Ball Mill and Microwave Assisted Synthetic Routes to Fluoxetine

Ricard Solà, Oliver B. Sutcliffe, Craig E. Banks and Beatriz Maciá*

Division of Chemistry and Environmental Science, Faculty of Science and Engineering, Manchester Metropolitan University, Oxford Road, M1 5GD, Manchester, UK.
E-mail: B.Macia-Ruiz@mmu.ac.uk

Abstract

Remarkable advances have been made in the development of an environmentally-friendly approach for the rapid and simple construction of the Active Pharmaceutical Ingredient (API) Fluoxetine (**1**). These include the use of ball milling and microwave irradiation as greener alternatives – compared to conventional heating – to provide the energy needed for the chemical transformations.

Keywords: mechanochemistry, ball mill, microwave, Fluoxetine, antidepressant

1. Introduction

Pharmaceutical manufacturing is the most solvent-intensive and the least efficient of all chemical industries in terms of waste generated per unit of product. Statistics compiled across the industry point to an average waste-to-product ratio of 200. In other words, factories generate 200 kilograms of waste for every kilogram of active pharmaceutical ingredient produced and the financial burden associated with the processing and disposal of these sizeable waste-streams is considerable (Rajagopal 2014). Furthermore, pharmaceutical manufacturing plants devote exorbitant amounts of money each year for the fuel and electricity they need to keep their facilities running (Galitsky et al. 2008). As a counter to this, various "green" approaches have become popular as a means to reduce the ecological impact of the pharmaceutical industry including the use of solvent-free synthetic procedures and alternative energy sources (Markarian 2016). In this context, mechanosynthesis [or synthesis in a ball mill (Tan et al. 2016)] and microwave assisted synthesis (Wagner 2006, Sekhon 2010), have recently become very popular as cleaner technologies in the pharmaceutical sector (Cernansky 2015).
Mechanosynthetic methods – grinding of (solid) reactants in a ball mill – avoid the use of solvents and at the same time utilize mechanical energy from the grinding for the formation/ breaking of new bonds (André et al. 2011, Baig et al. 2012, Bonnamour et al. 2013, James et al. 2012, Jones et al. 2014, Konnert et al. 2014, Konnert et al. 2016, Tan et al. 2014, Tan et al. 2016.). Similarly, microwave assisted synthesis is particularly interesting due to its high efficiency, leading to drastically reduced reaction times and higher yields, both of which result in energy savings. In addition, there is clear evidence that these technologies offer new

opportunities to the synthetic chemist in the form of complementary reactions that are not possible using conventional methods. As such, both mechano- and microwave assisted synthesis provide a general answer to the demands of pharmaceutical industry for cleaner, safer and efficient synthetic solutions. Their implementation into the pharmaceutical industry could lead to a decrease in the number of process operations, thus allowing both the simplification of the processes and the reduction of costs to the manufacturer and, ultimately, to the consumer (Bruckmann et al. 2008, Mikhailenko et al. 2004).

This work focuses on the synthesis of the antidepressant Fluoxetine (commercialised as Prozac), *via* environmentally-friendly ball milling and microwave assisted techniques. A simplified and fast synthetic pathway for the eco-friendly synthesis of Fluoxetine is here reported, where the utilisation of solvent and energy consumption have been minimized.

2. Materials and Methods

2.1. General instrumentation:

TLC: Thin layer chromatography (TLC) was run on silica gel 60 aluminium sheets, 0.25 mm thick (F_{254} *Merck KGaA*®). The components were visualized by UV light (254 nm), phosphomolybdic acid or $KMnO_4$ staining solutions.
IR: IR spectra were recorded on *Nicolet*® 380 FT/IR – Fourier Transform Infrared Spectrometer. Only the most significant frequencies have been considered for the characterisation, and have been reported in cm^{-1}.
NMR: ^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded on a *JEOL*® ECS-400 (400, 100.6 and 376.5 MHz, respectively) using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with TMS as internal standard ($CDCl_3$: δ 7.26 for ^{1}H-NMR, δ 77.0 for ^{13}C-NMR). Data are reported as follows: chemical shifts, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad), coupling constants (Hz), and integration.
Flash chromatography: Column chromatography was carried out using *Geduran*® Silica gel 60, 40-63 microns RE.
Melting points: Melting points were measured in a *Stuart*® SMP10 melting point apparatus and are not corrected.
GCMS: Low resolution mass spectra were recorded on a GC-MS spectrometer (*Hewlett Packard*® HP 5890 Series II GC System) equipped with a DB-5 column (*J&W Scientific*®, 30 m × 0.32 mm), connected to a *Hewlett Packard*® HP 5972 Series Mass Selective Detector. Helium was used as carrier gas at 10 psi, and the samples were ionized by an electronic impact (EI) source at 70 eV.
HRMS: High resolution mass spectra were obtained on a *Agilent Technologies*® 6540 Ultra-High-Definition (UHD) Accurate-Mass equipped with a time of flight (Q-TOF) analyzer and the samples were ionized by ESI techniques and introduced through a high pressure liquid

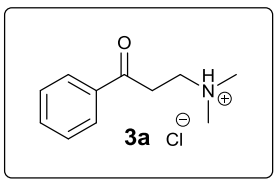
chromatography (HPLC) model *Agilent Technologies*® 1260 Infinity Quaternary LC system. Samples were eluted with mixture of MeOH and 0.1% formic acid, with a flow of 0.2 ml/min.
Shaker ball mill: Reactions in the shaker ball mill were carried out in a *Retsch*® MM200 (shaker mill) using a 25 mL stainless steel grinding jar provided with one stainless steel grinding ball of 2.5 cm of diameter.
Planetary ball mill: Reactions in the planetary ball mill were carried out in a *Retsch*® PM100 using a 50 mL stainless steel grinding jar and different sets of the grinding balls: (a) 2 stainless steel grinding balls of 1.5 cm diameter each, (b) 5 stainless steel grinding balls of 1 cm diameter each, (c) 10 stainless steel grinding balls of 0.8 cm diameter each, (d) 10 stainless steel grinding balls of 0.7 cm diameter each, (e) 5 stainless steel grinding balls of 0.6 cm diameter each, (f) 10 stainless steel grinding balls of 0.4 cm diameter each, or (d) 20 zirconium-coated grinding balls of 0.3 cm diameter each.
MW: The microwave irradiation was carried out in an *Anton Paar*® Monowave 300, Microwave Synthesis Reactor, using 10 and 30 mL glass vials sealed with a PTFE-coated silicone septum and closed with a snap cap made of PEEK.

