Supporting Information

An Efficient and Scalable Approach to the Synthesis of 3,5-Dichlorobenzoic Acid

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Content

1. General Remarks

Unless otherwise specified, dry solvents were used in all reactions. The chemicals were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded on a Bruke Avance operating at 400 or 600 MHz, ^{13}C NMR at 101 or 151 MHz, using TMS as an internal standard. The residual solvent signals were used as references for ^{1}H and ^{13}C NMR spectra and the chemical shifts were converted to the TMS scale (DMSO-d_6, 2.50 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, m = multiplet. The coupling constants *J* were given in Hertz. Column chromatography was performed using EM silica gel 60 (100−200 or 200−300 mesh).

2. Experimental equipment and product property

2.1 Preparation of 4-aminobenzoic acid

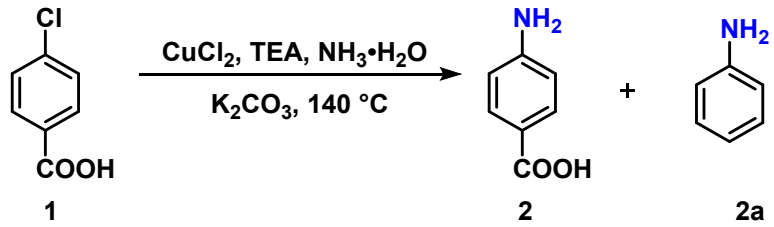


Figure S1 Reaction equipment of amination reaction

Figure S2 The product property of p-aminobenzoic acid

2.2 Preparation of 4-amino-3,5-dichlorobenzoic acid

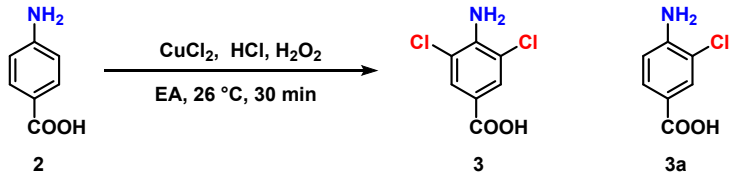
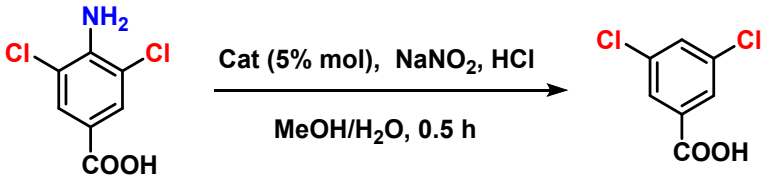


