Supplementary Information (SI) for Green Chemistry.
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Supplementary Material

Comparison of greenness and whiteness of selected mechanochemical and solution-based reactions using a new RGBsynt model

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1. Mechanochemical and in-solution synthesis procedures

General chemical methods

All commercially available reagents were of the highest purity, they were obtained from Fluorochem (Fluorochem Ltd, Hadfield, UK), Acros Organics (Thermo Fisher Scientific, Geel, Belgium), AmBeed (Ambeed, Inc., Arlington Heights, IL, USA) and Sigma-Aldrich (Merck Life Science Sp.z.o.o., Poznań, Poland) . All mechanochemical reactions were carried out in a vibratory ball-mill Retsch Mixer Mill MM 400 (Retsch GmbH, Haan, Germany) operated at 30 Hz. Reactions were conducted in stainless steel or PTFE jars with a volume of 10 mL or 35 mL, containing one stainless steel ball (ϕ_{ball} = 1.5 cm). Milling load is defined as the sum of the mass of the reactants per free volume in the jar and was equal to 15, 45 or 90 mg/ml. Total mass of reagents used was 125 mg (10 mL jar) or alternatively 500 mg, 1.5 g or 3 g (in 35 mL jar). All of the reactions using vibratory ball-mill were performed under air and ambient temperature.

HPLC analysis were performed by using Arc HPLC Core System (Waters Corporation, Milford, MA, USA) equipped with a UV/Vis Waters 2998 PDA spectrophotometric detector. Spectra were analyzed in 200-800 nm range with 1.2 nm resolution. Chromatographic separations were carried out using a Chromolith SpeedROD RP 18 column; 4.6 × 50 mm and 1.7 µm particle size. The column was maintained at 40°C, and eluted under gradient conditions from 95% to 0% of eluent A over 3 min, at a flow rate of 3 mL/min. Eluent A was water/formic acid (0.1%, *v*/*v*); eluent B was acetonitrile/formic acid (0.1%, *v*/*v*).

Mass spectra were recorded using a UPLC-MS/MS system consisted of a Waters Acquity Premier coupled to a Waters Xevo TQ-S Cronos mass spectrometer (electrospray ionization mode ESI). Chromatographic separations were carried out using the Acquity UPLC BEH (bridged ethylene hybrid) C18 column; 2.1 × 100 mm, and 1.7 µm particle size, equipped with Acquity UPLC BEH C18 VanGuard pre-column; 2.1 × 5 mm, and 1.7 µm particle size. The column was maintained at 40°C, and eluted under gradient conditions from 95% to 0% of eluent A over 10 min, at a flow rate of 0.3 mL/min. Eluent A was water/formic acid (0.1%, *v*/*v*); eluent B was acetonitrile/formic acid (0.1%, *v*/*v*). Chromatograms were recorded using Waters eλ PDA detector. Spectra were analysed in 200-500 nm range with 1.2 nm resolution and sampling rate 20 points/s. MS detection settings of Waters Xevo TQ-S Cronos mass spectrometer were as follows: source temperature 150°C, desolvation temperature 350°C, desolvation gas flow rate 600 L/h, cone gas flow 100 L/h, capillary potential 3.00 kV, cone potential 30 V. Nitrogen was used both as nebulizing and drying gas. The data were obtained in a scan mode ranging from 50 to 1000 m/z in 0.5 s time intervals. Data acquisition software was MassLynx V 4.2 (Waters).

^{1}H-NMR spectra were recorded using a JEOL JNM-ECZR500 RS1 (ECZR version) at 500 MHz (JOEL Ltd., Tokyo, Japan), respectively, and reported in ppm using deuterated solvent for calibration ($CDCl_3$ or DMSO-d_6).

Melting points (Mp) were determined with M-560 Büchi apparatus and are uncorrected.

General procedure for the mechanochemical *O*-alkylation of phenols with epichlorohydrin

Reactions were performed accordingly to previously reported procedure.[1] Different substituted phenol (1 equiv.) and previously grinded K_2CO_3 (3 equiv.) were introduced in a 35 mL PTFE jar (milling load 10 mg/mL) with one stainless steel ball (ϕ_{ball} = 1.5 cm). Then epichlorohydrin (1.2 equiv.) was added. The reaction was carried out for 140 minutes at rt. The mixture was solubilized in CH_2Cl_2 (15 mL) and the organic phase was washed with 2N NaOH aqueous solution (3 × 5 mL) saturated NaCl solution (1 × 5 mL), dried over Na_2SO_4 and finally filtered and concentrated under reduced pressure.

General procedure for the in-solution *O*-alkylation of phenols with epichlorohydrin

Reactions were performed accordingly to previously reported procedure.[2] Different substituted phenol (1 equiv.) and previously grinded K_2CO_3 (2.5 equiv.), KOH (0.5 equiv.) were suspended in 20 ml of acetone, Next, epichlorohydrin (2 equiv.) was slowly dropped to the mixture which was stirred at 60°C for 24 hours. Then, the inorganic residues were filtered off and the mixture concentrated under vacuum followed by re-solubilization in CH_2Cl_2 (20 ml) and washed with 2N NaOH aqueous solution (3 × 7 mL) and saturated NaCl solution (1 × 7 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude product was purified on silica gel with ethyl acetate/hexane (1/9, *v*/*v*) as eluting system.

General procedure for the mechanochemical *N*-alkylation of Boc-protected 4-aminopiperidine with oxirane

Reaction was performed accordingly to previously reported procedure.[1] 2-[([1,1'-Biphenyl]-2-yloxy)methyl] oxirane (424.5 mg, 1.88 mmol, 1 equiv.) and Boc-*N*-4-aminopiperidine (375.5 mg, 1.88 mmol, 1 equiv.) were introduced in a 35 mL PTFE jar (milling load 25 mg/mL) with one stainless steel ball ($\varnothing_{ball}$ = 1.5 cm) followed by addition of EtOH (80 µL, η = 0.1 µL·mg^{-1}) as liquid assistant. The reaction was carried out for 70 minutes at rt. Then, the product was solubilized in ethyl acetate (30 mL) and the organic phase was washed with $KHSO_4$ aqueous solution at pH = 3.5 (3 × 10 mL), saturated NaCl solution (1 × 10 mL), dried over Na_2SO_4 and finally filtered and concentrated under reduced pressure yielding compound *tert*-butyl {1-[3-([1,1'-biphenyl]-2-yloxy)-2-hydroxypropyl]piperidin-4-yl}carbamate as white powder (704.3 mg, yield 88%).

General procedure for the in-solution *N*-alkylation of Boc-protected 4-aminopiperidine with oxirane

Reaction was performed accordingly to previously reported procedure.[2] 4-Boc-*N*-aminopiperidine (0.85 g, 4.24 mmol, 1.2 equiv.) was dissolved in EtOH (15 mL), followed by addition of 2-[([1,1'-biphenyl]-2-yloxy)methyl] oxirane (0.8 g, 3.54 mmol, 1 equiv.) and the mixture was stirred under reflux for 4 hours. Inorganic residues were filtered off and organic mixture was concentrated under reduced pressure. The obtained crude product was purified using silica gel column chromatography with CH_2Cl_2/MeOH (9/1, *v*/*v*) as an eluting system yielding compound tert-butyl {1-[3-([1,1'-biphenyl]-2-yloxy)-2-hydroxypropyl]piperidin-4-yl}carbamate as white powder (1.17 g, yield = 78%).

General procedure for the mechanochemical *N*-alkylation of Boc-protected alicyclic diamines with (aryloxy)ethylbromide

Reactions were performed accordingly to previously reported procedure.[3] Commercially available alkylating agent 7-(2-bromoethoxy)-2,2-dimethyl-2,3-dihydrobenzofuran (1 equiv.) and Boc-protected alicyclic diamine (1.2 equiv.) were introduced in two 35 mL PTFE jars (milling load 15 mg/mL) with one stainless steel ball (φ_{ball} = 1.5 cm), followed by the addition of previously ground K_2CO_3 (3 equiv.) and KI (0.5 equiv.). The reaction was carried out for 210 min at rt. Then, the product was solubilized in CH_2Cl_2 (25 mL), and the organic phase was washed with $KHSO_4$ aqueous solution at pH = 3.5 (3 × 10 mL) and saturated NaCl solution (1 × 10 mL), dried over Na_2SO_4, and finally filtered and concentrated under reduced pressure.

General procedure for the in-solution *N*-alkylation of Boc-protected alicyclic diamines with (aryloxy)ethylbromide

Reactions were performed accordingly to previously reported procedure.[4] Commercial and Boc-protected alicyclic diamine (1 equiv.) was dissolved in acetone (15 ml). Then K_2CO_3 (3 equiv.) and catalytic amount of KI were added followed by dropwise addition of 7-(2-bromoethoxy)-2,2-dimethyl-2,3-dihydrobenzofuran (1.2 equiv.). The reaction was refluxed for 24 h. Inorganic residues were filtered off and organic mixture was concentrated under reduced pressure. The obtained crude product was purified using silica gel with CH_2Cl_2/MeOH as an eluting system.

General procedure for the mechanochemical nucleophilic aromatic substitution of (arylsulfonyl)isoindolines with piperazine

Reactions were performed accordingly to previously reported procedure.[5] Different substituted(arylsulfonyl)isoindolines (1 equiv.) and anhydrous piperazine (3 equiv.) were introduced in a 10 mL stainless steel jar (milling load 10 mg/mL) with one stainless steel ball (φ_{ball} = 1.5 cm) followed by the addition of MeCN (34 µL, η = 0.4 µL mg^{-1}) or DMSO (42 µL, η = 0.54 µL mg^{-1}) as a liquid assistant. The reaction was carried out for 1.5 h at 50 °C or 80 °C. After the addition of cold water (5 mL), the resulting mixture was transferred into a filtration funnel, washed with distilled water, and dried under reduced pressure. The products were purified via crystallization in ethanol.

General procedure for the in-solution nucleophilic aromatic substitution of (arylsulfonyl)isoindolines with piperazine

Different substituted (arylsulfonyl)isoindolines (1 equiv.) and anhydrous piperazine (6 equiv.) were solubilized in DMSO (8 mL). The reaction was carried out for 3 days at 90 °C. After the addition of cold water (10 mL), the resulting mixture was transferred into a filtration funnel, washed with distilled water, and dried under reduced pressure. The crude mixture was purified using silica gel column chromatography with CH_2Cl_2/MeOH (9/1, *v*/*v*).

General procedure for the mechanochemical sulfonylation of aliphatic primary amines with arylsulfonyl chlorides

Reactions were performed accordingly to previously reported procedure.[1,3] Aliphatic primary amine (1 equiv.), arylsulfonyl chloride (1 equiv.), and previously grinded K_2CO_3 (1 or 2 equiv.) were introduced in a 35 mL PTFE jar (milling load 15 or 25 mg/mL) with one stainless steel ball ($\varnothing_{ball}$ = 1.5 cm). The reaction was carried out for 1–5 min at rt. Then, the crude mixture was solubilized in ethyl acetate (25 mL) and the organic phase was washed with $KHSO_4$ aqueous solution at pH = 3.5 (3 × 10 mL), saturated NaCl solution (1 × 10 mL), dried over Na_2SO_4 and finally filtered and concentrated under vacuum.

General procedure for the mechanochemical sulfonylation of alicyclic secondary amines with arylsulfonyl chlorides

Reactions were performed accordingly to previously reported procedure.[5] Isoindoline derivative (1 equiv.), different fluoro-substituted benzenesulfonyl chloride (1.1 equiv.), and NaOH (3 equiv.) were introduced in a 35 mL SS jar (milling load 10 mg/mL) with one SS ball (φ_{ball} = 1.5 cm). The reaction was carried out for 5–7 min at rt. The mixture was transferred into a filtration funnel, washed with distilled water, and dried under reduced pressure.

General procedure for the in-solution sulfonylation of aliphatic primary and secondary amines with arylsulfonyl chlorides

Reactions were performed accordingly to previously reported procedure.[2] A mixture of amine (1 equiv.) in CH_2Cl_2 (4 mL), and TEA (3 equiv.) was cooled down (ice bath), and selected arylsulfonyl chloride (1.2 equiv.) was added in one portion. The reaction mixture was stirred for 2 hours under cooling. Then, the solvent was evaporated, and the crude mixture was purified using silica gel column chromatography with CH_2Cl_2/MeOH as an eluting system.

