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Supplementary Materials for

Digitization of multistep organic synthesis in reactionware for on-demand pharmaceuticals

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This PDF file includes:

Materials and Methods
Figs. S1 to S21
Tables S1 to S5
Caption for Movie S1

Other Supplementary Materials for this manuscript include the following:
(available at www.sciencemag.org/content/359/6373/314/suppl/DC1)

Movie S1
OpenSCAD libraries.zip
STL files.zip
Python Code

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1. General Experimental Remarks:

Solvents and reagents were used as received from commercial suppliers unless otherwise stated. Polypropylene feedstock for 3D printing was purchased from Barnes Plastic Welding Equipment Ltd., Blackburn, UK. 3D printing was achieved on an Ultimaker 2/2+ supplied by Ultimaker. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer at 298 K, and chemical shifts are reported in ppm relative to residual solvent (multiplicities are given as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, with coupling constants reported in Hz). Mass Spectra were recorded on a TOF MS (MicroTOF-Q MS) instrument equipped with an electrospray (ESI) source supplied by Bruker Daltonics Ltd. All analysis was collected in positive ion mode. The spectrometer was calibrated with the standard tune-mix to give a precision of ca.1.5 ppm in the region of m/z 100-3000. Percentage purity was assessed on a Dionex 3000 Ulitmate HPLC system comprising LPG-3400SD pump, DAD-3000 detector with a 13 μL flow cell, WPS-3000TFC analytical autosampler with fraction collector, and TCC-3000SD column thermostat, running Chromeleon 6.8. A reversed-phase C18 column (Purospher® STAR RP-18 endcapped (5 μm), 100 × 4.6 mm) was used.

2. Module / Cartridge Design and fabrication

2.1 General Remarks

All reactors used in this study were designed either using OpenSCAD open source script based 3D modeling software (www.openscad.org) or FreeCAD, open source GUI based 3D modeling software (www.freecadweb.org).The reactors were printed on Ultimaker 2 and 2+ 3D printers (https://ultimaker.com/), with nozzle diameter of 0.4 or 0.6 mm using polypropylene from a local supplier. The designs for the synthesis cartridges were exported as stereolithography (.stl) files and translated into 3D printer instruction files using software appropriate for the 3D printer, Cura (https://ultimaker.com/en/products/cura-software), a freely available 3D printer control software package developed by Ultimaker. These instruction files are then transferred to the 3D printer for fabrication. Devices were printed at 260°C on polypropylene plates to avoid warping (the use of a heating bed was unnecessary). To allow the introduction of necessary reagents, starting materials, or non-printed components the printing process was paused at pre-programmed intervals during the fabrication to allow their placement (see below). Once cartridge fabrication was complete the cartridges were flushed with a suitable inert gas (dry N_2 supplied by BOC.) and sealed prior to use.

2.2 Parametric module design

The OpenSCAD libraries used for the production of digital model files are provided as Supplementary Information. They are prefixed by "lib_" and are heavily commented. These libraries' purpose is to easily create high level objects (*e.g.* reactors, pipes, cannulas, etc.) which can be joined together *in silico* to create parametrically designed reactor / process modules. The modules / cartridges designed for these studies were composed of four libraries: lib_pipe (to create straight pipes), lib_bend_pipe (to create bent pipes), lib_canula (to connect two reactors), and lib_reactor (to create reactors). This allows modules to be created by specifying the required dimensions for a limited number of reaction parameters. The OpenSCAD command to create a cylindrical reactor is as follows (parameters are defined in table S1, below):

reactor(ed, id, h, flat_bot=false, open=false, adaptor_top=true, port_bot=true, adaptor_bot=false)

Table S1: Parameters required for the generation of a reactor module

Parameter	Units	Definition
ed	mm	Outer diameter of the reactor
id	mm	Inner diameter of the reactor
h	mm	Height of the reactor
flat_bot	true / false	Defines the bottom profile of the internal chamber; if 'true', the chamber bottom will be hemispherical in shape; if 'false' the chamber will have a flat bottom. Default set to false.
open	true / false	Defines whether the top of the chamber is open or closed. If true, the top of the reactor will be open. Default set to false.
adaptor_top	true / false	Defines the presence of an input / output port at the top of the chamber. If true and 'open' is false, creates an input at the top of the reactor. Default set to true.
port_bot	true / false	Defines the presence of an input / output port at the bottom of the chamber. If true, create a siphon output from the bottom of the reactor. Default set to true.
adaptor_bot	true / false	Defines the presence of an external port at the bottom of the chamber. If true, creates space for an adaptor at the bottom. Default set to false.

"Reactor" objects can then be modified to form the basis of a range of different modules. For example, co-axially oriented cylinders can be subtracted from main reaction volume to insert filters at defined positions. Radial-oriented cylinders (with respect to module axis) can also be subtracted from the walls of the reactor to create input holes as required by the specific synthesis requirements.

Reactors (or the modules built from them) can be connected to each other using the “cannula” and “pipe” libraries. For example, the bottom output of a reactor is connected to the input (the lowest entry point) of a transfer tube. The output of the transfer pipe will then lead to the inner volume of the next module. The OpenSCAD command to create a siphon transfer tube is as follows (parameters are defined in supplementary table S2, below):

cannula(vio, len, d, t);

Table S2: Parameters required for the generation of an inter chamber cannula

Parameter	**Units**	**Definition**
vio	mm	Vertical distance between input and output.
len	mm	Horizontal distance between input and output.
d	mm	Inner diameter of the tube.
t	mm	Thickness of the walls.

These parameters can then be defined to generate specific reactors or transfer tube objects, which can then be manipulated to produce the finalized cartridge devices (see Fig. S1).

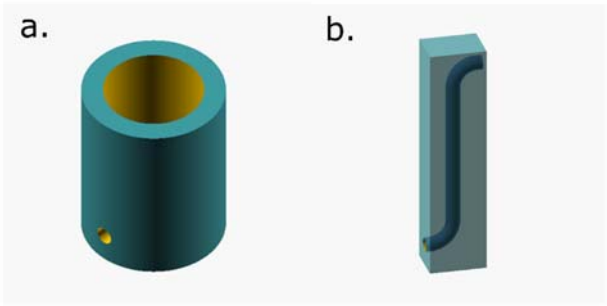


Fig. S1: OpenSCAD renderings of (a) Reactor defined by the following variables: *reactor*(ed=40, id=28, h=50, flat_bot=true, open=true, adaptor_top=true, port_bot=true, adaptor_bot=true); creating an open reactor of height 50 mm, external diameter 40 mm, internal diameter 28 mm, with a flat bottom and a siphon with space for an adaptor as an output, and (b) Transfer tube instance defined by the following variables: *cannula*(vio=40, len=10, d=3, t=3); creating a tube with 10 mm length, with an internal pipe diameter of 3 mm, and 40 mm vertical spacing between the input and the output.

Modular cartridges were 3D printed with openings to screw in standard Luer-lock connectors after tapping, and Tygon tubing (1/8 or 1/16" external diameter) were used to connect the modules. For liquid-liquid separation modules, TELOS Phase Separators (20 mm diameter) were used. For filtration modules, 20 mm glass filters (porosity 2) were used. While designing cartridges with embedded filters, a precise clearance between the filter disc and reactor walls has to be maintained to avoid leaks. We empirically found out that a filter enclosure diameter should be equal to the diameter of the filter + 0.85 mm (as set in the software), and the enclosure height should be equal to that of the filter itself. To insert filters during the 3D printing process, Cura's "Pause at Height" plugin was used, allowing the fabrication to be automatically halted at a desired point to allow the manual insertion of the non-printed component (See manuscript Fig. 4).

2.3 Baclofen Synthesis Modules

The modules designed for the translation of the end-to-end synthesis of Baclofen (see Fig. S2) are as follows:

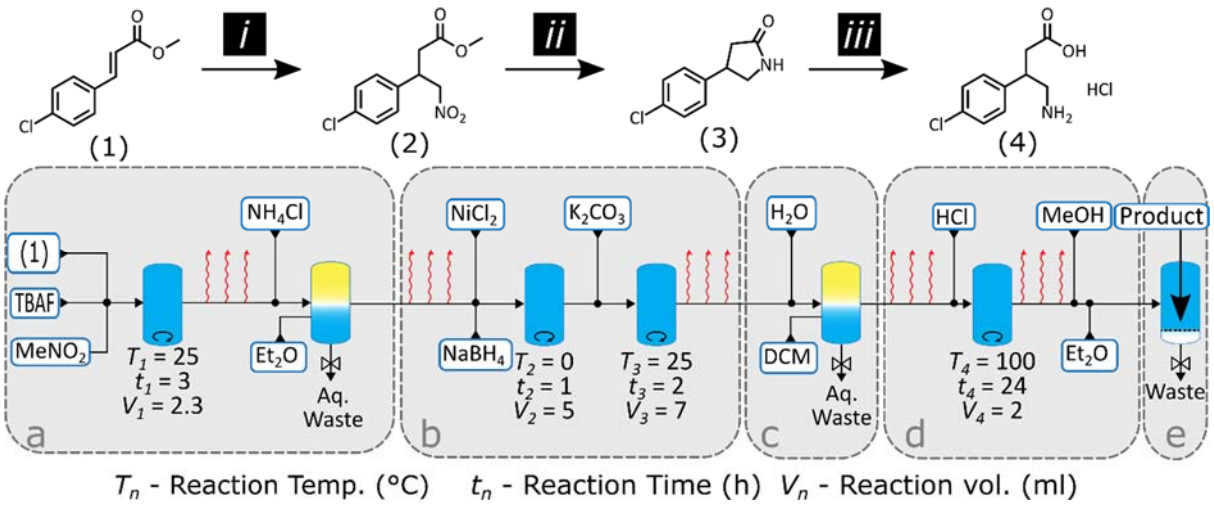


Fig. S2: Splitting of the end-to-end synthesis into five distinct multi-process modules, a – e.

2.3.1 Module (a): 1st Reaction; Concentration; Aqueous – Organic separation.

This module was based on a cylindrical, closed, round bottomed chamber with three inlet / outlet openings, one at the top of the module and two on either side of the vertical walls separated by a hydrophobic frit to achieve the necessary organic / aqueous separation. The volume below the frit was 4.9 mL and the volume above the frit was 3.2 mL. This module was designed for phase separations in which the organic layer is less dense than the aqueous layer, the mechanism for this separation is shown in Fig. S3,

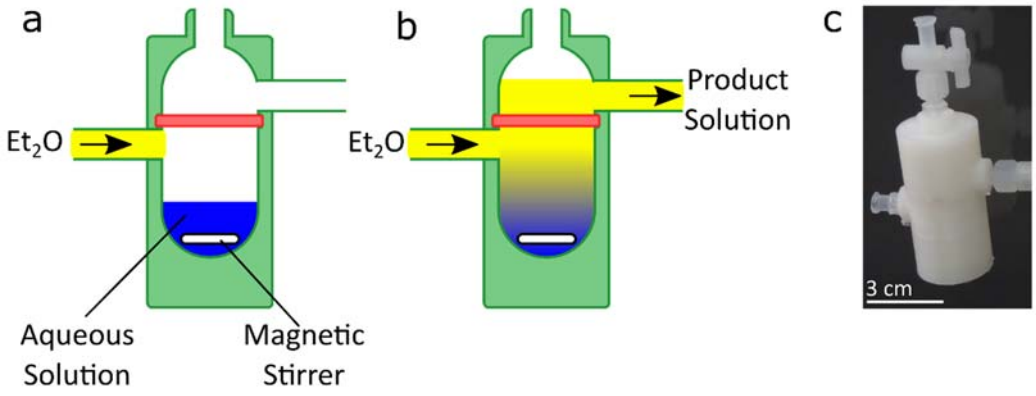


Fig. S3: Aqueous – organic phase separation mechanism of module **a**. Diethyl ether is added through the input port to mix with the aqueous phase already present under sufficient stirring to produce an efficiently mixed medium. Continuous input of solvent pushes the organic phase up through the hydrophobic frit which ensures that none of the aqueous material transfers into subsequent reaction chambers. This design was used for phase separations where the organic layer was less dense than the organic phase.

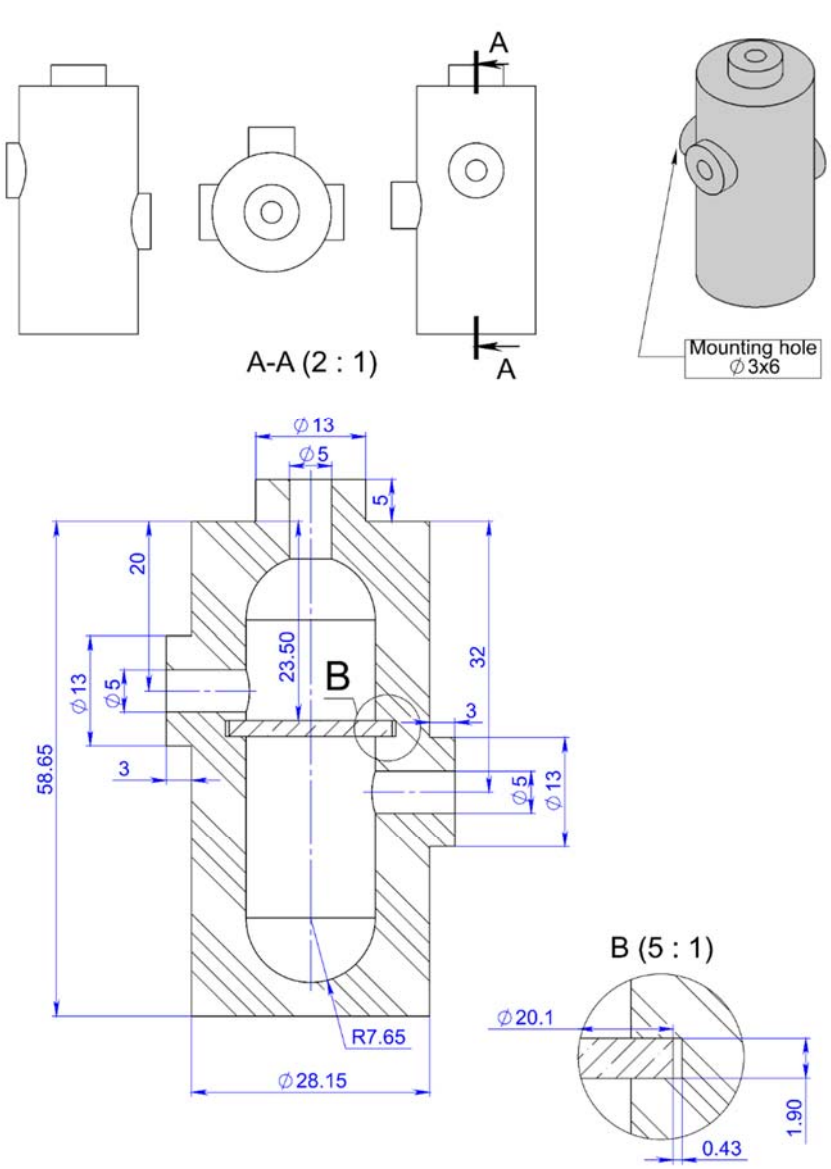


Fig. S4: Draft of module **a**. A mounting hole is included to allow the mounting of the module on racking by use of a M3 screw.

2.3.2 Module (b) & (d): Solvent removal and reactions 2 & 3.

This module was designed to have a large capacity to accommodate the excess solvent required for upstream extraction processes. It is based on a cylindrical, closed, round bottomed chamber with two inlet ports; one on the vertical wall of the chamber and one at the top of the module, and an outlet 'drain' at the bottom of the module, which consists of a bent pipe leading from the lowest point of the internal chamber to an outlet port located at the bottom of the vertical

wall of the chamber on the opposing side to the inlet port. The total volume of the chamber was 31.8 mL.

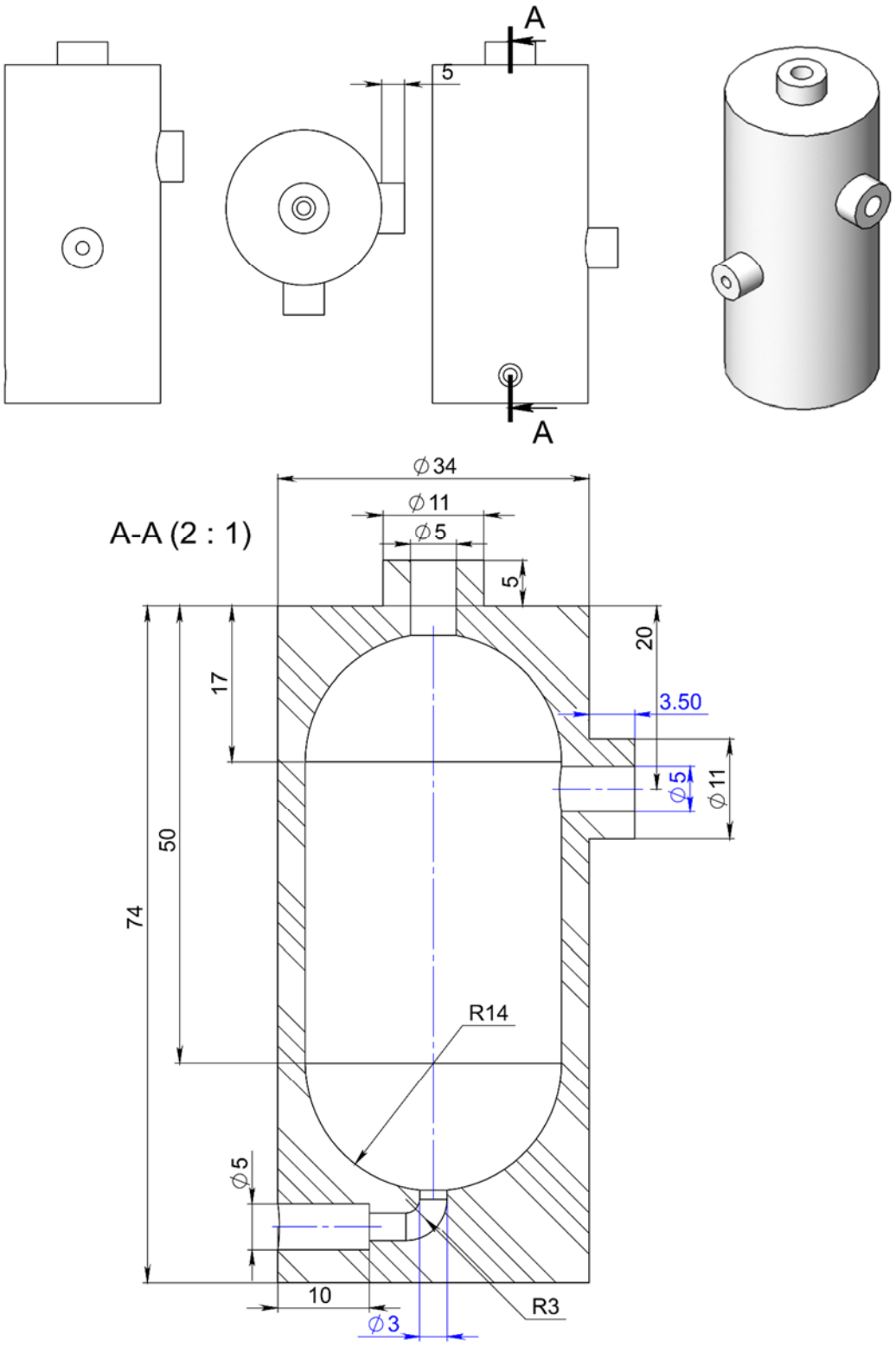


Fig. S5: Draft of modules **b** and **d**. A mounting hole is included to allow the mounting of the module on racking by use of a 3mm diameter screw.

2.3.3 Module c: Aqueous – Organic separation.

This module was based on a cylindrical, closed, round bottomed chamber with two inlet openings, one at the top of the module and one at the top of the vertical wall of the module. An outlet 'drain' at the bottom of the module consists of a bent pipe leading from the lowest point of the internal chamber to an outlet port located at the bottom of the vertical wall of the chamber on the opposing side to the inlet port. The internal chamber is divided by a hydrophobic frit placed at approximately one third of the full height of the internal chamber to achieve the necessary organic / aqueous separations. The volume below the frit was 2.1 mL and the volume above the frit was 4.7 mL. This module was designed for phase separations in which the organic layer is more dense than the aqueous layer, the mechanism for this separation is shown in Fig. S6,

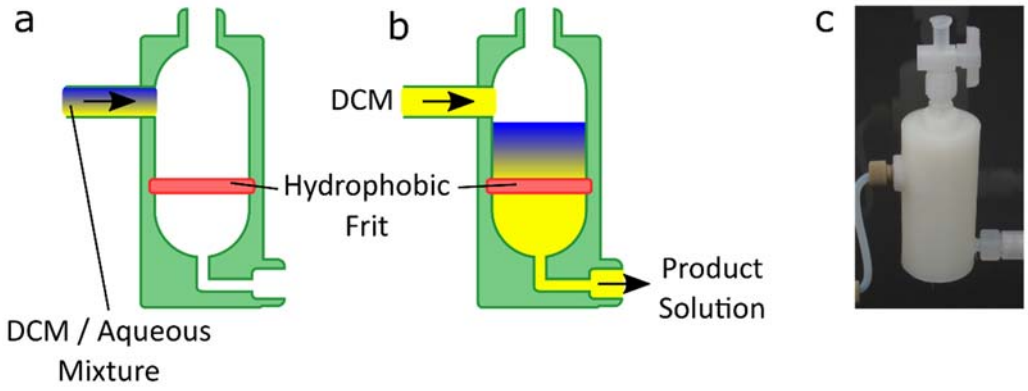


Fig. S6: Aqueous – organic phase separation mechanism of module **c**. A mixture of organic and aqueous phases are introduced. Continuous input of solvent pushes the organic phase down through the hydrophobic frit, ensuring that none of the aqueous material transfers into subsequent reaction chambers. This design was used for phase separations where the organic layer was more dense than the organic phase.

