as received unless otherwise indicated. The ethylenediamine, and starting materials of diazo compounds were purchased from GLR Innovations/TCI/Sigma and used without further purification. Copper(II) 2-ethylhexanoate was purchased from Sigma-Aldrich.

2. Preparation of Starting materials:

2.1. Preparation of α-diazo arylacetates (1a-1s)[1]:

a) Procedure for 1a:

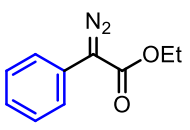


1a

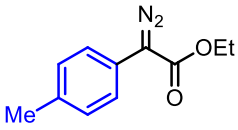
A solution of 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) (2.28 g, 15 mmol, 1.5 equiv) in anhydrous CH_3CN (10 mL) was added dropwise to a solution of ethyl phenyl acetate (1.64 g, 10 mmol, 1.0 equiv) and *p*-toluenesulfonyl azide (TsN_3) (2.37 g, 12 mmol, 1.2 equiv) in anhydrous CH_3CN (50 mL). Then, the reaction mixture was stirred at room temperature for 15 hours. After completion of the reaction, water (40 mL) was added, and the resulting mixture was extracted with diethyl ether (3 × 40 mL). The combined organic layers are washed with brine (40 mL) and dried over anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residual was purified by a silica gel column chromatography with petroleum ether (PE)/ethyl acetate (EA) (30:1) as the eluent (the eluent was PE/EA = 5:1.) to give **1a** as a red oil (1.73 g, 91% yield).

The same procedure was followed for the synthesis of other diazo compounds.

b) The diazo compounds employed in the reactions:



1a



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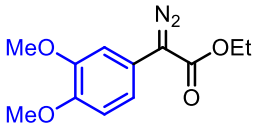

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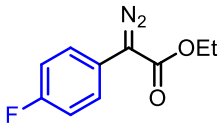

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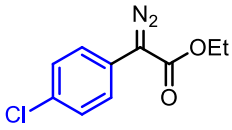

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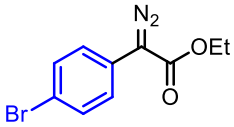

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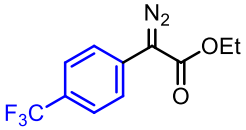

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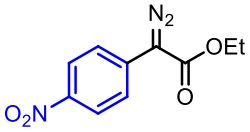

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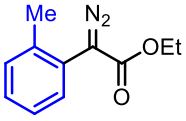

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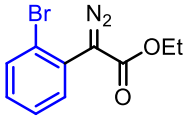

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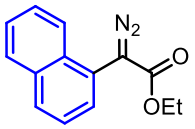

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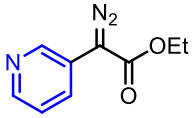

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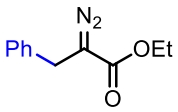

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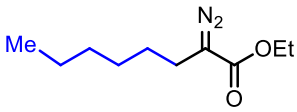

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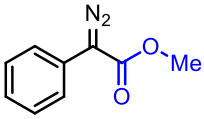

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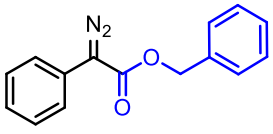

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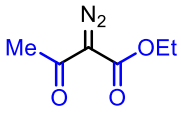

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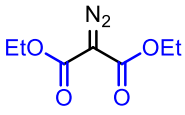

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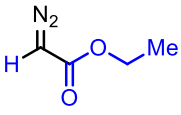
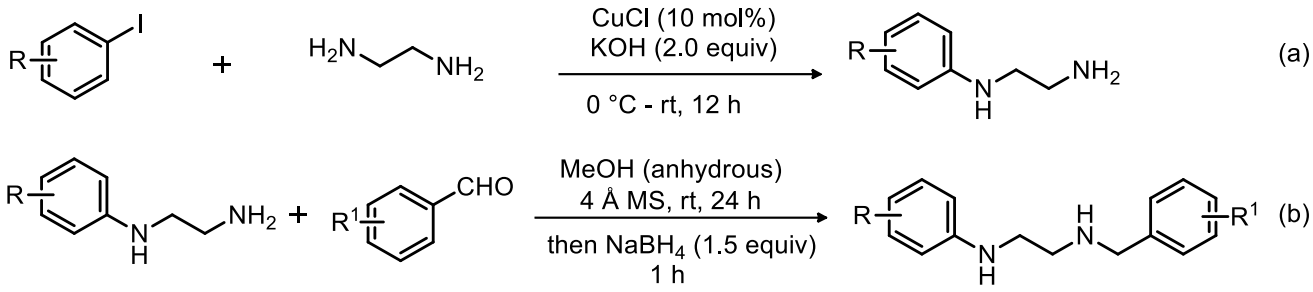


1s

2.2. Preparation of N^1,N^2-disubstituted diamines:[2]

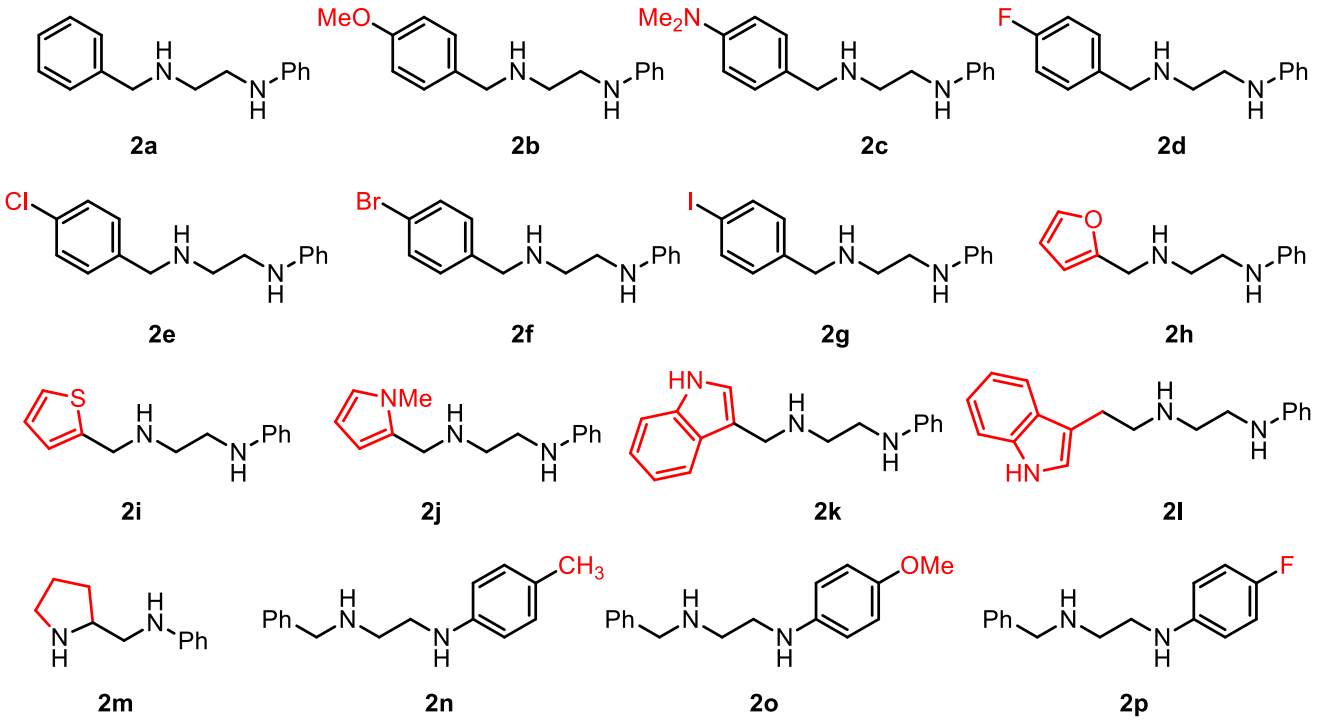


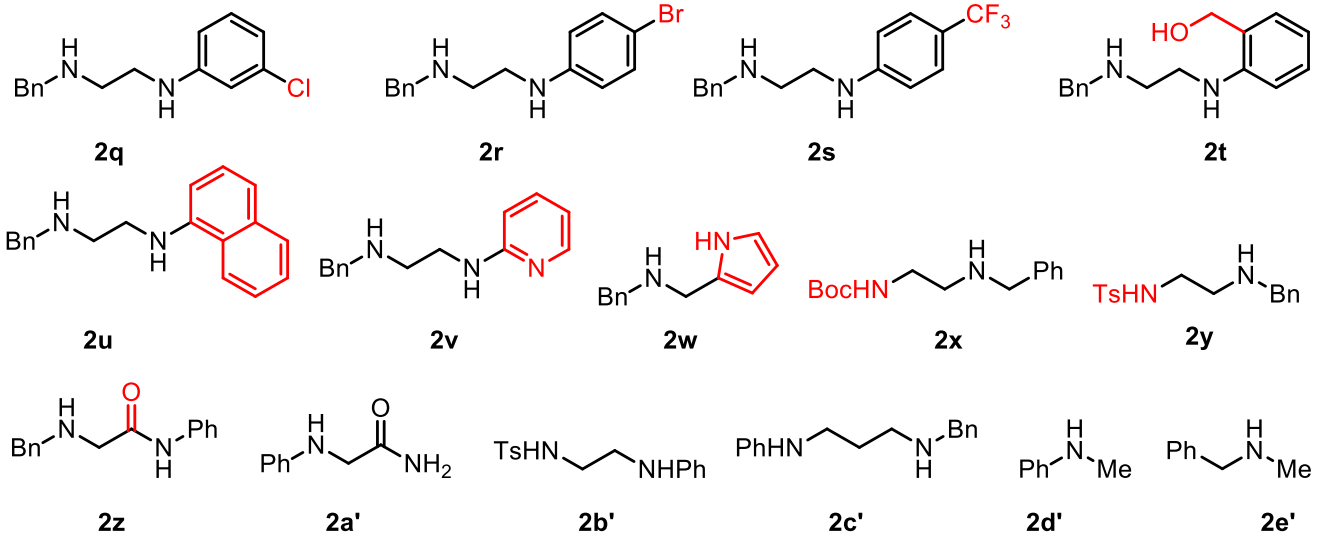
a) Step 1: In a round bottom flask charged with magnetic stirrer bar, CuCl (2.7 mmol), KOH (53 mmol) and iodobenzene derivatives (27 mmol), was added ethylenediamine (80 mmol) slowly at 0 °C. After being stirred overnight at room temperature, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (5 times). The combined organic layers were dried over Na_2SO_4, filtered off and concentrated in vacuo to give crud product which was used without purification for the next step.

b) Step 2: To the crude N-phenylethylenediamine derivatives (1.0 equiv) and 4 Å molecular sieves (powder, 200 mg per mmol) in dry methanol was added benzaldehyde (1.01 equiv) and the mixture was stirred at room temperature for 24 h. The mixture was then cooled to 0 °C, and was added $NaBH_4$ (1.5 equiv) portion wise and the reaction was stirred until completion. The reaction mixture was then filtered through a plug of Celite and the filtrate was evaporated under vacuo. The residue was then purified by flash column chromatography (DCM/MeOH) to afford pure *N^1*-benzyl-N^2-phenylethylenediamine.

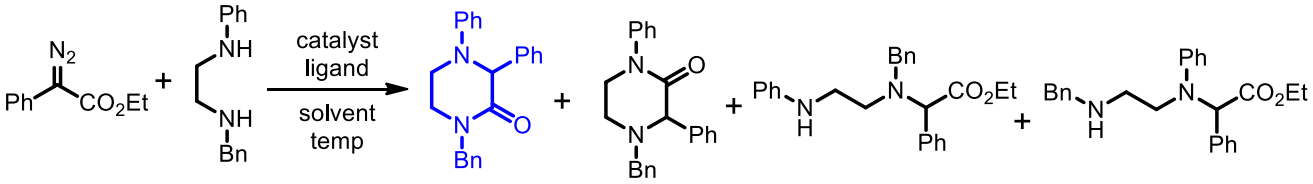
Following diamines were prepared using other reported procedures: **2l**,[3] (then reduction with $LiAlH_4$ in THF), **2m**[4] (then reduction with $LiAlH_4$ in THF), **2w**,[5] and **2z**.[3]

c) The diamine substrates employed in the reactions:





3. Optimization of reaction conditions:

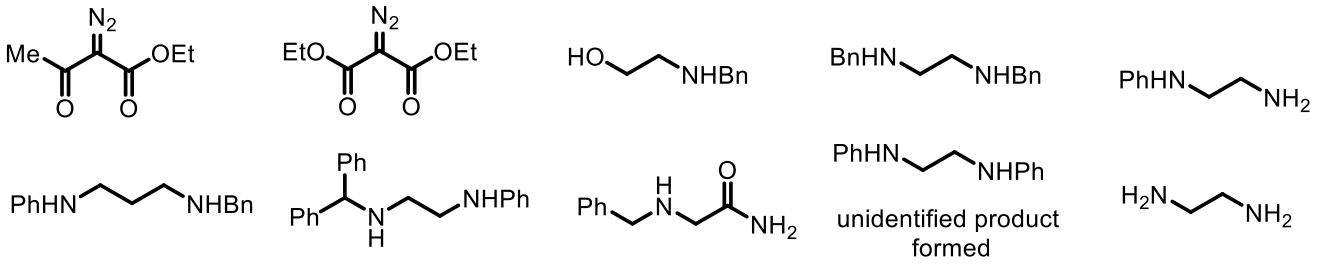


Entry	Catalyst (5 mol%)	Ligand (6 mol%)	Solvent	Temp	Yield of 3aa
1[b]	$Cu(hfacac)_2.xH_2O$	(*rac*)-BINOL	THF	60 °C	53%
2[c]	$Cu(hfacac)_2.xH_2O$	(*rac*)-BINOL	THF	60 °C	37%
3[d]	$Cu(hfacac)_2.xH_2O$	(*rac*)-BINOL	THF	60 °C	48%
4	$Cu(hfacac)_2.xH_2O$	(*rac*)-BINOL	THF	60 °C	54%
5	$Cu(hfacac)_2.xH_2O$ (10 mol%)	(*rac*)-BINOL (12 mol%)	THF	60 °C	39%
6	$Cu(hfacac)_2.xH_2O$	(*rac*)-BINOL	THF	RT	trace
7[e]	$Cu(hfacac)_2.xH_2O$	(*rac*)-BINOL	THF	60 °C	6%
8	$Cu(hfacac)_2.xH_2O$	-	THF	60 °C	44%
9	$Cu(hfacac)_2.xH_2O$	-	TFE	60 °C	44%
10	$Cu(hfacac)_2.xH_2O$	-	ACN	60 °C	20%
11	$Cu(hfacac)_2.xH_2O$	-	$CHCl_3$	60 °C	41%
12	$Cu(hfacac)_2.xH_2O$	-	Acetone	60 °C	17%
13	$Cu(hfacac)_2.xH_2O$	-	2-Me THF	60 °C	55%

14	$Cu(hfacac)_2.xH_2O$	-	DCE	60 °C	71%
15	$Cu(hfacac)_2.xH_2O$	(*rac*)-BINOL	DCE	60 °C	65%
16	$Cu(hfacac)_2.xH_2O$	1,10-Phenanthroline	DCE	60 °C	27%
17	$Cu(hfacac)_2.xH_2O$	2,2'-bipyridyl	DCE	60 °C	49%
18	$Cu(hfacac)_2.xH_2O$	dppe	DCE	60 °C	62%
19	$Cu(hfacac)_2.xH_2O$	dBbpy	DCE	60 °C	25%
20	$Cu(hfacac)_2.xH_2O$	*(rac)*-BINAP	DCE	60 °C	Trace
21[f]	$Cu(hfacac)_2.xH_2O$	-	DCE	60 °C	66%
22[g]	$Cu(hfacac)_2.xH_2O$	-	DCE	60 °C	69%
23	$Cu(hfacac)_2.xH_2O$ (10 mol%)	-	DCE	60 °C	58%
24	$Cu(acac)_2.xH_2O$	-	DCE	60 °C	61%
25	$Cu(OTf)_2$	-	DCE	60 °C	60%
26	-	-	DCE	60 °C	<5%
27	$Cu(CH_3CN)_4.PF_6$	-	DCE	60 °C	18%
28	$CuBr_2$	-	DCE	60 °C	60%
29	CuTc	-	DCE	60 °C	67%
30	$Rh(esp)_2$ (2 mol%)	-	DCE	60 °C	66%
31	CuI	-	DCE	60 °C	30%
32	CuBr (10 mol%)	-	DCE	60 °C	30%
33	$CuCl_2$ (10 mol%)	-	DCE	60 °C	52%
34	CuCl	-	DCE	60 °C	45%
35	Cu_2O (10 mol%)	-	DCE	60 °C	11%
36	$Pd(TFA)_2$	-	DCE	60 °C	<10%
37	$Zn(OTf)_2$	-	DCE	60 °C	<10%
38[b]	Cu(OAc)/10 mol%	-	DCE	60 °C	86%
39[b]	$Cu(OAc)_2.H_2O$	-	DCE	60 °C	80%
40[b]	**Cu(2-ethylhexanoate)$_2$**	**-**	**DCE**	**60 °C**	**91%**

[a]**Reaction condition**: **1a** (0.1 mmol), **2a** (2.0 equiv.), catalyst (5 mol%), ligand (6 mol%) in 1 mL solvent at indicated temp for 12 h. Yield calculated via ^{1}H NMR using 1,3,5-Trimethoxybenzene as internal standard. [b]Isolated Yield. [c]**2a** (1.2 equiv.). [d]**2a** (1.5 equiv.). [e]**2a** (1.0 equiv.) and **1a** (1.5 equiv.). [f]Under N_2. [g]Under O_2. CuTc = Copper(I)-thiophene-2-carboxylate TFE = 2,2,2-trifluoroethanol, DCE = Dichloroethane, ACN = acetonitrile, dppe = 1,2-Bis(diphenylphosphino)ethane, dBbpy = 4,4'-di-tert-butyl-2,2'-bipyridine, BINOL = 1,1'-Bi-2-naphthol, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

Unsuccessful substrates

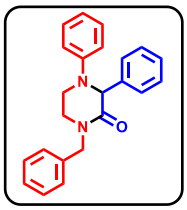


4. General Procedure A for the synthesis of 3aa-3nv, 4aw-4ac', 9 and 10:

In an oven-dried 25 mL Schlenk tube, charged with a magnetic stirrer bar, was added N^1, N^2-disubstituted ethylenediamine **2** (2.0 equiv.), Cu(2-ethylhexanoate)$_2$ (5 mol%) in dichloroethane (2.5-5 mL). To this was added the diazo compound **1** (0.25-0.50 mmol, 1.0 equiv.), and the reaction mixture was stirred at 60 °C for 12 hours. The solvent was evaporated under reduced pressure to afford the crude product. The crude product was purified by silica gel (100–200 mesh) column chromatography (Hexane/EtOAc) to afford corresponding piperazin-2-ones **3aa-3nv, 4aw-4ac', 9** and **10**.

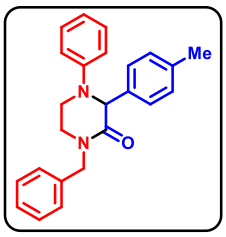
5. Characterization data

1-benzyl-3,4-diphenylpiperazin-2-one (3aa):



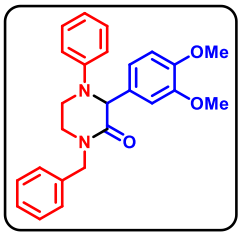
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (8% Ethyl acetate in Hexane) afforded the desired product **3aa** as a white solid (155.8 mg, 0.455 mmol, 91% yield). **m.p.**: 115 - 125 °C. R_f = 0.42 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.37 – 7.32 (m, 2H), 7.31 – 7.28 (m, 1H), 7.27 – 7.24 (m, 3H), 7.22 – 7.17 (m, 2H), 7.16 – 7.11 (m, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 2H), 5.44 (s, 1H), 4.69 (d, *J* = 14.8 Hz, 1H), 4.55 (d, *J* = 14.8 Hz, 1H), 3.67 – 3.61 (m, 1H), 3.51 – 3.43 (m, 2H), 3.33 – 3.25 (m, 1H). **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$):** δ 168.4, 147.9, 138.2, 136.4, 129.4, 128.8, 128.0, 127.9, 127.7, 126.7, 118.4, 113.2, 65.4, 49.8, 44.2, 43.5. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{23}N_2O$ 343.1810; found 343.1799. **IR:** ν(cm^{-1}) 2921, 2855, 1645, 1272.

1-benzyl-4-phenyl-3-(p-tolyl)piperazin-2-one (3ba):



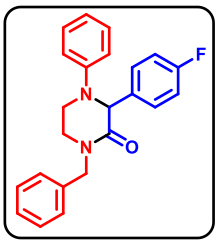
Prepared according to the general procedure **A** using **1b** (102.1 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (8% Ethyl acetate in Hexane) afforded the desired product **3ba** as a sticky solid (156.8 mg, 0.44 mmol, 88% yield). R_f = 0.48 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.22 (m, 3H), 7.21 – 7.16 (m, 2H), 7.15 – 7.11 (m, 4H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 7.9 Hz, 2H), 5.40 (s, 1H), 4.69 (d, *J* = 14.7 Hz, 1H), 4.50 (d, *J* = 14.7 Hz, 1H), 3.66 – 3.56 (m, 1H), 3.49 – 3.40 (m, 2H), 3.33 – 3.22 (m, 1H), 2.32 (s, 3H). **^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$):** δ 168.5, 147.9, 137.5, 136.5, 135.1, 129.4, 129.3, 128.7, 128.0, 127.7, 126.6, 118.3, 113.1, 65.2, 49.8, 44.1, 43.4, 21.1. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{25}N_2O$ 357.1967; found 357.1961. **IR:** ν(cm^{-1}) 3040, 2967, 1668, 1253.

1-benzyl-3-(3,4-dimethoxyphenyl)-4-phenylpiperazin-2-one (3ca):



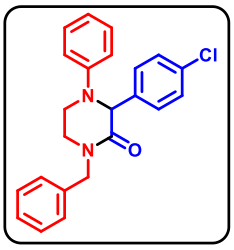
Prepared according to the general procedure **A** using **1c** (125.1 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (21% Ethyl acetate in Hexane) afforded the desired product **3ca** as a solid (195.2 mg, 0.485 mmol, 97% yield). **m.p.**: 123 - 138 °C. R_f = 0.457 (40% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.30 – 7.24 (m, 3H), 7.23 – 7.18 (m, 2H), 7.17 – 7.13 (m, 2H), 7.11 (d, *J* = 1.8 Hz, 1H), 6.97 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.82 – 6.76 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 2H), 5.36 (s, 1H), 4.62 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.65 – 3.59 (m, 1H), 3.53 – 3.42 (m, 2H), 3.35 – 3.26 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.4, 149.2, 148.7, 148.0, 136.5, 130.4, 129.3, 128.8, 128.0, 127.7, 118.8, 118.5, 113.4, 111.0, 109.9, 65.2, 56.0, 55.9, 49.9, 44.1, 43.6. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{27}N_2O_3$ 403.2022; found 403.2012. **IR:** ν(cm^{-1}) 2908, 2838, 1657, 1232.

1-benzyl-3-(4-fluorophenyl)-4-phenylpiperazin-2-one (3da):



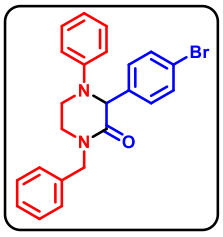
Prepared according to the general procedure **A** using **1d** (104.1 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (9% Ethyl acetate in Hexane) afforded the desired product **3da** as a sticky solid (173.0 mg, 0.48 mmol, 96% yield). R_f = 0.25 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.54 – 7.47 (m, 2H), 7.32 – 7.27 (m, 3H), 7.25 – 7.19 (m, 2H), 7.18 – 7.13 (m, 2H), 7.06 – 6.99 (m, 2H), 6.84 – 6.78 (m, 1H), 6.70 – 6.65 (m, 2H), 5.38 (s, 1H), 4.67 (d, *J* = 14.7 Hz, 1H), 4.58 (d, *J* = 14.7 Hz, 1H), 3.68 – 3.60 (m, 1H), 3.52 – 3.42 (m, 2H), 3.37 – 3.30 (m, 1H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -114.9. **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 168.2, 162.6 (d, *J* = 246.3 Hz), 147.8, 136.3, 133.9 (d, *J* = 2.8 Hz), 129.4, 128.8, 128.5 (d, *J* = 8.0 Hz), 128.1, 127.8, 118.8, 115.6 (d, *J* = 21.4 Hz), 113.5, 65.0, 50.0, 44.2, 43.7. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}FN_2O$ 361.1716; found 361.1707. **IR:** ν(cm^{-1}) 3035, 2925, 2861, 1647, 1270.

1-benzyl-3-(4-chlorophenyl)-4-phenylpiperazin-2-one (3ea):



Prepared according to the general procedure **A** using **1e** (56.1 mg, 0.25 mmol) and **2a** (113.1 mg, 0.5 mmol). Flash column chromatography (8% Ethyl acetate in Hexane) afforded the desired product **3ea** as a sticky solid (83.8 mg, 0.22 mmol, 89% yield). R_f = 0.25 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.27 (m, 5H), 7.25 – 7.19 (m, 2H), 7.18 – 7.13 (m, 2H), 6.84 – 6.79 (m, 1H), 6.67 (d, *J* = 8.0 Hz, 2H), 5.37 (s, 1H), 4.69 (d, *J* = 14.7 Hz, 1H), 4.56 (d, *J* = 14.7 Hz, 1H), 3.68 – 3.60 (m, 1H), 3.52 – 3.41 (m, 2H), 3.38 – 3.30 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 167.9, 147.7, 136.8, 136.2, 133.7, 129.4, 128.9, 128.8, 128.2, 128.0, 127.8, 118.9, 113.4, 65.0, 49.9, 44.2, 43.6. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}ClN_2O$ 377.1421; found 377.1413. **IR:** ν(cm^{-1}) 3065, 3035, 2972, 1669, 1254.

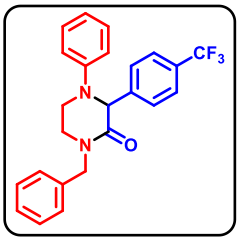
1-benzyl-3-(4-bromophenyl)-4-phenylpiperazin-2-one (3fa):



Prepared according to the general procedure **A** using **1f** (67.2 mg, 0.25 mmol) and **2a** (113.1 mg, 0.5 mmol). Flash column chromatography (8% Ethyl acetate in Hexane) afforded the desired product **3fa** as a sticky solid (88.5 mg, 0.21 mmol, 84% yield). R_f = 0.24 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.49 – 7.45 (m, 2H), 7.44 – 7.40 (m, 2H), 7.32 – 7.27 (m, 3H), 7.25 – 7.18 (m, 2H), 7.17 – 7.13 (m, 2H), 6.81 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 2H), 5.34 (s, 1H), 4.69 (d, *J* = 14.7 Hz, 1H), 4.55 (d, *J* = 14.7 Hz, 1H), 3.68 – 3.59 (m, 1H), 3.52 – 3.40 (m, 2H), 3.38 – 3.29 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):**

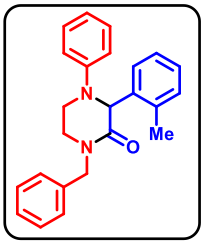
δ 167.8, 147.7, 137.4, 136.2, 131.9, 129.4, 128.8, 128.6, 128.0, 127.8, 121.9, 118.9, 113.4, 65.1, 50.0, 44.3, 43.6. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}BrN_2O$ 421.0916; found 421.0910. **IR:** ν(cm^{-1}) 3035, 2928, 2859, 1666, 1278, 1253.

1-benzyl-4-phenyl-3-(4-(trifluoromethyl)phenyl)piperazin-2-one (3ga):



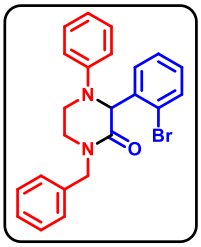
Prepared according to the general procedure **A** using **1g** (64.5 mg, 0.25 mmol) and **2a** (113.1 mg, 0.5 mmol). Flash column chromatography (9% Ethyl acetate in Hexane) afforded the desired product **3ga** as a sticky solid (68.7 mg, 0.167 mmol, 67% yield). R_f = 0.28 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.25 (m, 3H), 7.24 – 7.18 (m, 2H), 7.16 – 7.11 (m, 2H), 6.81 (t, *J* = 7.3 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 2H), 5.44 (s, 1H), 4.69 (d, *J* = 14.7 Hz, 1H), 4.54 (d, *J* = 14.7 Hz, 1H), 3.69 – 3.61 (m, 1H), 3.53 – 3.40 (m, 2H), 3.39 – 3.30 (m, 1H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -62.4. **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 167.6, 147.6, 142.5, 136.2, 130.2 (q, *J* = 32.2 Hz), 129.5, 128.8, 128.0, 127.9, 127.3, 126.9, 125.7 (d, *J* = 3.0 Hz), 124.2 (d, *J* = 271.9 Hz), 119.1, 113.5, 65.4, 50.0, 44.4, 43.7. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{22}F_3N_2O$ 411.1684; found 411.1680. **IR:** ν(cm^{-1}) 3066, 3034, 2938, 2878, 1670, 1252.

1-benzyl-4-phenyl-3-(o-tolyl)piperazin-2-one (3ia):



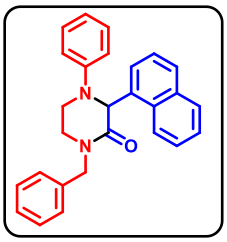
Prepared according to the general procedure **A** using **1i** (102.1 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (9% Ethyl acetate in Hexane) afforded the desired product **3ia** as a sticky solid (103.3 mg, 0.29 mmol, 58% yield). R_f = 0.257 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.25 (m, 4H), 7.24 – 7.15 (m, 6H), 7.14 – 7.08 (m, 1H), 6.84 (td, *J* = 7.3, 0.8 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.40 (s, 1H), 4.66 (d, *J* = 14.6 Hz, 1H), 4.61 (d, *J* = 14.6 Hz, 1H), 3.69 – 3.61 (m, 1H), 3.56 – 3.48 (m, 1H), 3.46 – 3.38 (m, 1H), 3.37 – 3.30 (m, 1H), 2.51 (s, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.6, 148.7, 138.1, 137.8, 136.6, 131.3, 129.3, 128.8, 128.3, 127.8, 127.7, 127.4, 125.9, 120.2, 116.3, 63.4, 50.1, 44.9, 44.1, 20.0. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{25}N_2O$ 357.1967; found 357.1966. **IR:** ν(cm^{-1}) 3053, 2969, 2935, 1662, 1292.

1-benzyl-3-(2-bromophenyl)-4-phenylpiperazin-2-one (3ja):



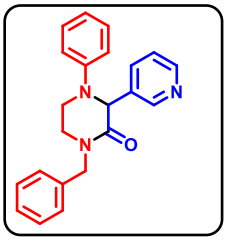
Prepared according to the general procedure **A** using **1j** (134.5 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (11% Ethyl acetate in Hexane) afforded the desired product **3ja** as a solid (176.9 mg, 0.42 mmol, 84% yield). **m.p.**: 95 - 103 °C. R_f = 0.15 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.60 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.37 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.36 – 7.30 (m, 3H), 7.29 – 7.25 (m, 2H + $CDCl_3$), 7.24 – 7.18 (m, 3H), 7.14 – 7.08 (m, 1H), 6.93 – 6.85 (m, 3H), 5.61 (m, 1H), 4.73 (d, *J* = 14.5 Hz, 1H), 4.59 (d, *J* = 14.5 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.59 – 3.51 (m, 1H), 3.50 – 3.43 (m, 1H), 3.41 – 3.33 (m, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 167.5, 148.7, 139.2, 136.5, 133.6, 129.4, 129.3, 129.2, 128.8, 128.4, 127.8, 127.5, 125.7, 121.2, 118.1, 65.2, 50.3, 46.4, 44.9. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}BrN_2O$ 421.0916; found 421.0906. **IR:** ν(cm^{-1}) 3027, 2907, 2824, 1641, 1261.

1-benzyl-3-(naphthalen-1-yl)-4-phenylpiperazin-2-one (3ka):



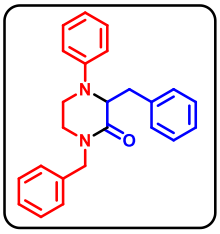
Prepared according to the general procedure **A** using **1k** (60.0 mg, 0.25 mmol) and **2a** (113.1 mg, 0.5 mmol). Flash column chromatography (10% Ethyl acetate in Hexane) afforded the desired product **3ka** as a white solid (63.7 mg, 0.162 mmol, 65% yield). **m.p.**: 142 - 146 °C. R_f = 0.5 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.54 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.50 (m, 3H), 7.43 – 7.36 (m, 1H), 7.34 – 7.27 (m, 3H), 7.23 – 7.15 (m, 4H), 6.83 (t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 1H), 4.71 (d, *J* = 14.6 Hz, 1H), 4.56 (d, *J* = 14.6 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.69 – 3.61 (m, 1H), 3.56 – 3.48 (m, 1H), 3.44 – 3.36 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.1, 148.1, 136.5, 135.3, 134.4, 131.7, 129.4, 128.9, 128.8, 128.7, 128.3, 127.8, 126.5, 126.0, 125.2, 125.1, 125.0, 119.8, 115.5, 63.3, 50.2, 45.0, 43.8. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{27}H_{25}N_2O$ 393.1967; found 393.1963. **IR:** ν(cm^{-1}) 3062, 2920, 2852, 1660, 1295.

1-benzyl-4-phenyl-3-(pyridin-3-yl)piperazin-2-one (3la):



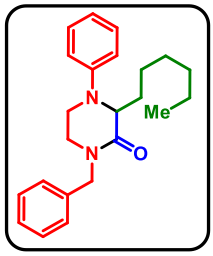
Prepared according to the general procedure **A** using **1l** (95.5 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (30% Ethyl acetate in Hexane) afforded the desired product **3la** as a red sticky (139 mg, 0.405 mmol, 81% yield). R_f = 0.2 (60% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.77 (s, 1H), 8.57 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.27 (m, 5H), 7.25 – 7.18 (m, 3H), 6.85 (t, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 2H), 5.43 (s, 1H), 4.69 (d, *J* = 14.6 Hz, 1H), 4.61 (d, *J* = 14.6 Hz, 1H), 3.69 – 3.60 (m, 1H), 3.55 – 3.49 (m, 1H), 3.48 – 3.43 (m, 1H), 3.42 – 3.36 (m, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 167.4, 149.1, 148.6, 147.6, 136.1, 135.1, 134.0, 129.5, 128.8, 128.1, 127.9, 123.5, 119.5, 114.2, 63.8, 50.1, 44.2, 43.9. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{22}N_3O$ 344.1763; found 344.1761. **IR:** ν(cm^{-1}) 3048, 2977, 2880, 2825, 1669, 1293, 1256.

1,3-dibenzyl-4-phenylpiperazin-2-one (3ma):



Prepared according to the general procedure **A** using **1m** (102 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (9% Ethyl acetate in Hexane) afforded the desired product **3ma** as a red sticky (58.8 mg, 0.165 mmol, 33% yield). R_f = 0.35 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 – 7.21 (m, 5H), 7.20 – 7.12 (m, 7H), 6.80 (t, *J* = 7.2 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 2H), 4.74 (d, *J* = 14.6 Hz, 1H), 4.66 (t, *J* = 4.8 Hz, 1H), 4.40 (d, *J* = 14.6 Hz, 1H), 3.38 – 3.27 (m, 3H), 3.25 – 3.17 (m, 1H), 3.14 – 3.06 (m, 1H), 2.76 – 2.69 (m, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 168.9, 147.9, 138.0, 136.4, 130.3, 129.5, 128.7, 128.2, 127.6, 126.7, 118.8, 114.5, 62.5, 50.1, 44.4, 42.4, 37.1. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{25}N_2O$ 357.1967; found 357.1966. **IR:** ν(cm^{-1}) 3037, 2974, 1654, 1257.

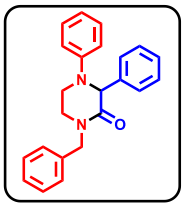
1-benzyl-3-hexyl-4-phenylpiperazin-2-one (3na):



Prepared according to the general procedure **A** using **1n** (99 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (8% Ethyl acetate in Hexane) afforded the desired product **3na** as a yellow oil (68.3 mg, 0.195 mmol, 39% yield). R_f = 0.6 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.28 (m, 3H), 7.27 – 7.21 (m, 4H), 6.86 – 6.79 (m, 3H), 4.81 (d, *J* = 14.6 Hz, 1H), 4.41 (d, *J* = 14.6 Hz, 1H), 4.28 (t, *J* = 6.4 Hz, 1H), 3.57 – 3.48 (m, 2H), 3.44 – 3.36 (m, 1H), 3.24 – 3.17 (m, 1H), 2.00 – 1.83 (m, 2H), 1.53 – 1.42 (m, 2H), 1.34 – 1.24 (m, 6H), 0.89 – 0.81 (m, 3H). **^{13}C{^{1}H} NMR (125 MHz,**

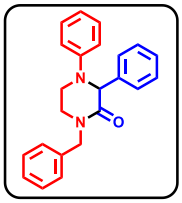
$CDCl_3$): δ 170.3, 148.6, 136.7, 129.4, 128.7, 128.1, 127.6, 119.1, 115.2, 61.4, 49.9, 44.4, 42.2, 32.0, 31.7, 29.3, 26.4, 22.6, 14.1. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{31}N_2O$ 351.2436; found 351.2441. **IR:** ν(cm^{-1}) 3038, 2935, 2871, 1655, 1257.

1-benzyl-3,4-diphenylpiperazin-2-one (3aa):



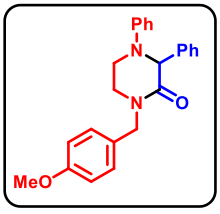
Prepared according to the general procedure **A** using **1o** (88.0 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (8% Ethyl acetate in Hexane) afforded the desired product **3aa** as a white solid (162.6 mg, 0.475 mmol, 95% yield). **m.p.**: 115 - 125 °C.

1-benzyl-3,4-diphenylpiperazin-2-one (3aa):



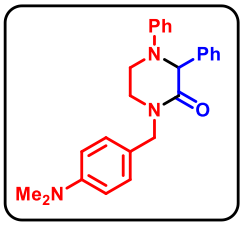
Prepared according to the general procedure **A** using **1p** (126.1 mg, 0.5 mmol) and **2a** (226.3 mg, 1.0 mmol). Flash column chromatography (8% Ethyl acetate in Hexane) afforded the desired product **3aa** as a white solid (166.0 mg, 0.485 mmol, 97% yield). **m.p.**: 115 - 125 °C.

1-(4-methoxybenzyl)-3,4-diphenylpiperazin-2-one (3ab):



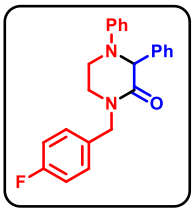
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2b** (256.3 mg, 1.0 mmol). Flash column chromatography (10% Ethyl acetate in Hexane) afforded the desired product **3ab** as a white solid (182.5 mg, 0.49 mmol, 98% yield). **m.p.**: 150 - 160 °C. R_f = 0.38 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.52 (d, *J* = 7.1 Hz, 2H), 7.36 – 7.32 (m, 2H), 7.31 – 7.27 (m, 1H), 7.23 – 7.19 (m, 2H), 7.11 – 7.07 (m, 2H), 6.82 – 6.77 (m, 3H), 6.68 (d, *J* = 7.9 Hz, 2H), 5.43 (s, 1H), 4.65 (d, *J* = 14.5 Hz, 1H), 4.47 (d, *J* = 14.5 Hz, 1H), 3.78 (s, 3H), 3.67 – 3.60 (m, 1H), 3.49 – 3.41 (m, 2H), 3.34 – 3.27 (m, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 168.3, 159.2, 147.9, 138.2, 129.5, 129.4, 128.8, 128.5, 127.8, 126.7, 118.4, 114.2, 113.2, 65.5, 55.3, 49.2, 44.3, 43.2. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{25}N_2O_2$ 373.1911; found 373.1915. **IR:** ν(cm^{-1}) 3032, 2931, 2837, 1653, 1314, 1221.

1-(4-(dimethylamino)benzyl)-3,4-diphenylpiperazin-2-one (3ac):



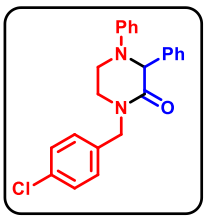
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2c** (269.4 mg, 1.0 mmol). Flash column chromatography (15% Ethyl acetate in Hexane) afforded the desired product **3ac** as a solid (175.4 mg, 0.455 mmol, 91% yield). **m.p.**: 135 - 140 °C. R_f = 0.38 (25% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.54 (d, *J* = 7.4 Hz, 2H), 7.36 – 7.28 (m, 3H), 7.23 – 7.19 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 2H), 6.78 (t, *J* = 7.1 Hz, 1H), 6.69 – 6.63 (m, 4H), 5.43 (s, 1H), 4.66 (d, *J* = 14.4 Hz, 1H), 4.40 (d, *J* = 14.4 Hz, 1H), 3.64 – 3.59 (m, 1H), 3.47 – 3.39 (m, 2H), 3.35 – 3.29 (m, 1H), 2.93 (s, 6H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 168.1, 150.2, 147.9, 138.3, 129.3, 128.7, 127.7, 126.7, 123.9, 118.2, 113.1, 112.6, 65.5, 49.2, 44.3, 42.8, 40.6. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{28}N_3O$ 386.2232; found 386.2227. **IR:** ν(cm^{-1}) 2905, 2863, 1655, 1282, 1214.

1-(4-fluorobenzyl)-3,4-diphenylpiperazin-2-one (3ad):



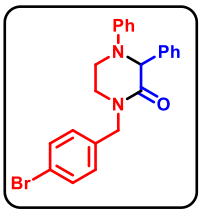
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2d** (244.3 mg, 1.0 mmol). Flash column chromatography (12% Ethyl acetate in Hexane) afforded the desired product **3ad** as a white solid (167.6 mg, 0.465 mmol, 93% yield). **m.p.**: 138 - 142 °C. R_f = 0.34 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.52 (d, *J* = 7.3 Hz, 2H), 7.37 – 7.29 (m, 3H), 7.25 – 7.20 (m, 2H), 7.14 – 7.11 (m, 2H), 6.96 (t, *J* = 8.6 Hz, 2H), 6.80 (t, *J* = 7.2 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 2H), 5.44 (s, 1H), 4.64 (d, *J* = 14.7 Hz, 1H), 4.55 (d, *J* = 14.7 Hz, 1H), 3.69 – 3.63 (m, 1H), 3.53 – 3.44 (m, 2H), 3.35 – 3.28 (m, 1H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -114.5. **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 168.4, 162.4 (d, *J* = 246.2 Hz), 147.9, 138.1, 132.3 (d, *J* = 3.1 Hz), 129.7 (d, *J* = 8.1 Hz), 129.4, 128.8, 127.9, 126.7, 118.6, 115.7 (d, *J* = 21.3 Hz), 113.3, 65.5, 49.2, 44.2, 43.6. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}FN_2O$ 361.1711; found 361.1715. **IR:** ν(cm^{-1}) 3048, 2899, 1647, 1217.

1-(4-chlorobenzyl)-3,4-diphenylpiperazin-2-one (3ae):



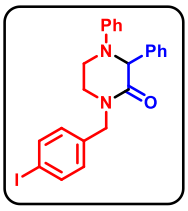
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2e** (260.7 mg, 1.0 mmol). Flash column chromatography (10% Ethyl acetate in Hexane) afforded the desired product **3ae** as a white solid (165.8 mg, 0.44 mmol, 88% yield). **m.p.**: 166 - 170 °C. R_f = 0.19 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 (d, *J* = 6.9 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.24 – 7.19 (m, 4H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.79 (t, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 2H), 5.42 (s, 1H), 4.61 (d, *J* = 14.8 Hz, 1H), 4.55 (d, *J* = 14.8 Hz, 1H), 3.68 - 3.63 (m, 1H), 3.52 – 3.44 (m, 2H), 3.32 – 3.25 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.4, 147.8, 138.0, 135.0, 133.6, 129.5, 129.4, 129.0, 128.8, 128.0, 126.7, 118.6, 113.3, 65.5, 49.3, 44.2, 43.7. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}ClN_2O$ 377.1415; found 377.1419. **IR:** ν(cm^{-1}) 3026, 2925, 2850, 1651, 1265, 1215.

1-(4-bromobenzyl)-3,4-diphenylpiperazin-2-one (3af):



Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2f** (305.2 mg, 1.0 mmol). Flash column chromatography (10% Ethyl acetate in Hexane) afforded the desired product **3af** as a brown solid (202.2 mg, 0.48 mmol, 96% yield). **m.p.**: 187 - 190 °C. R_f = 0.36 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.52 (d, *J* = 7.1 Hz, 2H), 7.41 – 7.35 (m, 3H), 7.34 – 7.29 (m, 2H), 7.25 – 7.19 (m, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 2H), 5.43 (s, 1H), 4.60 (d, *J* = 14.9 Hz, 1H), 4.54 (d, *J* = 14.9 Hz, 1H), 3.69 – 3.64 (m, 1H), 3.53 – 3.45 (, m, 2H), 3.33 – 3.26 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.4, 147.8, 138.0, 135.5, 131.9, 129.7, 129.4, 128.8, 128.0, 126.7, 121.7, 118.6, 113.3, 65.4, 49.4, 44.2, 43.7. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}BrN_2O$ 421.0921; found 421.0909. **IR:** ν(cm^{-1}) 3022, 2839, 1650, 1276, 1216.

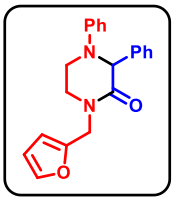
1-(4-iodobenzyl)-3,4-diphenylpiperazin-2-one (3ag):



Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2g** (352.2 mg, 1.0 mmol). Flash column chromatography (12% Ethyl acetate in Hexane) afforded the desired product **3ag** as a solid (210.7 mg, 0.45 mmol, 90% yield). **m.p.**: 188 - 193 °C. R_f = 0.2 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.61 – 7.58 (m, 2H), 7.53 – 7.51 (m, 2H), 7.37 – 7.31 (m, 3H), 7.24 – 7.20 (m, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.81 (t, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 2H), 5.44 (s, 1H), 4.59 (d, *J* = 14.9 Hz, 1H), 4.54 (d, *J* = 14.9

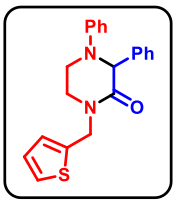
Hz, 1H), 3.69 – 3.64 (m, 1H), 3.54 – 3.45 (m, 2H), 3.33 – 3.26 (m, 1H). **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$):** δ 168.4, 147.8, 138.0, 137.9, 136.2, 129.9, 129.4, 128.8, 128.0, 126.7, 118.6, 113.2, 93.2, 65.4, 49.5, 44.2, 43.7. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}IN_2O$ 469.0771; found 469.0763. **IR:** ν(cm^{-1}) 3026, 2838, 1653, 1283, 1218.

1-(furan-2-ylmethyl)-3,4-diphenylpiperazin-2-one (3ah):



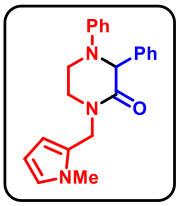
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2h** (216.2 mg, 1.0 mmol). Flash column chromatography (8% Ethyl acetate in Hexane) afforded the desired product **3ah** as a solid (141.2 mg, 0.425 mmol, 85% yield). **m.p.**: 88 - 95 °C. R_f = 0.34 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.51 – 7.49 (m, 2H), 7.36 – 7.27 (m, 4H), 7.24 – 7.19 (m, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 2H), 6.31 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.21 (d, *J* = 3.1 Hz, 1H), 5.41 (s, 1H), 4.73 (d, *J* = 15.3 Hz, 1H), 4.51 (d, *J* = 15.3 Hz, 1H), 3.71 – 3.63 (m, 1H), 3.56 – 3.43 (m, 3H). **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$):** δ 168.1, 150.0, 147.9, 142.6, 138.0, 129.4, 128.7, 127.8, 126.8, 118.5, 113.4, 110.5, 108.7, 65.3, 44.0, 43.8, 42.7. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{21}N_2O_2$ 333.1598; found 333.1601. **IR:** ν(cm^{-1}) 3034, 2935, 2863, 1651, 1286, 1233.

3,4-diphenyl-1-(thiophen-2-ylmethyl)piperazin-2-one (3ai):



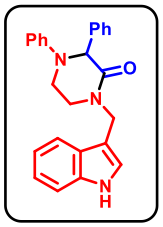
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2i** (232.3 mg, 1.0 mmol). Flash column chromatography (8% Ethyl acetate in Hexane) afforded the desired product **3ai** as a solid (158.5 mg, 0.455 mmol, 91% yield). **m.p.**: 113 - 120 °C. R_f = 0.4 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.52 – 7.50 (m, 2H), 7.36 – 7.27 (m, 3H), 7.24 – 7.19 (m, 3H), 6.92 (d, *J* = 3.6 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 2H), 5.41 (s, 1H), 4.84 (d, *J* = 15.1 Hz, 1H), 4.71 (d, *J* = 15.1 Hz, 1H), 3.68 – 3.65 (m, 1H), 3.55 – 3.48 (m, 2H), 3.47 – 3.42 (m, 1H). **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$):** δ 168.0, 147.9, 138.9, 138.0, 129.4, 128.7, 127.9, 127.0, 126.8, 125.8, 118.6, 113.5, 65.4, 44.7, 44.2, 43.5. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{21}H_{21}N_2OS$ 349.1375; found 349.1375. **IR:** ν(cm^{-1}) 2921, 2856, 1647, 1280, 1225.

1-((1-methyl-1H-pyrrol-2-yl)methyl)-3,4-diphenylpiperazin-2-one (3aj):



Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2j** (229.3 mg, 1.0 mmol). Flash column chromatography (14% Ethyl acetate in Hexane) afforded the desired product **3aj** as a solid (151.9 mg, 0.44 mmol, 88% yield). **m.p.**: 105 - 109 °C. R_f = 0.48 (25% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.53 (d, *J* = 6.9 Hz, 2H), 7.37 – 7.27 (m, 3H), 7.25 – 7.18 (m, 2H), 6.79 (t, *J* = 7.3 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 2H), 6.57 (t, *J* = 2.2 Hz, 1H), 6.10 – 6.07 (m, 1H), 6.05 – 6.02 (m, 1H), 5.40 (s, 1H), 4.67 (d, *J* = 15.1 Hz, 1H), 4.58 (d, *J* = 15.1 Hz, 1H), 3.72 – 3.65 (m, 1H), 3.50 – 3.33 (m, 3H), 3.31 (s, 3H). **$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$):** δ 167.7, 147.8, 138.2, 129.4, 128.8, 127.9, 126.6, 126.2, 123.7, 118.3, 113.0, 111.0, 106.9, 65.6, 44.1, 41.9, 40.9, 33.7. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{24}N_3O$ 346.1919; found 346.1918. **IR:** ν(cm^{-1}) 2925, 2854, 1655, 1294, 1220.

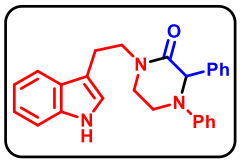
1-((1H-indol-3-yl)methyl)-3,4-diphenylpiperazin-2-one (3ak):



Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2k** (307.3 mg, 1.0 mmol). Flash column chromatography (25% Ethyl acetate in Hexane) afforded the desired product **3ak** as a sticky solid (106.8 mg, 0.28 mmol, 56% yield). R_f = 0.37 (40% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.25 (br s, 1H), 7.53 (d, *J* = 6.8 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.28 (m, 4H), 7.23 – 7.14 (m, 3H), 7.08 (d, *J* = 2.0 Hz, 1H), 7.05 – 6.98

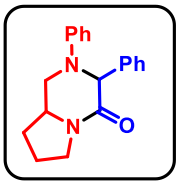
(m, 1H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 2H), 5.43 (s, 1H), 4.85 (d, *J* = 14.7 Hz, 1H), 4.77 (d, *J* = 14.7 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.46 – 3.31 (m, 3H). **$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$):** δ 168.1, 147.9, 138.3, 136.5, 129.3, 128.7, 127.8, 126.8, 126.7, 124.2, 122.4, 120.0, 119.1, 118.4, 113.3, 111.3, 110.6, 65.7, 44.1, 42.5, 41.2. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{24}N_3O$ 382.1914; found 382.1913. **IR:** ν(cm^{-1}) 3344, 3055, 2971, 1664, 1254.

1-(2-(1H-indol-3-yl)ethyl)-3,4-diphenylpiperazin-2-one (3al):



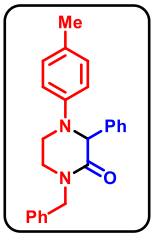
Prepared according to the general procedure **A** using **1a** (56 mg, 0.29 mmol) and **2l** (165 mg, 0.58 mmol). Flash column chromatography (22% Ethyl acetate in Hexane) afforded the desired product **3al** as a sticky solid (89.4 mg, 0.226 mmol, 78% yield). R_f = 0.51 (40% Ethyl acetate in Hexane). **^1H NMR (400 MHz, $CDCl_3$):** δ 7.82 (br s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 6.8 Hz, 2H), 7.37 – 7.29 (m, 4H), 7.23 – 7.14 (m, 3H), 7.11 – 7.05 (m, 1H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.66 – 6.59 (m, 3H), 5.34 (s, 1H), 3.94 – 3.85 (m, 1H), 3.65 – 3.56 (m, 1H), 3.55 – 3.46 (m, 1H), 3.41 – 3.27 (m, 2H), 3.14 – 3.06 (m, 1H), 3.00 (t, *J* = 6.8 Hz, 2H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$):** δ 168.2, 147.8, 138.4, 136.3, 129.3, 128.7, 127.7, 127.2, 126.8, 122.5, 122.0, 119.4, 118.5, 118.2, 113.0, 112.4, 111.3, 65.4, 48.2, 45.4, 44.0, 23.5. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{26}H_{26}N_3O$ 396.2070; found 396.2087. **IR:** ν(cm^{-1}) 3353, 3064, 3027, 2965, 2937, 1666, 1254.

