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Simple reversible fixation of magnetic catalyst in continuous flow system: Ultrafast reduction of nitroarenes and subsequent reductive amination using ammonia borane

Supporting Information

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General instrumentation

^{1}H NMR spectra were recorded in $CDCl_3$ (Cambridge isotope) at a Varian Mercury Plus 300MHz spectrometers. All spectra are referenced to $CDCl_3$ residual $CHCl_3$ peak (^{1}H-NMR δ = 7.26 ppm) .All chemical shifts are quoted in parts per million (ppm), measured from the center of the signal except in the case of multiplets of more than one proton, which are quoted as a range. Coupling constants are quoted to the nearest 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), heptet (hept.), multiplet (m), broad singlet (brs) and combinations thereof. GC analysis was carried out using Agilent 6890N equipped with HP 5-MS column (30.0 m × 320 μm × 0.25 μm) and the flame ionization detector. The maximum temperature was 310 °C and a gradient of 5 °C per minute was used. All the analysis was performed using anisole and 2-isopropylnaphtalene as internal standard and nitrogen as carrier gas. One type of syringe pumps employed was a Kd Scientific Instruments LEGATO 200 (syringe pump A) with a manual stepped motor and a customized syringe mount to hold multiple syringes at the same time. The second type were also multiple programmable Harvard Apparatus 11 Plus Syringe Pump (syringe pump B). – All chemicals were purchased from Sigma-Aldrich, TCI, Alfa-Aesar or Fisher Scientific and used without further purification. Dry methanol were purchased from J.T.Baker and stored over 3A molecular sieves.

Part numbers & vendors

Part	Details	Vendor	Item#	
Connectors	F Luer to 1/4-28 FB, F	REVODIX Inc.	P-628	
	Flangeless Fitting for 1/16” OD Tubing, Short		XP-235	
	ETFE Union for 1/16” OD Tubing		P-710	
	Flangeless Fitting for 1/8” OD Tubing		XP-301x	
	Flangeless Fitting for 1/16” OD Tubing		XP-201x	

	ETFE Tee for 1/16” OD Tubing		P-632	
BPRs	40 psi(2.8bar)		P-785	
Tubing	FEP TUBING, 1/16” OD, 0.030”ID(0.75mm)		1522	
	PFA Special Tubing Natural, OD: .125”,Wall: .030”	Swagelok	PFA-T2-030-100	
Syringe	5 mL, Model 1005 TLL SYR, NDL Sold Separately	Hamilton Company	81520	
	10 mL, Model 1010 TLL SYR, NDL Sold Separately		81620	

Flow reactor preparation – (Pd-Pt-Fe_3O_4 catalyst)

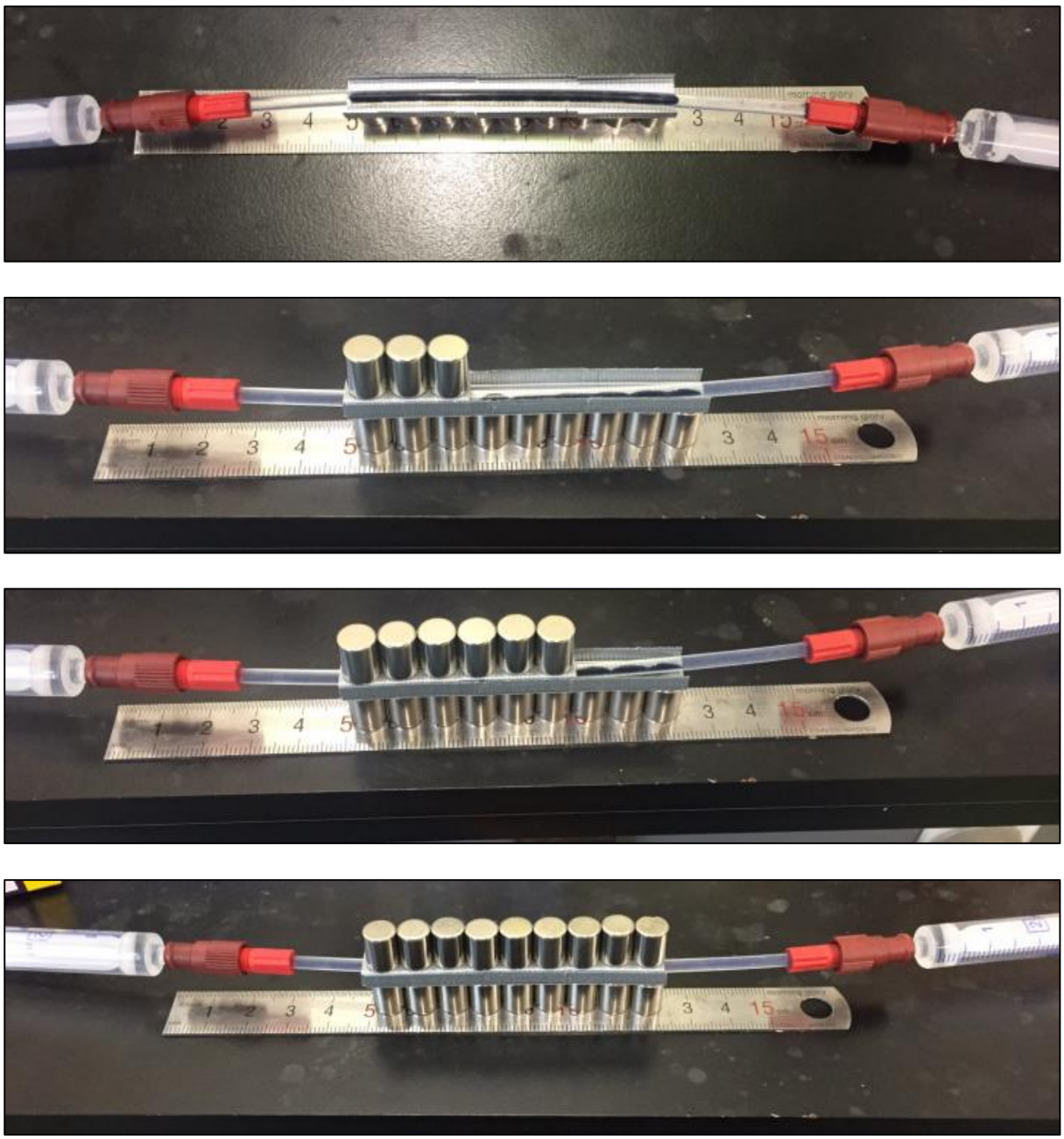


Figure 1. The procedure of magnetic nanoflakes fixation to tubes

General Procedure

Standard procedure A – Continuous flow reaction for the reduction of nitroarenes.

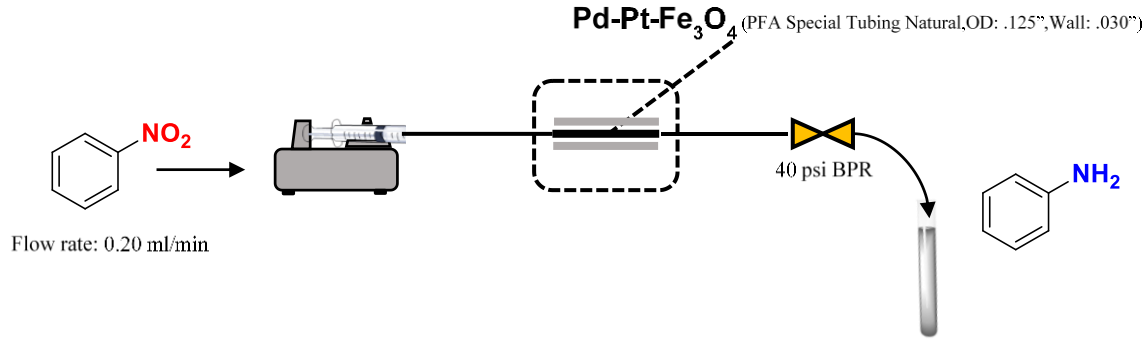


Diagram 1. Flow diagram for the procedure A.

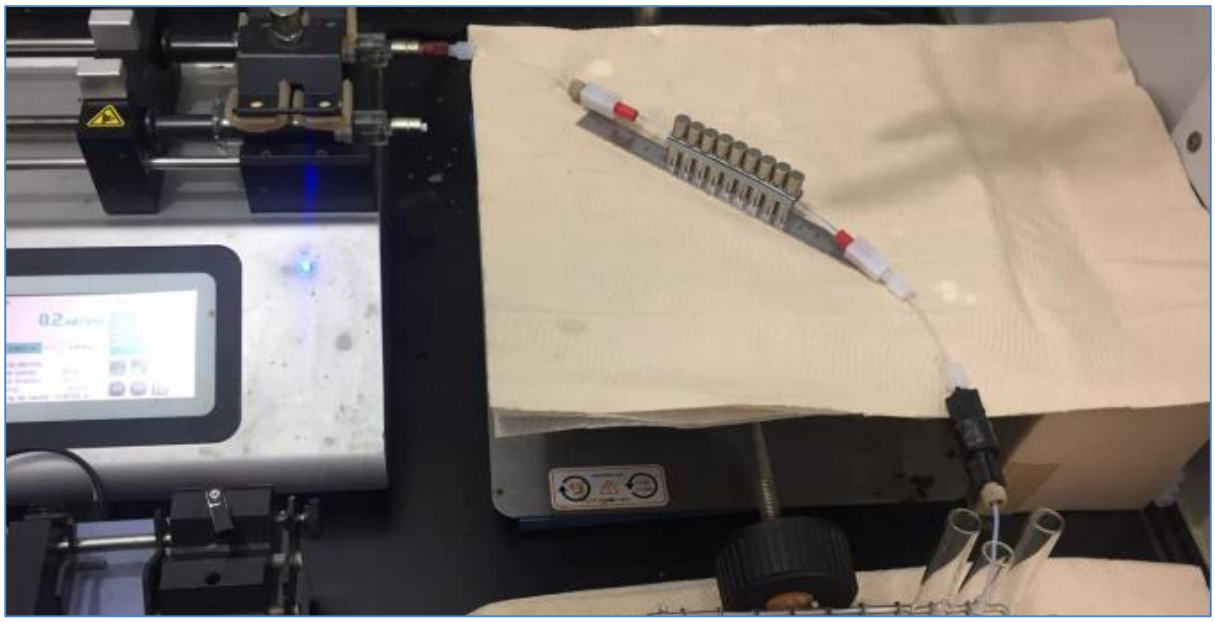


Figure 2. Flow setup for the reduction of nitroarenes

To the solution of nitrobenzene (1.0 equiv, 0.2 M) in dry methanol, ammonia borane (2.0 equiv, 0.4 M) and anisole (1.0 equiv) were added and the mixture was thoroughly mixed using a sonicator. This solution was then subjected to the continuous flow reactor using a syringe pump.

The flow rate of the reactor was set to 0.40 ml/min and the reaction was carried out at room temperature. The liquid samples were analyzed with a gas chromatography system (Agilent 6890N) equipped with HP 5-MS column (30.0 m × 320 µm × 0.25 µm) and the flame ionization detector. The yield of aniline was determined using anisole as an internal standard. The crude aniline was purified by silica gel column chromatography and characterized by ^{1}H NMR spectroscopy.

Standard procedure B – Continuous flow reaction for the reductive amination

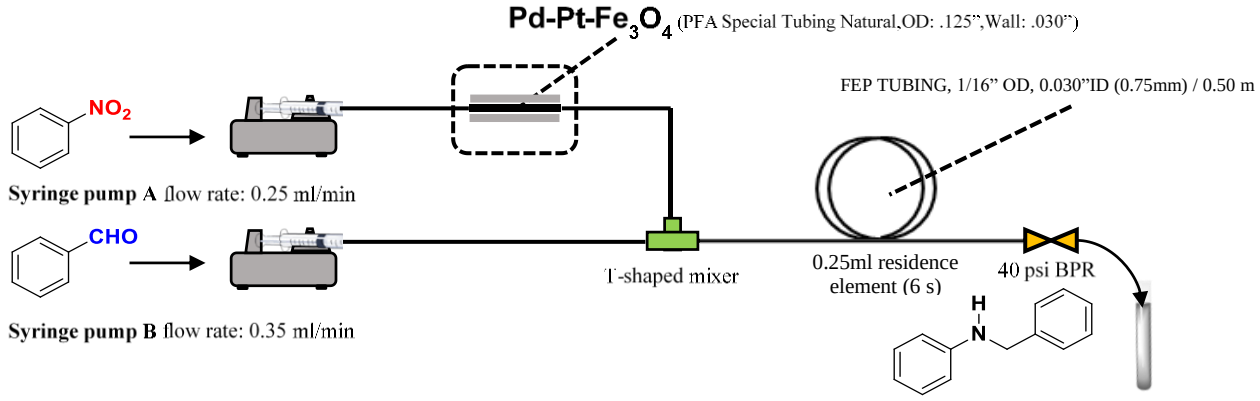


Diagram 2. Flow diagram for the procedure B.

