Supplementary Information

for

The synthesis of bupropion hydrochloride under greener and safer conditions utilizing flow technologies

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1 Experimental

1.1 General experimental

All batch processes were performed using traditional organic and synthetic chemistry techniques utilising typical glassware/equipment as found in standard synthetic laboratories. All starting materials and reagents required were purchased and used as received from commercial sources with no further purification. Where reactions were executed under inert conditions, a standard manifold line; connected to a nitrogen or argon cylinder; was used to supply the reaction vessel with an inert atmosphere (typically argon). Additionally, reaction vessels were either pre-dried in an oven kept at 80 ^{O}C overnight or flame-dried whilst under vacuum after which time they were allowed to cool down to ambient temperature under inert atmosphere.

Concentration under reduced pressure or *in-vacuo* denotes the removal of solvent under reduced pressures (approximately 20 mmHg) at temperatures between 40 ^{O}C and 60 ^{O}C depending on the identity of the solvent. This was performed utilizing a Heidolph HEI-VAP Core HL G1 rotary evaporator connected to a Hei-CHILL 250/600 chiller. Final drying and "high-vacuum" drying of products/intermediates was performed with the help of an oil pump connected to a manifold-line (approximately 1-2 mmHg) at ambient temperature.

Unless specified otherwise, yields were calculated from the immediate synthetic precursors. For convenience, all experiments described in this ESI are labelled with reference to the relevant table or scheme from the main manuscript where applicable.

1.2 Flow equipment

All flow-based experiments were performed using a Uniqsis Binary Pump Module or FlowSyn instrument equipped with 10mL or 50mL HPLC pump heads with appropriate accessories. Instruments were fitted with both standard 1/16" OD (1.0 mm ID) or 1/8" OD (1.5 mm ID) PTFE or SS tubing. Cartridge-based back-pressure regulators fitted with chemically resistant perfluoropolymer or Hastelloy components were utilised. Stand-alone Uniqsis 10 mL HPLC or Vapourtec SF-10 Peristaltic pumps were utilised where needed for additional reagent/solvent introduction. Packed bed reactors used in the experiments were OMNIFIT® glass columns with enhanced PEEK adjustable end fittings. A Uniqsis HotCoil flow reactor was fitted with the Uniqsis HotColumn housing with two different sized column holders 10 mm ID x 100 mm and 15 mm ID x 100 mm length columns. A maximum operating temperature of 150 ^{O}C with 362-psi (25 bar) or 217-psi (15 bar) pressure limit was used for 10- and 15-mm ID column reactors respectively. Coil reactors; 5, 25 or 52 mL 1/8" OD (1.5 mm ID) PTFE/PFA; with maximum operating temperatures of 150 ^{O}C and 145-psi (10 bar) pressure limits were used. A 14 mL 1/16" OD (1.0 mm ID) PTFE coil with maximum operating temperature of 150 ^{O}C and 362-psi (25 bar) pressure limit was used. The universal phase separator was purchased from Biotage® with a 70 mL capacity. An in-house developed triturator with ~120 mL capacity was used.[1] Zaiput laboratory scale SEP-10 (~0.5 mL internal volume, maximum 10 mL.min^{-1} flow rate) membrane separator (fitted with an OB900 S10 membrane) with maximum operating pressure of 290-psi (20 bar) and maximum temperature of 90 ^{O}C was used.

1.3 Characterisation

The retention factor (R_f) values reported are for thin layer chromatography (TLC) on aluminium-backed Macherey-Nagel Alugram Sil G/UV254 plates pre-coated with 0.25 mm silica gel 60.

^{1}H NMR (300 MHz or 400 MHz) and ^{13}C NMR (75 MHz or 101 MHz) spectra were recorded on a Bruker AVANCE-III-300 or a Bruker AVANCE-III-400 spectrometer at 300.13 and 400.13 MHz respectively using standard pulse sequences. ^{1}H NMR (600 MHz) spectra were recorded on a premium shielded Varian VNMRS 600 MHz spectrometer equipped with a Triple-Resonance Probe (5mm Auto HCN PFG). All spectra were recorded in deuterated solvents such as: deuterated chloroform ($CDCl_3$ at 7.26 ppm), deuterium oxide (D_2O at 4.79 ppm), deuterated dimethyl sulfoxide (d6-DMSO at 2.50 ppm) or deuterated methanol (d4-MeOD at 3.35 and 4.78 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) and multiplet (m). Coupling constants, *J*, are expressed in Hertz (Hz). In noted cases conversions were estimated from ^{1}H NMR by comparison of integral areas of starting materials and products. All NMR spectra recorded (^{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: a capillary voltage of 2.8 kV (positive mode) and 2.5 kV (negative mode), a sampling cone (ramped from 20 V – 40 V), an extraction cone 4 V, a source temperature of 100 ^{O}C, a desolvation temperature of 200 ^{O}C, cone gas of 100 L.h^{-1}, desolvation gas of 500 L.h^{-1}, inert gas source: nitrogen. Samples were made up in analytical grade acetonitrile, methanol and/or water combinations to an approximate concentration of 10 µg.mL^{-1}.

Infrared spectra were obtained on a Bruker ALPHA Platinum ATR spectrometer. The wavenumber (cm^{-1}) of absorptions is reported in the range of 400 – 3000 cm^{-1}. The signals are reported as relative intensity values.

Raman spectroscopy was performed on a WITec alpha300 RAS+ micro-Raman Confocal microscope with an objective of 50x, a 532 nm laser powered at 1 mW and an integration time of 60 seconds.

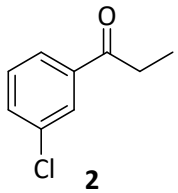
A Zeiss 540 Crossbeam FEGSEM instrument with Oxford Aztec EDS detector was used for microscopy images. Samples were prepared by fixating the specimen onto conductive carbon adhesive tape and excess particles were removed by air spray. Samples were coated using the thermal evaporation carbon rod coating method (the Brandley method).[2]

Powder X-ray diffraction was performed on a PANalytical X'pert PRO – Netherlands instrument fitted with a Cu Kα (λ = 0.154 nm) radiation source.

Single crystal diffraction data for **1a** was collected at 150(1) K using an Oxford Cryogenics Cryostat on a Rigaku XtaLAB Synergy R diffractometer, with a rotating-anode Cu X-ray source along with a HyPix CCD detector. Data reduction and absorption was carried out using the CrysAlisPro software package (version 1.171.40.23a).[3] The structure was solved with SHELXT-2013 by direct method using the OLEX2 interface.[4,5] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed in idealized positions and refined using riding models.

1.4 1st Generation batch processes

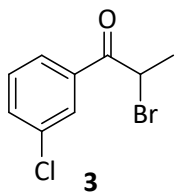
1.4.1 3'-Chloropropiophenone 2 (Starting material)



2

3'-Chloropropiophenone **2**: **Rf** 0.89 (Hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 1.9 Hz, 1H), 7.83 (ddd, *J* = 7.7, 1.6, 1.1 Hz, 1H), 7.52 (ddd, *J* = 7.9, 2.1, 1.1 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 2.98 (q, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.50, 138.48, 134.93, 132.86, 129.95, 128.18, 126.09, 31.99, 8.13; **IR ν_{max}/cm^{-1}** 2980 (w), 2938 (w), 1681 (s), 1571 (m), 1457 (m), 1423 (s), 1351 (m), 1211 (broad m), 1072 (m), 1023 (m), 998 (m), 972 (m), 896 (m), 775 (s), 679 (s), 470 (m), 409 (m).

1.4.2 2-Bromo-1-(3-chlorophenyl)propan-1-one 3 (Table 1, Entry 1)



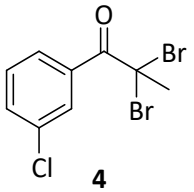
3

3'-Chloropropiophenone **2** (5.01 g, 29.7 mmol, 1.0 eq) was dissolved in 60 mL dichloromethane. Bromine liquid (1.70 mL, 32.6 mmol, 1.1 eq) was added dropwise over a period of 10 minutes to the reaction mixture. After all the bromine liquid was added, the reaction was allowed to stir for a further 30 minutes and quenched with 30 mL saturated K_2CO_3 (aq). The solvent was removed *in-vacuo* after which time the reaction mixture was extracted with ethyl acetate (3 × 30 mL) and the organic layers were combined and washed with 30 mL water and 30 mL brine. The organic layer was dried with anhydrous Na_2SO_4

(0.5 g) and concentrated *in vacuo* to afford 2-bromo-1-(3-chlorophenyl)propan-1-one **3** as a light yellow-oil in 87% yield. **Rf** 0.51 (50% MeOH:Hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (t, *J* = 1.9 Hz, 1H), 7.86 (ddd, *J* = 7.8, 1.7, 1.1 Hz, 1H), 7.53 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 5.21 (q, *J* = 6.6 Hz, 1H), 1.88 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.00, 135.55, 135.01, 133.52, 130.00, 128.90, 126.92, 41.29, 19.92; **IR ν_{max}/cm^{-1}** 1687 (s), 1570 (m), 1474 (w), 1443 (m), 1422 (m), 1377 (w), 1334 (m), 1229 (s), 1160 (m), 1076 (m), 996 (m), 959 (m), 901 (w), 801 (m), 738 (s), 696 (s), 671 (s), 644 (m), 556 (w), 465 (m), 417 (w); **HRMS m/*z* (ES+)** 248.1969 **[M + H]$^+$** (C_9H_9BrClO calculated as 248.5240).

Recorded spectra are consistent with previously reported data.[6]

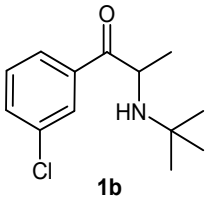
1.4.3 2,2-Dibromo-1-(3-chlorophenyl)propan-1-one 4 (Table 1, Entry 4)



4

3'-Chloropropiophenone **2** (1.00 g, 5.9 mmol, 1.0 eq) was dissolved in 12 mL dichloromethane. Bromine liquid (0.60 mL, 11.7 mmol, 2.0 eq) was added dropwise over a period of 10 minutes to the reaction mixture. After all the bromine liquid was added the reaction mixture was refluxed at 40 ^{O}C for 1 hour. The reaction mixture was allowed to cool down to ambient temperature after which it was stirred for an additional 11 hours and thereafter, quenched with 30 mL saturated K_2CO_3 (aq). The reaction mixture was extracted with dichloromethane (3 × 30 mL) and the organic layers were combined and washed with 30 mL water and 30 mL brine. The organic layer was dried with anhydrous Na_2SO_4 (0.5 g) and concentrated *in vacuo* to afford 2,2-dibromo-1-(3-chlorophenyl)propan-1-one **4** as a brown-oil in 78% yield. **Rf** 0.57 (Hexane); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (ddd, *J* = 8.9, 2.0, 1.0 Hz, 2H), 7.54 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.49 – 7.35 (m, 1H), 2.74 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 187.00, 134.20, 133.39, 133.26, 131.17, 129.44, 129.18, 57.36, 37.51; **IR ν_{max}/cm^{-1}** 2923 (m), 2852 (w), 1697 (s), 1569 (m), 1472 (m), 1434 (m), 1419 (m), 1377 (m), 1235 (s), 1131 (m), 1060 (s), 966 (m), 902 (m), 900 (m), 803 (s), 750 (m), 700 (s), 674 (s), 648 (m), 582 (s), 475 (m), 416 (w).

1.4.4 Bupropion 1b (Table 2, Entry 2)



1b

2-Bromo-1-(3-chlorophenyl)propan-1-one* **3** (6.40 g, 25.9 mmol, 1.0 eq) was dissolved in acetonitrile (53 mL) and transferred to a pressure tube. *tert*-Butylamine (8.4 mL, 5.80 g, 79.5 mmol, 3.1 eq) was added and the resultant reaction mixture allowed to stir for 4 hours at 95 ^{O}C. The reaction mixture was left to cool down to ambient temperature and concentrated under reduced pressure. The resulting residue was taken up in 30 mL saturated $NaHCO_3$ (aq) and extracted with ethyl acetate (3 × 30 mL) after which time the organic layers were combined, dried with anhydrous Na_2SO_4 (0.5 g), filtered and concentrated *in-vacuo* to afford the free base bupropion **1b** as a ginger-coloured oil in 86% yield. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.8 Hz, 1H), 7.91 – 7.82 (m, 1H), 7.54 (d, *J* = 10.5 Hz, 1H), 7.43 (s, 1H), 4.28 (q, *J* = 7.2 Hz, 1H), 1.24 (d, *J* = 7.1 Hz, 3H), 1.03 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 203.76, 136.61, 135.15, 133.20, 130.12, 128.42, 126.38, 52.21, 50.81, 29.71, 22.46; **HRMS m/*z* (ES+)** 240.1114 **[M + H]$^+$** ($C_{13}H_{19}ClNO$ calculated as 240.7510).

*Material purified by column chromatography prior to use.

Recorded spectra are consistent with previously reported data.[6, 8, 9]

Nucleophilic displacement solvent screen study

Several additional solvent systems were screened as depicted in **Table S1**, however, in all cases yields were either low or decomposition was observed.

Table S1. Additional solvent systems screened for the nucleophilic displacement[a]

Entry	Solvent	Precipitate	Bromine Intermediate 3 present	Crude Yield % 1b
1	Neat	Yes	No	54
2	MeOH	Yes (minimal)	No	-[b]
3	DCM	No	Yes (mostly)	48
4	95% ACN:H_2O	Yes	No	59
5	3:1 ACN:MeTHF[c]	Yes	No	Partial decomposition
6	1:1 EtOAc:H_2O[d]	No	Yes	Decomposed
7	92% Toluene:DMF	Yes	No	Partial Decomposition
8	1:1 ACN:TPGS-750-M (2.5% in H_2O)	No	Yes	Decomposed

[a]General reaction conditions: 95 ^{O}C, 4-hour reaction time, 0.5 M concentration, 3.0 equivalents of *tert*-butylamine [b]Unidentified product formed [c](MeTHF) 2-methyltetrahydrofuran [d]1.0 equivalent of TBAB phase-transfer catalyst added

*Decomposition study of 2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one **1b***

The decomposition of 2-(*tert*-butylamino)-1-(3-chlorophenyl)propan-1-one **1b** was investigated under both solvated and neat conditions. Free base bupropion **1b** was prepared as described in section **1.4.4**. For solvated conditions, a single NMR of free base bupropion **1b** sample was prepared (t = 0 hrs) in 600 µL d6-DMSO and incubated in a water bath held at 40 ^{O}C for a 48-h duration. The sample was resubmitted for NMR analysis at the following intervals: 1, 12, 24 and 48 hours (**Figure S1**).

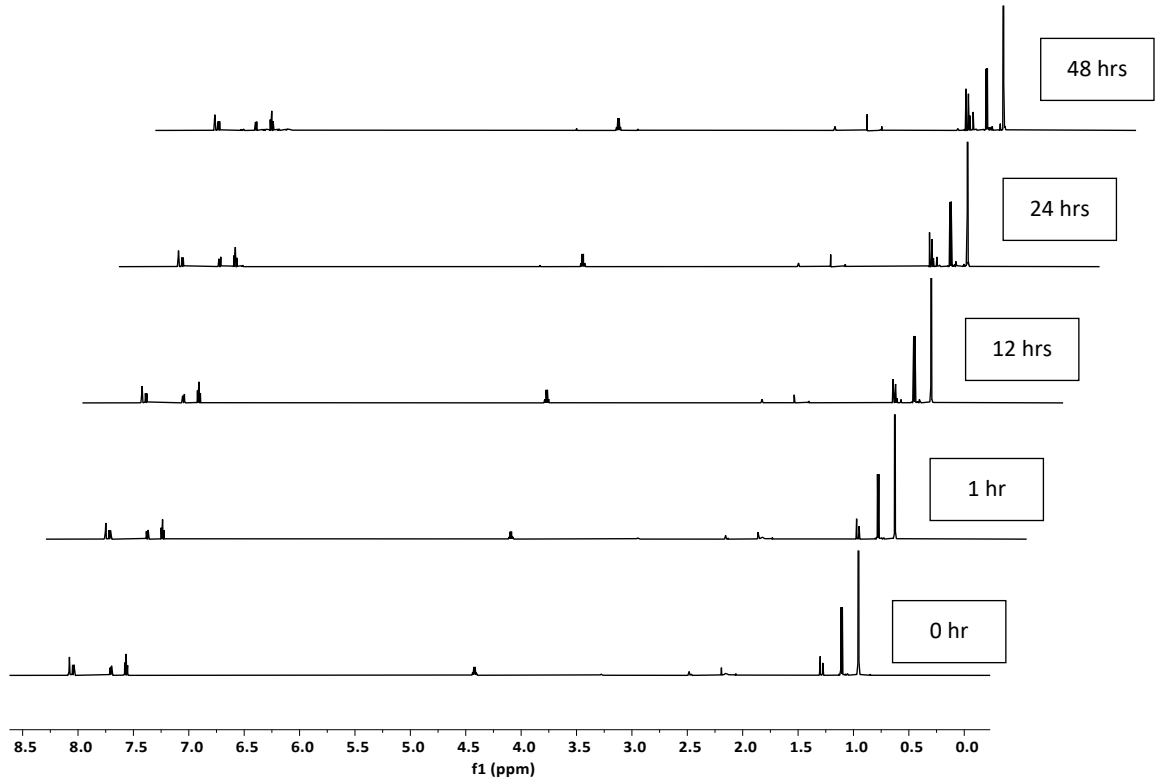


Fig S1. Stacked ^{1}H NMR spectra showing the decomposition of solvated **1b** over time

For neat conditions (**Figure S2**), 1 gram of the free base bupropion **1b** sample was incubated in a water bath held at 40 ^{O}C for a 48-hour duration and new NMR samples were prepared in 600 µL d6-DMSO at specified intervals (0, 1, 12, 24 and 48 hours).

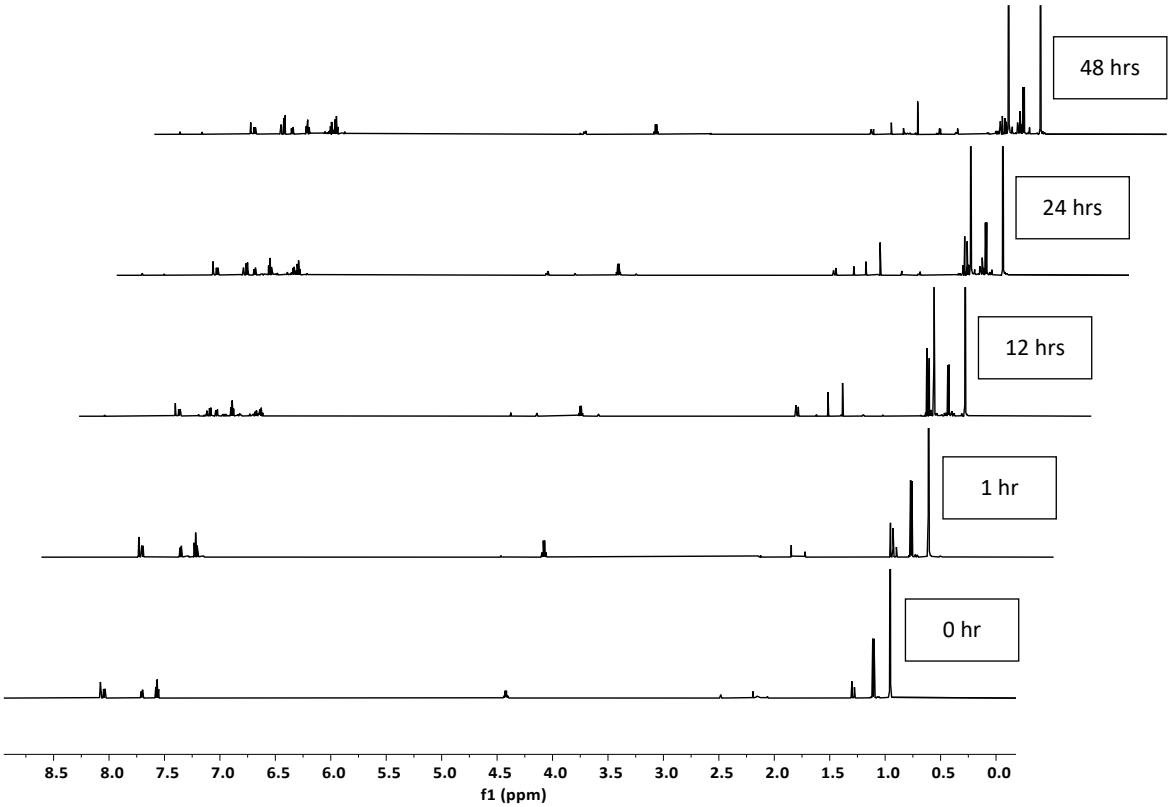
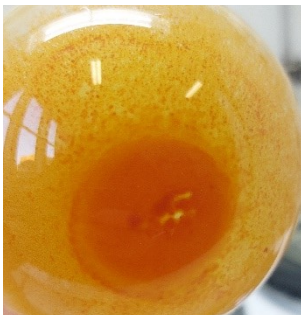


Fig S2. Stacked ^{1}H NMR spectra showing the decomposition of neat **1b** over time

The study shows that the free base bupropion **1b** readily decomposes under both solvated and neat conditions, with the rate of decomposition being faster under neat conditions with decomposition already observable after 1 hour. Furthermore, the decomposition of free base bupropion **1b** could also be noted visually by the conversion of the ginger-coloured oil to an orange solid (**Figure S3**).

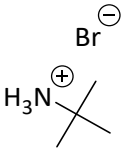
*Neat free base bupropion **1b** (t = 0 h)*



*Neat free base bupropion **1b** (t = 48 h)*

Fig S3. Decomposition of neat free base bupropion **1b** over time

1.4.5 *tert*-Butylammonium bromide (By-product of the nucleophilic substitution)



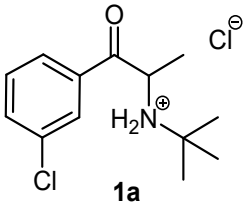
tert-Butylammonium bromide precipitates during the nucleophilic substitution step as a white solid by-product (**Figure S4**): **^{1}H NMR** (400 MHz, D_2O) δ 1.34 (s, 9H); **^{13}C NMR** (101 MHz, D_2O) δ 51.90, 26.57; **IR ν_{max}/cm^{-1}** 2975 (broad s), 2918 (m), 2886 (s), 2794 (m), 2695 (w), 2582 (m), 2487 (w), 2030 (w), 1606 (w), 1503 (m), 1475 (w), 1400 (m), 1376 (m), 1298 (m), 1213 (m), 445 (m), 424 (w).

Recorded spectra are consistent with previously reported data obtained for the chloride salt.[10]

Entry 2, Table 2 *Entry 4, Table 2* *Entry 9, Table 2*

Fig S4. Nucleophilic displacement reaction mixture after 4 hours

1.4.6 Bupropion hydrochloride 1a (Table 3, entry 3)^



1a

Free base bupropion* **1b** (1.24 g, 5.17 mmol, 1.0 eq) was suspended in 103 mL of diethyl ether (0.05 M). The reaction mixture was cooled to 0 ^{O}C and a 2.0 M hydrogen chloride in diethyl ether solution (5.2 mL, 10.4 mmol, 2.0 eq) was added dropwise to the mixture until precipitation started. Upon further stirring precipitation intensified. The mixture was left in a fridge (~ 4 ^{O}C) overnight after which time it was filtered and dried to afford bupropion hydrochloride **1a** as a white solid in 95% yield. **^{1}H NMR** (400 MHz, D_2O) δ 8.10 (t, *J* = 1.9 Hz, 1H), 8.00 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 1H), 7.76 (ddd, *J* = 8.1, 2.1, 1.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 5.17 (q, *J* = 7.2 Hz, 1H), 1.59 (d, *J* = 7.2 Hz, 3H), 1.33 (s, 9H); **^{13}C NMR** (101 MHz, D_2O) δ 196.17, 135.33, 134.95, 133.16, 130.81, 128.82, 127.40, 58.85, 53.58, 25.30, 17.57; **IR ν_{max}/cm^{-1}** 2842 (w), 2743 (broad m), 2667 (broad m), 2602 (broad m), 2449 (m), 2341 (w), 1687 (m), 1556 (m), 1457 (m), 1423 (m), 1407 (m), 1376 (m), 1280 (m), 1235 (s), 1208 (s), 1131 (m), 1074 (m), 1000 (m), 904 (m), 864 (w), 778 (m), 733 (m), 705 (m), 668 (m), 511 (m), 457 (m).

*Material was produced from purified (through column chromatography) 2-Bromo-1-(3-chlorophenyl)propan-1-one **3** starting material prior to use.^Reaction was scaled to match output scale of Stage 1 and 2 – for 1st Generation analysis in green chem metrics (CHEM21 toolkit).

Recorded spectra are consistent with previously reported data.[7, 11]

Validation of Zhejiang Apeloa Jiayuan Pharmaceutical Co Ltd. approach (US7737302B2) [12]

3'-Chloropropiophenone **2** (1.6866 g 10.00 mmol, 1.0 eq) was heated to 78 ^{O}C. Liquid bromine (0.48 mL, 9.34 mmol, 0.93 eq Br_2) was added dropwise with vigorous stirring. After complete addition, the reaction mixture was kept at 78 ^{O}C whilst stirring for an additional 3 hours to afford 2-bromo-1-(3-chlorophenyl)propan-1-one **3** (^{1}H NMR analysis showed ~20% conversion to unwanted 2,2-Dibromo-1-(3-chlorophenyl)propan-1-one **4**, **Figure S5**). The reaction mixture was allowed to cool down to 60 ^{O}C after which *tert*-butylamine (5.30 mL, 50.43 mmol, 5.0 eq) was added and the resultant mixture was refluxed for 5.5 hours at a temperature of 60 ^{O}C. Excess *tert*-butylamine was evaporated at 80 ^{O}C for 10 minutes after which time the resultant mixture was allowed to cool to ambient temperature and subsequently extracted with 15 mL of toluene and 3 mL water. The organic phase was collected, dried with anhydrous magnesium sulphate (0.2155 g) and filtered to obtain the free base bupropion **1b** solution (^{1}H NMR analysis showed minimal impurities and decomposition of **1b**, **Figure S5**). The solution was cooled down to 0 ^{O}C and treated with HCl gas (generated *in-situ* from sodium chloride and sulphuric acid) until a pH ≤ 4 was obtained. The resultant mixture was left in a fridge (4 ^{O}C) overnight after which it was filtered and dried to afford crude bupropion hydrochloride **1a** in 39% yield. The crude product **1a** was taken up in ethyl acetate (15 mL) pre-heated to 60 ^{O}C. Activated carbon (0.0526 g) was added and the mixture was stirred for 30 minutes after which it was filtered and allowed to cool to ambient temperature. Upon cooling, bupropion hydrochloride **1a** crystals formed (^{1}H NMR analysis showed minimal

impurities in **1a**, **Figure S5**) which was filtered and dried to obtain the final white solid **1a** in 21% yield based on 3'-chloropropiophenone **2**.

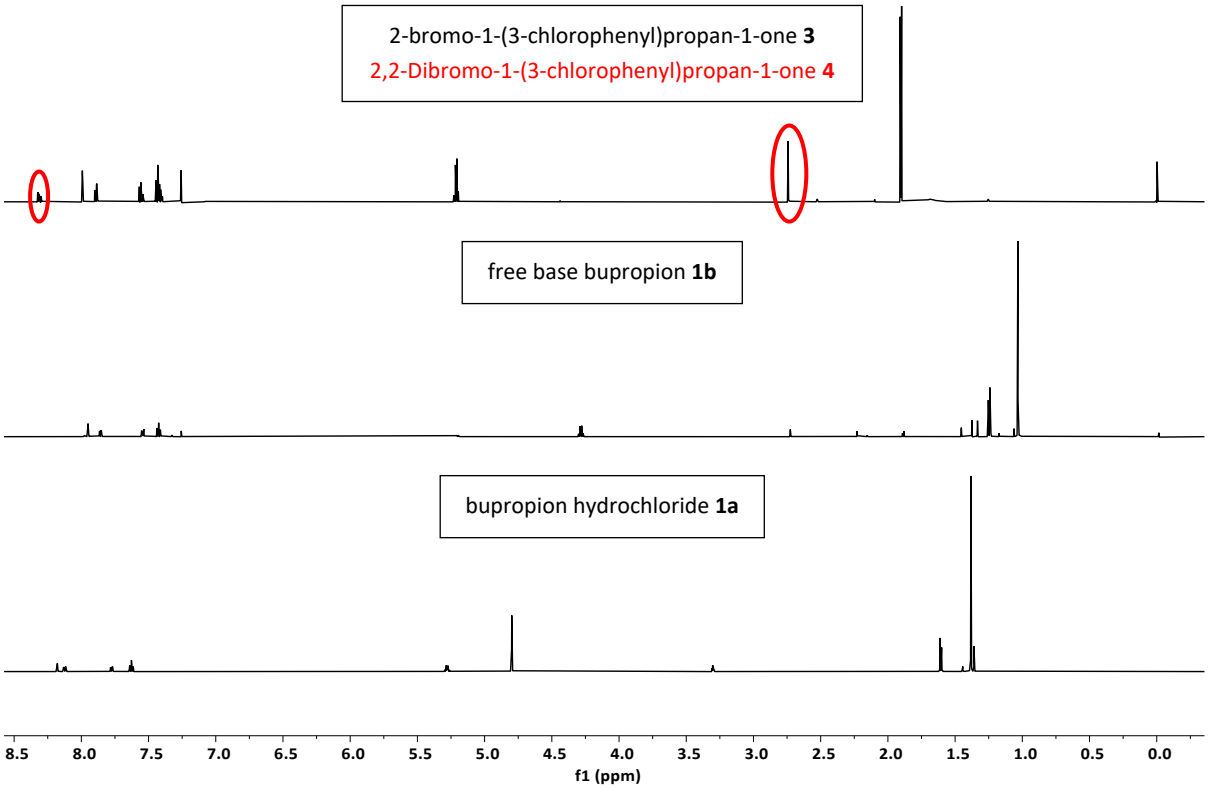


Fig S5. Stacked ^{1}H NMR results of the US7737302B2 patent validation

Solubility study of bupropion hydrochloride 1a

The solubility of bupropion hydrochloride salt **1a** was assessed in various solvents including methanol, acetone, water, ethanol, ethyl acetate, hexane, cyclohexane, diethyl ether and dimethyl sulfoxide (**Table S2**). The best solubility was observed in polar protic solvents such as methanol, ethanol and water. Appreciable solubility was also noted in polar aprotic dimethyl sulfoxide.