2,3-diphenylhexahydropyrrolo[1,2-a]pyrazin-4(1H)-one (3am):



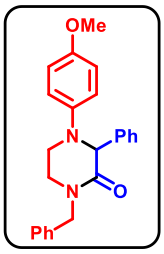
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2m** (176.2 mg, 1.0 mmol). Flash column chromatography (22% Ethyl acetate in Hexane) afforded the desired product **3am** as a gray powder (71.6 mg, 0.245 mmol, 49% yield). **m.p.**: 160 - 170 °C. R_f = 0.28 (40% Ethyl acetate in Hexane). **^1H NMR (400 MHz, $CDCl_3$):** δ 7.55 (d, *J* = 7.6 Hz, 2H), 7.37 – 7.27 (m, 3H), 7.23 – 7.16 (m, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 2H), 5.22 (s, 1H), 3.97 (dd, *J* = 10.1, 3.5 Hz, 1H), 3.93 – 3.84 (m, 1H), 3.64 – 3.56 (m, 1H), 3.52 – 3.44 (m, 1H), 3.12 (t, *J* = 10.5 Hz, 1H), 2.29 – 2.21 (m, 1H), 2.05 – 1.95 (m, 1H), 1.88 – 1.70 (m, 2H). **$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$):** δ 167.2, 147.9, 138.7, 129.3, 128.8, 127.8, 126.4, 118.1, 112.8, 65.7, 54.1, 51.1, 45.3, 30.8, 23.0. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{21}N_2O$ 293.1654; found 293.1653. **IR:** ν(cm^{-1}) 2960, 2916, 2849, 1657, 1249.

1-benzyl-3-phenyl-4-(p-tolyl)piperazin-2-one (3an):



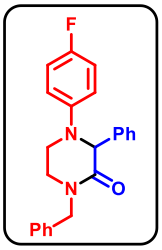
Prepared according to the general procedure **A** using **1a** (39 mg, 0.21 mmol) and **2n** (100 mg, 0.42 mmol). Flash column chromatography (9% Ethyl acetate in Hexane) afforded the desired product **3an** as a sticky solid (74.8 mg, 0.149 mmol, 71% yield). R_f = 0.42 (20% Ethyl acetate in Hexane). **^1H NMR (400 MHz, $CDCl_3$):** δ 7.51 (d, *J* = 7.3 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.28 – 7.24 (m, 3H + $CDCl_3$), 7.17 – 7.13 (m, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.60 (d, *J* = 8.6 Hz, 2H), 5.37 (s, 1H), 4.67 (d, *J* = 14.7 Hz, 1H), 4.57 (d, *J* = 14.7 Hz, 1H), 3.64 – 3.58 (m, 1H), 3.50 – 3.40 (m, 2H), 3.33 – 3.27 (m, 1H), 2.23 (s, 3H). **$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$):** δ 168.5, 145.8, 138.4, 136.5, 129.9, 128.8, 128.7, 128.1, 127.9, 127.8, 127.7, 126.9, 113.7, 65.7, 49.9, 44.4, 43.7, 20.3. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{25}N_2O$ 357.1961; found 357.1965. **IR:** ν(cm^{-1}) 3058, 2927, 2877, 1668, 1299.

1-benzyl-4-(4-methoxyphenyl)-3-phenylpiperazin-2-one (3ao):



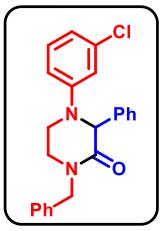
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2o** (256.3 mg, 1.0 mmol). Flash column chromatography (14% Ethyl acetate in Hexane) afforded the desired product **3ao** as a solid (137.7 mg, 0.37 mmol, 74% yield). **m.p.**: 95 - 101 °C. R_f = 0.316 (25% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.49 (d, *J* = 7.1 Hz, 2H), 7.36 – 7.27 (m, 6H), 7.22 – 7.17 (m, 2H), 6.81 – 6.76 (m, 2H), 6.72 – 6.67 (m, 2H), 5.26 (s, 1H), 4.67 (d, *J* = 14.7 Hz, 1H), 4.61 (d, *J* = 14.7 Hz, 1H), 3.73 (s, 3H), 3.60 – 3.54 (m, 1H), 3.51 – 3.44 (m, 1H), 3.42 – 3.35 (m, 1H), 3.34 – 3.28 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.5, 153.3, 142.6, 138.6, 136.6, 128.8, 128.6, 128.1, 127.8, 127.7, 127.3, 116.4, 114.8, 66.6, 55.7, 50.0, 45.1, 44.2. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{25}N_2O_2$ 373.1916; found 373.1914. **IR:** ν(cm^{-1}) 3047, 2982, 2828, 1665, 1291, 1246.

1-benzyl-4-(4-fluorophenyl)-3-phenylpiperazin-2-one (3ap):



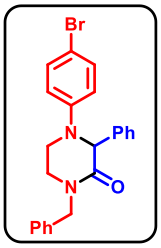
Prepared according to the general procedure **A** using **1a** (66.5 mg, 0.35 mmol) and **2p** (171 mg, 0.7 mmol). Flash column chromatography (10% Ethyl acetate in Hexane) afforded the desired product **3ap** as a solid (99.6 mg, 0.276 mmol, 79% yield). **m.p.**: 104 - 108 °C. R_f = 0.18 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.30 – 7.23 (m, 3H + $CDCl_3$), 7.18 – 7.13 (m, 2H), 6.93 – 6.85 (m, 2H), 6.64 – 6.58 (m, 2H), 5.30 (s, 1H), 4.67 (d, *J* = 14.7 Hz, 1H), 4.56 (d, *J* = 14.7 Hz, 1H), 3.62 – 3.55 (m, 1H), 3.52 – 3.36 (m, 2H), 3.33 – 3.26 (m, 2H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -126.1. **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 168.3, 156.6 (d, *J* = 237.6 Hz), 144.7, 144.6, 138.1, 136.4, 128.8 (d, *J* = 2.5 Hz), 128.1, 127.9 (d, *J* = 19.3 Hz), 127.0, 115.9, 115.7, 115.1 (d, *J* = 7.4 Hz), 66.2, 49.9, 44.9, 43.7. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}FN_2O$ 361.1716; found 361.1724. **IR:** ν(cm^{-1}) 3058, 2905, 1664, 1284, 1213.

1-benzyl-4-(3-chlorophenyl)-3-phenylpiperazin-2-one (3aq):



Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2q** (260.7 mg, 1.0 mmol). Flash column chromatography (10% Ethyl acetate in Hexane) afforded the desired product **3aq** as a solid (173.3 mg, 0.46 mmol, 92% yield). **m.p.**: 116 - 120 °C. R_f = 0.457 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.38 – 7.30 (m, 3H), 7.28 – 7.24 (m, 3H), 7.15 – 7.10 (m, 2H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.77 – 6.72 (m, 1H), 6.66 (t, *J* = 2.1 Hz, 1H), 6.52 – 6.48 (m, 1H), 5.42 (s, 1H), 4.71 (d, *J* = 14.7 Hz, 1H), 4.53 (d, *J* = 14.7 Hz, 1H), 3.67 – 3.57 (m, 1H), 3.52 – 3.42 (m, 2H), 3.34 – 3.24 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.0, 148.8, 137.4, 136.2, 135.2, 130.3, 128.9, 128.8, 128.1, 128.0, 127.8, 126.4, 118.1, 112.7, 111.1, 65.1, 49.8, 44.2, 43.1. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}ClN_2O$ 377.1421; found 377.1422. **IR:** ν(cm^{-1}) 3062, 3029, 2928, 2855, 1649, 1272, 1240.

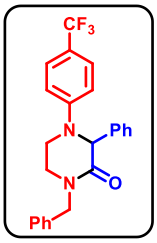
1-benzyl-4-(4-bromophenyl)-3-phenylpiperazin-2-one (3ar):



Prepared according to the general procedure **A** using **1a** (50.1 mg, 0.26 mmol) and **2r** (161 mg, 0.52 mmol). Flash column chromatography (10% Ethyl acetate in Hexane) afforded the desired product **3ar** as a solid (89.8 mg, 0.213 mmol, 82% yield). **m.p.**: 131 - 135 °C. R_f = 0.22 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.48 (d, *J* = 7.3 Hz, 2H), 7.37 – 7.29 (m, 3H), 7.28 – 7.23 (m, 5H), 7.15 – 7.12 (m, 2H), 6.52 (d, *J* = 8.9 Hz, 2H), 5.37 (s, 1H), 4.69 (d, *J* = 14.7 Hz, 1H), 4.53 (d, *J* = 14.7 Hz, 1H), 3.65 – 3.57 (m, 1H), 3.52 – 3.39 (m, 2H), 3.33 – 3.24 (m, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 168.0, 146.8, 137.6, 136.3, 132.1, 128.9,

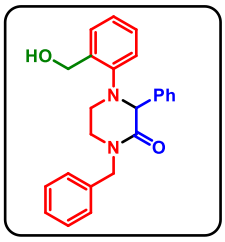
128.8, 128.1, 128.0, 127.8, 126.6, 114.7, 110.5, 65.4, 49.9, 44.4, 43.3. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{22}BrN_2O$ 421.0910; found 421.0930. **IR:** ν(cm^{-1}) 3025, 2917, 2857, 1649, 1298, 1218.

1-benzyl-3-phenyl-4-(4-(trifluoromethyl)phenyl)piperazin-2-one (3as):



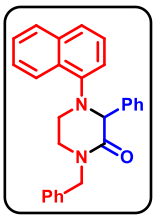
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2s** (294.3 mg, 1.0 mmol). Flash column chromatography (8% Ethyl acetate in Hexane) afforded the desired product **3as** as a sticky solid (166.2 mg, 0.405 mmol, 81% yield). R_f = 0.26 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.39 – 7.32 (m, 3H), 7.28 – 7.24 (m, 3H), 7.15 – 7.10 (m, 2H), 6.67 (d, *J* = 8.7 Hz, 2H), 5.50 (s, 1H), 4.73 (d, *J* = 14.8 Hz, 1H), 4.52 (d, *J* = 14.8 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.58 – 3.46 (m, 2H), 3.36 – 3.27 (m, 1H). **^{19}F NMR (376 MHz, $CDCl_3$):** δ -61.0. **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 167.8, 149.9, 137.0, 136.1, 129.0, 128.8, 128.2, 128.0, 127.8, 126.6 (q, *J* = 3.7 Hz), 126.3, 124.9 (q, *J* = 270.4 Hz), 119.6 (q, *J* = 32.7 Hz), 111.9, 64.9, 49.8, 44.3, 42.9. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{22}F_3N_2O$ 411.1679; found 411.1677. **IR:** ν(cm^{-1}) 3063, 3032, 2934, 1673, 1258.

1-benzyl-4-(2-(hydroxymethyl)phenyl)-3-phenylpiperazin-2-one (3at):



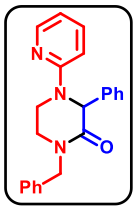
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2t** (256.3 mg, 1.0 mmol). Flash column chromatography (30% Ethyl acetate in Hexane) afforded the desired product **3at** as a solid (91.2 mg, 0.245 mmol, 49% yield). **m.p.**: 135 - 153 °C. R_f = 0.28 (40% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39 – 7.35 (m, 4H), 7.34 – 7.30 (m, 1H), 7.25 – 7.21 (m, 5H), 7.20 – 7.16 (m, 2H), 7.12 – 7.05 (m, 2H), 4.97 (s, 1H), 4.78 (d, *J* = 14.3 Hz, 1H), 4.75 – 4.67 (m, 2H), 4.46 (d, *J* = 11.2 Hz, 1H), 3.57 – 3.47 (m, 1H), 3.39 – 3.28 (m, 2H), 3.20 – 3.05 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.7, 147.6, 138.0, 136.7, 136.6, 129.0, 128.9, 128.8, 128.5, 128.3, 127.9, 127.8, 125.6, 122.7, 68.8, 62.7, 50.4, 47.9, 45.5. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{25}N_2O_2$ 373.1916; found 373.1934. **IR:** ν(cm^{-1}) 3367, 3034, 2921, 2852, 2803, 1631, 1281, 1243, 1080.

1-benzyl-4-(naphthalen-1-yl)-3-phenylpiperazin-2-one (3au):



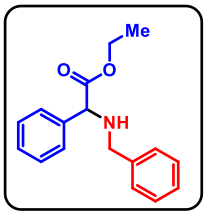
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2u** (276.3 mg, 1.0 mmol). Flash column chromatography (13% Ethyl acetate in Hexane) afforded the desired product **3au** as a sticky solid (139.3 mg, 0.355 mmol, 71% yield). R_f = 0.41 (25% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.28 (d, *J* = 8.0 Hz, 1H), 7.84 – 7.79 (m, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.41 – 7.37 (m, 5H), 7.36 – 7.31 (m, 2H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.25 – 7.18 (m, 3H), 6.97 (d, *J* = 6.5 Hz, 1H), 5.26 (s, 1H), 4.85 (d, *J* = 14.4 Hz, 1H), 4.68 (d, *J* = 14.4 Hz, 1H), 3.61 – 3.47 (m, 2H), 3.38 – 3.29 (m, 1H), 3.24 – 3.17 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.8, 145.8, 138.0, 136.7, 134.8, 129.2, 128.7, 128.5, 128.1, 127.7, 127.6, 126.0, 125.9, 125.5, 124.5, 123.2, 117.9, 67.5, 50.3, 47.3, 45.4. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{27}H_{25}N_2O$ 393.1967; found 393.1968. **IR:** ν(cm^{-1}) 3068, 3028, 2986, 2928, 1659, 1253.

1-benzyl-3-phenyl-4-(pyridin-2-yl)piperazin-2-one (3av):



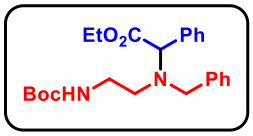
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2v** (227.3 mg, 1.0 mmol). Flash column chromatography (27% Ethyl acetate in Hexane) afforded the desired product **3av** as a sticky solid (49.7 mg, 0.145 mmol, 29% yield). R_f = 0.57 (40% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.19 – 8.16 (m, 1H), 7.53 – 7.49 (m, 2H), 7.44 – 7.39 (m, 1H), 7.36 – 7.32 (m, 2H), 7.31 – 7.28 (m, 1H), 7.27 – 7.23 (m, 3H), 7.18 – 7.14 (m, 2H), 6.65 – 6.61 (m, 1H), 6.41 (d, *J* = 8.6 Hz, 1H), 5.86 (s, 1H), 4.64 (s, 2H), 3.94 – 3.83 (m, 2H), 3.44 – 3.31 (m, 2H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.0, 157.2, 148.1, 137.7, 137.6, 136.4, 128.8, 128.1, 127.9, 127.7, 126.6, 113.5, 106.5, 62.6, 50.1, 43.9, 41.6. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{22}H_{22}N_3O$ 344.1763; found 344.1764. **IR:** ν(cm^{-1}) 3063, 3028, 2966, 2929, 1668, 1248.

ethyl 2-(benzylamino)-2-phenylacetate (4aw):



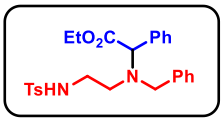
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2w** (186.2 mg, 1.0 mmol). Flash column chromatography (9% Ethyl acetate in Hexane) afforded the desired product **4aw** as a colourless oil (59.2 mg, 0.22 mmol, 44% yield). R_f = 0.657 (25% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 – 7.33 (m, 4H), 7.32 – 7.28 (m, 5H), 7.27 – 7.22 (m, 1H), 4.37 (s, 1H), 4.21 – 4.08 (m, 2H), 3.73 (s, 2H), 2.15 (br s, 1H), 1.19 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 173.0, 139.6, 138.2, 128.7, 128.5, 128.4, 128.1, 127.6, 127.2, 64.5, 61.2, 51.4, 14.2. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{20}NO_2$ 270.1494; found 270.1494. **IR:** ν(cm^{-1}) 3309, 3065, 2981, 2884, 2830, 1737, 1185.

ethyl 2-(benzyl(2-((tert-butoxycarbonyl)amino)ethyl)amino)-2-phenylacetate (4ax):



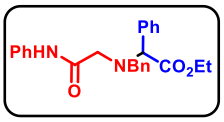
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2x** (250.3 mg, 1.0 mmol). Flash column chromatography (7% Ethyl acetate in Hexane) afforded the desired product **4ax** as a colourless oil (105.2 mg, 0.255 mmol, 51% yield). R_f = 0.29 (20% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.32 (m, 2H), 7.31 – 7.28 (m, 6H), 7.27 – 7.21 (m, 2H), 4.67 (br, 1H), 4.57 (s, 1H), 4.30 – 4.17 (m, 2H), 3.79 (d, *J* = 14.0 Hz, 1H), 3.73 (d, *J* = 13.9 Hz, 1H), 3.17 – 3.02 (m, 2H), 2.89 – 2.81 (m, 1H), 2.81 – 2.62 (m, 1H), 1.42 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 172.3, 156.1, 139.3, 136.6, 129.0, 128.9, 128.6, 128.5, 128.0, 127.3, 78.9, 67.1, 60.7, 55.4, 50.0, 38.5, 28.5, 14.4. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{33}N_2O_4$ 413.2440; found 413.2441. **IR:** ν(cm^{-1}) 3440, 3068, 2974, 1714, 1253, 1171.

ethyl 2-(benzyl(2-((4-methylphenyl)sulfonamido)ethyl)amino)-2-phenylacetate (4ay):



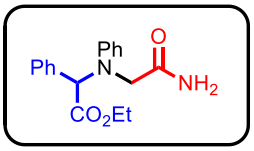
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2y** (304.4 mg, 1.0 mmol). Flash column chromatography (15% Ethyl acetate in Hexane) afforded the desired product **4ay** as a sticky solid (123.6 mg, 0.265 mmol, 53% yield). R_f = 0.43 (25% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57 – 7.53 (m, 2H), 7.38 – 7.32 (m, 3H), 7.31 – 7.24 (m, 3H), 7.22 – 7.13 (m, 6H), 4.99 (t, *J* = 4.6 Hz, 1H), 4.46 (s, 1H), 4.25 – 4.17 (m, 2H), 3.62 (s, 2H), 2.95 – 2.75 (m, 3H), 2.62 – 2.55 (m, 1H), 2.38 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 172.2, 143.1, 138.7, 136.8, 135.9, 129.6, 129.0, 128.9, 128.8, 128.7, 128.3, 127.5, 127.1, 67.0, 61.0, 55.5, 49.4, 40.7, 21.5, 14.3. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{26}H_{31}N_2O_4$ 467.2005; found 467.2008. **IR:** ν(cm^{-1}) 3276, 3034, 2969, 1717, 1253, 1163.

ethyl 2-(benzyl(2-oxo-2-(phenylamino)ethyl)amino)-2-phenylacetate (4az):



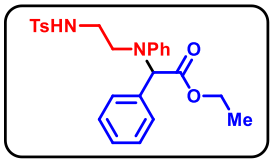
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2z** (240.3 mg, 1.0 mmol). Flash column chromatography (15% Ethyl acetate in Hexane) afforded the desired product **4az** as a sticky solid (66.4 mg, 0.165 mmol, 33% yield). R_f = 0.45 (25% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 9.20 (br s, 1H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.40 – 7.32 (m, 7H), 7.31 – 7.27 (m, 5H), 7.08 (t, *J* = 7.4 Hz, 1H), 4.66 (s, 1H), 4.29 – 4.23 (m, 2H), 3.89 (d, *J* = 13.3 Hz, 1H), 3.79 (d, *J* = 13.3 Hz, 1H), 3.49 (d, *J* = 17.1 Hz, 1H), 3.35 (d, *J* = 17.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 172.0, 169.4, 137.8, 137.4, 135.2, 129.2, 129.1, 129.0, 128.9, 128.8, 128.0, 124.0, 119.3, 68.0, 61.4, 57.8, 55.6, 14.3. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{27}N_2O_3$ 403.2022; found 403.2028. **IR:** ν(cm^{-1}) 3344, 3051, 2980, 1716, 1602, 1254, 1187.

ethyl 2-((2-amino-2-oxoethyl)(phenyl)amino)-2-phenylacetate (4aa'):



Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2a'** (150.1 mg, 1.0 mmol). Flash column chromatography (44% Ethyl acetate in Hexane) afforded the desired product **4aa'** as a solid (123.3 mg, 0.395 mmol, 79% yield). **m.p.**: 196 - 200 °C. R_f = 0.36 (60% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.89 (br s, 1H), 7.39 – 7.32 (m, 3H), 7.25 – 7.23 (m, 1H), 7.22 – 7.17 (m, 3H), 6.82 (t, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 2H), 5.49 (s, 1H), 5.40 (br s, 1H), 4.32 – 4.24 (m, 1H), 4.23 – 4.15 (m, 1H), 3.62 (d, *J* = 18.1 Hz, 1H), 3.56 (d, *J* = 18.1 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 174.3, 173.8, 147.2, 133.7, 129.7, 129.6, 129.5, 129.4, 119.3, 112.8, 66.6, 62.3, 51.5, 14.2. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{21}N_2O_3$ 313.1552; found 313.1555. **IR:** ν(cm^{-1}) 3387, 3164, 2983, 1730, 1647, 1278, 1240, 1156.

ethyl 2-((2-((4-methylphenyl)sulfonamido)ethyl)(phenyl)amino)-2-phenylacetate (4ab'):



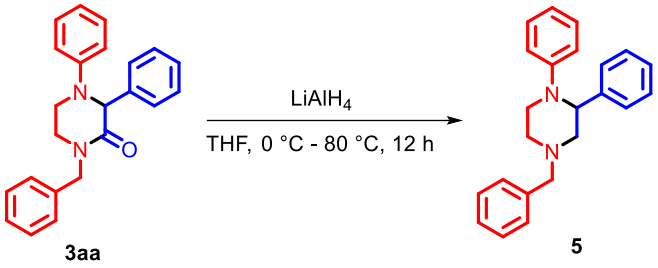
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2b'** (290.38 mg, 1.0 mmol). Flash column chromatography (14% Ethyl acetate in Hexane) afforded the desired product **4ab'** as a sticky solid (138.0 mg, 0.305 mmol, 61% yield). R_f = 0.34 (25% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.32 (m, 3H), 7.22 – 7.12 (m, 6H), 6.84 (t, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 2H), 5.68 – 5.63 (m, 1H), 5.40 (s, 1H), 4.36 – 4.24 (m, 2H), 3.32 – 3.24 (m, 1H), 3.23 – 3.15 (m, 1H), 3.03 – 2.94 (m, 1H), 2.87 – 2.79 (m, 1H), 2.37 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 173.2, 147.6, 142.9, 136.7, 135.0, 129.5, 129.3, 128.9, 128.9, 128.6, 127.0, 119.6, 115.8, 68.0, 61.8, 45.9, 40.5, 21.5, 14.2. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{25}H_{29}N_2O_4S$ 453.1848; found 453.1848. **IR:** ν(cm^{-1}) 3165, 3033, 2970, 2932, 1720, 1282, 1249, 1163.

6. Synthetic Transformations and the synthesis of Mianserin derivative

Scale up reaction of 3aa

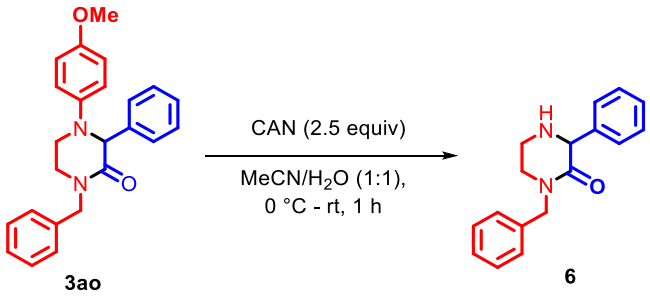
In a 50 mL round bottom flask was added N^1-benzyl-N^2-phenylethane-1,2-diamine **1a** (1.131 g, 5.0 mmol, 2.0 equiv), Cu(2-ethylhexanoate)$_2$ (43.7 mg) and 1,2-dichloroethane (25 mL). To this was added the ethyl phenyl diazoacetate **2a** (475.5 mg, 2.5 mmol, 1.0 equiv), and the reaction mixture was stirred at 60 °C for 12 hours. The solvent was evaporated under reduced pressure to afford the crude product. Then, the crude product was purified by silica gel (100 – 200 mesh) column chromatography (8% Ethyl acetate in Hexane) to afford compound **3aa** in 85% isolated yield.

4-benzyl-1,2-diphenylpiperazine (5):



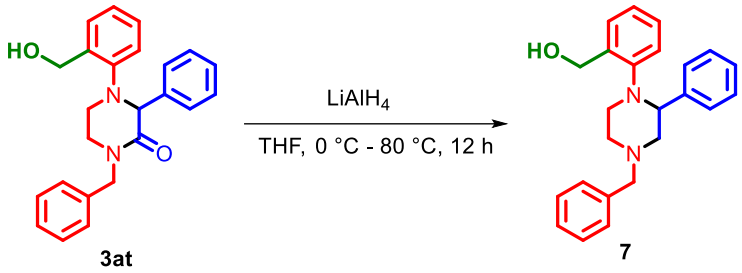
Following the reported procedure,[1] an oven-dried 25 mL Schlenk tube was charged with **3aa** (80.0 mg, 0.23 mmol) in THF (1 mL). To this was added $LiAlH_4$ (5 equiv) in THF at 0 °C slowly, and the reaction mixture was stirred for 12 h at 80 °C. Then, the reaction was quenched with a minimum amount of water (just for quenching of $LiAlH_4$), filtrated by Celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (6% Ethyl acetate in Hexane), affording the desired product **5** as a colourless oil (56.6 mg, 0.172 mmol, 75% yield). R_f = 0.48 (15% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.35 – 7.31 (m, 4H), 7.30 – 7.27 (m, 3H), 7.22 – 7.17 (m, 2H), 7.16 – 7.10 (m, 3H), 6.97 – 6.92 (m, 2H), 6.85 – 6.80 (m, 1H), 4.46 (dd, *J* = 7.7, 3.0 Hz, 1H), 3.62 (d, *J* = 13.1 Hz, 1H), 3.53 (d, *J* = 13.4 Hz, 1H), 3.51 – 3.45 (m, 1H), 3.25 – 3.17 (m, 1H), 2.94 – 2.88 (m, 1H), 2.83 – 2.76 (m, 1H), 2.67 – 2.60 (m, 1H), 2.53 (dd, *J* = 11.0, 7.9 Hz, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 151.3, 141.6, 137.9, 129.2, 128.7, 128.3, 128.1, 127.9, 127.2, 126.8, 121.3, 121.2, 63.0, 61.5, 61.0, 53.6, 52.9. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{23}H_{25}N_2$ 329.2018; found 329.2016. **IR:** ν(cm^{-1}) 3065, 3033, 2927, 2860, 1255.

1-benzyl-4-(2-(hydroxymethyl)phenyl)-3-phenylpiperazin-2-one (6):



Following the previously reported procedure,[6] A 50 mL round bottom flask was charged with a magnetic stirrer bar, **3ao** (111 mg, 0.298 mmol), and acetonitrile/water (1:1). The mixture was stirred at 0° C for 5 minutes, followed by the addition of CAN (408 mg, 2.5 equiv) in one portion. Then, the resulting mixture was stirred at room temperature for 1 hour. Then, the mixture was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with DCM (2 times), and the combined organic layers were washed with 5% aqueous Na_2SO_3 solution, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Flash column chromatography (2% MeOH in DCM) afforded the desired product **6** as a sticky solid (61.9 mg, 0.232 mmol, 78% yield). R_f = 0.52 (5% MeOH in DCM). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.46 – 7.41 (m, 2H), 7.39 – 7.33 (m, 4H), 7.32 – 7.27 (m, 4H), 4.65 (s, 3H), 3.47 – 3.39 (m, 1H), 3.27 – 3.20 (m, 1H), 3.16 – 3.09 (m, 1H), 3.07 – 2.99 (m, 1H), 2.08 (br, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 168.7, 140.0, 136.9, 128.7, 128.5, 128.4, 127.8, 127.6, 64.2, 50.3, 47.6, 41.5. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{19}N_2O$ 267.1497; found 267.1488. **IR:** ν(cm^{-1}) 3340, 3063, 3034, 2966, 1654, 1253.

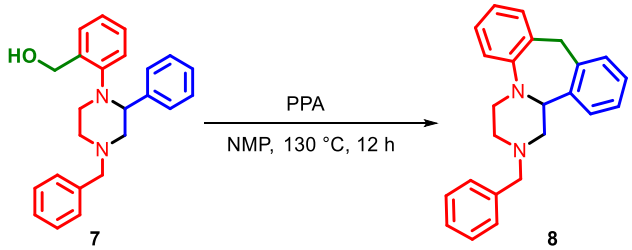
(2-(4-benzyl-2-phenylpiperazin-1-yl)phenyl)methanol (7):



3at **7**

Following the reported procedure,[1] an oven-dried 25 mL Schlenk tube charged with **3at** (253 mg, 0.68 mmol) in THF (1 mL) was reduced with $LiAlH_4$ (154 mg, 4.08 mmol) in THF at 0 °C. The reaction mixture was stirred for 12 h at 80 °C. After quenching with 1 mL of water, the mixture was filtrated by Celite, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (27% Ethyl acetate in Hexane), afforded the desired product **7** as an oil (180.3 mg, 0.503 mmol, 74% yield). R_f = 0.51 (40% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.37 – 7.29 (m, 4H), 7.28 – 7.22 (m, 3H), 7.16 – 7.10 (m, 3H), 7.09 – 7.04 (m, 2H), 7.03 – 6.99 (m, 1H), 6.96 – 6.91 (m, 1H), 4.92 (d, *J* = 13.6 Hz, 1H), 4.67 (d, *J* = 13.7 Hz, 1H), 4.32 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.61 (d, *J* = 13.0 Hz, 1H), 3.56 (d, *J* = 12.9 Hz, 1H), 3.24 – 3.17 (m, 1H), 3.05 – 2.92 (m, 3H), 2.49 (td, *J* = 11.4, 2.8 Hz, 1H), 2.42 – 2.35 (m, 1H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$):** δ 148.8, 140.0, 137.6, 136.1, 129.3, 128.4, 128.3, 128.2, 128.0, 127.6, 127.4, 127.3, 125.2, 123.3, 64.9, 64.8, 63.0, 61.8, 55.4, 53.7. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{27}N_2O$ 359.2123; found 359.2118. **IR:** ν(cm^{-1}) 3438, 3063, 2982, 1252.

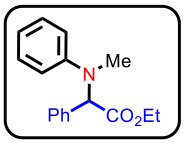
2-benzyl-1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepine (8):



7 **8**

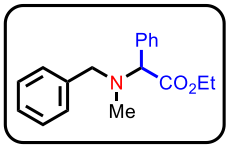
Following the modified procedure,[7] in a 25 ml round bottom flask charged with a magnetic stirrer bar was added piperazine derivative **7** (155 mg, 0.43 mmol) and polyphosphoric acid (1.8 g) in 1.5 mL NMP. The reaction mixture was stirred at 130 °C for 12 h. The reaction was quenched with ice, then DCM was added. The mixture was basified with 2N aqueous NaOH. The organic layer was separated from the aqueous layer, and subsequently extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in a vacuum. The residue was purified by flash column chromatography (15% ethyl acetate and Hexane), affording the desired product **8** as a sticky solid (72.1 mg, 0.211 mmol, 49% yield). R_f = 0.586 (25% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 7.20 – 7.15 (m, 1H), 7.14 – 7.09 (m, 2H), 7.08 – 7.03 (m, 2H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.99 – 6.94 (m, 1H), 6.87 (td, *J* = 7.3, 1.0 Hz, 1H), 4.84 (d, *J* = 12.5 Hz, 1H), 4.16 – 4.10 (m, 1H), 3.67 (d, *J* = 13.0 Hz, 1H), 3.54 (d, *J* = 13.0 Hz, 1H), 3.42 – 3.34 (m, 1H), 3.31 (d, *J* = 12.6 Hz, 1H), 3.26 – 3.19 (m, 1H), 3.01 – 2.91 (m, 2H), 2.55 – 2.48 (m, 1H), 2.41 – 2.32 (m, 1H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 148.8, 139.9, 139.4, 137.9, 137.7, 129.7, 129.3, 128.4, 128.2, 127.3, 127.2, 127.0, 126.6, 126.5, 122.3, 119.1, 66.6, 63.2, 62.9, 53.3, 51.3, 38.9. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{24}H_{25}N_2$ 341.2012; found 341.2015. **IR:** ν(cm^{-1}) 3062, 3030, 2958, 2813, 1256.

ethyl 2-(methyl(phenyl)amino)-2-phenylacetate (9):



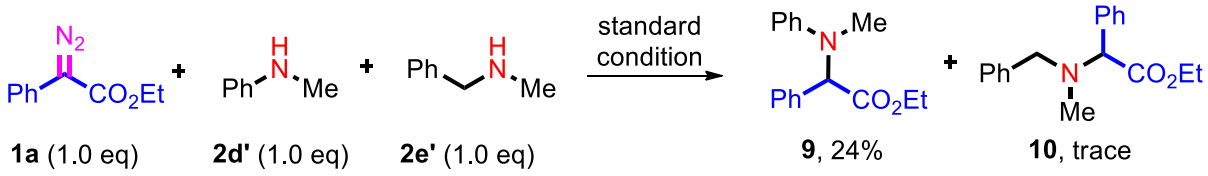
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2d'** (107.1 mg, 1.0 mmol). Flash column chromatography (2% Ethyl acetate in Hexane) afforded the desired product **9** as a yellow oil (55.2 mg, 0.205 mmol, 41% yield). R_f = 0.33 (5% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39 – 7.31 (m, 3H), 7.30 – 7.23 (m, 4H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.80 (t, *J* = 7.2 Hz, 1H), 5.63 (s, 1H), 4.32 – 4.19 (m, 2H), 2.79 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 171.8, 149.9, 136.0, 129.2, 128.6, 128.4, 128.0, 118.0, 113.4, 65.7, 61.0, 34.5, 14.2. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{20}NO_2$ 270.1494; found 270.1505. **IR:** ν(cm^{-1}) 3059, 2983, 2927, 2889, 1731, 1280, 1185.

ethyl 2-(benzyl(methyl)amino)-2-phenylacetate (10):



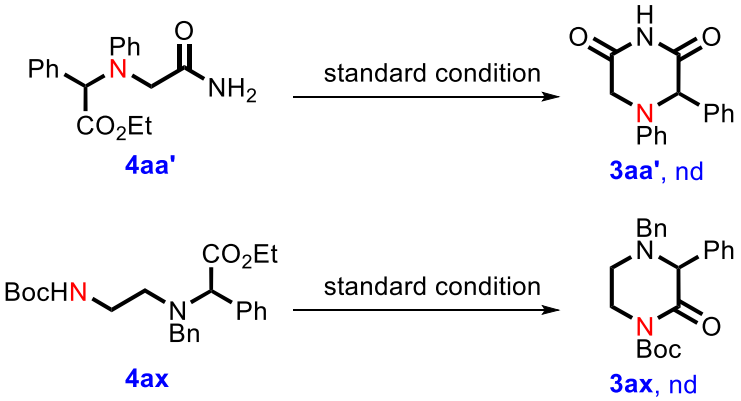
Prepared according to the general procedure **A** using **1a** (95.1 mg, 0.5 mmol) and **2e'** (121.1 mg, 1.0 mmol). Flash column chromatography (4% Ethyl acetate in Hexane) afforded the desired product **10** as a colorless oil (19.8 mg, 0.07 mmol, 14% yield). R_f = 0.25 (5% Ethyl acetate in Hexane). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 – 7.46 (m, 2H), 7.38 – 7.31 (m, 5H), 7.30 – 7.28 (m, 2H), 7.25 – 7.21 (m, 1H), 4.31 (s, 1H), 4.28 – 4.13 (m, 2H), 3.65 (d, *J* = 13.4 Hz, 1H), 3.54 (d, *J* = 13.4 Hz, 1H), 2.21 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$):** δ 171.0, 139.0, 136.9, 129.0, 128.9, 128.5, 128.3, 128.2, 127.1, 72.3, 60.8, 58.6, 39.2, 14.3. **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{18}H_{22}NO_2$ 284.1651; found 284.1648. **IR:** ν(cm^{-1}) 3030, 2931, 2850, 1716, 1254, 1169.

7. Control Experiments



1a (1.0 eq) **2d'** (1.0 eq) **2e'** (1.0 eq) **9**, 24% **10**, trace

Under the standard reaction condition, N-methylaniline **2d'** (11 mg, 0.1051 mmol, 1.0 equiv.), N-methylbenzylamine **2e'** (12.7 mg, 0.1051 mmol, 1.0 equiv.), were treated with the diazo compound **1a** (20 mg, 0.1051 mmol, 1.0 equiv), resulting in the desired product **9** in 24% yield while only a trace amount of insertion product **10** was observed.



Additionally, ethyl 2-((2-amino-2-oxoethyl)(phenyl)amino)-2-phenylacetate **4aa'** (20 mg, 0.064 mmol, 1.0 equiv.), and ethyl 2-(benzyl(2-((tert-butoxycarbonyl)amino)ethyl)amino)-2-

phenylacetate **4ax** (30 mg, 0.0725 mmol, 1.0 equiv.) were subjected under standard conditions. The desired products **3aa'** and **3ax** were not detected even after increasing the temperature.

8. XRD Data for 3aa

Crystals of compound **3aa** were grown from the solvent chloroform/hexane by slow evaporation method. A good quality yellow colour single crystal of size 0.15 x 0.18 x 0.19 mm, was selected under a polarizing microscope and was mounted on a glass fiber for data collection. Single crystal X-ray data for compound **3aa** were collected on the Rigaku Kappa 3 circle diffractometer equipped with the AFC12 goniometer and enhanced sensitivity (HG) Saturn724+ CCD detector in the 4x4 bin mode using the monochromated Mo-Kα radiation generated from the microfocus sealed tube MicroMax-003 X-ray generator equipped with specially designed confocal multilayer optics. Data collection was performed using ω-scans of 0.5° steps at 293(2) K. Cell determination, data collection and data reduction was performed using the Rigaku Crystal Clear-SM Expert 2.1 b24 software. Structure solution and refinement were performed by using SHELXTL-NT. Refinement of coordinates and anisotropic thermal parameters of non-hydrogen atoms were carried out by the full-matrix least-squares method. The hydrogen atoms attached to carbon atoms were generated with idealized geometries and isotropically refined using a riding model.

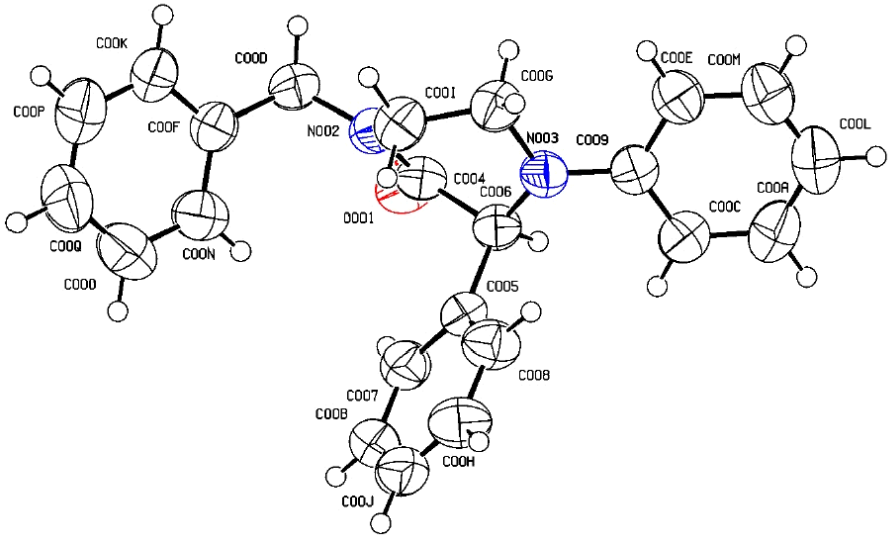


Figure 1: ORTEP diagram of the crystal structure of compound **3aa**

Table 2 Crystal data and structure refinement details for **3aa**

Compound	**3aa**
Empirical formula	$C_{23}H_{22}N_2O$
Formula weight	342.42
Crystal System	Orthorhombic

Space group	P c a 2_1
a (Å)	10.0123(6)
b (Å)	18.3467(8)
c (Å)	10.1070(4)
α (°)	90.00
β (°)	90.00
γ (°)	90.00
V (Å^3)	1856.58(16)
Z	4
D_c (g/cm^3)	1.225
F_{000}	728
μ (mm^{-1})	0.589
θ_{max} (°)	75.6450
Total reflections	5512
Unique reflections	2664
Obs. reflections [$I>2\sigma(I)$]	2384
R_{int}	0.0324
Goodness-of-fit	1.050
R_1 (F^2)	0.0359
wR^2 (F^2)	0.0956
CCDC No.	2321853

