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Supplementary information

An autonomous portable platform for universal chemical synthesis

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Supplementary Information for:

An autonomous portable platform for universal chemical synthesis

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1 General Experimental Remarks

1.1 Materials

Reagents and solvents were used as received from commercial suppliers unless otherwise stated.

1.2 NMR

NMR measurements were performed with Bruker Advance III HD 600 spectrometer operating at 600.1 and 150.9 MHz for ^{1}H and ^{13}C, respectively. Spectra were collected at 298 K, chemical shifts are reported in ppm, calibrated for the (residual) NMR solvent signal.

1.3 HPLC

HPLC analysis was performed on a Thermo Dionex Ultimate 3000 equipped with a LPG-3400 RS pump, a WPS-3000TRS autosampler, a TCC-3000SD column compartment and a DAD-3000 diode array detector. The HPLC was connected to a Bruker MaXis Impact quadrupole time-of-flight mass spectrometer with an electrospray source, operating in negative mode for small molecules and oligopeptides, and positive mode for oligonucleotides. The voltage of the capillary tip set at 4500 V, end plate offset at − 500 V, nebuliser at 1.6 bar, dry gas at 8.0 l/min, funnel 1 RF at 400 Vpp, funnel 2 RF at 400 Vpp, isCID energy at 0 eV, hexapole RF at 100 Vpp, ion energy 5.0 eV, low mass at 50 m/z, collision energy at 5 eV, collision cell RF at 200 Vpp, transfer time at 63.5 µs, and the pre-pulse storage time at 1.0 µs. The mass range was set to 50-2000 m/z for small molecules and oligopeptides, while 500-5000 m/z for oligonucleotides. Data was analysed using the Bruker DataAnalysis v4.1 software suite.

Small organic molecules

10 µL of each sample was injected on to an Agilent Porodhell 120 EC-C18 2.7 µm, 4.6 x 150 mm column, eluting at 1mL/min with mobile phase A being water + 0.1% formic acid and mobile phase B acetonitrile + 0.1% formic acid, detecting using UV (λ = 190, 214, 220 and 254 nm). The total run time was 26 minutes, with the LC method as follows - 0 min- 0% B, 4min – 10% B, 16 min – 70% B, 19 min – 100% B, 23 min – 0% B, 26 min – 0% B. Column compartment was set at 30 °C.

Oligonucleotides

10 µL of each sample was injected on to a Clarity 2.6 µm Oligo MS 100 Å (100 mm x 2.1 mm) column, eluting at 0.3 mL/min with *mobile phase A* being 100 mM hexafluoro isopropanol (HFIP)/ 4 mM triethylamine (TEA)/ 2% MeOH, and *mobile phase B* 100 mM hexafluoro isopropanol (HFIP)/ 4 mM triethylamine (TEA)/ 98% MeOH, detecting using UV (λ = 260 nm). The LC method was 95% A to 80% B over 30 mins. Column compartment was set at 50 °C.

1.4 3D printing

Reactionware

3D printing was done using a Ultimaker 2+ FDM. Polypropylene (PP) filament was purchased from Barnes Plastic Welding Equipment Ltd., Blackburn, UK. All prints were performed on a 12 mm PP sheet as a replacement of the standard glass bed. This is a necessary requirement to achieve a good adhesion of the first PP layer. The main 3D printer settings were: *Bed Temperature:* off (room temperature), *Nozzle temperature:* 260 ºC, *Speed:* 15 mm/s.

Sensor cases

3D Printing of accessories was performed on a Connex Objet 500 printer from Stratasys using the Fullcure 720 translucent resin for the major body of the printed parts. Once the print was finished, the supports were scraped manually before washing it thoroughly using a water jet cleaning station (Quill Vogue Polyjet). Then, the parts were placed in a 0.1 M $NaOH_{(aq)}$ bath for 30 min. Finally, the parts were again washed thoroughly in the cleaning station.

1.5 Laser Cutting

Laser-Cutting: was performed on a Monster1060 CO2 Laser system (ML1060 130 W) from Radecal with the RDWorksV8 software. The applied parameters to cut the 6 mm acrylic sheets were:

- *Laser power:* 50-65%
- *Speed:* 17 mm/s
- *Air:* On
- *Laser through mode:* Enabled
- *Air pressure:* 0.3 MPa
- *Flow rate:* 33 L/min

2 Software architecture

The portable platform was controlled adapting the previously published Chemical Description Language (χDL).[1,2]

2.1 Chemical Description Language (χDL)

Figure S1 represents the architecture used in χDL. The programming language contains three different modules of steps: base steps, utility steps and synthesis steps. Base steps execute a *Chempiler* object. The Chempiler library maps the platform graph to device drivers, providing a platform controller for χDL to execute steps with. This library is programmed to use *ChemputerAPI* (interface for custom-made devices, including the sensorhub shield) or *SerialLabware* (interface for commercial devices, handling different communication protocols) to communicate with the platform. Having this programming hierarchy, the user interacts solely with synthesis steps that will automatically execute operations on the specified platform. Utility steps are composed from base steps and other utility steps, while synthesis steps are constructed from utility steps and other synthesis steps. Currently χDL is composed of 82 different steps divided in 38 base steps (**Table S1**), 34 utility steps (**Table S2**), and 10 synthesis steps (**Table S3**).

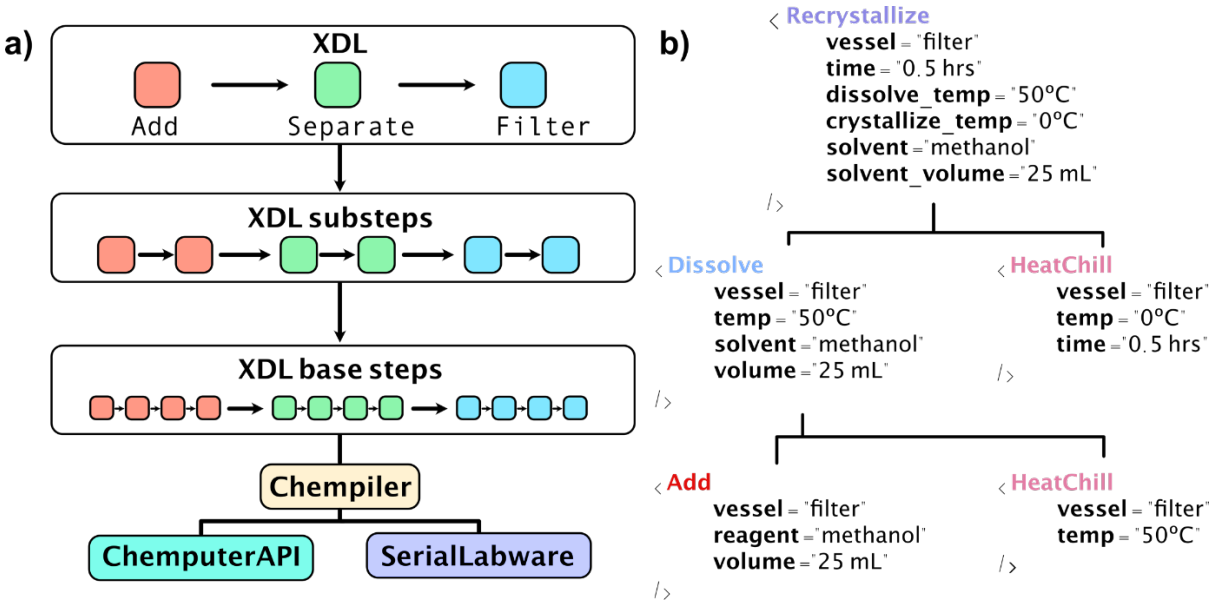


Figure S1. a) Software tree for χDL and b) an example of all the sub-steps to be executed to complete the synthesis step Recrystallize

Table S1. χDL base steps implemented in the portable platform

Step	Description	Step	Description
CChillerWaitforTemp	Waits for stirrer to reach the setpoint temperature	**CStirrerSetTemp**	Sets temperature on stirrer
CStartChiller	Starts recirculating pump	**CStirrerWaitForTemp**	Waits until the stirrer temperature reaches the setpoint
CStopChiller	Stops recirculation pump	**CStopHeat**	Stops heating operation of the stirrer
CBreakPoint	Execution is halted until operator resumes it	**CStopStir**	Stops stirring operation of the stirrer
CConnect	Connects two nodes together	**CStartVacuum**	Switches on vacuum pump
CMove	Moves a specified volume from one node to another	**CStopVacuum**	Switches off pump and vacuum pump to allow inert gas flow in
Confirm	Waits for user's confirmation	**CValveMoveToPosition**	Moves valve to given position
CSetRecordingSpeed	Set the time-lapse speed of the camera module	**CStirrerHeat**	Starts heating operation of the stirrer
CWait	Delays execution for the specified time	**CStir**	Starts stirring operation
CWaitUntil	Waits until a specified start time is reached	**CGetTemperature**	Gets the current temperature of the hotplate
CEvaporate	Detects evaporation based on pressure	**CIntervalReading**	Changes pressure readings frequency
CMonitorPressure	Starts monitoring the pressure in the given channels	**CPulse**	Vacuum pulses to the specify module
CSwitchArgon	Switches off pump and vacuum pump	**CPulseTransfer**	Vacuum pulses are used to transfer from module to module
CSwitchVacuum	Switches on vacuum pump	**CRestartMonitorPressure**	Restarts monitoring pressure
CTransferTo	Reads pressure changes to determine transfers completeness	**CWaitForStabilization**	Waits until pressure stabilizes after transfers
CStopMonitorPressure	Stops monitoring pressure in given channel	**CSwitchEmpty**	Closes gas inlet for the specified module
CSeStirRate	Sets stirring speed	**CSetStirRate**	Sets stir rate for hotplate
CSwitchPump	Switches on/off vacuum pump	**CStartRecording**	Starts recording
CSwitchStirrer	Switches on/off reagent/solvent stirrers	**CStopRecording**	Stops recording

Table S2. χDL utility steps implemented in portable platform

Step	Description	Step	Description
CleanBackbone	Moves 3 mL of a cleaning solvent to every available waste node	**StopPurge**	Switches pump off and de-energizes valves on the last cartridge
Wait	Waits for given time, changing the recording speed	**ShutDown**	Iterates through all the devices and switches them off
WaitUntil	Waits until a specified start time is reached, changing the recording	**Standby**	Moves solvent around backbone every specified time to prevent clogging.
Stir	Stirs the specified vessel	**SetStirRate**	Sets rate of stirring for a reactor, filter or rotary evaporator
HeatChillSetTemp	Sets stirrer temperature	**StartStir**	Starts stirring reactor, filter or rotary evaporator at given stir speed.
HeatChillToTemp	Heat/Chills vessel to given temp and leave heater/chiller on.	**StopStir**	Stops stirring reactor, filter or rotary evaporator.
StartHeatChill	Starts heating/Chilling the vessel to given temperature and gives the	**ApplyVacuum**	Applies vacuum to a given vessel for a specified time
StirrerReturnToRT	Stops heating the given vessel and let it cool down to RT (30ºC)	**StartVacuum**	Starts vacuum pump attached to given vessel.
StopHeatChill	Stop heater/chiller on given vessel.	**StopVacuum**	Stops vacuum pump attached to given vessel.
PrimePumpForAdd	Prime pump attached to given reagent flask in anticipation of reagent	**StartPurge**	Switches vacuum pump on the last cartridge
MonitorPressure	Start reading pressures on given vessels	**BubbleSolution**	Applies vacuum to a specified module to bubble inert gas through
StartCool	Start recirculation pump on given vessel	**FlushTubing**	Moves gas through backbone to remove residual liquid
StopCool	Stop recirculation pump	**RestartMonitorPressure**	Restarts monitoring pressure
SwicthArgon	Switches off vacuum pump, turns on gas inlet	**HeatChillReturnToRT**	Allows heater/chiller return to room temperature and then stop
SwitchVacuum	Switches on vacuum pump, turns off gas inlet	**StopMonitorPressure**	Stops monitoring pressure
Transfer	Transfers contents from one vessel to another using the vacuum pump	**SwitchArgon**	Turns on gas inlet to the specified module
Purge	Switch vacuum pump on the last cartridge for a given time	**WaitWhilePulse**	Waits for a given time while applying vacuum pulses to a module

Table S3. χDL synthesis steps implemented in the portable platform.

Step	Description
Add	Adds given volume of given reagent/solvent to given vessel
Dissolve	Dissolves contents of vessel in given solvent, at given temperature.
Dry	Dries given vessel by applying vacuum for a given time
Evaporate	Evaporates contents of give cartridge at given temperature
Filter	Filters contents of given cartridge and transfer them to the collector cartridge
HeatChill	Heat/Chills given cartridge to given temperature for given time
Precipitate	Induces precipitation by changing temperature in given cartridge
Recrystallize	Recrystallizes contents in given cartridge
Separate	Extracts/washes contents of cartridge with given solvent
WashSolid	Washes solid in given cartridge by adding solvent and filtering *n* times

2.2 Software workflow

The *portable platform* χDL that directly executes the abstract steps from the universal chemical language χDL includes a *cartridge generator* and *graph generator* packages to guarantee an autonomous execution of the chemical synthesis. In this sense, the χDL file, obtained from literature protocols[2], contains all the necessary chemical steps to be executed using the *portable platform χDL*. Simultaneously, this file automatically generates: a graph, containing all the positions of the monoliths, reagents and solvents to execute the reaction; and a first prototype of a reactionware monolith to execute the synthesis in, generated based on the back-end code of **ChemSCAD**.[2]

This workflow (**Figure S2**) generates 5 different files that are used for an automated synthesis:

1. **.xdl file:** A universal synthesis language file containing all the necessary steps for the synthesis, independent from the platform used.
2. **.json:** A platform specific graph with all the physical locations, connectivity, properties, and capabilities for each device that will be used in the synthesis.
3. **.xdlexe:** A platform specific executable file containing all the base steps that can be directly executed in the portable platform.
4. **.ccad:** An editable ChemSCAD file of a reactor prototype including all the chemical steps needed for the synthesis.
5. **.stl:** A 3D printable file of the reactors for

An example for the generation of all the necessary files and the execution of the Umifenovir synthesis is shown in **Figure S3**

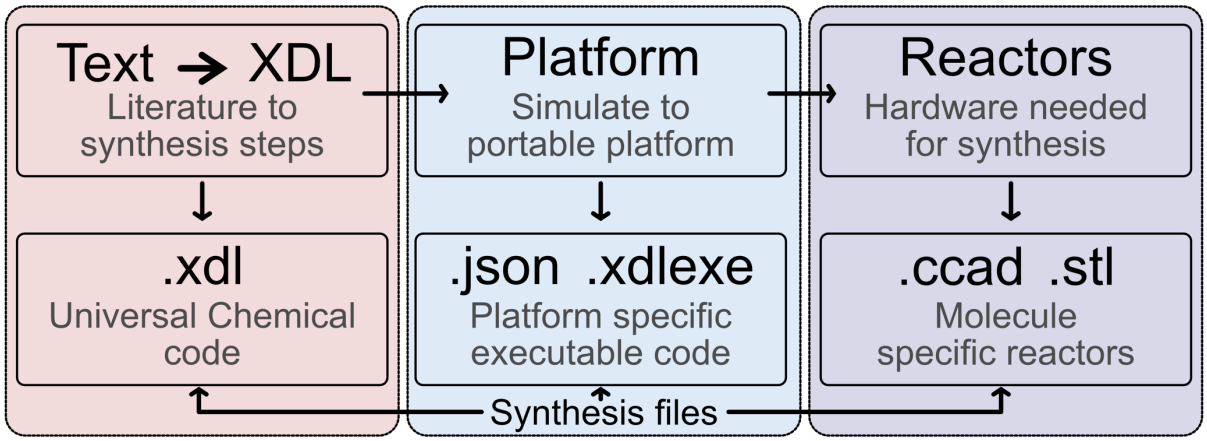


Figure S2. a) χDL steps containing parametric information for the synthesis of a targeted molecule, b) 3D modules generated based on the extracted parameters from the χDL file, and c) assembly of individual modules to produce a single STL file of a monolithic cartridge.

```
from os import path
from xdl import XDL
import ChemputerAPI
import SerialLabware
from chempiler import Chempiler
from baristabotxdl import BaristabotPlatform

experiment_name = 'Umifenovir-synthesis'
# Directory path
root = path.abspath(path.dirname(__file__))
# Output folder for log files
output_dir = path.join(root, 'logs')

# XDL file location
xdl_file = ('Umifenovir- synthesis.xdl')
# Instatiate xdl files with the respective platform
xdl = XDL(xdl=xdl_file, platform=BaristabotPlatform)

# Generates graph and STL files from XDL file
xdl.graph(save=experiment_name)

# Graph directory location
graph = path.join(root, f'{experiment_name}.json')
# Prepare file for execution in the specifed platform
xdl.prepare_for_execution(graph_file=graph, testing=True)
# Instantiate executable file with the specified platform
xdlexe = XDL(xdl_file + 'exe',platform=BaristabotPlatform)

# Compile Chempiler, ChemputerAPI and SerialLabware
c = Chempiler(experiment_name,
              graph,
              output_dir,
              simulation=False,
              device_modules=[ChemputerAPI, SerialLabware])

# Execute synthesis steps in the specified platform
xdlexe.execute(c)
```

Figure S3. An example for the generation of all the necessary files (.xdlexe, .json, .ccad, .stl) and the execution for the synthesis of Umifenovir

2.3 Cartridge generator

To automatically produce monolithic reactionware cartridges, a generator was programmed using Python. A χDL file contains a *Procedure* section with a list of all the synthesis steps needed to produce the targeted molecule. Considering reactionware systems are based on a workflow (i.e. linear synthesis) to create digital blueprints, this list of steps can be used to produce a first draft of monolithic designs containing all the necessary cartridges to execute the respective operations.

The *cartridge generator* iterates through all the steps present in the procedure section of the χDL file. For each step, it will assign what type of reactor is needed (i.e. reactor, filter or floating filter) based on the vessel's name and the executed function. All the parameters that are defined within this step are used to fine tune the geometric properties of the different modules. For example, if 25 mL of *solvent A* is added to *reactor*, then a reactor-type module with a volume of 25 mL is created. This process continues over all the χDL steps and finally all the modules are appended in the correct order to produce a single STL file for 3D printing using the backend software of **ChemSCAD** (Figure S4).[3] Once the modules are created, all the volumes are increased x 1.5 times. This is to prevent running synthetic procedures with 100% filled modules.

The software contains sanity checks at the end of the process to check the size of the reactors. Considering the modules are 3D printed, they are limited by the printing volume of the 3D printer used. In the case of Ultimaker 2+ the maximum printing height is ~ 200 mm, so this was used as a maximum height for the cartridges. If the cartridge is bigger than this size, the user can input a scale factor to reduce the volume/size of the monolith. When a scale factor is used, a new χDL file is created containing all the changed volumes to assure compatibility between the 3D printed reactors and the executable script.

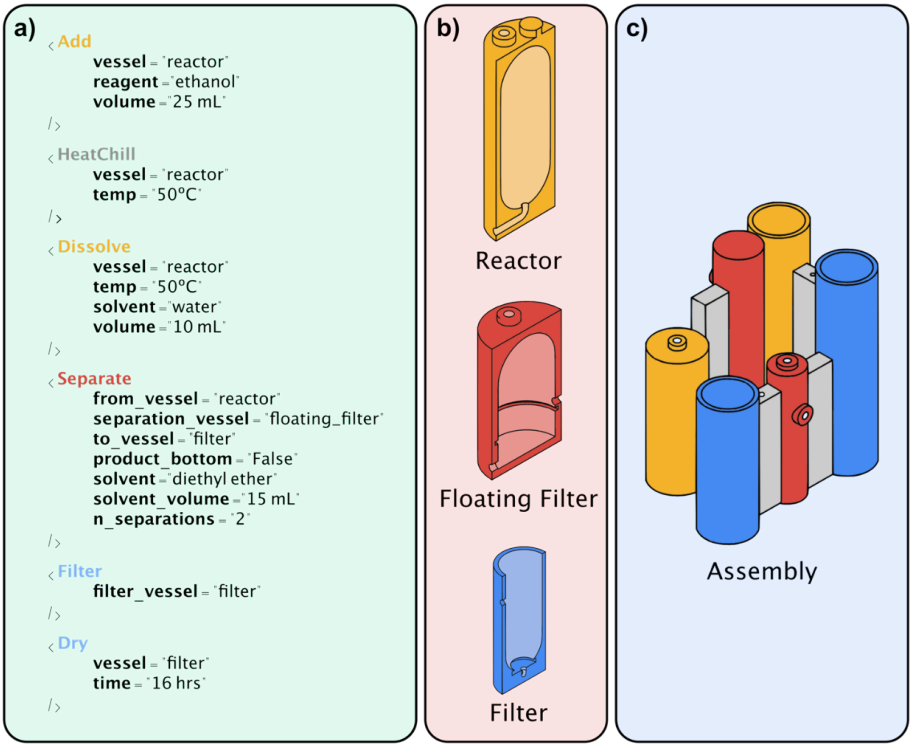


Figure S4. a) χDL steps containing parametric information for the synthesis of a targeted molecule, b) 3D modules generated based on the extracted parameters from the χDL file, and c) assembly of individual modules to produce a single STL file of a monolithic cartridge.

2.4 Graph generator

The portable platform is based on a graph containing all the topology information. In the directed multigraph each node represents a physical device location, including all the device properties and capabilities. This also includes reagents/solvents locations, as well as the connections between the pumps and the different modules. The physical operations carried out by the portable platform are fixed, considering all the chemical operations are extracted into the monolithic designs. This leads to having fixed elements in the graph, such as syringe pumps and the pneumatic manifold and the hotplate (Figure S5).

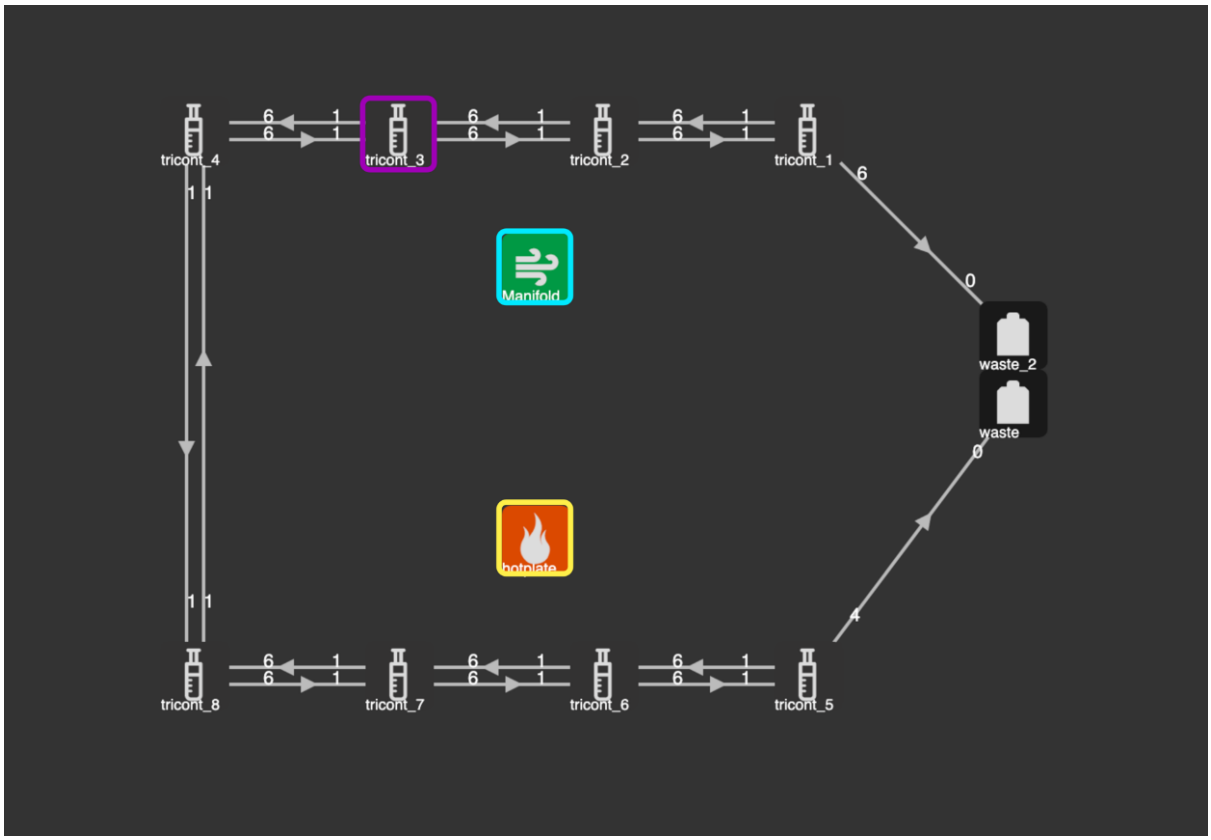


Figure S5. Portable platform graph template containing *C3000MP* Tricontinent syringe pumps (Purple), pneumatic supply (cyan) and IKA RCT Digital hotplate (yellow).

Once having a basic template, the information in the χDL file can be used to identify all the reagents, solvents and cartridges needed in the platform. The reactionware modules are obtained (in the correct sequential order) from the *CartridgeGenerator* (**Section 2.2**). Finally, all the necessary connections (i.e. pump valves ports, manifold ports, and connections in between reactionware modules) are added to obtain a graph ready to be used (Figure S6).

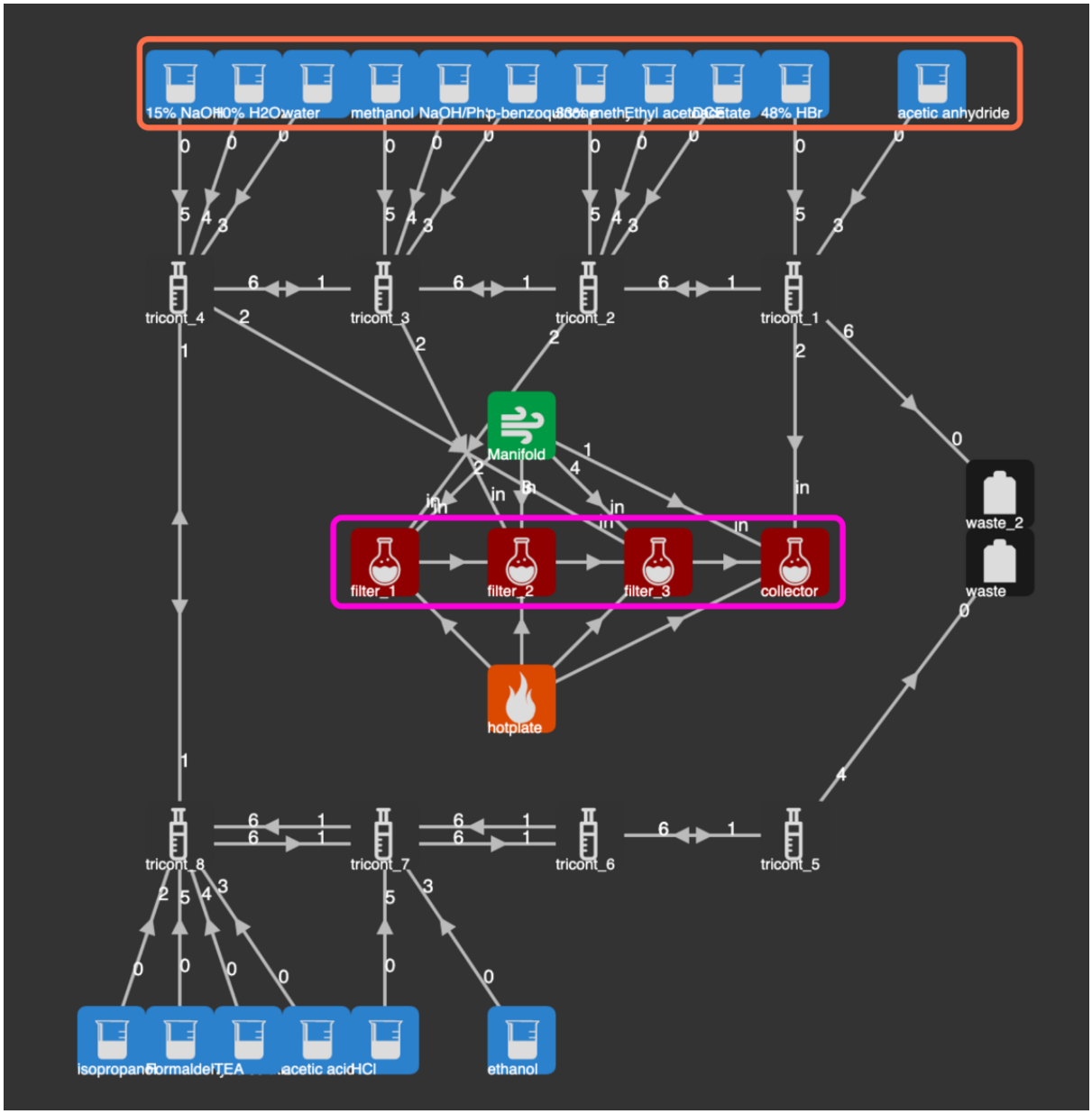


Figure S6. Full graph including reagents and solvents (orange rectangle) and reactionware modules (pink rectangle).