Figure S3 Reaction equipment of dichlorination reaction

Figure S4 The product property of 4-amino-3,5-dichlorobenzoic acid

2.3 Preparation of 3,5-dichlorobenzoic acid



3 4

Figure S5 Reaction equipment of deamination reaction

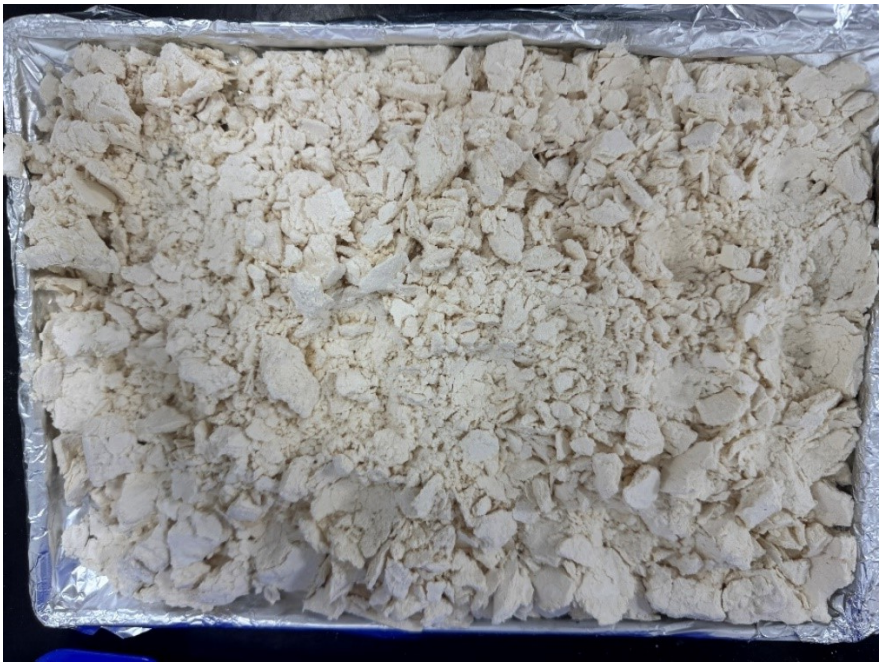


Figure S6 The product property of 3,5-dichlorobenzoic acid

3. Scalability & Green Metrics

Table Sl Process mass intensity (PMI) calculation

parameter	Step 1	Step 2	Step 3
Output	0.710 kg	0.719 kg	0.444 kg
Internal SM	-	0.600 kg (Step 1 product)	0.500 kg (Step 2product)
Total Input	24.58 kg	11.46 kg	9.66 kg
Recovery	86% (DCM)	78% (EA)	0%
Recovered Mass	10.26 kg	3.52 kg	0 kg
Net Input	14.32 kg	7.94 kg	9.66 kg

The amplification factor for each step: Step 1: Output 0.710 kg, requires provision of: 0.940 kg (for Step 2), amplification factor: 0.940 ÷ 0.710 = 1.324; Step 2: Output: 0.719 kg, requires provision of: 1.126 kg (for Step 3), amplification factor: 1.126 ÷ 0.719 = 1.566; Step 3: Output: 0.444 kg, needs to produce: 1.000 kg, amplification factor: 1.000 ÷ 0.444 = 2.252

$$PMI = \frac{total\ mass\ of\ process\ steps}{mass\ of\ product}$$

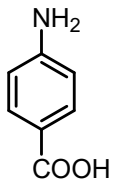
$$= \frac{14.32 \times 1.324 + (7.94 - 0.60) \times 1.566 + (9.66 - 0.50) \times 2.252}{1} = 51.48$$

$$\approx 51.5$$

$$E - factor = \frac{mass\ of\ tatal\ wastes}{mass\ of\ product}$$ =EffectivePMI-1=51.5-1=50.5

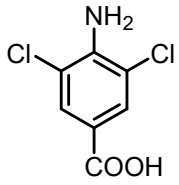
4. NMR data copies

4-aminobenzoic acid (2)[1]



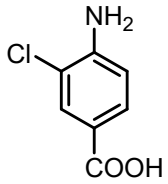
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 7.66 – 7.59 (m, 2H), 6.59 – 6.52 (m, 2H), 5.88 (s, 2H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 168.00, 153.65, 131.72, 117.35, 113.05.

4-amino-3,5-dichlorobenzoic acid (3)[2]



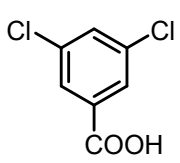
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (s, 2H), 6.34 (s, 2H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 166.02, 145.61, 129.70, 119.04, 117.60.

4-amino-3-chlorobenzoic acid (3a)[2]



^{1}H NMR (600 MHz, DMSO-d_6) δ 12.35 (s, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.61 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.15 (s, 2H). **^{13}C NMR (151 MHz, DMSO-d_6)** δ 166.96, 149.32, 131.10, 129.98, 118.80, 116.41, 114.61.

3,5-dichlorobenzoic acid (4)[3]



^{1}H NMR (400 MHz, DMSO-d_6) δ 13.68 (s, 1H), 7.91 (s, 1H), 7.85 (s, 2H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ 165.44, 135.01, 134.83, 132.76, 128.29.

5. Reference

1 Van Kalkeren, H. A.; Bruins, J. J.; Rutjes, F. P. J. T.; Van Delft, F. L. *Adv. Synth. Catal.* **2012**, *354*, 1417-1421.