Newly developed procedure for the mechanochemical *O*-alkylation of 1-naphthol with epichlorohydrin

1-Naphthol (152.28 mg, 1.056 mmol, 1 equiv.) and sodium tert-butoxide (152.26 mg, 1.584 mmol, 1.5 equiv.) were introduced in 35 mL stainless steel jar, charged with a stainless steel ball (φ_{ball} = 1.5 cm), and milled for 15 minutes. Subsequently epichlorohydrin (195.45 mg, 2.113 mmol, 2 equiv.) and K_2CO_3 (2 g) were added (milling load = 75 mg/mL) and milled for 90 minutes at room temperature. The resulting mixture was then solubilized in ethyl acetate (15 mL) and the organic layer was washed with 2M NaOH solution (3 × 5 mL), saturated solution of NaCl (2 × 3 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure yielding 2-[(naphthalen-1-yloxy)methyl]oxirane as yellow oil (181.89 mg, yield = 86%).

Synthesis procedure for the in-solution *O*-alkylation of 1-naphthol with epichlorohydrin

Reaction was performed accordingly to previously reported procedure.[6] Transfer 7.2 g (0.05 mol) of 1-naphthol, 5 g KOH to a round-bottom flask and add ethanol/H_2O (9:1), the mixture was stirred for 30 min at room temperature. After dissolution, add dropwise 12 mL (0.15 moles) epichlorhydrin slowly in 45 min and stirring was continued at room temperature for 7 h. The reaction is left under magnetic stirring at room temperature for 45 min. TLC is carried out in an eluent system (hexane/ethyl acetate 9:1) to monitor the end of the reaction. The reaction was finished with H_2O (50 mL) and extracted with chloroform (2×75 mL). The combined organic layers

were washed with water (5×100 mL) and sodium hydroxide solution (2×30 mL), and dried over sodium sulfate. Remove ethanol by vacuum evaporator and to give the glycidyl-α-naphthyl ether in 96% yield. Extract aqueous phase with ethyl ether. The ethyl ether extract is dried with anhydrous sodium sulfate. Filter and remove solvent to obtain the crude brown oil

Newly developed procedure for the mechanochemical *N*-alkylation of propan-2-amine with 2-[(naphthalen-1-yloxy)methyl]oxirane for obtaining propranolol

2-[(Naphthalen-1-yloxy)methyl]oxirane (229.28 mg, 1.145 mmol, 1 equiv.), propan-2-amine (270.72 mg, 4.580 mmol, 4 equiv.) and NaCl (0.75 g) were introduced in 35 mL stainless steel jar (milling load = 38 mg/mL), charged with a stainless steel ball (φ_{ball} = 1.5 cm), and milled for 90 minutes at room temperature. Then, a second and third portion of isopropylamine was added and reaction was left milling for another 90 minutes. Next, the resulting mixture was solubilized in saturated solution of $NaHCO_3$ (6 mL) and extracted with ethyl acetate (3 × 6 mL). The organic layer was washed with saturated solution of NaCl (2 × 3 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure yielding 1-(isopropylamino)-3-(naphthalen-1-yloxy) propan-2-ol (propranolol) as white powder (279.14 mg, yield = 94%).

Synthesis procedure for the in-solution *N*-alkylation of propan-2-amine with 2-[(naphthalen-1-yloxy)methyl]oxirane for obtaining propranolol

Reaction was performed accordingly to previously reported procedure.[7] 1.05 g of 2-[(Naphthalen-1-yloxy)methyl]oxirane dissolved in 10 mL of methanol was added to 15 mL of propan-2-amine (12 mM) and stirred at 45°C until obtaining the yellow-brown solution (48 h) and solution was cooled to 5°C. Then, 1.5 ml of HCl (2 M) was dropped slowly into the resulting mixture, followed by adding NaOH (2 M) until white precipitate appeared. The precipitate was washed by water, isolated by CC using a mixture of hexane/ethyl acetate (1/1, *v*/*v*). Finally, 0.738 g of 1-(isopropylamino)-3-(naphthalen-1-yloxy) propan-2-ol (compound 2) or propranolol was collected (yield = 54%).

Newly developed procedure for the mechanochemical *N*-alkylation of 1-benzo[*b*]thien-4-yl-piperazine with 7-(4-chlorobutoxy)quinolin-2(*1H*)-one for obtaining brexpiprazole

1-Benzo[*b*]thien-4-yl-piperazine hydrochloride (243.53 mg, 0.956 mmol, 1 equiv.), 7-(4-chlorobutoxy)quinolin-2(*1H*)-one (240.60 mg, 0.956 mmol, 1 equiv.) KI (15.87 mg, 0.096 mmol, 0.1 equiv.), and K_2CO_3 (2 g) were introduced in 35 mL stainless steel jar (milling load = 75 mg/mL), charged with a stainless steel ball (φ_{ball} = 1.5 cm), and milled for 90 minutes at room temperature. The resulting powder was washed with water (4 × 10 mL). The residue was suspended in mixture of ethanol, water and glacial acetic acid (2/3/0.05, *v*/*v*/*v*) and heated until completely dissolved. After cooling the clear liquid was poured into 10 mL of 5% NaOH solution, than the suspension was filtered and dried to obtain pure product (7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-quinolin-2(*1H*)-one, brexpiprazole) as white powder (389.57 mg, yield = 94%).

Synthesis procedure for the in-solution *N*-alkylation of 1-benzo[*b*]thien-4-yl-piperazine with 7-(4-chlorobutoxy)quinolin-2(*1H*)-one for obtaining brexpiprazole

Reaction was performed accordingly to previously reported procedure.[8] To a stirred suspension of 1-(1-benzothiophen-4-yl)piperazine hydrochloride (10.12 g, 0.040 mol), K_2CO_3 (6 g, 0.042 mol), and KI (7 g, 0.042 mol) in DMF (80 mL) was added 7-(4-chlorobutoxy)quinolin-2(*1H*)-one (10.0 g, 0.040 mol) at room temperature. The reaction mass temperature was raised to 70 °C and maintained for 10 h. When reaction completion was observed by TLC/HPLC, the reaction was quenched by addition of water (50 mL). The solid thus precipitated was filtered and washed with water. The crude product was purified in a mixture of CH_2Cl_2 and ethyl acetate, and the isolated solid was further purified by acid−base extraction. The purified product was dried in a vacuum oven at 60 °C to afford 7-{4-[4-(1-benzothiophen-4-yl)piperazin-1-yl]butoxy}-quinolin-2(*1H*)-one (brexpiprazole) as a white solid (14.9 g, yield = 84%).

Newly developed procedure for the mechanochemical nucleophilic aromatic substitution to obtain key intermediate for the synthesis of vortioxetine

1-Fluoro-2-nitrobenzene (72.26 mg, 0.512 mmol, 1 equiv.), 1-Boc-piperazine (286.18 mg, 1.536 mmol, 3 equiv.) and K_2CO_3 (141.56 mg, 1.024 mmol, 2 equiv.) were introduced in 35 mL stainless steel jar (milling load = 15 mg/mL), charged with a stainless steel ball (φ_{ball} = 1.5 cm), and milled for 180 minutes at room temperature. The resulting mixture was then solubilized in ethyl acetate (15 mL) and the organic layer was washed with water (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure yielding *tert*-butyl 4-(2-nitrophenyl)piperazine-1-carboxylate as yellow solid (149.54 mg, yield = 95%).

Synthesis procedure for the in-solution nucleophilic aromatic substitution to obtain key intermediate for the synthesis of vortioxetine

Reaction was performed accordingly to previously reported procedure.[9] *N*-Boc-piperazine (2.64g, 14.20 mmol, 2 equiv.) and potassium carbonate (1.96g, 14.20 mmol, 2 eg) were suspended in dry DMSO (40 mL). The corresponding fluoronitrobenzene (1.00g, 7.10 mmol, 1 equiv.) was added and the suspension was refluxed at 80 ◦C for 72 h. The reaction mixture was cooled to ambient temperature and acidified with 2 N HCl to a pH of 1. Phases were separated. The aqueous phase was extracted with diethyl ether. The organic phases were combined, washed with ice water and brine, dried over anhydrous sodium sulfate and filtered. The solvent was evaporated in vacuo yielding the pure products as orange oil (2.07 g (95%)).

Newly developed procedure for the mechanochemical sulfonylation of 2-aminopyridine with 4-nitrobenzenesulfonyl chloride to obtain key intermediate for the synthesis of sulfapyridine

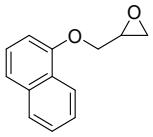
Pyridin-2-amine (94.50 mg, 1.004 mmol, 1 equiv.), 4-nitrobenzenesulfonyl chloride (289.25 mg, 1.305 mmol, 1.3 equiv.) and K_2CO_3 (416.26 mg, 3.012 mmol, 3 equiv.) were introduced in 35 mL stainless steel jar (milling load = 24 mg/mL), charged with a stainless steel ball (φ_{ball} = 1.5 cm), and milled for 15 minutes. The resulting powder was suspended in 10 mL of 5% HCl solution and then was filtered. The remaining residue was washed with water (2 × 10 mL) to yield desired 4-nitro-*N*-(pyridin-2-yl)benzenesulfonamide as yellow powder (241.13 mg, yield 86%).

Synthesis procedure for the in-solution sulfonylation of 2-aminopyridine with 4-nitrobenzenesulfonyl chloride to obtain key intermediate for the synthesis of sulfapyridine

Reaction was performed accordingly to previously reported procedure.[10] A solution of benzenesulfonyl chloride (2.64 g, 12 mmol) was slowly added under an ice bath to a solution of 2-aminopyridine (0.94 g, 10 mmol) in pyridine. The mixture was stirred at room temperature for 1 h. Ice water was added and the mixture was stirred vigorously until a large amount of solid was precipitated. After filtration, the crude product was obtained with yellow solid (yield 73.0%)

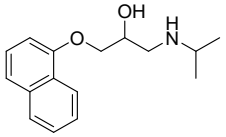
2. Characterization data for compounds synthesized by newly reported mechanochemical protocols

2-[(Naphthalen-1-yloxy)methyl]oxirane [CAS: 2461-42-9]



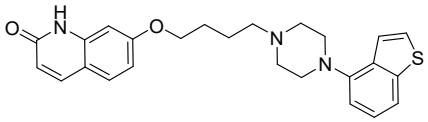
Yellow oil (181.89 mg, yield 86%). Molecular formula: $C_{13}H_{12}O_2$, MW: 200.24; monoisotopic mass: 200.08. UPLC/MS: t_R = 7.15 min, purity = 99%, $[M+MeCN+H]^+$ = 242.2 ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm 2.85 (dd, *J* = 4.9, 2.7 Hz, 1H), 2.96 (t, *J* = 4.6 Hz, 1H), 3.49 (ddt, *J* = 5.6, 4.0, 2.9 Hz, 1H), 4.14 (dd, *J* = 11.0, 5.6 Hz, 1H), 4.39 (dd, *J* = 11.0, 3.1 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 7.34–7.38 (m, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.47–7.52 (m, 2H), 7.77–7.82 (m, 1H), 8.28–8.33 (m, 1H). Data in agreement with literature.[6]

1-(Isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol (Propanolol) [CAS: 525-66-6]



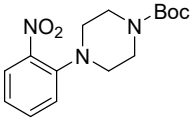
White powder (279.14 mg, yield 94%). Molecular formula: $C_{16}H_{21}NO_2$, MW: 259.35; monoisotopic mass: 259.16. UPLC/MS: t_R = 4.94 min, purity = 99%, $[M+H]^+$ = 260.3. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm 1.12 (dd, *J* = 6.2, 1.4 Hz, 6H), 2.83–2.98 (m, 4H), 3.01 (dd, *J* = 12.2, 3.4 Hz, 1H), 4.10–4.15 (m, 1H), 4.17–4.22 (m, 2H), 6.82 (d, *J* = 7.6 Hz, 1H), 7.33–7.38 (m, 1H), 7.41–7.45 (m, 1H), 7.45–7.50 (m, 2H), 7.77–7.81 (m, 1H), 8.22–8.25 (m, 1H). Mp: 97–99 °C. Data in agreement with literature.[7]