2.5 Step reaction classes

Step reaction can be added as a new type of steps within the χDL software suite. The class is composed of synthetic, utility or base steps and it is designed to contain all the minimum parameters necessary for the execution of a specific type of reaction. For example, the synthesis of oligopeptides is composed of four main processes: deprotection, coupling, washing, and cleavage. These procedures are repeated in an iterative fashion for a specified sequence until the final oligopeptide is completed and cleaved from the solid support. To write an executable file containing all the steps can be tedious and time consuming. However, since these are repetitive processes, they can be compressed into a single step reaction class (SPPS, Solid Phase Peptide Synthesis) that contains only the reaction scale and the sequence as minimum parameters. Having the oligopeptide sequence, χDL can generate all the necessary steps for completing the synthesis that include all χDL steps and base steps (Figure S7). Similarly for the synthesis of oligonucleotides, a different step reaction class can be programmed, to generate a complete executable script based solely on the input sequence.

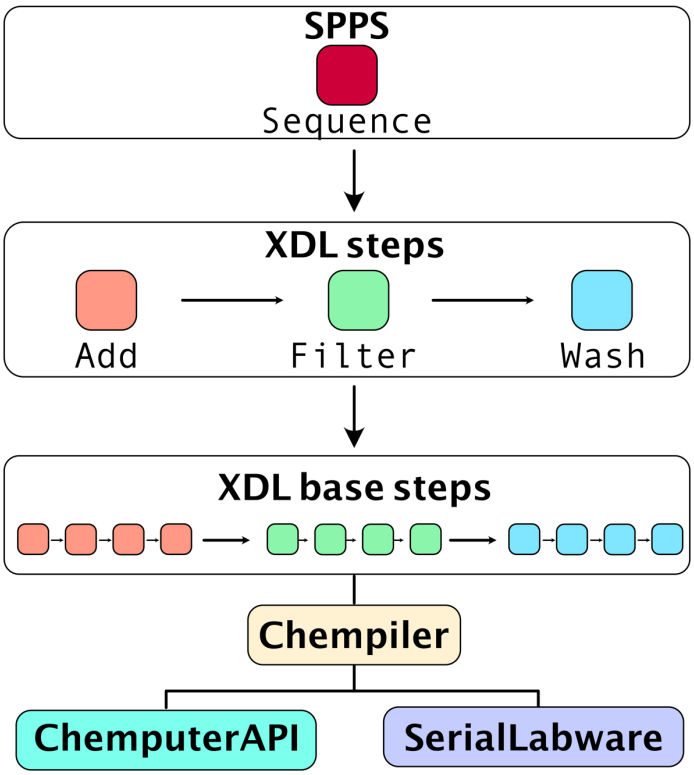


Figure S7. Software tree for a step-reaction class in χDL. The SPPS class inputs the minimum parameters for the synthesis of oligopeptides. Within this class there are several χDL steps for the deprotection, coupling and resin washing for the respective sequence. These steps are further divided in χDL base steps that are directly executed into the platform. The cycle is repeated for each amino acid specified in the sequence.

3 Portable platform Hardware Modules

3.1 Framework

The frame was built from OpenBuilds® parts (Table S4). The individual V-Slot rails were connected via L brackets and drop in tee nuts. To make a connection, the tee nut is simply placed in the V-Slot. When tightening the screw, the tee nut will turn inside the bottom slot and make a no-slip connection. More details on construction with OpenBuilds® parts can be found under https://openbuilds.com/. Then, the customized acrylic sheets (Figure S8) were added to the frame and locked in place using items in entries 1 and 2 from Table S1 (Figure S9b)

Table S4. Bill of materials for the portable platform frame.

Description	Manufacturer's Part Number	Amount	Supplier
Drop In Tee Nuts M5 Thread size	VSLOT-H-DT-M5	32	Ooznest
M5 Low Profile Bolts	VSLOT-S-B-LP-M5-8	32	Ooznest
V-Slot Linear Rail – 20x20mm black anodize, 250 mm	VSLOT-2040-O-B-200-299	6	Ooznest
V-Slot Linear Rail – 20x20mm black anodize, 310 mm	VSLOT-2040-O-B-300-399	4	Ooznest
V-Slot Linear Rail – 20x20mm black anodize, 330 mm	VSLOT-2040-O-B-300-399	4	Ooznest
V-Slot Linear Rail – 20x20mm black anodize, 600 mm	VSLOT-2040-O-B-600-699	2	Ooznest
Universal L brackets single clear anodise	VSLOT-B-UL-S-C	4	Ooznest
90 Degree Joining Plate	VSLOT-M-P-90-5-C	8	Ooznest
5 Hole T Joining Plate	VSLOT-M-P-T-5-C	2	Ooznest

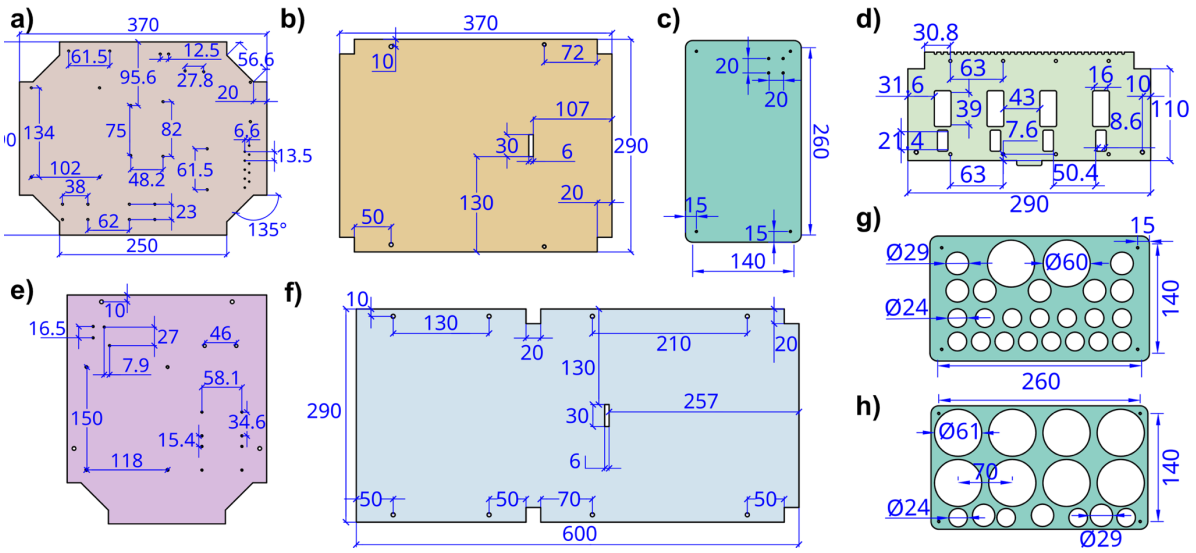


Figure S8. Acrylic designs for a) platform top, b) platform middle, c) bottom for solvents and reagents, d) back-pumps holder and e) platform back, f) bottom platform, g) reagents holder, and h) solvents holder acrylic plates used in portable platform. Units are in mm

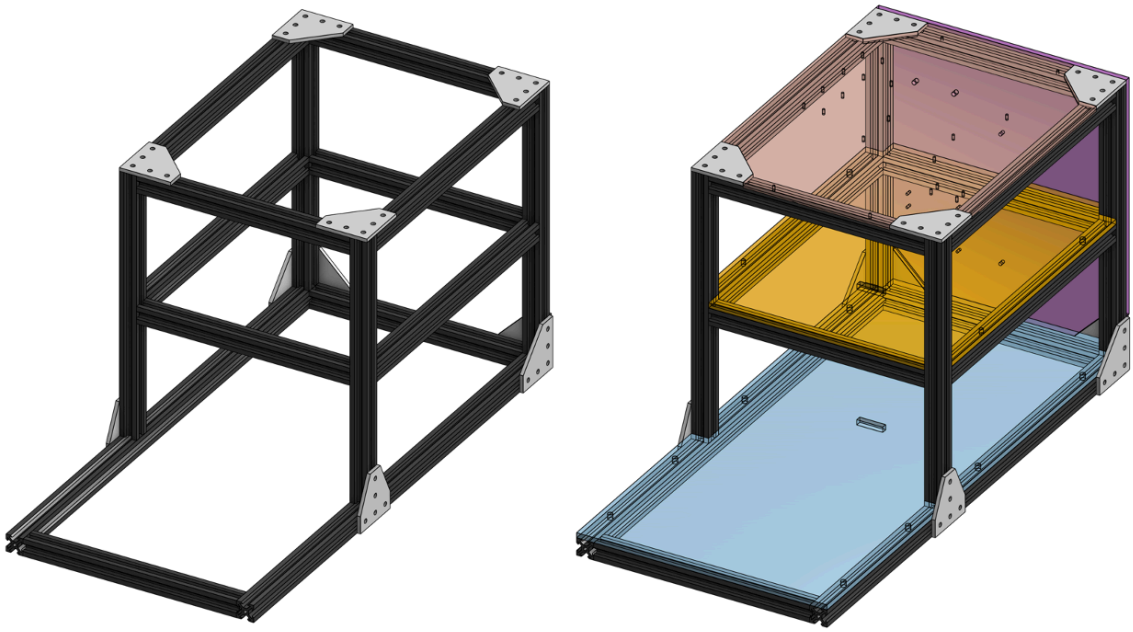


Figure S9. a) Fully assembled frame and b) including the acrylic sheets locked in place for Portable platform

3.2 Liquid Handling Backbone

Assembly

8x *C3000MP Syringe Pumps* were used in the platform equipped with 6-way distribution valves and 12.5 mL syringes (syringes are available in a wide range of volumes, from 50 µL to 12.5 mL). The pumps were organized into two stacks of 4 pumps each and fixed to the acrylic backplates using M3 screws. Based on manufacturer specifications, the media temperature should be between 15 ºC and 40ºC.

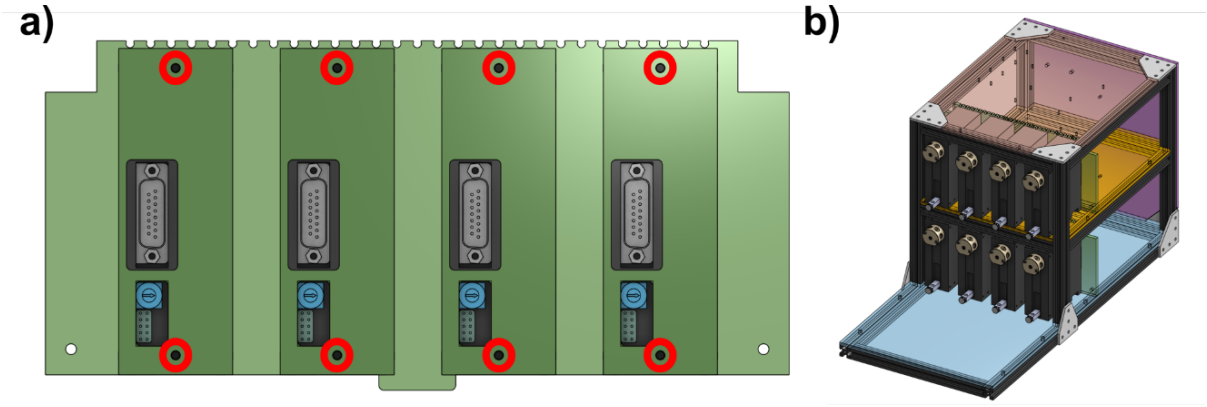


Figure S10. a) Red circles indicate the position of M3 screws to fix the syringe pumps onto the acrylic sheet. b) Isometric view on the assembly progress of the portable platform.

Tubing connections

To correctly assemble the backbone, all tubing must be cut with an appropriate tube cutter to provide perpendicular cut edge with no burrs.

Table S5 contains the bill of materials (BOM) needed to assemble the liquid handling backbone. Because of the size of the tubing, heterogenous mixtures are more likely to cause clogging.

Table S5. BOM used for Portable platform tubing

Supplier	Part #	Description	Quantity
Thames Restek	JR-T-6807-M25	Tubing, PTFE, 1/16" OD x 1.00 mm ID	N/A
Thames Restek	UPLT-115X	NUT, SUPER FLANGELESS 1/16-1/32in 1/4-28	N/A
Thames Restek	UPP-259X	SF Ferrule w/SS Ring 1/16in	N/A
Cole-Parmer	UY-02014-21	Idex P-675 Threaded Luer Adapter	N/A

Figure S11 represents the backbone of the portable platform system. The first and last syringe pump are connected to the same waste container and to another syringe pump, leaving 3 ports accessible for reagents/solvents and 1 port for a reactionware cartridge. For the remaining six syringe pumps, 2 ports are used to connect to the previous/next syringe pump, and 4 ports are open to connect to reagents, solvents or a reactionware module.

The number of possible reagents and solvents that can be used in the system, will vary depending on the number of cartridges present in the monolithic reactionware. This gives a minimum of 24 (monolith of 8 cartridges) and a maximum of 31 (monolith of 1 cartridge) reagents/solvents

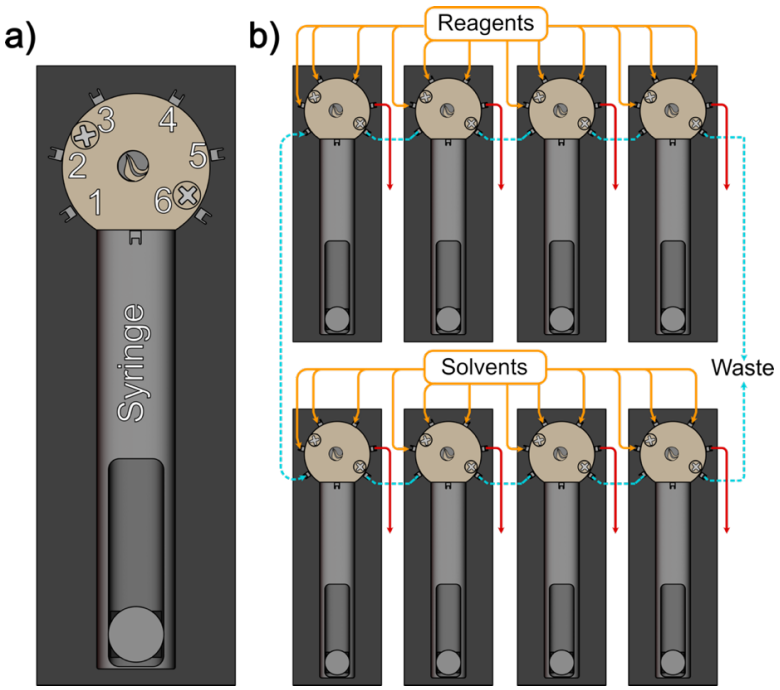


Figure S11. Representations of a) Port numbering in a 6-way distribution valve and syringe position in a Tricontinent syringe pump. b) Portable platform liquid handling backbone diagram

Tubing connections were put together following the instructions:

1. For all tubing connections going to the solvent/reagents flasks, a PTFE tube (
2. Table S5) was cut and a fitting and ferrule mounted to one end. The fitting was screwed into the respective port.
3. For tubing connections going into a reactionware cartridge, the other end of the tubing was passed through a hole drilled with a 1.6 mm drill bit into the luer lock cap.
4. For connections in between syringe pumps, a 125 mm 1.6 mm PTFE tubing piece (Entry 1,
5. Table S5) was cut and fittings and ferrules (Entry 2 and 3,
6. Table S5) were mounted on both ends. The pieces were connected to valve port number 1 and 6 of two different syringe pumps.

Electronics

To power and communicate with the 8 C300MP Tricontinent syringe pumps, a custom-designed board (PumpHub) was used along with a Serial-to-Ethernet interface converter module. Both components were fixed on the top acrylic plate (Figure S12).

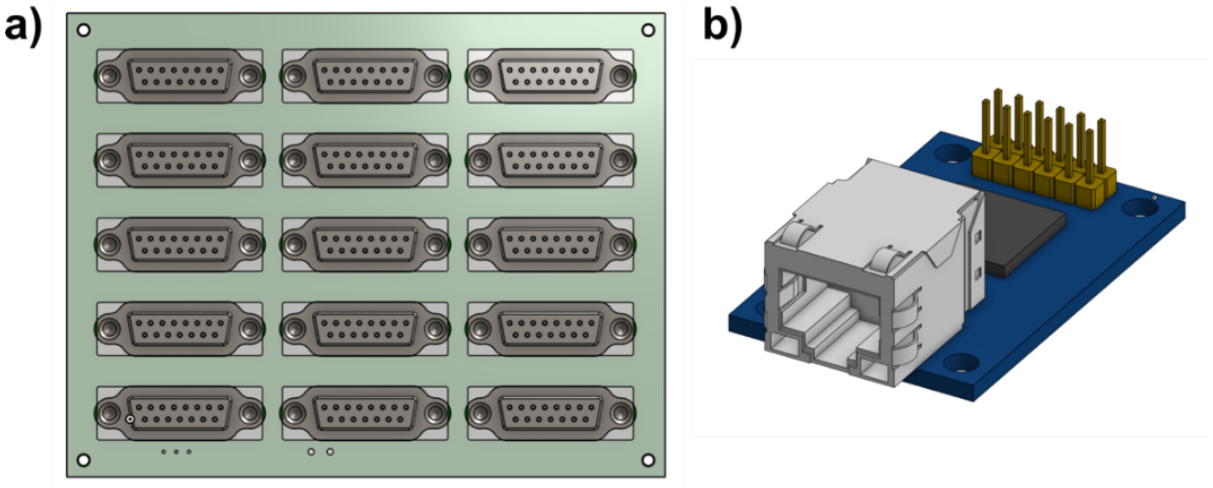


Figure S12. Representations of a) PumpHub for 15 different RS485 serial connections, and b) Wiznet WIZ107SR-TTL one port TTL level Serial-to-Ethernet plug in Module.

3.3 Cooling Unit

The cooling unit consists of two copper heat exchangers connected through a peristaltic pump (Figure S13, Table S7, Entry 3). One of the heat exchangers is immersed in the oil bath where the 3D printed reactors are located, while the remaining one is immersed in a cooling bath of ethylene glycol and dry ice. JULABO Thermal H10 bath fluid is recirculated between the cold bath and the oil batch using a peristaltic pump. Using this set-up, the oil bath can be cooled down to -13 ºC. Considering the poor thermal transfer of polypropylene, the solutions within the reactionware vessels must be immersed in the cold oil bath for ca. 20 mins for temperature equilibration.

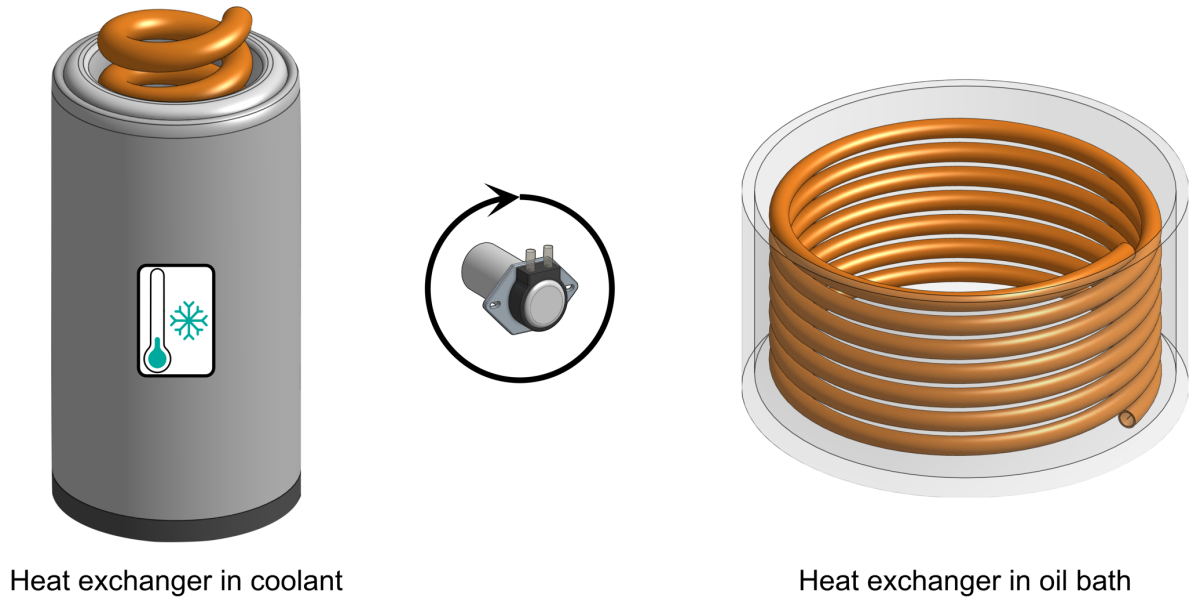


Figure S13. Representation of the cooling unit used in the portable platform. Two different heat exchangers are used, one in the oil bath to cool down the reactionware monolith, and a second one immersed in a cooling bath (dry ice in ethylene glycol). The two heat exchangers are connected through a peristaltic pump and filled with Julabo Thermal H-10 Bath Fluid to complete the closed system.

3.4 SensorHub

In order to facilitate the control of the pneumatics from the high-level Python-based code, a hardware interface controller was needed. We decided to implement it based on the widely used and easily available Arduino platform. Besides numerous obvious benefits, such as low price, easy availability and a huge ecosystem, an extra important reason for us was the ability to re-use the previously developed Commanduino framework[4] which made the integration of new sensors and actuators really fast and easy. We have chosen Arduino Mega2560 as the hardware platform due to a good combination of price, functionality, and robustness.

We developed a custom-made Arduino shield considering that: *i)* contains a relatively large number of on/off outputs to control the pneumatic valves, vacuum pump and peristaltic pump, considering that most common Arduino shields (e.g. RAMPS) usually have 2-4 on/off outputs; *ii)* integrates as many as possible I^2C-connected pressure sensors into the system since the BMP280 sensors contain only two choices for address configuration, extra I^2C connections are needed; and *iii)* includes an Ethernet port for communication with the portable platform since the Arduino Mega2560 has only serial-over-USB connectivity. The schematic for the developed shield is presented in **Figure S14**. Full schematic, 3D view and all the files needed to manufacture the board (Gerber, NC drill, pick and place, BoM) are available as part of the SI.

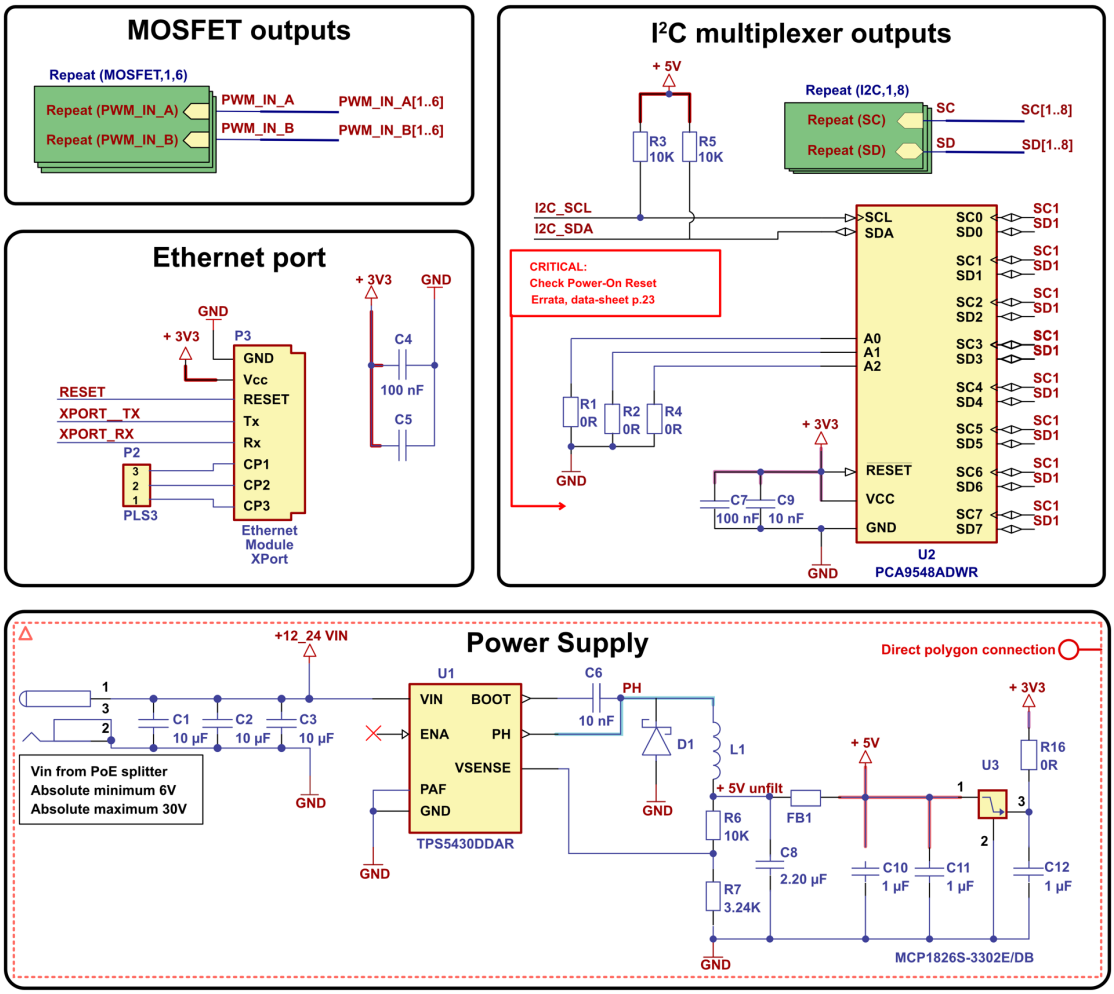


Figure S14. Schematic of the key components for the developed shield describing the connectivity for the a) MOSFETS output, b) I²C multiplexer outputs, c) Ethernet port, and d) Power supply of the custom-made Arduino shield.

The board layout is shown in **Figure S15**. The board has a built-in power supply based on TI TPS5430 buck regulator. The power supply accepts 6-30 V DC and outputs 5V DC at up to 3A max current. This 5V power supply is used to power the Arduino board itself as well as to provide power for the external sensors. Next, 5V are fed into the MCP1826 3.3 V LDO which powers the Ethernet to serial converter, I²C multiplexer chip and external sensor connectors. Si3900Dv double N-channel MOSFETs from Vishay with 1A peak current were used to control the pneumatic valves. MOSFETs' gates are controlled from Arduino digital outputs D0-D13. Each MOSFET channel is equipped with an LED that shows the output state as well as the diode-based back-EMF protection, which makes the use of inductive loads (solenoids, motors) safe. Each MOSFET output channel is terminated by a two-pin quick-connect terminal block having V_{in} connected to the other pin. This way full voltage swing from V_{in} to zero can be provided on any channel by applying PWM to the respective Arduino digital output.