Table S2. Estimated solubility of bupropion hydrochloride **1a** in different solvents[a]

Entry	Solvent	Estimated solubility (mg/mL)
1	Methanol	~ 347.0
2	Acetone	≤ 1.0
3	Water	~ 110.8
4	Ethanol	~ 113.1
5	Ethyl acetate	≤ 1.0
6	Hexane	≤ 1.0
7	Cyclohexane	≤ 1.0
8	Diethyl ether	≤ 1.0
9	Dimethyl sulfoxide	~ 181.0

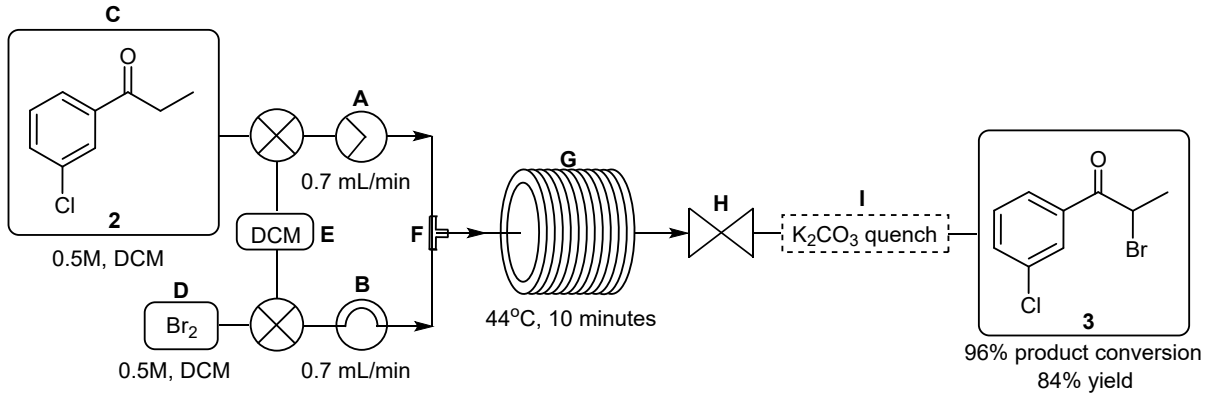
[a]General conditions: 1 mL of solvent was used and bupropion hydrochloride **1a** was added in small increments until dissolution stopped at room temperature (24 ^{O}C)

1.5 2nd Generation stand-alone flow processes

1.5.1 Stage 1 – Bromination

Scheme S1 (Table 4, entry 1 in main article) Flow reactor setup:

A stand-alone Uniqsis FlowSyn HPLC pump **A** and a Vapourtec SF-10 peristaltic pump **B** were connected upstream to two reservoirs (**C** and **D**, housing stock solutions of **2** and bromine respectively), via injection valves (reagent injection) (**Scheme S1**). The valves were also connected to a third reservoir **E** containing dichloromethane (solvent injection). The pumps were connected to a T-piece mixer **F** with standard PTFE tubing (1/16" OD & 1 mm ID) and thereafter connected in series to a 14 mL PTFE coil reactor (1/16" OD & 1 mm ID) **G** mounted on a Uniqsis HotCoil heating module. The reactor output was passed through a 5-bar cartridge-based back-pressure regulator **H** to an offline quench **I**. The flow system was pre-primed before execution of the reaction and washed post-reaction with a combined reactor and dead volume equivalent of dichloromethane. The system was stored in isopropyl alcohol when not in use.



Scheme S1. α-Bromination of 3'-chloropropiophenone **2** utilising molecular bromine

Preparation of stock solutions:

A 0.5 M stock solution of 3'-chloropropiophenone **2** was prepared by the dissolution of **2** (0.8451 g, 5.01 mmol, 1.0 eq) in dichloromethane and dilution to a total volume of 10.00 mL.

A 0.5 M stock solution of liquid bromine was prepared by dilution of bromine (0.26 mL, 5.04 mmol, 1.0 eq) in dichloromethane to a total volume of 10.00 mL.

General procedure:

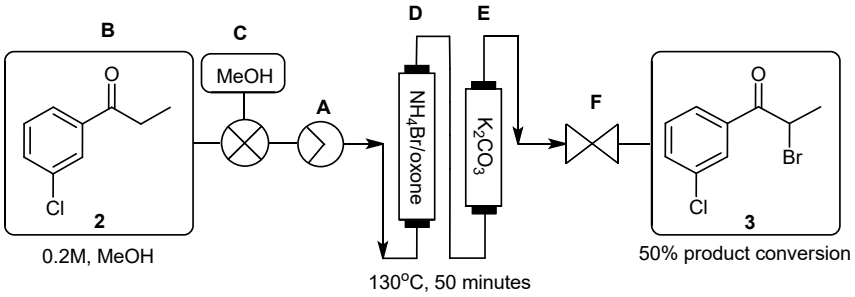
Stock solutions were prepared as described above. A total flow rate of 1.4 mL.min^{-1} (0.7 mL.min^{-1} per pump) was used to introduce 3 mL of each stock solution into the flow system after which time the injection valves were switched to the solvent reservoir containing dichloromethane which was used as a pushing solvent. The solutions were combined at the T-piece mixer and pumped through the coil reactor held at 44 ^{O}C (T_R = 10 min). Upon exiting the coil, the mixture was passed through the 5-bar back-pressure regulator and fed into a stirred solution of 50% saturated potassium carbonate. The resultant mixture was extracted and the organic layer collected. The aqueous layer was further extracted with 15 mL of dichloromethane. The organic layers were combined, dried with anhydrous Na_2SO_4 (0.5 g), filtered and concentrated *in-vacuo* to afford 2-bromo-1-(3-chlorophenyl)propan-1-one **3** in 84% isolated yield (96% conversion, as estimated by integral areas on ^{1}H NMR).

Scheme S2 (Table 4, entry 2 in main article)

Flow reactor setup:

A single pump from a Uniqsis BPM (HPLC) **A** was utilised (**Scheme S2**). The pump **A** was connected upstream to a reservoir **B** containing a stock solution of **2** via an injection valve (reagent injection), the injection valve was connected to a second reservoir **C** containing methanol (solvent injection). The pump was connected downstream to a 10.0 mm ID packed-bed reactor (OMNIFIT™) **D** housing excess ground-up ammonium bromide and oxone followed by a second 10.0 mm ID packed-bed reactor (OMNIFIT™) **E** housing excess potassium carbonate using standard PTFE tubing (1/16" OD & 1 mm ID). The column reactors were jacketed on a Uniqsis HotColumn module placed on a Uniqsis HotCoil heating module and the reactor outflow was connected to a standard 8-bar cartridge back-pressure regulator **F**. The column reactor volumes and subsequent

residence times were calculated as per OMNIFIT® instructions: volume (mL) = 0.7854 X bed length (cm). The flow system was pre-primed before execution of the reaction and again washed post-reaction with a combined reactor and dead volume equivalent of methanol. The system was stored in isopropyl alcohol when not in use.



Scheme S2. A-Bromination of 3'-chloropropiophenone **2** utilising NH4Br/oxone

Preparation of stock solution:

A 0.2 M stock solution of 3'-chloropropiophenone **2** was prepared by the dissolution of **2** (0.3423 g, 2.03 mmol, 1.0 eq) in methanol and dilution to a total volume of 10.00 mL.

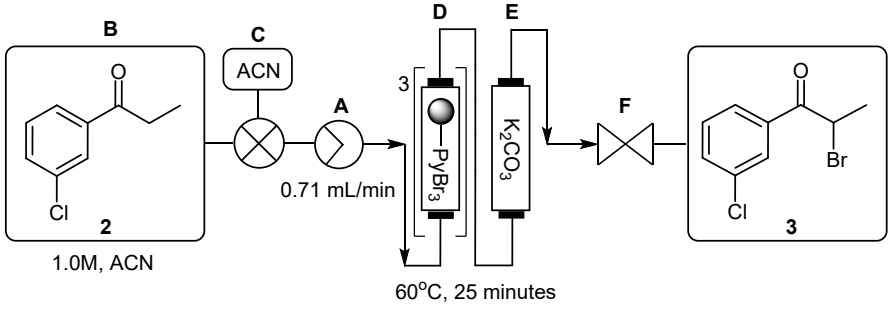
General procedure:

A stock solution was prepared as described above. A flow rate of 0.11 mL.min^{-1} was used to introduce 3 mL of the stock solution into the flow system after which time the injection valves were switched to the solvent reservoir containing methanol which was used as a pushing solvent. The solution was pumped through the first packed-bed reactor housing excess ammonium bromide/oxone held at 130 ^{O}C (T_R = 50 min), followed by the second PBR housing excess potassium carbonate at ambient temperature, thereafter it was passed through the back-pressure regulator. Unfortunately, as anticipated from the batch results, the reaction was characterized by severe precipitation ultimately leading to reactor fouling. ^{1}H NMR analysis of material isolated prior to the reaction aborting indicated a 50% conversion to 2-bromo-1-(3-chlorophenyl)propan-1-one **3**.

Scheme S3 (Table 4, Entry 3, Scheme 4 in main article)

Flow reactor setup:

A single pump from a Uniqsis BPM (HPLC) **A** was utilised for the chemical transformation described below. The pump **A** was connected upstream to a reservoir **B** containing a stock solution of **2** via an injection valve (reagent injection), the injection valve was connected to a second reservoir **C** containing acetonitrile (solvent injection) (**Scheme S3**). The pump was connected downstream through standard (1/16" OD & 1 mm ID) PTFE tubing to one 15.0 mm ID and two 10.0 mm ID packed-bed reactors (Omnifit^{TM}) in series **D** housing polymer supported pyridinium tribromide followed by a fourth 10.0 mm ID packed bed reactor (Omnifit^{TM}) housing potassium carbonate **E**. The column reactors were jacketed on a Uniqsis HotColumn module placed on a HotCoil heating module. The combined column reactor volumes and subsequent residence times were calculated as per OMNIFIT® instructions: volume (mL) = 0.7854 × bed length (cm). The reactor output was passed through a standard 8-bar cartridge back-pressure regulator **F**. The pyridinium tribromide PBR was flushed outside of the system with acetonitrile to minimise leached species within the system. The flow system was pre-primed before execution of the reaction and again washed post-reaction with a combined reactor and dead volume equivalent of acetonitrile. The system was stored in isopropyl alcohol when not in use (**Figure S6**).



Scheme S3. α-Bromination of 3'-chloropropiophenone **2** under flow conditions

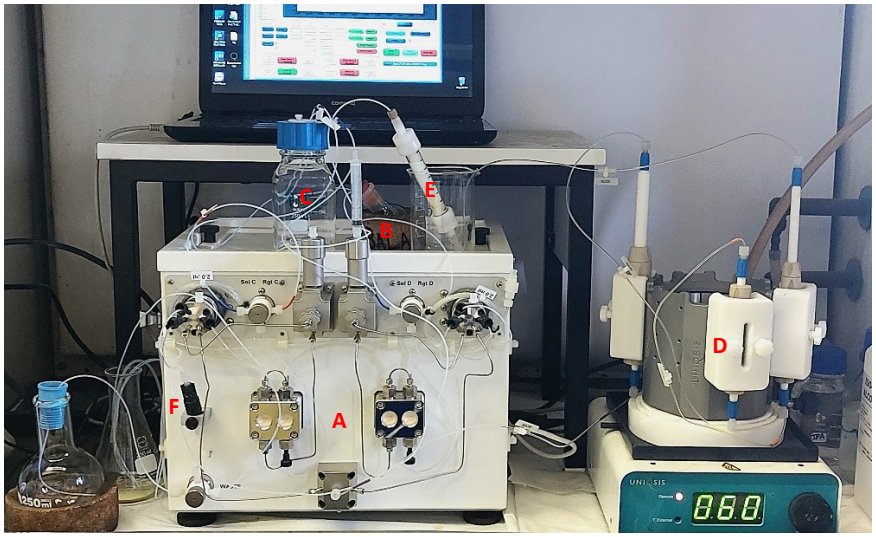


Fig S6. Reactor setup for flow bromination step with polymer bound pyridinium tribromide reagent

Preparation of stock solution:

A 1.0 M stock solution of 3'-chloropropiophenone **2** was prepared by the dissolution of **2** (2.5250 g, 14.97 mmol, 1.0 eq) in acetonitrile and dilution to a total volume of 15.00 mL.

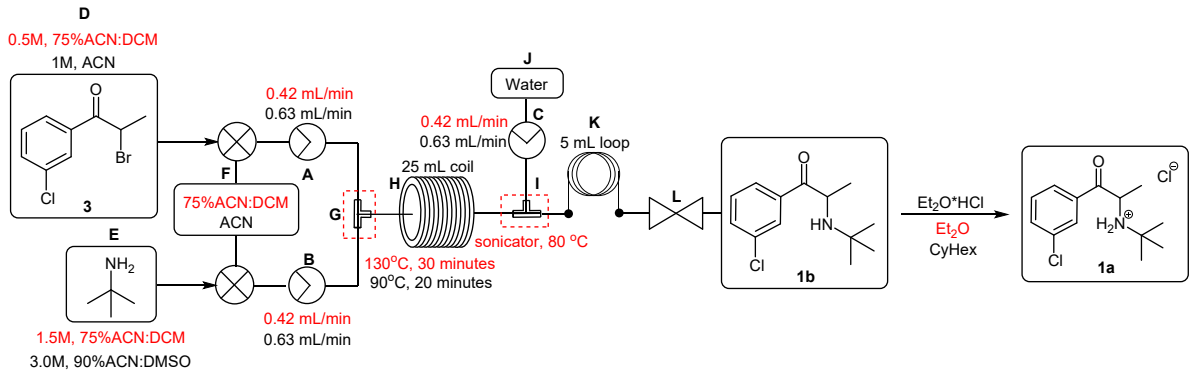
General procedure:

A stock solution was prepared as described above. A flow rate of 0.71 mL.min^{-1} was used to introduce 12 mL of the stock solution into the flow system after which time the injection valves were switched to the solvent reservoir containing acetonitrile which was used as a pushing solvent. The solution was pumped through the polymer-bound pyridinium tribromide packed-bed reactors (9.00 g, 18.0 mmol, 1.5 eq, 2 mmol.g^{-1}, 2.88 g Br_2) held at 60 ^{O}C (T_R = 25 min). Upon exiting, the mixture was passed through the potassium carbonate packed-bed reactor (4.6 g, 33.2 mmol, 2.8 eq) at ambient temperature after which time it was directed through the 8-bar back-pressure regulator. The resultant mixture was collected and concentrated *in-vacuo* to afford 2-bromo-1-(3-chlorophenyl)propan-1-one **3** as a light yellow oil in 81% isolated yield (98% conversion as estimated by integral areas on ^{1}H NMR).

1.5.2 Stages 2 & 3 – Nucleophilic substitution & salt formation

Scheme S4 – Red (Modification of Scheme 5 in main article) Flow reactor setup:

A Uniqsis Binary Pump Module (BPM) flow system, fitted with two 10 mL HPLC pump heads (**A** and **B**), along with a third stand-alone Uniqsis external pump (10 mL HPLC pump head) **C** were utilised (**Scheme S4 - Red**). The BPM pumps (**A** and **B**) were connected upstream to two reservoirs (**D** and **E**) containing stock solutions of **2** and *tert*-butylamine respectively (reagent injection), both valves were also connected to a third reservoir **F** containing 75% acetonitrile:dichloromethane (solvent injection). The flow streams were connected downstream at a T-piece mixer **G** using standard 1/16" OD & 1 mm ID PTFE tubing followed by a 25 mL (1/8" OD & 1.5 mm ID) PTFE coil reactor **H** mounted on a Uniqsis HotCoil heating module. The reactor outflow was combined with a third-stream delivering water from reservoir **J** via pump **C** at T-piece mixer **I**, this was followed by a 5 mL (1/8" OD & 1.5 mm ID) PTFE "dissolution" loop **K** and standard 8-bar cartridge back-pressure regulator **L**. The T-pieces (**G** and **I**) were suspended in a sonicating bath. The flow system was pre-primed before execution of the reaction and again washed post-reaction with a combined reactor and dead volume equivalent of 75% ACN:DCM. The system was stored in isopropyl alcohol when not in use.



Scheme S4. Nucleophilic substitution reaction for the formation of bupropion **1a** under flow conditions

Preparation of stock solutions:

A 0.5 M stock solution of 2-bromo-1-(3-chlorophenyl)propan-1-one* **3** was prepared by the dissolution of 1.2399 g (0.81 mL, 5.01 mmol, 1.0 eq) of **3** in 75% ACN:DCM (6.90 mL ACN and 2.30 mL DCM) and dilution to a volume of 10.00 mL.

*Material purified by column chromatography prior to use.

A 1.5 M stock solution of *tert*-butylamine was prepared by diluting *tert*-butylamine (1.60 mL, 15.23 mmol, 3.0 eq) in 75% ACN:DCM (6.30 mL ACN and 2.10 mL DCM) to total volume of 10.00 mL.

General procedure:

Stock solutions were prepared as described above. A flow rate of 0.84 mL.min^{-1} (0.42 mL.min^{-1} per pump) was used to introduce 2 mL of each of the stock solutions into the flow system after which time the injection valves were switched to the solvent reservoir containing 75% acetonitrile:dichloromethane which was used as a pushing solvent. The solutions were combined at the T-piece mixer (suspended in a sonicating bath T = 80 ^{O}C) and pumped through the coil reactor held at 130 ^{O}C (T_R = 30 min). Upon exiting the coil, the mixture was combined with the water quench line (pumping at 0.42 mL.min^{-1}, ~75 mL) at a T-piece mixer (suspended in the sonicating bath T = 80 ^{O}C) and passed through the "dissolution" loop held at room temperature prior to passage through the back-pressure regulator. The resultant mixture was collected and the organic solvent removed *in-vacuo*. The aqueous layer was extracted with dichloromethane (3 × 30 mL) combined and washed with a saturated solution of $NaHCO_3$ (30 mL). The organic layer was dried with anhydrous Na_2SO_4 (0.5 g) and concentrated *in vacuo* to afford the free base of bupropion **1b** in a yield of 81%. The free base **1b** (0.1939 g, 0.81 mmol, 1.0 eq) was then suspended in 16 mL diethyl ether (0.05 M) offline. The reaction mixture was cooled to 0 ^{O}C and a 2.0 M hydrogen chloride in diethyl ether solution (0.8 mL, 1.60 mmol, 2.0 eq) was added dropwise to the mixture until precipitation started. Upon further stirring precipitation intensified. The mixture was left in a fridge (~4 ^{O}C) overnight after which time it was filtered and dried to afford bupropion hydrochloride **1a** as a white solid in 62% yield.

Scheme S4 – Black (Modification of Scheme 5 in main article) Flow reactor setup:

A Uniqsis Binary Pump Module (BPM) flow system, fitted with two 10 mL HPLC pump heads (**A** and **B**), along with a third Uniqsis external FlowSyn pump **C** (10 mL HPLC pump head) was utilised (**Scheme S4 - Black**). The BPM pumps (**A** and **B**) were connected upstream to two reservoirs (**D** and **E**) containing stock solutions of **3** and *tert*-butylamine respectively (reagent injection), both valves were also connected to a third reservoir **F** containing acetonitrile (solvent injection). The flow streams were connected downstream at a T-piece mixer **G** using standard (1/16" OD & 1 mm ID) PTFE tubing followed by a 25 mL (1/8" OD & 1.5 mm ID) PTFE coil reactor **H** mounted on a Uniqsis HotCoil heating module. The reactor outflow was combined with a third-stream delivering water from reservoir **J** via pump **C** at T-piece mixer **I**, this was followed by a 5 mL (1/8" OD & 1.5 mm ID) PTFE "dissolution" loop **K** and subsequent standard 8-bar cartridge back-pressure regulator **L**. The flow system was pre-primed before execution of the reaction and again washed post-reaction with a combined reactor and dead volume equivalent of acetonitrile. The system was stored in isopropyl alcohol when not in use.

Preparation of stock solutions^:

A 1.0 M stock solution of 2-bromo-1-(3-chlorophenyl)propan-1-one* **3** was prepared by the dissolution of **3** (6.2191 g, 4.06 mL, 25.13 mmol, 1.0 eq) in acetonitrile and dilution to a total volume of 25.00 mL.

*Material purified by column chromatography prior to use.

A 3.0 M stock solution of *tert*-butylamine was prepared by diluting *tert*-butylamine (7.90 mL, 75.18 mmol, 3.0 eq) in 90% ACN:DMSO (15.40 mL ACN and 1.70 mL DMSO) to a total volume of 25.00 mL.

General procedure^:

Stock solutions were prepared as described above. A flow rate of 1.26 mL.min^{-1} (0.63 mL.min^{-1} per pump) was used to introduce 18.8 mL of each of the stock solutions into the flow system after which time the injection valves were switched to the solvent reservoir containing acetonitrile which was used as a pushing solvent. The solutions were combined at a T-piece mixer and pumped through the coil reactor held at 90 ^{O}C (T_R = 20 min). Upon exiting the coil, the mixture was combined with a water quench line (0.63 mL.min^{-1}, ~60 mL), passed through the "dissolution" loop at ambient temperature and subsequently through the 8-bar back-pressure regulator. The resultant mixture was collected, and the organic solvent removed *in-vacuo*. The aqueous layer was extracted with ethyl acetate (3 × 30 mL) combined and washed with 30 mL saturated aqueous $NaHCO_3$. The organic layer was dried with anhydrous Na_2SO_4 (0.5 g) and concentrated *in vacuo* to afford the free base bupropion **1b** in a yield of 98%. The free base **1b** (4.4317 g, 18.5 mmol, 1.0 eq) was suspended in 370 mL cyclohexane (0.05 M) offline. The reaction mixture was cooled to 0 ^{O}C and a 2.0 M hydrogen chloride in diethyl ether solution (18.80 mL, 37.60 mmol, 2.0 eq) was added dropwise to the mixture until precipitation started. Upon further stirring precipitation intensified. The mixture was left in a fridge (~4 ^{O}C) overnight after which time it was filtered and dried to afford bupropion hydrochloride **1a** as a white solid in 87% yield. ^ Reaction was scaled to match output scale of Stage 1 – Bromination (Table 4, Entry 3) for 2nd Generation analysis in green chem metrics (CHEM21 toolkit).

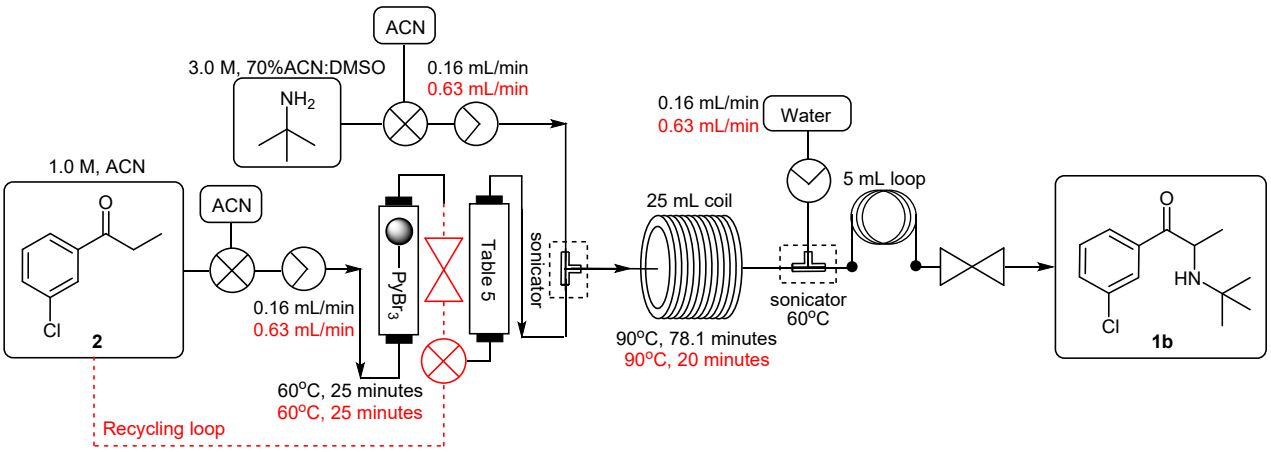
1.6 3rd Generation continuous flow process

1.6.1 Initial telescoping and scavenger screen

Scheme S5 – Black (Table 5, Entry 4, Scheme 6 – Black in main article)

Flow reactor setup:

A Uniqsis Binary Pump Module (BPM) flow system, fitted with two 10 mL HPLC pump heads (**A** and **B**), along with a third stand-alone Uniqsis external FlowSyn pump (10 mL HPLC pump head) **C** was utilised (**Scheme S5 - Black**). Pump **C** was connected upstream to a reservoir **D** containing a stock solution of **2** via an injection valve (reagent injection), the valve was also connected to a second reservoir **E** containing acetonitrile (solvent injection). Pump **C** was connected downstream using standard 1/16" OD & 1 mm ID PTFE tubing to a 10.0 mm ID packed-bed reactor **F** (OMNIFIT®) housing polymer supported pyridinium tribromide followed by a second 10.0 mm ID packed-bed reactor **G** (OMNIFIT®) housing potassium carbonate. The column reactors were jacketed on a Uniqsis HotColumn module and placed on a HotCoil heating module. The combined column reactor volumes and subsequent residence times were calculated as per OMNIFIT® instructions: volume (mL) = 0.7854 × bed length (cm). Pump **A** was connected upstream to reservoir **H** containing a stock solution of *tert*-butylamine via an injection valve (reagent injection), the valve was also connected to a second reservoir **I** containing acetonitrile (solvent injection). The outputs from the two flow lines (pumps **A** and **C**) were combined at a T-piece mixer **J** using standard (1/16" OD & 1 mm ID) PTFE tubing followed by a 25 mL (1/8" OD & 1.5 mm ID) PTFE coil reactor **K** mounted on a Uniqsis Polar Bear Plus module. The outflow was then combined with a line connecting reservoir **L** (containing water) via pump **B** at a T-piece mixer **M** followed by a 5 mL (1/8" OD & 1.5 mm ID) PTFE "dissolution" loop **N** and finally a standard 8-bar cartridge back-pressure regulator **O**. The T-pieces (**J** and **M**) were both suspended in a heated sonicating bath. The pyridinium tribromide PBR was flushed outside of the system with acetonitrile to minimise leached species within the system. The flow system was pre-primed before execution of the reaction and again washed post-reaction with a combined reactor and dead volume equivalent of acetonitrile. The system was stored in isopropyl alcohol when not in use.



Scheme S5. Nucleophilic substitution reaction for the formation of bupropion **1b** under flow conditions

Preparation of stock solutions:

A 1.0 M stock solution of 3'-chloropropiophenone **2** was prepared by dissolution of **2** (0.8451 g, 5.01 mmol, 1.0 eq) in acetonitrile and dilution to a total volume of 5.00 mL.

A 3.0 M stock solution of *tert*-butylamine was prepared by the dilution of *tert*-butylamine (3.20 mL, 30.46 mmol, 6.1 eq) in 6.8 mL of 70% ACN:DMSO to a total volume of 10.00 mL.

General procedure:

Stock solutions were prepared as described above. A flow rate of 0.16 mL.min^{-1} was used to introduce 3 mL of the 3'-chloropropiophenone **2** stock solution into the flow system. The solution was pumped through the polymer-bound pyridinium tribromide (2.25 g, 4.50 mmol, 1.5 eq, 2 mmol.g^{-1}, 0.72 g Br_2) packed-bed reactor held at 60 ^{O}C (T_R = 25 min). Upon exiting, the mixture was passed through the PBR housing ground-up potassium carbonate (4.60 g, 33.20 mmol, 2.8 eq) at ambient temperature after which time it was combined at a T-piece mixer (60 ^{O}C) with the *tert*-butylamine stock solution (0.16 mL.min^{-1}, delay = 47 min, 9 mL, 9.1 eq) and pumped through the coil reactor held at 90 ^{O}C (T_R = 78 min). Upon exiting the coil, the mixture was combined with a water quench line (0.16 mL.min^{-1}) at a T-piece mixer (60 ^{O}C), passed through the "dissolution" loop at ambient temperature prior to passage through the back-pressure regulator. The resultant mixture was collected, and the organic solvent removed *in-vacuo*. The aqueous layer was extracted with dichloromethane (3 × 30 mL) combined and washed with a saturated aqueous $NaHCO_3$ (30 mL). The organic layer was dried with anhydrous Na_2SO_4 (0.5 g) and concentrated *in vacuo* to afford the free base of bupropion **1b** in an isolated yield of 53%.