2.2. General methods and considerations:

All commercially available reagents were purchased from Aldrich, Acros, Alfa Aesar and Maybridge and used without further purification, unless stated otherwise.
Ball mill reactions: Before starting the grinding process, the grinding jar was flushed for 0.5 min with a stream of argon after all the reagents were added.
MW reactions: A dry MW-glass vial was filled with argon and sealed with a rubber septum. All the chemicals were added under argon atmosphere. The septum was quickly changed for a snap cap before putting the vial inside the Microwave Synthesis Reactor.

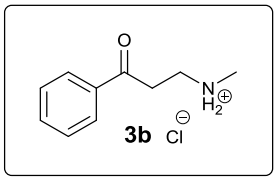
2.3. Experimental procedure and data of compounds

2.3.1. Mannich Reactions



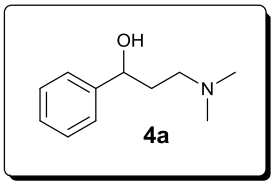
2.3.1.1. 3-(Dimethylamino)propiophenone hydrochloride (3a) (Istanbullu et al. 2015). Concentrated HCl (40 µL, 0.5 mmol) was added dropwise to a solution of acetophenone (961 mg, 8 mmol), dimethylamine hydrochloride (832 mg, 10 mmol) and paraformaldehyde (360 mg, 12 mmol) in ^{i}PrOH (4 mL) at RT under Ar atmosphere, in a 30 mL MW glass tube. The mixture was heated in the MW to 110 °C for 60 min and a solid precipitated inside the glass tube. The resulting solid was filtrated and washed with acetone and concentrated under vacuum. Pure 3-(dimethylamino)propiophenone hydrochloride (**3a**) was obtained as a white solid (1.099 g, 65%). **M_p** = 153–156 °C [lit. M_p = 153–154 °C (Roman et al. 2013)]. **IR** (ATR) 3400 (br), 2946, 2662, 1674, 1334, 1222, 958 cm^{-1}. **^{1}H NMR** (400 MHz,

CD_3OD) δ 8.80–7.20 (5H, m, Ar<u>H</u>), 4.45–2.25 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$N(CH_3)$_2$), 3.75 (6H, s, N(C<u>H</u>$_3$)$_2$). **^{13}C NMR** (100.6 MHz, CD_3OD) δ 198.3, 137.2, 135.0, 129.9, 129.3, 54.4, 43.9, 34.2. Data in agreement with the literature.

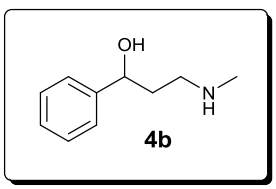


2.3.1.2. 3-(Methylamino)-1-phenylpropan-1-one hydrochloride (3b) (Hu et al. 2015). Concentrated HCl (125 μL, 1.5 mmol) was added dropwise to a solution of acetophenone (3.004 g, 25 mmol), methylamine hydrochloride (1.86 g, 27.5 mmol) and paraformaldehyde (1.05 g, 35 mmol) in EtOH (12.5 mL) at RT under Ar atmosphere, in a 30 mL MW glass tube. The mixture was heated in the MW to 130 °C for 5 h. The solvent was then concentrated under vacuum and the crude was purified by recrystallization (^{i}PrOH/AcOEt) to afford pure 3-(methylamino)-1-phenylpropan-1-one hydrochloride (**3b**) as a white solid (2.818 g, 57%). **M_p** = 113–118 °C [lit M_p = 113–115 °C (Hu et al. 2015)]. **IR** (ATR) 3390 (br), 2941, 2694, 2448, 1679, 1373, 1223, 749 cm^{-1}. **^{1}H NMR** (400 MHz, CD_3OD) δ 8.10–7.45 (5H, m, Ar<u>H</u>), 3.58–3.35 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$NCH_3), 2.77 (3H, s, NC<u>H</u>$_3$). **^{13}C NMR** (100.6 MHz, CD_3OD) δ 198.6, 137.2, 135.0, 129.9, 129.3, 45.5, 35.5, 34.1. Data in agreement with the literature.

2.3.2. Carbonyl reduction in the shaker mill



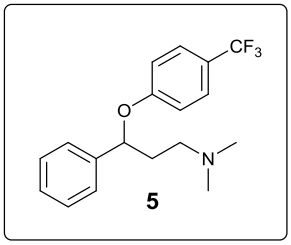
2.3.2.1. 3-Dimethylamino-1-phenylpropan-1-ol (4a) (Xu et al. 2015). Aminoketone hydrochloride **3a** (107 mg, 0.5 mmol) and $NaBH_4$ (25 mg, 0.65 mmol) were added into a 25 mL stainless steel grinding jar with a 25 mm Ø stainless steel ball. The grinding jar was flushed with a stream of argon and the mixture was shaken at 20.0 Hz for 25 min. The reaction crude was dissolved with water and acetone and transferred into a separating funnel. Concentrated HCl (5 mL) was added and the aqueous layer was washed with CH_2Cl_2 (3 × 20 mL) and the organic layer was discarded. A solution of NaOH 5 N (15 mL) was added to the aqueous layer, and was subsequently extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. To afford pure 3-dimethylamino-1-phenylpropan-1-ol (**4a**) as a white solid (86 mg, 96%). **M_p** = 45–47 °C [lit. M_p = 47–48 °C (Miyano et al. 1985)]. **R_f** (MeOH) = 0.25. **IR** (ATR) 3076 (br), 2970, 2821, 1602, 1450, 1027, 700 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.15 (5H, m, Ar<u>H</u>), 4.93 (1H, dd, *J* = 7.6, 4.0 Hz, C<u>H</u>OH), 2.68–2.44 (2H, m, C<u>H</u>$_2$CHOH), 2.30 (6H, s, N(C<u>H</u>$_3$)$_2$), 1.85–1.78 (2H, m, C<u>H</u>$_2$N(CH_3)$_2$). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 145.1, 128.1, 126.8, 125.5, 75.8, 58.4, 45.3, 34.5. Data in agreement with the literature.