The multiplication of the channels for the devices with similar addresses on the I²C bus is provided by a standard PCA9548 I²C multiplexer chip. PCA9548 has 8 fully independent outputs that can be connected to/disconnected from the bus in any possible combination. The chip itself is controlled over I²C as well. Each of eight I²C output channels is routed to a standard 4-way 2.54 mm pitch pin header accompanied with a 3-position pin header with a jumper to select between 3.3 and 5V power supply for each connected sensor. Using the

jumpers, every channel can be configured independently to use either 3.3 or 5V power and logic levels.

To provide Ethernet connectivity, a readily available *XPort* module from *Lantronics* was used. The initial configuration of the modules is done via the *DeviceInstaller* software provided by *Lantronics*. To fully utilize the board space, some of the unused Arduino digital and analog I/Os were routed to a separate set of standard pin headers along with power lines to allow easy connection of extra sensors/actuators. This feature was utilized later for the control of the conductivity sensor along with the pneumatic manifold for the Chemputer system.[5]

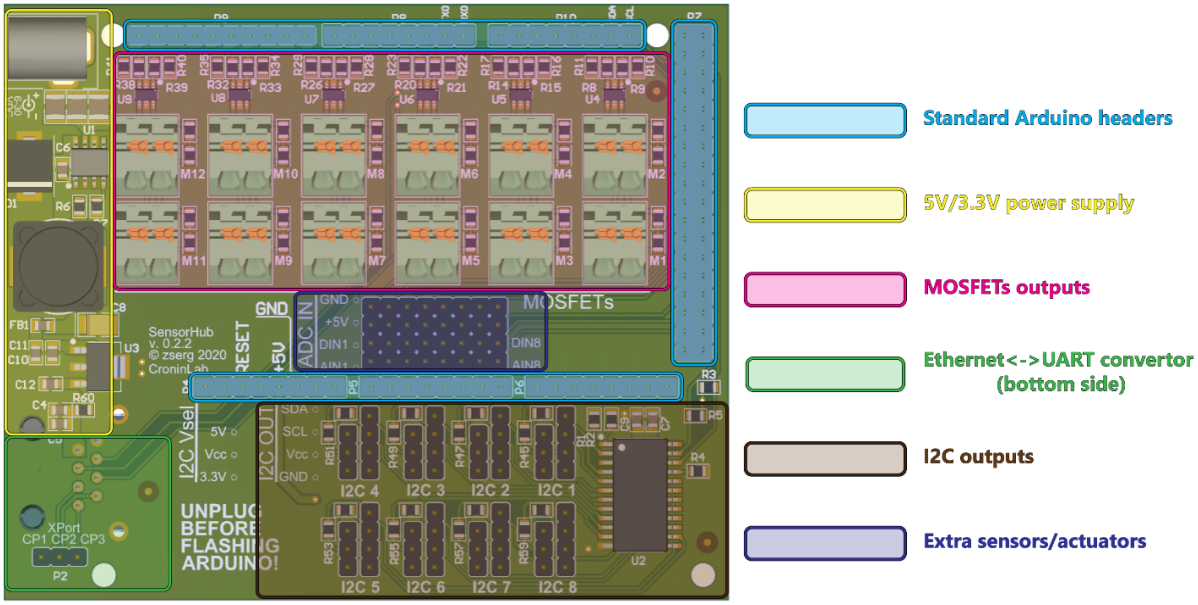


Figure S15. Layout describing the arrangement of the functional blocks on the customized Arduino shield

3.5 Pneumatics

Figure S16 shows a schematic of the pneumatic connections in the portable platform. For the inert gas supply (**Figure S16a**), the compressed argon supply after a secondary pressure regulator (1.2 bar) was connected to the system through a shut-off valve with the low side pressure relief. The output of the valve was connected to a multi-position manifold providing positive argon pressure for the reagent bottles. The outlet of the manifold was connected to the flow regulator that was used to adjust the flow rate of the argon gas coming into reaction chambers. The output of the flow regulator was connected to individual supply valves through another distribution manifold. The outlet of the manifold was vented to the atmosphere through a check valve.

For the vacuum line (**Figure S16b**), a compact diaphragm pump (TopsFlo TF30A-B) was used as a vacuum source. The pump was protected with two inline vacuum filters (SMC ZF series), one equipped with a standard filtering cartridge and another one – with basic alumina to neutralize acid vapors coming from the reaction mixtures. The outlet of the second filter was connected to a (dry ice/ethylene glycol cooled) trap which was also acting as a vacuum receiver. The outlet of the receiver was connected to the individual distribution valves via standard pneumatic manifold.

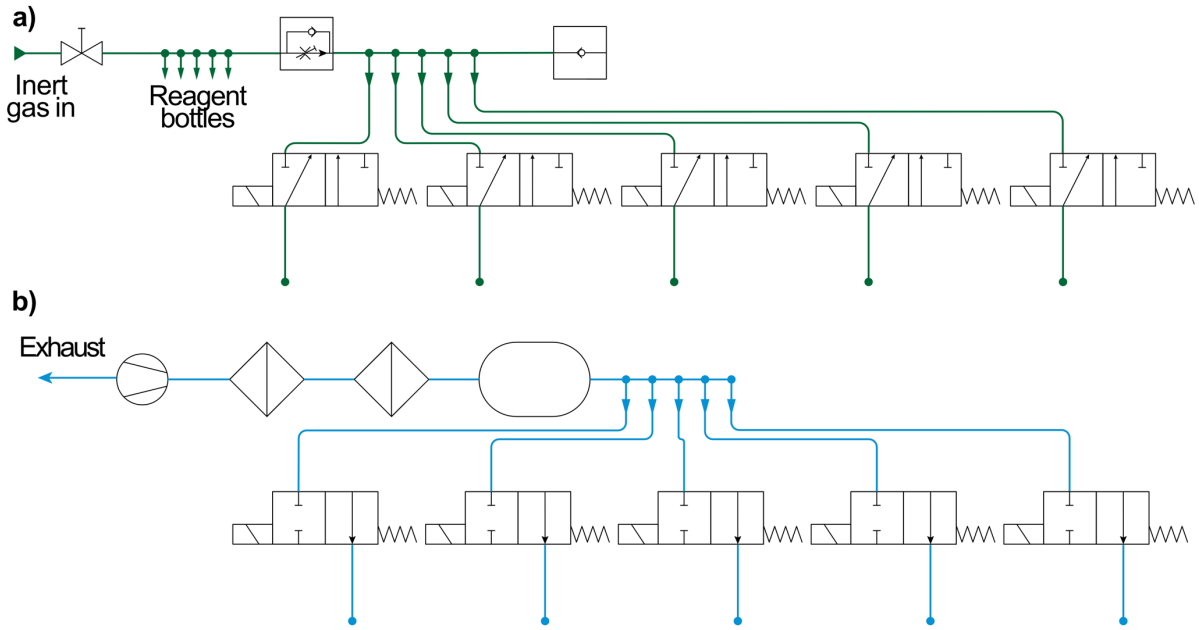


Figure S16. Schematics representing the pneumatic connectivity in the portable platform. a) the connections for the inert gas supply into the system, and b) the pneumatic connections for vacuum supply.

Operation example

The programable manifold was designed to control positive inert gas pressure as well as the vacuum supply (Figure S17). To provide this, the unit was designed to include ten 3/2 electromagnetic valves, five used as normally-closed with a common manifold (for the vacuum line) and five normally-open with individual baseplates (for the inert gas supply line). In the default state, when all the valves are de-energized, all the outputs are connected to the positive pressure inert gas supply via the normally-open valves. When a vacuum connection is needed, the normally-open inert gas supply valve for the required output is shut off, while the normally-closed vacuum supply line is opened, connecting the required output to the vacuum line. In the case where a particular output has to be shut off, it can be achieved by energizing only the inert gas supply valve

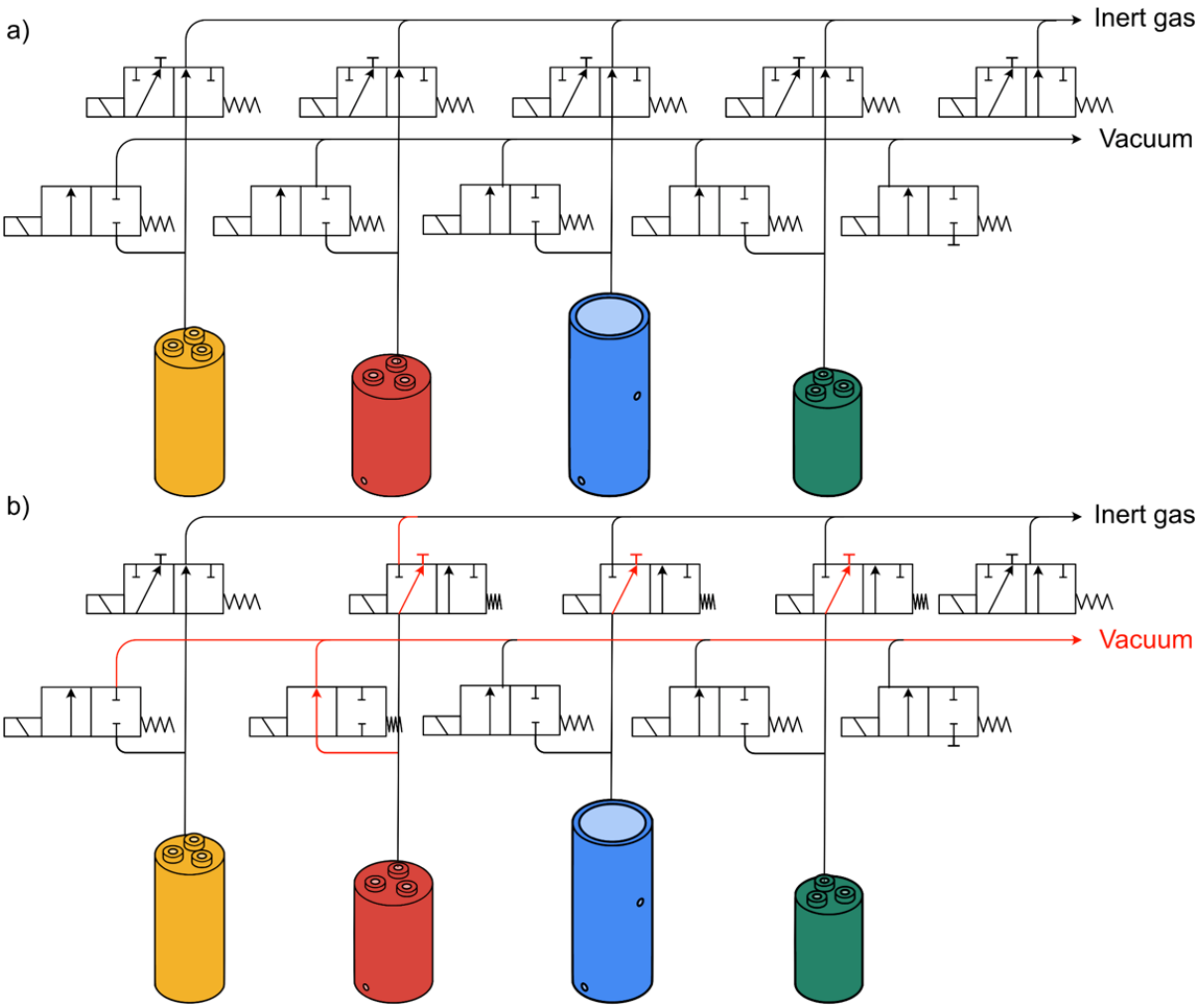


Figure S17. Scheme representing the gas/vacuum connections used for the synthesis of Phenelzine sulfate in the robotic platform. The manifold is based on two separate sets of solenoids dedicated for inert gas and vacuum. a) Original state of the manifold. All solenoid valves are deenergized, providing a continuous stream of inert gas to the individual modules, vacuum connection is shut off. b) Example of a liquid transfer from *module-1* to *module-2*. First the solenoid valves connected to *module-2*, *module-3*, and *module-4* are energized (blocking the flow of inert gas), then the solenoid valve connected to *module-2* is energized, going into a open state to the micropump to apply vacuum until the transfer is completed based on the pressure sensor readings.

Table S6. Materials used for the pneumatic manifold

Supplier	Part #	Description	Quantity
SMC Pneumatics	VV100-S41-05-M5	SMC V100 5-position valve manifold	1
SMC Pneumatics	VHK3-06F-06F	SMC finger valve	1
SMC Pneumatics	AS1002F-06	SMC flow regulator	1
RS Components	771-5658	SMC 4mm M5 one-touch male connector, inner hex, straight (SMC # KQ2S-04-M5A)	15
RS Components	771-5673	SMC 6mm M5 one-touch male connector, inner hex, straight (SMC # KQ2S-06-M5A)	2
Aliexpress	TF30A-B	Vacuum pump	1
Aliexpress	BMP280	Bosch BMP280 sensor	10
ColeParmer	WZ-45518-82	Male Luer Lock to Threaded Adapter	10
SMC Pneumatics	V114A-6LU-M5	SMC V100 pneumatic valve, 12V, with sub-plate	5
SMC Pneumatics	V114A-6LU	SMC V100 pneumatic valve, 12V	5
SMC Pneumatics	LVM11-6	SMC solenoid, 12V	5
RS Components	715-4084	Arduino Mega 2560	1

Electronics

To power and communicate with the pneumatic manifold, an Arduino fitted with a custom-designed shield was used (SensorHub). The shield consists of:

- 12 MOSFET outputs (12V, 2.5A), with back EMF protection diodes
- 8 I^2C channels (GND, +5V/3.3V)
- 4 connectors (GND, +5V, digital in, analog in)

Bosch BMP280 sensors were used to monitor pressure changes in the monolithic cartridges. The sensors were connected via the I^2C channels in the shield. The sensors were enclosed in a sealed (with epoxy resin) 3D printed case to minimize air leaking (Figure S18). Finally, a micropump was used as a vacuum supply. The micropump was controlled using one of the MOSFET channels.

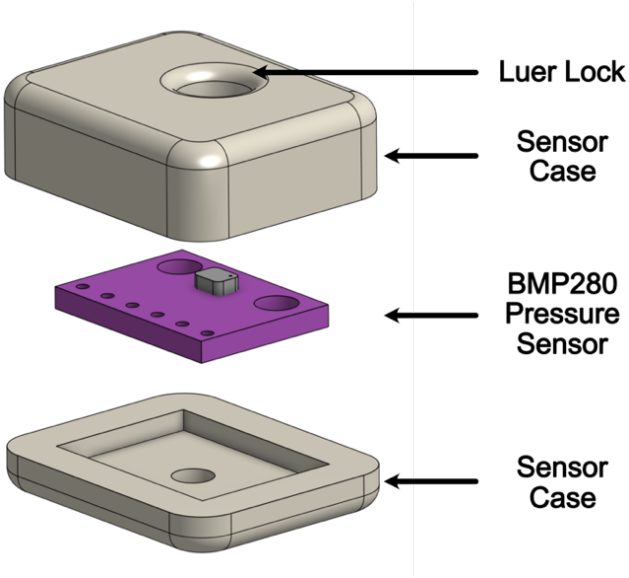


Figure S18. Exploded view of a BMP280 pressure sensor assembly showing the 3D printed cases, the sensor and the luer lock fitting space to attach it to the reactionware module.

3.6 Other components

To complete the functions provided in Portable platform the next components were added:

Table S7. Additional components used in Portable platform

Supplier	Part #	Description	Quantity
RS Components	705-9835	Power supply unit (PSU)	1
IKA	0025005221	RCT Digital Hot plate	1
TOPINCN	3016nyg9dt	12 V Peristaltic pump	1
Netgear	GS105E	5 Port Gigabit Ethernet Plus Switch	1
Wiznet	WIZ107SR	Serial-to-Ethernet plug	2

Switch

An Ethernet switch (Entry 4, Table S7) was included to communicate between the PC running the software and the Portable platform hardware. The switch provides 5 RJ-45 ports and has to be configured by browsing the configuration page and setting up the switch to the gateway address 192.168.1.1 and subnet mask 255.255.0.0 (see the suppliers manual for details).

Wiznet RS-232 to Ethernet Interface Converter Settings

1. The WIZnet configuration tool was installed
2. The "Direct IP Search" box was ticked, the factory IP address was inserted (192.168.11.1) and "Search" was clicked. The search returned the MAC address of the corresponding board in the "Board list". The board was selected, and the "Network" parameters were set as follows:
    a. "IP Configuration Method" was set to "Static".
    b. The "Local IP" was set to the respective address (see Table S8)
    c. The "Subnet" mask was set to 255.255.0.0.
    d. The "Gateway" was set to 192.168.1.1.
    e. The "Port" was set to 5000.
    f. The "Operation Mode" was set to "Server".
3. The "Serial" tab was selected next and the serial settings were configured according to the manufacturer's specifications of the device the serial-to-Ethernet converter will be connected to.

Table S8. Serial configuration for the used third-party devices.

Device	Speed	DataBit	Parity	Stop Bit	Flow	IP Address
PumpHub	9600	8	None	1	None	192.168.1.10
IKA RCT Digital	9600	7	Even	1	None	192.168.1.11

Table S9. Serial cables used to connect the third-party devices.

Device	Cable	CPC[a]
PumpHub	9 way D male to female RS232 serial cable, 1 m	CS24423
IKA RCT Digital	9 way D male to female RS232 serial cable, 1 m	CS24423

3.7 Complete assembly

Back acrylic sheet

After all components have been prepared, they were attached to the respective 6 mm acrylic sheets. The back BB-acrylic sheet is composed of the micropump, ethernet switch, Power Supply Unit (PSU), DC-DC Convertors (BC) and a shut-off valve for the inert gas inlet.

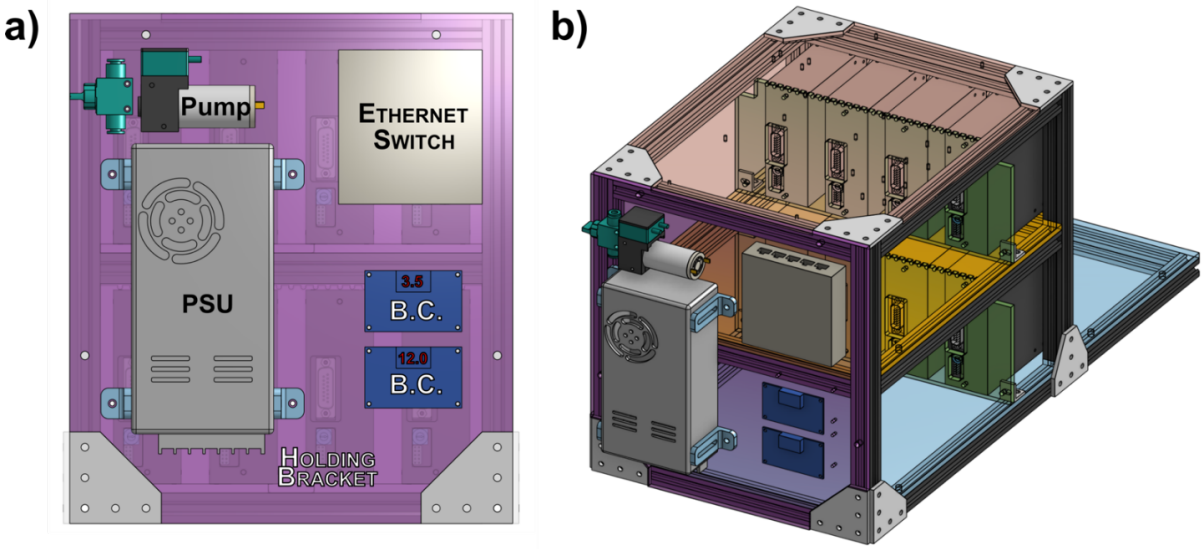


Figure S19. a) Back acrylic sheet filled with electronic components: PSU, Ethernet Switch, Buck Convertors (B.C., set at 3.5 and 12.0V), and a micropump. b) Isometric view on the assembly progress of Portable platform.

Top acrylic sheet

The top acrylic sheet is composed of the PumpHub, SensorHub, Pneumatic supply and the 2x Serial-to-Ethernet plugs. To control the inert gas flow, a flow regulator was also added.

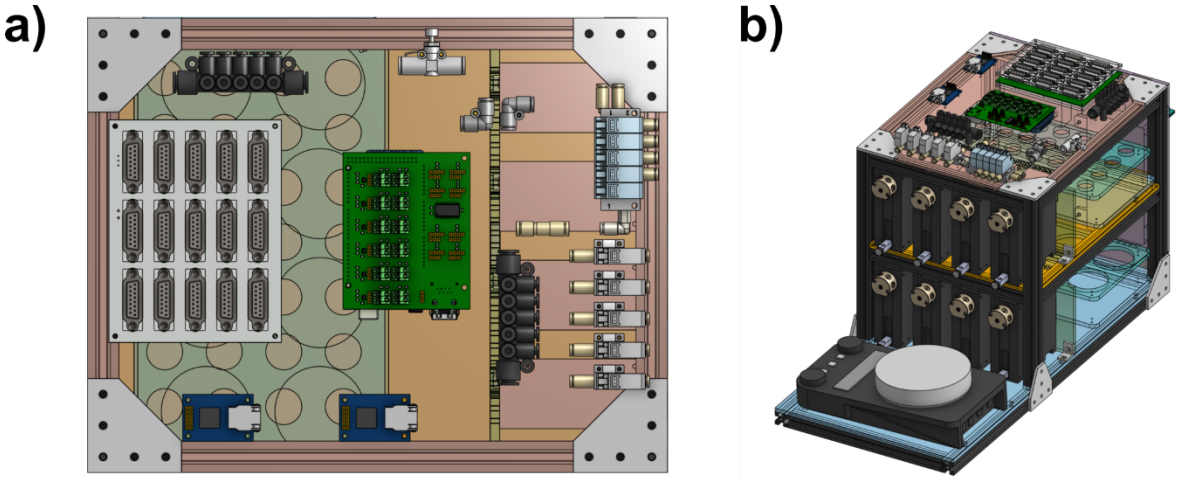


Figure S20. a) Components on tapped BB-top acrylic (Figure S8a). Components include: PumpHub, SensorHub, Serial-to-Ethernet convertor (S2E) and the pneumatic supply. b) Isometric view of the assembly progress of the portable platform.

4 Pressure profiles

Using the BMP280 sensor, pressure can be used to track important changes within the reactionware monolith. The pressure within the reactor is monitored in the background of the chemical process while the change (Δ) in pressure is calculated. Using this pressure difference single events can be identified. For example, Figure S21 shows how a standard transfer module-A → module-B works, the threshold is set at ΔP >= 65, where the vacuum is stopped, and the reactor is refilled with inert gas.

Similarly, pulse transfers (for slow additions from module-A to module-B without using the platform backbone, see Figure S22) can be detected based on the pressure change in the system. This kind of transfer is based on applying vacuum pulses to the receiving module and the threshold is set at ΔP <= -400, where, if detected, the transfer is complete, and the vacuum pulses are stopped.

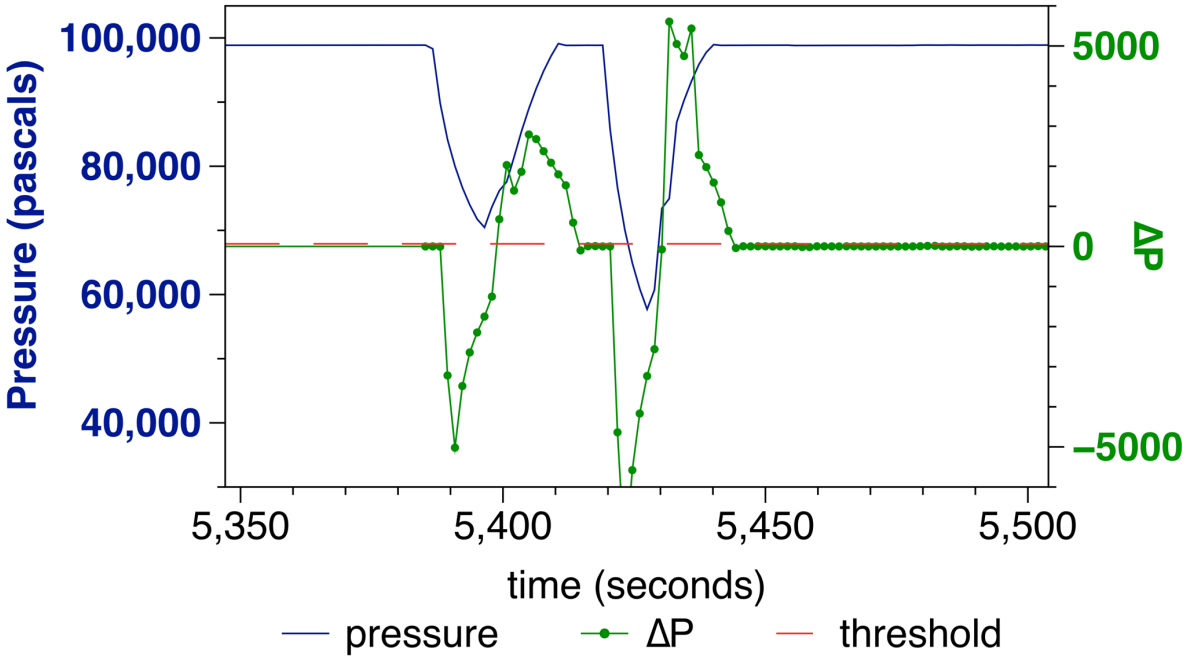


Figure S21. Pressure profile for a liquid transfer from module-A to module-B (blue), and pressure change (green) to determine when the transfer/filtration is finished depending on the stablished threshold (red).

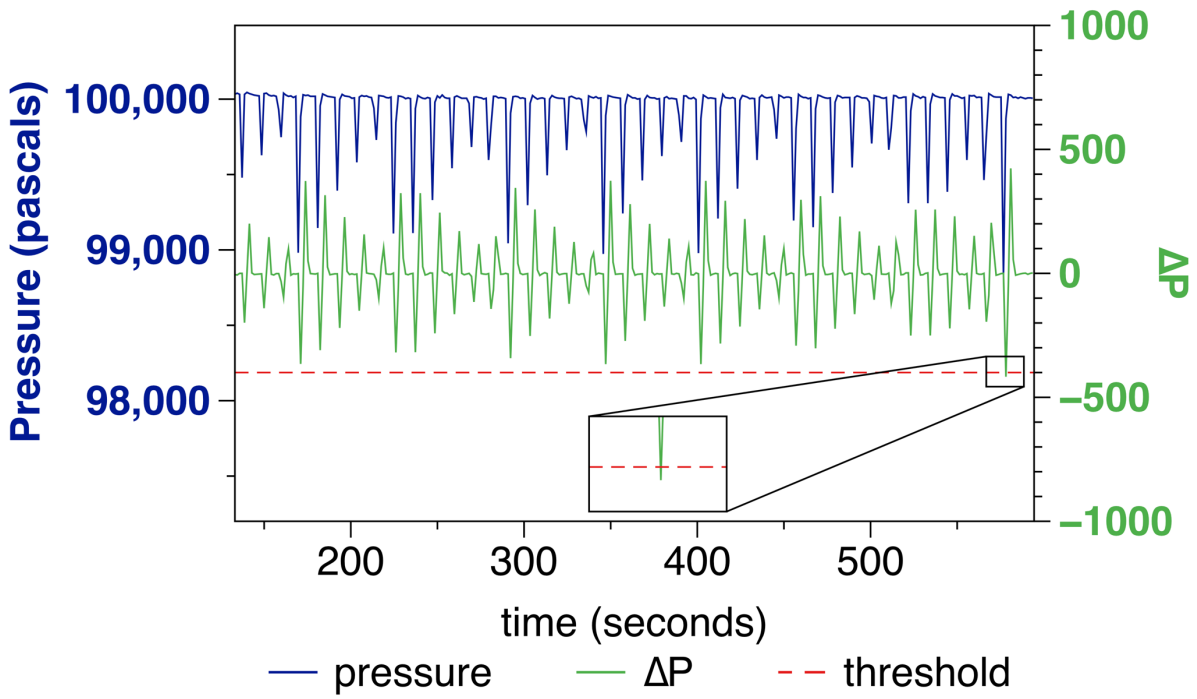
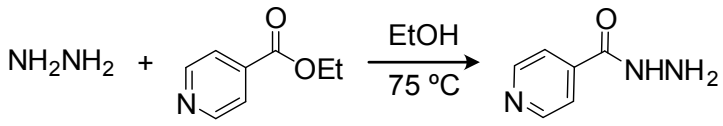


Figure S22. Pressure profile for a slow (pulse transfer) liquid transfer from module-A to module-B (blue), and pressure change (green) to determine when the transfer/filtration is finished depending on the stablished threshold (red).