7-{4-[4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(*1H*)-one (Brexpiprazole) [CAS: 913611-97-9]



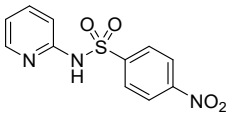
White powder (389.57 mg, yield 94%). Molecular formula: $C_{25}H_{27}N_3O_2S$, MW: 433.57; monoisotopic mass: 433.18. UPLC/MS: t_R = 5.46 min, purity = 99%, $[M+H]^+$ = 434.2. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm 1.72–1.80 (m, 2H), 1.84–1.92 (m, 2H), 2.51–2.57 (m, 2H), 2.73 (br. s., 4H), 3.19 (br. s., 4H), 4.10 (t, *J* = 6.3 Hz, 2H), 6.52–6.56 (m, 1H), 6.80 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 6.87–6.90 (m, 1H), 7.23–7.28 (m, 1H), 7.36–7.38 (m, 1H), 7.39–7.45 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 9.4 Hz, 1H), 12.50 (br. s., 1H). Mp: 180–182 °C. Data in agreement with literature.[8]

Tert-butyl 4-(2-nitrophenyl)piperazine-1-carboxylate [CAS: 170017-73-9]



Orange oil (149.54 mg, yield 95%). Molecular formula: $C_{15}H_{21}N_3O_4$, MW: 307.35; monoisotopic mass: 307.15. UPLC/MS: t_R = 9.52 min, purity = 97%, $[M+H]^+$ = 308.2. ^{1}H-NMR (500 MHz, $CDCl_3$) δ ppm 1.46 (s, 9H), 3.00 (br. s., 4H), 3.53–3.61 (m, 4H), 7.08 (d, *J* = 0.8 Hz, 1H), 7.13 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.44–7.51 (m, 1H), 7.77 (dd, *J* = 8.1, 1.6 Hz, 1H). Data in agreement with literature.[9]

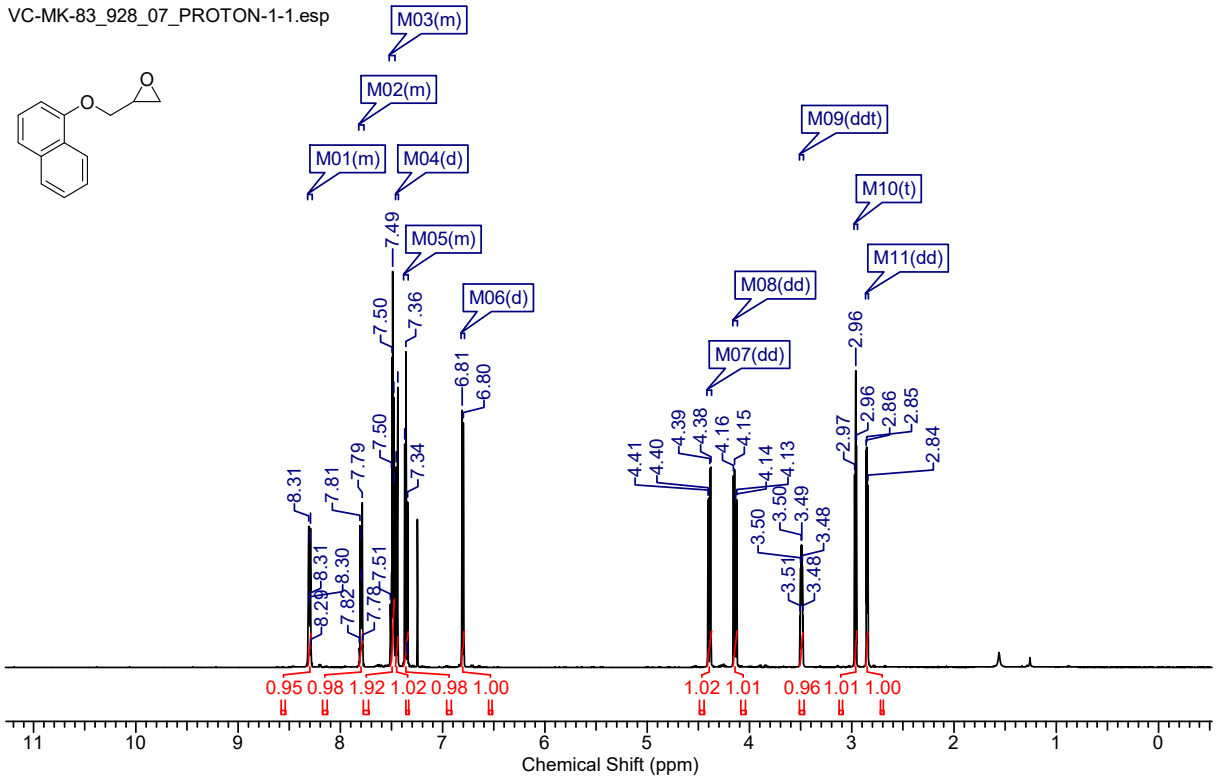
4-Nitro-*N*-(pyridin-2-yl)benzenesulfonamide [CAS: 1028-11-1]



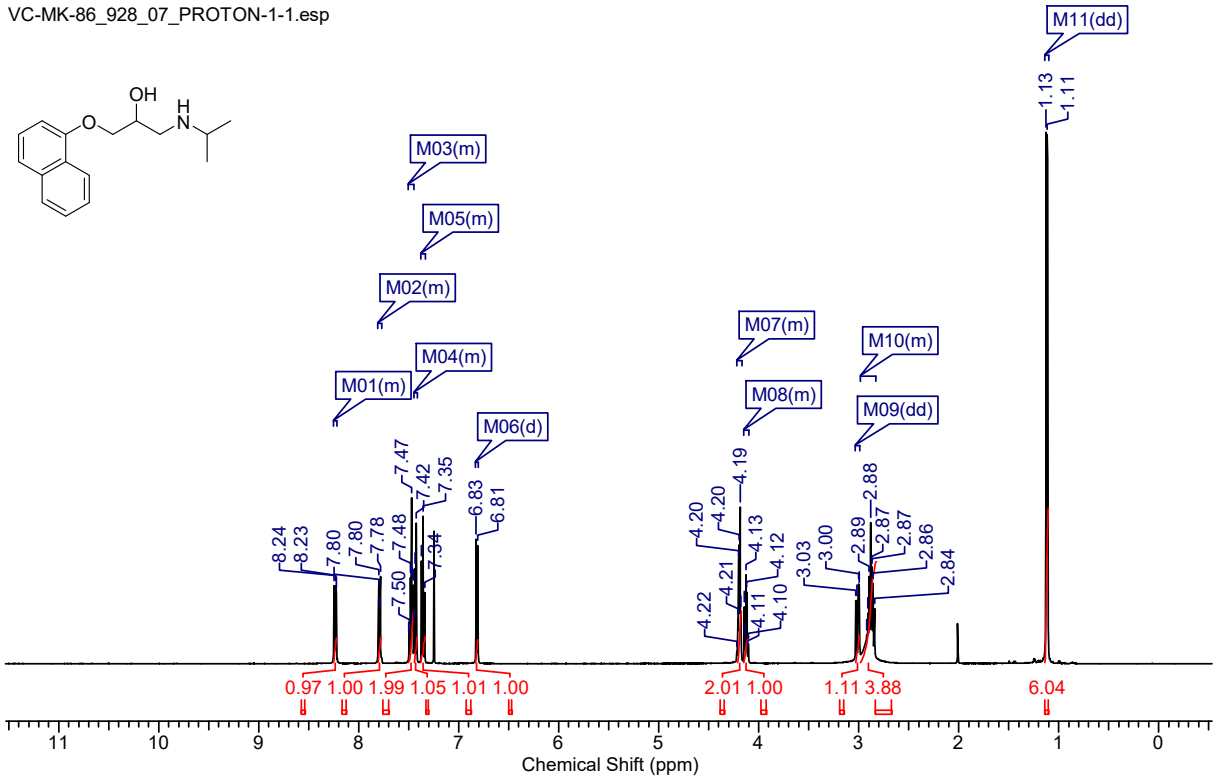
Yellow powder (241.13 mg, yield 86%). Molecular formula: $C_{11}H_9N_3O_4S$, MW: 279.27; monoisotopic mass: 279.03. UPLC/MS: t_R = 4.78 min, purity = 100%, $[M+H]^+$ = 280.1. ^{1}H-NMR (500 MHz, DMSO-d_6) δ ppm 6.83 (br. s., 1H), 7.23 (d, *J* = 6.5 Hz, 1H), 7.78 (br. s., 1H), 7.91 (br. s., 1H), 8.05 (d, *J* = 6.4 Hz, 2H), 8.30 (d, *J* = 6.7 Hz, 2H),12.99 (br. s., 1H). Mp: 183–184 °C. Data in agreement with literature.[10]

3. ^{1}H-NMR spectra of newly synthesized compounds using mechanochemistry

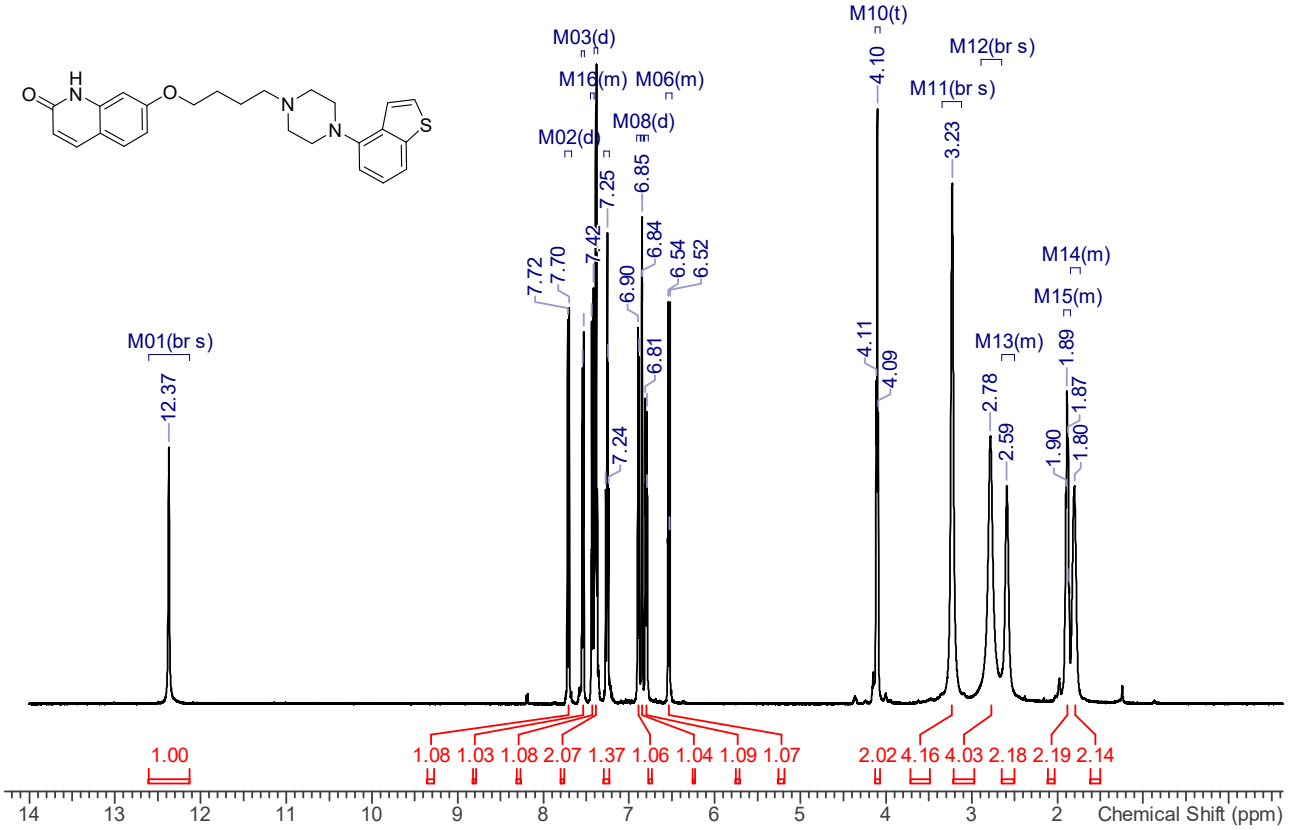
2-[(Naphthalen-1-yloxy)methyl]oxirane (500 MHz, $CDCl_3$)