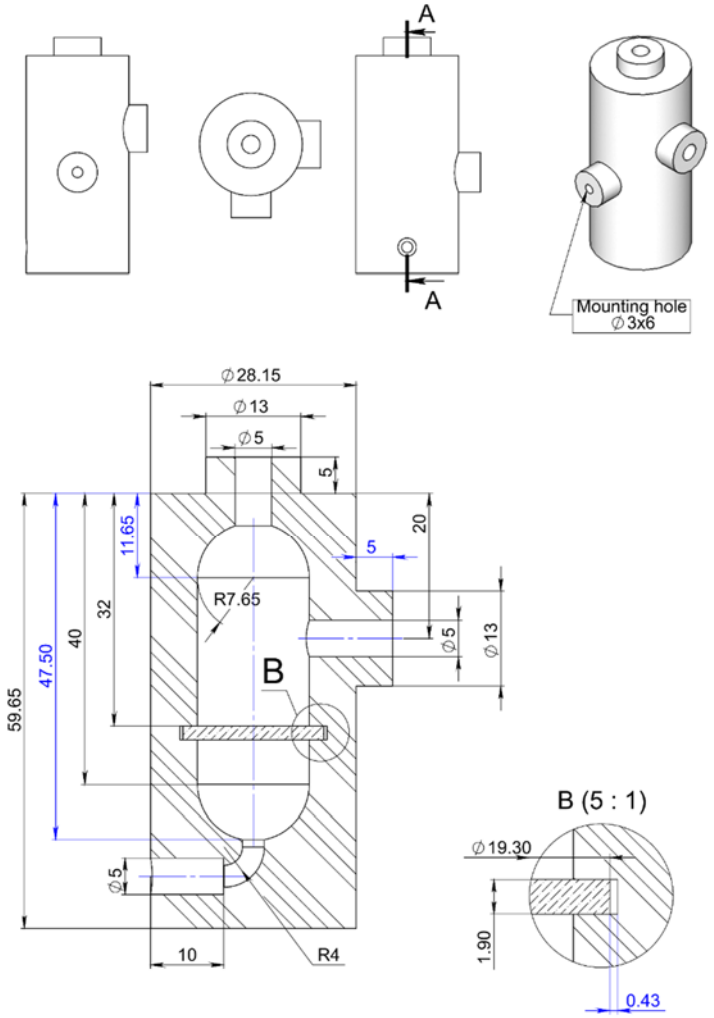


Fig. S7: Draft of module **c**. A mounting hole is included to allow the mounting of the module on racking by use of a M3 screw.

2.3.4 Module e: Filtration module.

This module was based on a cylindrical, open-topped, round bottomed chamber with one inlet opening at the top of the vertical wall of the module. An outlet 'drain' at the bottom of the module which consists of a bent pipe leading from the lowest point of the internal chamber to an outlet port located at the bottom of the vertical wall of the chamber on the opposing side to the inlet port. At the bottom of the chamber a fritted glass filter is present which is inserted during the fabrication process. The total volume of the chamber was 8.0 mL.

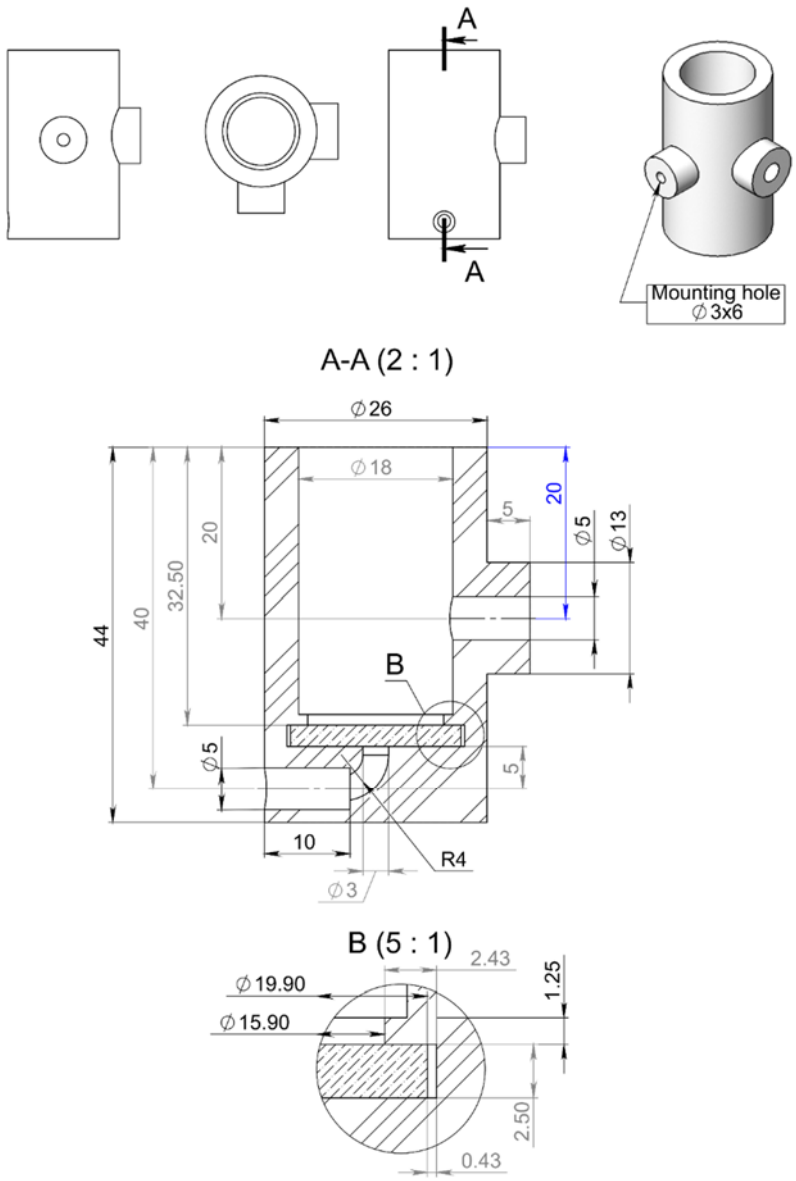


Fig. S8: Draft of module **e**. A mounting hole is included to allow the mounting of the module on racking by use of a M3 screw.

2.4 Baclofen Monolithic Synthesis Cartridge.

Once the designs for the modules necessary for the synthesis of baclofen were tested (see above), these modules were combined in OpenSCAD, with minor modifications, to produce a monolithic cartridge for the complete synthesis of baclofen. The modules were connected to each other either by directly connecting the outlet and inlet ports designed in the original modules or via siphon channels connecting drain outlets at the bottom of module to input port at the top of the subsequent module. The orientation of the inputs and outputs were rotated around the central axis of each module as required to minimise the footprint of the final

cartridge. Minor optimisations were also made based on the experience of the use of the modular system For example the space below the hydrophobic filter in module **c** was removed. The cartridge was designed such that all non-printed parts were at the same height from the base of the cartridge to minimise the number of pauses required during fabrication.

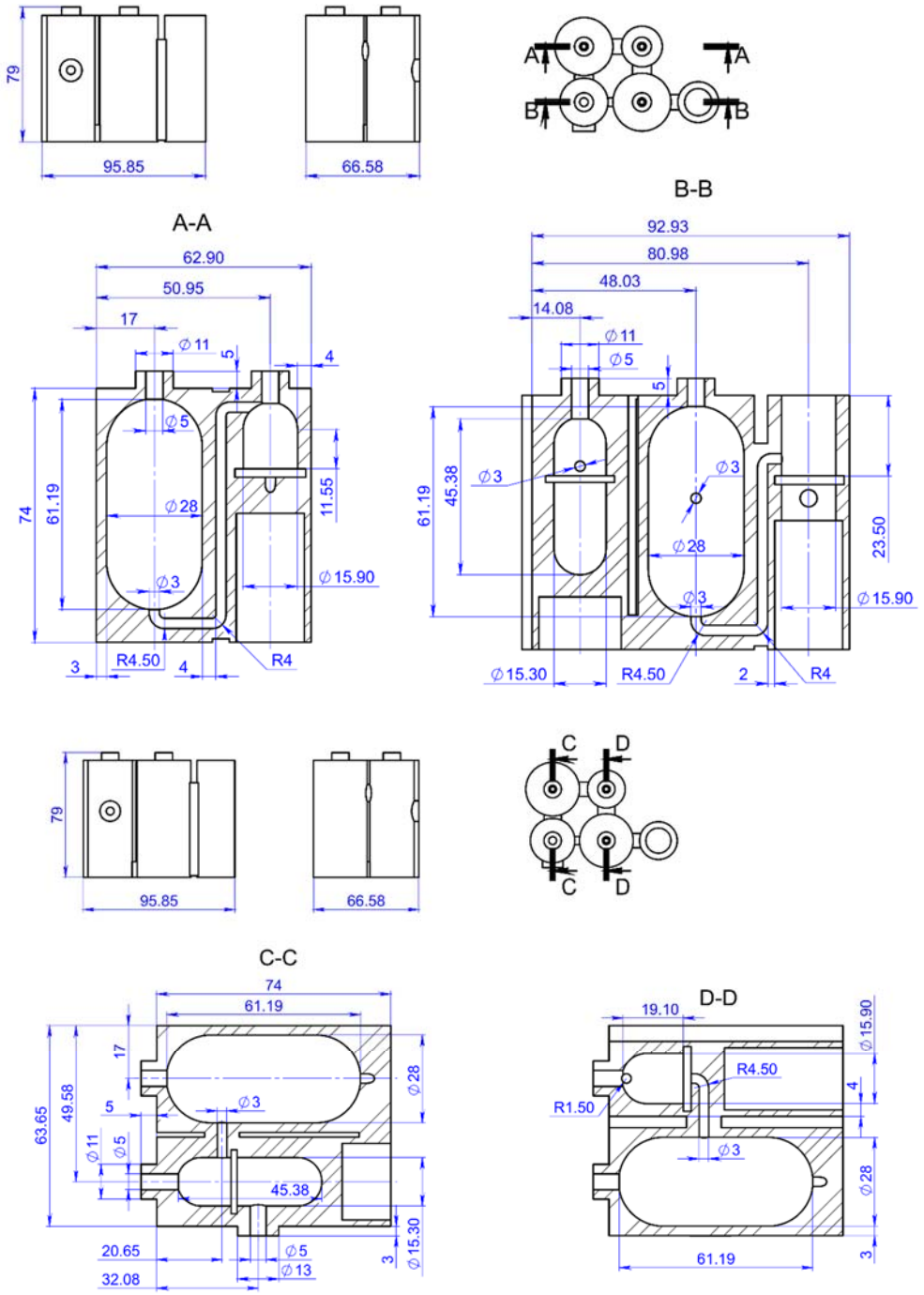


Fig. S9: Draft of monolithic reaction cartridge, showing vertical section views through the design.

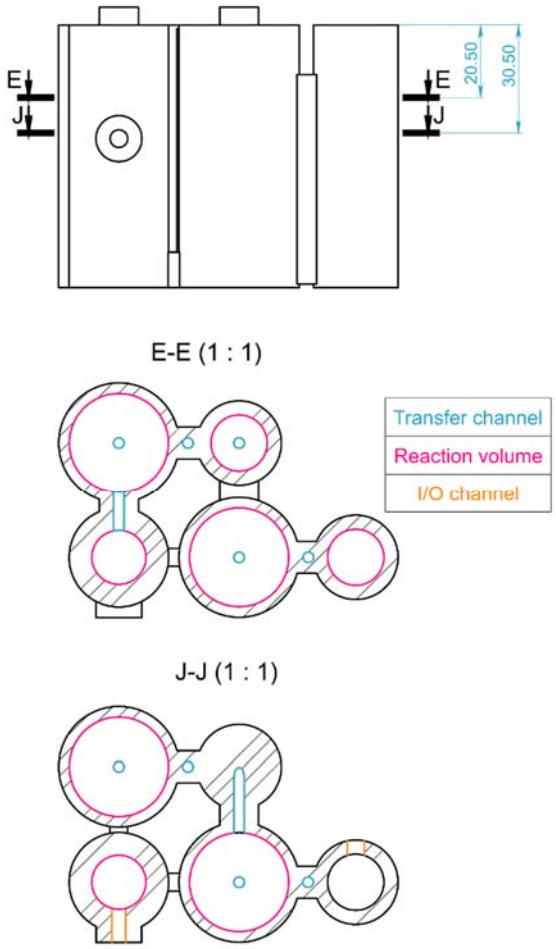


Fig. S10: Technical Diagram of Monolithic reaction cartridge, showing horizontal section views through the design.

2.5 Module / Cartridge inlets & outlets

In order to interface the synthesis cartridges with the external fluid handling of the system, each design was produced with openings suitable for tapping to produce a ¼" UNF thread which could be fitted with polypropylene adapters for Luer-lock fittings (supplied by Cole Parmer, see Fig. S11) allowing ease of connection to external fluidics. These Luer-lock interfaces proved to be solvent tight and gas tight under the conditions of the syntheses presented.

The tapped openings could be also fitted with barbed fittings for directly connecting cartridges to external tubing, or standard flangeless fittings for interfacing with external tubing. Individual modules could be connected directly by fitting a ¼" UNF to female Luer adaptor on one module

into a male Luer to ¼" UNF adaptor on the next module, reducing the flow path for reaction media through the modular systems.

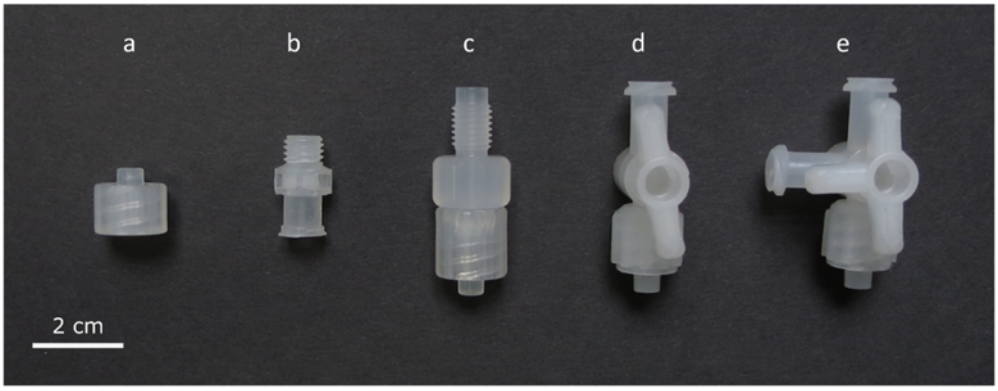


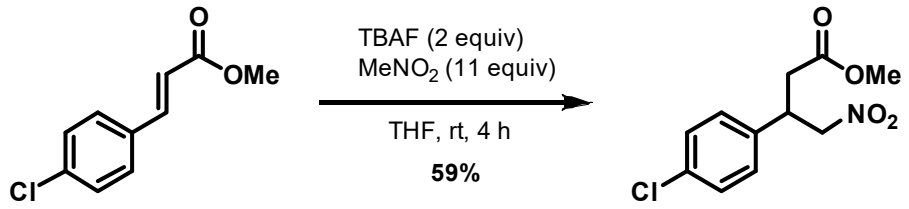
Fig. S11: Polypropylene adaptors used to interface 3D printed modules / cartridges with external liquid handling. (a) Male Luer stopper. (b) ¼" UNF to female Luer connector (c) ¼" UNF to male Luer connector (d) single input female to male Luer connector with valve (e) double input (female) to single output (male) Luer connector with T - valve.

3. Traditional / Polypropylene synthesis / analysis

Given below are the details of the synthetic procedure for the test reactions in both polypropylene and glass reactors conducted for each step of the three syntheses considered. The diagnostic ^{1}H and ^{13}C NMR spectra shown are taken from glassware reactions but comparison of spectra from both regimes confirmed the identity of products obtained.

3.1 Synthesis of (±) – Baclofen

3.1.1 Baclofen Reaction 1



Traditional (glassware) synthesis

In a 25 mL round bottomed flask, methyl 4-chlorocinnamate (1.0 g, 5.10 mmol) followed by nitromethane (3.0 mL, 56.1 mmol, 11 equiv) were added into a 1 M solution of tetrabutylammonium fluoride in THF (10.2 mL, 10.2 mmol, 2 equiv). The reaction was stirred over 4 hours at room temperature. Afterwards, the resulting yellow crude mixture was quenched with an aqueous solution of HCl (2 M) until a colorless solution was obtained. The solvents were removed under reduced pressure and the residual reaction mixture was purified by flash chromatography (Petrol. / EtOAc 10 : 1 and then 4 : 1). The desired γ-nitro ester was obtained (771 mg, 3.0 mmol, **59%**) as a colorless oil.

Polypropylene test reaction:

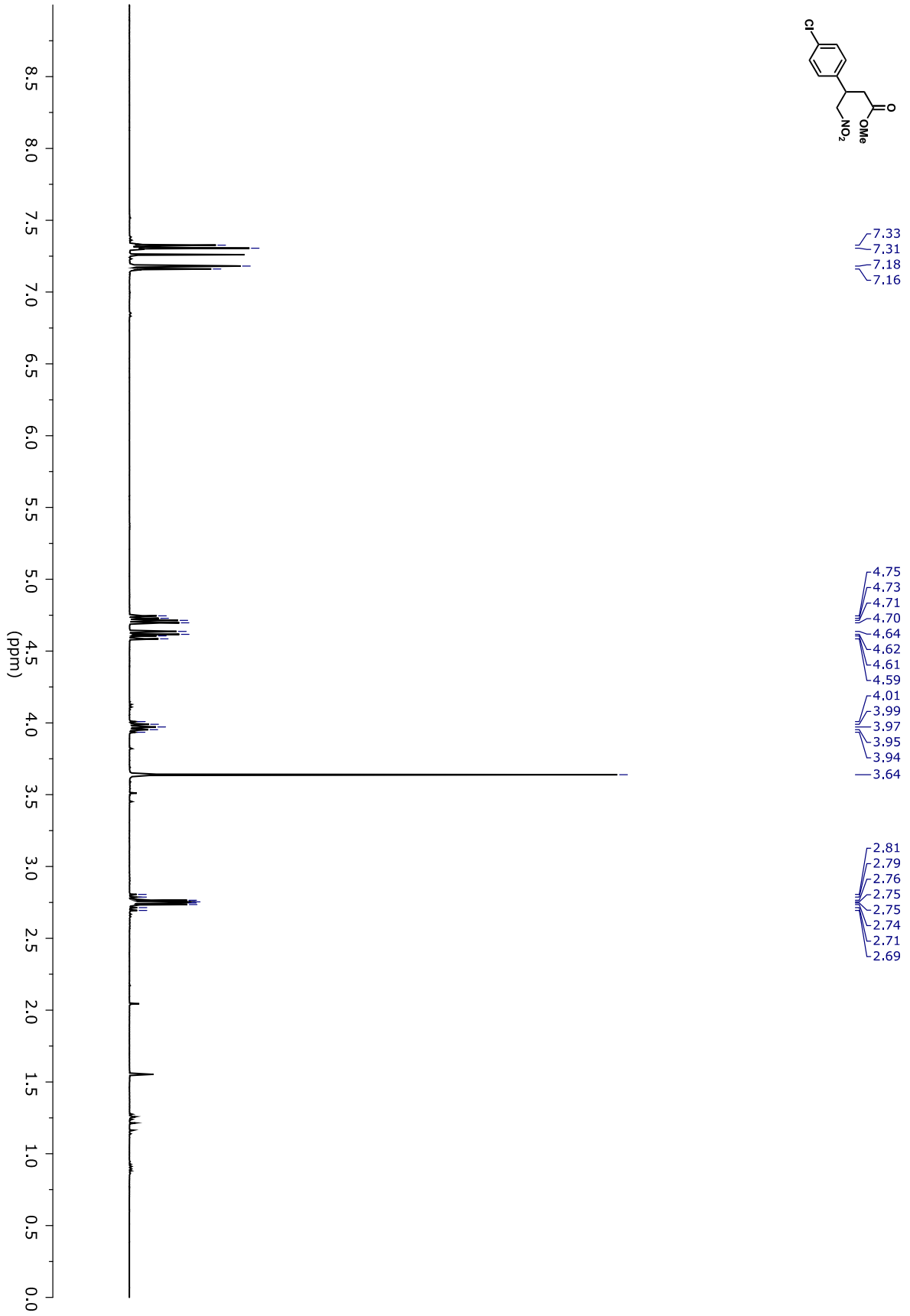
In an 11 mL polypropylene reactionware vessel, methyl 4-chlorocinnamate (100 mg, 0.51 mmol) followed by nitromethane (0.3 mL, 5.61 mmol, 11 equiv) were added into a 1 M solution of tetrabutylammonium fluoride in THF (1.0 mL, 1.02 mmol, 2 equiv). The reaction was stirred over 4 hours at room temperature. Afterwards, the resulting yellow crude mixture was quenched with an aqueous solution of HCl (2 M) until a colorless solution was obtained. The solvents were removed under reduced pressure and the residual reaction mixture was purified by flash chromatography (Petrol. /EtOAc 10: 1 and then 4: 1). The desired γ-nitro ester was obtained (62 mg, 0.24 mmol, **47%**) as a colorless oil.