5 Manual Syntheses

5.1 Isoniazid



Ethyl isonicotinate (3 mL, 20 mmol), hydrazine hydrate (1.5 mL, 31 mmol) and ethanol (12 mL) were added to *module-1*. The monolith was heated to 70 - 75 ºC and kept at this temperature for 4 hrs with stirring. After the reaction was completed, the reaction was cooled down to RT and stirred for 30 mins. The solution was filtered and the solid was washed with ethanol (5 mL). To recrystallize the product, methanol (25 mL) was added to *module-1* and the reactionware was heated to 70 - 75 ºC for 20 mins to dissolve the crude product. Then, the reactionware was cooled down to 0 ºC and kept at 0 ºC for 30 mins. Finally, the solution was filtered and the solid was dried for 10 hrs under vacuum to give Isoniazid as a white solid (2.0 g, 73 % yield)

^{1}H NMR: (600 MHz, D_2O) δ 8.59 (d, *J* = 5.7 Hz, 2H), 7.60 (d, *J* = 5.6 Hz, 2H)

^{13}C{^{1}H} NMR: (151 MHz, D_2O) δ = 121.0, 140.0, 149.0, 166.6.

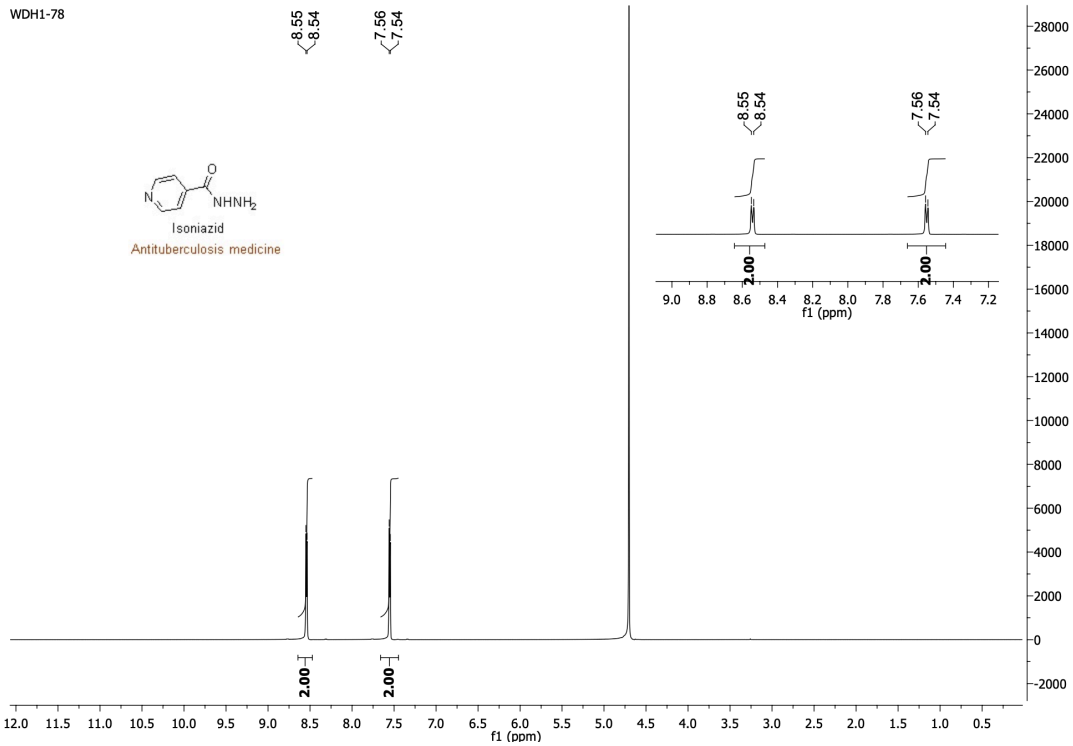
HPLC-UV/Vis retention time: 4.5 min

ESI $(M+H)^+$: expected: 138.06 Da, observed: 138.07 Da

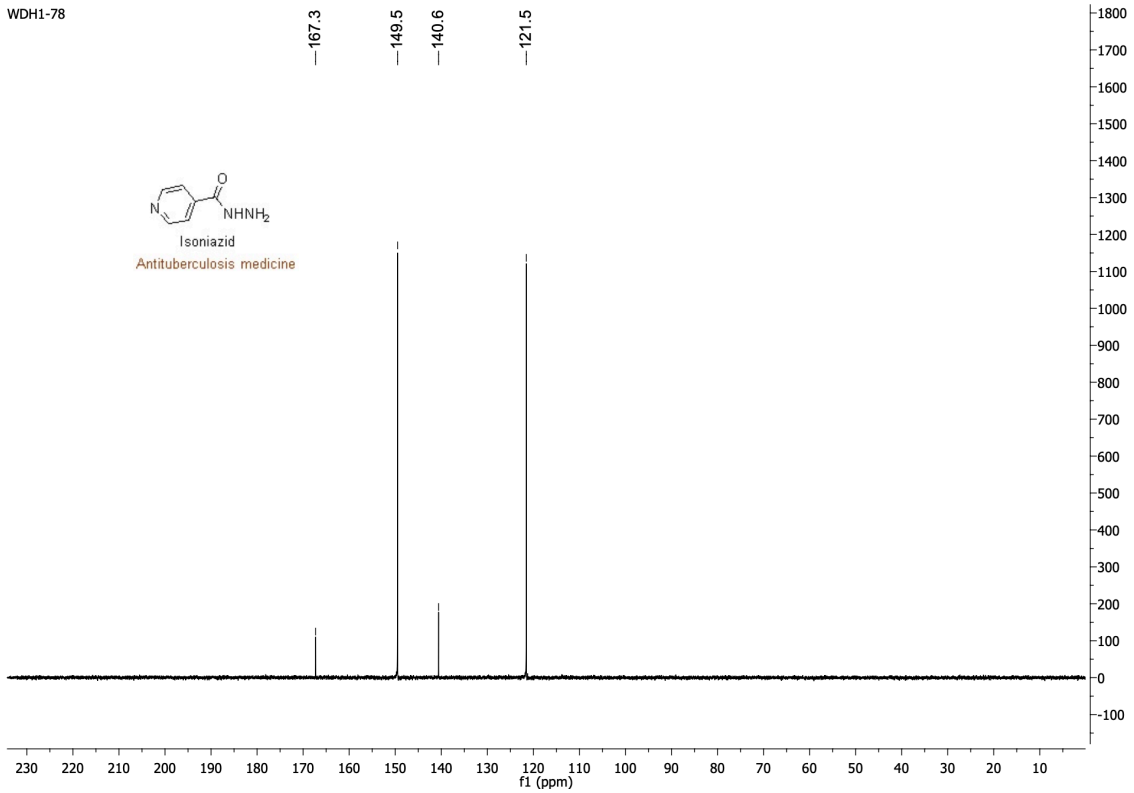
Table S10. Table of operations for the synthesis of Isoniazid

Process	Reagent	To	Temp (°C)	Stir Rate (rpm)	Pressure(mbar)	Time (min)
Add	EtOH (12 mL)		RT	0	Atmospheric	0.5
Add	Ethyl isonicotinate (3.0 g, 3.0 mL)		RT	250	Atmospheric	0.5
Add	Hydrazine hydrate (1.5 g, 1.5 mL)		RT	250	Atmospheric	0.5
Heat	-		70 - 75	250	Atmospheric	40
Stir	-		70 - 75	250	Atmospheric	240
Cool	-		RT	250	Atmospheric	40
Stir	-		RT	250	Atmospheric	30
Filter	-		RT	250	Atmospheric	1
Add	EtOH (3 mL)	**Module 1**	RT	250	Atmospheric	0.5
Stir	-		RT	250	Atmospheric	2
Filter	-		RT	250	Atmospheric	1
Add	EtOH (35 mL)		RT	250	Atmospheric	0.5
Heat	-		70 - 75	250	Atmospheric	40
Stir	-		70 - 75	250	Atmospheric	10
Cool	-		0	250	Atmospheric	40
Stir	-		0	250	Atmospheric	30
Filter	-		0	250	Atmospheric	2
Dry	-		RT	0	100	720

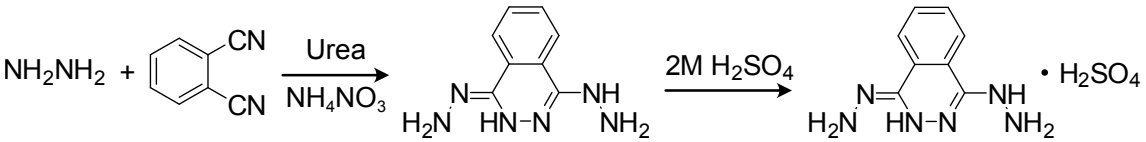
^{1}H NMR



$^{13}C\{^{1}H\}$ NMR:



5.2 Dihydralazine sulfate



1, 4-dicyanobenzene (2.56 g, 20 mmol), urea (7.3 g, 122 mmol), NH_4NO_3 (0.5 g, 6 mmol) and hydrazine hydrate (7.3 mL, 150 mmol) were added to *module-1*. The monolith was heated to 100 ºC and kept at this temperature for 3 hrs. The reactionware was cooled to RT and water (10 mL) was added to *module-1*. The solution was filtered and the solid was washed with water (10 mL). 2M H_2SO_4 (12.5 mL) was added to *module-1* slowly. The monolith was heated to 100 ºC for 1 hr. The solution was filtered, and cooled down to RT. Once the solution has been cooled down, it was filtered and washed with 5 mL of water twice. Dihydralazine sulfate (2.1g, 72% yield, was obtained as a yellow solid after drying under vacuum for 10 hrs.

^{1}H NMR: (600 MHz, D_2O) δ 8.22 (m, 2H), 8.16 (m, 2H)

^{13}C{^{1}H} NMR: (151 MHz, D_2O) δ = 119.8, 123.4, 134.8.

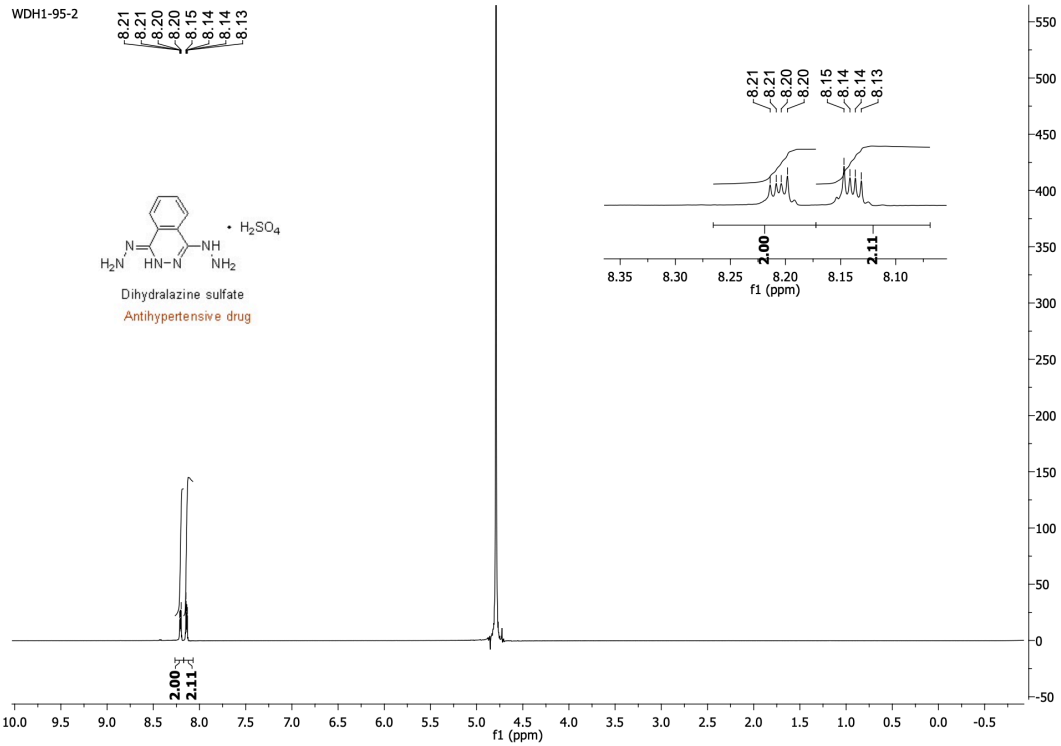
HPLC-UV/Vis retention time: 0.45 min, purity: > 99 % (at 254 nm).

ESI(M+H)$^+$: expected: 191.1045 Da, observed: 191.1093 Da

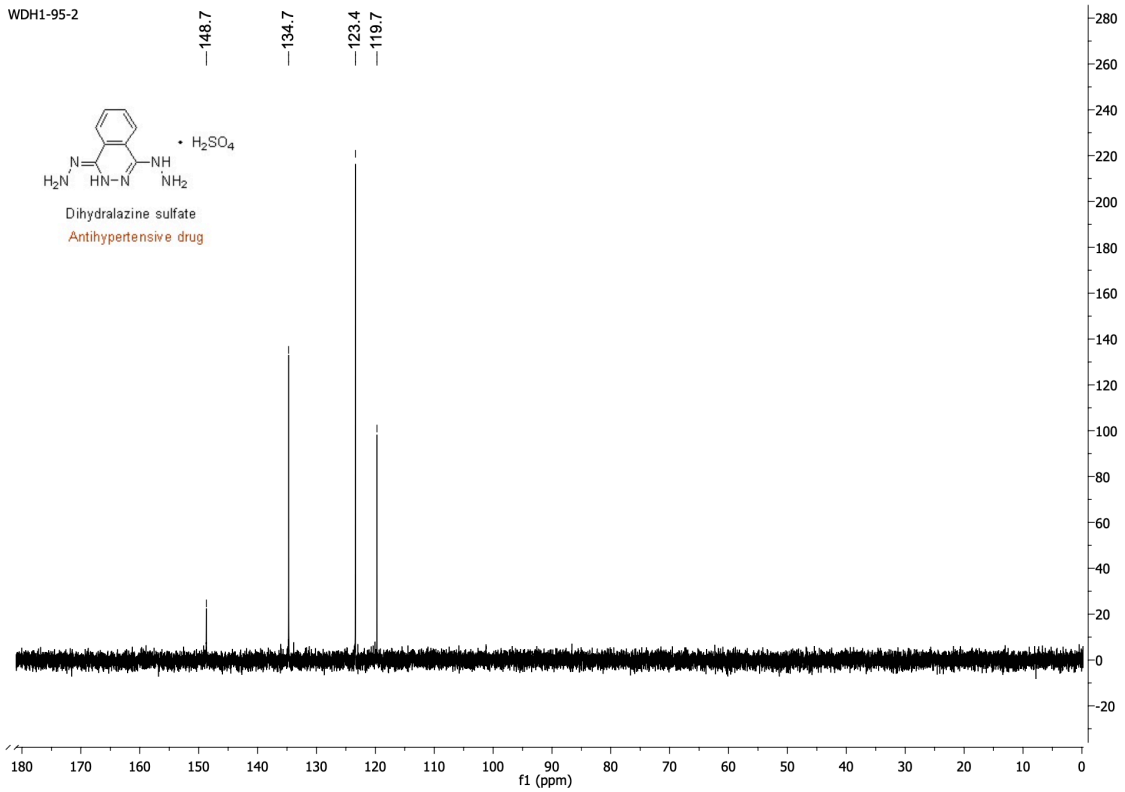
Table S11. Table of operations for the synthesis of Dihydralazine sulfate

Process	Reagent	To	Temp (°C)	Stir Rate (rpm)	Pressure(mbar)	Time (min)
Add	RM1 (2.56 g), Urea (7.3 g) and NH_4NO_3 (0.5 g)		RT	0	Atmospheric	0.5
Add	Hydrazine hydrate (7.3 g, 7.3 mL)		RT	250	Atmospheric	0.5
Heat	-		100	450	Atmospheric	40
Stir	-		100	450	Atmospheric	180
Cool	-		RT	450	Atmospheric	40
Add	Water (10 mL)	Module 1	RT	450	Atmospheric	0.5
Stir	-		RT	450	Atmospheric	5
Filter	-		RT	250	Atmospheric	5
Add	Water (10 mL)		RT	250	Atmospheric	0.5
Filter	-		RT	250	Atmospheric	5
Add	2M H_2SO_4 (25 mL)		RT	250	Atmospheric	0.5
Heat	-		100	450	Atmospheric	40
Stir	-		100	450	Atmospheric	60
Transfer	-		100	250	Atmospheric	15
Cool	-		RT	250	Atmospheric	40
Stir	-		RT	250	Atmospheric	60
Filter	-		RT	250	Atmospheric	2
Add	Water (5 mL)	Module 2	RT	450	Atmospheric	0.5
Stir	-		RT	450	Atmospheric	5
Filter	-		RT	250	Atmospheric	5
Add	Water (5 mL)		RT	250	Atmospheric	0.5
Filter	-		RT	250	Atmospheric	5
Dry	-		RT	0	100	720

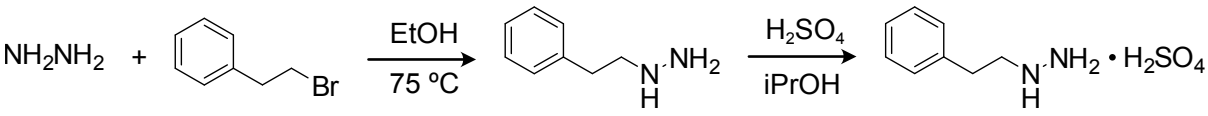
[1]H NMR



[13]C{[1]H} NMR:



5.3 Phenelzine sulfate



Ethanol (16 mL) and hydrazine hydrate (2.9 mL, 60 mmol) were added to *module-1*. The reactionware was heated to 75 ºC, and 2-bromoethylbenzene (1.84 mL, 10 mmol) was added to *module-1* slowly, and the cartridge was kept at that temperature for 2 h. The reactor was cooled down to RT and EtOH was evaporated under vacuum. Diethyl ether (15 mL) was added to *module-1* to extract compound **Error! Reference source not found.**, and transferred to *m odule-2*. Water (10 mL) was added to *module-1* and transferred to module-3, to push residual diethyl ether from *module-2*. Diethyl ether was evaporated under vacuum at 35 ºC. Isopropanol (20 mL) was added to *module-3* to dissolve the product, then a H_2SO_4-isopropanol mixture (1:5, 6 mL) was added to *module-3* slowly, and the solution was stirred for 2 hrs at RT. Hexane (5 mL) was added to *module-3* and stirred for 30 mins. The solution was filtered and washed with hexanes (10 mL) twice. Phenelzine sulfate was obtained as a pale yellow solid (1.2g, 51% yield) after drying for 10 hrs.

^{1}H NMR: (600 MHz, D_2O) δ 7.42 (m, 2H), 7.36 (m, 3H), 3.43 (t, J = 7.5 Hz, 2H), 3.03 (t, J = 7.5 Hz, 2H).

^{13}C{^{1}H} NMR: (151 MHz, D_2O) δ = 30.6, 52.1, 127.3, 128.8, 136.6.

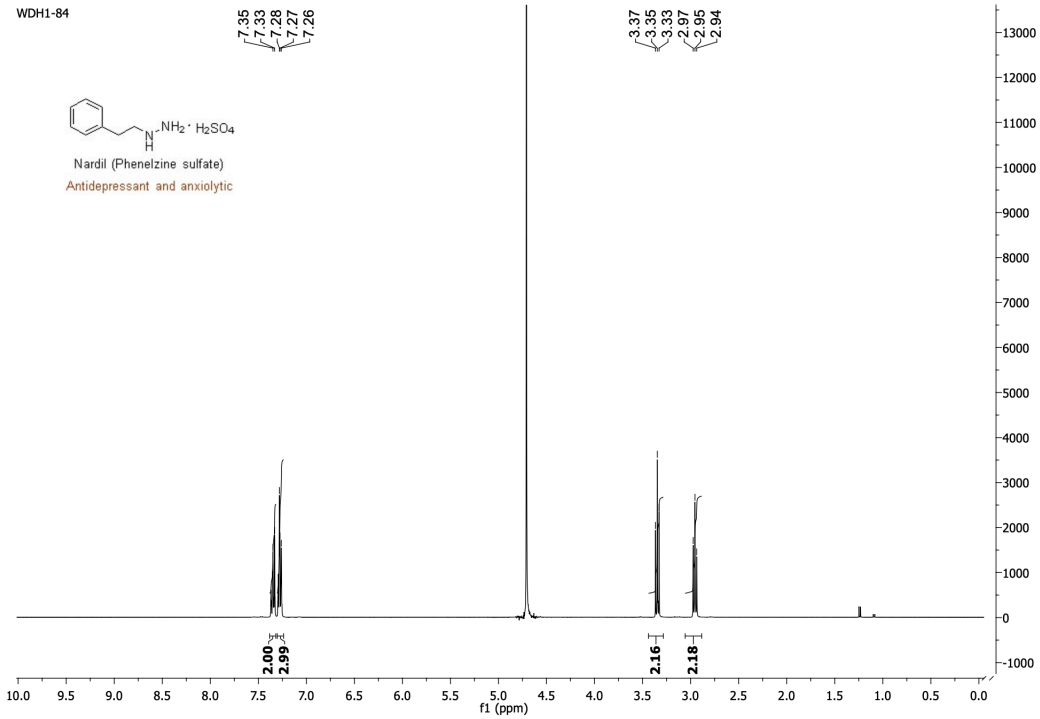
HPLC-UV/Vis retention time: 8.3 min, purity: > 99 % (at 254 nm).

ESI(M+H)$^+$: expected: 137.1034 Da, observed: 137.1077 Da

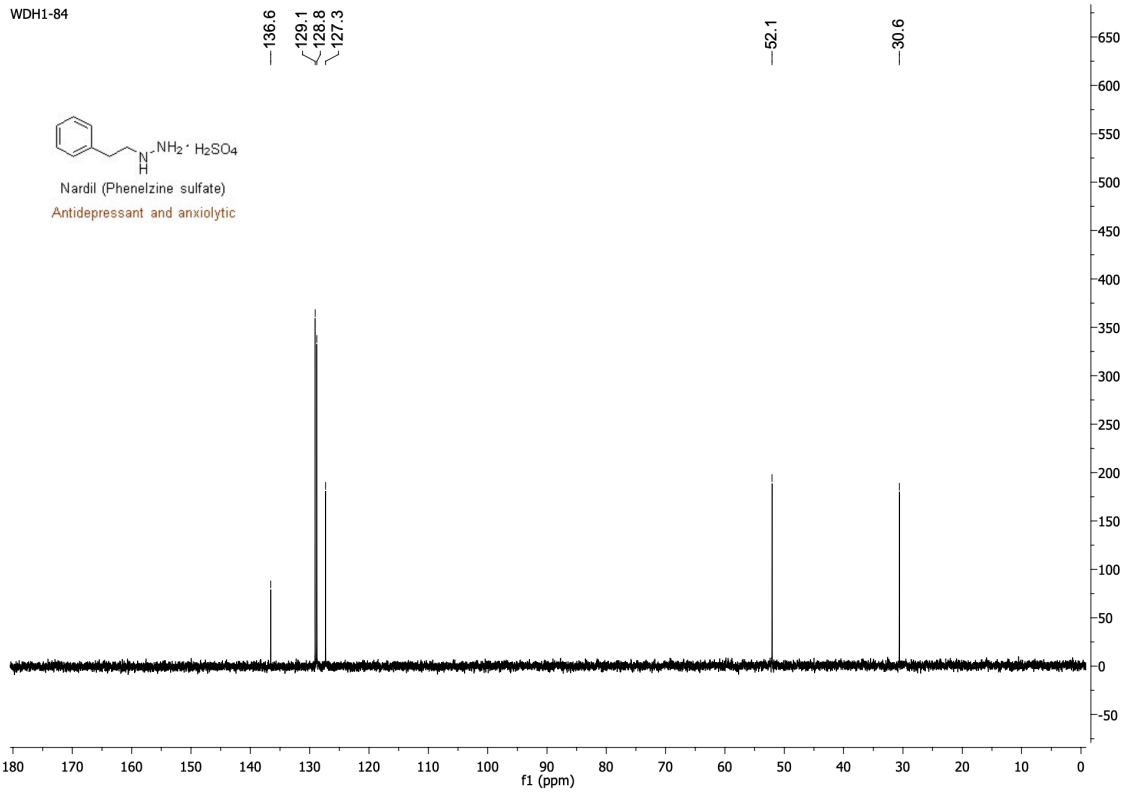
Table S12. Table of operations for the synthesis of Phenelzine sulfate

Process	Reagent	To	Temp (°C)	Stir Rate (rpm)	Pressure (mbar)	Time (min)
Add	EtOH (16 mL)		RT	0	Atmospheric	0.5
Add	hydrazine hydrate (2.9 mL)		RT	250	Atmospheric	0.5
Heat	-		75 - 80	250	Atmospheric	40
Add	2-bromoethylbenzene (1.8 mL)		75 - 80	250	Atmospheric	30
Heat	-	**Module 1**	75 - 80	250	Atmospheric	120
Cool	-		40 - 45	250	Atmospheric	15
Dry	-		40 - 45	250	120	180
Cool	-		RT	250	Atmospheric	15
Add	Et_2O (20 mL)		RT	250	Atmospheric	0.5
Stir	-		RT	250	Atmospheric	10
Transfer	-	**Module 2**	RT	0	Atmospheric	5
Add	Et_2O (20 mL)	**Module 1**	RT	250	Atmospheric	0.5
Stir	-	**Module 2**	RT	250	Atmospheric	5
Transfer	-		RT	0	Atmospheric	5
Add	H_2O (10 mL)	**Module 1**	RT	0	Atmospheric	0.5
Transfer	-	**Module 2**	RT	0	Atmospheric	5
Transfer	-		RT	0	Atmospheric	5
Dry	-		RT	250	200	60
Add	^{i}PrOH (20 mL)		RT	250	Atmospheric	0.5
Add	$H_2SO_{4(c)}$ (1 mL)		RT	250	Atmospheric	10
Stir	-		RT	250	Atmospheric	120
Add	Hexane (5 mL)	**Module 3**	RT	250	Atmospheric	0.5
Stir	-		RT	250	Atmospheric	30
Filter	-		RT	250	Atmospheric	5
Add	Hexane (10 mL)		RT	250	Atmospheric	0.5
Filter	-		RT	250	Atmospheric	5
Dry	-		RT	0	100	120

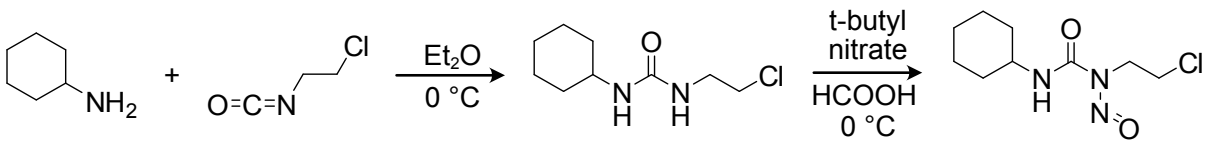
^{1}H NMR



$^{13}C\{^{1}H\}$ NMR:



5.4 Lomustine



Diethyl ether (20 mL), 2-chloroethyl isocyanate (1.05 mL, 10 mmol) were added to *module-1*. The reactionware was cooled down to 0 ºC, and cyclohexylamine (0.5M, 20 mL, 10 mmol) was added slowly. The solution was stirred for 3 hrs, filtered, and washed with diethyl ether twice (5 mL). The obtained solid was dried for 1 hr under vacuum. Formic acid (18 mL) was added to *module-1*, and the solution was cooled down to 0 ºC, before adding t-butyl nitrate (1.8 mL, 13.5 mmol). The solution was stirred for 2 hrs at 0→25ºC. Water (36 mL) was added to *module-1*, and the solution was stirred for and extra 1 hr. After that the solution was filtered, and washed with water (three times, 5 mL). The obtained pale-yellow solid was dried under vacuum for 10 hrs to yield Lomustine (1.6g, 69 % yield)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 6.80 (b, 1H), 4.21 (t, J = 6.6 Hz, 2H), 3.94 – 3.87 (m,1H), 3.52 (t, J = 6.7 Hz, 2H), 2.10 – 2.04 (m, 2H), 1.82 – 1.76 (m, 2H), 1.71 – 1.63 (m, 1H), 1.50 – 1.40 (m, 2H), 1.37 – 1.21 (m, 3H).