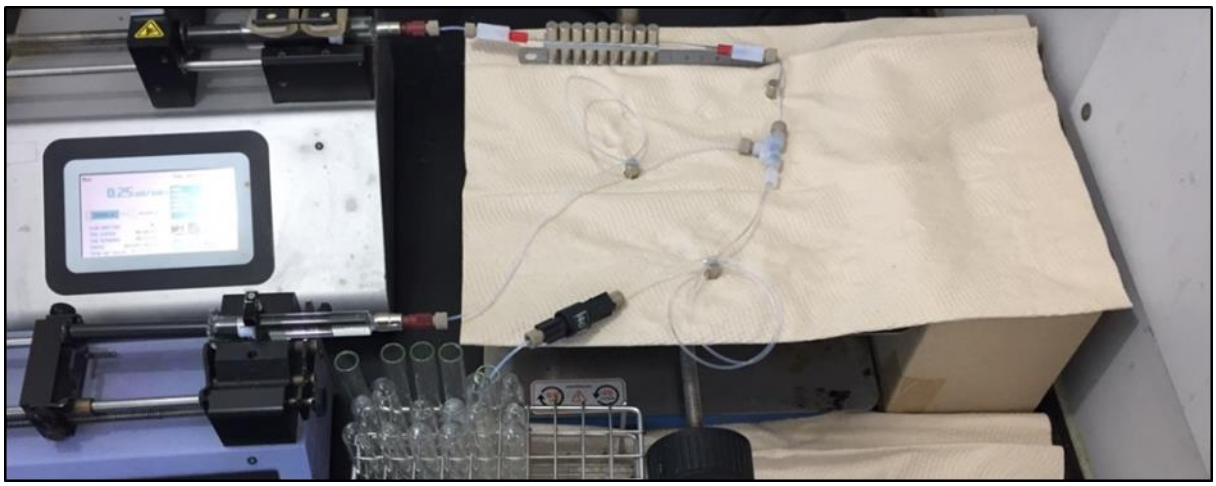


Figure 3. Flow setup for the reductive amination

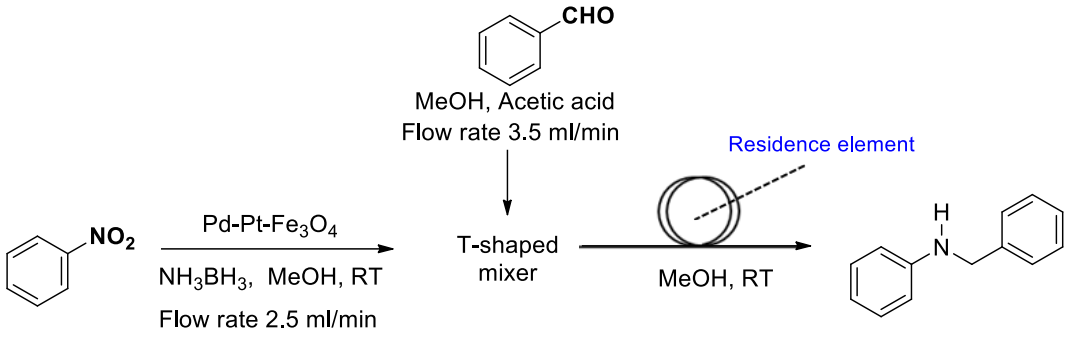
A: To a solution of nitrobenzene (1.0 equiv, 0.2 M) in dry methanol, ammonia borane (5.0 equiv, 1 M) and 2-isopropylnaphtalene (1.0 equiv) were added and the mixture was thoroughly mixed using a sonicator. This solution was then subjected to the continuous flow reactor using a syringe pump **A**.

B: To a methanolic solution of benzaldehyde (3.5 equiv, 0.7 M), acetic acid 10 % (v/v) was charged and the reaction mixture was thoroughly mixed using a sonicator. This solution was then subjected to the continuous flow reactor using a syringe pump **B**.

The flow rates were set to 0.25 ml/min and 0.35 ml/min for the syringe pump **A** and **B**, respectively and both the solutions were combined at a T-shaped mixer at room temperature. The effective residence time was 6 sec with 0.5 m tubing. The samples were analyzed with a gas chromatography system (Agilent 6890N) equipped with HP 5-MS column (30.0 m × 320 µm × 0.25 µm) and the flame ionization detector. The yield of amine was determined using 2-isoproplynaphtalene as an internal standard. After completion of the reaction, methanol was removed under reduced pressure and the residue was poured

into water and extracted with DCM (3 X 15 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ Solution (15 mL) and separated, dried over Na_2SO_4, filtered, and concentrated affording the crude product. The crude amine was purified by silica gel column chromatography and characterized by ^1H NMR spectroscopy.

Table 1. Yields by varying residence element



Entry	Residence Element (meter)	Residnce time (s)	Yied[a] (%)
1	0.25	3	49
2	0.5	6	>99
3	1	13	>99

Reaction conditions: 40 psi BPR, room temperature, syringe A: $PhNO_2$ (1.0 equiv) + NH_3BH_3 (2.0 equiv) in MeOH (0.2 M based upon nitrobenzene) with Pd-Pt-Fe_3O_4 80 mg (0.360 mmol). Syringe B: PhCHO (3.5 equiv) + acetic acid (10%) in MeOH (0.7 M). [a] Yield determined by GC analysis using 2-isopropylnaphthalene as an internal standard.

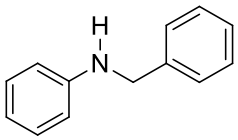
Synthesis of the Pd–Pt–Fe_3O_4

The synthesis of Pd-Pt-Fe_3O_4 was performed as follows:

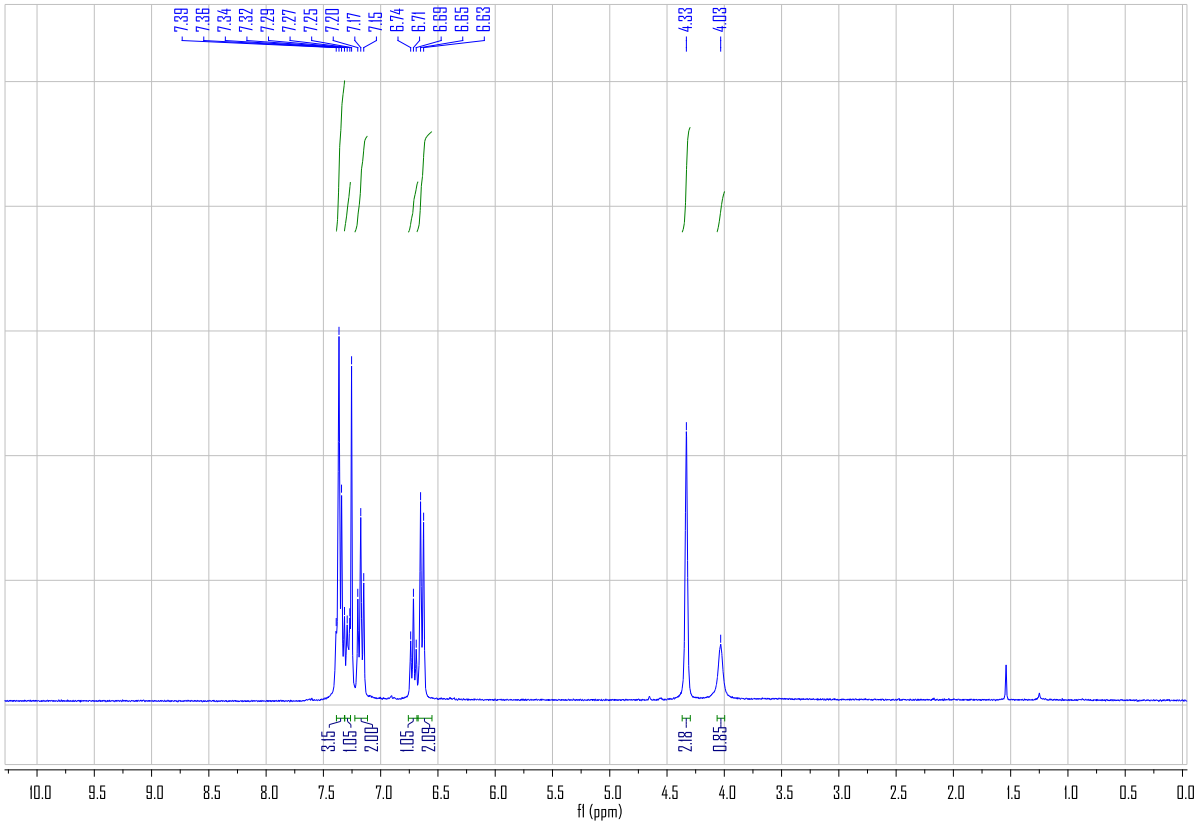
First 800 mg of potassium platinochloride (K_2PtCl_4), 340 mg of palladium(II) chloride ($PdCl_2$) and 1.00 g of polyvinylpyrrolidone (PVP) (Mw ~10,000) were dissolved in 80 mL of ethylene glycol (EG) in a 250 mL round-bottom flask. This mixture was sonicated for 10 min and heated for 1 h at 100°C in oil bath with magnetic stirring. Meanwhile, 1.00g of Fe_3O_4 was dissolved in 300 mL of EG in a two-necked 500 mL round-bottom flask and then ultrasonication performed for 40 min. Next, with vigorously stirring of the Fe_3O_4 solution with a mechanical stirrer, the prepared platinum and palladium precursor solution was injected dropwise. The resulting solution was further processed at 100°C for an additional 24 h. Afterward, the resultant sample could be retrieved via centrifugation and washing with absolute ethanol. Finally, the product was obtained via drying on a rotary evaporator.

Spectroscopic data

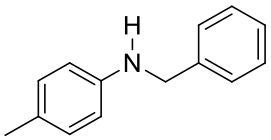
^{1}H NMR of N-benzylaniline (3a)



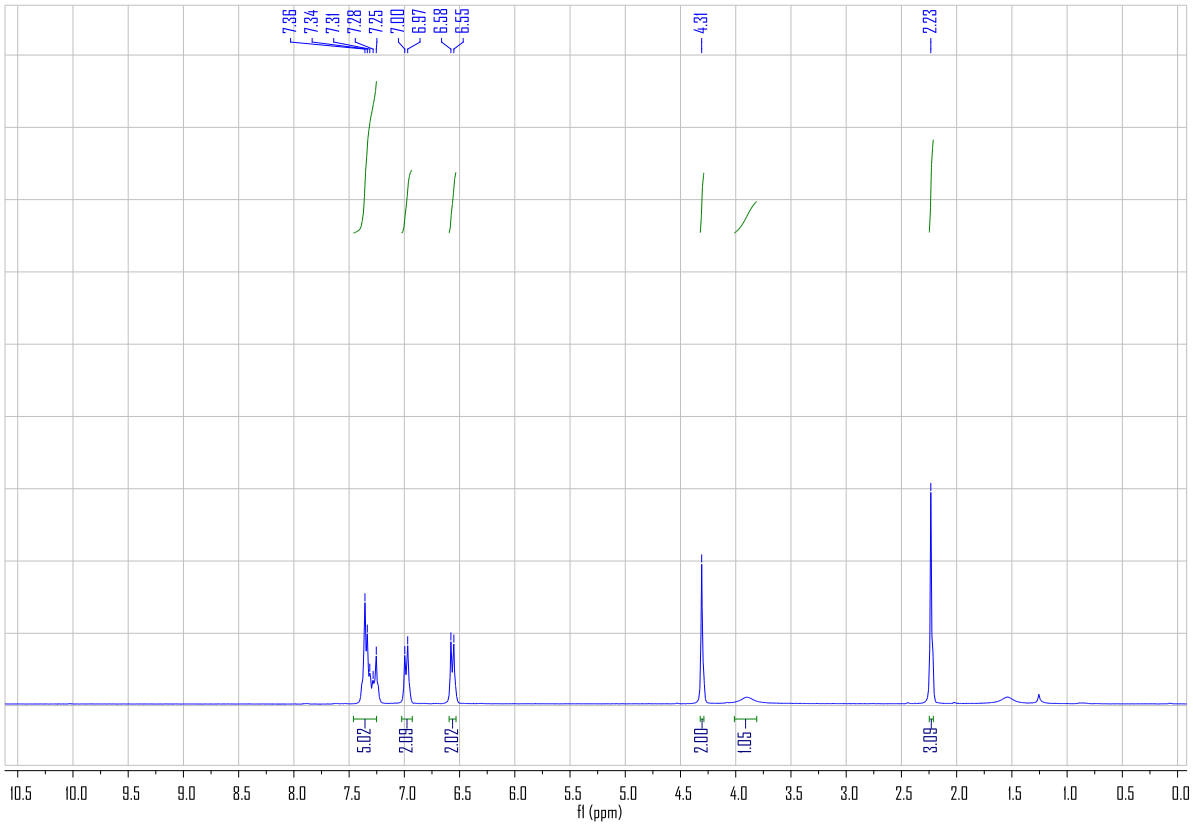
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 3H), 7.32 – 7.26 (m, 1H), 7.17 (t, *J* = 7.8 Hz, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 7.9 Hz, 2H), 4.33 (s, 2H), 4.03 (s, 1H).