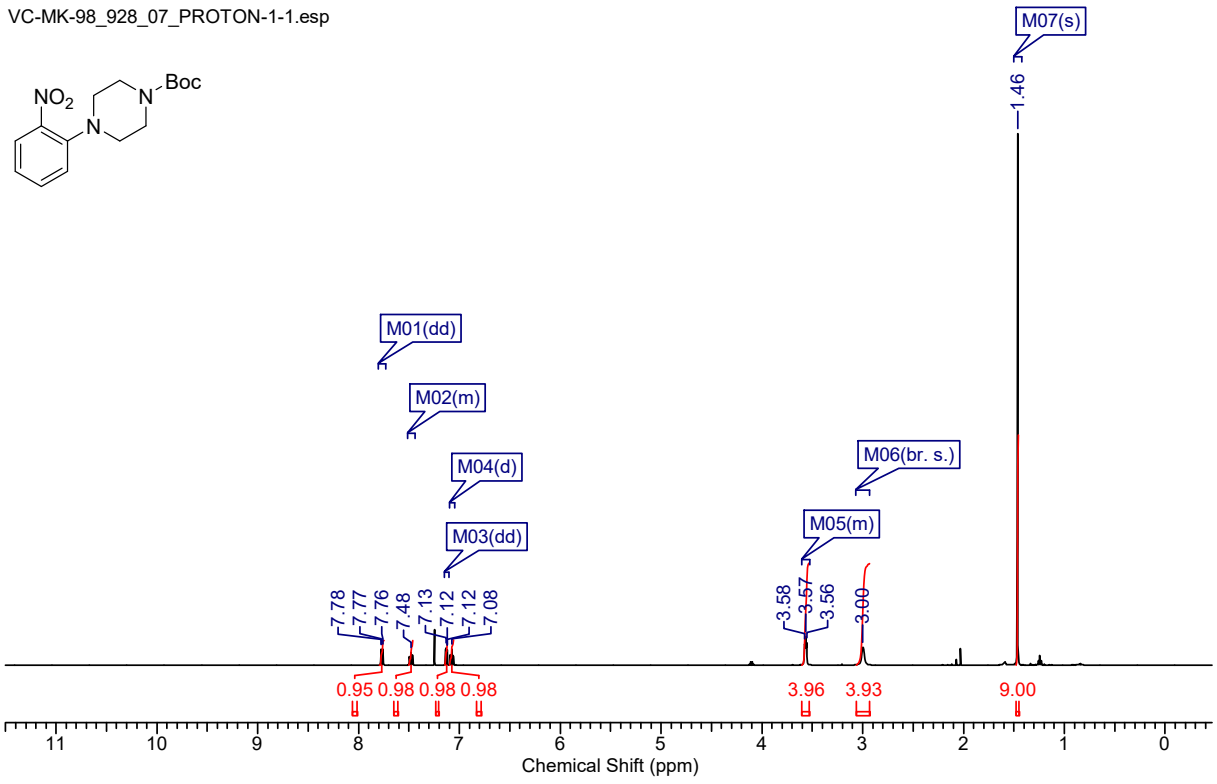
1-(Isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol (Propanolol, 500 MHz, $CDCl_3$)



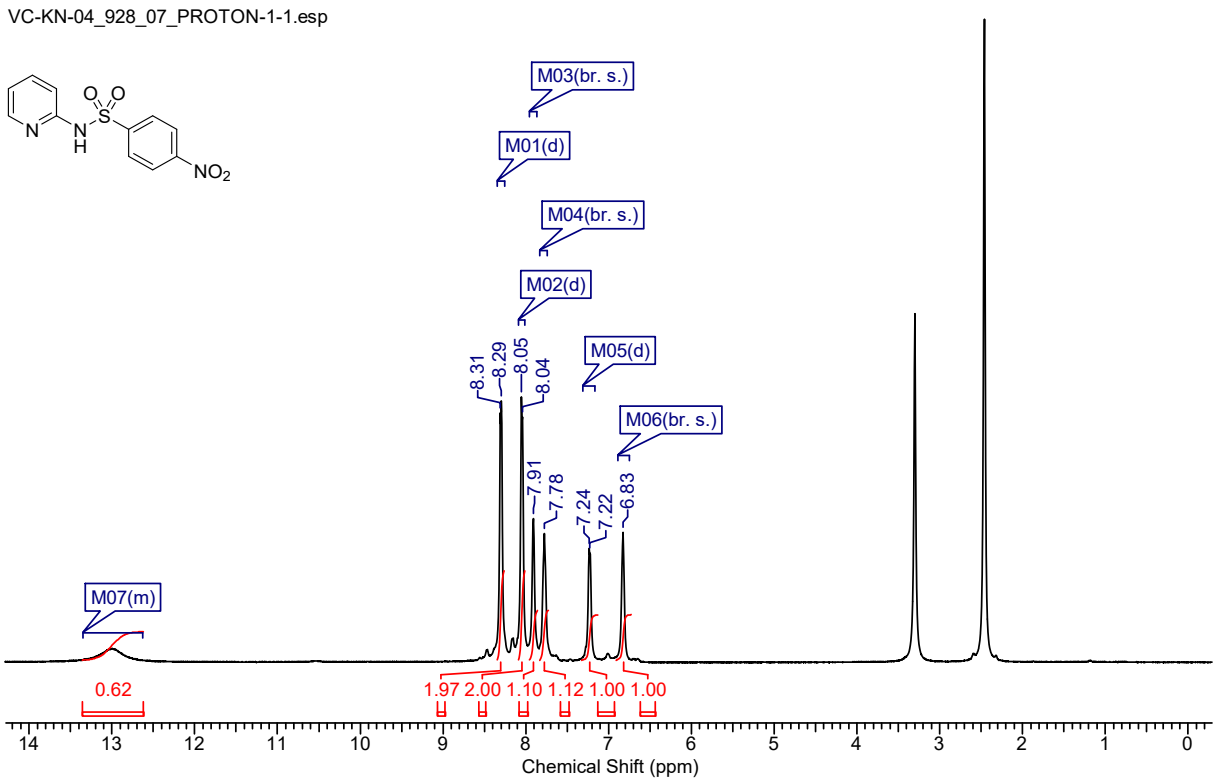
7-{4-[4-(Benzo[*b*]thiophen-4-yl)piperazin-1-yl]butoxy}quinolin-2(*1H*)-one (Brexpiprazole, 500 MHz, $CDCl_3$)



Tert-butyl 4-(2-nitrophenyl)piperazine-1-carboxylate (500 MHz, $CDCl_3$)

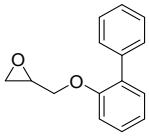
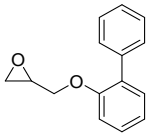
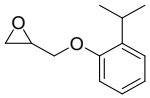
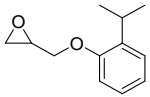
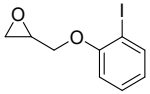
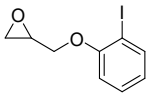
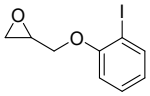


4-Nitro-*N*-(pyridin-2-yl)benzenesulfonamide (500 MHz, DMSO-d_6)



4. Data related to the literature study

Table 1-SI. Literature review on reaction conditions for the alkylation of 2-substituted phenols with epichlorohydrine in solution.

Products	Reagents (equiv.)	Solvent	Temp./time	Isolation procedure	Yields	Scale	Reference
	phenol (1) epichlorohydrine (12) tetramethylammonium chloride(0.01) NaOH (1)	DMSO/ Toluene (1/4, *v*/*v*)	100 °C/1 h	Dilution (hexane and DCM) Acidification with 1M HCl Washing (H_2O) Concentration	90	119.64 g	[11]
	phenol (1) epichlorohydrine (3) NaOH (1.2)	EtOH	20 °C/9.5 h	Concentration Extraction (EtOAc) Washing with brine Column chromatography hexane/EtOAc (2/1, *v*/*v*)	88	6.61 g	[12]
	phenol (1) epichlorohydrine (2) K_2CO_3 (4)	Acetone	80 °C/16 h	Filtration Column chromatography petroleum ether/acetone (100/1, *v*/*v*)	81	-	[13]
	phenol (1) epichlorohydrine (4) tetra(n-butyl)ammonium hydrogensulfate (0.04) NaOH (8.3)	H_2O	25 °C/18 h	Extraction (EtOAc) Concentration Column chromatography	12	176 mg	[14]
	phenol (1) epichlorohydrine (3) NaOH (1.4)	H_2O	50 °C/2.5 h	Extraction (DCM) Concentration Distillation	75	4.5 g	[15] [16]
	phenol (1) epichlorohydrine (1.5) NaOH (1.6)	H_2O	25° C/16 h	Extraction ($CHCl_3$) Washing with H_2O Concentration Distillation	45	2.5 g	[17]
	phenol (1) epichlorohydrine (5) NaH (1.1)	DMF	70 °C/2 h	Concentration Dissolution ($CHCl_3$) Washing with 10% NaOH, H_2O and brine	80	20.0 g	[18]

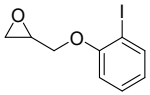
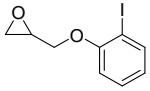
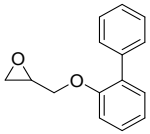
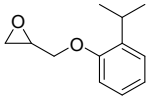
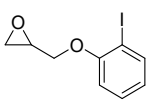
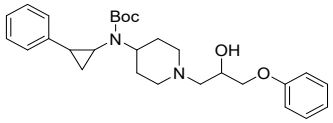
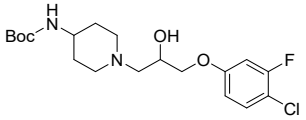
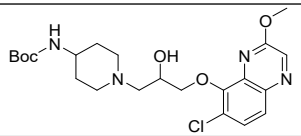
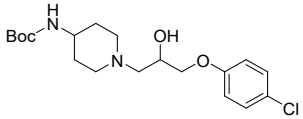
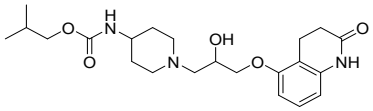
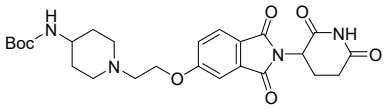
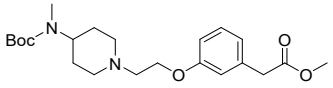
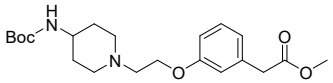
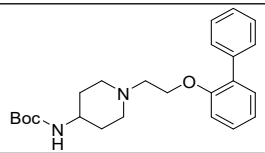
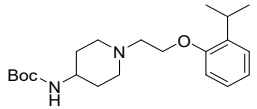
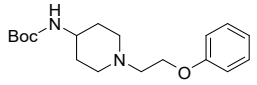
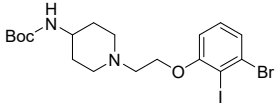
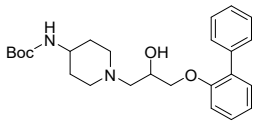
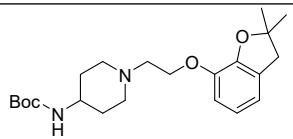
				Concentration Distillation			
	phenol (1) epichlorohydrine (2) Cs_2CO_3 (1.2)	ACN_{anh}	70 °C/12 h	Dilution (H_2O) Extraction (Et_2O) Washing with brine Concentration Column chromatography (hexane)	-	-	[19]
	phenol (1) epichlorohydrine (3) NaOH (1.4)	H_2O	50 °C /1.5 h	Dilution (H_2O) Extraction (EtOAc) Washing with brine Concentration Column chromatography Petroleum ether/EtOAc (78/22, *v*/*v*)	38	9.6 g	[20]
arithmetic mean					63.71		
geometric mean					54.71		
median					77.50		
	Phenol (1) Epichlorohydrine (2) K_2CO_3 (2.5) KOH (0.5)	Acetone	60 °C/24 h	Filtration Condensation Dissolution (DCM) Washing with 2M NaOH aqueous solution and brine Concentration Column chromatography EtOAc/hexane (1/9, *v*/*v*)	62	0.82 g	In-house protocol[1]
	phenol (1) epichlorohydrine (2) K_2CO_3 (2) KI (0.015)	Acetone	60 °C/24 h	Filtration Condensation Column chromatography EtOAc/hexane (1/9, *v*/*v*)	40	0.56 g	In-house protocol[2]
	phenol (1) epichlorohydrine (2) K_2CO_3 (2) KI (0.015)	Acetone	60 °C/24 h	Filtration Condensation Column chromatography EtOAc/hexane (1/9, *v*/*v*)	65	0.82 g	In-house protocol[2]