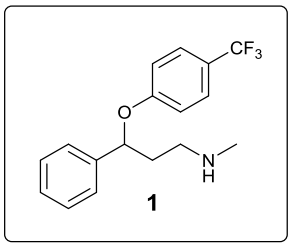
2.3.2.2. 3-Methylamino-1-phenylpropan-1-ol (4b) (Calow et al. 2014). Aminoketone hydrochloride **3b** (105 mg, 0.5 mmol) and $NaBH_4$ (39 mg, 1.0 mmol) were added into a 25 mL stainless steel grinding jar with a 25 mm Ø stainless steel ball. The grinding jar was flushed with a stream of

argon and the mixture was shaken at 20.0 Hz for 5 min. The reaction crude was dissolved with water and acetone and transferred into a separating funnel. Concentrated HCl (5 mL) was added and the aqueous layer was washed with CH_2Cl_2 (3 × 20 mL) and the organic layer was discarded. A solution of NaOH 5 N (15 mL) was added to the aqueous layer, and was subsequently extracted with CH_2Cl_2 (4 × 25 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum to afford pure 3-methylamino-1-phenylpropan-1-ol (**4b**) as a white solid (73 mg, 83%). **M_p** = 66–73 °C [lit. M_p = 50–60 °C (Mathad et al. 2005)]. **R_f** (AcOEt/MeOH 1:1) = 0.20. **IR** (ATR) 3281, 2927, 2793, 1600, 1450, 1080, 1080 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.20 (5H, m, ArH), 4.94 (1H, dd, *J* = 8.8, 3,2 Hz, CHOH), 3.95 (1H, s (broad), NH), 2.94–2.83 (2H, m, CH_2CHOH), 2.45 (3H, s, NCH_3), 1.90–1.73 (2H, m, CH_2NCH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 145.1, 128.2, 126.9, 125.6, 75.6, 50.5, 36.8, 36.0. Data in agreement with the literature.

2.3.3. MW-assisted copper catalysed *O*-arylation



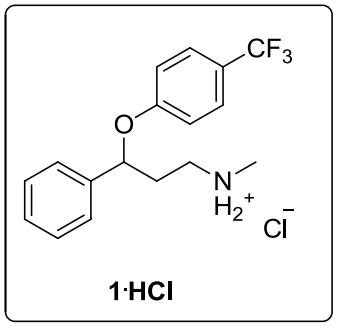
2.3.3.1. 3-Dimethylamino-1-phenyl-1-(4-trifluoromethylphenoxy)propane (5) (Andersen et al. 2014). 4-Iodobenzotrifluoride (40 µL, 0.275 mmol) was added dropwise to a solution of amino alcohol **4a** (45 mg, 0.25 mmol), CuI (5 mg, 0.025 mmol) and Cs_2CO_3 (163 mg, 0.50 mmol) in *o*-xylene (2.5 mL) at RT under Ar atmosphere, in a 10 mL MW glass tube. The mixture was heated in the MW using the following heating program: 120 °C for 10 min, then 150 °C for 10 min and last 200 °C for 3 h. After that time, GC-MS analysis confirmed 99% conversion. The resulting solution was filtrated through a plug of Celite® and eluted with EtOAc. After concentrating the solvent under vacuum, pure 3-dimethylamino-1-phenyl-1-(4-trifluoromethylphenoxy)propane (**5**) was obtained as a brown oil (84 mg,99%). **R_f** (CH_2Cl_2/MeOH 95:5) = 0.25. **IR** (ATR) 2946, 2768, 1614, 1517, 1323, 1248, 1108 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45–6.88 (9H, m, ArH), 5.28 (1H, dd, *J* = 8.4, 5.2 Hz, CHOAr), 2.50–2.36 (2H, m, CH_2CHOAr), 2.25 (6H, s, $N(CH_3)_2$), 2.30–1.94 (2H, m, $CH_2N(CH_3)_2$). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 160.6, 141.1, 128.7, 127.8, 126.7 (q, *J* = 15.2 Hz), 125.8, 123.0, 122.7 (q, *J* = 129.6 Hz), 115.8, 78.5, 55.7, 45.4, 36.7. **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –61.52. **HRMS** (+ESI): *m/z* calculated for $C_{18}H_{21}NOF_3$ $[M+H]^+$: 324.1575. Found: 324.1572. Data in agreement with the literature.



2.3.3.2. *N*-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine (1) (Siddappa et al. 2014). 4-Iodobenzotrifluoride (40 µL, 0.275 mmol) was added dropwise to a solution of amino alcohol **4b** (41 mg, 0.25 mmol), CuI (5 mg, 0.025 mmol) and Cs_2CO_3 (163 mg, 0.50 mmol) in *o*-xylene (2.5 mL) at RT under Ar atmosphere, in a 10 mL MW glass tube. The mixture was heated in the MW using the following

heating program: 120 °C for 10 min, then 150 °C for 10 min and last 200 °C for 2 h. After that time, GC-MS analysis confirmed full conversion. The resulting solution was filtrated through a plug of Celite® and eluted with EtOAc. After concentrating the solvent under vacuum, pure *N*-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine (**1**) was obtained as a yellow oil (81 mg, >99%). $\mathbf{R_f}$ (CH_2Cl_2/MeOH 95:5) = 0.25. **IR** (ATR) 2927, 2849, 1613, 1516, 1323, 1107 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–6.82 (9H, m, ArH), 5.27 (1H, dd, *J* = 8.4, 4.8 Hz, CHOAr), 3.03 (1H, s(broad), NH), 2.82–2.70 (2H, m, CH_2CHOAr), 2.41 (3H, s, NCH_3), 2.30–1.98 (2H, m, CH_2NCH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 160.3, 140.5, 128.8, 128.0, 126.8 (q, *J* = 15.2 Hz), 125.7, 122.9 (q, *J* = 130.0 Hz), 115.8, 78.2, 47.8, 37.7, 35.7, 30.9. **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –61.44. Data in agreement with the literature.