Scheme S5 – Red (Entry 6, Table 5, Scheme 6 – Red in main article)

Flow reactor setup:

A Uniqsis Binary Pump Module (BPM) flow system, fitted with two 10 mL HPLC pump heads (**A** and **B**), along with a third stand-alone 10 mL Uniqsis HPLC pump **C** was utilised (**Scheme S5 – Red, Figure S7**). Pump **C** was connected upstream to a reservoir **D** containing a stock solution of **2** via an injection valve (reagent injection), the valve was also connected to a second reservoir **E** containing acetonitrile (solvent injection). The pump **C** was connected downstream using standard 1/16" OD & 1 mm ID PTFE tubing to a 10.0 mm ID packed-bed reactor **F** (Omnifit™) housing polymer supported pyridinium tribromide followed by a standard 8-bar cartridge back-pressure regulator **P** and subsequent manual selector valve **Q**. The selector valve **Q** was connected to both reservoir **D** (recycling) and a second 10.0 mm ID packed-bed reactor **G** (Omnifit™) housing potassium carbonate. The column reactors were jacketed on a Uniqsis HotColumn module placed on a Uniqsis HotCoil heating module. The combined column reactor volumes and subsequent residence times were calculated as per OMNIFIT® instructions: volume (mL) = 0.7854 × bed length (cm). The outputs from the two flow lines (pumps **A** and **C**) were combined at a T-piece mixer **J** using standard 1/16" OD & 1 mm ID PTFE tubing followed by a 25 mL PTFE (1/8" OD & 1.5 mm ID) coil reactor **K** mounted on a Uniqsis Polar Bear Plus module. The outflow was then combined with a flow line connecting reservoir **L** (containing water) via pump **B** at a T-piece mixer **M** followed by a 5 mL PTFE (1/8" OD & 1.5 mm ID) "dissolution" loop **N** and finally a standard 8-bar cartridge back-pressure regulator **O**. The T-pieces (**J** and **M**) were both suspended in a heated sonicating bath. The pyridinium tribromide PBR was flushed outside of the system with acetonitrile to minimise leached

species within the system. The flow system was pre-primed before execution of the reaction and again washed post-reaction with a combined reactor and dead volume equivalent of acetonitrile. The system was stored in isopropyl alcohol when not in use.

Fig S7. Reactor setup for initial flow telescoping with recycling

Preparation of stock solutions:

A 1.0 M stock solution of 3'-chloropropiophenone **2** was prepared by the dissolution of **2** (0.8495 g, 5.04 mmol, 1.0 eq) in acetonitrile and dilution to a total volume of 5.00 mL.

A 3.0 M stock solution of *tert*-butylamine was prepared by dilution of *tert*-butylamine (8.00 mL, 76.13 mmol, 15.1 eq) in 70% ACN:DMSO to a total volume of 25.00 mL.

General procedure:

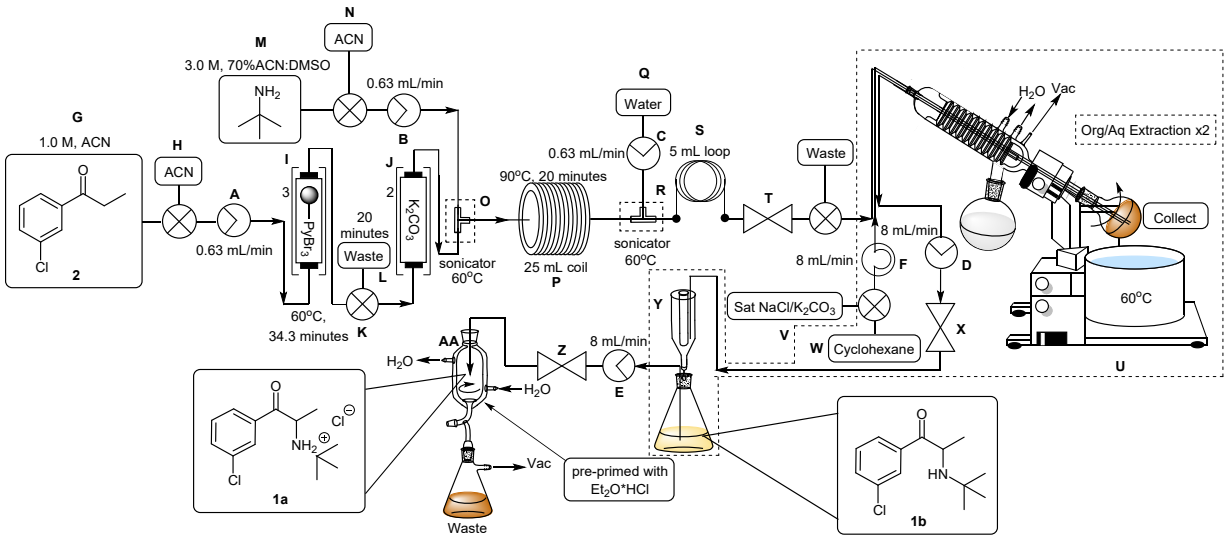
Stock solutions were prepared as described above. A flow rate of 0.63 mL.min^{-1} was used to recycle 3 mL of the 3'-chloropropiophenone **2** stock solution through polymer-bound pyridinium tribromide (2.25 g, 4.50 mmol, 1.5 eq, 2 mmol.g^{-1}, 0.72 g Br_2) housed in a packed-bed reactor held at 60 ^{O}C (T_R = 25 min for a total recycling time of 48 min, ~4 cycles). Upon completion of the recycle, the manual valve was used to direct the flow stream through the scavenger PBR (4.60 g, 33.20 mmol, 2.8 eq) held at room temperature after which time it was combined with the *tert*-butylamine stock solution stream (0.63 mL.min^{-1}, delay = 50 min, 20 mL, 20.3 eq) at a T-piece mixer (60 ^{O}C) and pumped through the coil reactor held at 90 ^{O}C (T_R = 20 min). Upon exiting the coil, the mixture was combined with a water quench line (0.63 mL.min^{-1}) at a T-piece mixer (60 ^{O}C), followed by the "dissolution" loop at ambient temperature and finally the back-pressure regulator. The resultant mixture was collected, and the organic solvent removed *in-vacuo*. The aqueous layer was extracted with dichloromethane (3 × 30 mL) combined and washed with a saturated solution of aqueous $NaHCO_3$ (30 mL). The organic layer was dried with anhydrous Na_2SO_4 (0.5 g) and concentrated *in vacuo* to afford free base bupropion **1b** in an isolated yield of 77%.

1.6.2 Telescoped process

Scheme S6 (Scheme 7, Figure 1 in main article)

Flow reactor setup:

The telescoped process was performed using a Uniqsis Binary Pump Module (BPM) flow system, fitted with two 10 mL HPLC pumpheads (**A** and **B**), along with three stand-alone 10 mL Uniqsis HPLC pumps (**C**, **D** and **E**) and a stand-alone Vapourtec SF-10 peristaltic pump (**F**) (**Scheme S6**). All pumps were plumbed with standard (1/16" OD & 1 mm ID) PTFE tubing unless stated otherwise.



Scheme S6. Generation 3 – Final telescoped process

Pump **A** was connected upstream to a reservoir **G** containing a stock solution of **2** via an injection valve (reagent injection), the valve was also connected to a second reservoir **H** containing acetonitrile (solvent injection). Pump **A** was connected downstream using standard PTFE tubing (1/16" OD & 1 mm ID) to 3 packed-bed reactors (Omnifit™, 2 x 15 mm ID and 1 x 10 mm ID) **I** connected in series housing polymer supported pyridinium tribromide followed by two packed-bed reactors (Omnifit™, 2 x 15 mm ID) **J** also connected in series housing potassium carbonate. The column reactors were jacketed on a Uniqsis HotColumn module placed on a Uniqsis HotCoil heating module. The combined column reactor volumes and subsequent residence times were calculated as per OMNIFIT® instructions: volume (mL) = 0.7854 × bed length (cm). A manual selector valve **K** was inserted directly after the packed-bed reactors **I** housing the polymer supported pyridinium tribromide and could be directed to a waste reservoir **L** or to the packed bed reactors **J** housing the potassium carbonate. The pyridinium tribromide PBRs were flushed outside of the system prior to commencement of the reaction (to waste reservoir **L**) with acetonitrile to minimise leaching within the system.

Pump **B** was connected upstream to reservoir **M** containing a stock solution of *tert*-butylamine via an injection valve (reagent injection), the valve was also connected to a second reservoir **N** containing acetonitrile (solvent injection). The outputs from the two flow lines (pumps **A** and **B**) were combined at a T-piece mixer **O** using standard PTFE tubing (1/16" OD & 1 mm ID) followed by a 25 mL (1/8" OD & 1.5 mm ID) PTFE coil reactor **P** mounted on a Uniqsis Polar Bear Plus module. The outflow was then combined with a line connected to reservoir **Q** (containing water) via pump **C** at a T-piece mixer **R**, followed by a 5 mL (1/8" OD & 1.5 mm ID) PTFE "dissolution" loop **S** and finally a standard 8-bar cartridge back-pressure regulator **T**. The T-pieces (**O** and **R**) were both suspended in a sonicating bath.

The collection outlet was plumbed directly to a 500 mL evaporation flask mounted on a Heidolph rotary evaporator **U**. A Vapourtec peristaltic pump **F** equipped with standard (1/16" OD & 1 mm ID) tubing fitted with an automatic selector valve, was also plumbed into the 500 mL collection flask. The automatic selector valve was connected up stream to two reservoirs **V** (Sat NaCl/K_2CO_3) and **W** (Cyclohexane). Finally, a stand-alone 10 mL Uniqsis HPLC pump **D** was also plumbed into the 500 mL collection flask. Pump **D** was connected downstream to an 8-bar cartridge based back pressure regulator **X** followed by a Biotage® phase separator **Y**. The organic phase from the Biotage® phase separator **Y** was passed, via pump **E** through an 8-bar cartridge based back pressure regulator **Z** prior to collection in a pre-cooled in-line triturator **AA** for the final salt formation. The flow system was pre-primed before execution of the reaction and again washed post-reaction with a combined reactor and dead volume equivalent of acetonitrile. The system was stored in isopropyl alcohol when not in use.

Preparation of stock solutions:

A 1.0 M stock solution of 3'-chloropropiophenone **2** was prepared by the dissolution of **2** (4.2475 g, 25.2 mmol, 1.0 eq) in acetonitrile and dilution to a total volume of 25.00 mL.

A 3.0 M stock solution of *tert*-butylamine was prepared by diluting *tert*-butylamine (31.52 mL, 300 mmol, 11.8 eq) in 70% ACN:DMSO to a total volume of 100.00 mL.

General procedure:

A 1.0 M 3'-chloropropiophenone **2** (2.5 g, 14.8 mmol, 1 eq) stock solution (in 15 mL ACN) was pumped through 3 packed bed reactors (2 x 15.0 mm & 1 x 10.0 mm) housing a combined 1.5 equivalents of pyridinium tribromide (11.25 g, 22.5 mmol, 1.52 eq, 2 mmol.g^{-1}, 3.60 g Br_2) (T_R = 34.3 min, Temp = 60 ^{O}C), which was followed by 2 PBR's (2 x 15.0 mm) housing excess crushed potassium carbonate (30.0 g, 217.1 mmol, 14.5 eq). *NOTE: the flow stream was initially directed to the waste reservoir located after the PBR's housing the pyridinium tribromide for 20 min and thereafter when the reagent plug was calculated to start exiting the PBR's the flow stream was switched (using a manual selector valve) to direct the stream to the PBR's housing potassium carbonate. This operation was performed as a precaution to prevent unwanted leaching from the polymer supported pyridinium bromide into the potassium carbonate PBR's.* The reaction mixture exiting the column was combined with the 3.0 M stock solution (85 mL) of *tert*-butylamine (18.7 g, 26.8 mL, 255.0 mmol, 17.2 eq) in 70% ACN:DMSO at a T-piece submerged in a sonicating bath (T = 60 ^{O}C). The resulting mixture was subsequently passed through the PTFE coil reactor (T_R = 20 min, Temp = 90 ^{O}C) prior to being quenched with distilled water (0.63 mL.min^{-1}, 104 mL) at the second T-piece mixer (submerged in the sonicating bath T = 60 ^{O}C) which was followed by the 5 mL PTFE "dissolution" loop and thereafter the 8-bar cartridge type back-pressure regulator prior to collection in the evaporation flask mounted on the rotary evaporator. Upon complete collection, the ACN and unreacted *tert*-butylamine was removed under reduced pressure. Thereafter, cyclohexane was pumped into the rotary evaporator using the second line (8 mL.min^{-1}, 90 mL) followed by a saturated solution of sodium chloride and potassium carbonate (8 mL.min^{-1}, 50 mL NaCl & 50 mL K_2CO_3). The rotatory evaporator was set to rotate (250 rpm) to mix the phases, thereafter the rotation was stopped to allow phase separation and finally the organic phase was pumped out of the rotary evaporator using the third line (8 mL.min^{-1}). The resultant mixture was fed into a Biotage® phase separator allowing for the removal of any remaining traces of the aqueous phase and subsequent collection of the organic layer. A second extraction was performed in a similar fashion (90 mL) and the organic fractions were combined and pumped into a cooled (T = 0 ^{O}C) in-line triturator pre-primed with 12 mL of cyclohexane. A 2.0 M hydrogen chloride in diethyl ether solution (12.3 mL, 0.9 g, 24.6 mmol, 1.7 eq) was added dropwise to the mixture until precipitation started. Upon further stirring precipitation intensified. The mixture was filtered and dried to afford bupropion hydrochloride **1a** as a white solid (2.54 g) in a 62% isolated yield. Additional information: priming and pushing solvent – ACN (190 mL), combined reactor volumes ~ 85.00 mL, system dead- and connecter-tubing volume ~ 10 mL, clean-up and storing solvent – IPA (40 mL).

1.7 4th Generation staggered flow process

1.7.1 Initial investigation

We investigated the 3rd generation process to determine whether the loss in yield and purity was arising as a result of one or more of the downstream processing operations. Our investigation; initially conducted only on the second nucleophilic substitution step utilizing un-columned brominated material **3** prepared under batch conditions; aimed to evaluate the effect of the in-line trituration step, the use of excess *tert*-butylamine, the water quench line and the liquid-liquid extraction performed with the rotary evaporator (**Table S3**, **Scheme S7**).

Table S3. Flow nucleophilic displacement of bromine utilising different work-up procedures[a]

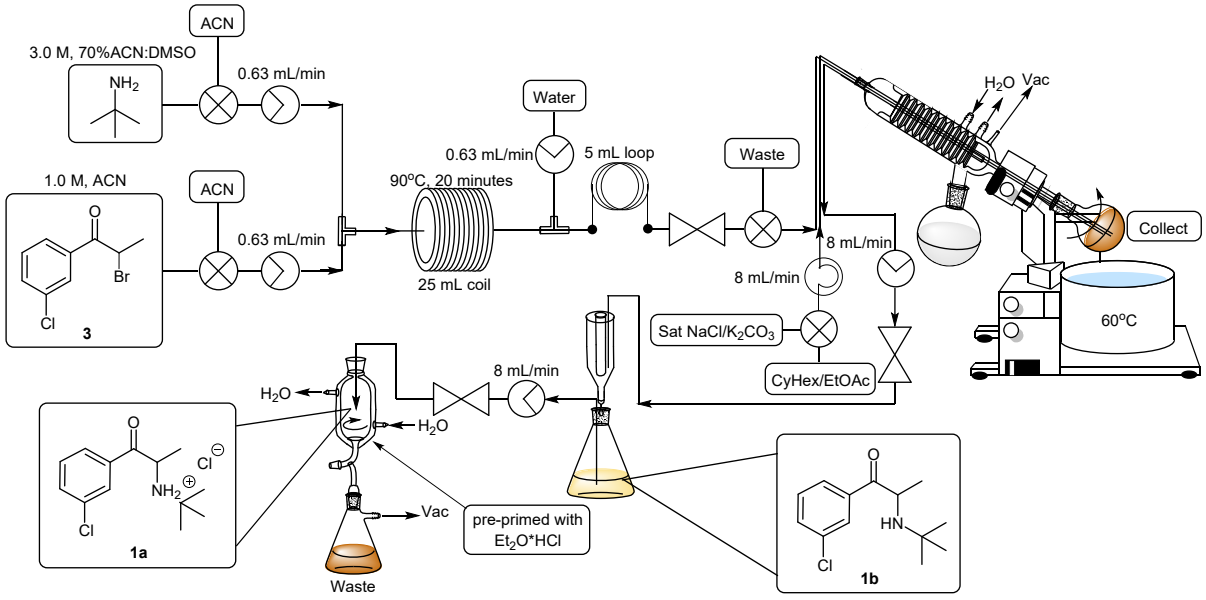
Entry	Source of 3 [b]	Excess *tert*-butylamine (Yes/No)	Quench type	Extraction (off-line/in-line)	Trituration[c] (off-line/in-line)	Yield %[d]	
						1b	1a
1	Batch	No	H_2O	Off-line	Off-line	91	80
2	Batch	No	None	Off-line	In-line	93	74
3	Batch	No	H_2O	In-line	Off-line	87	73
4[e]	Batch	Yes	H_2O	Off-line	Off-line	69	83
5[f]	Flow	No	H_2O	In-line	Off-line	91	75[g]

[a]General reaction conditions: 1.0 M stock solution of bromine intermediate **3**, 3.0 M *tert*-butylamine, 90 ^{O}C, 20-minute residence time, 4.5-gram theoretical scale of **1b** [b]Reaction material was purified via simple extraction prior to usage [c]Performed with Et_2O* HCl in Et_2O [d]Isolated yield [e]Excess *tert*-butylamine 17.2 equivalents [f]89% conversion to **1b**, 11% Bromine intermediate **3** [g]Salt formation facilitated by *in-situ* generation of HCl gas

Notably, in all instances, the need for the sonicating bath was diminished as little to no precipitate formation was observed during the flow process, this is possibly because the brominated material **3** was extracted with water, removing unwanted bromide species, as part of the downstream processing for stage 1. Upon evaluation of the results obtained, several conclusions could be drawn. Firstly, neither the liquid-liquid extraction performed with the utilization of the rotary evaporator, nor the in-line trituration step (**Table S3**, Entries 2 & 3) led to significant variations in the yields. Furthermore, the use of the water quench-line did not prove to be problematic as near comparable yields were obtained for both the free base **1b** and salt **1a** (**Table S3**, Entries 1 & 2). Interestingly though, the use of excess *tert*-butylamine (17.2 eq) appeared to negatively impact the yield of the free base **1b** (**Table S3**, Entry 4).

We hypothesized that the lower yields in the third generation might be linked to the absence of a work-up step between stages 1 and 2 and the use of excess *tert*-butylamine.

Practically, this could readily be overcome by including an inline extraction between stages 1 and 2, which would subsequently lead to the use of less *tert*-butylamine in the second stage. This led to a short re-investigation of the first bromination step integrating a rotary evaporator and a Zaiput™ membrane separator. In this iteration, the PBR housing excess potassium carbonate was removed, and the resulting reaction mixture was washed with a saturated solution of potassium carbonate in the rotary evaporator instead. Utilising these conditions, the nucleophilic substitution reaction was again investigated using flow generated bromine intermediate **3** to ascertain whether the starting material used led to any changes in the isolated yields of **1b** and **1a** (Entry 5). Although comparable isolated yields were obtained for both **1b** and **1a** we noticed upon further inspection that there was still incomplete conversion. We hypothesized that a moderate increase in the stochiometric excess of *tert*-butylamine from 3.0 to 4.0 equivalents would diminish this problem and lead to full conversion to the free base **1b**.



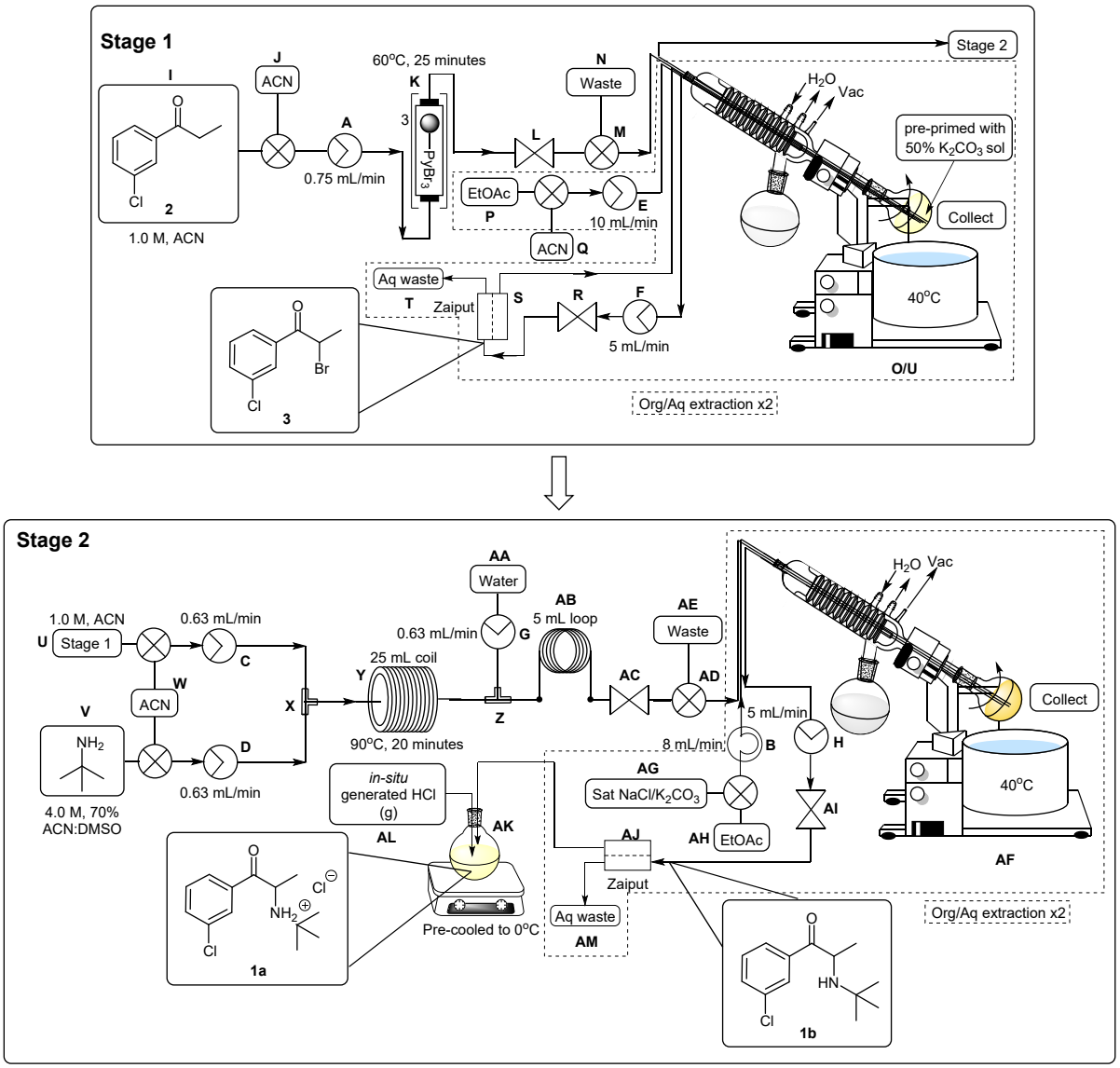
Scheme S7. Nucleophilic substitution reaction with integrated flow work-up

1.7.2 Final telescoped process

Scheme S8 (Scheme 8 in main article)

Flow reactor setup:

The telescoped process utilised two Uniqsis Binary Pump Modules (BPM) flow system, fitted with either 10 mL or 50 mL HPLC pump heads (**C** & **D**), along with five stand-alone 10 mL or 50 mL Uniqsis HPLC pumps (**A, E, F, G** & **H**) and a stand-alone Vapourtec SF-10 peristaltic pump (**B**). All flow lines were comprised of (1/16" OD & 1 mm ID PTFE tubing) unless stated otherwise (**Scheme S8**).



Scheme S8. Generation 4 – Final telescoped process

A Uniqsis stand-alone pump **A** was connected upstream to a reservoir **I** containing a stock solution of **2** via an injection valve (reagent injection), the valve was also connected to a second reservoir **J** containing acetonitrile (solvent injection). Pump **A** was connected downstream to 3 packed-bed reactors (2 x 15 mm ID and 1 x 10 mm ID) **K** (Omnifit^{TM}) connected in series housing polymer supported pyridinium tribromide followed by an 8-bar cartridge based back pressure regulator **L** and a manual selector value **M** with two outlet pathways. One pathway was connected to a waste collection flask **N** and the other was plumbed directly into a 500 mL evaporation flask mounted on a Heidolph rotary evaporator **O**. The column reactors were jacketed on a Uniqsis HotColumn module placed on a Uniqsis HotCoil heating module. The combined column reactor volumes and subsequent residence times were calculated as per OMNIFIT® instructions: volume (mL) = 0.7854 × bed length (cm). A second Uniqsis standalone 50 mL HPLC pump **E** was plumbed downstream into the rotary's 500 mL evaporation flask **O**, and upstream to reservoirs containing ethyl acetate **P** and acetonitrile **Q** via a selector valve. A third Uniqsis standalone pump **F** was plumbed upstream to the 500 mL evaporation flask **O**. Downstream the pump **F**, directed the flow stream through an 8-bar cartridge based back pressure regulator **R** followed by a Zaiput separator **S** fitted with a OB900 S10 membrane. The line carrying the organic phase from the Zaiput was plumbed back into the Heidolph rotary evaporator fitted with a new evaporation flask **U** and the aqueous phase was plumbed into a waste collection reservoir **T**. The second pump **E** was used to introduce, from reservoir **Q**, acetonitrile into the new flask **U** to obtain the desired concentration (1.0 M) for the second stage of the synthesis. The pyridinium tribromide PBRs were flushed outside of the system prior to commencement of the reaction (to waste reservoir **L**) with acetonitrile to minimise leaching within the system.

Uniqsis Binary pump module pumps **C** and **D** were connected upstream to stock solutions of **3** (from stage 1, **U**) and tert-butylamine in 70% ACN:DMSO (**V**) respectively via selector valves (reagent injection). The selector valves were also both connected to a third reservoir **W** housing acetonitrile (solvent injection). The outputs of pump heads **C** and **D** were combined at a T-piece mixer **X** prior to passage through a 25 mL (1/8" OD & 1.5 mm ID) PTFE coil reactor **Y** mounted on a Uniqsis Polar Bear Plus heating module. The output flow stream was then combined with a quench line from a Uniqsis HPLC pump **G** at a second T-piece mixer **Z**, pump **G** was connected upstream to a reservoir **AA** containing water. Thereafter, the combined flow line was passed through a 5 mL (1/8" OD & 1.5 mm ID) PTFE mixing loop **AB** an 8-bar cartridge back-pressure regulator **AC** and finally a manual selector value **AD** with two outlet pathways. One pathway was connected to a waste collection flask **AE** and the other was plumbed directly into a 500 mL evaporation flask mounted on a Heidolph rotary evaporator **AF**. A Vapourtec SF-10 peristaltic pump **B** was plumbed directly into the 500 mL evaporation flask, and connected upstream to two reservoirs containing saturated NaCl/K_2CO_3 **AG** and ethyl acetate **AH** respectively. A second Uniqsis standalone 10 mL HPLC pump **H** was plumbed directly from the 500 mL evaporation flask. Downstream the pump directed the flow stream through an 8-bar cartridge based back pressure regulator **AI** followed by a Zaiput separator **AJ** fitted with a OB900 S10 membrane. The line carrying the organic phase from the Zaiput was plumbed into a round-bottom flask **AK** connected to hydrogen chloride gas generator **AL** and the aqueous phase was directed to a waste reservoir **AM**. The flow system was pre-primed before execution of the reaction and again washed post-reaction with a combined reactor and dead volume equivalent of acetonitrile. The system was stored in isopropyl alcohol when not in use.

Preparation of stock solutions:
A 1.0 M stock solution of 3'-chloropropiophenone **2** was prepared by the dissolution of **2** (4.2475 g, 25.2 mmol, 1.0 eq) in acetonitrile and dilution to a total volume of 25.00 mL.

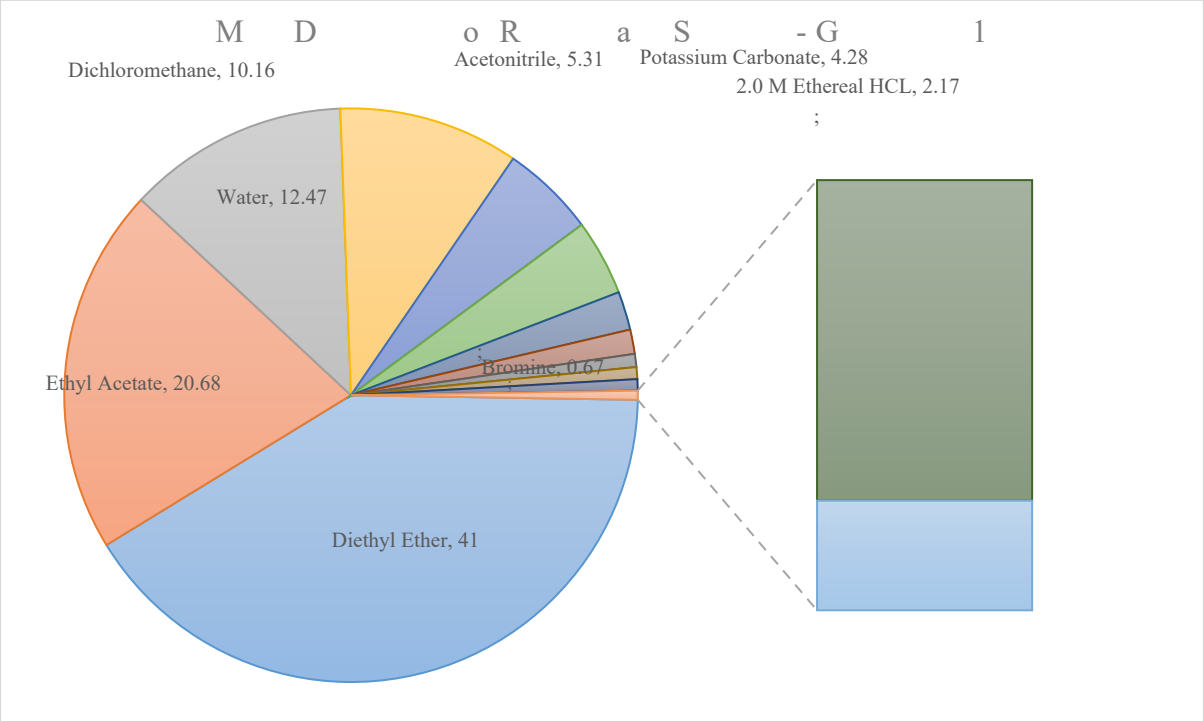
A 4.0 M stock solution of *tert*-butylamine was prepared by diluting *tert*-butylamine (7.31 g, 10.50 mL, 100 mmol, 4.1 eq) in 70% ACN:DMSO and dilution to a total stock solution volume of 25.00 mL.