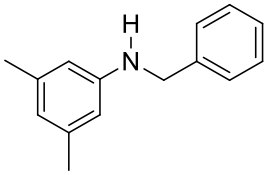
^{1}H NMR of N-benzyl-4-methylaniline (3b)



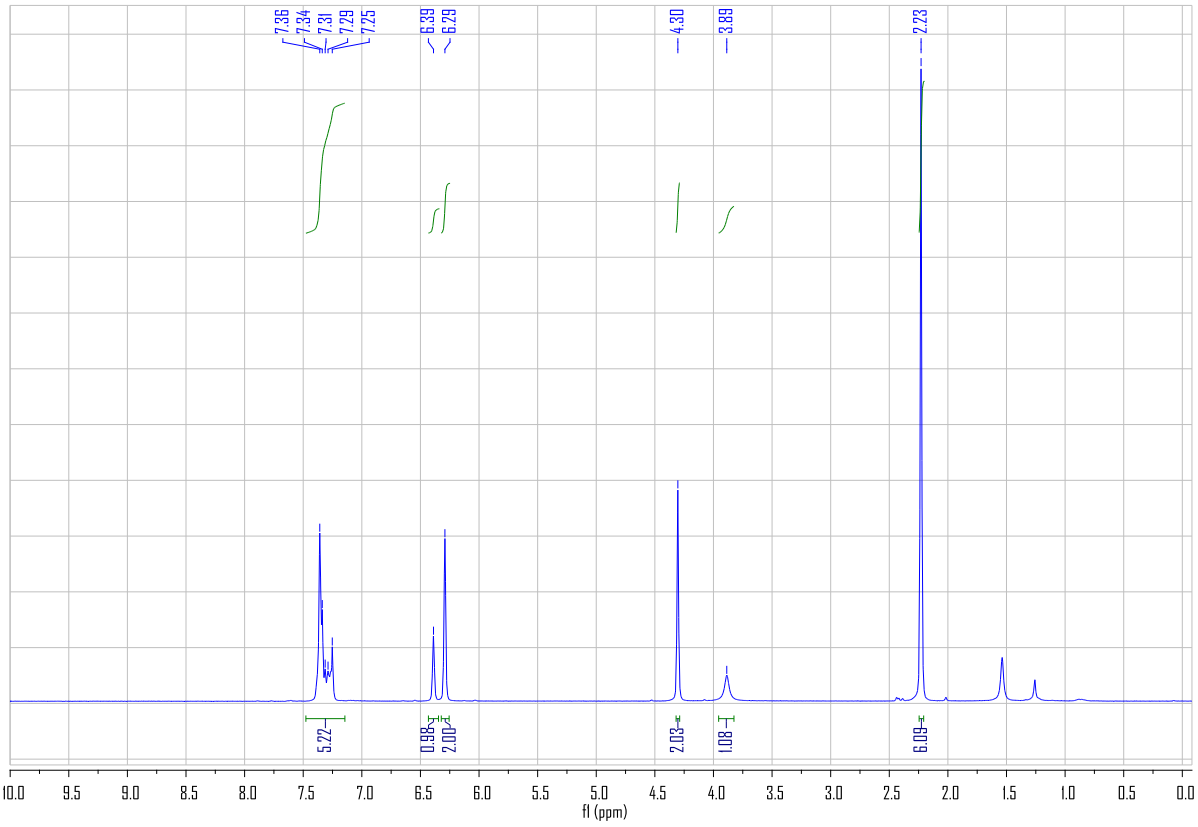
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.25 (m, 5H), 6.98 (d, *J* = 7.9 Hz, 2H), 6.57 (d, *J* = 8.0 Hz, 2H), 4.31 (s, 2H), 3.91 (s, 1H), 2.23 (s, 3H).



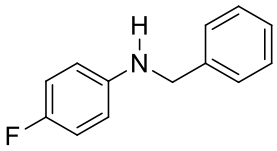
^{1}H NMR of N-benzyl-3,5-dimethylaniline (3c)



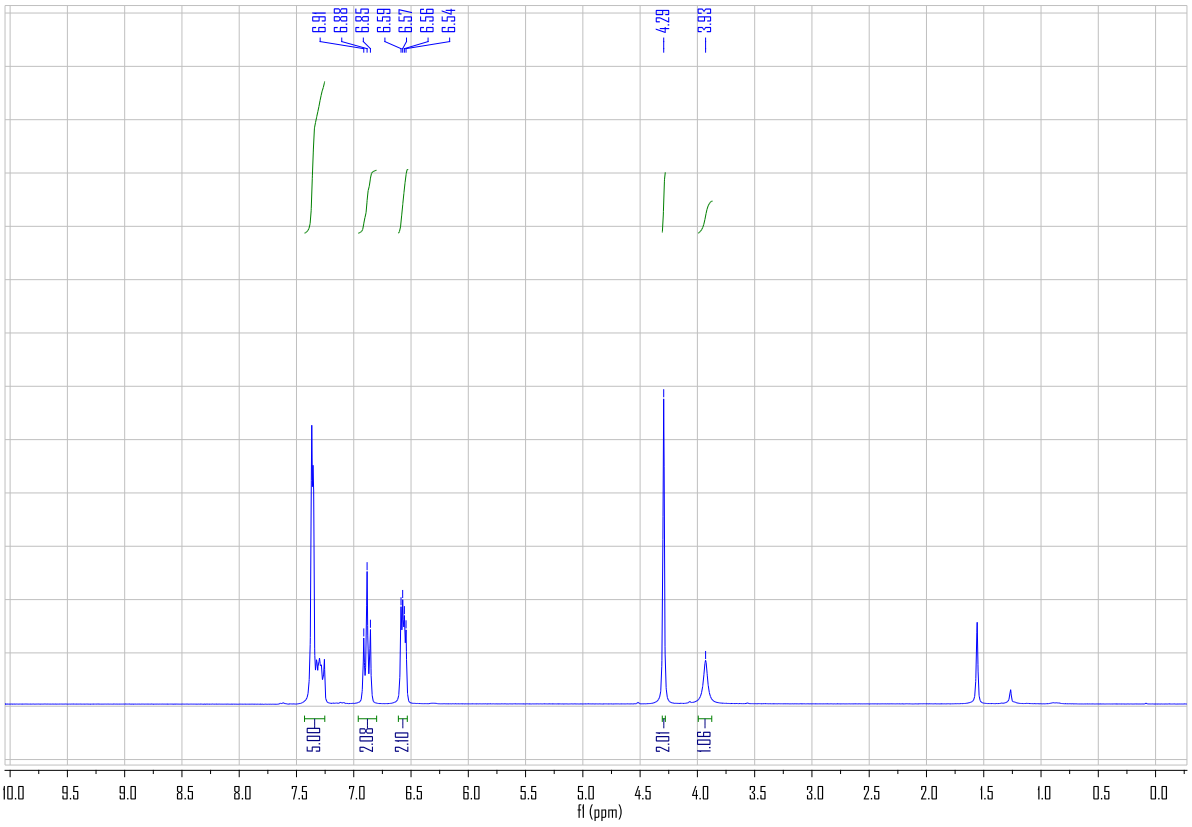
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.14 (m, 5H), 6.39 (s, 1H), 6.29 (s, 2H), 4.30 (s, 2H), 3.89 (s, 1H), 2.23 (s, 6H).0



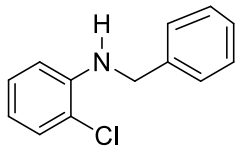
^{1}H NMR of N-benzyl-4-fluoroaniline (3d)



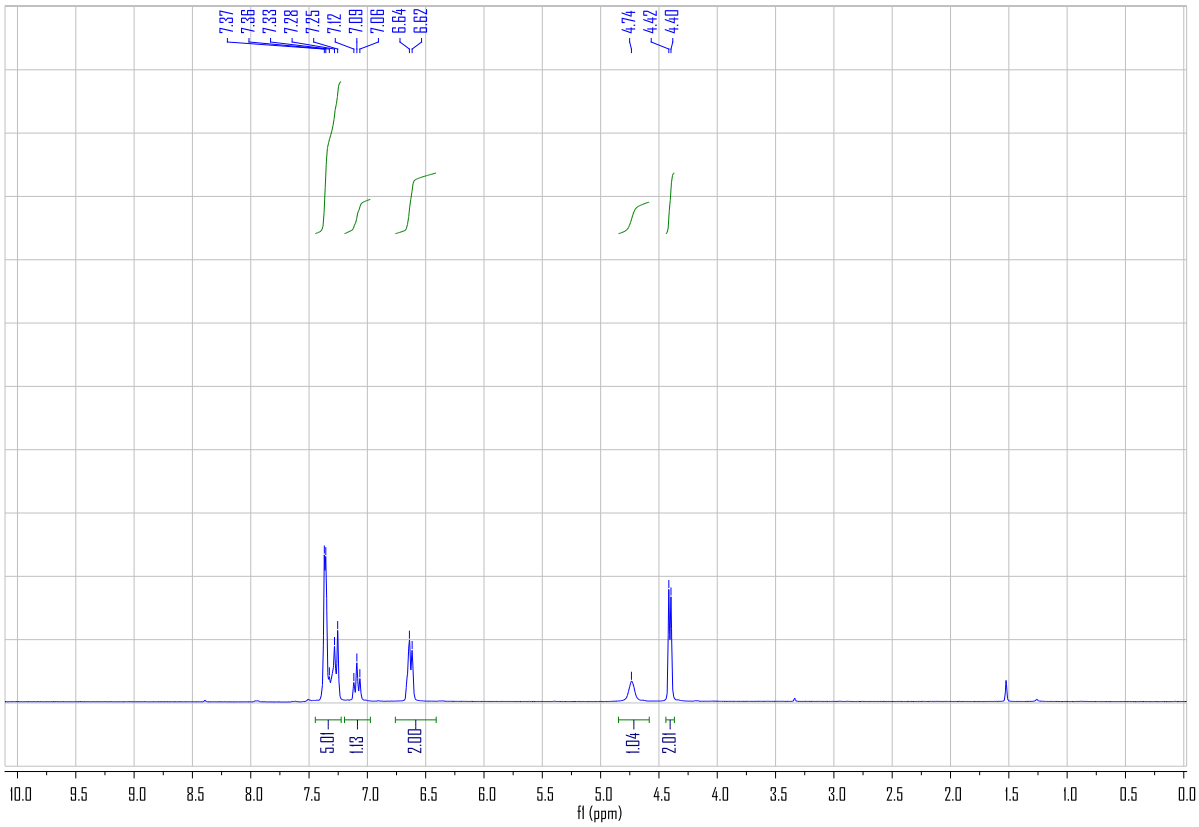
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.25 (m, 5H), 6.88 (t, *J* = 8.7 Hz, 2H), 6.57 (dd, *J* = 8.8, 4.3 Hz, 2H), 4.29 (s, 2H), 3.93 (s, 1H).



