Supplementary Information

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1. General experimental details

All flow based experiments were performed using a Uniqsis FlowSyn SS instrument fitted with standard PTFE and SS tubing. Back pressure regulators are fitted with chemically resistant perfluoropolymer or Hastelloy components.

Glass columns used in the experiments are OMNIFIT glass columns with enhanced PEEK adjustable end fittings. The FlowSyn column housing fitted in the flow reactor accepts 10 mm in diameter x 100 mm columns and is adjustable for different column sizes. The columns can operate under a maximum operating temperature of 150 ^{o}C with a 600-psi pressure limit.

The mixer block used is machined from borosilicate glass and is chemically inert, the mixer block incorporates 1 mm in diameter channels with active mixing geometries. The total mixing volume is 2 mL and has a maximum operating temperature of 150 ^{o}C and a maximum operating pressure of 600 psi.

PTFE and SS coils with 14 mL and 20 mL volumes respectively were used. The internal diameters of the coils were 1 mm. Operating temperature of up to 150 ^{o}C - 160 ^{o}C were used.

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker AVANCE-III-300 Bruker AVANCE-III-400 spectrometers at 300.13 and 400.13 MHz respectively using standard pulse sequences. All spectra were recorded in deuterated chloroform ($CDCl_3$ at 7.26 ppm), deuterium oxide (D_2O at 4.79 ppm) or deuterated dimethyl sulfoxide (d6-DMSO at 2.50 ppm) in 5 mm NMR spectroscopy tubes. Chemical shifts, δ, are reported in parts per million (ppm), and splitting patterns are given as singlet (s), doublet (d), triplet (t), quartet (q), broad (b) or multiplet (m). Coupling constants, *J,* are expressed in hertz (Hz). In noted cases conversions were determined from ^{1}H NMR spectra by comparison of integral areas of starting materials and products. All NMR spectra (^{1}H and ^{13}C NMR) were compared to known literature spectra.

High-resolution mass spectra were recorded on a Waters Synapt G2 Mass Spectrometer at 70 eV and 200 mA. For analysis, the instrument was operated under the following conditions: capillary voltage 2.8 kV (positive mode), 2.5 kV (negative mode), sampling cone

(ramped from 20 V - 40 V), extraction cone 4 V, source temperature 100°C, desolvation temperature 200°C, Cone gas 100 L/h, desolvation gas 500 L/h, MS gas: nitrogen. Samples were made up in acetonitrile (containing 0.1 % formic acid) to an approximate concentration of 10 µg/mL.

2. Synthetic procedures in batch

2.1. 2-((4-Chloro-2 nitrophenyl)amino)benzoic acid 4

A mixture of anthranilic acid **2** (1 eq, 4.41 mmol, 0.615 g), 2-bromo-5-chloronitrobenzene **3** (1.1 eq, 4.85 mmol, 1.13 g), anhydrous potassium carbonate (2 eq, 8.82 mmol, 1.22 g), and copper powder (0.2 eq, 1.0 mmol, 0.066 g) were mixed together in iso-propanol (15 mL) and refluxed for 12 hours under an inert atmosphere. The solvent was removed under reduced pressure and water was added to the reaction mixture. The mixture was filtered and the filtrate was acidified with aqueous hydrochloric acid (2 M) to a pH 3 - 4. The precipitate was collected and recrystalized in EtOH/water to afford 2-((4-chloro-2 nitrophenyl)amino)-benzoic acid **4** as orange needles in 80% yield. **mp** 245 - 247 ^{o}C; **Rf** 0.65 (5 % MeOH: DCM); **^{1}H NMR** (300 MHz, DMSO) δ 13.49 (br s, 1H), 11.08 (s, 1H), 8.14 (s, 1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.63 (s, 2H), 7.57 – 7.47 (m, 2H), 7.12 (t, *J* = 6.6 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO) δ 169.2, 142.1, 137.8, 137.5, 136.5, 135.7, 134.1, 132.3, 125.9, 123.8, 122.7, 121.3, 119.4; **IR ν_{max}/cm^{-1}** (2853, 1671, 1580, 1503, 1406, 1346, 1260, 1153, 863, 818, 740, 622, 516); **HRMS m/z (EI)** 293.0302.

2.2. 2-((2-Amino-4-chlorophenyl)amino)benzoic acid 5

A mixture of 2-(4-chloro-2-nitroanilino)benzoic acid **4** (1 eq, 1.71 mmol, 0.491 g) and aqueous ammonia (2 M, 25 mL) was warmed to 80 ^{o}C. Sodium dithionite (6 eq, 10.2 mmol, 1.78 g) was then added portion-wise to the red/crimson solution affording a colour change from red to yellow (±15 minutes). Decolourising charcoal was added and the mixture was filtered whilst hot. The filtrate was adjusted to a pH 4.5 with glacial acetic acid and the product collected by filtration. Recrystallization in MeOH/water afforded the pure 2-(2-amino-4-chloro-anilino) benzoic acid **5** as a white-yellow solid in 65 % yield; **mp** 198 – 200 °C; **Rf** 0.39 (3:1 EtOAc/Hexanes); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.86

(dd, *J* = 8.0 & 1.7 Hz, 1H), 7.29 (ddd, *J* = 8.7, 7.1 & 1.7 Hz), 7.03 (d, *J* = 8.3 Hz, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 6.68 (ddd, *J* = 8.1, 7.1 & 1.1 Hz, 1H), 6.62 – 6.50 (m, 2H), 5.19 (s, 2H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 170.5, 149.3, 146.3, 134.5, 132.0, 130.5, 128.0, 124.3, 116.7, 116.2, 114.7, 113.7, 112.4; **IR ν_{max}/cm^{-1}** 3456, 1663, 1620, 1572, 1500, 1444, 1336, 1244, 1156, 1089, 1043, 915, 847, 785, 744 and 660; **HRMS m/z (EI)** 245.0502.

2.3. 8-Chloro-5H-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one 6

A mixture of 2-(2-amino-4-chloroanilino) benzoic acid **5** (1 eq, 0.77 mmol, 0.21 g) and xylenes 50 mL were heated under Dean Stark conditions for 96 hours. The reaction mixture was cooled, evaporated to dryness *in vacuo* and the resulting residue was washed with hot aqueous ammonia (2 M, 2 × 25 mL). The product was recrystallized from acetone/water to afford pure 8-chloro-10,11- dihydro-5*H*-dibenzo[*b, e*][1, 4] diazepine-11-one **6** in a 74 % yield as light yellow platelets. **mp** 232 - 235 °C; **Rf** 0.81 (5 % MeOH/DCM); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 9.91 (s, 1H), 7.97 (s, 1H), 7.68 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.41 – 7.28 (m, 1H), 6.98 (m, *J* = 10.6 Hz, 4H), 6.90 (t, *J* = 7.5 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ168.1, 150.3, 139.2, 133.9, 132.7, 131.7, 126.7, 124.4, 122.8, 121.5, 121.4, 120.9, 119.6; **IR ν_{max}/cm^{-1}** 3357, 3177, 3053, 2927, 1656, 1590, 1495, 1463, 1370, 1301, 1248, 1215, 1132, 946, 862, 814, 745, 684, 639, 601, 507, 457; **HRMS m/z (EI)** 245.0497.