2 Kim, D. Sarkar, Y. Kim, M. H. Park, M. Yoon, Y. Kim and M. Kim, *J. Ind. Eng. Chem.*, **2017**, 53, 171 —176

3 Wang, CC., Zhang, GX., Zuo, ZW. et al. *Sci. China Chem*. **2021**, 64, 1487–1492.

6. NMR Spectra

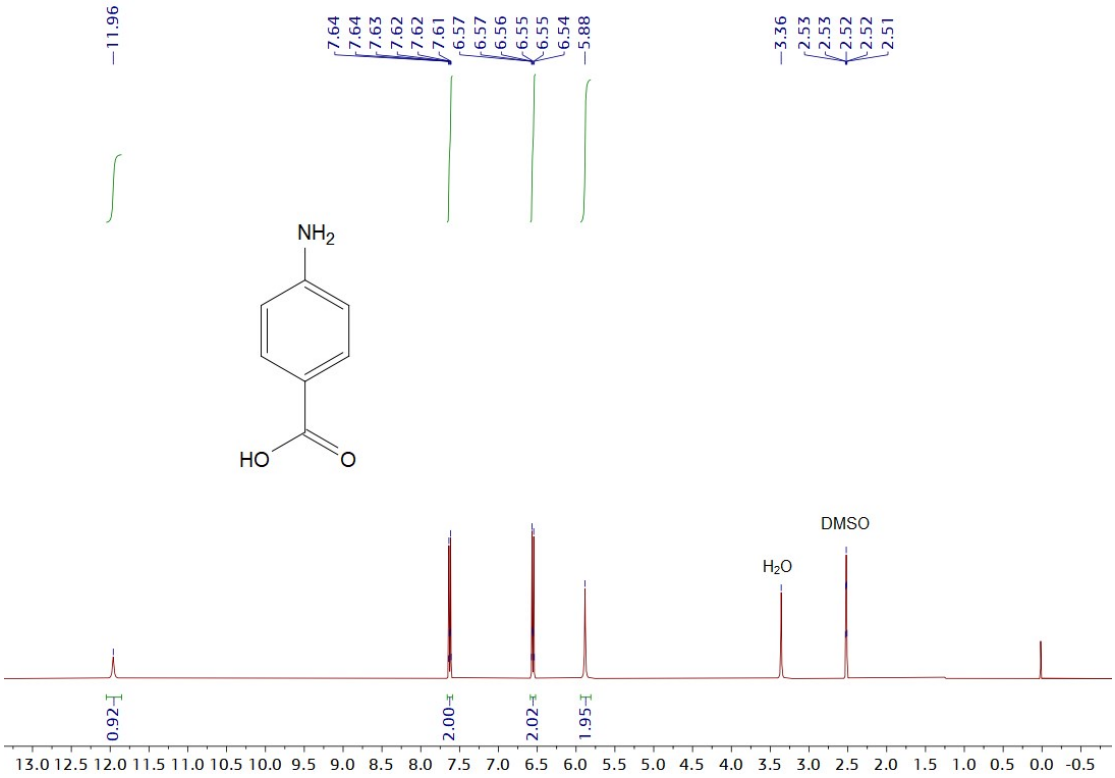


Figure S7 ^{1}H NMR spectrum of compound **2** (DMSO, 400 MHz)