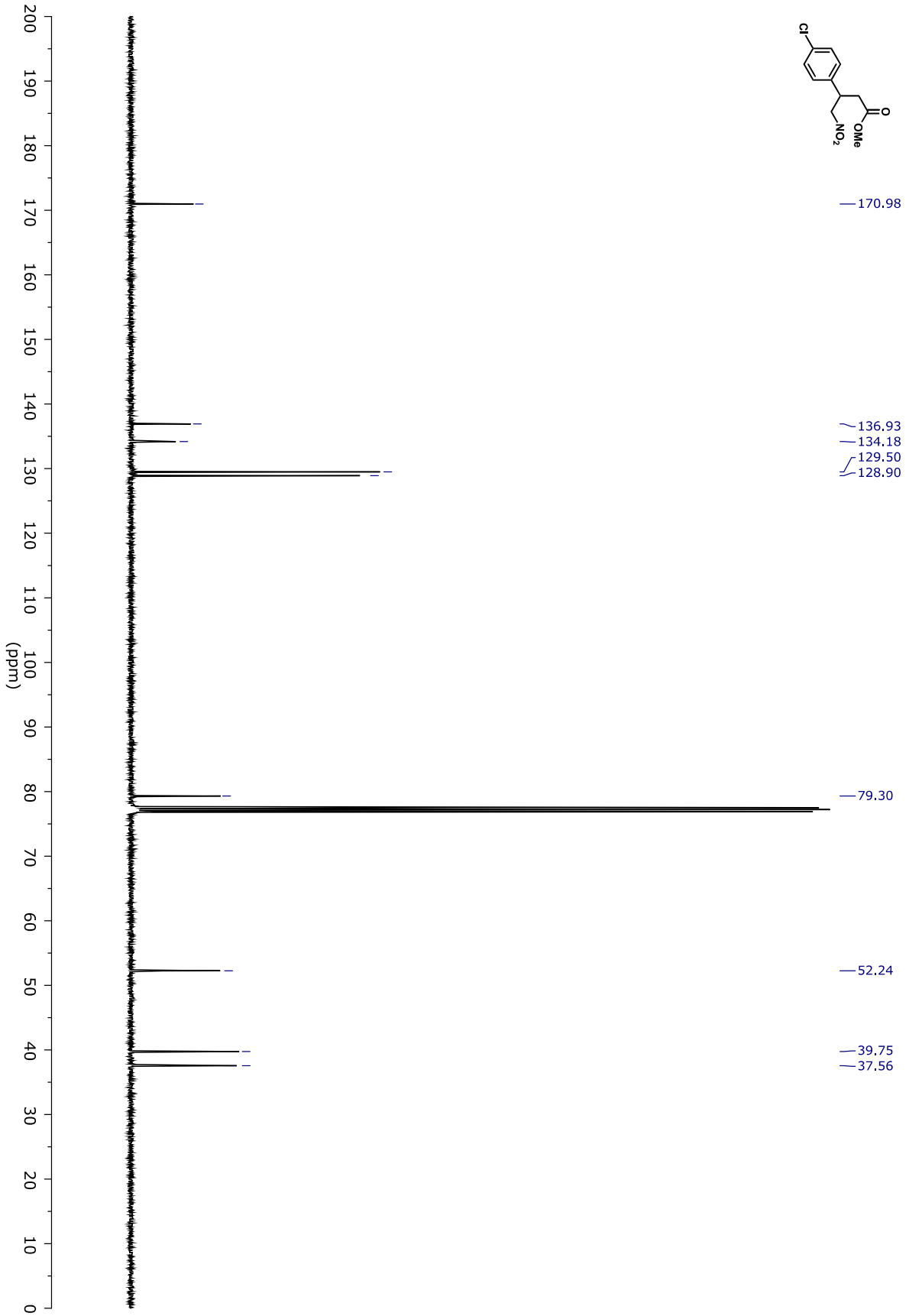
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (2 H, d, *J* = 8.8 Hz), 7.17 (2 H, d, *J* = 8.4 Hz), 4.72 (1 H, m), 4.61 (1 H, m), 3.97 (1 H, q, *J* = 7.6 Hz), 3.13 (3 H, s), 2.75 (2 H, m).

^{13}C NMR (101 MHz, $CDCl_3$): 171.0, 136.9, 134.2, 129.5, 128.9, 79.3, 52.2, 39.8, 37.4.

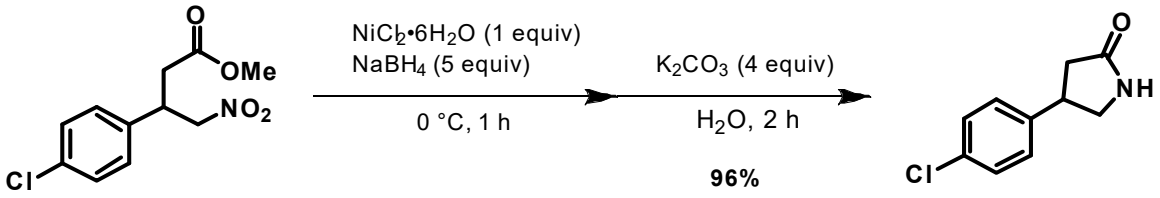
IR (ν_{max}): 3005, 2955, 1732, 1551, 1493, 1437, 1377, 1267, 1225, 1198, 1169, 1096, 1015, 880, 829, 733, 648 cm^{-1}.

HRMS (ESI) calculated for $C_{11}H_{12}NO_4N^{35}ClNa$ $[M + Na]^+$ 280.0347, found 280.0340. Δ = 2.5 ppm.


Cl
O
OMe
NO2
7.33
7.31
7.18
7.16
4.75
4.73
4.71
4.70
4.64
4.62
4.61
4.59
4.01
3.99
3.97
3.95
3.94
3.64
2.81
2.79
2.76
2.75
2.75
2.74
2.71
2.69
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


Cl
O
OMe
NO2
170.98
136.93
134.18
129.50
128.90
79.30
52.24
39.75
37.56
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

3.1.2 Baclofen Reaction 2



Traditional (glassware) synthesis

In a 25 mL round bottomed flask, $NaBH_4$ (142 mg, 3.75 mmol, 5 equiv) was added in portions into a solution of the nitro ester (193 mg, 0.75 mmol) and $NiCl_2 \cdot 6H_2O$ (178 mg, 0.75 mmol, 1 equiv) in MeOH (10 mL). The reaction was stirred over 30 minutes at 0 °C. After quenching the crude mixture with a solution of K_2CO_3 (415 mg, 3.0 mmol, 4 equiv) in water (5 mL) for 2 hours, the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The solvents were evaporated *in vacuo* to obtain the desired γ-lactam (140 mg, 0.72 mmol, **96%**) as a white solid.

Polypropylene test reaction:

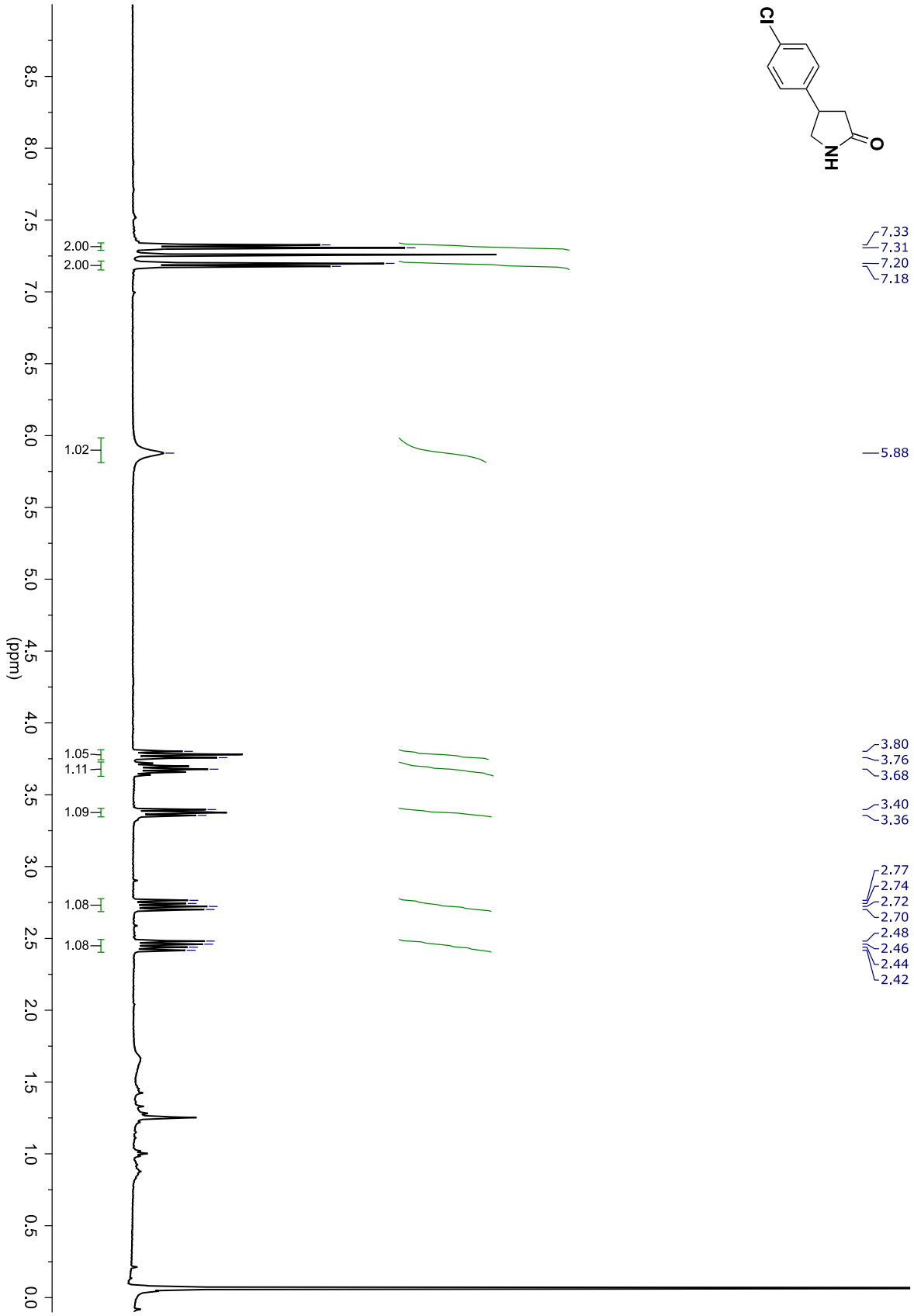
In an 11 mL polypropylene reactionware vessel, $NaBH_4$ (59 mg, 1.6 mmol, 4 equiv) was added in portions into a solution of the nitro ester (100 mg, 0.39 mmol) and $NiCl_2 \cdot 6H_2O$ (93.0 mg, 0.39 mmol, 1 equiv) in MeOH (4 mL). The reaction was stirred over 30 minutes at 0 °C. After quenching the crude mixture with a solution of K_2CO_3 (221 mg, 1.6 mmol, 4 equiv) in water (2.0 mL) for 2 hours. The aqueous phase was extracted with CH_2Cl_2 (5 mL) and transferred into the next cartridge through the hydrophobic filter disc. The solvents were evaporated *in vacuo* to obtain the desired γ-lactam (60 mg, 0.31 mmol, **80%**) as a white solid.

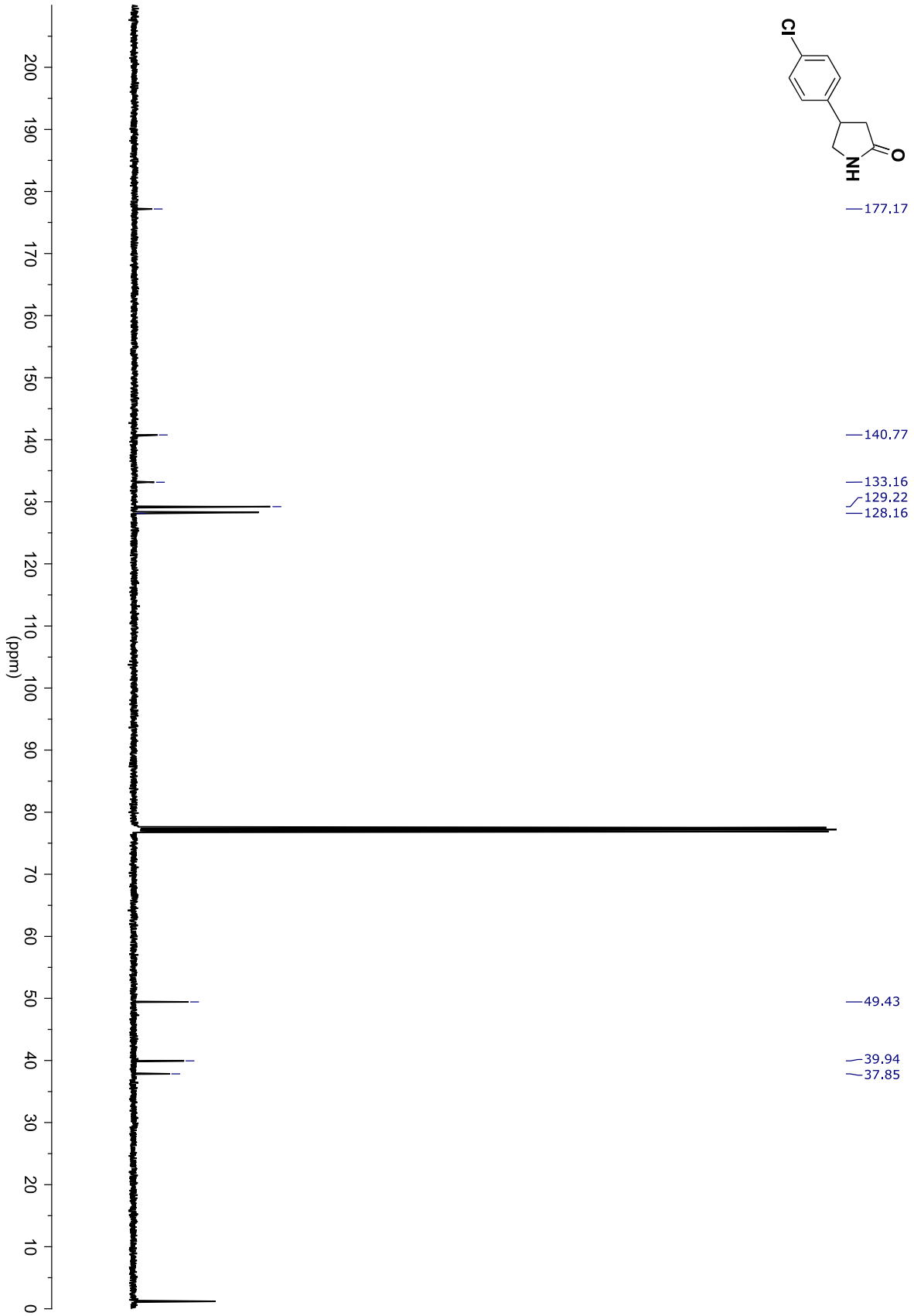
m.p. 113 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (2 H, d, *J* = 8.0 Hz), 7.19 (2 H, d, *J* = 8 Hz), 5.88 (1 H, br), 3.80 – 3.76 (1 H, m), 3.68 (1 H, q, *J* = 8 Hz), 3.40 – 3.36 (1 H, m), 2.74 (1 H, dd, *J* = 16.8, 8.8 Hz), 2.45 (1 H, dd, J = 16.8, 8.8 Hz).

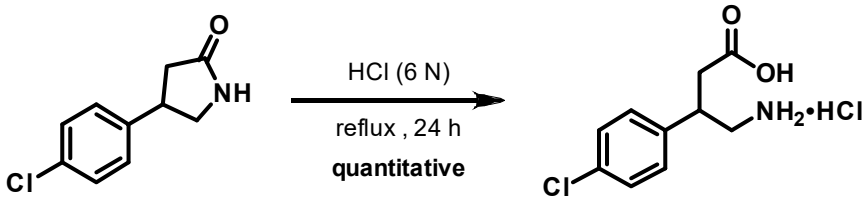
^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.2, 140.8, 133.2, 129.2, 128.2, 49.4, 39.9, 37.9.

IR (ν_{max}): 3195, 2934, 2359, 2245, 2045, 2029, 1967, 1688, 1493, 1456, 1404, 1346, 1260, 1088, 1013, 887, 800 cm^{-1}.


Cl
O
NH
2.00
2.00
1.02
1.05
1.11
1.09
1.08
1.08
7.33
7.31
7.20
7.18
5.88
3.80
3.76
3.68
3.40
3.36
2.77
2.74
2.72
2.70
2.48
2.46
2.44
2.42
(ppm)


Cl
NH
O
177.17
140.77
133.16
129.22
128.16
49.43
39.94
37.85
(ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

3.1.3 Baclofen Reaction 3



Traditional (glassware) synthesis

In a 10 mL round bottomed flask, the γ-lactam (80 mg, 0.41 mmol) was mixed in an aqueous solution of HCl (6 M, 2.5 mL). The reaction mixture was then refluxed over 24 hours. The resulting mixture was cooled down to room temperature and carefully concentrated under vacuum to afford (±)-baclofen (101 mg, 0.40 mmol, **quantitative yield**).

Polypropylene test reaction:

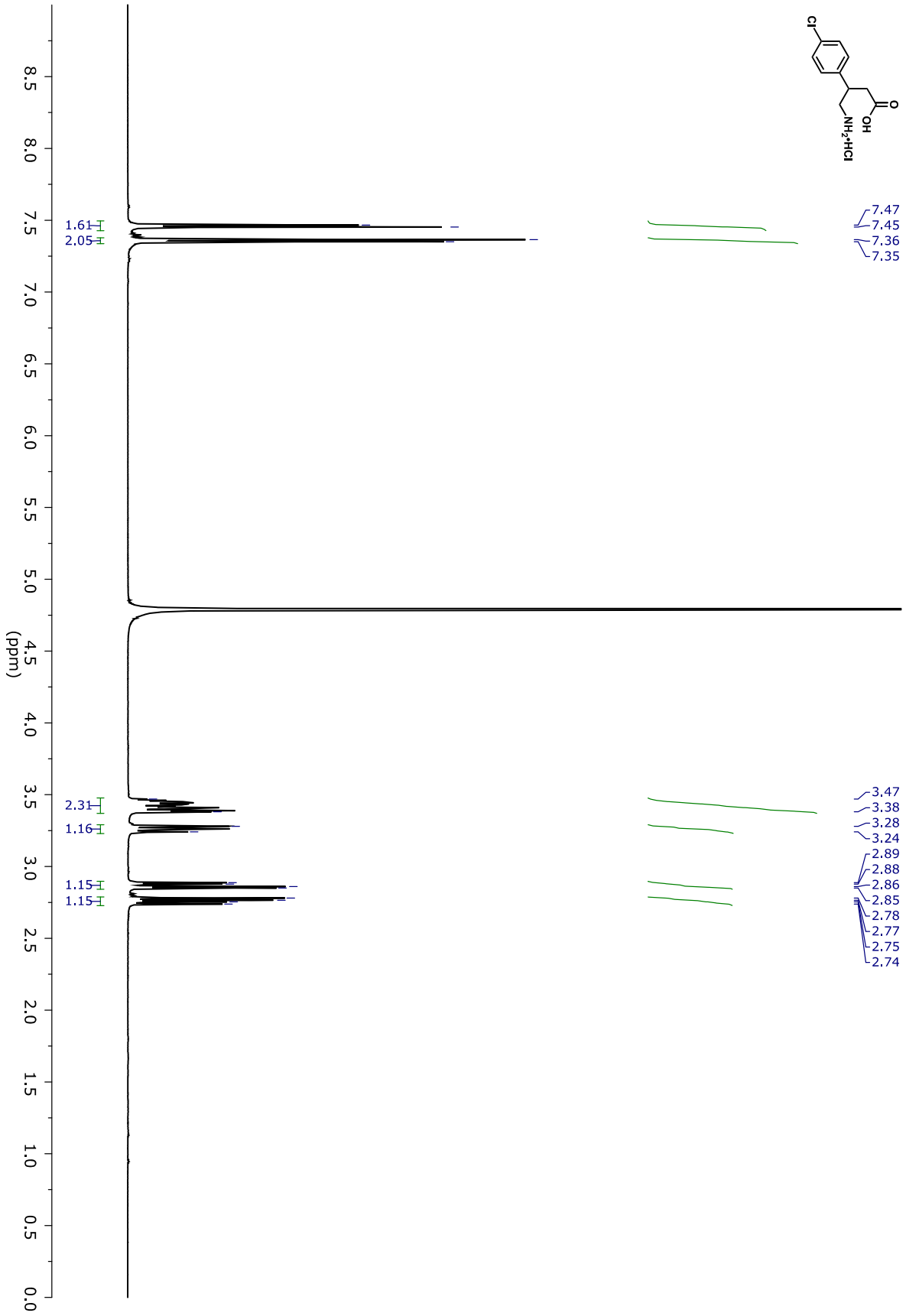
In an 11 mL polypropylene reactionware vessel, the γ-lactam (32 mg, 0.16 mmol) was mixed in an aqueous solution of HCl (6 M, 1.3 mL). The reaction mixture was then refluxed over 24 hours. The resulting mixture was cooled down to room temperature and carefully concentrated under vacuum to afford baclofen (39 mg, 0.16 mmol, **quantitative yield**).