2.4. 8-Chloro-11-(4-methylpiperazin-1-yl)-5*H*-dibenzo[*b,e*][1,4]diazepine 1

To a solution of piperazine (8 eq, 2.5 mmol, 0.27 mL) in anhydrous 1,4-dioxane (3.5 mL) under argon was added titanium tetrachloride (2 eq, 0.64 mmol, 0.070 mL). The mixture was warmed to 50 - 55 ^{o}C and a solution of 8-chloro-10,11- dihydro-5*H*-dibenzo[*b, e*][1, 4] diazepine-11-one **6** (1 eq, 0.32 mmol, 0.071 g) in anhydrous 1,4-dioxane (3.5 mL) was added. The mixture was heated at reflux for 24 hours after which time it was evaporated to dryness under vacuum. The residue was partitioned between ethyl acetate (20 mL) and aqueous hydrochloric acid (2 M, 10 mL) then filtered under vacuum. The aqueous phase was extracted with ethyl acetate to remove unreacted lactam prior to being basified with sodium hydroxide to pH 14 and extracted with ethyl acetate. The organic layers were combined and dried over sodium sulfate and evaporated to dryness *in vacuo.* The product was purified via column chromatography (20% MeOH/DCM) to afford clozapine **1** in 69 %

yield; **mp** 182 - 184 °C; **Rf** 0.66 (20 % MeOH/DCM); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 10.7, 4.6 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 6.97 (m, 2H), 6.83 – 6.74 (m, 2H), 6.57 (d, *J* = 8.3 Hz, 1H), 4.89 (s, 1H), 3.67 (s, 4H), 2.81 (s, 4H), 2.52 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9, 152.9, 141.7, 140.7, 132.1, 130.3, 129.1, 126.7, 123.3, 123.3, 123.2, 120.2, 120.2, 54.8, 45.9, 29.6; **IR ν_{max}/cm^{-1}** 3284, 2923, 1598, 1557, 1457, 1370, 1286, 1227, 1132, 1079, 1000, 929, 873, 833, 777, 671, 577, 525; **HRMS m/z (EI)** 327.1396.

3. Flow based procedures

3.1. Preparation of stock solutions for stage 1

Stock solutions of both starting materials were prepared by dissolution in IPA. Anthranilic acid **2** (3.66 mmol, 0.501 g) was dissolved in 24 mL of IPA to prepare a concentration of 0.15 M. 2-Bromo-4-chloro-2-nitrobenzene **3** (3.94 mmol, 0.933 g) was dissolved in 26 mL of IPA to prepare a concentration 0.15 M.

3.2. Flow synthesis of 2-((4-Chloro-2-nitrophenyl)amino)benzoic acid 4

A stock solution of 0.3 M concentration of the starting materials was prepared by dissolving anthranilic acid **2** (1 eq, 1.2 mmol, 0.17 g) and 2-bromo-4-chloro-2-nitrobenzene **3** (1,2 eq, 1.4 mmol, 0.35 g) in IPA (8.5 mL). The stock solution inlets were connected via selector valves to HPLC pumps followed by a T-piece mixer which was in turn connected to a column reactor packed with excess amounts of potassium carbonate and copper powder (prepared by grinding together with a mortar and pestle). The outlet was passed through a 100 psi back pressure regulator with the addition of a recycling loop which was achieved by placing the outlet line into the starting material stock reservoir. IPA was employed as the pushing solvent and a flow rate of 0.125 mL min^{-1} was used affording a residence time of 27 minutes. The reaction was run for 3.5 hours after which time it was stopped and processed following the method described in the batch method. A yield of 38 % was obtained.

3.3. Hybrid synthesis of 2-((4-Chloro-2-nitrophenyl)amino)benzoic acid 4

The general batch procedure described in 1.1 was carried out. Once the reaction was completed (4 hrs for pentanol and 12 hrs for IPA), water was pumped into the reaction

mixture precipitating unreacted 1-bromo-4-chloro-2-nitrobenzene **3**, the solution was then pumped into in-line triturator (Figure 1) fitted with an overhead stirrer which was pre-primed with 6M HCl (50 mL) and cooled to 0 ˚C (Figure 2). The desired 2-((4-chloro-2 nitrophenyl)amino)-benzoic acid **4** precipitated as an orange solid and the filtrate was removed via vacuum filtration. The product **4** was dried under vacuum after which time ammonia/acetone was added to the in-line triturator to dissolve the starting material for the next stage. (Isolated yield 80 % when run as a standalone stage).

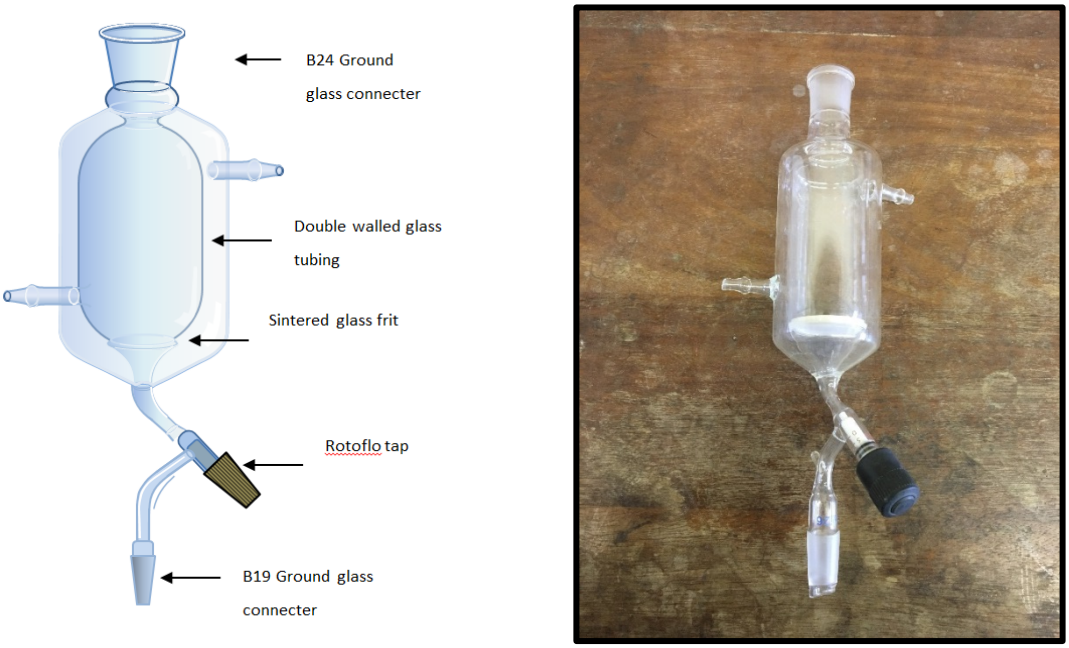


Figure 1: Schematic diagram of the in-line triturator

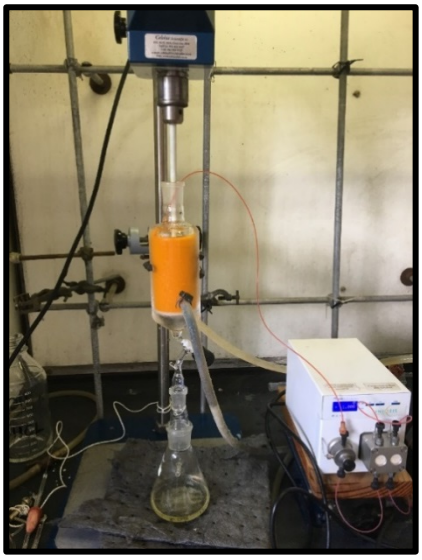


Figure 2: In-line triturator with the precipitated 2-((4-chloro-2 nitrophenyl)amino)-benzoic acid **4** (Stage 1)

3.4. Preparation of stock solutions for stage 2

Stock solutions of both starting reagents were prepared by dissolution in acetone, 2 M NH_3(aq) as solvent. Starting material A 2-(4-chloro-2-nitroanilino)benzoic acid **4** (3.42 mmol, 1.02 g) was dissolved in Acetone/NH_3(aq) 1:1 (50 mL) to prepare a concentration of 0.0625 M. Starting material B (Sodium dithionite) (24 mmol, 4.2 g) was dissolved in Water/NH_3(aq) 1:1 (80 mL) to prepare a concentration of 0.3 M.