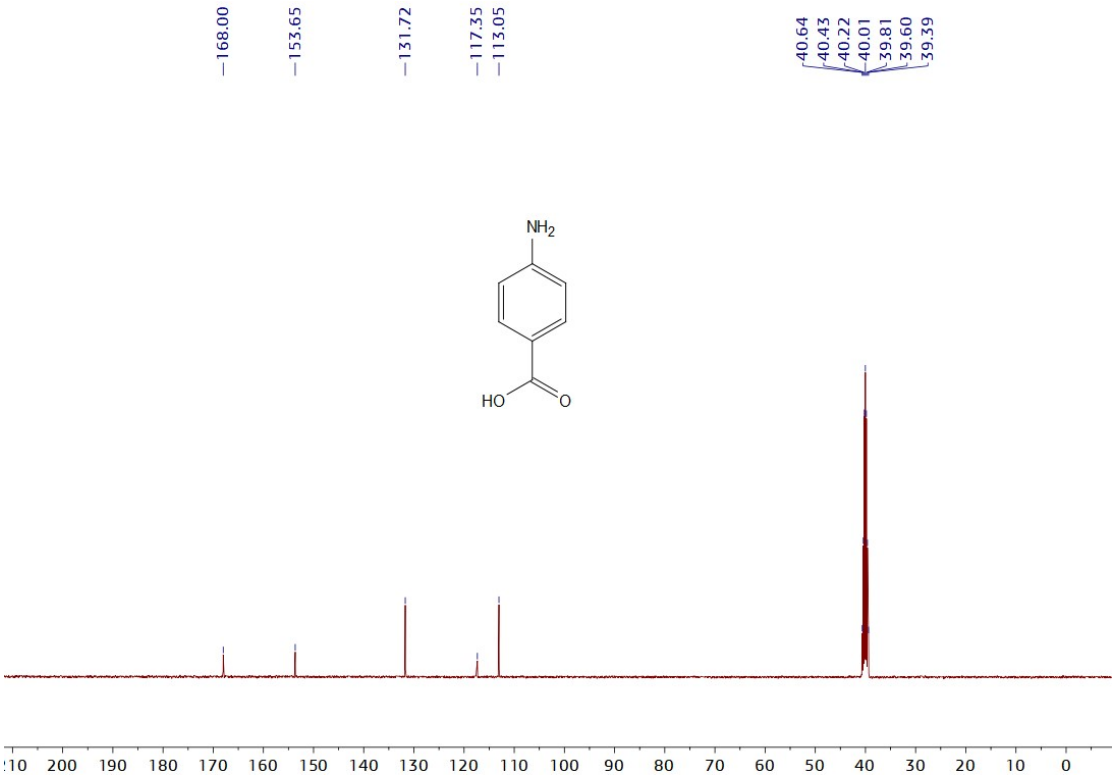


Figure S8 ^{13}C NMR spectrum of compound **2** (DMSO, 101 MHz)

