Supporting Information

A General Nickel-Catalyzed Highly Regioselective Hydroarylation of Unactivated Alkenes Enabled by Picolinamide Auxiliary

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1. General Remarks

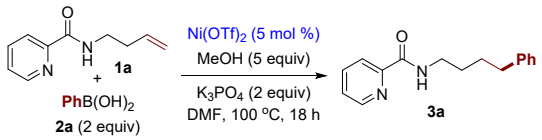
All the manipulations were performed in an argon-filled glovebox, unless mentioned otherwise. Anhydrous solvent was purchased from commercial sources and transferred under argon atmosphere. Alkene substrates were prepared according to previously reported procedures, all arylboronic acids was purchased from commercial sources and used without further purification.

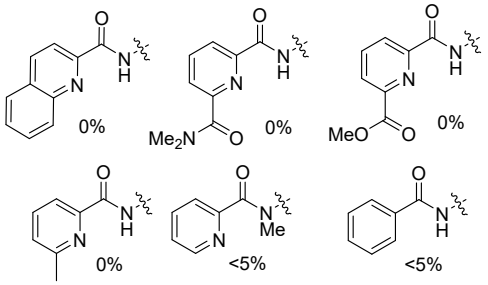
^{1}H NMR, ^{13}C NMR spectra were recorded using Bruker 400 MHz NMR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were referenced to resonances of the residual protons in the deuterated solvents. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br = broad singlet and m = multiplet. GC-MS analysis was performed on Shimadzu GC-2010 gas chromatography coupled to a Shimadzu QP2010 mass selective detector. Analytical HPLC/MS was performed with an Agilent 6520 Series HPLC.

2. Condition Optimization

In order to identify the optimal conditions for the designed regioselective hydroarylation, amide **1a** bearing picolinamide auxiliary (PA) and phenyl boronic acid **2a** was chosen as the model substrates. After carefully evaluation of reaction parameters, it was noticed that the desired hydrophenylation product **3a** could be isolated with excellent yield (93%) in our hand, and the optimal conditions was shown in Table S1. During this process, the following five points should be highlighted. (1) No external ligand was necessary and the use of $Ni(OTf)_2$ is best for the transformation, although the employment of air-sensitive and expensive $Ni(COD)_2$ could also give rise to the same result (entries 2-3). As a comparison, the use of other nickel salts which include $NiCl_2$ or $NiBr_2$ only led to inferior yield (entry 1 vs. 4). (2) Control experiments confirmed that both solvent and base has great influence for the hydrophenylation, and the use of polar solvent DMF and K_3PO_4 as base is optimal (entries 6-9). (3) a small amount of MeOH is good for the yield (entries 10-11). (4) Both the temperature and reaction time is also inevitable for obtaining the anticipated efficiency (entries 12-13). (5) The auxiliary plays a very decisive role for this process, as attempting to utilize other similar ones led to the complete shutdown of the transformation (entry 14). As demonstrated later, the PA auxiliary could be easily removed under basic conditions.

Table S1 Optimal conditions.[a]

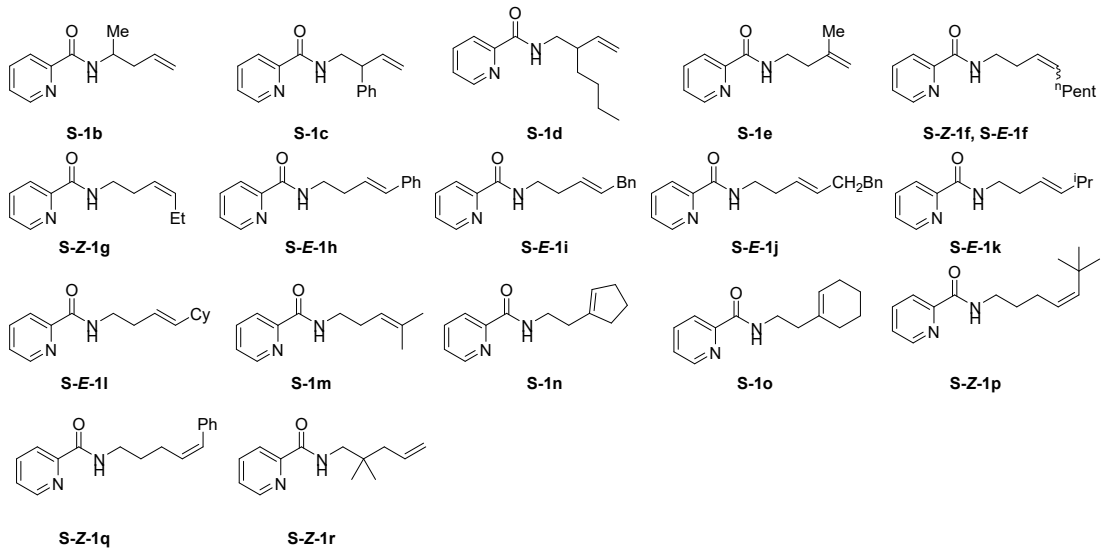


Entry	Deviation from standard conditions	Yield **3a** (%)[b]
1	none	93
2	No $Ni(OTf)_2$	0
3	$Ni(COD)_2$ instead of $Ni(OTf)_2$	93
4	$NiCl_2$, $NiBr_2$ instead of $Ni(OTf)_2$	<55
5	1,4-dioxane instead of DMF	42
6	MeCN instead of DMF	NR
7	*t*-BuOH instead of DMF	82
8	Cs_2CO_3 instead of K_3PO_4	84
9	$KHCO_3$ instead of K_3PO_4	88
10	No MeOH	78
11	MeOH instead of DMF	86
12	80 °C instead of 100 °C	59
13	12 h instead of 18 h	87
14		

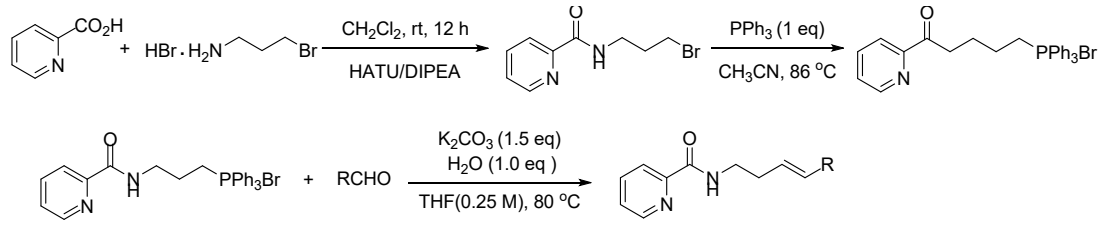
[a] Conditions: 1**a** (0.20 mmol), **2a** (2.0 equiv), $Ni(OTf)_2$ (0.01 mmol, 5 mol %), K_3PO_4 (2.0 equiv), N,N-dimethylformamide (DMF) (1.0 mL), MeOH (6 mmol, 30 equiv) at 100 °C for 24 hours. [b] Isolated yield. NR = no reaction.

3. Alkene Substrate Synthesis

Table S2. Picolinamide-containing alkene substrates **S-1b – S-*Z*-1r.**



The synthesis of compounds **S-*E*-1j** and **S-*E*-1l**.

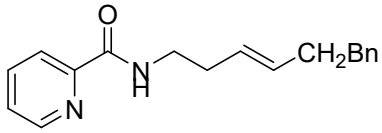


To a 50 mL flask was added 3-bromopropylamine hydrobromide (1.0 eq), picolinic acid (1.2 eq), HATU (1.1 eq), DIPEA (2 eq) and CH_2Cl_2 (30 mL). The reaction mixture was left to stir for 12 h. After that, the reaction mixture was diluted with EtOAc (100 mL) and washed with brine (3×100 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated, and carried forward to the next step without further purification. [1]

PPh_3 (30 mmol, 1.0 eq), CH_3CN (150 mL) was added to the resulting solution and then the reaction vessel was allowed to heat to reflux under argon for 48 h. After this time, the reaction vessel was cooled to room temperature, removed solvent by vacuum. Then added aldehyde (30 mmol, 1.0 eq), K_2CO_3 (45 mmol, 1.5 eq), H_2O (30 mmol, 1.0 eq) in THF (80 mL) was stirred at 80 °C for 12 h. After that, the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered and

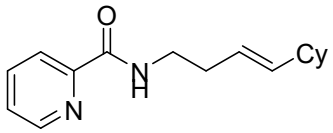
concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography (ethyl acetate:hexanes = 1:8) to give the desired product.

(*E*)-N-(6-phenylhex-3-en-1-yl)picolinamide (S-*E*-1j)



The title compound was isolated as yellow oil after chromatography on silica with ethyl acetate/hexane (1:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J = 4.8, 0.6 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.09 (br, 1H), 7.94 – 7.78 (m, 1H), 7.41 (m, 1H), 7.36 – 7.21 (m, 2H), 7.21 – 7.08 (m, 3H), 5.65 – 5.53 (m, 1H), 5.44 (m, 1H), 3.44 (dd, J = 13.1, 6.8 Hz, 2H), 2.66 (dd, J = 15.6, 8.3 Hz, 2H), 2.43 – 2.20 (m, 4H). ^{13}C NMR (101 MHz, CDCl3) δ 164.3, 150.1, 148.1, 141.9, 137.4, 131.8, 128.5, 128.3, 126.6, 126.2, 125.9, 122.3, 39.1, 35.9, 29.3, 27.6. GC-MS (EI): Calcd for $C_{18}H_{20}N_2O$:280.16, found: 280.19.

(*E*)-N-(4-phenylbut-3-en-1-yl)picolinamide (S-*E*-1l)



The title compound was isolated as a yellow oil after chromatography on silica with ethyl acetate/hexane (1:8).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.51 (m, 1H), 8.20 (m, 1H), 8.12 (br, 1H), 7.84 (m, 1H), 7.41 (m, 1H), 5.47 – 5.22 (m, 2H), 3.50 (dd, J = 13.0, 6.8 Hz, 2H), 2.39 (m, 2H), 2.30 – 2.15 (m, 1H), 1.69 – 1.53 (m, 6H), 1.28 – 1.12 (m, 4H), 1.04 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 150.1, 148.0, 139.1, 137.4, 126.1, 123.8, 122.2, 39.3, 36.5, 33.3, 27.8, 26.0, 25.9. GC-MS (EI): Calcd for $C_{18}H_{20}N_2O$:258.17, found:258.19.

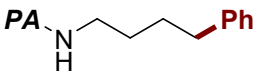
Table S3. Reference containing synthetic/characterization data for known substrates.

Alkene substrates	Reference
S-1b - S-1g	*Cell Rep. Phys. Sci.* **2021**, *2*, 100574.
S-1h, S-1i, S-1k	*Nat. Commun.* **2021**, *12*, 6280.
S-1n	*Org. Lett.* **2016**, *18*, 5014.
S-1o, S-Z-1p	*J. Am. Chem. Soc.* **2019**, *141*, 8758.
S-Z-1q, S-Z-1r	*Nat. Commun.* **2021**, *12*, 6280.

4. General Procedure for the Nickel(II)-Catalyzed Hydroarylation of Alkeny Amines

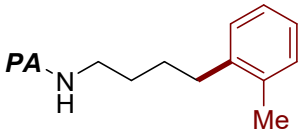
In an argon-filled glovebox, $Ni(OTf)_2$ (0.01 mmol, 5 mol%), K_3PO_4 (0.4 mmol, 2.0 eq), alkene substrate (0.2 mmol, 1.0 eq), appropriate aryl boronic nucleophile (0.4 mmol, 2 eq), DMF (1 mL) and MeOH (243.0 μL, 30 eq) were added to a 10 mL schlenk flask. The reaction mixture was stirred at 100 °C for 18 h and the resulting solution was concentrated in vacuum. The crude product was purified by column chromatography on silica gel with a mixture of ethyl acetate and hexane as eluent. The conditions for flash chromatography and data for characterization of the products are listed below.

N-(4-phenylbutyl)picolinamide (3a)



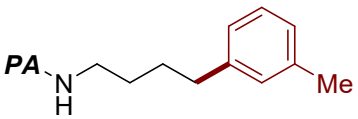
The title compound was isolated as yellow oil (93% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 4.5 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.03 (br, 1H), 7.80 (m, 1H), 7.37 (dd, J = 6.9, 5.2 Hz, 1H), 7.33 – 7.17 (m, 2H), 7.15 (d, J = 7.0 Hz, 3H), 3.49 – 3.44 (m, 2H), 2.64 (t, J = 7.2 Hz, 2H), 1.79 – 1.53 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 150.1, 148.1, 142.2, 137.4, 128.5, 128.4, 126.1, 125.8, 122.2, 39.3, 35.6, 29.3, 28.8. GC-MS (EI): Calcd for $C_{16}H_{18}N_2O$:254.14, found:254.20.

N-(4-(*o*-tolyl)butyl)picolinamide (3b)



The title compound was isolated as yellow oil (93% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.2 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.12 (br, 1H), 7.87 – 7.82 (m, 1H), 7.44 – 7.40 (m, 1H), 7.25 – 7.03 (m, 4H), 3.55 – 3.50 (m, 2H), 2.66 (t, J = 7.4 Hz, 2H), 2.30 (s, 3H), 1.87 – 1.58 (m, 4H);^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 149.9, 148.0, 140.3, 137.5, 135.9, 130.2, 128.9, 126.1, 126.0, 125.9, 122.3, 39.4, 32.9, 29.6, 27.6, 19.3. GC-MS (EI): Calcd for $C_{17}H_{20}N_2O$: 268.16, found: 268.23.

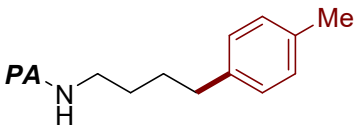
N-(4-(*m*-tolyl)butyl)picolinamide (3c)



The title compound was isolated as yellow oil (86% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H

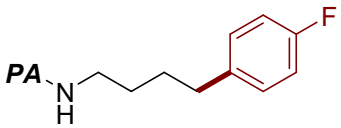
NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.1 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.10 (br, 1H), 7.86 (t, J = 7.7 Hz, 1H), 7.43 (dd, J = 7.4, 4.9 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.02 – 6.93 (m, 2H), 3.78 – 3.52 (m, 2H), 2.63 (t, J = 7.2 Hz, 2H), 2.32 (s, 3H), 1.98 – 1.59 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 149.8, 147.6, 142.2, 137.9, 129.3, 129.3, 128.3, 126.6, 126.3, 125.5, 122.6, 39.5, 35.5, 29.3, 28.9, 21.5. GC-MS (EI): Calcd for $C_{17}H_{20}N_2O$: 268.16, found: 268.23.

N-(4-(*p*-tolyl)butyl)picolinamide (3d)



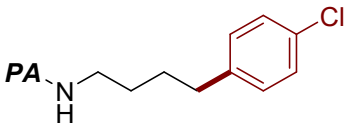
The title compound was isolated as yellow oil (89% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.7 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.09 (br, 1H), 7.84 (m, 1H), 7.41 (dd, J = 7.5, 4.8 Hz, 1H), 7.08 (s, 4H), 3.52 – 3.47 (m, 2H), 2.63 (t, J = 7.1 Hz, 2H), 2.31 (s, 3H), 1.89 – 1.55 (m, 4H);^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 150.0, 148.0, 139.1, 137.4, 135.3, 134.1, 129.1, 128.3, 126.1, 122.3, 39.4, 35.1, 29.3, 28.9, 21.0. GC-MS (EI): Calcd for $C_{17}H_{20}N_2O$: 268.16, found: 268.23.

N-(4-(4-fluorophenyl)butyl)picolinamide (3e)



The title compound was isolated as yellow oil (89% yield) after chromatography on silica with ethyl acetate/hexane (1:6).^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, J = 4.7, 0.7 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.09 (br, 1H), 7.85 (m, 1H), 7.43 (m, 1H), 7.18 – 7.05 (m, 2H), 7.03 – 6.85 (m, 2H), 3.49 (m, 2H), 2.64 (t, J = 7.1 Hz, 2H), 1.86 – 1.43 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 162.5, 160.1, 150.0, 148.0, 137.8, 137.6, 129.8, 129.8, 126.2, 122.4, 115.2, 115.0, 39.3, 34.8, 29.3, 28.9. GC-MS (EI): Calcd for $C_{16}H_{17}FN_2O$: 272.13, found: 272.15.

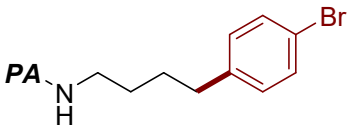
N-(4-(4-chlorophenyl)butyl)picolinamide (3f)



The title compound was isolated as yellow oil (87% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.3 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.09 (br, 1H), 7.88 – 7.84 (m, 1H), 7.45 – 7.41 (m, 1H), 7.24 – 7.22 (m, 2H), 7.10 (d, J = 8.3 Hz, 2H), 3.49 (m, 2H), 2.64 (t, J = 7.2 Hz, 2H), 1.93 – 1.48 (m, 4H); ^{13}C

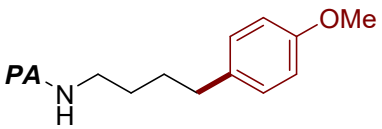
NMR (101 MHz, $CDCl_3$) δ 164.1, 149.8, 147.8, 140.6, 137.8, 131.6, 129.8, 128.5, 126.3, 122.5, 39.3, 34.9, 29.2, 28.7. GC-MS (EI): Calcd for $C_{16}H_{17}ClN_2O$: 288.10, found: 288.13.

N-(4-(4-bromophenyl)butyl)picolinamide (3g)



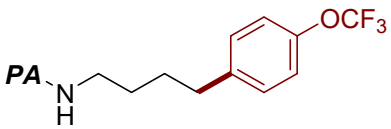
The title compound was isolated as green oil (78% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, CDCl3) δ 8.53 (d, J = 4.6 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.05 (s, 1H), 7.86 – 7.81 (m, 1H), 7.45 – 7.34 (m, 3H), 7.05 (d, J = 8.3 Hz, 2H), 3.48 (m, 2H), 2.61 (t, J = 7.1 Hz, 2H), 1.75 – 1.53 (m, 4H); ^{13}C NMR (101 MHz, CDCl3) δ 164.2, 149.9, 148.0, 141.0, 137.3, 131.3, 130.2, 126.1, 122.2, 119.5, 39.1, 34.9, 29.1, 28.5. GC-MS (EI): Calcd for $C_{16}H_{17}BrN_2O$: 332.05, found: 332.11.

N-(4-(4-methoxyphenyl)butyl)picolinamide (3h)



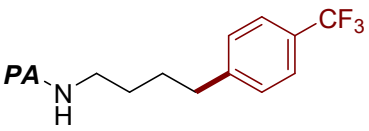
The title compound was isolated as green oil (84% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.5 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 8.06 (br, 1H), 7.83 (dd, *J* = 11.1, 4.3 Hz, 1H), 7.41 (dd, *J* = 7.2, 4.9 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H), 3.51 – 3.46 (m, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 1.71–1.64 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 157.8, 150.1, 148.0, 137.5, 134.3, 129.4, 126.1, 122.3, 113.8, 55.3, 39.4, 34.7, 29.3, 29.0. GC-MS (EI): Calcd for $C_{17}H_{20}N_2O_2$: 284.15, found: 284.16.

N-(4-(4-(trifluoromethoxy)phenyl)butyl)picolinamide (3i)



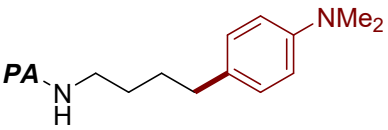
The title compound was isolated as yellow oil (86% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.6 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.11 (br, 1H), 7.88 – 7.84 (m, 1H), 7.45 – 7.41 (m, 1H), 7.19 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 3.62 – 3.39 (m, 2H), 2.67 (t, J = 7.2 Hz, 2H), 1.81 – 1.56 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 149.9, 147.9, 147.5, 140.9, 137.7, 129.7, 126.3, 124.4, 122.5, 121.9, 121.0, 119.3, 116.8, 39.3, 34.9, 29.3, 28.7. GC-MS (EI): Calcd for $C_{17}H_{17}F_3N_2O_2$: 338.12, found: 338.15.

N-(4-(4-(trifluoromethyl)phenyl)butyl)picolinamide (3j)



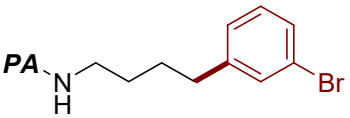
The title compound was isolated as yellow oil (84% yield) after chromatography on silica with ethyl acetate/hexane (1:6).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.3 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.10 (br, 1H), 7.82 (m, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.40 (m, 1H), 7.30 – 7.18 (m, 2H), 3.49 (m, 2H), 2.69 (t, J = 7.2 Hz, 2H), 1.82 – 1.52 (m, 4H);^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 149.8, 148.1, 146.3, 137.6, 134.4, 128.8, 126.3, 125.4, 125.3, 122.4, 39.3, 35.4, 29.3, 28.5. GC-MS (EI): Calcd for $C_{17}H_{17}F_3N_2O_2$: 322.13, found: 322.16.

N-(4-(4-(dimethylamino)phenyl)butyl)picolinamide (3k)



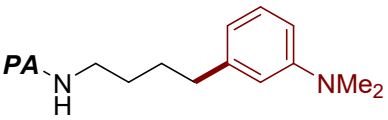
The title compound was isolated as a yellow oil (83% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.7 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.05 (br, 1H), 7.83 (m, 1H), 7.47 – 7.34 (m, 1H), 7.06 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 3.51 – 3.47 (m, 2H), 2.91 (s, 6H), 2.58 (t, J = 7.0 Hz, 2H), 1.78 – 1.62 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 150.1, 149.1, 148.1, 137.4, 130.4, 129.1, 126.1, 122.2, 113.1, 41.0, 39.4, 34.5, 29.3, 29.1. GC-MS (EI): Calcd for $C_{18}H_{23}N_3O$: 297.18, found: 297.20.

N-(4-(3-bromophenyl)butyl)picolinamide (3l)



The title compound was isolated as yellow oil (83% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (m, 1H), 8.13 (dd, J = 7.8, 0.9 Hz, 1H), 8.01 (br, 1H), 7.79 – 7.75 (m, 1H), 7.36 – 7.33 (m, 1H), 7.28 – 7.20 (m, 2H), 7.14 – 6.98 (m, 2H), 3.43 (m, 2H), 2.56 (t, J = 7.2 Hz, 2H), 1.72 – 1.46 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 150.0, 148.0, 144.6, 137.5, 131.5, 130.0, 129.0, 127.2, 126.2, 122.5, 122.3, 39.2, 35.2, 29.3, 28.6. GC-MS (EI): Calcd for $C_{16}H_{17}BrN_2O$: 332.05, found: 332.11.

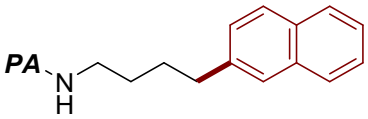
N-(4-(3-(dimethylamino)phenyl)butyl)picolinamide (3m)



The title compound was isolated as yellow oil (91% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 4.2 Hz, 1H),

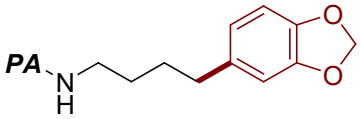
8.12 (d, J = 7.8 Hz, 1H), 7.99 (br, 1H), 7.78 – 7.73 (m, 1H), 7.34 – 7.31 (m, 1H), 7.11 – 7.02 (m, 1H), 6.52 (dd, J = 10.7, 4.3 Hz, 3H), 3.45 – 3.40 (m, 2H), 2.86 (s, 6H), 2.55 (t, J = 7.3 Hz, 2H), 1.73 – 1.50 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 150.6, 150.1, 148.0, 143.2, 137.4, 129.1, 126.1, 122.2, 117.3, 113.1, 110.6, 40.9, 40.9, 39.4, 36.1, 29.4, 28.9. GC-MS (EI): Calcd for $C_{18}H_{23}N_3O$: 297.18, found: 297.20.

N-(4-(naphthalen-2-yl)butyl)picolinamide (3n)



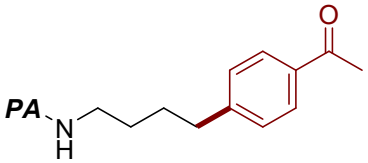
The title compound was isolated as brown oil (88% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J = 4.7, 0.6 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.06 (br, 1H), 7.86–7.75 (m, 4H), 7.62 (s, 1H), 7.47–7.39 (m, 3H), δ 7.33 (dd, J = 8.4, 1.6 Hz, 1H), 3.52 (dd, J = 13.3, 6.9 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H), 1.88–1.68 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 150.1, 148.1, 139.7, 137.4, 133.7, 132.1, 128.0, 127.7, 127.5, 127.4, 126.5, 126.1, 126.0, 125.2, 122.3, 39.4, 35.7, 29.4, 28.7. GC-MS (EI): Calcd for $C_{20}H_{20}N_2O$: 304.16, found: 304.18.

N-(4-(benzo[d][1,3]dioxol-5-yl)butyl)picolinamide (3o)



The title compound was isolated as brown oil (88% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 3.9 Hz, 1H), 8.20 (d, J = 7.7 Hz, 1H), 8.07 (br, 1H), 7.85 (t, J = 7.5 Hz, 1H), 7.42 (dd, J = 7.1, 4.8 Hz, 1H), 6.94 – 6.52 (m, 3H), 5.91 (s, 2H), 3.57 – 3.40 (m, 2H), 2.59 (t, J = 6.9 Hz, 2H), 1.72 – 1.58 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 149.9, 147.9, 147.6, 145.6, 137.7, 136.1, 126.2, 122.5, 121.2, 108.9, 108.2, 100.8, 39.4, 35.3, 29.2, 29.1. GC-MS (EI): Calcd for $C_{17}H_{18}N_2O_3$: 298.13, found: 298.17.

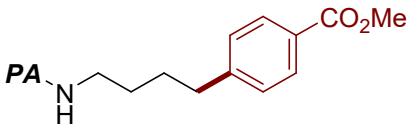
N-(4-(4-acetylphenyl)butyl)picolinamide (3p)



The title compound was isolated as green oil (88% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.2 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 8.08 (br, 1H), 7.88–7.82 (m, 3H), 7.42 – 7.39 (m, 1H), 7.27–7.24 (m, 2H), 3.51 – 3.46 (m, 2H), 2.71 (t, J = 7.4 Hz, 2H), 2.56 (s, 3H), 1.77 – 1.63 (m, 4H); ^{13}C NMR

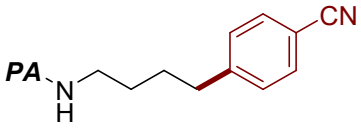
(101 MHz, $CDCl_3$) δ 197.9, 164.3, 149.9, 148.0, 148.0, 137.5, 135.1, 128.6, 126.2, 122.3, 39.2, 35.60, 29.3, 28.4, 26.6. GC-MS (EI): Calcd for $C_{18}H_{20}N_2O_2$: 296.15, found: 296.18.

Methyl 4-(4-(picolinamido)butyl)benzoate (3q)



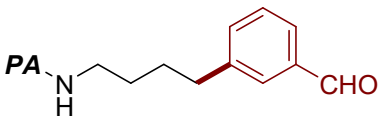
The title compound was isolated as yellow oil (88% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.7 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.08 (br, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.86 – 7.82 (m, 1H), 7.47 – 7.36 (m, 1H), 7.24 (d, J = 8.2 Hz, 2H), 3.89 (s, 3H), 3.52 – 3.47 (m, 2H), 2.72 (t, J = 7.4 Hz, 2H), 1.85 – 1.60 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 164.3, 149.9, 148.0, 147.8, 137.6, 129.8, 128.5, 127.9, 126.2, 122.4, 52.1, 39.2, 35.6, 29.3, 28.5. GC-MS (EI): Calcd for $C_{18}H_{20}N_2O_3$: 312.15, found: 312.12.

N-(4-(4-cyanophenyl)butyl)picolinamide (3r)



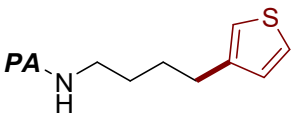
The title compound was isolated as green oil (75% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.7 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.08 (br, 1H), 7.87 – 7.83 (m, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.45–7.41 (m, 1H), 7.28 (d, J = 8.1 Hz, 2H), 3.53 – 3.48 (m, 2H), 2.73 (t, J = 7.3 Hz, 2H), 1.76 – 1.67 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ164.4, 150.0, 148.1, 147.9, 137.5, 132.3, 129.3, 126.2, 122.3, 119.2, 109.8, 39.1, 35.7, 29.3, 28.3. GC-MS (EI): Calcd for $C_{17}H_{17}N_3O$: 279.14, found: 279.24.

N-(4-(3-formylphenyl)butyl)picolinamide (3s)



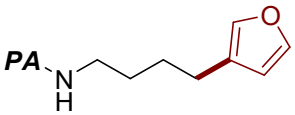
The title compound was isolated as yellow oil (84% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.52 (d, J = 4.2 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 8.07 (br, 1H), 7.82 (dd, J = 11.0, 4.4 Hz, 1H), 7.68 (dd, J = 5.0, 2.0 Hz, 2H), 7.49 – 7.34 (m, 3H), 3.52 – 3.47 (m, 2H), 2.74 (t, J = 7.4 Hz, 2H), 1.88 – 1.59 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 164.4, 150.0, 148.1, 143.3, 137.4, 136.6, 134.8, 129.4, 129.1, 127.7, 126.2, 122.3, 39.2, 35.2, 29.3, 28.6. GC-MS (EI): Calcd for $C_{17}H_{18}N_2O_2$: 282.14, found: 282.12.

N-(4-(thiophen-3-yl)butyl)picolinamide (3t)



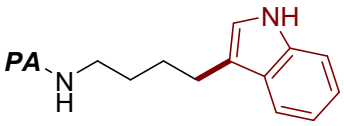
The title compound was isolated as green oil (84% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.1 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.08 (br, 1H), 7.86 – 7.82(m, 1H), 7.43 – 7.40 (m, 1H), 7.28 – 7.16 (m, 1H), 6.94 (d, J = 4.3 Hz, 2H), 3.52 – 3.46 (m, 2H), 2.69 (t, J = 7.2 Hz, 2H), 1.89 – 1.59 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 150.0, 148.0, 142.5, 137.5, 128.3, 126.2, 125.4, 122.3, 120.2, 39.3, 29.9, 29.3, 28.0. GC-MS (EI): Calcd for $C_{15}H_{18}N_2S$:260.09, found: 260.12.

N-(4-(furan-3-yl)butyl)picolinamide (3u)



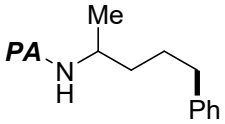
The title compound was isolated as yellow oil (69% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 4.1 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.11 (br, 1H), 7.88 – 7.84 (m, 1H), 7.45 – 7.43 (m, 1H), 7.34 (d, J = 1.6 Hz, 1H), 7.22 (s, 1H), 6.27 (s, 1H), 3.52 – 3.47 (m, 2H), 2.48 (t, J = 6.7 Hz, 2H), 1.74 – 1.55 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 149.9, 147.9, 142.8, 139.0, 137.7, 126.2, 124.8, 122.5, 111.0, 39.3, 29.3, 27.4, 24.5. GC-MS (EI): Calcd for $C_{14}H_{16}N_2O_2$: 244.12, found: 244.23.

N-(4-(1*H*-indol-3-yl)butyl)picolinamide (3v)



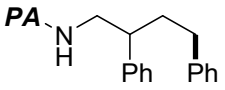
The title compound was isolated as brown oil (58% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.52 (m, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.16 (d, J = 15.8 Hz, 2H), 7.90 – 7.86 (m, 1H), 7.46 – 7.42 (m, 2H), 7.31 (d, J = 8.3 Hz, 1H), 7.21 – 7.13 (m, 1H), 7.03 (dd, J = 8.3, 1.5 Hz, 1H), 6.49 – 6.47 (m, 1H), 3.51 (dd, J = 13.1, 6.8 Hz, 2H), 2.76 (t, J = 7.3 Hz, 2H), 1.79 (m, 2H), 1.74 – 1.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 150.0, 148.0, 137.3, 134.5, 133.4, 128.0, 126.0, 124.3, 122.9, 122.1, 119.8, 110.8, 102.2, 39.4, 35.6, 29.4, 29.2. GC-MS (EI): Calcd for $C_{18}H_{19}N_3O$: 293.15, found: 293.13.

N-(5-phenylpentan-2-yl)picolinamide (3w)



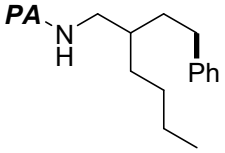
The title compound was isolated as brown oil (57% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, J = 2.9, 1.9 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.95 – 7.71 (m, 2H), 7.44 – 7.37 (m, 1H), 7.27 – 7.06 (m, 5H), 4.25 – 4.19 (m, 1H), 2.63 (t, J = 7.5 Hz, 2H), 1.83 – 1.66 (m, 2H), 1.64 – 1.52 (m, 2H), 1.34 – 1.10 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 150.2, 148.0, 142.3, 137.4, 128.5, 128.3, 126.1, 125.8, 122.3, 45.2, 36.6, 35.8, 28.0, 21.1. GC-MS (EI): Calcd for $C_{17}H_{20}N_2O$: 268.16, found: 268.19.

N-(2,4-diphenylbutyl)picolinamide (3x)



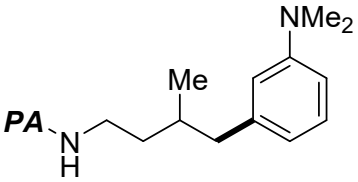
The title compound was isolated as brown oil (76% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (dd, J = 4.4, 1.2 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.91 (br, 1H), 7.75 – 7.70 (m, 1H), 7.34 – 7.24 (m, 3H), 7.21 – 7.13 (m, 5H), 7.12 – 6.97 (m, 3H), 3.87 – 3.71 (m, 1H), 3.48 – 3.43 (m, 1H), 2.99 – 2.76 (m, 1H), 2.54 – 2.30 (m, 2H), 2.10 – 1.86 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 149.9, 148.1, 142.4, 142.1, 137.4, 128.9, 128.5, 128.4, 128.0, 126.9, 126.1, 125.9, 122.3, 45.6, 45.2, 35.3, 33.5. GC-MS (EI): Calcd for $C_{22}H_{22}N_2O$: 330.17, found: 330.20.

N-(2-phenethylhexyl)picolinamide (3y)



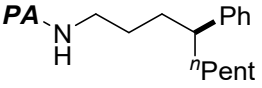
The title compound was isolated as green oil (87% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 – 8.51 (m, 1H), 8.19 (dd, J = 4.8, 3.9 Hz, 1H), 8.08 (br, 1H), 7.82 (m, 1H), 7.40 (m, 1H), 7.31 – 7.08 (m, 5H), 3.48 – 3.44 (m, 2H), 2.75 – 2.59 (m, 2H), 1.76 – 1.51 (m, 3H), 1.40 – 1.36 (m, 2H), 1.31 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 150.1, 148.0, 142.6, 137.5, 128.5, 128.4, 126.1, 125.8, 122.3, 42.6, 37.9, 33.9, 33.1, 31.6, 28.9, 23.1, 14.2. GC-MS (EI): Calcd for $C_{20}H_{26}N_2O$: 310.20, found: 310.22.

N-(4-(3-(dimethylamino)phenyl)-3-methylbutyl)picolinamide (3z)



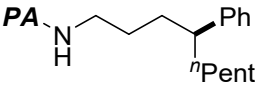
The title compound was isolated as green oil (65% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J = 4.7, 0.7 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.00 (br, 1H), 7.86 – 7.81 (m, 1H), 7.43 – 7.39 (m, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.62 (m, 3H), 3.59 (m, 1H), 3.47 (m, 1H), 2.94 (s, 6H), 2.66 – 2.61 (m, 1H), 2.46 – 2.40(m, 1H), 1.94 – 1.85 (m, 1H), 1.79 – 1.65 (m, 1H), 1.54 – 1.44 (m, 1H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 150.6, 150.0, 148.0, 141.7, 137.3, 128.8, 126.0, 122.1, 117.8, 113.6, 110.4, 44.0, 40.7, 37.5, 36.3, 32.8, 19.5. GC-MS (EI): Calcd for $C_{19}H_{25}N_3O$: 311.20, found: 311.22.

N-(4-phenylnonyl)picolinamide (3aa) (from *Z*)



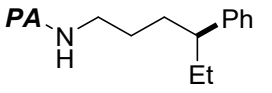
The title compound was isolated as brown oil (94% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 – 8.50 (m, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.97 (br, 1H), 7.84 – 7.80 (m, 1H), 7.41 – 7.37 (m 1H), 7.33 – 7.23 (m, 2H), 7.22 – 7.09 (m, 3H), 3.53 – 3.30 (m, 2H), 2.61 – 2.34 (m, 1H), 1.79 – 1.70 (m, 1H), 1.66 – 1.48 (m, 4H), 1.47 – 1.36 (m, 1H), 1.31 – 1.07 (m, 6H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 150.1, 148.0, 145.7, 137.4, 128.4, 127.7, 126.1, 126.0, 122.3, 45.9, 39.6, 37.0, 34.2, 32.0, 27.9, 27.3, 22.6, 14.1. GC-MS (EI): Calcd for $C_{21}H_{28}N_2O$: 324.22, found: 324.23.

N-(4-phenylnonyl)picolinamide (3ab) (from *E*)



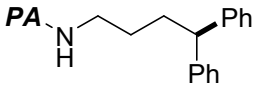
The title compound was isolated as brown oil (92% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 4.7 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.99 (br, 1H), 7.82 – 7.77 (m, 1H), 7.39 – 7.35(m 1H), 7.26 (dd, J = 10.4, 4.4 Hz, 2H), 7.21 – 7.04 (m, 3H), 3.42 – 3.35 (m, 2H), 2.52 – 2.47 (m, 1H), 1.78 – 1.69 (m, 1H), 1.64 – 1.48 (m, 3H), 1.45 – 1.32 (m, 1H), 1.29 – 0.98 (m, 7H), 0.80 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 150.0, 148.0, 145.6, 137.4, 128.3, 127.7, 126.1, 126.0, 122.2, 45.8, 39.6, 37.0, 34.2, 31.9, 27.8, 27.3, 22.6, 14.1. GC-MS (EI): Calcd for $C_{21}H_{28}N_2O$: 324.22 found: 324.24.

N-(4-phenylhexyl)picolinamide (3ac) (from *Z*)



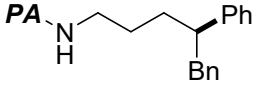
The title compound was isolated as brown oil (51% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.7 Hz, 1H), 8.18 (d, J = 7.9 Hz, 1H), 7.96 (br, 1H), 7.83 (m, 1H), 7.44 – 7.36 (m, 1H), 7.31 – 7.23 (m, 2H), 7.22 – 7.08 (m, 3H), 3.55 – 3.32 (m, 2H), 2.52 – 2.33 (m, 1H), 1.88 – 1.69 (m, 2H), 1.63 – 1.57 (m, 2H), 1.52 (m, 2H), 0.76 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 150.0, 147.9, 145.3, 137.3, 128.3, 127.7, 126.0, 126.0, 122.1, 47.6, 39.4, 33.7, 29.7, 27.8, 12.1. GC-MS (EI): Calcd for $C_{18}H_{22}N_2O$: 282.17, found: 282.22.