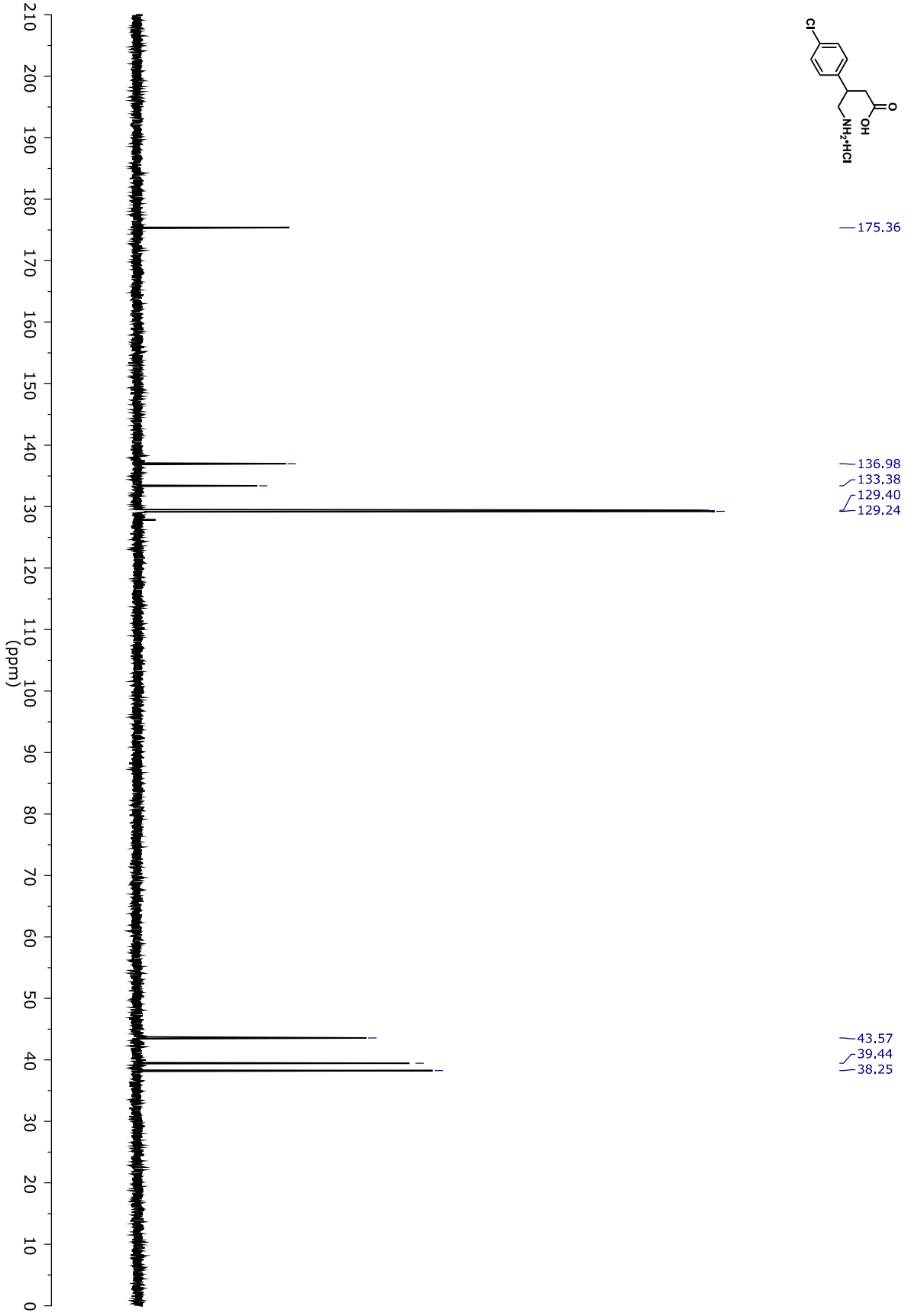
m.p. 192 - 194 °C.

^{1}H NMR (600 MHz, D_2O): δ = 7.46 (2 H, d, *J* = 8.4 Hz), 7.36 (2 H, d, *J* = 8.4 Hz), 3.47 – 3.38 (2 H, m), 3.28 – 3.24 (1 H, m), 2.87 (1 H, dd, *J* = 15.6, 5.4 Hz), 2.77 (1 H, dd, *J* = 16.2, 9.0 Hz).

^{13}C NMR (150 MHz, D_2O): δ = 175.4, 137.0, 133.4, 129.4, 129.2, 43.6, 39.4, 38.3.

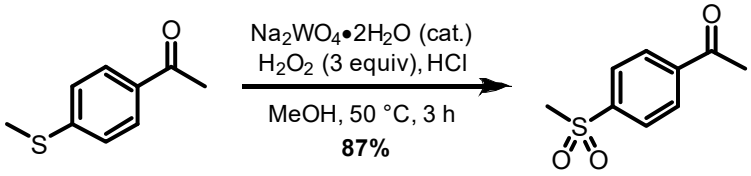
IR (ν_{max}):3700, 3074, 1765, 1591, 1514, 1493, 1408, 752, 700 cm^{-1}.


Cl
O
OH
NH2•HCl
7.47
7.45
7.36
7.35
3.47
3.38
3.28
3.24
2.89
2.88
2.86
2.85
2.78
2.77
2.75
2.74
1.61
2.05
2.31
1.16
1.15
1.15
(ppm)


Cl
O
OH
NH2·HCl
175.36
136.98
133.38
129.40
129.24
43.57
39.44
38.25
(ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

3.2 Synthesis of Zolimidine

3.2.1 Zolimidine Reaction 1



Traditional (glassware) synthesis

In a 25 mL round bottom flask containing 4-(methylthio)-acetophenone (250 mg, 1.50 mmol), sodium tungstate dihydrate (49.8 mg, 0.150 mmol, 10 %mol), methanol (2 mL), and aqueous conc. HCl (1-2 drops) was added aqueous H_2O_2 (30%, w/v, 500 µL, 4.50 mmol, 3 equiv) and the resulting solution heated to 50 °C. After 3 hours, the reaction was concentrated *in vacuo* and the resulting residue partitioned between an aqueous solution of NaOH (0.5 M, 20 mL) and EtOAc (20 mL). The aqueous phase was separated and extracted using EtOAc (2 ×10 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 4-(methylsulfonyl)-acetophenone (258 mg, 1.30 mmol, **87%**) as a white solid.

Polypropylene test reaction:

In a polypropylene reactionware vessel containing 4-(methylthio)-acetophenone (100 mg, 0.60 mmol), sodium tungstate dihydrate (20 mg, 0.06 mmol), methanol (2 mL), and aqueous conc. HCl (1-2 drops) was added aqueous H_2O_2 (30%, w/v, 200 µL, 1.80 mmol) and the resulting solution heated to 50 °C. After 3 hours, the reaction was concentrated *in vacuo* and the resulting residue partitioned between aqueous solution of NaOH (0.5 M, 20 mL) and EtOAc (20 mL). The aqueous phase was extracted using EtOAc (2 ×10 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford 4-(methylsulfonyl)-acetophenone (119 mg, 0.60 mmol, **76%**) as a white solid.

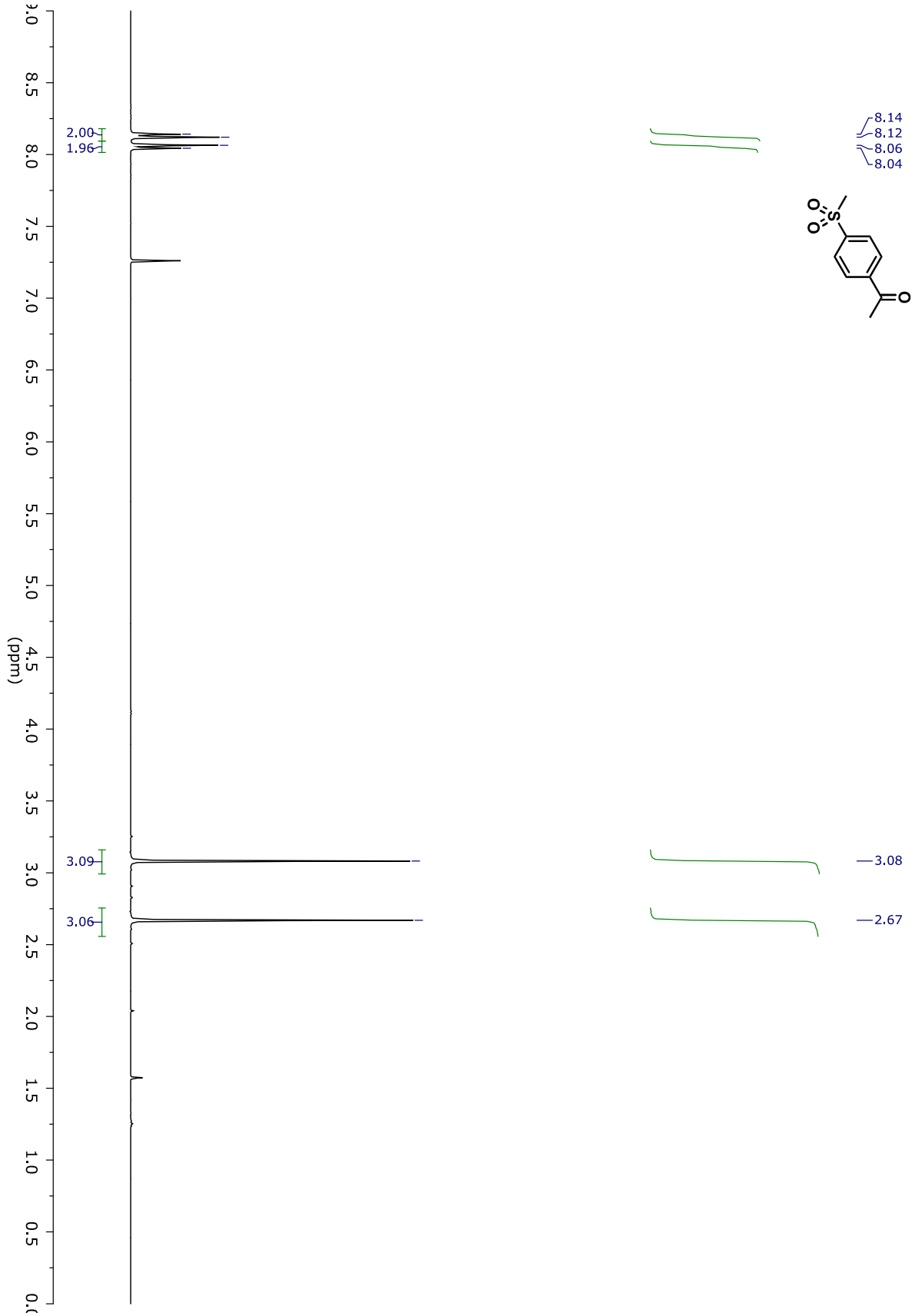
m.p. = 132 – 135 °C

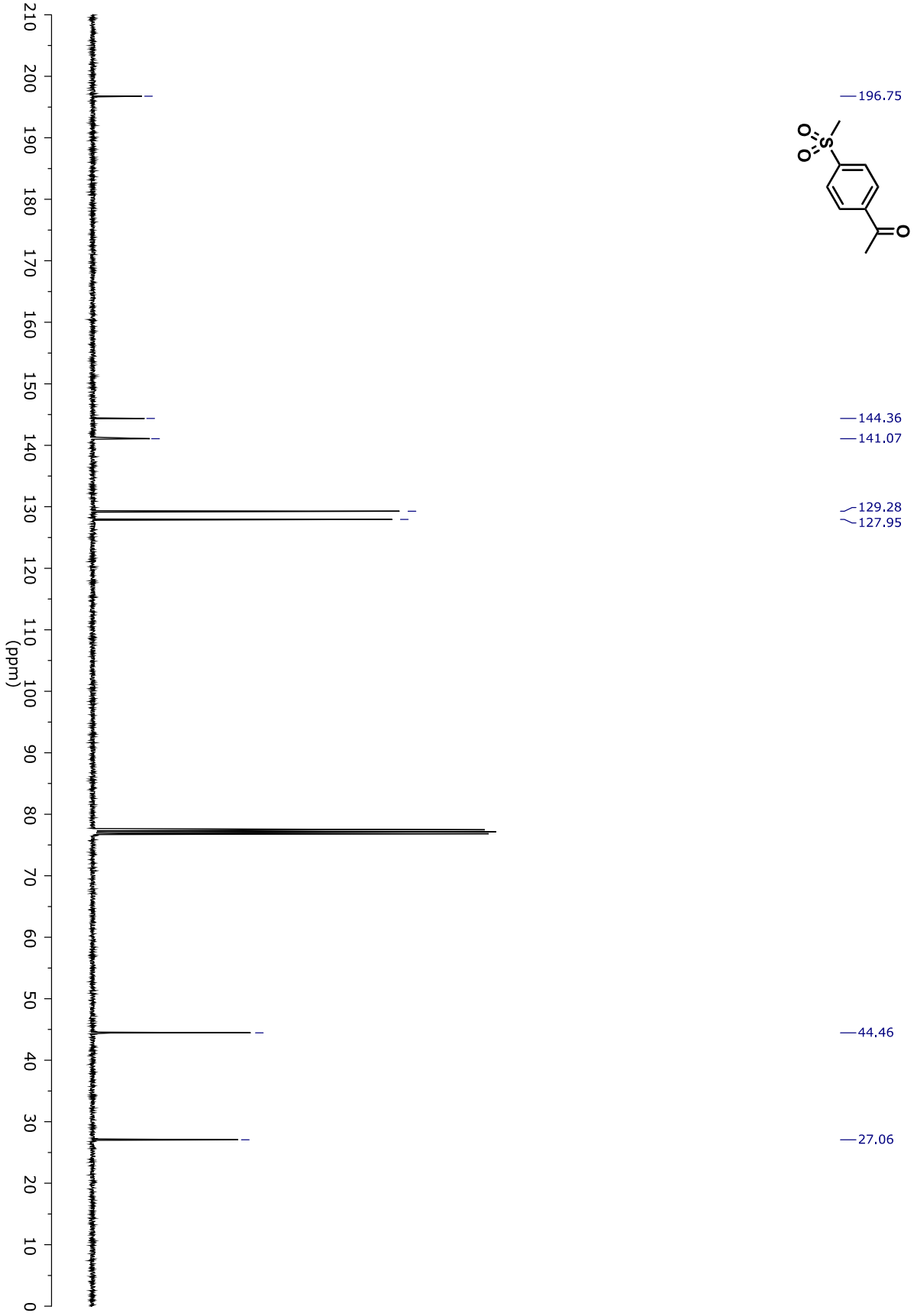
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 – 8.10 (2 H, m), 8.09 – 8.02 (2 H, m), 3.08 (3 H, s), 2.67 (3 H, s).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.8, 144.4, 141.1, 129.3, 128.0, 44.5, 27.1.

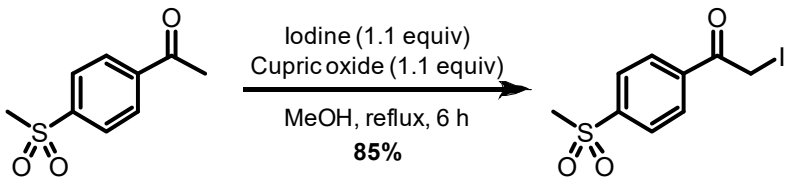
IR (υ_{max}): 1687, 1396, 1310, 1295, 1289, 1259, 1173, 1149, 1090, 963, 779, 748, 618 cm^{-1}.

HRMS (**EI**) calculated for $C_9H_{10}O_3S$ $[M]^+$: 198.0351, found 198.0351. Δ = 0 ppm.


2.00
1.96
3.09
3.06
8.14
8.12
8.06
8.04
3.08
2.67
(ppm)


196.75
144.36
141.07
129.28
127.95
44.46
27.06
(ppm)

3.2.2 Zolimidine Reaction 2



Traditional (glassware) synthesis

In a 25 mL round bottom flask containing acetophenone (100 mg, 0.50 mmol), iodine (141 mg, 0.55 mmol), and cupric oxide (44.1 mg, 0.55 mmol) was added methanol (2.5 mL) and the resulting suspension heated to reflux. After 6 hours, the reaction was filtered through a pad of Celite®, eluting with methanol. The filtrate was concentrated *in vacuo* and the residue dissolved in ethyl acetate, which was then washed with an aq. sodium thiosulfate (10%, w/v, 10 mL) solution, brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography on silica gel (methylene chloride – ethyl acetate, 9:1) afforded α-iodoketone (122 mg, 0.38 mmol, **85%**) as an off white solid.

Polypropylene test reaction:

In a polypropylene reactionware vessel containing acetophenone (100 mg, 0.50 mmol), iodine (140 mg, 0.55 mmol), and cupric oxide (44.0 mg, 0.55 mmol) was added methanol (2.5 mL) and the resulting suspension heated to 70 °C. After 6 hours, the reaction was filtered through a pad of Celite®, eluting with methanol. The filtrate was concentrated *in vacuo* and the residue dissolved in EtOAc, which was then washed with an aqueous sodium thiosulfate (10%, w/v, 10 mL) solution, brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography on silica gel (CH_2Cl_2 / EtOAc: 9:1) afforded α-iodoketone (61 mg, 0.19 mmol, **38%**) as an off white solid.

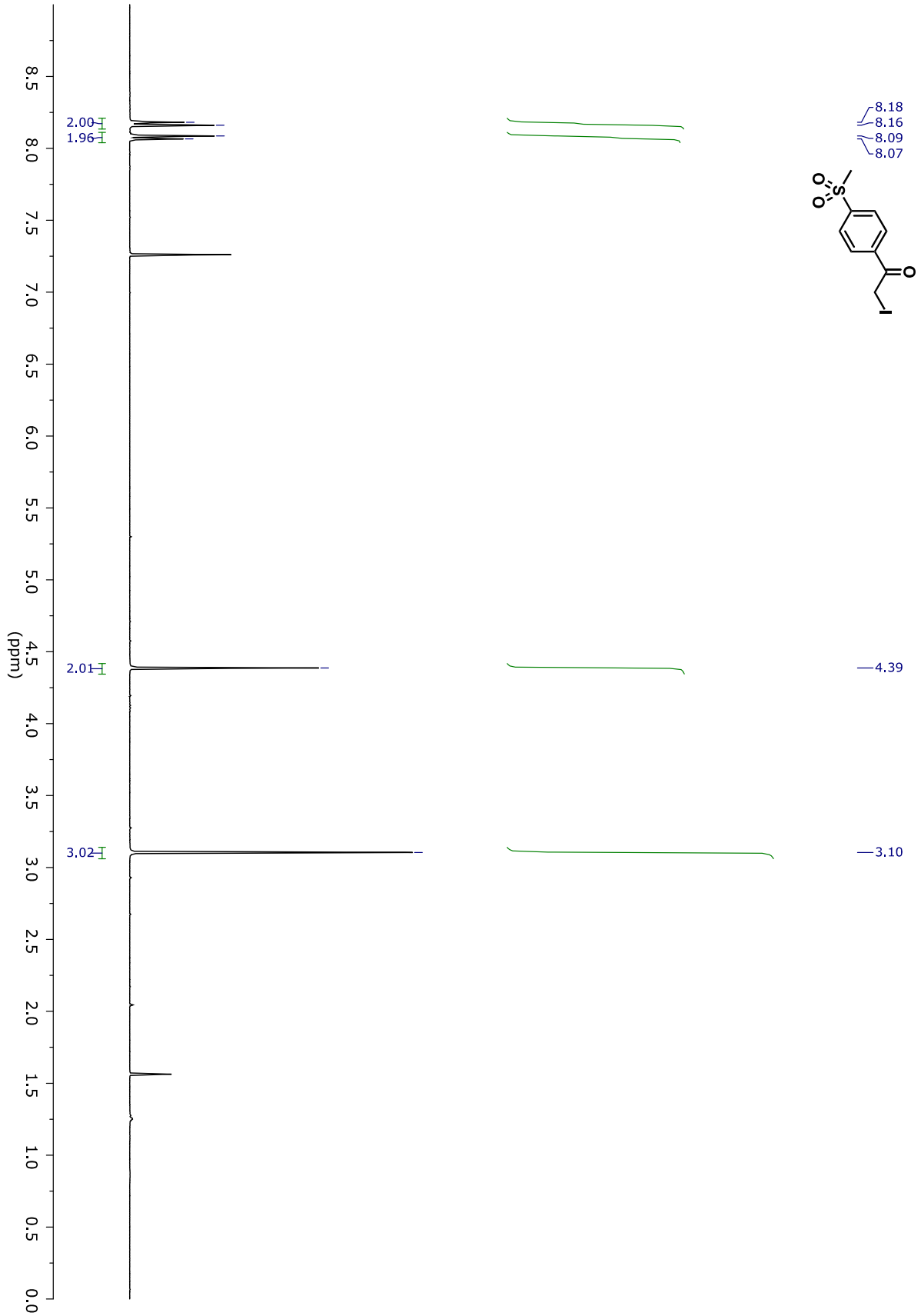
m.p. 134 – 136 °C.