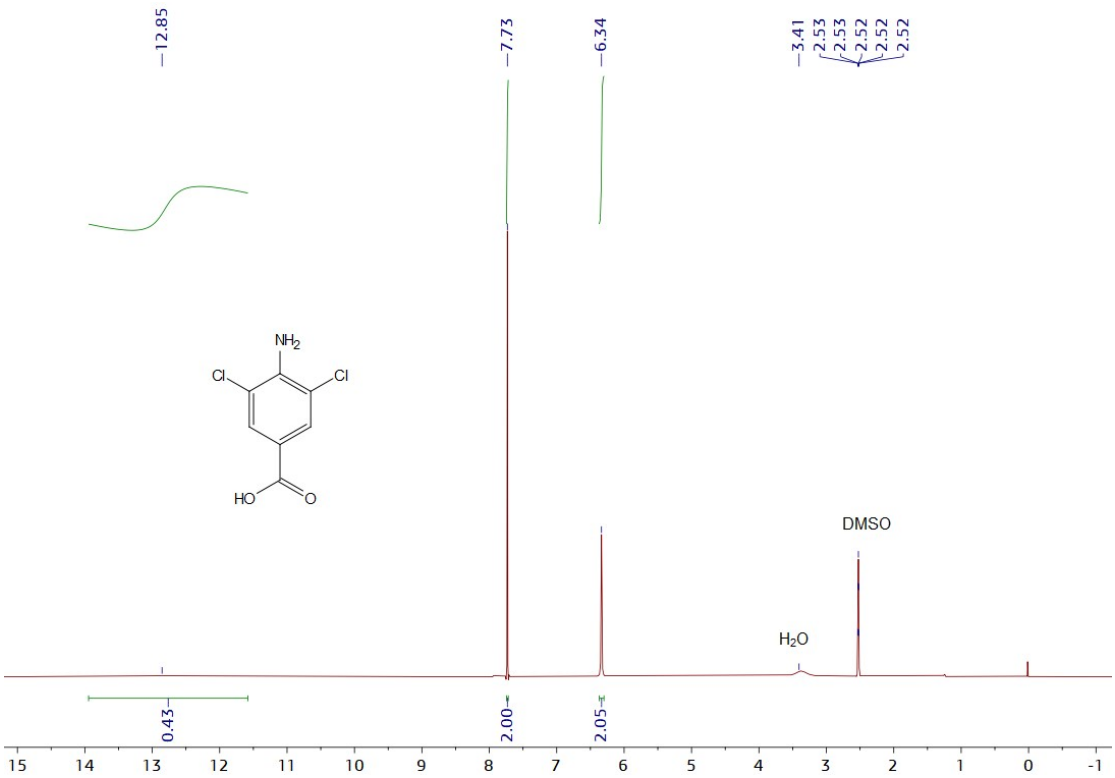


Figure S9 ^{1}H NMR spectrum of compound **3** (DMSO, 400 MHz)

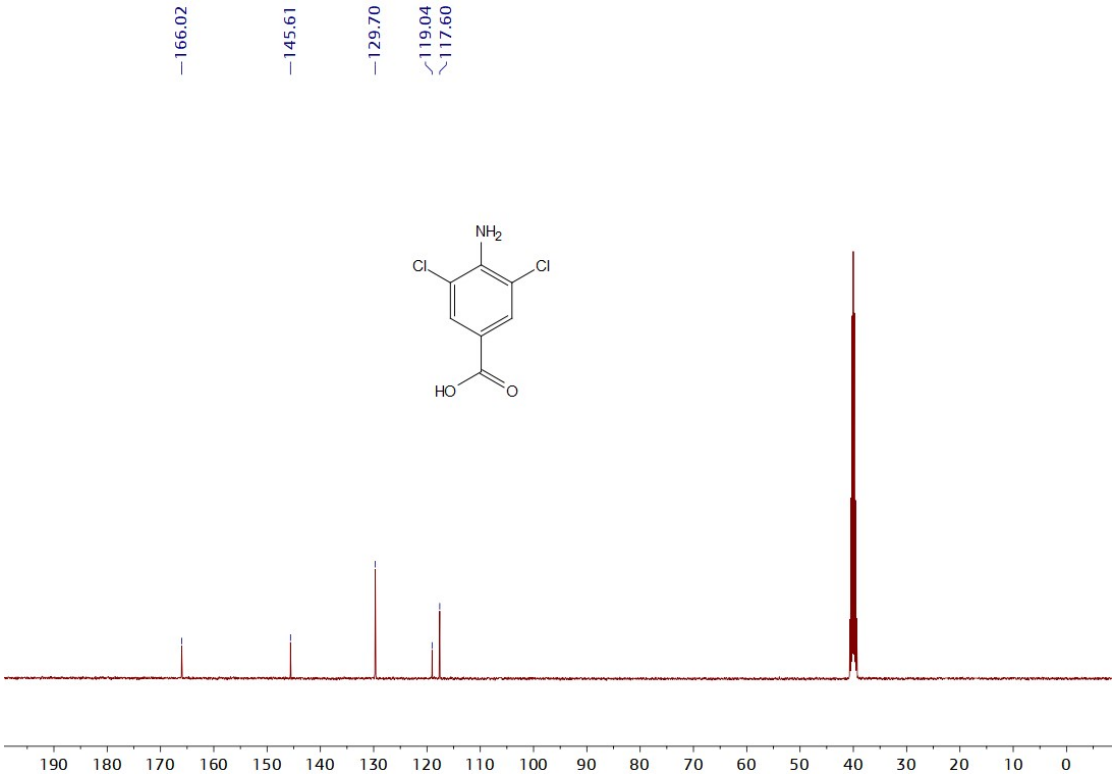


Figure S10 ^{13}C NMR spectrum of compound **3** ($CDCl_3$, 101 MHz)