9. Reference

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10. NMR Spectra

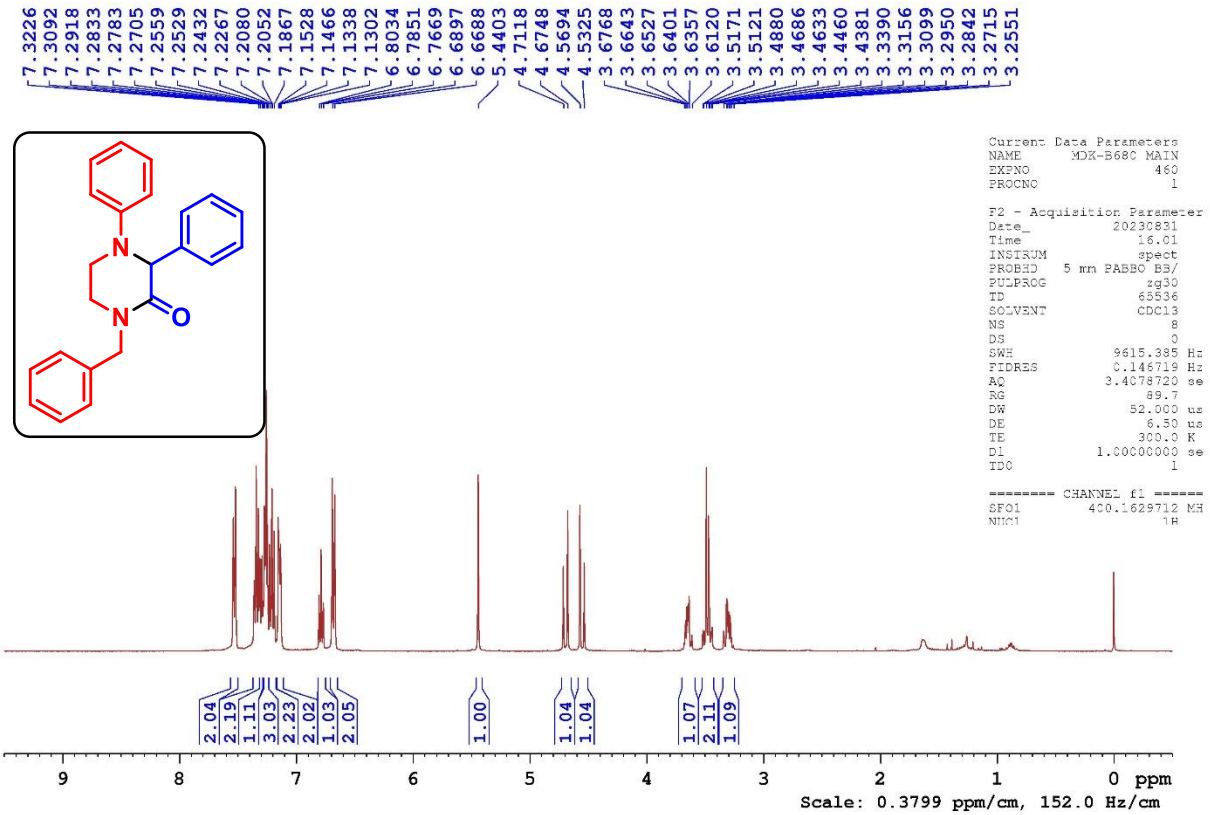


Figure S-01: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3aa**

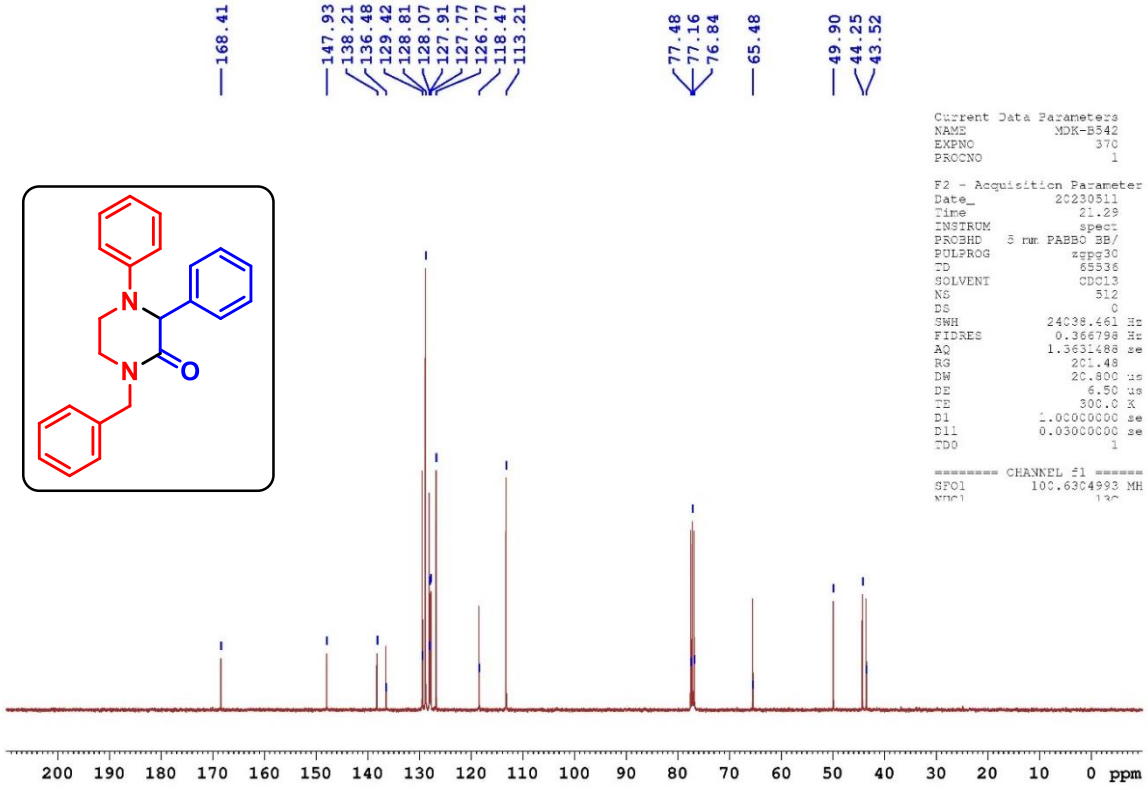


Figure S-02: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3aa**

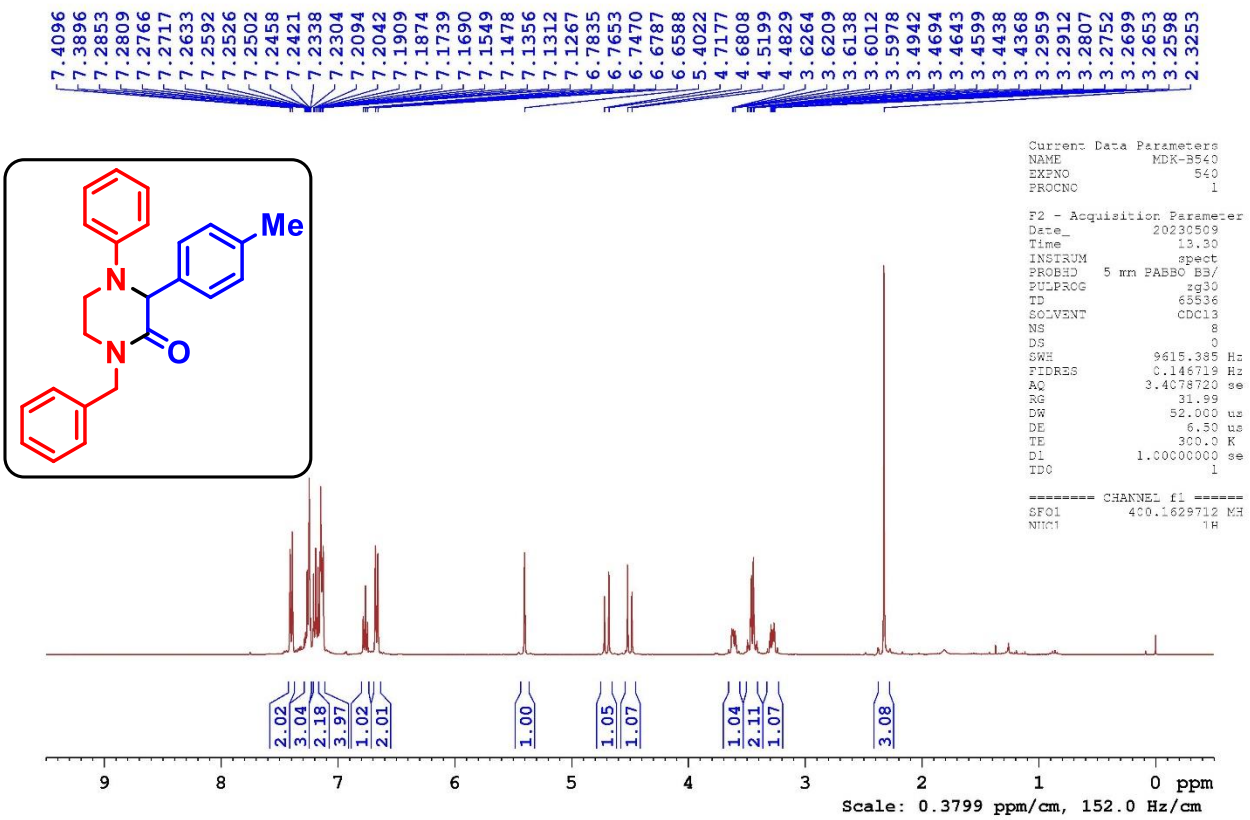


Figure S-03: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ba**

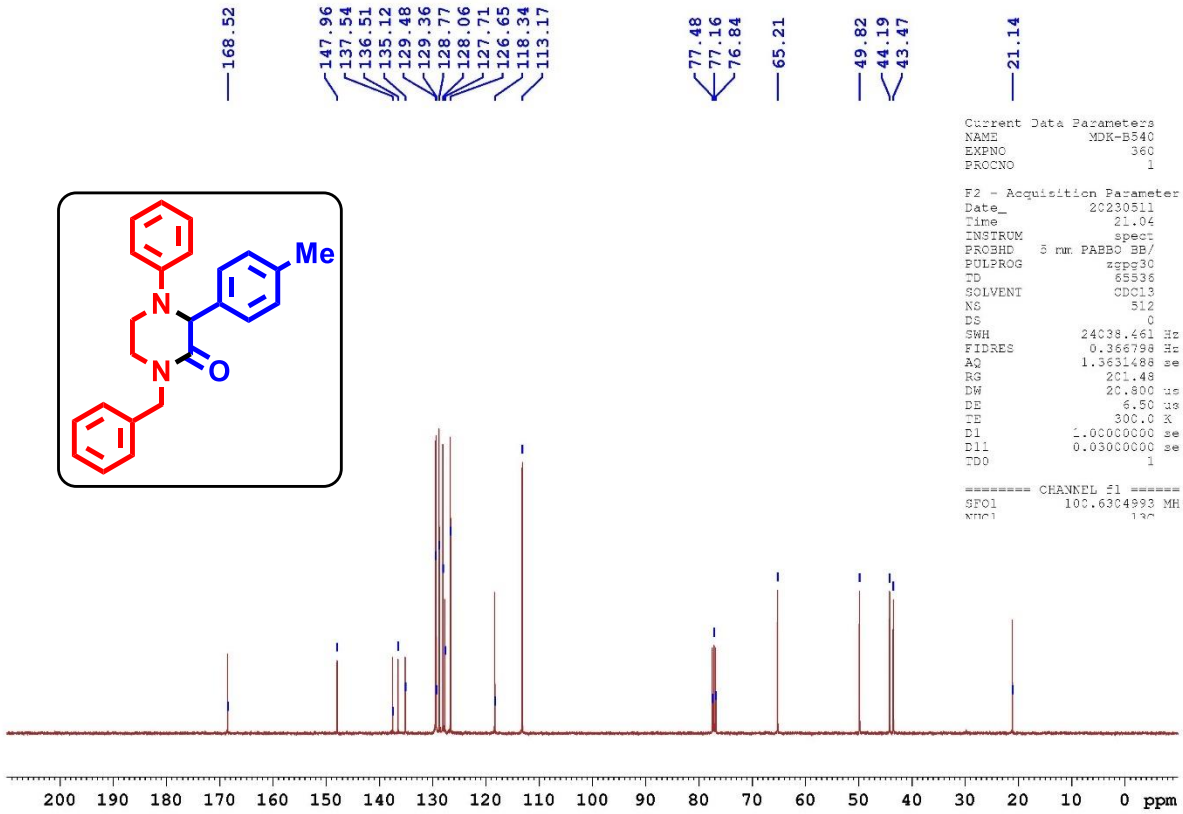


Figure S-04: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ba**

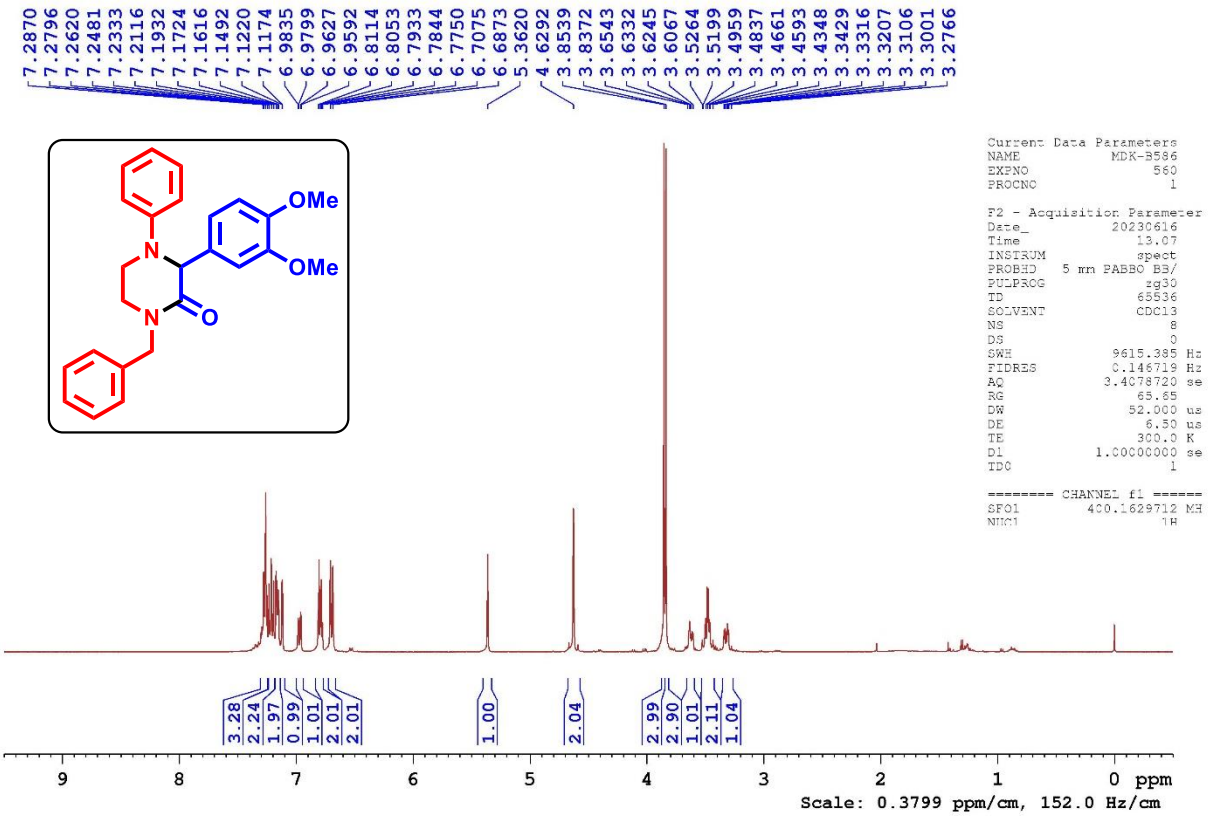


Figure S-05: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ca**

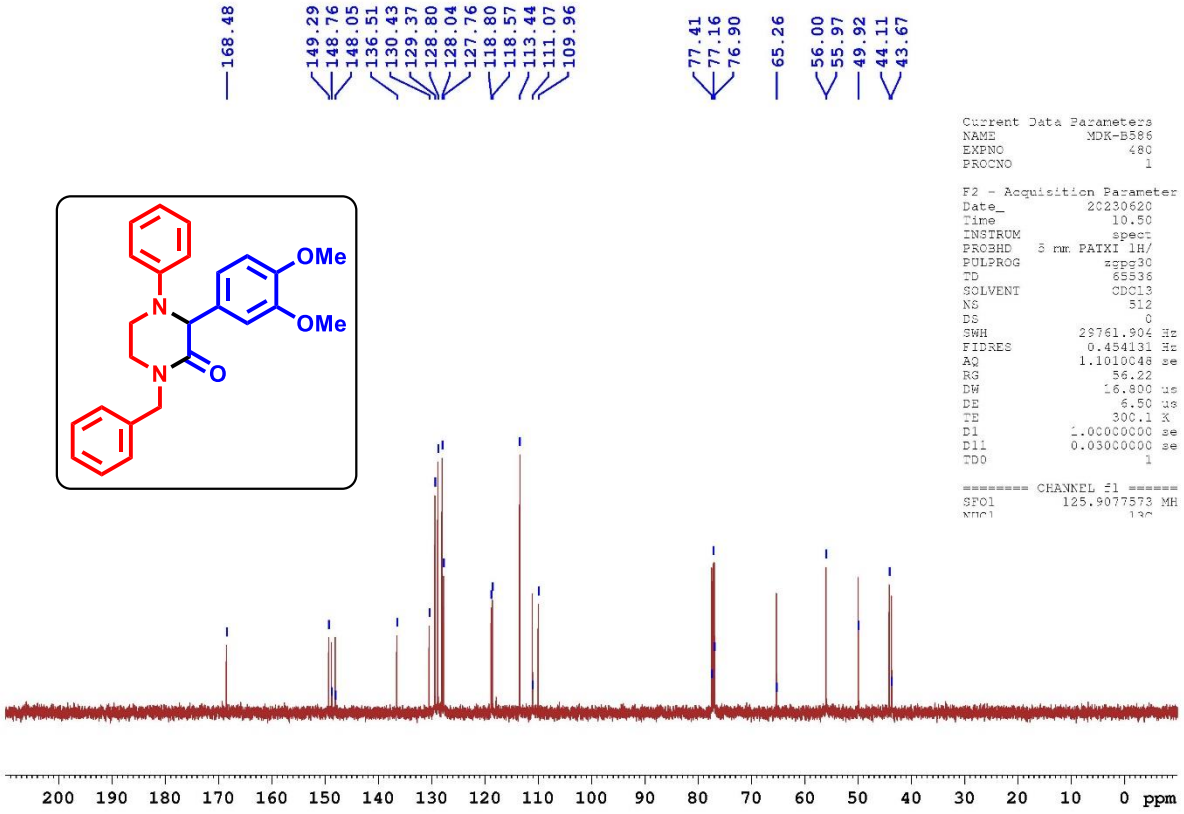


Figure S-06: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3ca**

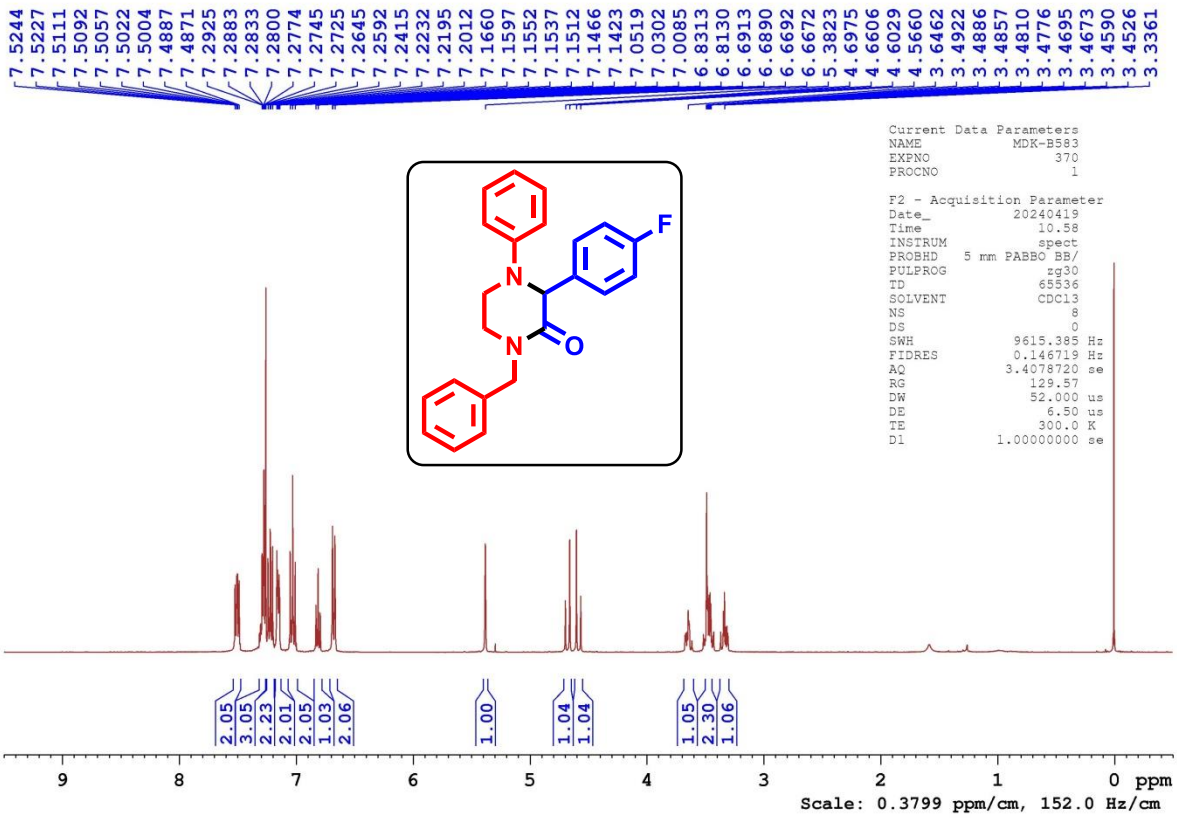


Figure S-07: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3da**

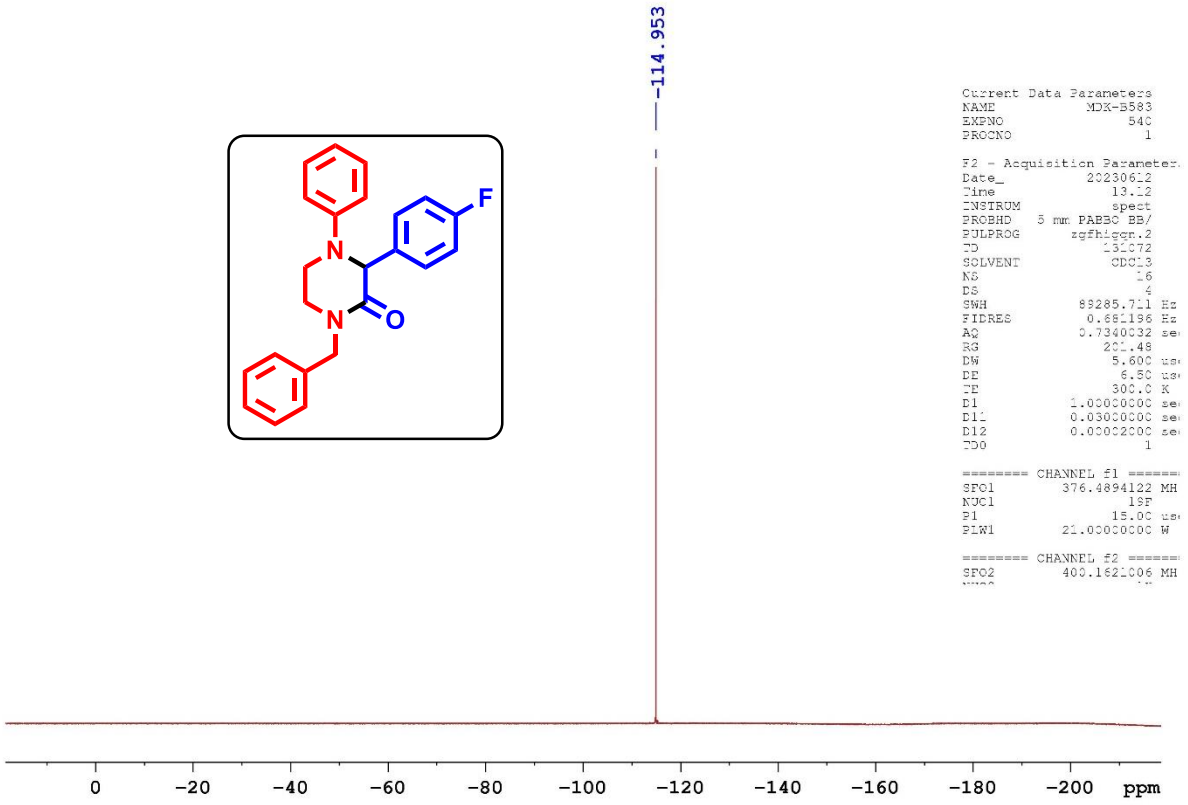


Figure S-08: ^{19}F NMR (376 MHz, $CDCl_3$) spectrum of compound **3da**

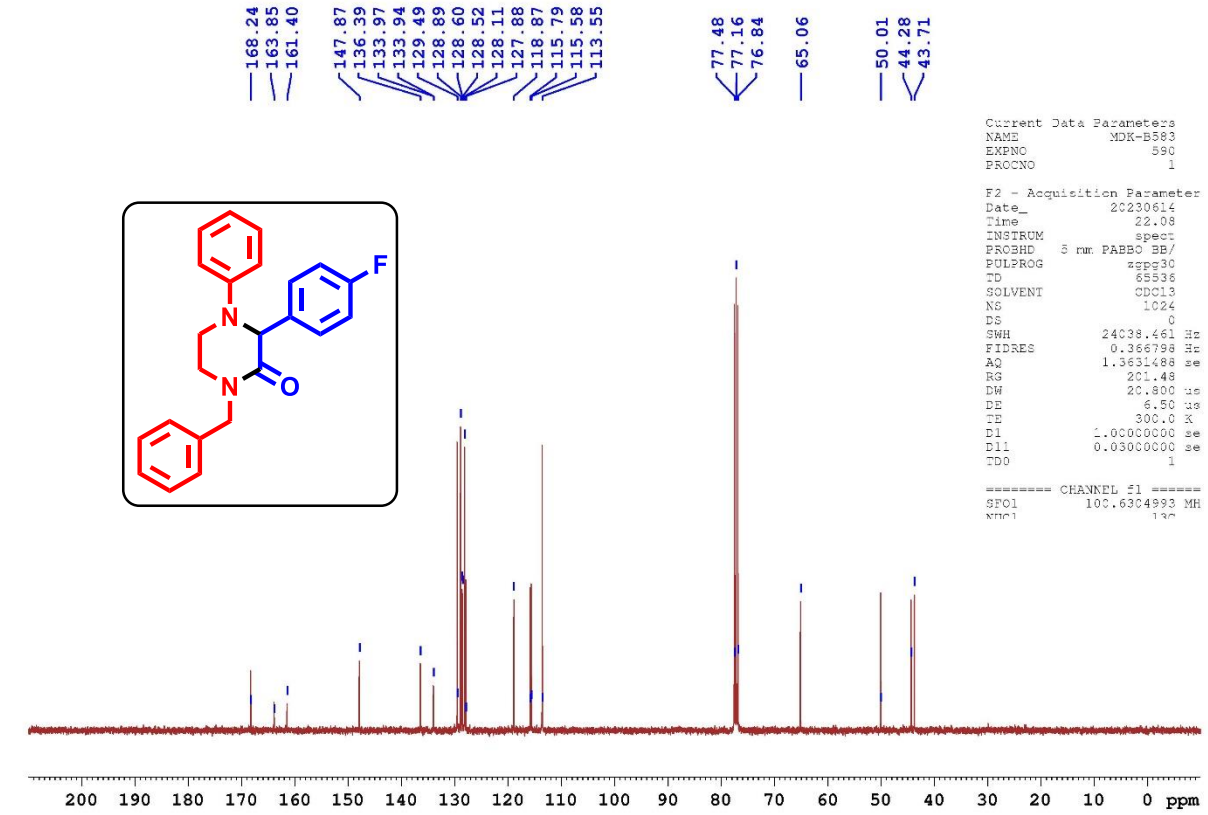


Figure S-09: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3da**

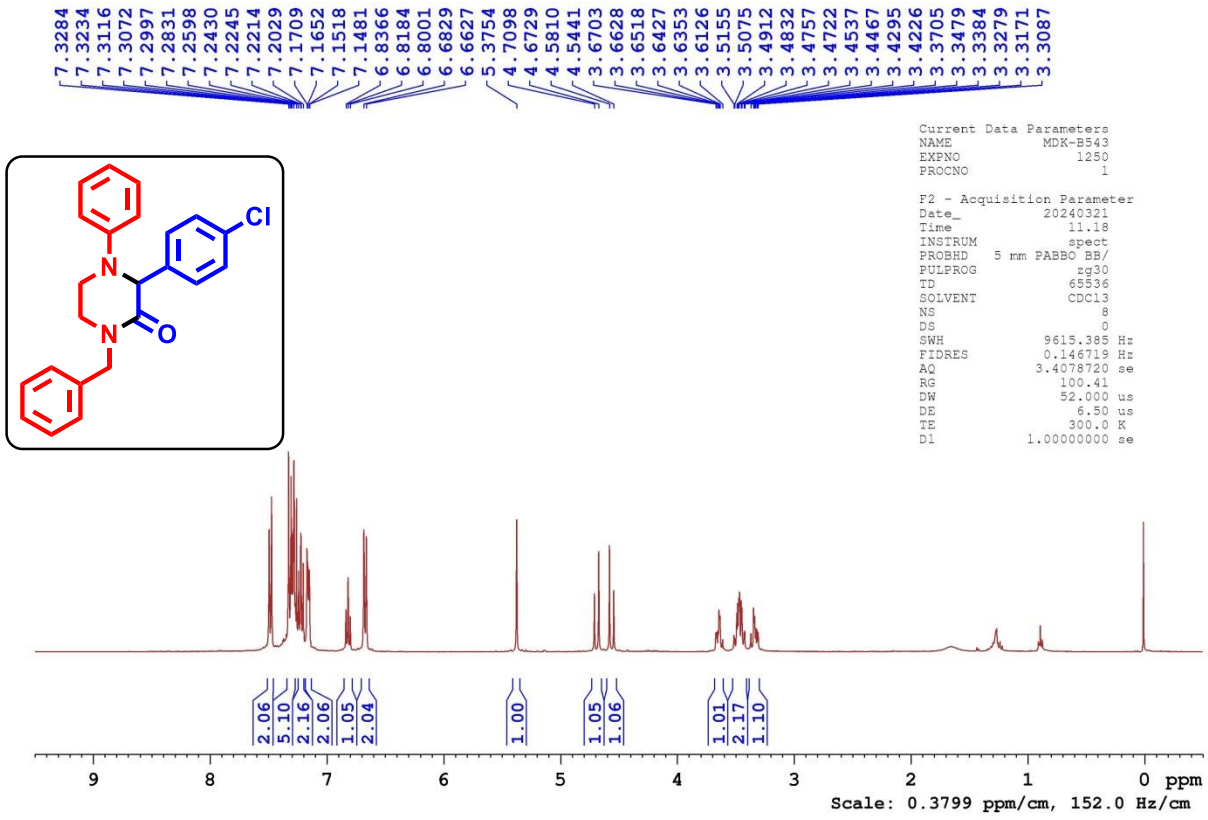


Figure S-10: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ea**

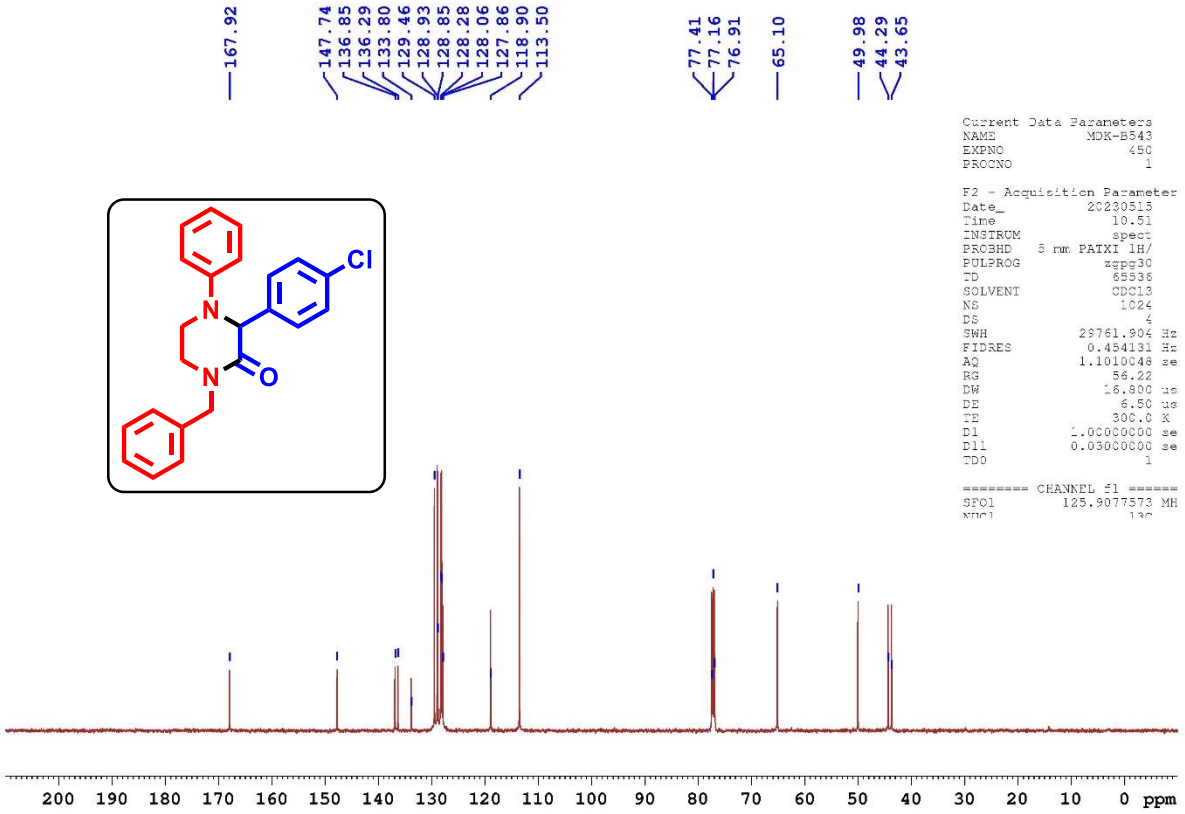


Figure S-11: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3ea**

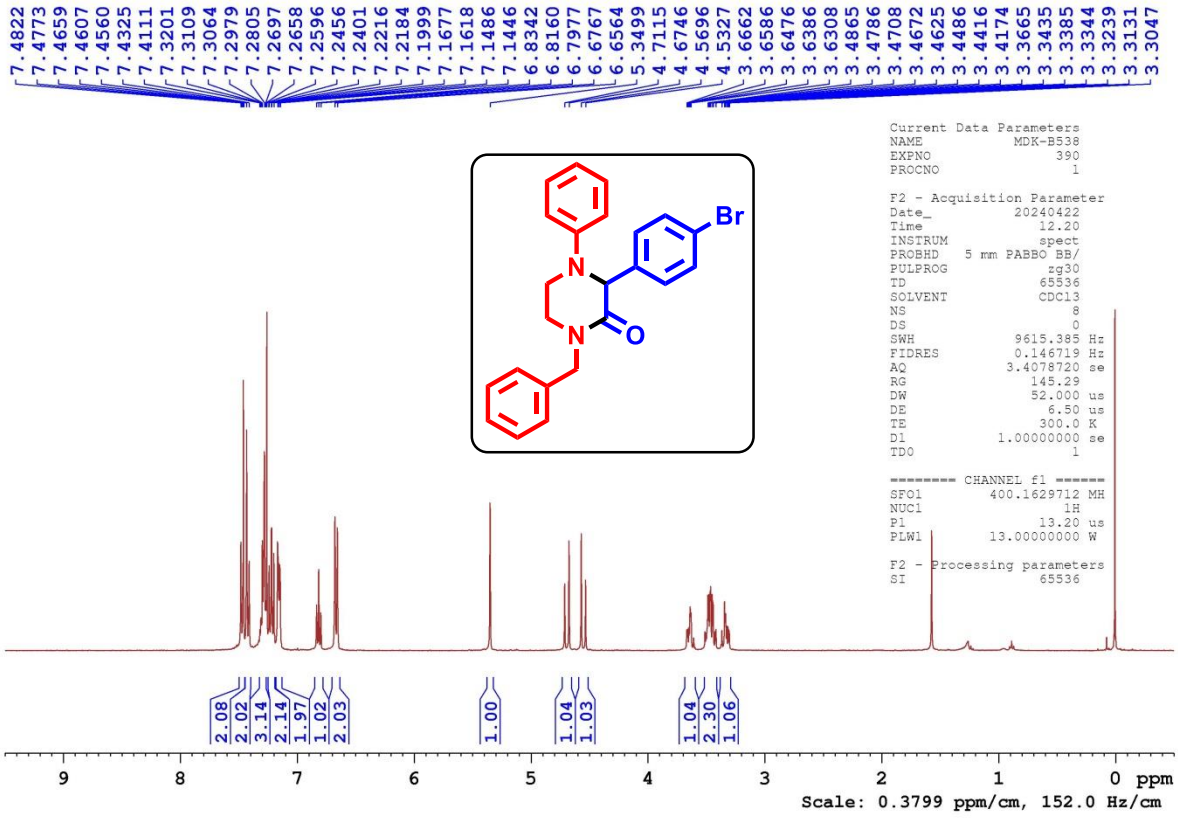


Figure S-12: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3fa**

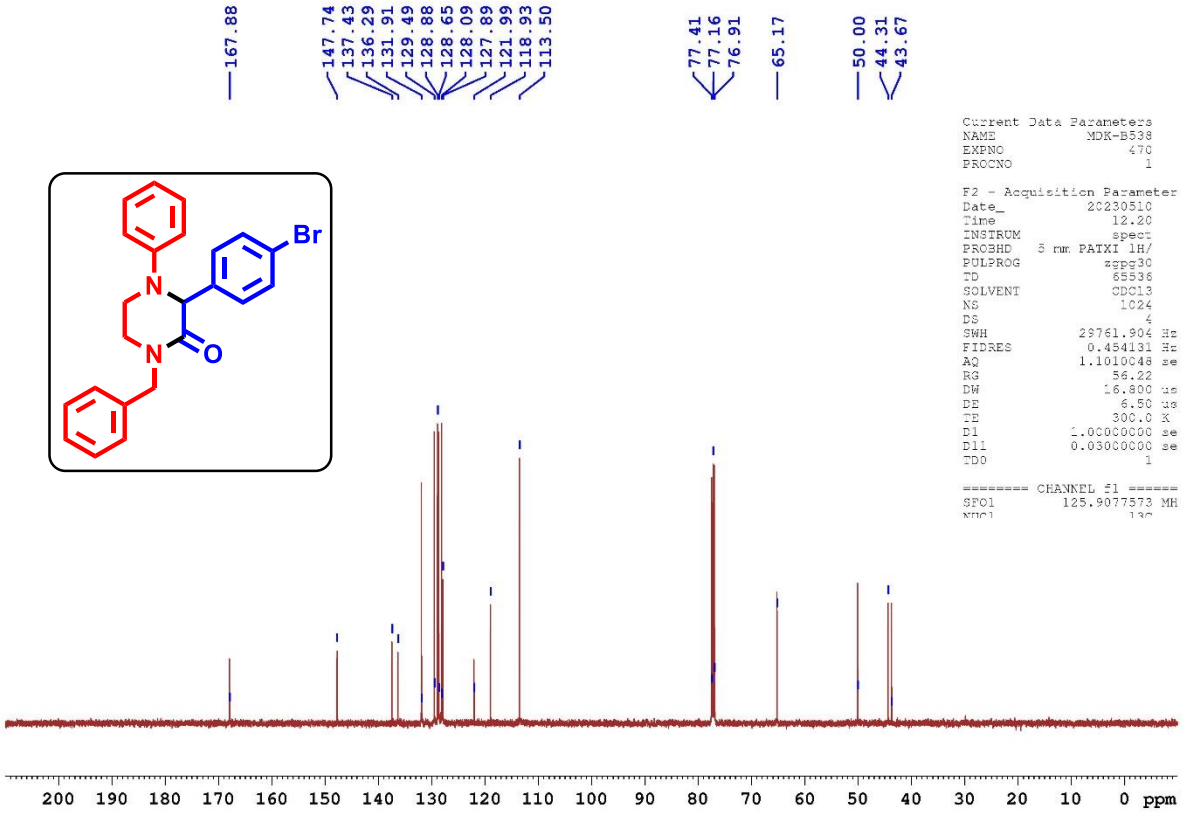


Figure S-13: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3fa**

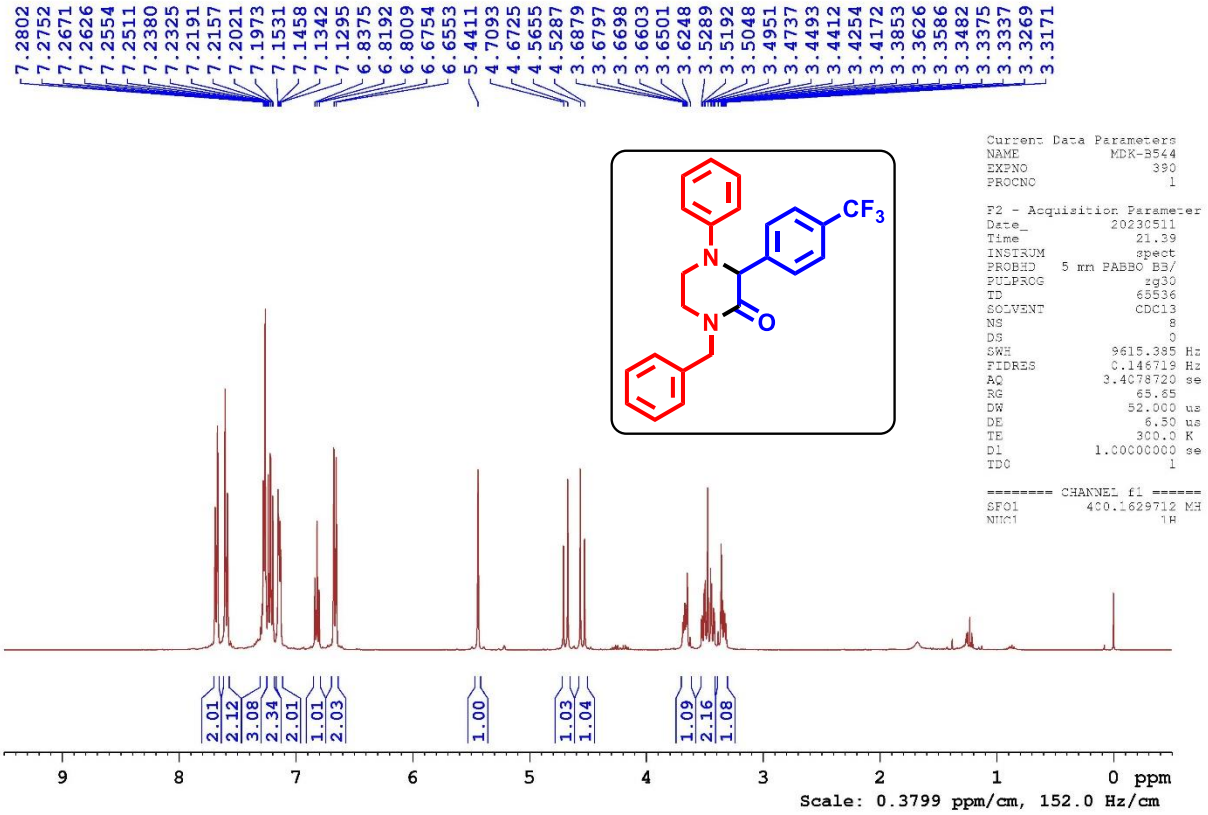


Figure S-14: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ga**

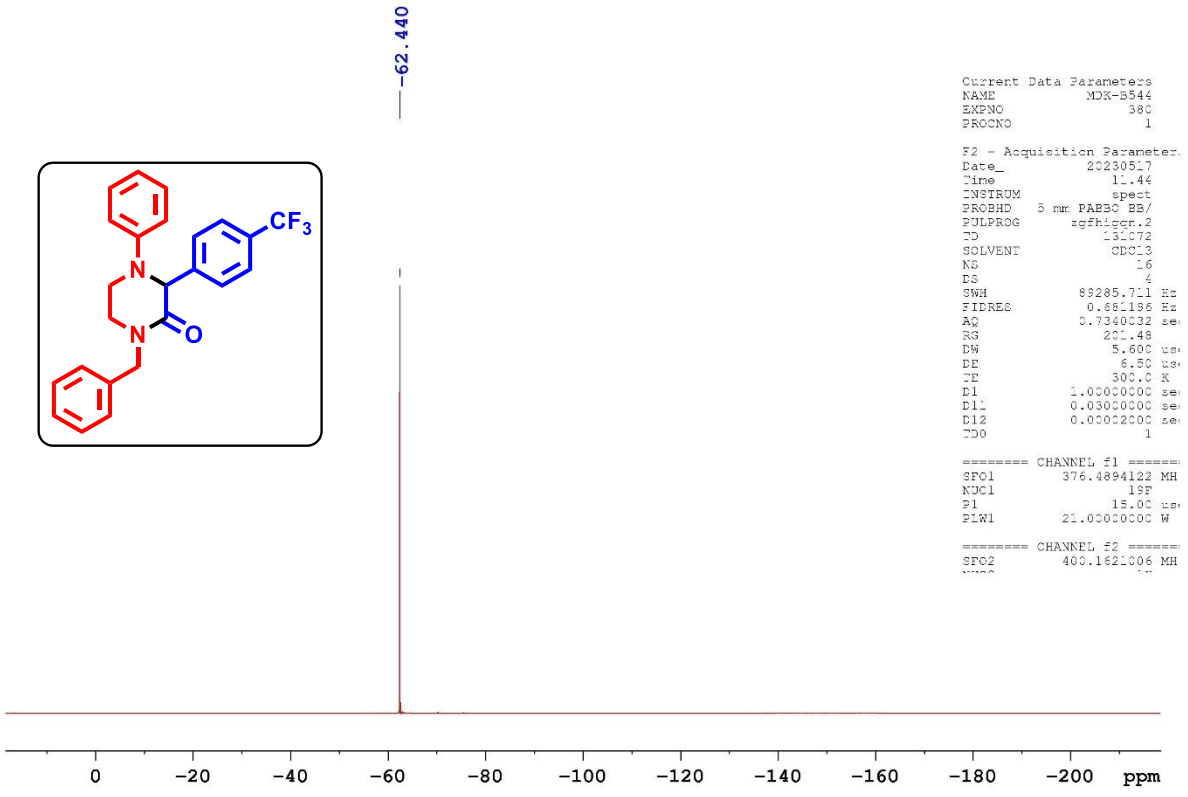


Figure S-15: ^{19}F NMR (376 MHz, $CDCl_3$) spectrum of compound **3ga**

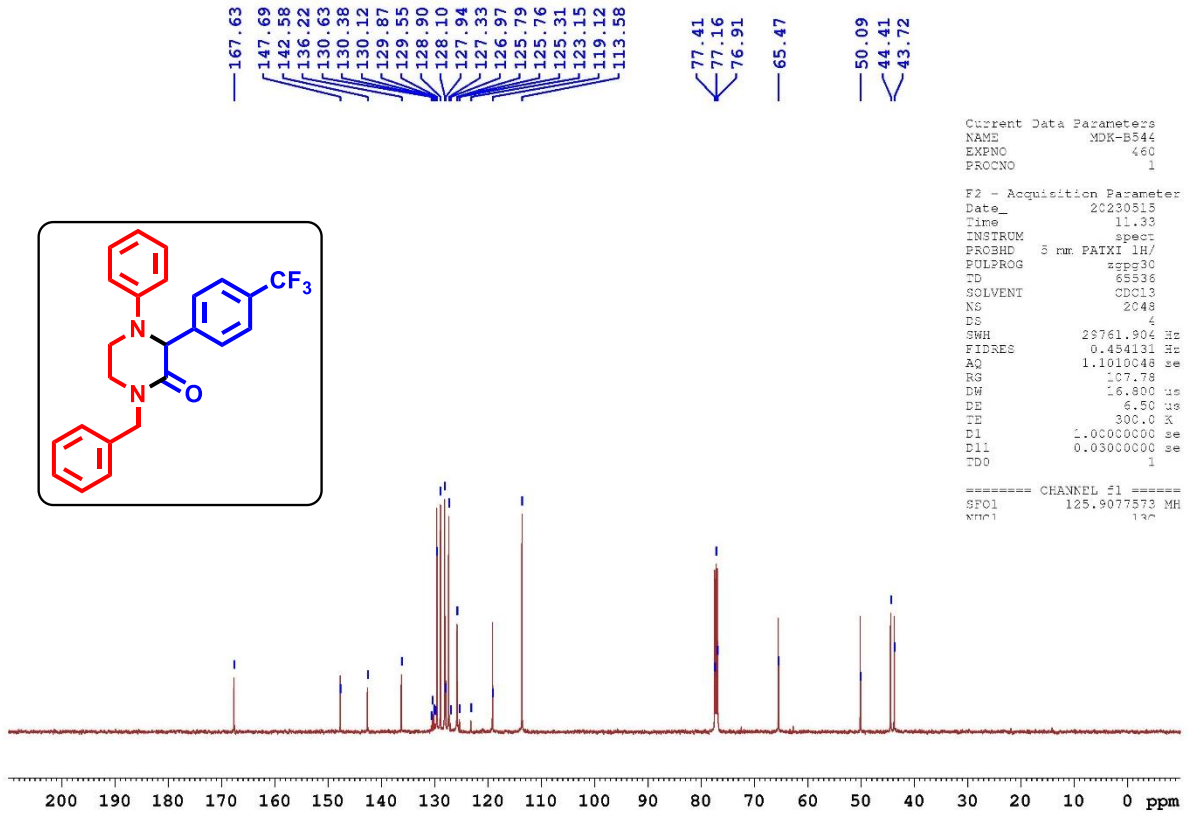


Figure S-16: $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3ga**

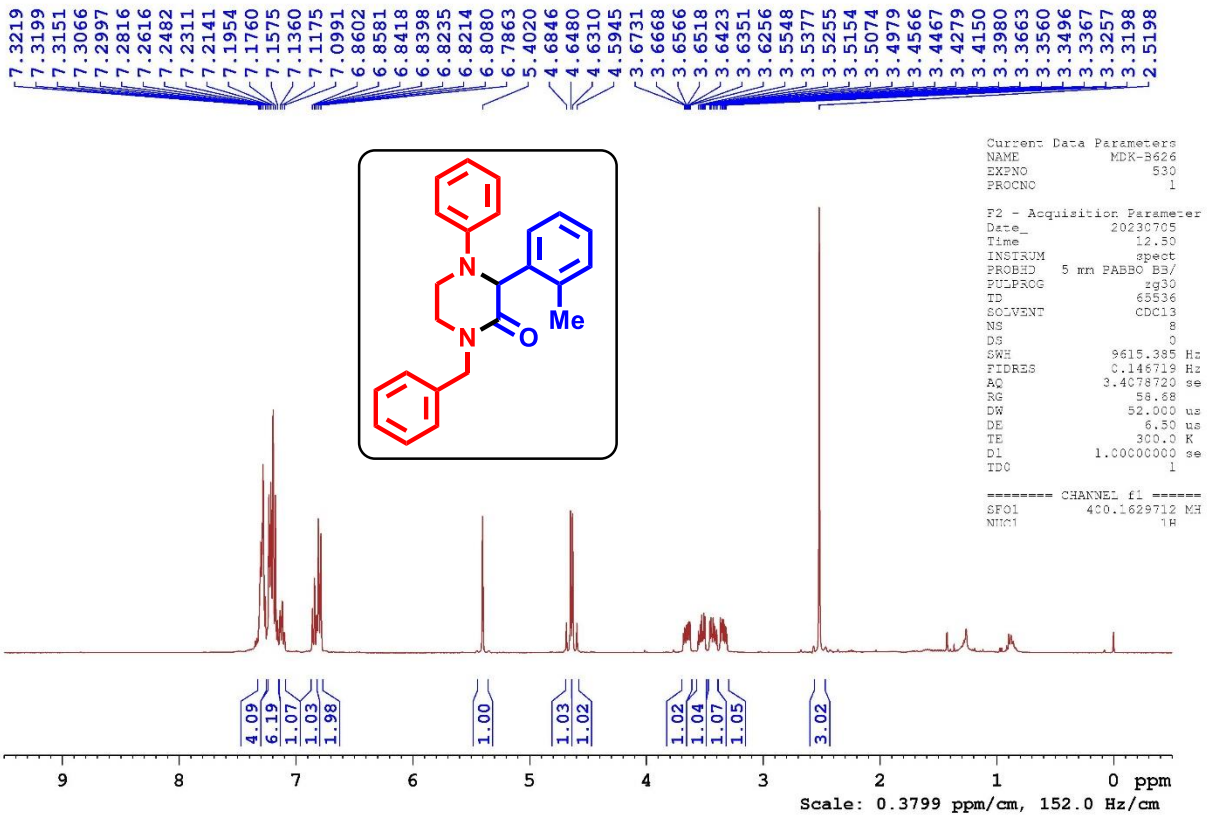