N-(4,4-diphenylbutyl)picolinamide (3ad) (from *E*)



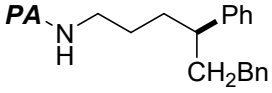
The title compound was isolated as brown oil (81% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.0 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.03 (br, 1H), 7.82 (m, 1H), 7.44 – 7.36 (m, 1H), 7.30 – 7.20 (m, 8H), 7.20 – 7.05 (m, 2H), 3.93 (t, J = 7.9 Hz, 1H), 3.49 (m, 2H), 2.21 – 2.03 (m, 2H), 1.71 – 1.53 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 150.0, 147.9, 144.7, 137.3, 128.5, 127.8, 126.2, 126.0, 122.2, 51.0, 39.3, 32.9, 28.3. GC-MS (EI): Calcd for $C_{22}H_{22}N_2O$: 330.17, found: 330.20.

N-(4,5-diphenylpentyl)picolinamide (3ae) (from *E*)



The title compound was isolated as yellow oil (65% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.7 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 7.94 (br, 1H), 7.83 (m, 1H), 7.40 (m, 2H), 7.26 (t, J = 7.4 Hz, 3H), 7.18 (m, 3H), 7.15 – 7.08 (m, 3H), 7.06 – 6.95 (m, 2H), 3.47 – 3.29 (m, 2H), 3.01 – 2.71 (m, 3H), 1.86 – 1.64 (m, 2H), 1.56 – 1.37 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 150.1, 148.0, 144.6, 140.5, 137.4, 129.2, 128.4, 128.1, 127.8, 126.3, 126.1, 125.9, 122.2, 47.8, 43.9, 39.4, 32.8, 27.8. GC-MS (EI): Calcd for $C_{23}H_{24}N_2O$: 344.19, found: 344.22.

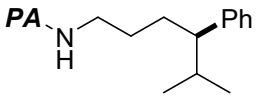
N-(4,6-diphenylhexyl)picolinamide (3af) (from *E*)



The title compound was isolated as yellow oil (95% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (m, 1H), 8.19 (dd, J = 7.8, 0.8 Hz, 1H), 8.00 (br, 1H), 7.82 (m, 1H),

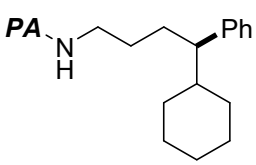
7.40 (m, 1H), 7.33 (t, J = 7.4 Hz, 2H), 7.25 (m, 3H), 7.22 – 7.16 (m, 3H), 7.13 – 7.05 (m, 2H), 3.52 – 3.29 (m, 2H), 2.68 – 2.52 (m, 1H), 2.50 – 2.41 (m, 2H), 2.02 – 1.87 (m, 2H), 1.84 – 1.75 (m, 1H), 1.73 – 1.62 (m, 1H), 1.60 – 1.50 (m, 1H), 1.49 – 1.36 (m, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 150.0, 148.0, 145.0, 142.4, 137.3, 128.5, 128.4, 128.3, 127.8, 126.2, 126.0, 125.7, 122.2, 45.3, 39.4, 38.6, 34.3, 33.8, 27.8. GC-MS (EI): Calcd for $C_{24}H_{26}N_2O$: 358.20, found: 358.22.

N-(5-methyl-4-phenylhexyl)picolinamide (3ag) (from *E*)



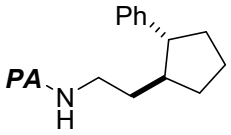
The title compound was isolated as yellow oil (92% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 – 8.47 (m, 1H), 8.16 (dd, J = 4.8, 4.0 Hz, 1H), 7.95 (br, 1H), 7.81 (m, 1H), 7.38 (m, 1H), 7.31 – 7.23 (m, 2H), 7.21 – 7.14 (m, 1H), 7.11 (dd, J = 5.1, 3.2 Hz, 2H), 3.39 (m, 2H), 2.27 (m, 1H), 1.99 – 1.74 (m, 2H), 1.71 – 1.59 (m, 1H), 1.50 – 1.34 (m, 2H), 0.94 (d, J = 6.7 Hz, 3H), 0.70 (d, J = 6.7 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 150.1, 148.0, 144.1, 137.3, 128.5, 128.1, 126.0, 126.0, 122.2, 52.9, 39.5, 33.5, 30.3, 28.1, 21.1, 20.8. GC-MS (EI): Calcd for $C_{19}H_{24}N_2O$: 296.19, found: 296.23.

N-(4-cyclohexyl-4-phenylbutyl)picolinamide (3ah) (from *E*)



The title compound was isolated as yellow oil (57% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.3 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.93 (br, 1H), 7.82 (m, 1H), 7.40 (dd, J = 6.6, 4.9 Hz, 1H), 7.26 (t, J = 7.4 Hz, 2H), 7.17 (t, J = 7.3 Hz, 1H), 7.10 (d, J = 7.1 Hz, 2H), 3.38 (m, 2H), 2.32 (m, 1H), 1.98 – 1.85 (m, 2H), 1.80 – 1.54 (m, 4H), 1.47 – 1.32 (m, 4H), 1.29 – 1.15 (m, 1H), 1.13 – 1.01 (m, 2H), 0.90 (m, 1H), 0.83 – 0.69 (m, 1H)；^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 150.1, 148.0, 144.3, 137.4, 128.6, 128.1, 126.1, 125.9, 122.2, 52.1, 43.3, 39.6, 31.5, 31.1, 30.0, 28.1, 26.6. GC-MS (EI): Calcd for $C_{22}H_{28}N_2O$: 336.22, found: 336.24.

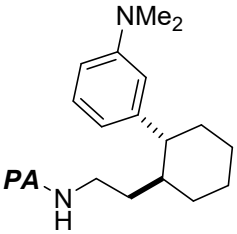
N-(2-(2-phenylcyclopentyl)ethyl)picolinamide (3ai)



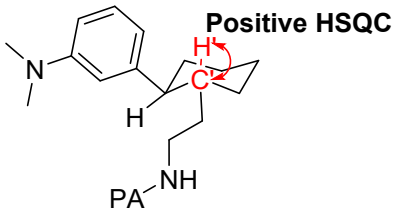
The title compound was isolated as yellow oil (89% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.2 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.91

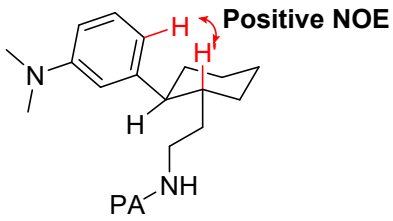
(br, 1H), 7.82 (m, 1H), 7.40 (m, 1H), 7.34 – 7.13 (m, 5H), 3.50 – 3.29 (m, 2H), 2.67 – 2.48 (m, 1H), 2.25 – 1.88 (m, 3H), 1.84 – 1.64 (m, 4H), 1.60 – 1.35 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 150.0, 148.0, 145.2, 137.5, 128.5, 127.6, 126.2, 126.1, 122.3, 53.4, 53.4, 46.2, 46.2, 38.8, 38.8, 35.6, 35.6, 34.4, 32.4, 32.4, 32.3, 24.2, 24.2. GC-MS (EI): Calcd for $C_{19}H_{22}N_2O$: 294.17, found: 294.22.

N-(2-(2-(3-(dimethylamino)phenyl)cyclohexyl)ethyl)picolinamide (3aj)



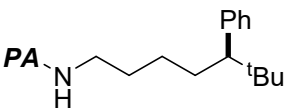
The title compound was isolated as yellow oil (54% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 4.7 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.81 (m, 1H), 7.47 – 7.34 (m, 1H), 7.16 (t, J = 7.9 Hz, 1H), 6.72 – 6.46 (m, 3H), 3.45 (m, 1H), 3.29 (m, 1H), 2.93 (s, 6H), 2.18 (m, 1H), 2.12 – 2.01 (m, 1H), 1.93 – 1.76 (m, 3H), 1.71 – 1.60 (m, 1H), 1.59 – 1.41 (m, 2H), 1.40 – 1.31 (m, 2H), 1.30 – 1.23 (m, 1H), 1.11 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 150.6, 150.1, 148.0, 147.4, 137.3, 129.2, 126.0, 122.1, 110.6, 51.5, 40.8, 40.2, 37.3, 36.2, 34.2, 32.8, 32.4, 26.9, 26.5. GC-MS (EI): Calcd for $C_{22}H_{29}N_3O$: 351.23, found: 351.24.





1D ^{13}C DEPT 90 and 2D NMR analysis was used to determine the relative stereochemistry of the cyclic product. First, the chemical shift of C' was determined by 1D 13C DEPT 90. The H' was properly assigned in the ^{1}H spectrum using HSQC to identify the positive correlation between the C' and the H'. Finally, the positive NOE correlation corresponding between the H' and the H, demonstrating they are on the same side of the ring, was observed, which indicating the Ni-Ph species underwent a syn-insertion process.

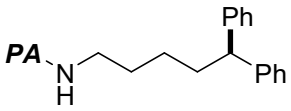
N-(6,6-dimethyl-5-phenylheptyl)picolinamide (3ak) (from *Z*)



The title compound was isolated as yellow oil (78% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 4.3 Hz, 1H), 8.18 (d, J = 7.8 Hz,

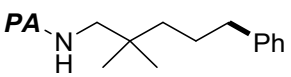
1H), 7.95 (br, 1H), 7.86 – 7.78 (m, 1H), 7.41 – 7.38 (m, 1H), 7.31 – 7.20 (m, 2H), 7.18 – 7.14 (m, 1H), 7.12 (dd, J = 6.5, 5.2 Hz, 2H), 3.49 – 3.09 (m, 2H), 2.31 (m, 1H), 1.88 – 1.69 (m, 2H), 1.64 – 1.43 (m, 2H), 1.20 – 1.08 (m, 2H), 0.85 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 150.1, 147.9, 142.9, 137.2, 127.5, 125.9, 125.8, 122.1, 56.6, 39.30, 33.7, 29.6, 28.9, 28.3, 25.8. GC-MS (EI): Calcd for $C_{21}H_{28}N_2O$: 324.22, found: 324.20.

N-(5,5-diphenylpentyl)picolinamide (3al) (from *Z*)



The title compound was isolated as yellow oil (77% yield) after chromatography on silica with ethyl acetate/hexane (1:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.6 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.06 (br, 1H), 7.88 – 7.84(m, 1H), 7.48 – 7.39 (m, 1H), 7.35 – 7.23 (m, 8H), 7.22 – 7.13 (m, 2H), 3.92 (t, J = 7.8 Hz, 1H), 3.47 – 3.42 (m, 2H), 2.15 – 2.09 (m, 2H), 1.77 – 1.64 (m, 2H), 1.43 – 1.35 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 149.8, 146.3, 141.3, 141.0, 137.9, 130.3, 129.5, 129.4, 128.6, 128.5, 128.1, 128.0, 127.9, 124.7, 119.0, 65.5, 43.4, 37.8, 36.2, 33.0. GC-MS (EI): Calcd for $C_{23}H_{24}N_2O$: 344.19, found: 344.22.

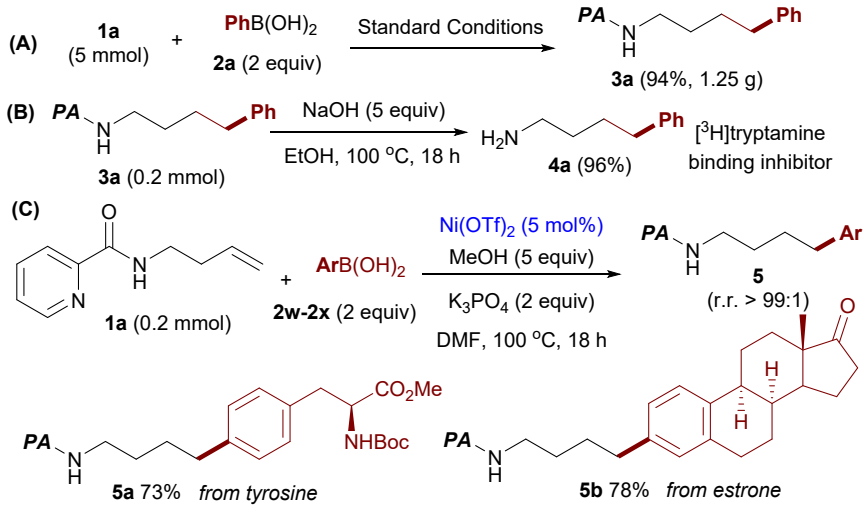
N-(2,2-dimethyl-5-phenylpentyl)picolinamide (3am)



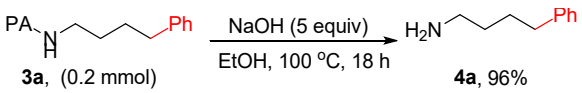
The title compound was isolated as yellow oil (90% yield) after chromatography on silica with ethyl acetate/hexane (1:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.0 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.16 (br, 1H), 7.82 – 7.86(m, 1H), 7.43 – 7.41(m, 1H), 7.31 – 7.22 (m, 2H), 7.19 – 7.14(m, 3H), 3.30 (d, J = 6.6 Hz, 2H), 2.60 (t, J = 7.7 Hz, 2H), 1.77 – 1.58 (m, 2H), 1.42 – 1.31 (m, 2H), 0.95 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 150.1, 148.1, 142.6, 137.4, 128.4, 128.3, 127.8, 126.1, 125.7, 122.3, 49.2, 39.7, 36.7, 34.6, 29.7, 26.0, 25.1. GC-MS (EI): Calcd for $C_{19}H_{24}N_2O$: 296.19, found: 296.22.

5. Synthetic Utilities

To further demonstrate the synthetic utility of our strategy, a gram scale reaction was first conducted. As depicted in Scheme S1-A, the desired **3a** could be isolated with 94% yield under standard conditions (1.25 g). Furthermore, the PA auxiliary can be facilely removed under the conditions of base,[16] providing a new way for the preparation of **4a** that can act as a [^{3}H]tryptamine binding inhibitor (Scheme S1-B).[2c] Eventually, our method can be applied for the modification of bioactive derivatives. For the use of arylboronic acids **2w**–**2x** derived from estrone and tyrosine, bearing with different functional group as arylation source, they all proceeded smoothly and products **5a**–**5b** could be isolated with good yields, highlighting the synthetic potential of our strategy (Scheme S1-C).

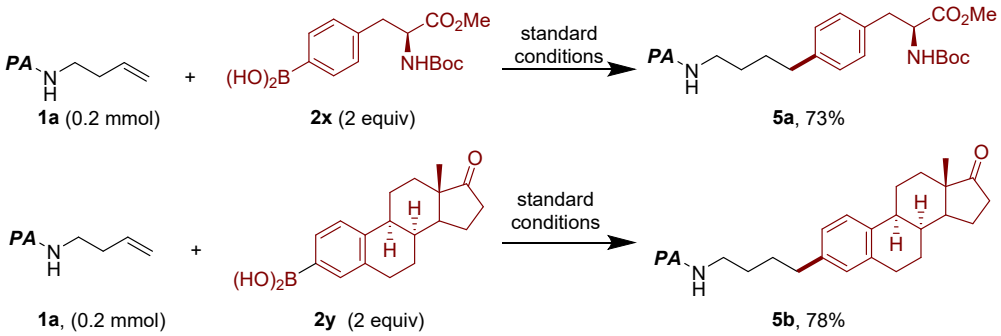


Scheme S1 Synthetic utilities.

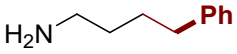


Removal of picolinic acid directing group was carried out by adapting a literature procedure.[2] To an oven-dried schlenk flask was added the hydroarylation product **3a** (0.2 mmol, 1.0 eq), NaOH (1 mmol, 5 eq), and EtOH (1 mL). The resulting mixture was stirred at 100 °C for 18 h. After this time, the reaction mixture was allowed to cool to room temperature, diluted by addition of EtOAc (5 mL) and H_2O (2 mL × 2). The aqueous layers

were combined and extracted with EtOAc (10 mL × 2). The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo to give pure orimary amine product.

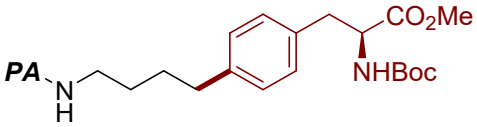


4-Phenylbutan-1-amine (4a)



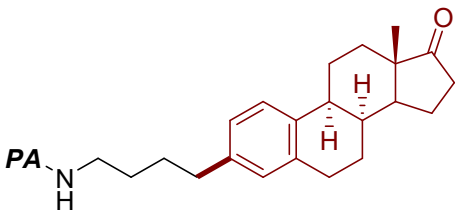
The title compound was obtained as colorless oil (96% yield). ^{1}H NMR (400 MHz, CDCl3) δ 7.28 – 7.18 (m, 5H), 2.73 (t, J = 7.1 Hz, 2H), 2.62 (t, J = 7.6 Hz, 2H), 1.71 – 1.40 (m, 6H). The NMR spectras of the product **4a** match the previously described in literature. [3]

Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-(4-(picolinamido)butyl)phenyl)propanoate (5a)



The title compound was isolated as yellow oil (73% yield) after chromatography on silica with ethyl acetate/hexane (1:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, J = 4.7, 0.7 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.05(br 1H), 7.81 (t, J = 7.7 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.08 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 7.8 Hz, 2H), 4.65 – 4.42 (m, 1H), 3.68 (s, 3H), 3.47 (m, 2H), 3.06 – 2.97 (m, 2H), 2.61 (t, J = 7.0 Hz, 2H), 1.73 – 1.58 (m, 4H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 164.3, 155.1, 150.0, 148.0, 140.9, 137.4, 133.4, 129.3, 128.6, 126.1, 122.2, 79.9, 54.5, 52.2, 39.3, 37.9, 35.1, 29.3, 28.7, 28.3. HRMS (ESI) m/z calculated for $C_{25}H_{33}N_3O_5$ $[M+Na]^+$ 478.2312, found: 478.2312.

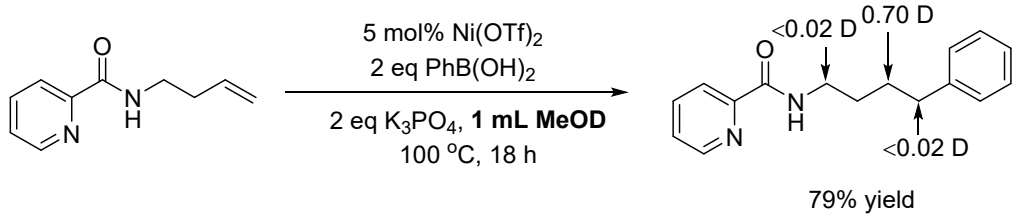
N-(4-((8*R*,9*S*,13*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl)butyl)picolinamide (5b)

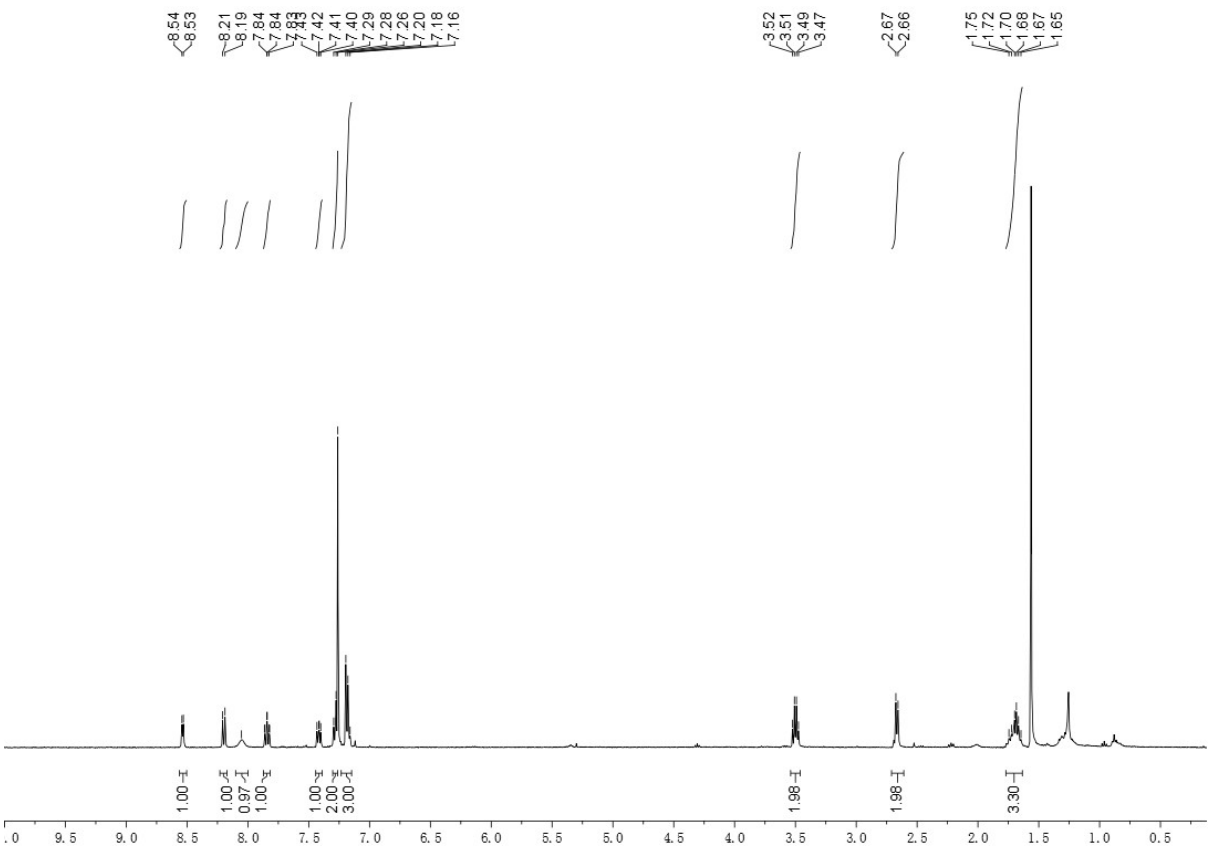


The title compound was isolated as yellow oil (78% yield) after chromatography on silica with ethyl acetate/hexane (1:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.6 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.06 (br, 1H), 7.84 (t, J = 7.7 Hz, 1H), 7.41 (dd, J = 7.5, 4.8 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 3.50 (m, 2H), 2.93 – 2.77 (m, 2H), 2.61 (t, J = 7.0 Hz, 2H), 2.53 – 2.46 (m, 1H), 2.45 – 2.34 (m, 1H), 2.27 (t, J = 10.4 Hz, 1H), 2.20 – 2.09 (m, 1H), 2.08 – 1.85 (m, 3H), 1.78 – 1.68 (m, 4H), 1.61 (d, J = 11.5 Hz, 2H), 1.53 – 1.46 (m, 2H), 1.42 (t, J = 4.9 Hz, 1H), 1.26 (t, J = 6.9 Hz, 1H), 0.90 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 150.1, 148.0, 139.6, 137.4, 137.2, 136.4, 129.1, 126.1, 125.9, 125.3, 122.2, 53.5, 50.6, 48.1, 44.4, 39.4, 38.3, 35.9, 35.0, 31.7, 29.4, 29.4, 28.8, 26.6, 25.8, 21.6, 13.9. HRMS (ESI) m/z calculated for $C_{28}H_{34}N_2O_2$ $[M+Na]^+$ 453.2512, found: 453.2512.

6. Deuterium Labelling Experiment

To further study the reaction mechanism, deuterium labelling experiment has been conducted. The sum of deuterium was less than one, suggesting that the proton source might come from MeOH and H_2O (probably formed *in situ* via the trimerization of $PhB(OH)_2$).





7. References

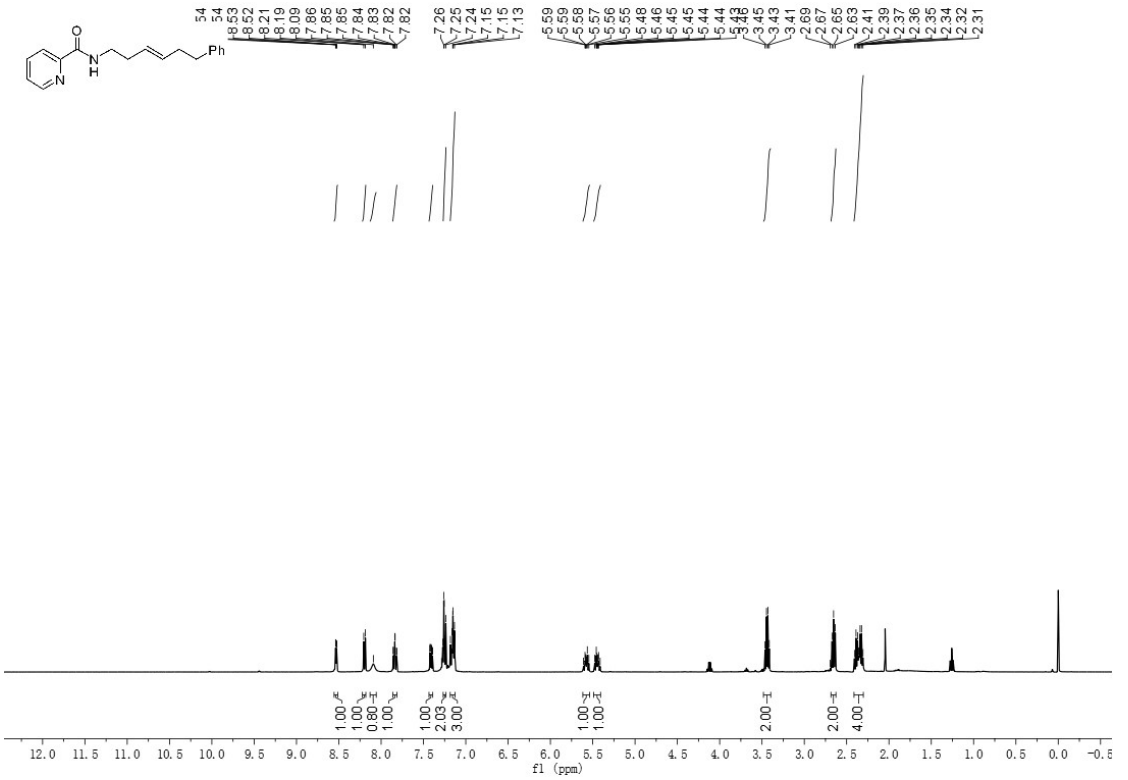
[1] B. S. Schreib, M. Fadel, E. M. Carreira, *Angew. Chem. Int. Ed.* **2020**, *59*, 7818.

[2] J. Derosa, V. T. Tran, M. N. Boulous, J. S. Chen, K. M. Engle, *J. Am. Chem. Soc*. **2017**, *139*, 10657.

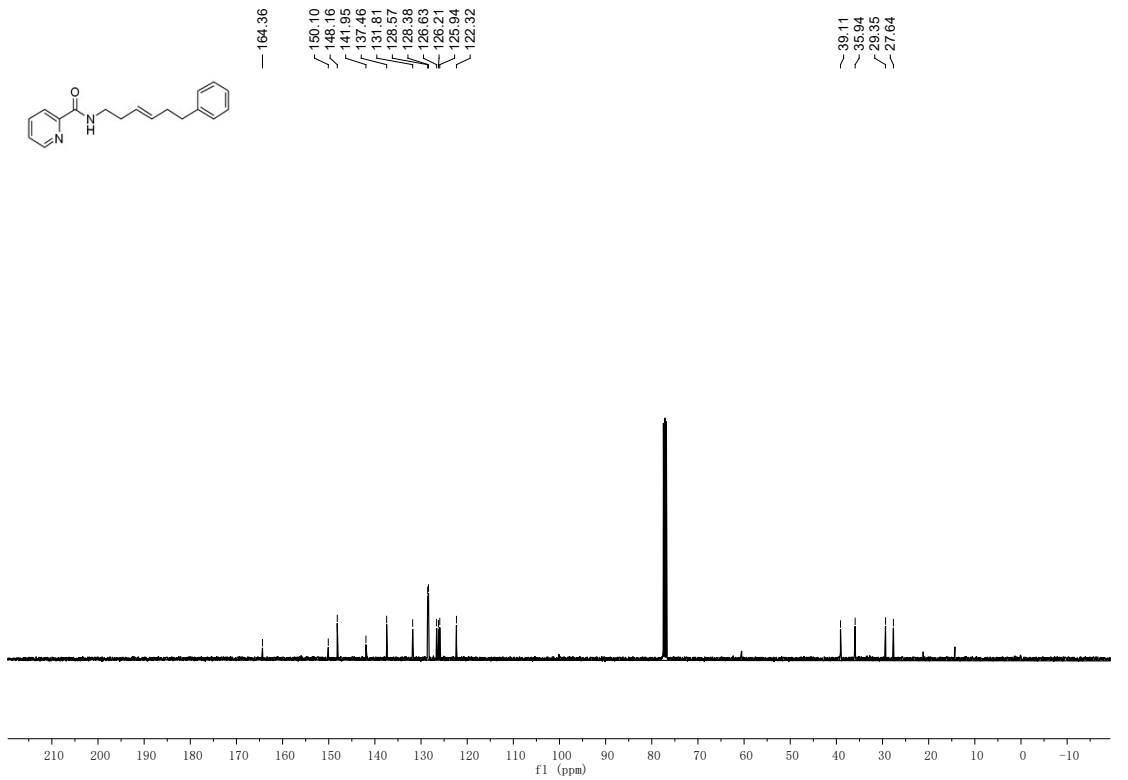
[3] Y. Shimizu, H. Morimoto, M. Zhang, T. Ohshima, *Angew. Chem. Int. Ed.* **2012**, *51*, 8564.

8. NMR Spectra

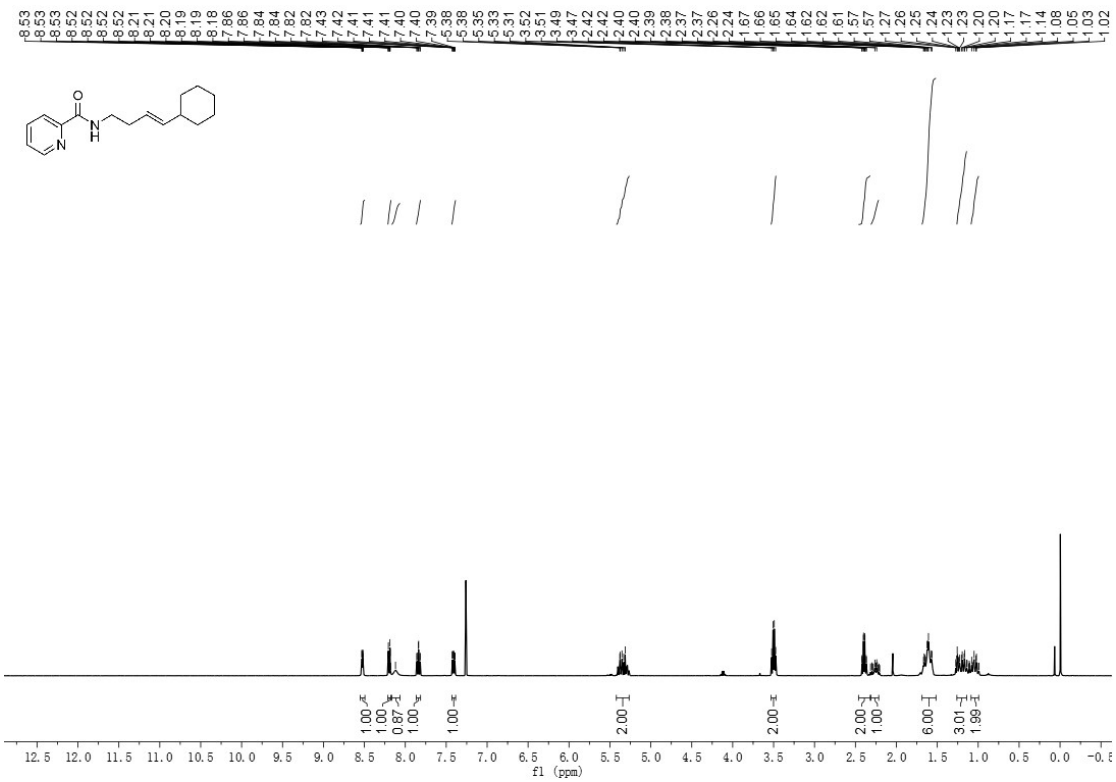
^{1}H NMR (400 MHz, $CDCl_3$) of **S-*E*-1j**



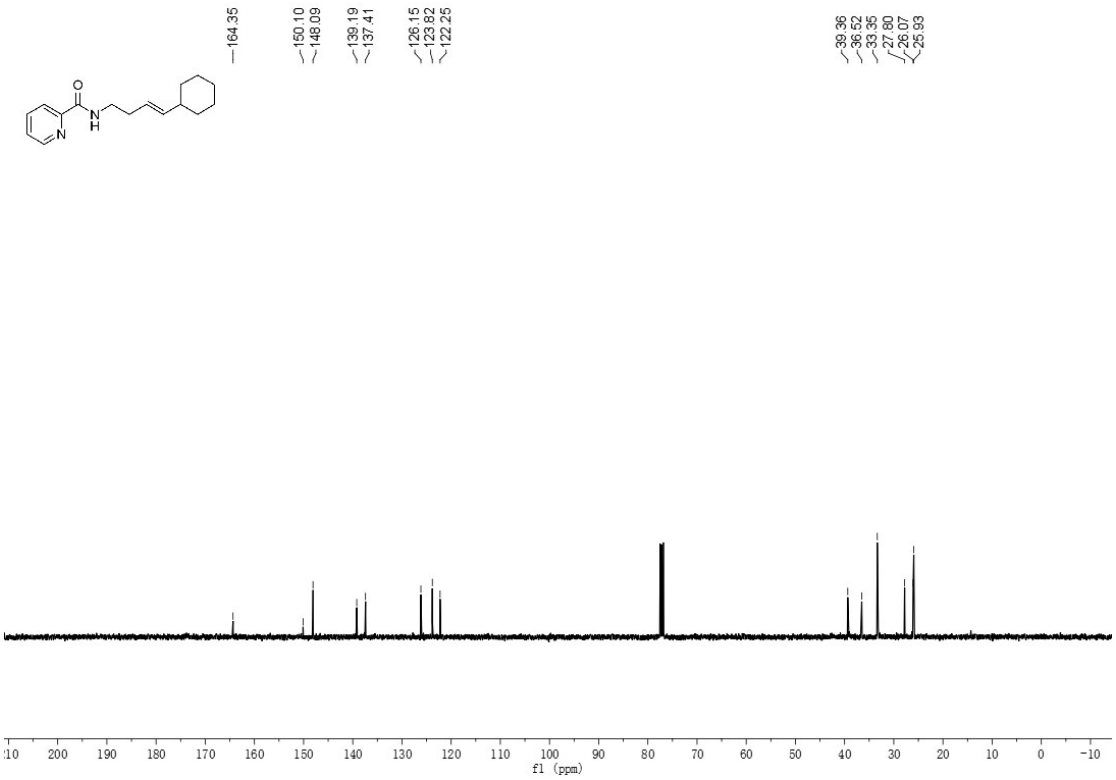
^{13}C NMR (101 MHz, $CDCl_3$) of **S-*E*-1j**



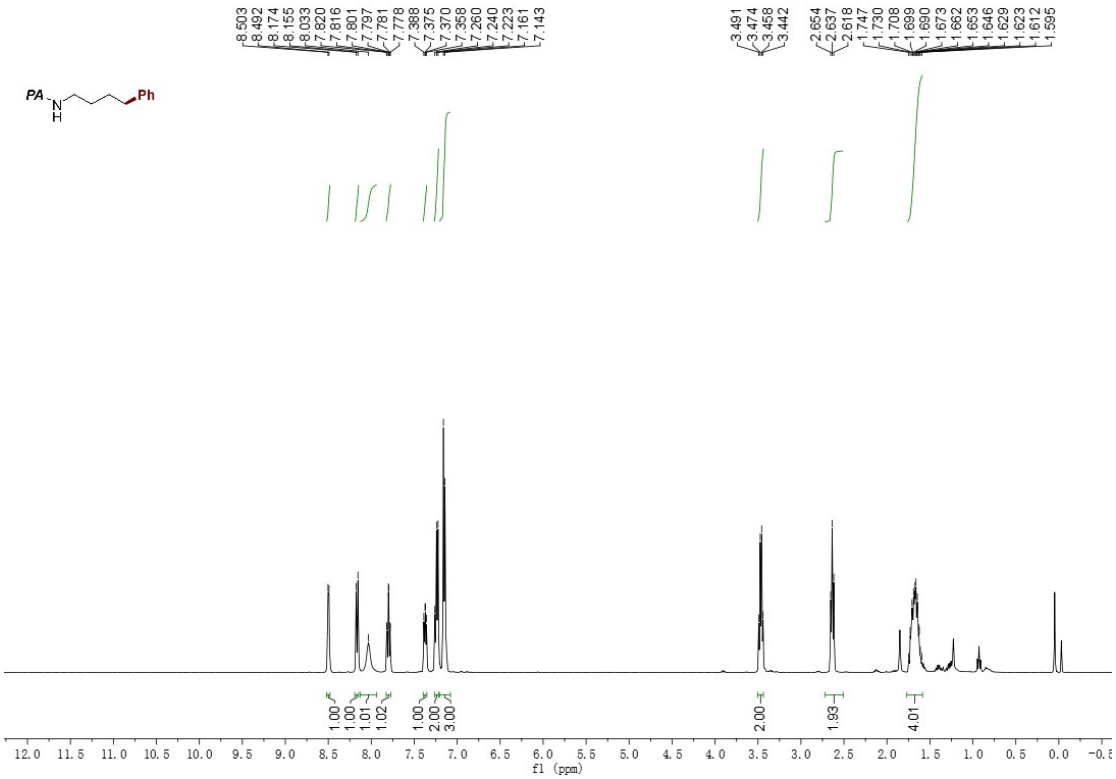
^{1}H NMR (400 MHz, $CDCl_3$) of **S-*E*-1l**