3.5. 2-((2-Amino-4-chlorophenyl)amino)benzoic acid 5

Starting reagents were prepared per the procedure in 2.4. The starting material stocks (A + B) were connected to two HPLC pumps via selector valves followed by a 2 mL mixing chip prior to passage through a 100 psi back pressure regulator. A known volume of each starting reagent was pumped at a flow rate of 1.3 mL min^{-1} at ambient temperature. The stock solution B was also used as the pushing solvent facilitated but the insertion of the pushing solvent inlet lines into the B stock reservoir. A post collect of 8 mL was inserted at the end of the reaction. The product was collected in the in-line triturator pre-primed with 50 mL, 6 M acetic acid and cooled to 0 ˚C. Following precipitation of **5** the filtrate was removed via vacuum filtration. The product was left to dry under vacuum for 12 hours. Anhydrous THF was added to the triturator to dissolve the product for stage 3. (Isolated yield 79 % when run as a standalone stage)

Figure 1: Reaction setup for stage 2 connected to in-line triturator

3.6. Preparation of stock solutions for stage 3

Stock solution of the starting material was prepared via dissolution in anhydrous THF. The starting material 2-(2-amino-4-chloroanilino) benzoic acid **5** (0.76 mmol, 0.21 g) was dissolved in 5 mL THF to prepare a stock solution of 0.15 M.

3.7. 8-Chloro-5H-dibenzo[*b,e*][1,4]diazepin-11(10*H*)-one

A 0.15 M stock solution of the starting material was prepared by dissolution in dry THF. The solution was pumped continuously through a column reactor packed with polymer supported EDC (1,5 eq for each run) connected to a recycling loop (Figure 3). The reactor was primed with dry THF for 20 minutes prior to reaction start. The flow rate was set to 0.25 mL/min overall. The reaction was recycled for 6 hours after which time a conversion by ^{1}H NMR spectroscopy of ≥85 % was observed. After recycling was complete the column was washed with THF. The solution was passed through a solvent swapper (Figure 4) and enriched with anhydrous toluene achieved by introducing a toluene line into the reaction stream via a t-piece adaptor prior to passage through the swapper. The flow rate of the THF line was set at 0.2 mL/min and that of the toluene at 0.8 mL/min (A total of 15 mL THF and 60 mL Toluene were used), the solvent swapper was heated to 40 ˚C and Argon was used as the carrier gas. The remaining solvent in the reaction column was pumped out in intervals of 5 minutes. The solution was collected and directly used in stage 4. (Isolated yield 76 % when run as a standalone stage). Table 1 highlights the development of the solvent swopping process when using pure THF and toluene as feedstocks.

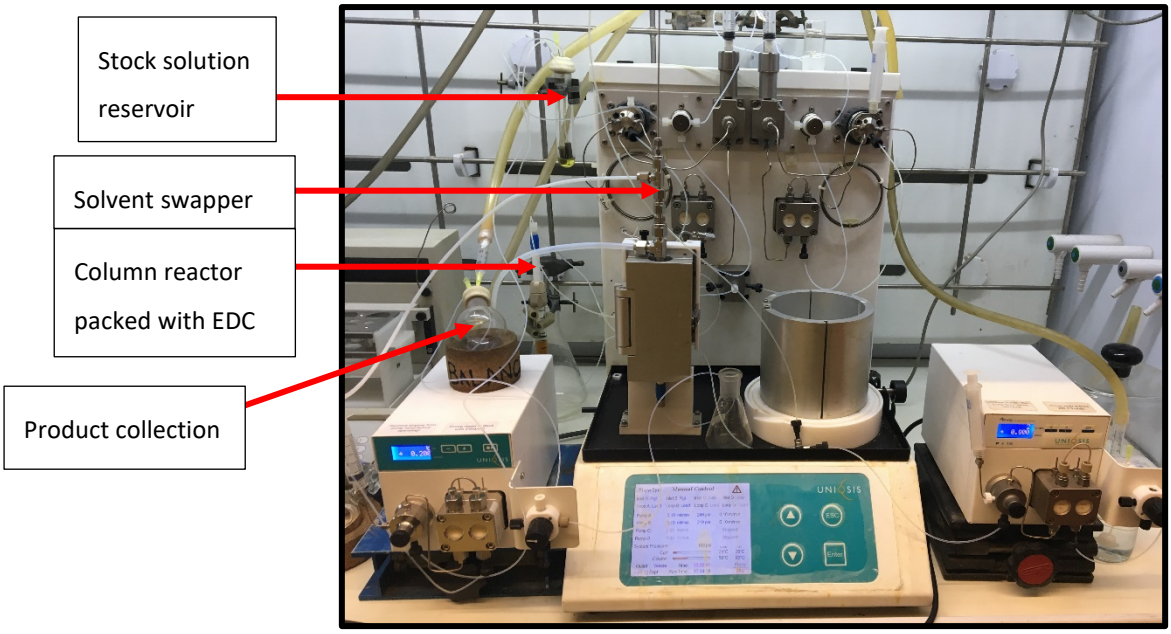


Figure 2: Flow reactor setup for stage 3 along with in-line solvent swapper

Table 1: Optimisation of solvent swap from THF to toluene.

Test number	THF: Toluene ratio	Temp	Flow rate	Time (min)	THF remaining[a]
1	1: 1	RT	1 mL/min	15	69 %
2	1: 1	RT	0.5 mL/min	15	63 %
3	1: 1	RT	0.25 mL/min	25	63 %
4	1: 1	RT	0.5 mL/min	15	22 %[b]
5	1: 1	40	0.5 mL/min	15	35 %
6	1: 1	60	0.5 mL/min	15	25 %
7	1: 2	RT	1 mL/min	15	31 %
8	1: 2	RT	0.5 mL/min	15	33 %
9	1: 2	RT	0.25 mL/min	25	28 %
10	1: 2	40	0.5 mL/min	15	35 %

11	1: 2	60	0.5mL/min	15	25 %
12	1: 4	RT	0.5 mL/min	15	10 %[b]
13	1: 4	RT	0.5 mL/min	15	10 %
14	1: 4	40	0.5 mL/min	15	0 %
15	1: 4	60	0.5 mL/min	15	0 %

[a] Standalone pump was connected to the bottom of the column reactor and switched on to pump out the solvent mix.

[b] Solvent swapper was run for 5 min before turning on the standalone pump.