Figure S-17: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ia**

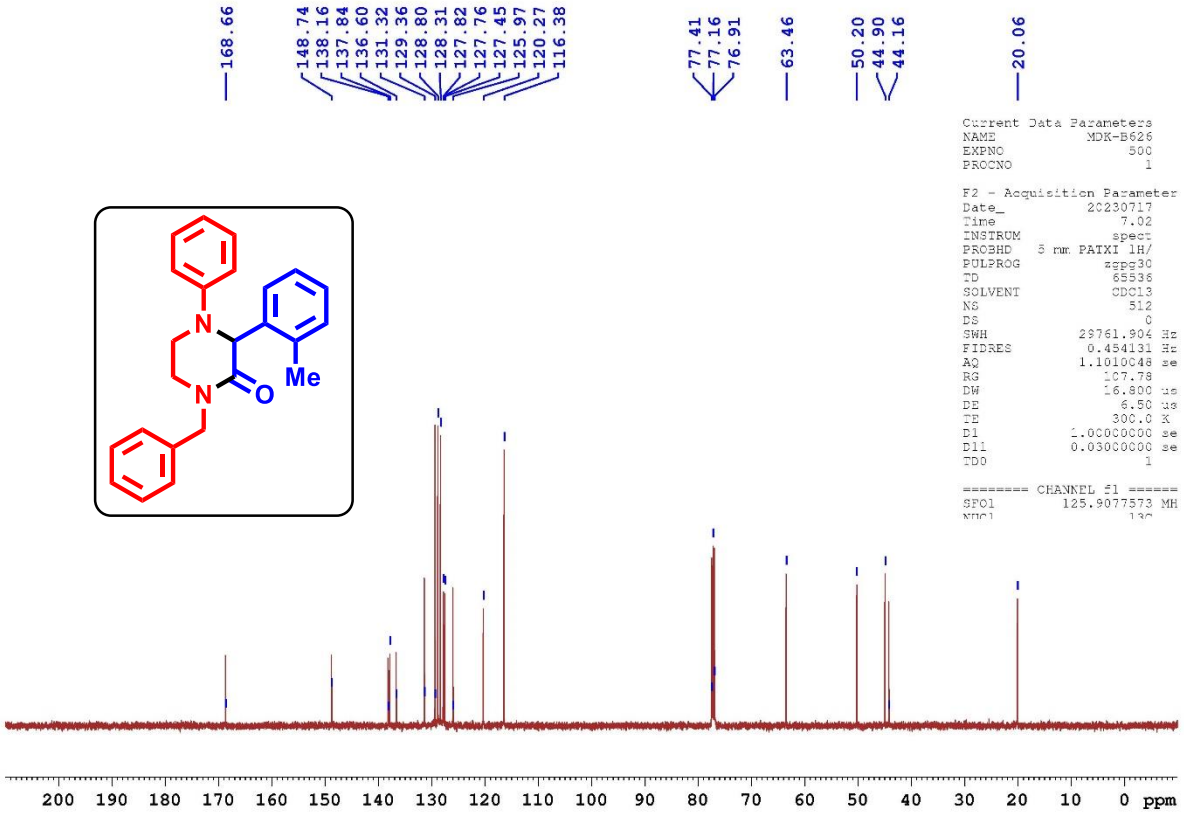


Figure S-18: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3ia**

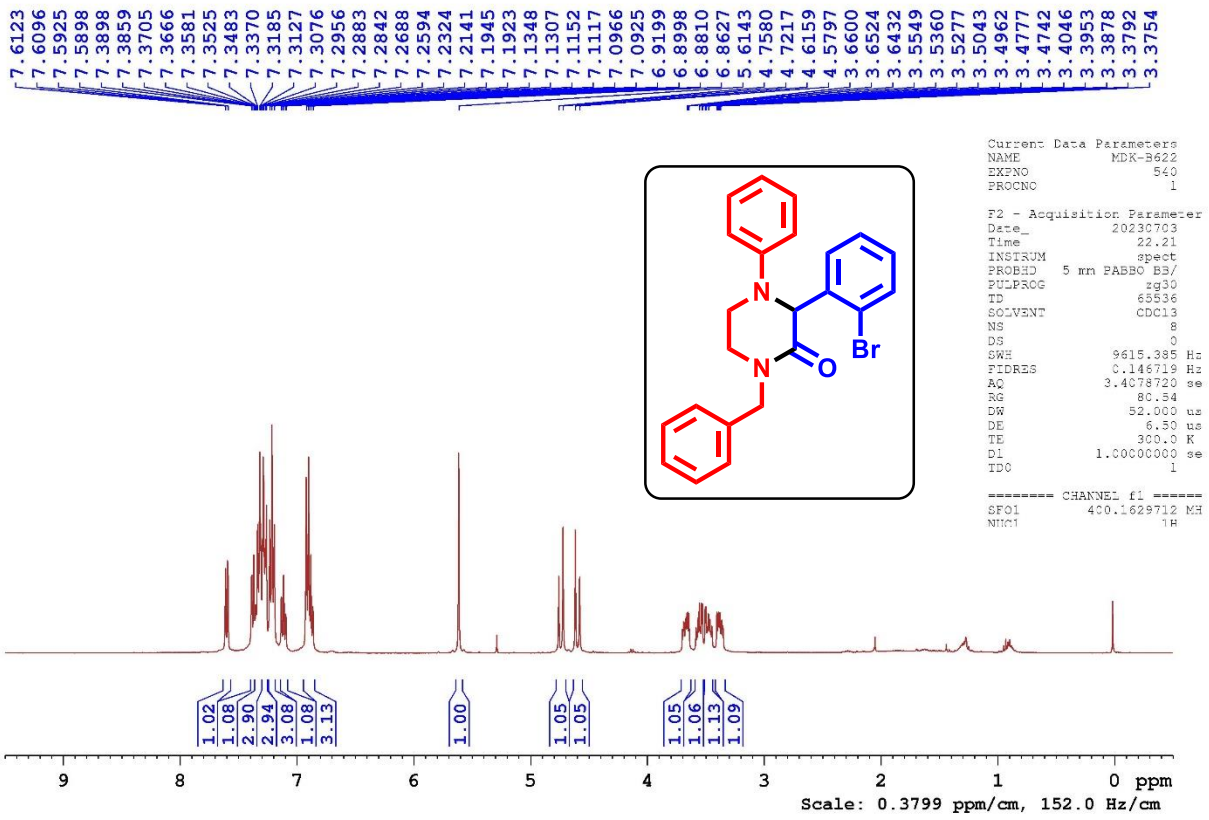


Figure S-19: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ja**

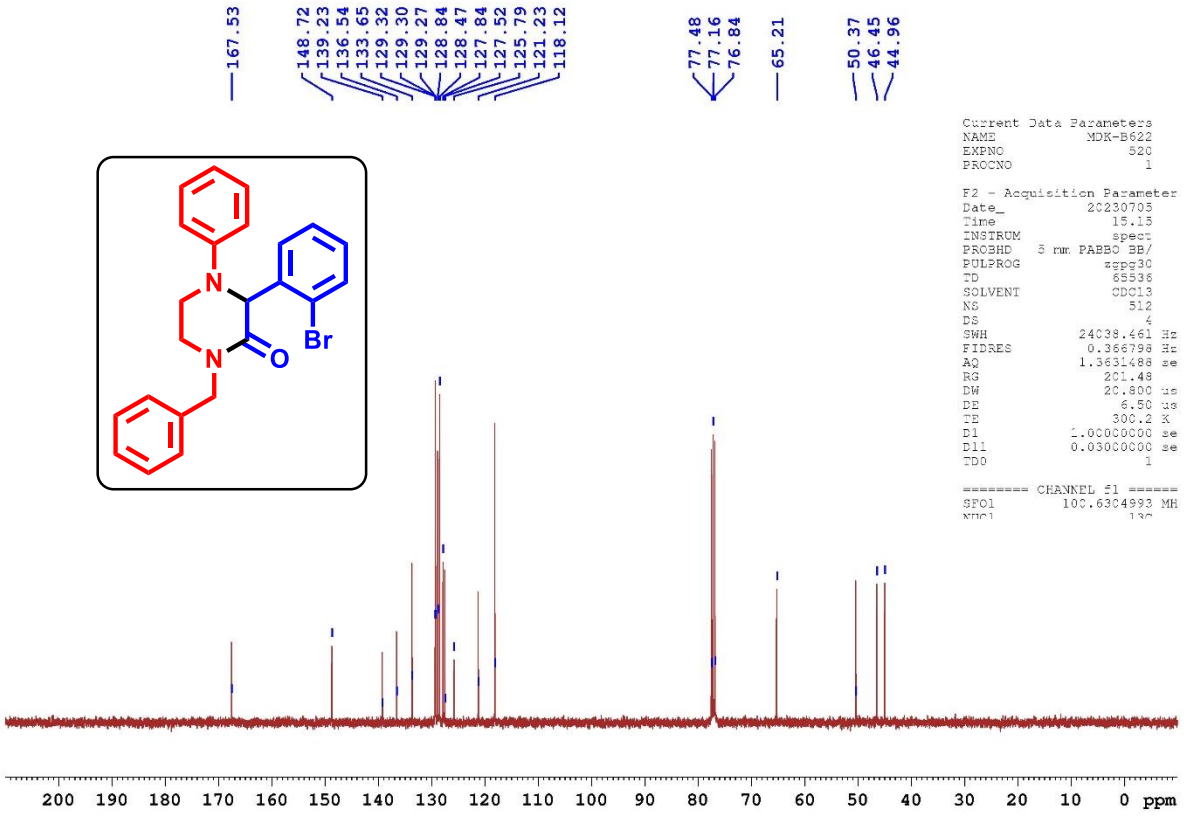


Figure S-20: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ja**

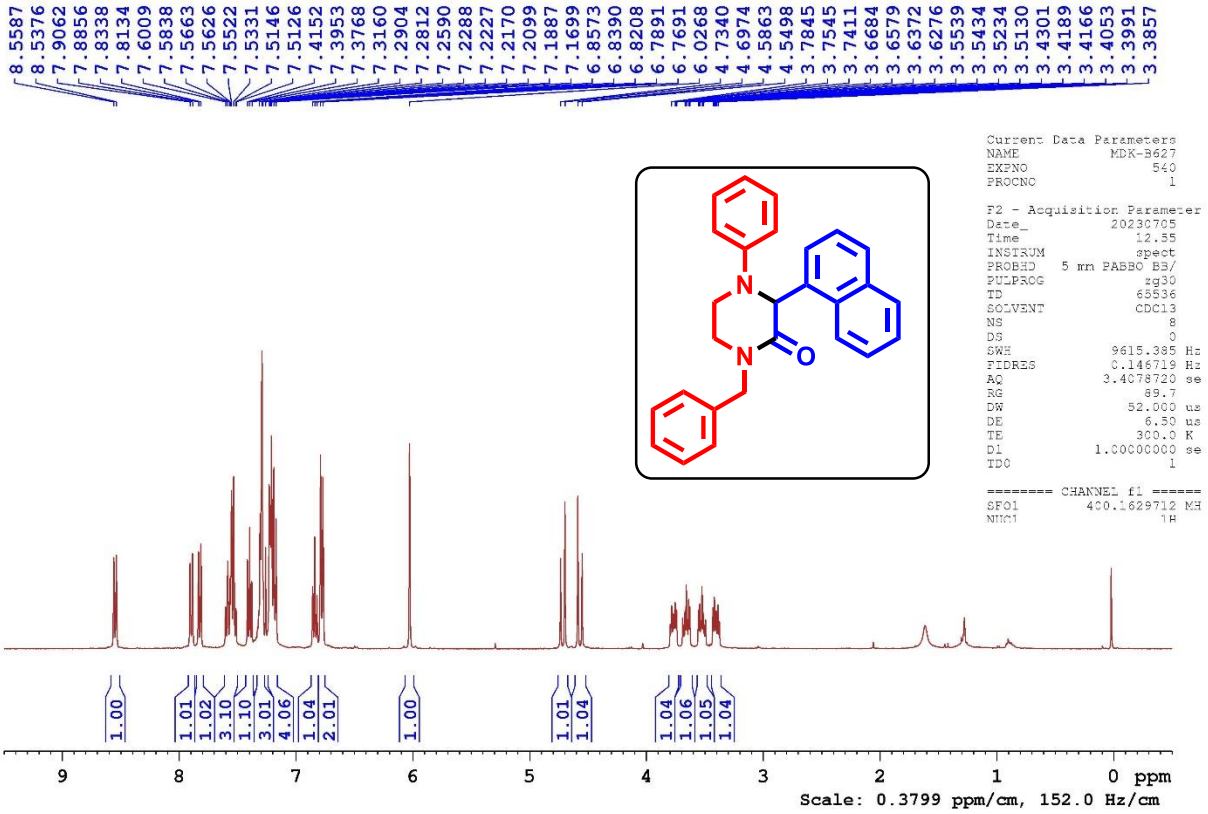


Figure S-21: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ka**

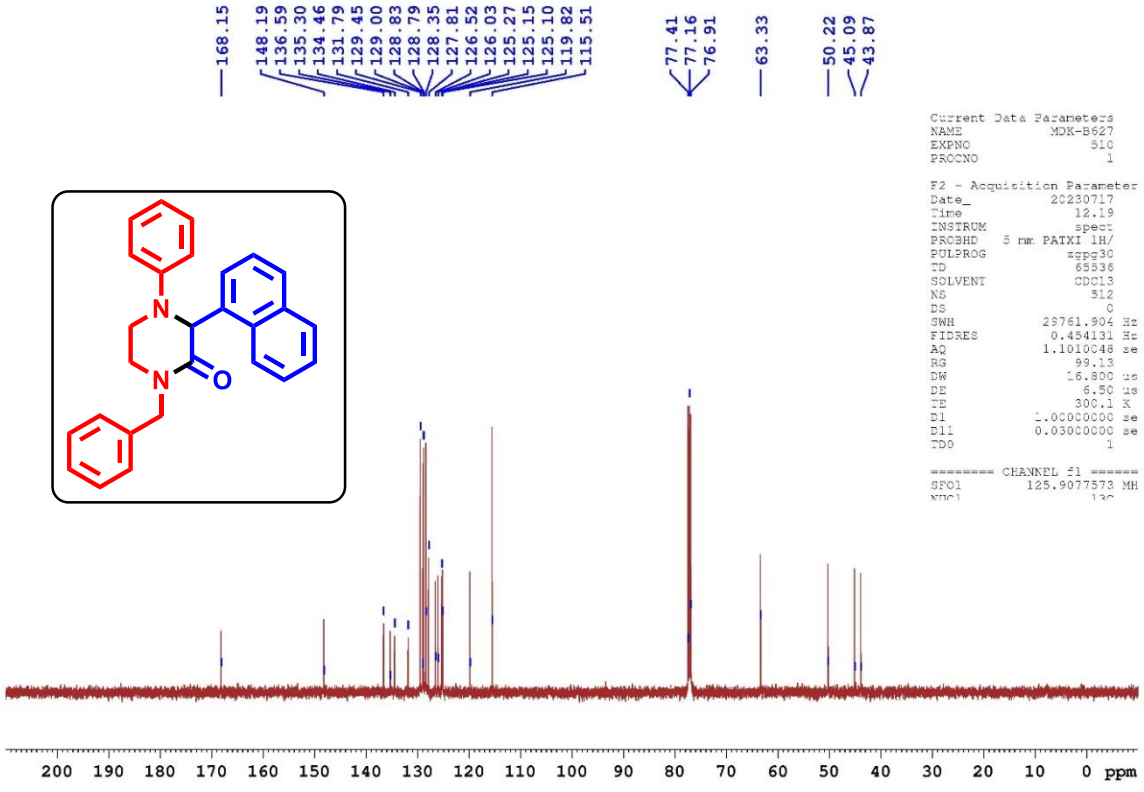


Figure S-22: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3ka**

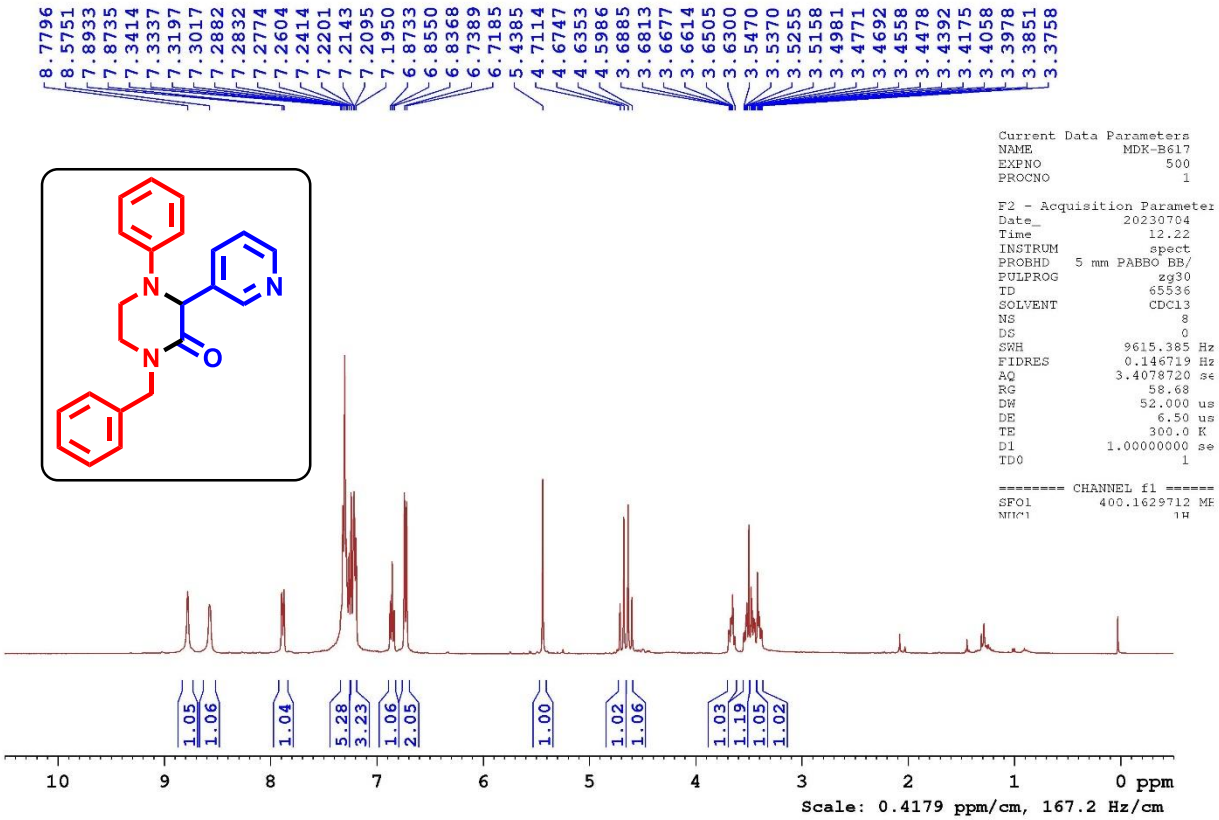


Figure S-23: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3la**

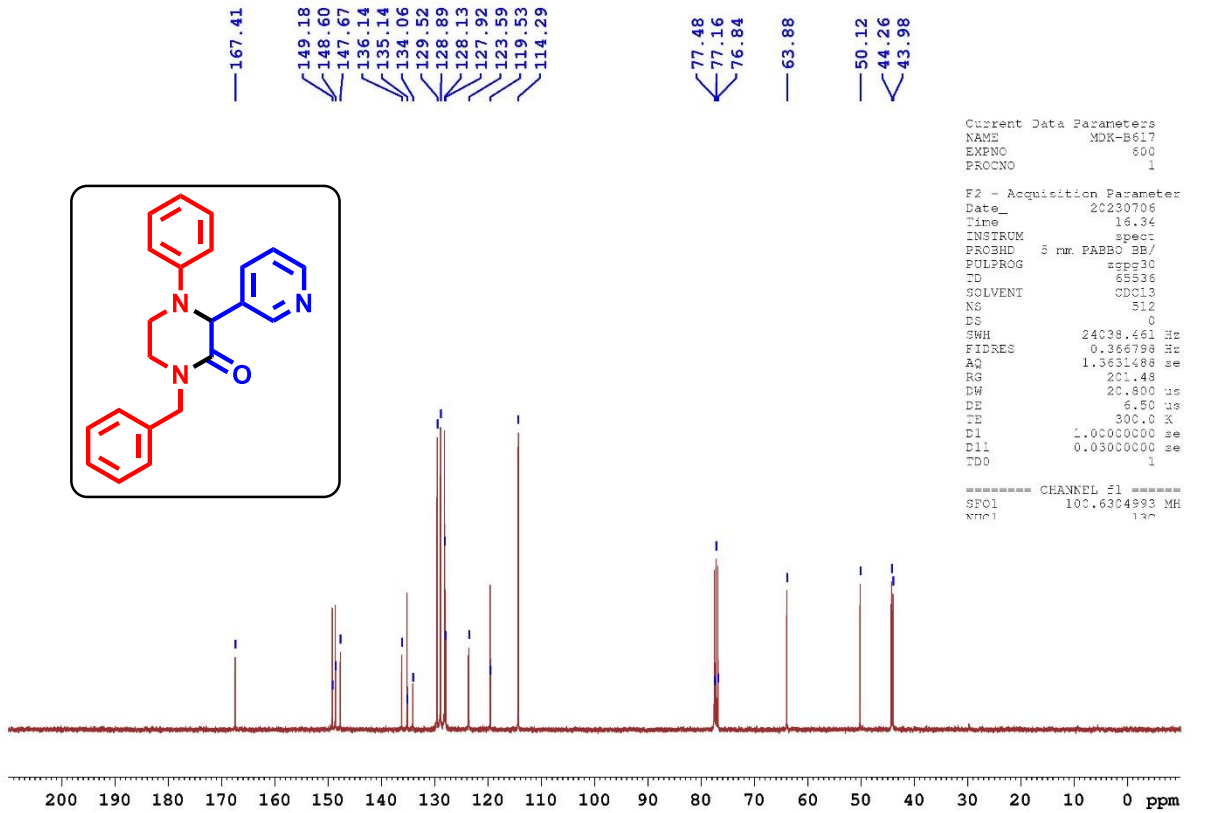


Figure S-24: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3la**

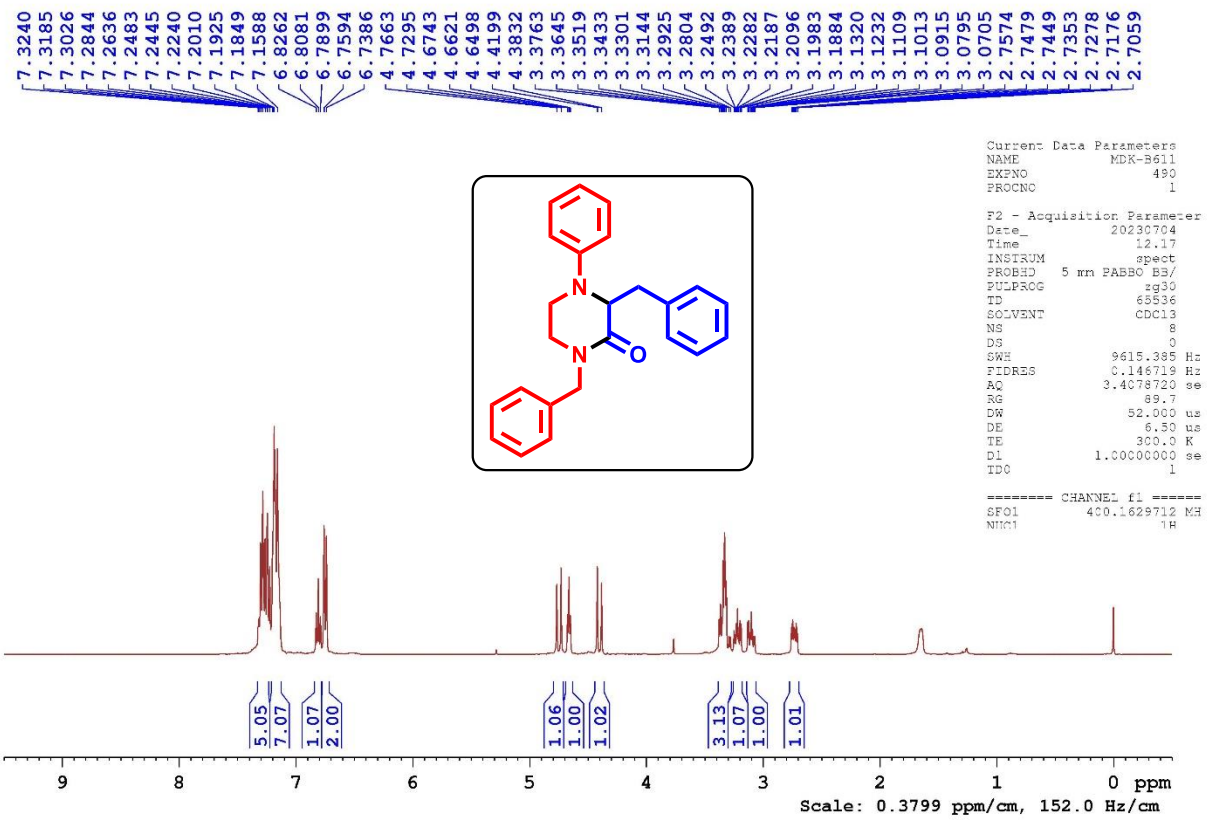


Figure S-25: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ma**

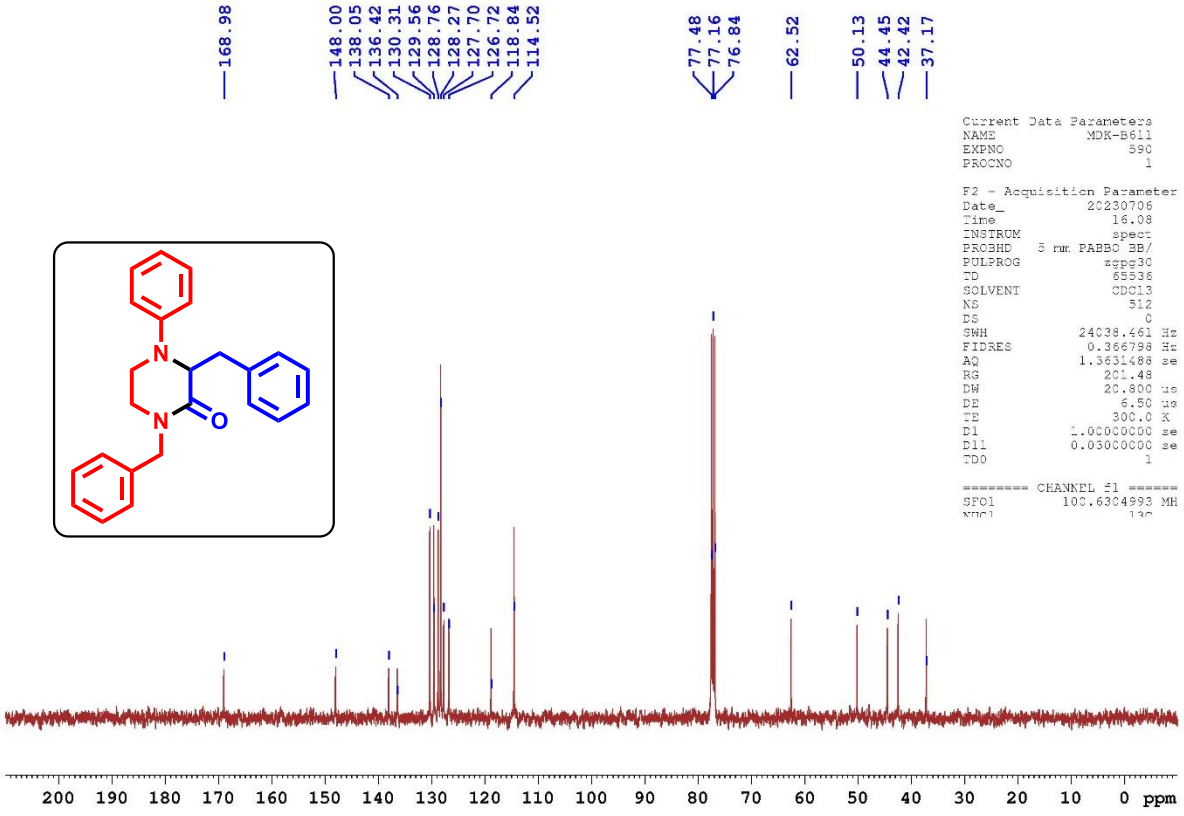


Figure S-26: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ma**

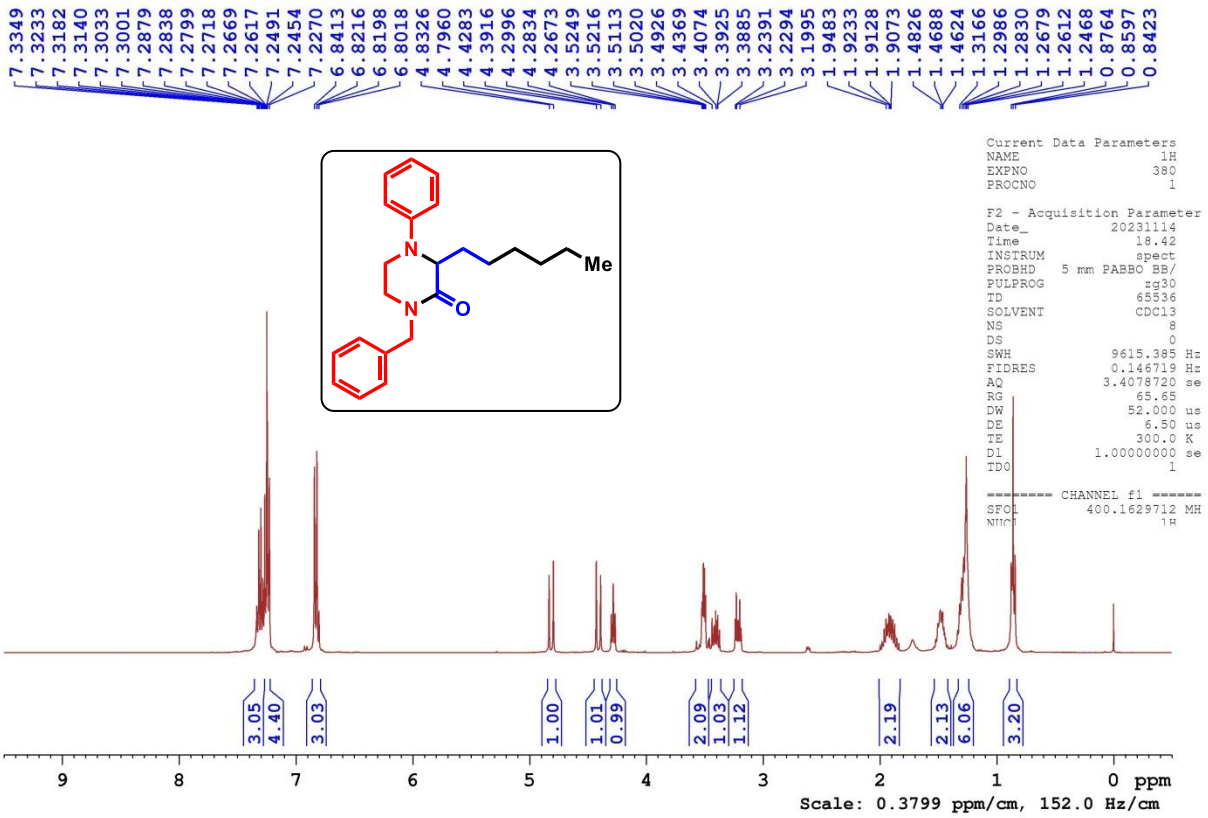


Figure S-27: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3na**

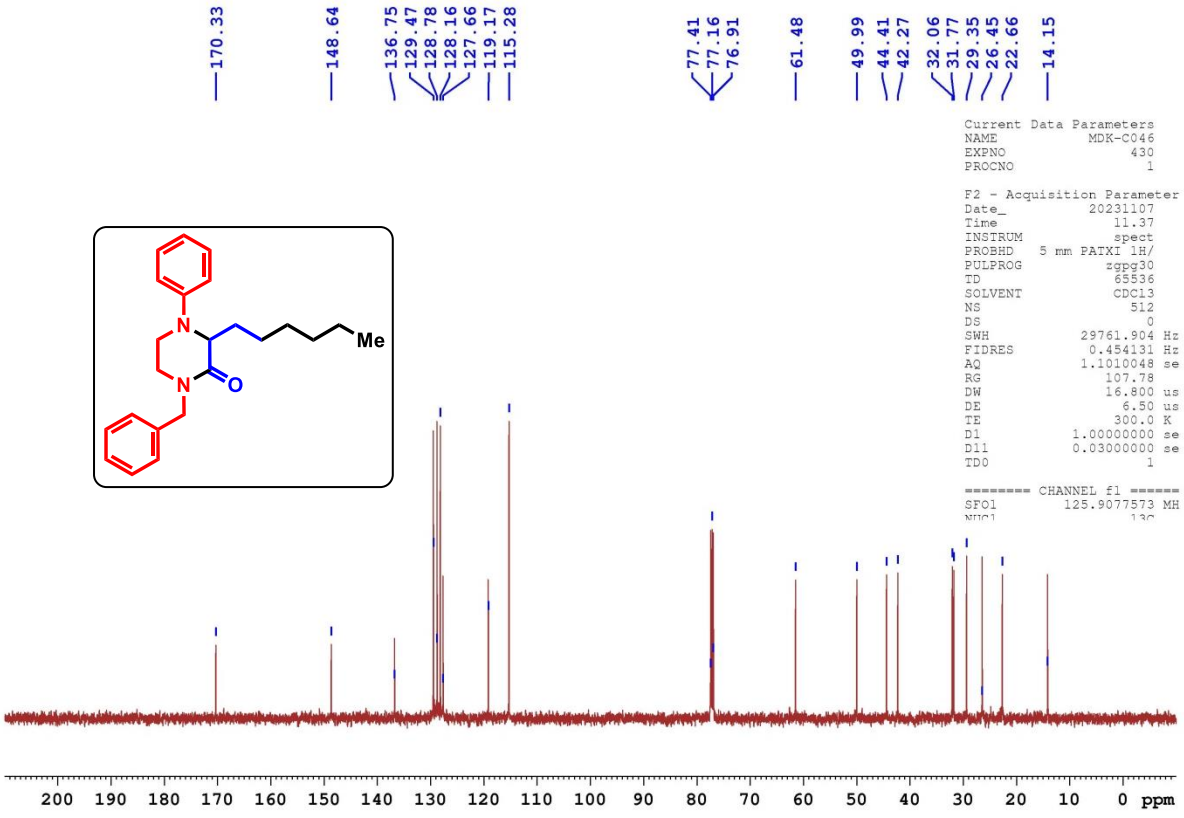


Figure S-28: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3na**

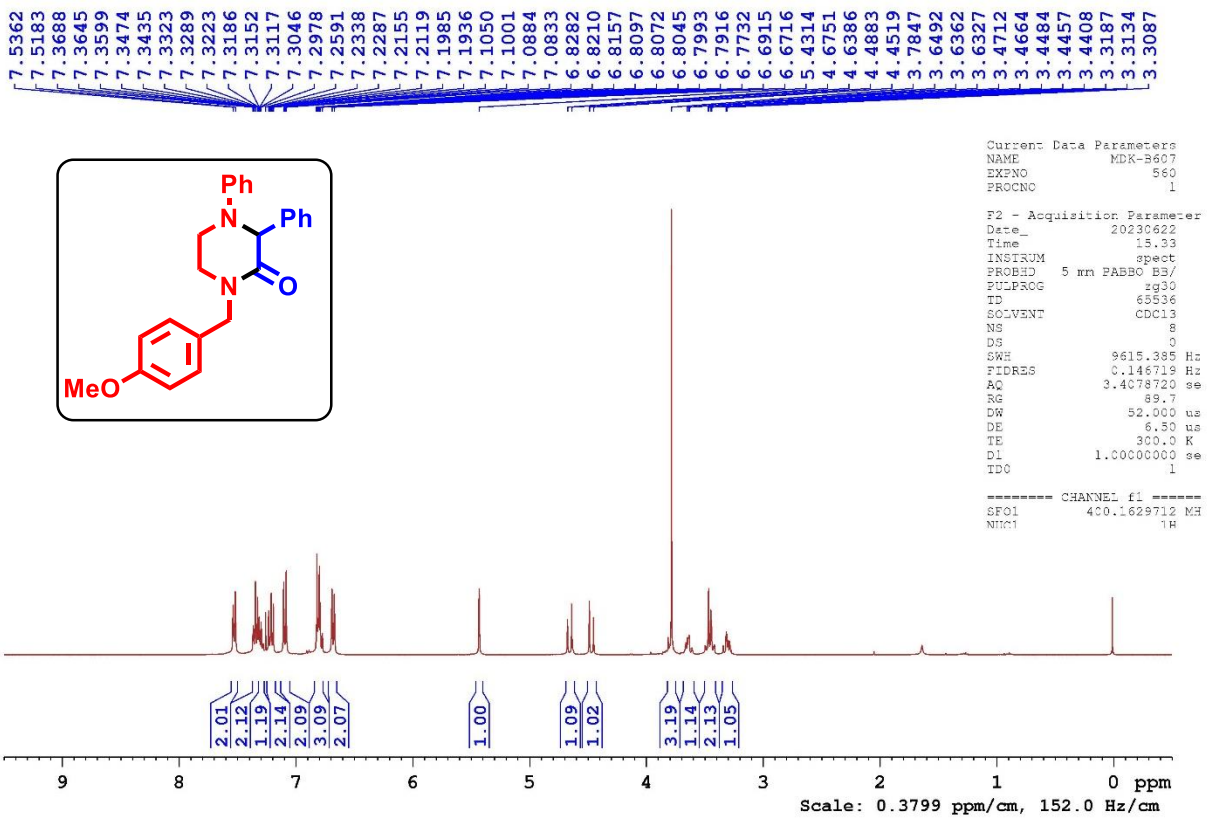


Figure S-29: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ab**

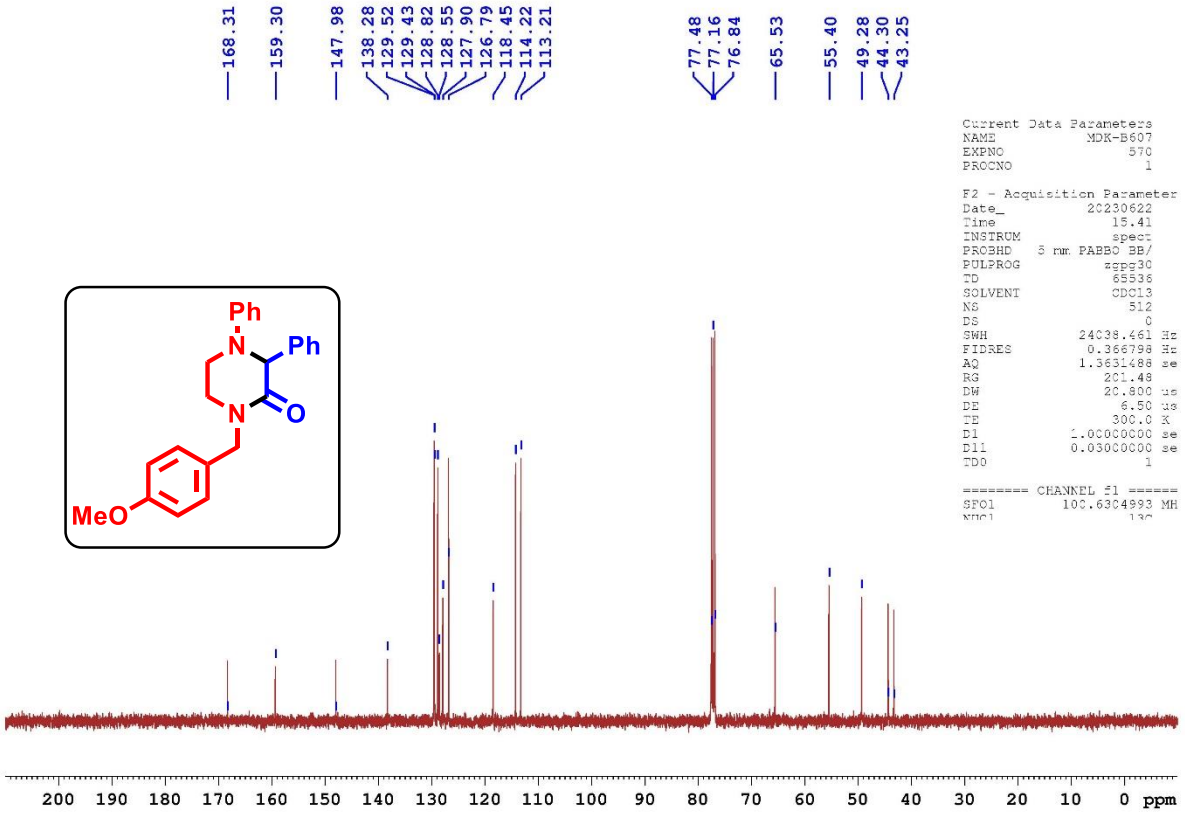


Figure S-30: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ab**

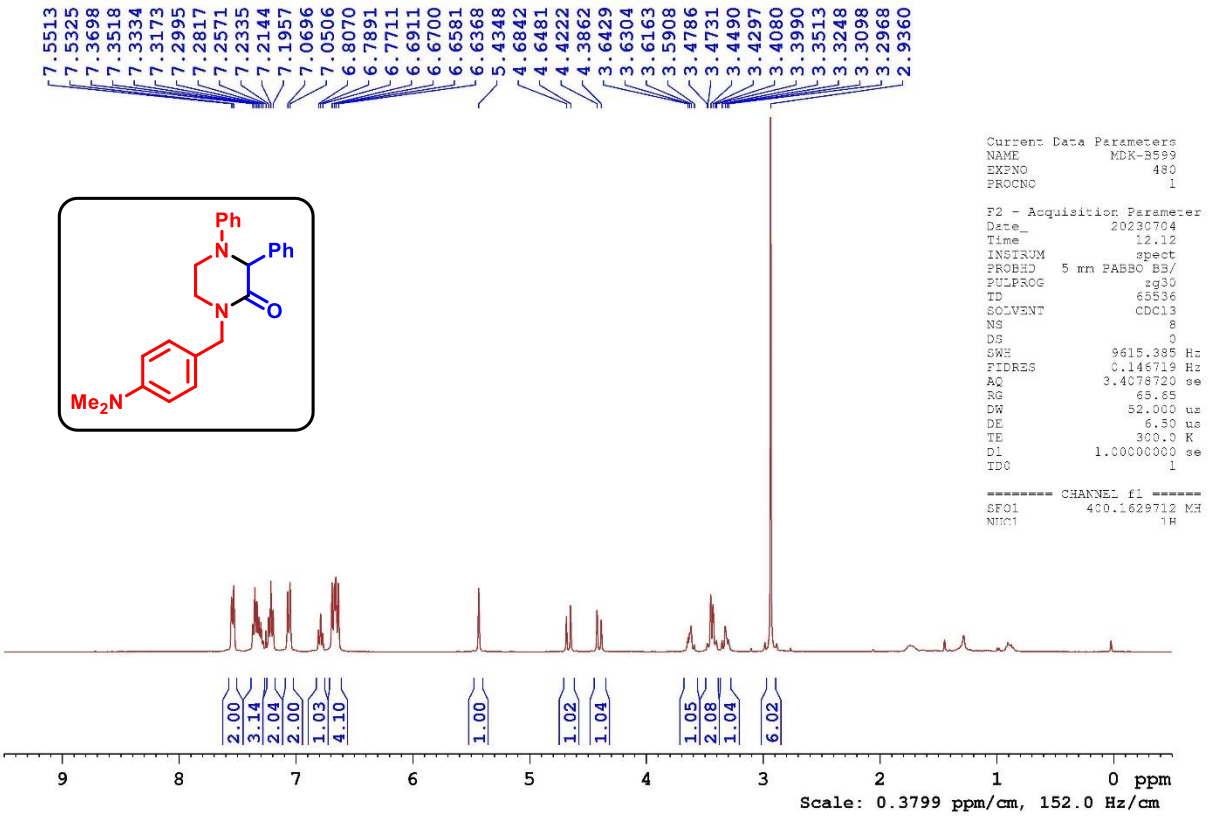


Figure S-31: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ac**

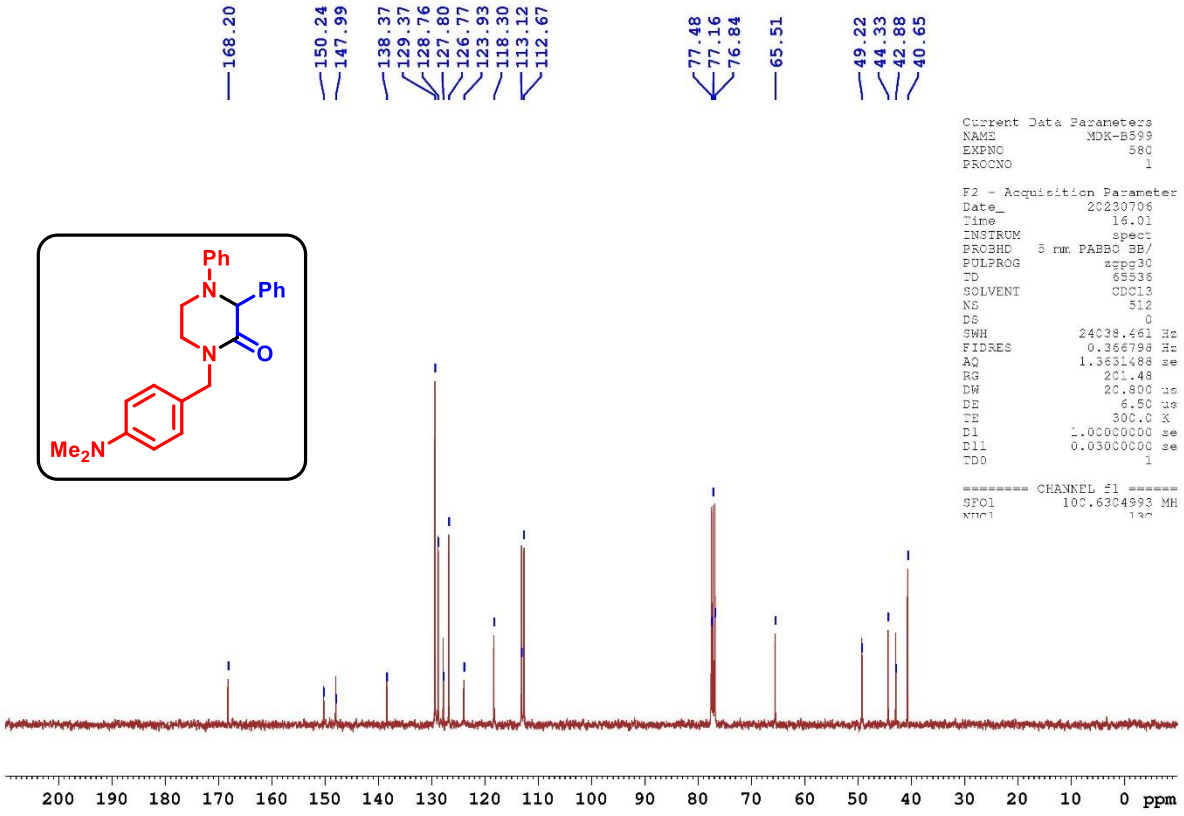


Figure S-32: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ac**

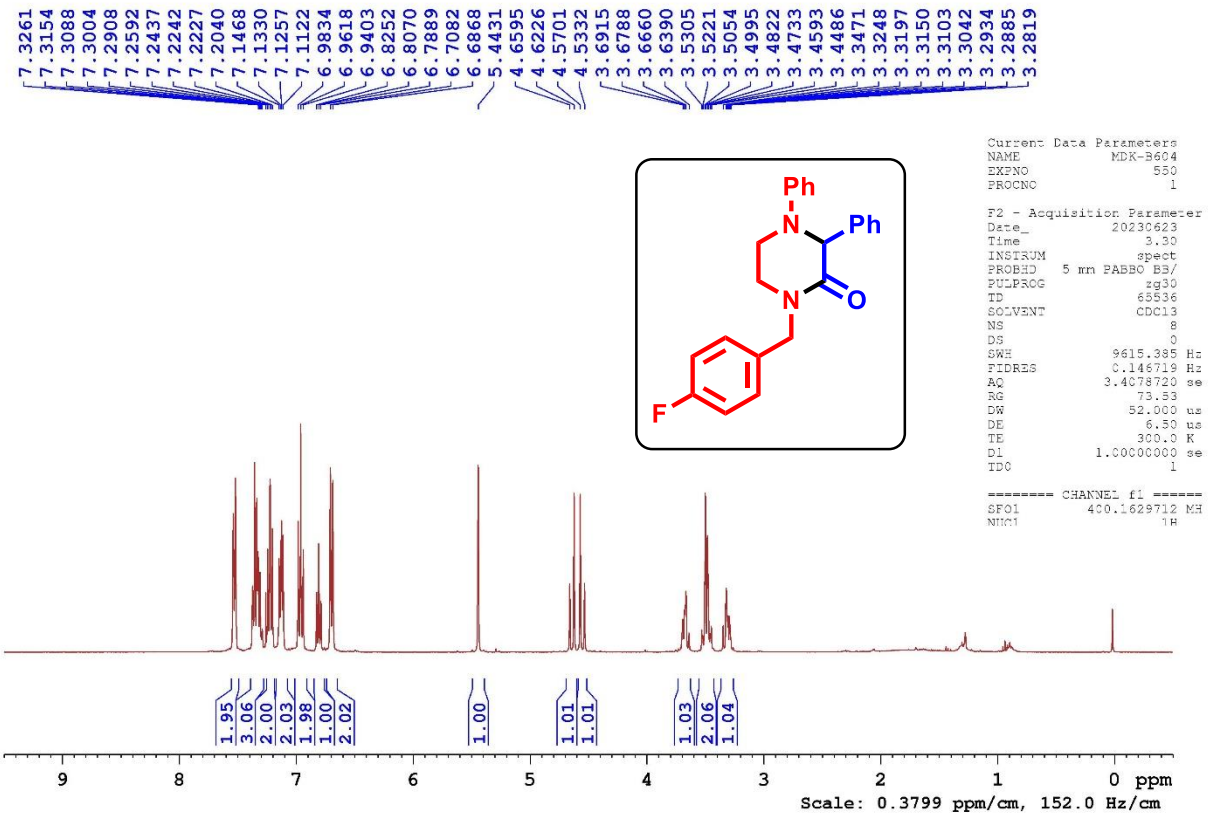


Figure S-33: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ad**

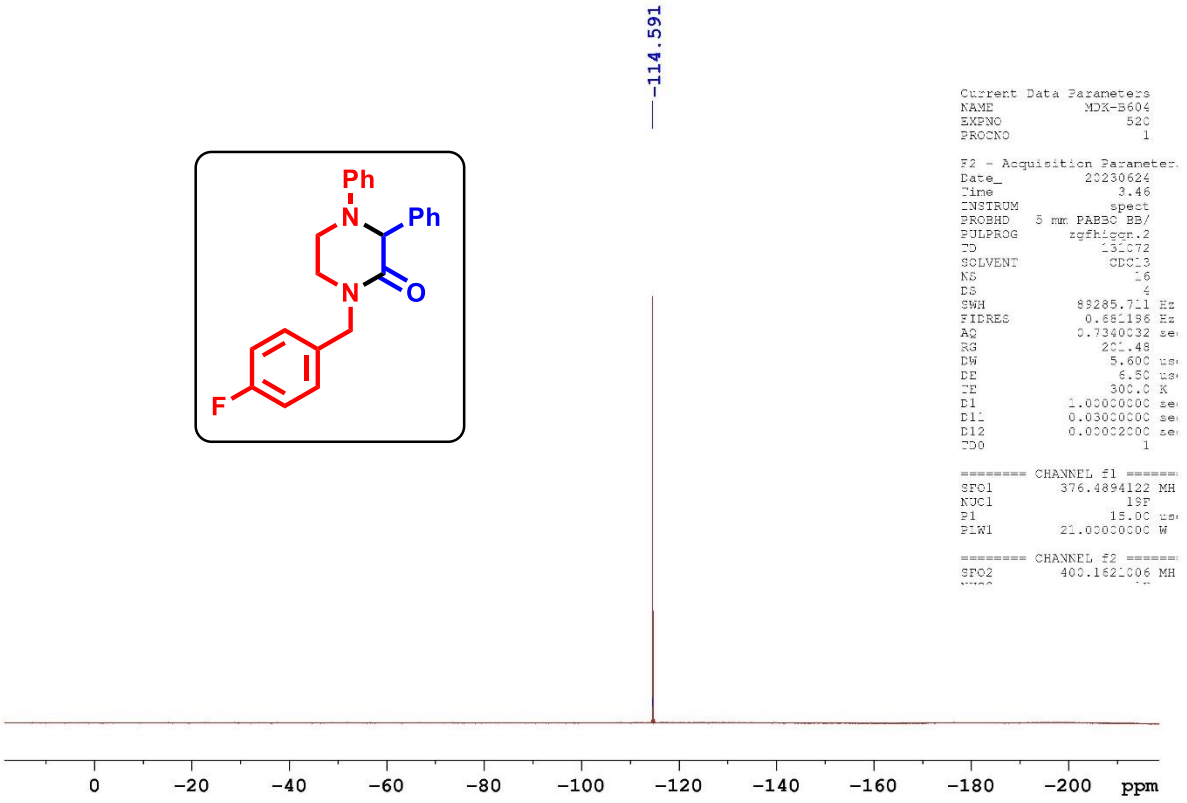


Figure S-34: ^{19}F NMR (376 MHz, $CDCl_3$) spectrum of compound **3ad**