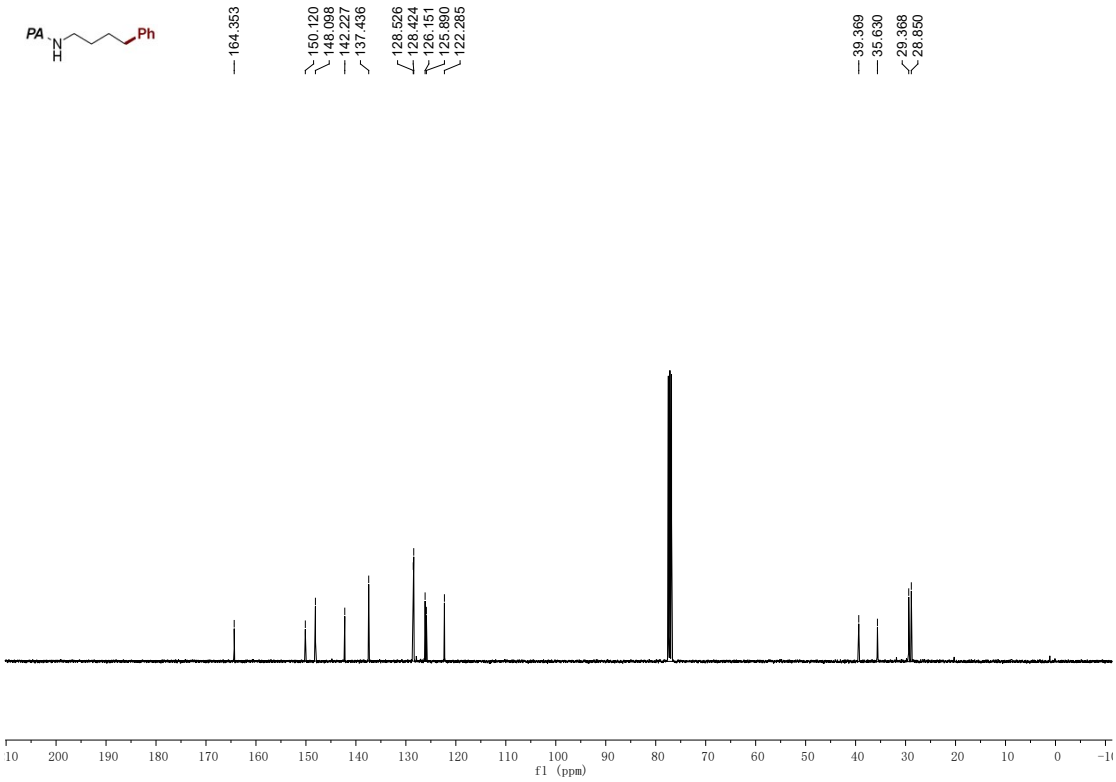
^{13}C NMR (101 MHz, $CDCl_3$) of **S-*E*-1l**



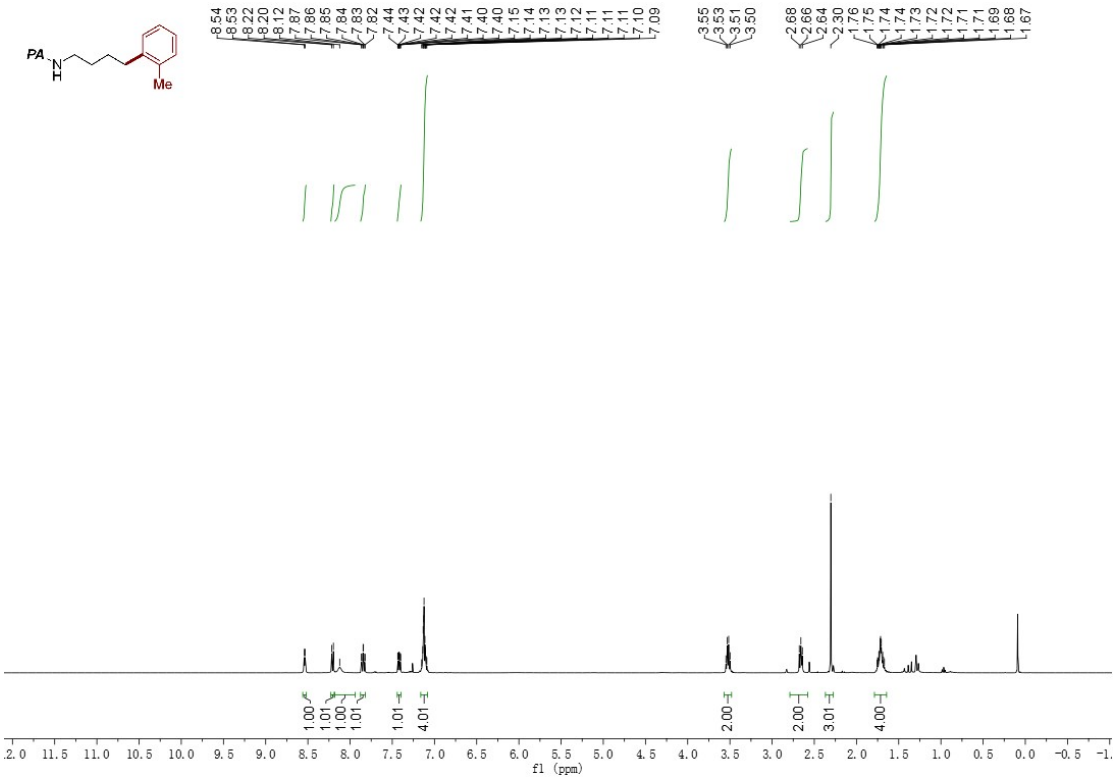
^{1}H NMR (400 MHz, $CDCl_3$) of **3a**



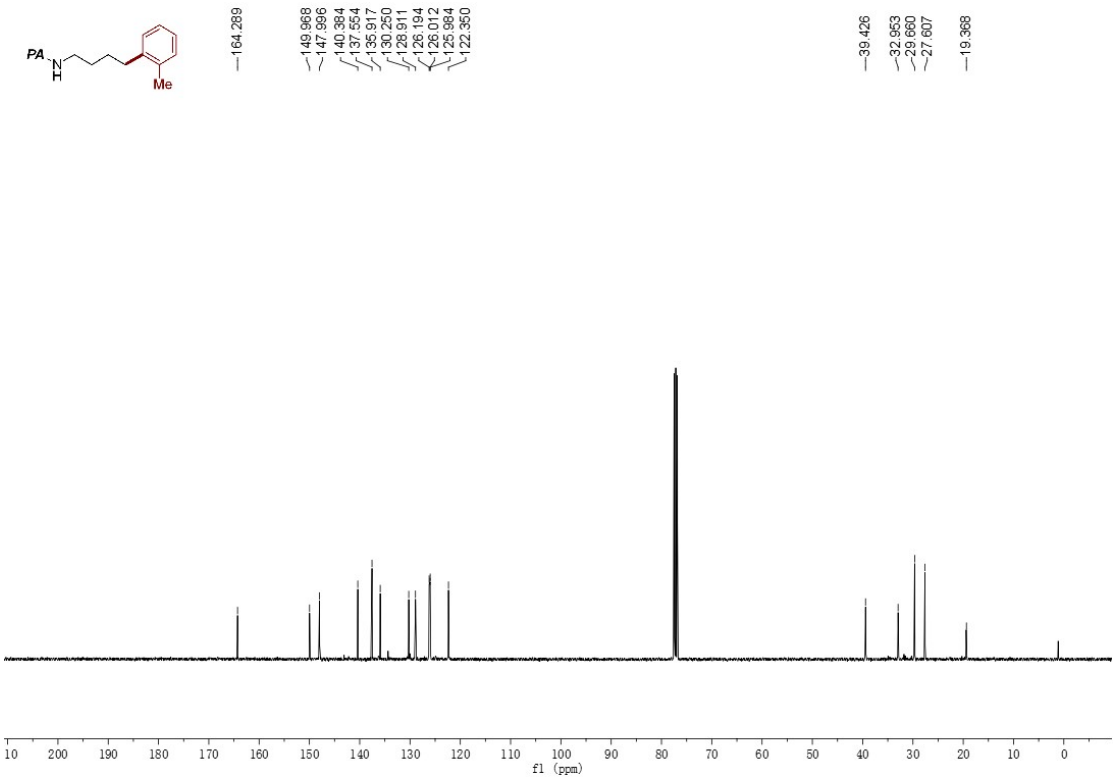
^{13}C NMR (101 MHz, $CDCl_3$) of **3a**



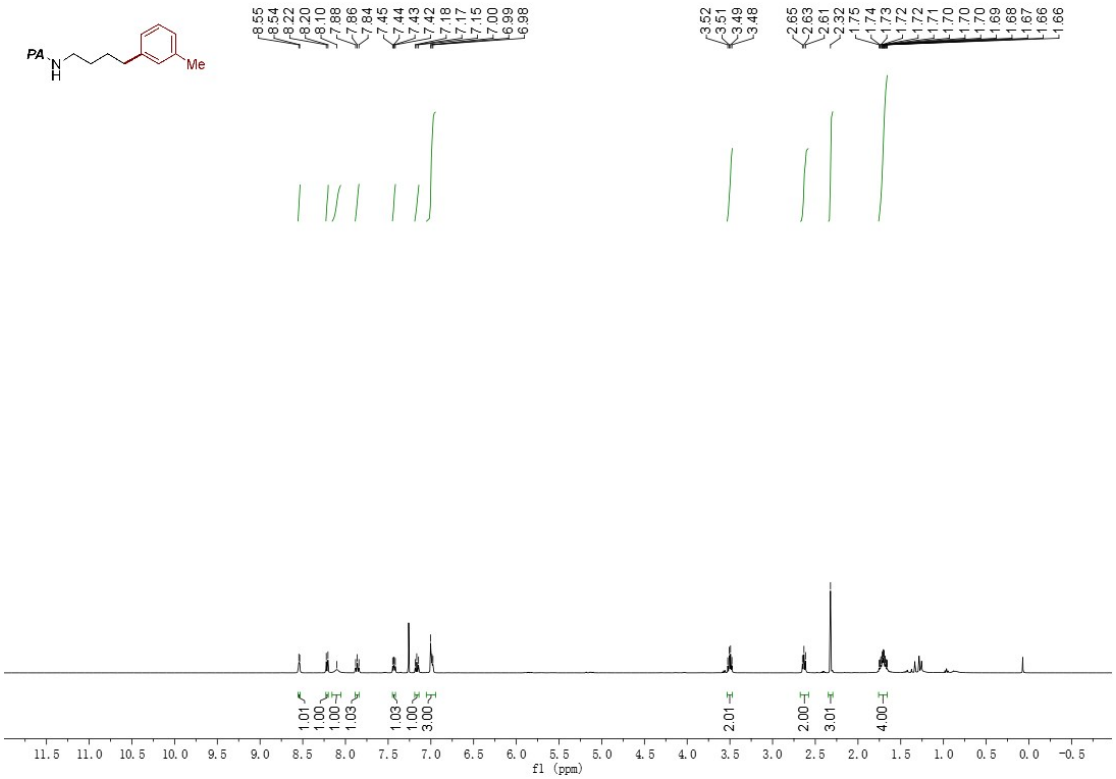
^{1}H NMR (400 MHz, $CDCl_3$) of **3b**



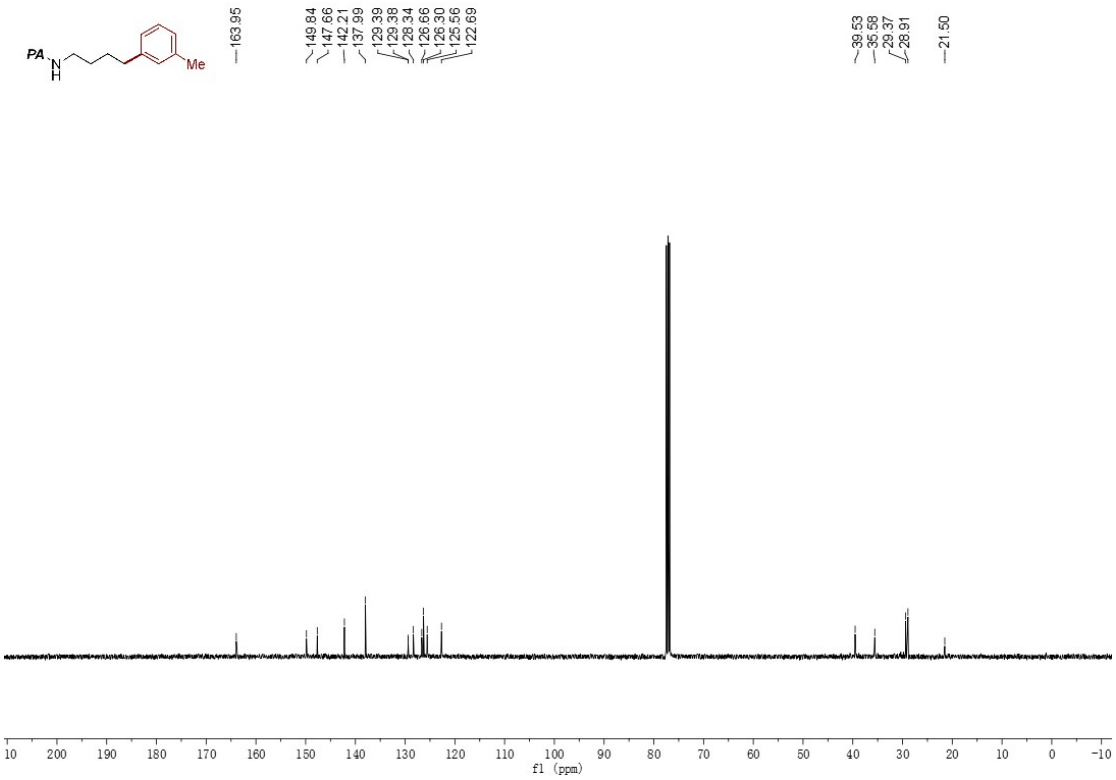
^{13}C NMR (101 MHz, $CDCl_3$) of **3b**



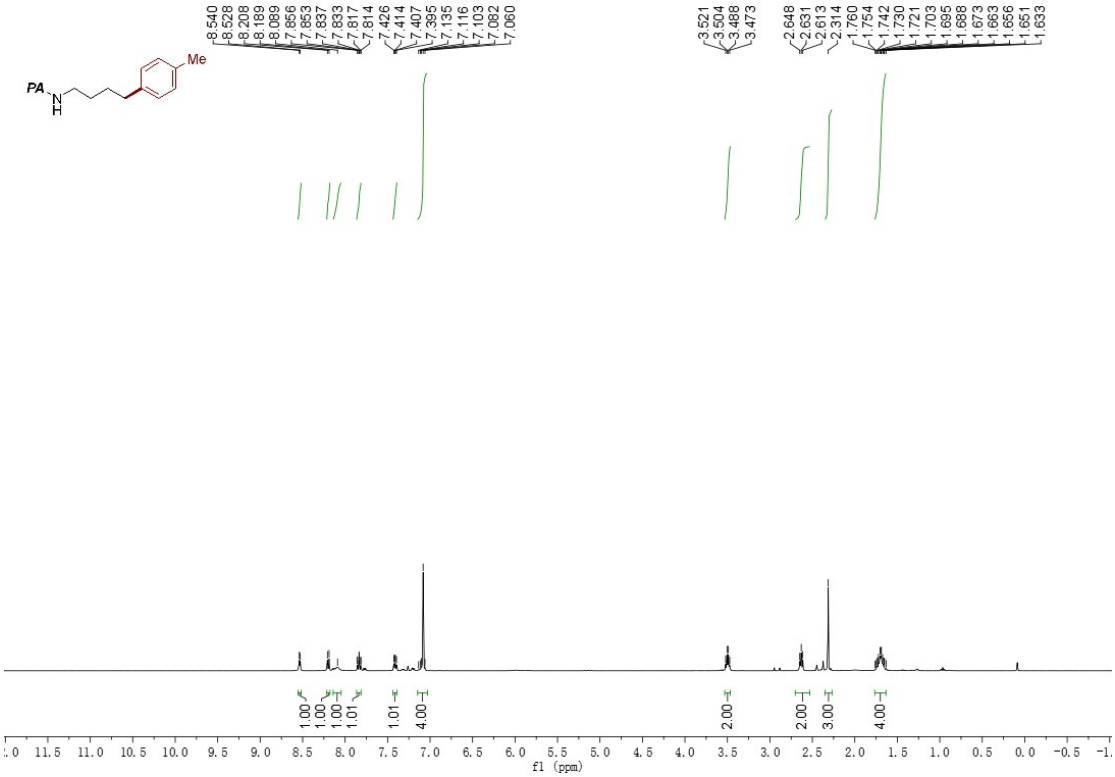
^{1}H NMR (400 MHz, $CDCl_3$) of **3c**



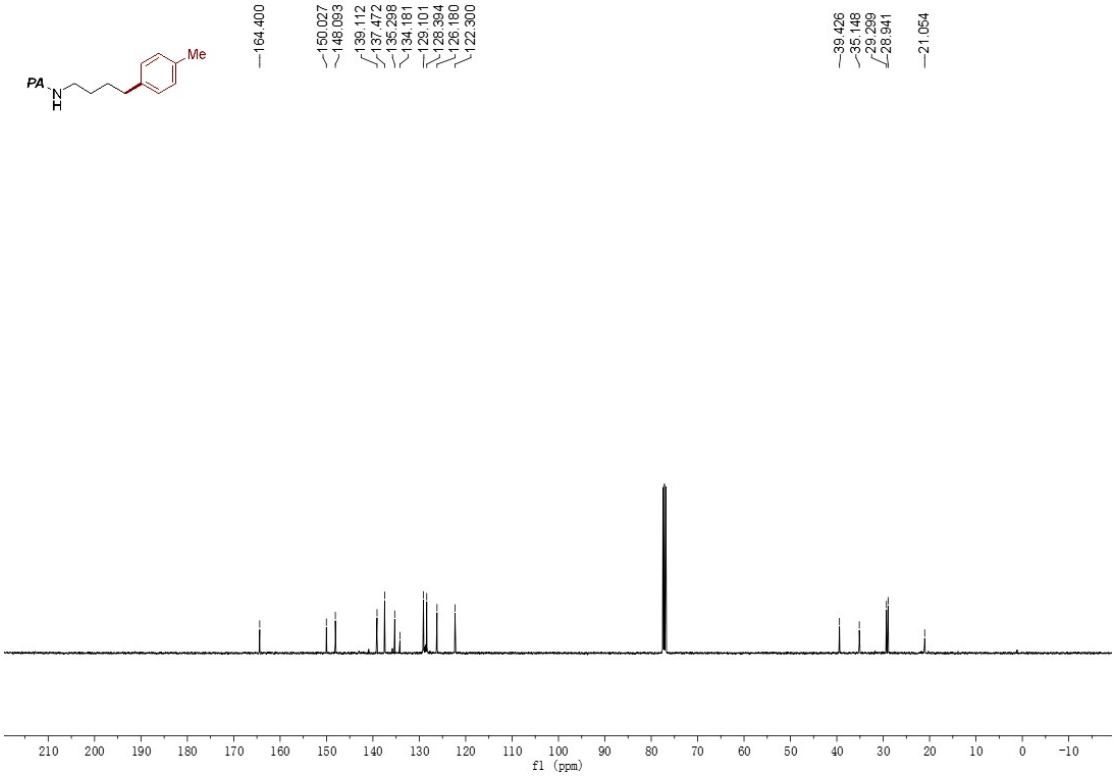
^{13}C NMR (101 MHz, $CDCl_3$) of **3c**



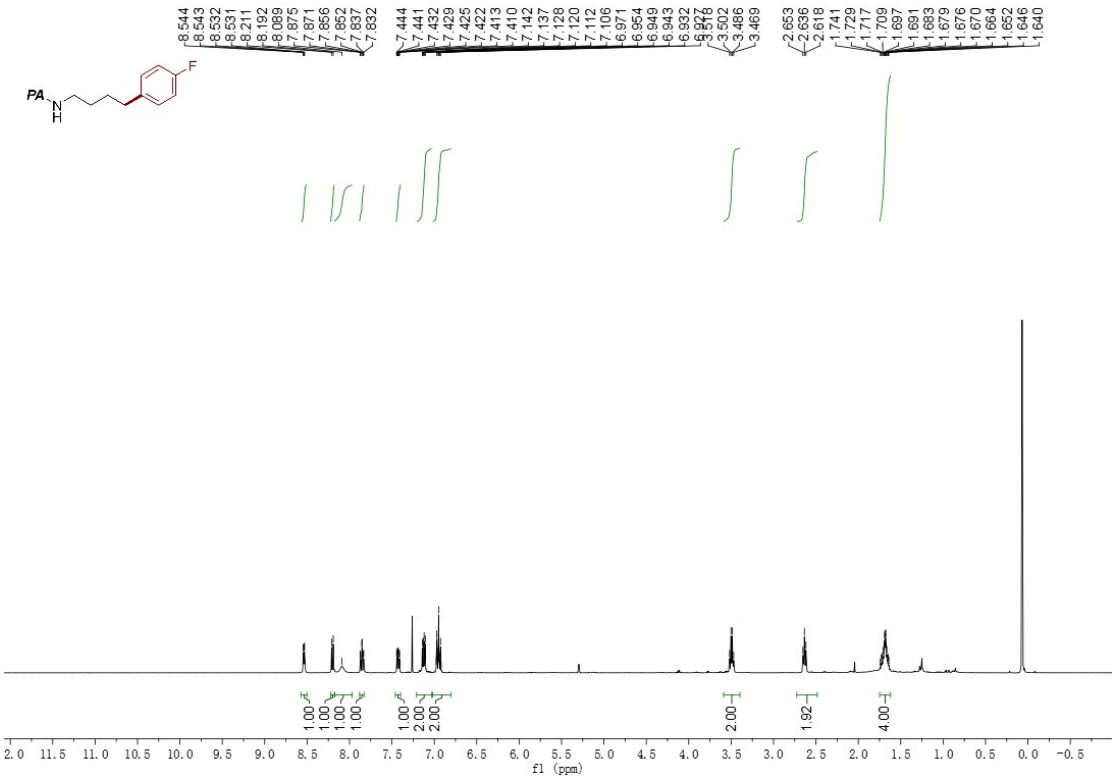
^{1}H NMR (400 MHz, $CDCl_3$) of **3d**



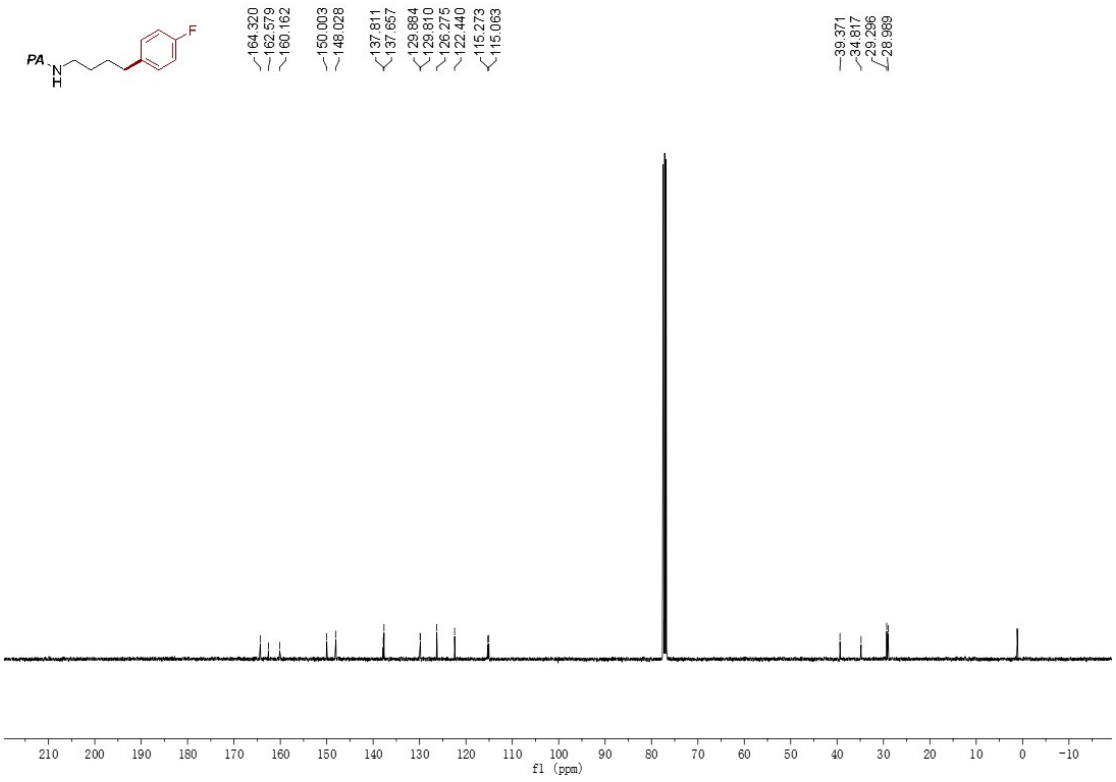
^{13}C NMR (101 MHz, $CDCl_3$) of **3d**



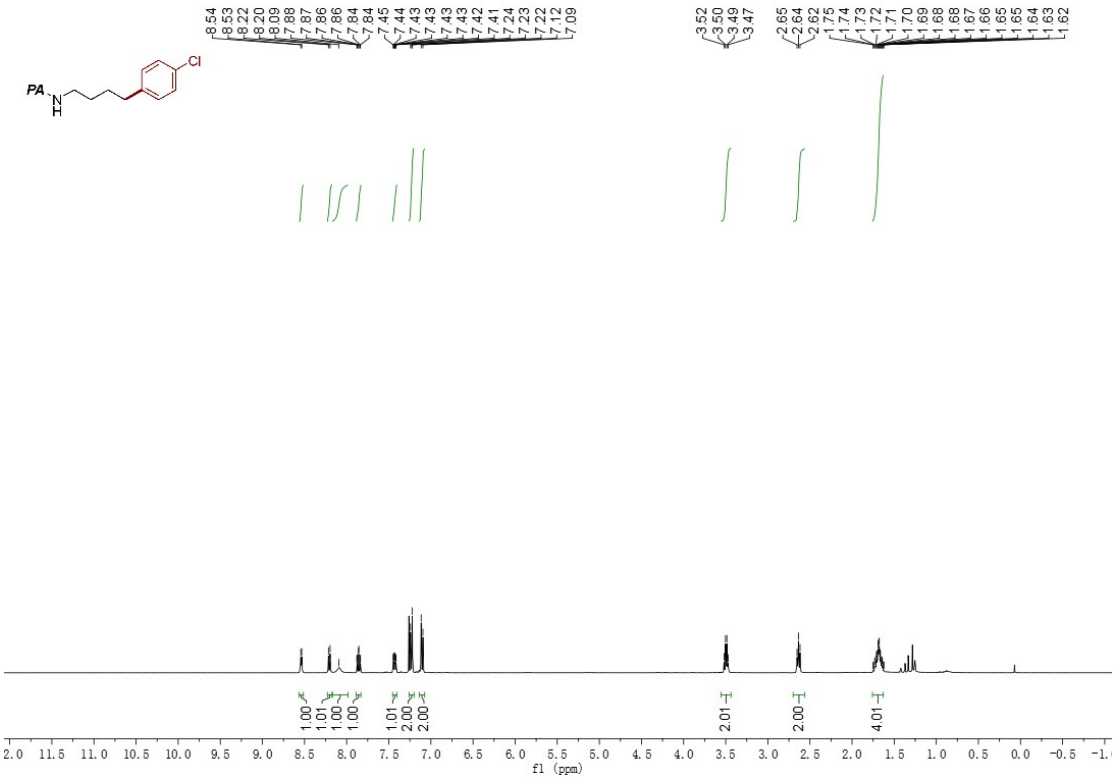
^{1}H NMR (400 MHz, $CDCl_3$) of **3e**



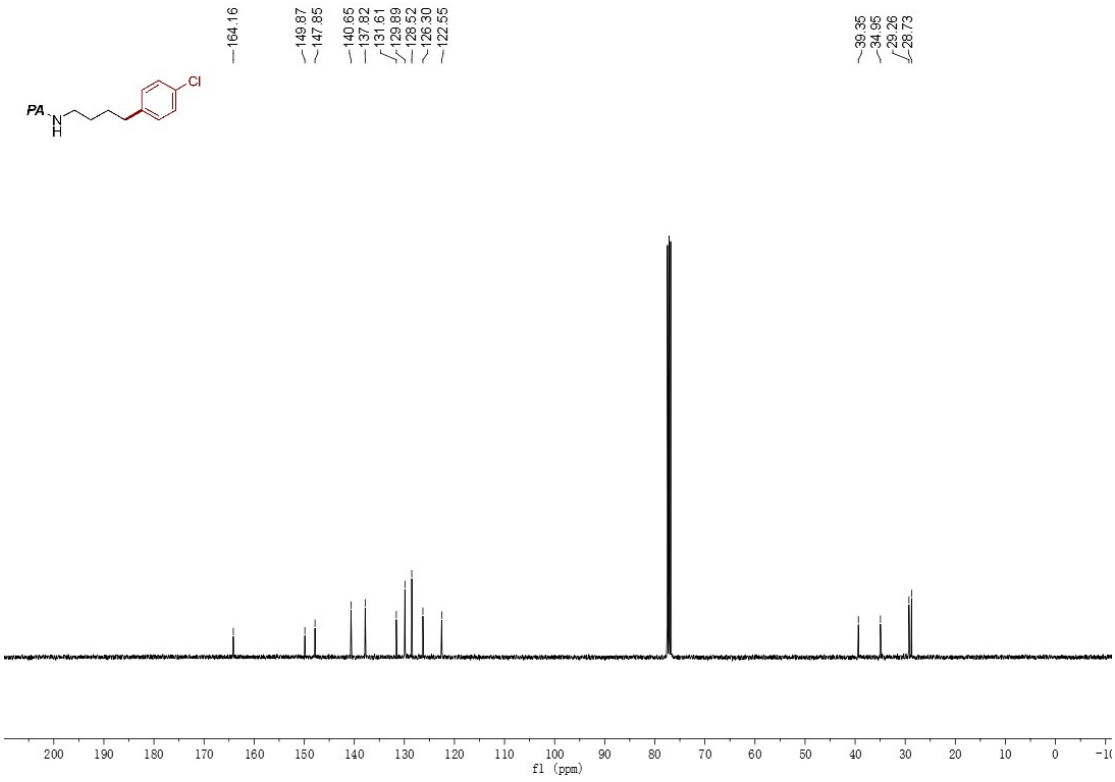
^{13}C NMR (101 MHz, $CDCl_3$) of **3e**



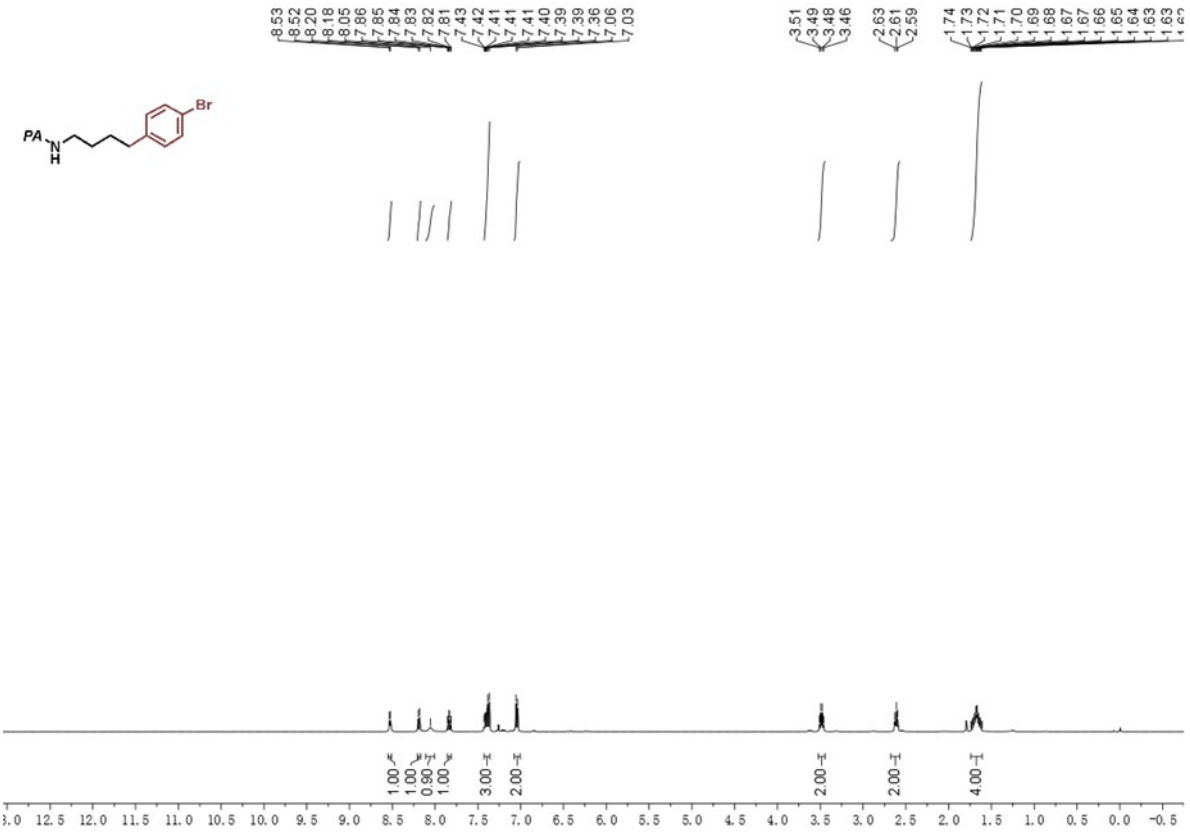
^{1}H NMR (400 MHz, $CDCl_3$) of **3f**



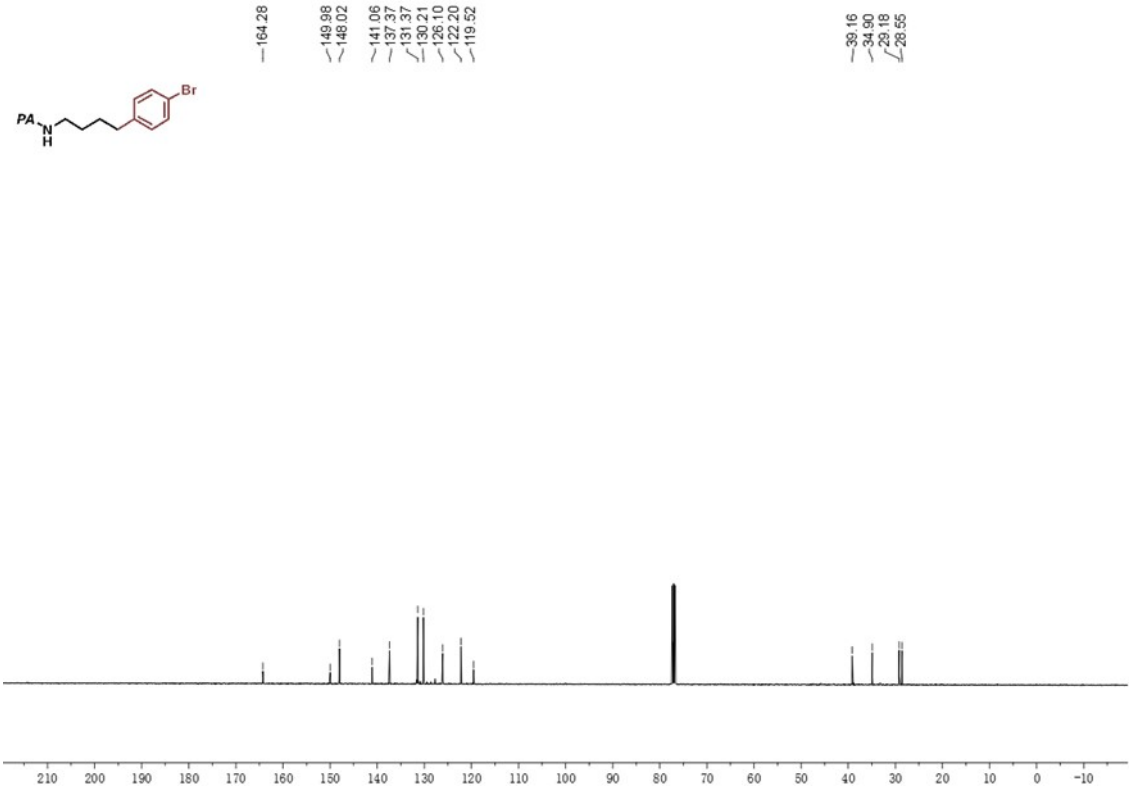
^{13}C NMR (101 MHz, $CDCl_3$) of **3f**