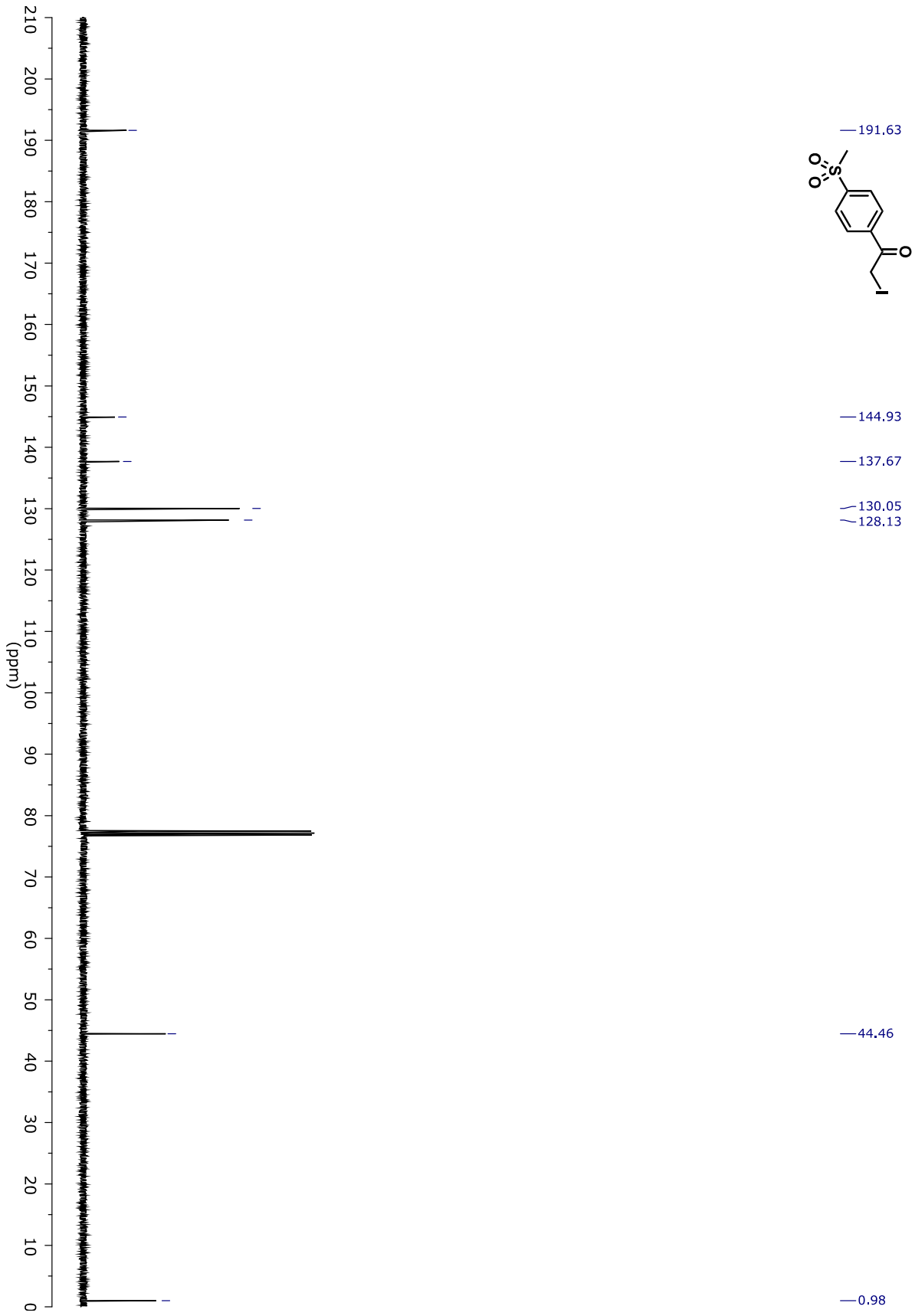
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (2 H, d, *J* = 8.4 Hz), 8.08 (2 H, d, *J* = 8.3 Hz), 4.39 (2 H, s), 3.10 (3 H, s).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 191.6, 144.9, 137.6, 130.1, 128.4, 44.5, 1.0.

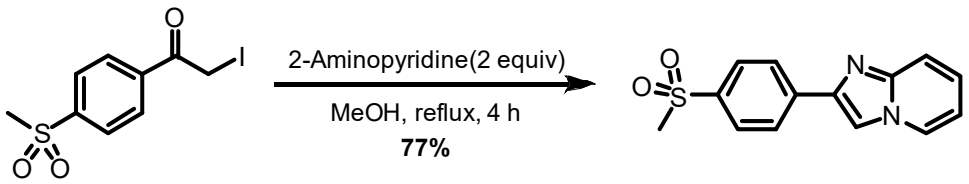
IR (υ_{max}): 1674, 1319, 1298, 1267, 1151, 1009, 963, 786, 737 cm^{-1}.

HRMS (ESI) calculated for $C_9H_{10}IO_3SNa$ $[M+Na]^+$:346.9215, found 346.9214. Δ = 0.3 ppm.


8.18
8.16
8.09
8.07
2.00
1.96
2.01
3.02
4.39
3.10
(ppm)


191.63
144.93
137.67
130.05
128.13
44.46
0.98
(ppm)

3.2.3 Zolimidine Reaction 3



Traditional (glassware) synthesis

In a 25 mL round bottom flask containing a solution of α-iodoketone (40.0 mg, 0.123 mmol) in methanol (5 mL) was added 2-aminopyridine (23.3 mg, 0.25 mmol, 2 equiv) and the resulting solution heated to reflux. After 4 hours, the reaction was concentrated *in vacuo* and purified by flash chromatography on silica gel (CH_2Cl_2 / EtOAc: 4:1 to 1:1). Zolimidine was obtained (26 mg, 0.10 mmol, **77%**) as an off white solid.

Polypropylene test reaction:

In a polypropylene reactionware vessel containing a solution of α-iodoketone (40 mg, 0.13 mmol) in methanol (3 mL) was added 2-aminopyridine (24.0 mg, 0.25 mmol, 2 equiv) and the resulting solution heated to 50 °C. After 18 hours, the reaction was concentrated *in vacuo* and purified by flash chromatography on silica gel (CH_2Cl_2 / EtOAc: 4:1 to 1:1). Zolimidine was obtained (28 mg, 0.10 mmol, **82%**) as an off white solid.

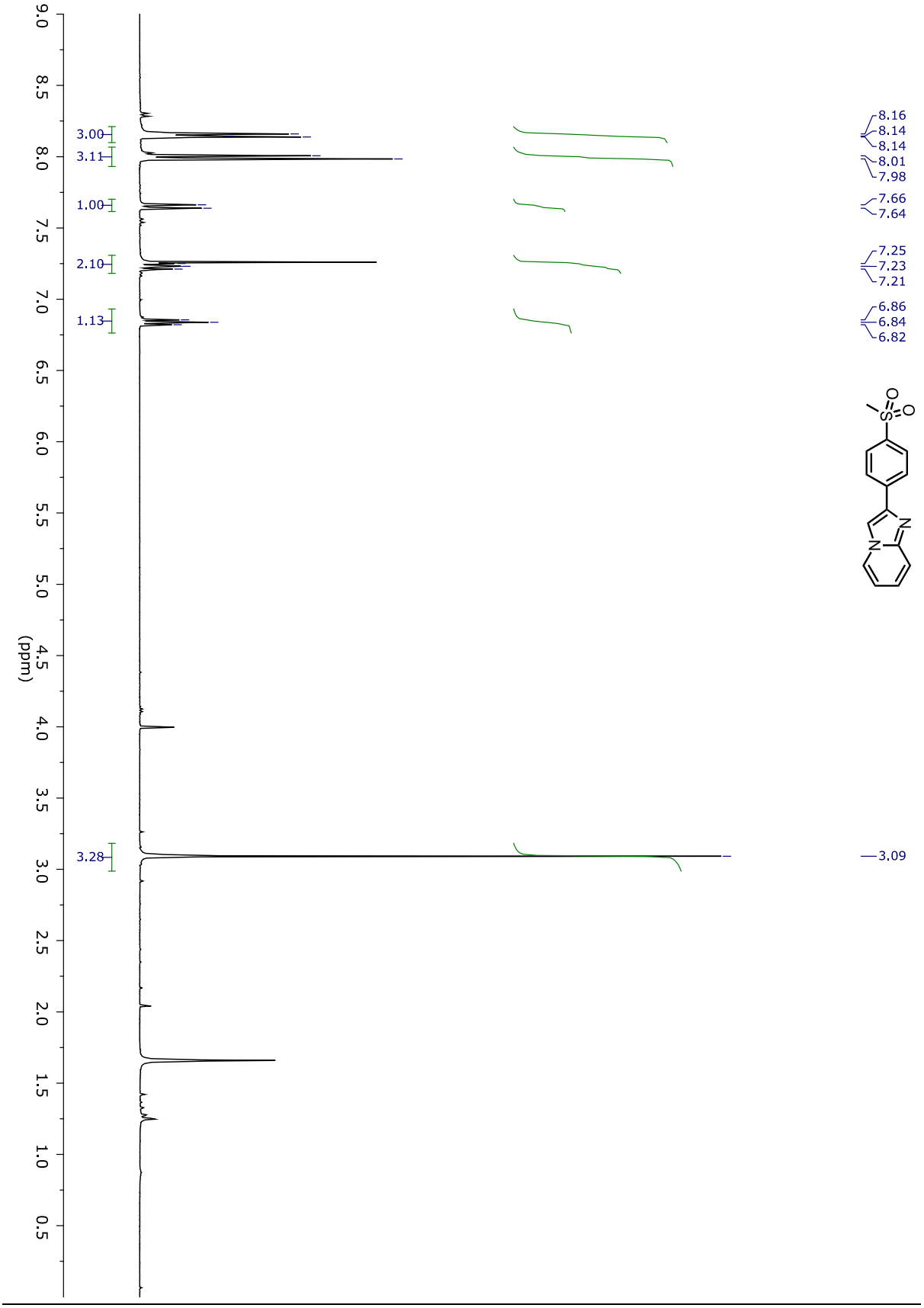
m.p. 240 – 242 °C.

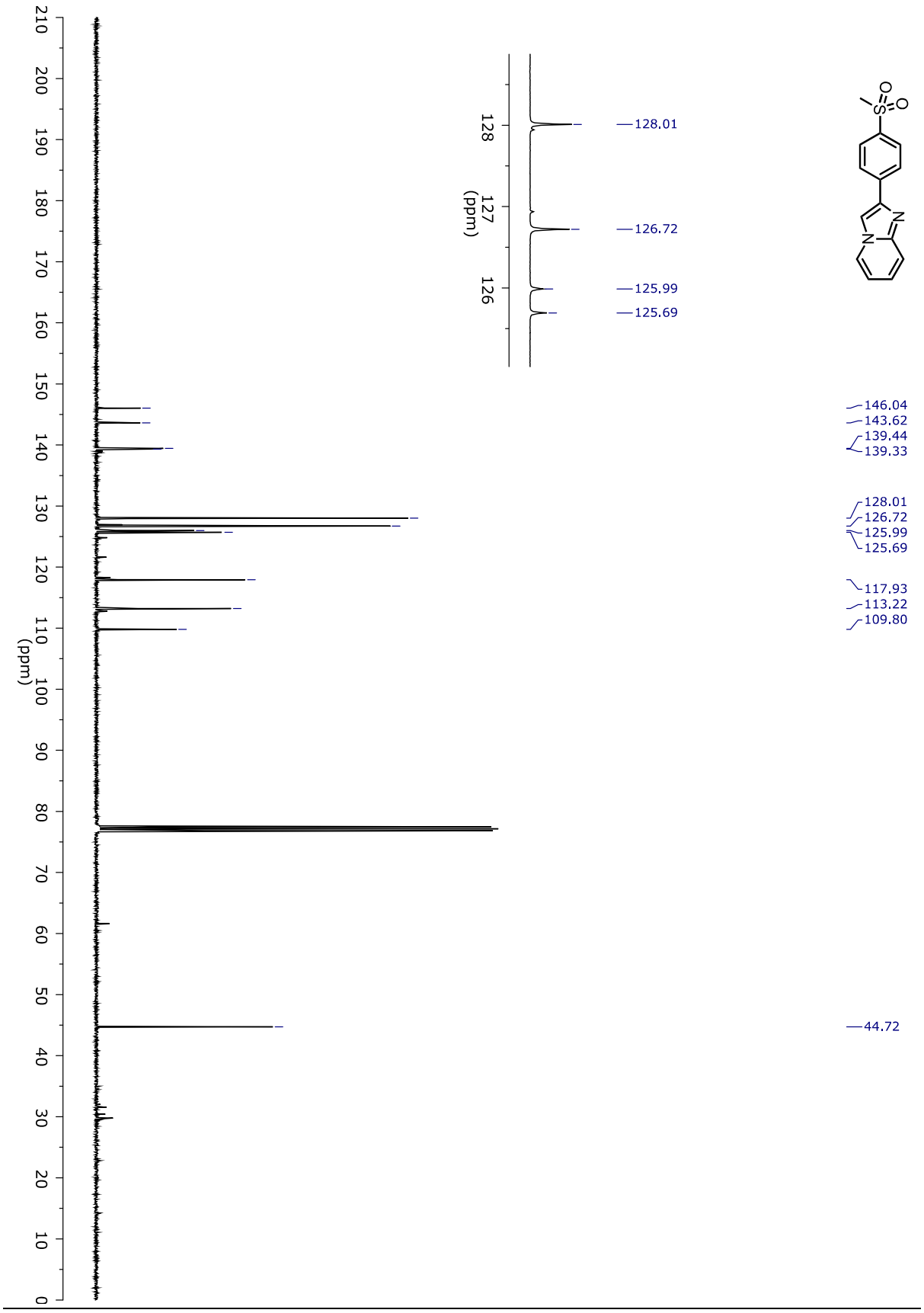
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 – 8.10 (3 H, m), 8.06 – 7.93 (3 H, m), 7.65 (1 H, d, *J* = 9.1 Hz), 7.31 – 7.18 (1 H, m), 6.84 (1 H, t, *J* = 6.8 Hz), 3.10 (3 H, s).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.0, 143.6, 139.4, 139.3, 128.0, 126.7, 126.0, 125.7, 117.9, 113.2, 109.8, 44.7.

IR (υ_{max}): 1303, 1150, 775, 748, 606 cm^{-1}.

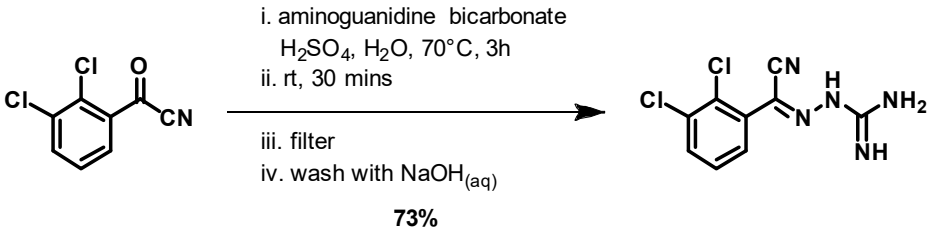
HRMS (ESI) calculated for $C_{14}H_{13}N_2O_2S$ [M + H^+] 273.0692, found 273.0698. Δ = 2.2 ppm.


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
(ppm)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
3.00
3.11
1.00
2.10
1.13
3.28
8.16
8.14
8.14
8.01
7.98
7.66
7.64
7.25
7.23
7.21
6.86
6.84
6.82
3.09
O
S
O
N
N


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)
128
127
126
(ppm)
128.01
126.72
125.99
125.69
O
O
S
N
N
146.04
143.62
139.44
139.33
128.01
126.72
125.99
125.69
117.93
113.22
109.80
44.72

3.3 Synthesis of Lamotrigine

3.3.1 Lamotrigine Reaction 1



Traditional (glassware) synthesis

To a stirred mixture of aminoguanidine bicarbonate (250 mg, 0.96 mmol) in sulfuric acid (4 mL 50:50 v/v with H_2O) was added 2,3-dichlorobenzoyl cyanide (250 mg, 1.27 mmol, 1.32 equiv). The reaction mixture was then heated to 70 °C for 3 hours. The reaction was then cooled to 0 °C and stirred for 30 mins. The precipitate was filtered and washed with water (2 × 10 mL) before being solubilized in methanol. The removal of volatiles were proceeded under *vacuo* to afford 2-(2,3-dichlorophenyl)-2-(guanidinylimino)acetonitrile (230 mg, 0.90 mmol, **73%**) as an off-white amorphous solid.

Polypropylene test reaction:

To a stirred mixture of aminoguanidine bicarbonate (250 mg, 0.96 mmol) in sulfuric acid (4 mL 50:50 v/v with H_2O) in a polypropylene reaction vessel was added 2,3-dichlorobenzoyl cyanide (250 mg, 1.27 mmol). The reaction mixture was then heated to 70 °C for 5 hours. The reaction was then cooled to 0 °C and stirred for 30 mins. The precipitate was filtered and washed with water (2 × 10 mL) before being solubilised in methanol. The removal of volatiles were proceeded under *vacuo* to afford 2-(2,3-dichlorophenyl)-2-(guanidinylimino)acetonitrile as (190 mg, 0.74 mmol, **59%**) an off-white amorphous solid.

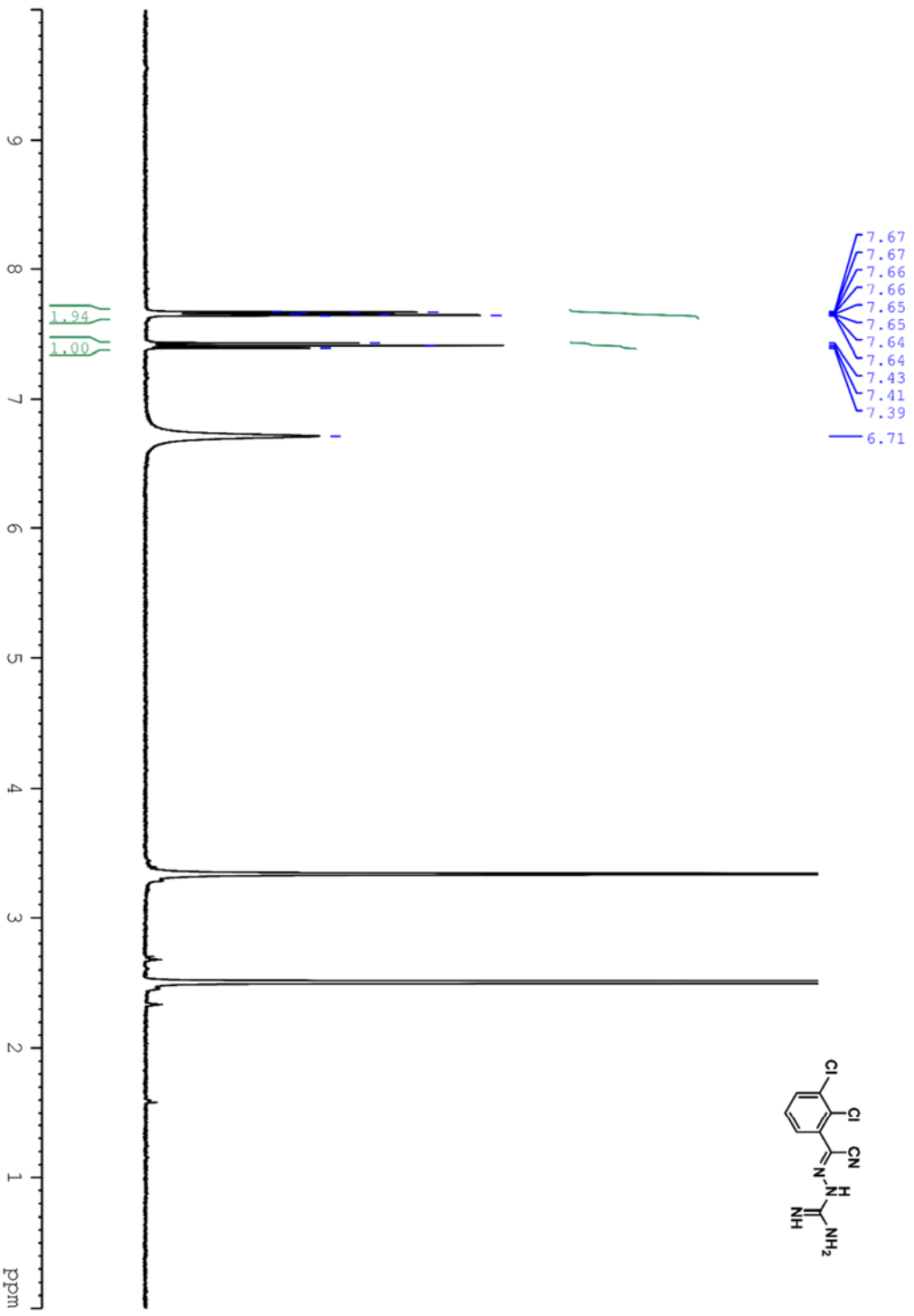
m.p. 175-177 C.