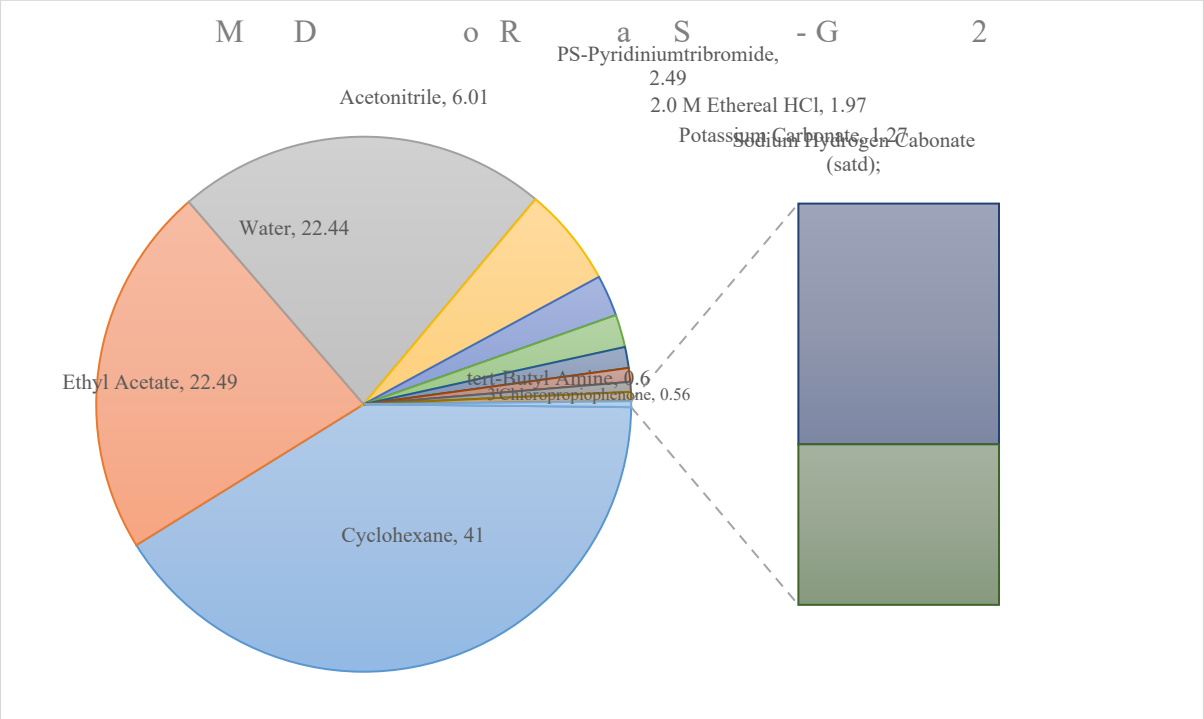
General procedure:
A 1.0 M 3'-chloropropiophenone **2** stock solution (15 mL, 2.5 g, 14.8 mmol, 1 eq) was pumped through the pack-bed reactors (2 x 15.0 mm & 1 x 10.0 mm) housing a combined 1.5 equivalents of pyridinium tribromide (11.25 g, 22.5 mmol, 1.52 eq, 2 $mmol.g^{-1}$, 3.60 g Br_2) (T_R = 25 min, Temp = 60 ^{O}C). The reactor output stream was pumped (0.75 $mL.min^{-1}$) into the rotary evaporator (pre-primed with 60 mL 50% aqueous potassium carbonate) while rotating at 250 rpm. After collection was completed, the acetonitrile solvent was removed *in vacuo* (40 ^{O}C water bath) and ethyl acetate (30 mL, 8.0 $mL.min^{-1}$) was pumped into the rotary evaporator through the second line. The rotatory evaporator was set to rotate at 250 rpm for 5 min to facilitate the required extraction, thereafter the biphasic mixture was pumped through the Zaiput membrane separator (at 5.0 $mL.min^{-1}$) prior to collection in two separate flasks. The extraction was repeated (30 mL EtOAc, 8.0 $mL.min^{-1}$) after which time the system was cleaned with 5 mL EtOAc and 5 mL H_2O, the organic fractions combined, dried with 0.5 g of Na_2SO_4, filtered and pumped back into the rotary evaporator fitted with a new evaporation flask. The ethyl acetate solvent was removed *in vacuo* and acetonitrile (13 mL) was pumped in to afford a 1.0 M stock solution of bromine intermediate **3**.

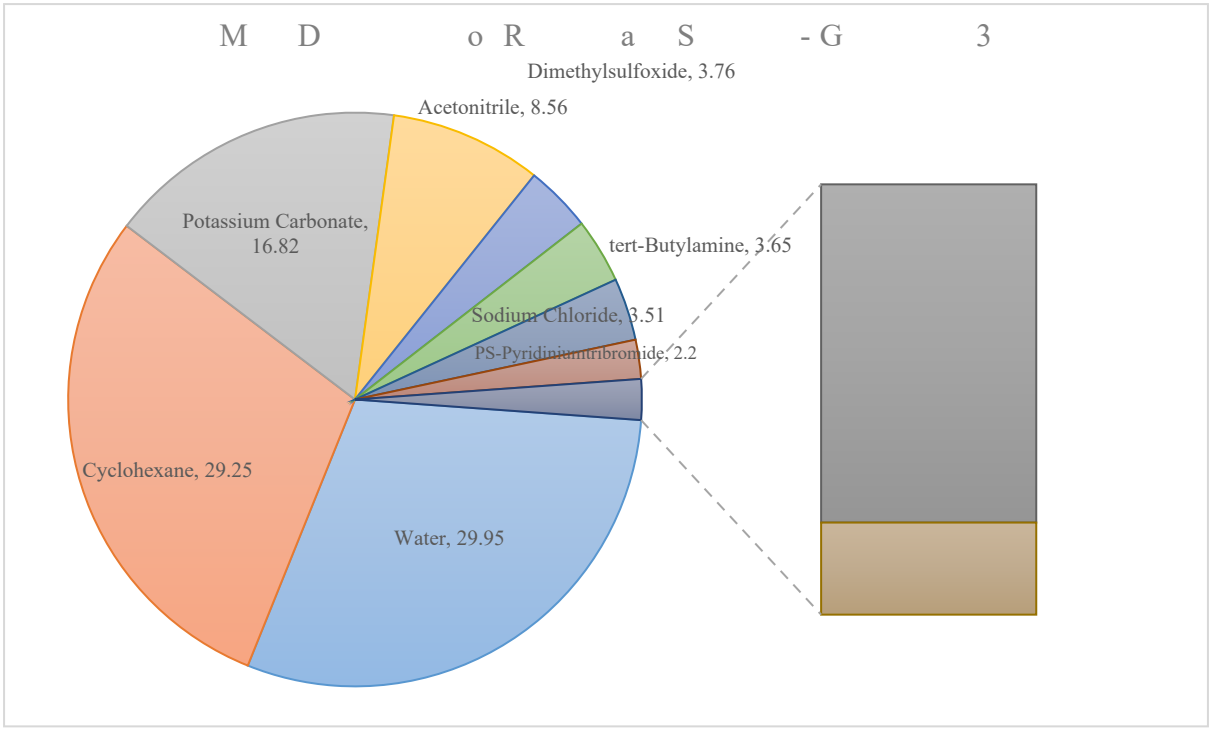
The stock solution of **3** (FR = 0,63 $mL.min^{-1}$) was combined with the *tert*-butylamine stock solution (FR = 0,63 $mL.min^{-1}$) (15 mL, 4.39 g, 6.31 mL, 60 mmol, 4.1 eq) at a T-piece mixer. The resulting mixture was subsequently passed through the PTFE coil reactor (T_R = 20 min, Temp = 90 ^{O}C) prior to being quenched with water (0.63 $mL.min^{-1}$, 50 mL) at the second T-piece mixer. Thereafter, the flow stream was passed through the 5 mL PTFE "dissolution" loop followed by the back-pressure regulator prior to collection in the evaporation flask mounted on the rotary evaporator. Upon complete collection, the ACN and unreacted *tert*-butylamine were removed under reduced pressure (40 ^{O}C rotary water bath temperature). Thereafter, ethyl acetate was pumped into the rotary evaporator using the second line (8 $mL.min^{-1}$, 30 mL) followed by a saturated aqueous solution of sodium chloride and potassium carbonate (8 $mL.min^{-1}$, 10 mL NaCl & 10 mL K_2CO_3). The rotatory evaporator was set to rotate at 250 rpm for 5 min to facilitate the required mixing, thereafter the biphasic mixture was fed through the Zaiput membrane separator (5 $mL.min^{-1}$) using the third line allowing for the separation of the two phases. The Zaiput output streams were collected in separate collection flasks. A second extraction was performed in a similar fashion (30 mL EtOAc, 8.0 $mL.min^{-1}$) and the system was washed with 5 mL EtOAc and 5 mL H_2O. The organic fractions were combined, dried with 0.5 g of anhydrous Na_2SO_4, filtered and pumped into a pre-cooled (0 ^{O}C) round bottom flask fitted with 1/8" PTFE tube for delivery of hydrogen chloride gas which was generated *in situ*. The system was washed with 5 mL EtOAc. The hydrogen chloride gas was generated off-line by the reaction of 11.0407 g of NaCl and 5 mL of H_2SO_4. The gas was

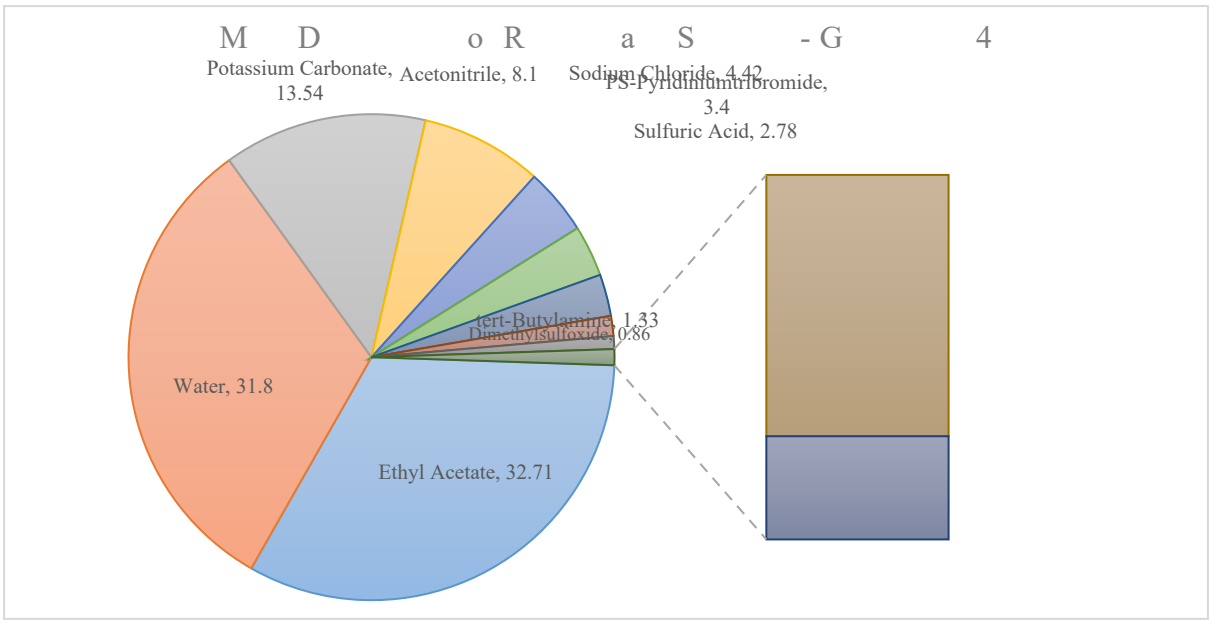
allowed to bubble into the solution (0.21 M) until no more gas evolution was noted. The mixture was left in a fridge (4 ^{O}C) overnight prior to filtration and dried to afford bupropion hydrochloride **1a** as a white solid in 69% yield (2.8402 g). Additional information: priming and pushing solvent – ACN (140 mL), combined reactor volumes – 60.00 mL, system dead- and connecter-tubing volume – 10 mL, clean-up and storing solvent – IPA (40 mL).

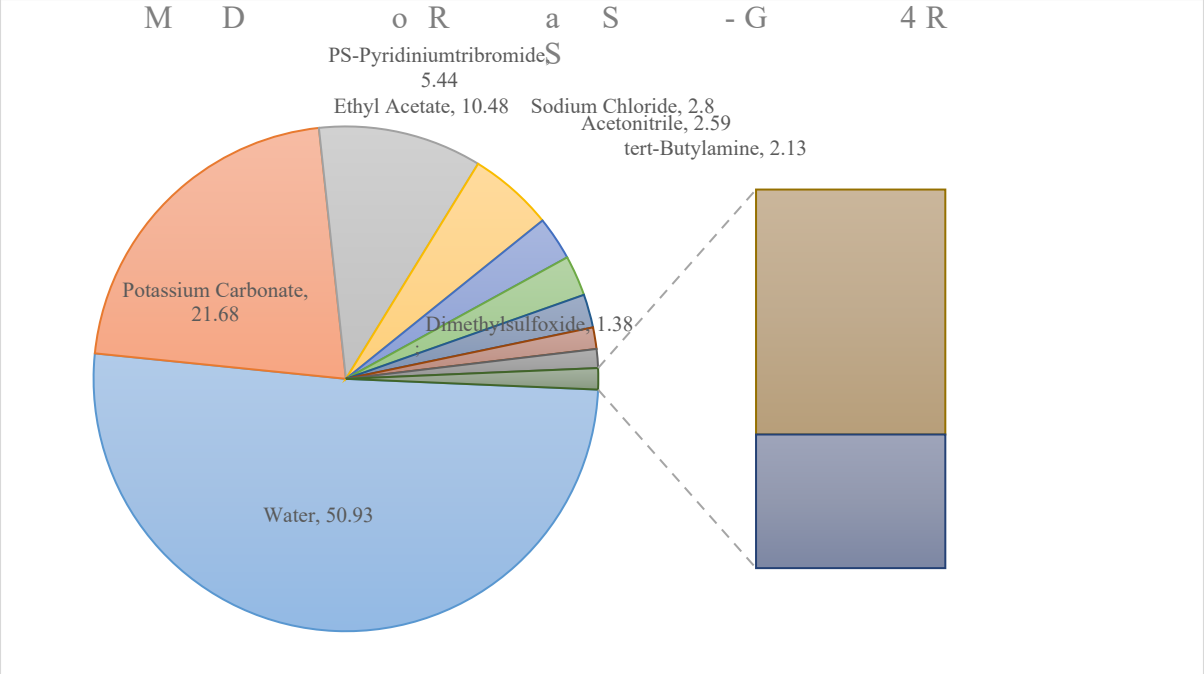
1.8 Distribution of raw materials






M D o R a S - G 3
Dimethylsulfoxide, 3.76
Acetonitrile, 8.56
Potassium Carbonate, 16.82
tert-Butylamine, 3.65
Sodium Chloride, 3.51
PS-Pyridiniumtribromide, 2.2
Cyclohexane, 29.25
Water, 29.95


M D o R a S - G 4
Potassium Carbonate, 13.54
Acetonitrile, 8.1
Sodium Chloride, 4.42
PS-Pyridiniumtribromide, 3.4
Sulfuric Acid, 2.78
tert-Butylamine, 1.33
Dimethylsulfoxide, 0.86
Water, 31.8
Ethyl Acetate, 32.71



Scenario representing an 80% recovery of ethyl acetate and acetonitrile and 2.0 equivalents of HCl.

1.9 Green Metrics

Green metrics were assessed using the CHEM21 toolkit.[13] A zero and first pass assessment was conducted for generations 1 to 4 and contrasted against first pass assessments of previously reported approaches. The assessments are summarised in the separate Excel spreadsheet included as part of the ESI. In instances where values of reagents and solvents were not reported in prior art, we elected to use a value of zero so as to not unfairly penalise the approach being assessed. Descriptions of metrics employed for this analysis have also been included in the Excel spreadsheet. In instances of the 1st and 2nd generation reactions procedures were scaled to match the outputs generated in previous steps.

The following analyses can be found in the excel spreadsheet:

Zero Pass Generation 1
First Pass Generation 1
Zero Pass Generation 2
First Pass Generation 2
Zero Pass Generation 3
First Pass Generation 3
Zero Pass Generation 4
First Pass Generation 4
First Pass Generation 4 Scenario (Refers to a hypothetical scenario wherein 80% ethyl acetate and acetonitrile are recycled)
First Pass Perrine
First Pass Hurst and Sherwood
First Pass Ley
First Pass Z.A.J. Pharmaceutica
First Pass Z.A.J. Validation (Analysis using in-house validation results of the Z.A.J. Pharmaceutica approach)

1.9.1 Comparison of generation 4 with previously reported processes

The original Burroughs Wellcome Co. approach afforded **1a** in a good overall yield of 71% over three discrete stages[9] (based on results of in-house validation, description in the original patent does not provide sufficient detail for direct analysis). Critically, the approach makes use of molecular bromine which is flagged by red H&S codes linked to toxicity (H330) and environmental implications (H400) as well as dichloromethane and diethyl ether which are categorised as hazardous and highly hazardous solvents respectively. The use of dichloromethane notably is becoming more contentious with the US environmental protection agency currently proposing a widespread ban its use under the US governments toxic substances control act.[36] In addition, the process utilised a 3-fold excess of

tert-butylamine which is flagged by an amber H&S code linked to toxicity (H331) and from an energy perspective the approach requires undesirable refluxing in stage 2.

Perrine and co-workers in 2000 reported an improved process affording **1a** in 80% yield.[11] Molecular bromine and dichloromethane were again employed, but the nucleophilic substitution was conducted in NMP. The authors rationalised that NMP afforded an advantage by significantly reducing the reaction time for stage 2 from hours to only 10 min. Unfortunately, the use of NMP is highly problematic. It is flagged by a red H&S code linked to long-term toxicity (H360D) and in 2020 was placed on the REACH list restricting its marketing and use both as a pure solvent and as a mixture in the European Union.[37] In addition, it has also been flagged as a substance of very high concern by ChemSec.[38] Its use imparts several additional penalties; notably its removal in downstream processing is energy and waste intensive requiring, in the case of the Perrine and co-workers report, eight organic/aqueous extractions and the additional time required for complete removal could potentially impact the final product yield and purity as the free base **1b** is known to be unstable.[39] In addition, the *tert*-butylamine is used in 8-fold excess also adding to the waste burden (PMI_{TOTAL} = 174.2). Finally, although the authors switched to aqueous HCl for the final salt formation they elected to persist with the use of diethyl ether as an extractive solvent.

Thereafter, in 2008 the Zhejiang Apeloa Medical Technology Co Ltd filed a patent reporting an efficient approach with a low overall PMI score of 17.4.[40] A solvent free approach was adopted but once again molecular bromine was utilised, and in this instance the risk was elevated as neat bromine is charged directly into neat 3'-chloropropiophenone **2** at temperatures in excess of the boiling point of bromine (75 vs. 58.8 °C). The process also requires refluxing of both stages 1 and 2 for an extended period of time (> 8.5 h) resulting in a red flag in terms of energy usage, and finally, use is made of dichloromethane and/or toluene, both of which have amber H-codes, as an extracting solvent in several iterations of the method. We felt that the approach raised several red flags, notably, in our experience elevated temperatures in the first stage promotes unwanted dibromination **4** and extended heating in stage 2 promotes the decomposition of the free base **1b**. We elected to validate the approach in-house on a 1.7-gram scale, and in our hands, we were unable to replicate the process as described. Critically, the first stage afforded ~20% of the unwanted dibrominated product **4** (as estimated by integral areas in ^{1}H NMR) and we were only able to isolate bupropion HCl **1a** in an overall yield of 21%. As an additional note, the addition of bromine to **2** at elevated proved to be extremely vigorous even on gram scale.

The 2018 flow synthesis by the Ley group afforded the free base **1b** in 80% yield (conversion to the salt form **1a** not reported). The process was fully telescoped with integrated downstream processing improving the safety profile by reducing chemical exposure and the volume of material undergoing reaction at any point in time.[19] Critically, like Perrine[11] the translation made use of molecular bromine, dichloromethane and NMP, but in this instance the stoichiometric excess of *tert*-butylamine was reduced to 3.0 equivalents. The approach has a high waste burden (PMI = 566.1), but it should be noted that high level process optimisation was not the objective of the study, which was instead focused on the testing and demonstration of an across-the-world automation and optimization platform.

Hurst and Sherwood in 2022[41] reported an elegant green synthesis of bupropion hydrochloride **1a** (68% overall yield). In their approach they elected to use *N*-bromosuccinamide in the presence of catalytic ammonium acetate as an alternative to molecular bromine and all reaction and work-up solvents were switched to green alternatives (ethyl acetate, cyrene and water). The use of an NBS bromination mitigated the safety risks associated with molecular bromine but led to an increased waste burden due to the formation of the succinimide by-product and an increase in energy usage as the reaction time increased from 40 min to 70 min. The group also resorted to increasing the stoichiometric excess of *tert*-butylamine to 8 equivalents to allow appreciable conversion rates for the second stage. The final product isolation step was also red flagged as it requires an energy intensive evaporation of water to recover the final salt **1a**. Surprisingly, despite the many interventions to improve greenness the process PMI (167.7) was higher than ideal for a green process.

1.9.2 Solvent recovery study and 4th Generation scenario

Analysis of the final 4th generation staggered flow process led to a short investigation on the solvent recoverability of the ethyl acetate and acetonitrile solvents employed during the process. Solvent mixtures were prepared so as to mimic as accurately as possible the remaining solutions after solvent evaporation was completed on the rotary evaporator in-process. The solutions were placed on the rotary evaporator off-line in order to determine how much of the desired solvents could be recovered. These conditions and corresponding findings have been summarized in **Table S4** below.

Table S4. Solvent recovery study on mimicked 4th Generation process[a]

Stage	Solvent	Quantities added (g or mL)	Vacuum pressure (mbar)	Time (min)	Post-processing	Percentage recovery (%)	Conclusion[b]
1	ACN	-58.96 g ACN (75 mL) -30 mL sat K_2CO_3 -30 mL H_2O	200	40	Dried with Na_2SO_4 and filtered	89	ACN recovered contains water (~5%) + impurity
	EtOAc	58.70 g EtOAc (65 mL)	190	30	None	97	EtOAc recovered contains little to no impurities
2	ACN	-70.02 g ACN (89.1 mL) -6.3 mL *tert*-butylamine -50 mL H_2O -2.6 mL DMSO	Decreased slowly over 15 minutes from 800 to 200, 200 for remaining 25 minutes.	40	Dried with Na_2SO_4 and filtered	90	ACN recovered contains water (~8%) and *tert*-butylamine (~2.1%)
					Heated additionally at 50 ^{O}C for 15 minutes.	85	ACN recovered contains water (~7%) and *tert*-butylamine (~1.8%)
					Nitrogen assisted open evaporation for 20 minutes.	32	ACN recovered contains water (~10.3%) and *tert*-butylamine (~1.3%)

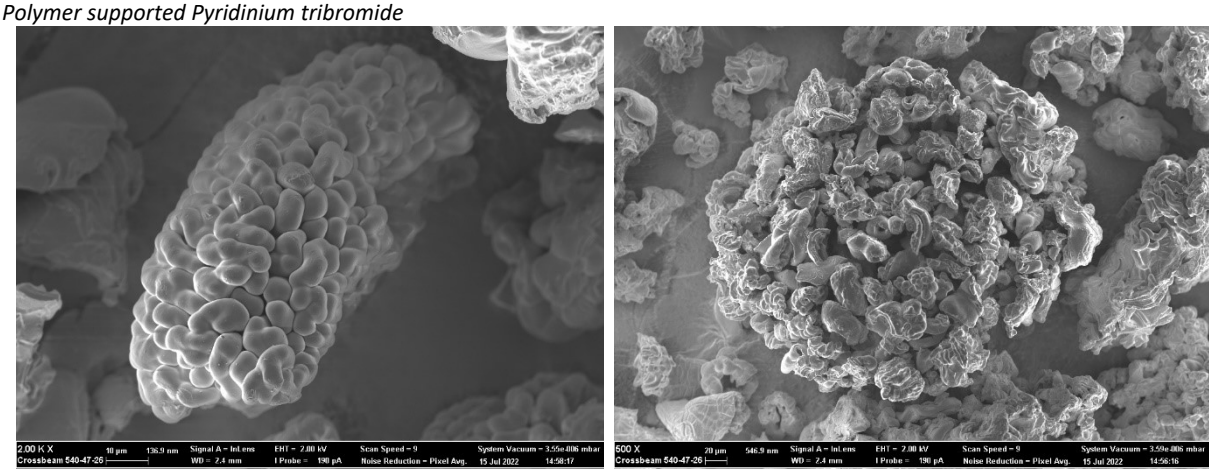
[a]General conditions: Rotary evaporator bath was set to 40 ^{O}C and HeiCHILL accessory was held at a temperature of -3.5 ^{O}C [b]^{1}H NMR analysis was conducted on isolated solvent and calculations were performed using integral areas

Inspection of the results led to the assumption that a maximum solvent recovery of 80% for both EtOAc and ACN may be possible, as such we assumed an 80% recovery of both EtOAc and ACN when calculating the metrics for the hypothetical 4th generation recycling scenario. A second assumption was made with regards to the quantity of hydrogen chloride gas used; which was estimated based upon stochiometric equivalents used in generations 2 and 3.

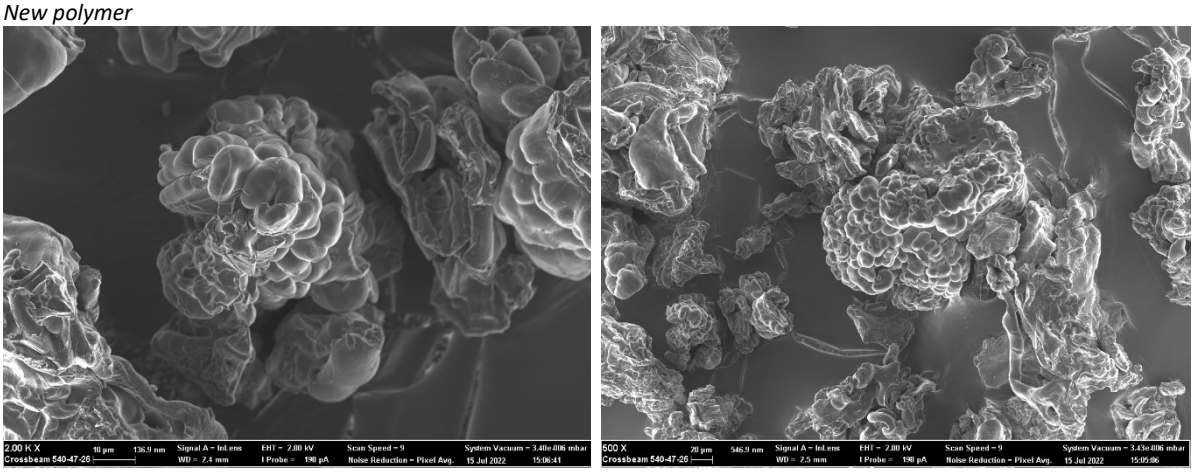
1.10 Characterization data

1.10.1 Scanning Electron Microscopy images

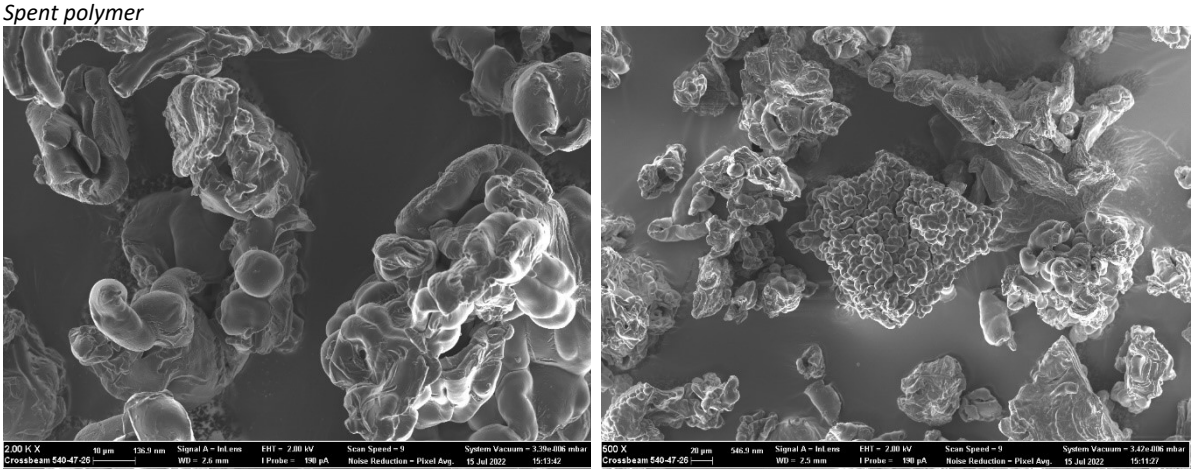
Polymer supported Pyridinium tribromide



New polymer



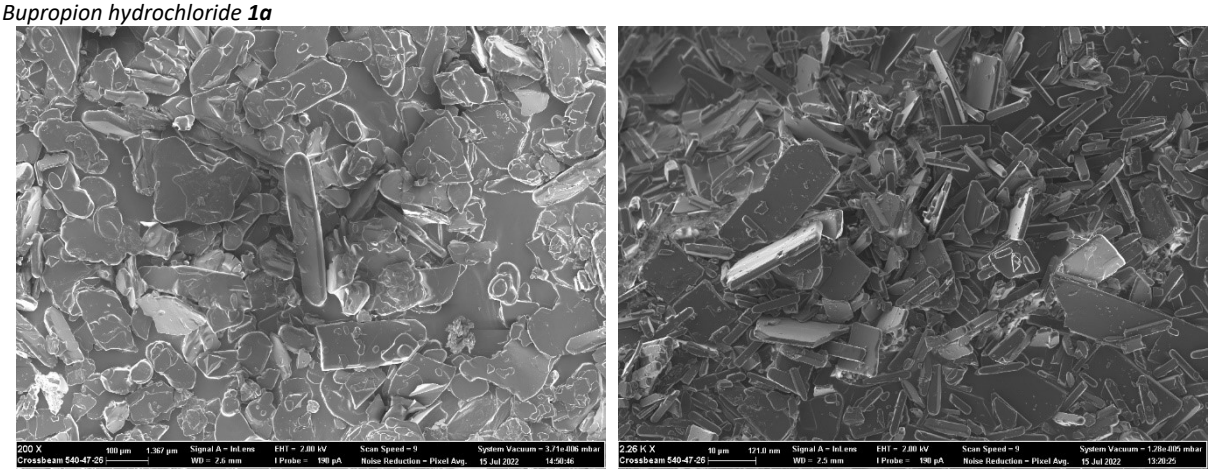
Spent polymer



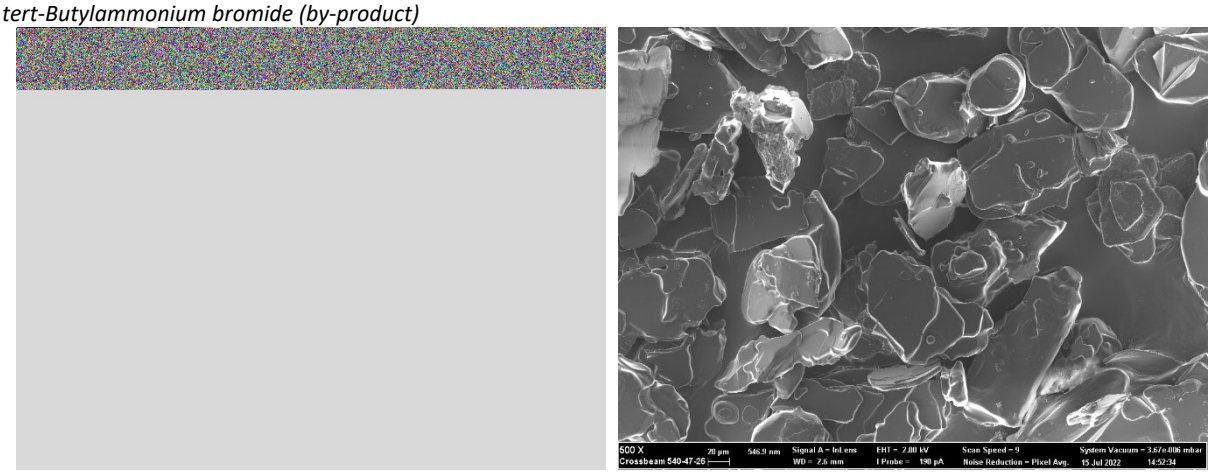
Regenerated polymer

From the images above, no distinct difference is noted between the new polymer, spent polymer or regenerated polymer. It can be assumed that the polymer backbone remains intact after the reaction has occurred and after it has been regenerated.