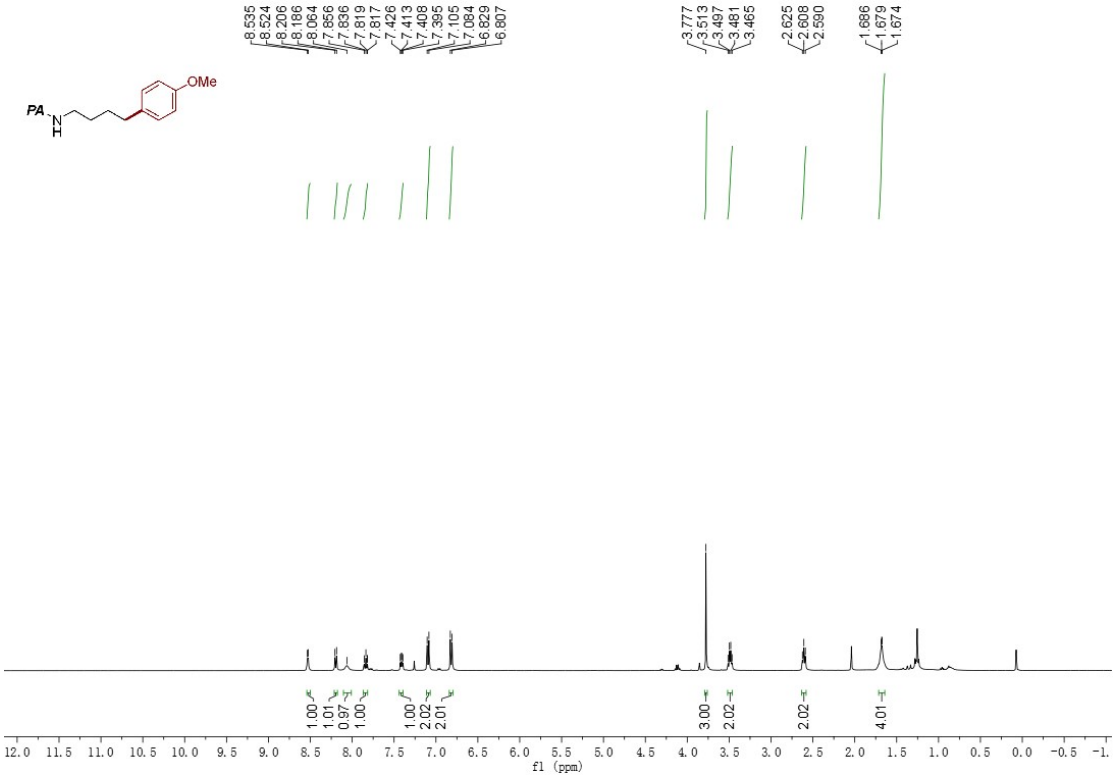
^{1}H NMR (400 MHz, $CDCl_3$) of **3g**



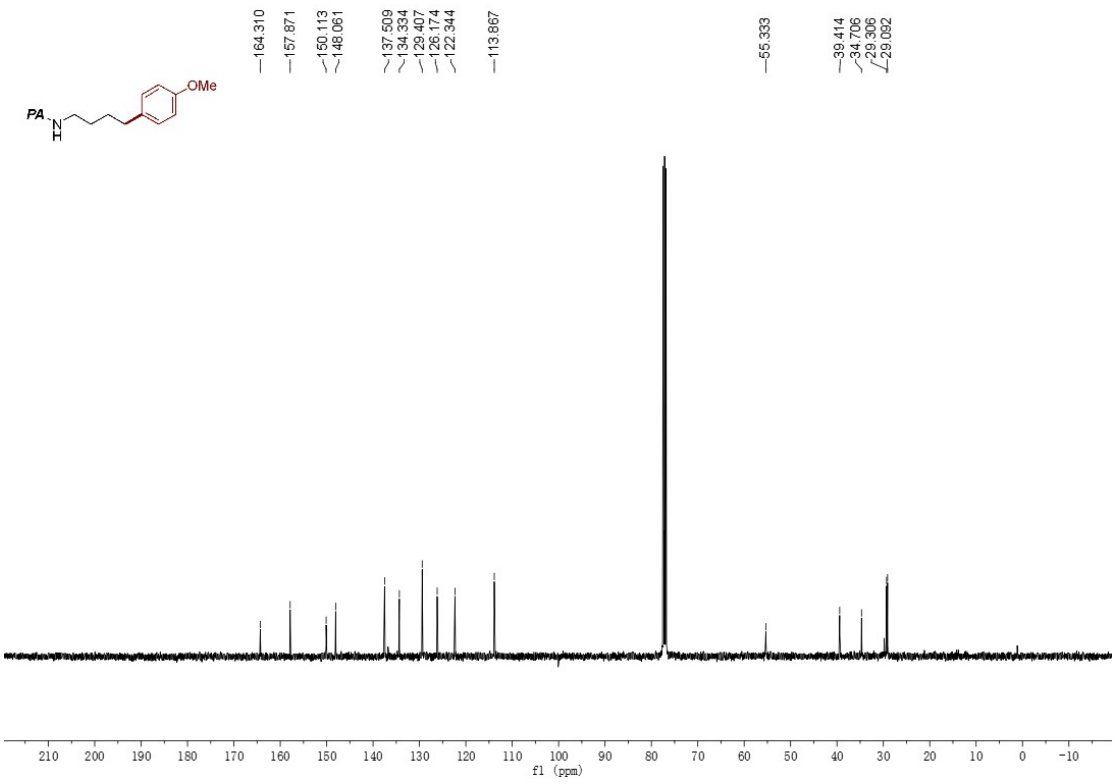
^{13}C NMR (101 MHz, $CDCl_3$) of **3g**



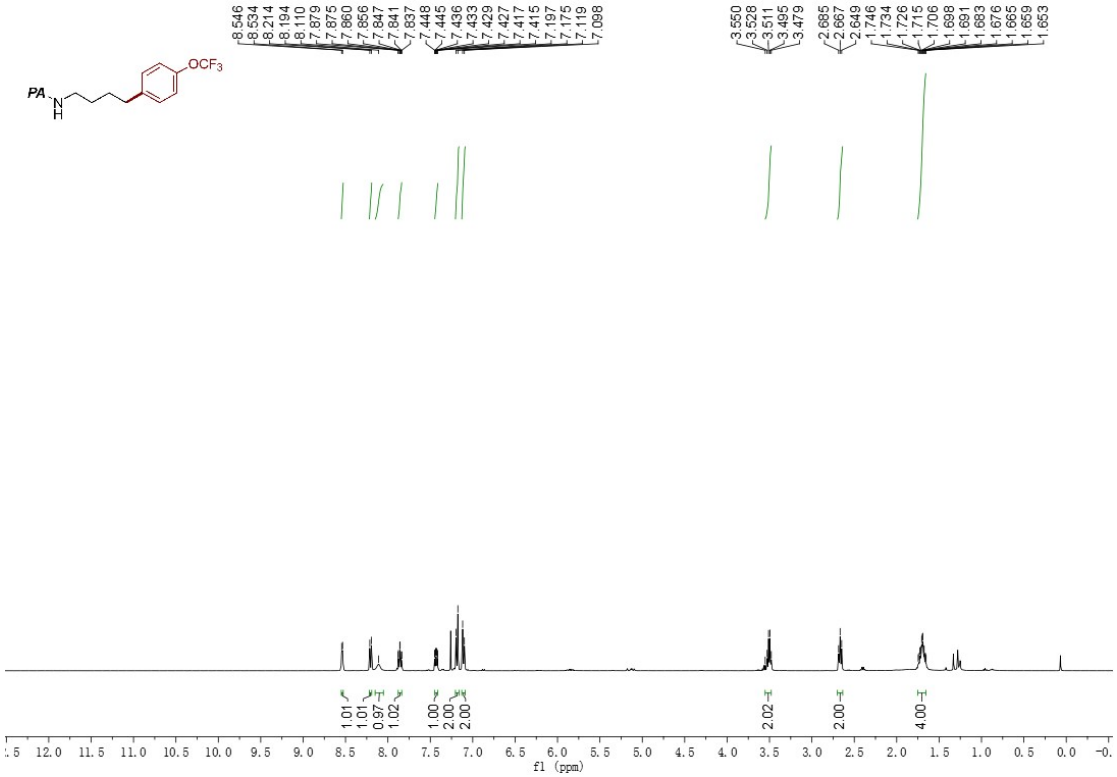
^{1}H NMR (400 MHz, $CDCl_3$) of **3h**



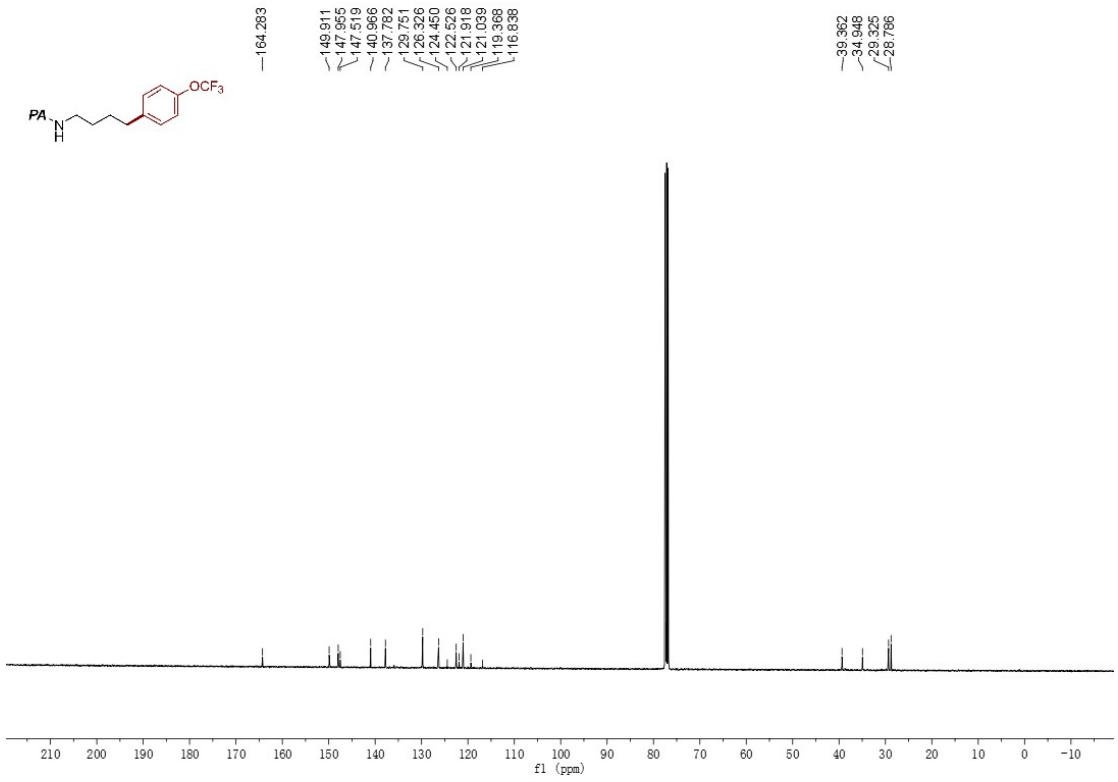
^{13}C NMR (101 MHz, $CDCl_3$) of **3h**



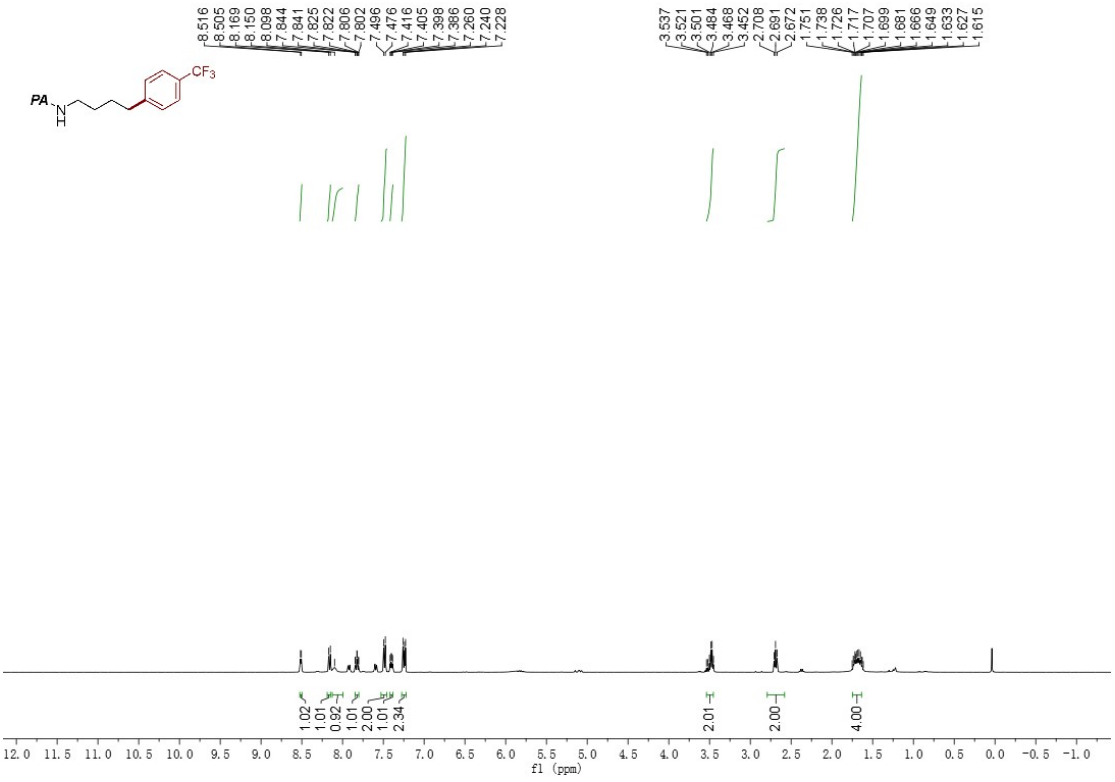
^{1}H NMR (400 MHz, $CDCl_3$) of **3i**



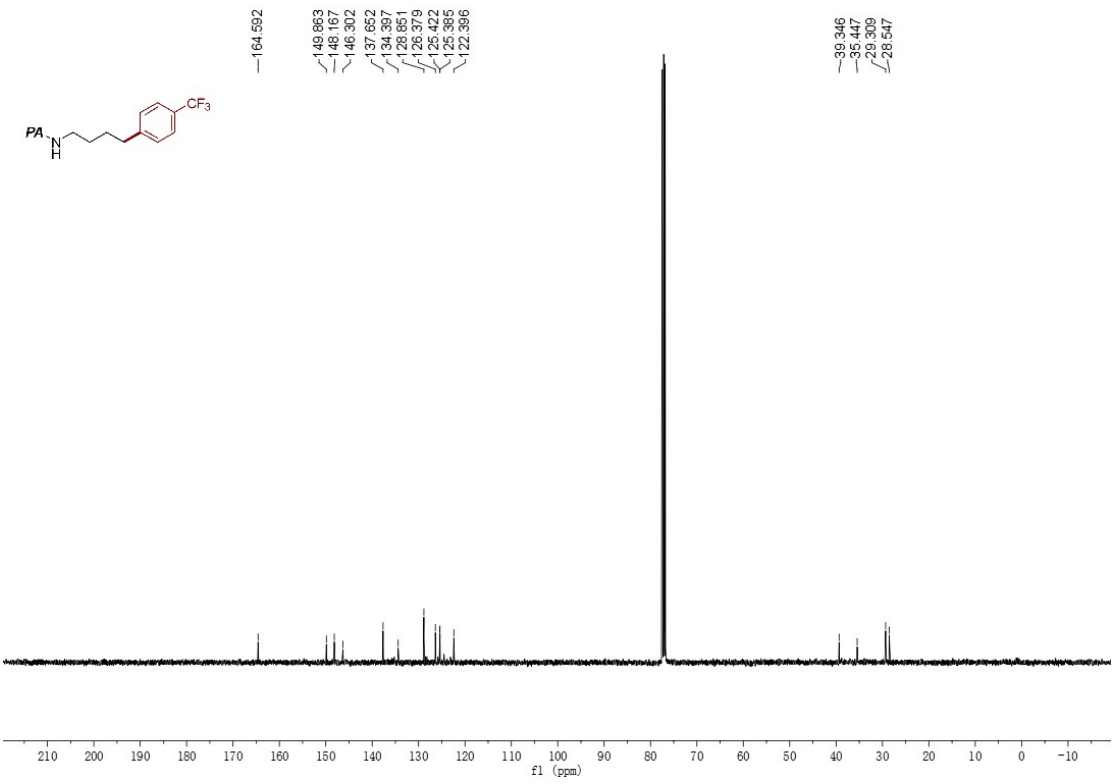
^{13}C NMR (101 MHz, $CDCl_3$) of **3i**



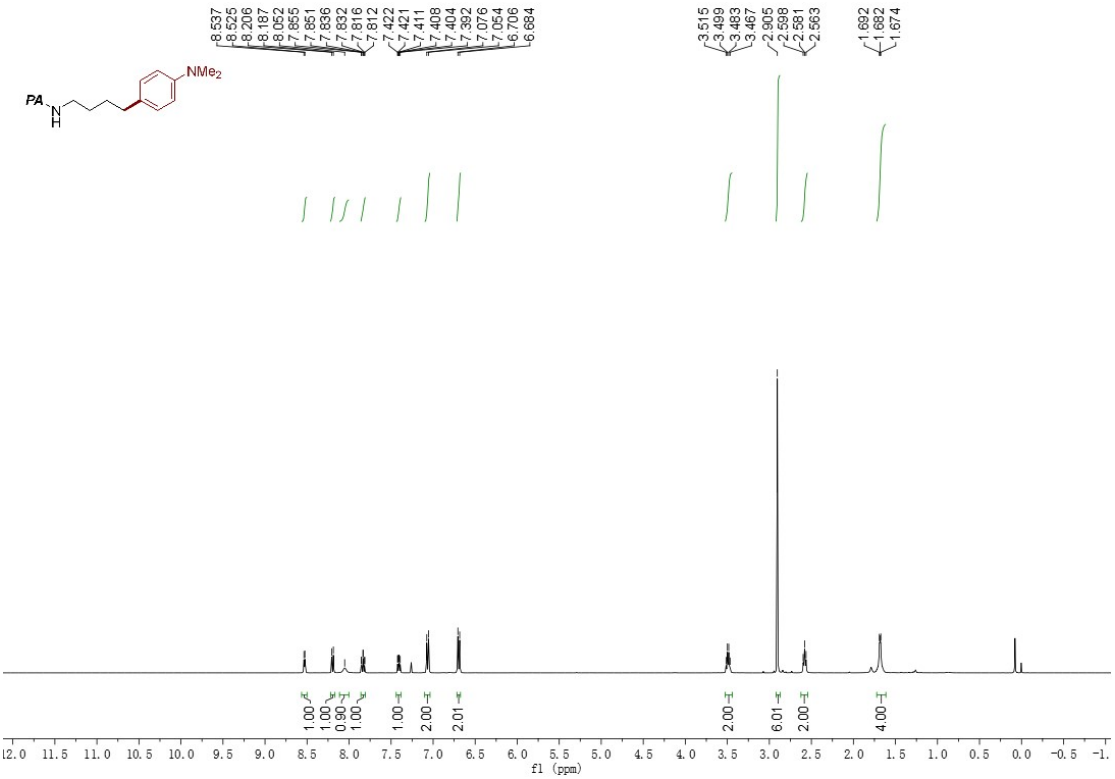
^{1}H NMR (400 MHz, $CDCl_3$) of **3j**



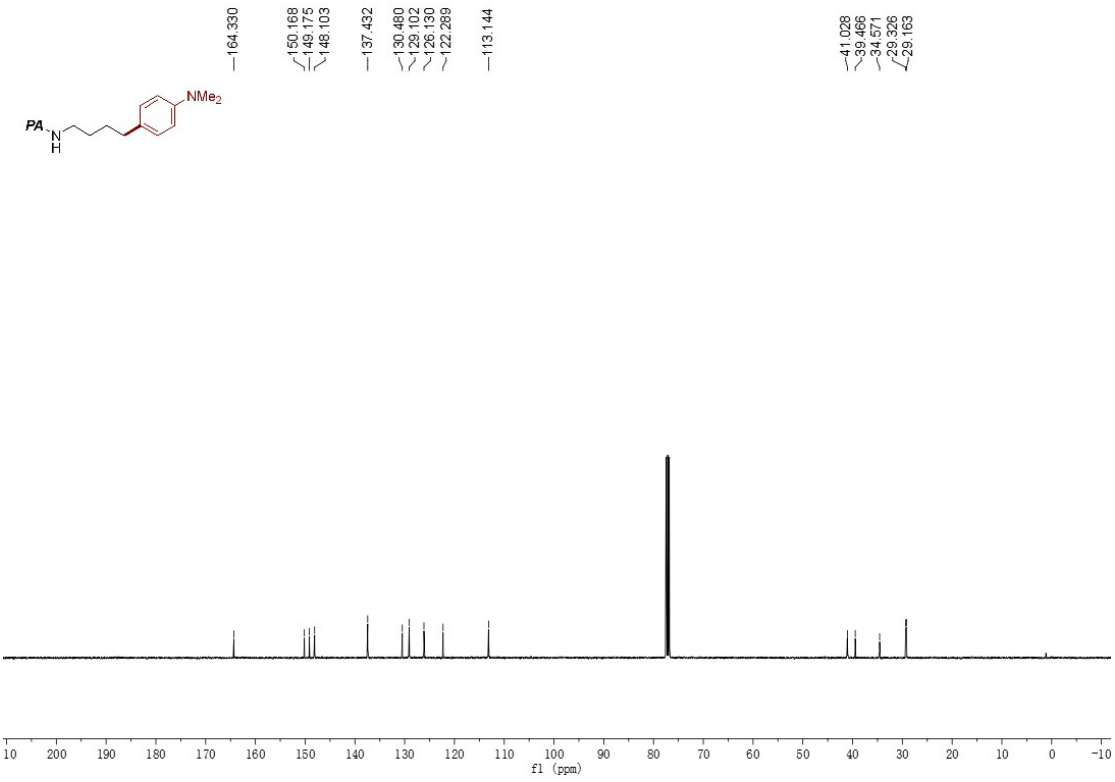
^{13}C NMR (101 MHz, $CDCl_3$) of **3j**



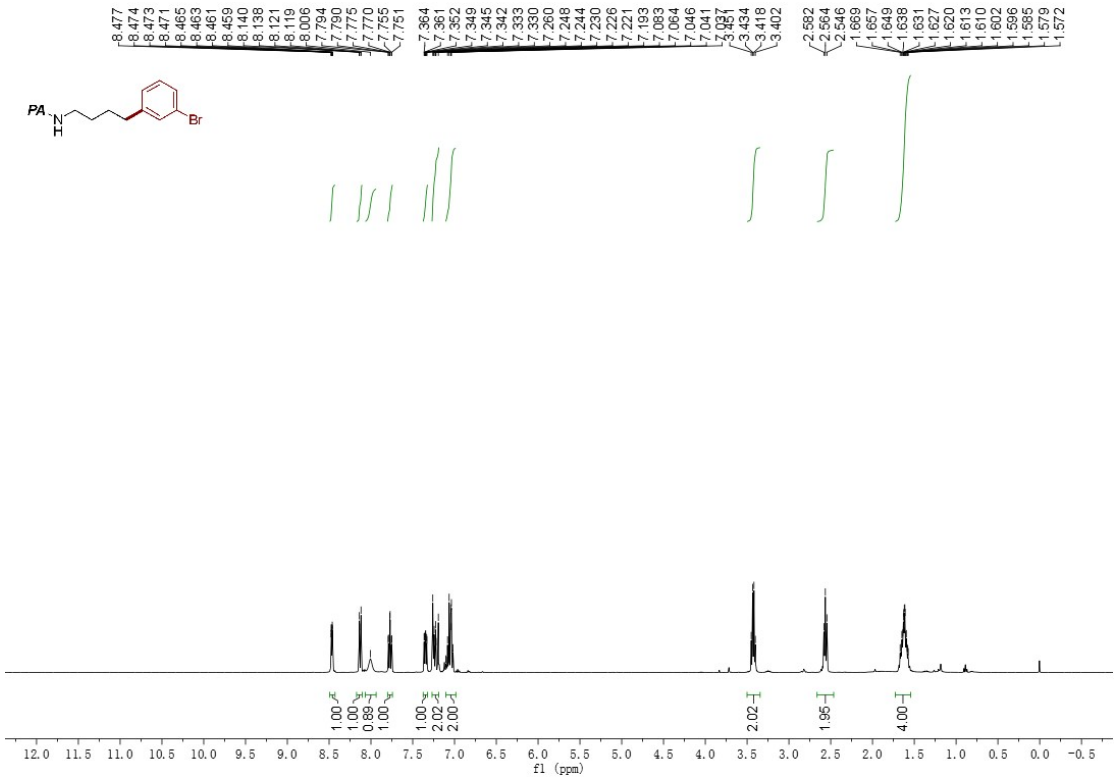
^{1}H NMR (400 MHz, $CDCl_3$) of **3k**



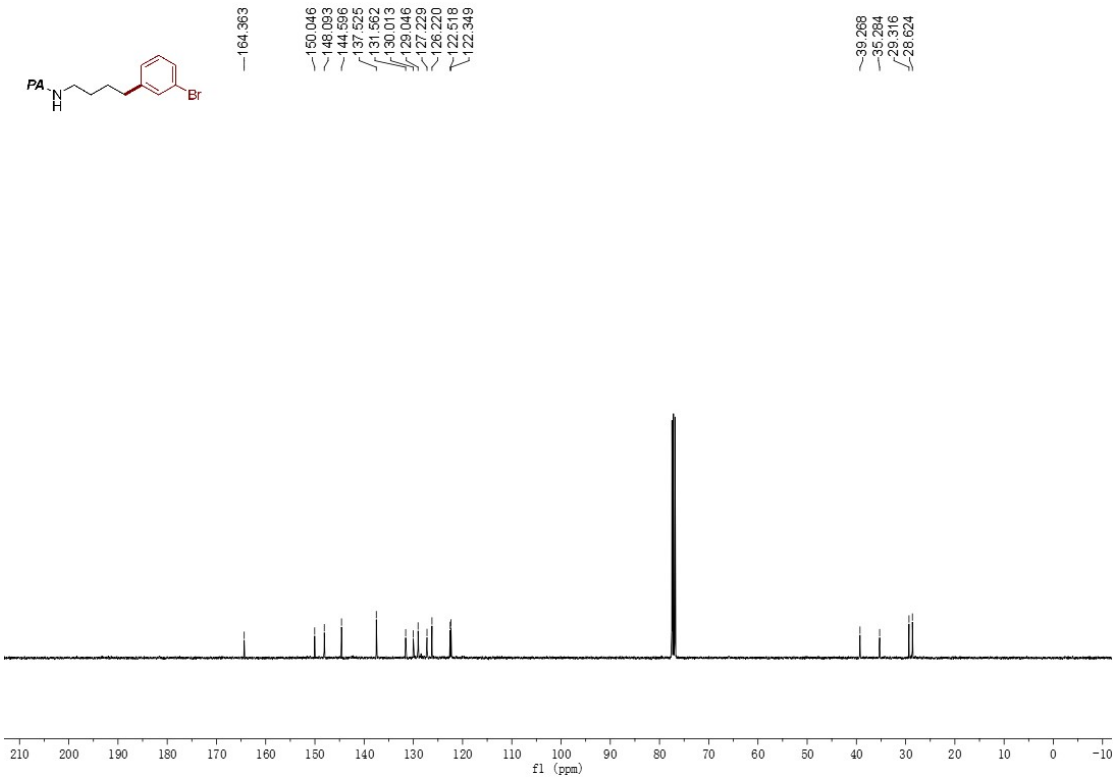
^{13}C NMR (101 MHz, $CDCl_3$) of **3k**



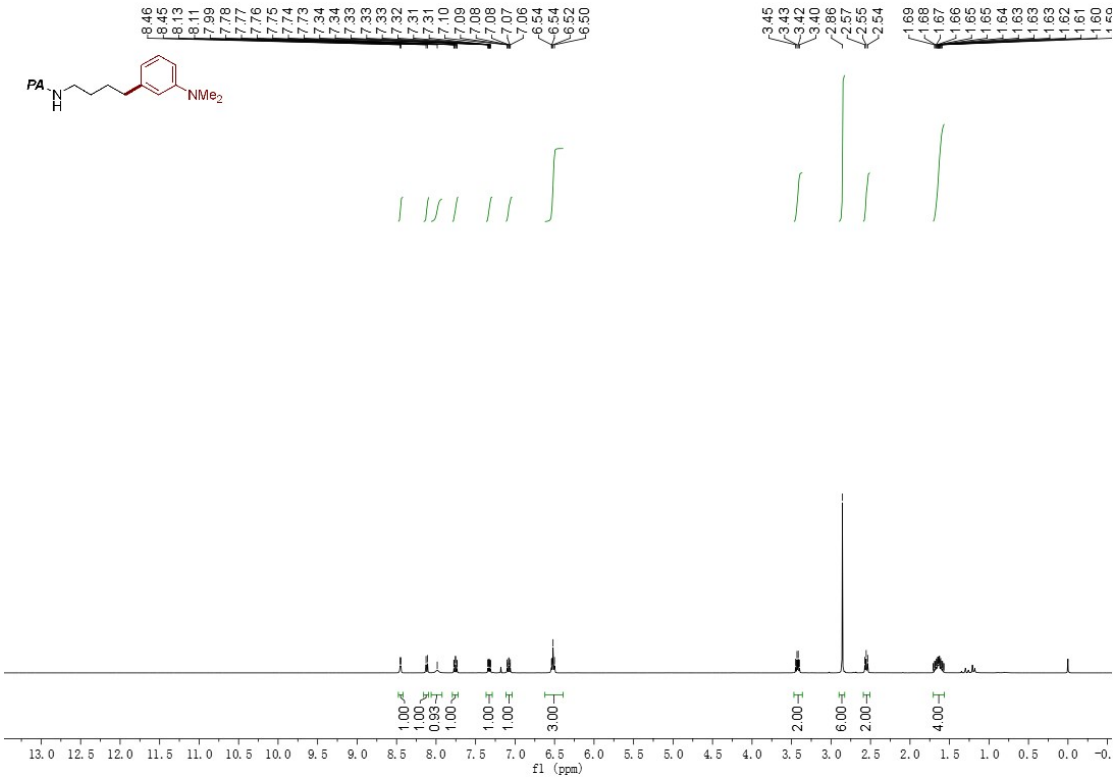
^{1}H NMR (400 MHz, $CDCl_3$) of **3l**



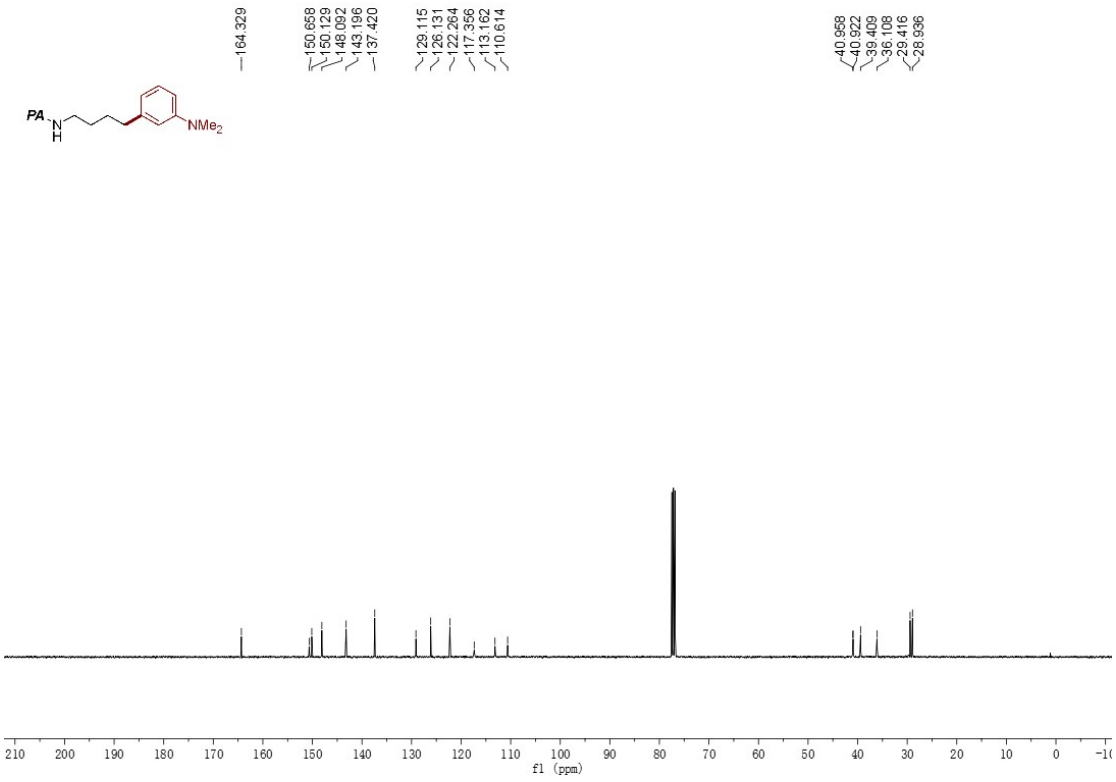
^{13}C NMR (101 MHz, $CDCl_3$) of **3l**



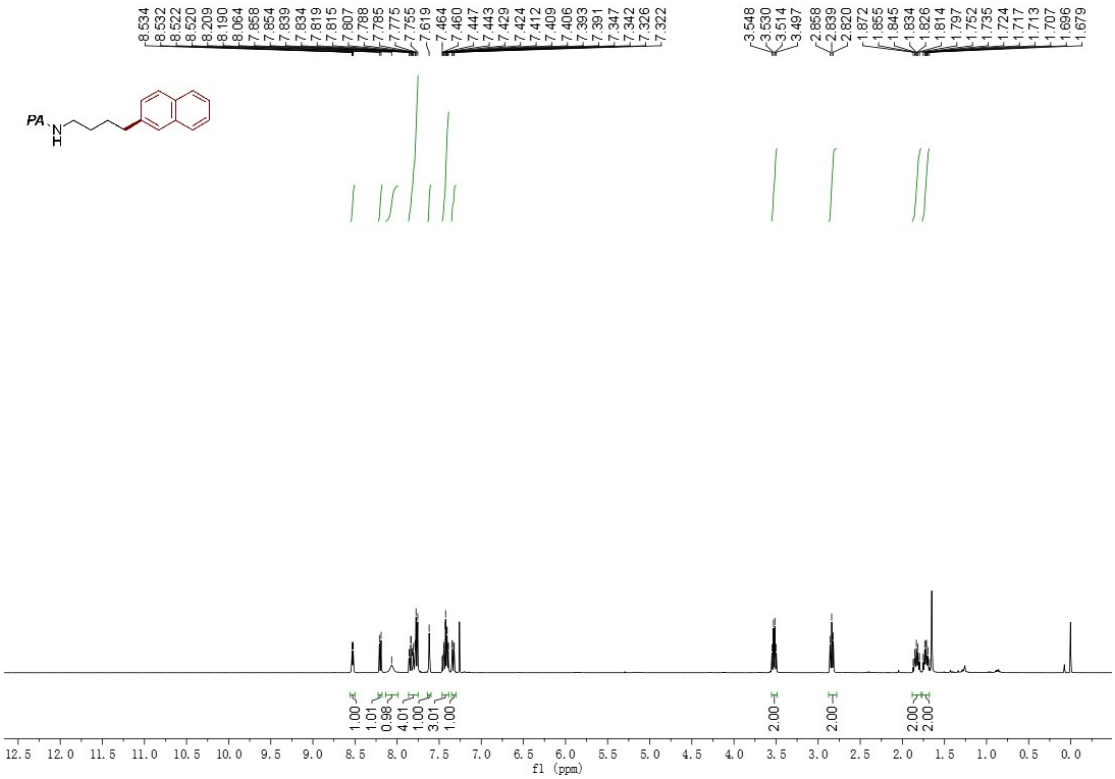
^{1}H NMR (400 MHz, $CDCl_3$) of **3m**



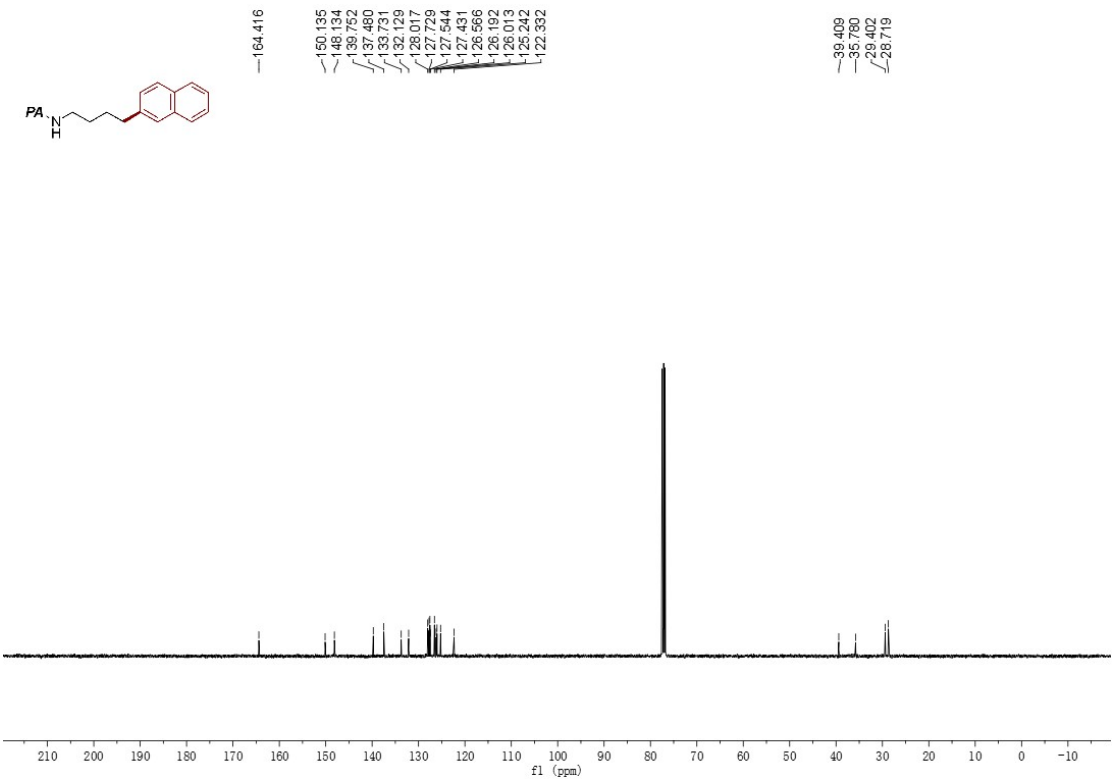
^{13}C NMR (101 MHz, $CDCl_3$) of **3m**