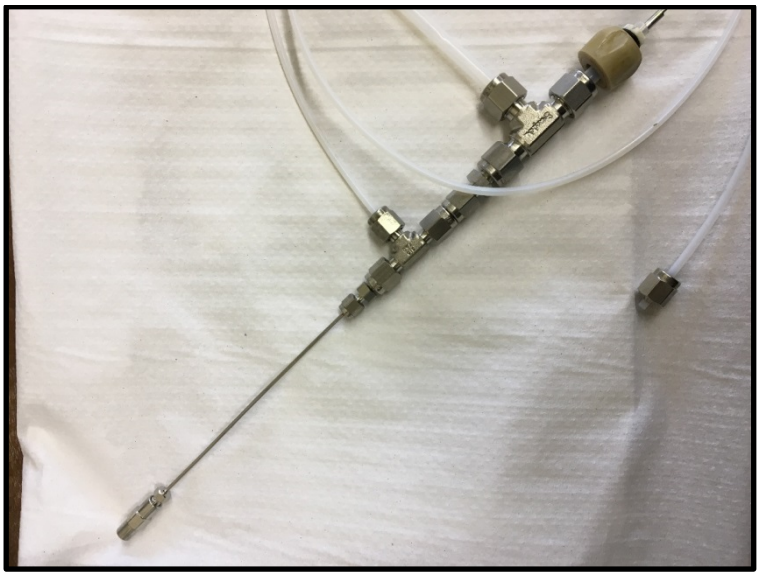


Figure 4: Solvent swapper used in stage 3 to exchange between THF and toluene

3.8. 8-Chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine 1

The material collected from stage 3 was pumped into a round bottom flask. Titanium tetrachloride (2 eq, 1.52 mmol, 0.28 g) and N-methylpiperazine (8 eq, 6.08 mmol, 0.609 g) were introduced to the flask under argon at room temperature. The resulting solution was refluxed for 24 hours and processed as described in the batch procedure in 1.4. An overall yield of 72 % (0.18 g) was obtained over 2 stages.

4. Comparison of Reaction times and Yields between batch procedure and hybrid procedure

Table 1: Comparison of Batch and hybrid results

	Literature Results	Batch Procedure	Hybrid Procedure
Stage 1	74 % RT = 4 hours	80 % RT = 12 hours	80 % RT = 12 hours
Stage 2	64 % RT = 15 minutes	65 % RT = 15 minutes	79 % RT = 92 seconds
Stage 3	79 % RT = 96 hours	74 % RT = 96 hours	72 % two stages RT = 30 hours
Stage 4	69 % RT = 12 hours	69 % RT = 24 hours	
Total	25.8 % RT = 112.25 hours	27 % RT = 132.25 hours	45 % RT = 44 hours

5. Scanning Electron Microscope Images

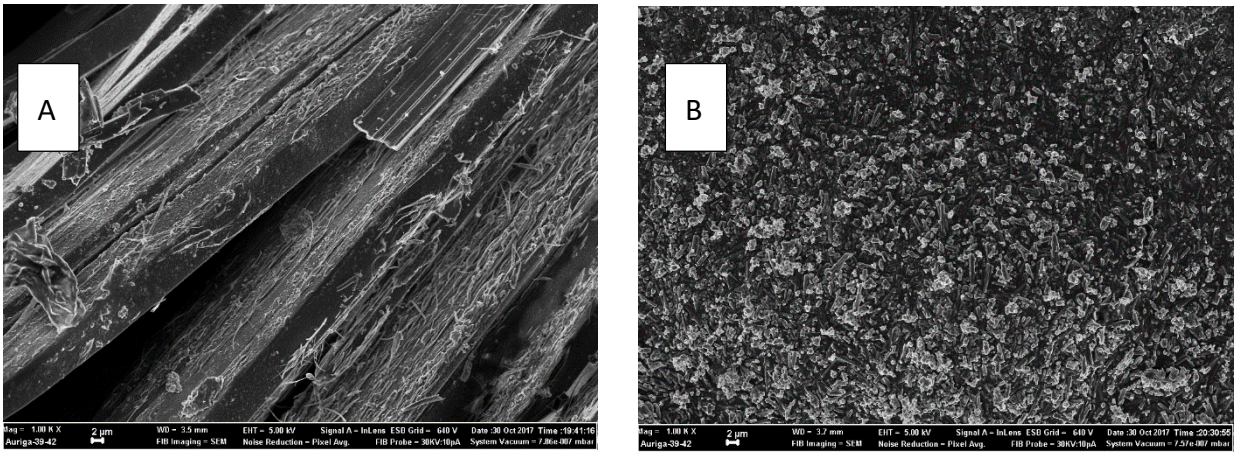


Figure 5.1: SEM scans of diarylamine [4] recrystallized [**A**] and triturated [**B**] (1000 × magnification)

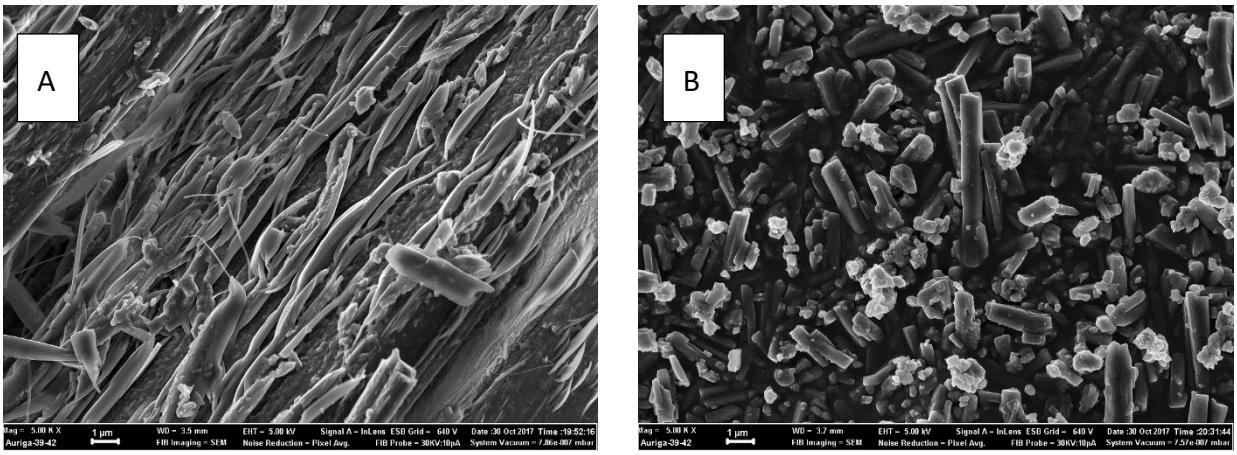


Figure 5.2: SEM scans of diarylamine [4] recrystallized [**A**] and triturated [**B**] (5000 × Magnification)