2.3.4. *N*-demethylation

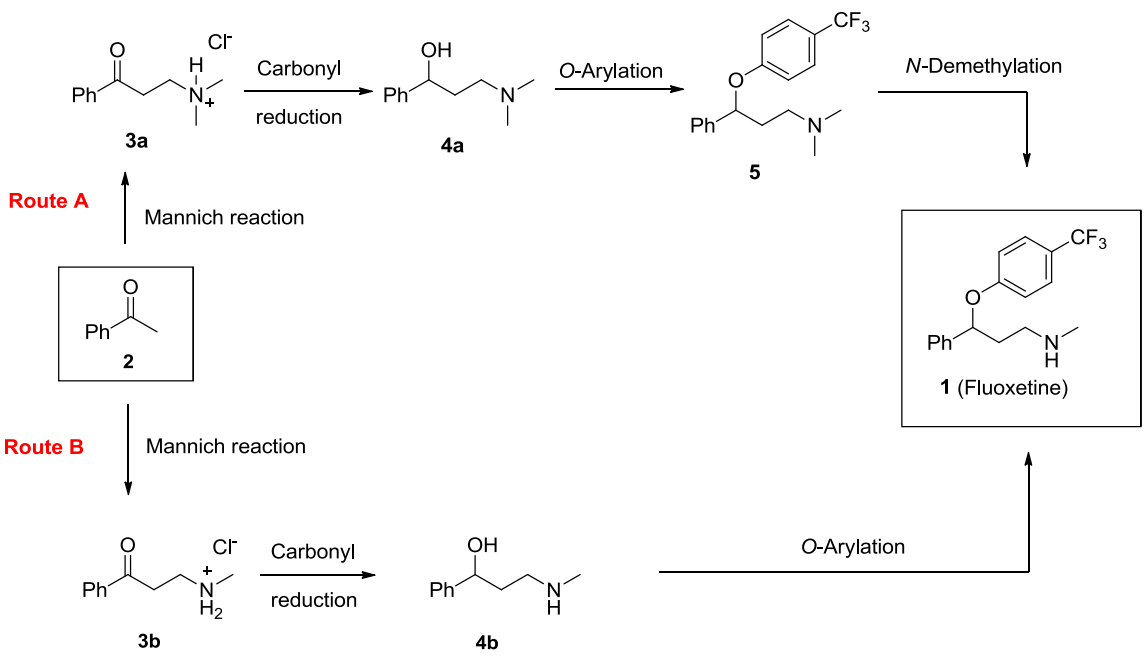


1·HCl

2.3.4.1. *N*-methyl-3-(4-trifluoromethylphenoxy)-3-phenylpropylamine hydrochloride / Fluoxetine hydrochloride (1·HCl) (Chang et al 2006). α-Chloroethyl chloroformate (108 µL, 1.0 mmol) was added dropwise to a solution of 3-dimethylamino-1-phenyl-1-(4-trifluoromethylphenoxy)propane (**5**) (81 mg, 0.25 mmol) in dichloroethane (2.5 mL) at RT under argon atmosphere, in a 10 mL MW glass tube. The mixture was heated in the MW at 120 °C for 1 h and at 150 °C for 1 h. The resulting solution was concentrated under vacuum and heated (MW) with MeOH (2.5 mL) at 120 °C for 1 h. The crude oil was purified by recrystallization (EtOAc/hexane) to afford of pure Fluoxetine hydrochloride (**1·HCl**) (66 mg, 76%) as a white solid. $\mathbf{M_p}$ = 152–154 °C [lit. $\mathbf{M_P}$ = 156–158 °C (Srivastava et al. 2004)]. $\mathbf{R_f}$ (CH_2Cl_2/MeOH 95:5) = 0.30). **IR** (ATR) 2858, 2730, 2450, 1614, 1517, 1325, 1241, 1107 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.69 (2H, s (broad), NH_2), 7.45–6.85 (9H, m, ArH), 5.46 (1H, dd, *J* = 7.6, 4.0 Hz, CHOAr), 3.20–3.05 (2H, m, CH_2CHOAr), 2.63 (3H, s, NCH_3), 2.58–2.37 (2H, m, CH_2NCH_3). **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 159.6, 139.0, 129.0, 128.4, 126.8 (q, *J* = 15.2 Hz), 125.7, 123.3 (q, *J* = 129.6 Hz), 122.8, 115.8, 76.9, 46.1, 34.5, 33.0. **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –61.54. Data in agreement with the literature.

3. Results and Discussion

Two synthetic routes (A and B) for the preparation of racemic Fluoxetine (Jakobsen et al. 1991, Fuller et al. 1991, Molloy et al. 1982, Wirth et al. 2000) have been studied (Scheme 1). Both pathways consist of a Mannich condensation, a carbonyl reduction, *O*-arylation and, in the case of Route A, a final *N*-demethylation reaction.



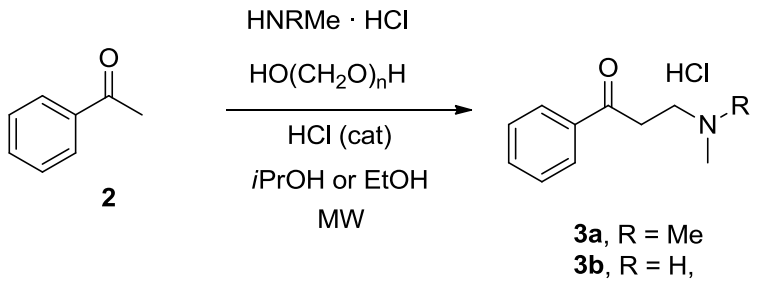
Scheme 1 – Fluoxetine synthetic pathways evaluated in this study

The Mannich condensation between acetophenone (**2**) and dimethyl- or methylamine hydrochlorides has been previously described under conventional heating conditions, to provide adducts **3a** (Abid et al. 2005, Borah at al. 2015, Cablewski et al. 1994, Kaiser et al. 2006) and **3b** (Liu et al. 2005), respectively.

The analogous Mannich reactions were attempted under mechanochemical conditions, using both a shaker and a planetary mill. A wide screening of various grinding parameters and reaction conditions was performed; unfortunately, no conversion higher than 10% was achieved for either **3a** or **3b**.

Next, we performed the reactions under microwave irradiation, which provided higher yields in shorter times than the corresponding reactions under conventional heating (Abid et al. 2005, Borah at al. 2015, Cablewski et al. 1994, Kaiser et al. 2006, Liu et al. 2005). Thus, the reaction of **2** with 1.25 eq of dimethylamine hydrochloride and 1.50 eq of paraformaldehyde in isopropanol, provided the hydrochloride salt **3a** in 65% yield in only 1 h at 110 ºC (entry 1, Table 1). Longer reaction times did not improve the yield of the reaction (entry 2, Table 1). Similarly, the synthesis of **3b** was achieved in 40% yield, using ethanol as solvent and microwave assisted heating at 130 °C (entry 3, Table 1). In this case, the yield of the reaction could be improved to 57% with longer reaction times (5 h, entry 4, Table 1).

Table 1 – MW assisted Mannich reaction for the synthesis of **3a** and **3b**.[a]



Entry	HNRMe (eq)	$HO(CH_2O)_nH$ (eq)	Solvent	T (°C)	Product	Time (h)	Yield (%)[b]
1	$HNMe_2$ (1.25)	1.50	*i*PrOH	110	**3a**	1	65
2	$HNMe_2$ (1.25)	1.50	*i*PrOH	110	**3a**	4	59
3	H_2NMe (1.10)	1.40	EtOH	130	**3b**	2	40
4	H_2NMe (1.10)	1.40	EtOH	130	**3b**	5	57
[a] Reaction Conditions: **2** (1 eq), HNRMe, paraformaldehyde, solvent, MW . [b] Isolated yield.							