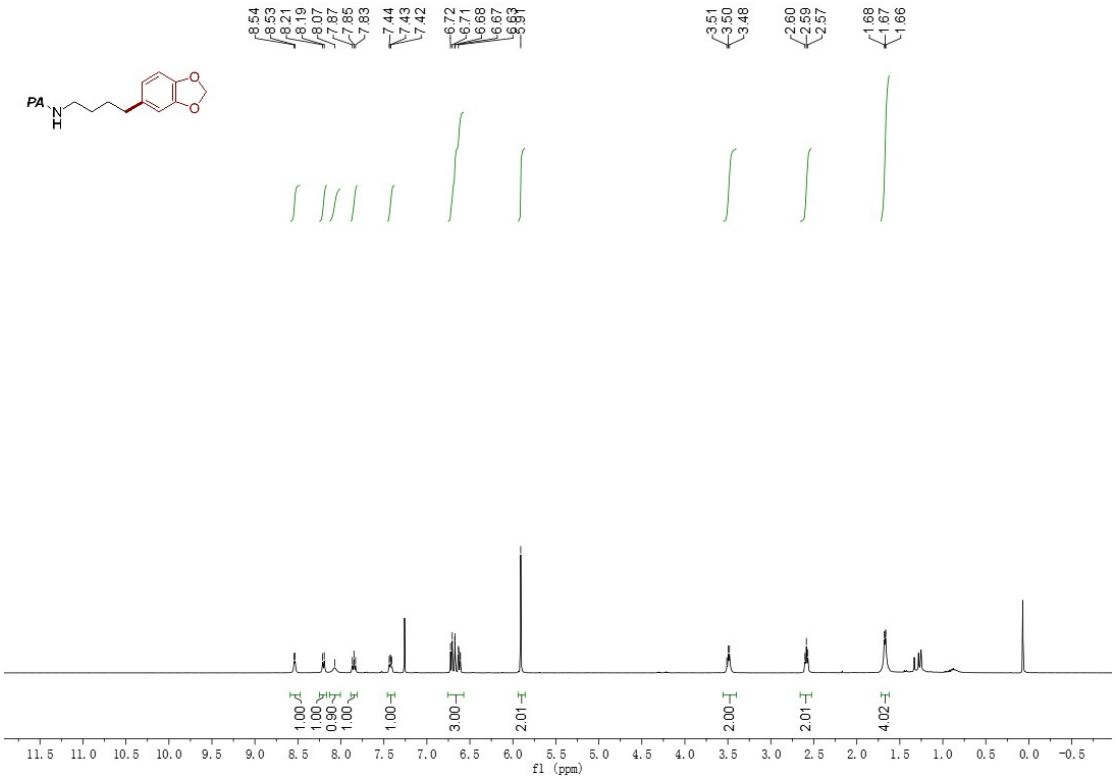
^{1}H NMR (400 MHz, $CDCl_3$) of **3n**



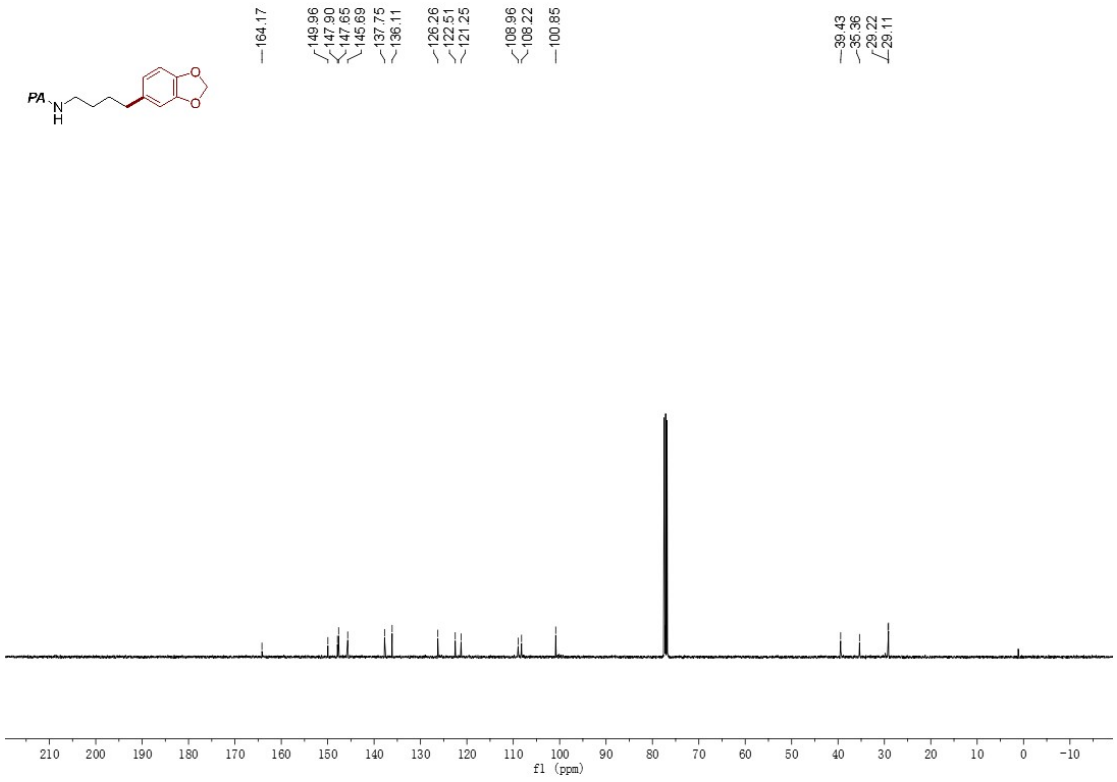
^{13}C NMR (101 MHz, $CDCl_3$) of **3n**



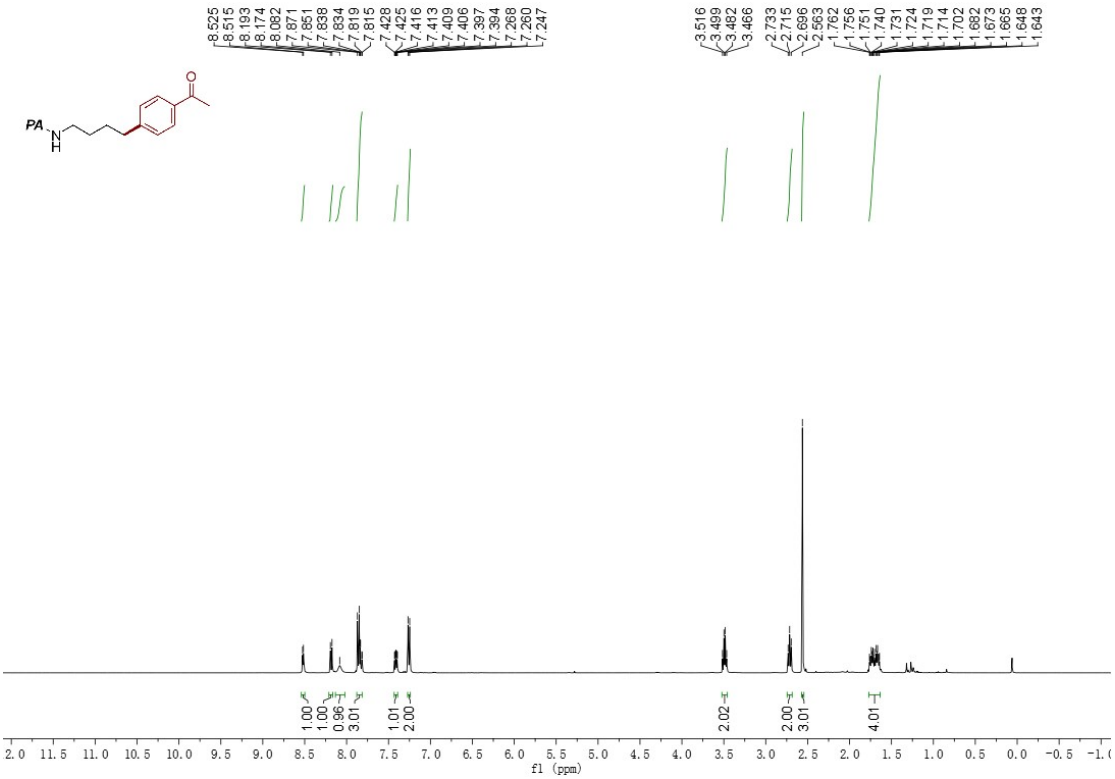
^{1}H NMR (400 MHz, $CDCl_3$) of **3o**



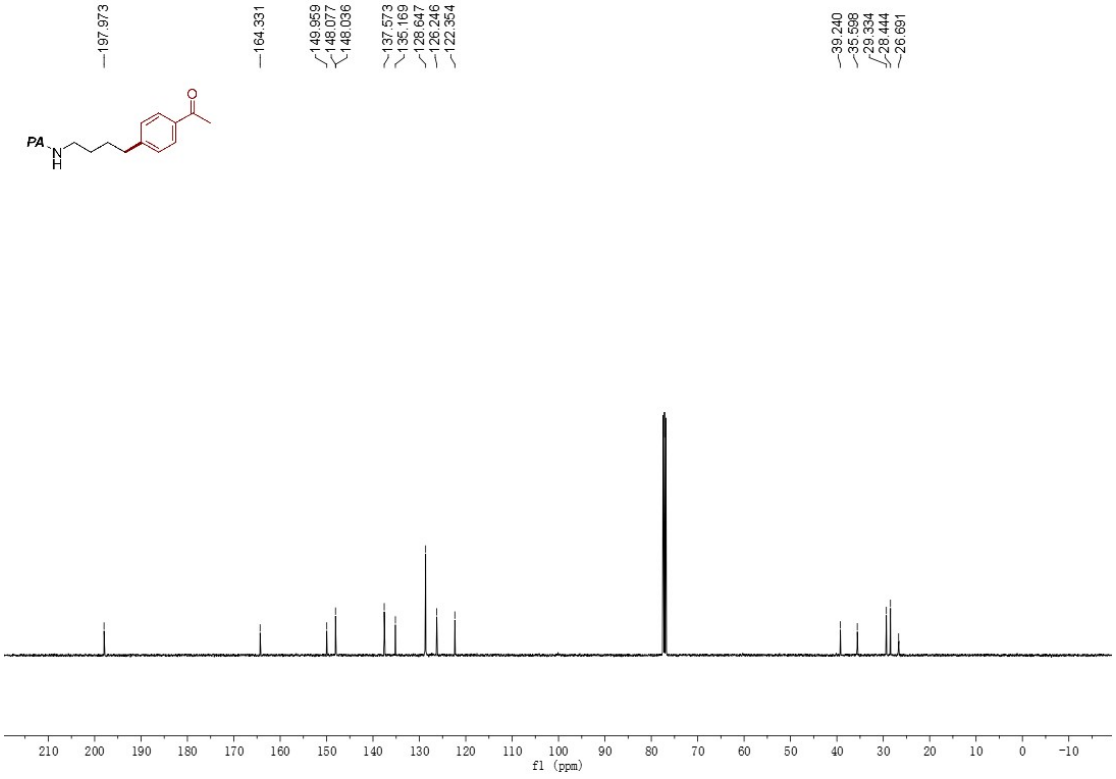
^{13}C NMR (101 MHz, $CDCl_3$) of **3o**



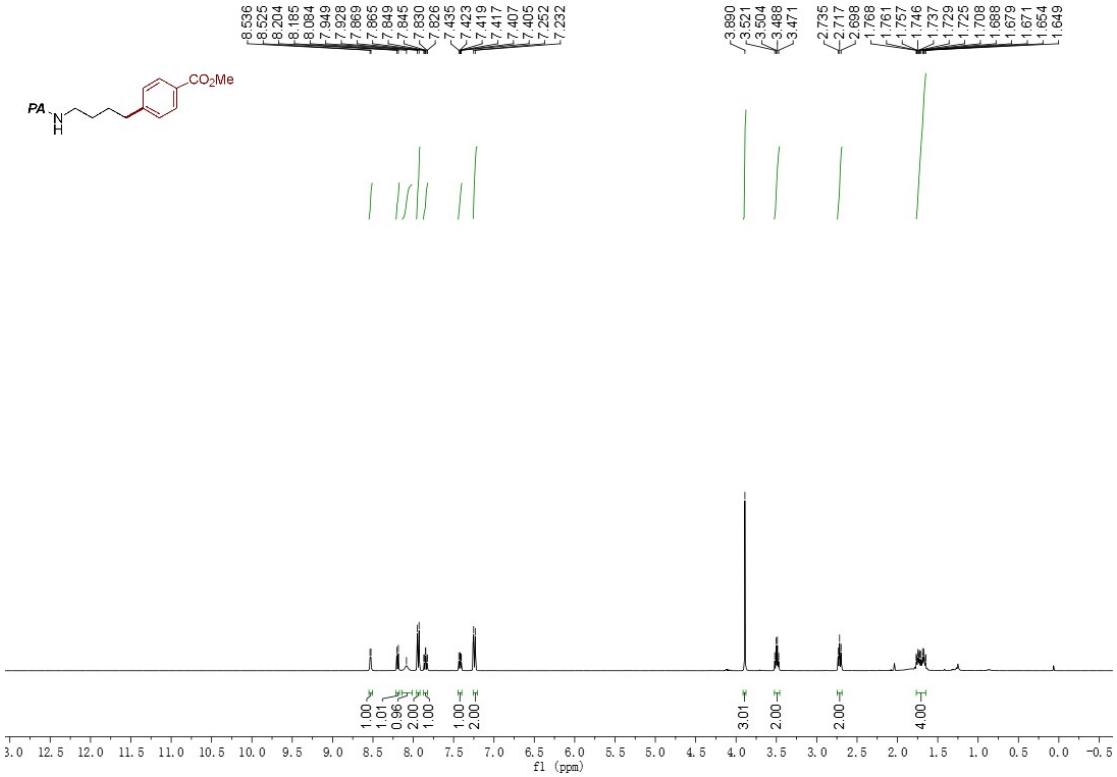
^{1}H NMR (400 MHz, $CDCl_3$) of **3p**



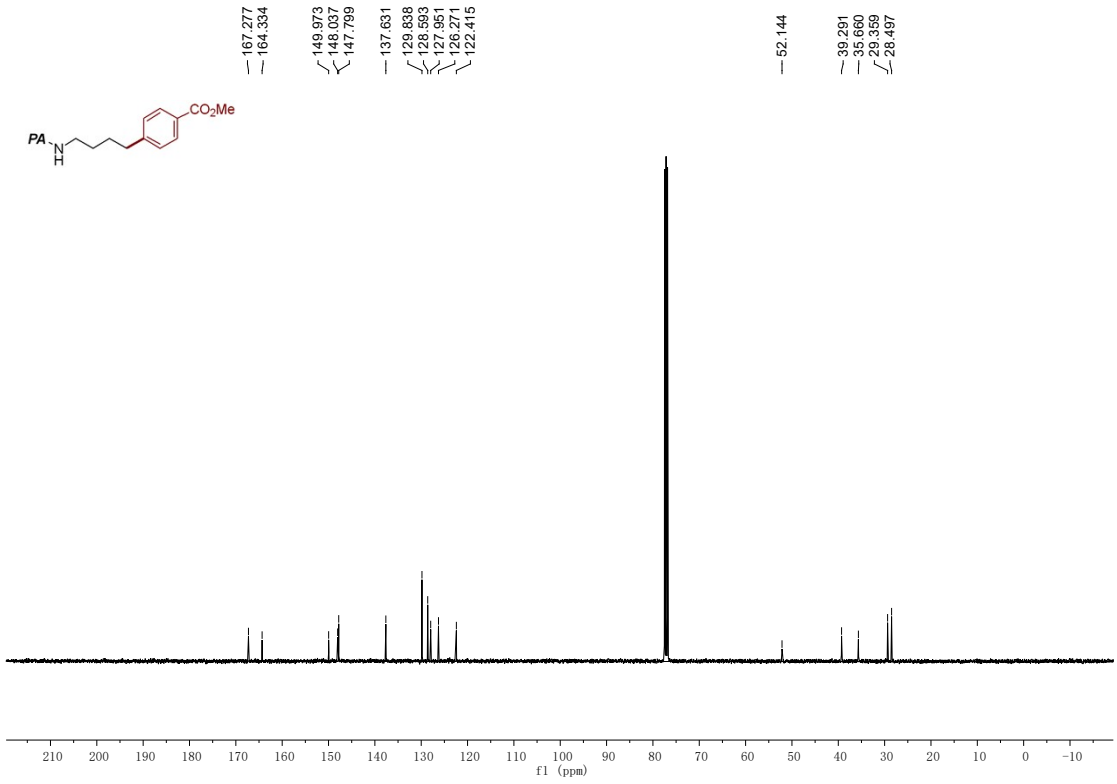
^{13}C NMR (101 MHz, $CDCl_3$) of **3p**



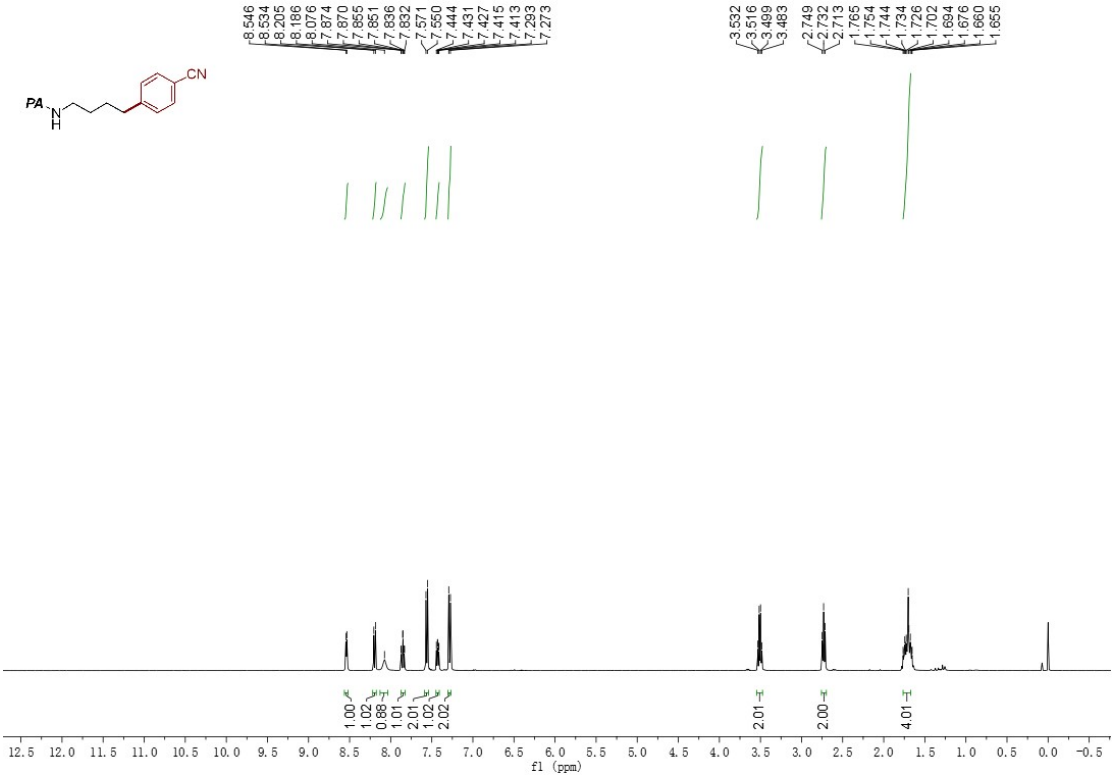
^{1}H NMR (400 MHz, $CDCl_3$) of **3q**



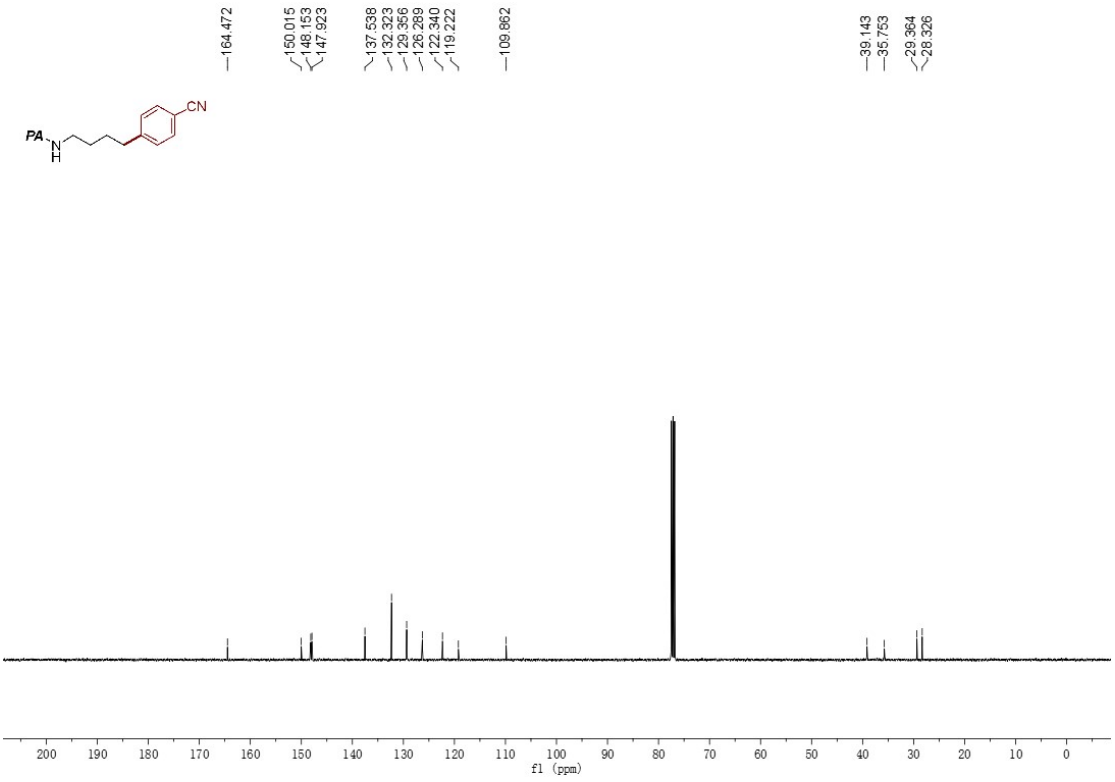
^{13}C NMR (101 MHz, $CDCl_3$) of **3q**



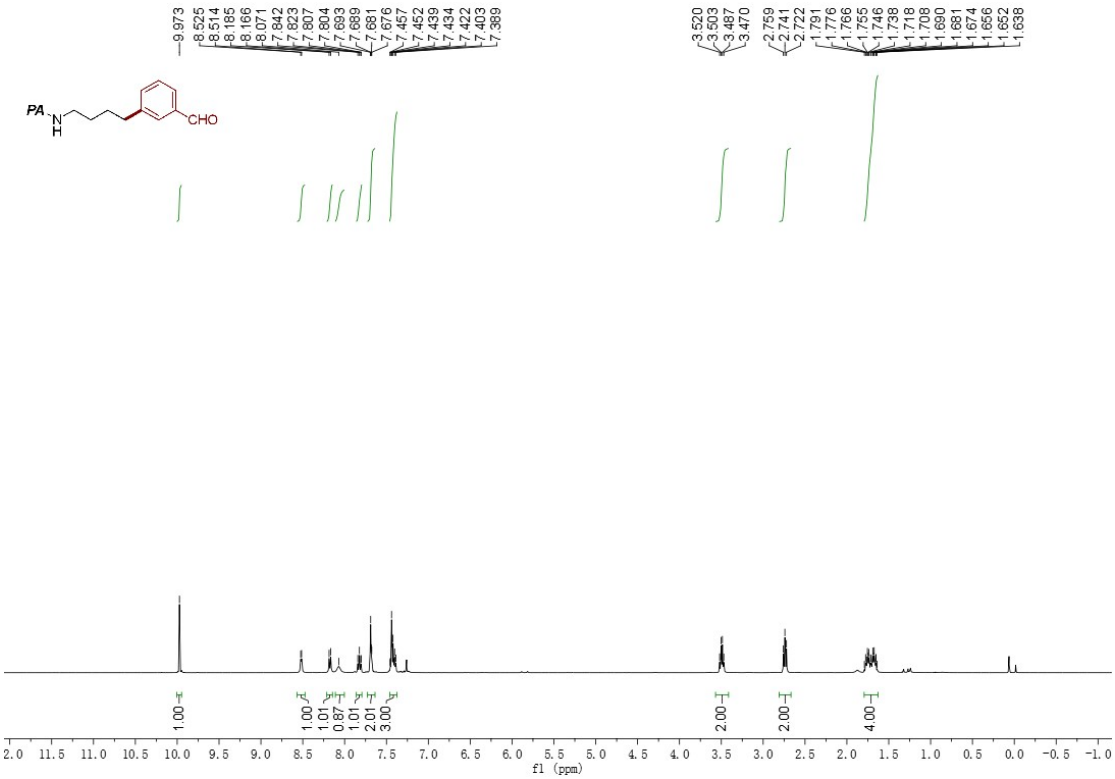
^{1}H NMR (400 MHz, $CDCl_3$) of **3r**



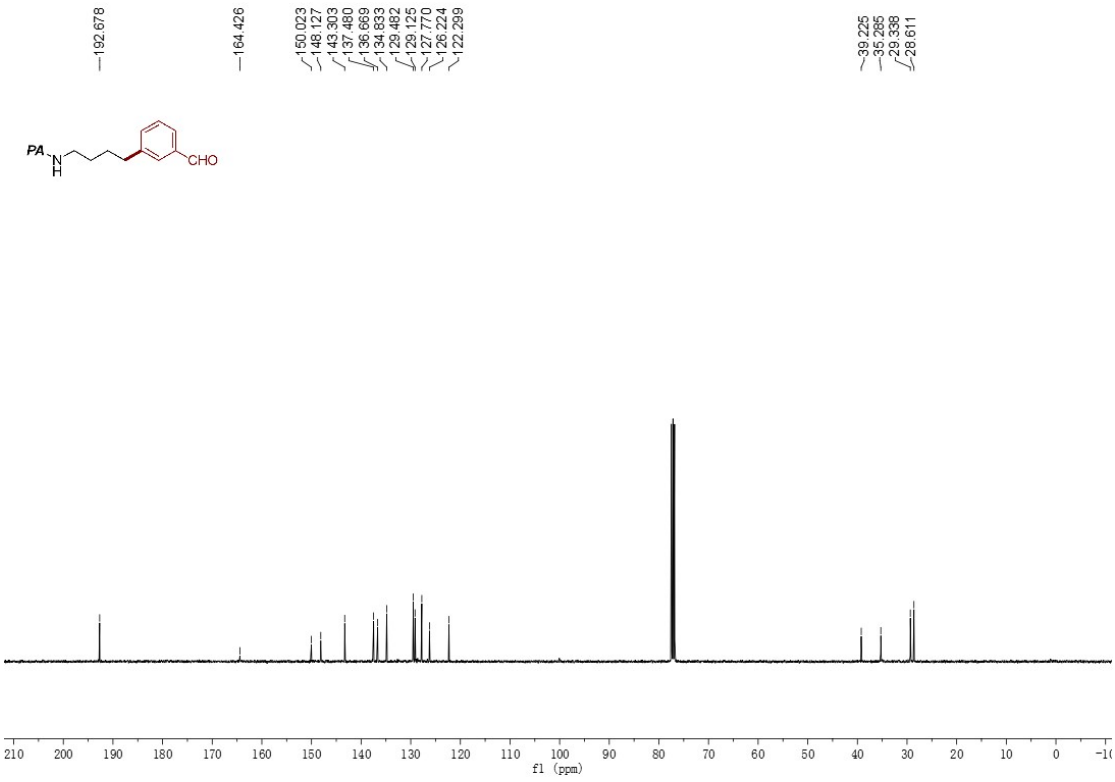
^{13}C NMR (101 MHz, $CDCl_3$) of **3r**



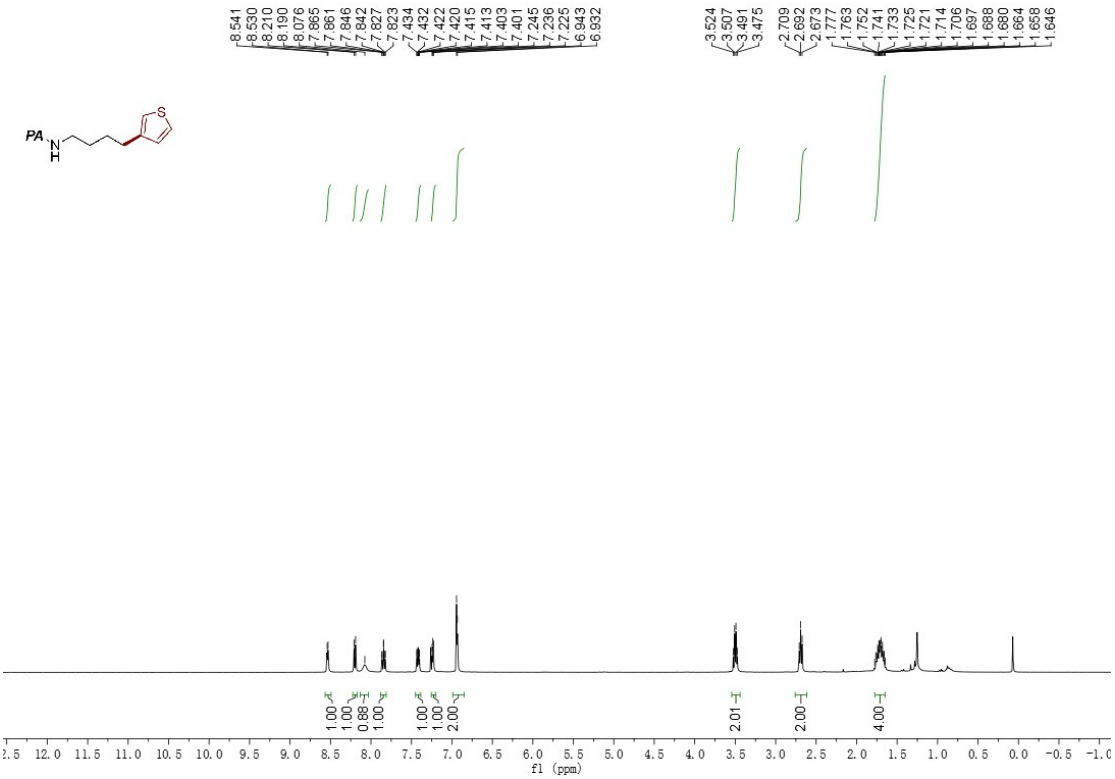
^{1}H NMR (400 MHz, $CDCl_3$) of **3s**



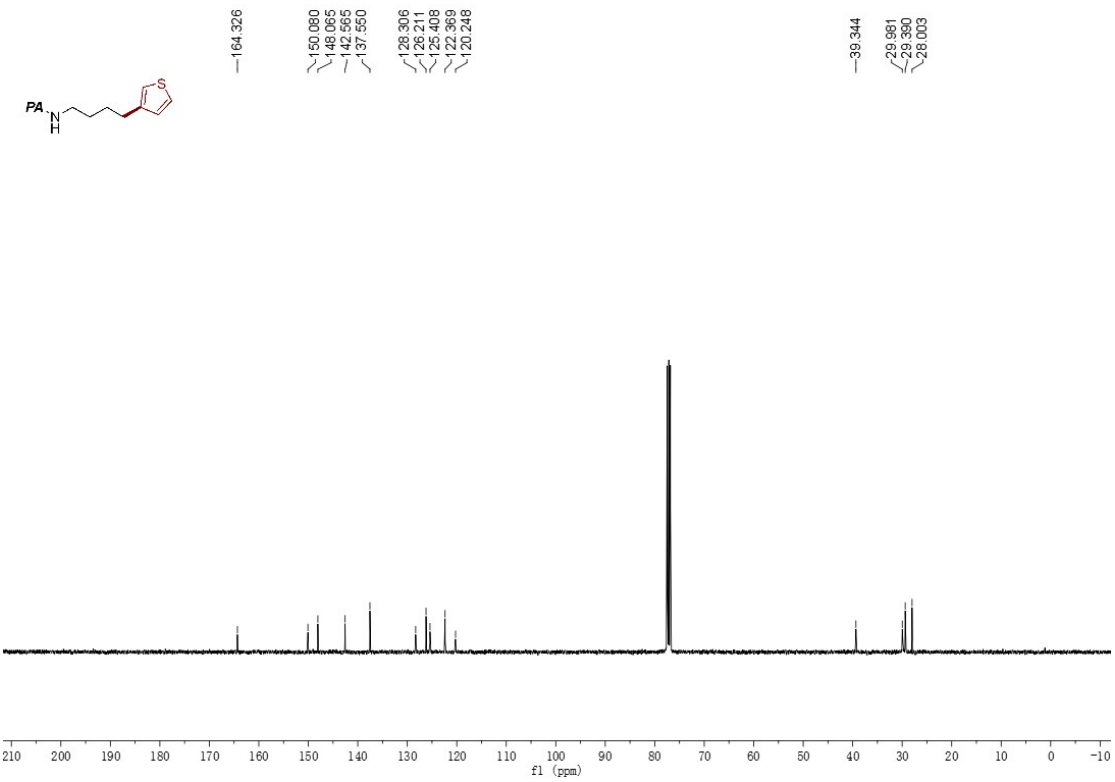
^{13}C NMR (101 MHz, $CDCl_3$) of **3s**



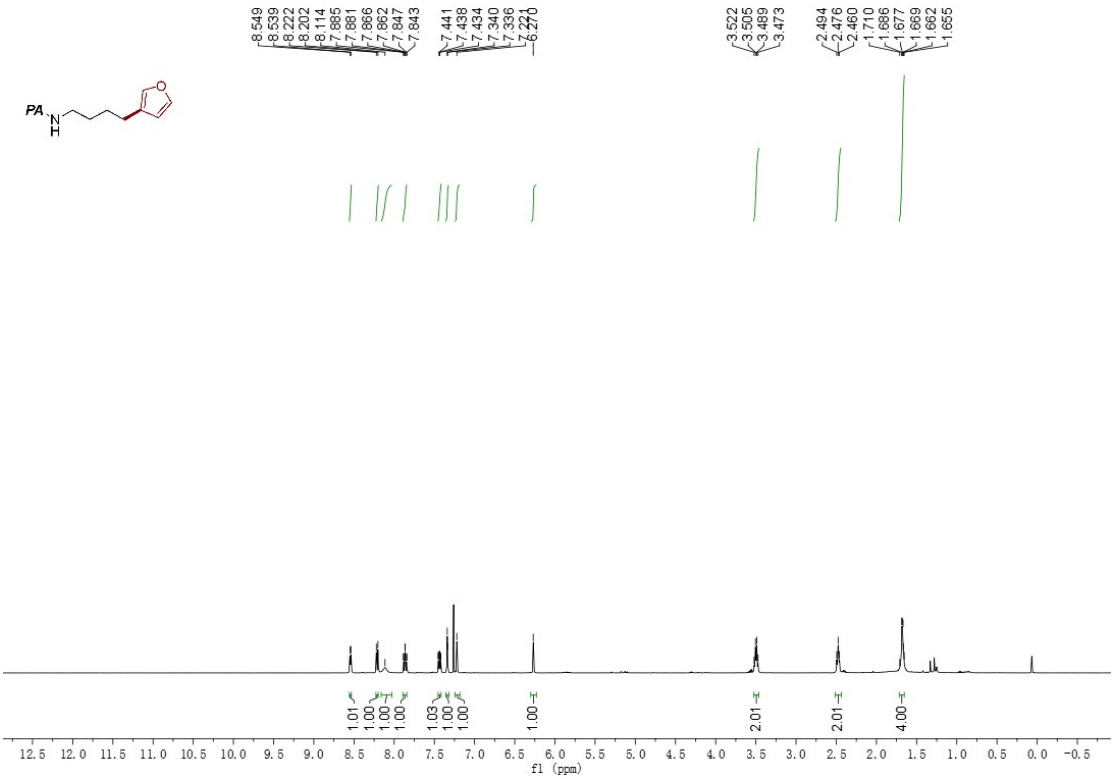
^{1}H NMR (400 MHz, $CDCl_3$) of **3t**



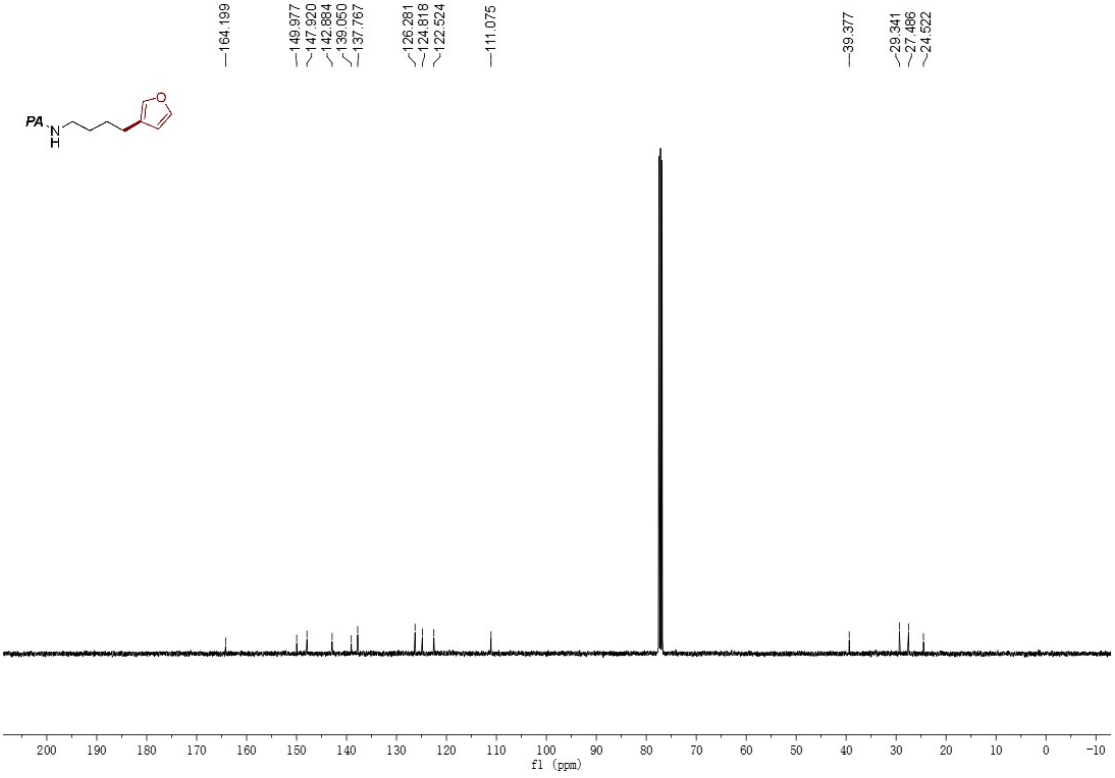
^{13}C NMR (101 MHz, $CDCl_3$) of **3t**