^{13}C{^{1}H} NMR: (151 MHz, $CDCl_3$) δ = 151.3, 49.5, 39.6, 38.4, 32.6, 24.9, 24.3.

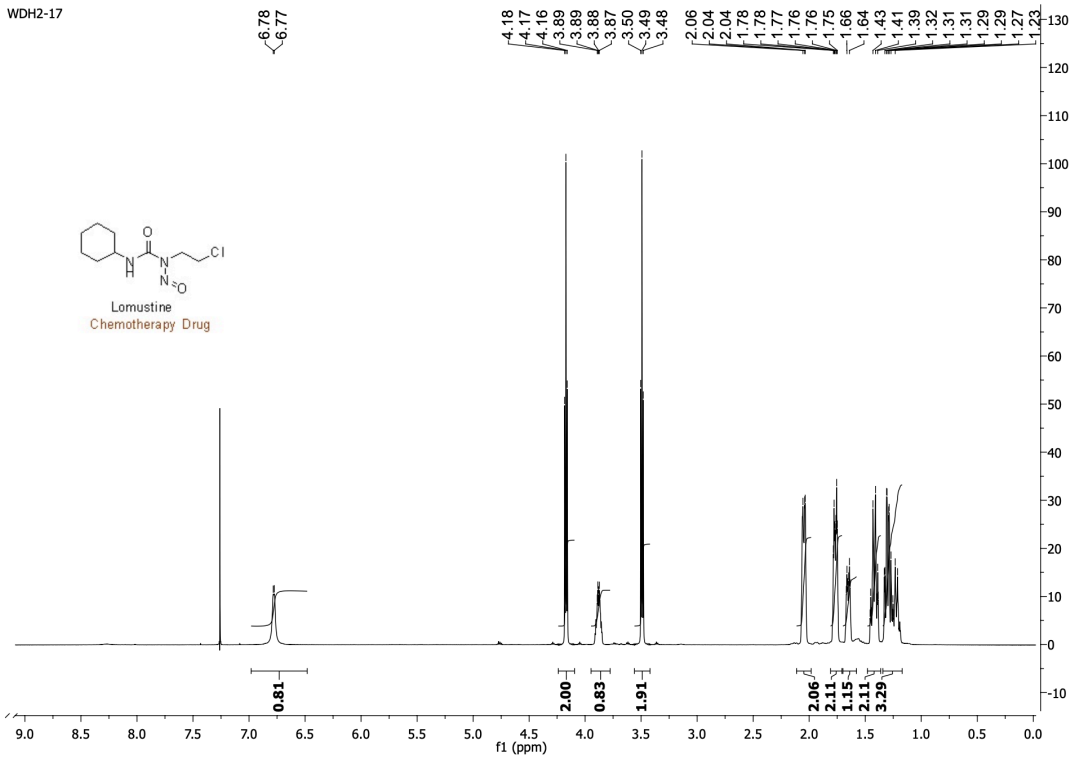
HPLC-UV/Vis retention time: 1.8 min, purity: > 99 % (at 254 nm).

ESI(M+H)$^{+}$: expected: 234.1009 Da, observed: 234.1056 Da

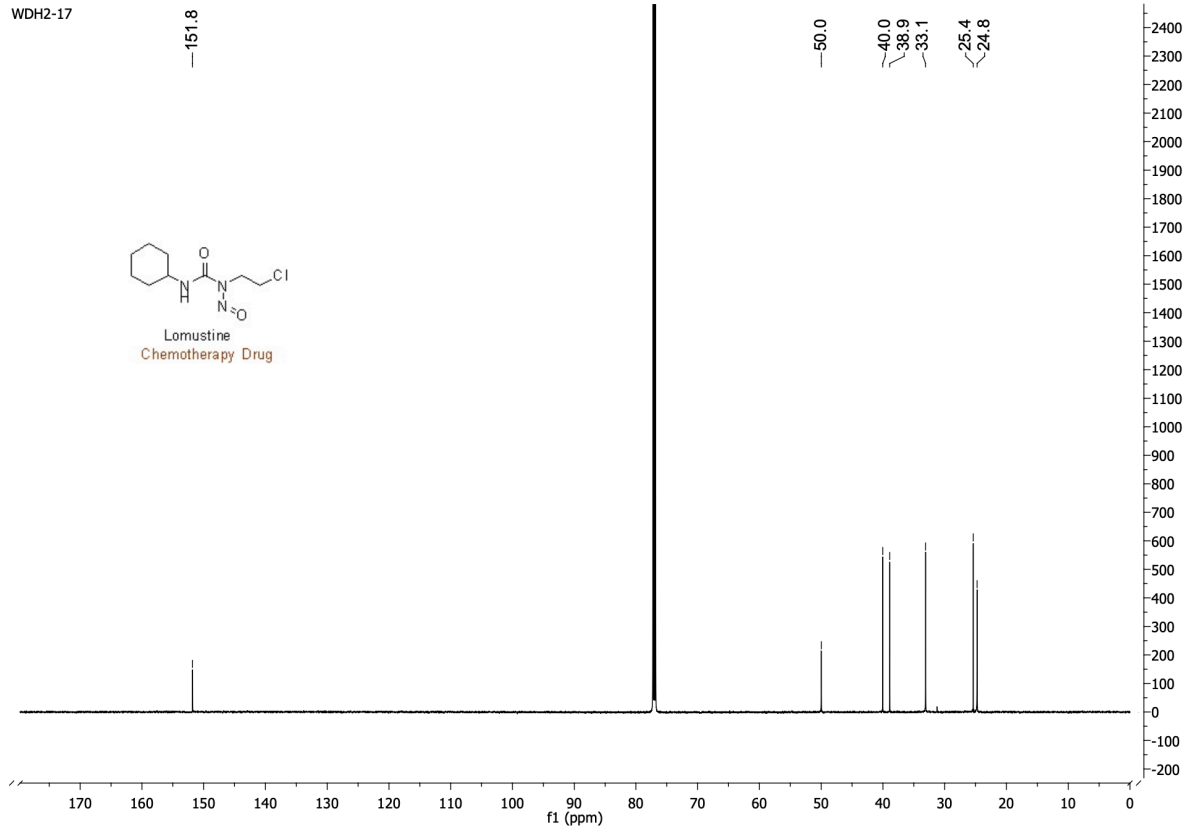
Table S13. Table of operations for the synthesis of Lomustine

Process	Reagent	To	Temp (°C)	Stir Rate (rpm)	Pressure(mbar)	Time (min)
Add	Et_2O (20 mL)		RT	0	Atmospheric	0.5
Add	2-Chloroethyl isocyanate (1.05 g)		RT	250	Atmospheric	0.5
Cool	-		0 - 5	250	Atmospheric	30
Add	Cyclohexanamine (1.00 g) in Et_2O (20 mL)		0 - 5	400	Atmospheric	10
Stir	-		0 - 5	400	Atmospheric	180
Filter	-	**Module 1**	0 - 5	250	Atmospheric	2
Add	Et_2O (3 mL)		0 - 5	250	Atmospheric	0.5
Stir	-		0 - 5	250	Atmospheric	2
Filter	-		0 - 5	250	Atmospheric	2
Dry	-		RT	0	100	60
Add	HCOOH (16 mL)		RT	0	Atmospheric	0.5
Stir	-		RT	250	Atmospheric	5
Transfer	-	**Module 2**	RT	250	Atmospheric	2
Add	HCOOH (2 mL)	**Module 1**	RT	250	Atmospheric	30
Stir	-		RT	250	Atmospheric	5
Transfer	-	**Module 2**	RT	250	Atmospheric	2
Cool	-	**Module 2**	0 - 15	250	Atmospheric	20
Add	Tert-butyl Nitrite (1.8 mL)	**Module 2**	0 - 15	250	Atmospheric	10
Stir	-		0 - 15	250	Atmospheric	60
Add	Water (36 mL)	**Module 2**	0 - 15	250	Atmospheric	10
Stir	-		0 - 15	250	Atmospheric	30
Filter	-		0 - 15	250	Atmospheric	2
Add	Water (5 mL)	**Module 2**	0 - 15	250	Atmospheric	0.5
Filter	-		0 - 15	250	Atmospheric	2
Dry	-		RT	0	100	720

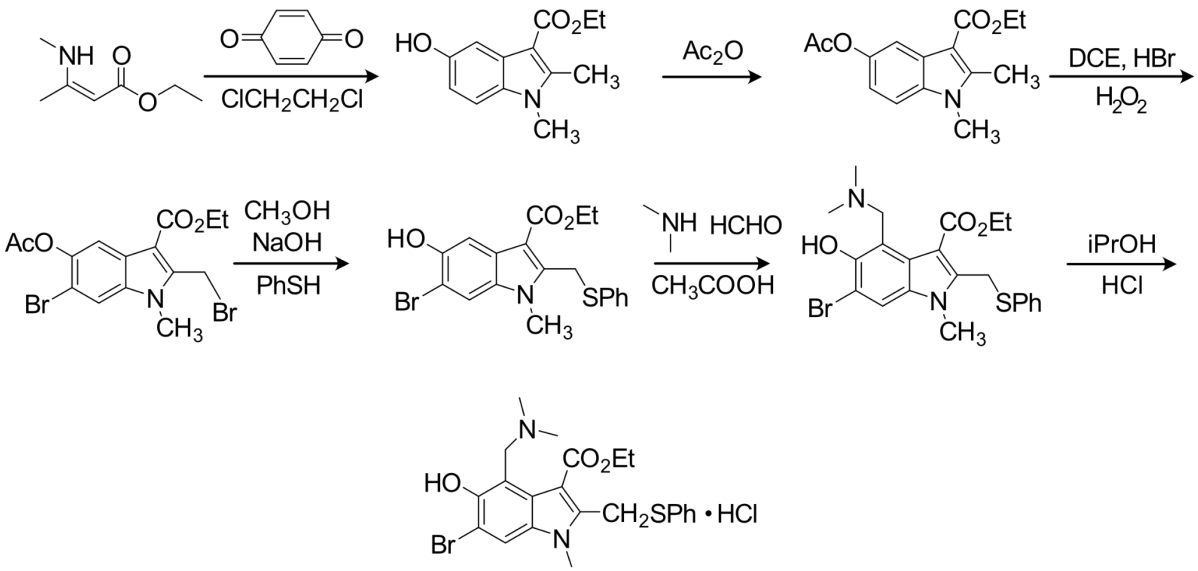
^{1}H NMR



$^{13}C\{^{1}H\}$ NMR:



5.5 Umifenovir



Ethyl 5-acetoxy-1,2-dimethyl-1H-indole-3-carboxylate (Umifenovir-A)

$ZnCl_2$ (160 mg) was added to *module-2*. A solution of p-benzoquinone (2.56 g in 10 mL of 1,2-dichloroethane) was added to *module-2*. The monolith was cooled down to 0-5 ºC and the enamine was added to *module-2* slowly. Once the transfer was completed, the reaction mixture was heated to 75 ºC and kept at this temperature for 1 h. Then, the monolith was cooled down naturally to room temperature, and it was stirred for 30 mins at this temperature. Finally, the solution was filtered and dry under vacuum for 1 h to obtain a grey solid.

Ethyl 5-hydroxy-1,2-dimethyl-1H-indole-3-carboxylate (Umifenovir -B)

1, 2-dichloroethane (15 mL), acetic anhydride (3 mL) and triethylamine (4.5 mL) were added to *module-2*. The reaction mixture was stirred at room temperature for 2 h. Then, the solvent was evaporated at 50 ºC for 1 h under vacuum (100 mbar). Methanol (8 mL) was added to *module-2*, and it was evaporated at 50 ºC for 1 h under vacuum (100 mbar). After evaporation, methanol (4 mL) was added to *module-2*, and the solution was cooled down to room temperature and kept at this temperature for 30 mins. The reaction mixture was filtered and washed twice with methanol (2 mL) and one time with 50% methanol (4 mL). Finally, the grey solid was dried under vacuum at 50 ºC for 3 h.

Ethyl 5-acetoxy-6-bromo-2-(bromomethyl)-1-methyl-1*H*-indole-3-carboxylate (Umifenovir-C)

1,2-dichloroethane (10 mL) was added to *module-2* with stirring to dissolve Umifenovir-B. Once the solid was dissolved, 48% HBr (3 mL) was added to *module-2*, and the monolith was heated to 70 ºC. Then, 10% H_2O_2 (9 mL) was added within 30 mins, and the reaction was stirred at 70 ºC for 1 h. The monolith was cooled down to room temperature, and it was stirred at this temperature for 1h. The solution was filtered, and methanol (15 mL) was added to the residual solid in *module-2*, and the reaction mixture was stirred for 30 mins. This process was repeated twice. Finally, the pale-red solid was dried under vacuum at 50 ºC for 3 h.

Ethyl 5-acetoxy-6-bromo-1-methyl-2-((phenylthio)methyl)-1H-indole-3-carboxylate (Umifenovir-D)

A mixture solution of PhSNa / NaOH in methanol was prepared by mixing NaOH (745 mg), thiophenol (0.79 mL) and methanol (20 mL). PhSNa/ NaOH solution (22 mL) was added to *module-2* containing Umifenovir-C. The reaction mixture was stirred at room temperature for 2 h. Then, acetic acid (3 mL) was added to *module-2* slowly, and the reaction was stirred for 1 h. Finally, the solution was filtered, the yellow solid was washed with water (3 mL), and it was dried under vacuum at 50 ºC for 3 h.

Ethyl 6-bromo-4-((dimethylamino)methyl)-5-hydroxy-1-methyl-2-((phenylthio)methyl)-1H-indole-3-carboxylate (Umifenovir-E)

A solution containing 40% dimethylamine (1.2 mL), acetic acid (5 mL) and 37% formaldehyde (0.7 mL) was prepared and added to *module-2* containing Umifenovir-D. The reaction mixture was heated to 65 ºC and stirred at this temperature for 2 h. Water (5 mL) was added to *module-2*. 15% NaOH (35 mL) was added to *module-3*, and the monolith was cooled down to 0-5 ºC for 30 mins. Once cooled, the solution in *module-2* was transferred to *module-3* and it was stirred at this temperature for 30 mins. Finally, the solution was filtered, washed with water (15 mL), and dried under vacuum at 40 ºC for 3 h to obtain a pale yellow solid.

Umifenovir

Isopropanol (5 mL) was added to *module-3* containing Umifenovir-E, and the monolith was heated to 70 ºC. Once at this temperature, conc. HCl (1 mL) was added to *module-3* slowly. The reaction mixture was stirred at this temperature for 30 mins, before it was cooled down to room temperature naturally. At room temperature, the solution was stirred for 30 mins and then filtered and washed with isopropanol (3 mL). Finally, the yellow-white (**1.3 g, 10 % yield**) solid was dried under vacuum for 3 h.

^{1}H NMR (600 MHz, DMSO) δ 9.42 (s, 1H), 9.13 (s, 1H), 8.03 (s, 1H), 7.43 – 7.22 (m, 5H), 4.91 (s, 2H), 4.74 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 2.73 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, DMSO): 165.1, 148.9, 144.2, 134.3, 132.7, 131.3, 129.2, 127.6, 125.3, 60.4, 53.1, 42.2, 29.8, 13.9.

HPLC-UV/Vis retention time: 12.45 min, purity (> 99%)

ESI(M+H)$^{+}$: expected: 477.0848, observed: 477.4221

Table S14. Table of operations for the synthesis of Umifenovir using a reactionware cartridge

Reaction	Process	Reagent	To	Temp (°C)	Stir Rate (rpm)	Pressure(mbar)	Time (min)
Step 1	Add	Ethyl acetoacetate (4.1 mL)	Module 1	RT	0	Atmospheric	0.5
	Add	33% Ethylamine ethanol (4.9 mL)		RT	250	Atmospheric	20
	Stir	-		RT	250	Atmospheric	180
	Evaporate	-		50	250	100	30
	Evaporate	-		80	250	100	60
Step 2	Cool	-	Module 2	0 - 5	250	Atmospheric	40
	Add	$ZnCl_2$ (160 mg)		0 - 5	250	Atmospheric	0.5
		p-Benzoquinone (2.56 g) in DCE (10 mL)		0 - 5	250	Atmospheric	0.5
	Stir	-		0 - 5	250	Atmospheric	15
	Transfer	The solution of Module 1		0 - 5	250	Atmospheric	10
	Heat	-		70 - 75	250	Atmospheric	30
	Stir	-		70 - 75	250	Atmospheric	60
	Cool	-		RT	250	Atmospheric	30
	Stir	-		RT	250	Atmospheric	30
	Filter	-		RT	250	Atmospheric	30
Step 3	Add	DCE (15 mL)	Module 2	RT	250	Atmospheric	0.5
		Acetic anhydride (3 mL)		RT	250	Atmospheric	0.5

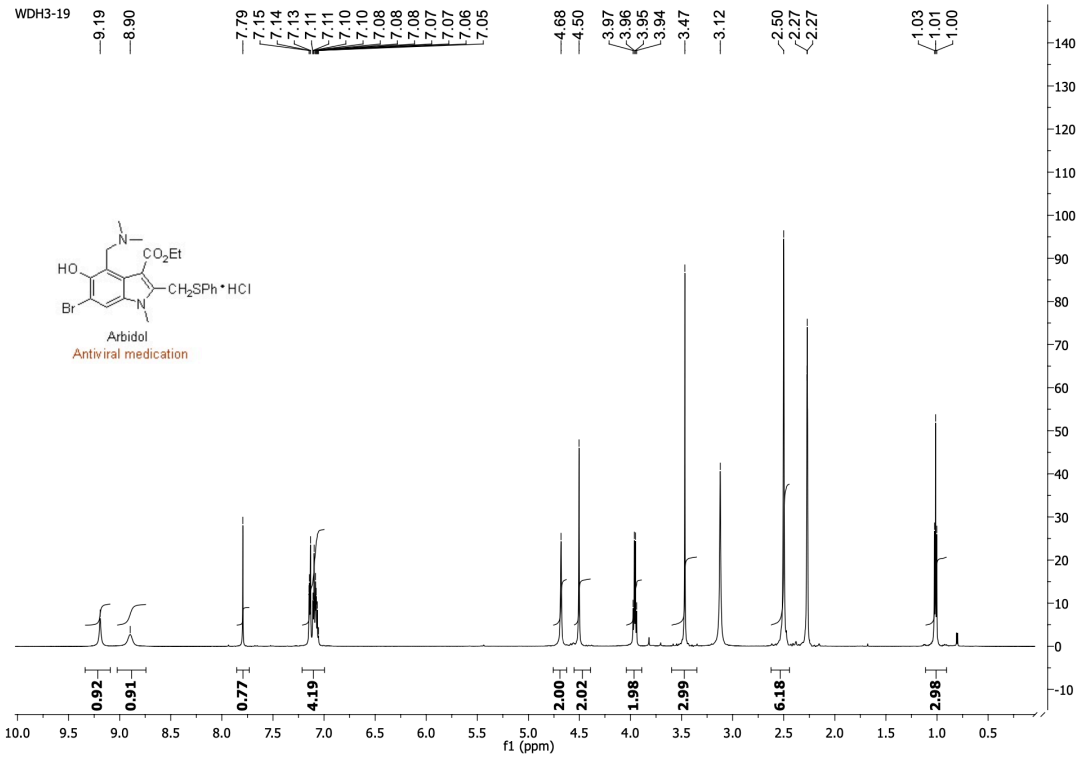
	Triethylamine (4.5 mL)	RT	250	Atmospheric	0.5
Stir	-	RT	250	Atmospheric	120
Evaporate	-	50	250	100	60
Add	MeOH (8 mL)	50	250	Atmospheric	0.5
Evaporate	-	50	250	100	60
Add	MeOH (4 mL)	50	250	Atmospheric	0.5
Cool	-	RT	250	Atmospheric	15
Stir	-	RT	250	Atmospheric	30
Filter	-	RT	0	Atmospheric	5
Add	MeOH (4 mL)	RT	250	Atmospheric	0.5
Filter	-	RT	0	Atmospheric	5
Add	50% MeOH (4 mL)	RT	250	Atmospheric	0.5
Filter	-	RT	0	Atmospheric	5
Dry	-	50	0	<100	180
Add	DCE (10 mL)	RT	250	Atmospheric	0.5
Add	48% HBr	RT	250	Atmospheric	0.5
Step 4	**Module 2**				
Heat	-	70	250	Atmospheric	30
Add	10% H_2O_2 (9 mL)	70	250	Atmospheric	30

	Stir	-		70	250	Atmospheric	60
	Cool	-		RT	250	Atmospheric	30
	Stir	-		RT	250	Atmospheric	60
	Filter	-		RT	0	Atmospheric	10
	Add	MeOH (15 mL)		RT	0	Atmospheric	0.5
	Stir	-		RT	250	Atmospheric	30
	Filter	-		RT	0	Atmospheric	10
	Add	MeOH (15 mL)		RT	0	Atmospheric	0.5
	Stir	-		RT	250	Atmospheric	30
	Filter	-		RT	0	Atmospheric	10
	Dry	-		50	0	<100	180
	Add	The solution of NaOH (745 mg), MeOH (25 mL) and PhSH (0.79 mL)		RT	0	Atmospheric	0.5
	Stir	-		RT	250	Atmospheric	120
Step 5	**Add**	CH_3COOH (3 mL)	**Module 2**	RT	250	Atmospheric	5
	Stir	-		RT	250	Atmospheric	60
	Filtrate	-		RT	0	Atmospheric	10
	Add	Water (3 mL)		RT	0	Atmospheric	0.5

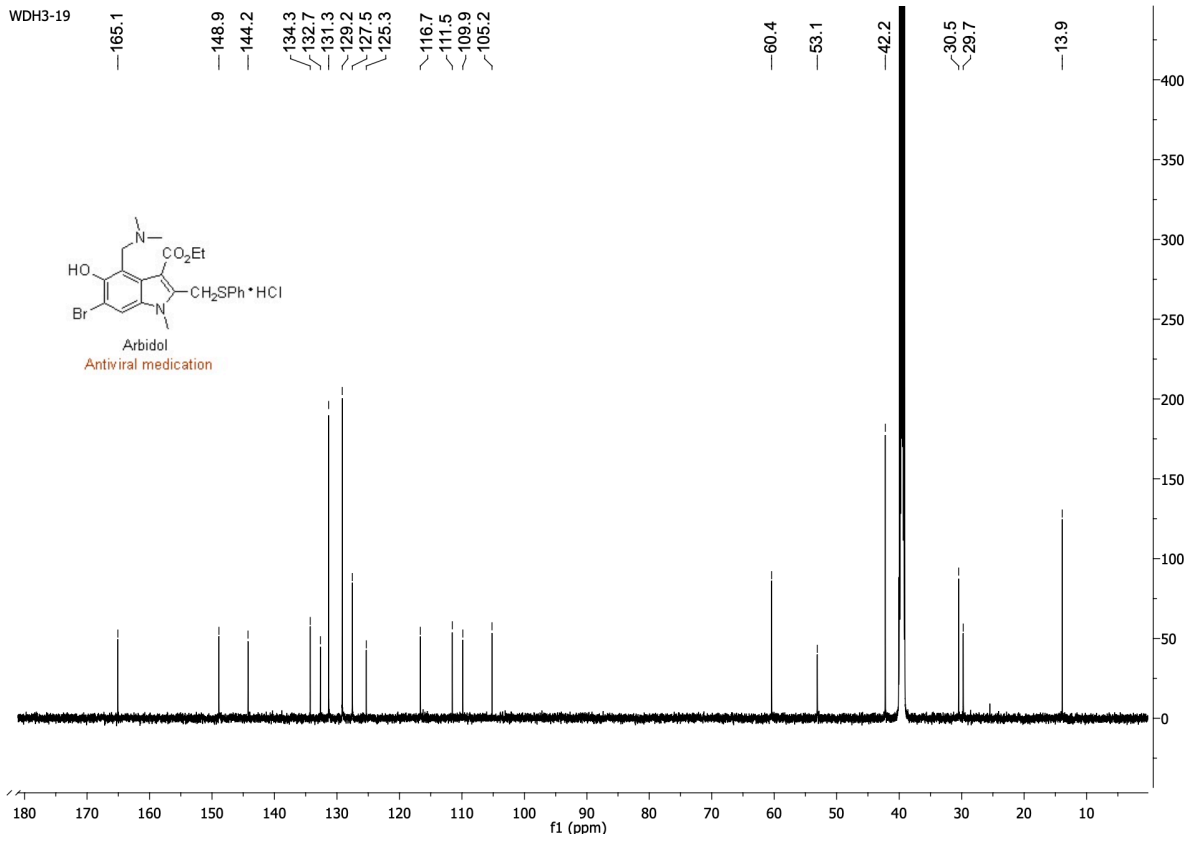
	Stir	-		RT	250	Atmospheric	5
	Filter	-		RT	0	Atmospheric	10
	Dry	-		50	0	<100	180
Step 6	**Add**	The mixture of CH_3COOH (5 mL), 40% Dimethylamine (1.2 mL) and 37% HCHO (0.7 mL)		RT	0	Atmospheric	0.5
	Heat	-		65	250	Atmospheric	25
	Stir	-	**Module 2**	65	250	Atmospheric	120
	Cool	-		0 - 5	250	Atmospheric	40
	Add	Water (5 mL)		0 - 5	250	Atmospheric	0.5
	Add	15% NaOH (35 mL)	**Module 3**	0 - 5	250	Atmospheric	0.5
	Stir	-		0 - 5	250	Atmospheric	30
	Transfer	The solution of Module 2		0 - 5	250	Atmospheric	30
	Stir	-		0 - 5	250	Atmospheric	30
	Filter	-		0 - 5	250	Atmospheric	30
	Add	Water (5 mL)	**Module 3**	RT	0	Atmospheric	0.5
	Stir	-		RT	250	Atmospheric	5
	Filter	-		RT	0	Atmospheric	10
	Dry	-		40	0	<100	180

	Add	iPrOH (5 mL)		RT	0	Atmospheric	0.5
	Heat	-		70	250	Atmospheric	30
	Add	Con. HCl (1 mL)		70	250	Atmospheric	5
	Stir	-		70	250	Atmospheric	30
	Cool	-		RT	250	Atmospheric	30
Step 7	**Stir**	-	**Module 3**	RT	250	Atmospheric	30
	Filter	-		RT	250	Atmospheric	30
	Add	^{i}PrOH (3 mL)		RT	0	Atmospheric	0.5
	Stir	-		RT	250	Atmospheric	5
	Filter	-		RT	0	Atmospheric	10
	Dry	-		40	0	<100	180

[1]H NMR

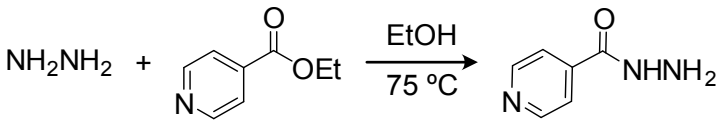


[13]C{[1]H} NMR:

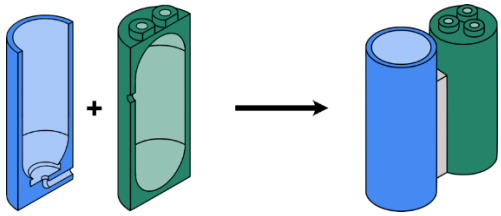


6 Automated small molecule syntheses

6.1 Isoniazid



Synthesis cartridge



The monolithic cartridge is composed of a filter reactor and a reactor connected with a siphon. *Module-1* (filter-reactor) is designed to contain all the synthetic procedures, while *module-2* is used to collect, and extract waste from the system.