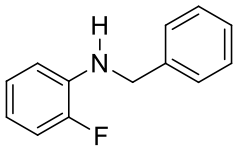
^{1}H NMR of N-benzyl-2-chloroaniline (3e)



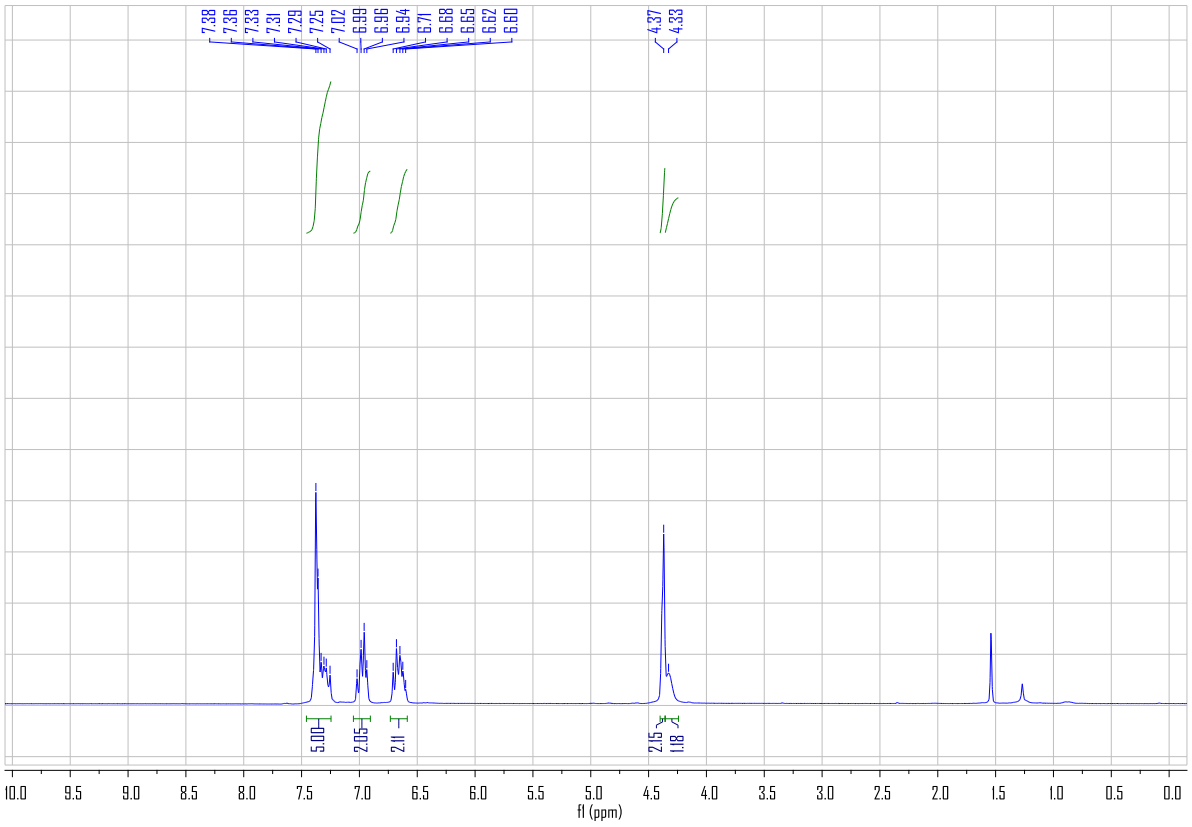
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.22 (m, 5H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.63 (d, *J* = 7.0 Hz, 2H), 4.74 (s, 1H), 4.41 (d, *J* = 5.5 Hz, 2H).



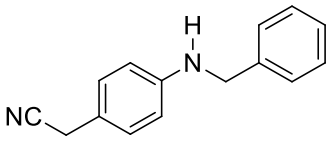
^{1}H NMR of N-benzyl-2-fluoroaniline (3f)



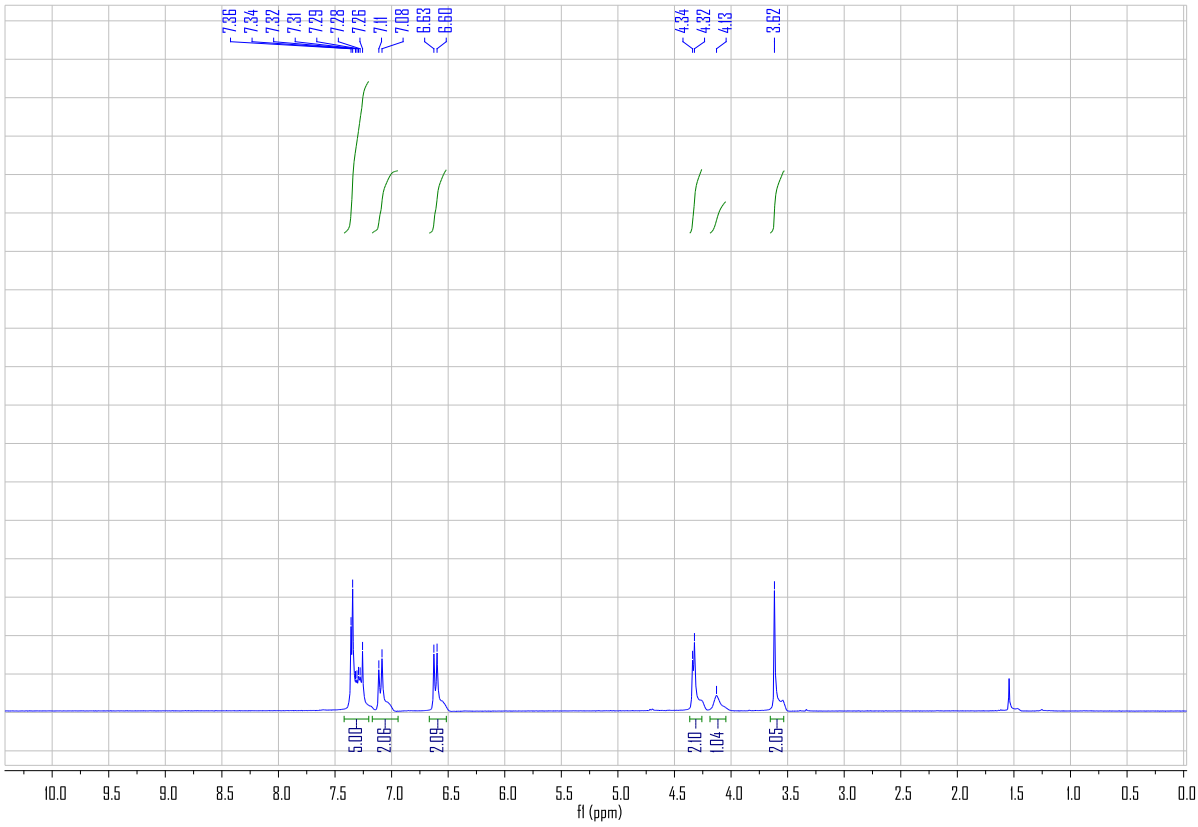
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.25 (m, 5H), 6.98 (dd, J = 16.7, 8.7 Hz, 2H), 6.73 – 6.59 (m, 2H), 4.37 (s, 2H), 4.33 (s, 1H).



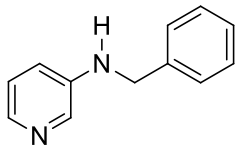
^{1}H NMR of N-benzyl-4-(isocyanomethyl)aniline (3g)



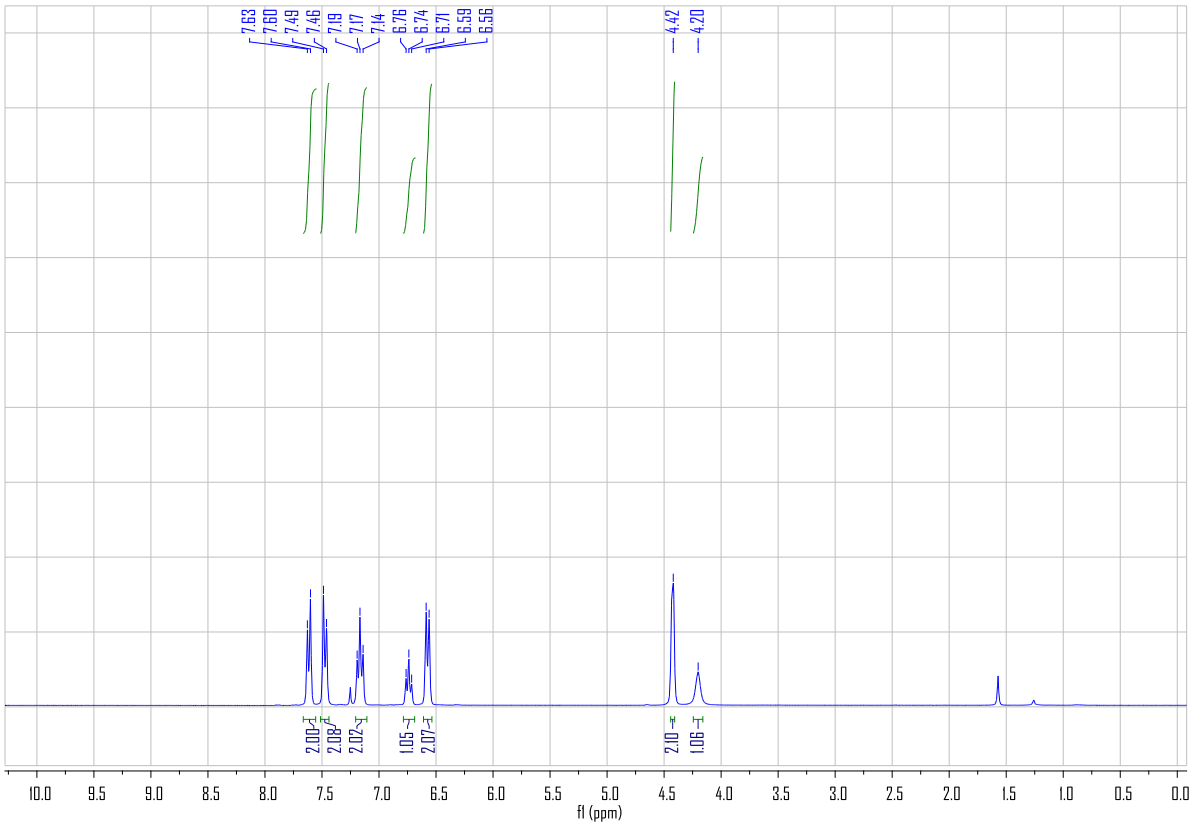
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.20 (m, 5H), 7.10 (d, J = 8.4 Hz, 2H), 6.61 (d, J = 8.5 Hz, 2H), 4.33 (d, J = 5.0 Hz, 2H), 4.13 (s, 1H), 3.62 (s, 2H).



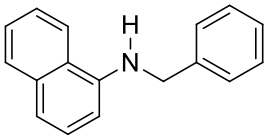
^{1}H NMR of N-benzylpyridin-3-amine (3h)



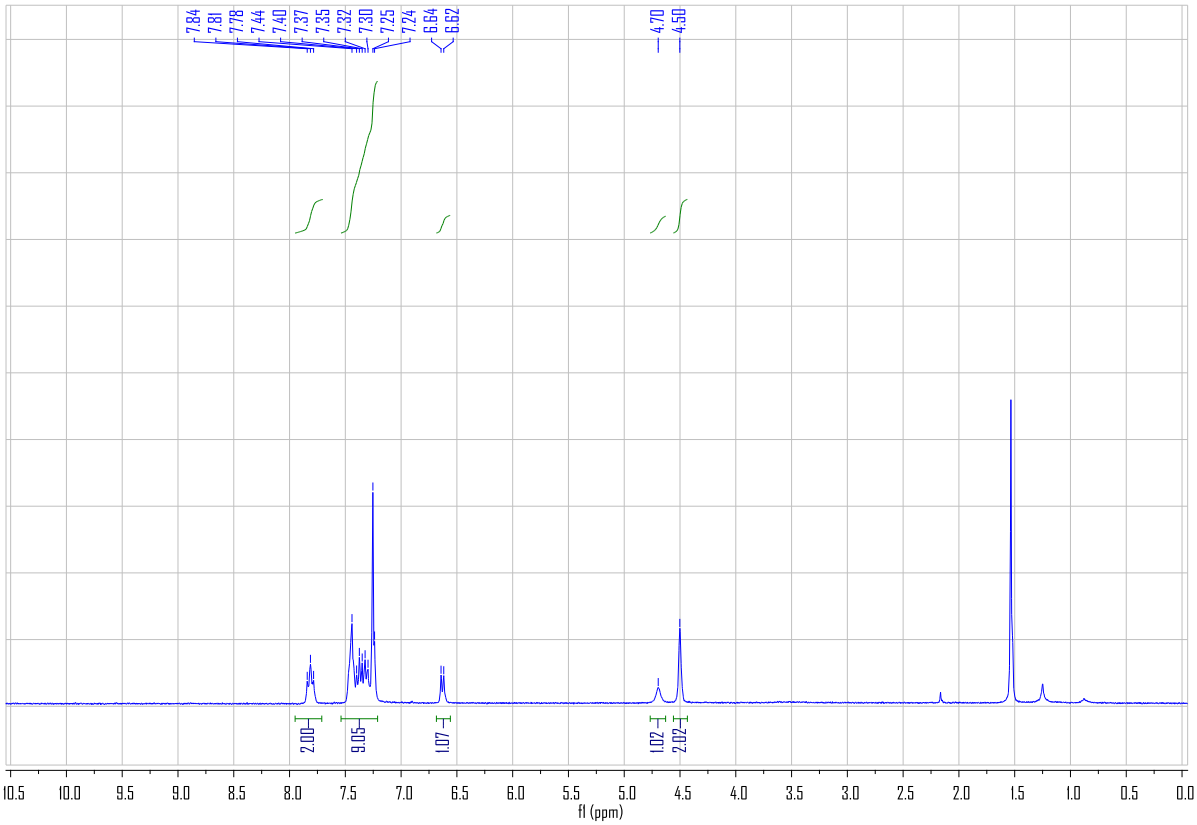
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.17 (t, *J* = 7.8 Hz, 2H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 2H), 4.42 (s, 2H), 4.20 (s, 1H).