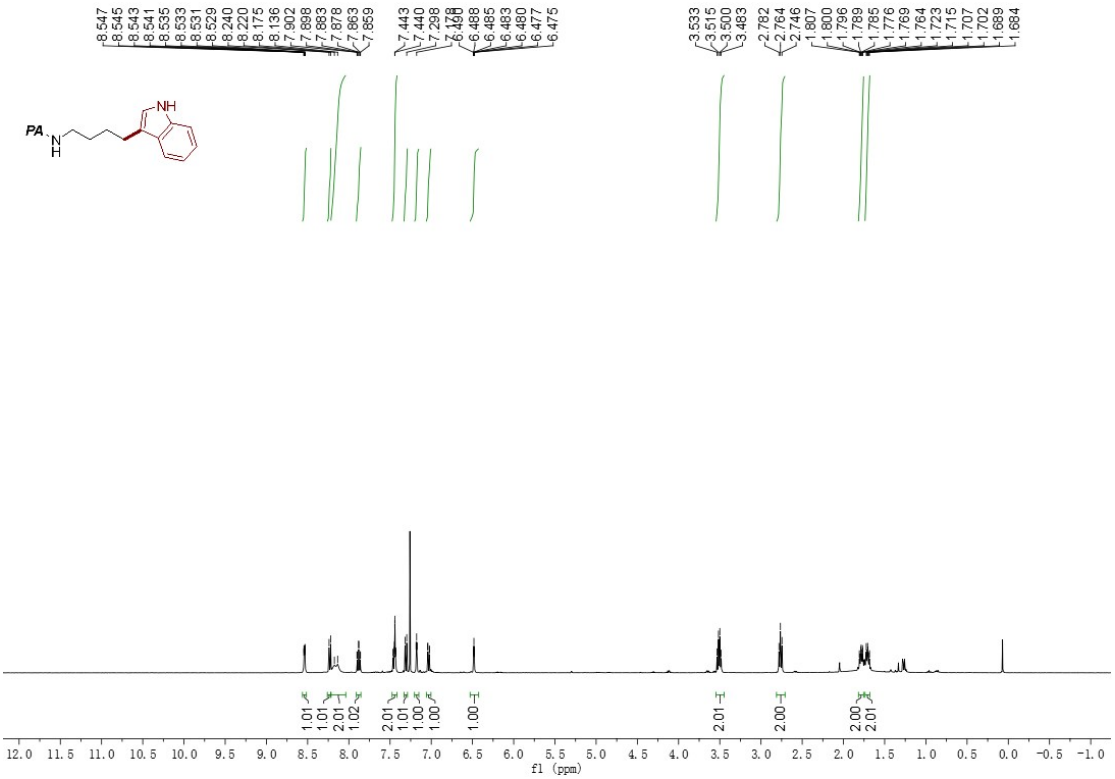
^{1}H NMR (400 MHz, $CDCl_3$) of **3u**



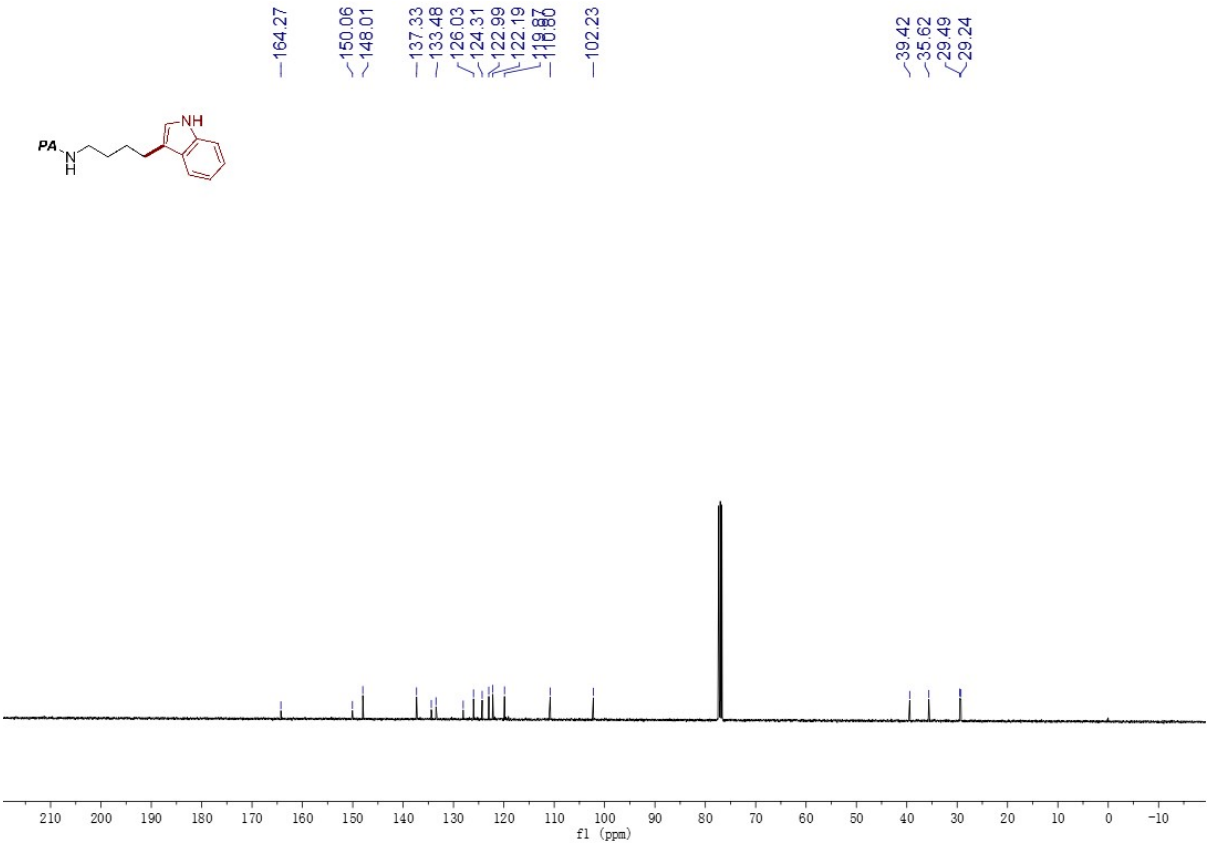
^{13}C NMR (101 MHz, $CDCl_3$) of **3u**



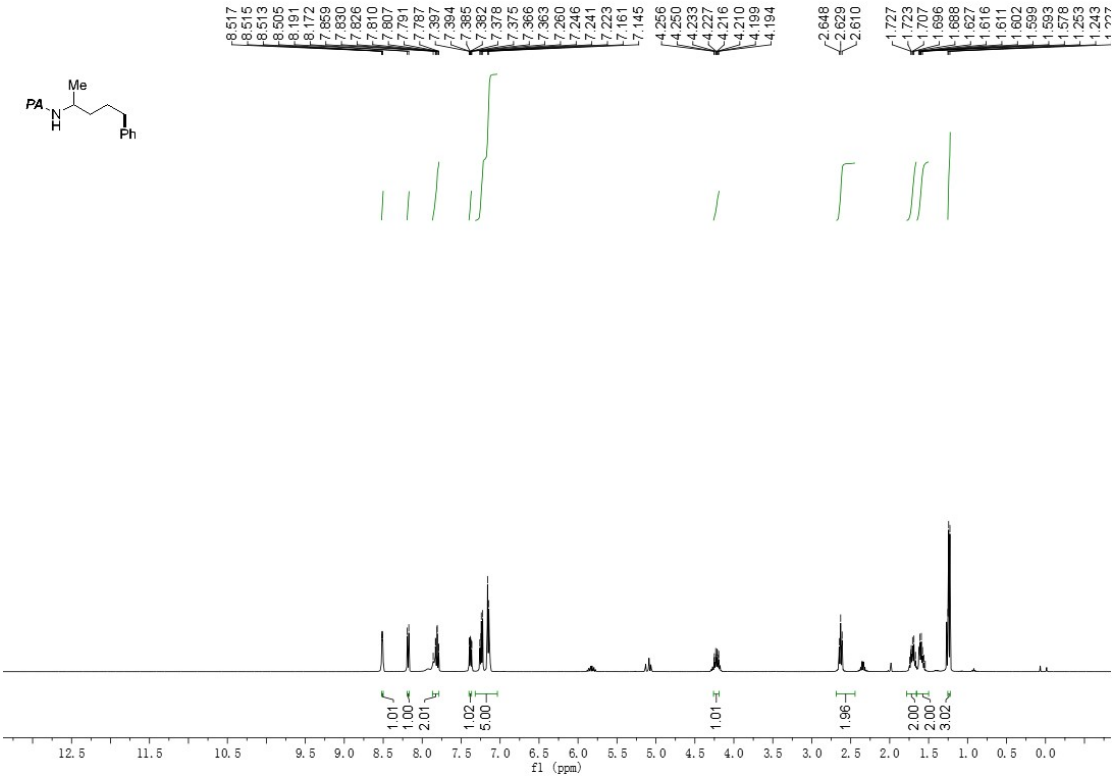
^{1}H NMR (400 MHz, $CDCl_3$) of **3v**



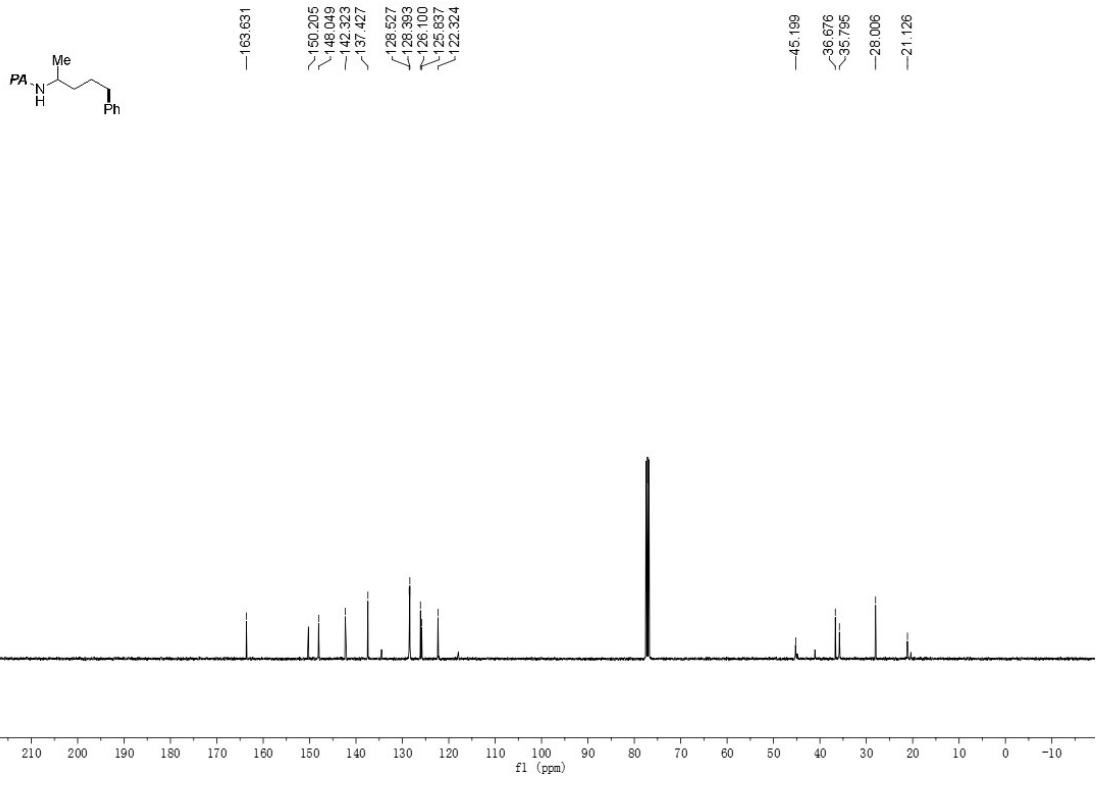
^{13}C NMR (101 MHz, $CDCl_3$) of **3v**



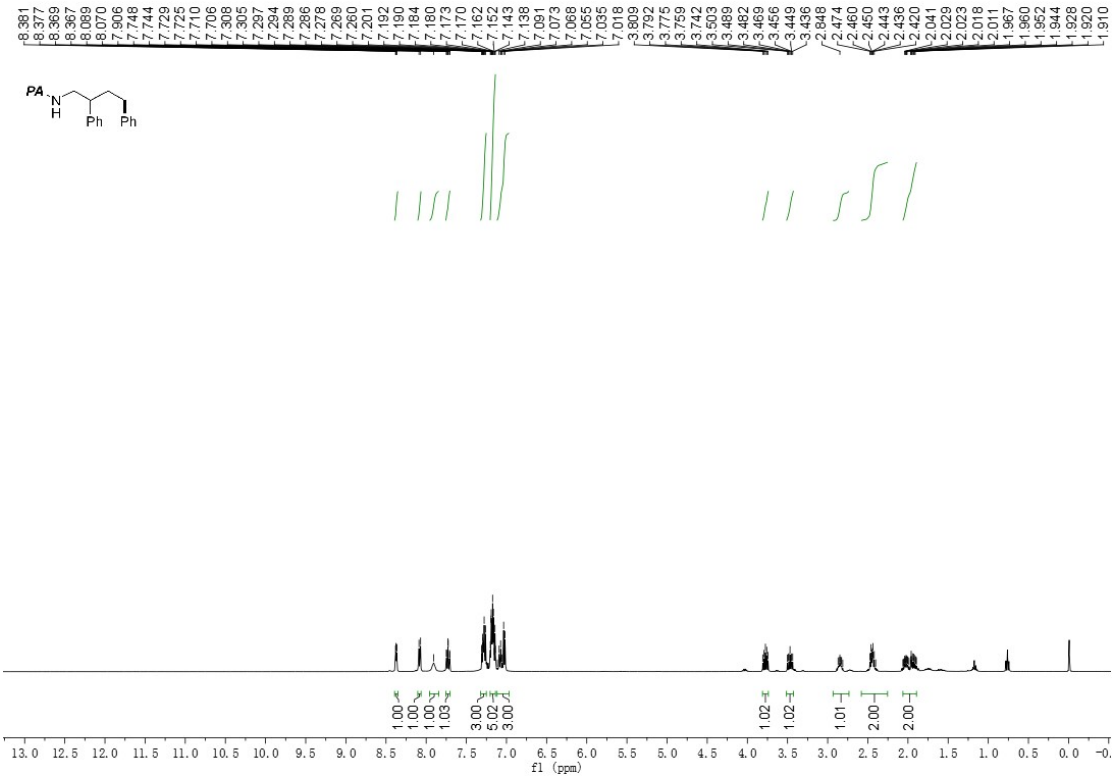
^{1}H NMR (400 MHz, $CDCl_3$) of **3w**



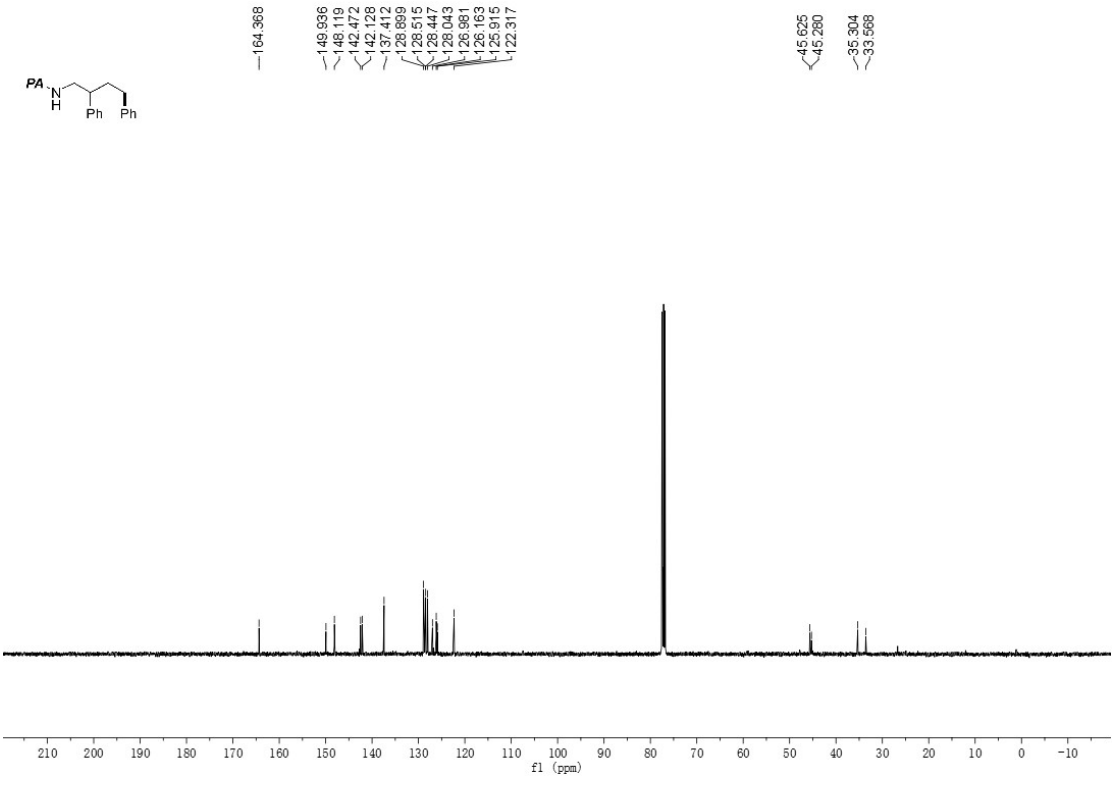
^{13}C NMR (101 MHz, $CDCl_3$) of **3w**



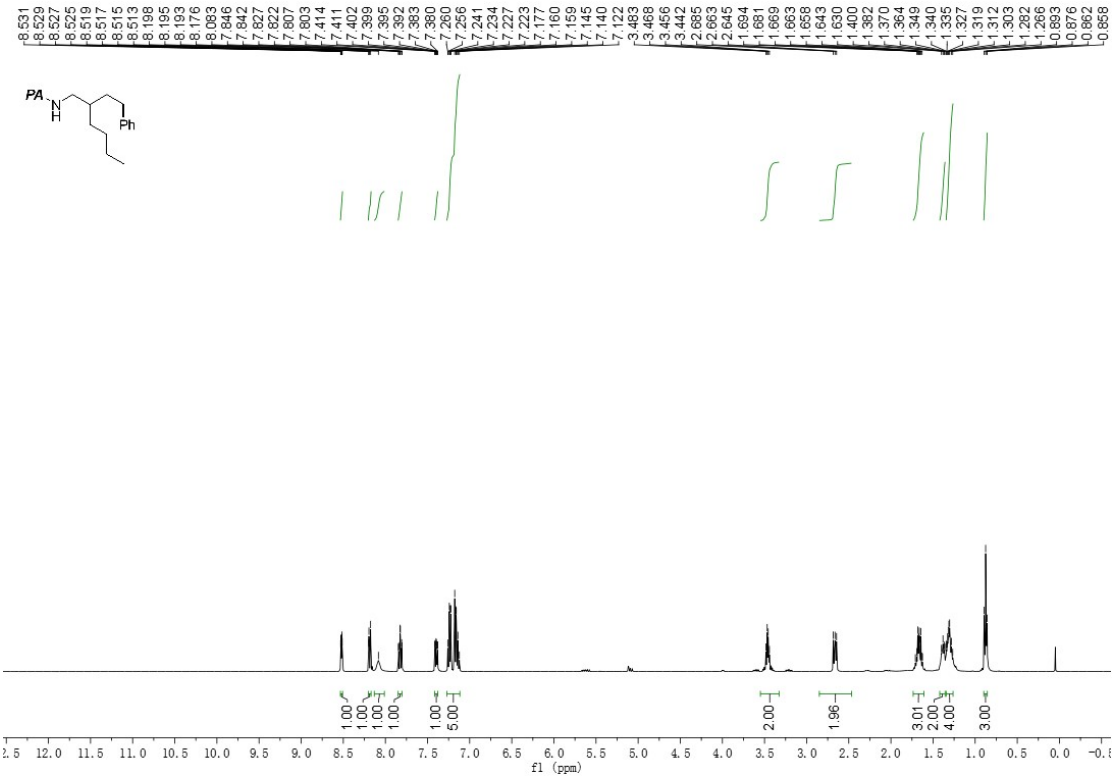
^{1}H NMR (400 MHz, $CDCl_3$) of **3x**



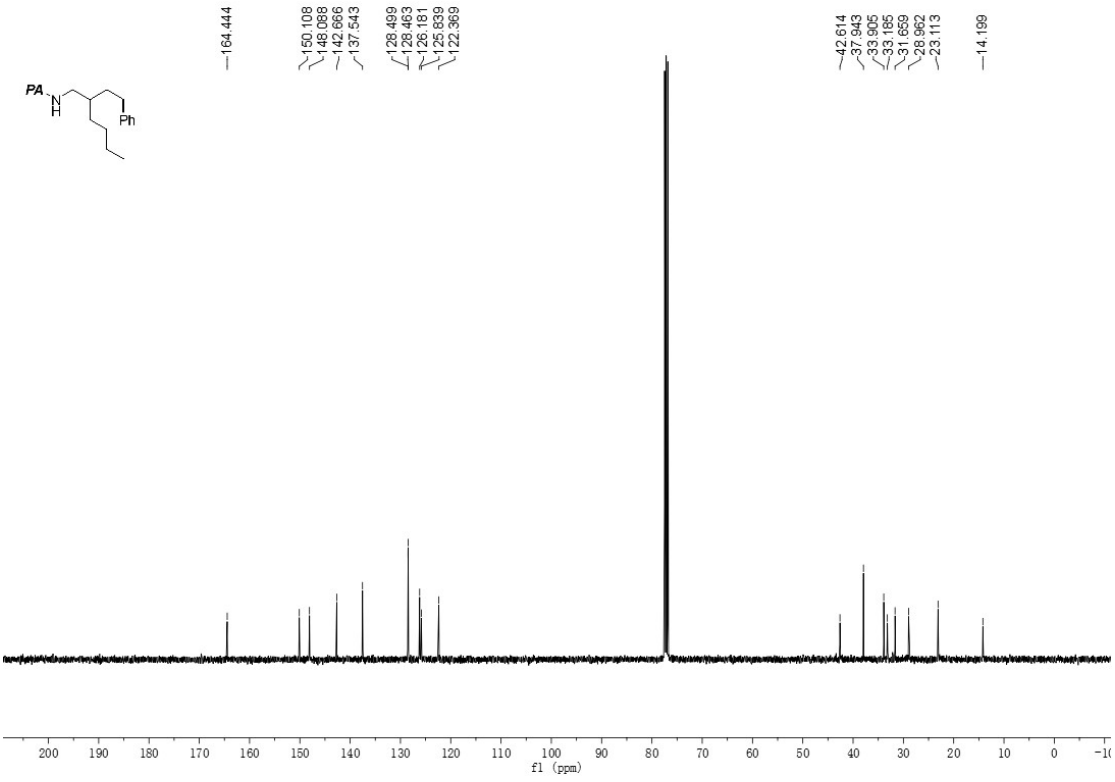
^{13}C NMR (101 MHz, $CDCl_3$) of **3x**



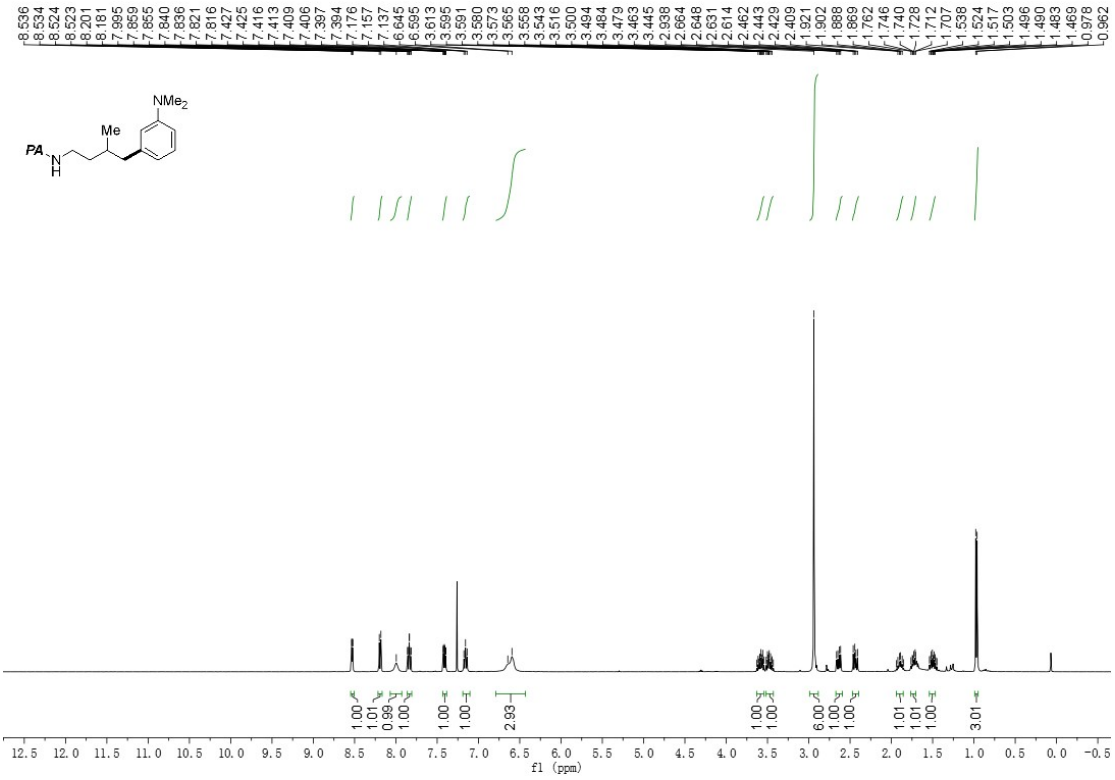
^{1}H NMR (400 MHz, CDCl3) of **3y**



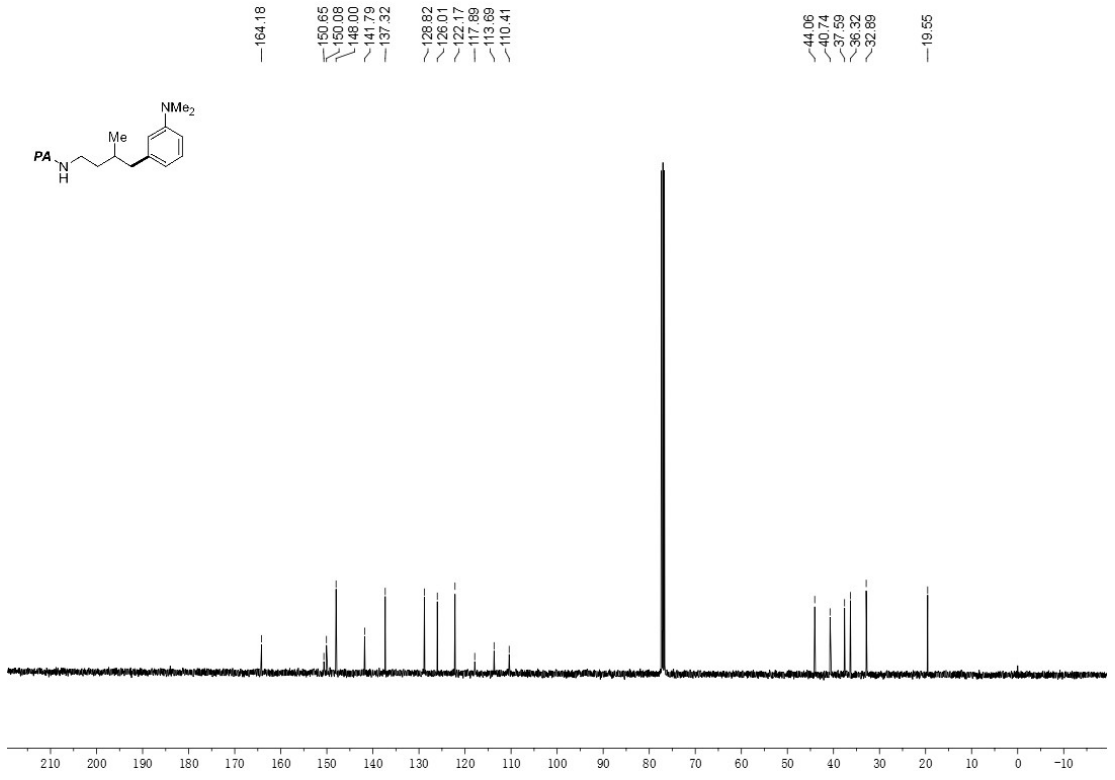
^{13}C NMR (101 MHz, $CDCl_3$) of **3y**



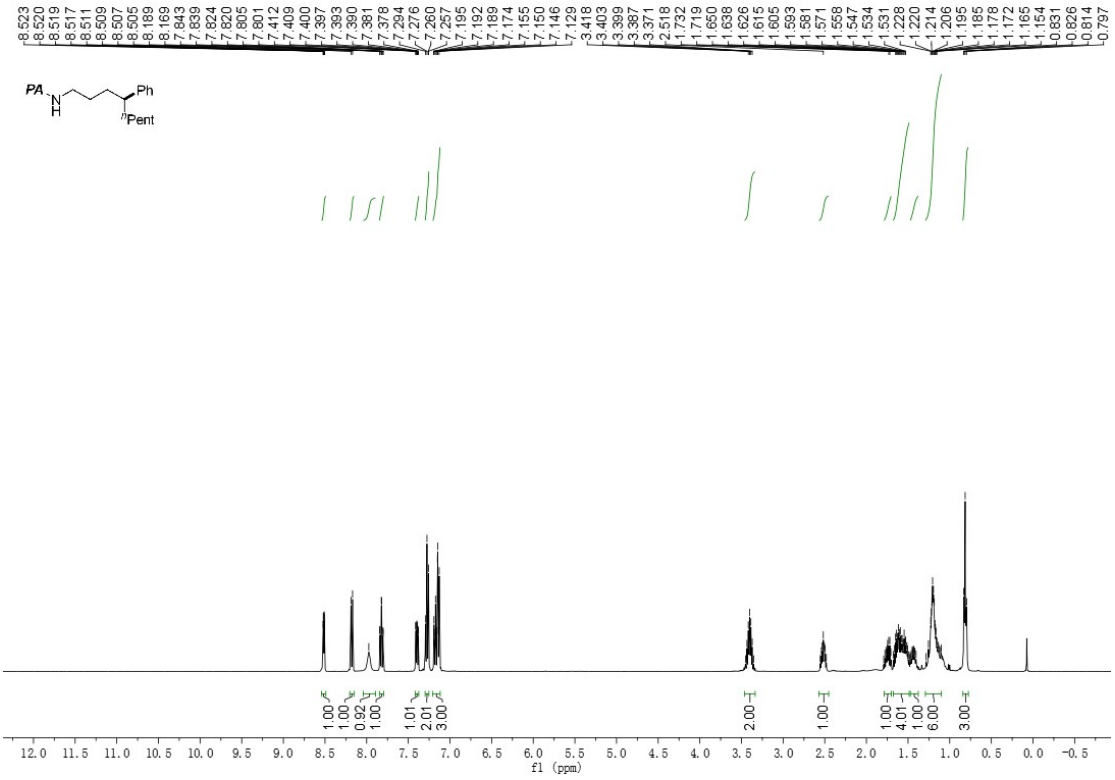
^{1}H NMR (400 MHz, $CDCl_3$) of **3z**



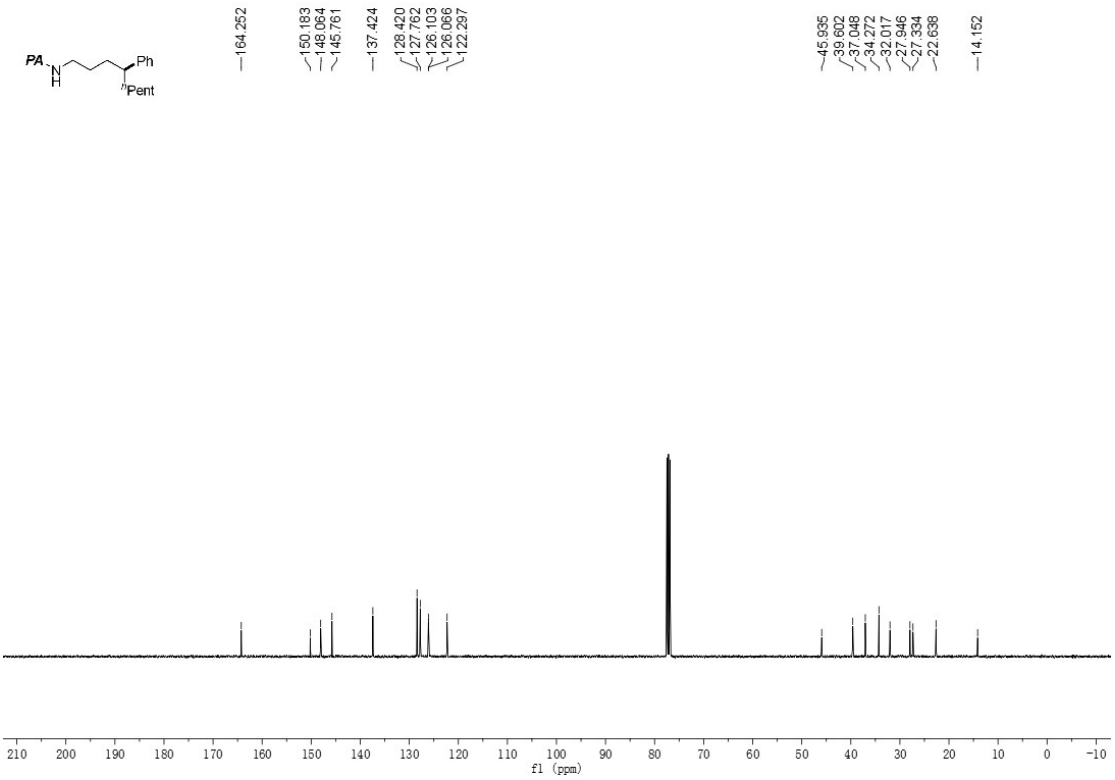
^{13}C NMR (101 MHz, $CDCl_3$) of **3z**



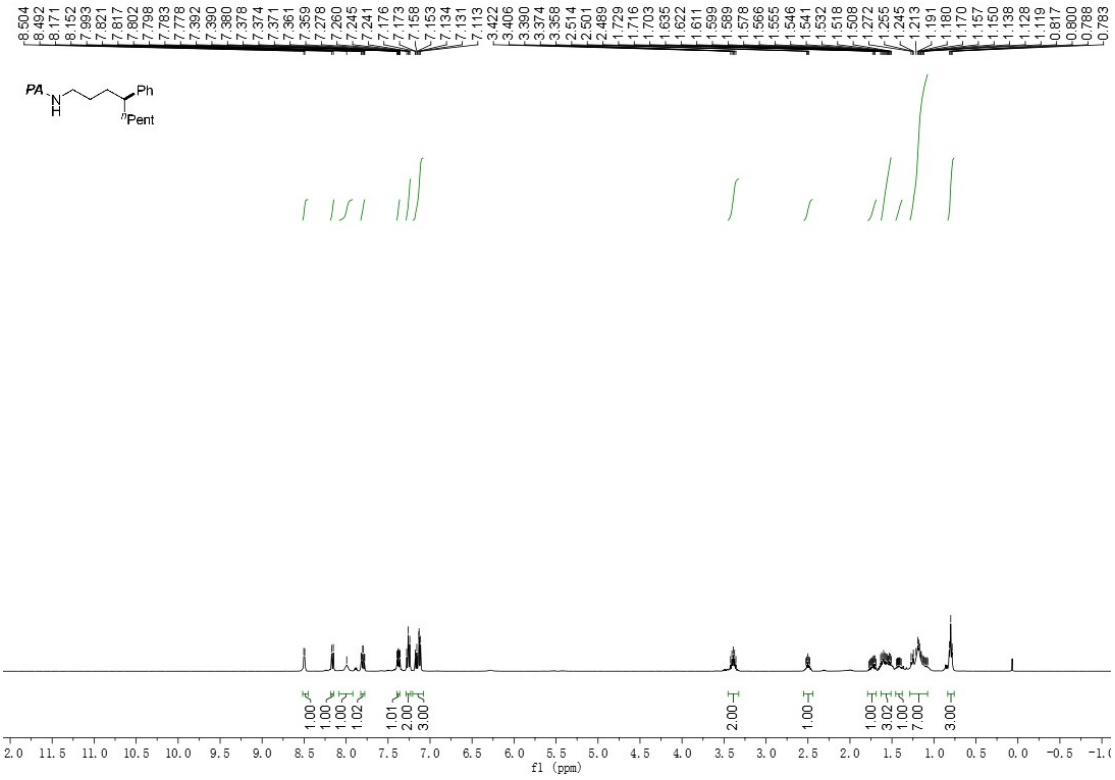
^{1}H NMR (400 MHz, $CDCl_3$) of **3aa (from *Z*)**



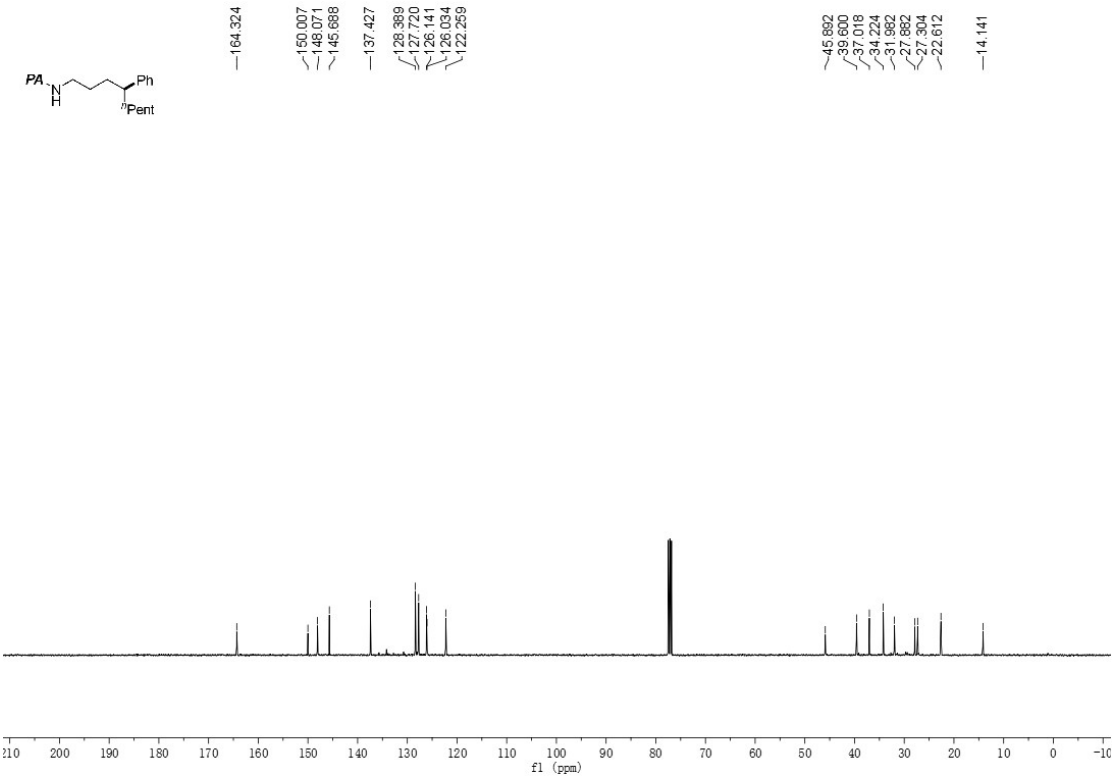
^{13}C NMR (101 MHz, $CDCl_3$) of **3aa (from *Z*)**