Synthesis description

Ethyl isonicotinate (3 mL, 20 mmol), hydrazine hydrate (1.5 mL, 31 mmol) and ethanol (12 mL) were added to *module-1*. The monolith was heated to 75 ºC and was kept at this temperature for 4 hrs. After the reaction was completed, the reaction mixture was cooled down to 40ºC and stirred for 30 mins at that temperature. The solution was filtered and washed with ethanol (5 mL). To recrystallize the product, methanol (25 mL) was added to *module-1* to dissolve the product and the reactionware was heated to 60 ºC for 20 mins. Then, the cartridge was cooled down to 8 ºC and stirred at that temperature for 30 mins. Finally, the solution was filtered and dried for 10 hrs under vacuum. Isoniazid was obtained as a white solid (2.0 g, 73% yield)

^{1}H NMR: (600 MHz, D_2O) δ 8.59 (d, J = 5.7 Hz, 2H), 7.60 (d, J = 5.6 Hz, 2H)

^{13}C{^{1}H} NMR: (151 MHz, D_2O) δ = 121.0, 140.0, 149.0, 166.6.

HPLC-UV/Vis retention time: 0.6 min, purity: > 99 % (at 254 nm).

ESI(M+H)$^{+}$: expected: 138.066 Da, observed: 138.0705 Da

XDL file

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Hardware Graph

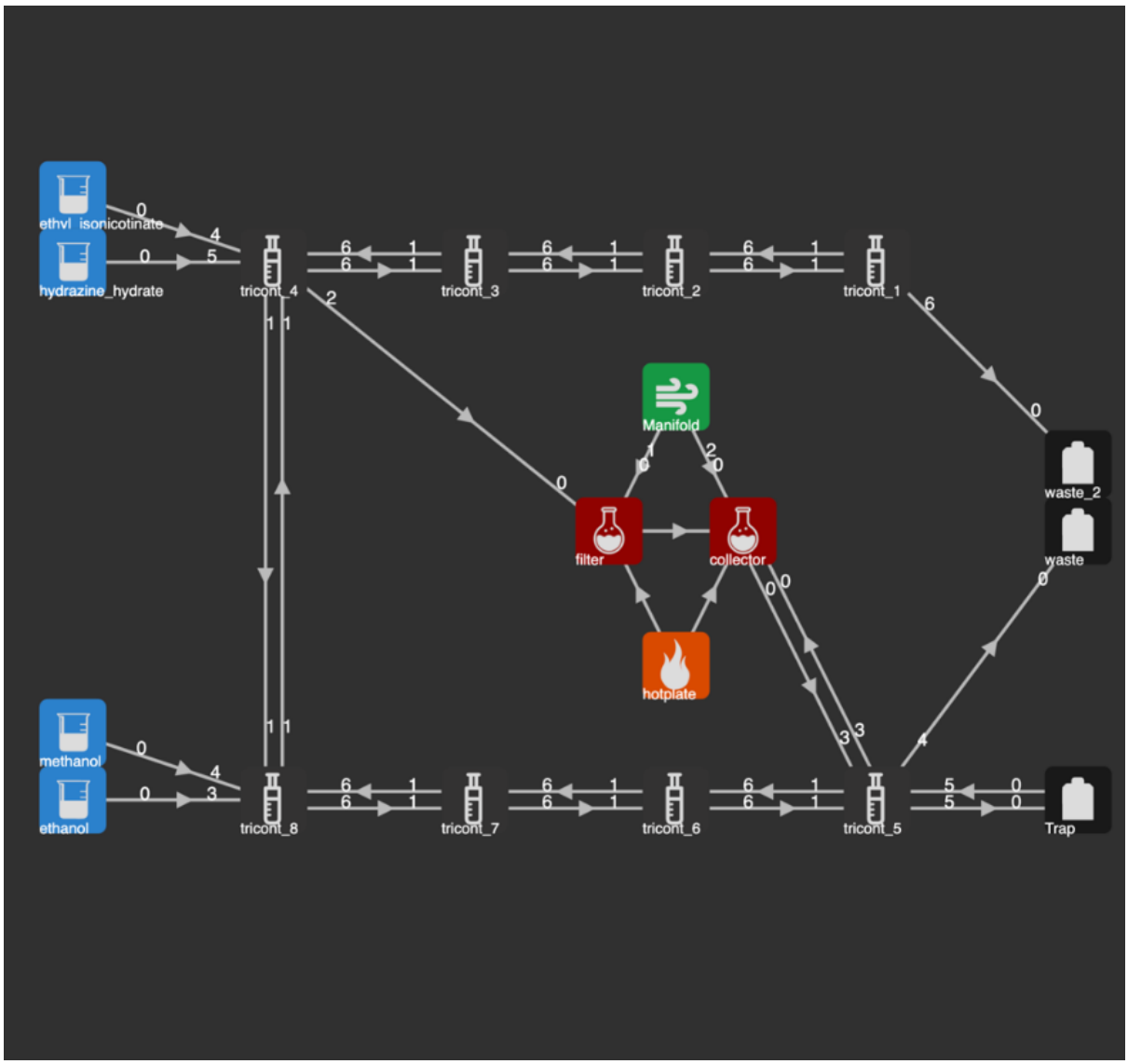


Figure S23. Graph describing all the physical elements and connections between them for the synthesis of Isoniazid

Pressure profile fingerprint

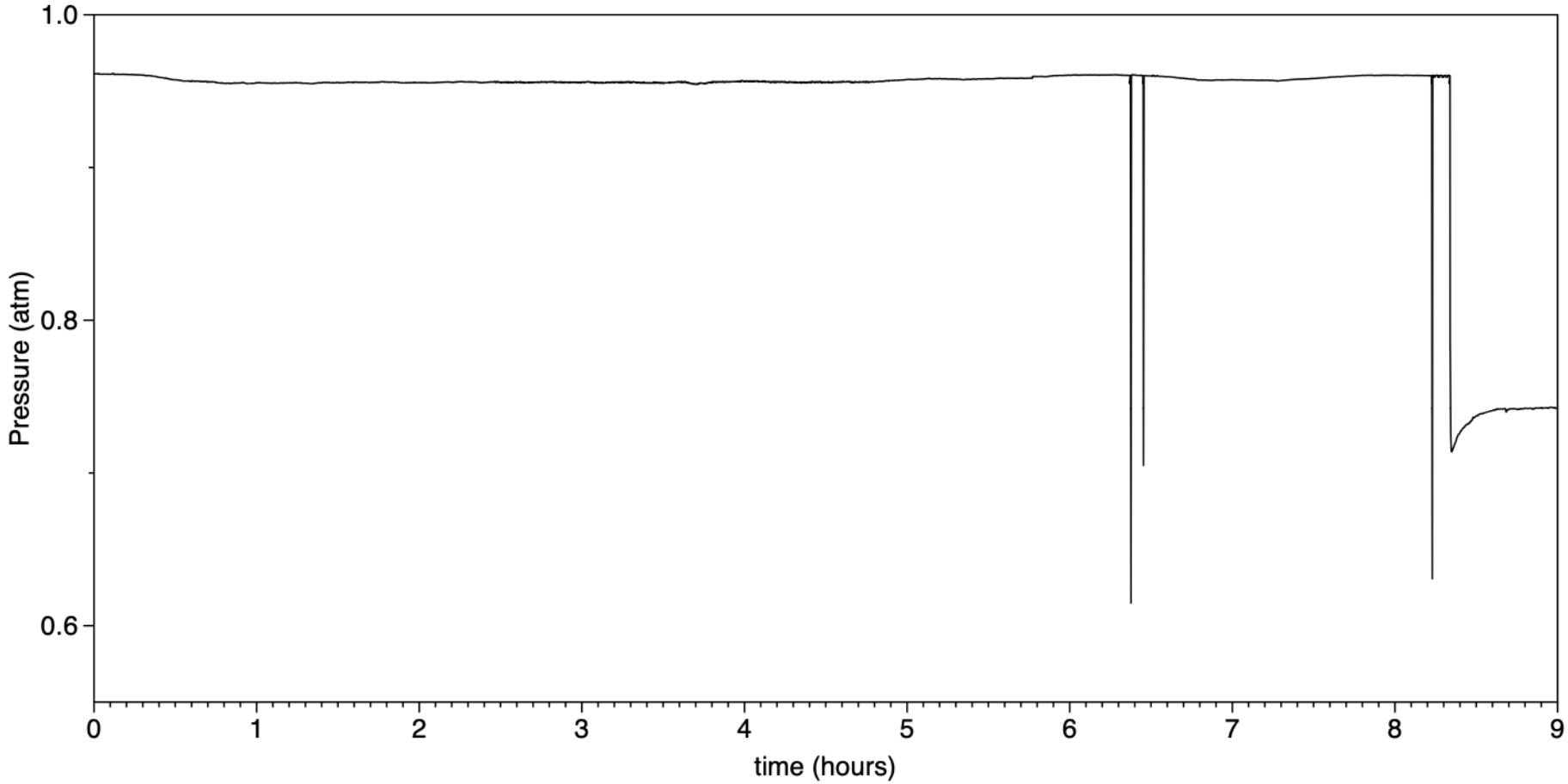
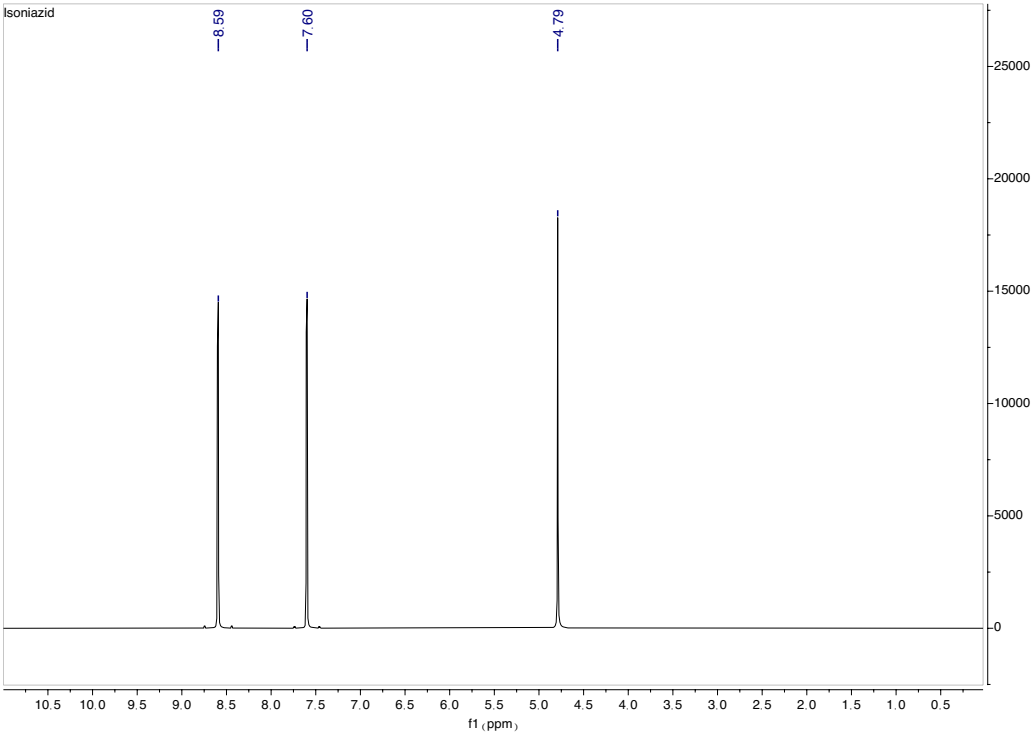
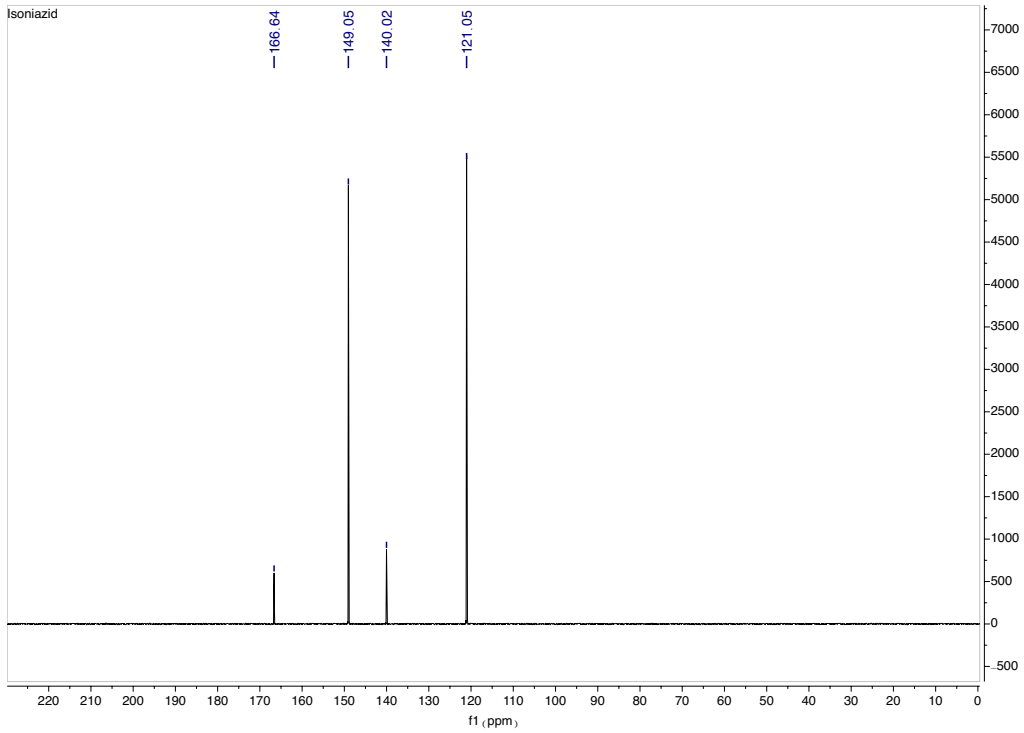


Figure S24. Pressure profile for the synthesis of Isoniazid

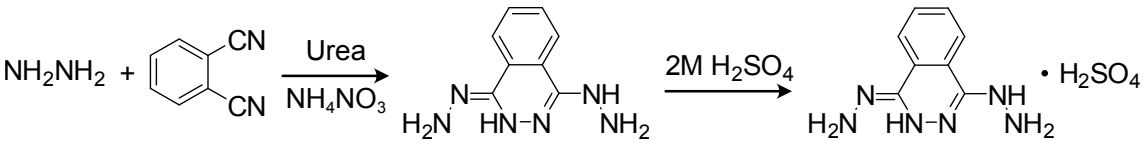
^{1}H NMR



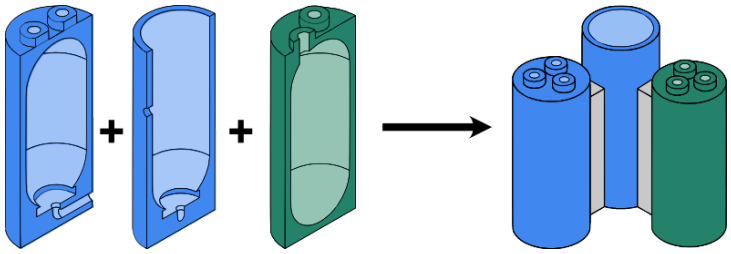
$^{13}C\{^{1}H\}$ NMR:



6.2 Dihydralizine sulfate



Synthesis cartridge



The monolithic cartridge is composed of two filter reactors (blue) and a reactor (green) connected with siphons. Module-1 and module-2 contain all the synthesis steps, while module-3 is used to collect, and extract waste from the system.

Synthesis description

The monolith was preloaded with 1,4-dicyanobenzene (1.28g, 10 mmol) and urea (3.65g, 61 mmol). The system was purged with nitrogen by applying vacuum to it for 60 seconds and refilling back with nitrogen until pressure is stabilized for three times. Hydrazine hydrate (3.65 mL, 75 mmol) was added to *module-1* while stirring. The monolith was heated to 100ºC and kept at this temperature for 3 hrs. The reactionware is cooled to 30ºC and water (10 mL) was added to *module-1*. The solution was filtered (to *module-3*) and washed with water (10 mL, x2). All the solvent waste was removed from the system. 2M H_2SO_4 (12.5 mL) was added to *module-1* over 10 mins while stirring at 500 rpm. The monolith was heated to 100 ºC for 1 hr. The solution was filtered, while it is hot (transferred to *module-2*), where it has been cooled down to 30 ºC. Once the solution was cooled down, the precipitate formed was filtered off and washed with 5 mL of water twice. Dihydralazine sulfate (2.1g, 72% yield) was obtained as a yellow solid after drying under vacuum for 10 hrs.

^{1}H NMR: (600 MHz, D_2O) δ 8.22 (m, 2H), 8.16 (m, 2H)

^{13}C{^{1}H} NMR: (151 MHz, D_2O) δ = 119.82, 123.46, 134.76.

HPLC-UV/Vis retention time: 0.45 min, purity: > 99 % (at 254 nm).

ESI(M+H)$^+$: expected: 191.1045 Da, observed: 191.1093 Da

XDL file

```
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    <Purge
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    />
    <Add
      reagent="hydrazine_hydrate"
      vessel="filter"
      volume="3.65 mL"
      stir="True"
      priming_volume="1 mL"
    />
    <HeatChill
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      temp="100°C"
      time="3 hrs"
      stir="true"
      track="True"
    />
    <HeatChill
      vessel="filter"
      temp="30°C"
      time="5 mins"
      stir="true"
    />
    <Add
      reagent="water"
      vessel="filter"
      volume="10 mL"
      stir="True"
      stir_speed="500 RPM"
    />
    <Filter
      filter_vessel="filter"
    />
    <WashSolid
      vessel="filter"
      solvent="water"
      volume="10 mL"
      washes="2"
    />
    <Add
      reagent="2M_H2SO4"
      vessel="filter"
      volume="12.5 mL"
      time="10 mins"
      stir="True"
      stir_speed="500 RPM"
    />
    <HeatChill
      vessel="filter"
      temp="100°C"
      time="1 hrs"
      stir="true"
    />
    <Transfer
```

```
      to_vessel="filter_2"
    />
    <HeatChill
      vessel="filter"
      temp="30°C"
      time="1 hrs"
      stir="true"
    />
    <Filter
      filter_vessel="filter_2"
    />
    <WashSolid
      vessel="filter_2"
      solvent="water"
      volume="5 mL"
      washes="2"
    />
    <Dry
      vessel="filter_2"
      time="10 hrs"
    />
  </Procedure>
</Synthesis>
```

Hardware Graph

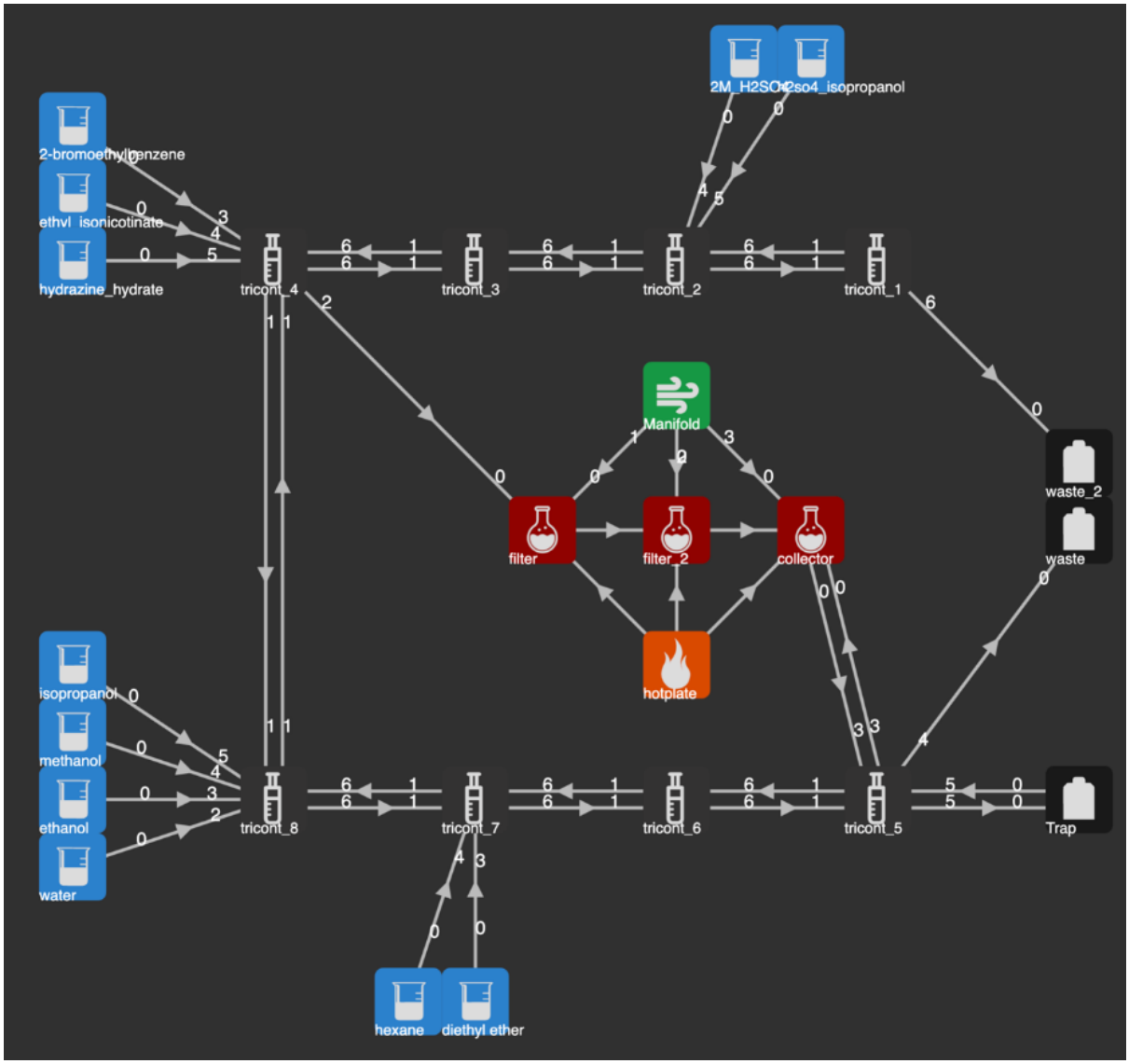


Figure S25. Graph describing all the physical elements and connections between them for the synthesis of Isoniazid and Dihydralizine

Pressure profile fingerprint

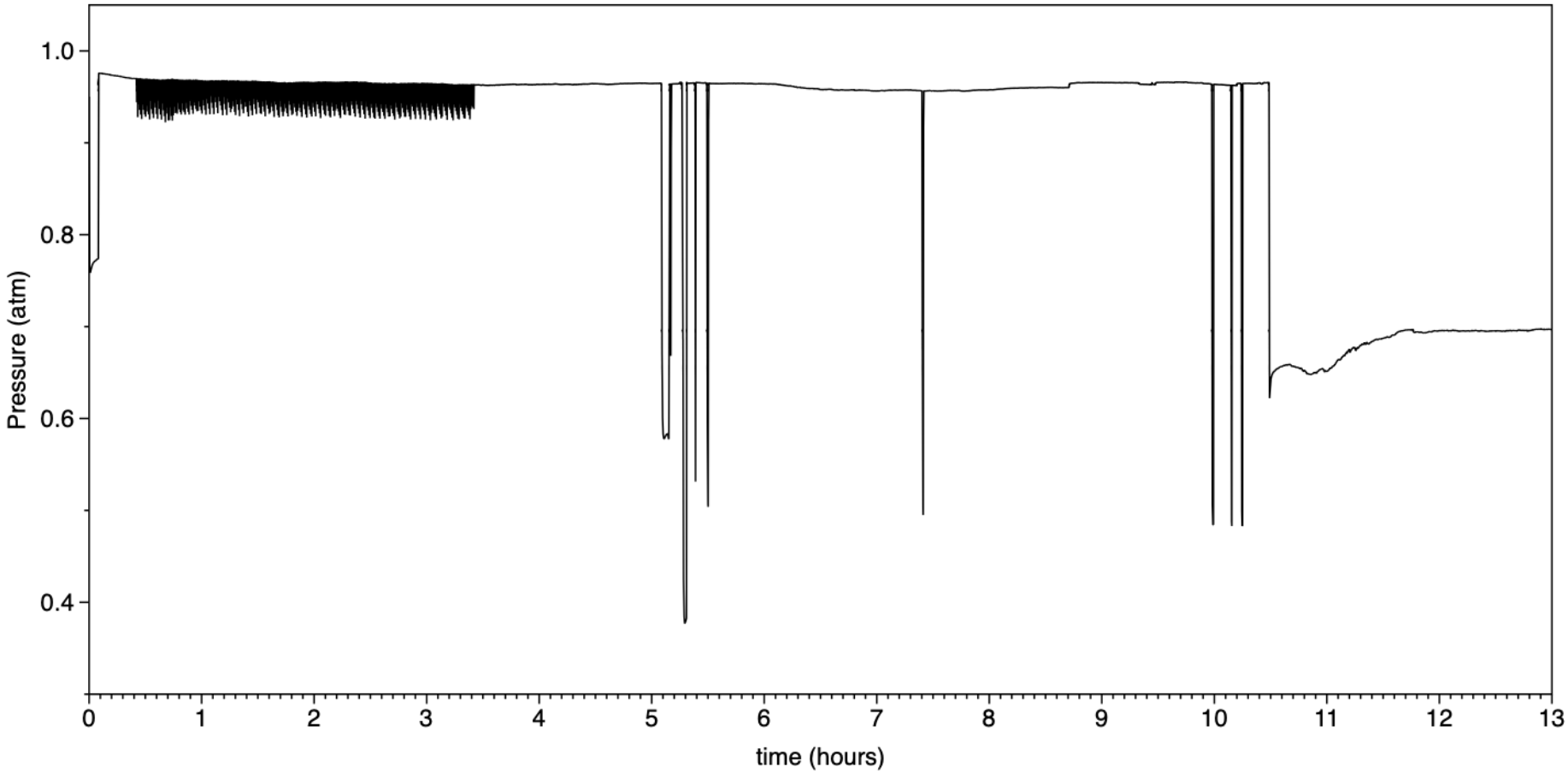
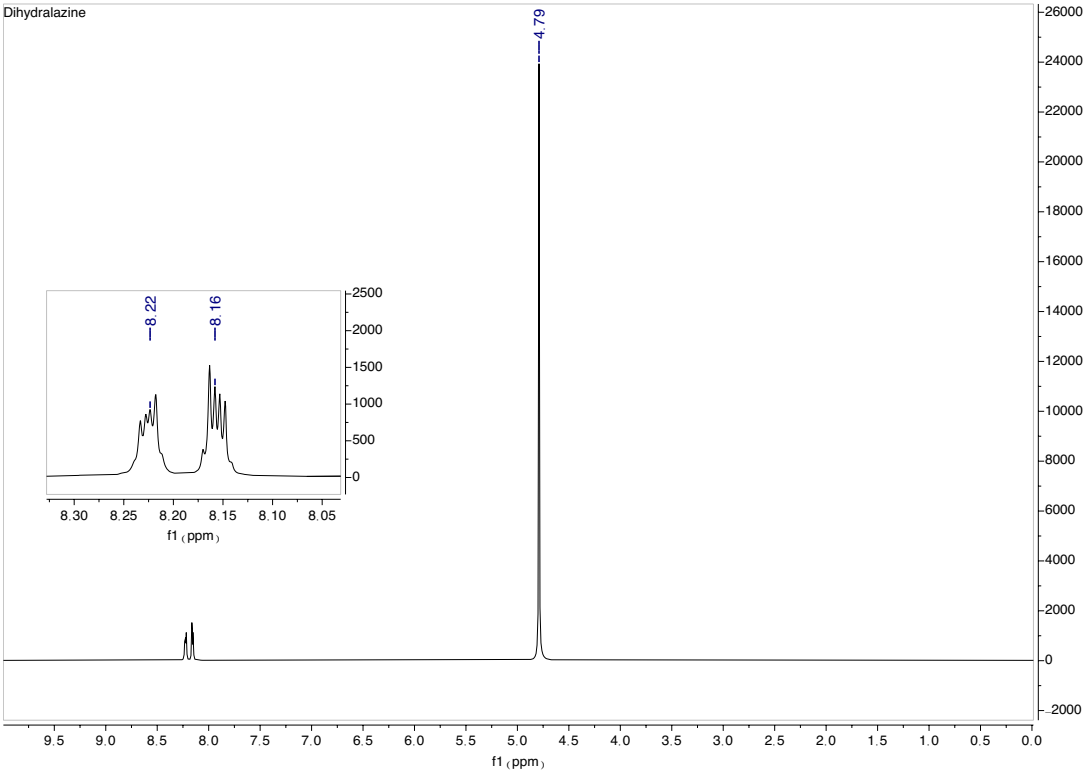
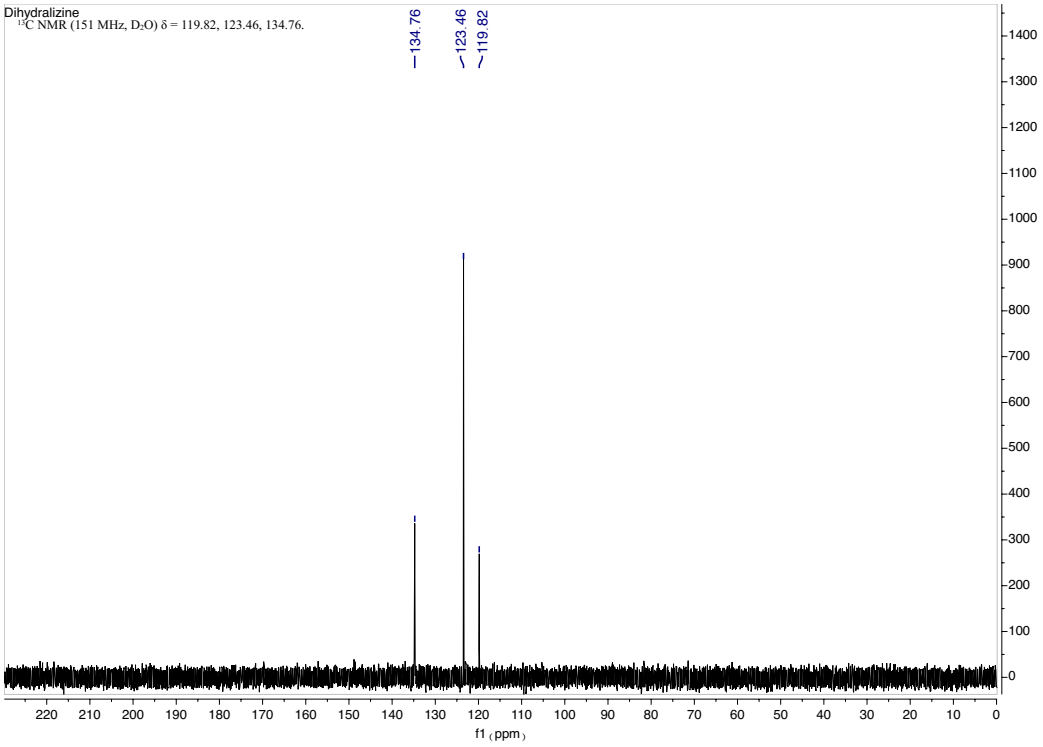