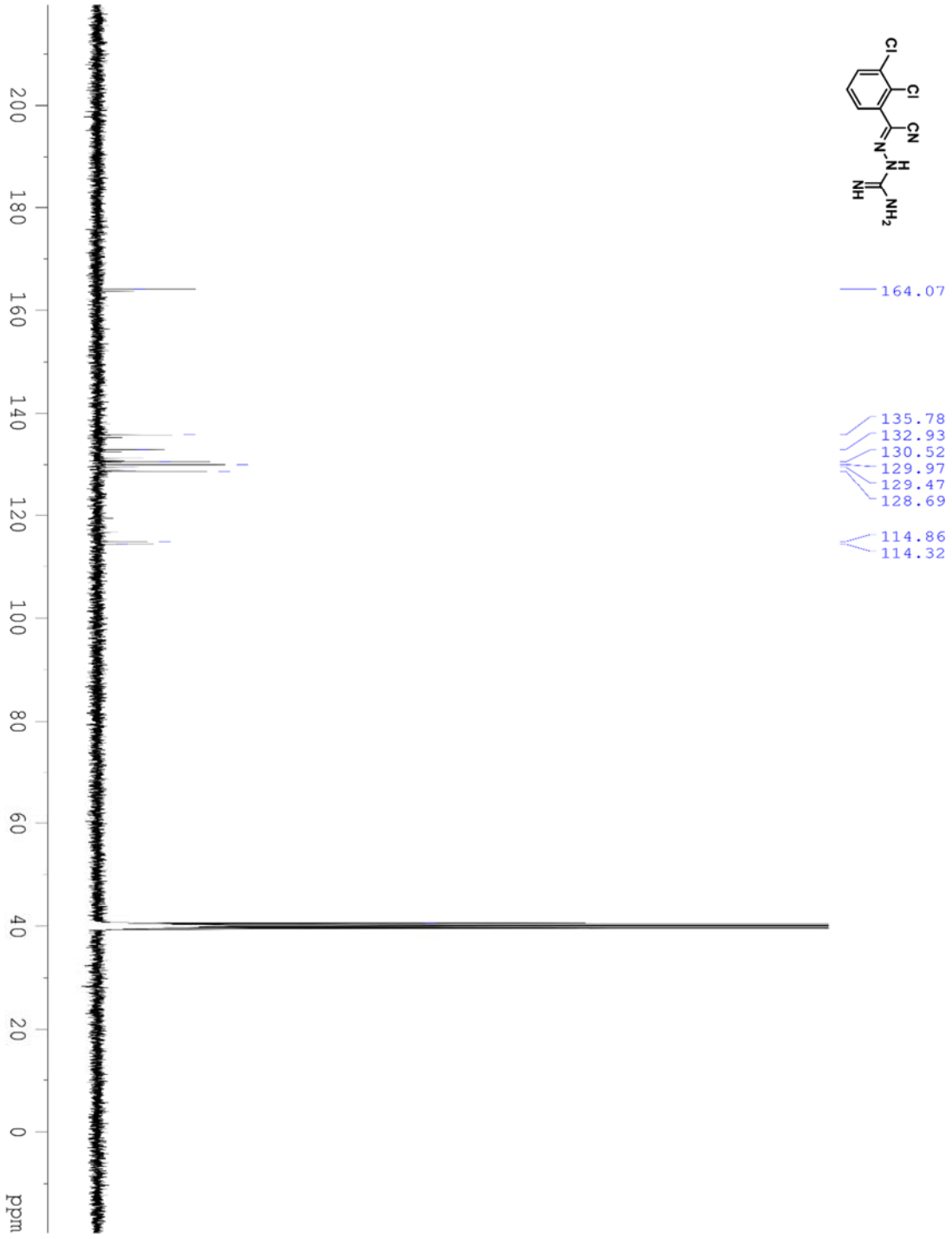
^{1}H NMR (400 MHz, DMSO-d^6): δ = 7.65 (2 H, m), 7.41 (1 H, dd, *J*=7.9Hz), 6.71 (1 H, br, N–H).

^{13}C NMR (101 MHz, DMSO-d^6): δ = 164.1, 135.8, 132.9, 130.5, 130.0, 129.5, 128.7, 114.9, 114.3.

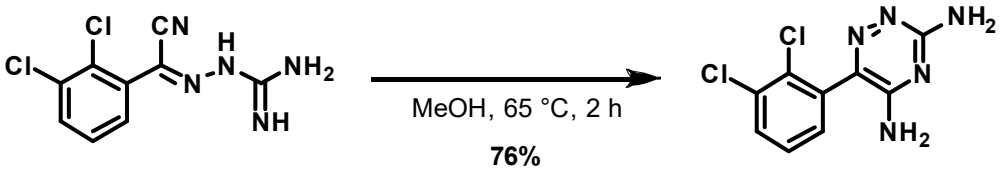
IR (υ_{max}): 3167, 3082, 3072, 3061, 1734, 1707, 1593, 1581, 1548, 1454, 1433, 1410, 1400, 1298, 1284, 1261, 1197, 1168, 1138, 1116, 1099, 1068, 1053, 1014, 976, 829, 812, 790, 744, 705, 682, 661, 628, 615 cm^{-1}.

HRMS (ESI) calculated for $C_9H_8N_5Cl_2$ $[M + H]^+$: 256.0151, found 256.0143. Δ = 3.1 ppm.


1.94
1.00
7.67
7.67
7.66
7.66
7.65
7.65
7.64
7.64
7.43
7.41
7.39
6.71
ppm
Cl
Cl
CN
N
H
N
NH
NH2


Cl
Cl
CN
N
H
N
NH
NH2
164.07
135.78
132.93
130.52
129.97
129.47
128.69
114.86
114.32
200
180
160
140
120
100
80
60
40
20
0
ppm

Lamotrigine reaction 2



Traditional (glassware) synthesis

2-(2,3-dichlorophenyl)-2-(guanidinylimino)acetonitrile (300 mg, 1.17 mmol) was suspended in NaOH (1 M) solution and stirred for 30 mins. The solid was then filtered and washed with water (2 × 10 mL). The resulting solid was solubilised in methanol (6 mL) and heated to 65 °C for 2 hours after which activated carbon (20 mg) was added and the solution was stirred for a further 15 mins before being hot filtered through celite®. The resulting solution was cooled to 0 °C causing a white precipitate to form, which was filtered and washed with cold methanol to yield lamotrigine (230 mg, 0.9 mmol, **76%**).

Polypropylene test reaction:

2-(2,3-dichlorophenyl)-2-(guanidinylimino)acetonitrile (400 mg, 1.56 mmol) was suspended in NaOH (1 M) solution and stirred for 30 mins. The solid was then filtered and washed with water (2 × 10 mL). The resulting solid was solubilised in methanol (6 mL) and heated to 55 °C for 6 hours. After which, activated carbon (20 mg) was added and the solution was stirred for a further 15 mins before being hot filtered through celite®. The resulting solution was cooled to 0 °C causing a white precipitate to form, which was filtered and washed with cold methanol to yield (280 mg, 1.09 mmol, **70%**).

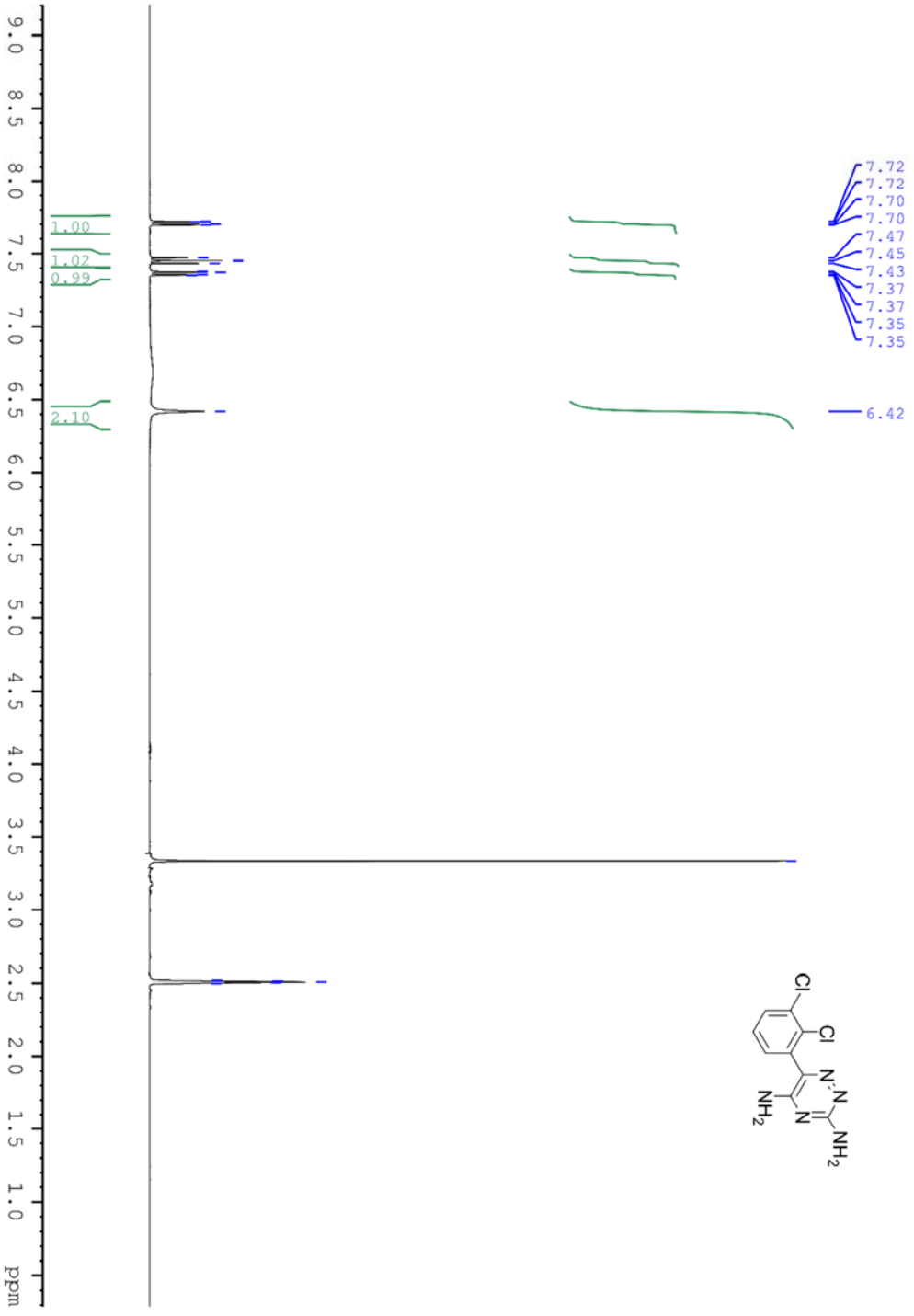
m.p. 214-216 °C.

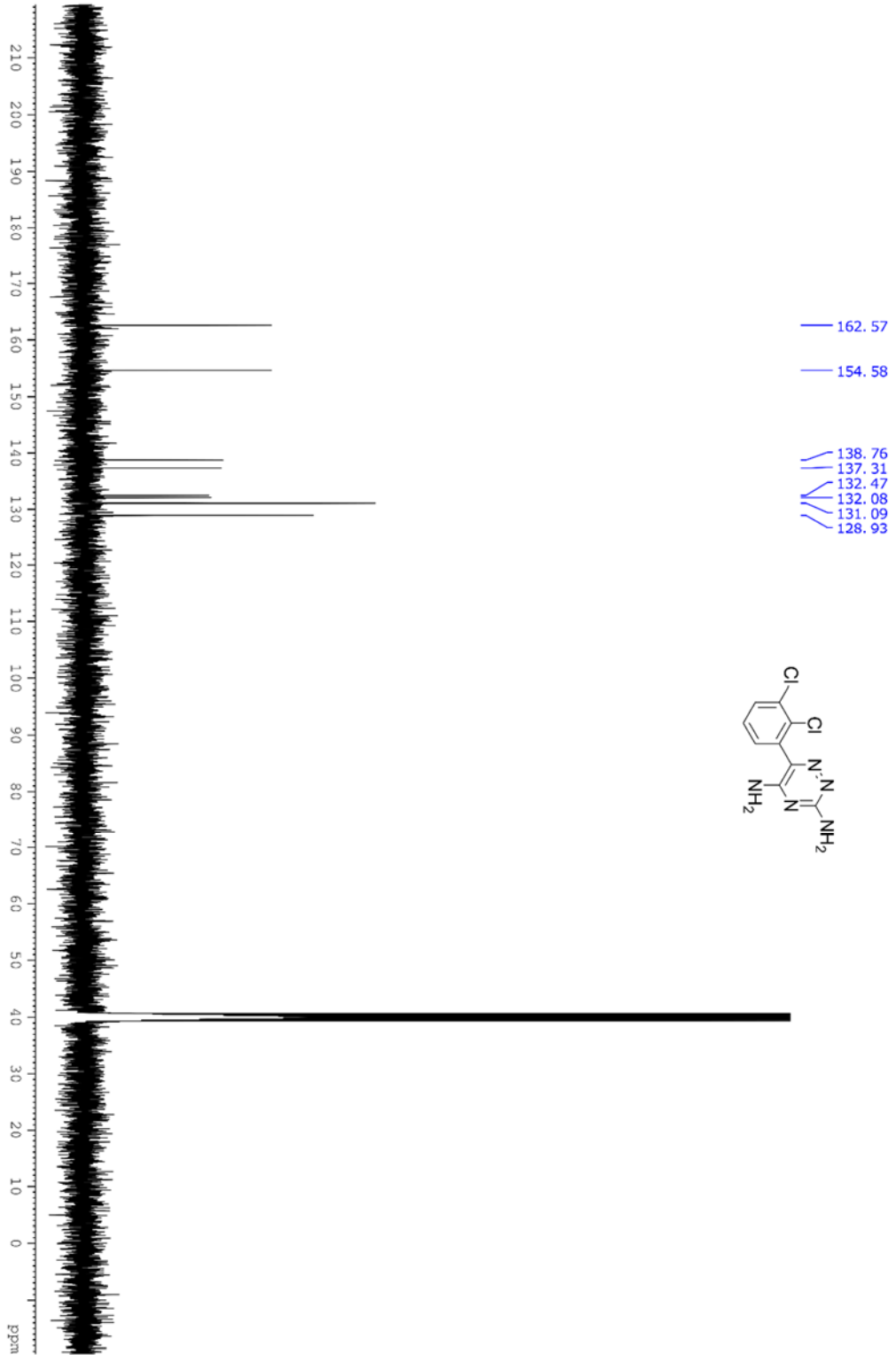
^{1}H NMR (400 MHz, DMSO-d^{6}): δ = 7.71 (1 H, dd, J_1 = 8.0 Hz, J_2=1.6 Hz), 7.45 (1 H, dd, J_1 = 8.0 Hz, J_2 = 7.6 Hz), 7.36 (1 H, dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz), 6.42 (2 H, s).

^{13}C NMR (101 MHz, DMSO-d^{6}): δ 162.6, 154.6, 138.8, 137.3, 132.5, 132.1, 131.1, 128.9.

IR (υ_{max}): 3495, 3356, 3101, 1672, 1614, 552, 1464, 1431, 1410, 1161, 1114, 1018, 810, 788, 769, 738, 721, 605 cm^{-1}.

HRMS (ESI) calculated for $C_9H_7N_5Cl_2Na$ $[M + Na]^+$: 277.9971, found 277.9927. Δ = 16.8 ppm.


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.02
0.99
2.10
7.72
7.72
7.70
7.70
7.47
7.45
7.43
7.37
7.37
7.35
7.35
6.42
Cl
Cl
N
N
NH2
N
NH2


162.57
154.58
138.76
137.31
132.47
132.08
131.09
128.93
Cl
Cl
N
N
N
NH2
NH2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

4. Modular / Monolithic Synthesis of (±)-Baclofen.

4.1 Module / Monolith preparation and configuration

As part of the development of the Baclofen synthesis cartridge the synthesis was performed using the modules **a** – **e** (described in section 2.3). First, the modules were used independently to validate the procedures necessary for each stage of the synthesis, and subsequently the modules were connected with pieces of Tygon tubing to simulate the final cartridge. The inlet and outlet ports in the fluidic pathway of the reaction sequence of the modules were fitted with ¼" UNF to either female (for inlet ports) or male (for the outlet ports) Luer-lock adaptors to allow the modules to be connected together, whilst the top inlet / outlet ports were fitted universally with ¼" UNF to female Luer-lock adaptors. These adaptors were then fitted with either single input female to male Luer-lock connector with valve (modules **a** and **c**) or double input (female) to single output (male) Luer-lock connectors with T – valves (modules **b** and **d**). At the start of the reaction procedure all ports except the initial inlet port are sealed. Care must be taken with the order of opening / closing of individual modules to atmosphere / vacuum to avoid premature transfer of material to subsequent chambers. Starting materials and reagents were prepared and loaded into polypropylene syringes (1, 2, 5 or 20mL capacity, Fig.S12) either prior to beginning the synthesis or immediately prior to use. Solutions prepared in advance were stored at 4 °C prior to use in the synthesis.

Fig. S12: Polypropylene syringes used for starting material and reagents. Left to right; 1 mL, 2 mL, 5 mL and 20 mL capacity.

4.2 Cooling and heating configurations

The cooling and heating of the reaction cartridge necessary for the synthesis of (±)Baclofen was achieved by immersing the lower portion of the reaction cartridge (or individual reaction module in the case of the modular implementation) in either an ice bath (cooling) or a sand bath (heating) as shown below (Fig.S13). For cooling operations the monolithic cartridge was submerged such that the lower 3 cm of the device was under the surface of the water / ice mixture to ensure the entire reaction mixture reached a sufficiently low temperature. For heating operations a sufficient quantity of sand was used such that the lower 2 cm of the device were covered. Care must be taken that the coverage of the monolithic device is uniform. For some heating operations a polypropylene syringe barrel containing glass wool was attached to the appropriate chamber to act as a condenser in the case where vapors escaped the reaction vessel (Fig S13 (C)).

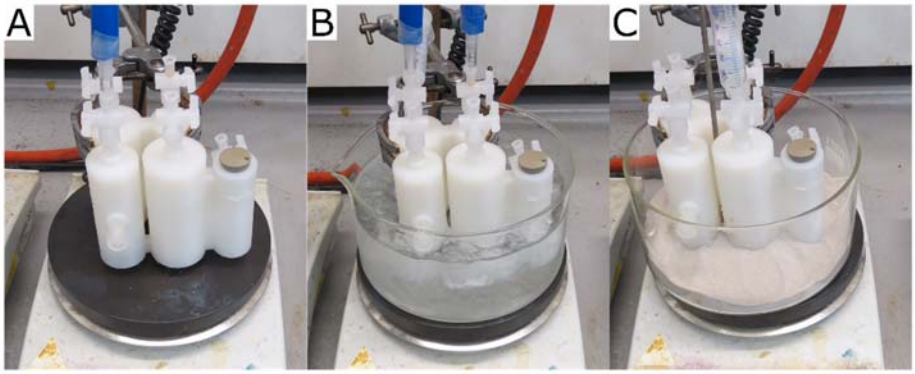


Fig. S13: Configuration of Monolithic reaction cartridge for; (A) room temperature operations, (B) ice cooled operations, and (C) heated operations.

For heating and cooling operations the module was allowed to equilibrate for 15 minutes with the external environment stable at the prescribed temperature before continuing with the operations in the procedure. Heating of the sand bath was controlled by an Asynt-HP1 digital stirrer hotplate with an external temperature probe (Asynt-TC1) submerged in the sand bath.