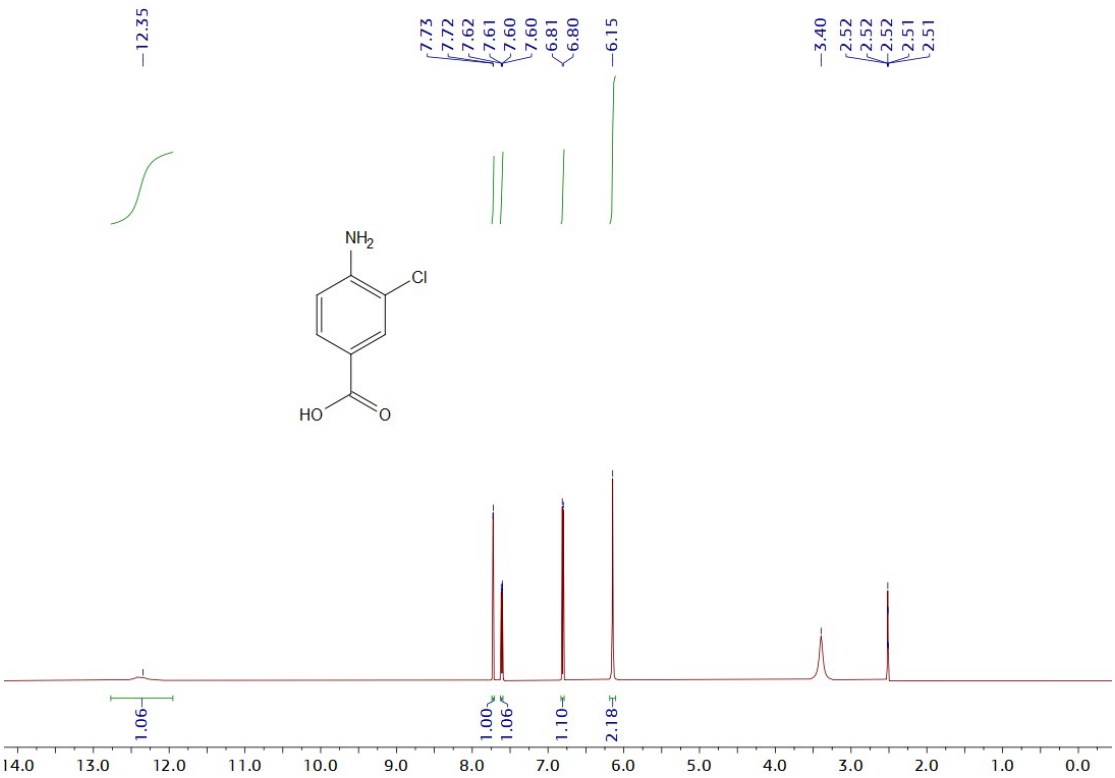


Figure S11 ^{1}H NMR spectrum of compound **3b** (DMSO, 600 MHz)