*Bupropion hydrochloride **1a***



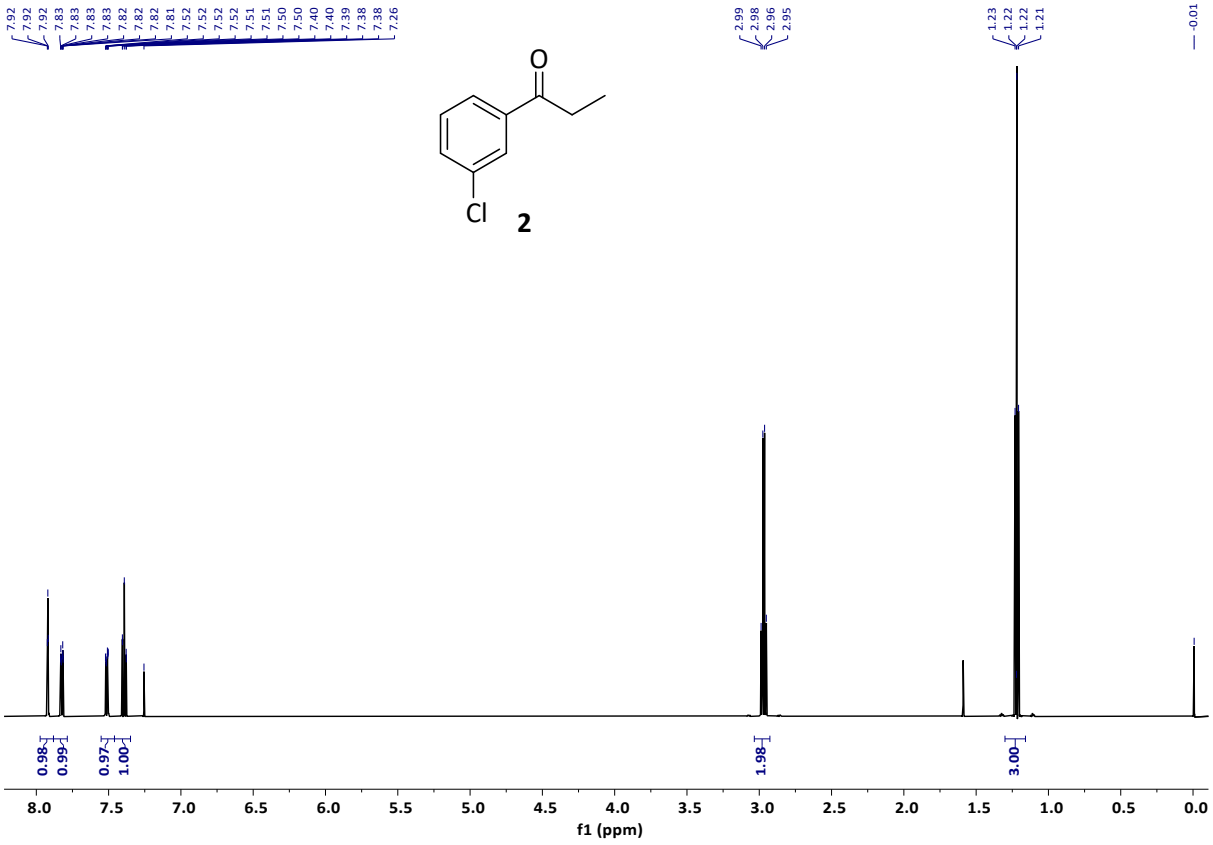
tert-Butylammonium bromide (by-product)



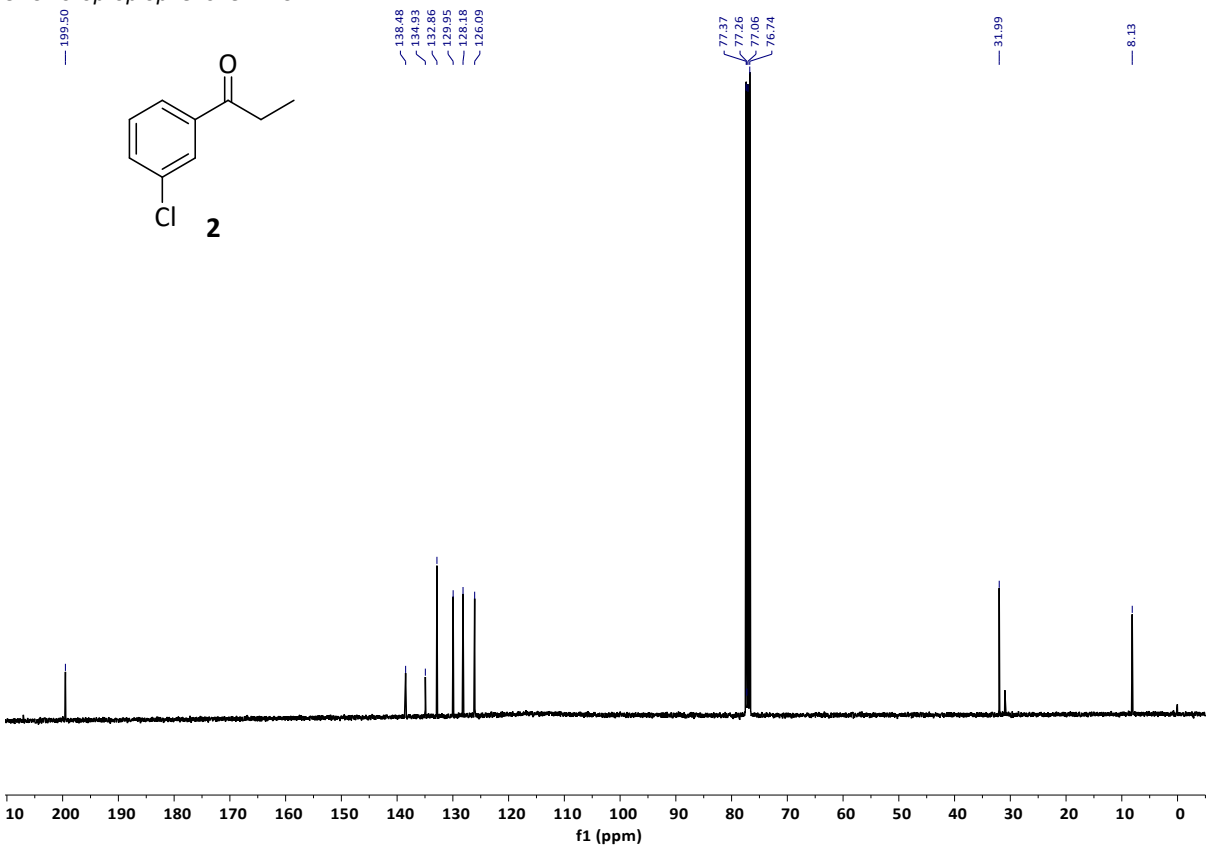
1.10.2 NMR spectra

<u>^{1}H, ^{13}C, DEPT, COSY and NOESY NMR</u>

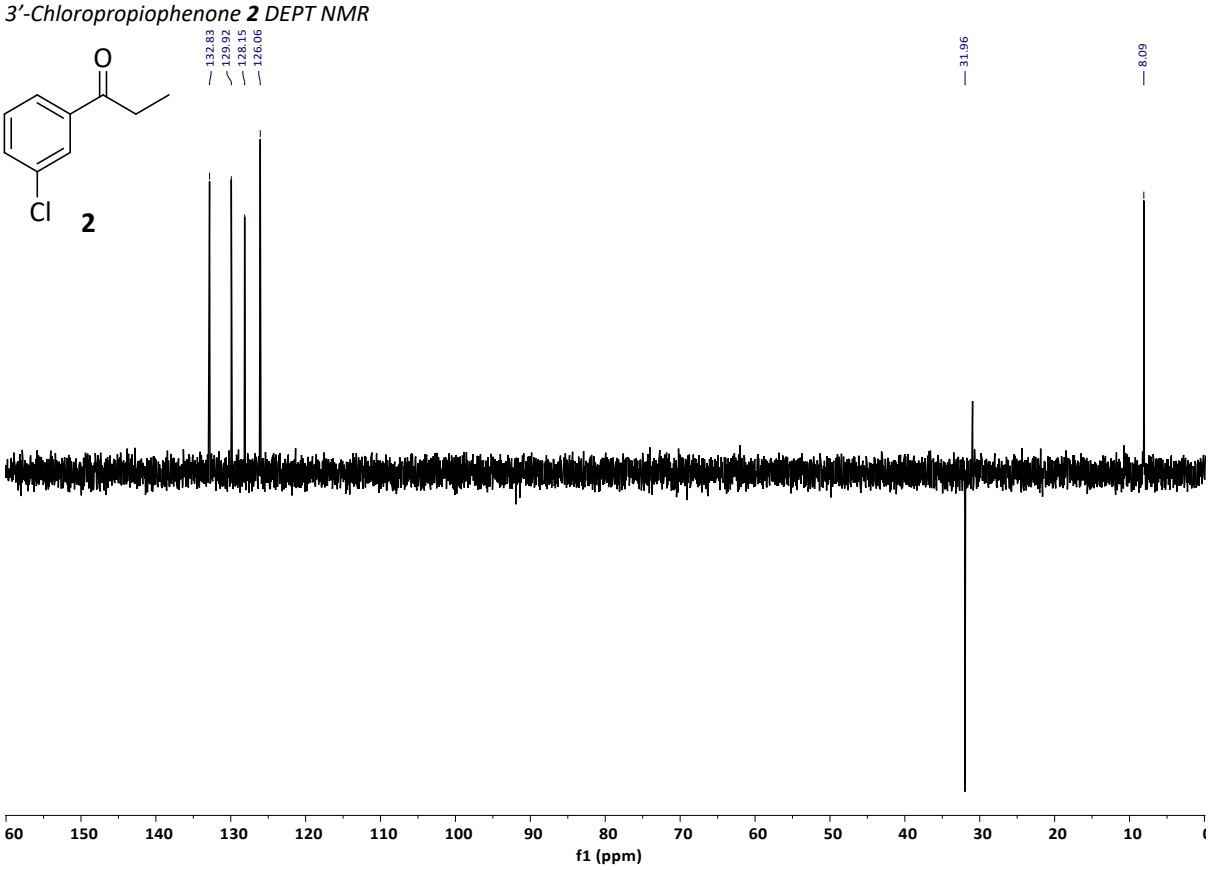
*3'-Chloropropiophenone **2** ^{1}H NMR*



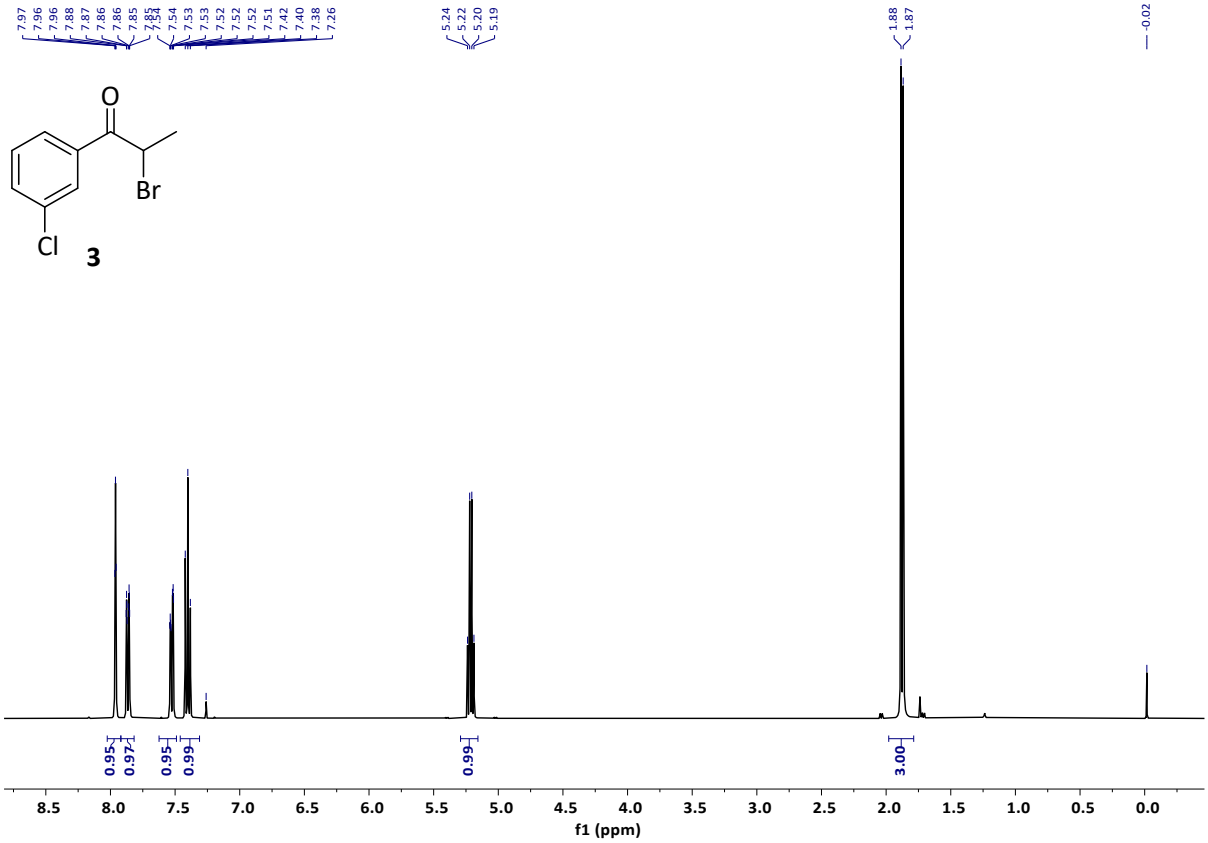
*3'-Chloropropiophenone **2** ^{13}C NMR*



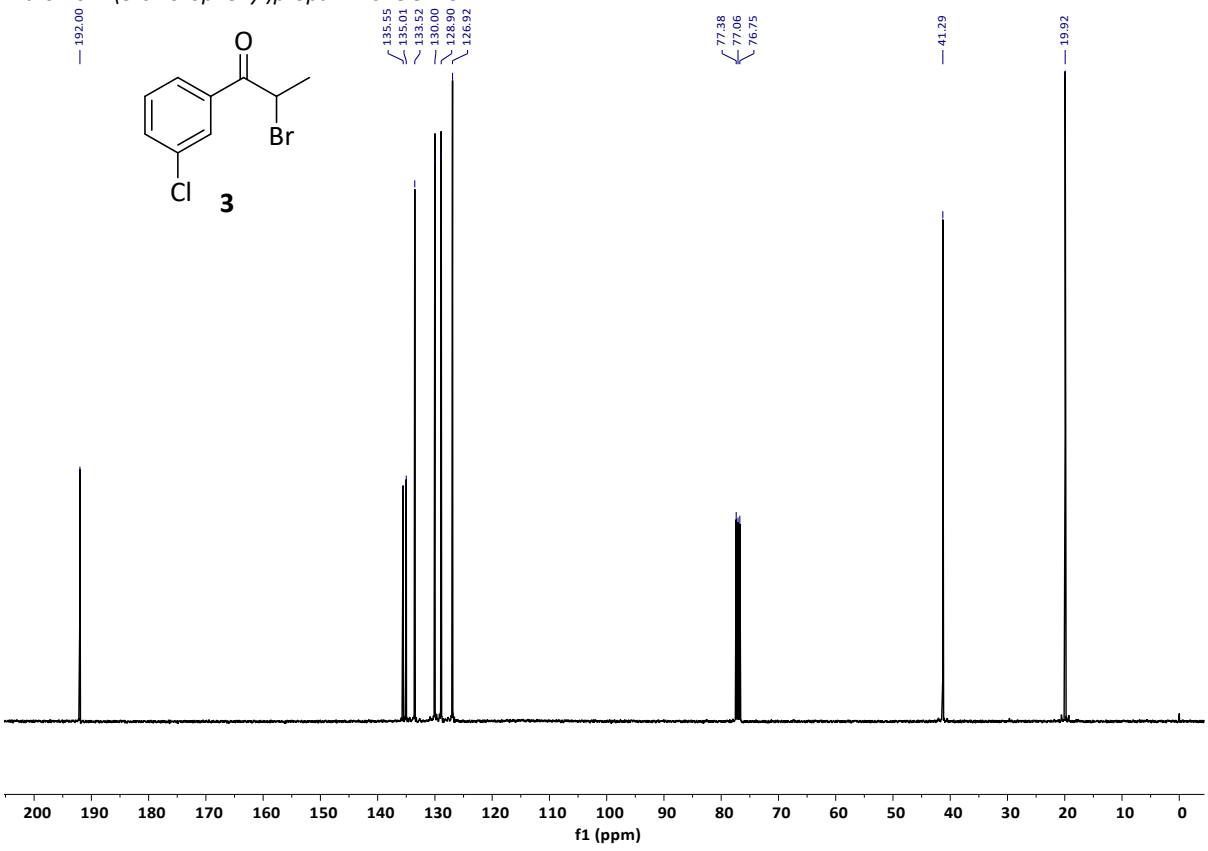
*3'-Chloropropiophenone **2** DEPT NMR*



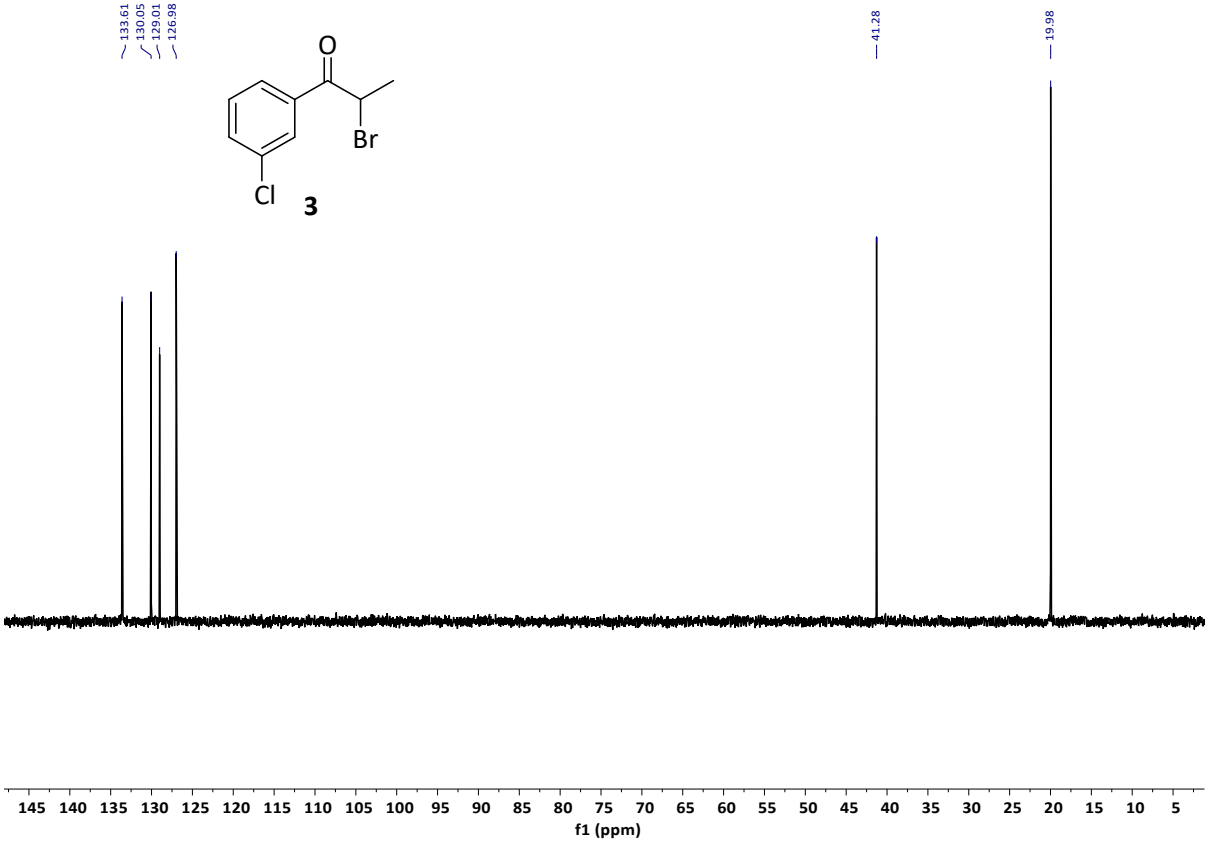
*2-bromo-1-(3-chlorophenyl)propan-1-one **3** ^{1}H NMR*



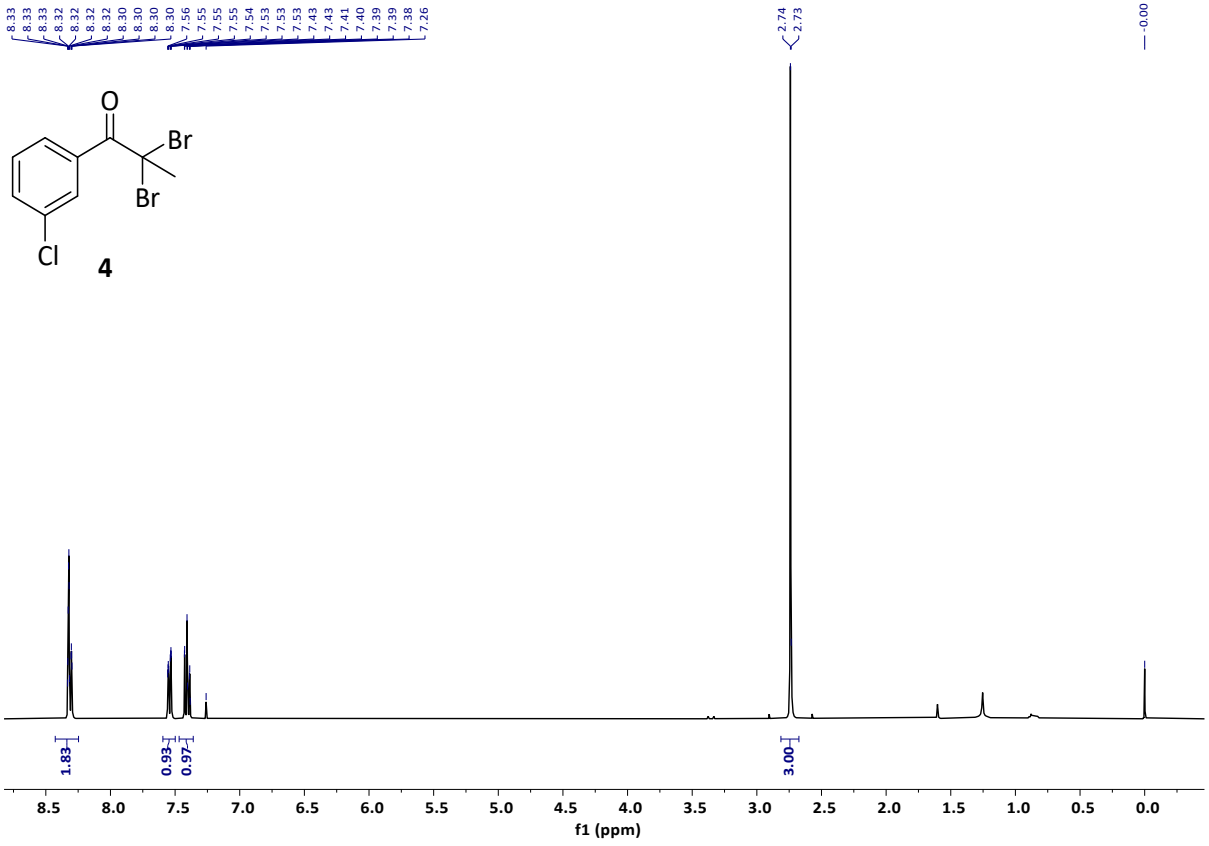
*2-bromo-1-(3-chlorophenyl)propan-1-one **3** ^{13}C NMR*



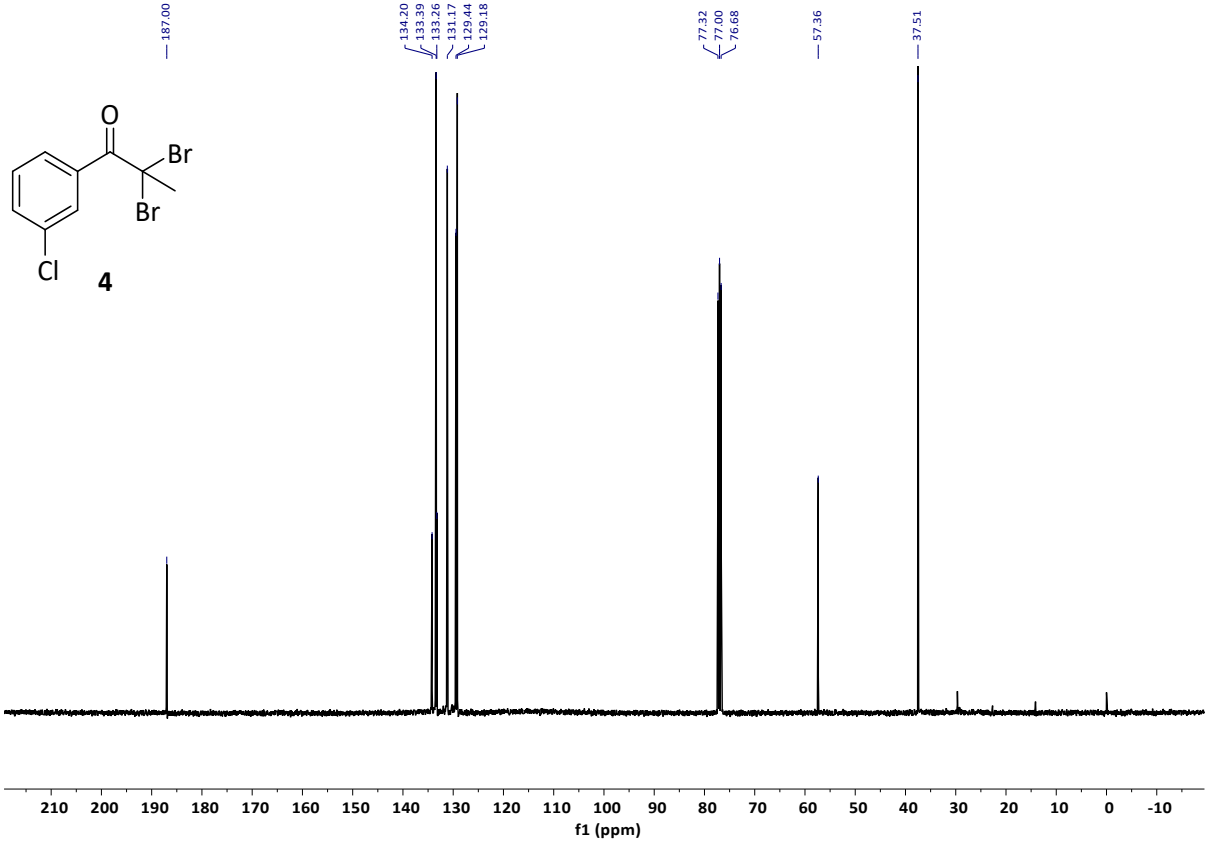
*2-bromo-1-(3-chlorophenyl)propan-1-one **3** DEPT NMR*