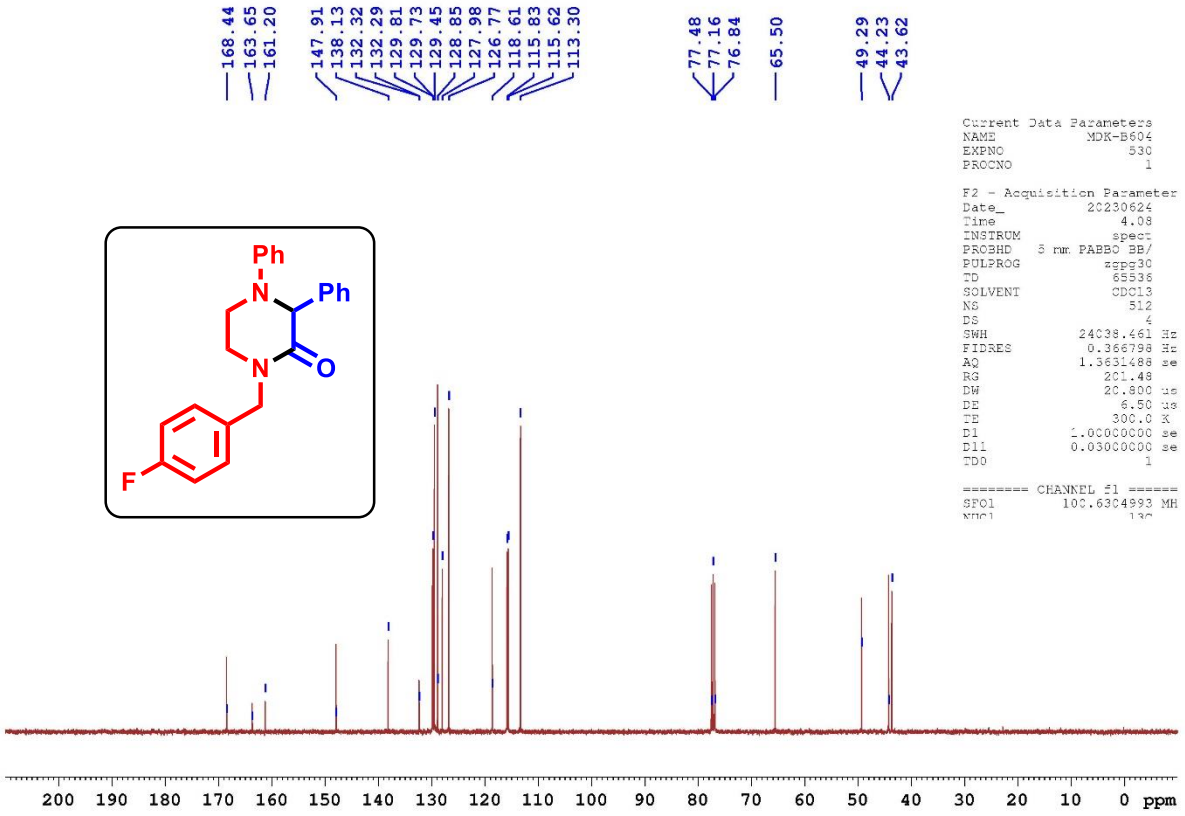


Figure S-35: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ad**

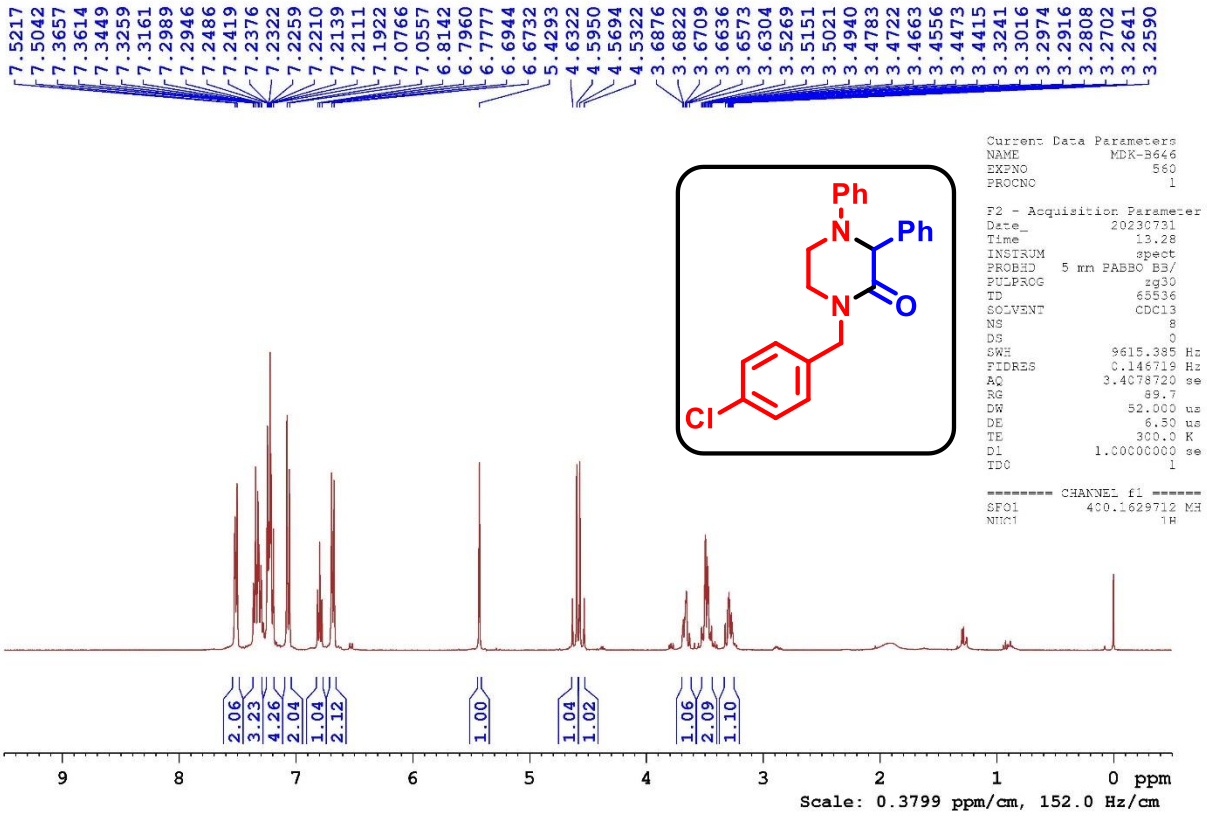


Figure S-36: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ae**

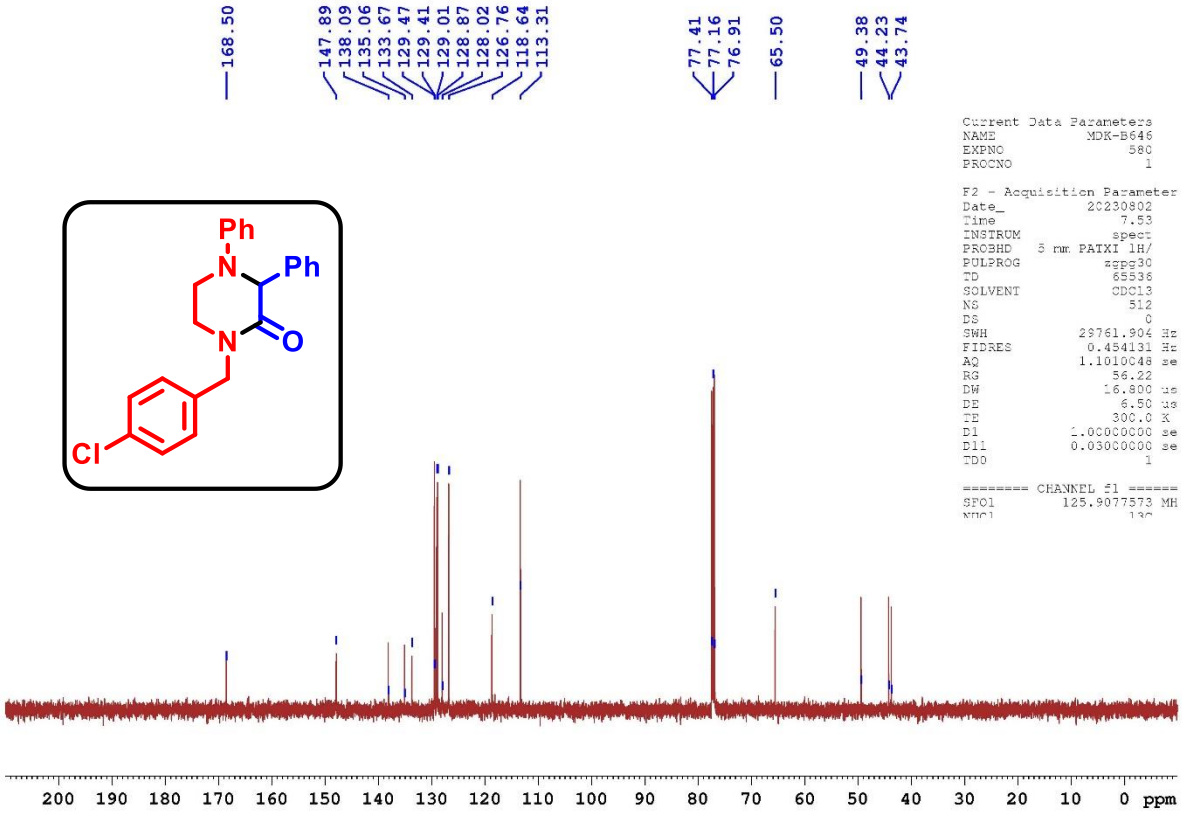


Figure S-37: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3ae**

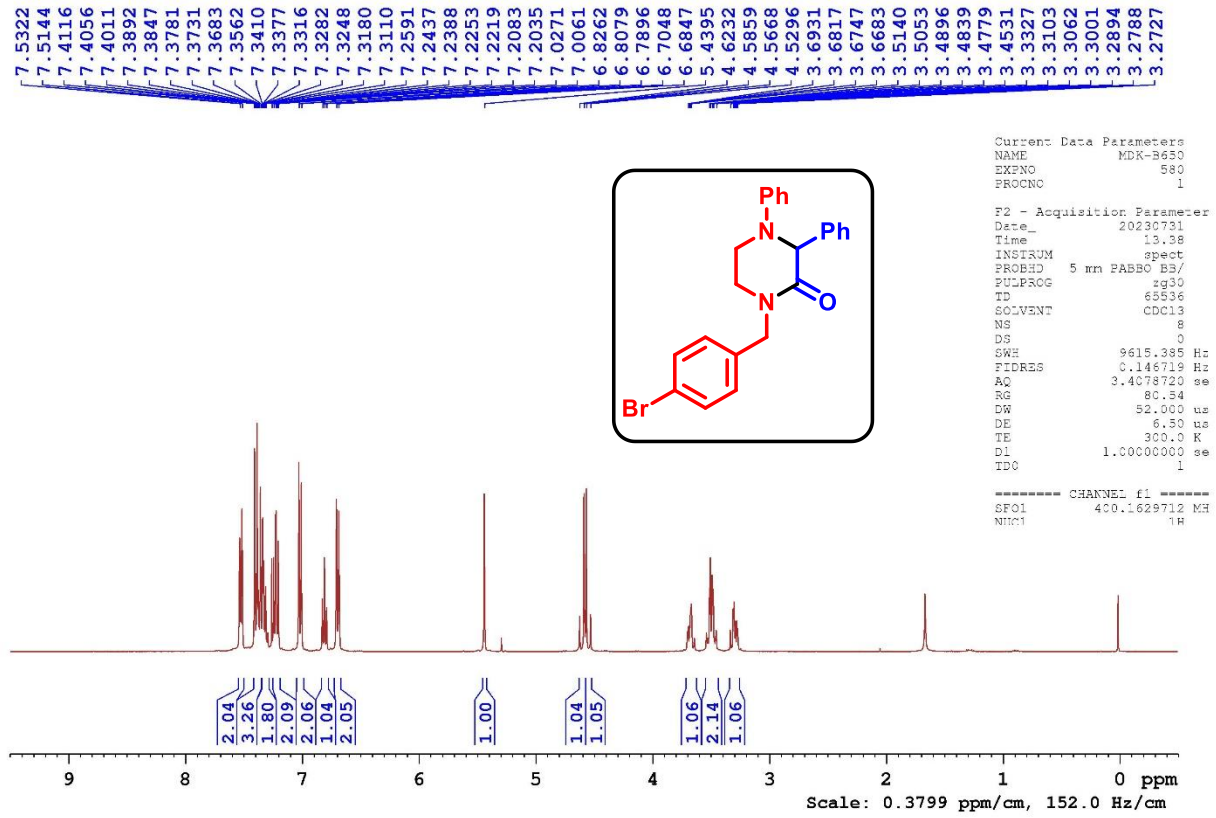


Figure S-38: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3af**

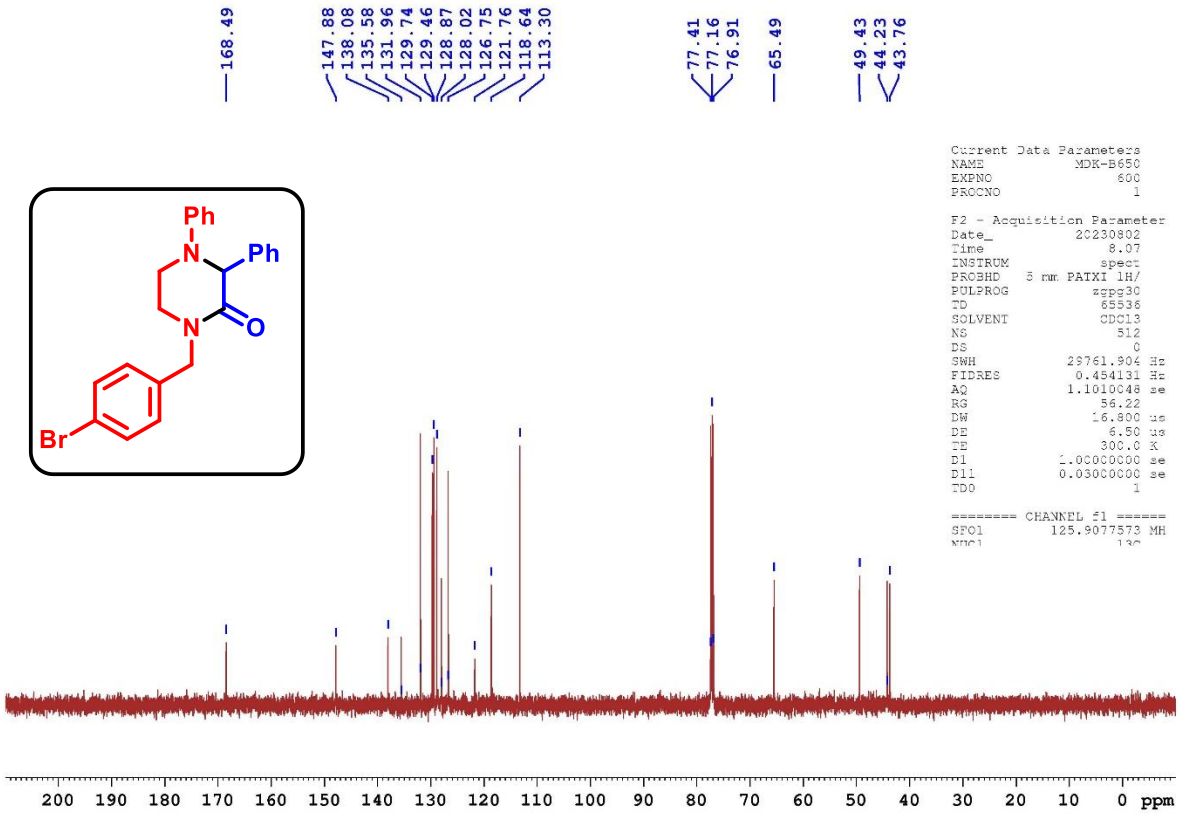


Figure S-39: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3af**

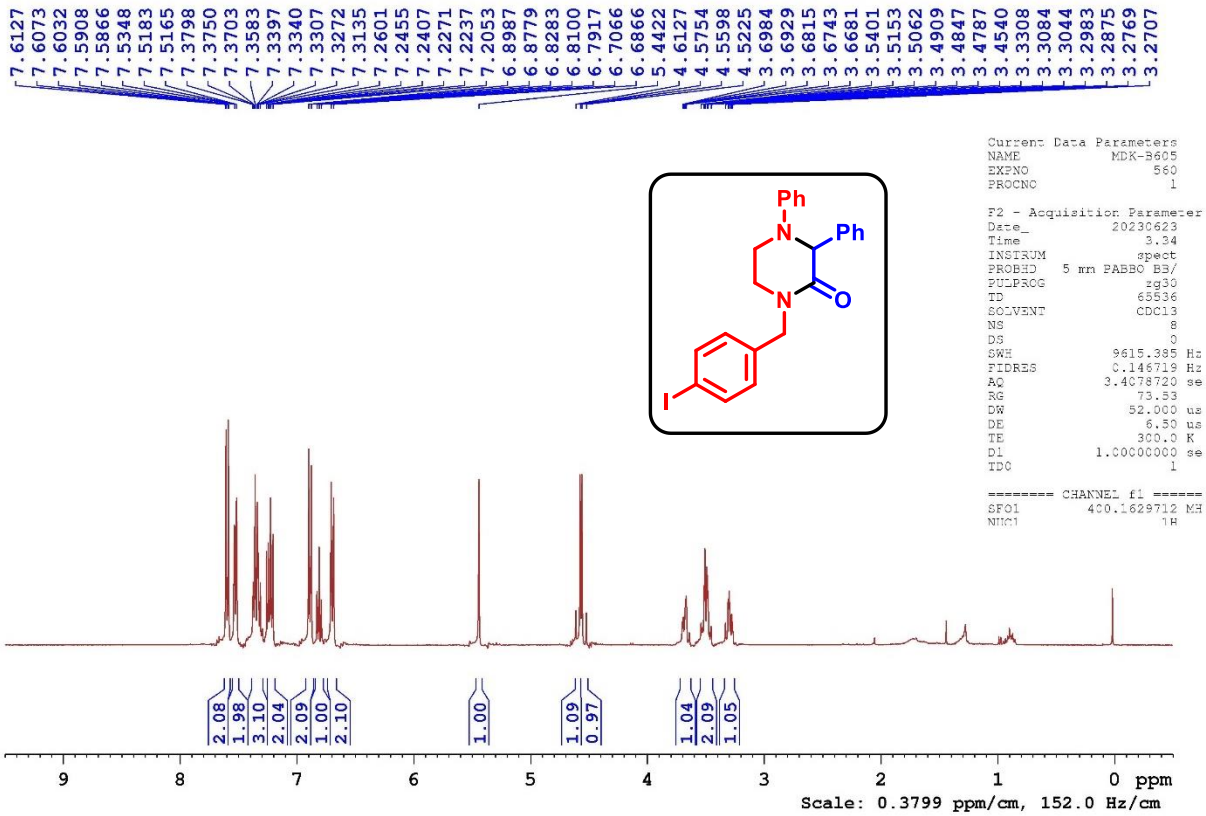


Figure S-40: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ag**

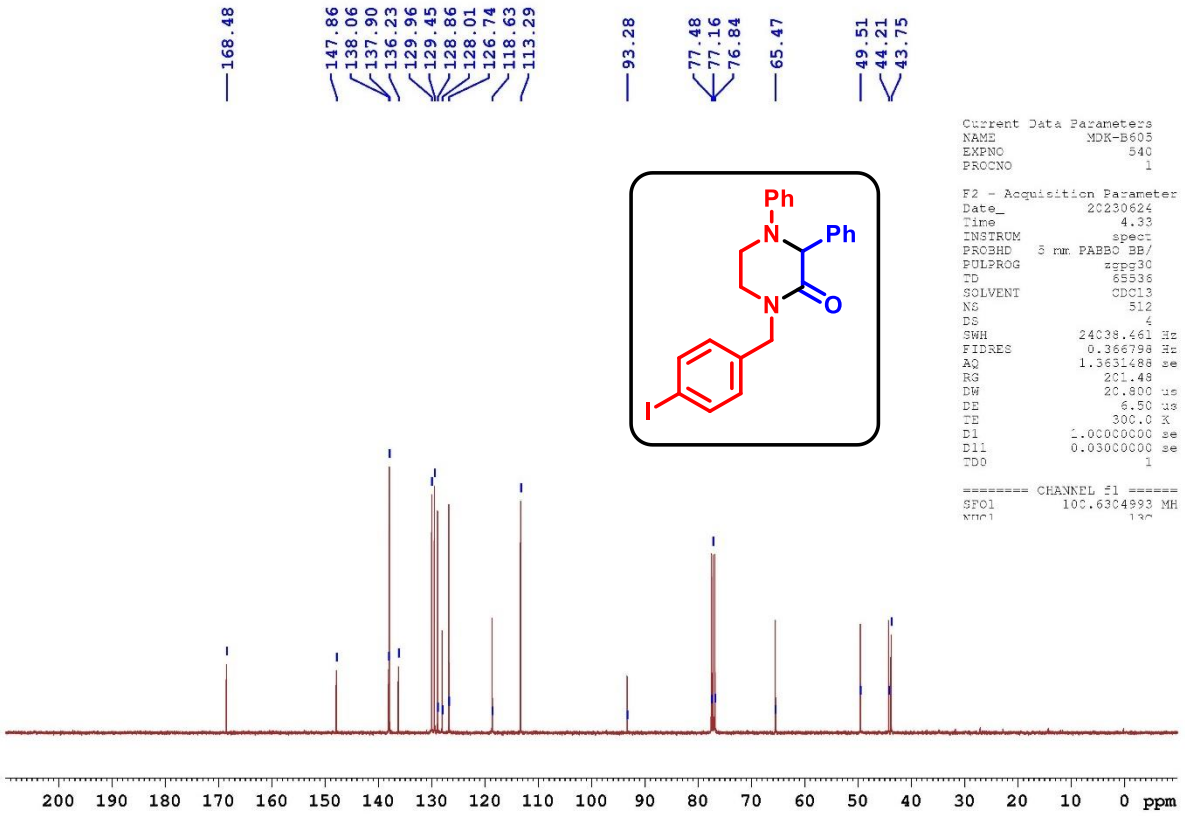


Figure S-41: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ag**

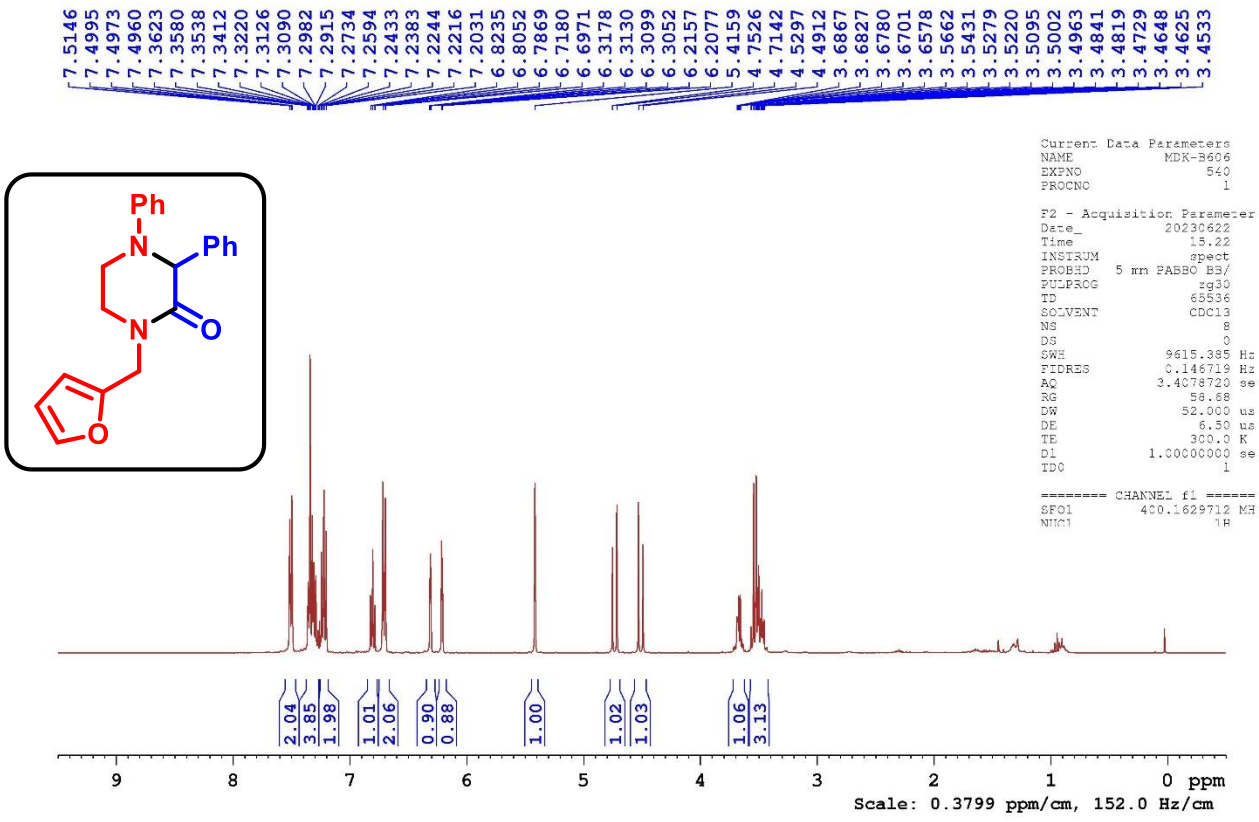


Figure S-42: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ah**

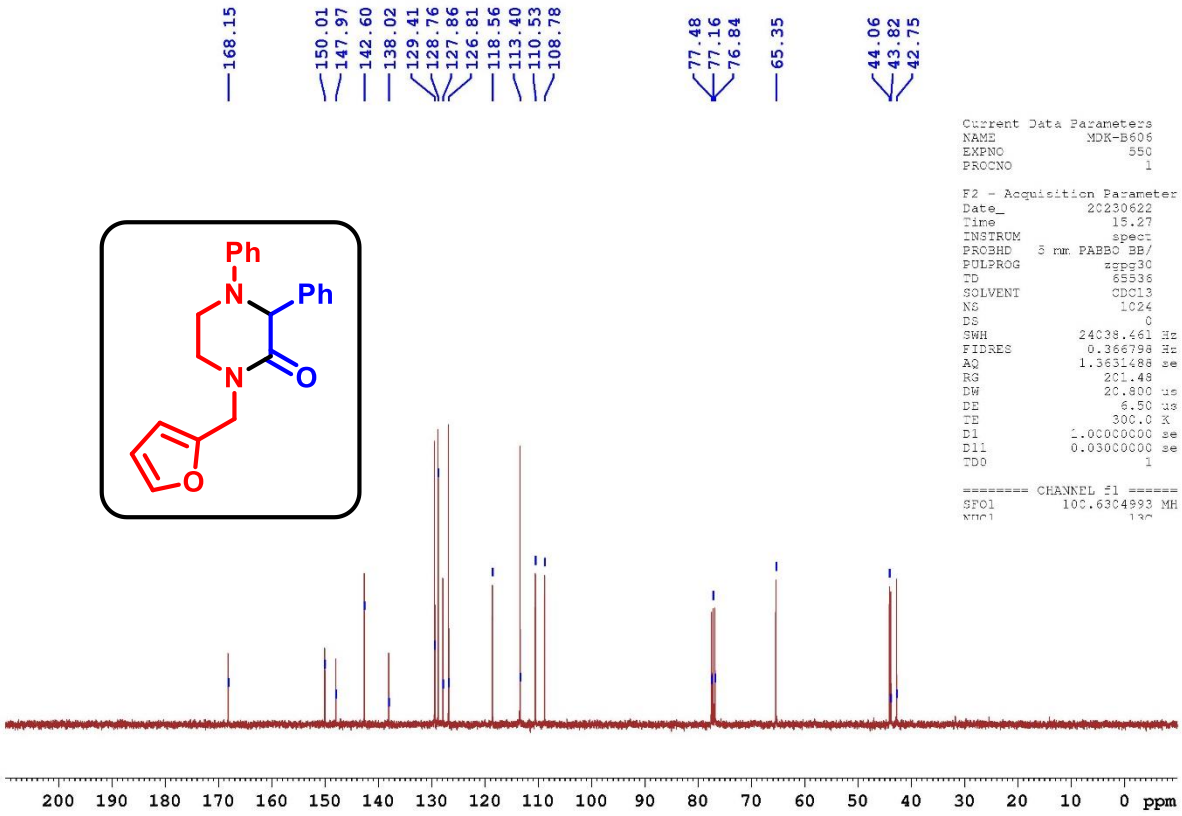


Figure S-43: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ah**

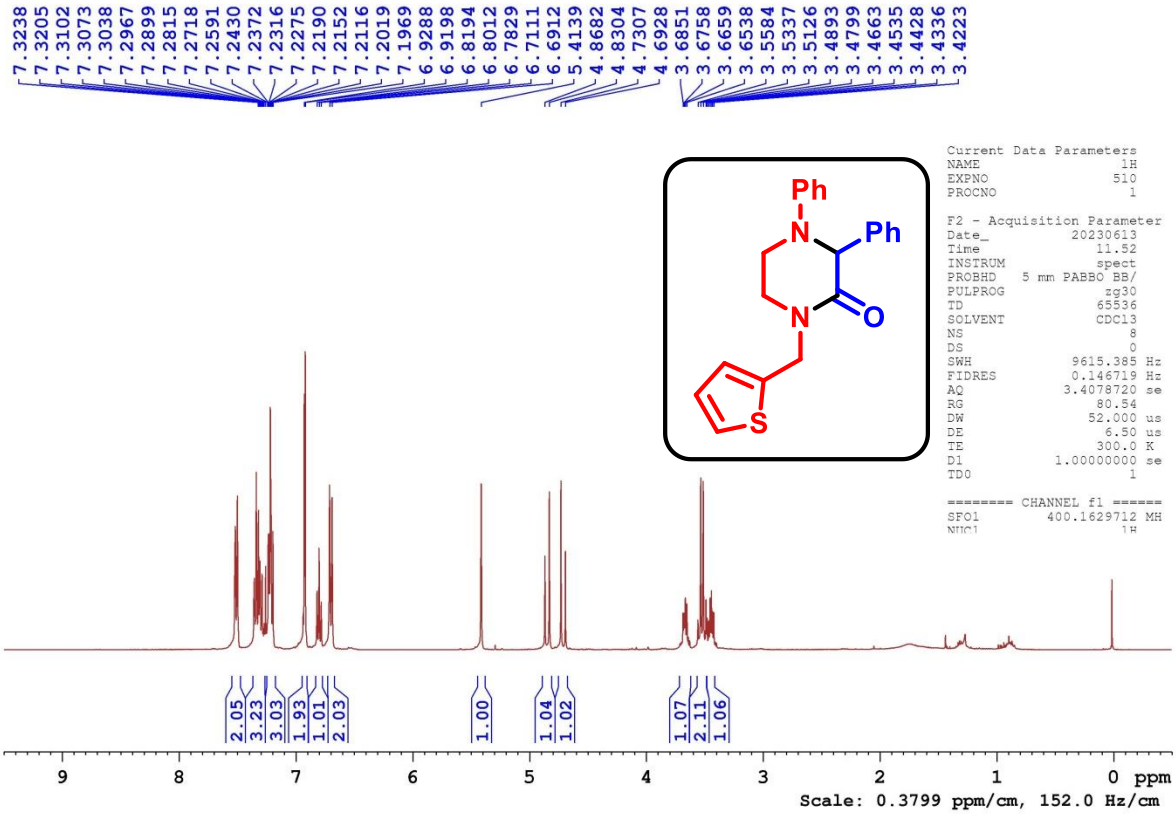


Figure S-44: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ai**

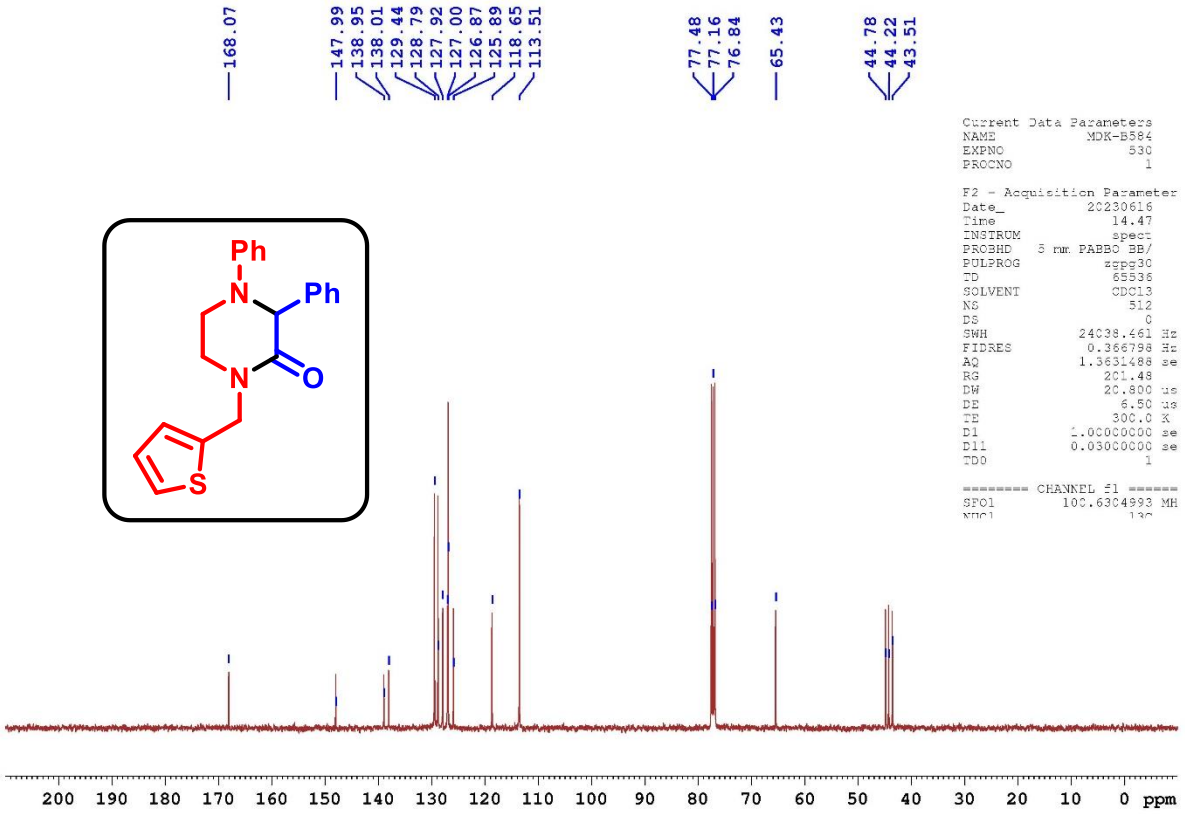


Figure S-45: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ai**

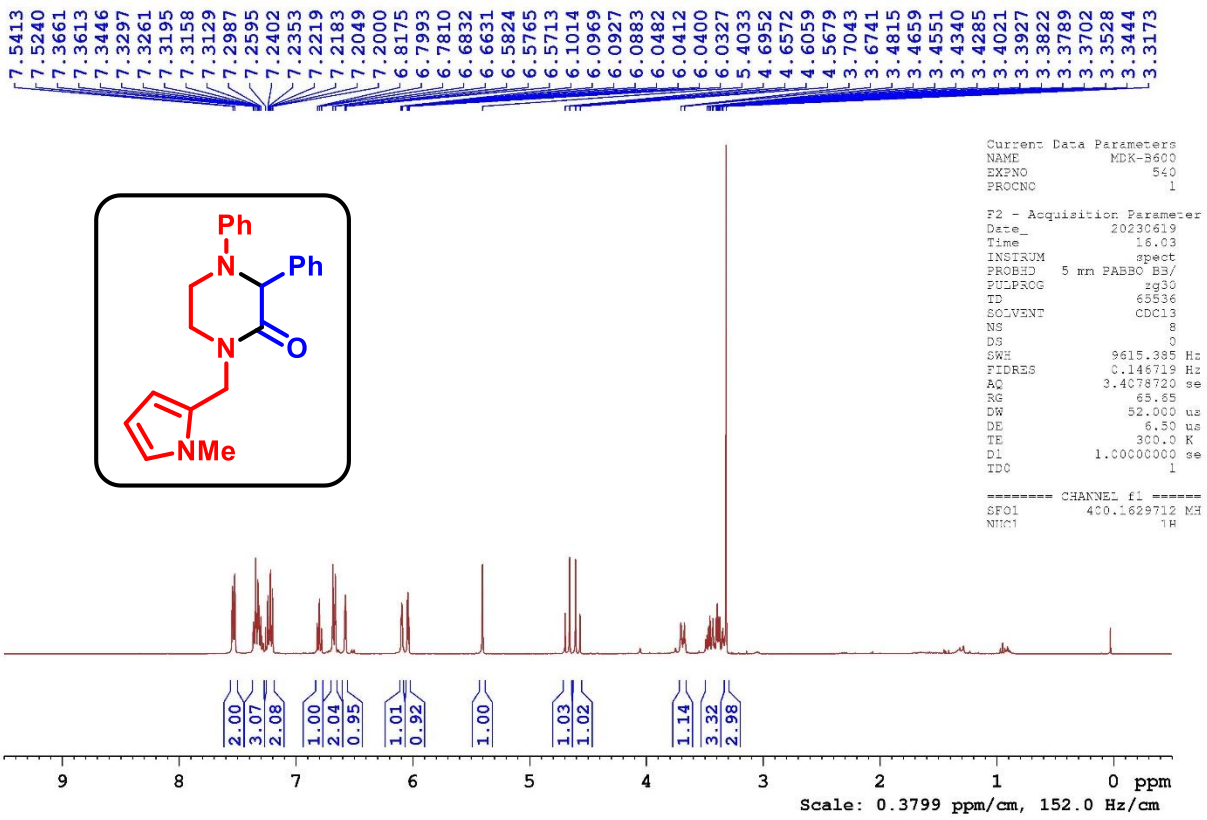


Figure S-46: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3aj**

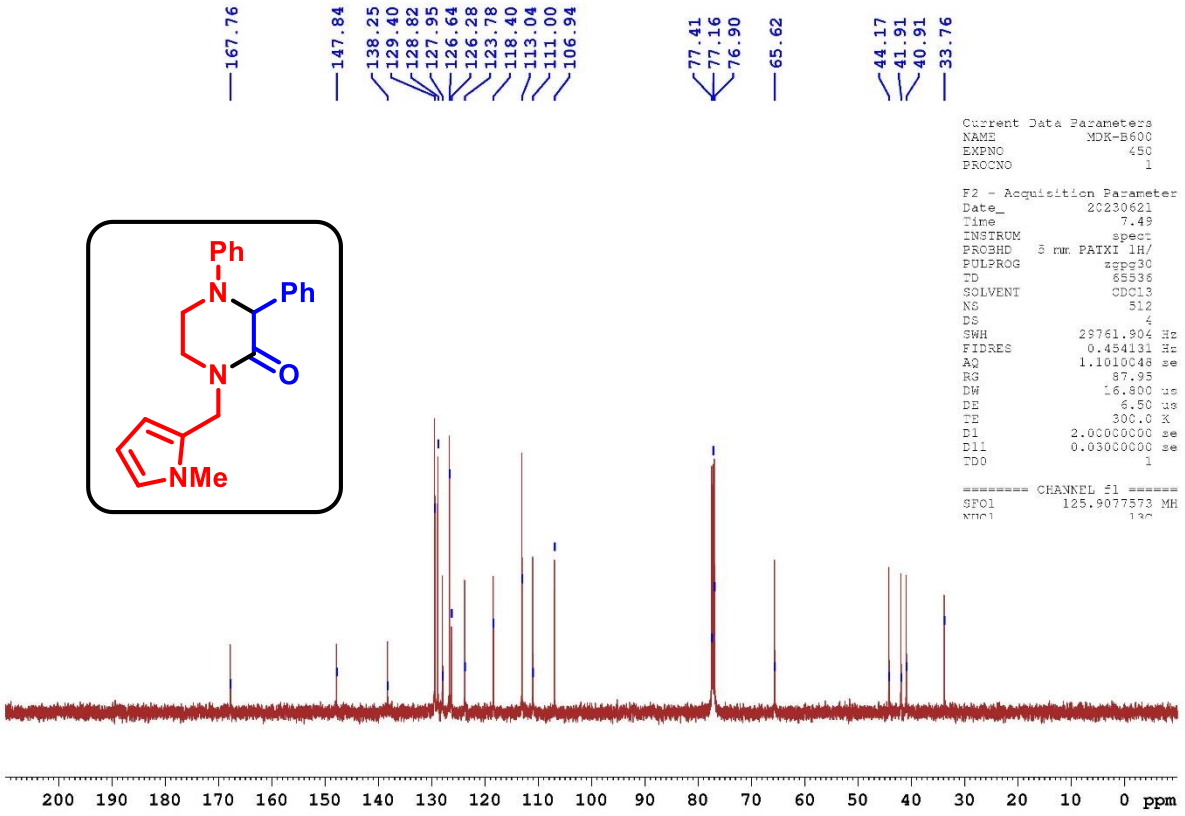


Figure S-47: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3aj**

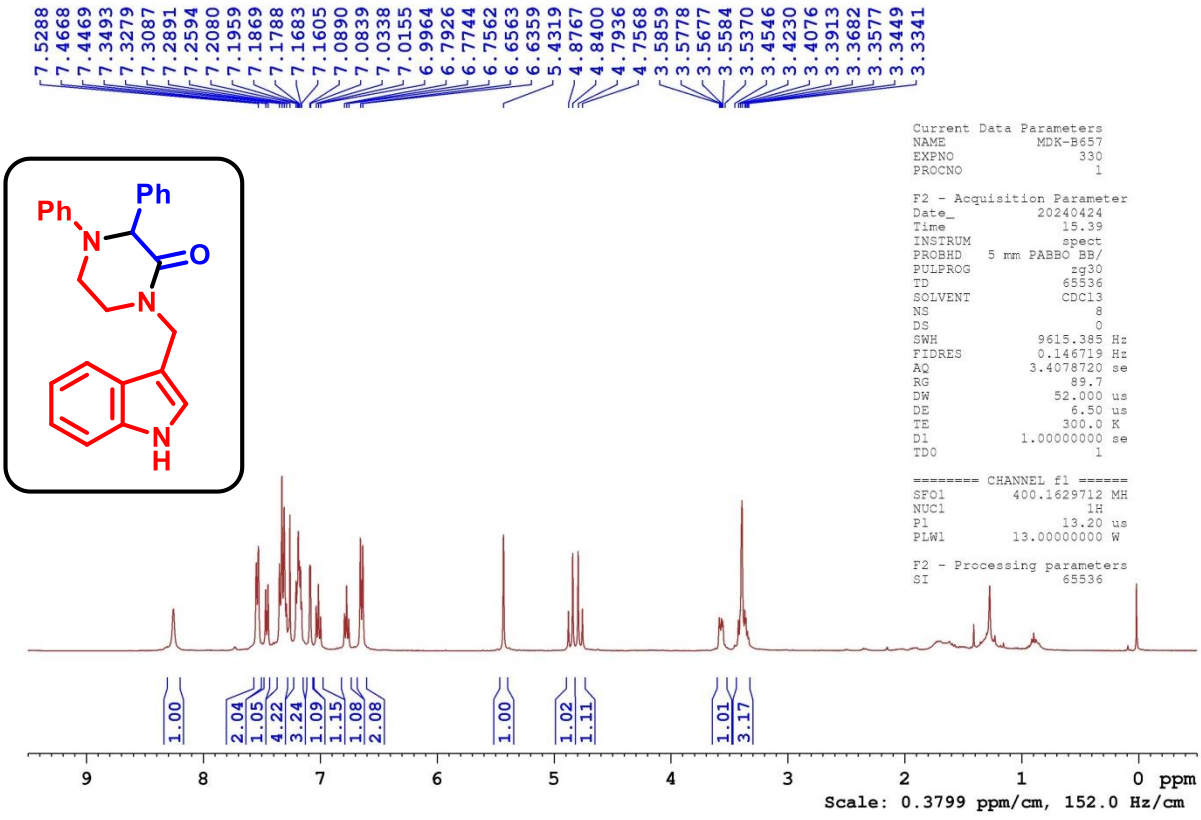


Figure S-48: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ak**

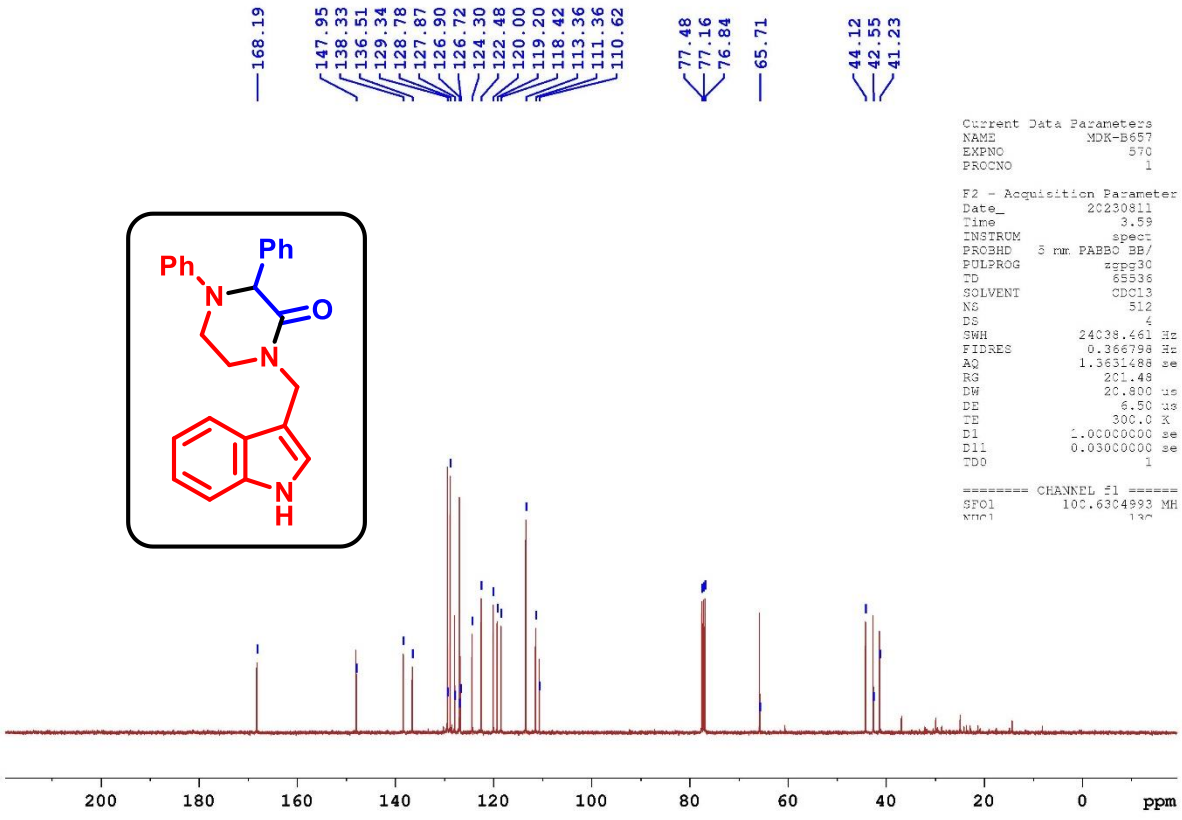


Figure S-49: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ak**

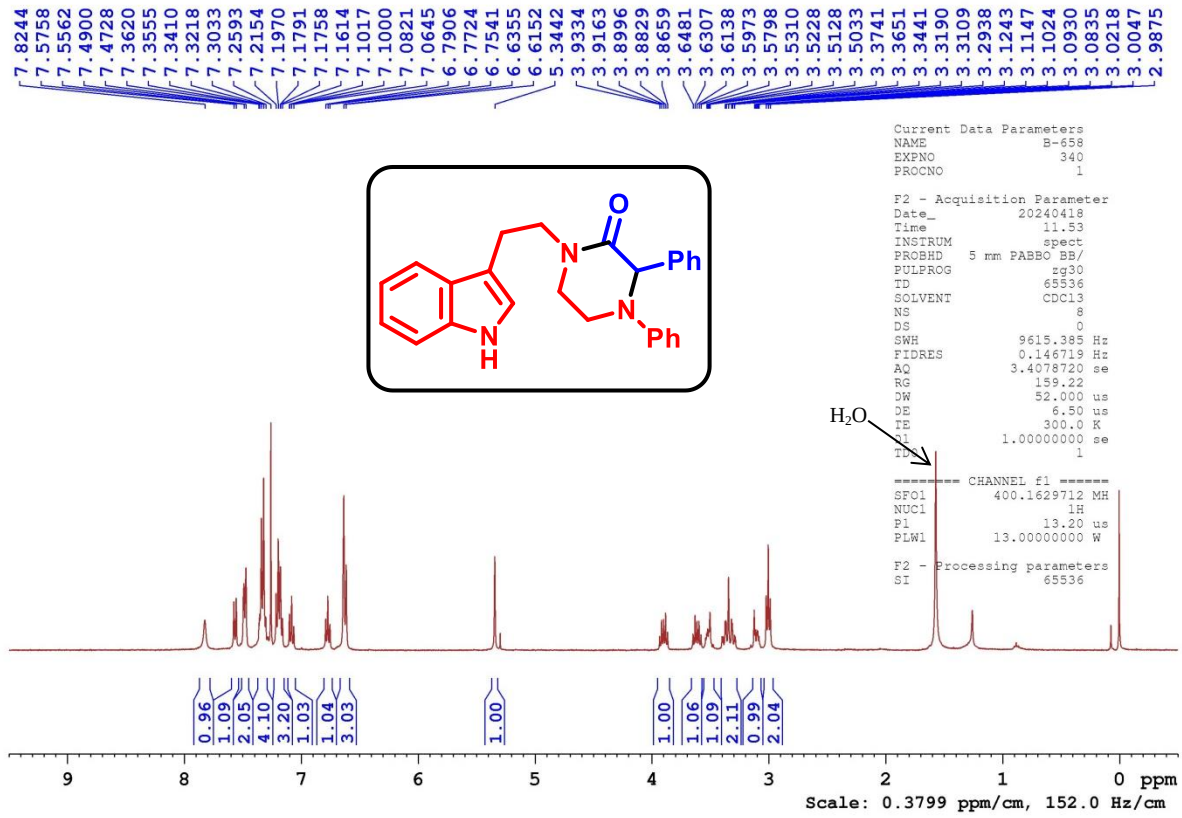


Figure S-50: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3al**

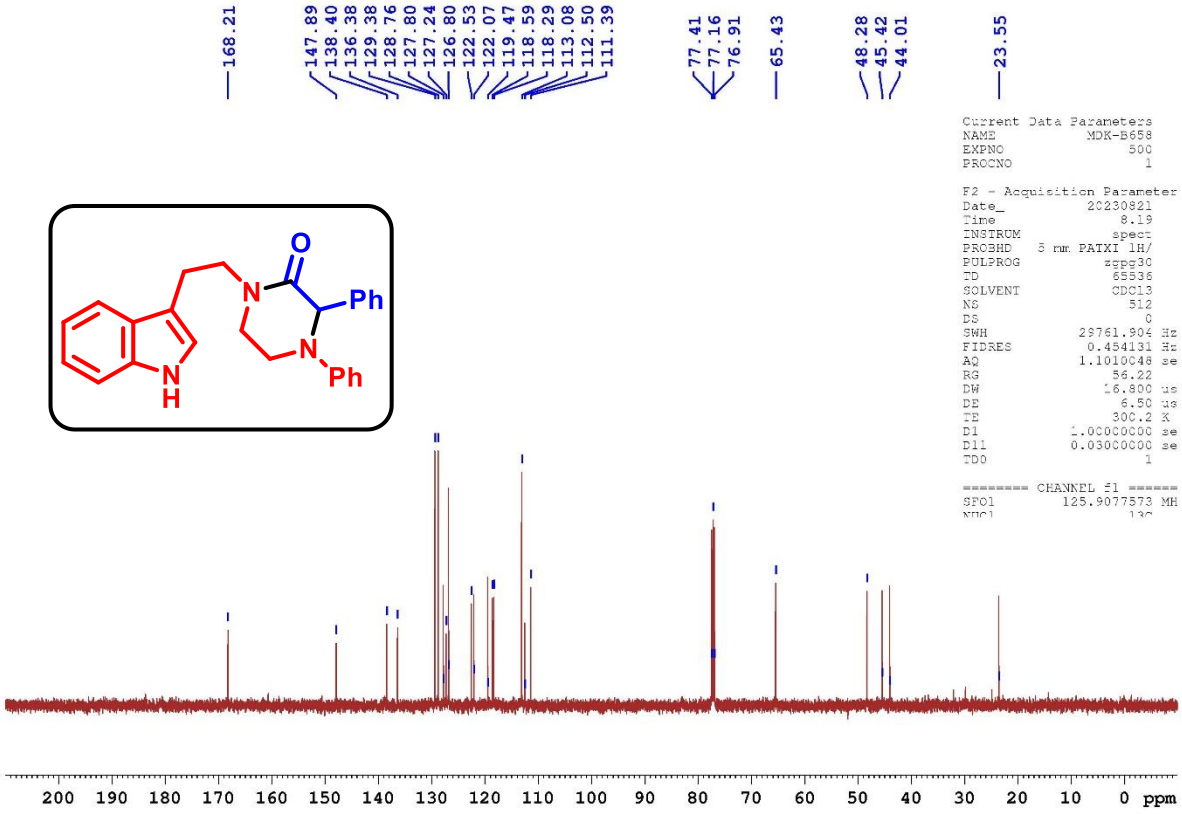


Figure S-51: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3al**

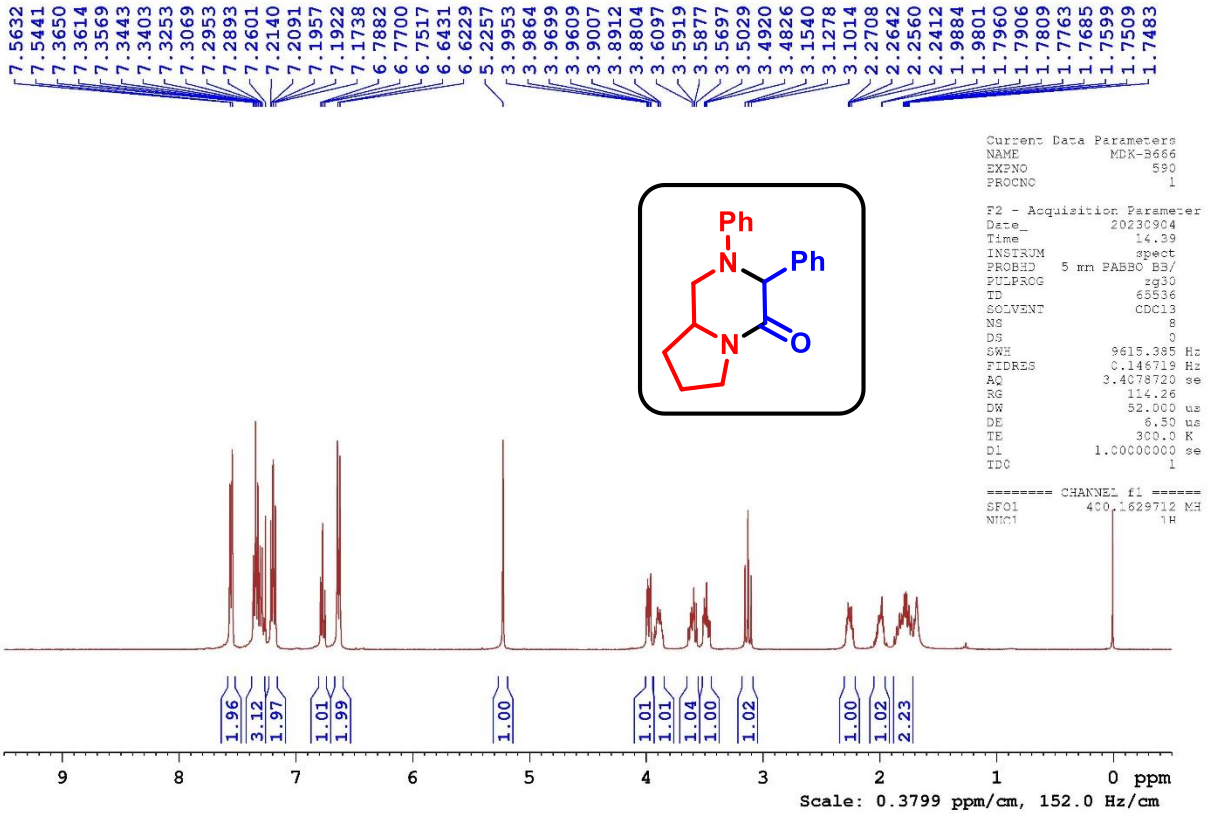