Table 2-SI. Literature review on reaction conditions for the *N*-alkylation of secondary amines in solution

Products	Reagents (equiv.)	Solvent	Temp./time	Isolation procedure	Yields	Scale	Reference
	Oxirane (1) Amine (1) K_2CO_3 (2)	ACN	80 °C/14 h	Filtration Concentration Column chromatography PE/EtOAc (5/1, *v*/*v*)	64	400 mg	[21]
	Oxirane (1) Amine (1)	DMF	100 °C/12 h	Dilution (H_2O) Precipitation Filtration Washing with H_2O	99	1 g	[22]
	Oxirane (1) Amine (1) K_2CO_3 (2)	ACN	80 °C/72 h	Concentration Column chromatography (10% 2M NH_3 in MeOH/DCM	75	0.59 g	[23]
	Oxirane (2) Amine (1)	DMF	100 °C/12 h	Dilution (H_2O) Precipitation Filtration Washing with H_2O	73	0.7 g	[22]
	Oxirane (1.1) Amine (1)	*i*PrOH	83 °C/24 h	Diltration Dissolution (EtOH) Acidification (HCl in EtOH) Filtration Washing with ether	60	3.2 g	[24]
	Alkylating agent (1) Amine (1) K_2CO_3 (3) KI (1)	ACN	70 °C/2 h	Dilution (H_2O) Extraction (DCM Reverse phase flash column chromatography ACN/0.1% formic acid in H_2O, (0% to 100%)	70	1.402 g	[25]
	Alkylating agent (1) Amine (1.1) K_2CO_3 (1.4)	DMF	25 °C/16 h	Concentration Dissolution (H_2O and EtOAc) Extraction Washing with H_2O and brine Condensation Column chromatography	89	562 mg	[26]

	Alkylating agent (1) Amine (1) DIPEA (2)	DMF	25 °C/30 h	Dissolution (aqueous $NaHCO_3$ solution) Extraction (EtOAc) Condensation Column chromatography	70	1.12 g	[26]
	Alkylating agent (1.2) Amine (1) K_2CO_3 (3)	Acetone	60 °C/48 h	Filtration Concentration Column chromatography DCM/MeOH (9/0.7, *v*/*v*)	77	1.2 g	[27]
	Alkylating agent (1.2) Amine (1) K_2CO_3 (3)	Acetone	60 °C/48 h	Filtration Concentration Column chromatography DCM/MeOH (9/0.7, *v*/*v*)	72	0.8 g	[27]
	Alkylating agent (1.2) Amine (1) K_2CO_3 (3)	Acetone	60 °C/24 h	Filtration Concentration Column chromatography DCM/MeOH (9/0.7, *v*/ *v*)	70	3.0 g	[4]
	Alkylating agent (1.2) Amine (1) K_2CO_3 (3)	Acetone	60 °C/24 h	Filtration Concentration Column chromatography DCM/MeOH (9/0.7, *v*/*v*)	62	2.2 g	[4]
arithmetic mean					74.70		
geometric mean					73.93		
median					72.50		
	Oxirane (1) Amine (1.2)	EtOH	80 °C/4 h	Filtration Concentration Column chromatography DCM/MeOH (9/1, *v*/*v*)	78	1.17 g	[1]
	Alkylating agent (1.2) Amine (1) K_2CO_3 (3) KI (catalytic)	Acetone	70 °C/24 h	Filtration Concentration Column chromatography DCM/MeOH (9/0.7, *v*/*v*)	70	1.366 g	[4]

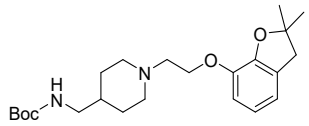
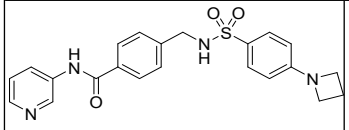
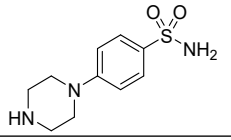
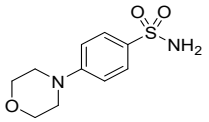
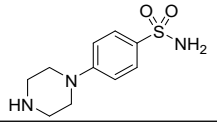
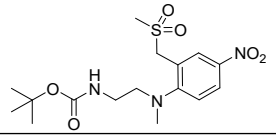
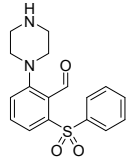
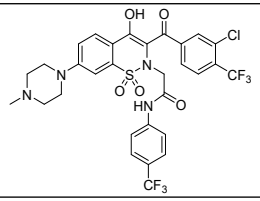
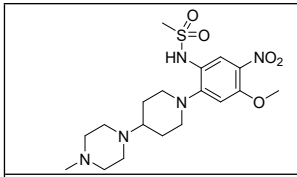
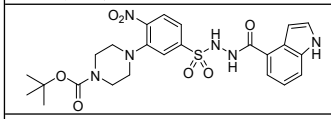
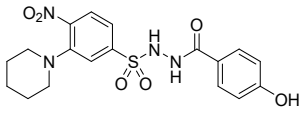
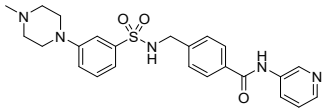
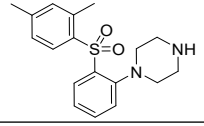
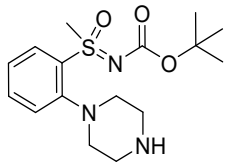
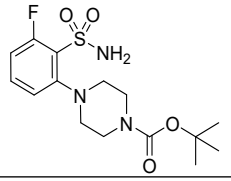
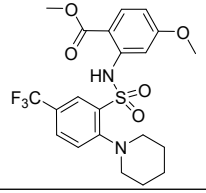
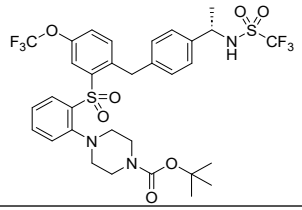
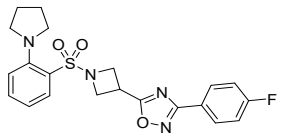
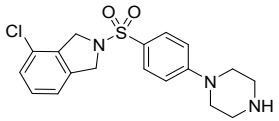
	Alkylating agent (1.2) Amine (1) K_2CO_3 (3) KI (catalytic)	Acetone	70 °C/24 h	Filtration Concentration Column chromatography DCM/MeOH (9/0.7, *v*/*v*)	77	1.454 g	[4]

Table 3-SI. Literature review on reaction conditions for the aromatic nucleophilic substitution in solution.

Product	Reagents (equiv.)	Solvent	Temp./time	Isolation procedure	Yields	Scale	Reference
	Fluoro-derivative (1) Secondary amine (7) K_2CO_3 (3)	DMA	120 °C/20 h	Precipitation with H_2O Filtration Crystallization (ACN)	64	0.2 g	[28]
	Fluoro-derivative (1), Secondary amine (4),	H_2O	100 °C/24 h	Filtration Washing with H_2O and toluene	94	32.3 g	[29]
	Fluoro-derivative (1), Secondary amine (36),	-	130 °C/72 h	Concentration Precipitation with DCM Filtration Crystallization (EtOH) Filtration	73	5.59 g	[30]
	Fluoro-derivative (1), Secondary amine (4),	H_2O	100 °C/16 h	Filtration Washing with H_2O and toluene	90	5.54 g	[31]
	Fluoro-derivative (1), Secondary amine (1.2), K_2CO_3 (1.5)	DMF_{anh}	95 °C/16 h	Dilution with H_2O Extraction with EtOAc Washing with brine Concentration	94	11.7 g	[32]
	Fluoro-derivative (1), Secondary amine (2.5), K_2CO_3 (2)	ACN	90 °C/16 h	Partial solvent evaporation Dilution with H_2O Extraction (DCM) Column chromatohraphy DCM/MeOH (15/1, *v*/*v*)	79	1.28 g	[33]
	Fluoro-derivative (1), Secondary amine (5), K_2CO_3 (3)	DMSO	80 °C/9 h	Concentration Preparative HPLC $H_2O/CH_3CN/CH_3OH$ (44/28/28 to 0/50/50, *v*/*v*)	41	47 mg	[34]

	Fluoro-derivative (1), Secondary amine (1), K_2CO_3 (2)	DMF	80 °C/16 h	Extraction with H_2O and DCM Concentration Crystallization (methyl tert-butyl ether)	53	240 mg	[35]
	Fluoro-derivative (1), Secondary amine (1.5), K_2CO_3 (2)	DMF	rt/16 h	Dilution (H_2O) Extraction (EtOAc) Column chromatography	44	1.2 g	[36]
	Fluoro-derivative (1), Secondary amine (1.2), K_2CO_3 (2.5)	MeOH	rt/16 h	Dilution with H_2O Extraction (EtOAc) Washing with brine Concentration Flash column chromatography DCM/MeOH (50/1, *v*/*v*)	51	240 mg	[36]
	Fluoro-derivative (1), Secondary amine (62)	DMSO	130 °C/72 h	Concentration Dilution (H_2O) Filtration Washing with H_2O Column chromatography 5-10% of MeOH/DCM followed by 1% aqueous NH_3/10% MeOH/DCM	33	45 mg	[37]
	Fluoro-derivative (1), Secondary amine (5), K_2CO_3 (1.2)	DMSO	100 °C/16 h	Precipitation Filtration Washing with H_2O	96	0.57 g	[38]
	Fluoro-derivative (1), Secondary amine (4)	Neat	110 °C/18 h	Dissolution (H_2O and EtOAc) Extraction (EtOAc) Washing with brine Concentration Flash column chromatography EtOAc in heptane (0% with gradient towards 100%), then MeOH in EtOAc, (0% with gradient	68	4.5 g	[39]

				towards 100%) Concentration Dissolution (DCM) Filtration Concentration			
	Fluoro-derivative (1), Secondary amine (1), DIPEA (1.5)	1,4-dioxane	110 °C/3 h	Concentration Column chromatography 0-45% MBTE in DCM	39	796 mg	[39]
	Fluoro-derivative (1), Secondary amine (3.5)	THF	60 °C/144 h	Concentration Column chromatography (0-50% EtOAc/isohexanes)	60	52 mg	[40]
	Fluoro-derivative (1), Secondary amine (8)	ACN	80 °C/88 h	preparative TLC PTLC EtOAc/hexane (1/1, *v*/*v*)	37	0.096 g	[41]
	Fluoro-derivative (1), Secondary amine (54), NaH (10)	-	80 °C/16 h	Concentration Dissolution (H_2O) Extraction (DCM) Washing with brine Flash column chromatography	16	7 mg	[42]
arithmetic mean					60.71		
geometric mean					55.33		
median					60.40		
	Fluoro-derivative (1) Secondary amine (6)	DMSO	90 °C/72 h	Dilution (H_2O) Filtration Washing (H_2O) Column chromatography (DCM/MeOH (9/1, *v*/*v*)	48	68.9 mg	in-house data