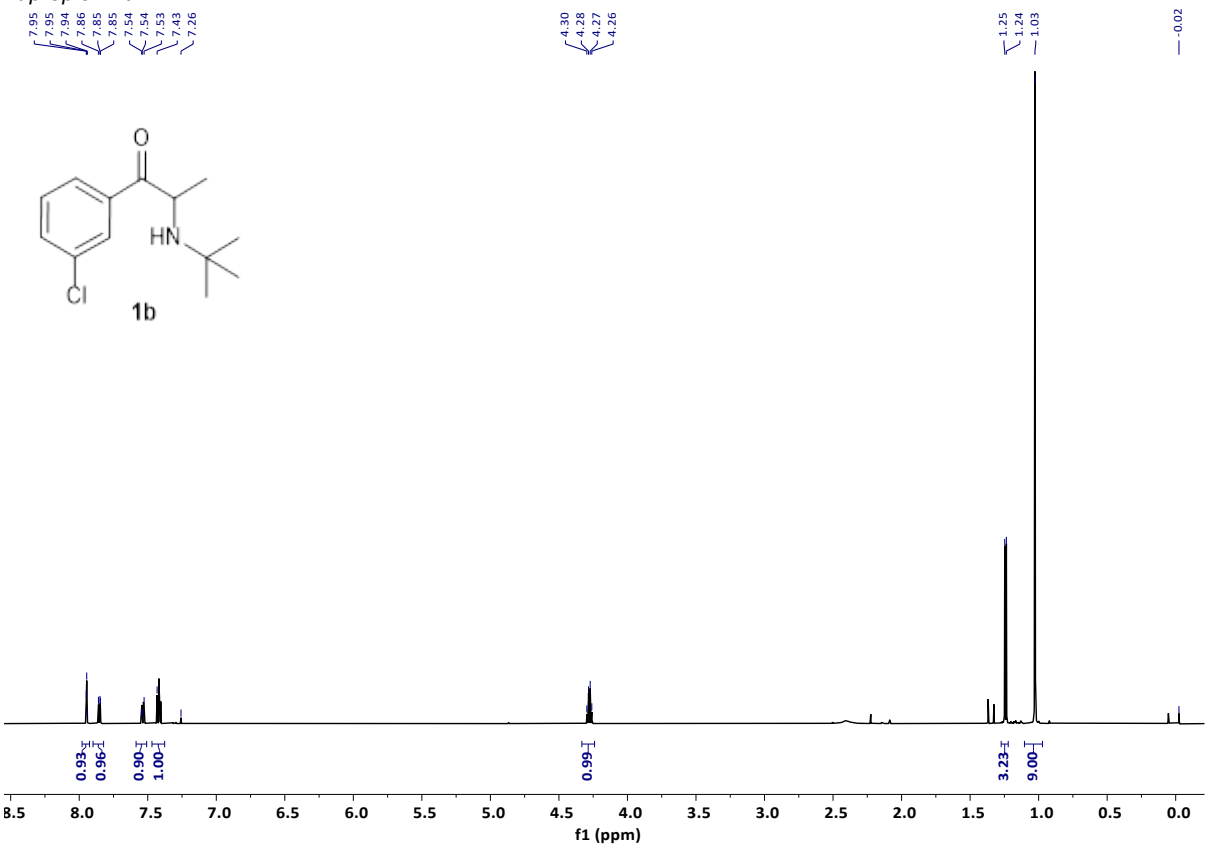
*2,2-dibromo-1-(3-chlorophenyl)propan-1-one **4** ^{1}H NMR*



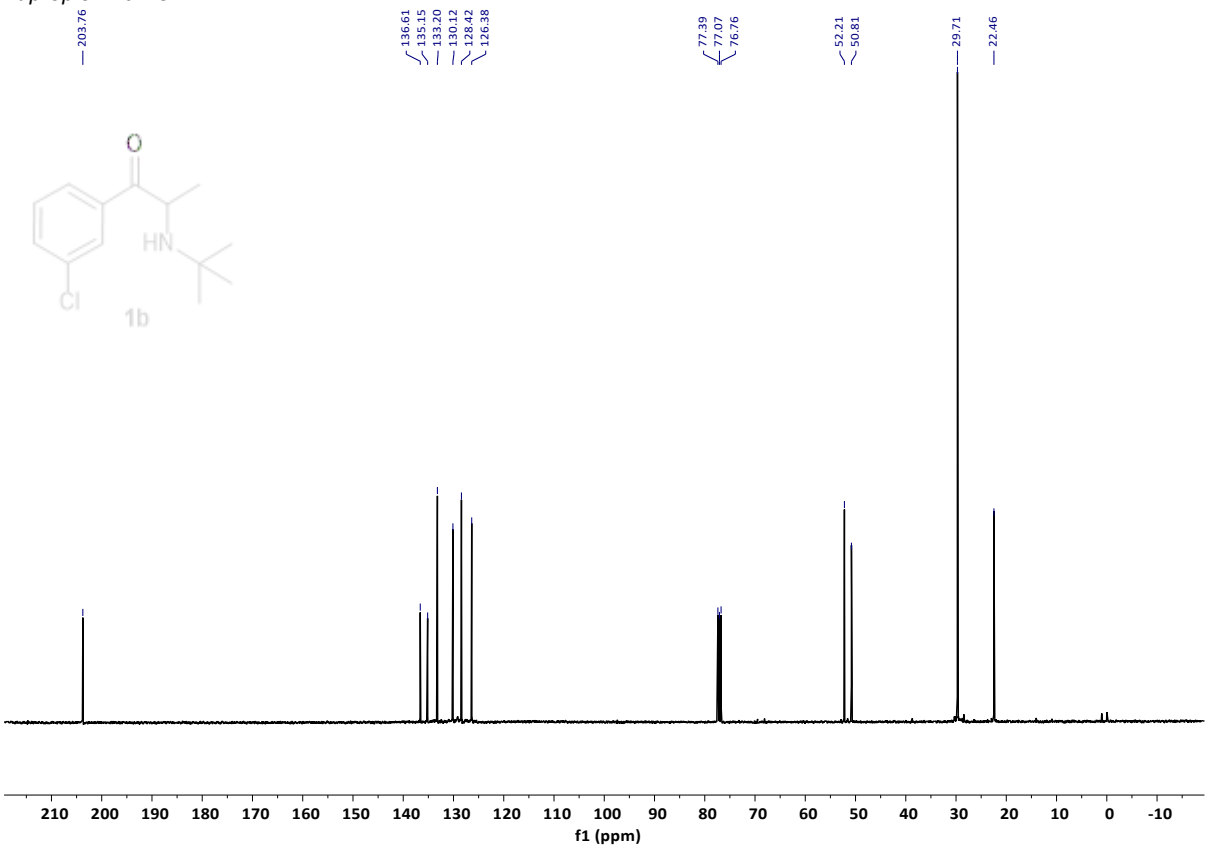
2,2-dibromo-1-(3-chlorophenyl)propan-1-one ***4*** *^{13}C NMR*



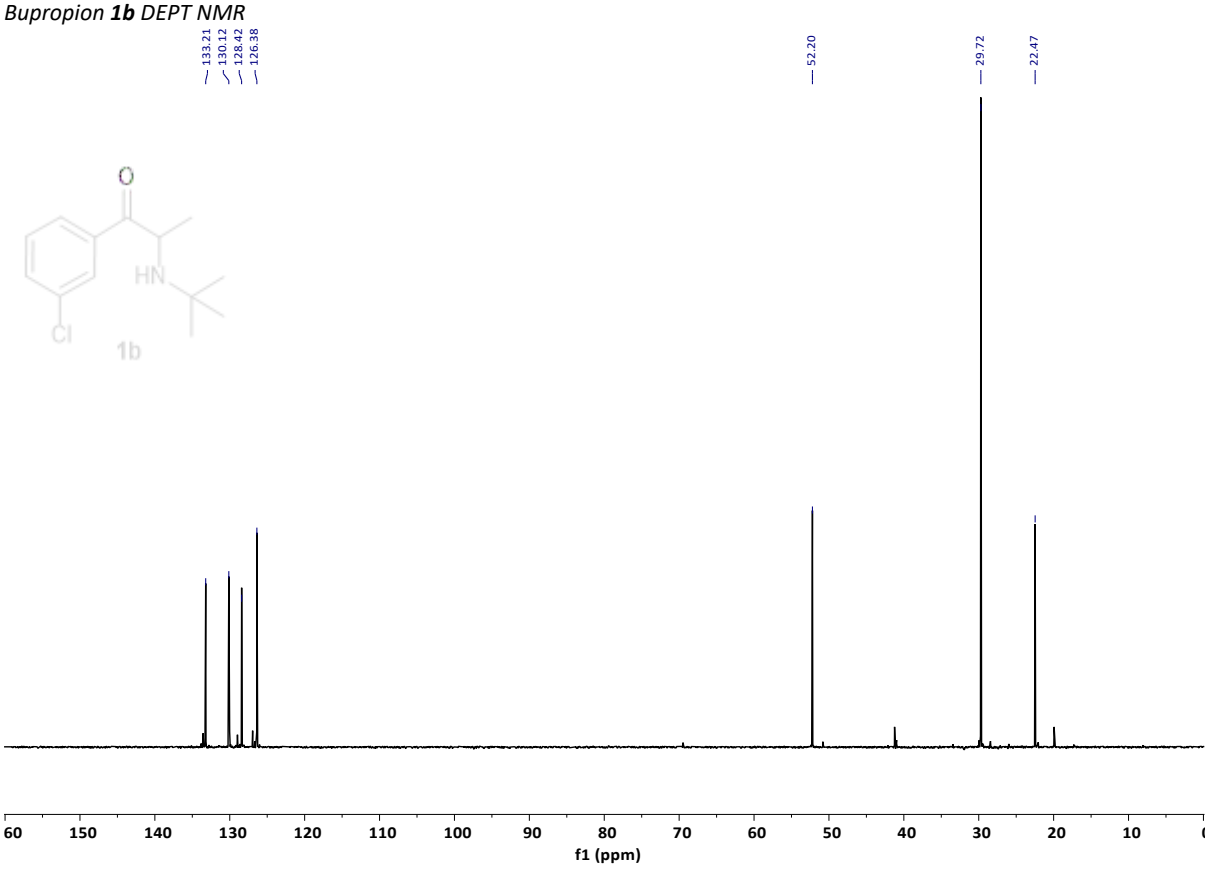
Bupropion ***1b*** *^{1}H NMR*



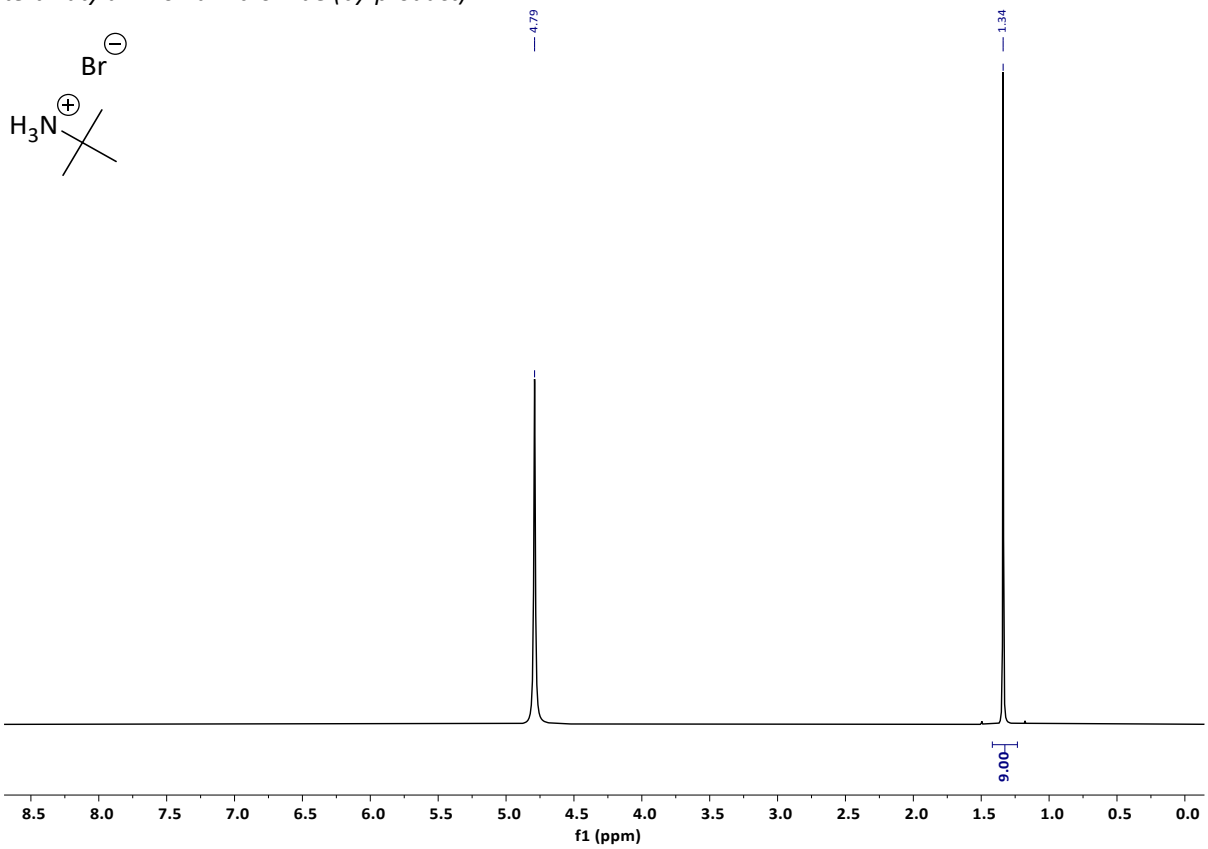
*Bupropion **1b** ^{13}C NMR*



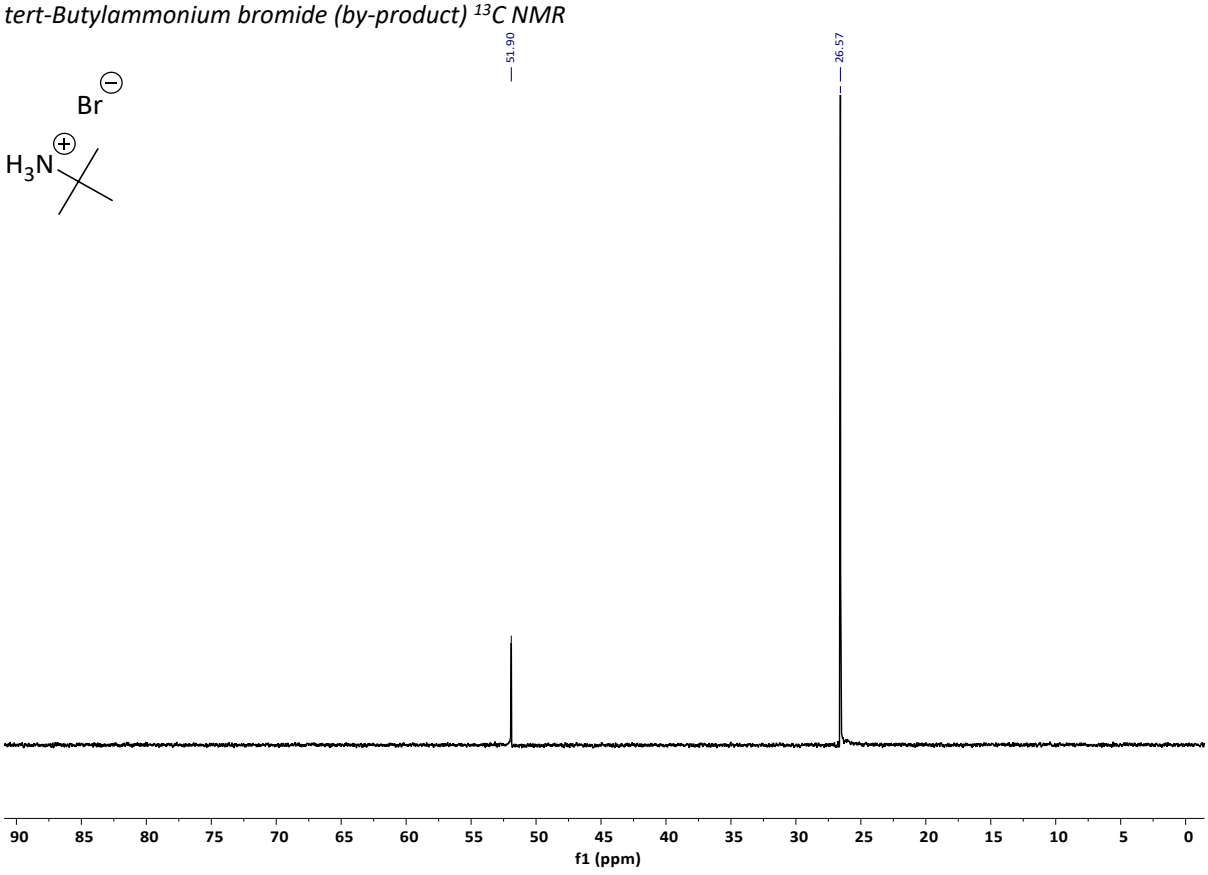
*Bupropion **1b** DEPT NMR*



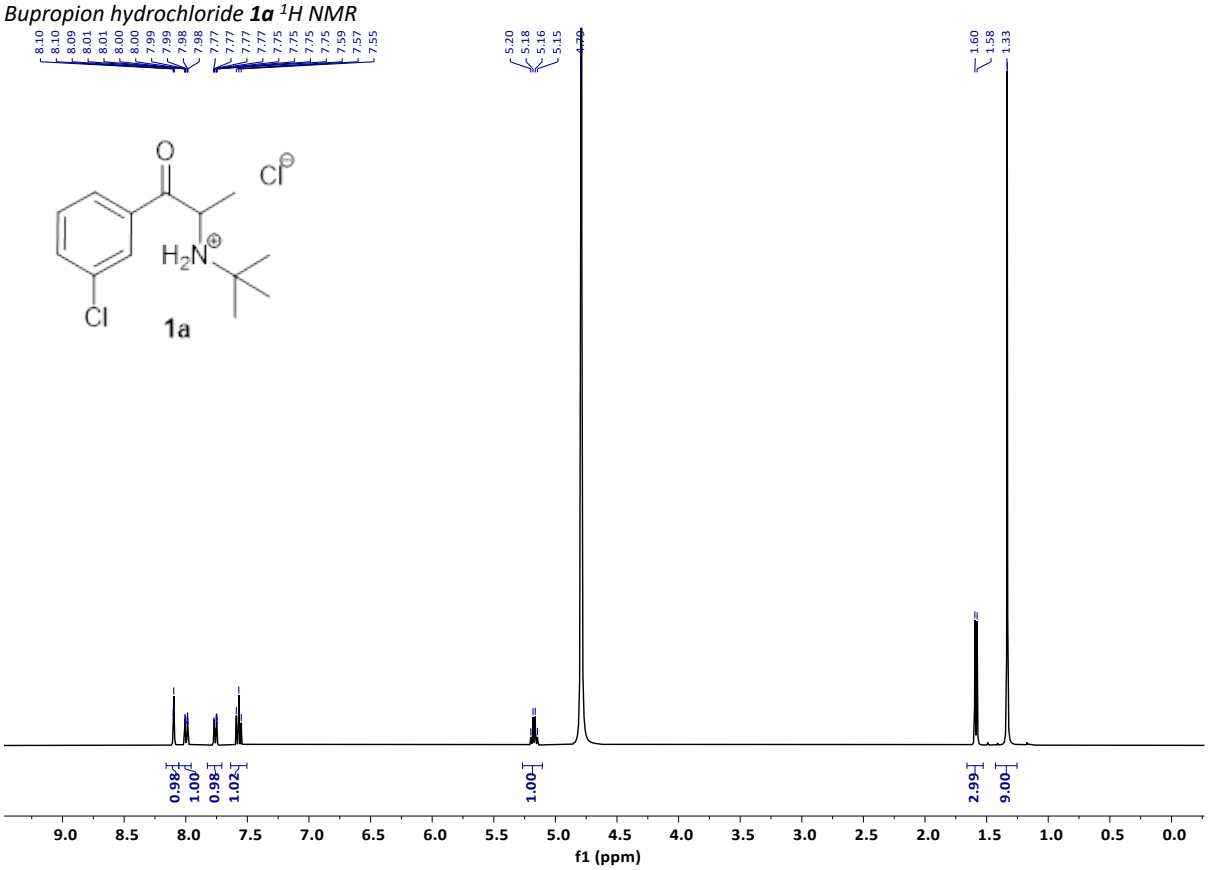
tert-Butylammonium bromide (by-product) ^{1}H NMR



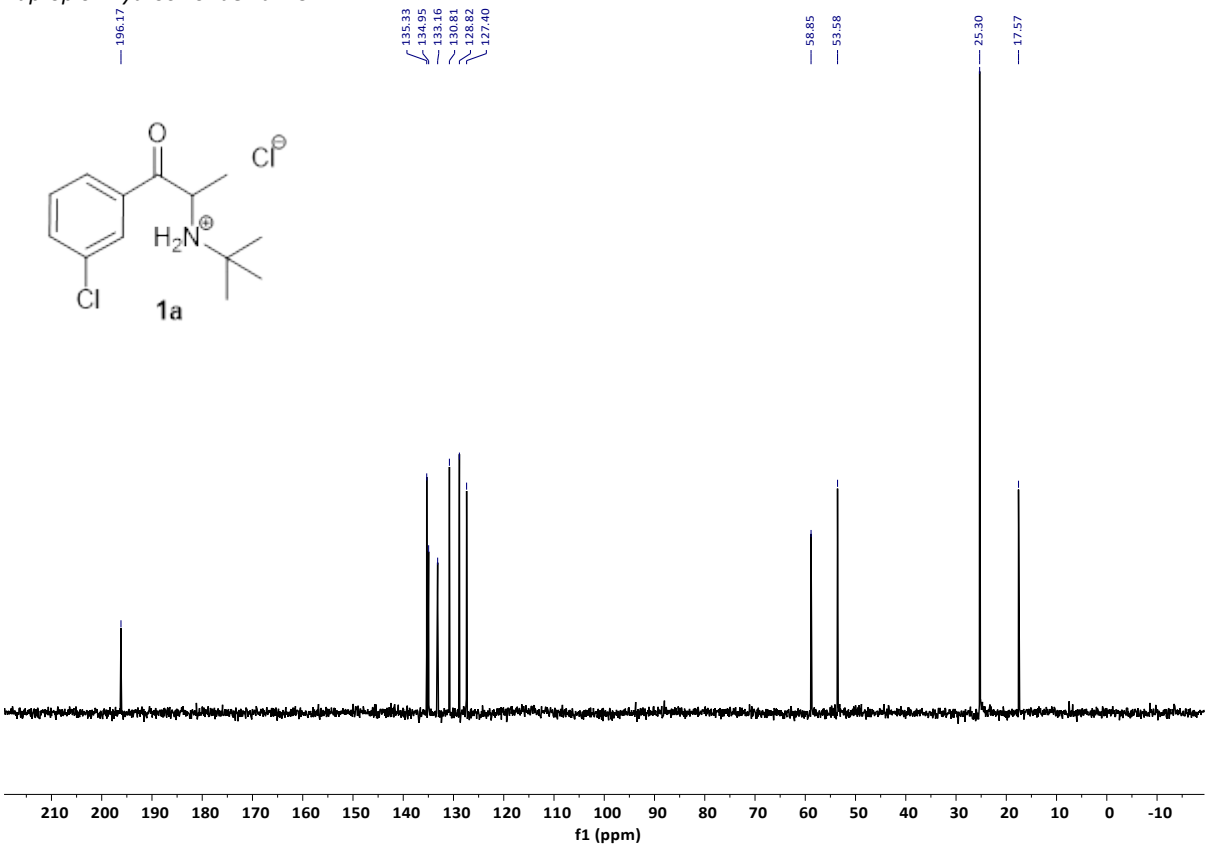
tert-Butylammonium bromide (by-product) ^{13}C NMR



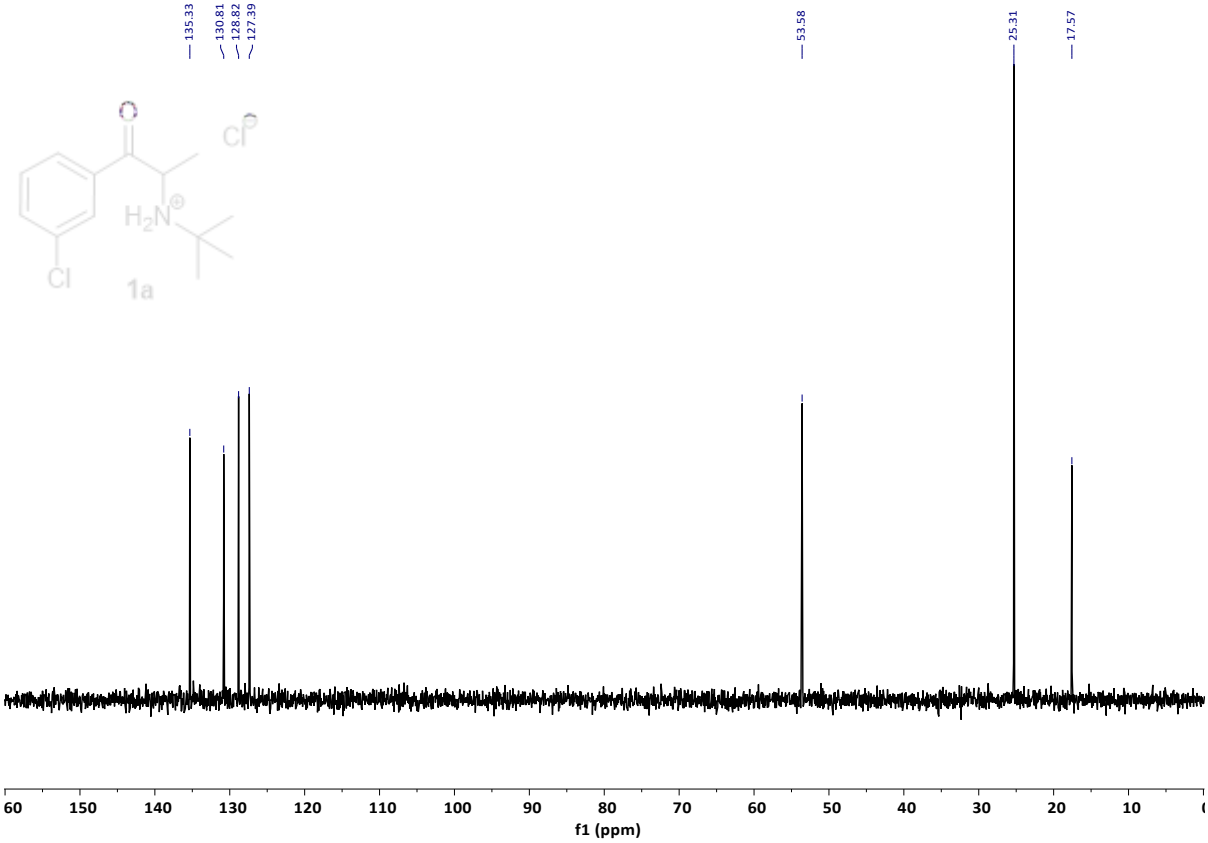
*Bupropion hydrochloride **1a** ^{1}H NMR*