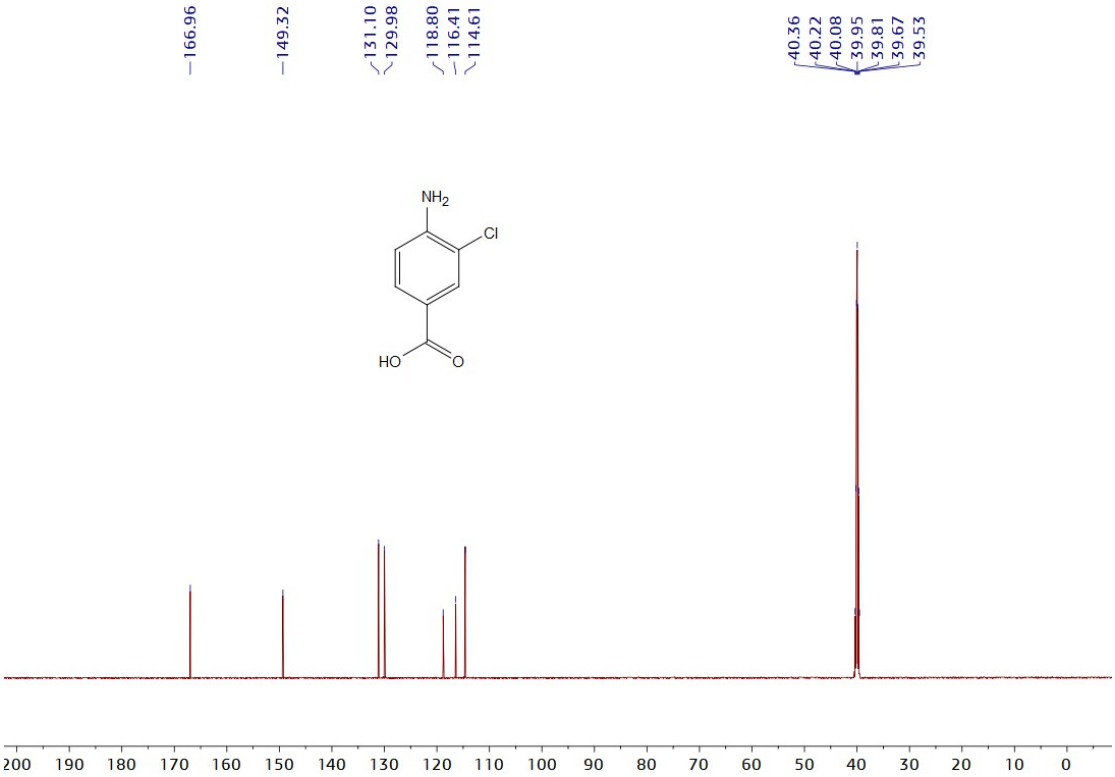


Figure S12 ^{13}C NMR spectrum of compound **3b** (DMSO, 151 MHz)