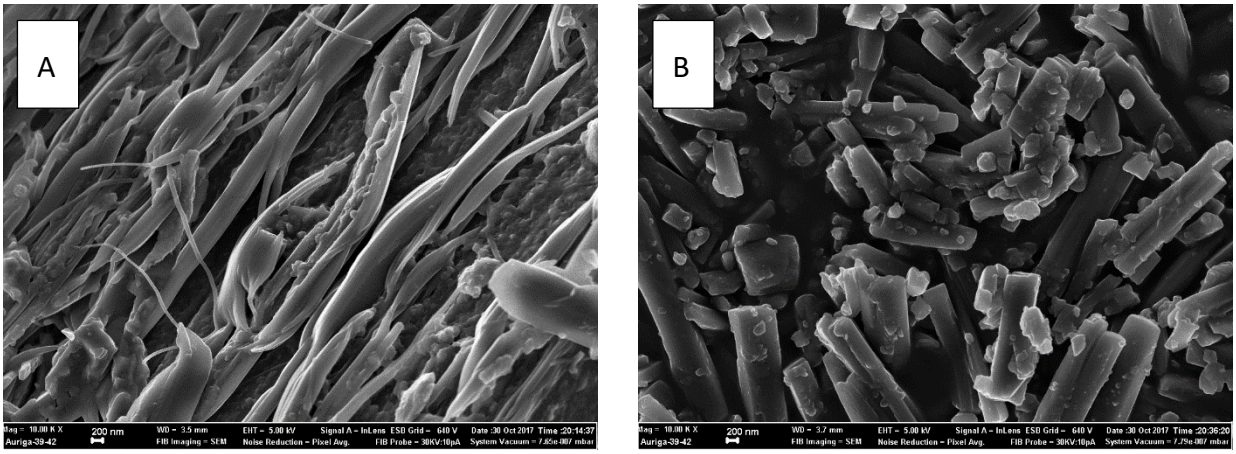


Figure 5.3: SEM scans of diarylamine [4] recrystallized [**A**] and triturated [**B**] (10000 × magnification)

5.2 Stage 2 SEM images

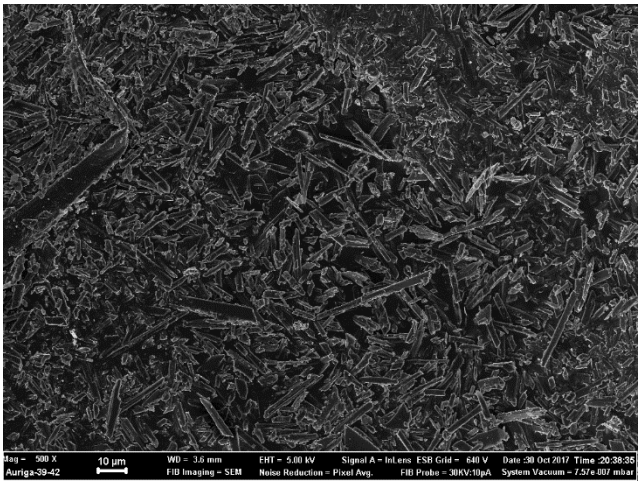


Figure 5.4: SEM scans of [5] triturated (500 × magnification)

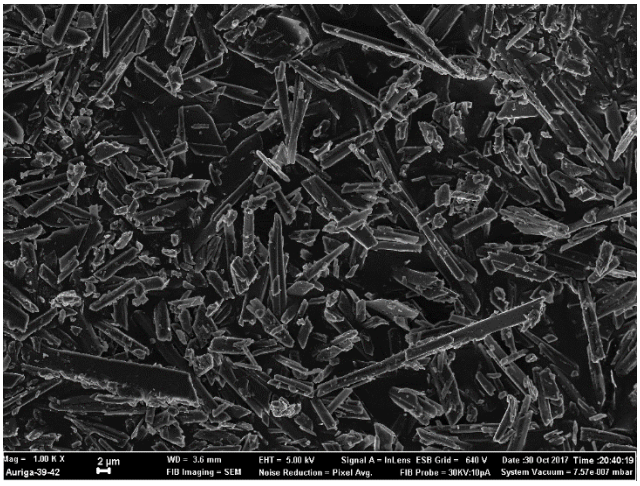


Figure 5.5: SEM scans of [5] triturated (1000 × magnification)

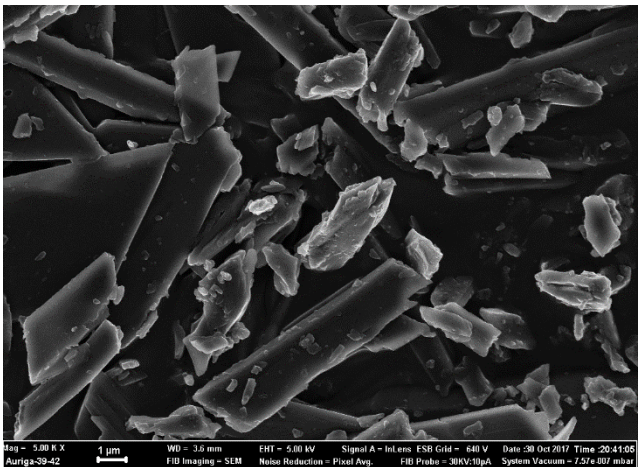
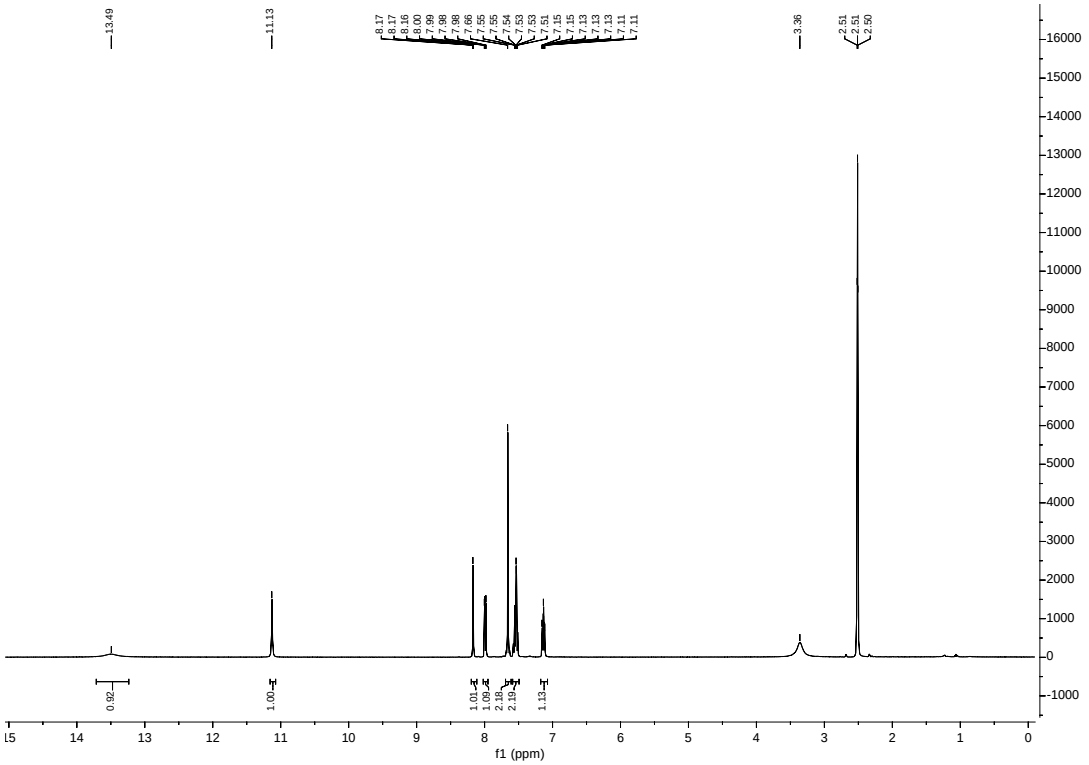
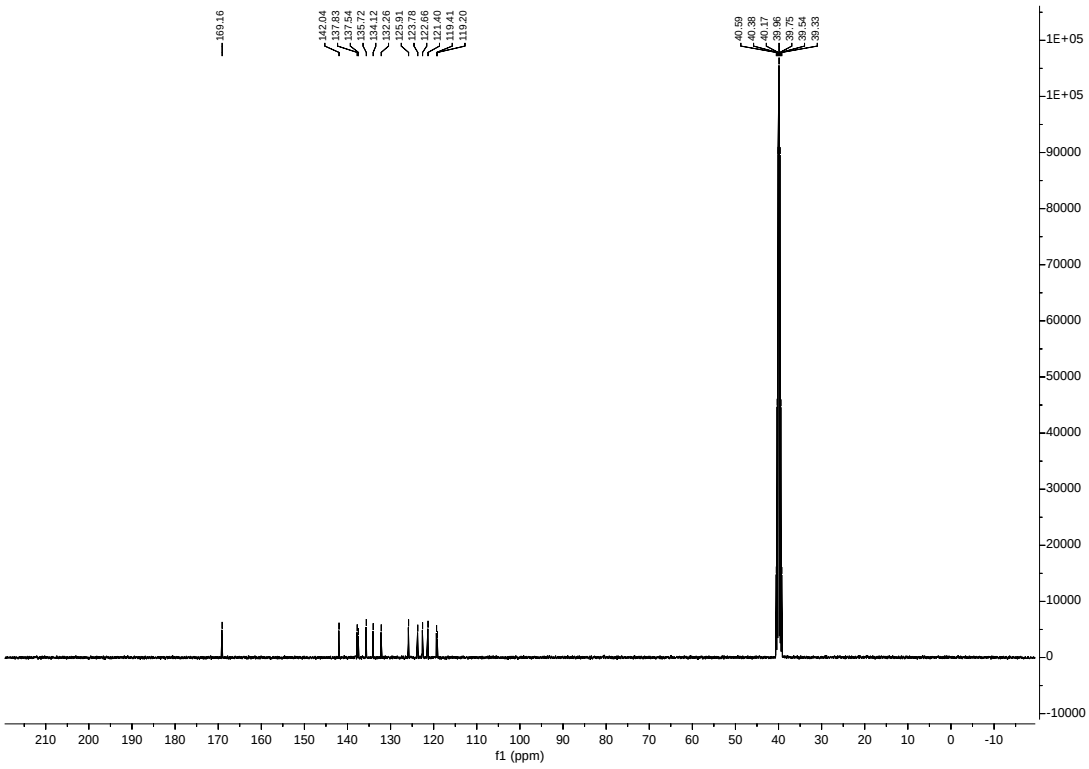