Heat flow from the sand bath to the monolithic polypropylene walls of the reactor cartridge was modelled for cartridges of varying sizes (100mg starting material scale as designed, along with reactors at 1.25x and 1.5x) to confirm that no adjustment in the heating protocol is required based on the size of reactor for reaction scales tested in this study (Fig. S13). Simulations were performed using SolidWorks CAD software package. Models were meshed with curvature-driven mesh (element size varying from 5 to 1 mm with 8 elements fitted per arc). The

simulation was run in transient mode (900 seconds with 30 second step) with direct sparse solver. 2000 W heating was applied from the bottom plane of the sand bath. Initial temperature was set to 290 K for both sand and model. No thermal contact resistance between sand and model was defined.

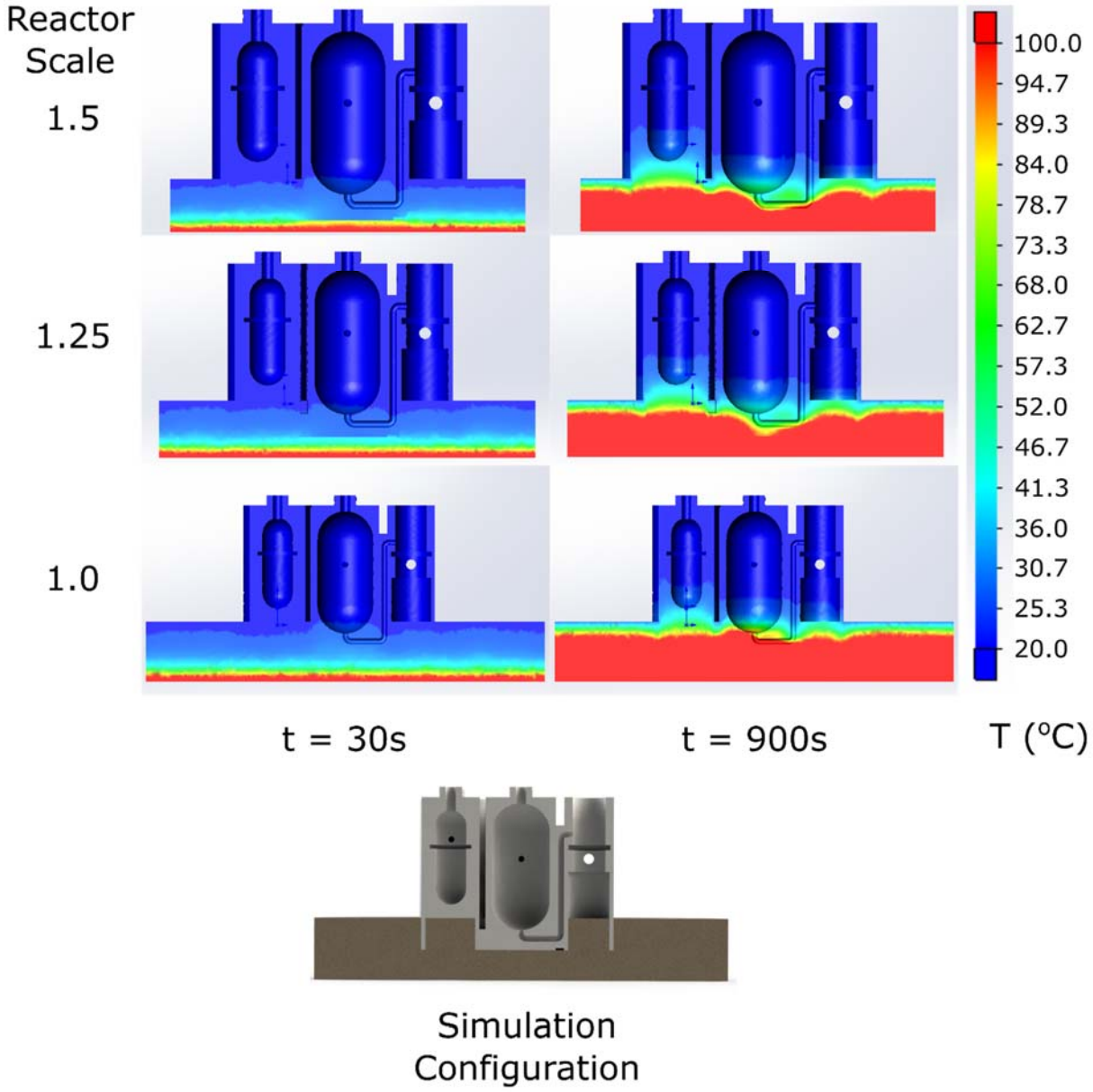


Fig. S14: Simulations of heat transfer from sand bath to monolithic reactionware cartridge at different reactor scales.

4.3 Checklist of important considerations.

To ensure the successful completion of the synthesis of (±)baclofen in the monolithic device, care must be taken that the following are rigorously checked / adhered to:

- **During 3D printing of the monolithic device care should be taken that the printing is not paused for too long (>30 minutes) for the insertion of non-printed parts to ensure successful printing of the device.**
- **After fabrication of the monolithic device it must be thoroughly checked for leaks to ensure the reaction sequence is not contaminated from the outside environment and that the fluidic transfers from chamber to chamber will occur smoothly.**
- **Ensure all reagent solution concentrations are correct.**
- **Ensure that the correct solution is used for each stage in the synthesis and that the order of reagent addition is as described in table S3 below.**
- **Ensure that magnetic stirring bars have been added to all the necessary module chambers.**
- **Once stirring is turned on the chambers with magnetic stirring bars should be checked to ensure the bars are in motion.**
- **When preparing the device for heating / cooling, ensure the device is not in contact with the bottom of the ice / sand bath to ensure uniform temperature distribution around the device.**
- **For heated and cooled operations ensure sufficient time has been left to allow reaction mixtures to achieve a stable temperature before continuing with the procedure.**
- **Care must be taken that the valve positions defined in table S3 are adhered to in order to prevent premature transfer of material from one chamber to the next.**
- **Care must be taken not to exceed the flow rates specified for extraction operations as elevated pressures can force aqueous phase through the hydrophobic frits leading to inefficient separation.**

4.4 Synthetic procedure.

The procedure for the modular synthesis is given below, firstly as prose and then as an itemized list of precise operation (table S3) which, when followed allow the operator to conduct the synthesis of (±)baclofen in the monolithic implementation with minimal human interaction. We have also developed a precise digital code (using the programming language python) that can accompany the synthesis and be loaded into a digital stirrer hotplate to automatically perform the hotplate operations at the appropriate times. This code is available from the authors upon request.

The valve on the top port of the first module is opened to avoid buildup of pressure within the device as material is added. This port is connected to a slight overpressure of nitrogen supplied *via* Schlenk line. Solutions of methyl 4-chloro-cinammate (0.5 M, 100 mg, 0.5 mmol) and tetra butyl ammonium fluoride (TBAF) (1 M, 1 mL, 1 mmol) in THF and 0.3 mL of nitromethane (5.6 mmol) are introduced sequentially into the first reaction chamber. This reaction mixture is stirred for 3 hours. Once the reaction is complete the chamber is put under vacuum (*via* the aforementioned Schlenk line) for 1 hour to evaporate a significant proportion of the THF present. A 2 M aqueous solution of NH_4Cl (2 mL) is then introduced to ensure that the tetrabutyl ammonium ions remain in the aqueous phase of the subsequent ether extraction. Once this has stirred for 10 minutes, 20 mL of Et_2O is flowed through the reaction chamber at a rate of 1 mL/min under stirring. The less dense etheric phase rises through the hydrophobic frit and drains into the next reaction chamber, ensuring none of the aqueous material is carried through into the next reaction chamber. Once all the ether has been pumped through the chamber any remaining liquid (aqueous phase and excess Et_2O) is drawn back through the inlet opening before carrying on to the next stage of the reaction. Once in the second chamber, (b), the extraction solvent is evaporated under reduced pressure. Once the solvent has been removed a solution of $NiCl_2{\cdot}6H_2O$ (137 mg, 0.6 mmol) in methanol (2 mL) is introduced to the chamber and the reaction chamber cooled to 0 °C. A freshly prepared solution of $NaBH_4$ (90 mg, 2.4 mmol) in ethanol (3 mL) is then introduced to the dropwise at a rate of 0.5 mL/min. The reduction reaction is allowed to continue for 1 hour before being brought up to room temperature and a 2 mL aqueous solution of K_2CO_3 (200 mg, 1.4 mmol) is introduced to the chamber. The reaction is then stirred for 1 hour to ensure complete conversion of the material to the corresponding lactam. Vacuum is again applied to the chamber along with mild heating (40 °C) for 1 hour to gently remove the alcohols present in the solvent mixture. Once the

reaction mixture has reduced sufficiently in volume, further water is added to the chamber followed by CH_2Cl_2 (20 mL) at a rate of 1 mL/min. The openings of the chamber are arranged such that the introduction of the extraction solvent pushed the material through the fluidic channel connecting module (b) with module (c). The organic layer is transferred directly to the upper chamber, and passes through the frit and flows directly into the next reaction chamber, (d). After the completion of the organic phase transfer, the solvent is removed under a flow of air. An aqueous 6 M HCl solution (3 mL) is added to the reaction chamber and the mixture heated to 100 °C for 24 hours. After cooling the acidic medium is again removed under a flow of air along with heating (70 °C), followed by the addition of MeOH (3mL) to the chamber to dissolve the reaction residue. Diethyl ether (20 mL) is added and the chamber is pressurized to transfer the slurry through to the final (filtration) cartridge, (e). The Baclofen product can be recovered as a white microcrystalline solid (56 mg, representing a 44% yield over three reaction steps based on starting material (methyl 4-chlorocinnamate). Purity of the final product was assessed by HPLC as ≥95%.

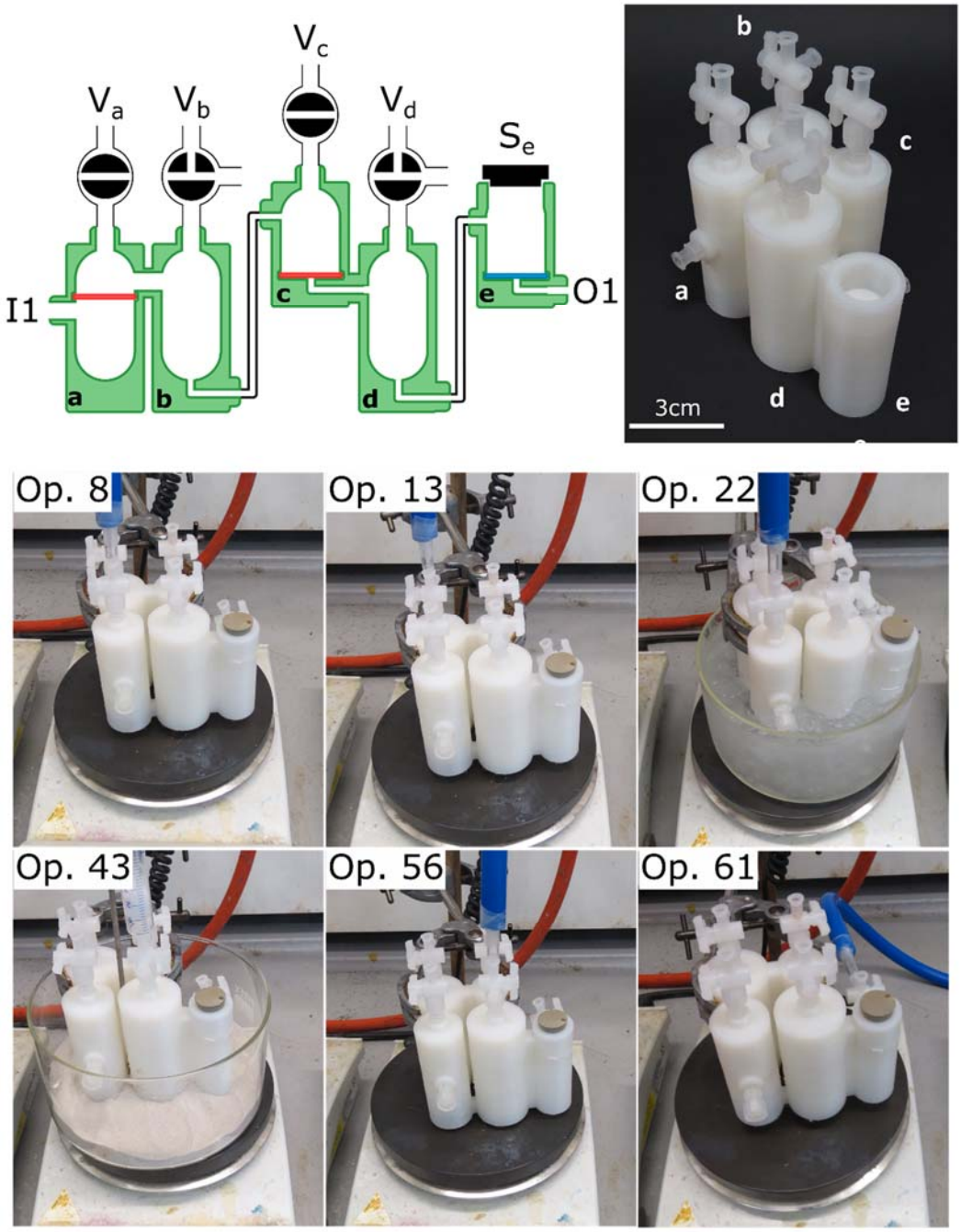


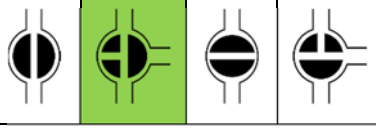
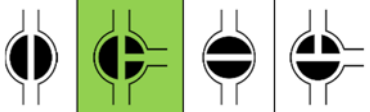
Fig. S15: Top left, schematic diagram of modular / monolithic synthesis cartridge indicating the placement of 2- and 3- way Luer adaptor valves on modules (**a**) – (**d**). Top right; as-printed monolithic cartridge fitted with valve Luer adaptors. Below, photographs illustrating the process at various stages corresponding to the numbered operations given in table S3.

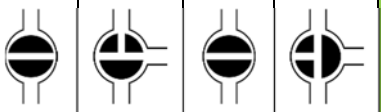
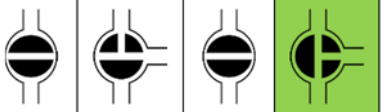
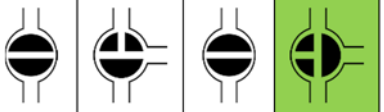
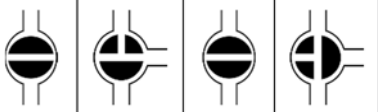
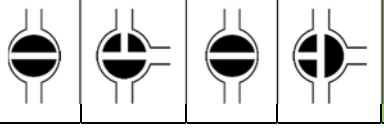
Table S3: Individual operations for the synthesis of (±)-baclofen in modular / monolithic implementation.

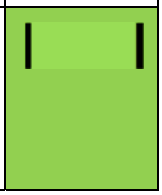
Op.	Time (hh:mm)	Action	Valve Position				Stopper
			V_a	V_b	V_c	V_d	Se
Reagent Solutions							
-	Prepare prior to synthesis	R1: 1 mL methyl 4-chloro-cinammate in THF (0.5M, 0.5 mmol), in a 2 mL syringe	-	-	-	-	-
-	Prepare prior to synthesis	R2: 1 mL TBAF in THF (1 M 1 mL, 1 mmol), in a 2 mL syringe	-	-	-	-	
-	Prepare prior to synthesis	R3: 0.3 mL nitromethane in a 1 mL syringe	-	-	-	-	-
-	Prepare prior to synthesis	R4: 2 mL NH_4Cl_{aq} (2 M) in a 3 mL syringe	-	-	-	-	-
-	Prepare prior to synthesis	R5: 20 mL Et_2O in a 20 mL syringe	-	-	-	-	-
-	Prepare prior to synthesis	R6: $NiCl_2 \cdot 6H_2O$ (137 mg, 0.6 mmol) in methanol (2 mL) in a 3 mL syringe	-	-	-	-	-
-	Prepare Fresh (Op. 23)	R7: $NaBH_4$ (90 mg, 2.4 mmol) in ethanol (3 mL) in a 3 mL syringe	-	-	-	-	-
-	Prepare prior to synthesis	R8: K_2CO_3 (200 mg, 1.4 mmol) in H_2O (2 mL) in a 3 mL syringe	-	-	-	-	-

Op.	Time (hh:mm)	Action	Valve Position				Stopper
			V_a	V_b	V_c	V_d	Se
-	Prepare prior to synthesis	R9: 20 mL dichloromethane in a 20 mL syringe	-	-	-	-	-
-	Prepare prior to synthesis	R10: 6 M HCl (3 mL) in a 5 mL syringe	-	-	-	-	-
-	Prepare prior to synthesis	R11: MeOH (3 mL), in a 5 mL syringe	-	-	-	-	-
-	Prepare prior to synthesis	R12: 20 mL Et_2O in a 20 mL syringe	-	-	-	-	-
Begin Synthesis: Room Temperature Configuration							
1	00:00	Open V_a					
2	00:00	Apply N_2 on Va					
3	00:01	Introduce R1 through I1 over 1 second					
4	00:01	Introduce R2 through I1 over 1second					
5	00:01	Introduce R3 through I1 over 1 second					
6	00:01	Stirrer ON RPM: 500					
7	03:00	Stop N_2 on Va					
8	03:00	Apply vacuum to Va					
9	05:00	Stop vacuum to Va					

Op.	Time (hh:mm)	Action	Valve Position				Stopper
			V_a	V_b	V_c	V_d	Se
10	05:00	Apply N_2 to Va					
11	05:00	Introduce R4 through I1 over 2 seconds					
12	05:11	Stop N_2 to Va					
13	05:11	Close V_a, open V_b					
14	05:11	Introduce R5 through I1 in 20 min					
15	05:32	Stirrer OFF					
16	05:32	Empty chamber 1 of module (a)					
17	05:33	Stirrer: ON RPM: 500					
18	05:33	Apply vacuum to V_b					
19	06:33	Stop vacuum on V_b					
20	06:34	Open V_a					
21	06:34	Introduce R6 through V_b over 5 seconds					
Cooling Configuration							
22	06:34	Cool to 0 °C					
23	06:47	Prepare solution R7					
24	06:49	Adjust V_b					
25	06:49	Introduce R7 to V_b over 5 minutes					

Op.	Time (hh:mm)	Action	Valve Position				Stopper
			V_a	V_b	V_c	V_d	Se
26	06:54	Adjust V_b					
Room Temperature Configuration							
27	06:54	Stop cooling					
28	07:09	Wait until temperature reaches RT					
29	07:09	Adjust V_b					
30	07:09	Introduce R8 to V_b in 2 seconds					
Heating Configuration							
31	08:09	Adjust V_a and V_b					
32	08:09	Apply vacuum to Vb					
33	08:09	Heating to 40°C					
34	10:09	Stop heating					
35	10:24	Stop vacuum to V_b					
36	10:24	Apply N_2 to V_b					
37	10:24	Adjust V_b, Vc and V_d					
38	10:25	Introduce R9 through Vb in 20 minutes					
39	10:45	Adjust V_b and V_c, Remove stopper from module (e)					
40	10:45	Apply partial vacuum to V_d					

Op.	Time (hh:mm)	Action	Valve Position				Stopper
			V_a	V_b	V_c	V_d	Se
41	12:45	Stop vacuum to Vd					
42	12:45	Replace stopper from module (e)					
43	12:45	Fit condenser to top outlet of module (d)					
44	12:45	Adjust V_d					
45	12:45	Introduce R10 to Vd in 2 seconds					
46	12:45	Adjust V_d					
47	12:45	Heat to 100°C					
48	36:45	Set heating to 70°C					
49	36:45	Wait until heating reaches 70°C					
50	37:00	Remove stopper from module (e)					
51	37:00	Remove condenser from Vd					
52	37:00	Apply vacuum to Vd					
53	40:00	Heating: OFF					
54		Allow to cool to room temperature					
55	40:15	Stop vacuum to V_d					
56	40:15	Replace stopper from module (e)					

Op.	Time (hh:mm)	Action	Valve Position				Stopper
			V_a	V_b	V_c	V_d	Se
57	40:15	Adjust V_d					
58	40:15	Introduce R11 to V_d in 2 seconds					
59	40:20	Introduce R12 to V_d in 5 minutes					
60	40:25	Adjust V_d					
61	40:25	Replace outlet Luer stopper with filtrate collector in O1					
62	40:25	Apply N_2 to V_d					
63	40:25	Stop N_2 to V_d					
64	40:25	Remove Stopper from module (e) to retrieve product from filter					

4.5 (±)-Baclofen reaction stage NMR comparisons.