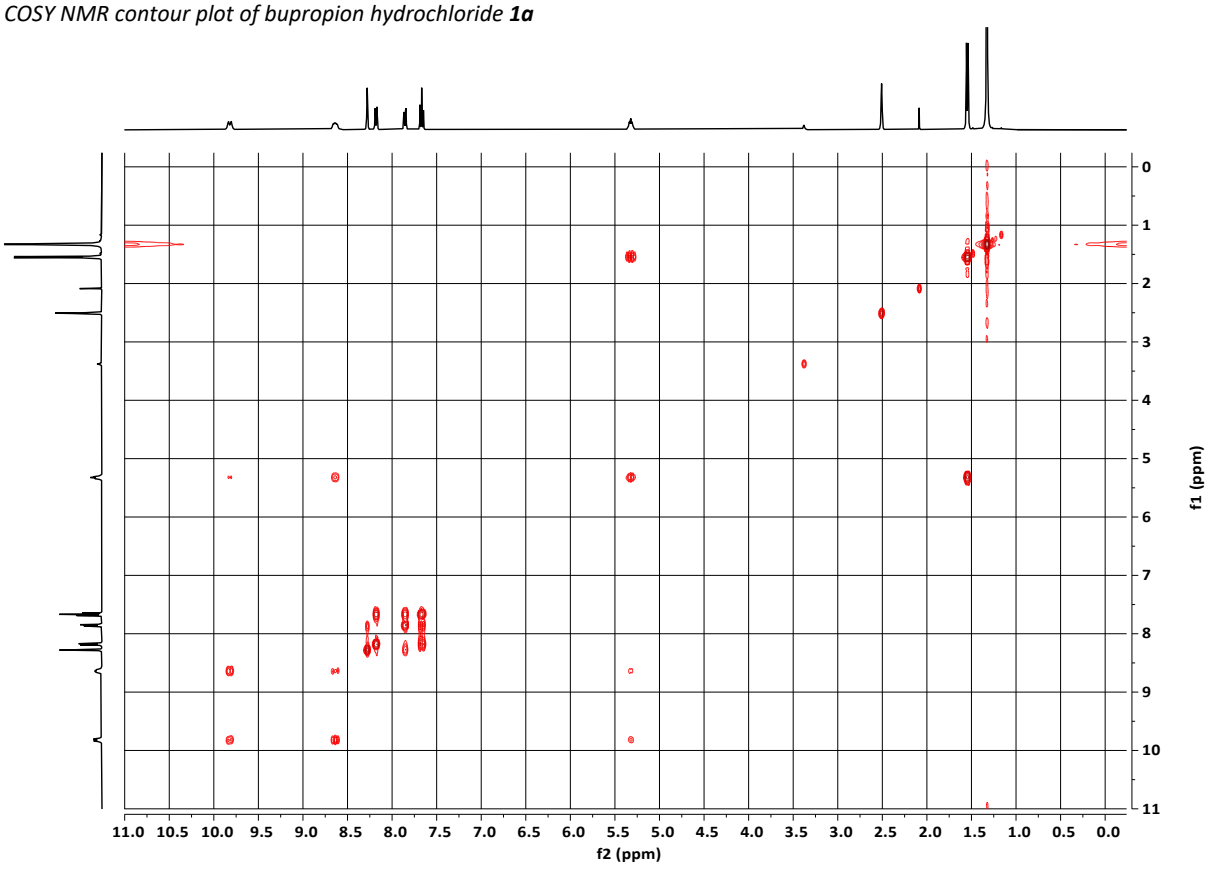
*Bupropion hydrochloride **1a** ^{13}C NMR*



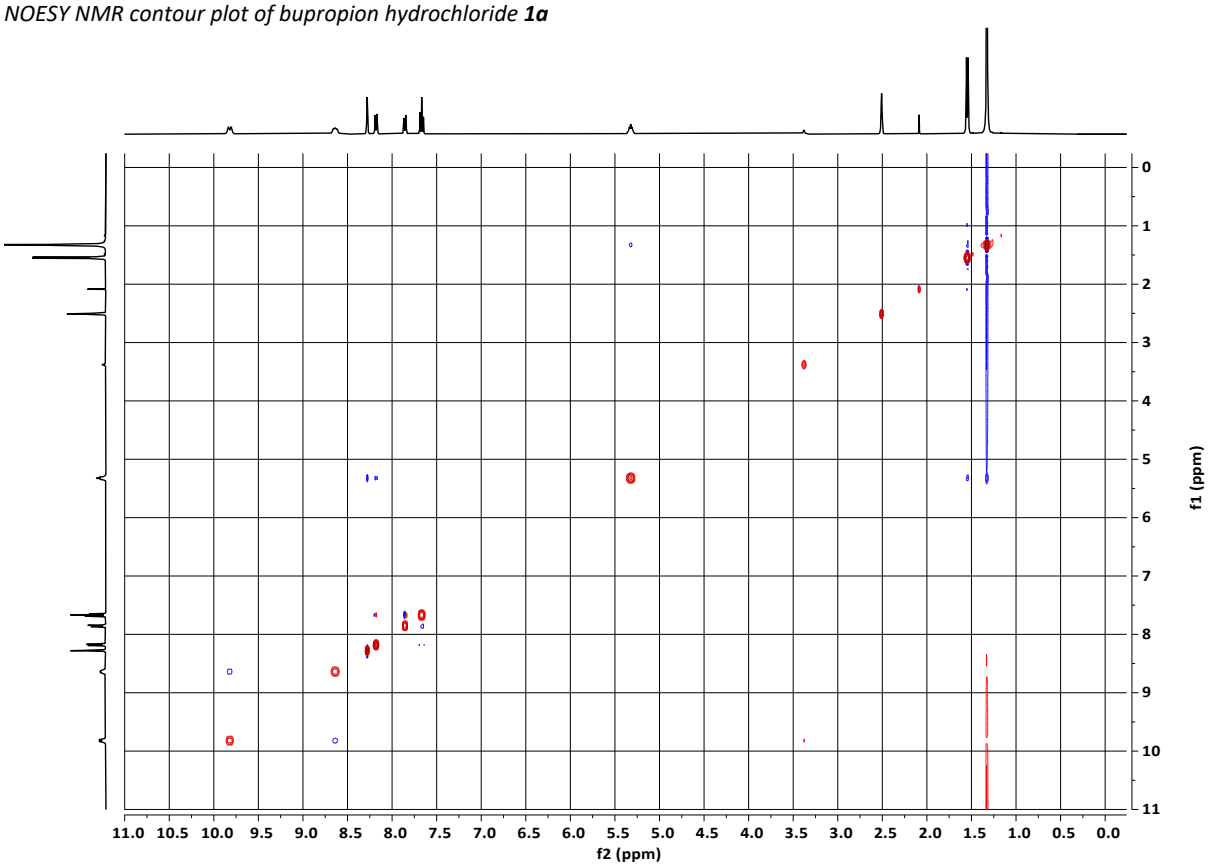
*Bupropion hydrochloride **1a** DEPT NMR*



*COSY NMR contour plot of bupropion hydrochloride **1a***



*NOESY NMR contour plot of bupropion hydrochloride **1a***



1H quantitative NMR

For quantitative NMR analysis the external calibrant and internal calibrant (ECIC) method was used and the results were summarised in **Table S5**.[14]

Purity of bupropion hydrochloride **1a** in the weighed sample was determined using the following formula:

$$\%purity = \frac{m(BHCl)}{m(Sam)} = \frac{[m(DMS) * Mr(BHCl) * I(BHCl) * \#(DMS)]}{[m(Sam) * Mr(DMS) * I(DMS) * \#(BHCl)]} * P(DMS)$$

Where: m(BHCl) = mass of bupropion hydrochloride in the sample
m(DMS) = accurately weighed mass of dimethyl sulfone as external standard
Mr(BHCl) = the molar mass of bupropion hydrochloride ($C_{13}H_{19}Cl_2NO$ = 276.20 g/mol)
Mr(DMS) = the molar mass of dimethyl sulfone ($(CH_3)_2SO_2$ = 94.13 g/mol)
I(BHCl) = integrated area for bupropion hydrochloride signal
I(DMS) = integrated area for dimethyl sulfone external standard 3.00 ppm
#(BHCl) = number of protons accounting for the integrated area of bupropion hydrochloride
#(DMS) = the number of protons accounting for the integrated area for dimethyl sulfone
P(DMS) = purity of dimethyl sulfone (>98%)

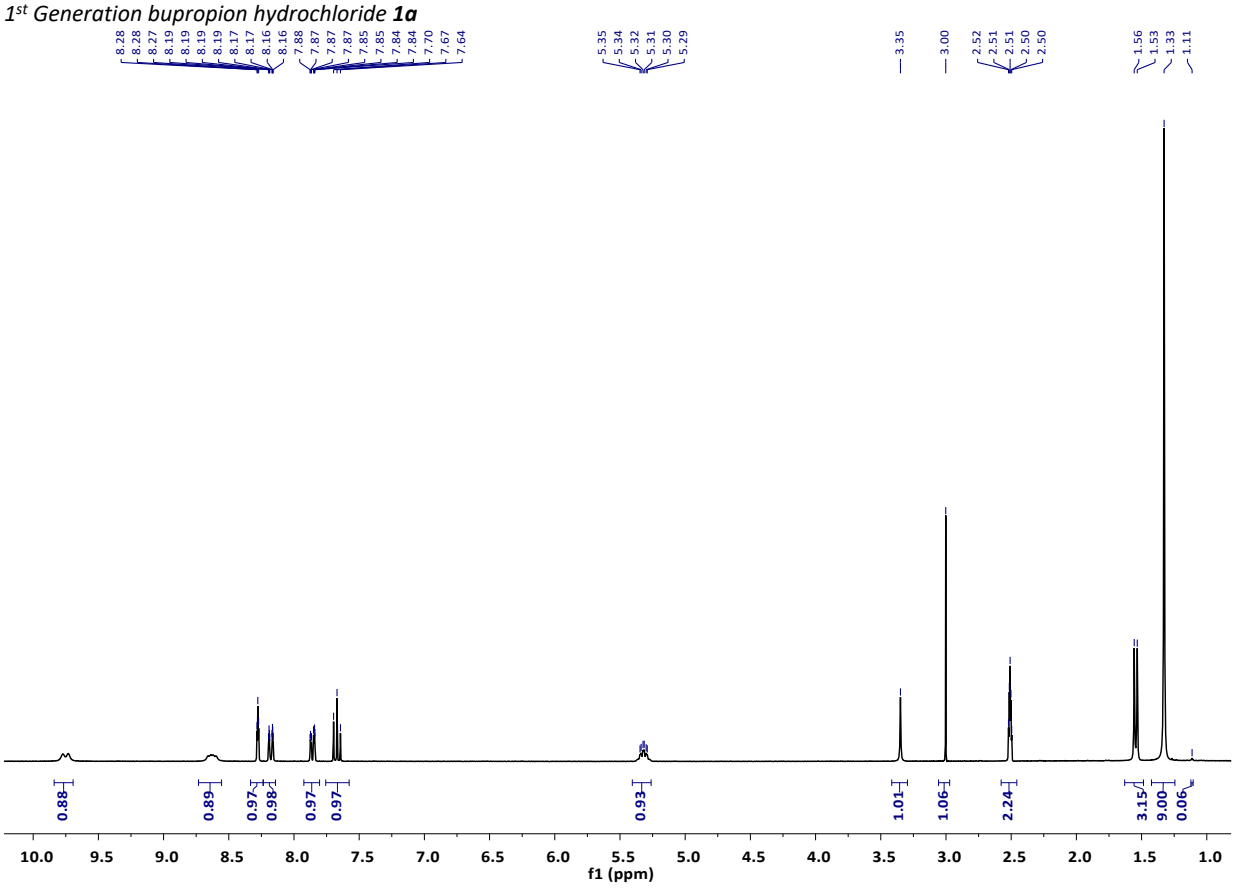
Physical appearance: Fine white powder (not free flowing)

Table S5. Percentage purity of Bupropion hydrochloride **1a** across Generations 1-4

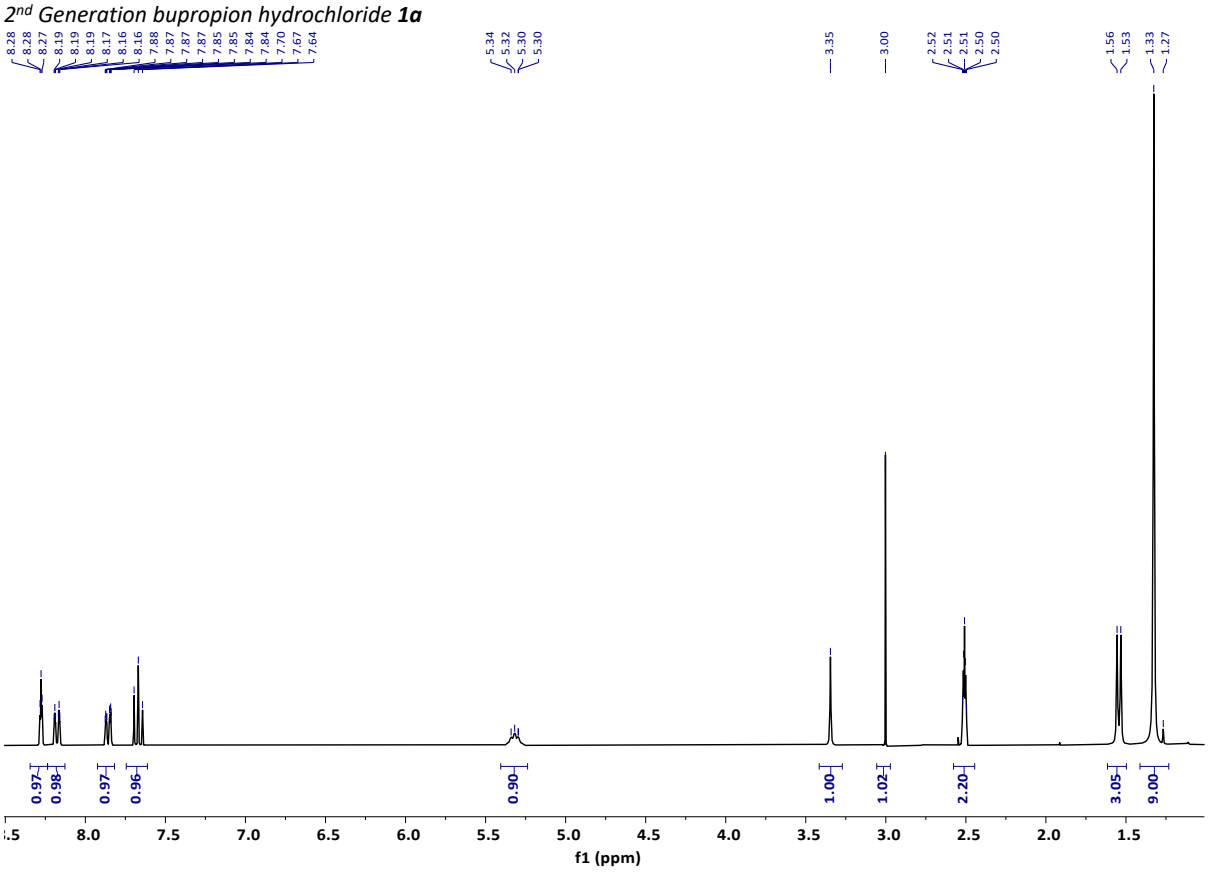
		Generation 1		**Generation 2**		**Generation 3**		**Generation 4**	
Identity	δ / ppm	m / mg	% m/m	m / mg	% m/m	m / mg	% m/m	m / mg	% m/m
DMS[a]	3.00	0.63		0.63		0.63		0.63	
BHCl[b]	Range	10.7	96.6152	10.5	99.9868	10.5	86.7324	10.9	97.7642
Imp 1[c]	3.35								

[a]Dimethylsulfone calibrant (Stock solution was prepared: 4,2 mg in 2 mL deuterated DMSO of which 0,3 mL) [b]Bupropion hydrochloride **1a** – 17 protons used for the calculations with 2 protons (NH_2) omitted [c]Water impurity contaminant from ampule *d6*-DMSO – omitted in calculations

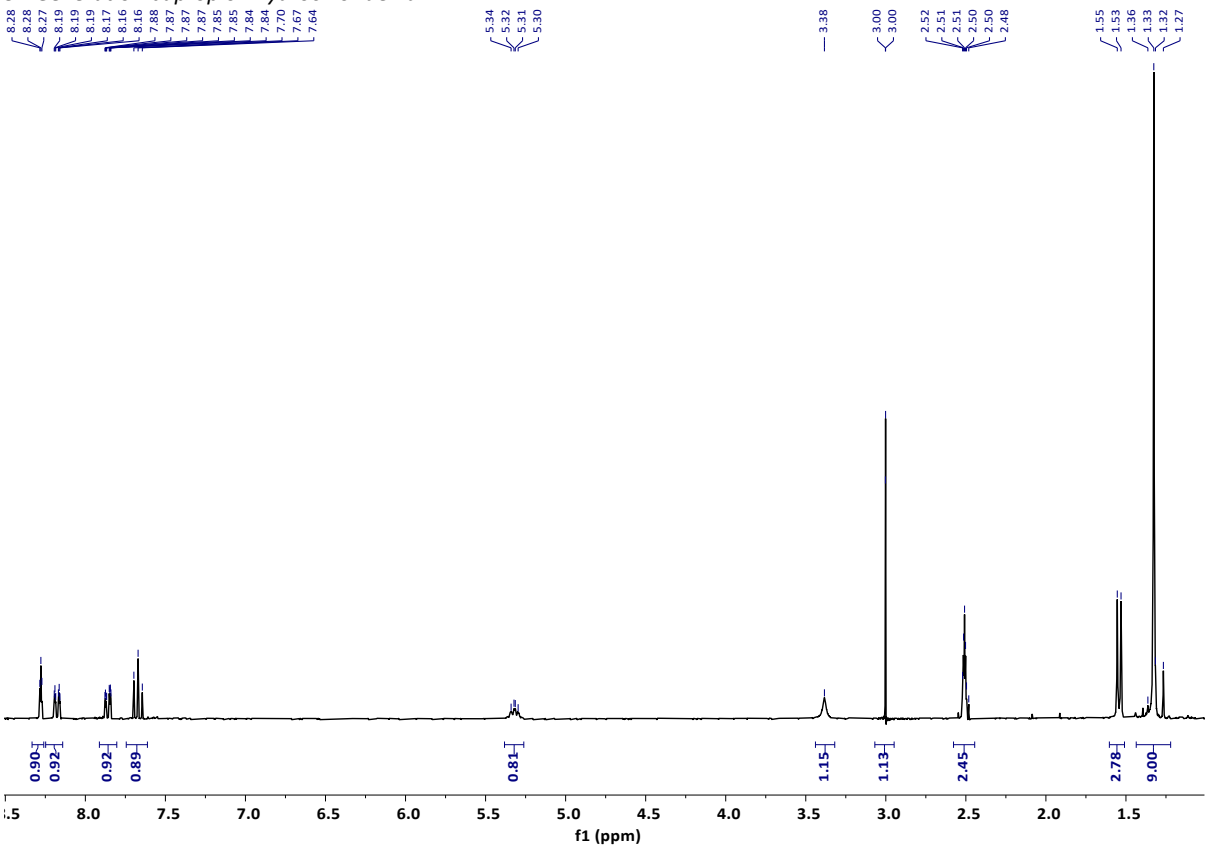
1st Generation bupropion hydrochloride ***1a***



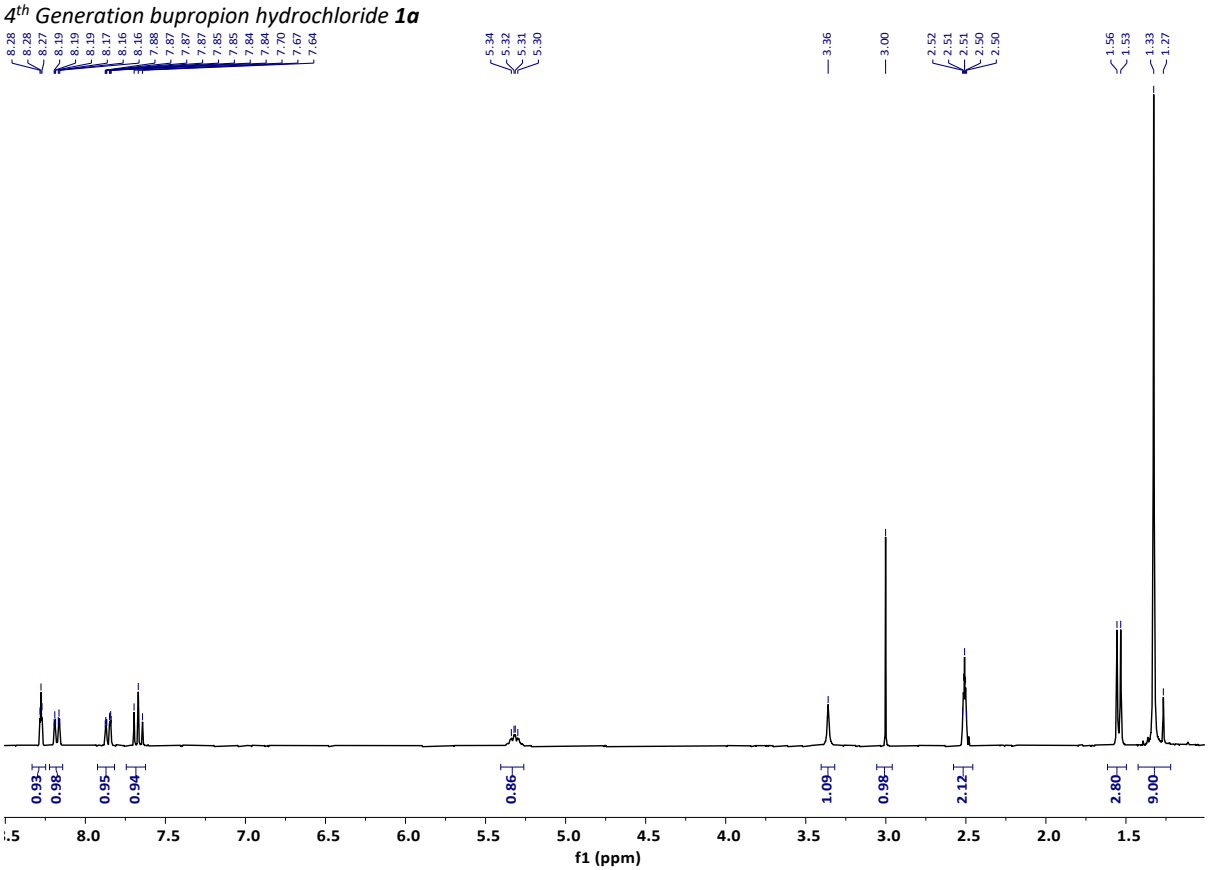
2nd Generation bupropion hydrochloride ***1a***