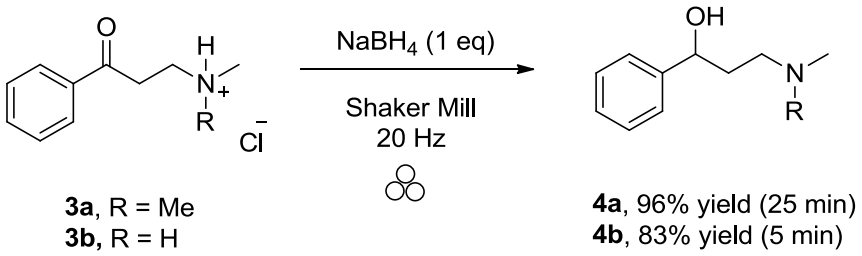
We studied the reduction of **3a-b** to their corresponding alcohols **4a-b** (Scheme 1). Mack et al. (2007) described a solvent-free method for the reduction of carbonyl compounds (non-functionalised aldehydes and ketones) using $NaBH_4$ as a reducing agent in a high-speed ball mill (HSBM). A similar procedure was reported by Cho et al. (2006) and Shalbaf (2010) in a pestle and mortar, using $NaBH_4$ in the presence of some activators, such as PTSA, H_3BO_3, benzoic acid, or Al_2O_3, which provided shorter reactions times and higher yields.

Based on these literature precedents, we envisioned that the development of a ball milling methodology for the reduction of amino ketones **3a-b** under solvent-free conditions could be feasible.

The reduction reactions of **3a-b** using $NaBH_4$ were studied in both in a shaker and a planetary ball mill, using stainless steel grinding jars in both cases. Different parameters were scrutinized, such as (i) the number and size of the stainless steel grinding balls (in the case of the planetary mill, zirconium coated grinding balls were also evaluated); (b) reaction scale; (c) liquid assisted grinding (using 100 μL of MeOH per mmol of substrate); (c) equivalents of $NaBH_4$; (d) reaction time and (e) different work-up procedures (filtration, wash, acid/base extraction, etc).

The shaker mill – equipped with a single steel ball of 2.5 cm of diameter in the 25 mL grinding jar – proved more efficient than the planetary mill. After 25 min of grinding at 20.0 Hz in the shaker mill, salt **3a** fully reacted to the corresponding aminoalcohol **4a**, using 1 eq of $NaBH_4$ and in the absence of solvent. Next, a mere acid/base extraction provided the product **4a** in 96% yield

(Scheme 2). This methodology reduces the reaction time to 25 min, compared to 15 h needed in the solution-based reactions described in the literature (Jakobsen et al. 1991).
Under analogous conditions the reduction of **3b** was completed after 5 min of grinding, providing **4b** in 83% yield. (Scheme 2).



Scheme 2 – Carbonyl reduction in the ball mill

The absence of solvent to act as a heat-sink for the system is an obvious concern and we therefore tracked the temperature increase in the system with the aid of an IR thermometer for the reduction of **3a**. As represented in Figure 1 below, the temperature of the grinding ball, and both inside and outside walls of the grinding jar increases by an average of 4.5 °C during the 25 min of grinding due to friction. We believe this increase is not significant and is not a determining factor for the reaction. When the reaction was performed in intervals of 5 min, leaving the system enough time to cool down to room temperature, analogous results were obtained.

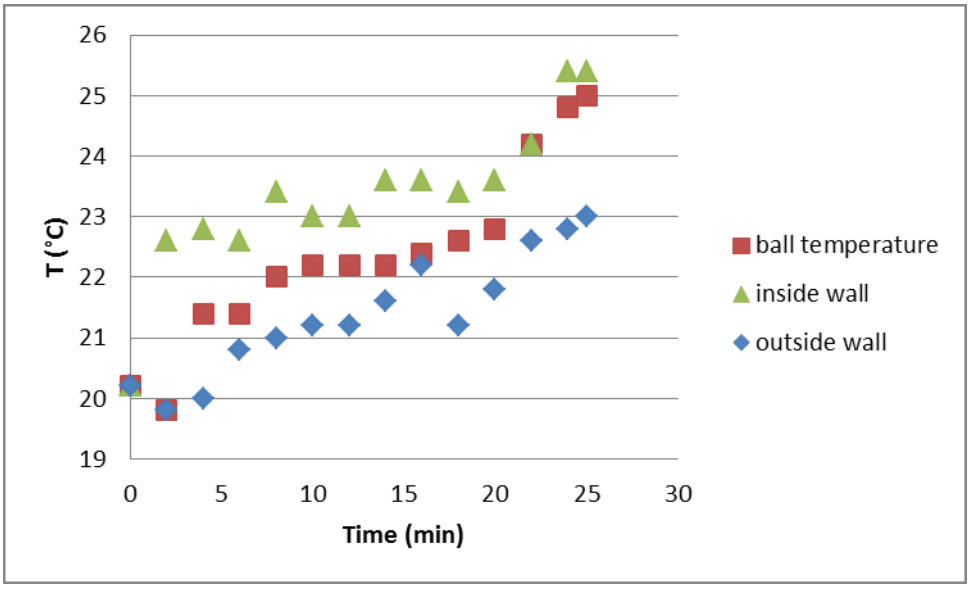


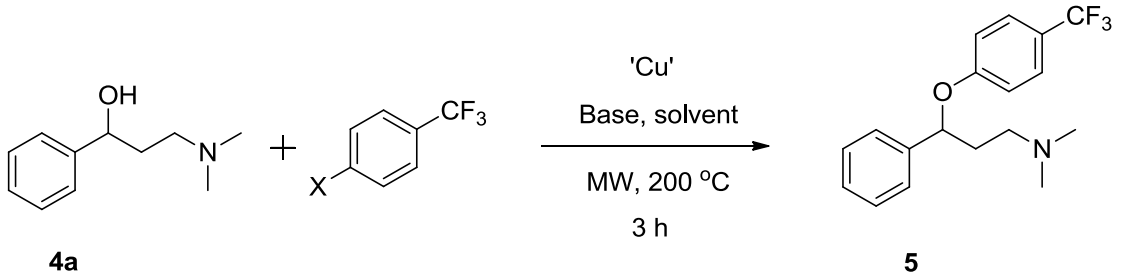
Figure 1 – Temperature of the grinding ball and inside and outside walls of the grinding jar for the reduction of **3a** to **4a**.

With amino alcohols **4a-b** in hand, we continued with the optimization of the third step of the synthetic sequence (Scheme 1). The SN_2 reactions of the corresponding mesylated derivatives **4**, using *p*-trifluoromethylphenol as nucleophile, have been previously described (O'Brien et al. 2002). Likewise, Mitsunobu procedures (Rej et al. 2013) are also known for the synthesis of **5** and **1** from **4a-b**, respectively. However, these methods are unfavourable due to the high levels of waste generated.