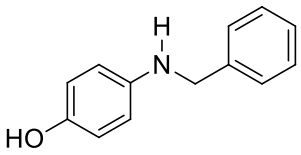
^{1}H NMR of N-benzylnaphthalen-1-amine (3i)



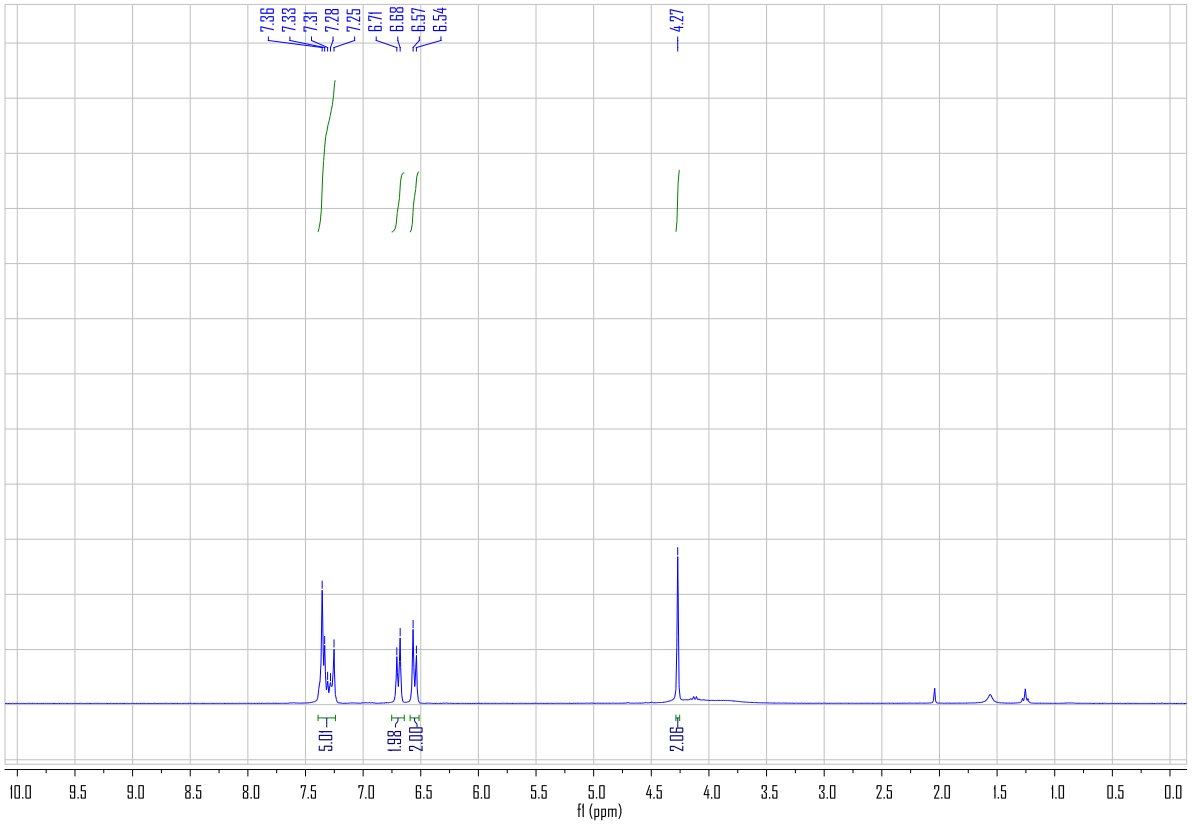
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (t, *J* = 8.6 Hz, 2H), 7.33 (ddd, *J* = 25.5, 18.7, 8.4 Hz, 9H), 6.63 (d, *J* = 7.3 Hz, 1H), 4.70 (s, 1H), 4.50 (s, 2H).



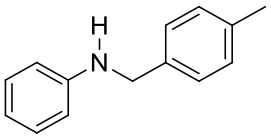
^{1}H NMR of 4-(benzylamino)phenol (3j)



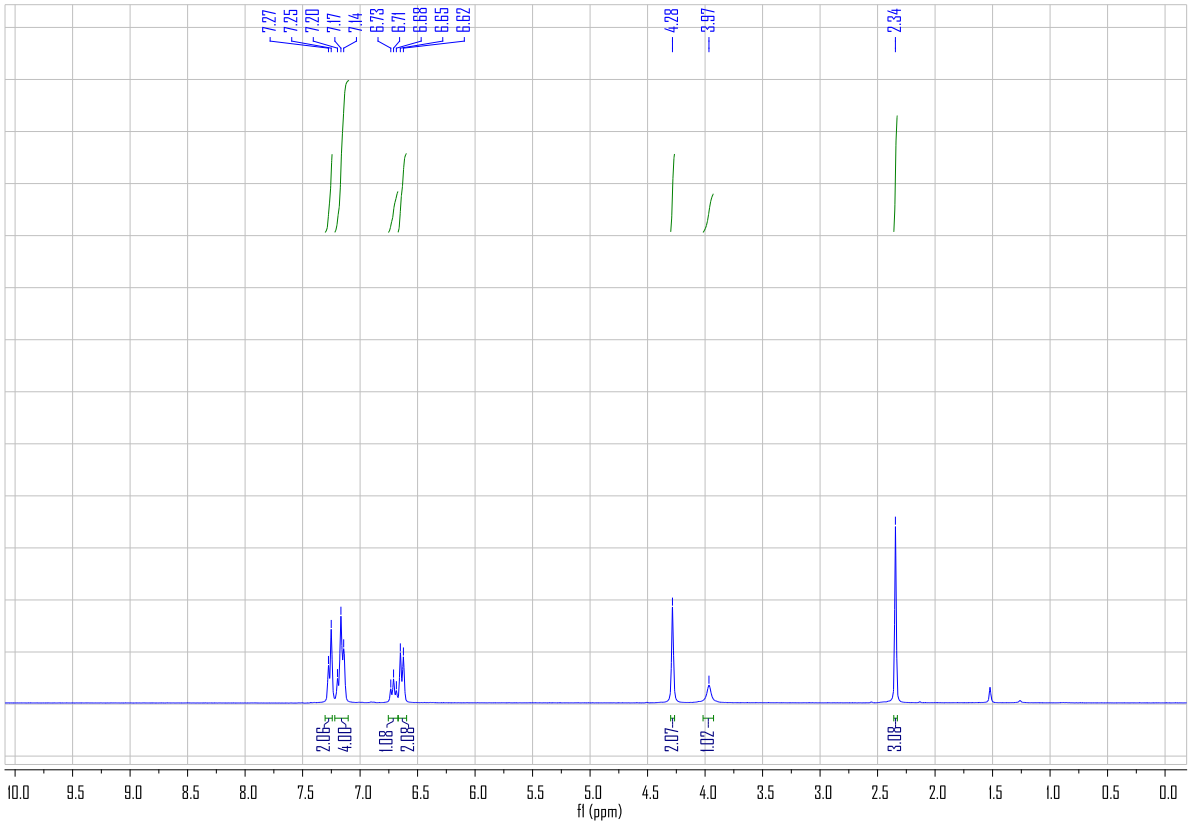
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 5H), 6.69 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 8.7 Hz, 2H), 4.27 (s, 2H).



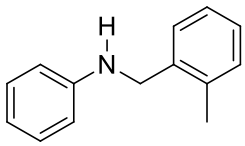
^{1}H NMR of N-(4-methylbenzyl)aniline (3k)



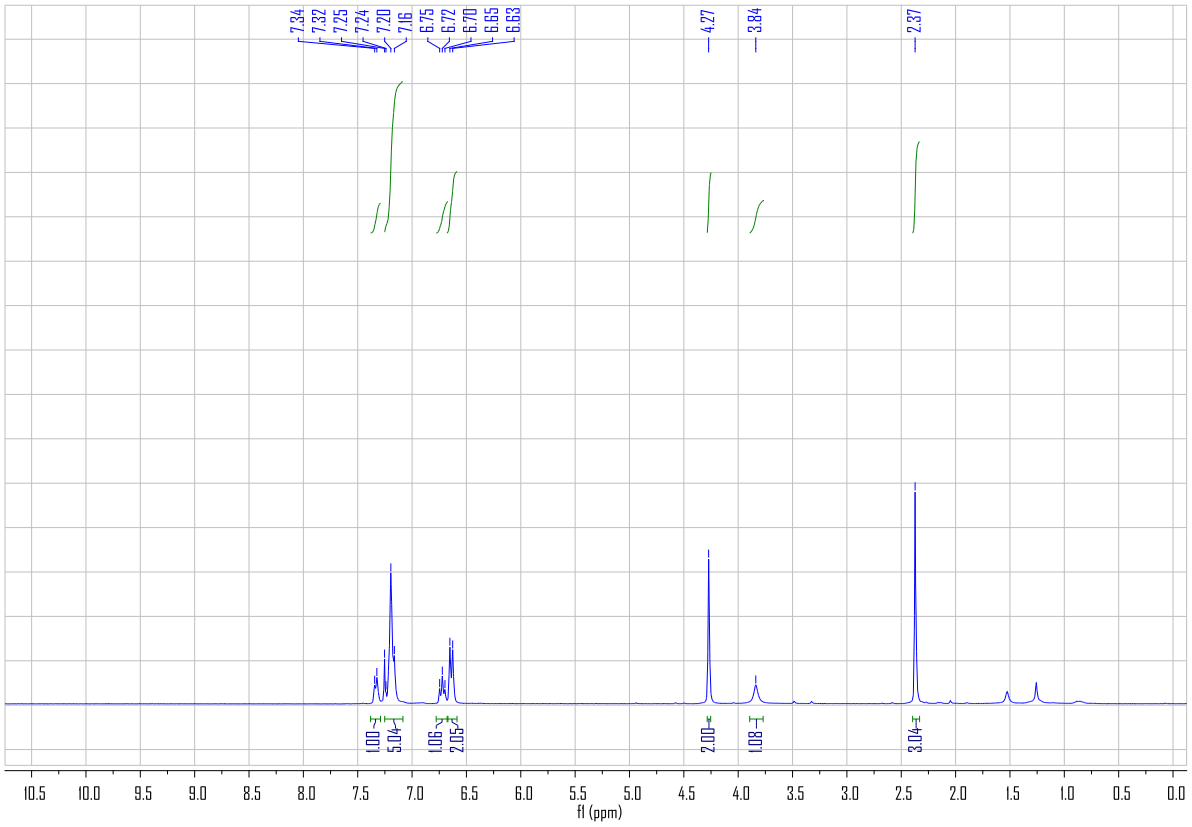
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.2 Hz, 2H), 7.17 (t, *J* = 8.1 Hz, 4H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 2H), 4.28 (s, 2H), 3.97 (s, 1H), 2.34 (s, 3H).



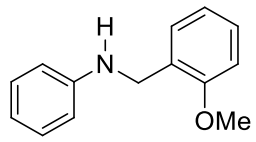
^{1}H NMR of N-(2-methylbenzyl)aniline (3l)



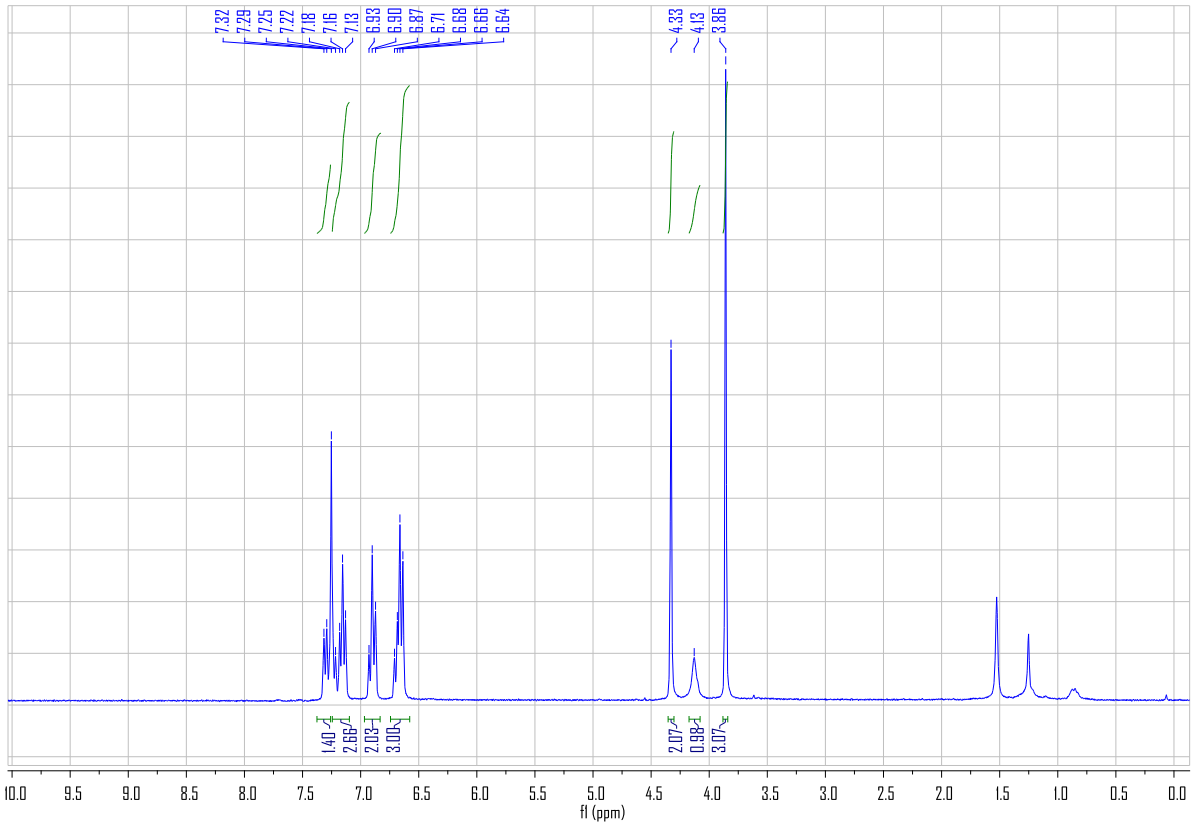
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 6.0 Hz, 1H), 7.25 – 7.08 (m, 5H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 2H), 4.27 (s, 2H), 3.84 (s, 1H), 2.37 (s, 3H).