3rd Generation bupropion hydrochloride ***1a***

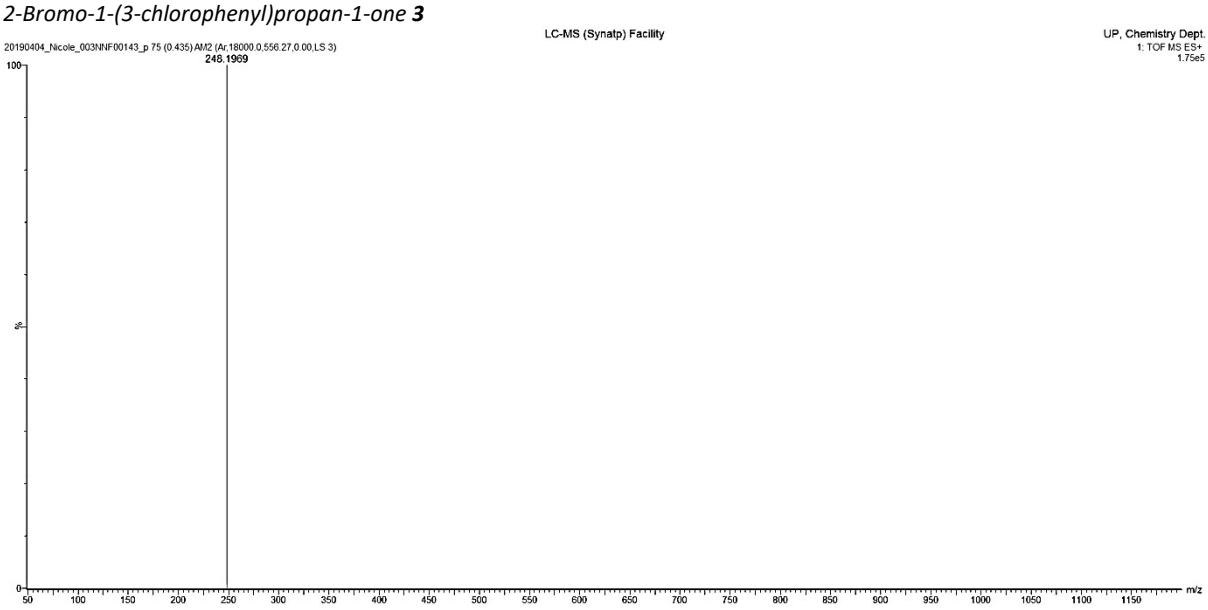


4th Generation bupropion hydrochloride ***1a***

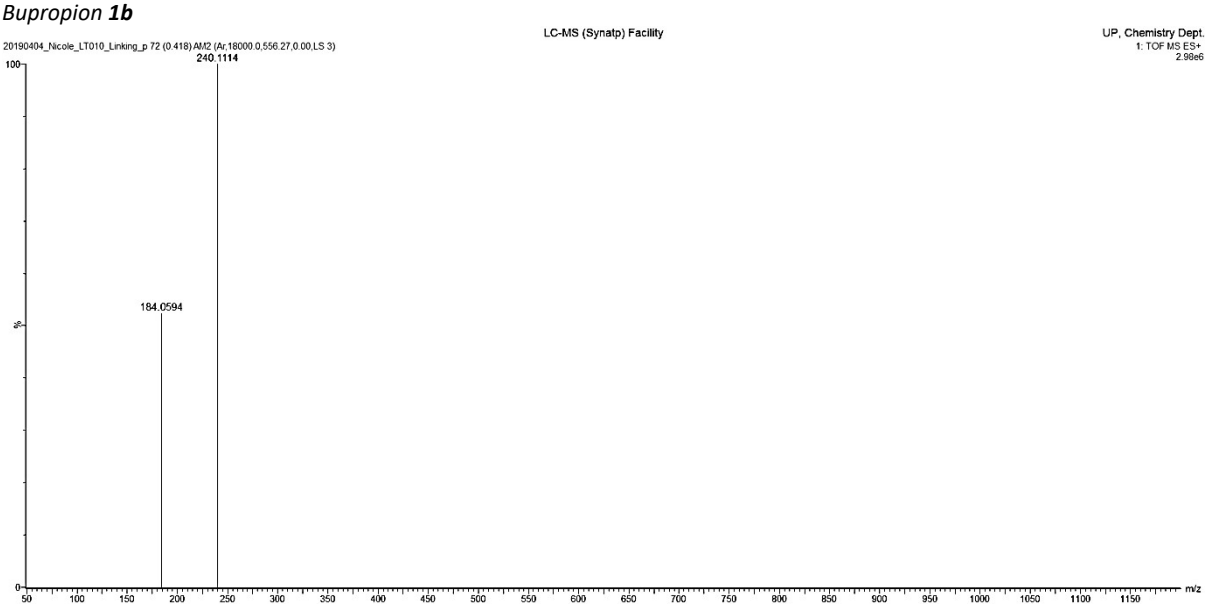


1.10.3 HRMS spectra

*2-Bromo-1-(3-chlorophenyl)propan-1-one **3***

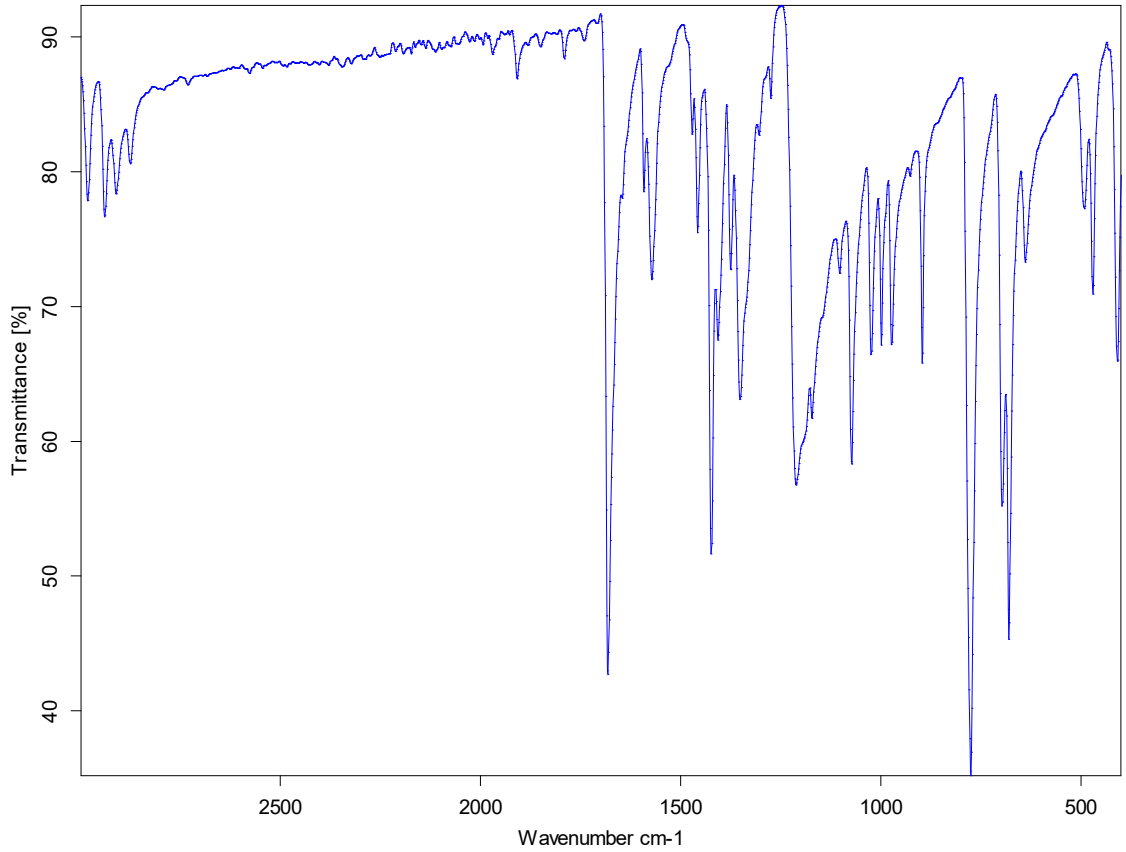


*Bupropion **1b***

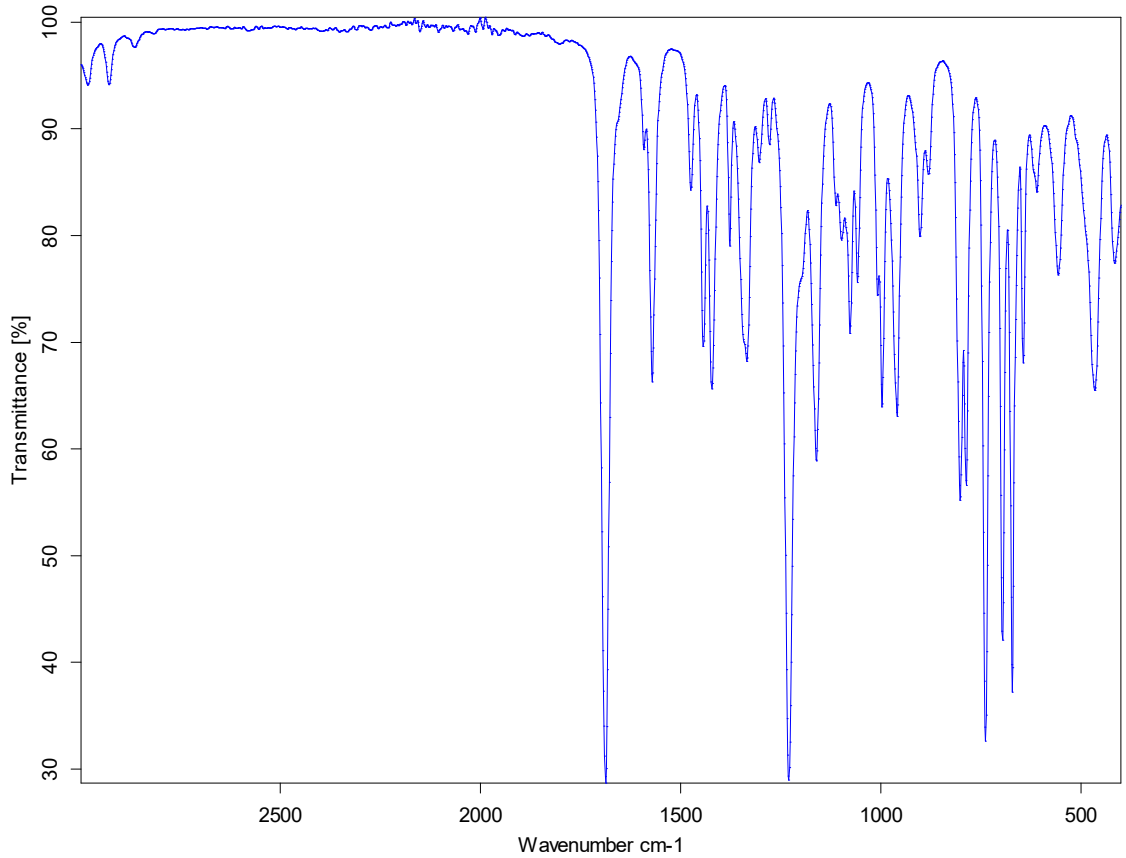


1.10.4 FTIR spectra

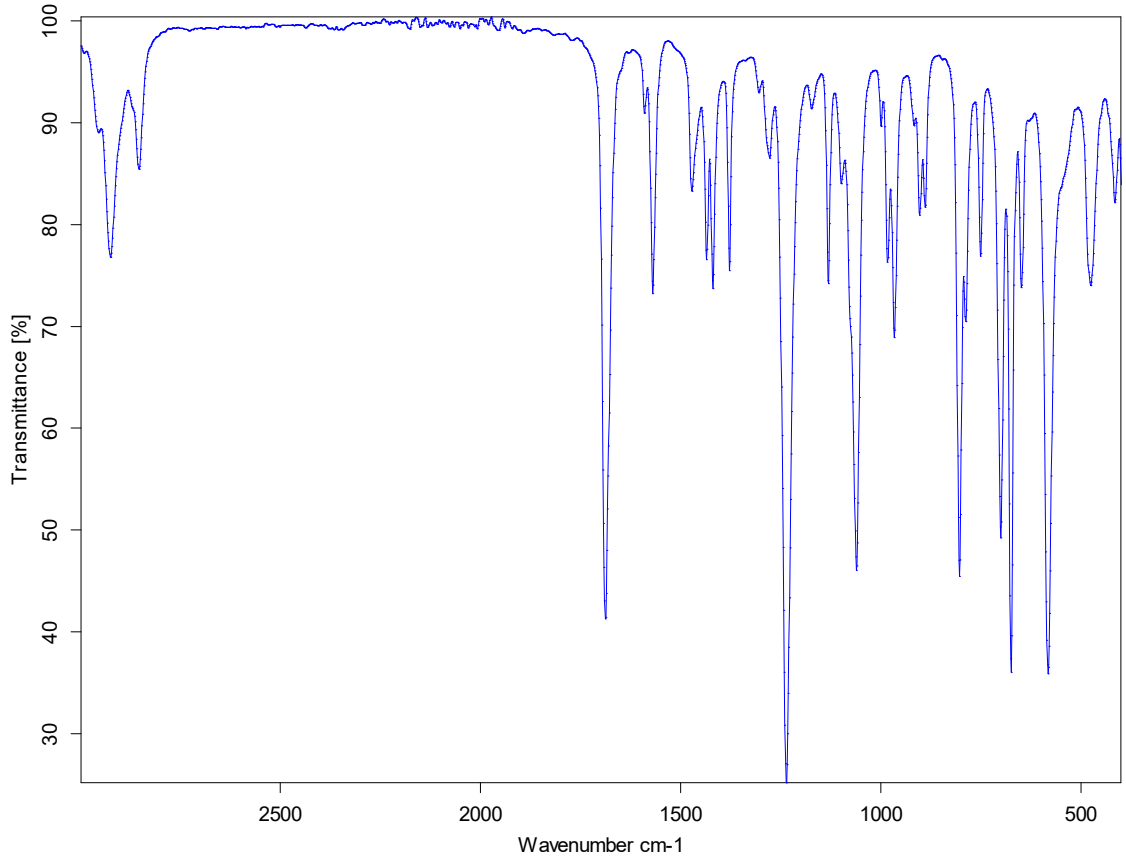
3'-Chloropropiophenone ***2***



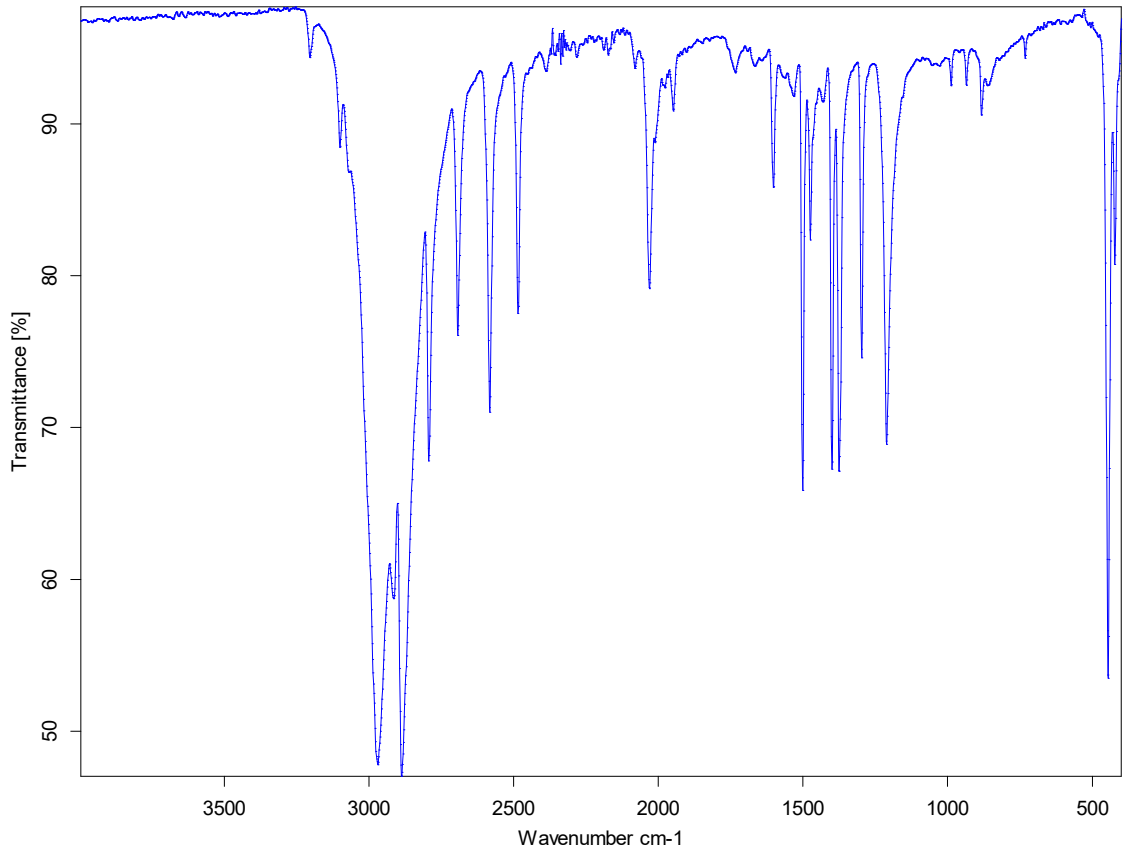
2-Bromo-1-(3-chlorophenyl)propan-1-one ***3***



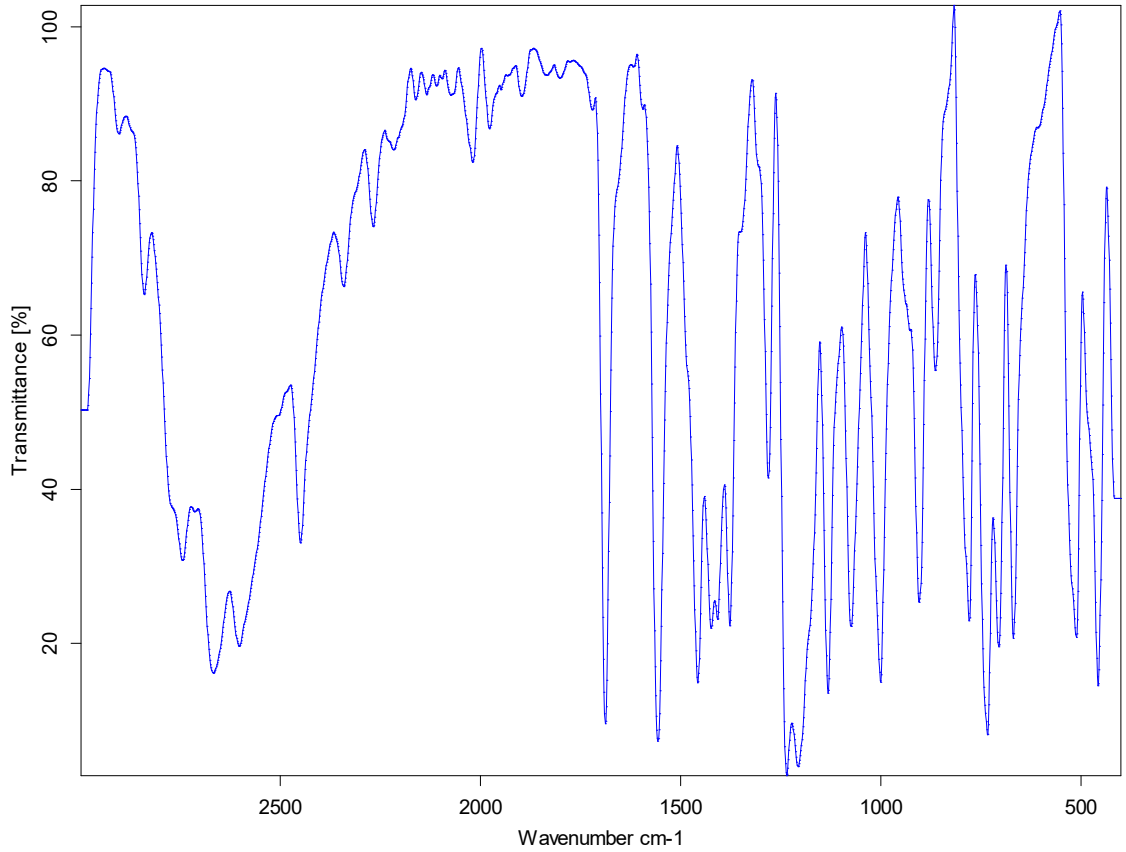
2,2-Dibromo-1-(3-chlorophenyl)propan-1-one ***4***



tert-Butylammonium bromide (by-product)



*Bupropion hydrochloride **1a***



1.10.5 PXRD and SCXRD data

PXRD

*Bupropion hydrochloride **1a***

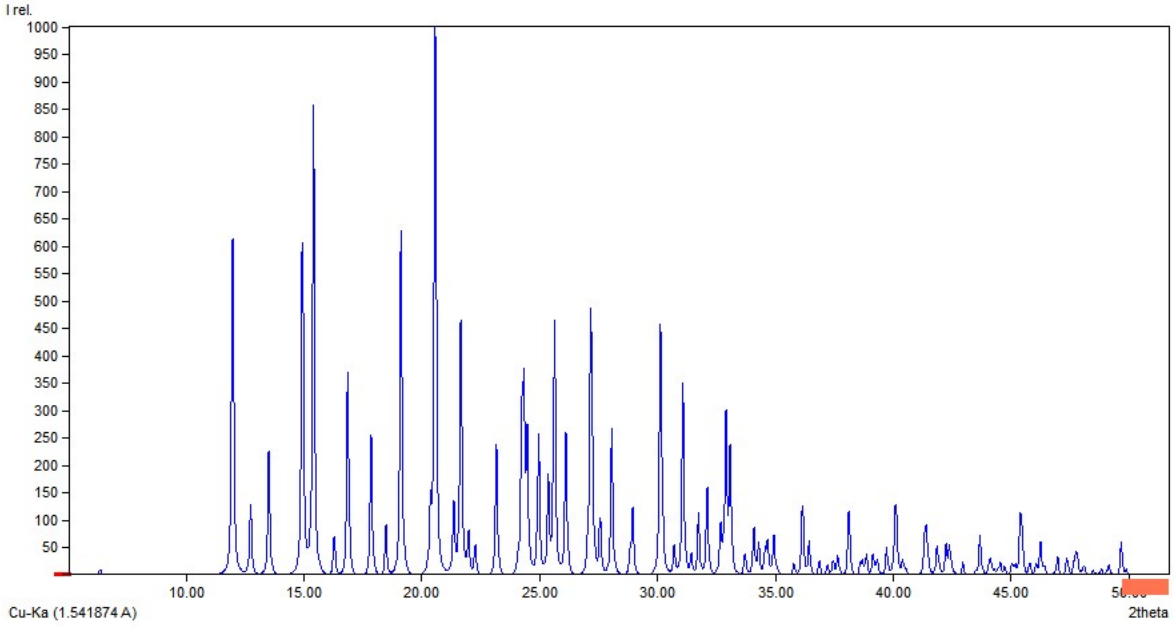


Table S6. List of the Most Intense Peaks (% Relative Intensity) in the Experimental PXRD Pattern of Bupropion HCl **1a**

Scattering Angle (degrees 2Θ)	Relative Intensity (%)	Scattering Angle (degrees 2Θ)	Relative Intensity (%)	Scattering Angle (degrees 2Θ)	Relative Intensity (%)	Scattering Angle (degrees 2Θ)	Relative Intensity (%)

11,98	61,36	23,18	23,56	32,12	16,08	39,74	4,91
12,74	13,1	24,05	2,92	32,7	9,99	40,12	13,76
13,52	22,47	24,3	45,2	32,91	29,86	40,41	2,92
14,94	60,47	24,47	28,76	33,09	24,79	41,4	10,97
15,17	5,11	24,96	25,41	33,72	4,21	41,88	5,52
15,41	83,94	25,38	18,34	34,1	8,72	42,26	5,71
16,29	6,78	25,64	46,98	34,3	6,1	42,4	5,71
16,87	36,12	26,12	26,23	34,65	7,26	42,97	2,12
17,86	25,33	26,99	4,32	34,94	7,24	43,7	7,12
18,48	8,87	27,19	52,68	36,17	12,72	44,12	3,27
19,12	62,86	27,39	3,91	36,45	6,03	44,54	2,39
20,4	16,7	27,57	10,36	36,88	2,55	45,06	2,31
20,58	100	28,07	26,36	37,46	2,59	45,43	12,89
21,36	13,7	28,95	12,38	37,65	3,44	45,81	2,17
21,49	4,31	30,14	47,71	38,13	11,53	46,09	2,15
21,66	48,1	30,72	5,62	38,67	3,04	46,26	6,07
21,85	3,49	31,09	34,56	38,87	3,87	46,99	3,27
21,98	8,43	31,44	4,01	39,16	3,7	47,38	3,2
22,27	5,35	31,75	11,11	39,32	3,15	47,78	4,89

Recorded PXRD pattern was consistent with previously reported data.[15]

tert-Butylammonium bromide (by-product)

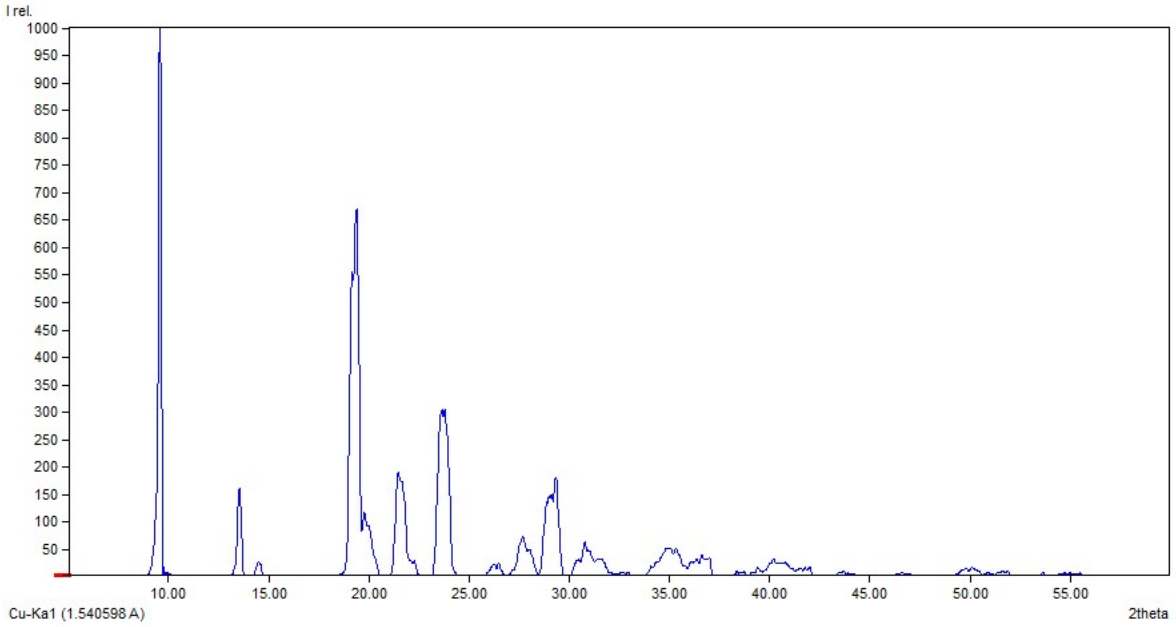


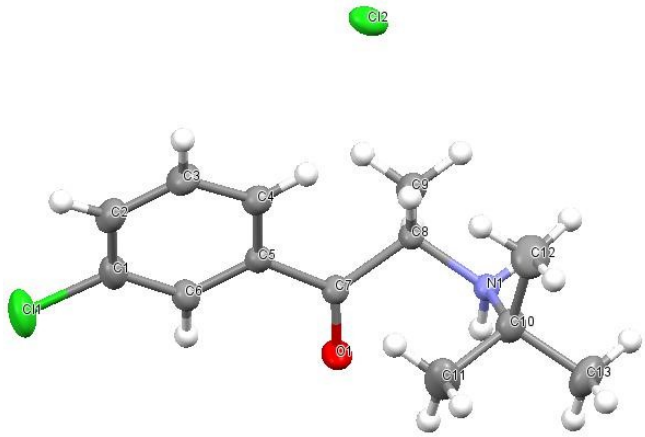
Table S7. List of the Most Intense Peaks (% Relative Intensity) in the Experimental PXRD Pattern of *tert*-butylammonium bromide (by-product)

Scattering Angle (degrees 2Θ)	Relative Intensity (%)	Scattering Angle (degrees 2Θ)	Relative Intensity (%)	Scattering Angle (degrees 2Θ)	Relative Intensity (%)	Scattering Angle (degrees 2Θ)	Relative Intensity (%)
8,68	1,43	19,8	12,23	27,7	7,79	34,09	1,66
9,59	100	21,48	19,81	28,03	5,68	34,9	5,61
9,94	1,64	21,62	18,67	28,99	15,53	35,02	5,72
10,31	1,1	21,79	6,87	29,09	16,04	35,34	5,42
10,5	1,1	22,27	3,67	29,22	7,43	36,12	3,12

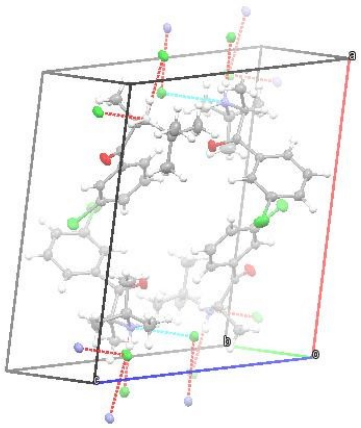
11,71	0,98	23,65	31,67	29,35	19,01	36,35	3,47
13,56	16,89	23,8	31,29	30,45	4,05	36,65	3,95
14,49	3,13	24,02	11,21	30,78	6,78	36,97	3,58
19,2	56,93	26,25	2,54	30,99	5,55	38,4	1,14
19,4	68,65	26,49	2,59	31,42	3,66	38,57	1,22

SCXRD

Bupropion hydrochloride ***1a***



Asymmetric unit



Packing

Table S8. Comparison of crystal cell data for different solid forms of bupropion hydrochloride **1a**

Form	**Bupropion·HCl form I**	**Bupropion·HCl form II**	**Bupropion·HCl form III**	**Bupropion·HCl form IV**	**This work**
Space group	Monoclinic $P2_1/c$	Orthorhombic *Pbca*	Triclinic $P\bar{1}$	Triclinic $P\bar{1}$	Monoclinic $P2_1/c$
a [Å]	14.326(2)	27.2853(5)	7.7477(2)	7.5154(3)	14.2321(2)
b [Å]	8.753(2)	8.7184(3)	8.1124(1)	7.8712(3)	8.7149(2)
c [Å]	11.885(3)	12.0422(3)	13.1768(3)	13.7033(6)	11.7513(2)
α [deg]	90	90	117.02(2)	88.12(3)	90
β [deg]	78.07(2)	90	81.34(2)	86.41(2)	101.879(2)
γ [deg]	90	90	89.00(2)	67.78(2)	90
V [Å^3], *Z*	1458.2, 4	2864.7, 8	725.9, 2	748.9, 2	1426.32, 4
V/Z	365	358	363	374	357

The crystal structure obtained corresponds well to that of bupropion hydrochloride form I (Monoclinic $P2_1/c$ space group) as published in 2009 by Elisabetta Maccaroni and co-authors.[15]

1.10.6 Raman spectroscopy

tert-Butylammonium bromide (by-product)

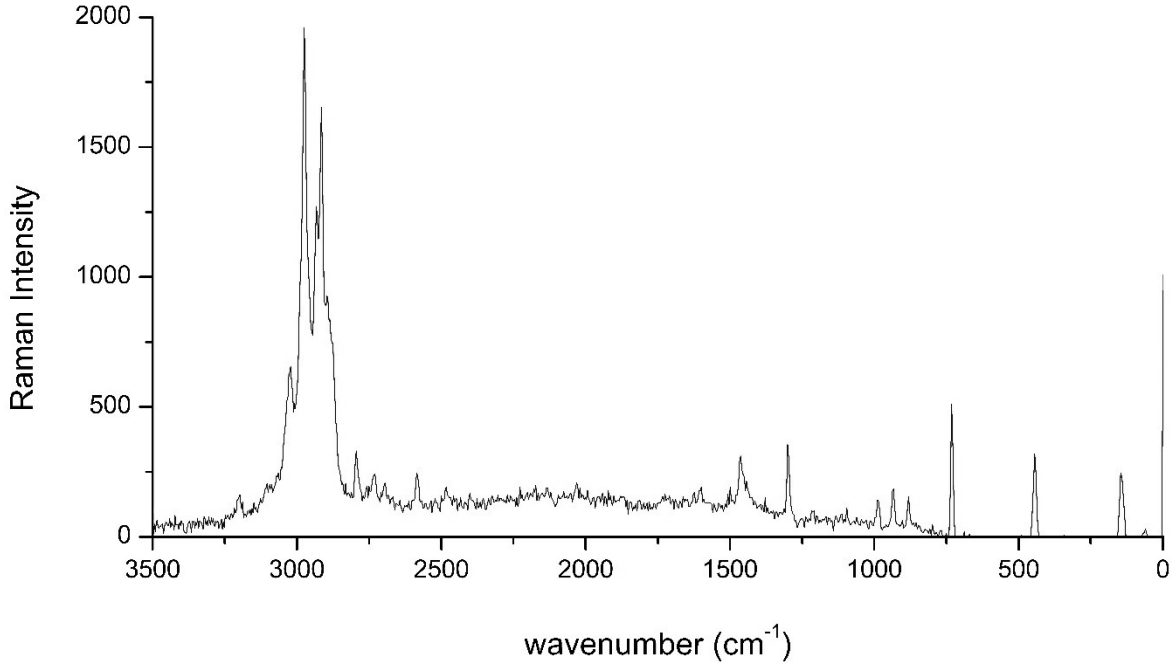


Table S9. Most prominent Raman peak positions for *tert*-butylammonium bromide

Frequency (cm^{-1})	Relative intensity (%)	Assignment
732	26	C-Br
1300	18	C-C, CH_3
2896	47	Sp^3-C (CH_3)
2916	84	Sp^3-C (CH_3)
2976	100	Amine (N-H)

*Bupropion hydrochloride **1a***

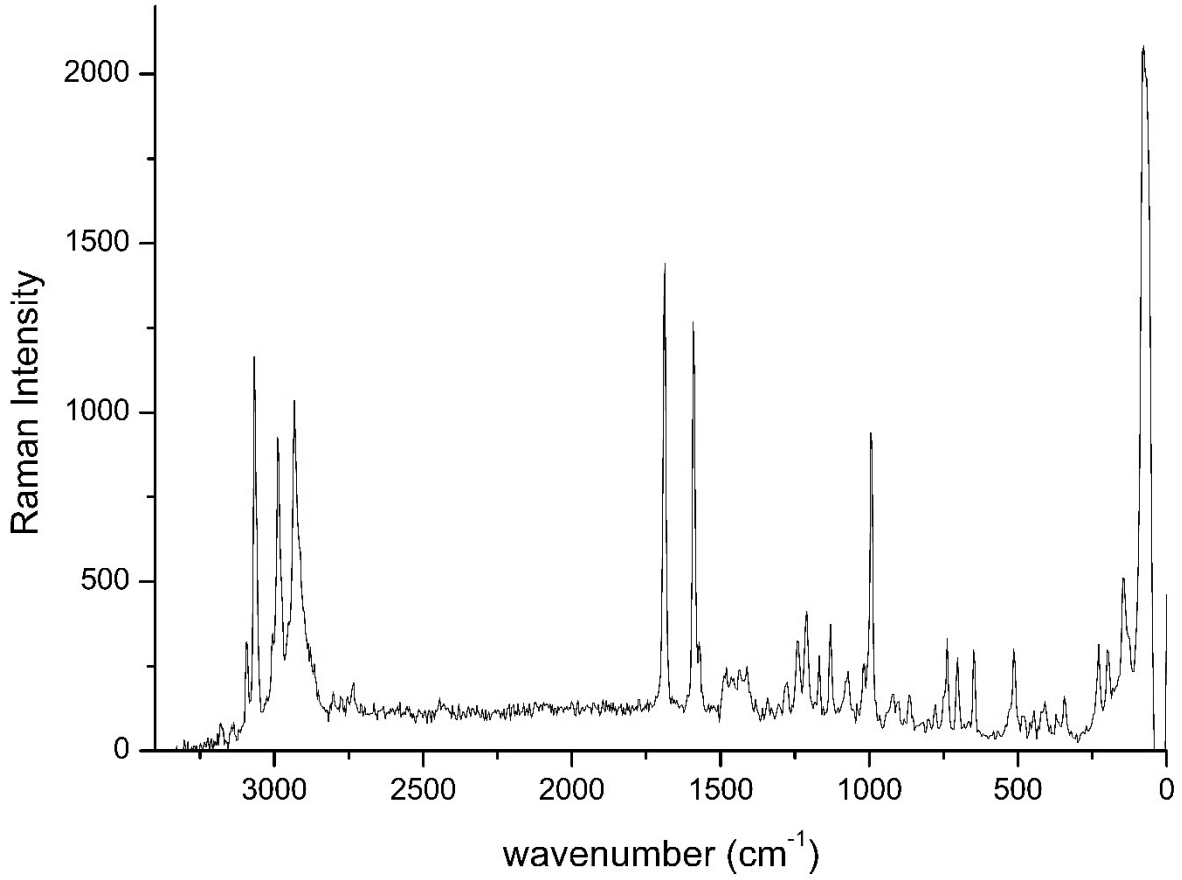


Table S10. Most prominent raman peak positions for bupropion hydrochloride **1a**

Frequency (cm^{-1})	Relative intensity (%)	Assignment
77	100	Lattice vibrations
994	45	Aromatic ring (CH), C-Cl
1592	61	Aromatic ring (C=C)
1686	69	Ketone (C=O)
2933	50	Sp^3-C (CH_3)
2989	44	Sp^3-C (CH_3)
3068	56	Aromatic (CH), amine (NH)

The frequencies and relative intensities corresponds well with those reported in the literature for form I of bupropion hydrochloride **1a**.[18]

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