Figure S-52: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3am**

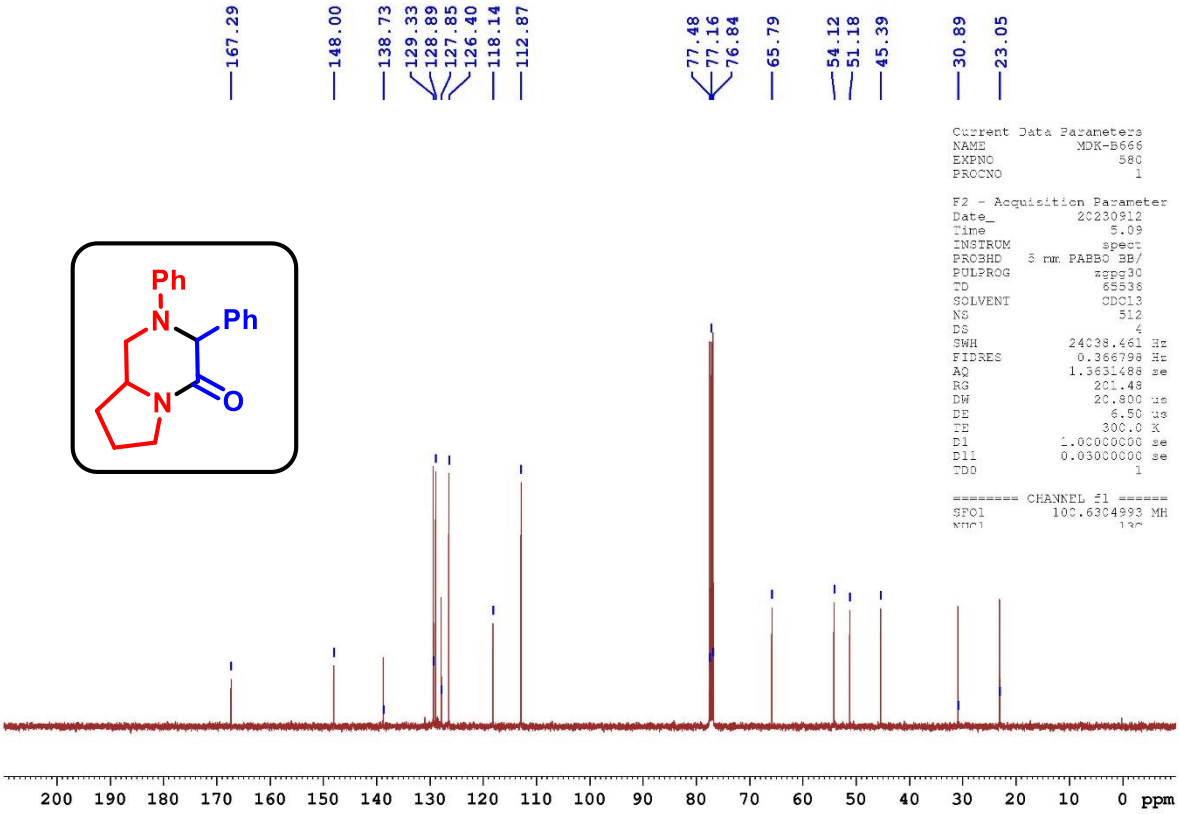


Figure S-53: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3am**

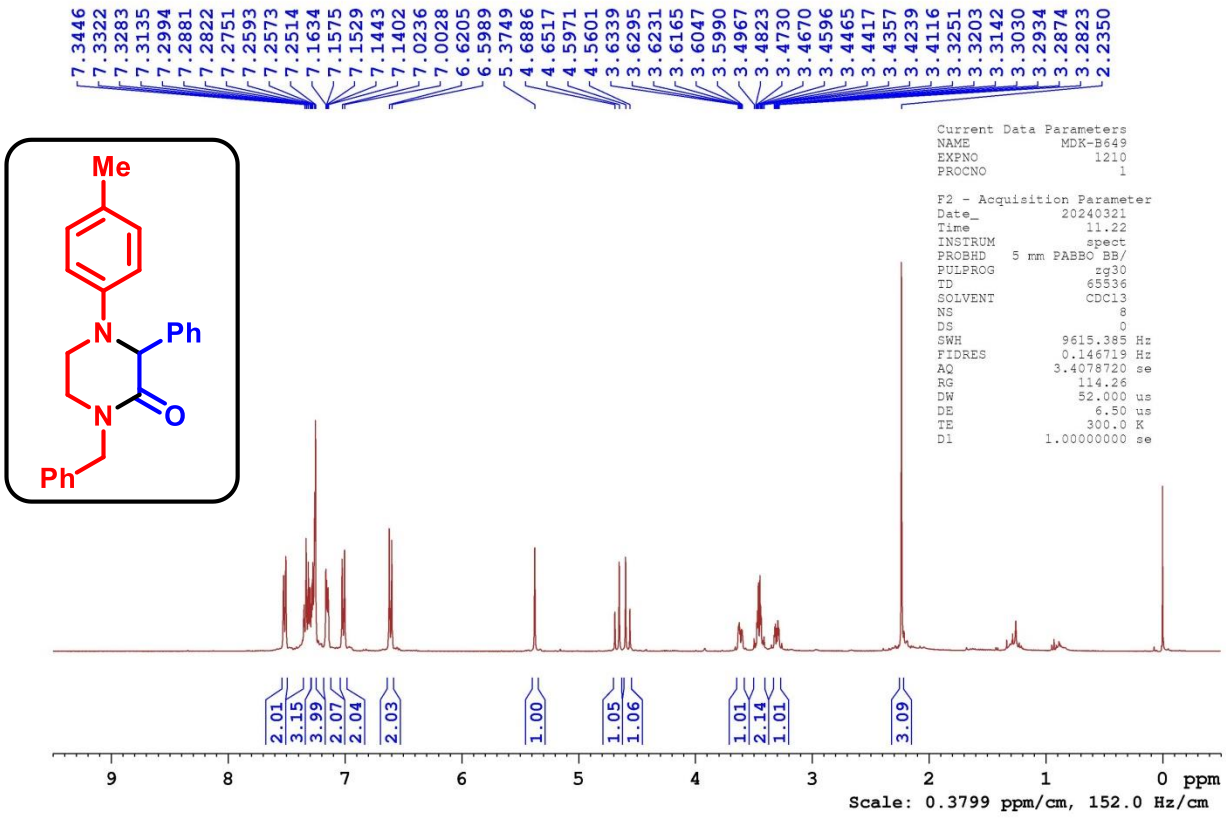


Figure S-54: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3an**

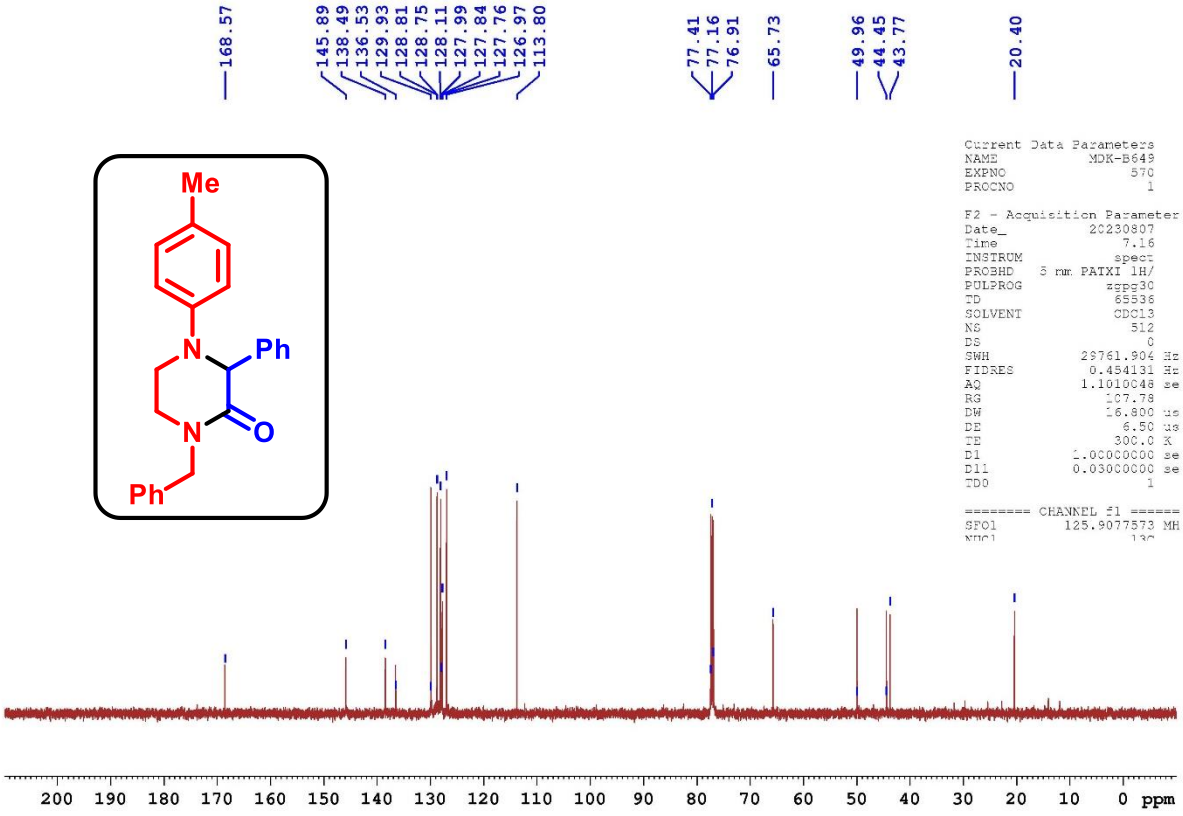


Figure S-55: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3an**

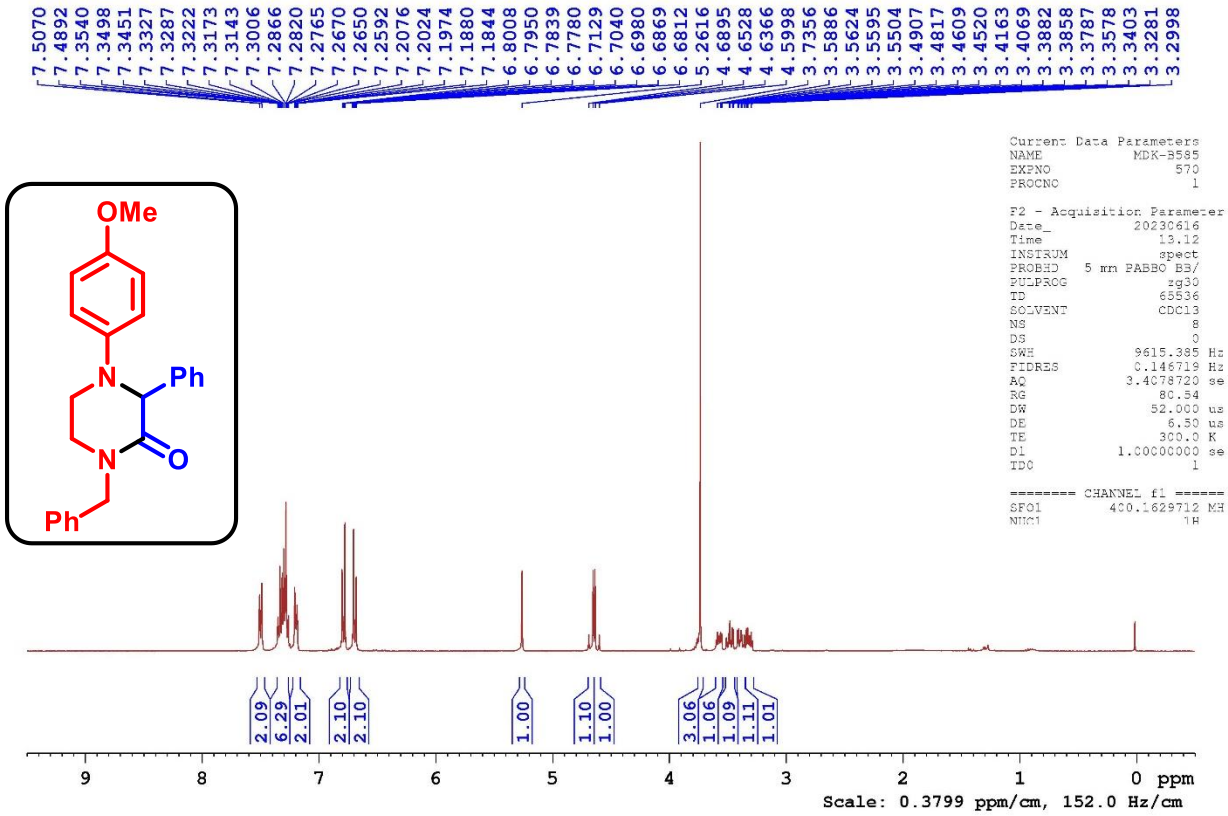


Figure S-56: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ao**

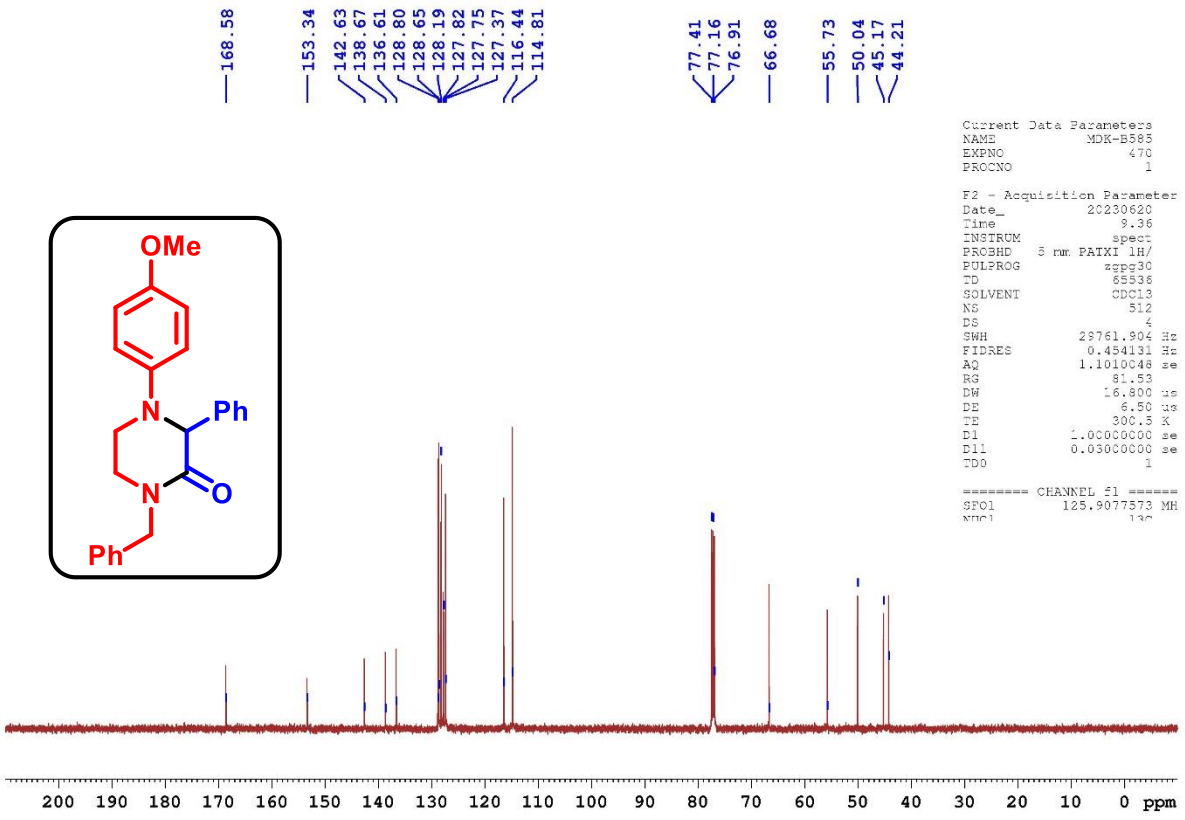


Figure S-57: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3ao**

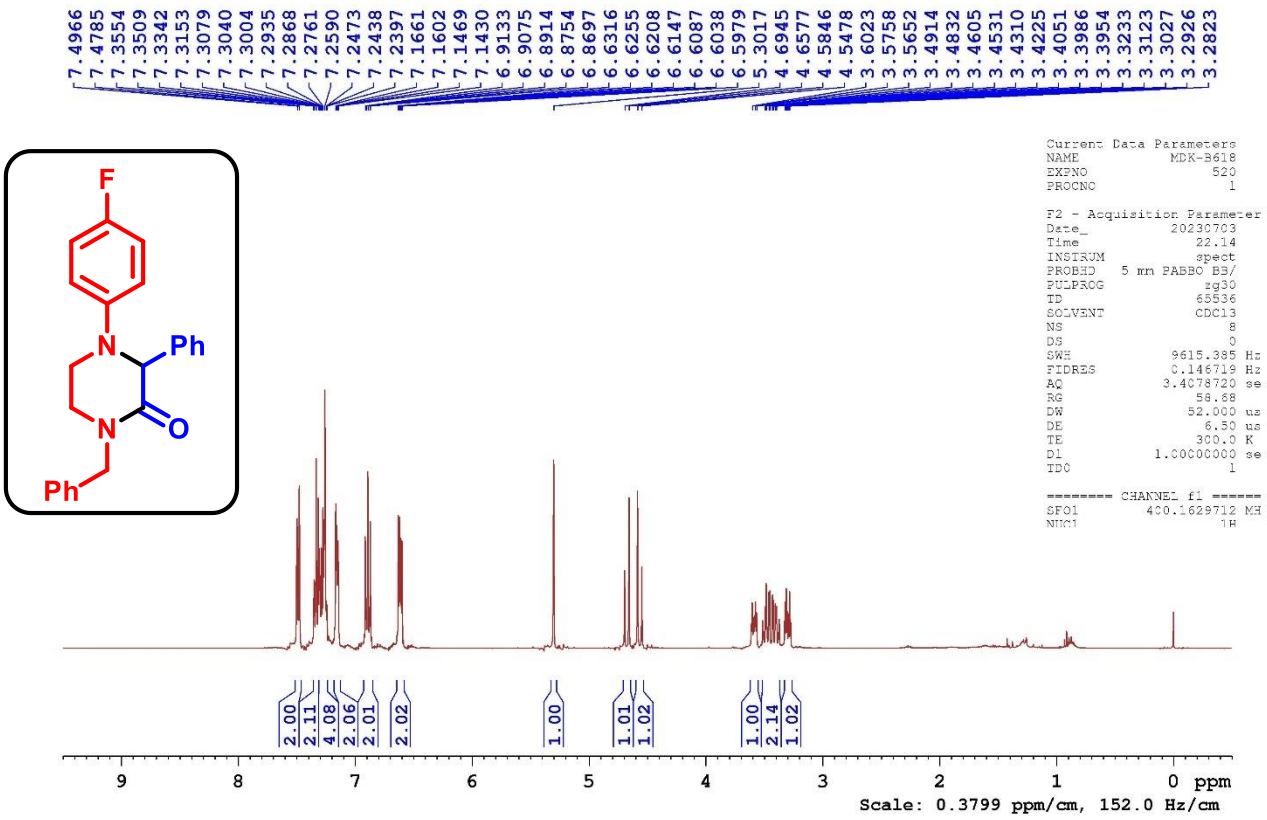


Figure S-58: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ap**

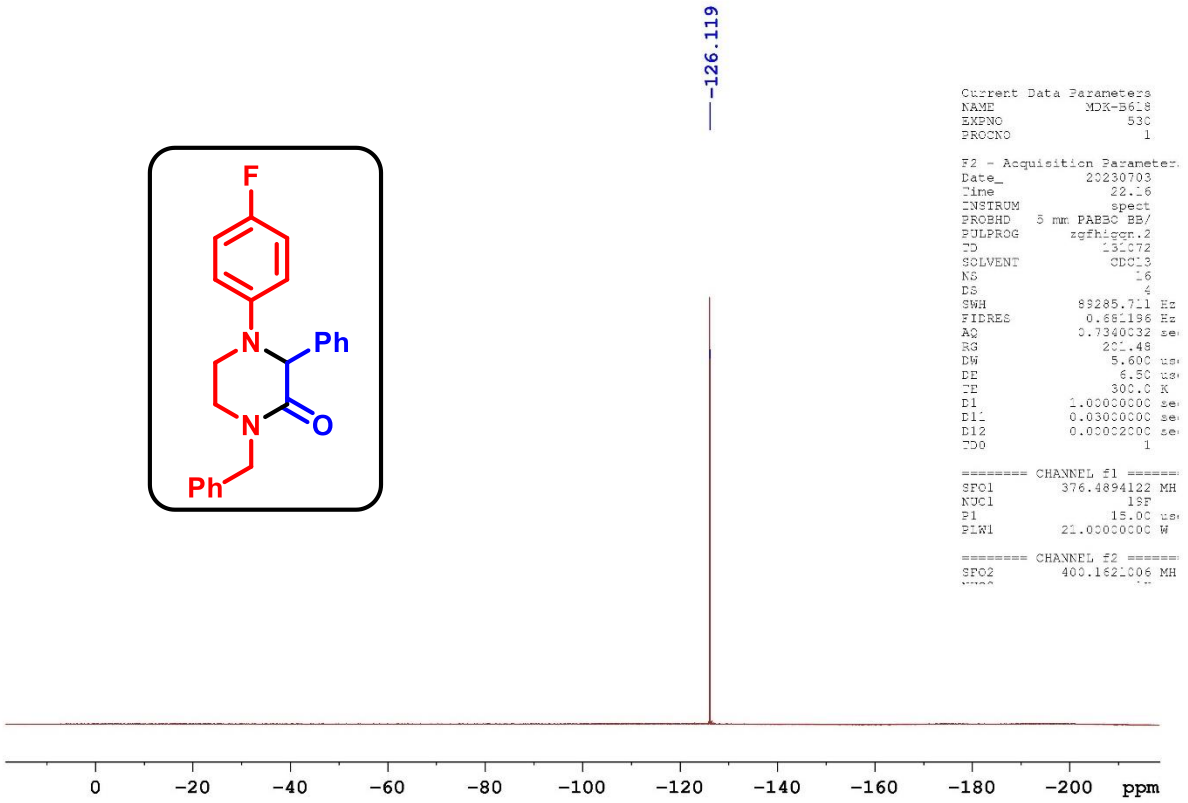


Figure S-59: ^{19}F NMR (376 MHz, $CDCl_3$) spectrum of compound **3ap**

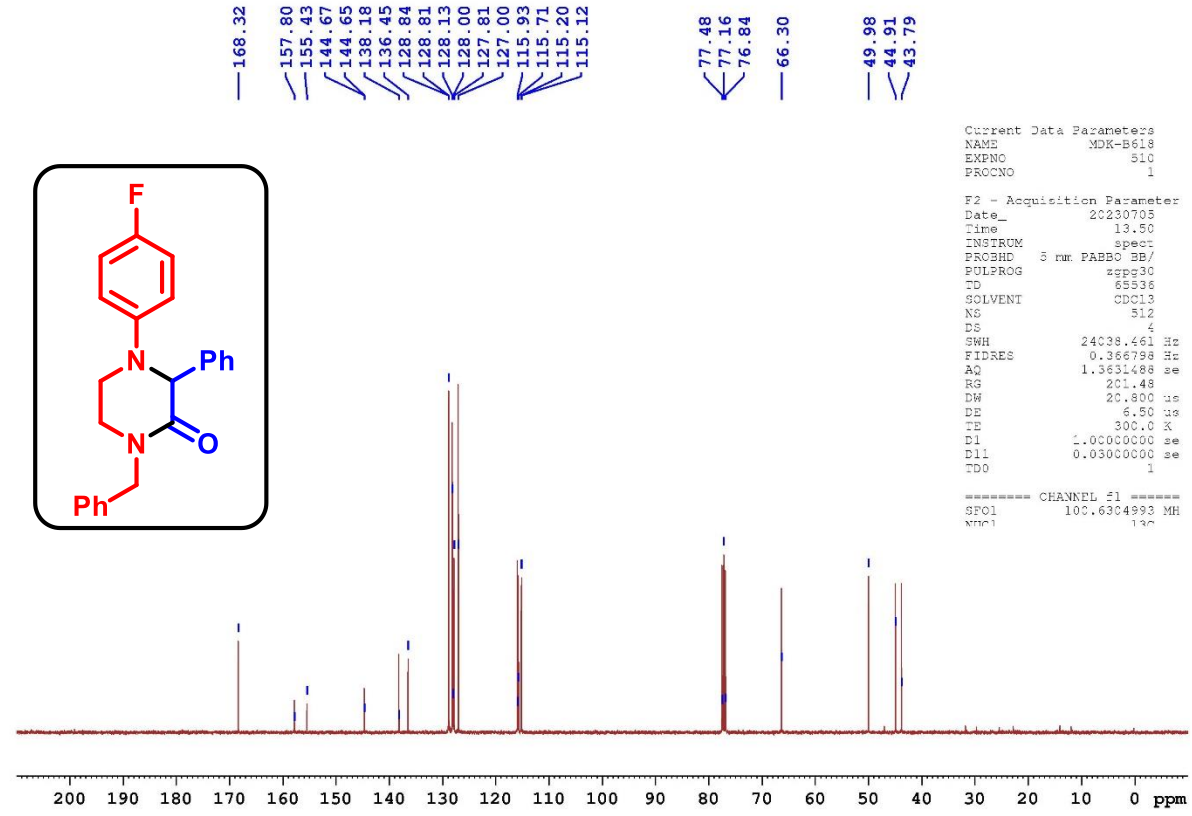


Figure S-60: $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ap**

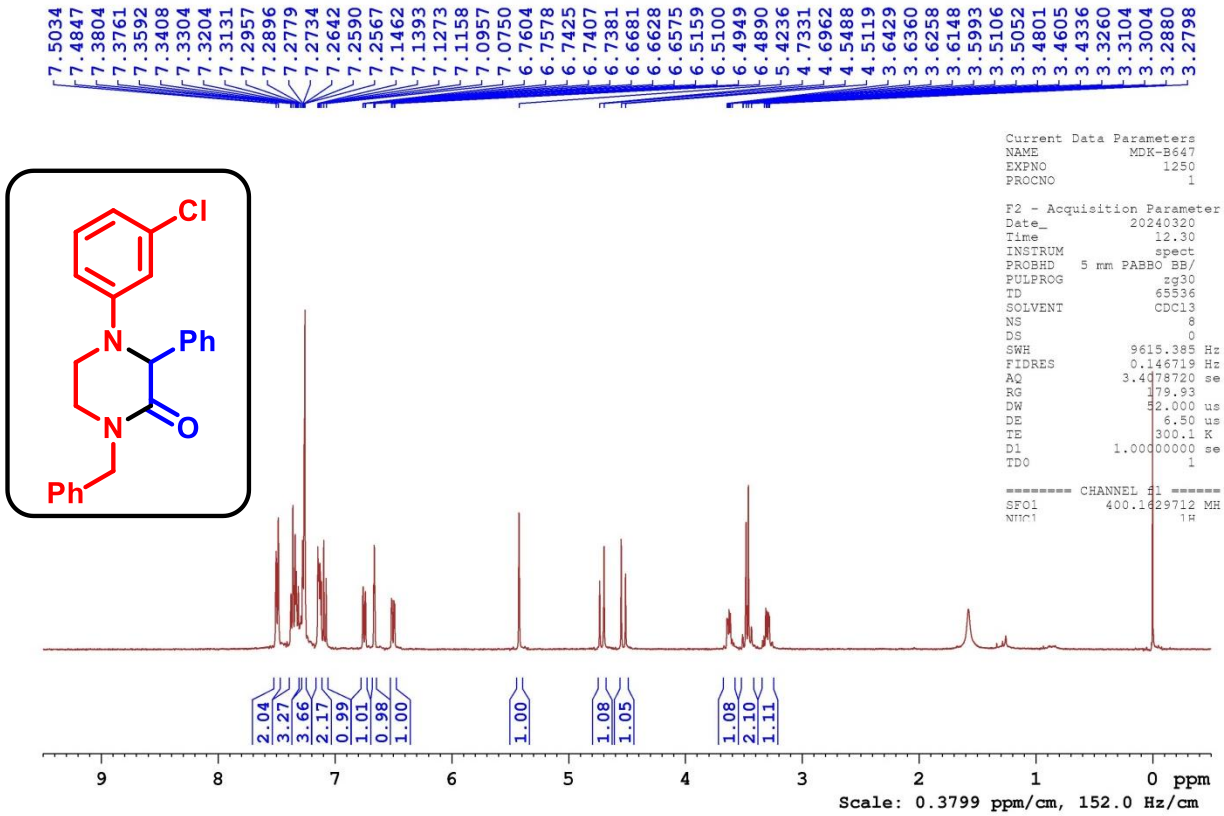


Figure S-61: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3aq**

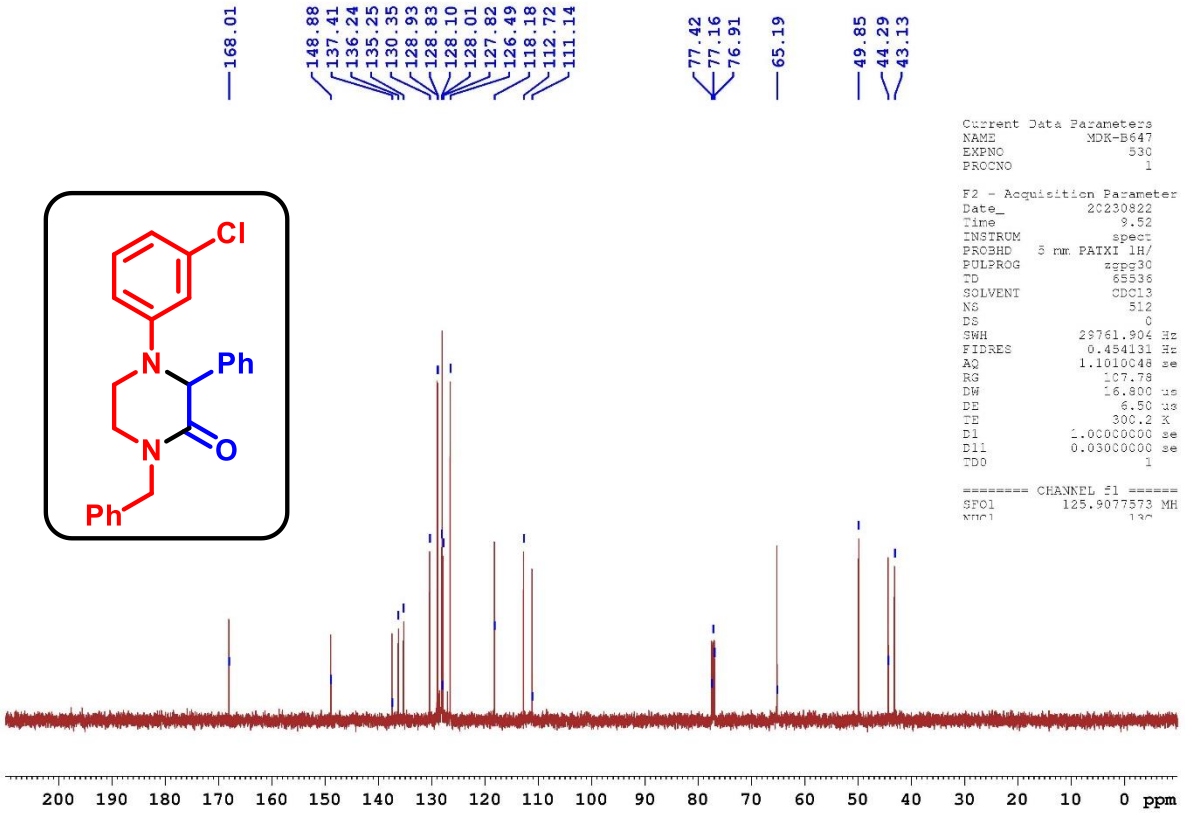


Figure S-62: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3aq**

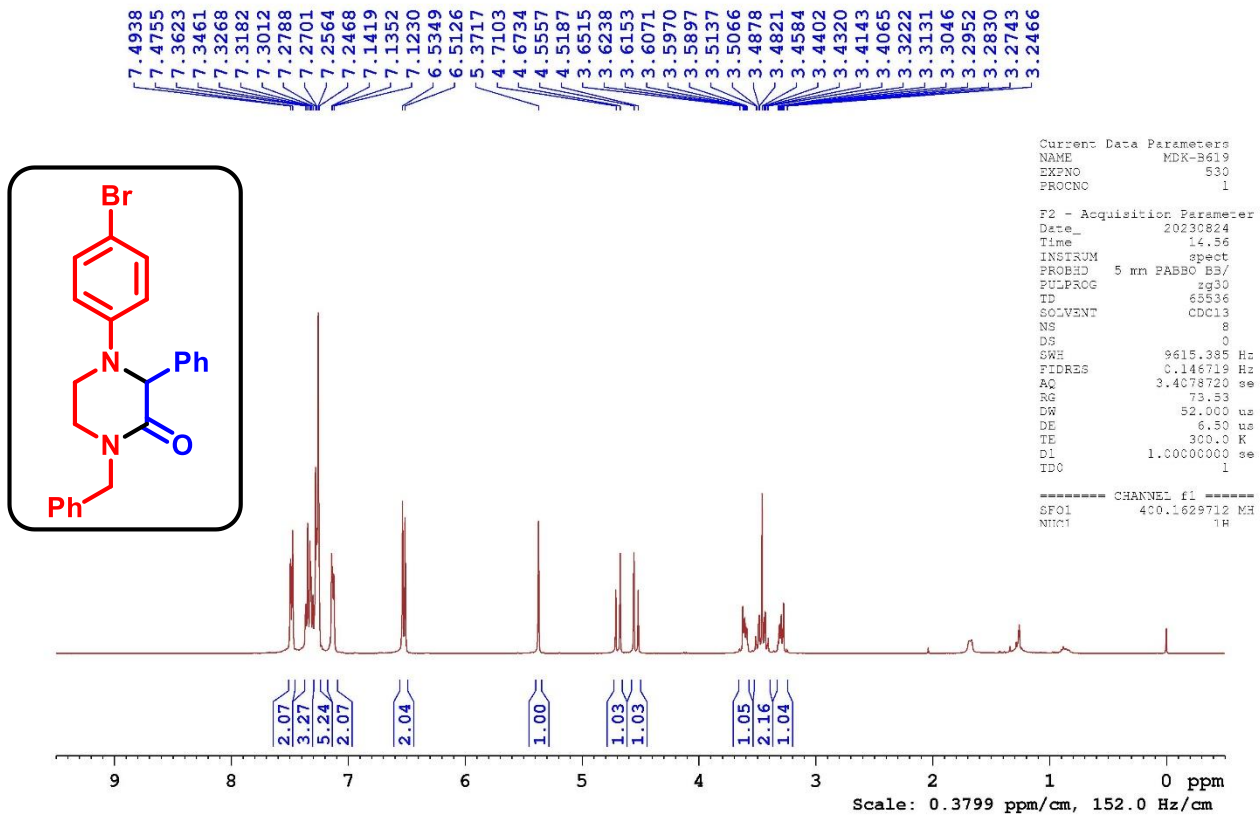


Figure S-63: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ar**

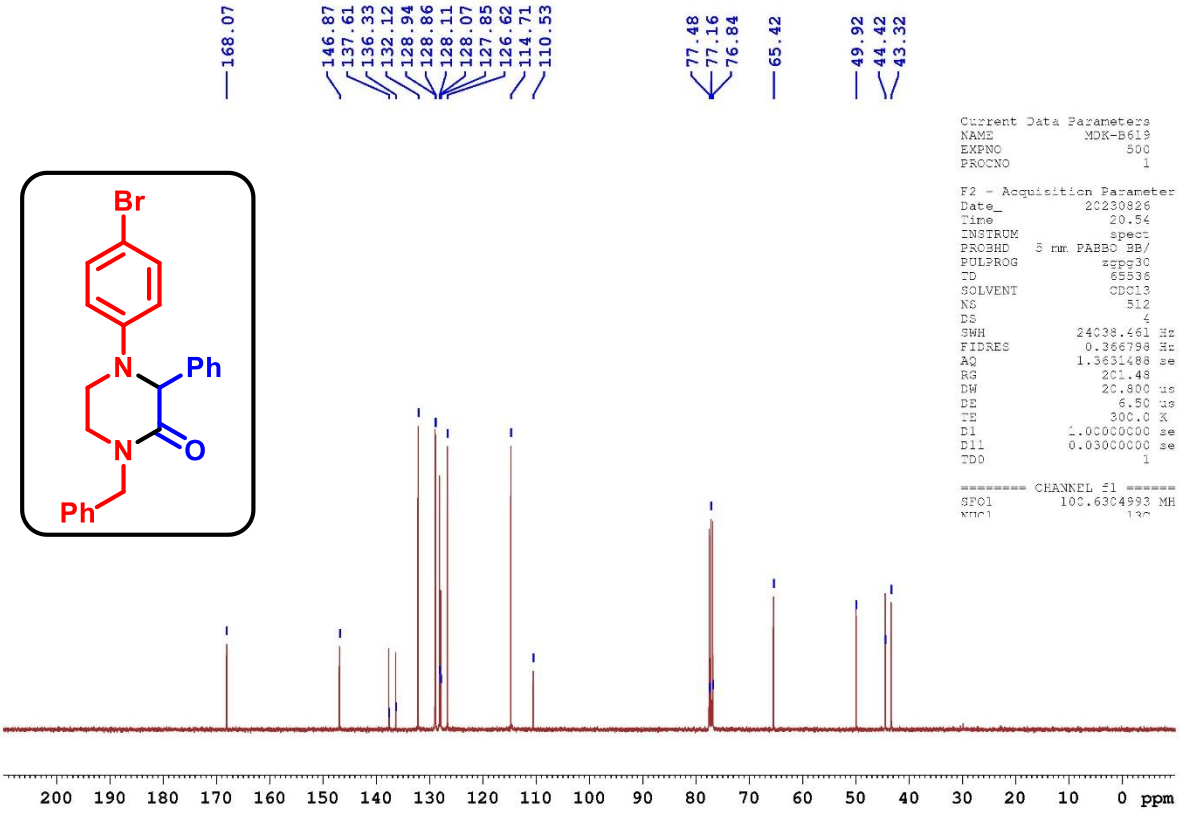


Figure S-64: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3ar**

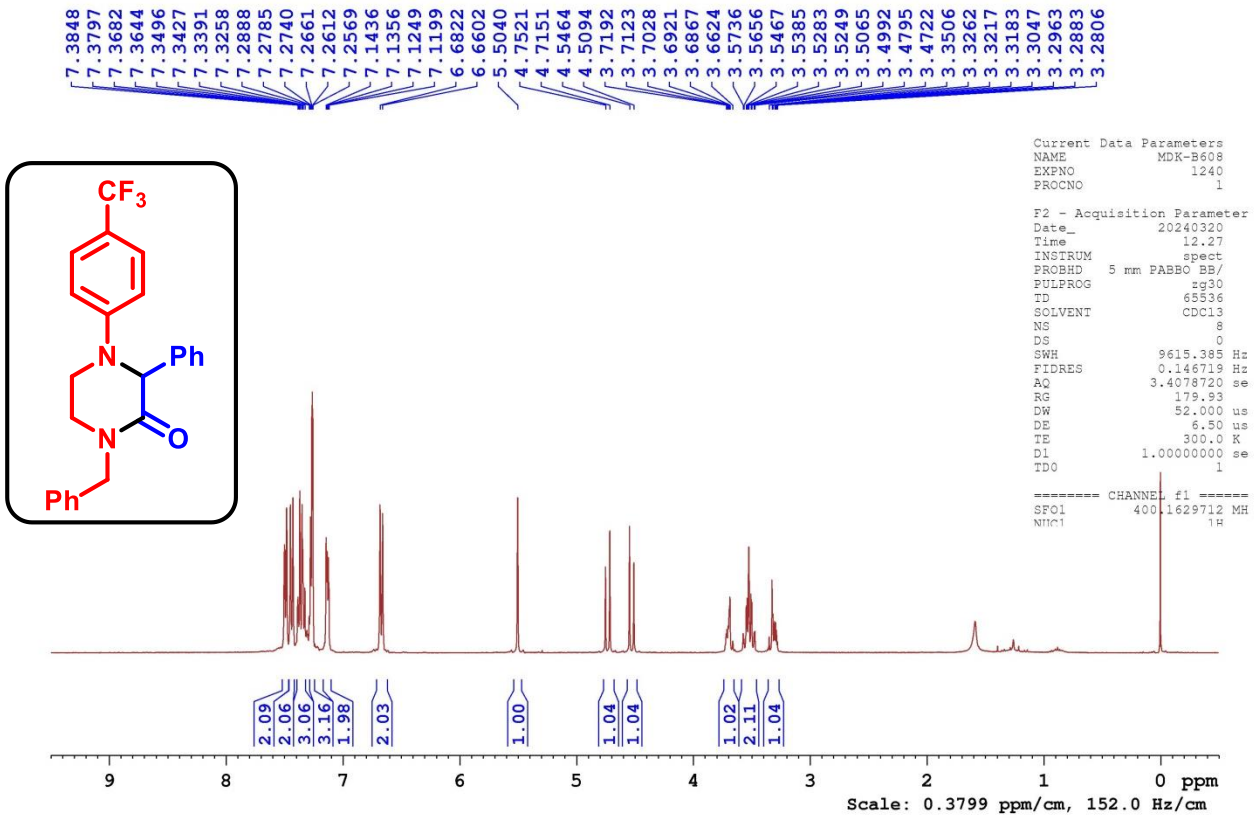


Figure S-65: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3as**

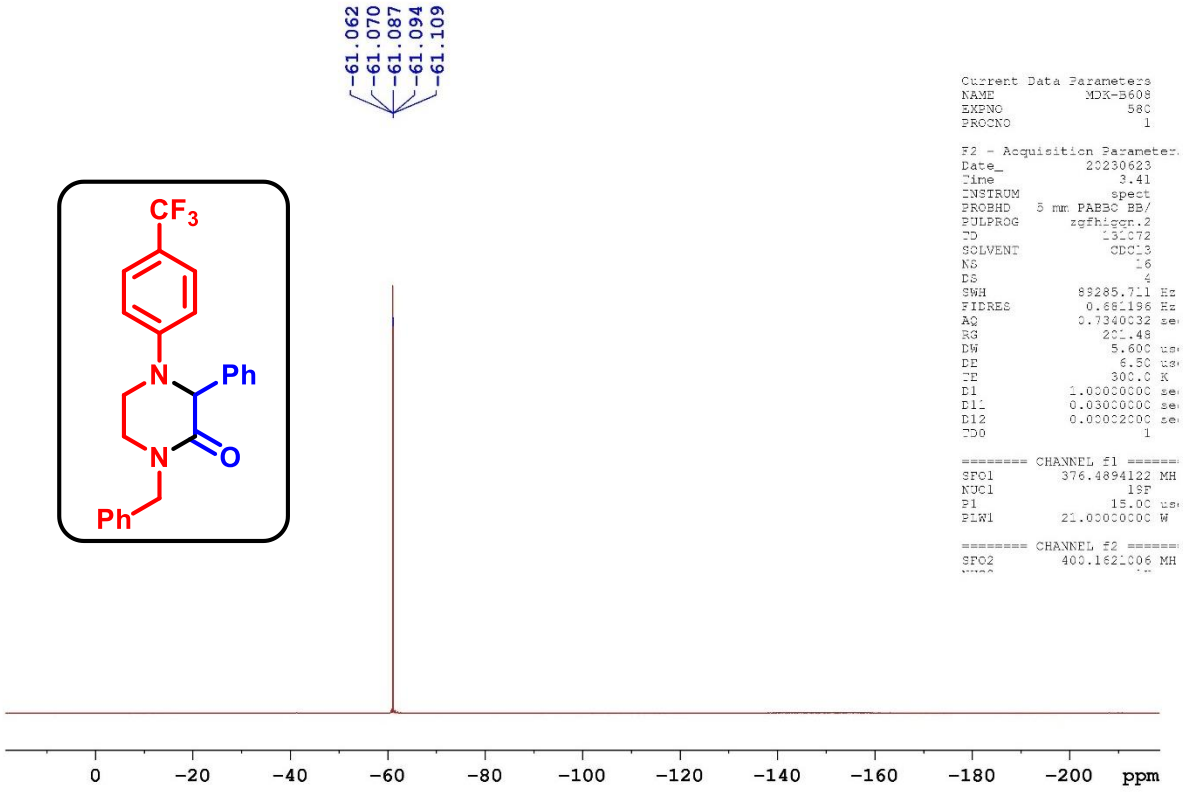


Figure S-66: ^{19}F NMR (376 MHz, $CDCl_3$) spectrum of compound **3as**

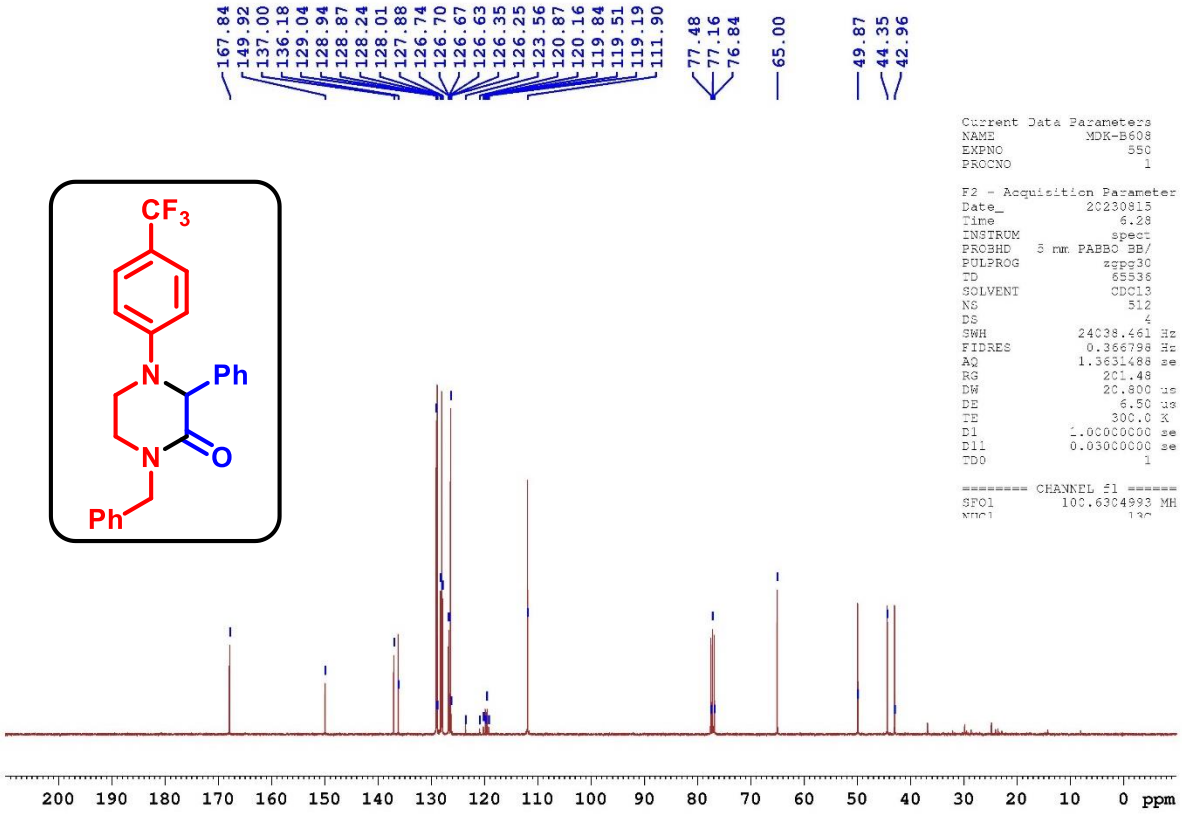


Figure S-67: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3as**

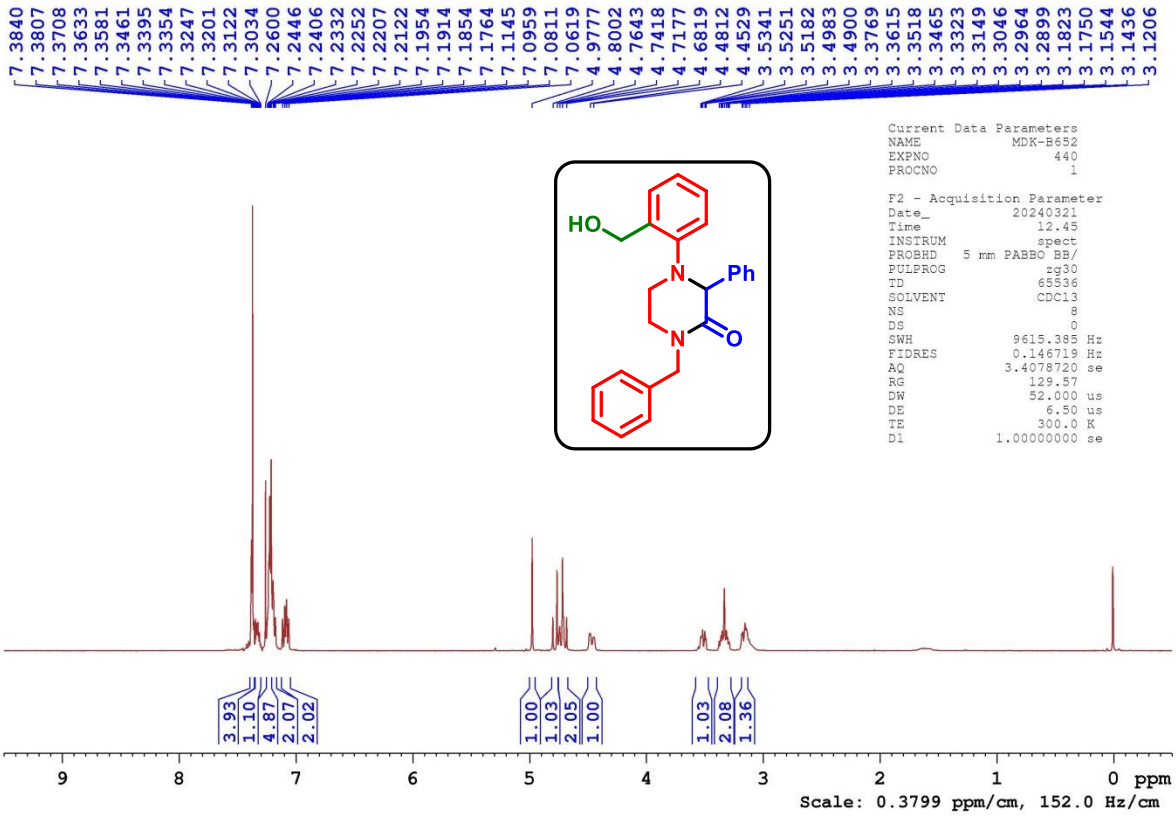


Figure S-68: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3at**

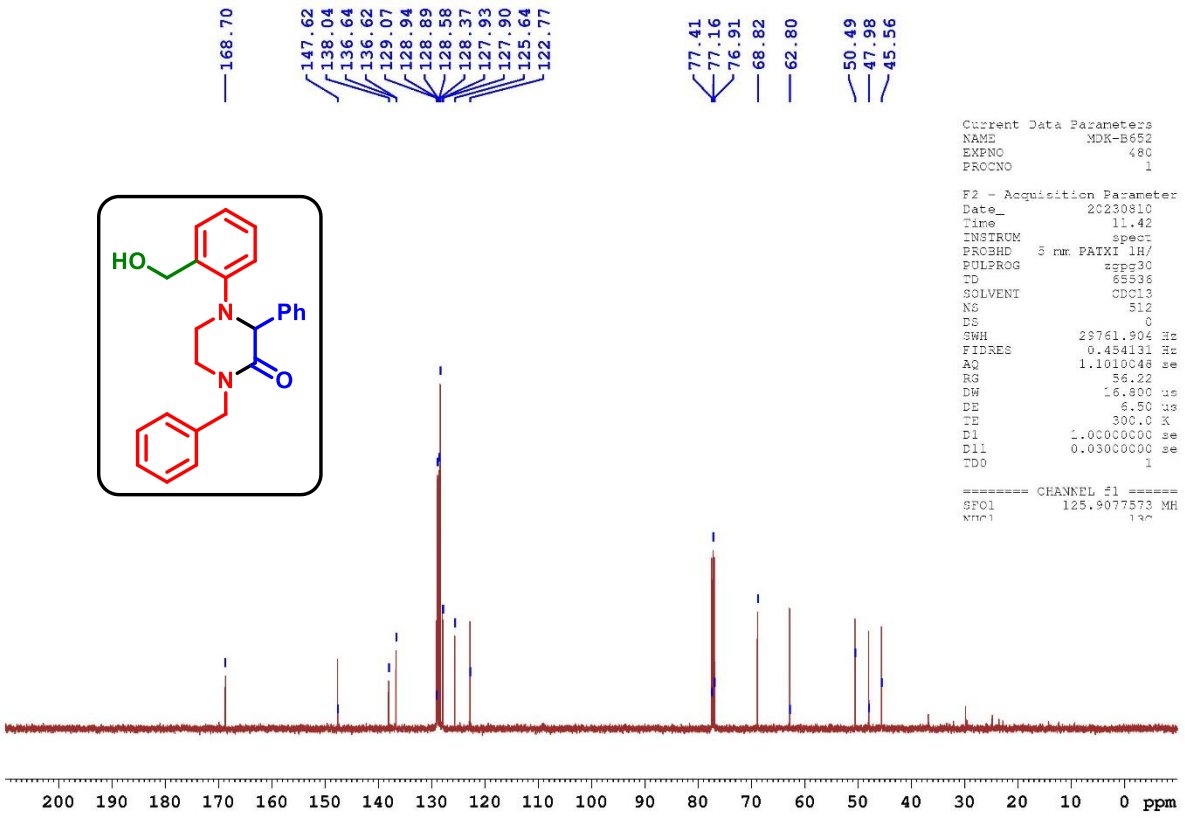


Figure S-69: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3at**