Figure S26. Pressure profile for the synthesis of Dihydralizine

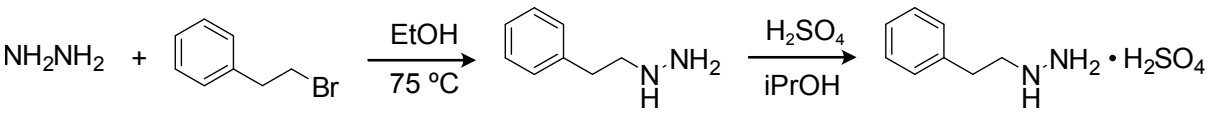
[1]H NMR:



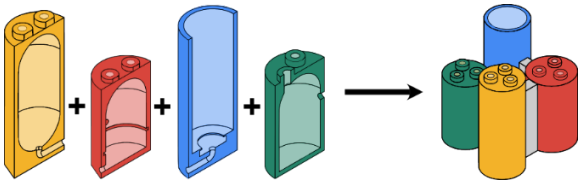
[13]C{[1]H} NMR:



6.3 Phenelzine sulfate



Synthesis cartridge



The monolithic cartridge is composed of one reactor (yellow), a floating filter reactor (red), a filter reactor (blue) and a reactor (green) connected with siphons. Module-1 and module-2 are design for the synthesis of Phenelzine, module-3 for the synthesis of Phenelzine sulfate**,** and module-3 is used to collect, and extract waste from the system.

Synthesis description

The monolith was purged with nitrogen three times (vacuum for 60 seconds each cycle). Ethanol (10 mL) and hydrazine hydrate (2.9 mL, 60 mmol) were added to *module-1*. The reactionware was heated to 75 ºC, and 2-bromoethylbenzene (1.84 mL, 10 mmol) was added to *module-1* over 2 mins. Ethanol (5 mL) was added to *module-1*, and the system was kept at 75 ºC for 2 hrs while applying vacuum pulses of 1 seconds every 60 seconds in *module-1*. The reactor was cooled down to 40 ºC and vacuum was applied to *module-1* for 2.5 hrs to evaporate the solvent. Diethyl ether (15 mL) was added to module-1 to extract Phenelzine and transferred to module-2. The extraction was repeated twice. Water (10 mL) was added to *module-1* and transferred to *module-3*, to push residual diethyl ether from *module-2*. Vacuum was applied to *module-3*, to evaporate diethyl ether, for 2.5 hours, while heating to 35 ºC. Isopropanol (20 mL) was added to *module-3*. Then, a H_2SO_4-isopropanol mixture (1:5, 6 mL) was added to module-3 over 5 mins, and the solution was stirred for 2 hrs. Hexane (5 mL) was added to module-3 and stirred for 30 mins. The solution was filtered (transferred to *module-4* for collection) and washed with hexanes (10 mL) twice. Phenelzine sulfate was obtained as a pale yellow solid (1.2g, 51% yield) after drying for 10 hrs.

^{1}H NMR: (600 MHz, D_2O) δ 7.42 (m, 2H), 7.36 (m, 3H), 3.43 (t, J = 7.5 Hz, 2H), 3.03 (t, J = 7.5 Hz, 2H).

^{13}C{^{1}H} NMR: (151 MHz, D_2O) δ = 30.6, 52.1, 127.3, 128.8, 136.6.

HPLC-UV/Vis retention time: 8.3 min, purity: > 99 % (at 254 nm).

ESI(M+H)$^+$: expected: 137.1034 Da, observed: 137.1077 Da

XDL file

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      vessel="reactor"
    />
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      vessel="reactor"
      volume="10 mL"
    />
    <Add
      reagent="hydrazine_hydrate"
      vessel="reactor"
      volume="2.9 mL"
      stir="True"
      priming_volume="1 mL"
    />
    <HeatChill
      vessel="reactor"
      temp="75°C"
      time="1 min"
      stir="true"
    />
    <Add
      reagent="2-bromoethylbenzene"
      vessel="reactor"
      volume="1.84 mL"
      stir="True"
      time="2 mins"
      stir_speed="400 RPM"
      priming_volume="1 mL"
    />
    <Add
      reagent="ethanol"
      vessel="reactor"
      volume="5 mL"
      stir="True"
      stir_speed="400 RPM"
    />
    <HeatChill
      vessel="reactor"
      temp="75°C"
      time="2 hrs"
      stir="true"
      track="true"
    />
    <Evaporate
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      solvent="ethanol"
      temp="40°C"
      time="2.5 h"
      mode="manual"
    />
    <SeparateReactionware
      from_vessel="reactor"
      separation_vessel="floating_filter"
      to_vessel="filter"
```

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  product_phase="top"
  solvent="diethyl ether"
  solvent_volume="15 mL"
  repeats="2"
/>
<Add
  reagent="water"
  vessel="reactor"
  volume="10 mL"
  stir="True"
  stir_speed="400 RPM"
/>
<Transfer
  from_vessel="reactor"
  to_vessel="floating_filter"
  time="10 seconds"
/>
<Transfer
  from_vessel="floating_filter"
  to_vessel="filter"
  time="10 seconds"
/>
<Evaporate
  rotavap_name="filter"
  solvent="diethyl ether"
  temp="35°C"
  time="2.5 h"
  mode="manual"
/>
<Add
  reagent="isopropanol"
  vessel="filter"
  volume="20 mL"
  stir="True"
  stir_speed="400 RPM"
/>
<Add
  reagent="h2so4_isopropanol"
  vessel="filter"
  volume="6 mL"
  time="5 mins"
  stir="True"
  stir_speed="400 RPM"
/>
<Wait
  time="2 hrs"
/>
<Add
  reagent="hexane"
  vessel="filter"
  volume="5 mL"
  stir="True"
/>
<Stir
  vessel="filter"
  time="30 mins"
  stir_speed="400 RPM"
/>
```

```
    <Filter
      filter_vessel="filter"
    />
    <WashSolid
      vessel="filter"
      solvent="hexane"
      volume="10 mL"
      washes="1"
    />
    <Dry
      vessel="filter"
      time="10 hrs"
    />
  </Procedure>
</Synthesis>
```

Hardware Graph

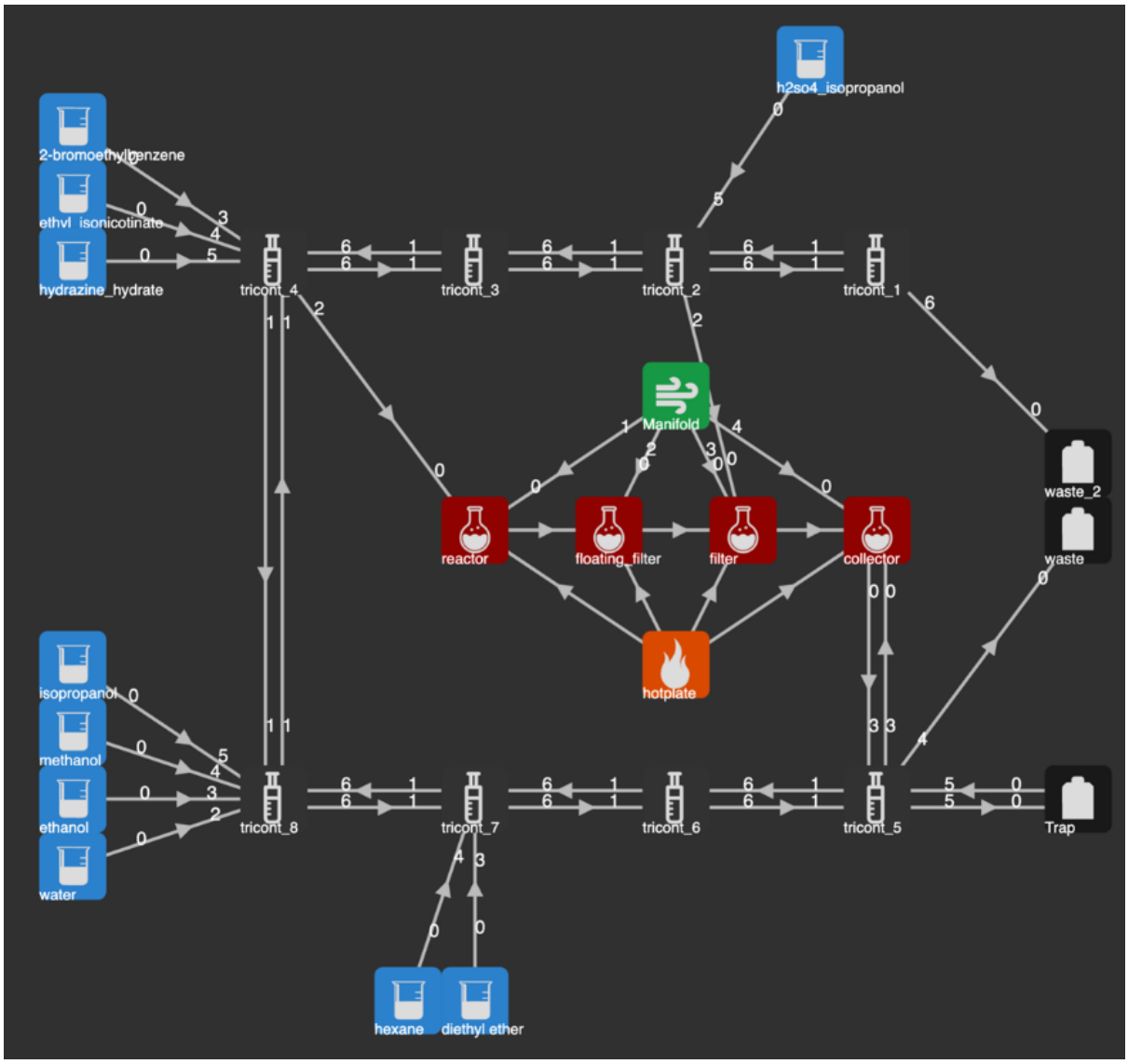


Figure S27. Graph describing all the physical elements and connections between them for the synthesis of Isoniazid, Dihydralizine, and Phenelzine sulfate

Pressure profile fingerprint

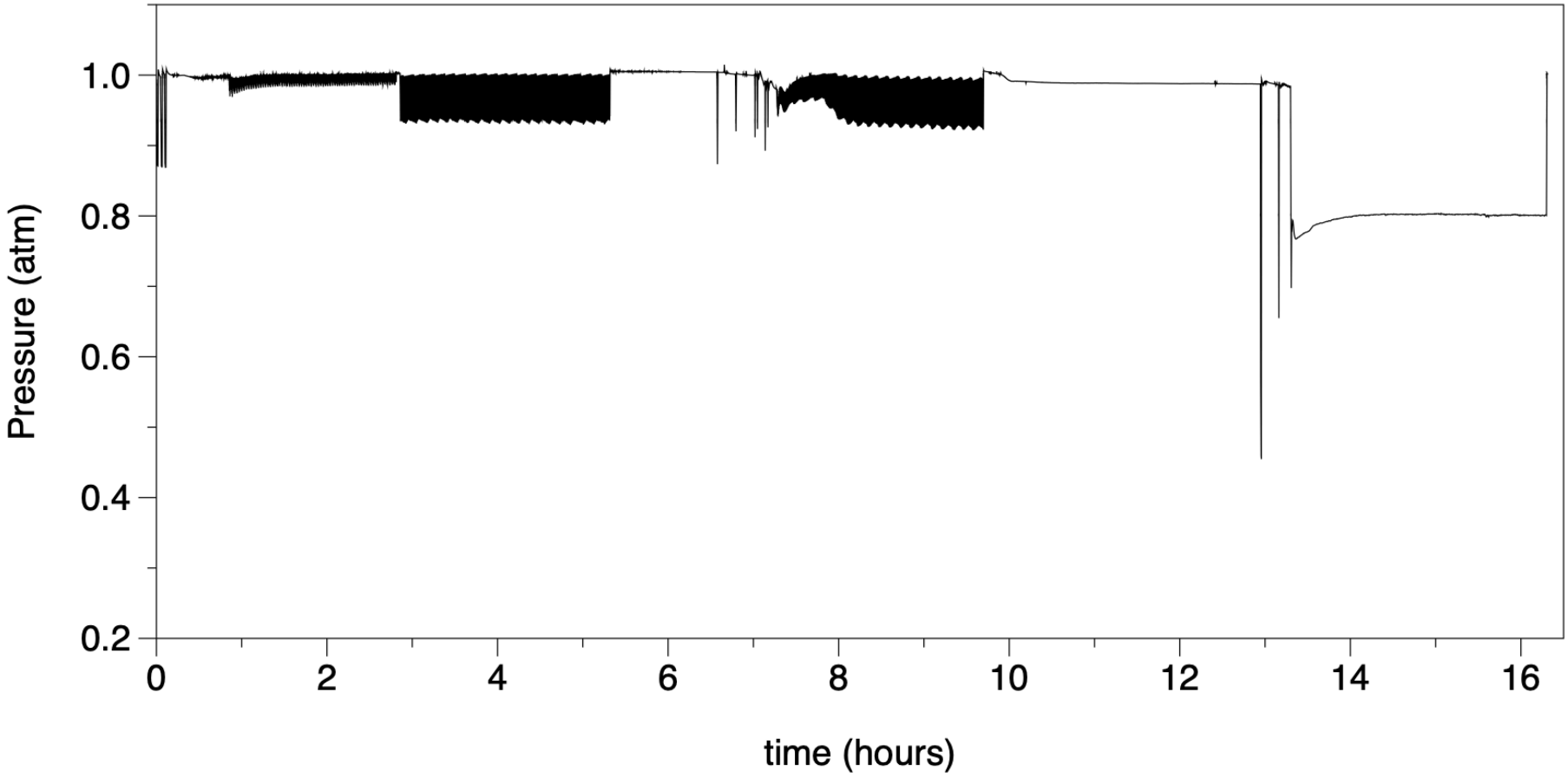
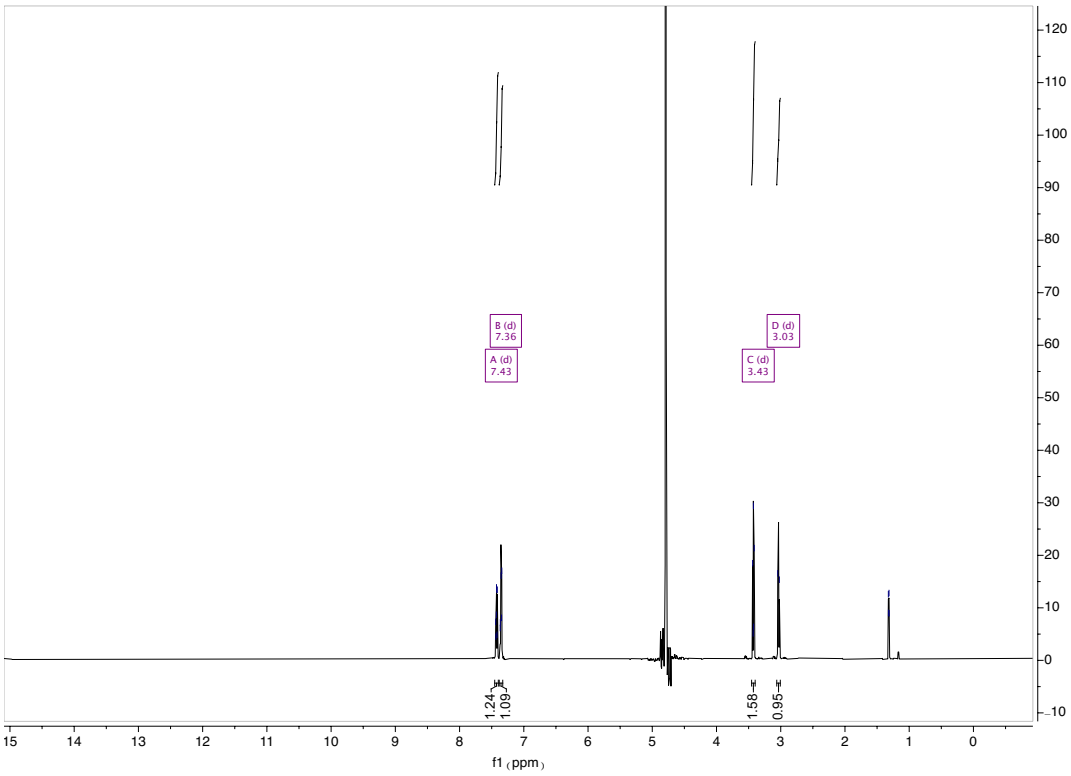
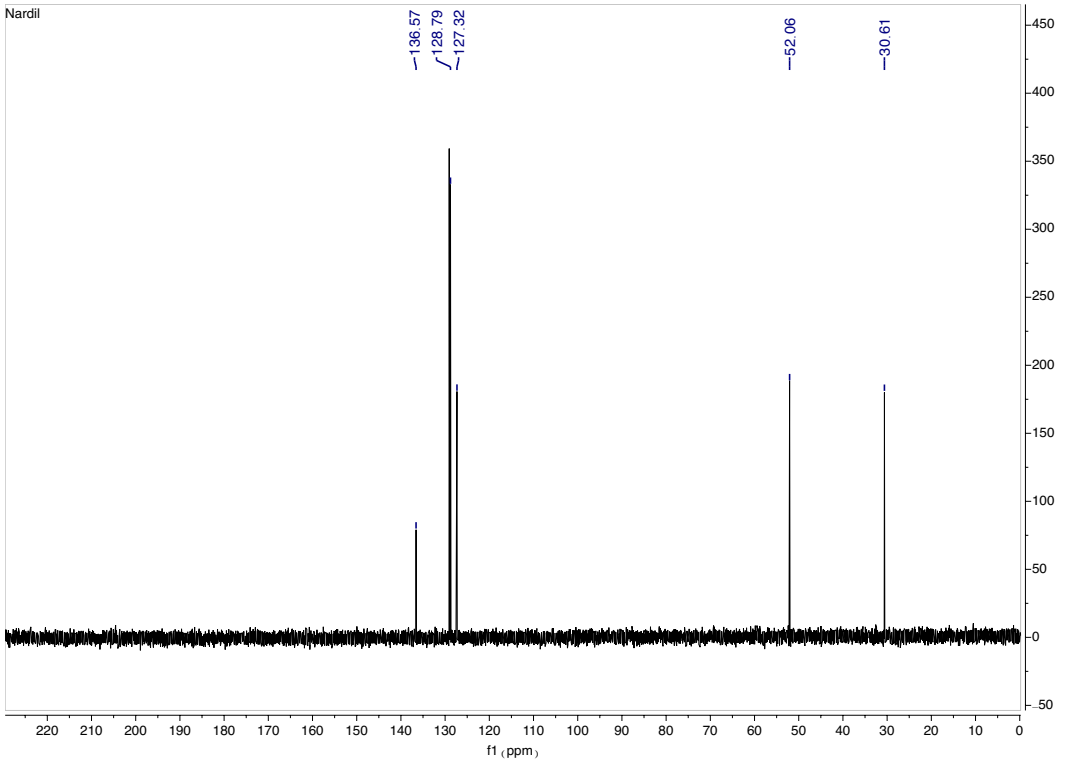


Figure S28. Pressure profile for the synthesis of Phenelzine sulfate

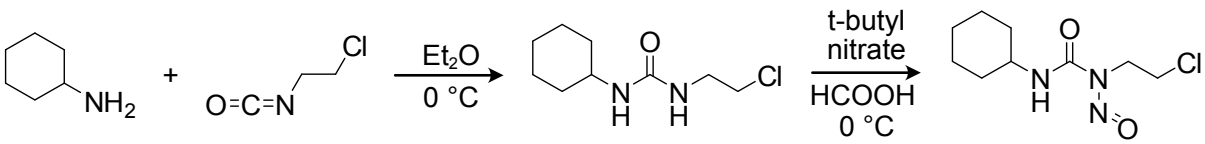
^{1}H NMR:



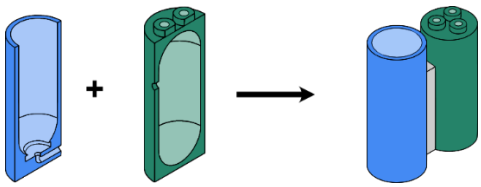
$^{13}C\{^{1}H\}$ NMR:



6.4 Lomustine



Synthesis cartridge



The monolithic cartridge is composed of one filter reactor (blue) containing all synthetic steps of Lomustine, and a reactor (green) that is used to collect, and extract waste from the system.

Synthesis description

The monolith was purged with nitrogen three times (vacuum for 60 seconds followed by refilling with nitrogen until the pressure is stabilized). Diethyl ether (20 mL), 2-chloroethyl isocyanate (1.05 mL, 10 mmol) were added to *module-1*. The reactionware was cooled down to 5 ºC, and cyclohexylamine (0.5M, 20 mL, 10 mmol) was added over 5 mins. The solution was stirred for 3 hrs, filtered, and washed with diethyl ether twice (5 mL). The obtained solid was dried for 1 hr under vacuum. Formic acid (18 mL) was added to *module-1*, and the solution was cooled down to 5 ºC, followed by adding t-butyl nitrate (1.8 mL, 13.5 mmol). The solution was stirred for 2 hrs at 0→25ºC. Water (36 mL) was added to *module-1*, and the solution was stirred for an extra 1 hr. The solution was filtered, and the obtained precipitate was washed with water (three times, 5 mL). The obtained pale yellow solid was dried under vacuum for 10 hrs to yield compound **5** (1.6g, 69 % yield)

^{1}H NMR: (600 MHz, $CDCl_3$) δ 6.80 (b, 1H), 4.21 (t, J = 6.6 Hz, 2H), 3.94 – 3.87 (m,1H), 3.52 (t, J = 6.7 Hz, 2H), 2.10 – 2.04 (m, 2H), 1.82 – 1.76 (m, 2H), 1.71 – 1.63 (m, 1H), 1.50 – 1.40 (m, 2H), 1.37 – 1.21 (m, 3H).

^{13}C{^{1}H} NMR: (151 MHz, $CDCl_3$) δ = 151.3, 49.5, 39.6, 38.4, 32.6, 24.9, 24.3.

HPLC-UV/Vis retention time: 1.8 min, purity: > 99 % (at 254 nm).