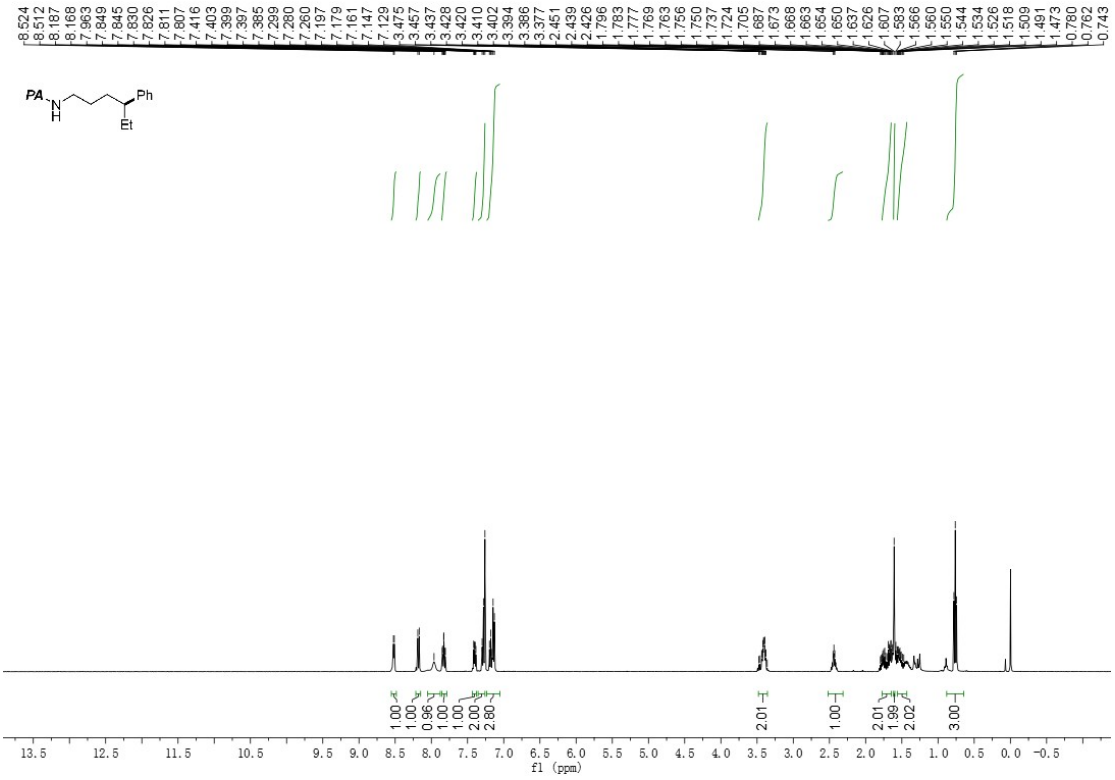
^{1}H NMR (400 MHz, $CDCl_3$) of **3ab (from *E*)**



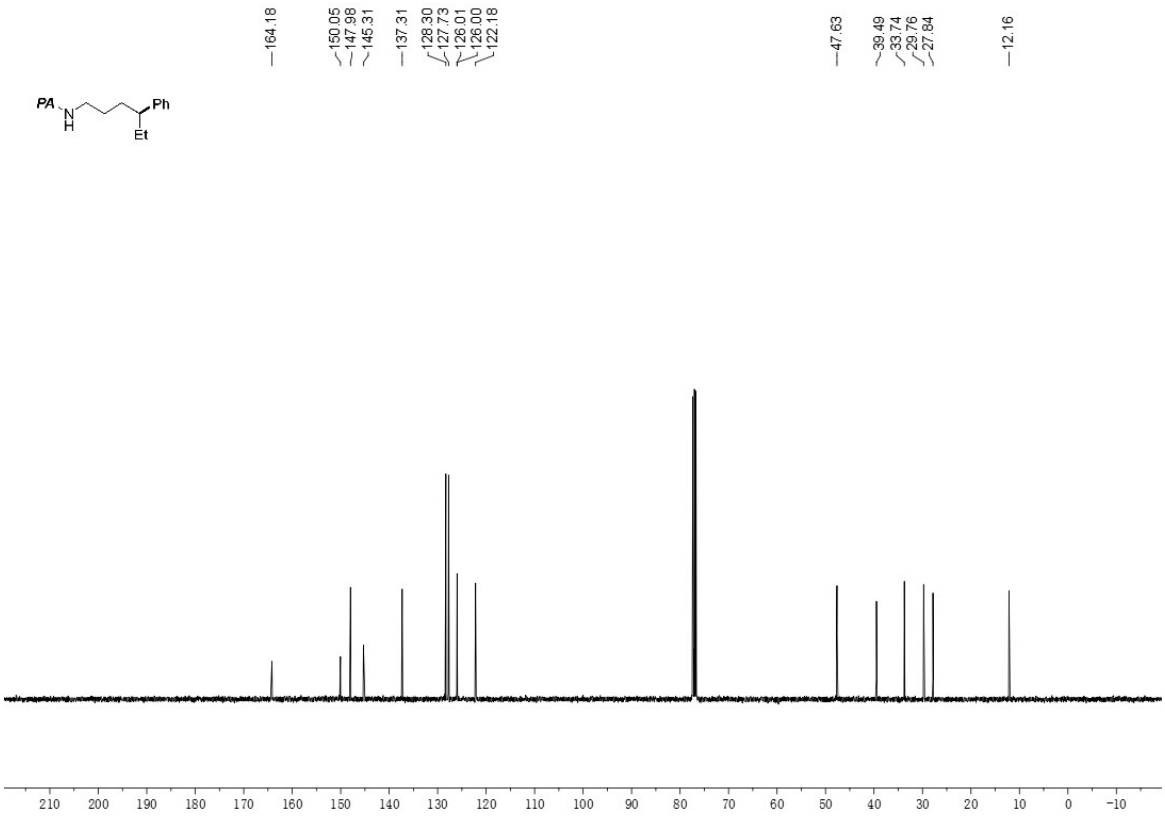
^{13}C NMR (101 MHz, $CDCl_3$) of **3ab (from *E*)**



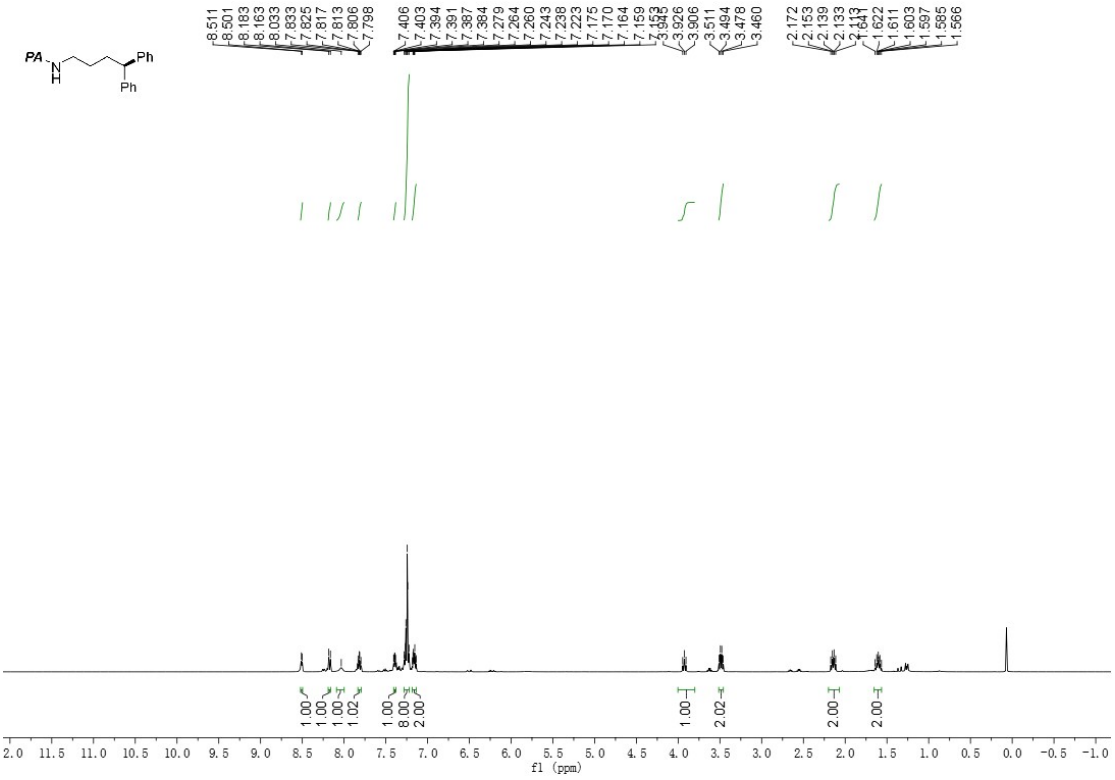
^{1}H NMR (400 MHz, $CDCl_3$) of **3ac (from *Z*)**



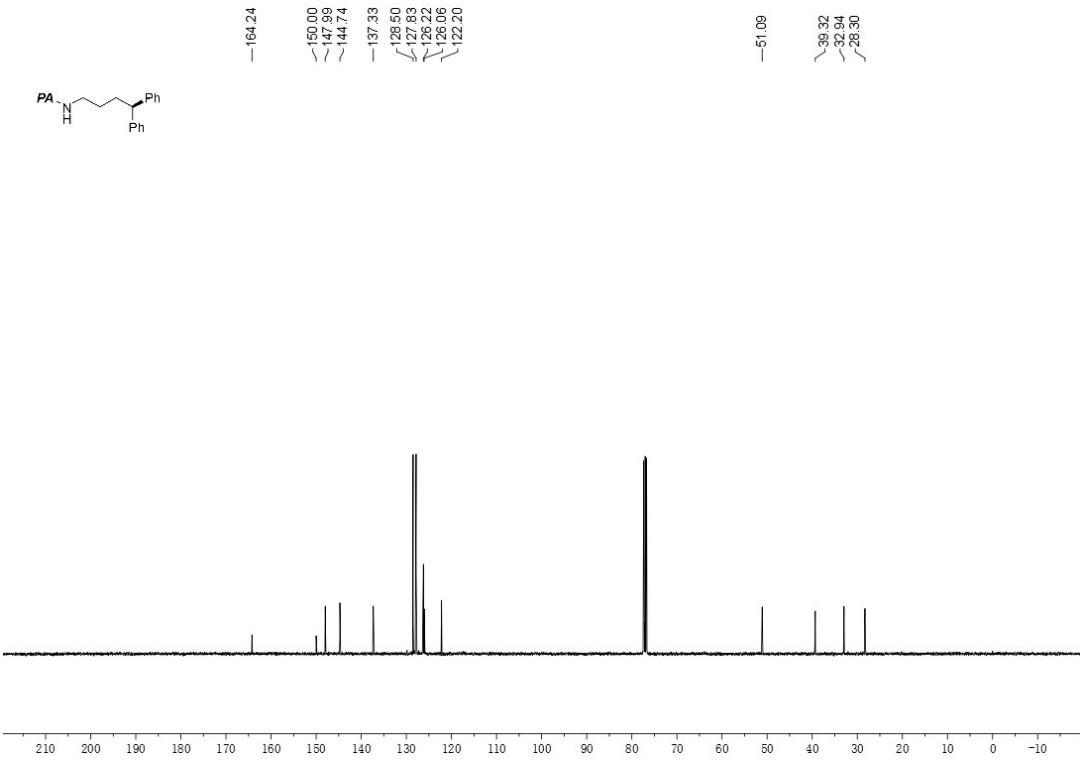
^{13}C NMR (101 MHz, $CDCl_3$) of **3ac (from *Z*)**



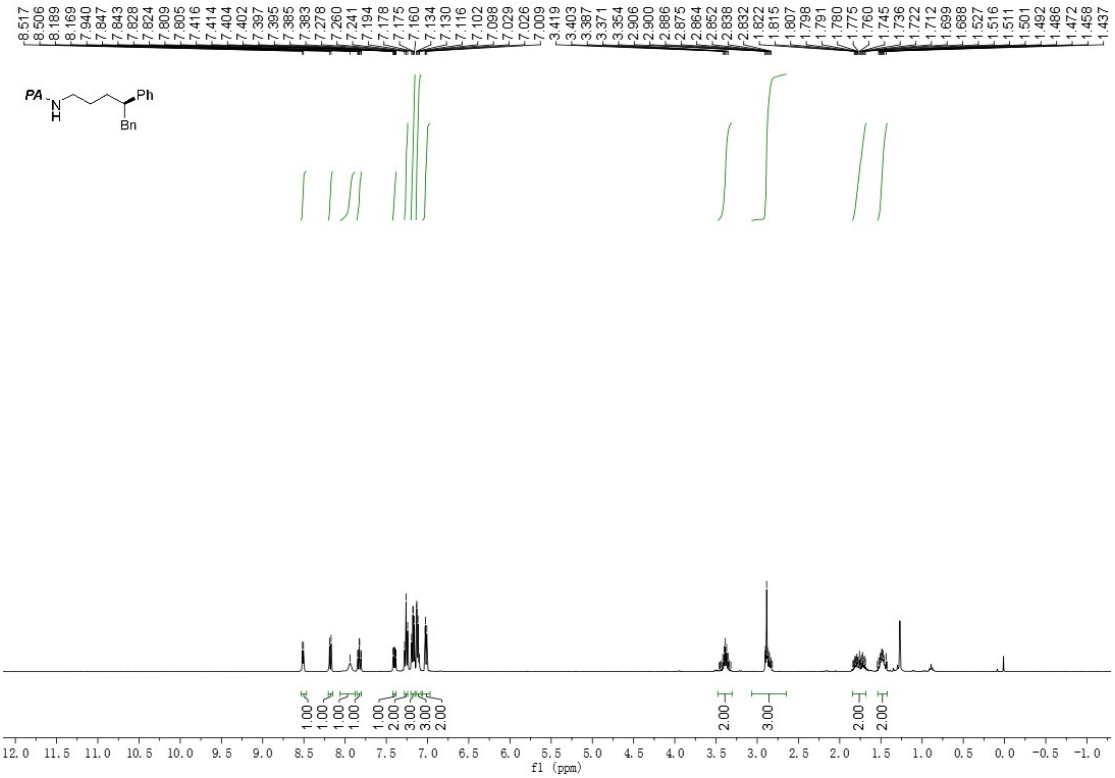
^{1}H NMR (400 MHz, $CDCl_3$) of **3ad (from *E*)**



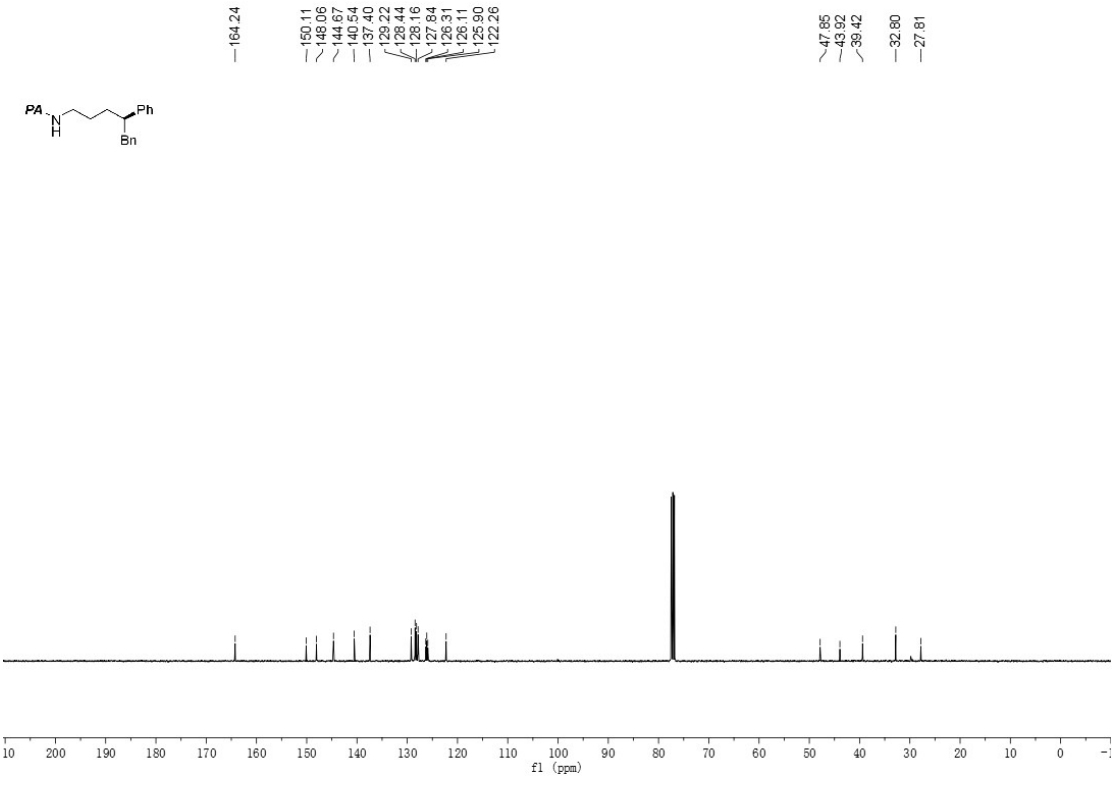
^{13}C NMR (101 MHz, $CDCl_3$) of **3ad (from *E*)**



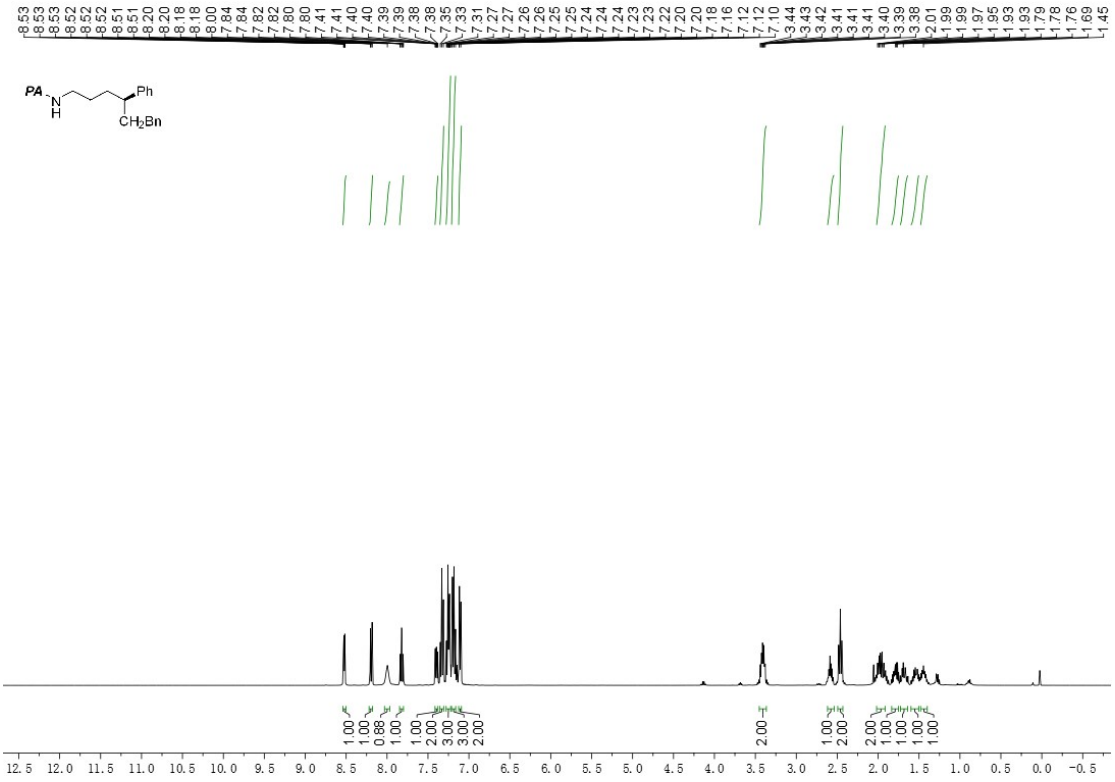
^{1}H NMR (400 MHz, $CDCl_3$) of **3ae (from *E*)**



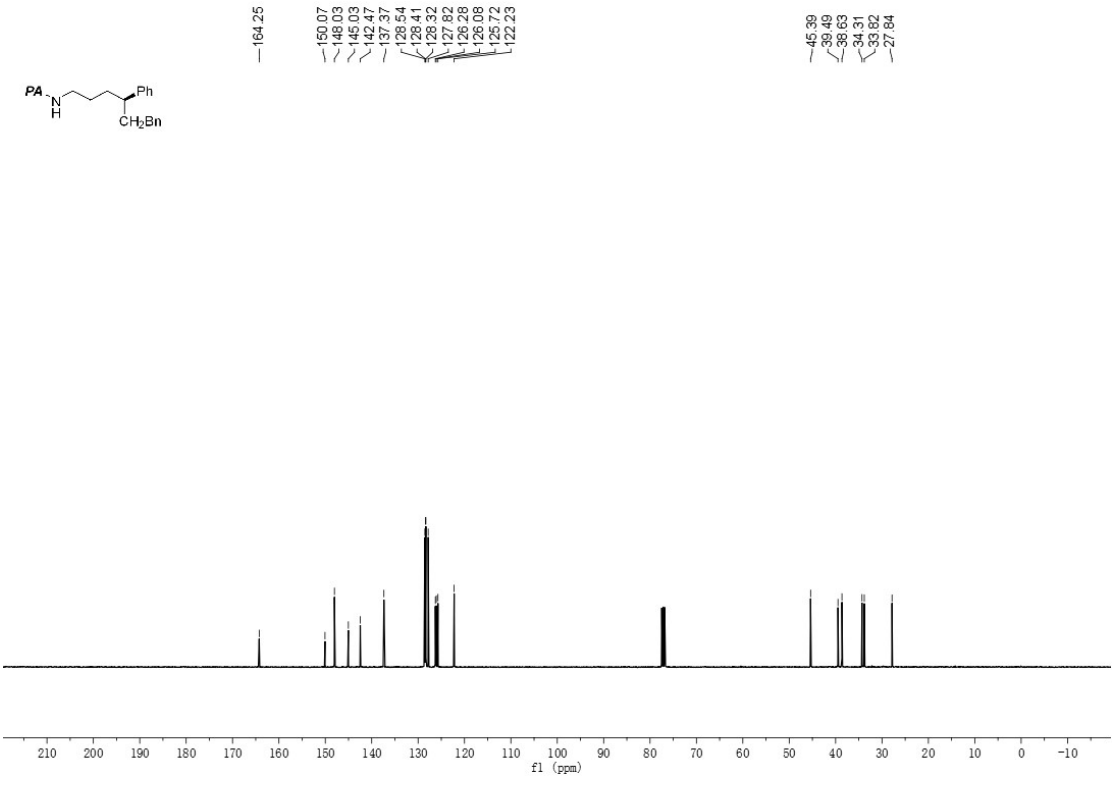
^{13}C NMR (101 MHz, $CDCl_3$) of **3ae (from *E*)**



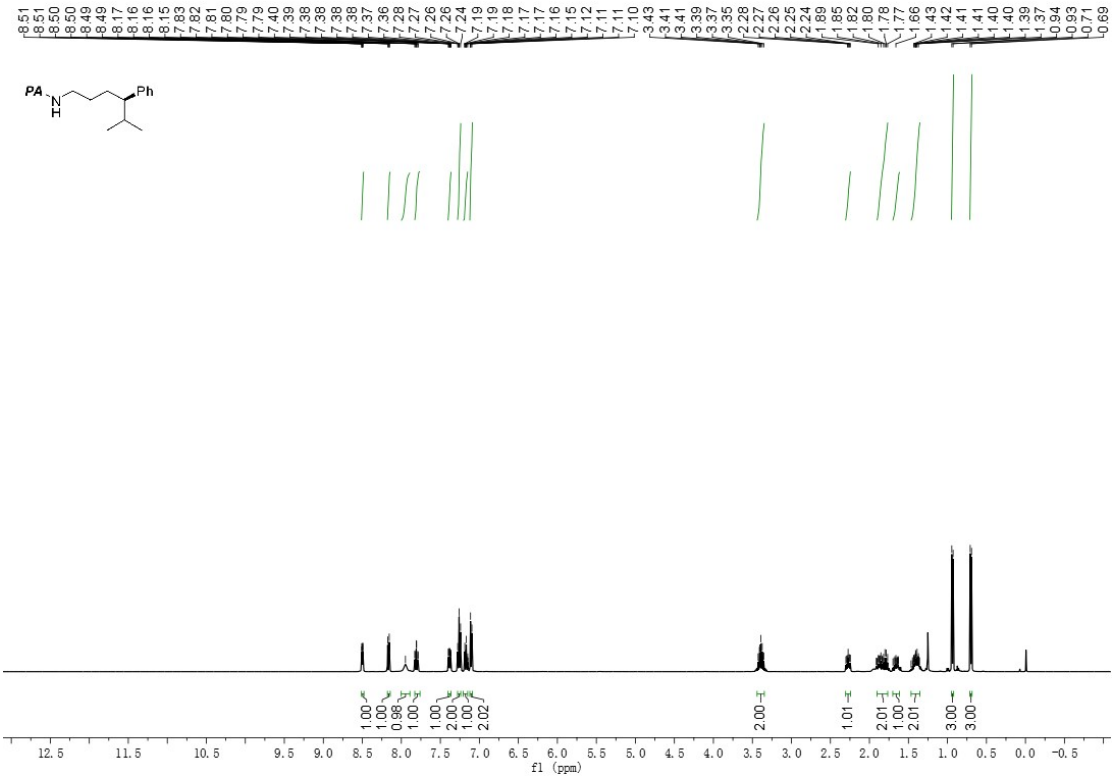
^{1}H NMR (400 MHz, $CDCl_3$) of **3af (from *E*)**



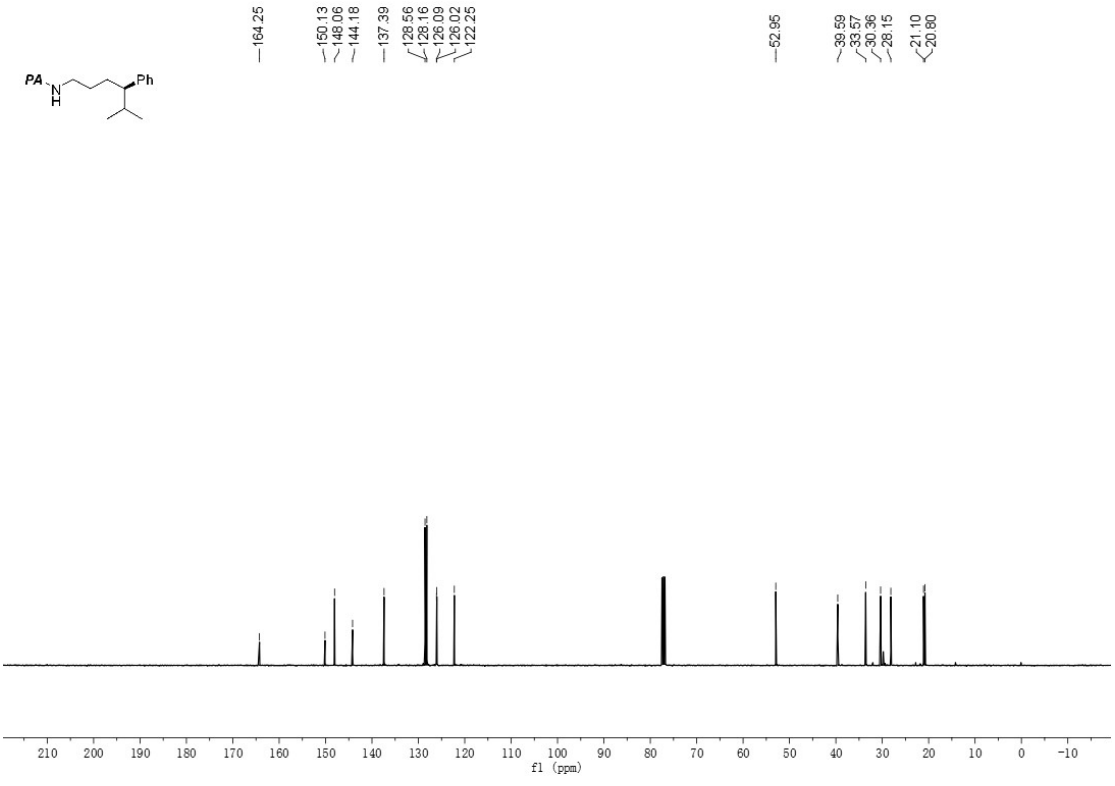
^{13}C NMR (101 MHz, $CDCl_3$) of **3af (from *E*)**



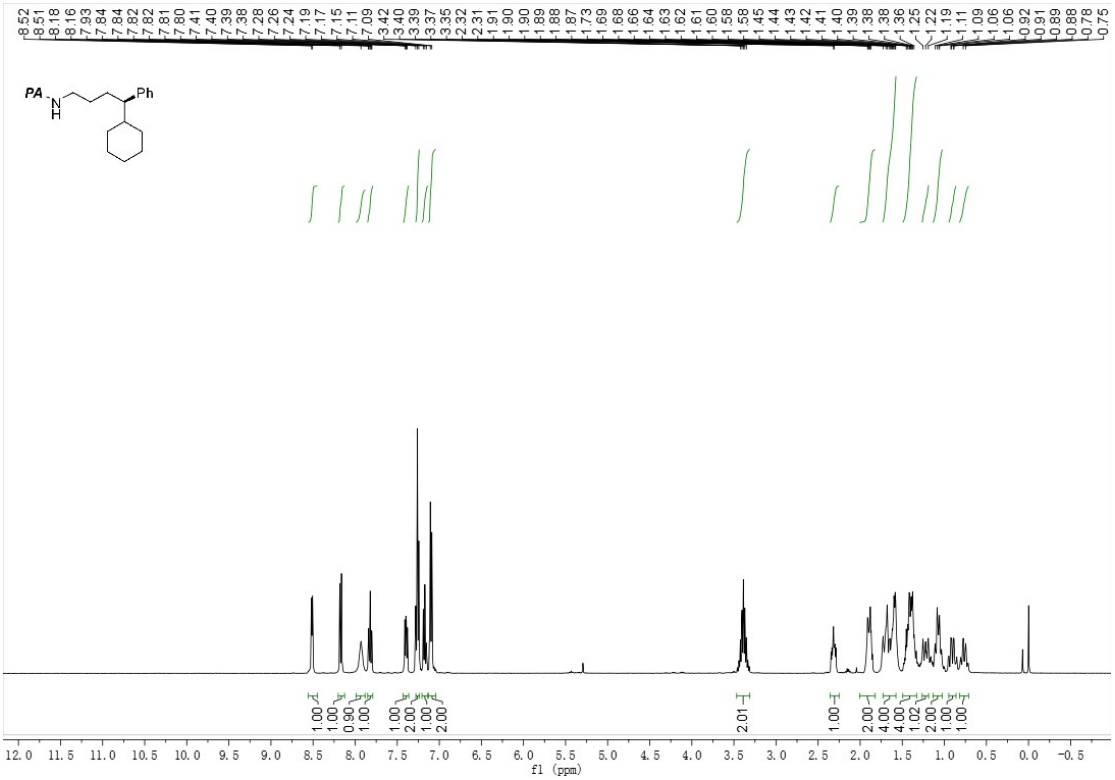
^{1}H NMR (400 MHz, $CDCl_3$) of **3ag (from *E*)**



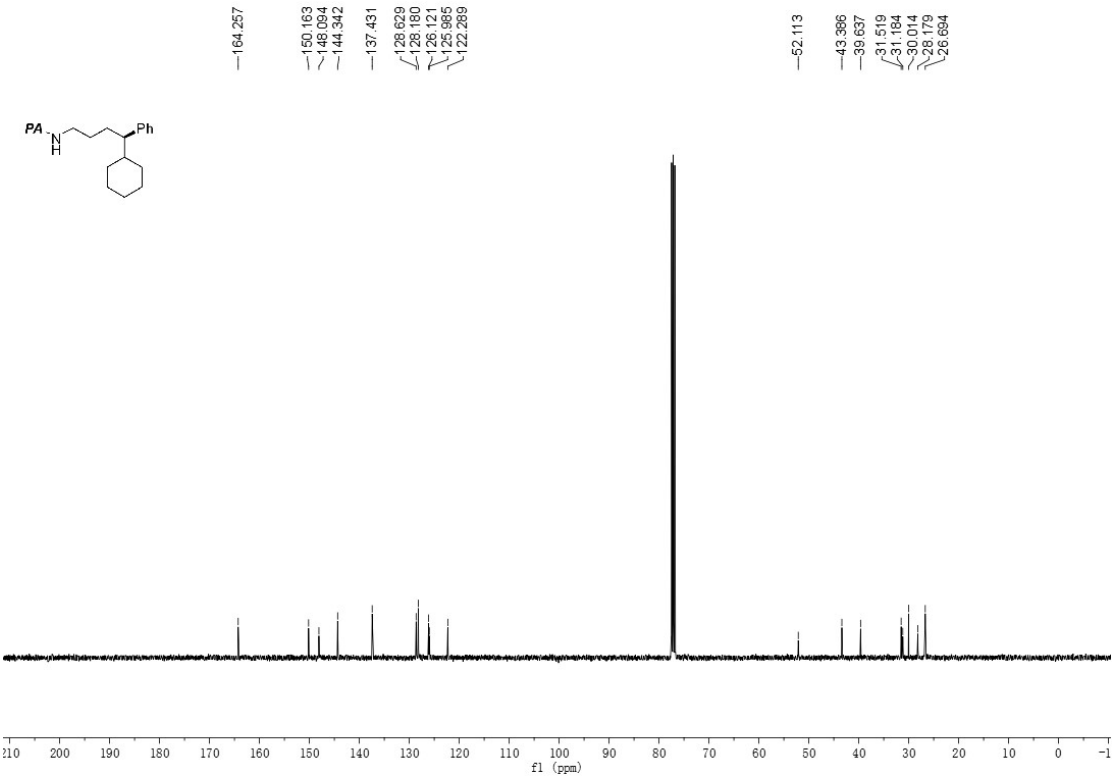
^{13}C NMR (101 MHz, $CDCl_3$) of **3ag (from *E*)**



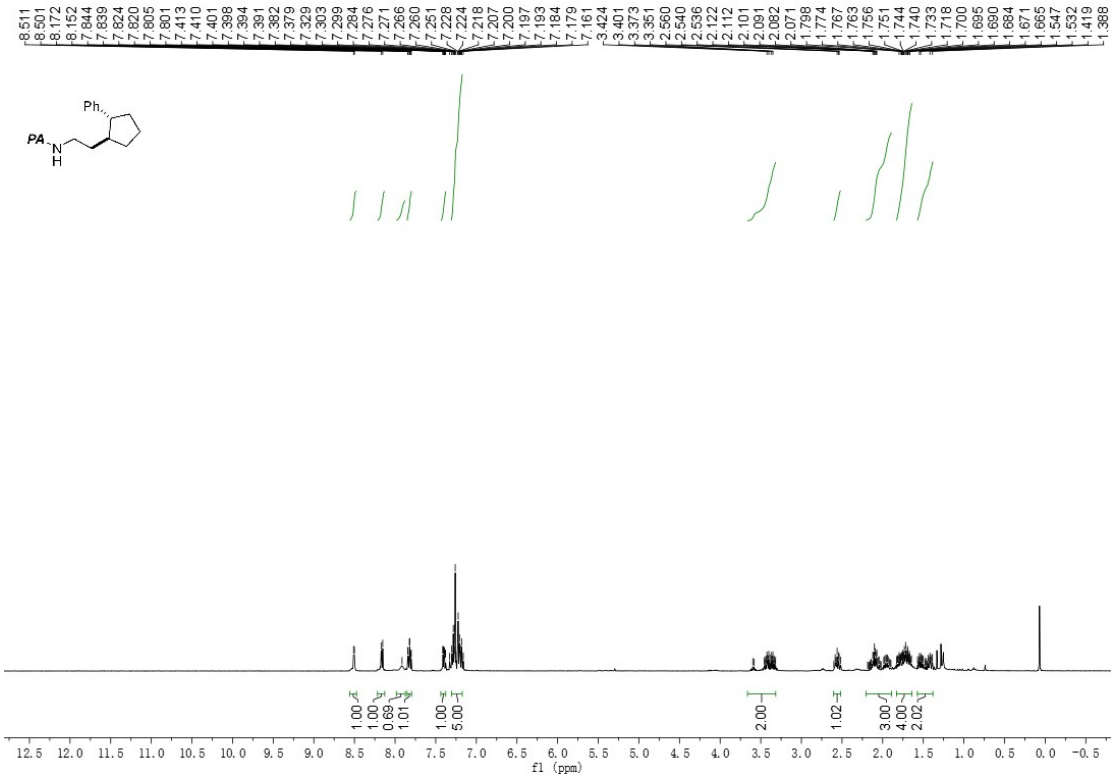
^{1}H NMR (400 MHz, $CDCl_3$) of **3ah (from *E*)**



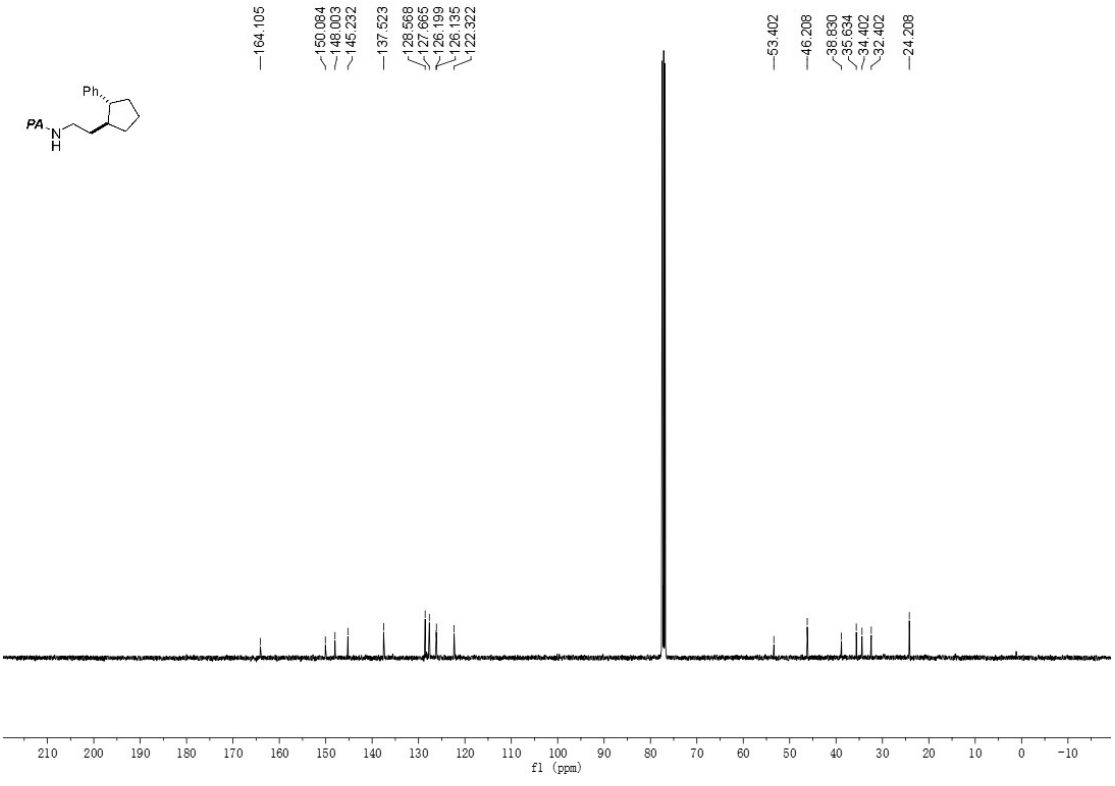
^{13}C NMR (101 MHz, $CDCl_3$) of **3ah (from *E*)**