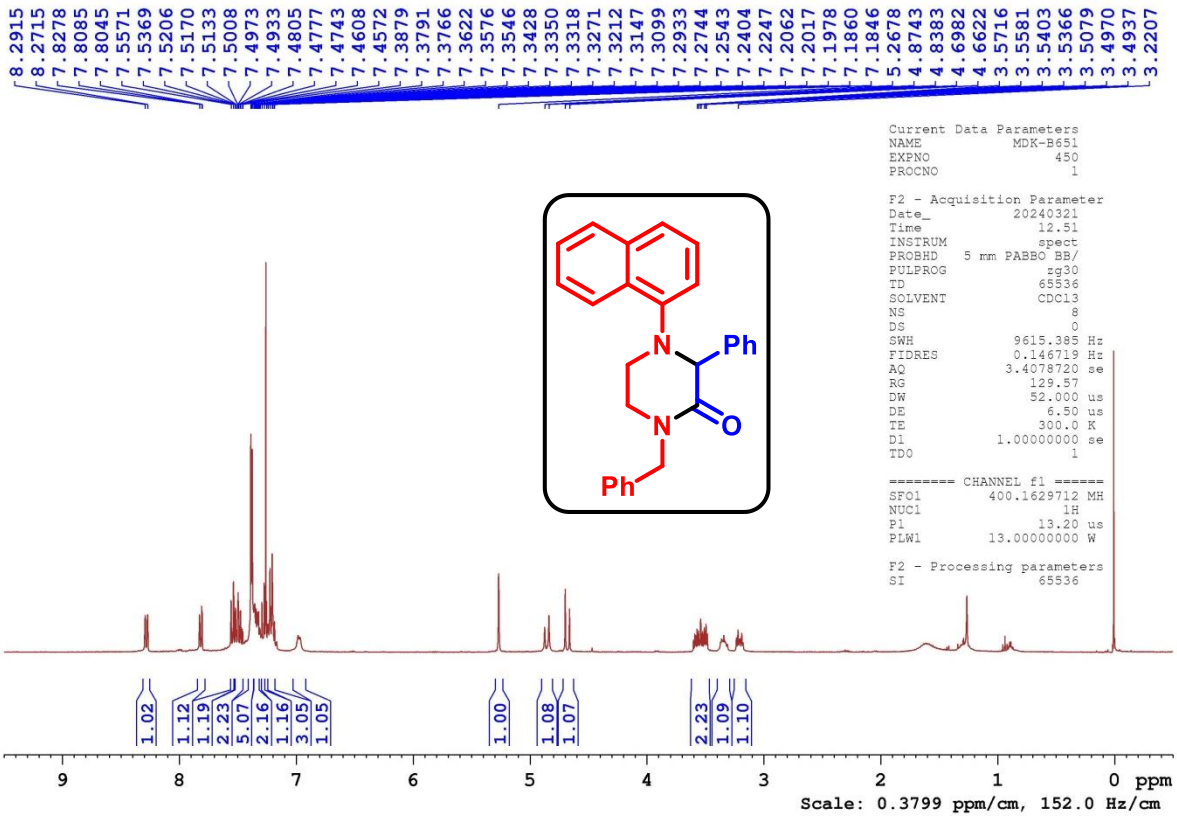


Figure S-70: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3au**

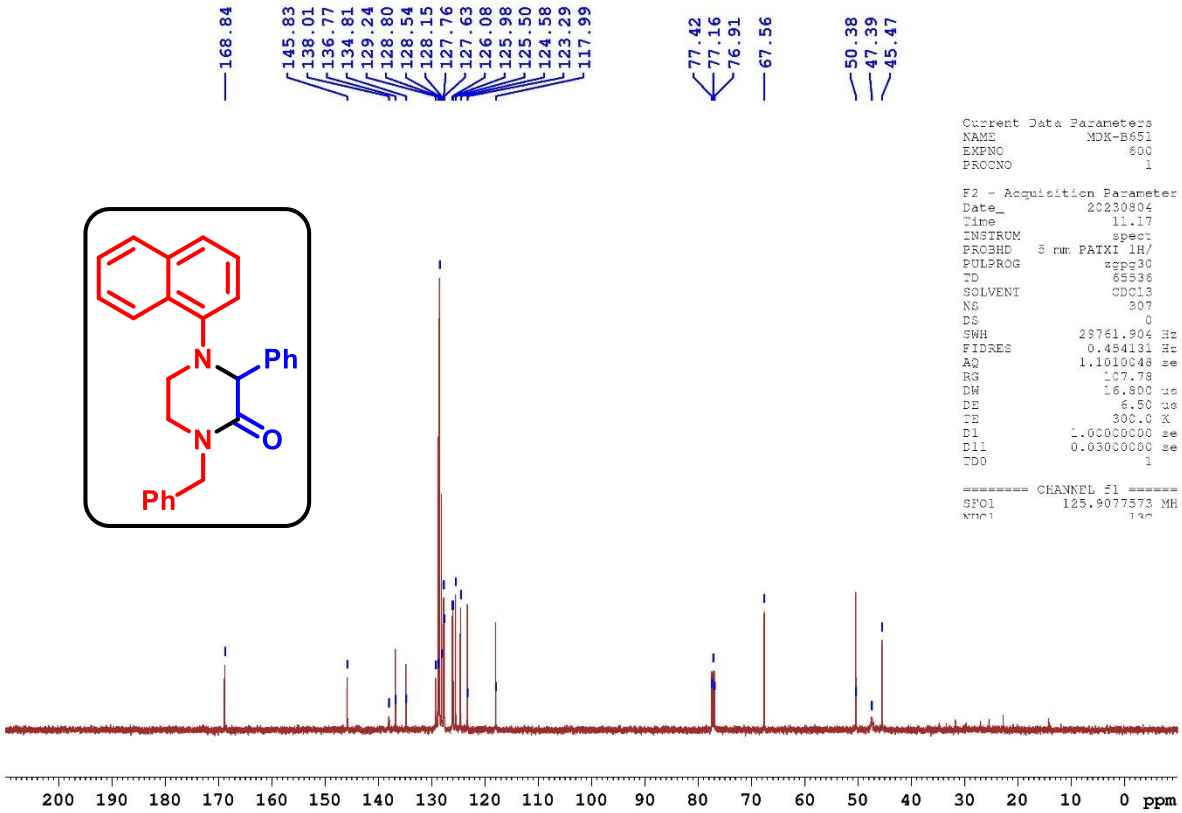


Figure S-71: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3au**

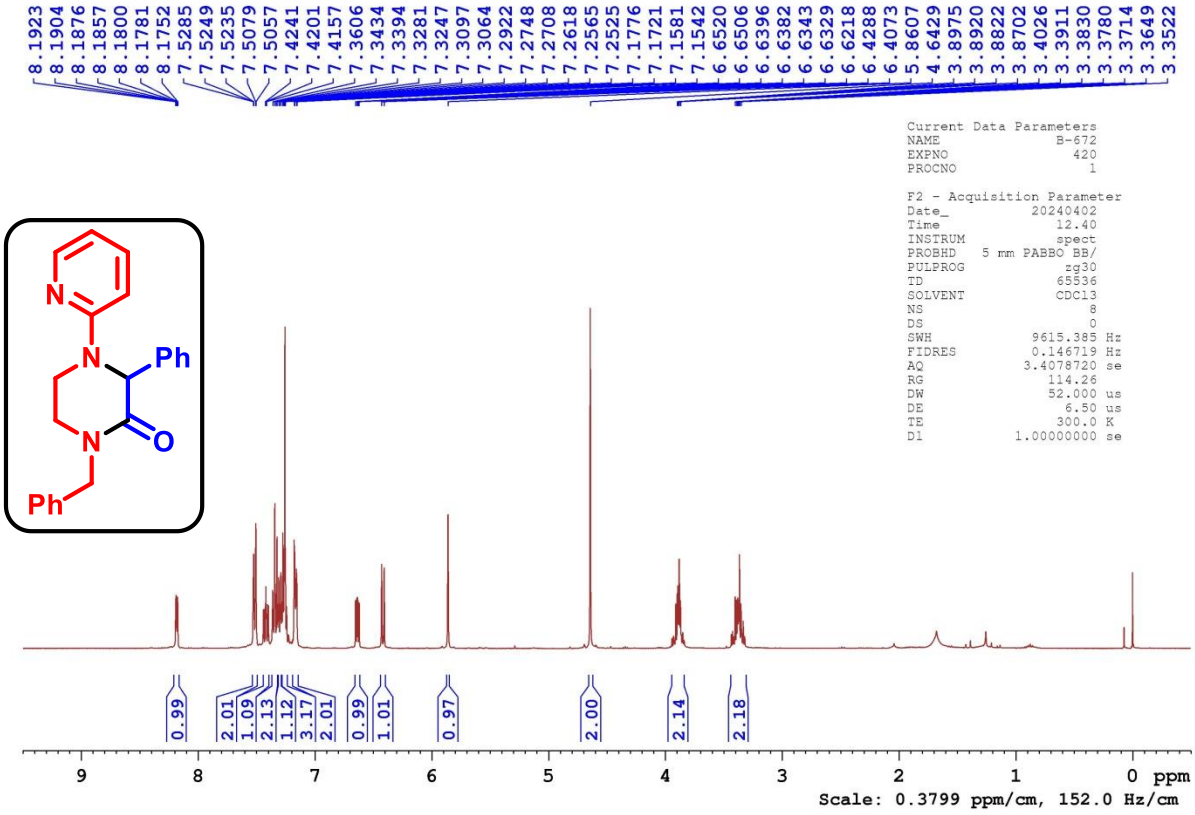


Figure S-72: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3av**

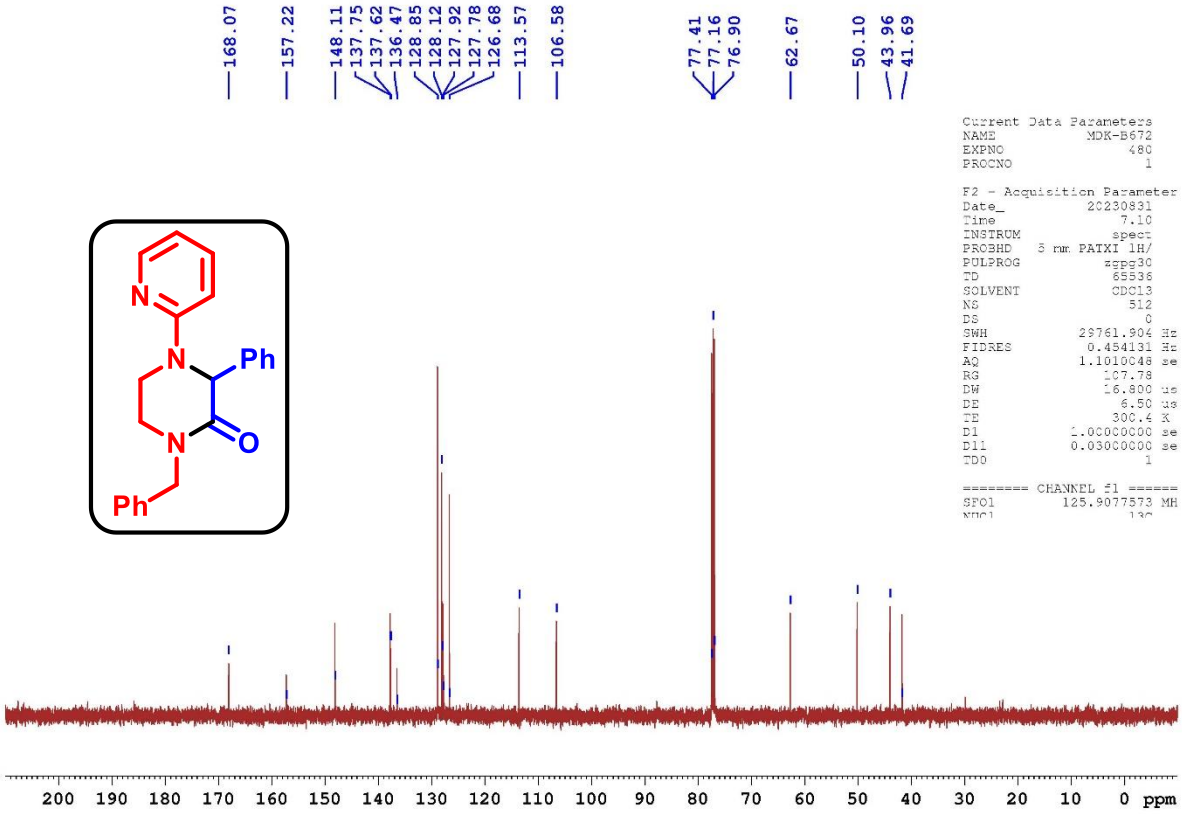


Figure S-73: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **3av**

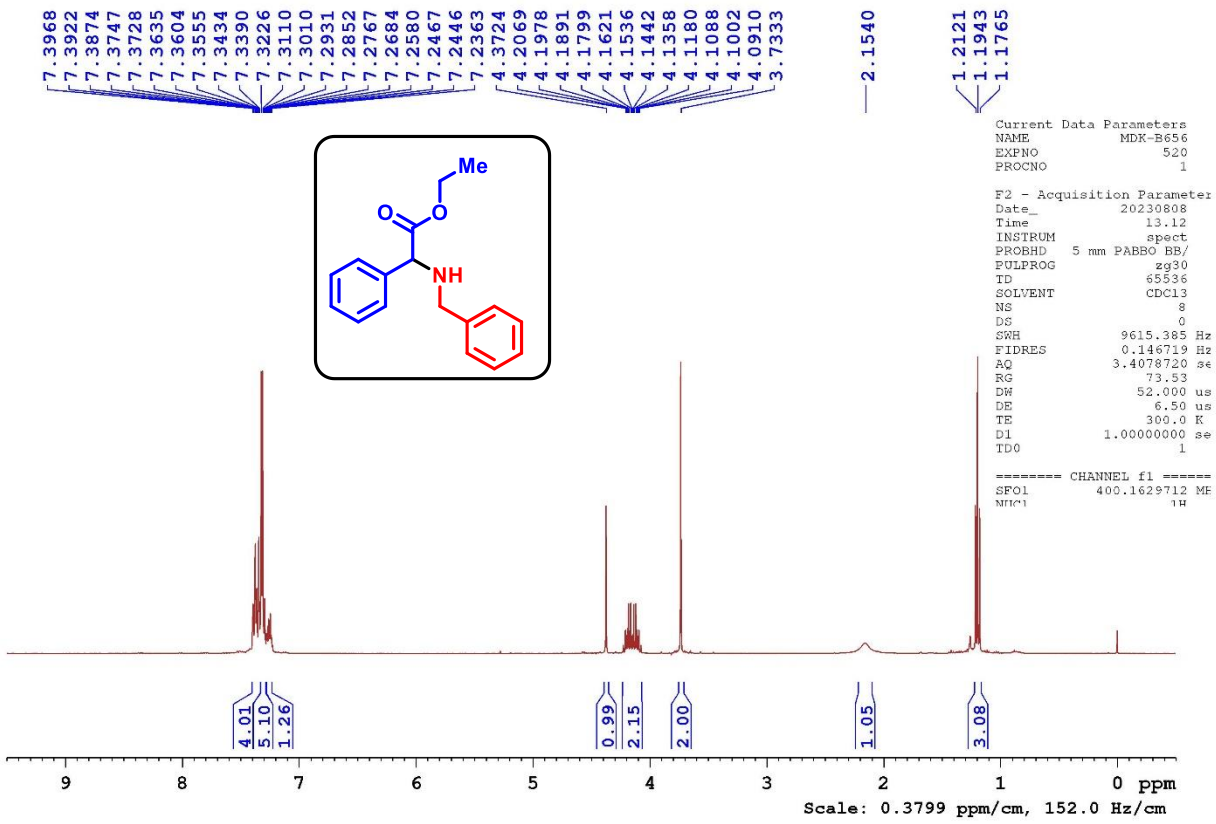


Figure S-74: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4aw**

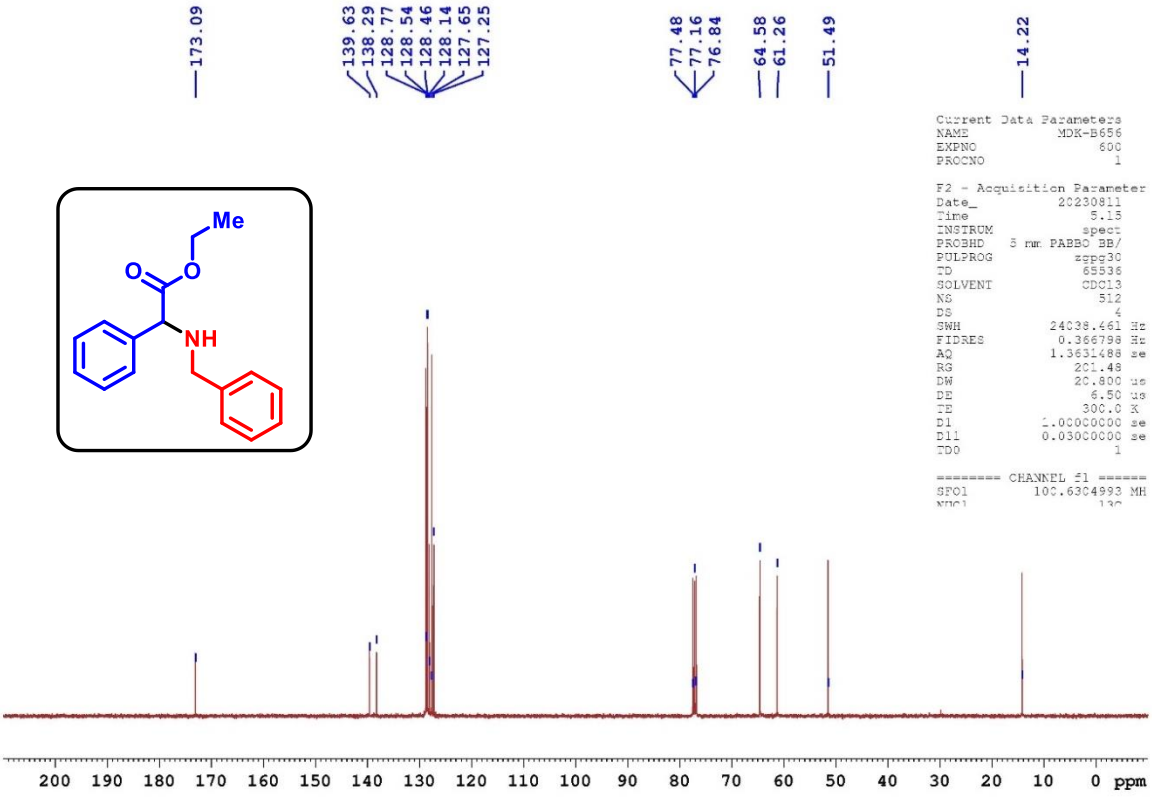


Figure S-75: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **4aw**

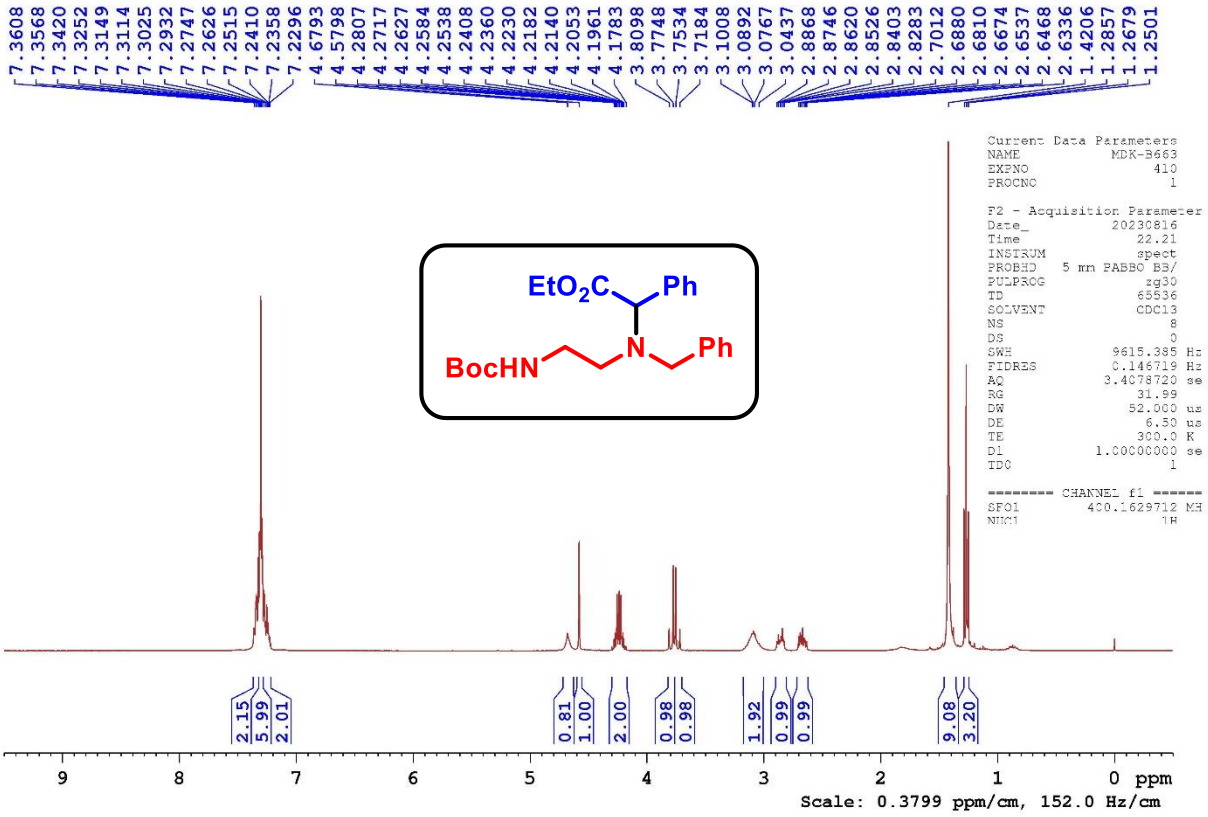


Figure S-76: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4ax**

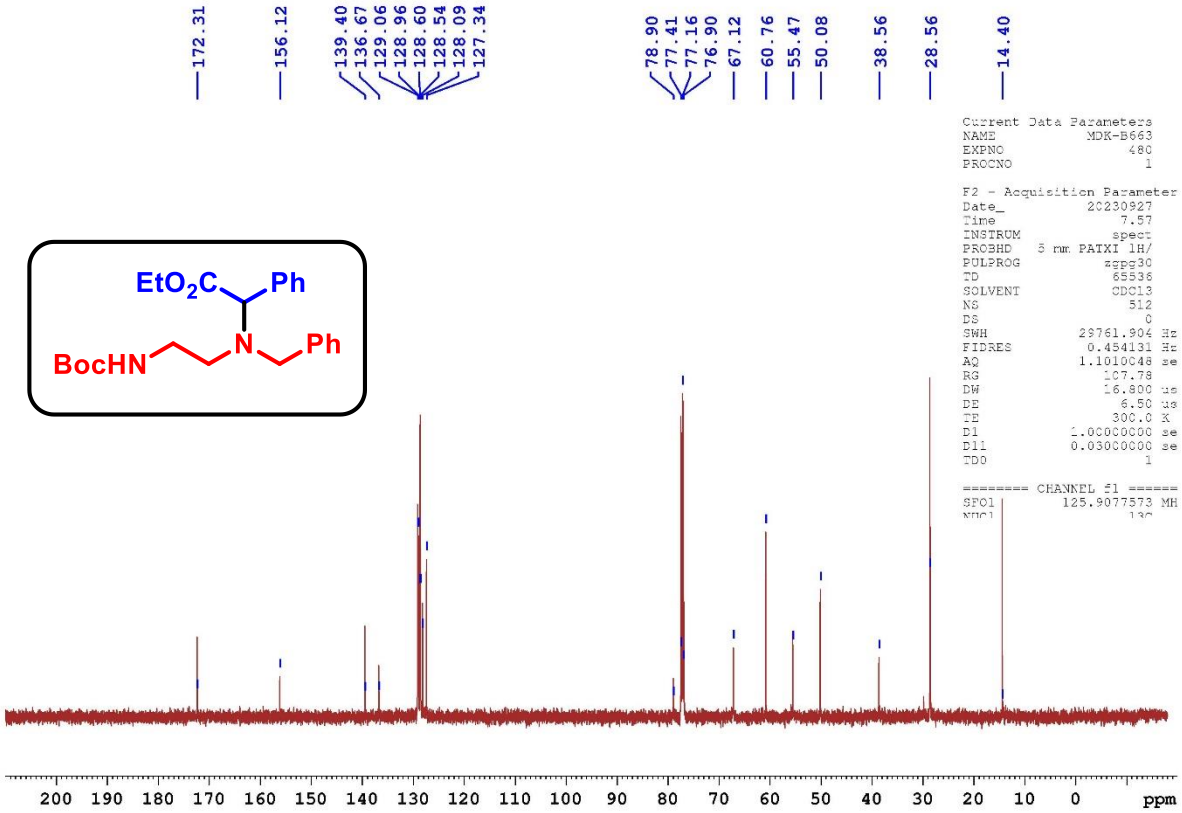


Figure S-77: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4ax**

Figure S-78: ^{1}H-^{13}C HSQC Spectra of **4ax** in $CDCl_3$ at 400 MHz

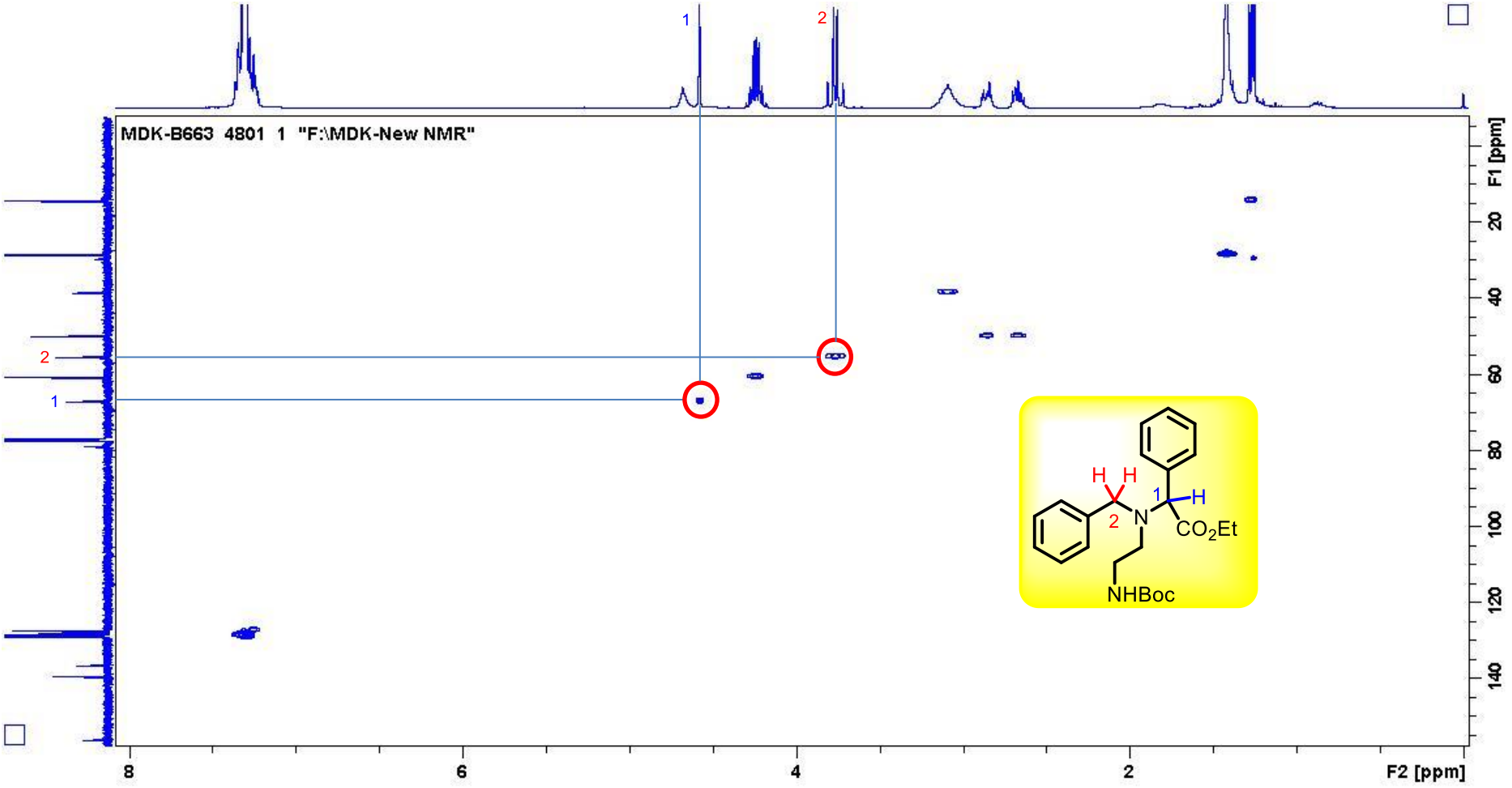
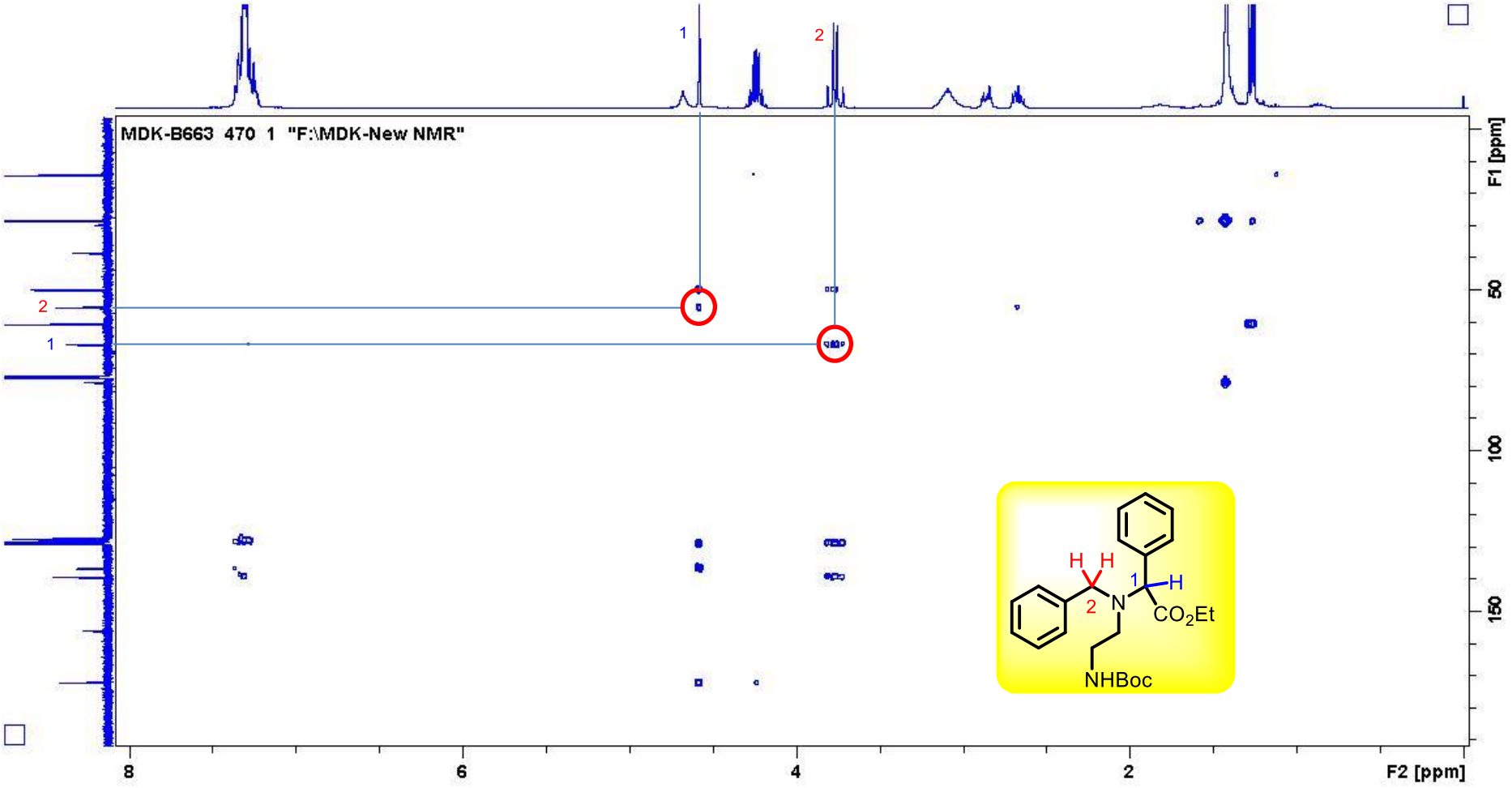


Figure S-79: ^{1}H-^{13}C HMBC Spectra of **4ax** in $CDCl_3$ at 400 MHz



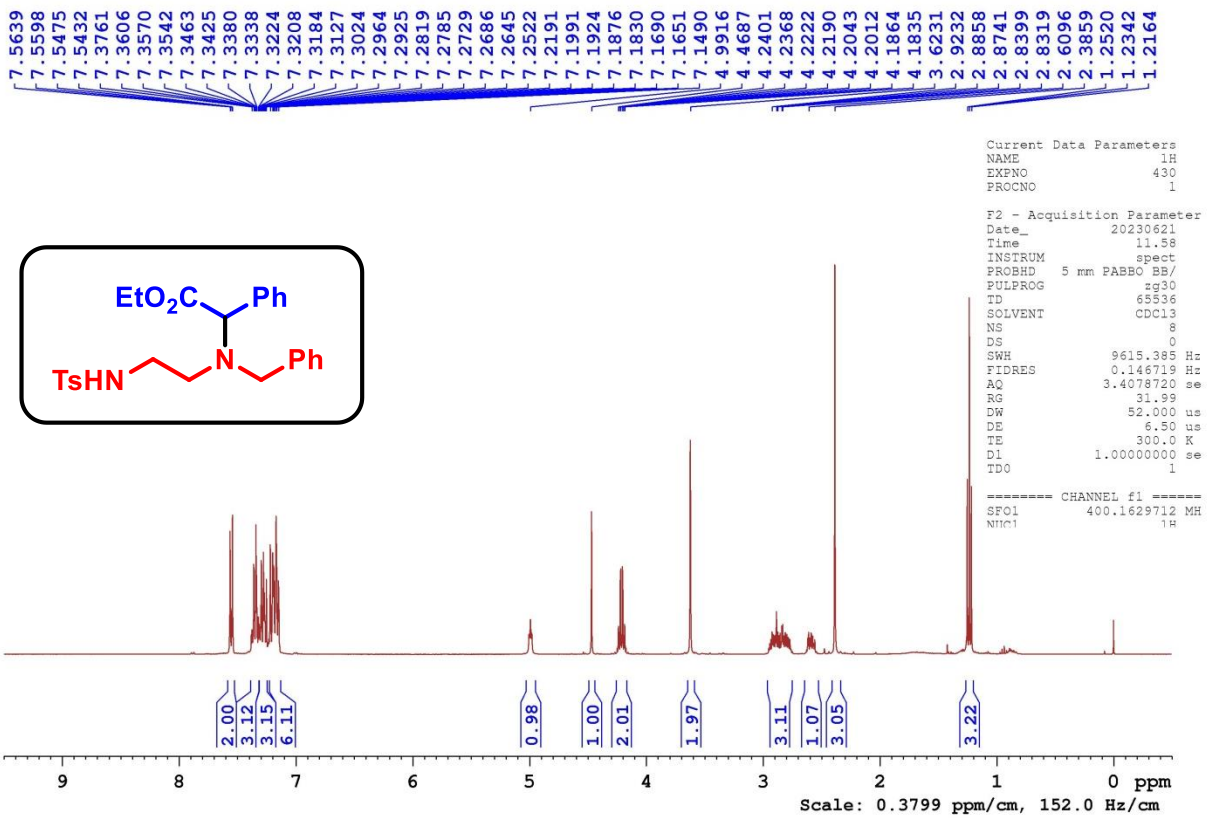


Figure S-80: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4ay**

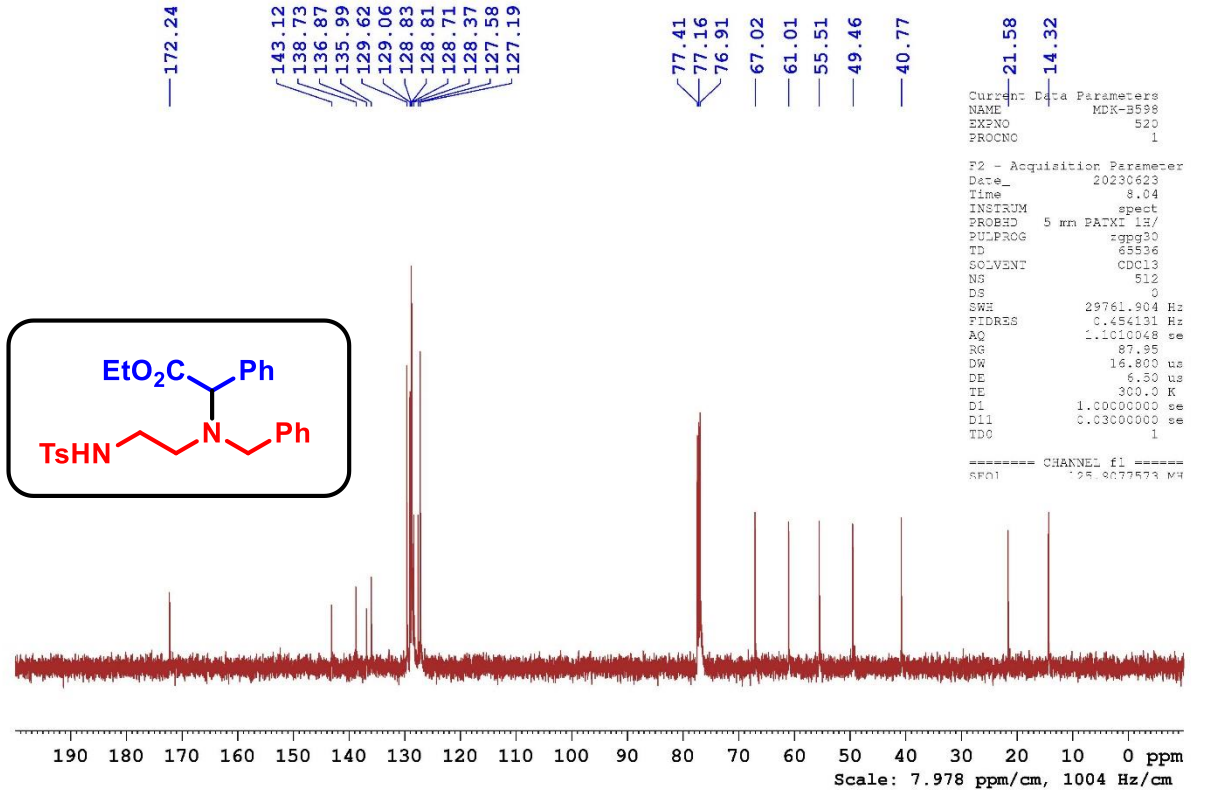


Figure S-81: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4ay**

Figure S-82: ^{1}H-^{13}C HSQC Spectra of **4ay** in $CDCl_3$ at 400 MHz

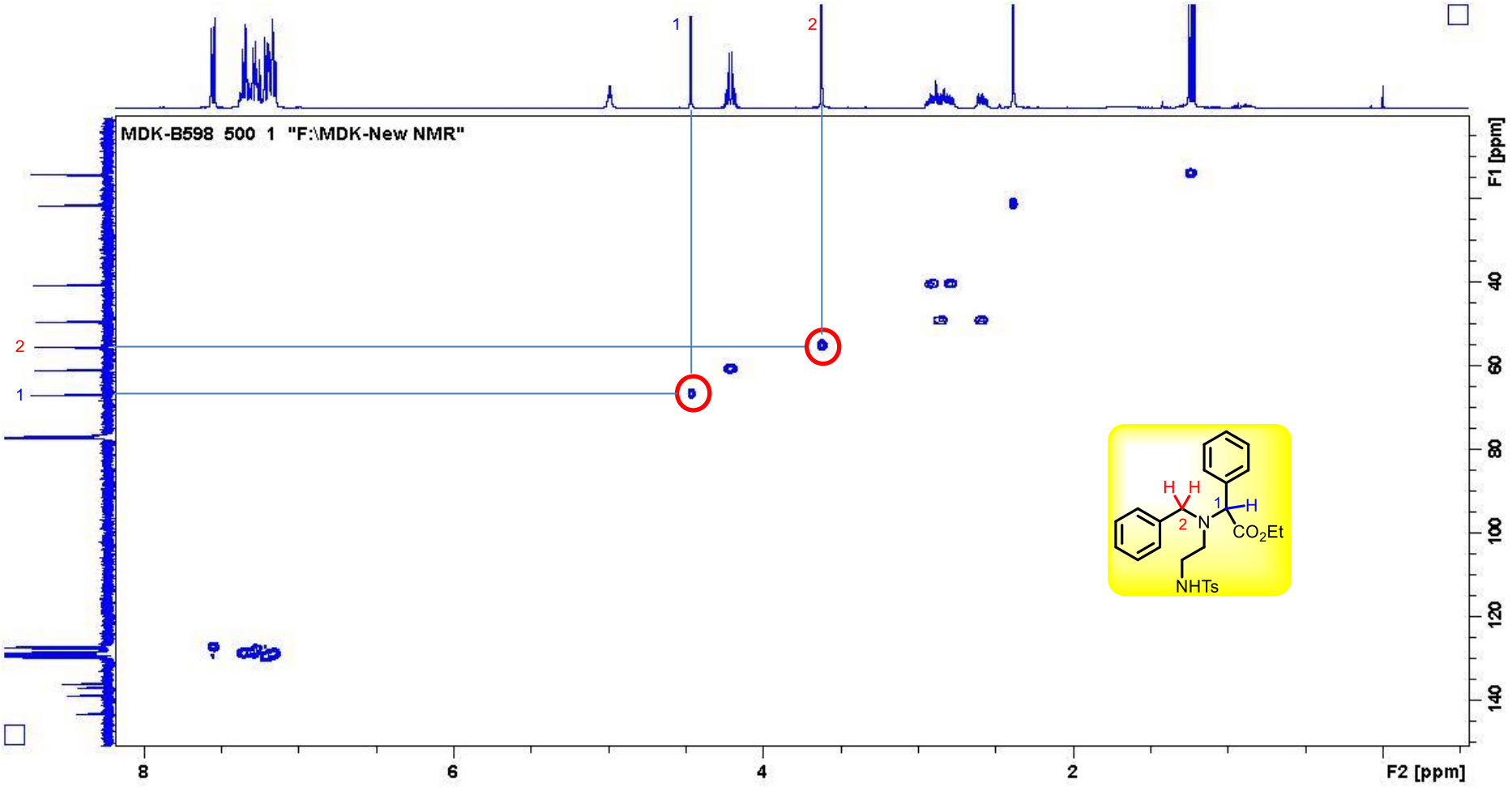
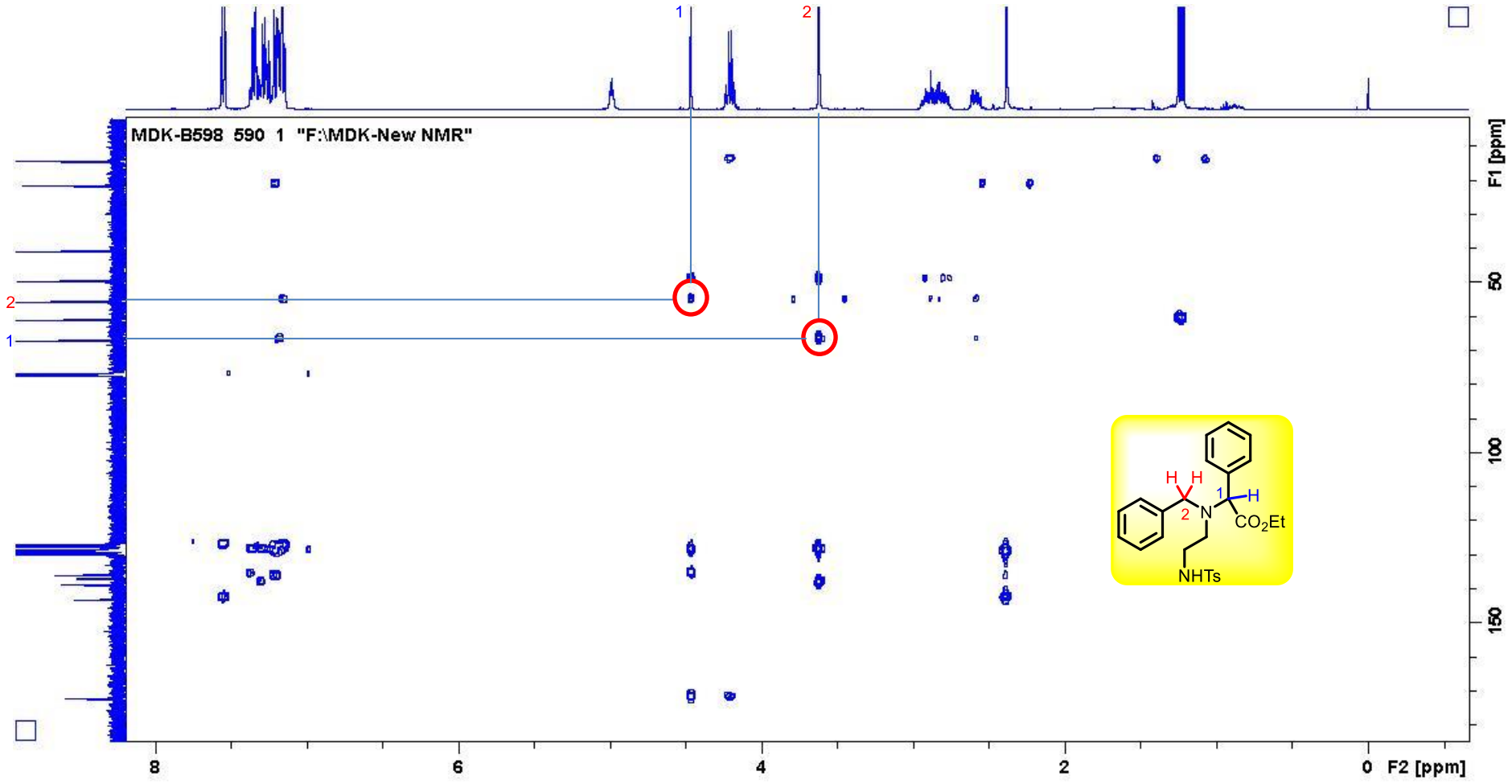


Figure S-83: ^{1}H-^{13}C HMBC Spectra of **4ay** in $CDCl_3$ at 400 MHz



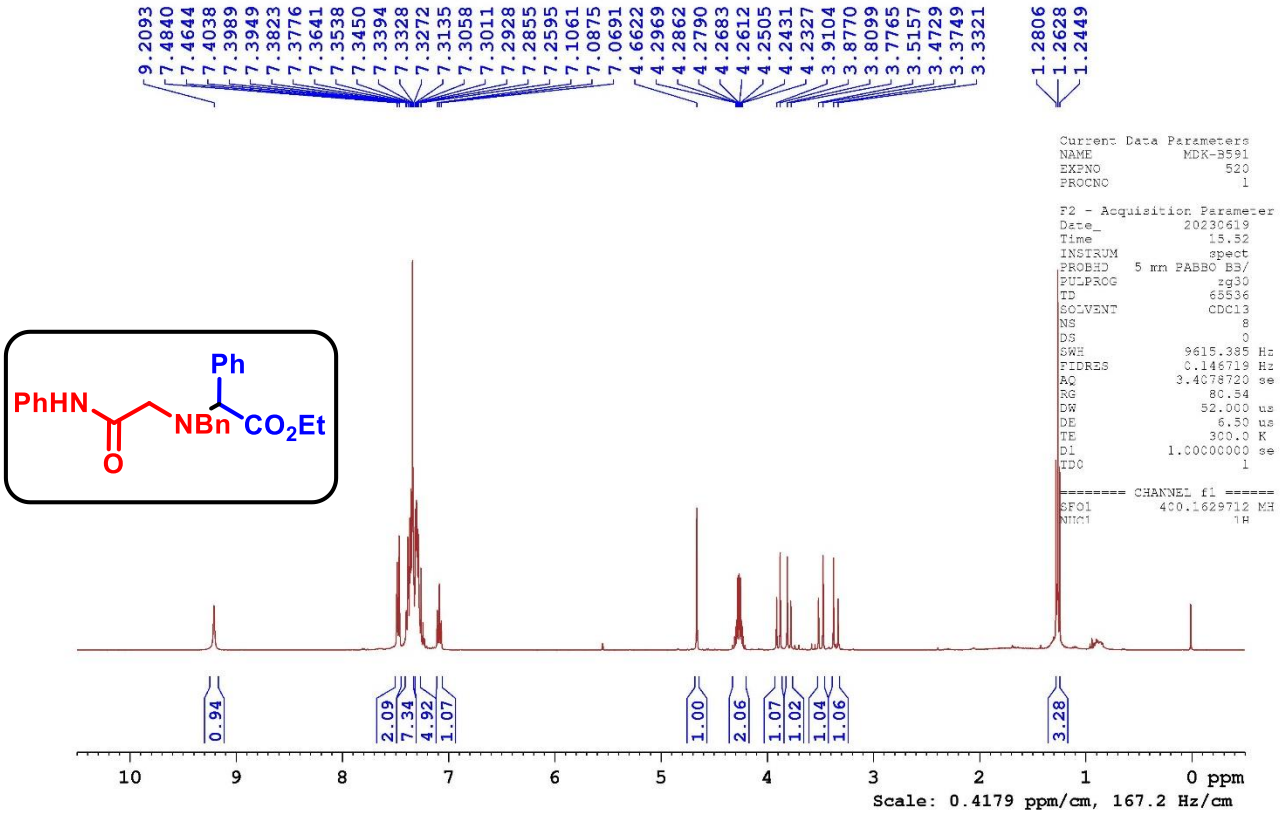


Figure S-84: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4az**

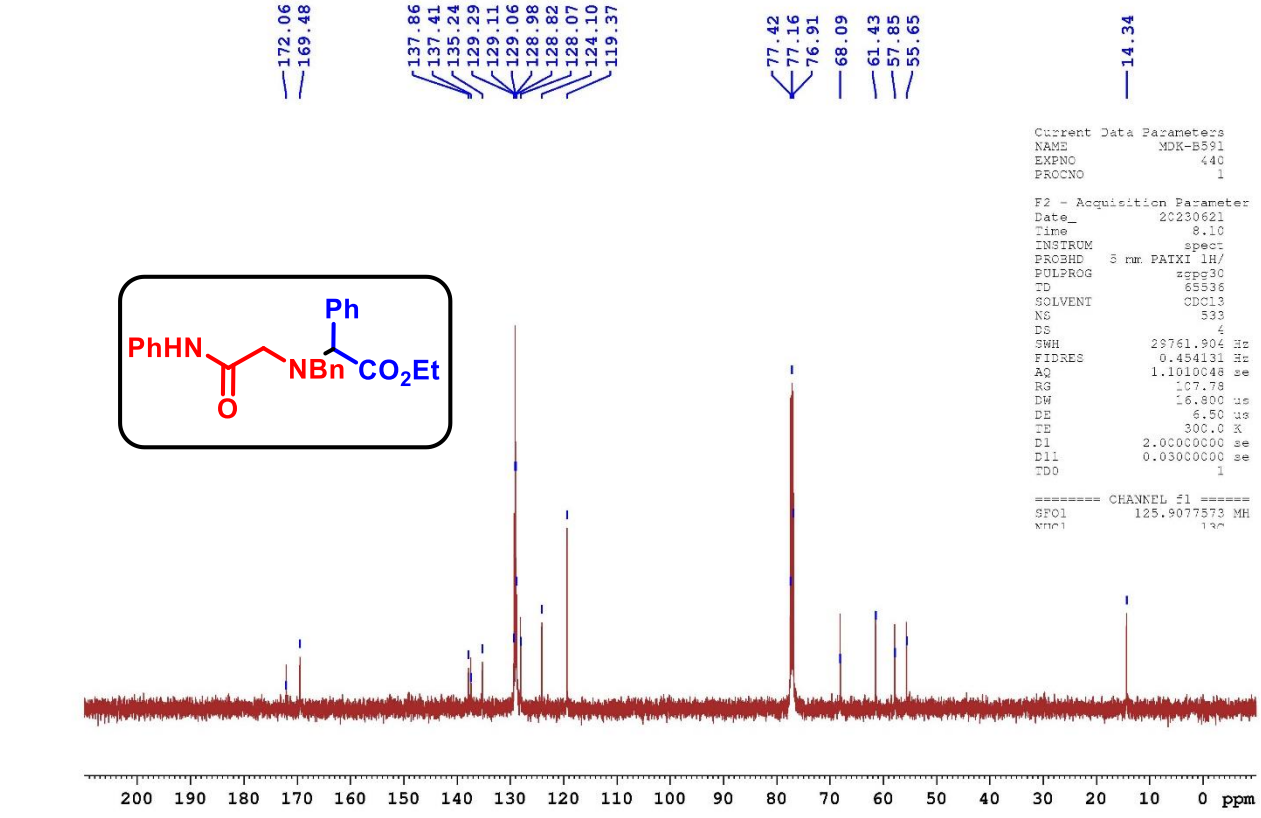


Figure S-85: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4az**

Figure S-86: ^{1}H-^{13}C HSQC Spectra of **4az** in $CDCl_3$ at 400 MHz

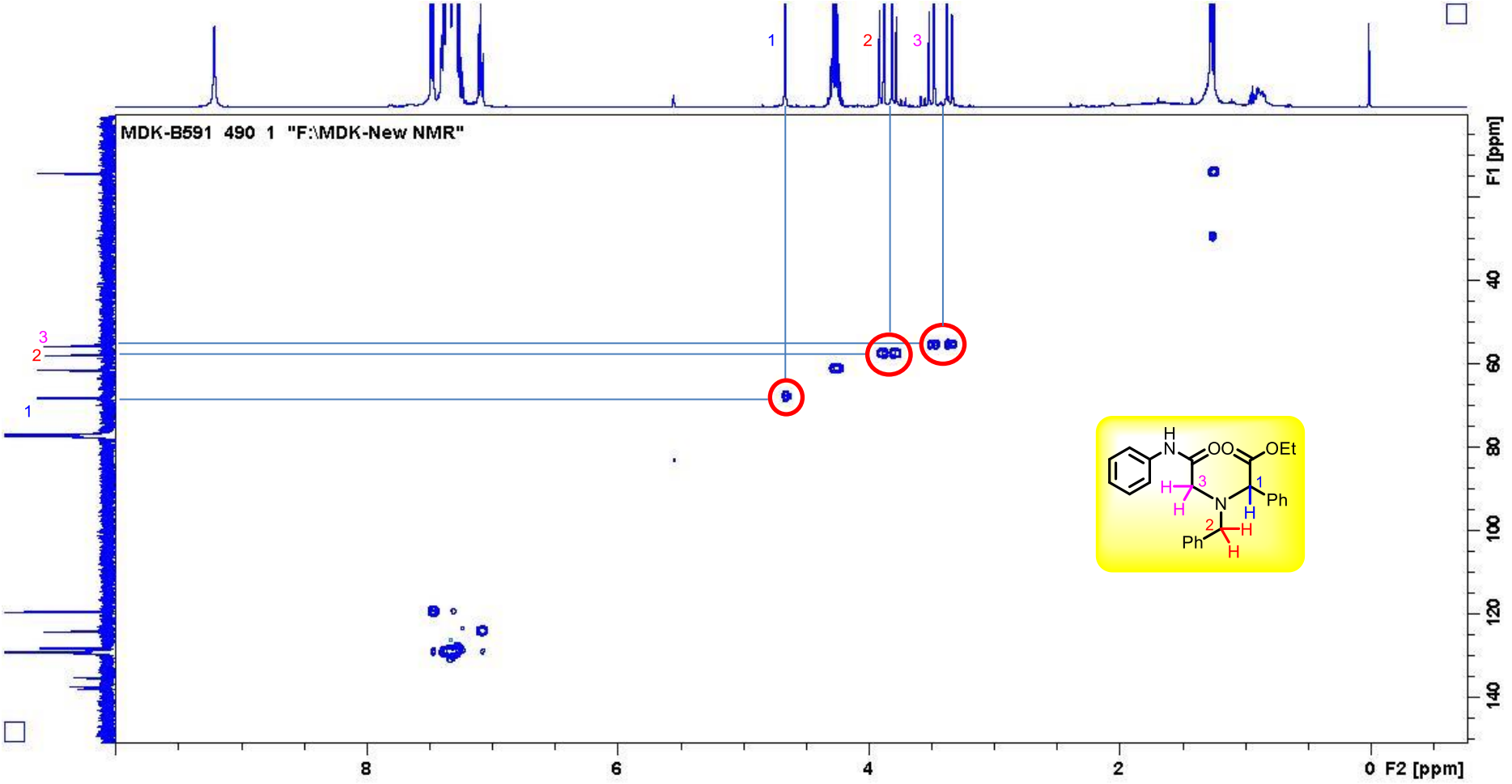
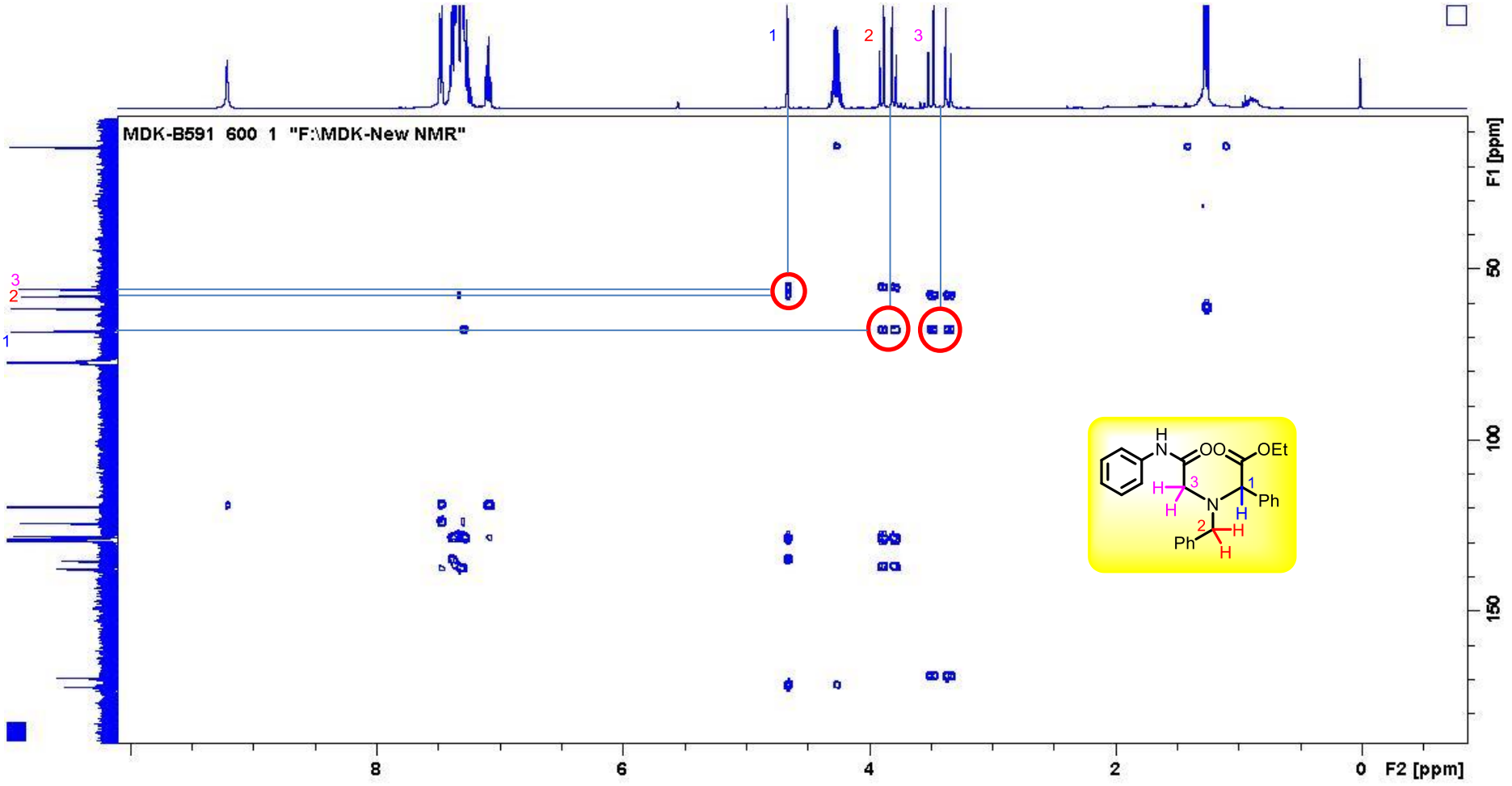