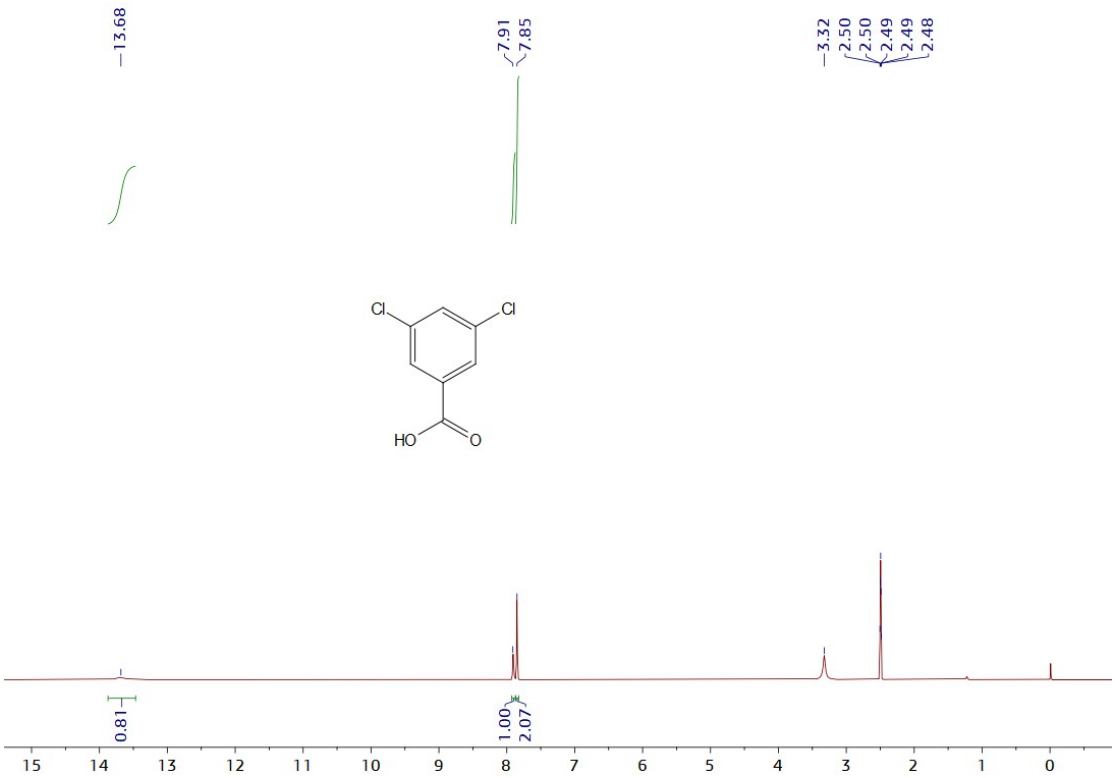


Figure S13 ^{1}H NMR spectrum of compound **4** (DMSO, 400 MHz)

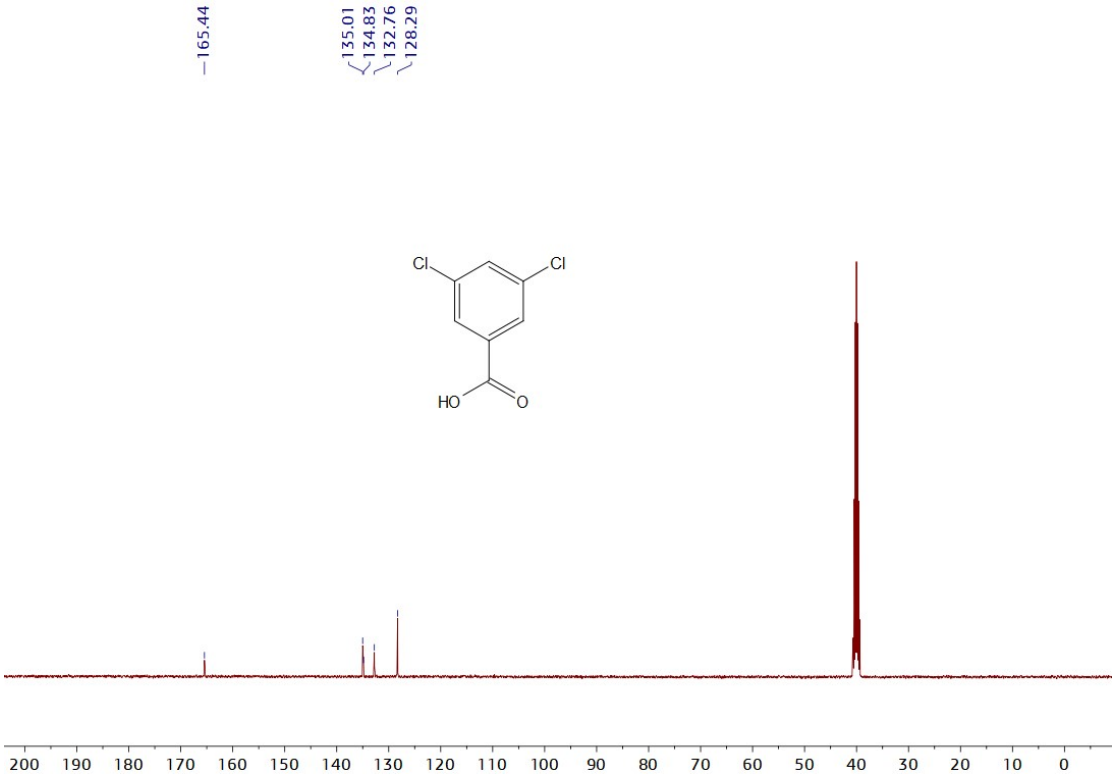


Figure S14 ^{13}C NMR sspectrum of compound **4** (DMSO, 101 MHz)