Thus, we focused our efforts in the development of an efficient *O*-arylation procedure of **4a-b**, using aryl halides as coupling partners. Based on the knowledge that i) *O*-arylation reactions of aliphatic alcohols can be readily performed in the presence of catalytic amounts of CuI and 1,10-phenantroline as ligand (Altman et al. 2008, Vorogushin et al. 2005, Wolter et al. 2002, Wu et al. 2011); ii) the *O*-arylation reactions of certain aminoalcohols are also known to proceed under copper catalysis in the absence of ligands (Job et al. 2002, Shafir et al. 2007), we carried out an extensive investigation to perform the *O*-arylation reaction of **4a-b** under mechanochemical conditions. Varying bases, metal salts (copper, palladium and nickel) and ligands (1,10-phenantroline, 2,2'-bipyridine, NHC ligands, etc.) were evaluated as catalysts, under both solid grinding and liquid assisted grinding conditions (both planetary and shaker mill were tested). Unfortunately, no higher conversions than 20% were reached in any case and starting materials were recovered.

The use of Microwave assisted heating, however, provided better results and the *O*-arylation of **4a** could be successfully carried out under copper catalysis (Table 2).

Table 2 – Optimisation of the *O*-arylation reaction of **4a** in the MW.[a]



4a **5**

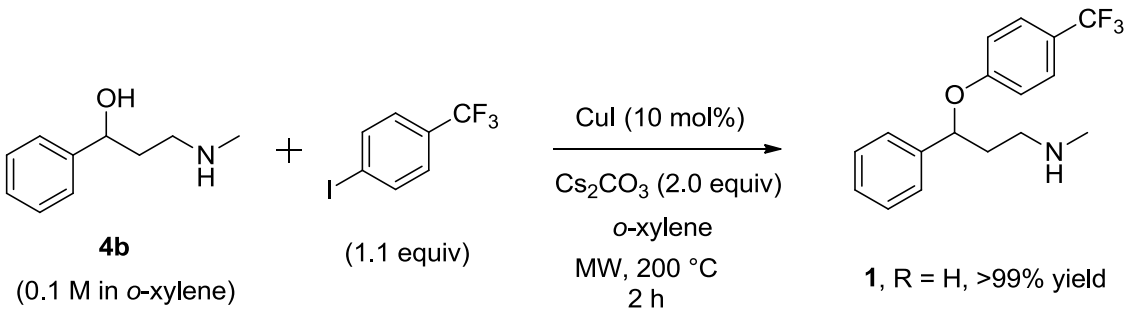
Entry	X	Copper salt (mol%)	Ligand (mol%)	Base	Solvent	Conv (%)[b]
1	I	CuI (10)	1,10-phenanthroline (10)	Cs_2CO_3	toluene	60
2	I	CuI (10)	2,2'-bipyridine (10)	Cs_2CO_3	toluene	73
3	I	CuI (10)	2,2'-bipyridine (10)	KOH	toluene	0
4	I	CuI (10)	2,2'-bipyridine (10)	Cs_2CO_3	*o*-xylene	98
5	I	CuI (10)	-	Cs_2CO_3	*o*-xylene	99
6	**I**	**CuCl (10)**	**-**	**Cs_2CO_3**	***o*-xylene**	**99**

7	I	CuI (5)	-	Cs_2CO_3	*o*-xylene	90
8[c]	I	CuCl (10)		Cs_2CO_3	*o*-xylene	23
9	Br	CuI (10)	-	Cs_2CO_3	*o*-xylene	51
10	Cl	CuI (10)	-	Cs_2CO_3	*o*-xylene	1
[a] Reaction conditions: **4a** (1.0 eq, 0.1 M), $X(C_6H_4)CF_3$ (1.1 eq), copper salt, ligand, Cs_2CO_3(2.0 eq), solvent, 200 °C, MW, 3 h. [b] Conversion determined by CG. [c] Conventional reflux conditions.						

The reaction of **4a** with 4-iodobenzotrifluoride, in the presence of 10 mol% CuI and 1,10-phenanthroline or 2,2'-bipyridine as ligand provided 60 and 73% conversion, respectively, when Cs_2CO_3 was used as base and toluene as solvent (entries 1-2). Using 2,2'-bipyridine as ligand, other bases were also evaluated, but lower conversions were obtained in all cases. Intriguingly, no conversion was observed when KOH was used as base (entry 3). Other solvents were also tested in the reaction; while 1,2-dichlorobenzene, DMF and ethylbenzene all gave lower conversions than toluene (63-81%), *o*-xylene proved more efficient (entry 4). Next, we observed that the reaction was equally effective in the absence of ligand (entry 5) and that no regioselectivity issues (*N*-arylation versus *O*-arylation) arose. A meticulous screening of copper sources revealed that CuCl was also a suitable salt for the reaction (entry 6). Lowering the catalyst loading from 10 to 5 mol% caused a drop in the conversion of the reaction (entry 7). For comparison, we performed our optimized reaction under conventional heating (reflux conditions) and only 23% conversion was observed after 3 h (entry 8).

Lastly, we evaluated the use of other aryl halides as coupling partners (entries 9-10). Under the optimized conditions, the reaction of **4a** with 4-bromobenzotrifluoride proceeded in 51% conversion (entry 9), while for the 4-chlorobenzotrifluoride, no product was observed (entry 10). Higher temperatures and longer reaction times did not improve these results.

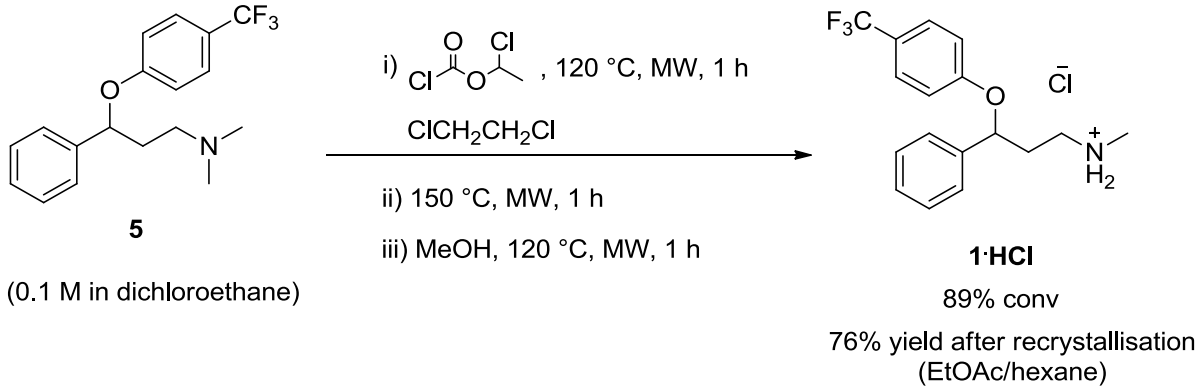
Satisfyingly, when the *O*-arylation reaction of **4b** was performed using the optimized conditions (entry 6, Table 2) full conversion and excellent regioselectivity were obtained after only 2 h of heating at 200 °C. A simple filtration through a plug of Celite gave Fluoxetine **1** in quantitative yield (Scheme 3).