Figure S-87: ^{1}H-^{13}C HMBC Spectra of **4az** in $CDCl_3$ at 400 MHz



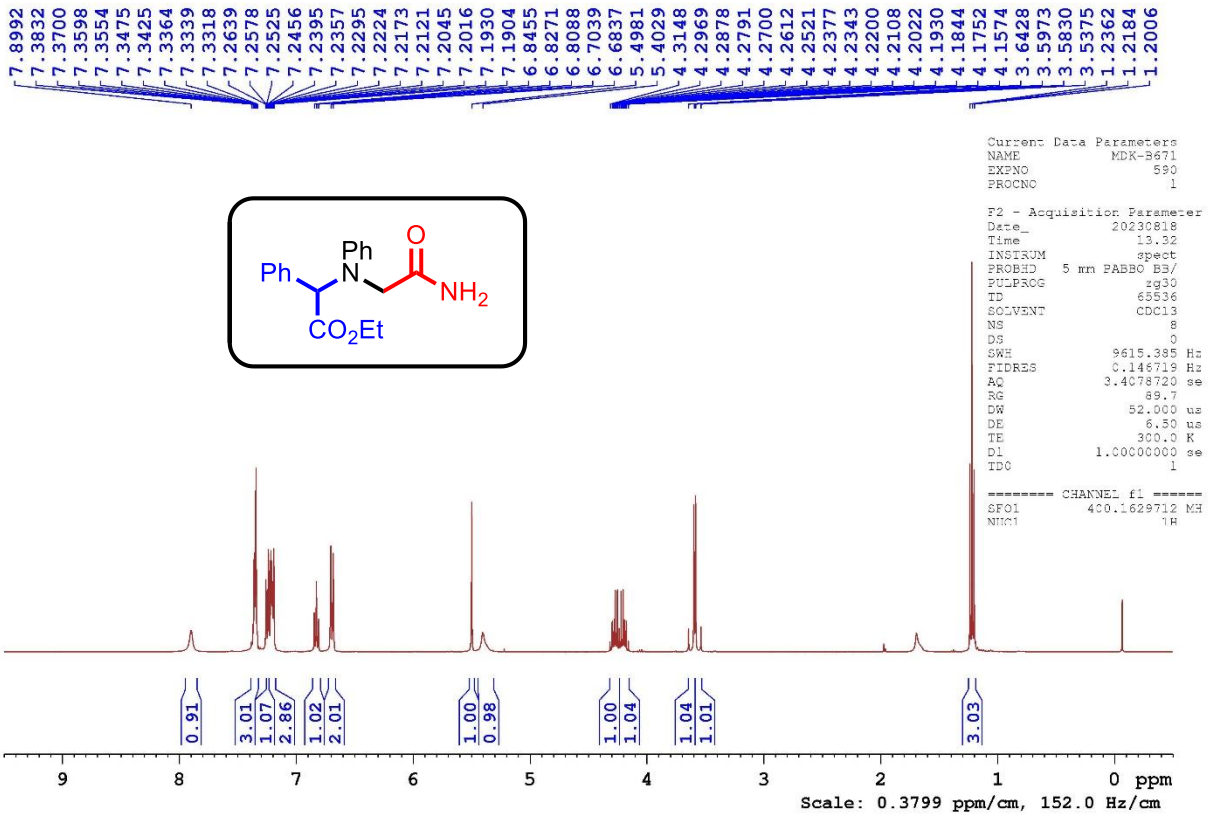


Figure S-88: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4aa'**

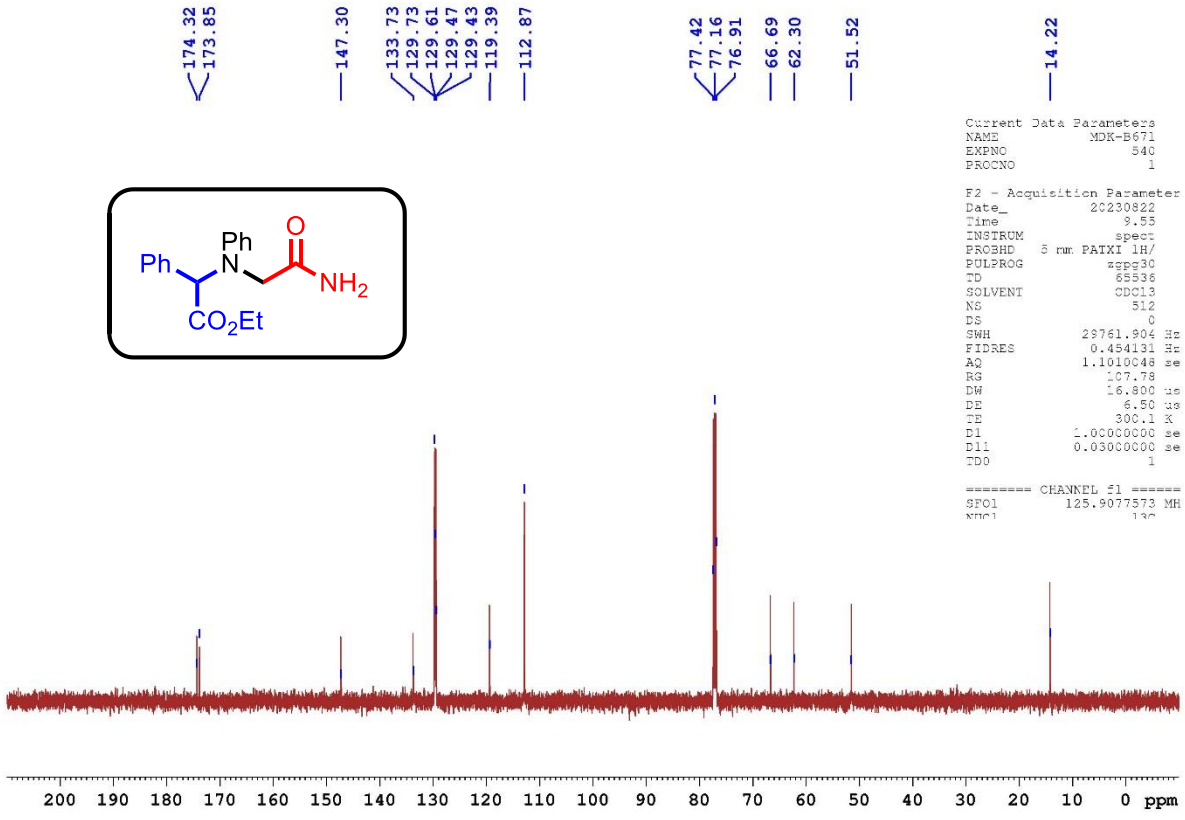


Figure S-89: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4aa'**

Figure S-90: ^{1}H-^{1}H NOESY Spectra of **4aa'** in $CDCl_3$ at 400 MHz

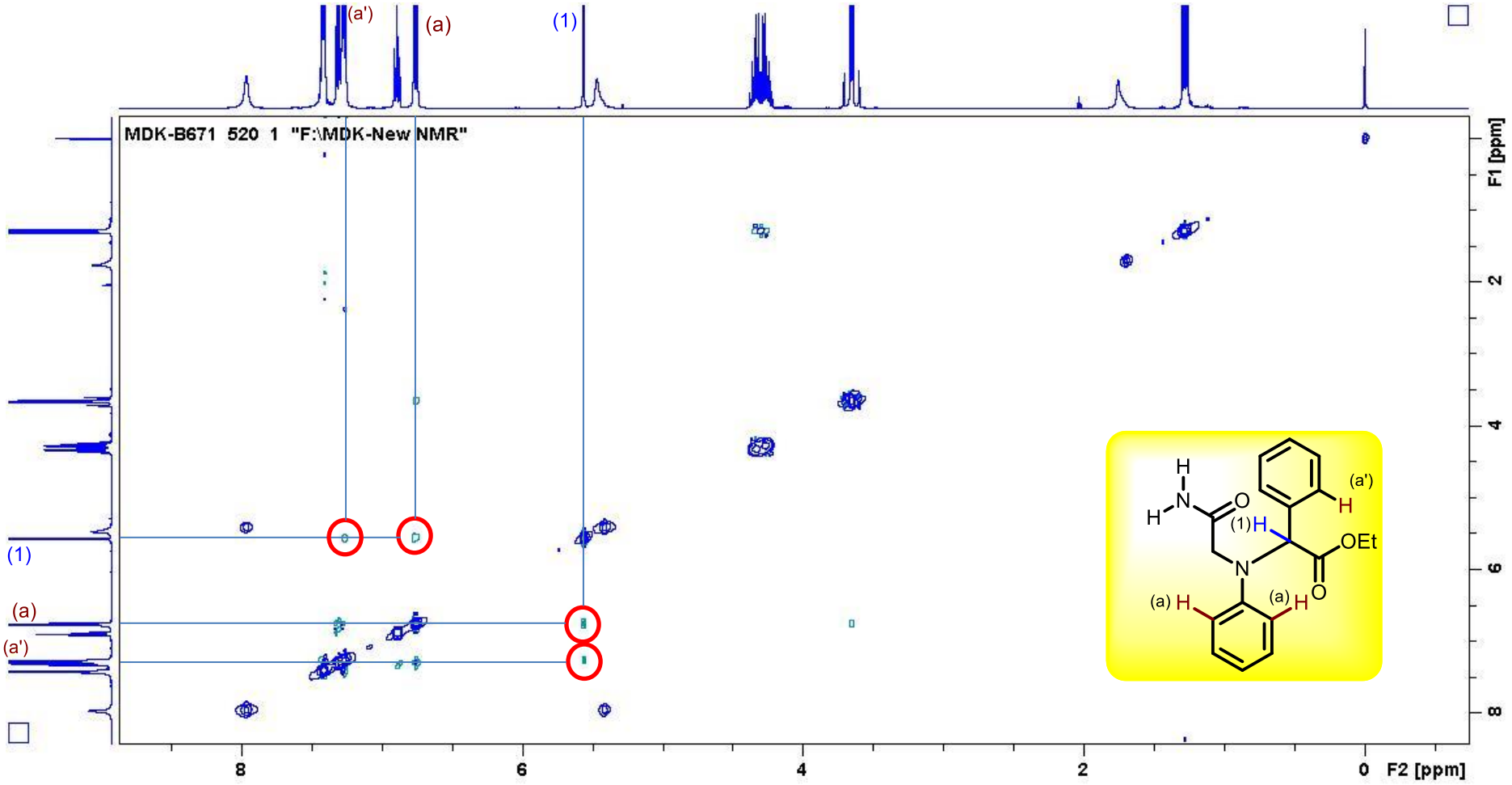


Figure S-91: ^{1}H-^{13}C HSQC Spectra of **4aa'** in $CDCl_3$ at 400 MHz

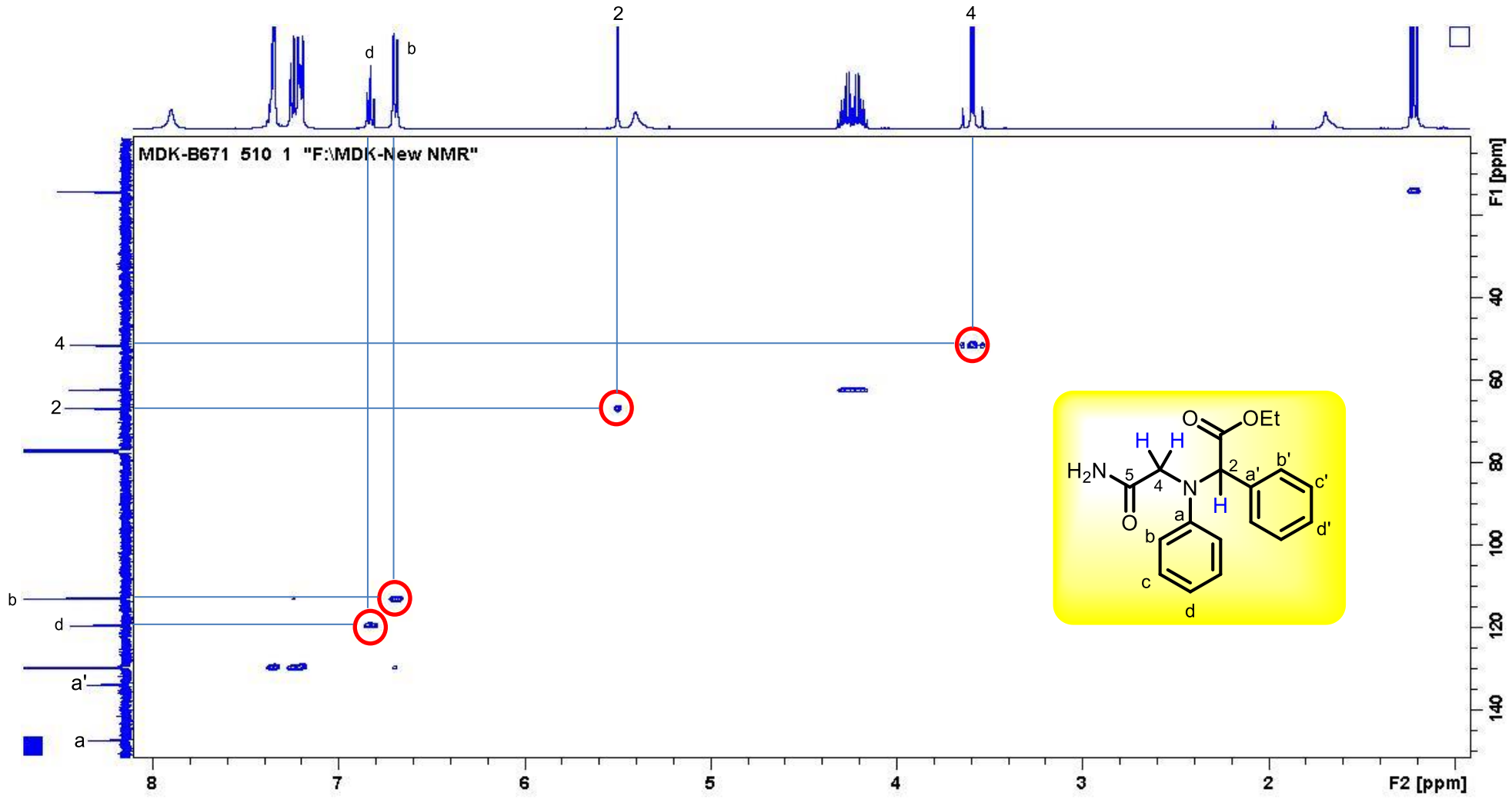
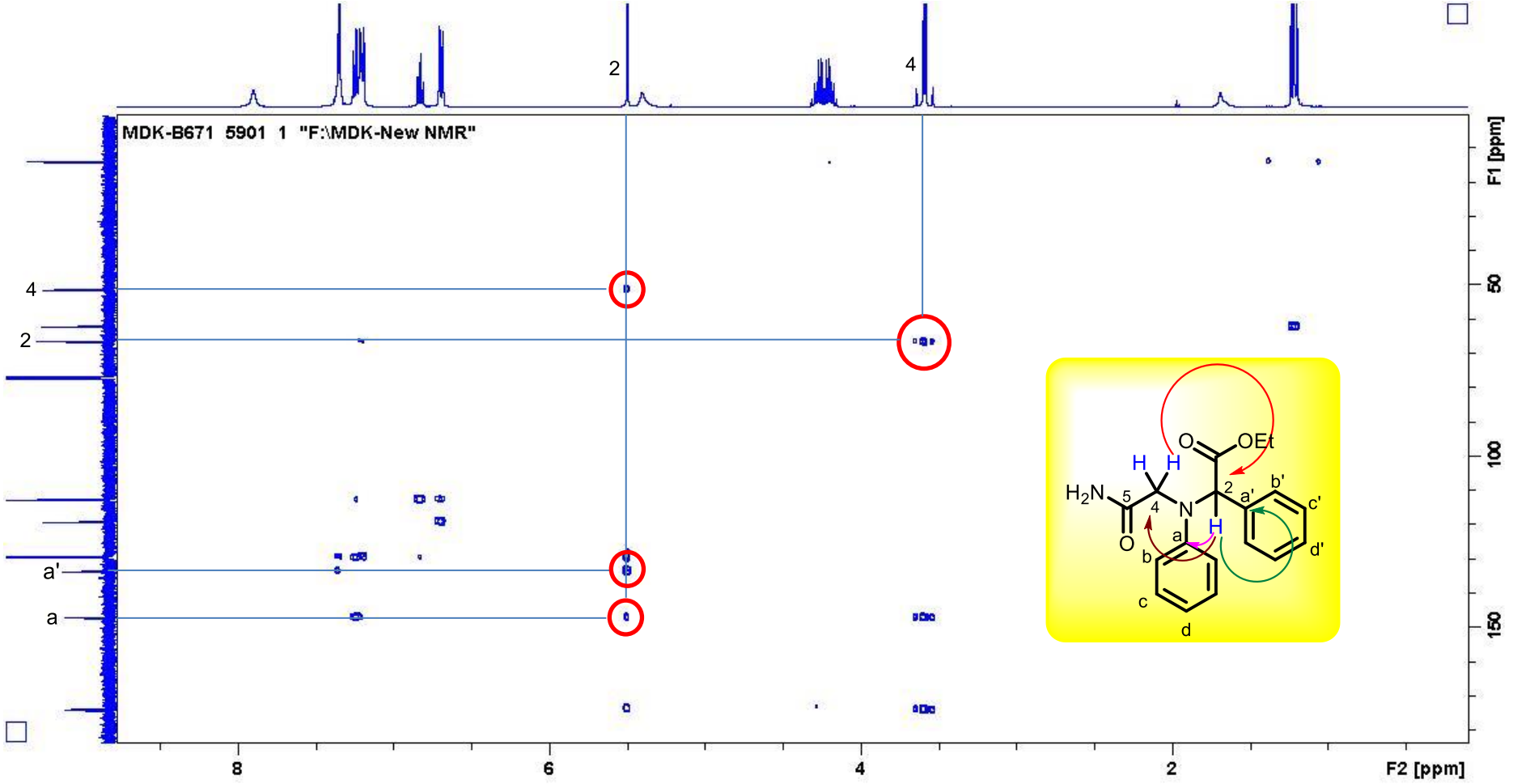


Figure S-92: ^{1}H-^{13}C HMBC Spectra of **4aa'** in $CDCl_3$ at 400 MHz



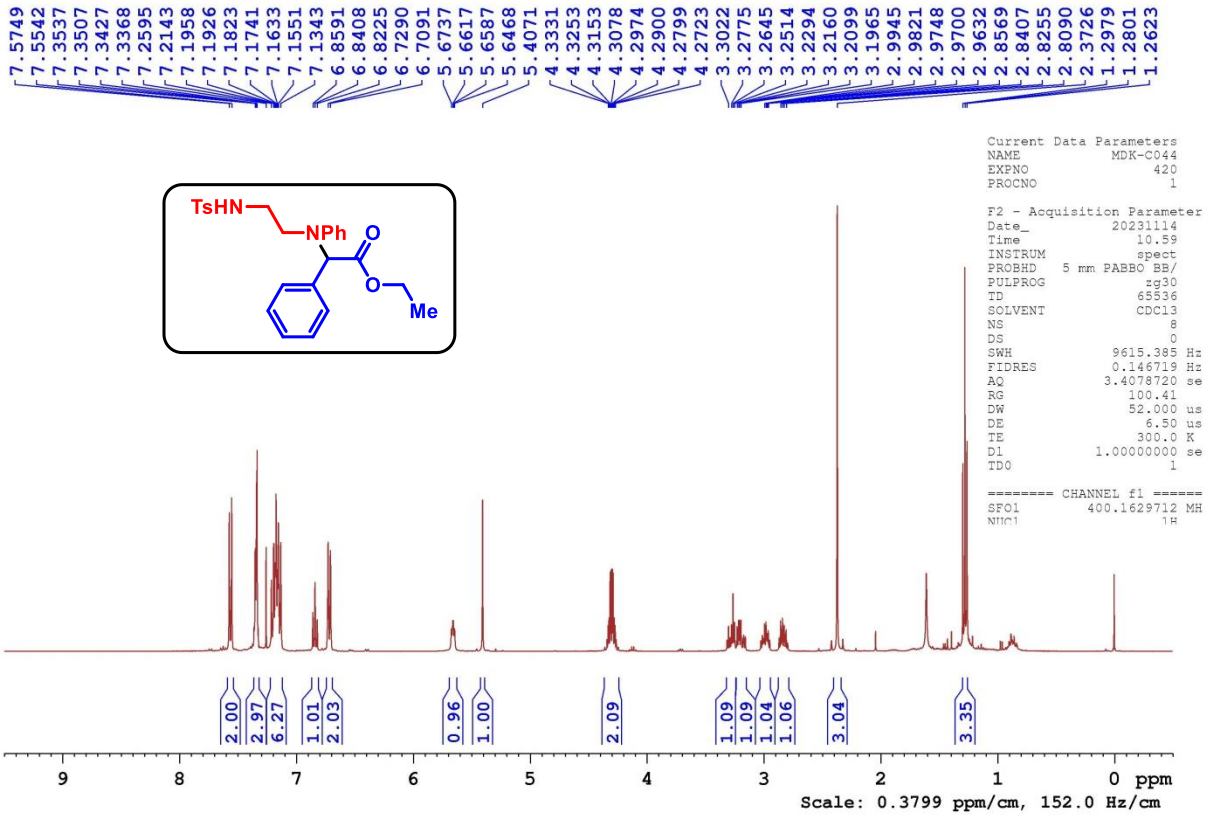


Figure S-93: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4ab'**

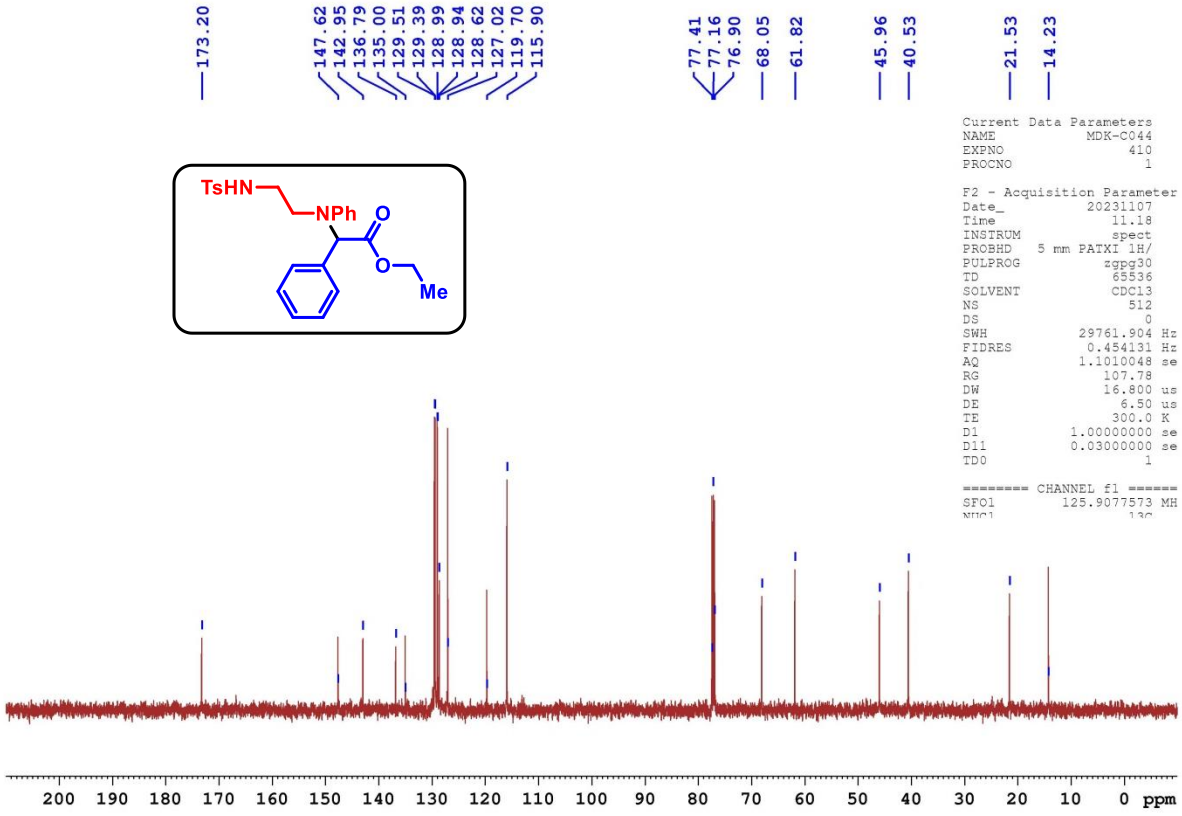


Figure S-94: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **4ab'**

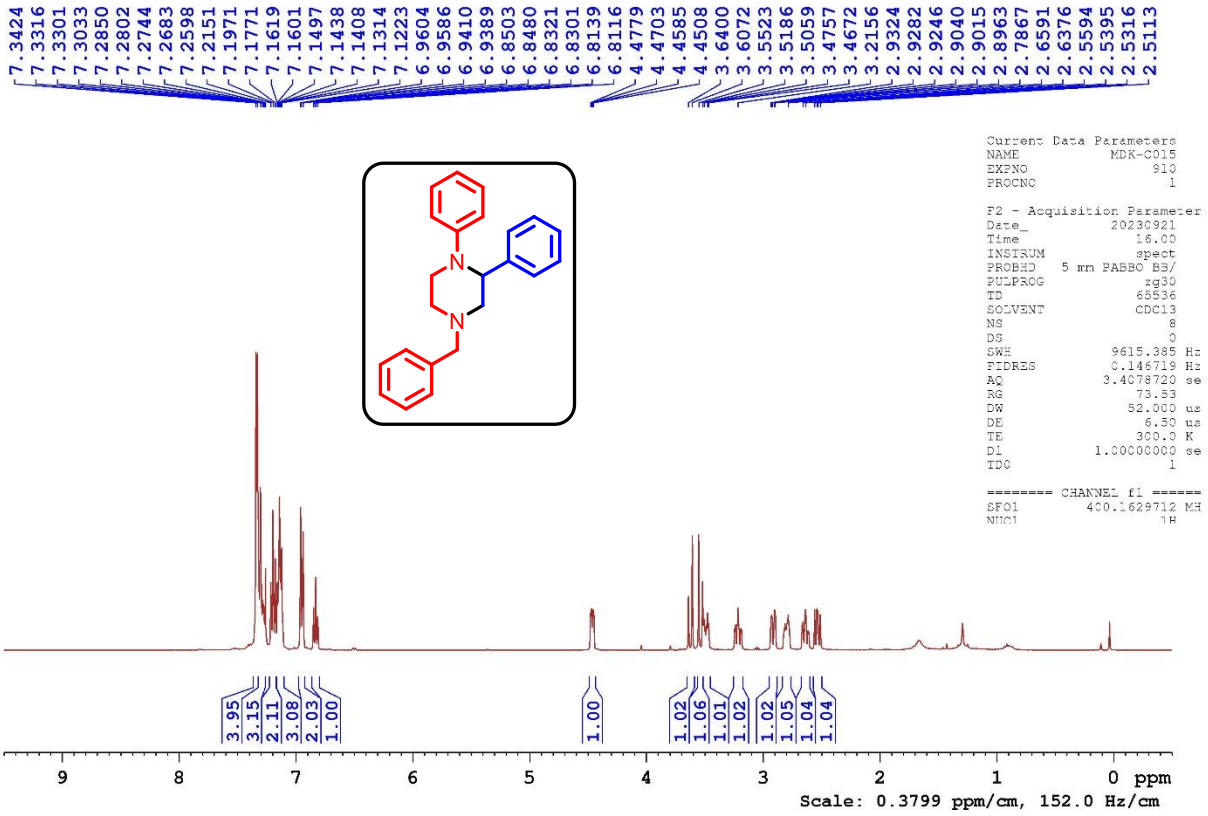


Figure S-95: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5**

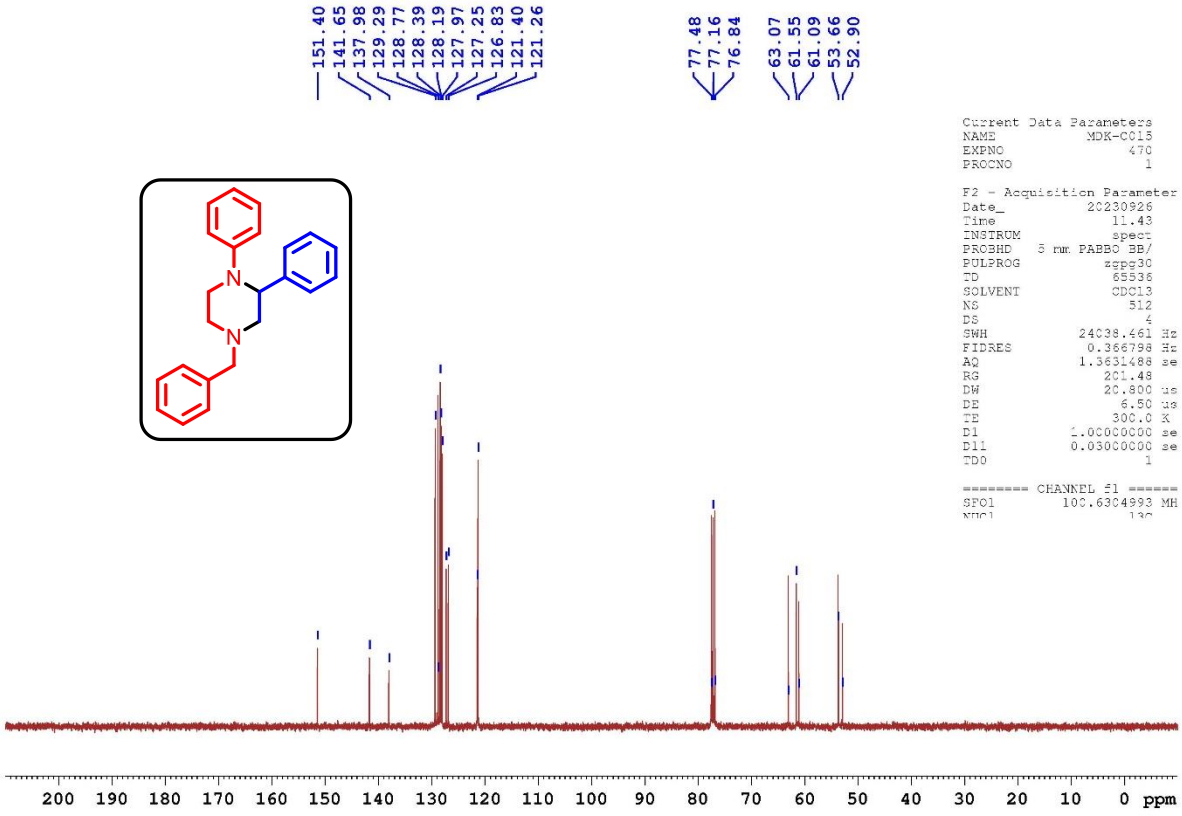


Figure S-96: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **5**

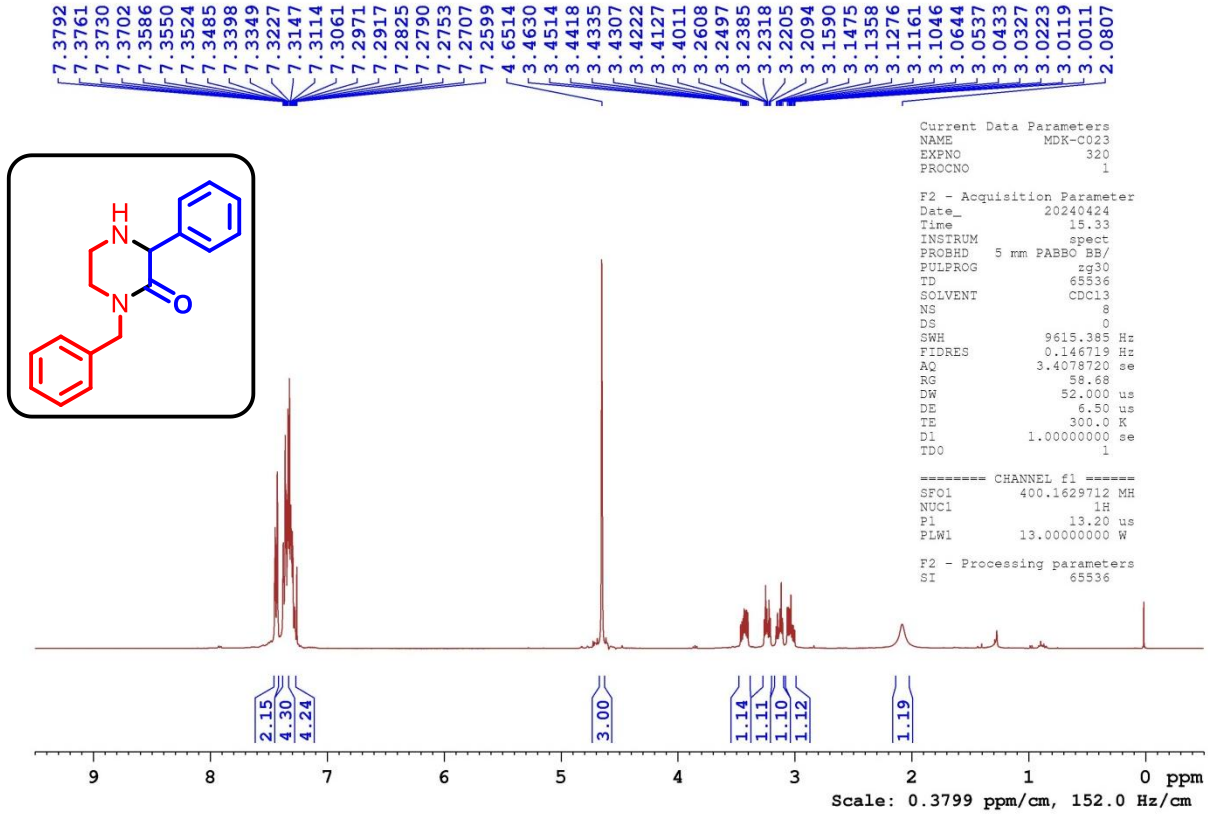


Figure S-97: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **6**

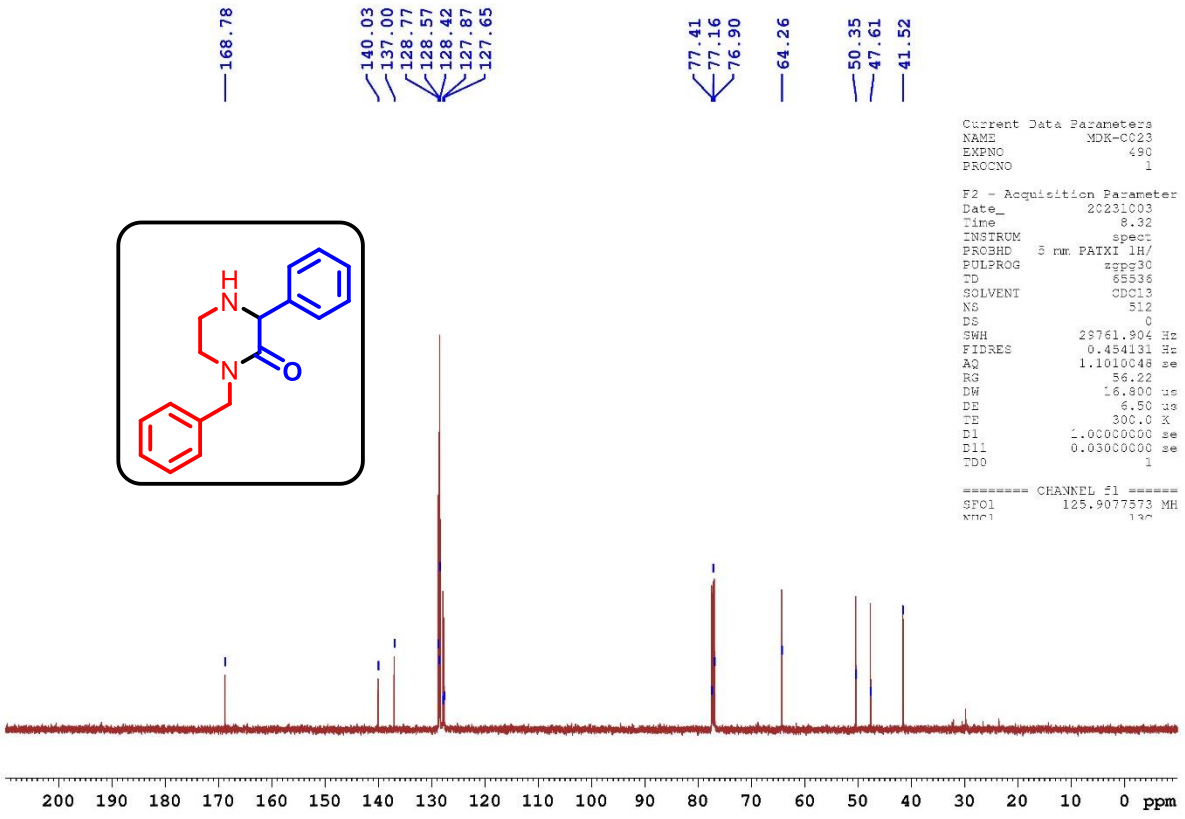


Figure S-98: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **6**

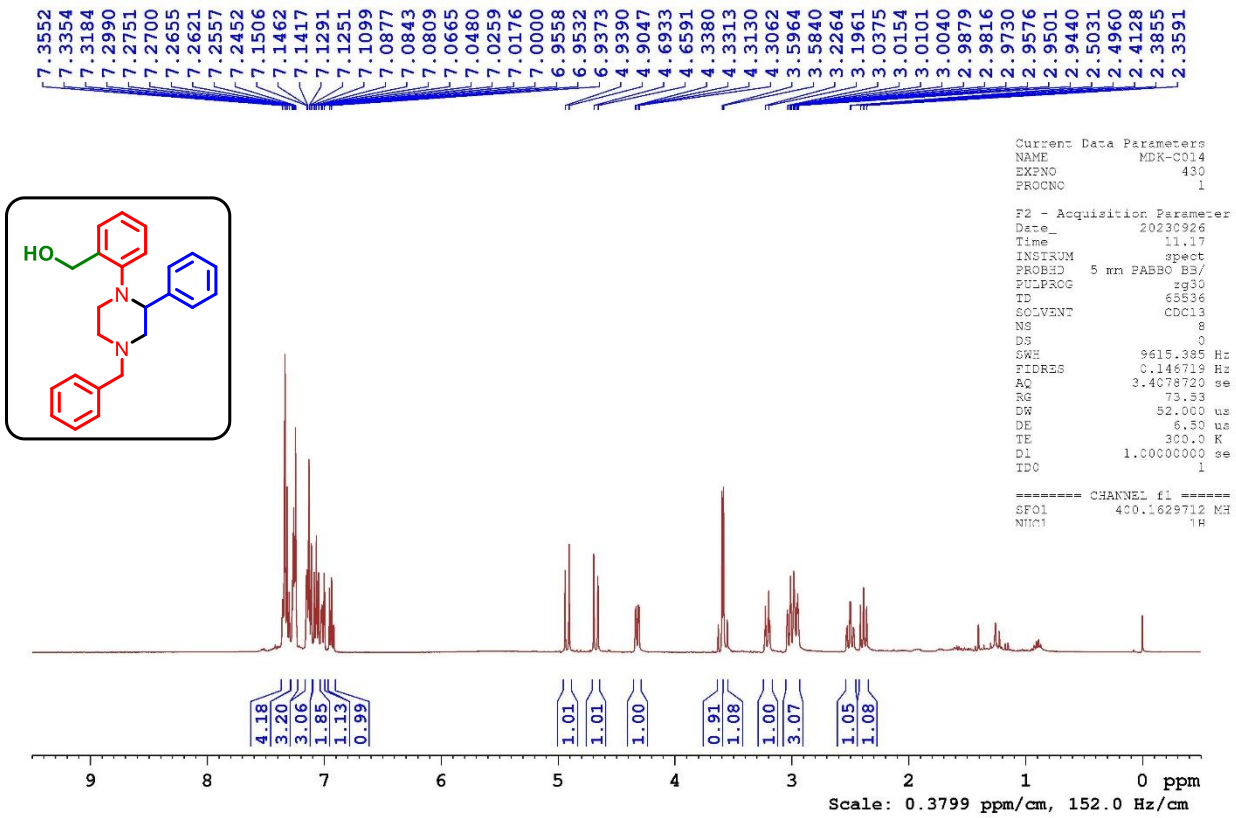


Figure S-99: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **7**

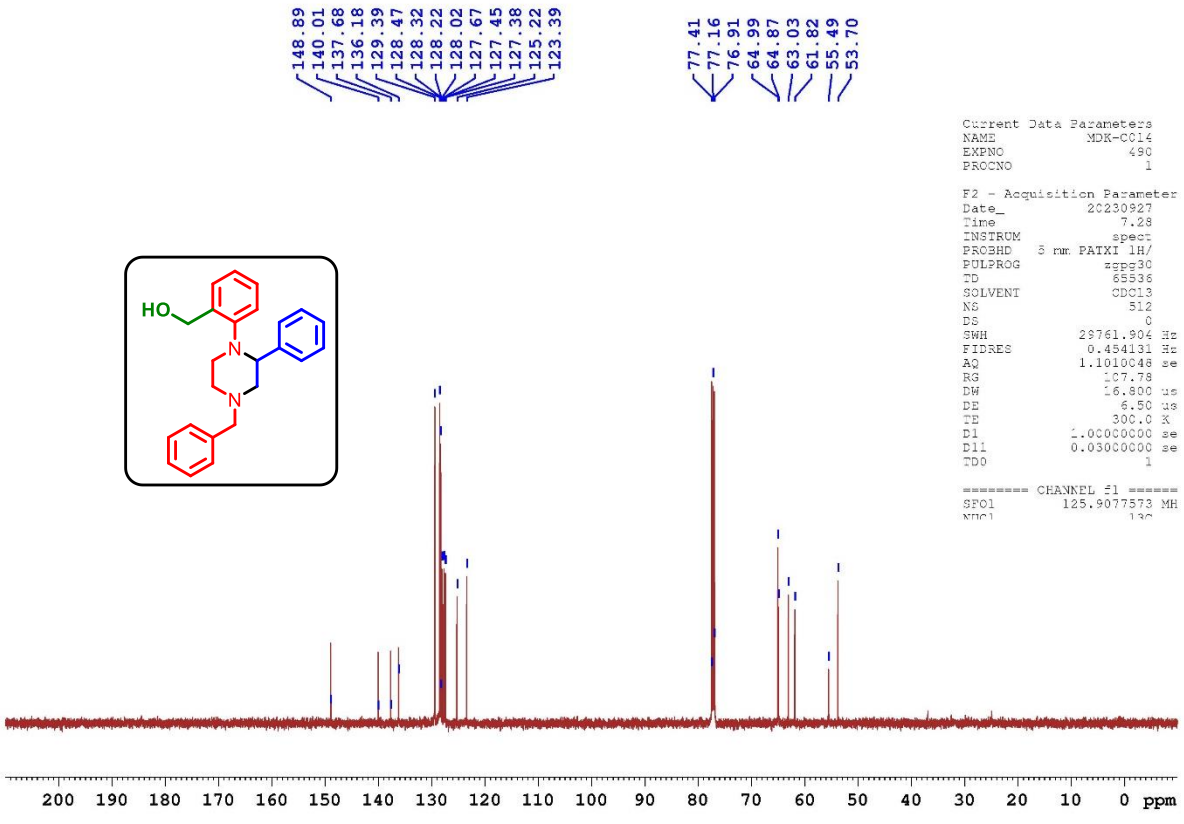


Figure S-100: $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) spectrum of compound **7**

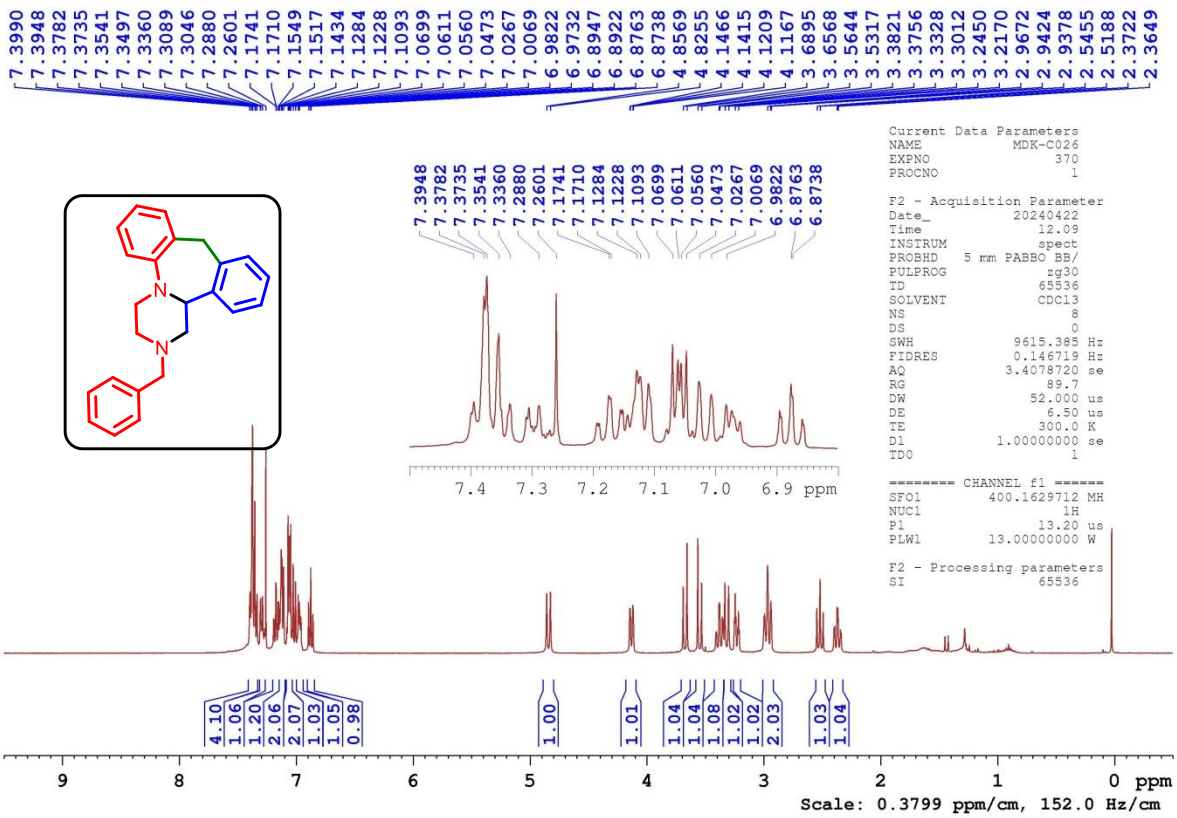


Figure S-101: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8**

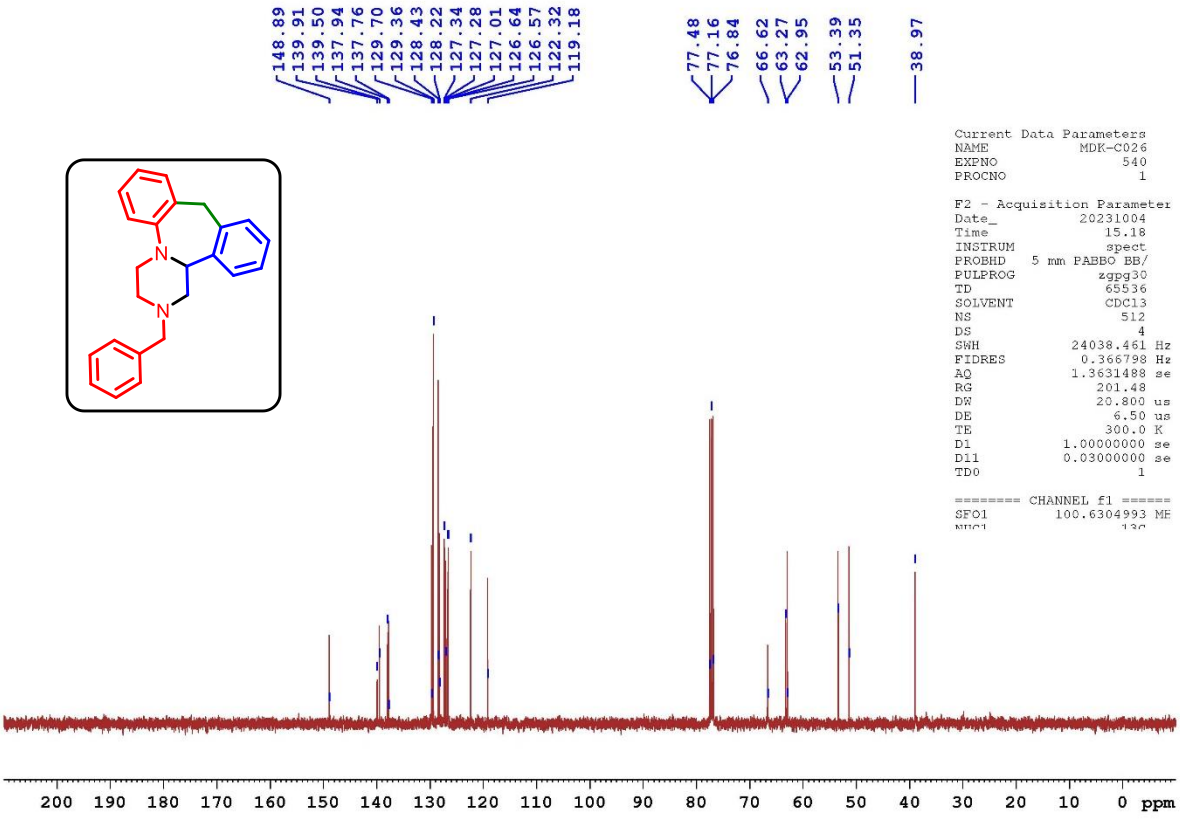


Figure S-102: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **8**

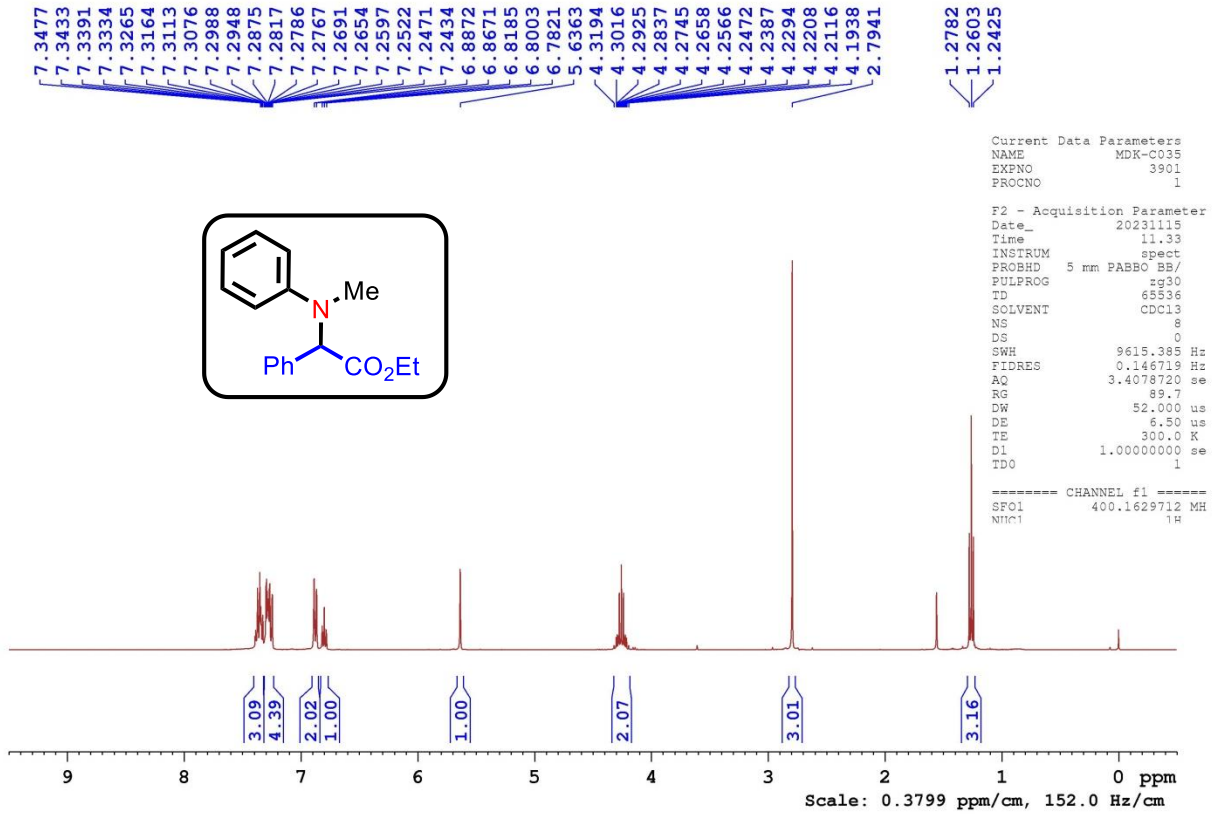


Figure S-103: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9**

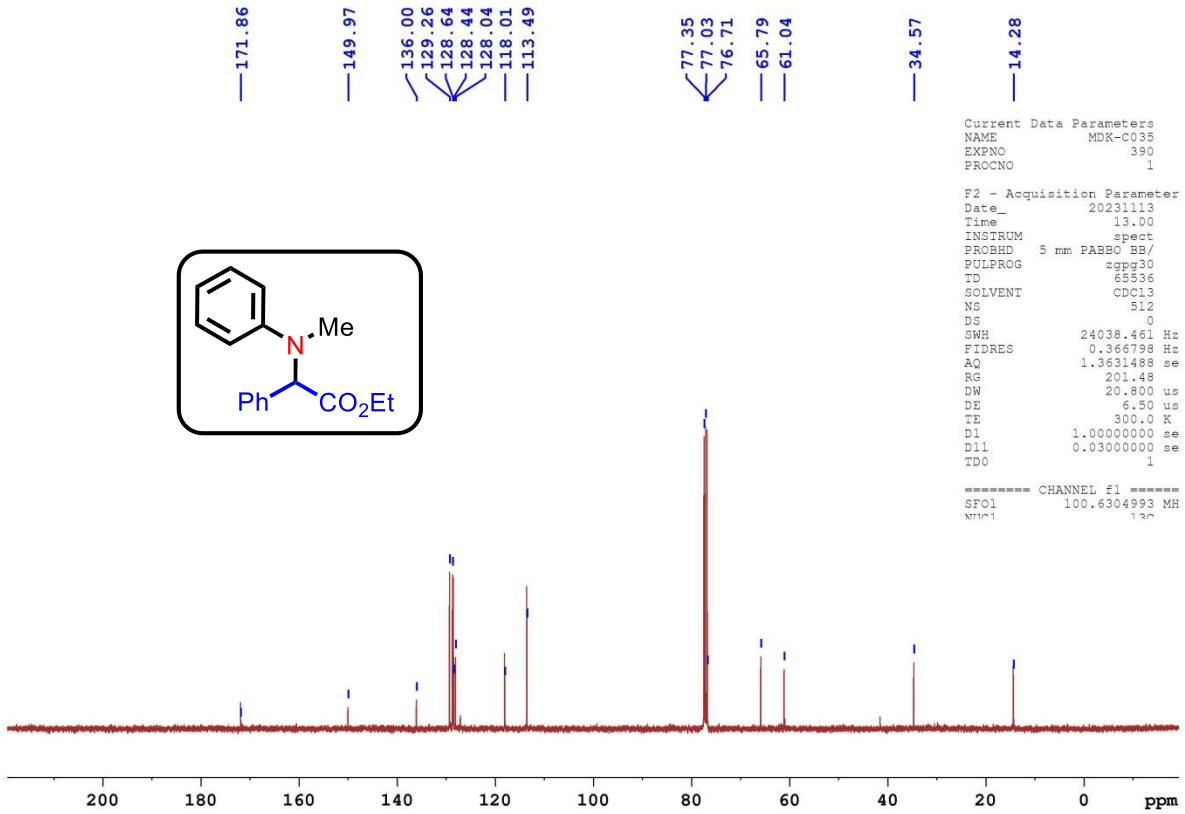


Figure S-104: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **9**

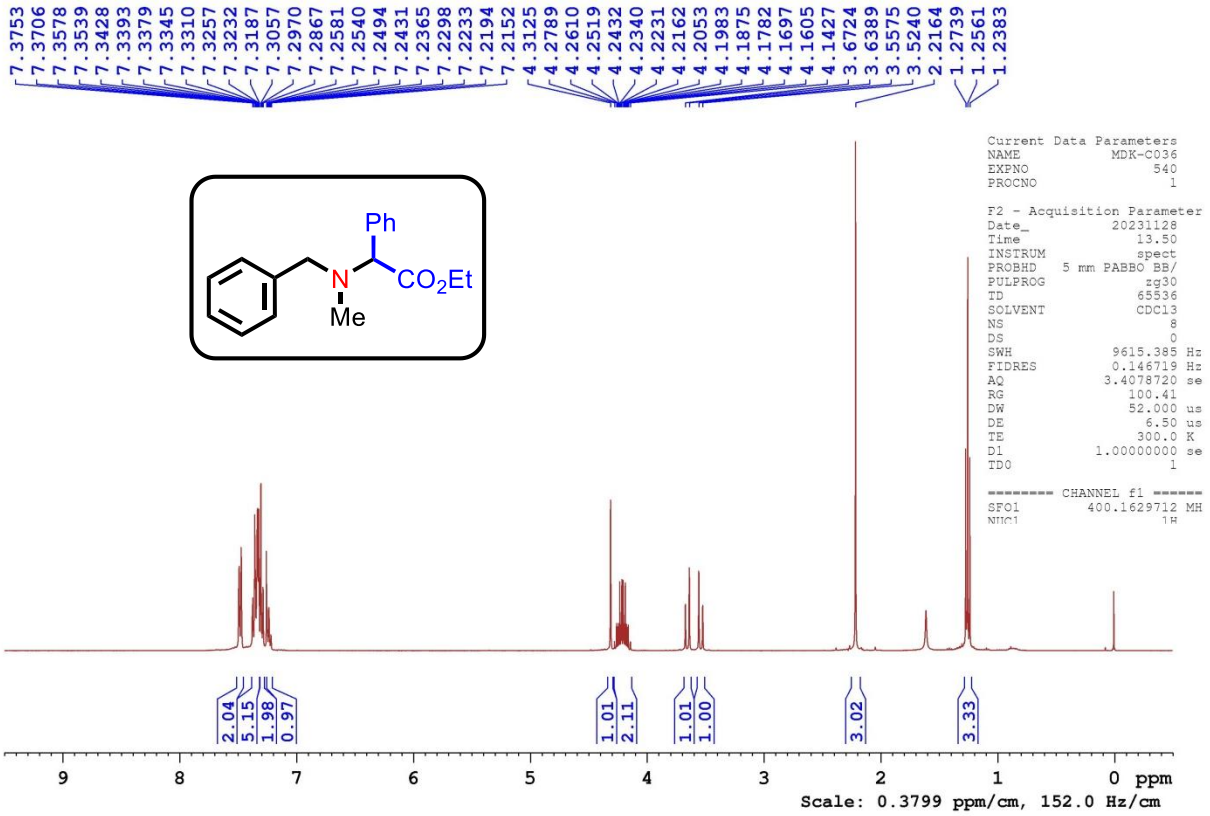


Figure S-105: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **10**

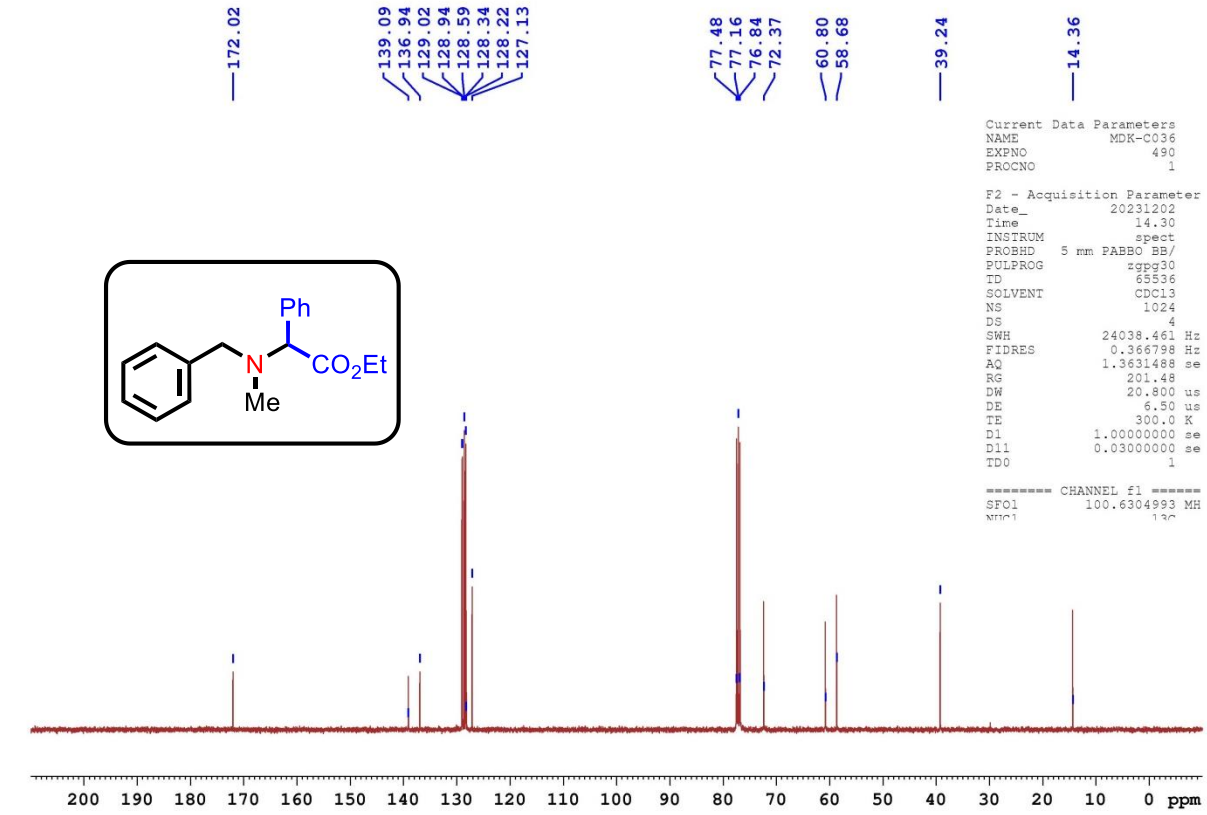


Figure S-106: $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **10**