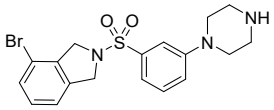
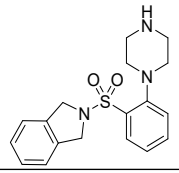
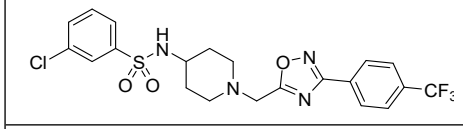
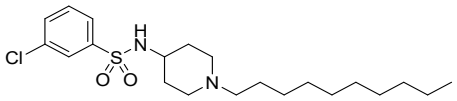
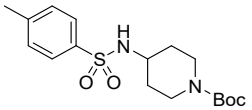
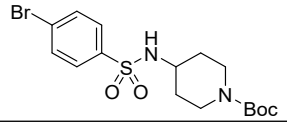
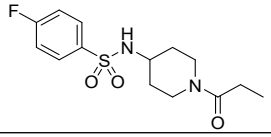
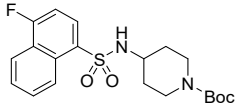
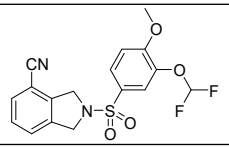
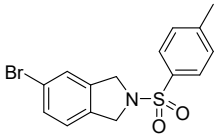
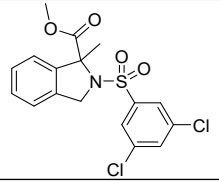
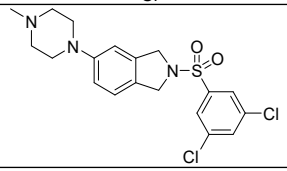
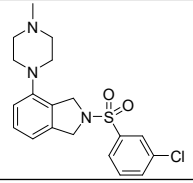
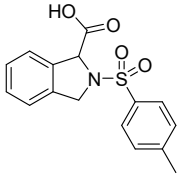
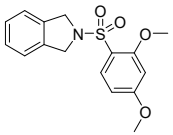
	Fluoro-derivative (1) Secondary amine (6)	DMSO	90 °C/72 h	Dilution (H_2O) Filtration Washing (H_2O) Column chromatography DCM/MeOH (9/1, *v*/*v*)	84	33 mg	in-house data
	Fluoro-derivative (1) Secondary amine (6)	DMSO	90 °C/72 h	Dilution (H_2O) Filtration Washing (H_2O) Column chromatography DCM/MeOH (9/1, *v*/*v*)	66	98.6 mg	in-house data

Table 4-SI. Literature review on reaction conditions for the sulfonylation of different primary and secondary amines in solution.

Product	Reagents (equiv.)	Solvent	Temp./time	Isolation procedure	Yields	Scale	Reference
	Primary amine (1) Arylsulfonyl chloride (1.1) TEA (3)	DCM_{anh}	25 °C/12 h	Washing with 10% citric acid solution and brine Concentration Crystallization	66	83 mg	[43]
	Primary amine (1) Arylsulfonyl chloride (1.1) TEA (3)	DCM	25 °C/48 h	Dissolution (DCM) Washing with H_2O Concentration Column chromatography DCM/MeOH MeOH (100/1, *v*/*v*)	31	186.7 mg	[44]
	Primary amine (1) Arylsulfonyl chloride (1.1) DIPEA (2)	DCM_{anh}	25 °C/10 h	Quenching (H_2O) Extraction (DCM) Washing with brine Condensation Column chromatography hexane/EtOAc (4/1, *v*/*v*)	88	468 mg	[45]
	Primary amine (1) Arylsulfonyl chloride (1) pyridine (3)	THF	25 °C/3 h	Condensation Flash column chromatography	53	550 mg	[46]
	Primary amine (1) Arylsulfonyl chloride () TEA (2)	ACN	-	-	82	-	[47]
	Primary amine (1) Arylsulfonyl chloride (1) TEA (1)	THF	25 °C/17 h	Concentration Dissolution (DCM) Washing H_2O and brine Concentration	90	15 g	[48]
	Secondary amine (1) Arylsulfonyl chloride (1) TEA (1.5)	DCM	25 °C/8 h	Concentration Column chromatography	69	1.3 g	[49]

	Secondary amine (1) Arylsulfonyl chloride (1.1) DIPEA (3) 4-DMAP (0.3)	THF/ACN (2.5/1, *v*/*v*)	25 °C/16 h	Concentration Dissolution (H_2O) Extraction (EtOAc) Washing with brine Concentration filtration with PE	94	700 mg	[50]
	Secondary amine (1) Arylsulfonyl chloride (1) DIPEA (3) 4-DMAP (0.1)	DCM/THF (1/1, *v*/*v*)	25 °C/16 h	Concentration Flash column chromatography hexane/EtOAc (20/1, *v*/*v*)	50	0.18 g	[51]
	Secondary amine (1) Arylsulfonyl chloride (1) TEA (1.8)	DCM	25 °C/16 h	Condensation Flash column chromatography EtOAc/TEA/hexane (60/1/39, *v*/*v*)	56	17 mg	[52]
	Secondary amine (1) Arylsulfonyl chloride (1.2) TEA (3)	DCM	0 °C/5 h	Condensation Preparative column chromatography DCM/MeOH (9/0.5, *v*/*v*)	85	203 mg	[53]
	Secondary amine (1) Arylsulfonyl chloride (1.1) Na_2CO_3 (2)	H_2O	25 °C/20 h	Dissolution (H_2O) Washing with EtOAc Acidification (concentrated HCl) Extraction (DCM) Concentration Preparative HPLC	10	0.047 g	[54]
	Secondary amine (2) Arylsulfonyl chloride (1) TEA (2)	ACN	25 °C/18 h	Dilution (EtOAc) Washing with 1M aqueous HCl solution, saturated $NaHCO_3$ solution and brine Concentration	-	-	[55]
arithmetic mean					64.30		
geometric mean					56.22		
median					67.20		

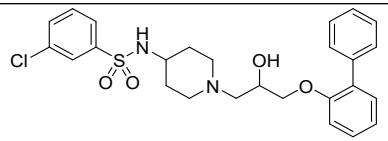
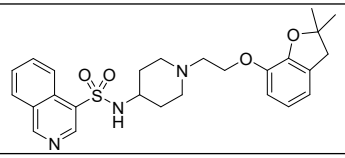
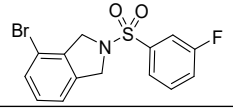
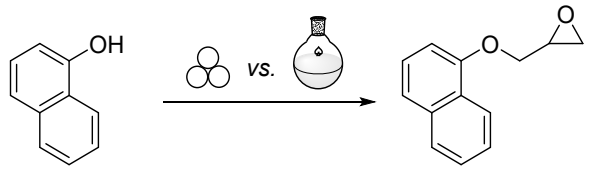
	Primary amine (1) Arylsulfonyl chloride (1.2) TEA (3)	DCM	0 °C/2 h	Concentration Column chromatography DCM/MeOH (9/0.5 *v*/*v*)	72	330 mg	In-house protocol[1]
	Primary amine (1) Arylsulfonyl chloride (1.2) TEA (3)	DCM	0 °C/2 h	Concentration Column chromatography DCM/MeOH (9/0.5 *v*/*v*)	73	242.1 mg	In-house protocol[4]
	Secondary amine (1) Arylsulfonyl chloride (1.2) TEA (3)	DCM	0 °C/2 h	Concentration Column chromatography DCM/MeOH	62	280 mg	In-house data[5]

Table 5-SI. Literature review on reaction conditions for the *O*-alkylation in the synthesis of propranolol in solution.



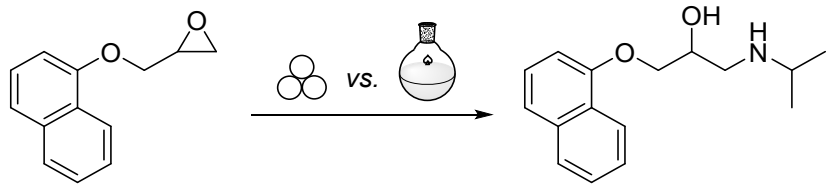
Reagents (equiv.)	Solvent	Temp./time	Isolation procedure	Yields	Scale	Reference
Phenol (1) Epichlorohydrine (2) K_2CO_3 (14) NaO*t*Bu (1.5)		r.t./1 h 45 min	Dissolution (EtOAc) Washing with 2M NaOH aqueous solution and brine Concentration	86	181.9 mg	In-house protocol
Phenol (1) Epichlorohydrine (3) KOH (2)	EtOH/H_2O (9/1, *v*/*v*)	r.t./8.5 h	Dilution (H_2O) Extraction ($CHCl_3$) Washing with H_2O and aqueous NaOH solution Concentration	96	9.62 g	[6]
Phenol (1) Epichlorohydrine (1.5) K_2CO_3 (4) NaOH (1) TBAB (0.1)	Solvent-free conditions	MW irradiation 116 °C/2 min	Dissolution Extraction (Et_2O) Washing with H_2O Concentration Flash chromatography hexane/EtOAc (10/1, *v*/*v*)	96	3.84 g	[56]
Phenol (1) Epichlorohydrine (2.5) NaOH (1.6) PEG 6000 (0.02)	H_2O	65 °C/5 h	Washing with H_2O Concentration	95	286.5 g	[57]
Phenol (1) Epichlorohydrine (3) TBAB (0.01)	ACN	reflux/5 h	Dilution (H_2O and NaOH aqueous solution) Washing with H_2O Concentration	96	-	[57]
Phenol (1) Epichlorohydrine (3.2) NaOH (1.1)	EtOH	MW irradiation 30 °C/12 min	Filtration Extraction (Et_2O) Washing with NaOH aqueous	93	12.95 g	[58]

KI (0.04)			solution and H_2O Concentration			
Phenol Epichlorohydrine K_2CO_3	Acetone	reflux/12 h	-	90	-	[59]
Phenol (1) Epichlorohydrine (1.5) K_2CO_3 (2)	2-butanone$_{anh}$	reflux/12 h	Filtration Concentration Column chromatography EtOAc/PE (1/19, *v*/*v*)	90	6.3 g	[60]
Phenol (1) Epichlorohydrine (2) KOH (1)	MeOH	60 °C /0.5 h	Washing with brine Extraction (DCM) Concentration Column chromatography hexane/EtOAc (16/1, *v*/*v*)	88	0.88 g	[61]
Phenol (1) Epichlorohydrine (1) NaH (1.1, 60% in mineral oil)	DMF$_{anh}$	60 °C /16 h	Quenching with aqueous saturated NH_4Cl solution Concentration Dispersion in H_2O Extraction (Et_2O) Washing with 1M aqueous NaOH solution and brine Concentration Flash column chromatography EtOAc/PE (40/60 to 30/70 over 10 column volumes)	88	2.44 g	[62]
Phenol (1) Epichlorohydrine (1.5) K_2CO_3 (2)	ACN	reflux/16 h	Cooling Filtration Concentration Column chromatography (EtOAc/hexane (1/19, *v*/*v*)	80	400 mg	[63]
Phenol (1) Epichlorohydrine (3) KOH (3)	DMSO	r.t./17 h	Dilution (H_2O) Extraction ($CHCl_3$) Washing with 1 N aqueous NaOH solution, H_2O and brine Condensation	78	3.26 g	[64]
Phenol (1)	H_2O	60 °C	Extraction (EtOAc)	76	19.7 g	[65]

Epichlorohydrine (3.2) NaOH (2)			Washing with brine Concentration Flash chromatography EtOAc/PE (1/10, *v*/*v*)			
Phenol (1) Epichlorohydrine (5) NaH (1.5, 60% in mineral oil)	DMF	25 °C /12 h	Dilution (H_2O) Extraction (EtOAc) Condensation Column chromatography Et_2O/hexane (3/7, *v*/*v*)	76	1.08 g	[66]
Phenol (1) Epichlorohydrine (1.2) CsF (3)	DMF_{anh}	50 °C /19.5 h	Dilution (H_2O) Precipitation Extraction (EtOAc) Concentration Filtration through silica (EtOAc/heptane (1/1, *v*/*v*) Flash column chromatography (EtOAc/heptane (1/9, *v*/*v*)	72	764 mg	[66]
Phenol (1) Epichlorohydrine (5) NaH (1.5, 60% in mineral oil)	DMF	25 °C /12 h	Dilution (H_2O) Extraction (EtOAc) Washing with brine Condensation Column chromatography Et_2O/hexane (3/7, *v*/*v*)	71	-	[67]
Phenol (1) Epichlorohydrine (1.3) NaOH (1.3)	H_2O	reflux/6 h	Extraction (Et_2O) Concentration Flash chromatography hexane/EtOAc (10/1, *v*/*v*))	69	26.25 g	[68]
Phenol (1) Epichlorohydrine (2) NaH (2)	DMF_{anh}	80 °C /5 h	Dilution (H_2O) Extraction (Et_2O) Concentration Flash chromatography EtOAc/hexane (1/9, *v*/*v*)	61	1.69 g	[69]
Phenol (1) Epichlorohydrine (4) K_2CO_3 (2)	Acetone	reflux/12 h	Filtration Concentration Dissolution (toluene) Washing with H_2O and 1 N aqueous	61	12.2 g	[70]