Figure 5.6: SEM scans of [5] triturated (5000 × magnification)

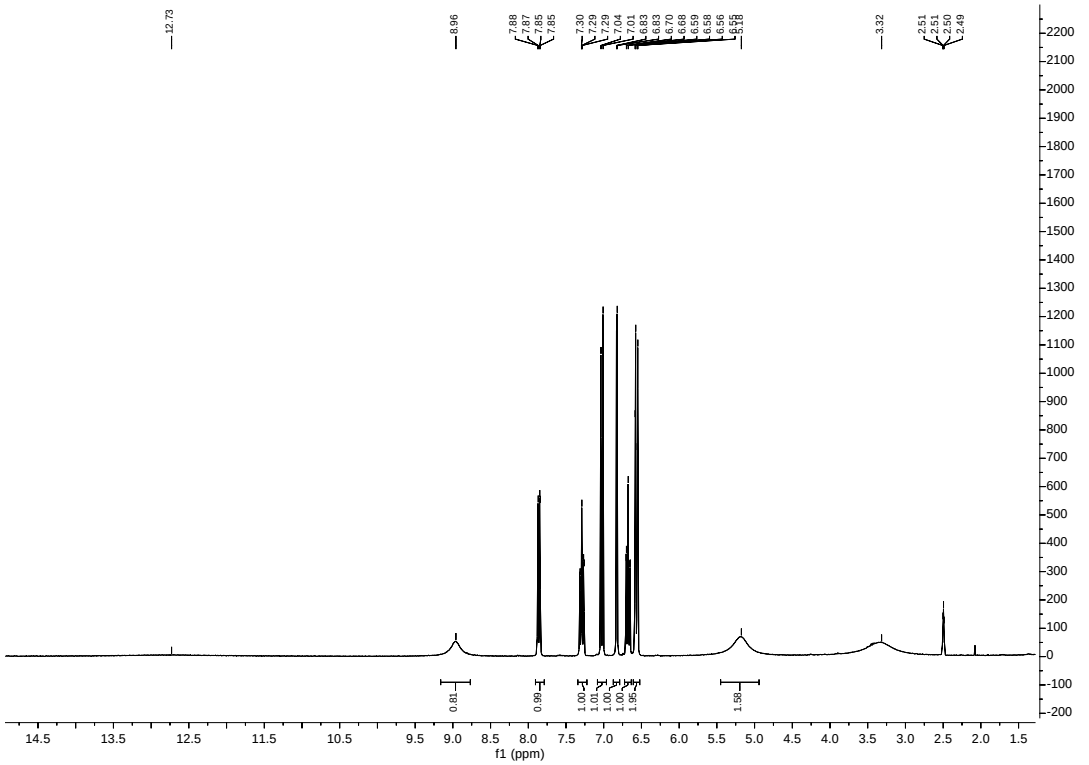
6. NMR and MS spectra

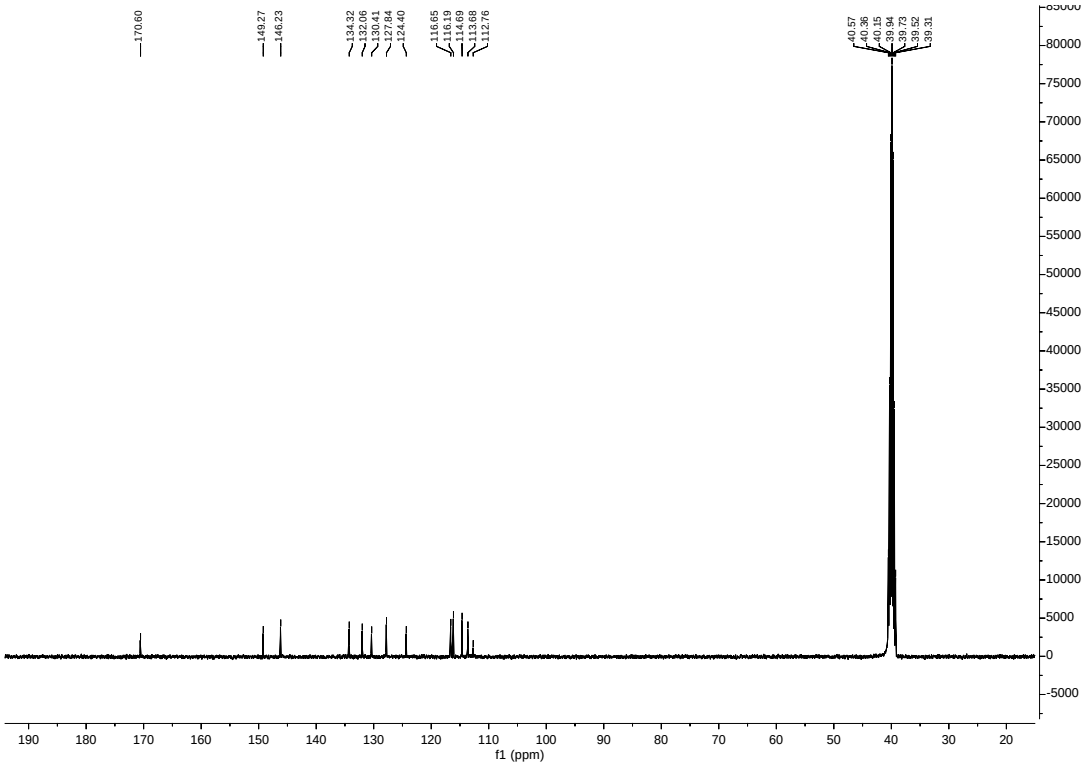
6.1 ^{1}H and ^{13}C NMR spectra of 2-((4-chloro-2-nitrophenyl)amino)-benzoic acid 4