Scheme 3 – MW assisted *O*-Arylation of **4b**.

The last step in our synthetic pathway (Scheme 1) was the *N*-demethylation of intermediate **5**. In 1984, Olofson and Senet described the use of α-chloroethyl chloroformate for the selective *N*-dealkylation of tertiary amines (Olofson et al. 1984). Some years later, in 2000, Ohkuma et al. successfully applied this methodology to the *N*-demethylation of **5** that allowed the isolation of fluoxetine hydrochloride (**1·HCl**) in 96% yield (Ohkuma et al. 2000).

After several unsuccessful attempts to reproduce Ohkuma's experiments, we decided to investigate the reaction in the ball mill and the microwave reactor. Thus, the reaction was attempted in the solid state, using both planetary and shaker ball mills, although negligible conversions (<3%) were obtained in all cases. Fortunately, the reaction could be optimized under microwave assisted heating. Thus, irradiation of **5** (120-150 ºC for 2 h) with α-chloroethyl chloroformate (4.0 eq), in dichloroethane as solvent, followed by reaction with MeOH (MW, 120 ºC, 1 h) afforded the desired Fluoxetine hydrochloride (**1·HCl**) in 89% conversion and 76% yield after recrystallization (Scheme 4). Longer reaction times did not improve the conversion of the reaction.



Scheme 4 – *N*-demethylation reaction with MW assisted heating

4. Conclusions

In summary, Fluoxetine hydrochloride (**1·HCl**) and Fluoxetine (**1**) have been obtained with an overall yield of 47% through Route A or B, respectively. The use of ball milling and microwave assisted heating implies a substantial improvement compared to the previously described synthetic methodologies based on conventional heating methods, not only by allowing higher yields and shorter reaction times, but also by reducing the amount of solvent necessary for the process and simplifying the number of technological steps in the procedure. This work expands the applicability of ball milling and microwave assisted reactions in total synthesis and opens up new possibilities for greener chemistry.

5. Acknowledgements

MMU is thanked for funding RS's scholarship. BM thanks the European Commission for a Marie Curie Career Integration Grant, the EPSRC for a First Grant and the RS for a travel grant. G. P. Howell is thanked for helpful comments on the manuscript.

6. References

Abid, M., Azam, A., 2005. Synthesis and antiamoebic activities of 1-*N*-substituted cyclised pyrazoline analogues of thiosemicarbazones. Bioorgan. Med. Chem. 13, 2213–2220.

Altman, R. A., Shafir, A., Choi, A., Lichtor, P. A., Buchwald, S. L., 2008. An improved Cu-based catalyst system for the reactions of alcohols with aryl halides. J. Org. Chem. 73, 284–286.

Andersen, J., Stuhr-Hansen, N., Zachariassen, L. G., Koldso, H., Schiott, B., Stromgaard, K., Kristensen, A. S., 2014. Molecular basis for selective serotonin reuptake inhibition by the antidepressant agent fluoxetine (Prozac). Mol. Pharmacol. 85, 703–714.

André, V., Hardeman, A., Halasz, I., Stein, R. S., Jackson, G. J., Reid, D. G., Duer, M. J., Curfs, C., Duarte, M. T., Friščić, T., 2011. Mechanosynthesis of the metallodrug bismuth subsalicylate from Bi_2O_3 and structure of bismuth salicylate without auxiliary organic ligands. Angew. Chem. Int. Ed. 50, 7858–7861.

Baig, R. B. N., Varma, R. S. 2012. Alternative energy input: mechanochemical, microwave and ultrasound-assisted organic synthesis. Chem. Soc. Rev. 41, 1559–1584.

Bonnamour, J., Métro, T.-X., Martínez, J., Lamaty, F., 2013. Environmentally benign peptide synthesis using liquid-assisted ball-milling: application to the synthesis of Leu-enkephalin. Green Chem. 15, 1116–1120.

Borah, A., Goswami, L., Neog, K., Gogoi, P., 2015. DMF dimethyl acetal as carbon source for α-methylation of ketones: a hydrogenation–hydrogenolysis strategy of enaminones. J. Org. Chem. 80, 4722−4728.

Bruckmann, A., Krebs, A., Bolm, C., 2008. Organocatalytic reactions: effects of ball milling, microwave and ultrasound irradiation. Green Chem. 10, 1131–1141.

Cablewski, T., Faux, A. F., Strauss, C. R., 1994. Development and application of a continuous microwave reactor for organic synthesis. J. Org. Chem. 59, 3408–3412.

Calow, A. D. J., Fernández, E., Whiting, A., 2014. Total synthesis of fluoxetine and duloxetine through an in situ imine formation/borylation/transimination and reduction approach Org. Biomol. Chem. 12, 6121–6127.

Cernansky, R., 2015. Chemistry: Green refill. Nature 519, 379–380.

Chang, M.-Y., Lin, C.-Y., Pai, C.-L. 2006. CAN-mediated oxidative cleavage of 4-aryl-3,4-dihydroxypiperidines. Tetrahedron Lett. 47, 2565–2568.

Cho, B. T., Kang, S. K., Kim, M. S., Ryu, S. R., An, D. K., 2006. Solvent-free reduction of aldehydes and ketones using solid acid-activated sodium borohydride. Tetrahedron, 62, 8164–8168.

Fuller, R. W., Wong, D. T., Robertson, D. W., 1991. Fluoxetine, a selective inhibitor of serotonin uptake. Med. Res. Rev. 11, 17−34.

Galitsky, C., Chan, S.-c., Worrell, E., Masanet, E., 2008. Energy efficiency improvement and cost saving opportunities for the pharmaceutical industry. An ENERGY STAR® guide for energy and plant managers. Lawrence Berkeley National Laboratory, Berkeley, California. Report LBNL-57260.

Hu, Q., Zhang, Z., Liu, Y., Imamoto, T., Zhang, W., 2015. $ZnCl_2$-Promoted asymmetric hydrogenation of β-secondary-amino ketones catalyzed by a P-chiral Rh–bisphosphine complex. Angew. Chem. Int. Ed. 54, 2260–2264.

Istanbullu, H., Erzurumlu, Y., Kirmizibayrak, P. B., Erciyas, E., 2015. Evaluation of alkylating and intercalating properties of Mannich bases for cytotoxic activity. Lett. Drug Des. Discov. 11, 1096–1106.

Jakobsen, P., Drejer, J. U. S. Patent 5,019,592, issued May 28, 1991.