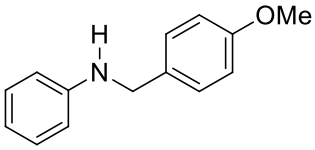
^{1}H NMR of N-(2-methoxybenzyl)aniline (3m)



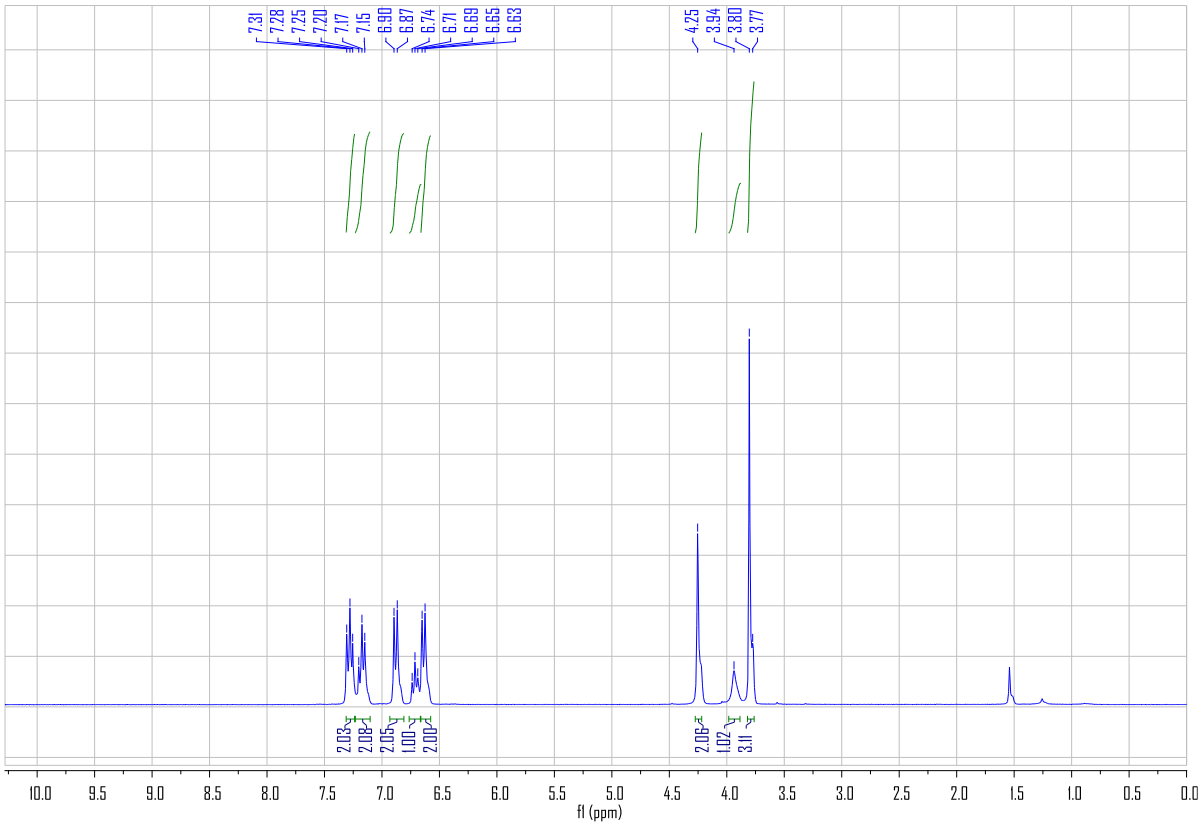
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.3 Hz, 1H), 7.17 (dd, *J* = 16.7, 9.2 Hz, 3H), 6.90 (t, *J* = 8.5 Hz, 2H), 6.67 (dd, *J* = 14.1, 7.5 Hz, 3H), 4.33 (s, 2H), 4.13 (s, 1H), 3.86 (s, 3H).



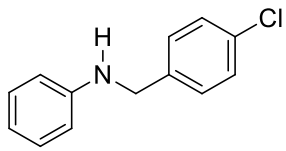
^{1}H NMR of N-(4-methoxybenzyl)aniline (3n)



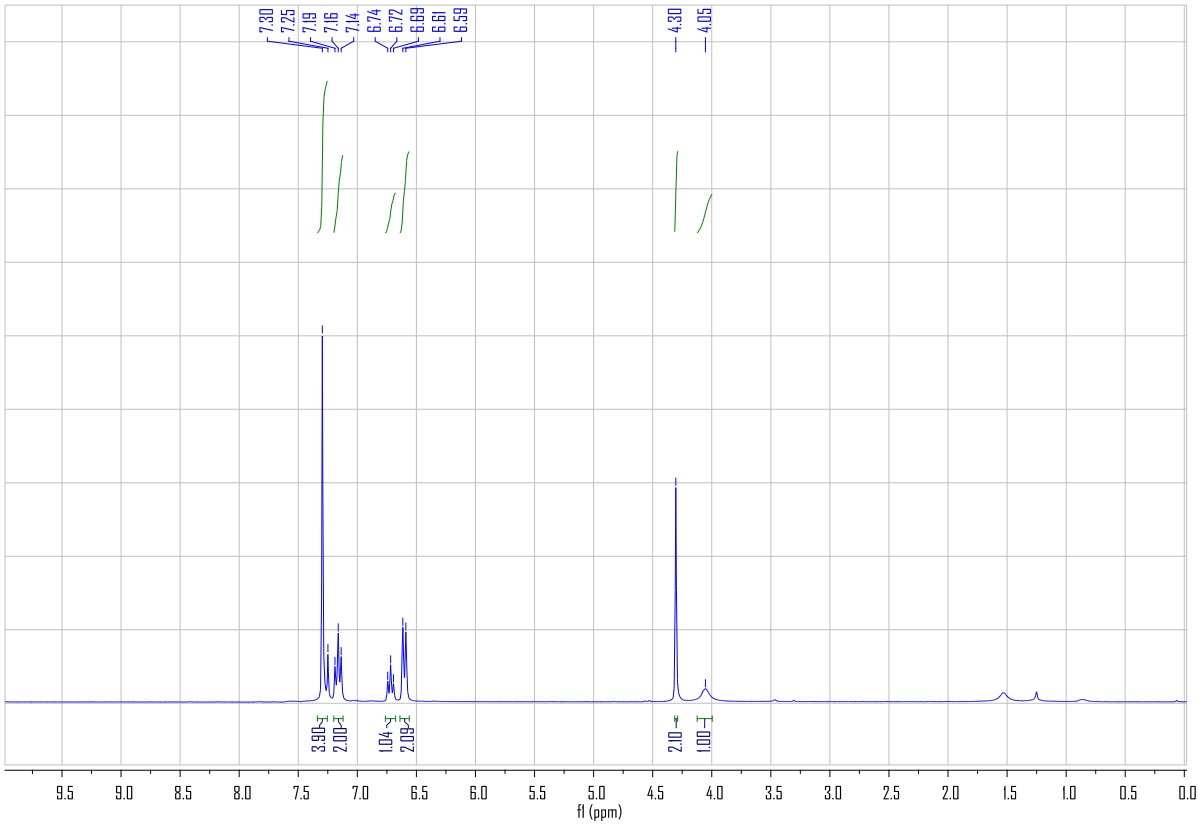
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 2H), 7.18 (t, *J* = 7.9 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 2H), 4.25 (s, 2H), 3.94 (s, 1H), 3.79 (d, *J* = 8.8 Hz, 3H).



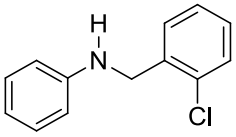
^{1}H NMR of N-(4-chlorobenzyl)aniline (3o)



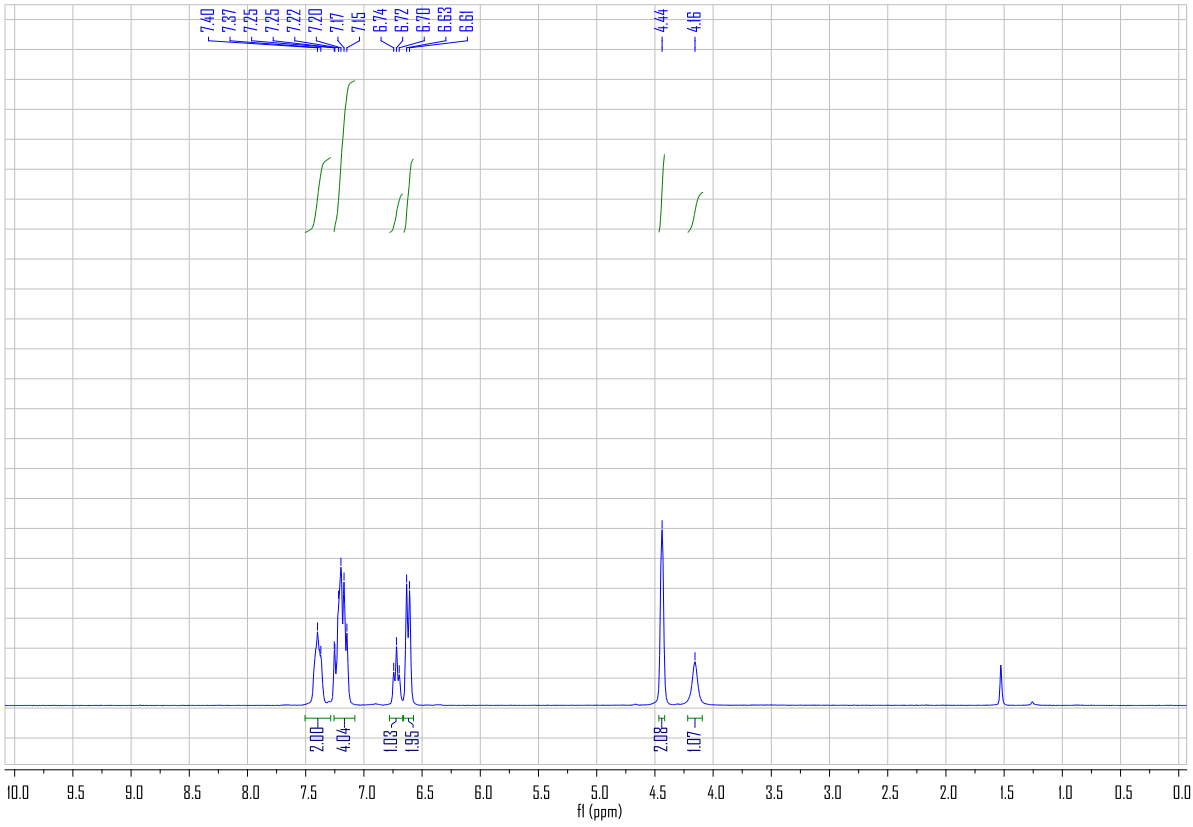
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 4H), 7.16 (t, *J* = 7.9 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.60 (d, *J* = 7.7 Hz, 2H), 4.30 (s, 2H), 4.05 (s, 1H).