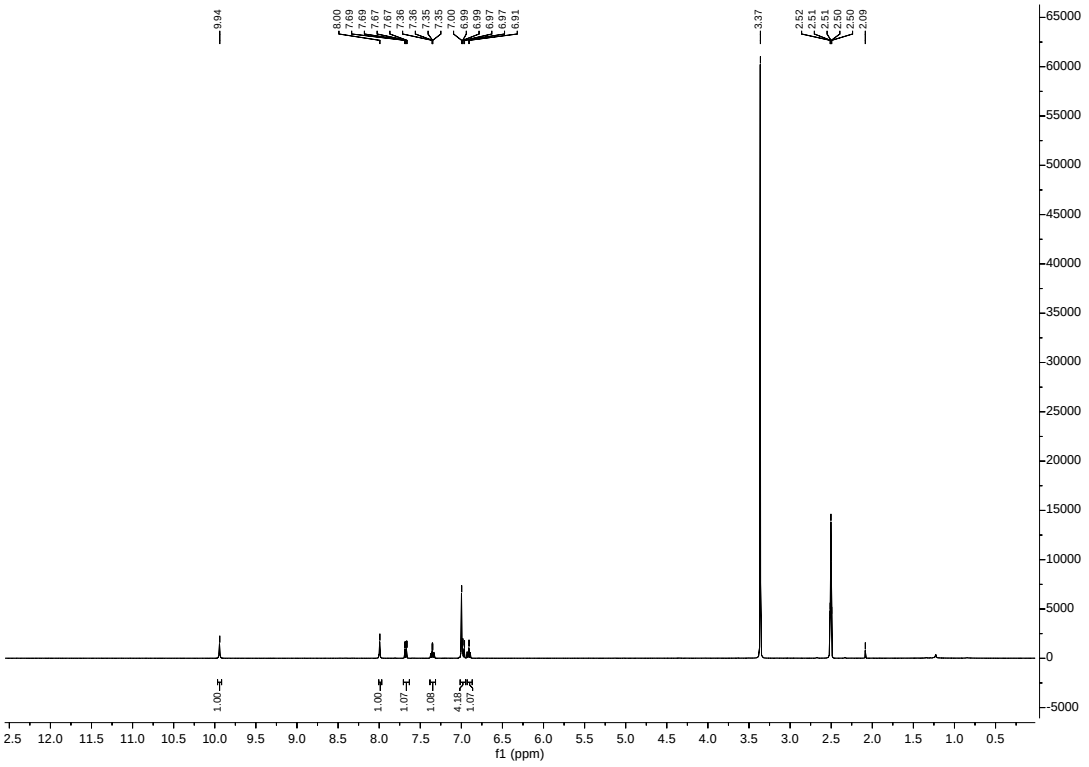


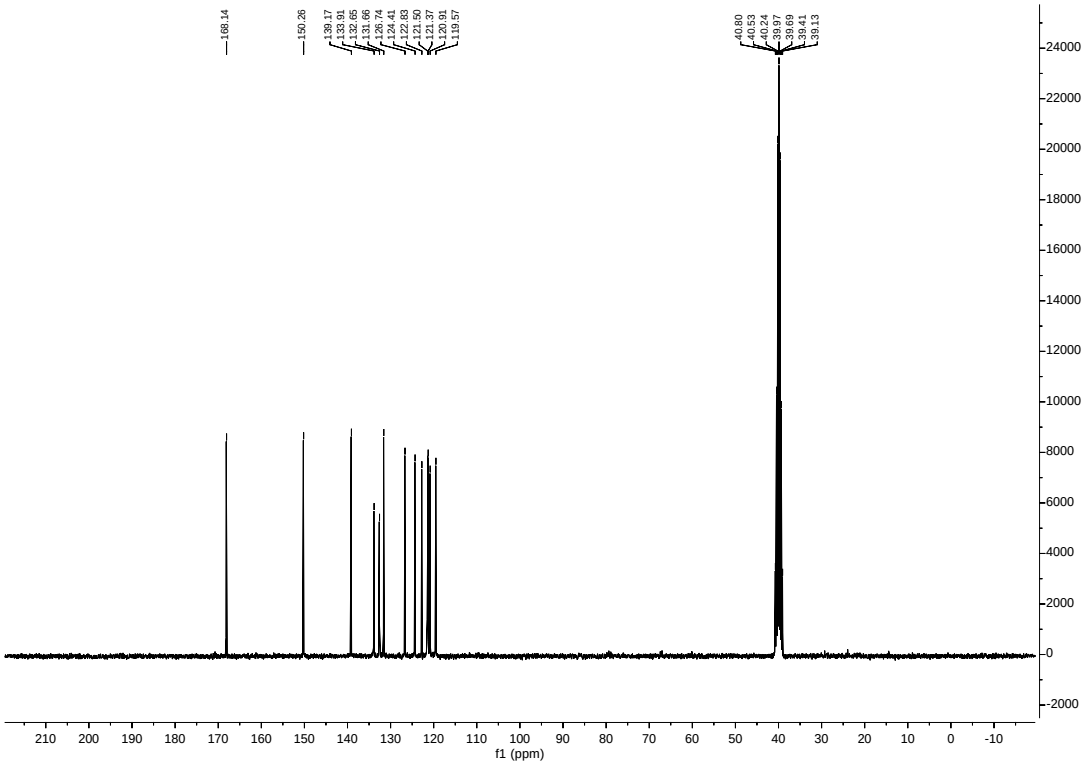
6.2 ^{1}H and ^{13}C NMR spectra of 2-((2-amino-4-chlorophenyl)amino)benzoic acid 5