			NaOH solution Concentration Column chromatography ($CHCl_3$)			
Phenol (1) Epichlorohydrine (2.5) NaOH (1.5)	H_2O	85 °C /11 h	Washing with H_2O and brine Distillation	57	22.8 g	[71]
Phenol (1) Epichlorohydrine (1.2) NaH (1.3)	DMF_{anh}/THF_{anh} (5/1, *v*/*v*)	50 °C /16 h	Dilution (H_2O) Precipitation Extraction (EtOAc) Concentration Filtration through silica EtOAc/heptane (1/1, *v*/*v*) Flash column chromatography EtOAc/heptane (1/9, *v*/*v*))	50	4.0 g	[72]
Phenol (1) Epichlorohydrine (1.5) NaOH (1.2)	H_2O	r.t./5 h	Extraction (DCM) Washing with 5% aqueous NaOH solution and brine Concentration Column chromatography	34	3.4 g	[73]
Phenol (1) Epichlorohydrine (1.1) NaOH (1.2)	DMF/H_2O (2/1, *v*/*v*)	r.t./121.5 h	Extraction (DCM) Washing with H_2O Concentration column chromatography hexane/EtOAc (9/1, *v*/*v*)	11	467 mg	[74]

Table 6-SI. Literature review on reaction conditions for the *N*-alkylation in the synthesis of propranolol

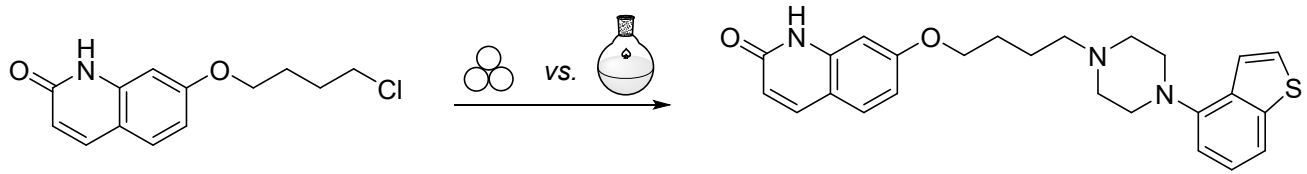


Reagents (equiv.)	Solvent	Temp./time	Isolation procedure	Yields	Scale	Reference
Oxirane (1) Isopropylamine (16) NaCl AcOH (0.1)		r.t./4.5 h	Dissolution (saturated solution of $NaHCO_3$) Extraction (EtOAc) Washing with brine Concentration	94	279.1 mg	in-house protocol
Oxirane (1) Isopropylamine (1)	H_2O	reflux/3 h	Concentration	100	78 mg	[75]
Oxirane (1) Isopropylamine (79)	H_2O	reflux/1 h	Concentration	99	384 mg	[76]
Oxirane (1) Isopropylamine (5) AcOH (0.1) H_2O (0.1)	-	r.t./8 h	Concentration	99	770 mg	[77]
Oxirane (1) Isopropylamine (2) $CaCl_2$ (1)	ACN	r.t./8 h	Dilution (H_2O) Extraction (Et_2O) Concentration Crystallization (Et_2O)	93	0.24 g	[69]
Oxirane (1) Isopropylamine (4.24)	MeOH	50 °C/12-24 h	Concentration Column chromatography (EtOAc)	93	200.6 mg	[66]
Oxirane (1) Isopropylamine (1.5) DIPEA (0.4)	Toluene	35 °C/6 h	Cooling Precipitation Filtration	93	192 g	[57]
Montmorillonite K 10 (10% *w*/*w*) Oxirane (1) Isopropylamine (1)	neat condition	r.t./1.5 h	Dilution (Et_2O) Filtration Washing with Et_2O	92	670 mg	[78]

			Concentration Column chromatography EtOAc/hexane (1/20, *v*/*v*)			
Oxirane (1) Isopropylamine (1) $CeCl_3 \cdot 7H_2O$ (0.1)	Glycerine	r.t./0.5 h	Extraction (EtOAc) Washing with H_2O and brine Concentration Column chromatography EtOAc/PE (3/7, *v*/*v*)	90	233.4 mg	[79]
Oxirane (1) Isopropylamine (2) nano Fe_3O_4 (10 mol%)	neat condition	r.t./20 h	Dilution (EtOAc) Concentration Column chromatography EtOAc/hexane (2/8, *v*/*v*)	85	220 mg	[80]
Oxirane (1) Isopropylamine (10)	DCM	r.t./30 h	Concentration Dilution (H_2O) Extraction (EtOAc) Washing with H_2O and brine Flash column chromatograph EtOAc/PE (75/25, *v*/*v*)	83	0.535 mg	[81]
Oxirane (1) Isopropylamine (11.2)	EtOH	reflux/3 h	Concentration Dissolution (DCM) Extraction with 0.2 N HCl Washing with DCM Neutralization (1 N aqueous NaOH solution) Extraction with DCM Concentration	77	214 mg	[82]
Oxirane (1) Isopropylamine (1) $Zn(ClO_4)_2 \cdot 7H_2O$ (2 mol%)	neat condition	r.t./1 h	Dilution (Et_2O) Washing with H_2O Concentration	72	189 mg	[83]
Oxirane (1) Isopropylamine (1.6) Silica gel	MW neat condition	-/0.5 h	Extraction (Et_2O) Condensation Dissolution (Et_2O) Precipitation with concentrated HCl Filtration	67	1.74 g	[56]
Oxirane (1)	MeOH	45 °C /48 h	Cooling to 5 °C	54	0.74 g	

Isopropylamine (2.3)			Precipitation with HCl (2 M) and NaOH (2 M) Washing with H_2O Column chromatography hexane/EtOAc (5/5, *v*/*v*)			[7]

Table 7-SI. Literature review on reaction conditions for the *N*-alkylation in the synthesis of brexpiprazole in solution.



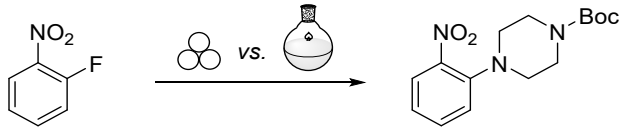
Reagents (equiv.)	Solvent	Temp./time	Isolation procedure	Yields	Scale	Reference
1-(benzo[b]thiophen-4-yl)piperazine hydrochloride (1) 7-(4-chlorobutoxy)quinolin-2(1H)-one (1) K_2CO_3 (15) KI (0.1)		r.t./1.5 h	Washing with H_2O Dissolution EtOH/ H_2O/AcOH (2/3/0.05, *v*/*v*/*v*) Precipitation (5% NaOH solution) Filtration	94	389.6 mg	In-house protocol
1-(benzo[b]thiophen-4-yl)piperazine hydrochloride (1.1) 7-(4-chlorobutoxy)quinolin-2(1H)-one (1) Na_2CO_3 (3)	H_2O/MeOH (2/1, *v*/*v*)	70 °C/16.5 h	Cooling to 0°C Filtration	96	20.7 g	[84]
1-(benzo[b]thiophen-4-yl)piperazine hydrochloride (1.1) 7-(4-chlorobutoxy)quinolin-2(1H)-one (1) K_2CO_3 (3) NaI (1)	DMF	90 °C/3 h	Dilution (H_2O) Filtration Washing with H_2O	94	80.98 g	[85]
1-(benzo[b]thiophen-4-yl)piperazine hydrochloride (1.1) 7-(4-chlorobutoxy)quinolin-2(1H)-one (1) K_2CO_3 (3) NaI (1.1)	DMF	80 °C/2 h	Precipitation with H_2O Filtration Washing Dissolution (DCM/MeOH) Concentration Column chromatography DCM/MeOH (100/3, *v*/*v*) Concentration Crystallization (EtOH)	88	13.6 g	[86]
1-(benzo[b]thiophen-4-yl)piperazine hydrochloride (1) 7-(4-chlorobutoxy)quinolin-2(1H)-one (1)	DMF	70 °C/10 h	Dilution (H_2O) Filtration Washing with H_2O	77	13.2 g	[8]

K_2CO_3 (1.1)			Dissolution (DCM) Filtration Concentration Dissolution (EtOAc) Cooling Precipitation Filtration Acid-base purification			
1-(benzo[b]thiophen-4-yl)piperazine hydrochloride (1.1) 7-(4-chlorobutoxy)quinolin-2(1H)-one (1) K_2CO_3 (1.2)	H_2O/EtOH (3/7, *v*/*v*)	reflux	Cooling to 10°C Filtration Dissolution (DCM) Washing with H_2O Concentration Dissolution in DMSO/EtOH (1/1, *v*/*v*) Filtration	82	146.29 g	[87]
1-(benzo[b]thiophen-4-yl)piperazine hydrochloride (1.1) 7-(4-chlorobutoxy)quinolin-2(1H)-one (1) K_2CO_3 (1.1) KI (1.1)	DMF	100 °C/2 h	Dilution (H_2O) Cooling to 10 °C Precipitation Filtration Washing with H_2O and EtOH Dissolution in EtOH/AcOH (13/1, *v*/*v*) Acidification (concentrated HCl) Precipitation Cooling to 10 °C Filtration Washing with EtOH Dissolution in EtOH/H_2O (1.5/1, *v*/*v*) Filtration Dissolution Neutralization (25% aqueous NaOH solution) Precipitation with H_2O Filtration	83	14.3 g	[88]

			Washing with H_2O			
1-(benzo[b]thiophen-4-yl)piperazine hydrochloride (1) 7-(4-chlorobutoxy)quinolin-2(1H)-one (1.1) $NaHCO_3$ NaI (0.5)	DMF	95 °C/7 h	Cooling Precipitation with H_2O Filtration Washing	71	120 g	[86]
1-(benzo[b]thiophen-4-yl)piperazine (1.2) 7-(4-chlorobutoxy)quinolin-2(1H)-one (1) K_2CO_3 (1.1) NaI (1.1)	DMF	90 °C/3 h	Cooling Precipitation with H_2O Filtration Washing with H_2O and EtOH Dissolution in EtOH/AcOH (8/1, *v*/*v*) Filtration Washing with EtOH Dissolution in EtOH/H_2O |(4/1, *v*/*v*) Filtration Neutralization (5% aqueous $NaHCO_3$ solution) Dilution (H_2O) Cooling Filtration Washing (H_2O)	67	23 g	[89]
1-(benzo[b]thiophen-4-yl)piperazine (1.2) 7-(4-chlorobutoxy)quinolin-2(1H)-one (1) K_2CO_3 (1.1) NaI (1.1)	DMF	95 °C/3 h	Cooling Precipitation with H_2O Filtration Washing with H_2O and EtOH Dissolution EtOH/AcOH (13.33/1, *v*/*v*) Acidification (concentrated HCl) Precipitation Cooling Filtration Washing with EtOH Dissolution in EtOH/H_2O (32/1 *v*/*v*) Filtration	64	110 g	[89]

			Neutralization (5% aqueous $NaHCO_3$ solution) Dilution (H_2O) Cooling Filtration Washing (H_2O) Dissolution (EtOH) Filtration Washing (EtOH)			
7-hydroxy-2-quinolone (1.1) 1-bromo-4-chlorobutane (1.2) 1-(benzo[*b*]thiophen-4-yl)piperazine hydrochloride (1) K_2CO_3 (2.5)	H_2O/EtOH (5/6, *v*/*v*)	reflux/11 h	Concentration Cooling to 50 °C Dissolution (EtOAc) Cooling to 20 °C Filtration Washing with EtOH	54	14.5 g	[90]

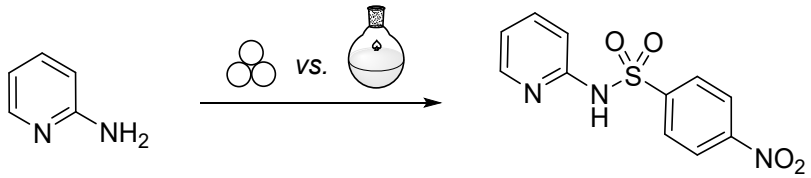
Table 8-SI. Literature review on reaction conditions for the aromatic nucleophilic substitution in the synthesis of vortioxetine intermediate in solution.