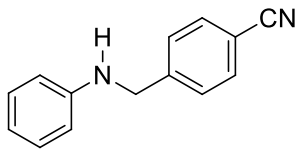
^{1}H NMR of N-(2-chlorobenzyl)aniline (3p)



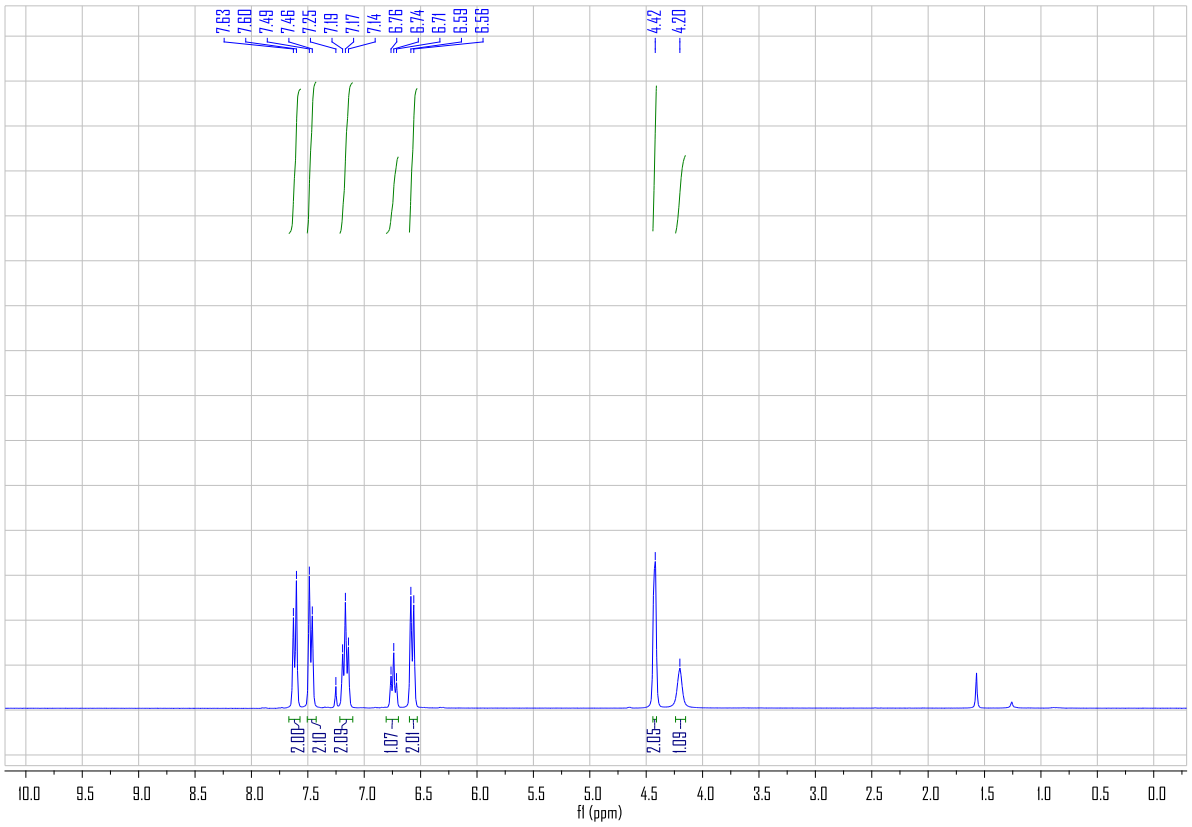
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.5 Hz, 2H), 7.26 – 7.08 (m, 4H), 6.72 (t, *J* = 7.1 Hz, 1H), 6.62 (d, *J* = 7.5 Hz, 2H), 4.44 (s, 2H), 4.16 (s, 1H).



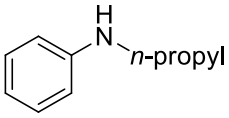
^{1}H NMR of 4-((phenylamino)methyl)benzonitrile (3q)



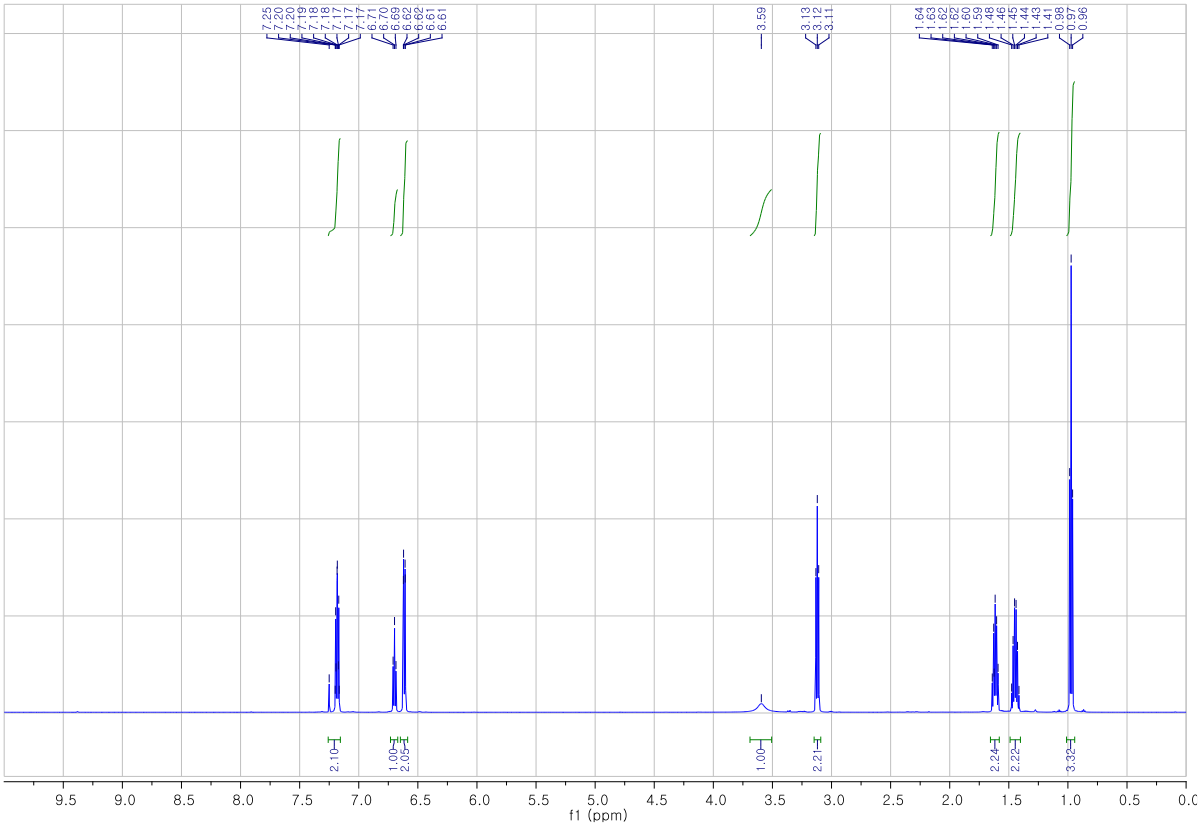
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.17 (t, J = 7.8 Hz, 2H), 6.74 (t, J = 7.3 Hz, 1H), 6.57 (d, J = 7.8 Hz, 2H), 4.42 (s, 2H), 4.20 (s, 1H).



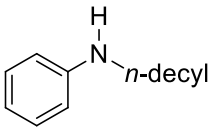
^{1}H NMR of N-butylaniline (3r)



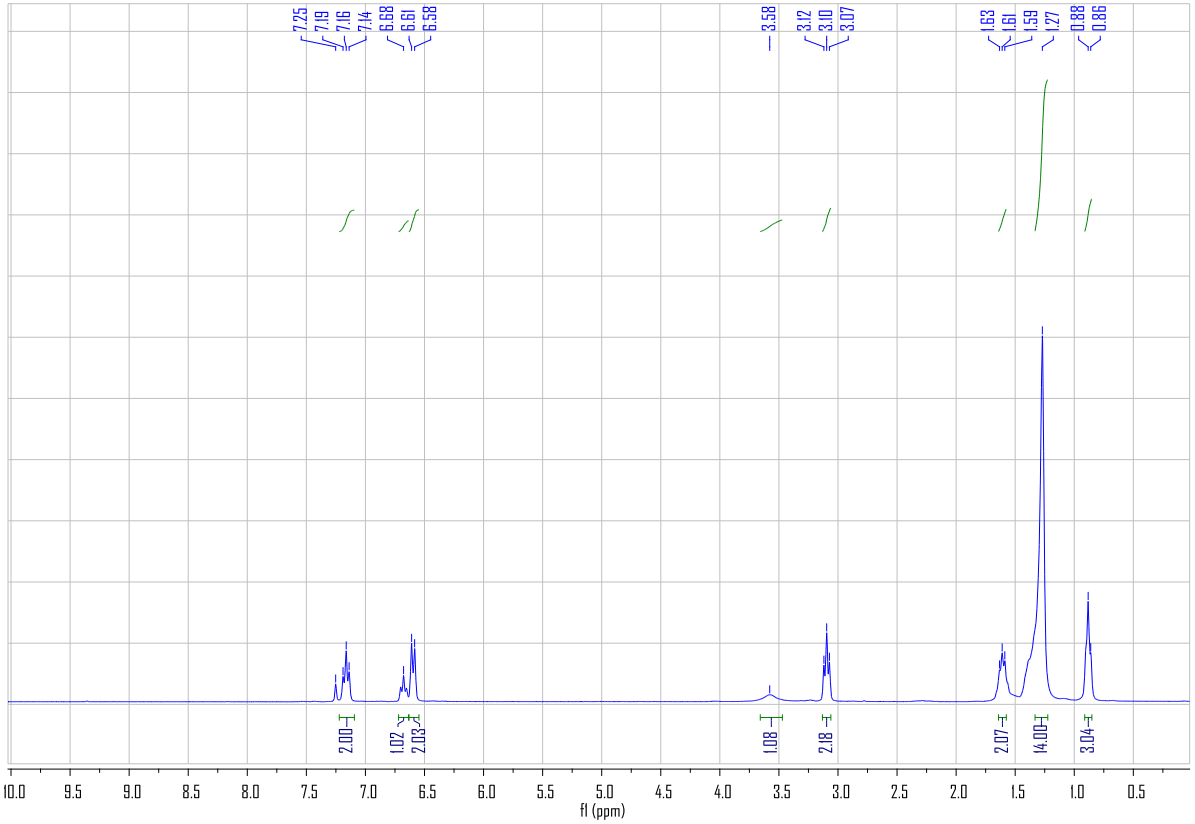
1H NMR (600 MHz, cdcl3) δ 7.21 – 7.16 (m, 2H), 6.70 (t, J = 7.3 Hz, 1H), 6.61 (dd, J = 8.4, 0.8 Hz, 2H), 3.59 (s, 1H), 3.12 (t, J = 7.1 Hz, 2H), 1.62 (dt, J = 20.1, 7.3 Hz, 2H), 1.49 – 1.40 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).



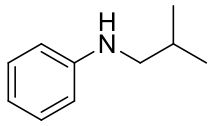
^{1}H NMR of N-decylaniline (3s)



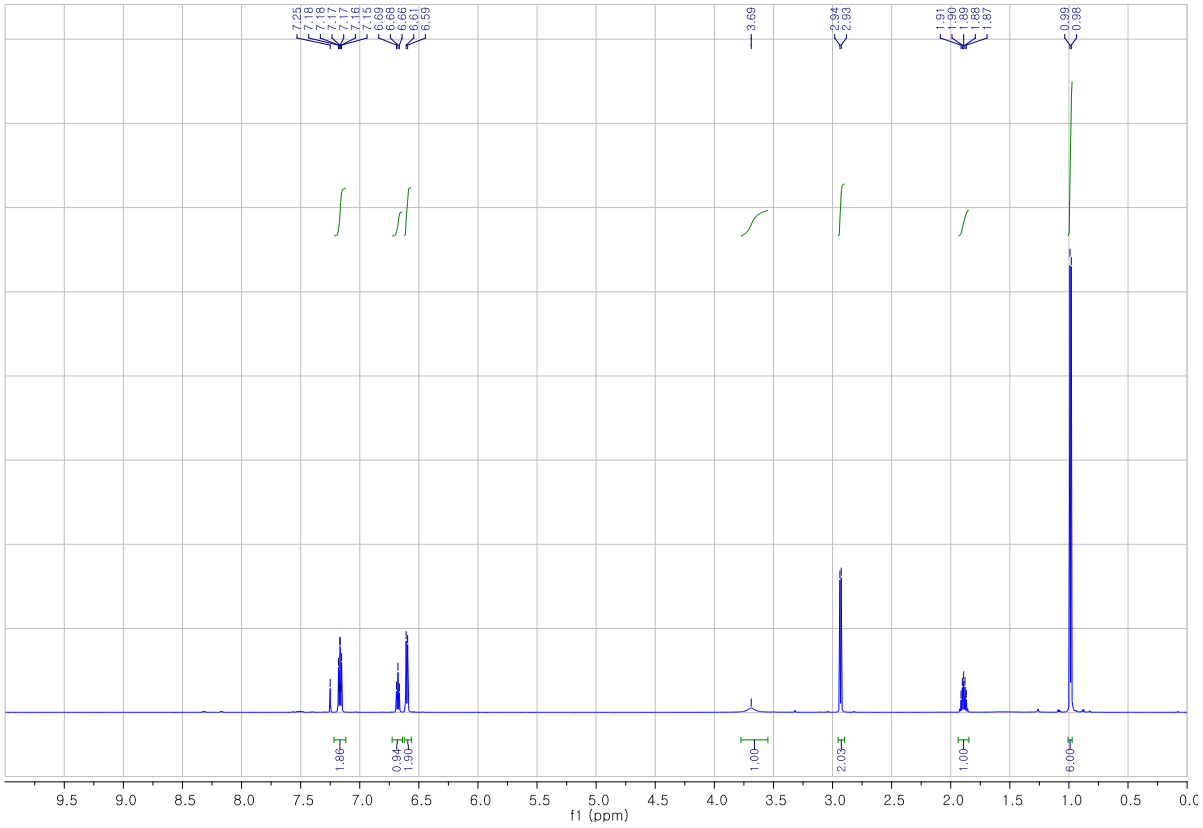
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.7 Hz, 2H), 6.68 (s, 1H), 6.60 (d, *J* = 7.6 Hz, 2H), 3.58 (s, 1H), 3.10 (t, *J* = 7.0 Hz, 2H), 1.64 – 1.58 (m, 2H), 1.27 (s, 14H), 0.87 (d, *J* = 6.5 Hz, 3H).