At the modular development stage, samples of crude reaction mixture for (±)-baclofen reactions 1 and 2 were taken from the modular and monolithic reactors during the synthesis to ascertain the success of each reaction and assess the suitability of continuation to subsequent phases of the process. This comparison was carried out by ^{1}H NMR;

(±)-Baclofen reaction 1

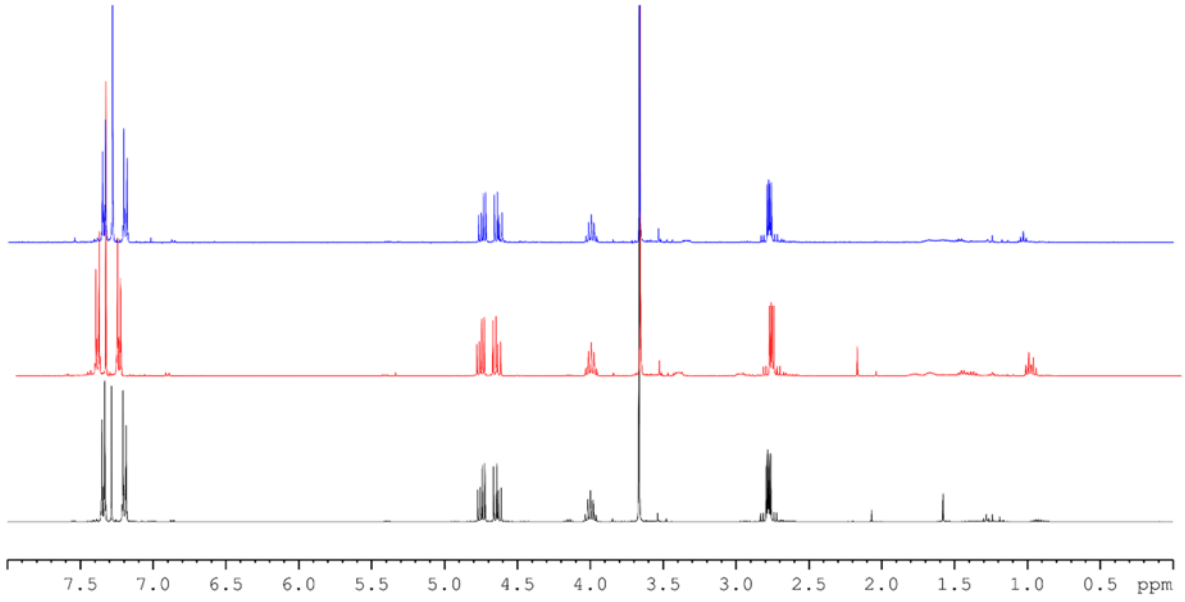


Fig. S16: ^{1}H NMR Comparison of polypropylene module (blue trace), glassware crude (red trace) and glassware purified (black trace) product of (±)-baclofen reaction 1.

(±)-Baclofen reaction 2

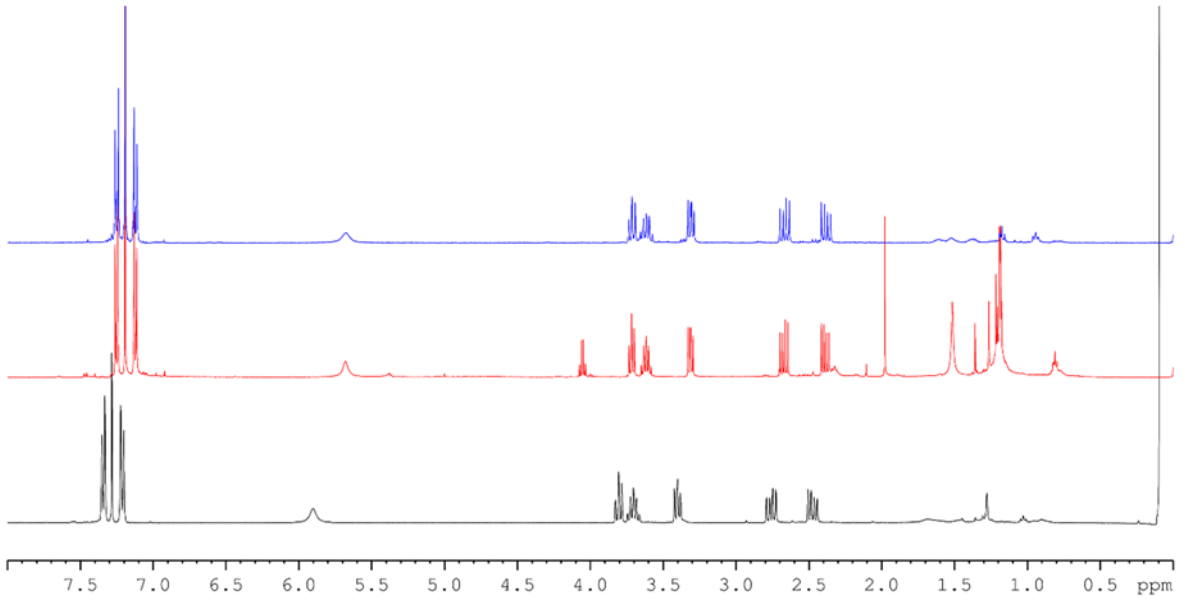


Fig. S17: ^{1}H NMR Comparison of polypropylene module (blue trace), glassware crude (red trace) and glassware purified (black trace) product of (±)-baclofen reaction 2.

(±)-Baclofen reaction 3

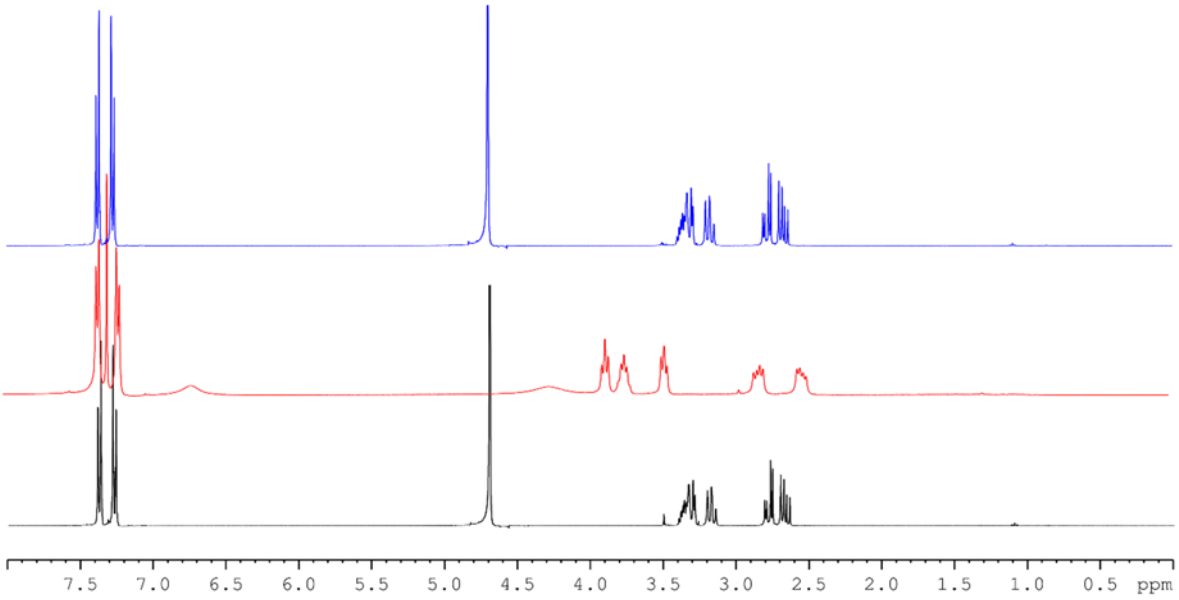


Fig. S18: ^{1}H NMR Comparison of polypropylene module (blue trace) glassware crude (red trace, peaks shifted slightly due to presence of excess HCl in sample) and glassware purified (black trace) of (±)-baclofen product.

4.6 HPLC analysis of Cartridge Synthesized Baclofen.

Material collected from the modular and cartridge synthesis of Baclofen was analysed using a Dionex 3000 Ulitmate HPLC system comprising LPG-3400SD pump, DAD-3000 detector with a 13 µL flow cell, WPS-3000TFC analytical autosampler with fraction collector, and TCC-3000SD column thermostat, running Chromeleon 6.8. A reversed-phase C18 column (Purospher® STAR RP-18 endcapped (5 µm), 100 × 4.6 mm).

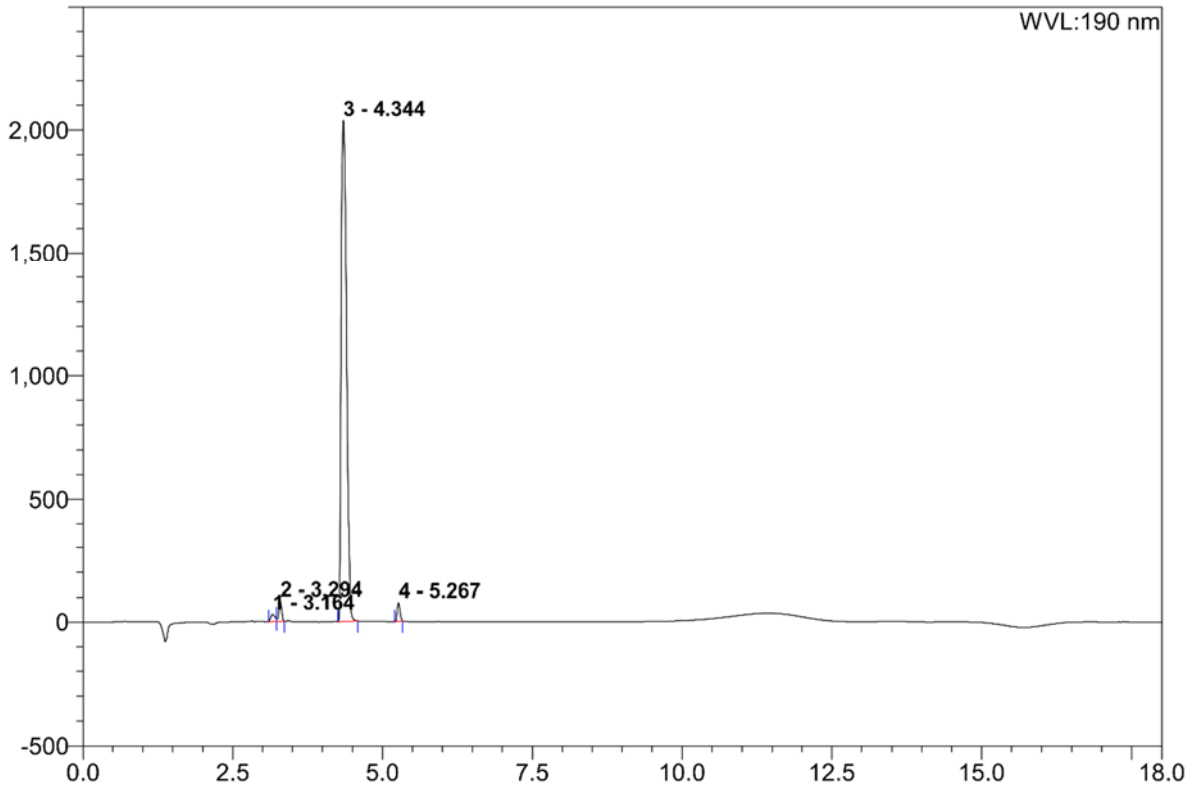


Fig. S19: Integrated HPLC trace for sample obtained from the cartridge synthesis on Baclofen. Peak 3 (retention time 4.344 minutes) represents Baclofen and has a peak area equivalent to 95.03% of the total area of the trace.

4.7 Baclofen Synthesis Scaling Experiments

The synthesis procedure described above for (±)-baclofen was carried out using the quantities of starting materials, reagents, and solvents given in table S4 below. The 300 mg scale reaction was carried out in a modified device in which the capacity of the initial reaction chamber was increased to 6.5 mL to accommodate extra reaction medium. The .stl and OpenSCAD files for this modified cartridge are available as supplementary files.

Table S4: Reagent quantities for different reaction scale syntheses of (±)-baclofen.

Reagent	Quantity		
methyl 4-chloro-cinammate	100 mg (1 mL 0.5 M in THF)	200 mg (1mL 1.0 M in THF)	300 mg (1.5 mL 1.0 M in THF)
TBAF (1M in THF)	1 mL	2 mL	3 mL
$MeNO_2$	0.3 mL	0.6 mL	0.9 mL
2 M $NH_4Cl_{(aq)}$	2 mL	3 mL	3 mL
Et_2O (1st extraction)	20 mL	25 mL	30 mL
$NiCl_2 \cdot 6H_2O$	137 mg	274 mg	411 mg
$NaBH_4$	90 mg	180 mg	270 mg
MeOH ($NiCl_2 \cdot 6H_2O$ solvent)	2 mL	3 mL	4 mL
EtOH ($NaBH_4$ solvent)	3 mL	6 mL	9 mL
K_2CO_3	200 mg	400 mg	600 mg
H_2O	2 mL	4 mL	6 mL
CH_2Cl_2	20 mL	25 mL	30 mL
6 M HCl	3 mL	4 mL	4 mL
MeOH (final product solvent)	3 mL	4 mL	6 mL
Et_2O (crystallization antisolvent)	20 mL	20 mL	20 mL
(±)-baclofen hydrochloride	56 mg	98 mg	133 mg

5. Single Module Synthesis of Lamotrigine.

Lamotrigine synthesis was carried out in a single filtration module (see Fig. S16) in which each of the operations was carried out as follows. During fabrication of the module solid reagents aminoguanidine bicarbonate (250 mg, 0.96 mmol) and 2,3-dichlorobenzoyl cyanide (250 mg, 1.27 mmol) along with a PTFE coated magnetic stirring bar were added subsequent to the addition of the fritted glass filter. Once the module had finished printing all outlets were fitted with ¼" UNF threaded Luer lock adaptors and the cartridge sealed. To initiate the reaction the input and roof adaptors were unsealed and a solution of H_2SO_4 (4 mL 50:50 V/V with H_2O) was introduced into the module at a rate of 0.5 mL/min under stirring. The reaction module was then heated to 70 °C for 3 hours. Once the reactor had cooled to room temperature the reaction mixture was washed with 20 mL H_2O and 20 mL 2 M NaOH solution, followed by a further 20 mL H_2O, with washings being removed *via* the drain at the bottom of the filtration cartridge. The valve on the module drain was then closed and 5 mL of MeOH introduced into the module. The module was then fitted with a condenser similar to that shown in the baclofen synthesis above and the module heated to 55 °C for 6 hours. The reactor was then cooled to 0 °C under continuous stirring before the valve on the module drain was again opened and the methanolic solution removed. The solid material inside the module was then washed with further cold methanol to yield lamotrigine as a pale yellow solid (112 mg, 0.44 mmol, **46%**).

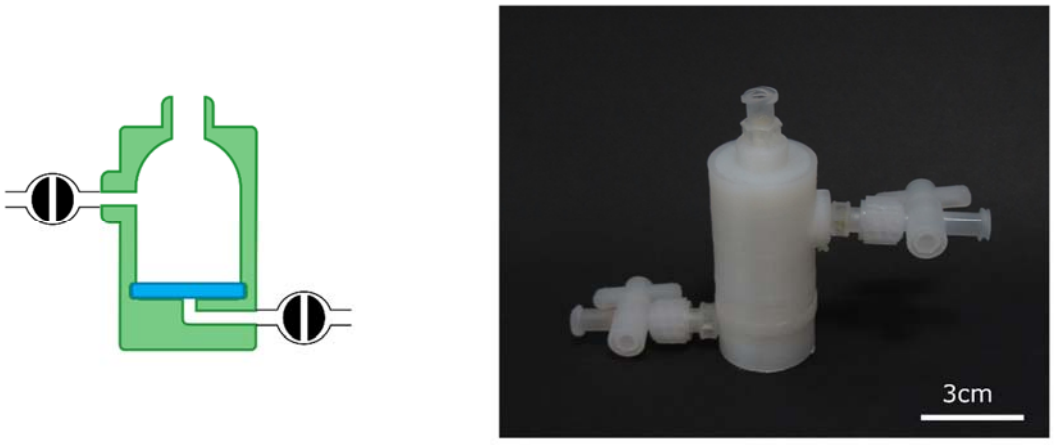


Fig. S20: Schematic diagram (left) and photograph (right) of filtration module used to achieve the synthesis of lamotrigine.

6. Economic Analysis.

For the application of our approach to fine chemical manufacture, consideration must be given to the economic incentives of adopting our methodology - given the up-front costs of cartridge development for any given process (although it should be noted that these costs are one – off costs, and once a process is digitized it can be stored indefinitely and re-used on-demand.). The costs of traditional bench scale synthesis broadly increase in proportion to the quantity (number of units) of material produced, whereas the up-front cost of the digitization process coupled with savings achieved in both labor and infrastructure costs mean that with increasing scale the cost per unit of the cartridge approach will decrease. This means there will be a 'digitization-zone' for fine chemical synthesis between bespoke bench small scale syntheses and reactor scale production i.e. between mg-kg scale, where the use of the cartridge based approach will be economically favorable (Fig. S17)

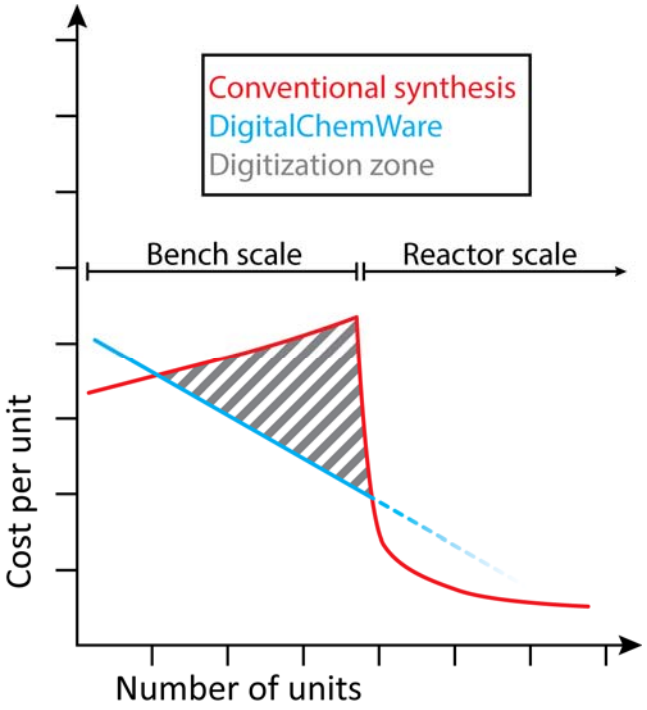


Fig. S21: Illustration of the per unit cost of production for fine chemical manufacture *via* traditional bench, and DigitalChemWare cartridge approaches, highlighting the 'digitization zone' where use of our methodology would be economically advantageous.

As a preliminary analysis of these considerations we have taken two potential regimes for sub-pilot-reactor scale production of an arbitrary fine chemical product. For simplicity this analysis excludes capital expenditure in the setting up of the production facilities in each of the cases,

although it is to be expected that a facility designed to implement cartridge based manufacture would require relatively less investment than a traditional synthetic chemistry laboratory.

Including **cost per gram** for bench (C_B) and **cost per gram** for Digitized Cartridges (C_D), assuming a digitization cost D

Equation 1 $T = \frac{D}{C_B - C_D}$

Breakdown for the costs with Labor costs (L_B, L_R), Infrastructure costs (I_B, I_R), Reagent Costs (R) and Yield (Y)

Equation 2 $C_B = \frac{L_B + I_B + R}{Y}$

Equation 3 $C_D = \frac{L_D + I_D + R}{Y}$

Equation 4 $C_B - C_D = \frac{(L_B + I_B) - (L_D + I_D)}{Y}$

Then the threshold is

Equation 5 $T = \frac{D \times Y}{(L_B + I_B) - (L_D + I_D)}$

Where D is the digitization cost, Y is the reaction yield, L_B and L_D are the labour costs for the reaction on the bench and in reactionware respectively, I_B and I_D are the infrastructure costs for the bench and reactionware respectively.

The actual values of these variables will depend on the economic situation, with a large variety of factors influencing them. We took a rough estimate of the costs incurred for each of these variables based on our own experience of the digitization of the baclofen synthesis, its operation, and discussions with representatives of CRO chemical manufacturing companies and Sigma Millipore. We can provide an illustrative case of where the application of our digitization methodology becomes economically viable for a given product, assuming a digitization cost in the region of $ 50k. Table S5 below sets out the parameters used in our illustration

Table S5: Variables used in the following illustration of the threshold profitability for an arbitrary fine chemical product.

Per day	**Bench scale**	**Reactionware**
Labor(L)	350 $	150 $
Infrastructure (I)	2100 $	750 $
Cost	2500 $	900 $
Reagents (R)	50 $	50 $
# Reactions	2 (1.25 g scale)	10 (0.25 mg scale)
Yield	2.5 g	2.5 g
Cost $	1000 / g	360 /g

Movie S1. This cartoon animation depicts the passage of the reagents and operations that are automatically carried out within the digitally defined reactionware cartridge as the operator adds the various reagents and follows the instructions for running the process, resulting in the production of the solid material at the end of the process.