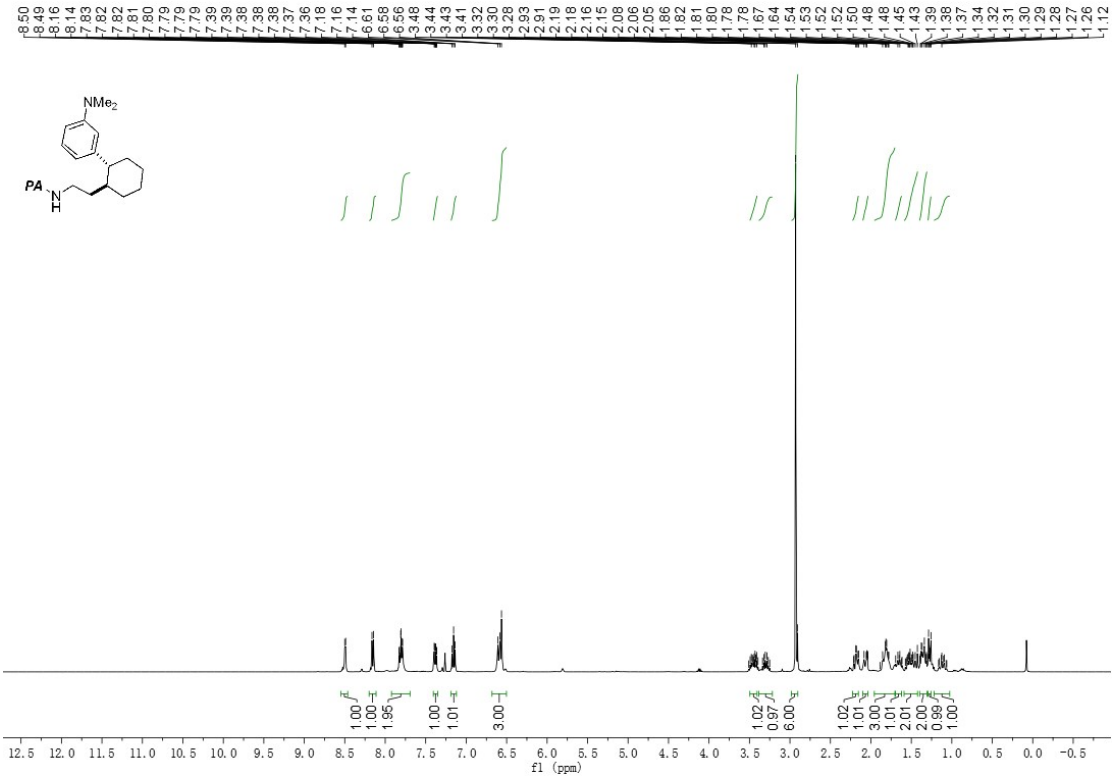
^{1}H NMR (400 MHz, $CDCl_3$) of **3ai**



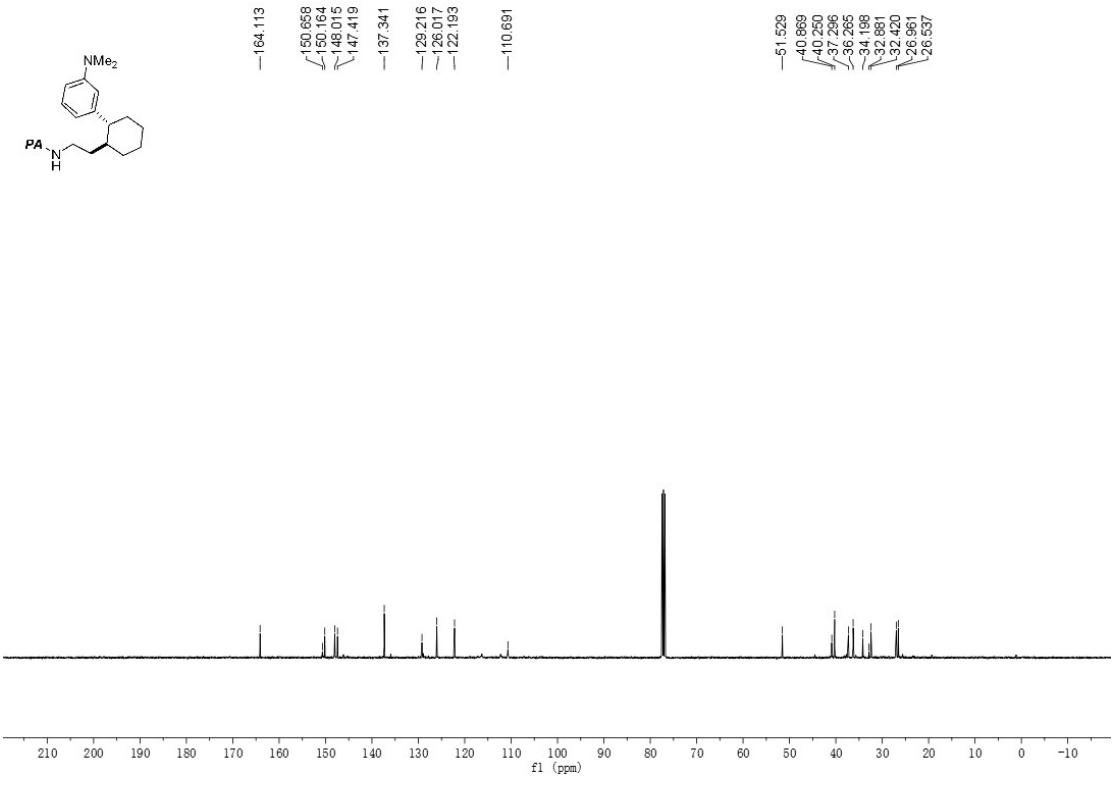
^{13}C NMR (101 MHz, $CDCl_3$) of **3ai**



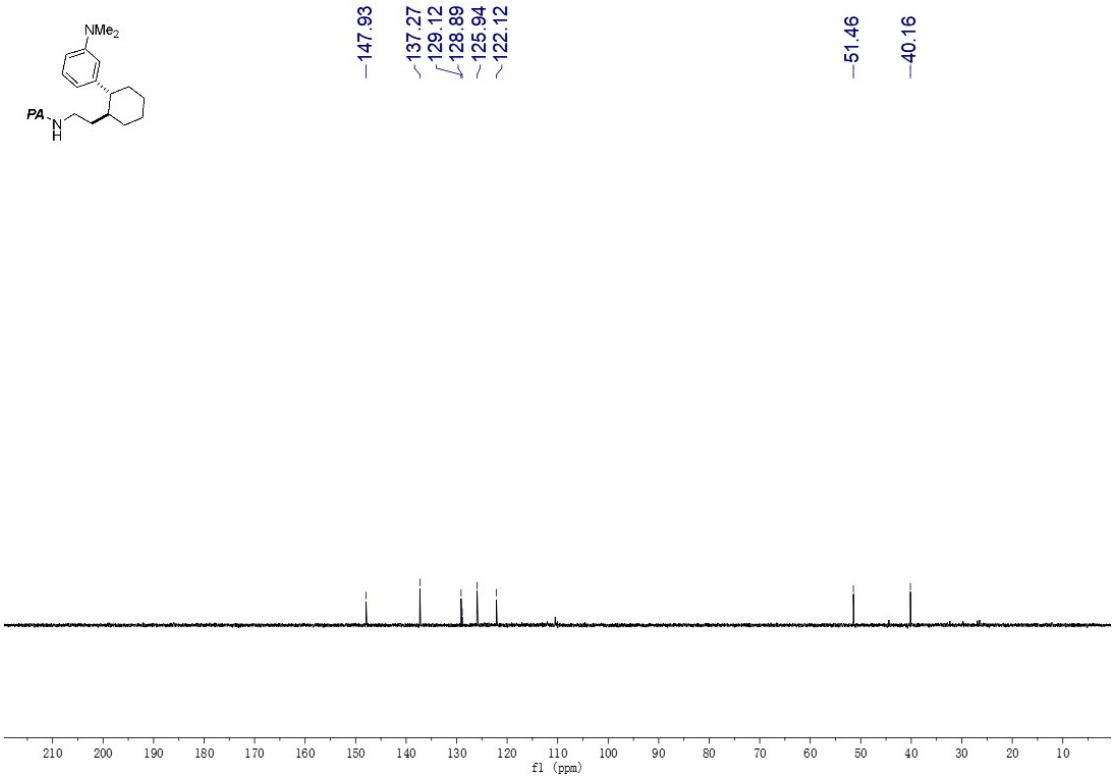
^{1}H NMR (400 MHz, $CDCl_3$) of **3aj**



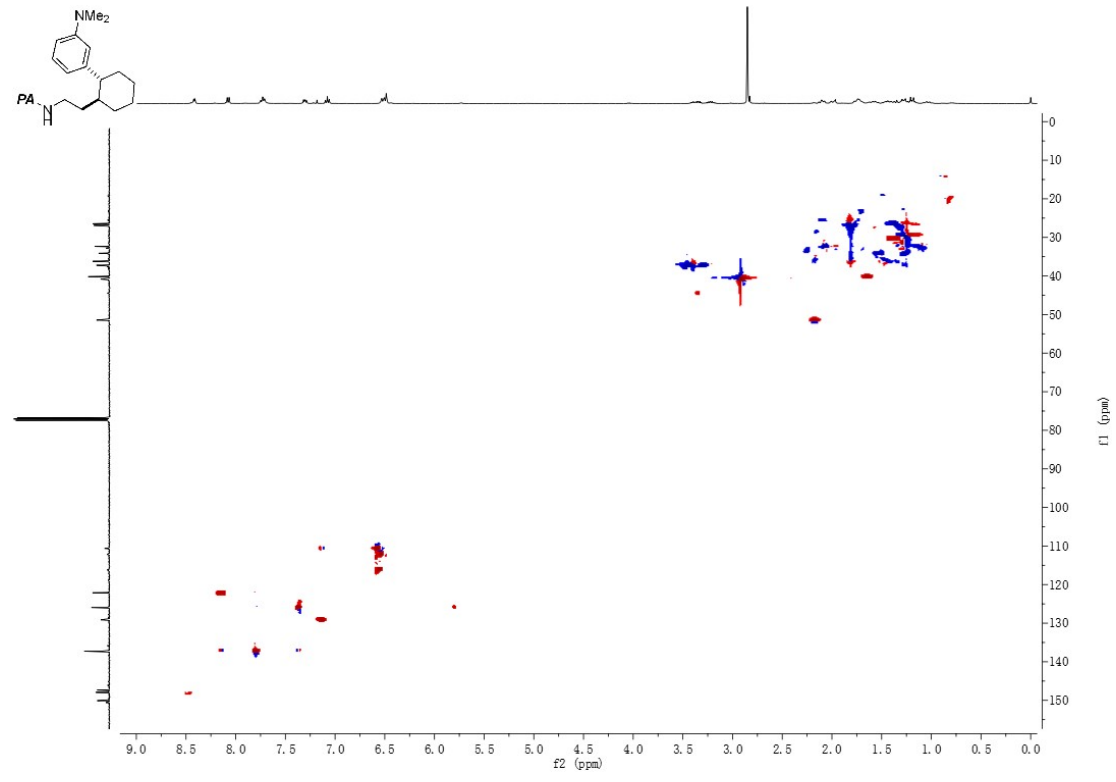
^{13}C NMR (101 MHz, $CDCl_3$) of **3aj**



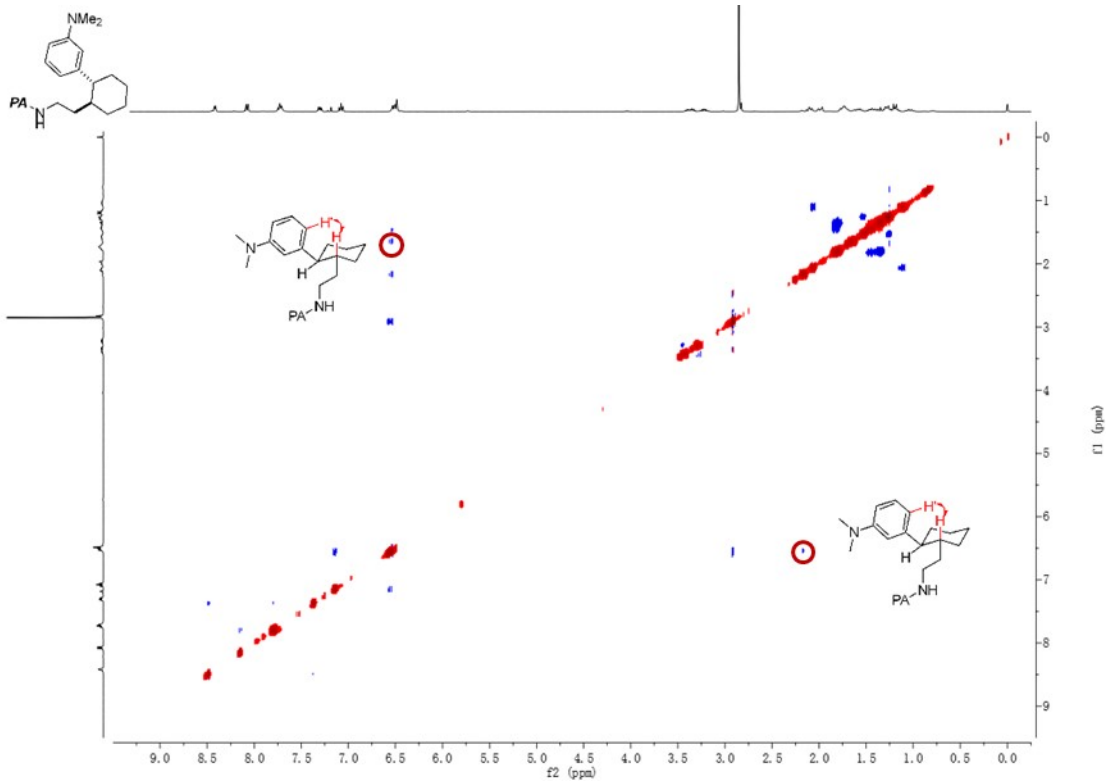
1D ^{13}C DEPT 90 of **3aj**



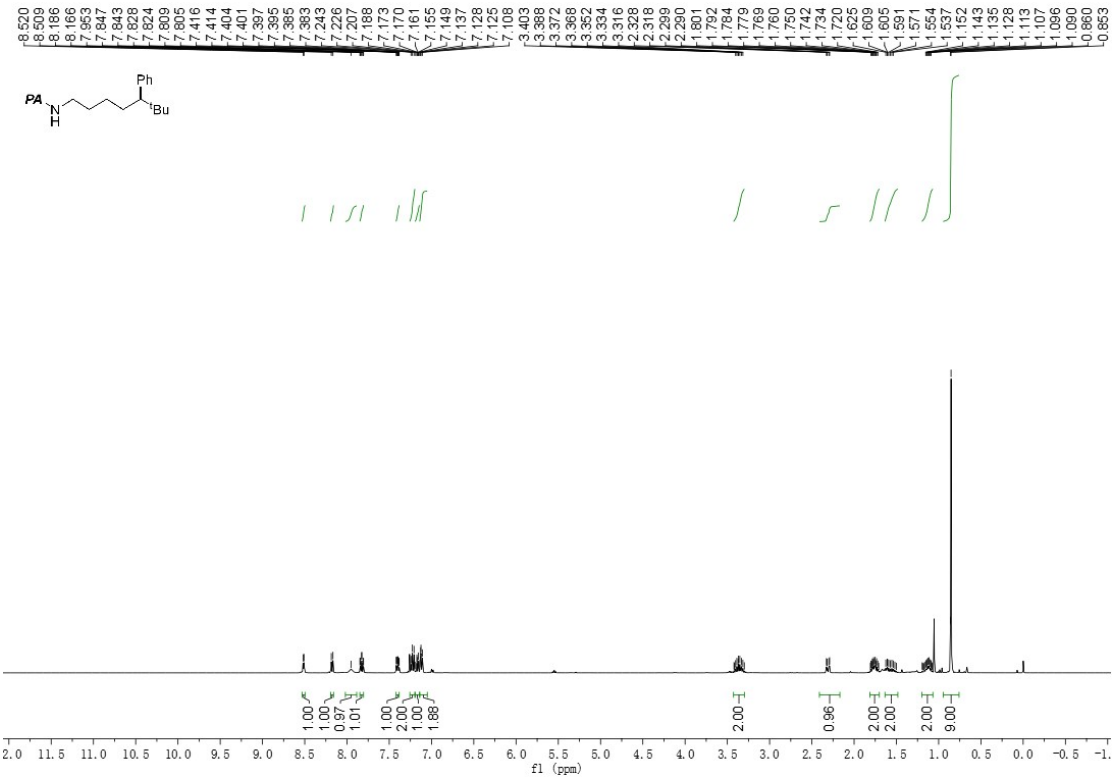
HSQC of **3aj**



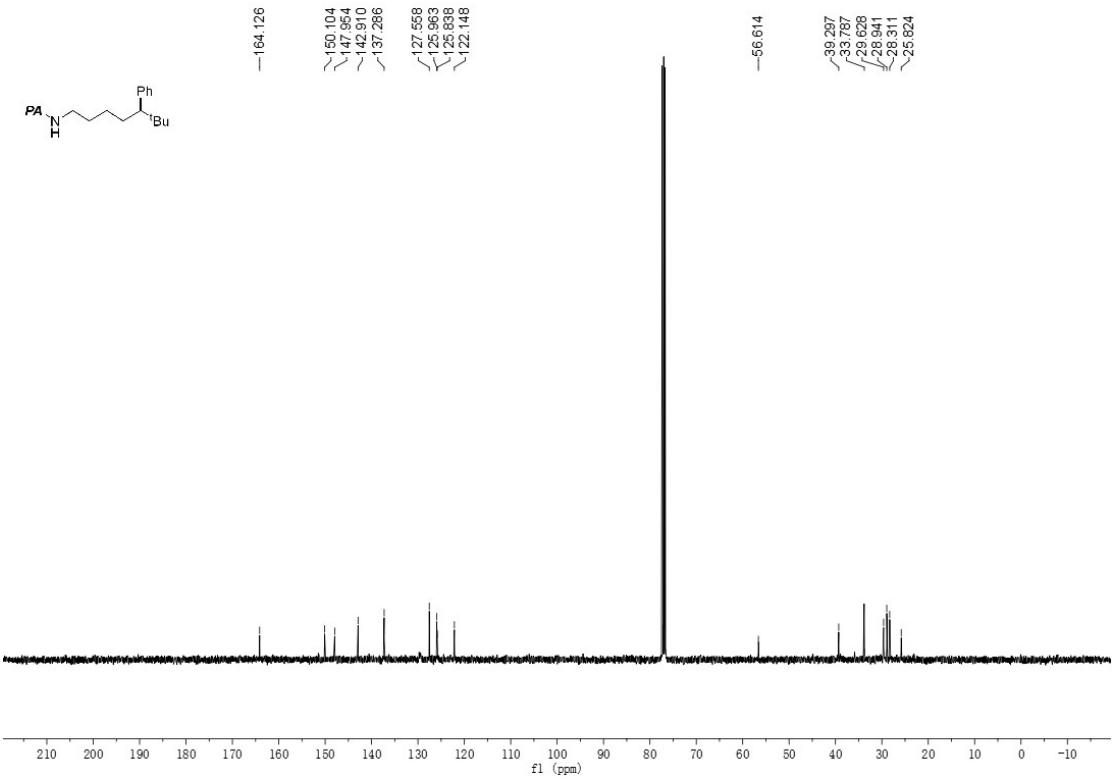
NOE of **3aj**



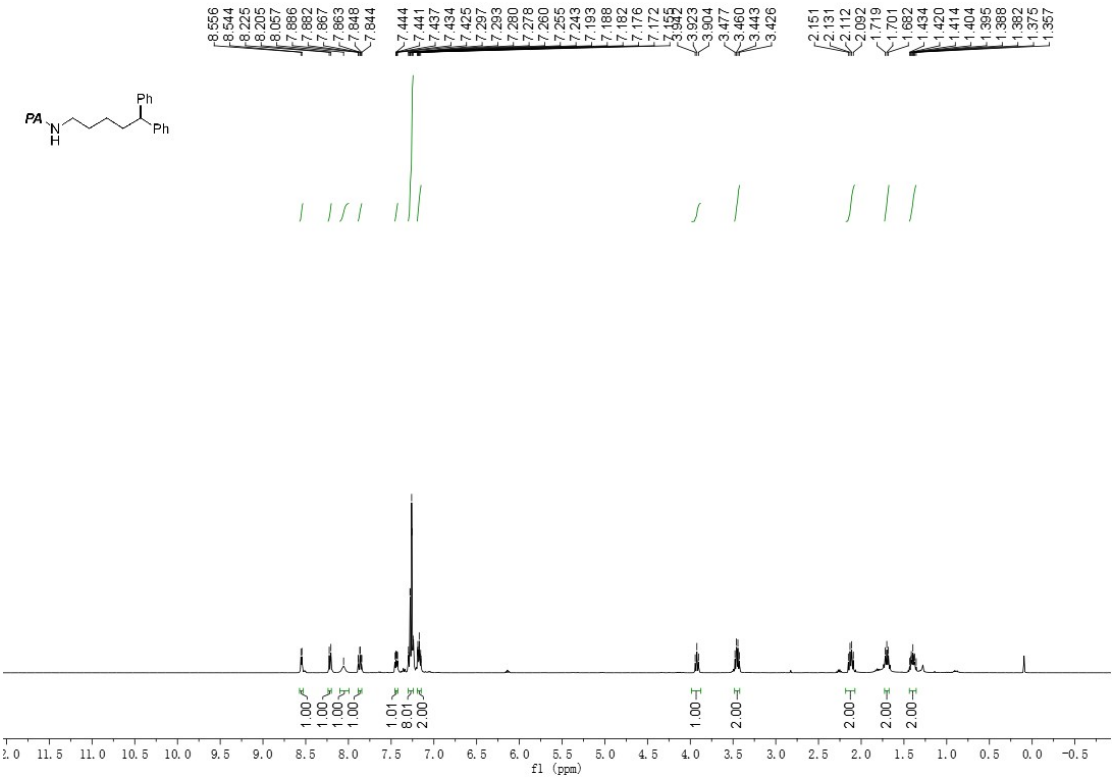
^{1}H NMR (400 MHz, $CDCl_3$) of **3ak**



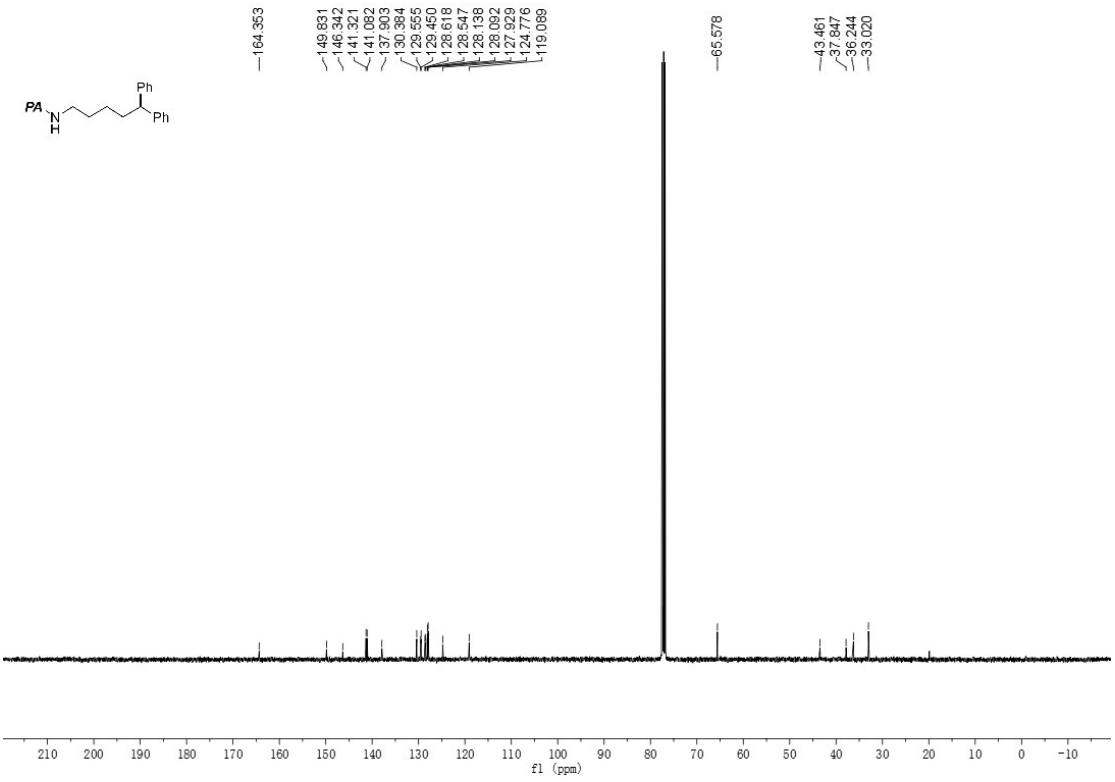
^{13}C NMR (101 MHz, $CDCl_3$) of **3ak**



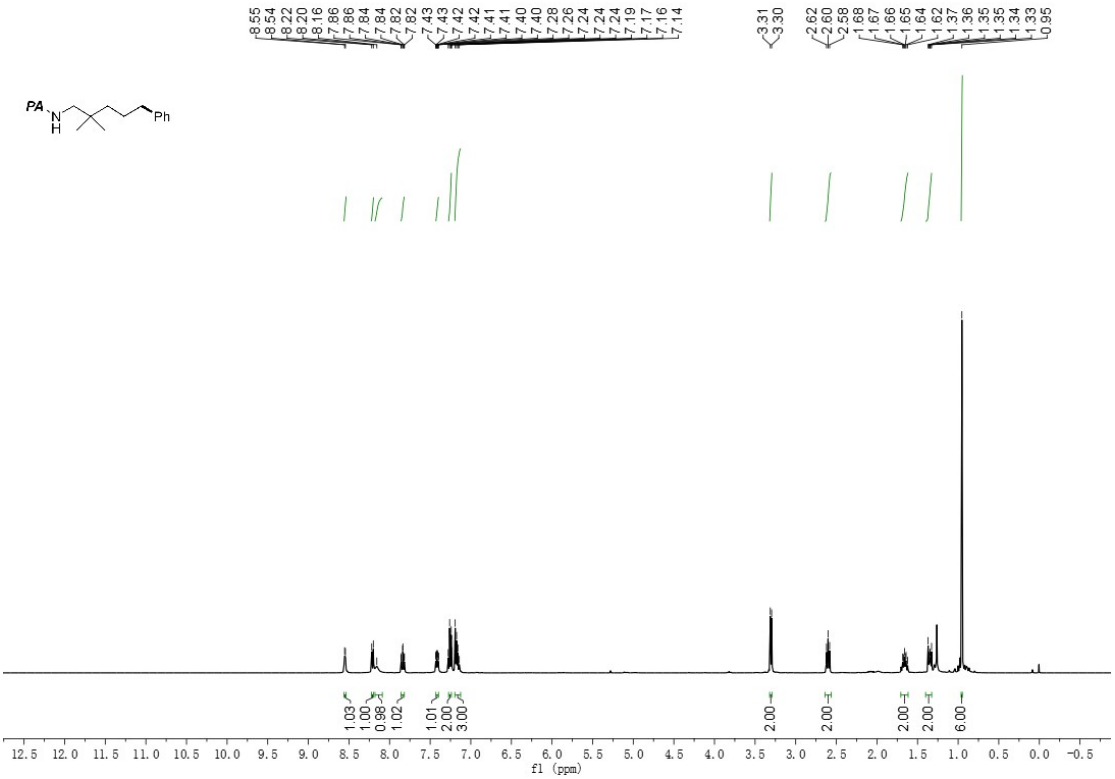
^{1}H NMR (400 MHz, $CDCl_3$) of **3al**



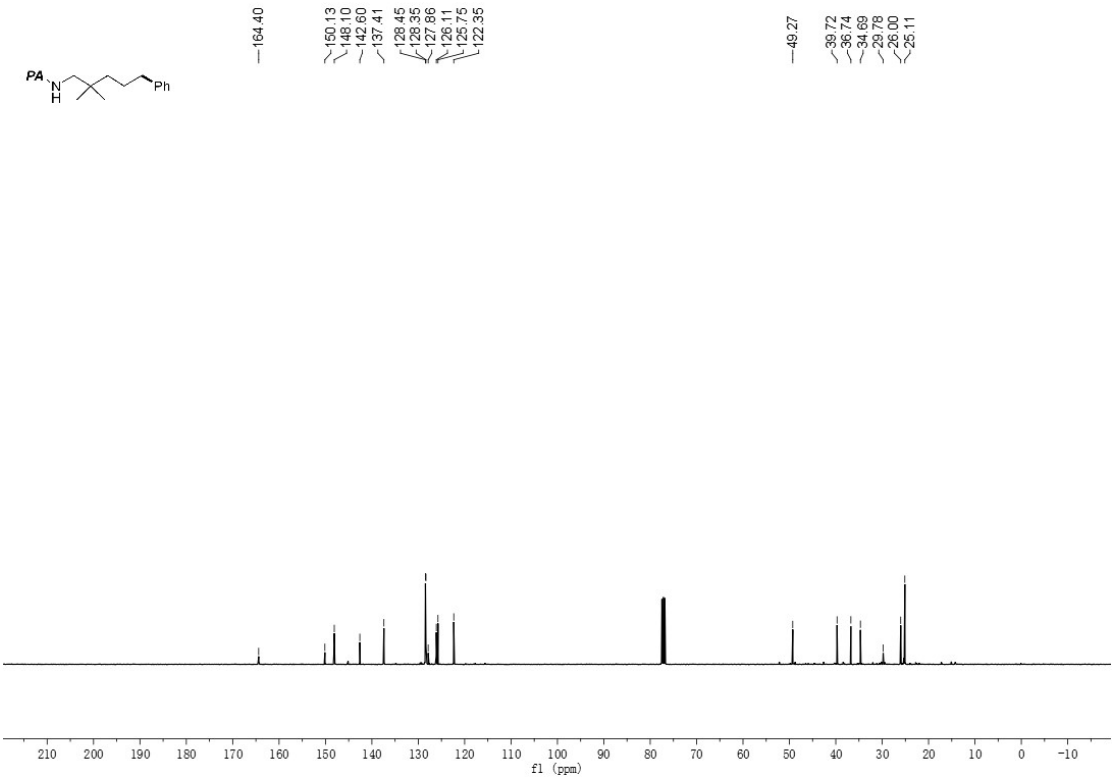
^{13}C NMR (101 MHz, $CDCl_3$) of **3al**



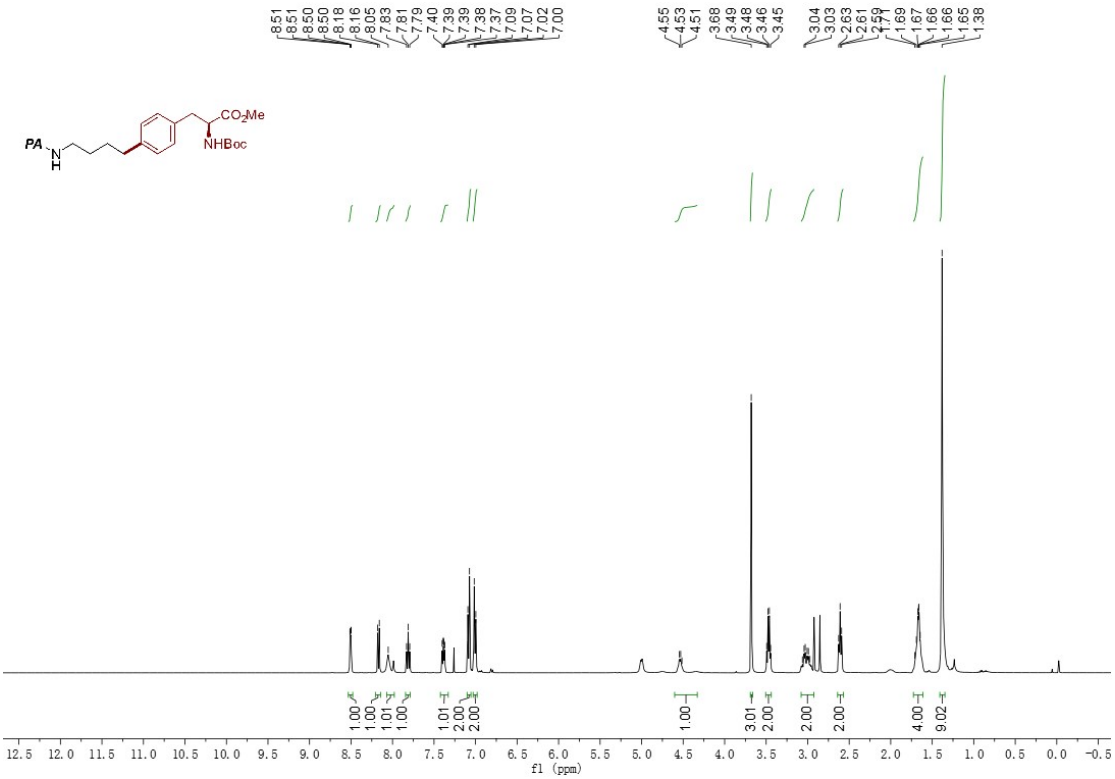
^{1}H NMR (400 MHz, $CDCl_3$) of **3am**



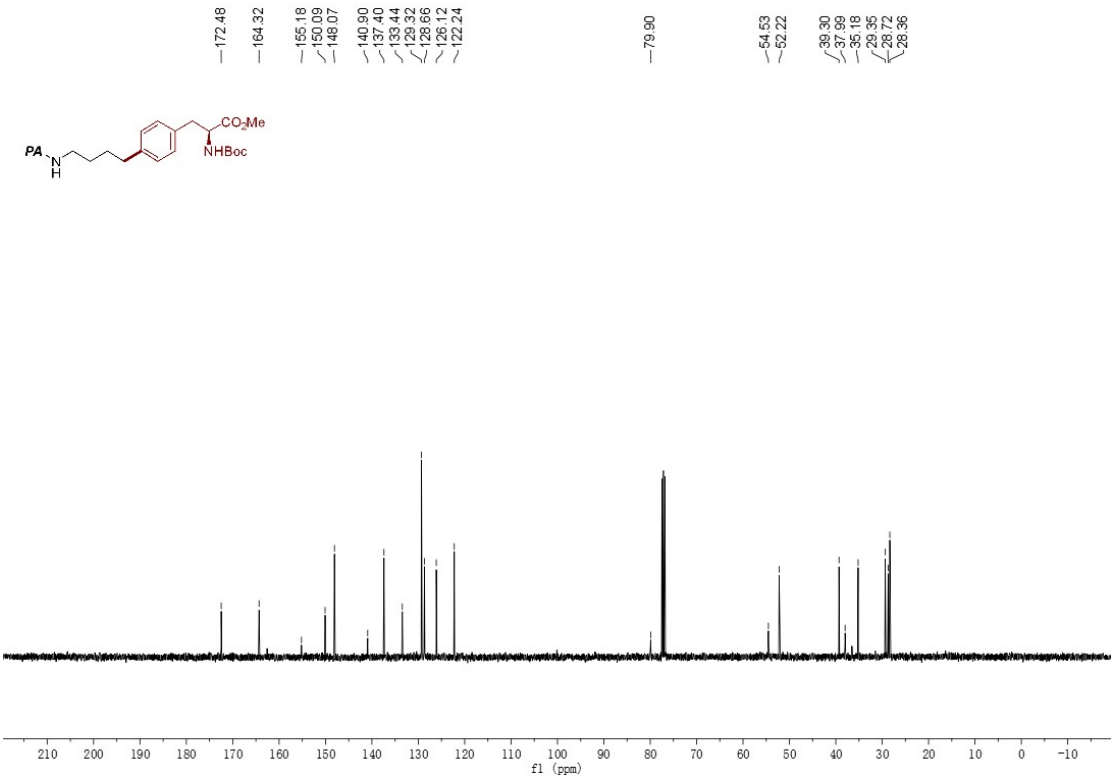
^{13}C NMR (101 MHz, $CDCl_3$) of **3am**



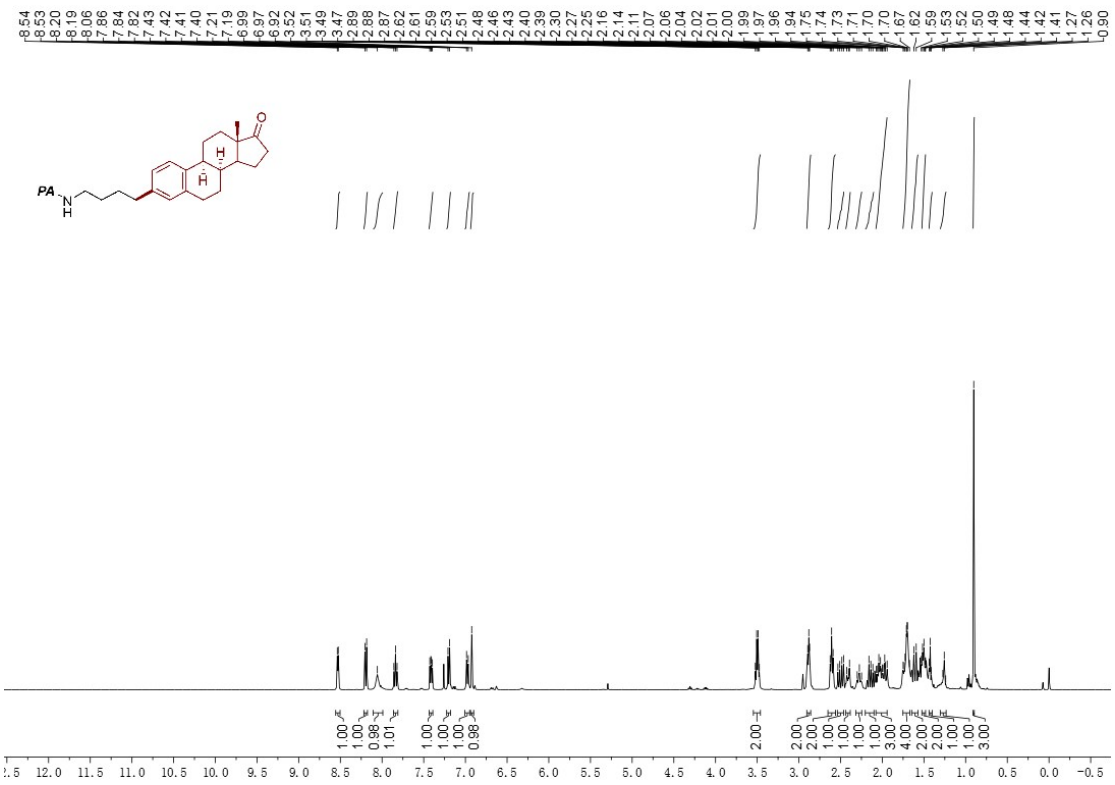
^{1}H NMR (400 MHz, $CDCl_3$) of **5a**



^{13}C NMR (101 MHz, $CDCl_3$) of **5a**



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



^{13}C NMR (101 MHz, $CDCl_3$) of **5b**