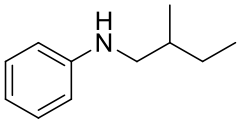
^{1}H NMR of N-Isobutylaniline (3t)



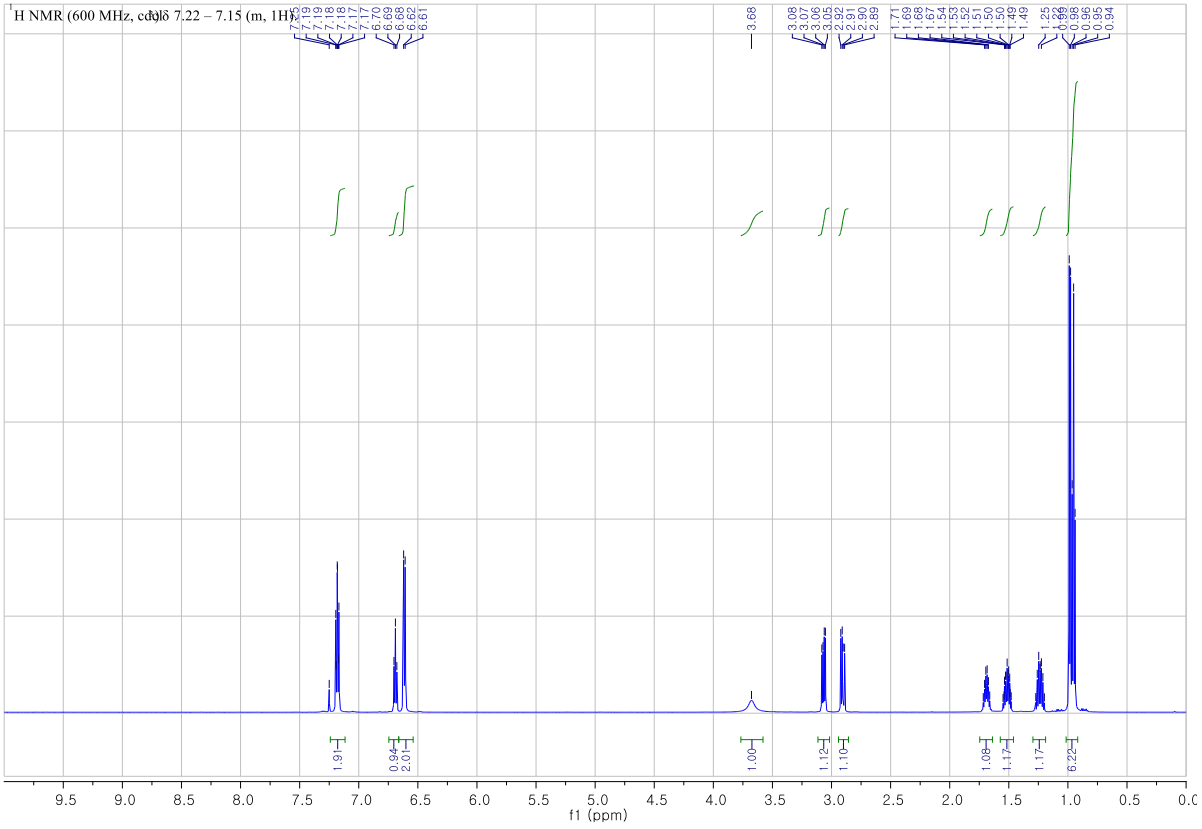
1H NMR (600 MHz, cdcl3) δ 7.20 – 7.13 (m, 2H), 6.68 (t, J = 7.3 Hz, 1H), 6.60 (d, J = 7.7 Hz, 2H), 3.69 (s, 1H), 2.93 (d, J = 6.8 Hz, 2H), 1.89 (dt, J = 13.4, 6.7 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H).



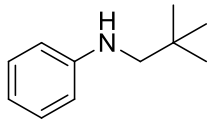
^{1}H NMR of N-(2-methylbutyl)aniline (3u)



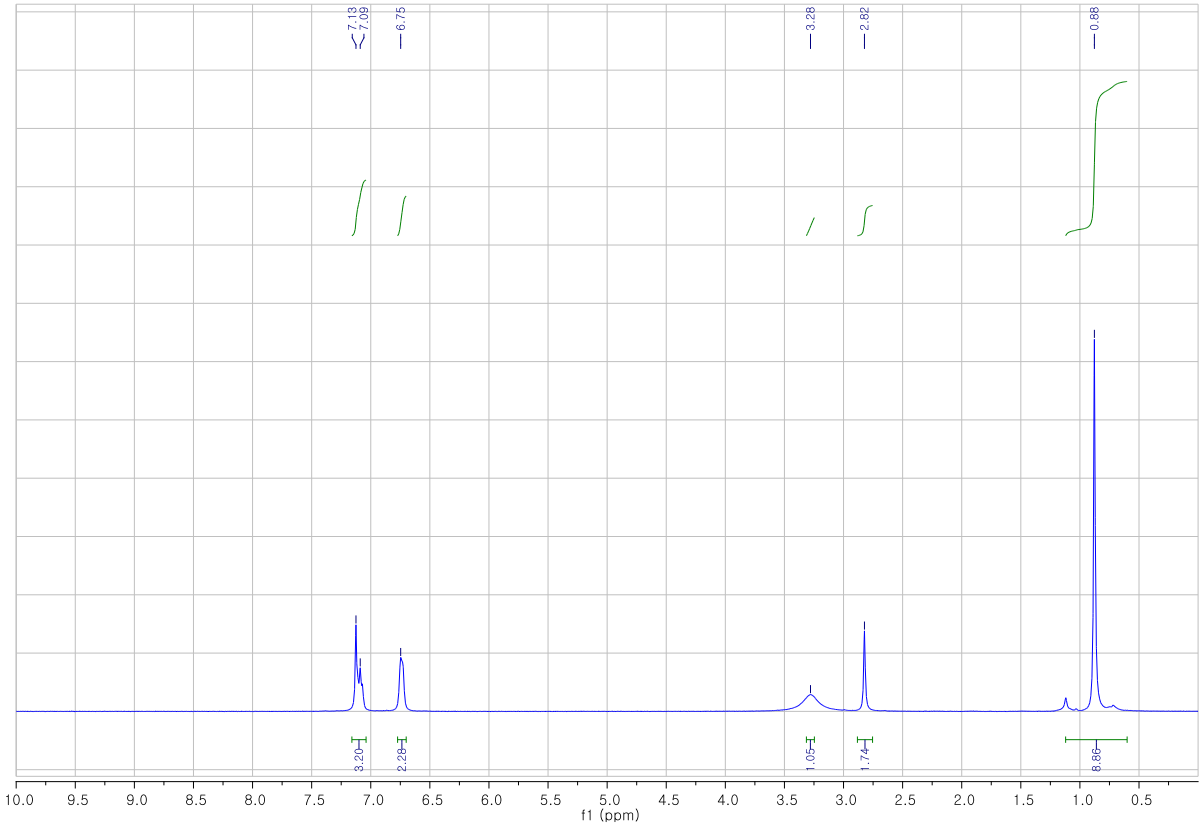
1H NMR (600 MHz, cdcl3) δ 7.22 – 7.15 (m, 2H), 6.69 (t, J = 7.3 Hz, 1H), 6.61 (d, J = 7.7 Hz, 2H), 3.68 (s, 1H), 3.07 (dd, J = 12.2, 6.0 Hz, 1H), 2.91 (dd, J = 12.2, 7.2 Hz, 1H), 1.69 (td, J = 13.1, 6.7 Hz, 1H), 1.57 – 1.45 (m, 1H), 1.32 – 1.16 (m, 1H), 1.03 – 0.91 (m, 6H).



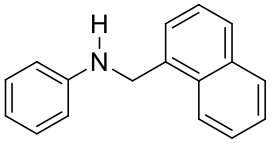
^{1}H NMR of N-neopentylaniline (3v)



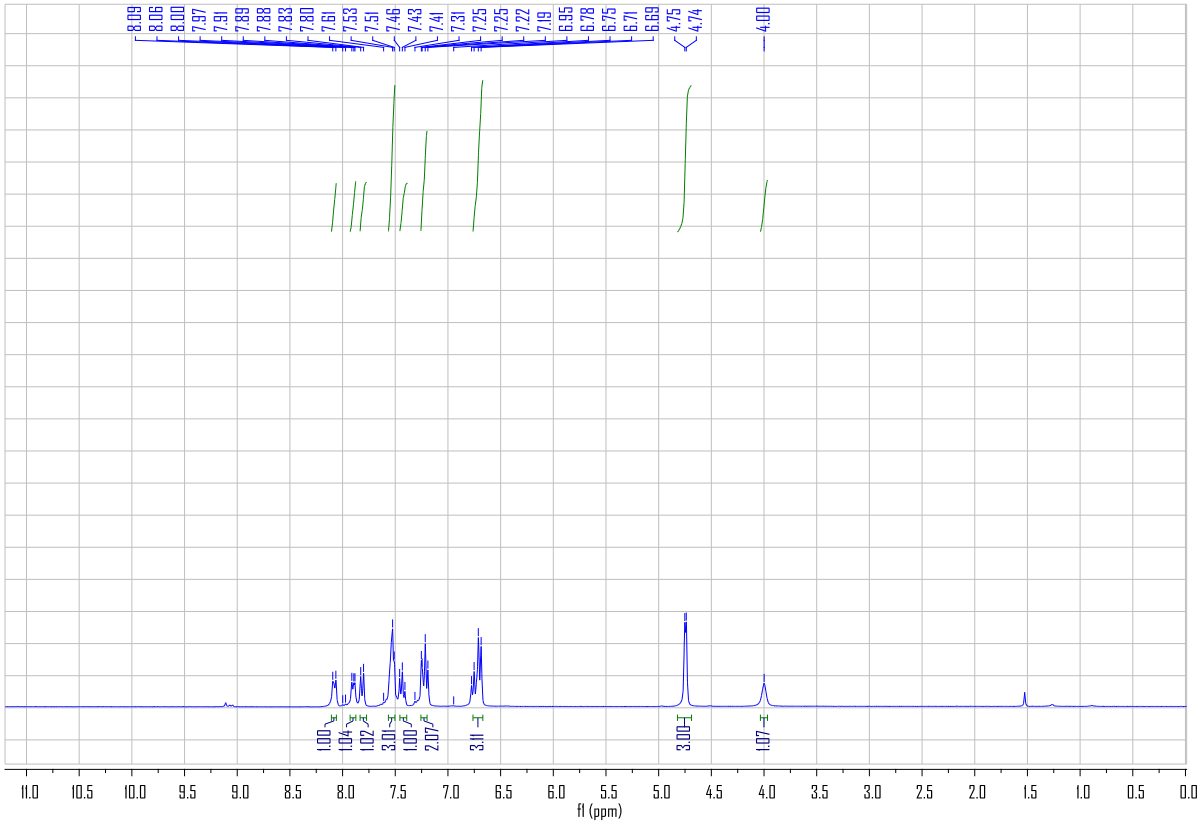
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 14.4 Hz, 3H), 6.75 (dd, 2H), 3.28 (s, 1H), 2.82 (s, 2H), 0.88 (s, 9H).



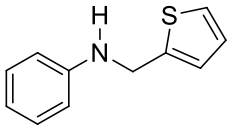
^{1}H NMR of N-(naphthalen-1-ylmethyl)aniline (3w)



^{1}H NMR (300 MHz, cdcl$_3$) δ 8.08 (d, *J* = 8.8 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.52 (d, *J* = 4.6 Hz, 3H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.26 – 7.20 (m, 2H), 6.76 – 6.67 (m, 3H), 4.74 (d, *J* = 4.2 Hz, 3H), 4.00 (s, 1H).



^{1}H NMR of N-(thiophen-2-ylmethyl)aniline (3x)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.15 (m, 3H), 7.08 – 6.92 (m, 2H), 6.76 (t, *J* = 7.3 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 2H), 4.52 (s, 2H), 4.04 (s, 1H).