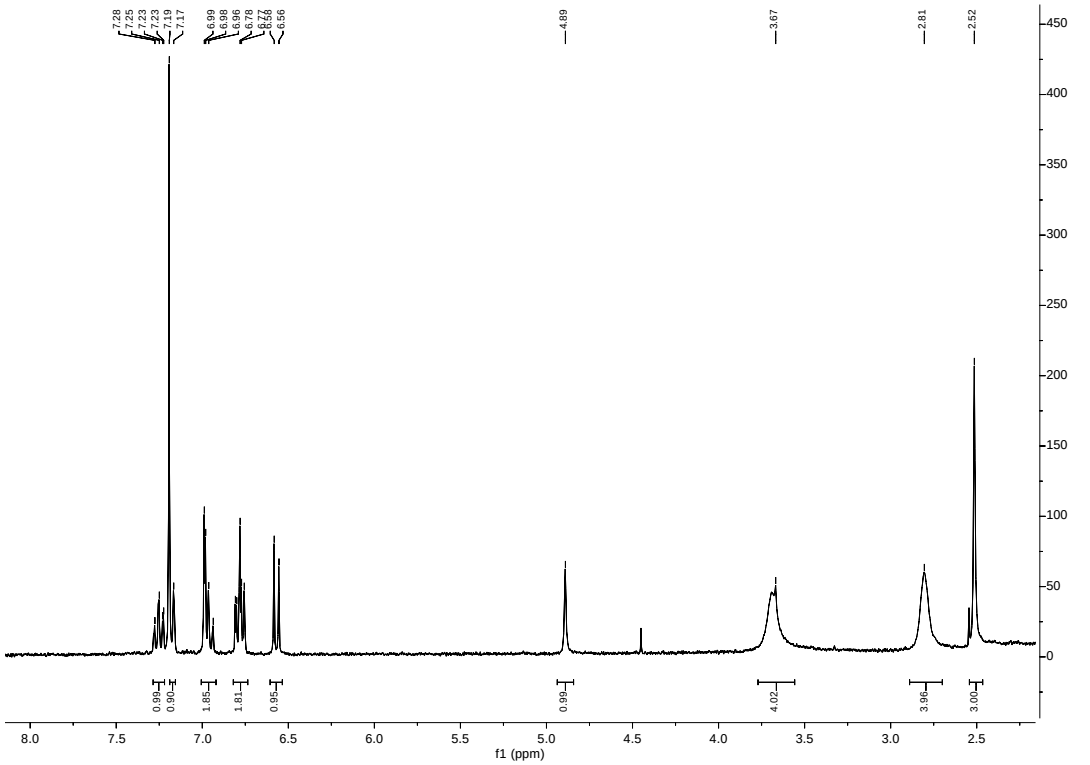


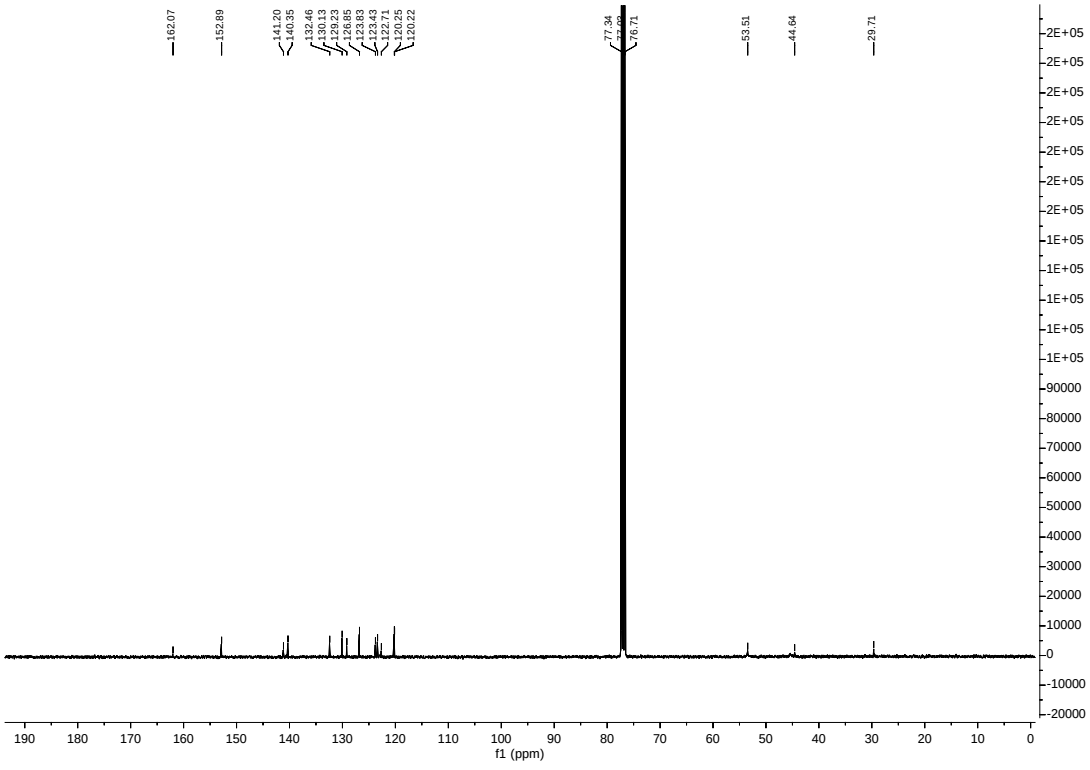
6.3 ^{1}H and ^{13}C NMR spectra of 8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11(10*H*)-one 6



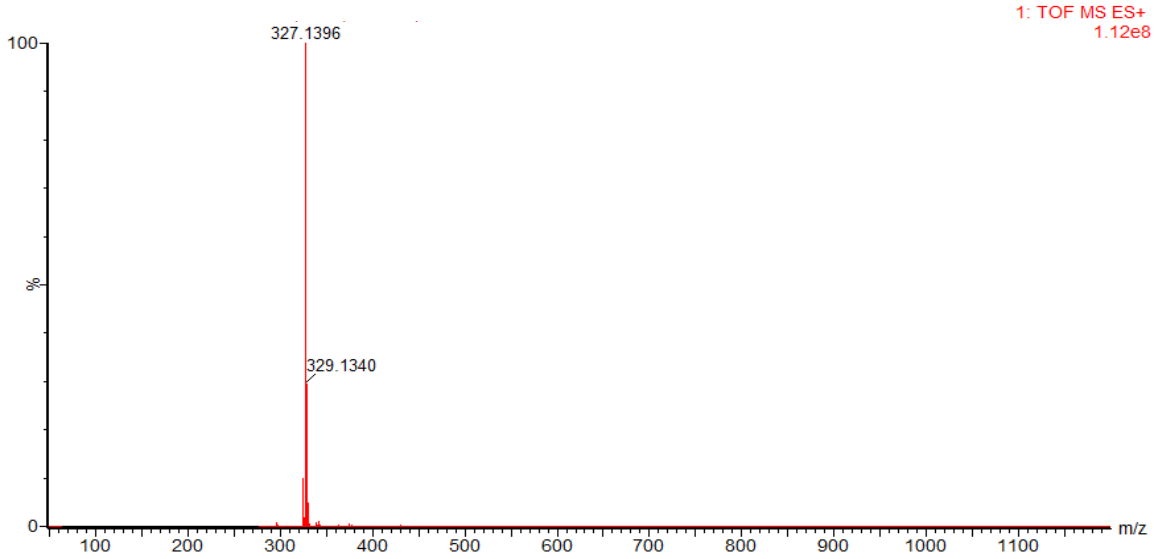


6.4 ^{1}H and ^{13}C NMR spectra of Clozapine 1





6.5 Mass spectrometry of Clozapine 1



(M^+ 100%, $C_{18}H_{19}ClN_4$ requires 327.1376)