James, S. L., Adams, C. J., Bolm, C., Braga, D., Collier, P., Friščić, T., Grepioni, F., Harris, K. D. M., Hyett, G., Jones, W., Krebs, A., Mack, J., Maini, L., Orpen, A. G., Parkin, I. P., Shearouse, W. C., Steed, J. W., Waddell, D. C., 2012. Mechanochemistry: opportunities for new and cleaner synthesis. Chem. Soc. Rev. 41, 413–447.

Job, G. E., Buchwald, S. L., 2002. Copper-catalyzed arylation of β-amino alcohols. Org. Lett. 4, 3703–3706.

Jones, W., Eddleston, M. D. 2014. Introductory lecture: Mechanochemistry, a versatile synthesis strategy for new materials. Faraday Discuss. 170, 9–34.

Kaiser, S., Smidt, S. P., Pfaltz, A., 2006. Iridium catalysts with bicyclic pyridine–phosphinite ligands: asymmetric hydrogenation of olefins and furan derivatives. Angew. Chem. Int. Ed. 45, 5194–5197.

Konnert, L., Reneaud, B., Figueiredo, R. M., Campagne, J.-M., Lamaty, F., Martínez, J., Colacino, E., 2014. Mechanochemical preparation of hydantoins from amino esters: application to the synthesis of the antiepileptic drug phenytoin. J. Org. Chem. 79, 10132–10142.

Konnert, L., Dimassi, M., Gonnet, L., Lamaty, F., Martínez, J., Colacino, E., 2016. Poly(ethylene) glycols and mechanochemistry for the preparation of bioactive 3,5-disubstituted hydantoins. RSC Adv 6, 36978–36986.

Liu, D., Gao, W., Wang, C., Zhang, X., 2005. Practical synthesis of enantiopure γ-amino alcohols by rhodium-catalyzed asymmetric hydrogenation of β-secondary-amino ketones. Angew. Chem. Int. Ed. 44, 1687–1689.

Mack, J., Fulmer, D., Stofel, S. Santos, N., 2007. The first solvent-free method for the reduction of esters. Green Chem. 9, 1041–1043.

Markarian, J., 2016. Reducing the environmental impact of manufacturing. Pharm. Technol. 40, 36–38.

Mathad, V. T., Ghanta, M. R., Govindan, S., Macharla, P., Nalivela, V. U.S. Patent 034860, issued September 27, 2005.

Mikhailenko, M. A., Shakhtshneider, T. P., Boldyrev, V. V., 2004. On the mechanism of mechanochemical synthesis of phthalylsulphathiazole. J. Mater. Sci. 39, 5435–5439.

Miyano, S., Lu, L. D. L., Viti, S. M., Sharpless, K. B., 1985. Kinetic resolution of racemic β-hydroxy amines by enantioselective *N*-oxide formation. J. Org. Chem. 50, 4350–4360.

Molloy, B. B., Schmiegel, K. K. U.S. Patent 4,314,081, issued February 2, 1982.

O'Brien, P., Phillips, D. W., Towers, T. D., 2002. An azetidinium ion approach to 3-aryloxy-3-aryl-1-propanamines. Tetrahedron Lett. 43, 7333–7335.

Ohkuma, T., Ishii, D., Takeno, H., Noyori, R., 2000. Asymmetric hydrogenation of amino ketones using chiral $RuCl_2$(diphophine)(1,2-diamine) complexes. J. Am. Chem. Soc. 122, 6510–6511.

Rajagopal, R., 2014. Sustainable value creation in the fine and speciality chemicals industry. John Wiley & Sons Ltd.

Rej, R. K., Das, T., Hazra, S., Nanda, S., 2013. Chemoenzymatic asymmetric synthesis of fluoxetine, atomoxetine, nisoxetine, and duloxetine. Tetrahedron-Asymmetr. 24, 913–918.

Roman, G., Mares, M., Nastasa, V., 2013. A novel antifungal agent with broad spectrum: 1-(4-biphenylyl)-3-(1H-imidazol-1-yl)-1-propanone. Arch. Pharm. 346, 110–118.

Sekhon, B. S., 2010. Microwave-assisted pharmaceutical synthesis: an overview. Int. J. Pharm. Tech. Res. 2, 827–833.

Shafir, A., Lichtor, P. A., Buchwald, S. L., 2007. *N*- versus *O*-Arylation of aminoalcohols: orthogonal selectivity in copper-based catalysts. J. Am. Chem. Soc. 129, 3490–3491.

Shalbaf, H., 2010. Reduction of aldehydes and ketones with $NaBH_4/Al_2O_3$ under solvent-free conditions. Asian J. Chem. 22, 6761–6764.

Siddappa, R. K. G., Chang, C.-W., Chein, R.-J., 2014. From precursor to catalyst: the involvement of $[Ru(\eta5\text{-}Cp^*)Cl_2]_2$ in highly branch selective allylic etherification of cinnamyl chlorides. Tetrahedron Lett. 55, 1031–1035.

Srivastava, S., Bhandari, K., Shankar, G., Singh, H. K., Saxena, A. K., 2004. Synthesis, anorexigenic activity and QSAR of substituted aryloxypropanolamines. Med. Chem. Res. 13, 631–642.

Tan, D., Štrukil, V., Mottillo, C., Friščić, T., 2014. Mechanosynthesis of pharmaceutically relevant sulfonyl-(thio)ureas. Chem. Commun. 50, 5248–5250.

Tan, D.; Loots, L., Friščić, T., 2016. Towards medicinal mechanochemistry: evolution of milling from pharmaceutical solid form screening to the synthesis of active pharmaceutical ingredients (APIs). Chem. Commun. 52, 7760–7781.

Vorogushin, A. V., Huang, X. H., Buchwald, S. L., 2005. Use of tunable ligands allows for intermolecular Pd-catalyzed C−O bond formation. J. Am. Chem. Soc. 127, 8146–8149.

Wagner, R. in Microwave-assisted synthesis in the pharmaceutical industry a current perspective and future prospects. Drug Discovery World, July 2006.

Wirth, D. D., Miller, M. S., Boini, S. K., Koenig, T. M., 2000. Identification and comparison of impurities in fluoxetine hydrochloride synthesized by seven different routes. Org. Proc. Res. Devel. 4, 513−519.

Wolter, M., Nordmann, G., Job, G. E., Buchwald, S. L., 2002. Copper-catalyzed coupling of aryl iodides with aliphatic alcohols. Org. Lett. 4, 973–976.

Wu, X. X., Fors, B. P., Buchwald, S. L., 2011. A single phosphine ligand allows palladium-catalyzed intermolecular C-O bond formation with secondary and primary alcohols. Angew. Chem. Int. Ed. 50, 9943–9947.

Xu, W., Langer, R., 2015. Probing the effect of heterocycle-bonding in PNX-type ruthenium pre-catalysts for reactions involving H_2. Dalton Trans. 44, 16785–16790.