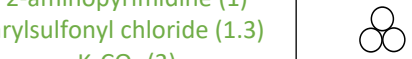


Reagents (equiv.)	Solvent	Temp./time	Isolation procedure	Yields	Scale	Reference
1-Fluoro-2-nitrobenzene (1) *N*-Boc-piperazine (3) K_2CO_3 (2)		r.t./3 h	Dissolution (EtOAc) Washing with H_2O Concentration	95	149.5 mg	In-house protocol
1-Fluoro-2-nitrobenzene (1) *N*-Boc-piperazine (1.1) K_2CO_3 (1.2)	DMF	50 °C/17 h	Dilution (H_2O) Extraction (toluene) Concentration	99	21.7 g	[91]
1-Fluoro-2-nitrobenzene (1) *N*-Boc-piperazine (1) DIPEA (1.2)	DMF	80 °C/16 h	Dilution (H_2O) Extraction (EtOAc) Washing with brine Concentration	99	10.9 g	[92]
1-Fluoro-2-nitrobenzene (1) *N*-Boc-piperazine (2) K_2CO_3 (2)	DMSO	80 °C/12 h	Dilution (Et_2O) Acidification (1 N HCl) Extraction (Et_2O)	> 95	-	[93]
1-Fluoro-2-nitrobenzene (1) *N*-Boc-piperazine (2) K_2CO_3 (2)	$DMSO_{anh}$	80 °C/72 h	Acidification (2 N HCl to a pH of 1) Extraction (Et_2O) Washing with H_2O and brine Concentration	95	2.07 g	[9]
1-Fluoro-2-nitrobenzene (1) *N*-Boc-piperazine (2) K_2CO_3 (2)	$DMSO_{anh}$	80 °C/72 h	Dilution (Et_2O) Acidification (2 N HCl to a pH of 1) Extraction (Et_2O) Washing with H_2O and brine Concentration	95	2.07 g	[94]
1-Fluoro-2-nitrobenzene (1) *N*-Boc-piperazine (1.1) Cs_2CO_3 (2)	DMF	80 °C/12 h	Concentration Column chromatography hexane/EtOAc	92	2 g	[95]
1-Fluoro-2-nitrobenzene (1)	ACN	80 °C/4 h	Dilution (H_2O)	87	0.72 g	

N-Boc-piperazine (1) K_2CO_3 (3)			Extraction (EtOAc) Concentration Flash column chromatohraphy (0-10% EtOAC in hexane)			[96]
1-fluoro-2-nitrobenzene (1) *N*-Boc-piperazine (1) K_2CO_3 (4)	ACN	80 °C/16 h	Filtration Washing with ACN Concentration	-	-	[97]

Table 9-SI. Literature review on reaction conditions for the sulfonylation in the synthesis of sulfasalazine intermediate in solution.



Reagents (equiv.)	Solvent	Temp./time	Isolation procedure	Yields	Scale	Reference
2-aminopyrimidine (1) arylsulfonyl chloride (1.3) K_2CO_3 (3)		r.t./15 min	Dissolution (5% aqueous HCl solution) Filtration Washing with H_2O	86	241.1 mg	In-house protocol
2-aminopyrimidine (1) arylsulfonyl chloride (1.2)	1,4-dioxane$_{anh}$	95 °C/15 min	Precipitation with H_2O Filtration Washing with H_2O Crystallization (80% 1,4-dioxane)	84	235.42 g	[98]
2-aminopyrimidine (1) arylsulfonyl chloride (1.2)	pyridine	25 °C/1 h	Precipitation with H_2O Filtration	73	2.04 g	[99]
2-aminopyrimidine (1) arylsulfonyl chloride (1)	DCM	25 °C/16 h	Quenching with H_2O Washing with H_2O and brine Concentration Crystallization (MeOH/DCM)	65	0.41 g	[100]
2-aminopyrimidine (1) arylsulfonyl chloride (1.5)	pyridine	0 °C/2 h	Precipitation with H_2O Filtration Crystallization (MeOH/DCM)	63	3.52 g	[10]
2-aminopyrimidine (1) arylsulfonyl chloride (2.6)	pyridine	0 °C/24 h	Filtration Washing with H_2O Crystallization EtOAc/toluene (1/3, *v*/*v*)	61	7.7 g	[101]
2-aminopyrimidine (1) arylsulfonyl chloride (1)	pyridine	80 °C/2 h	Precipitation with H_2O Filtration Washing with H_2O	60	0.76 g	[102]
2-aminopyrimidine (1) arylsulfonyl chloride (2.1)	THF/DCM (1/2, *v*/*v*)	reflux/2 h	Filtration Dissolution	47	2.79 g	[103]

TEA (2.2)			MeOH and sodium methoxide (> 10 eq) Concentration Neutralization (HCl 1 N) Precipitation Filtration Washing with H_2O			

5. Additional data on the assessment with RGBsynt

Table 10-SI. Values of the parameters used in the assessment for all compared synthesis methods.

	Procedure	R1: Yield (%)	R2: Purity (%)	G1/B1: E-factor	G2: ChlorTox (g)	B2: Time-efficiency (h)	G3/B3: Energy (EED)
				O-alkylation - mechanochemistry (Mech. O)			
old	Mech. O1	83	99	158.05	40.53	3.42	46.21
old	Mech. O2	65	100	131.43	37.19	3.42	46.21
old	Mech. O3	84	99	129.05	36.02	3.42	46.21
new	Mech. O4	86	99	119.96	25.29	2.83	42.06
	Average	**79.5**	**99.25**	**134.63**	**34.76**	**3.27**	**45.17**
				O-alkylation - in-solution (Sol. O)			
old	Sol. O1	62	96	499.70	360.04	28.25	138.19
old	Sol. O2	40	96	543.66	367.47	28.25	138.19
old	Sol. O3	65	97	498.80	359.34	28.25	132.88
new	Sol. O4	96	98	100.24	17.89	10.42	83.93
	Average	**65.75**	**96.75**	**410.60**	**276.18**	**23.79**	**123.30**
				N-alkylation - mechanochemistry (Mech. N)			
old	Mech. N1	88	97	138.39	23.72	2.25	37.50
old	Mech. N2	84	96	152.64	38.63	4.58	53.50
old	Mech. N3	81	96	152.84	38.53	4.58	53.50
new	Mech. N4	94	99	114.11	51.93	6.08	61.64
new	Mech. N5	94	99	190.78	8.26	4.17	34.71
	Average	**88.2**	**97.4**	**149.75**	**32.21**	**4.33**	**48.17**
				N-alkylation - in-solution (Sol. N)			
old	Sol. N1	78	98	728.58	352.22	8.17	74.32
old	Sol. N2	70	97	717.33	345.54	28.17	138.00
old	Sol. N3	77	95	716.42	344.88	28.17	138.00
new	Sol. N4	54	99	495.79	287.84	52.17	187.79
new	Sol. N5	77	100	84.55	51.45	16.75	106.41

	Average	**71.2**	**97.8**	**548.53**	**276.38**	**26.69**	**128.90**
			Nucleophilic aromatic substitution - mechanochemistry (Mech. SNAr)				
old	Mech. SNAr1	81	100	47.47	6.25	4.17	34.71
old	Mech. SNAr2	88	100	46.79	5.73	4.17	34.71
old	Mech. SNAr3	84	100	47.49	6.27	4.17	34.71
new	Mech. SNAr4	95	97	193.18	37.46	4.08	50.50
	Average	**87**	**99.25**	**83.73**	**13.93**	**4.15**	**38.66**
			Nucleophilic aromatic substitution - in-solution (Sol. SNAr)				
old	Sol. SNAr1	55	97	953.32	356.97	75.92	226.54
old	Sol. SNAr2	48	98	949.03	357.11	75.92	226.54
old	Sol. SNAr3	66	97	918.79	355.51	75.92	226.54
new	Sol. SNAr4	95	99	257.38	43.72	72.87	221.95
	Average	**66**	**97.75**	**769.63**	**278.33**	**75.16**	**225.39**
			Sulfonylation - mechanochemistry (Mech. S)				
old	Mech. S1	84	98	129.83	20.87	1.17	27.04
old	Mech. S2	76	99	112.37	13.93	1.17	27.04
old	Mech. S3	79	100	50.89	0.71	0.75	14.72
new	Mech. S4	86	100	104.39	2.50	1.33	19.61
	Average	**81.25**	**99.25**	**99.37**	**9.50**	**1.11**	**22.10**
			Sulfonylation - in-solution (Sol. S)				
old	Sol. S1	80	98	715.86	343.20	6.08	61.64
old	Sol. S2	73	96	741.43	362.63	6.08	61.64
old	Sol. S3	62	99	739.36	360.99	6.08	61.64
new	Sol. S4	73	97	157.49	4.37	1.83	21.64
	Average	**72**	**97.5**	**588.54**	**267.80**	**5.02**	**51.64**

6. Guidelines for the categorization of electrical instruments

The following classification of instruments is only a suggestion; depending on the circumstances and actual energy consumption parameters, it is recommended to develop own classifications. It is also possible to change the weight values (1,2,3,4), e.g. to ones that differ to a greater extent.

Table 11-SI. Energy-consumption categories of electrical instruments and examples of EED calculations

Category*	**Potential instruments****	**Example 1**	**Example 2**	**Example 3**
Low-power instruments, <100 W (weight = 1)	pH-meter, balance, magnetic stirrer without heating, rotavapor, UV lamp, portable electrophoresis system, etc.	2 instruments (pH-meter and balance), EED input: 2 x 1 = 2	2 instruments (pH-meter and balance), EED input: 2 x 1 = 2	2 instruments (pH-meter and balance), EED input: 2 x 1 = 2
Medium-power instruments, 100-250 W (weight = 2)	centrifuge, grinder, ball mill, heating bath, ultrasonic bath, vacuum pump, magnetic stirrer with heating, etc.	1 instrument (centrifuge), EED input: 1 x 2 = 2	2 instruments (centrifuge and ball mill), EED input: 2 x 2 = 4	3 instruments (centrifuge, ball mill, vacuum pump), EED input: 3 x 2 = 6
High-power instruments, 250-1000 W (weight = 3)	fume hood, large centrifuge, chiller, freezer, chromatograph, spectrophotometer, fluorimeter, large-scale electrophoresis system, small-scale mass spectrometer, small-scale GC-MS, etc.	2 instruments (fume hood and freezer), EED input: 2 x 3 = 6	3 instruments (fume hood, freezer, HPLC), EED input: 3 x 3 = 9	3 instruments (fume hood, freezer, HPLC), EED input: 3 x 3 = 9
Very high-power instruments, >1000 W (weight = 4)	NMR spectrometer, large-scale mass spectrometer, liquid chromatographs and electrophoresis systems coupled to MS detector (HPLC-MS, CE-MS), etc.			1 instrument (NMR spectrometer), EED input: 1 x 4 = 4
	Total EED input	2 + 2 + 6 = 10	2 + 4 + 9 = 15	2 + 6 + 9 + 4 = 21
	Total procedure time	1 h	1 h	2 h
	EED	$10 \times \sqrt{1} = 10$	$15 \times \sqrt{1} = 15$	$20 \times \sqrt{2} = 29.7$

* - assigned based on the approximated average electric power (W), the relationship between the weight assigned to the category and electric power is not linear to approximate the actual energy consumption - it was assumed that highly energy-intensive instruments (NMR, MS, etc.) are usually used for a shorter time than less energy-intensive ones that are the basic equipment (magnetic stirrer, heating bath, vacuum pump, etc.).
** - based on the literature[104] and our best knowledge, computers included as the integral parts of the research instrumentations.

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