ESI(M+H)$^{+}$: expected: 234.1009 Da, observed: 234.1056 Da

XDL file

```
<Synthesis>
  <Procedure>
    <Purge
      vessel="filter"
    />
    <Add
      reagent="diethyl ether"
      vessel="filter"
      volume="20 mL"
    />
    <Add
      reagent="2-chloroethyl isocyanate"
      vessel="filter"
      volume="1.05 mL"
      stir="true"
      priming_volume="0.5 mL"
    />
    <HeatChill
      vessel="filter"
      temp="5°C"
      time="5 min"
      stir="true"
    />
    <Add
      reagent="0.5M cyclohexylamine"
      vessel="filter"
      volume="20 mL"
      time="5 min"
      stir="True"
    />
    <Wait
      time="3 hrs"
    />
    <Filter
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    />
    <WashSolid
      vessel="filter"
      solvent="diethyl ether"
      volume="5 mL"
    />
    <Dry
      vessel="filter"
      temp="25 °C"
      time="1 hrs"
    />
    <Add
      reagent="formic acid"
      vessel="filter"
      volume="18 mL"
      stir="True"
    />
    <HeatChill
      vessel="filter"
      temp="5°C"
      time="5 min"
      stir="true"
```

```
    />
    <Add
      reagent="t-butyl nitrite"
      vessel="filter"
      volume="1.8 mL"
      time="1 min"
      stir="True"
      priming_volume="1 mL"
    />
    <Stir
      vessel="filter"
      time="2 hrs"
      continue_stirring="true"
    />
    <Add
      reagent="water"
      vessel="filter"
      volume="36 mL"
      stir="True"
    />
    <Stir
      vessel="filter"
      time="1 hrs"
    />
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      vessel="filter"
      solvent="water"
      volume="5 mL"
    />
    <Dry
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      temp="25 °C"
      time="10 hrs"
    />
  </Procedure>

</Synthesis>
```

Hardware graph

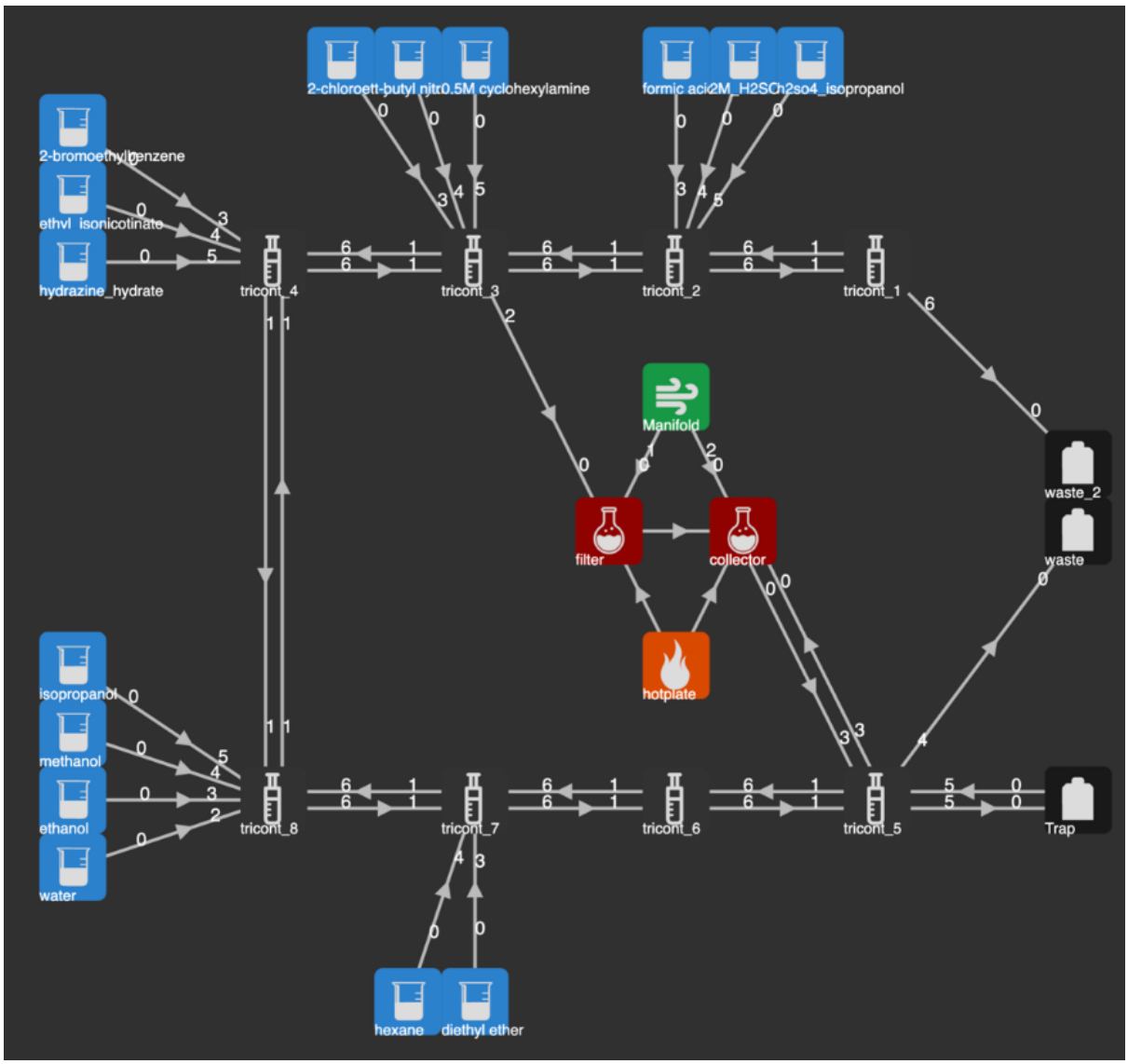


Figure S29. Graph describing all the physical elements and connections between them for the synthesis of Isoniazid, Dihydralizine, Phenelzine sulfate, and Lomustine

Pressure profile fingerprint

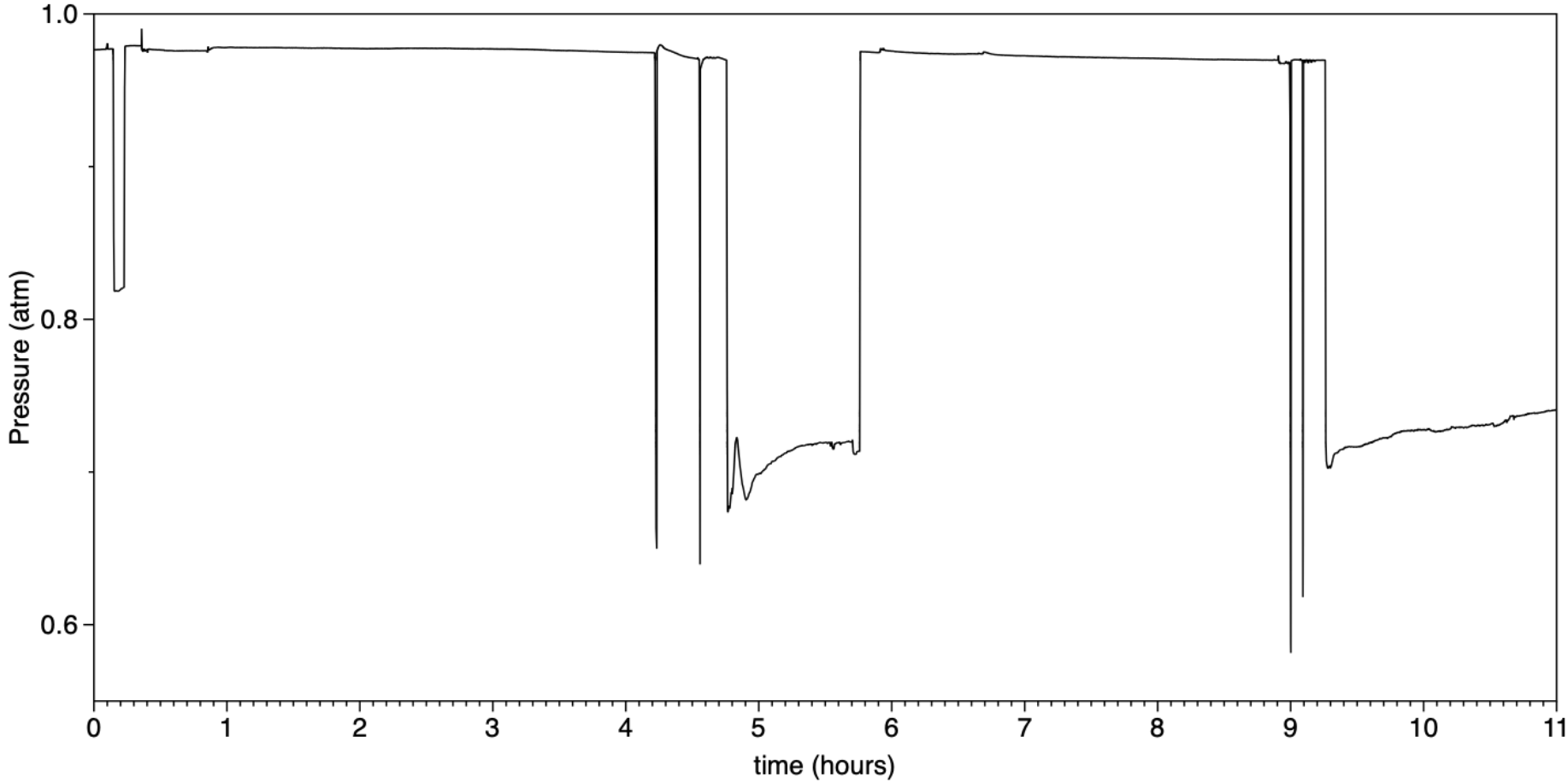
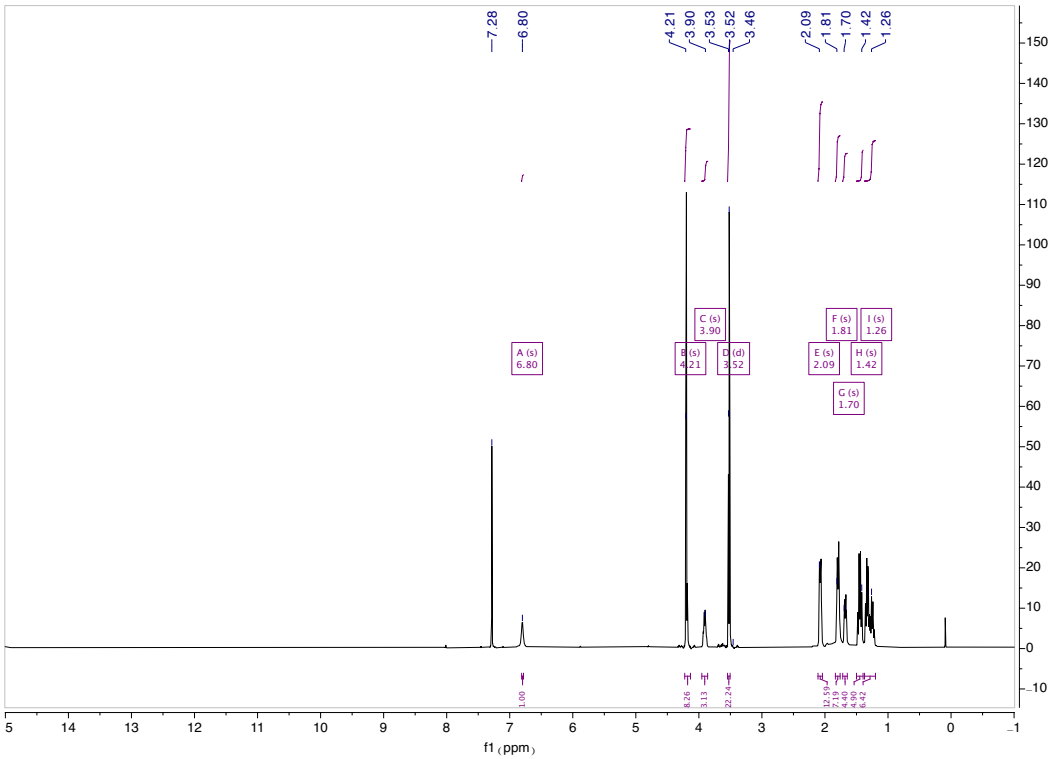
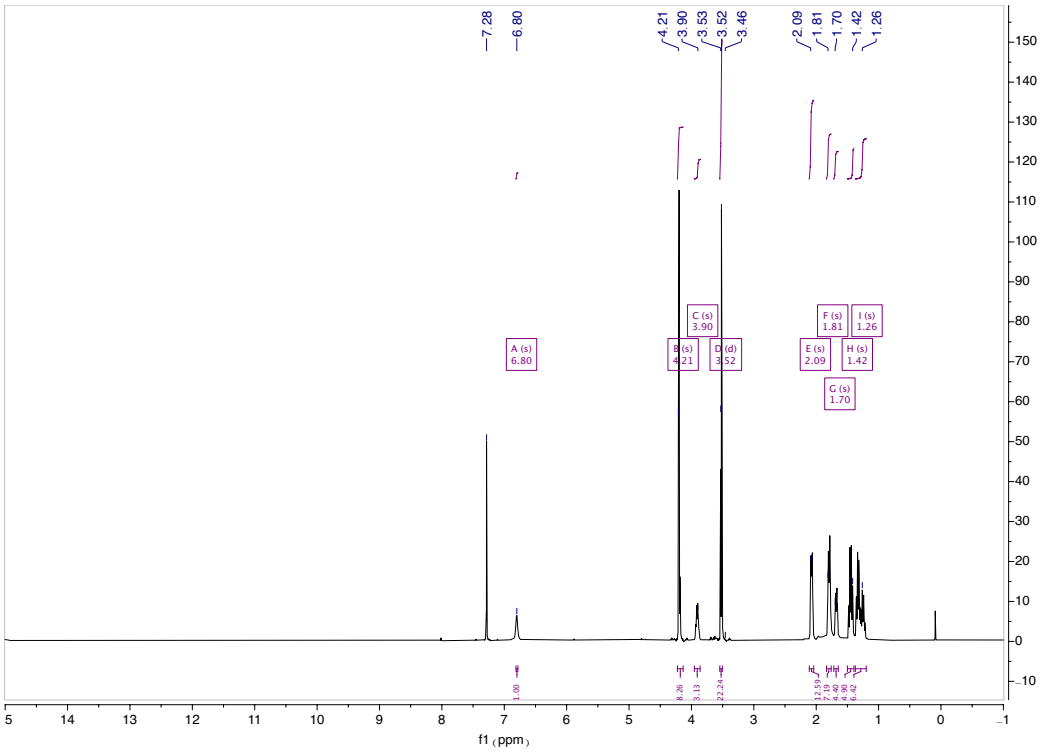


Figure S30. Pressure profile for the synthesis of Lomustine

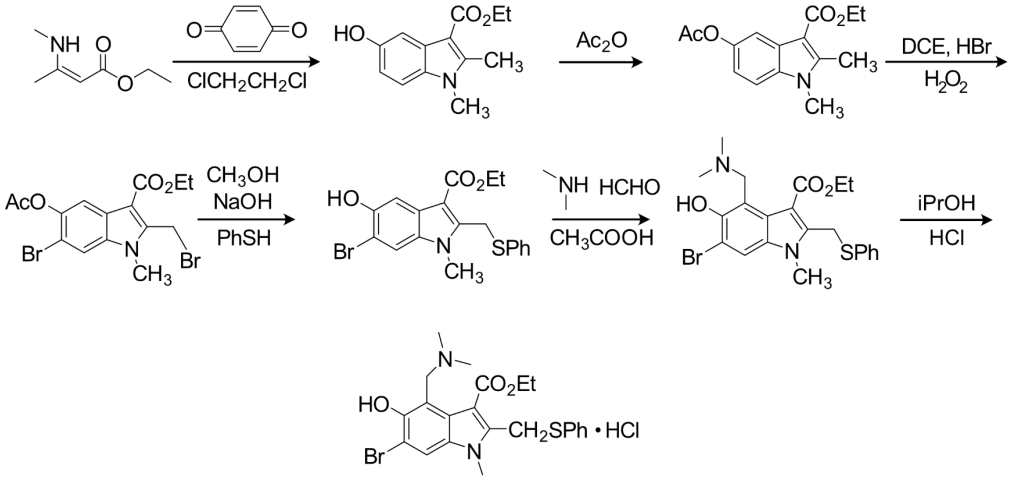
[1]H NMR:



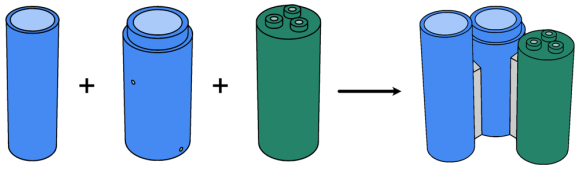
[13]C{[1]H} NMR:



6.5 Umifenovir



Synthesis cartridge



The monolithic cartridge is composed of two filter reactors (blue) and a reactor (green) that is used to collect, and extract waste from the system.

Synthesis description

Ethyl 5-acetoxy-1,2-dimethyl-1H-indole-3-carboxylate (Umifenovir-A)

$ZnCl_2$ (160 mg) was pre-loaded to *module-1*. A solution of p-benzoquinone (7 mL, 3.32 g in 13 mL of 1,2-dichloroethane) was added to *module-1*. The monolith was cooled down to 6 ºC for 30 mins and then, the enamine (4.9 mL) was added to *module-1* within 10 mins. The monolith was heated to 75 ºC and kept at this temperature for 2 h and stirred at 200 rpm. Then, the monolith was cooled down to 30 ºC and heating was stopped. The solution was stirred at 200 rpm for 1 h. Finally, the solution was filtered and dry under vacuum for 1 h to obtain a grey-yellow solid.

Ethyl 5-hydroxy-1,2-dimethyl-1H-indole-3-carboxylate (Umifenovir-B)

1,2-dichloroethane (15 mL), acetic anhydride (3 mL) and triethylamine (4.5 mL) were added to *module-2*. The reaction mixture was stirred at room temperature for 2 h. Then, DCE was evaporated at 60 ºC for 2 h under vacuum pulses (4 s vacuum, 6 s waiting). Methanol (8 mL) was added to *module-1*, and it was evaporated first at 60 ºC for 1 h under vacuum pulses (4 s vacuum, 6 s waiting), and then at 60 ºC under vacuum for 2 h. After evaporation, methanol (4 mL) was added to *module-1*, and the solution was cooled down to 25 ºC, heating was turned off and the solution was stirred for 1 h. The reaction mixture was filtered and washed twice with methanol (2 mL) and one time with 50% methanol (4 mL). Finally, the grey solid was dried under vacuum for 3 h.

Ethyl 5-acetoxy-6-bromo-2-(bromomethyl)-1-methyl-1*H*-indole-3-carboxylate (Umifenovir -C)

1,2-dichloroethane (10 mL) was added to *module-2*, and the solution was stirred at 200 rpm for 30 mins to dissolve Umifenovir-B. Then, 48% HBr (2.8 mL) was added to *module-1*, and the monolith was heated to 70 ºC. 10% H_2O_2 (9 mL) was added within 30 mins, and the reaction was stirred at 70 ºC for 2 h. DCE was evaporated at 60 ºC using vacuum pulses (3 s vacuum, 6 s waiting). Then, the monolith was cooled down to 30 ºC, and it was stirred at this temperature for 1h. The solution was filtered, and methanol (15 mL) was added to the residual solid in *module-1*, and the reaction mixture was stirred for 30 mins. This process was repeated twice. Finally, the white-red solid was dried under vacuum for 1 h.

Ethyl 5-acetoxy-6-bromo-1-methyl-2-((phenylthio)methyl)-1H-indole-3-carboxylate (Umifenovir-D)

A mixture solution of PhSNa/NaOH in methanol was prepared by mixing NaOH (1.49 g), thiophenol (1.6 mL) and methanol (40 mL). PhSNa/ NaOH solution (22 mL) was added to *module-1* containing Umifenovir-C. The reaction mixture was stirred at room temperature for 2 h. Then, acetic acid (3 mL) was added to *module-1* slowly, and the reaction was stirred for 1 h. Finally, the solution was filtered, the yellow solid was washed with water (3 mL), and it was dried under vacuum at for 1 h.

Ethyl 6-bromo-4-((dimethylamino)methyl)-5-hydroxy-1-methyl-2-((phenylthio)methyl)-1H-indole-3-carboxylate (Umifenovir-E)

A solution containing 40% dimethylamine (2.4 mL), acetic acid (10 mL) and 37% formaldehyde (1.4 mL) was pre-prepared. 7 mL of this solutions were added to *module-1* containing Umifenovir-D. The reaction mixture was heated to 65 ºC and stirred at this temperature for 3 h. Water (5 mL) was added to *module-1*. 15% NaOH (35 mL) was added to *module-2*, and the monolith was cooled down to 6 ºC for 30 mins. Once cooled, the solution in *module-2* was transferred to *module-2* and it was stirred for 30 mins. Finally, the solution was filtered, washed with water (15 mL), and dried under vacuum at for 2 h to obtain a pale yellow solid.

Umifenovir

Isopropanol (5 mL) was added to *module-2* containing Umifenovir-E, and the monolith was heated to 70 ºC. Once at this temperature, conc. HCl (1 mL) was added to *module-2* within 5 mins. The reaction mixture was stirred at this temperature for 30 mins, before it was cooled down to 30º C, turning off the heating. Then, the solution was stirred for 30 mins and then filtered and washed with isopropanol (3 mL). Finally, the yellow-white (**0.75 g, 5.6 % overall yield**) solid was dried under vacuum for 3 h.

^{1}H NMR (600 MHz, DMSO) δ 9.42 (s, 1H), 9.13 (s, 1H), 8.03 (s, 1H), 7.43 – 7.22 (m, 5H), 4.91 (s, 2H), 4.74 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 2.73 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, DMSO): 165.1, 148.9, 144.2, 135.6, 132.7, 131.3, 129.2, 127.6, 124.5, 117.9, 111.5, 109.2, 104.9, 60.5, 53.5, 42.7, 31.0, 29.4, 13.9.

HPLC-UV/Vis retention time: 12.8 min, purity (> 95%)

ESI(M+H)$^{+}$: expected: 477.0848, observed: 477.1102

XDL file

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      far_waste="waste_3"
      n_cleans="2"/>
    <CleanBackbone
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      near_waste='waste_3'
      far_waste="waste_3"
      n_cleans="3"/>
    <HeatChill
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      temp="6 °C"
      time="0.5 hrs"
      stir="true"
      stir_speed="150 RPM"
    />
    <Add
      reagent="DCE"
      vessel="filter_1"
      volume="1 mL"
      priming_volume="1.0 mL"
      stir="True"
      stir_speed="150 RPM"
    />
    <Add
      reagent="enamine"
      vessel="filter_1"
      volume="4.9 mL"
      prime="False"
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      stir="True"
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    />
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      n_cleans="2"/>
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  stir_speed="150 RPM"
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/>
<Filter
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  stir="true"
  removes="None"
/>
<WashSolid
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  solvent="methanol"
  volume="5 mL"
  washes="3"
/>
<Dry
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  time="1 hrs"
/>
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/>
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/>
<Stir
  vessel="filter_1"
  time="0.5 hrs"
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/>
<Add
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  vessel="filter_2"
  volume="3 mL"
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/>
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  volume="4.5 mL"
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  stir="True"
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/>
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```

```
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  far_waste="waste_2"/>
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  stir_speed="200 RPM"
/>
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  time="2 hrs"
  mode="pulse"
/>
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  vessel="filter_2"
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  priming_volume="1.0 mL"
  stir="True"
/>
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  solvent="methanol"
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  mode="pulse"
/>
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  mode="manual"
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  stir="true"
  continue_heatchill="False"
/>
<Stir
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  time="1 hrs"
  stir_speed="200 RPM"
/>
<Filter
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  removes="None"
/>
```

```
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  volume="5 mL"
  washes="3"
/>
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  vessel="filter_1"
  solvent="methanol"
  volume="4 mL"
  washes="2"
/>
<WashSolid
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  solvent="50% methanol"
  volume="5 mL"
  washes="1"
/>
<Dry
  vessel="filter_1"
  time="3 hrs"
/>
<Confirm
  msg="STEP-3 COMPLETED, Grey white solid?"
/>
<Add
  reagent="DCE"
  vessel="filter_1"
  volume="10 mL"
  priming_volume="1.0 mL"
  stir="True"
/>
<Stir
  vessel="filter_1"
  time="0.5 hrs"
/>
<Add
  reagent="48% HBr"
  vessel="filter_2"
  volume="2.8 mL"
  priming_volume="1.0 mL"
  stir="True"
/>
<CleanBackbone
  solvent="water"
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  far_waste="waste_2"/>
<HeatChillToTemp
  vessel="filter_2"
  temp="70°C"
  stir="true"
/>
<Add
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  vessel="filter_1"
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  time="30 mins"
  priming_volume="1.0 mL"
```

```
  stir="True"
/>
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  far_waste="waste_2"/>
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<HeatChill
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  temp="70°C"
  stir="true"
  stir_speed="600 RPM"
  time="2 hrs"
/>
<Evaporate
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  solvent="DCE"
  temp="60°C"
  time="2 hrs"
  mode="pulse"
  pulse_time="3 seconds"
/>
<HeatChillToTemp
  vessel="filter_2"
  temp="30°C"
  stir="true"
  continue_heatchill="False"
/>
<Stir
  vessel="filter_1"
  time="1 hrs"
/>
<Filter
  filter_vessel="filter_1"
  stir="true"
/>
<WashSolid
  vessel="filter_2"
  solvent="DCE"
  volume="3 mL"
  washes="2"
/>
<Add
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  vessel="filter_2"
  volume="15 mL"
  priming_volume="1.0 mL"
  stir="True"
/>
<Stir
  vessel="filter_1"
  time="0.5 hrs"
/>
<Filter
  filter_vessel="filter_1"
```

```
  stir="true"
/>
<Add
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  vessel="filter_2"
  volume="15 mL"
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  stir="True"
/>
<Stir
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  time="0.5 hrs"
/>
<Filter
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  stir="true"
/>
<Dry
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  time="1 hrs"
/>
<Confirm
  msg="STEP-4 COMPLETED, Pale red solid?"
/>
<Add
  reagent="NaOH/PhSNa/MeOH"
  vessel="filter_1"
  volume="22 mL"
  priming_volume="1.0 mL"
  stir="True"
/>
<CleanBackbone
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  far_waste="waste_2"/>
<Stir
  vessel="filter_2"
  time="2 hrs"
/>
<Add
  reagent="acetic acid"
  vessel="filter_1"
  volume="3 mL"
  time="10 mins"
  priming_volume="1.0 mL"
  stir="True"
/>
<CleanBackbone
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  far_waste="waste_2"/>
<Stir
  vessel="filter_2"
  time="2 hrs"
/>
<Filter
  filter_vessel="filter_1"
  stir="true"
```

```
/>
<WashSolid
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  solvent="water"
  volume="3 mL"
  washes="2"
/>
<Dry
  vessel="filter_1"
  time="1 hrs"
/>
<Confirm
  msg="STEP-5 COMPLETED, yellow solid?"
/>
<Add
  reagent="Formaldehyde solution"
  vessel="filter_1"
  volume="7 mL"
  priming_volume="1.0 mL"
  stir="True"
/>
<HeatChill
  vessel="filter_1"
  temp="65°C"
  time="3 hrs"
  stir="true"
/>
<HeatChillToTemp
  vessel="filter_1"
  temp="30°C"
  stir="true"
  continue_heatchill="False"
/>
<Add
  reagent="water"
  vessel="filter_1"
  volume="5 mL"
  priming_volume="1.0 mL"
  stir="True"
/>
<Add
  reagent="15% NaOH"
  vessel="filter_2"
  volume="35 mL"
  priming_volume="1.0 mL"
  stir="True"
/>
<CleanBackbone
  solvent="water"
  near_waste="waste"
  far_waste="waste"/>
<CleanBackbone
  solvent="isopropanol"
  near_waste="waste"
  far_waste="waste"/>
<HeatChill
  vessel="filter_1"
  temp="6°C"
```

```
  time="0.5 hrs"
  stir="true"
/>
<Transfer
  from_vessel="filter_1"
  to_vessel="filter_2"
  stir="True"
/>
<Stir
  vessel="filter_2"
  time="1 hrs"
  stir_speed="500 RPM"
/>
<Filter
  filter_vessel="filter_2"
  stir="true"
/>
<WashSolid
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  solvent="water"
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/>
<Dry
  vessel="filter_2"
  time="2 hrs"
/>
<Confirm
  msg="STEP-6 COMPLETED, pale yellow solid?"
/>
<Add
  reagent="isopropanol"
  vessel="filter_2"
  volume="5 mL"
  stir="true"
/>
<HeatChillToTemp
  vessel="filter_2"
  temp="70°C"
  stir="true"
/>
<Add
  reagent="HCl"
  vessel="filter_2"
  time="5 mins"
  volume="1 mL"
  stir="true"
/>
<CleanBackbone
  solvent="water"
  near_waste="waste"
  far_waste="waste"/>
<HeatChill
  vessel="filter_2"
  temp="70°C"
  time="1 hrs"
  stir="true"
/>
<HeatChillToTemp
```

```
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      temp="30°C"
      stir="true"
      continue_heatchill="False"
    />
    <Stir
      vessel="filter_2"
      time="1 hrs"
    />
    <Filter
      filter_vessel="filter_2"
      stir="true"
    />
    <WashSolid
      vessel="filter_2"
      solvent="isopropanol"
      volume="3 mL"
    />
    <Dry
      vessel="filter_2"
      time="3 hrs"
    />
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</Synthesis>
```

Hardware graph

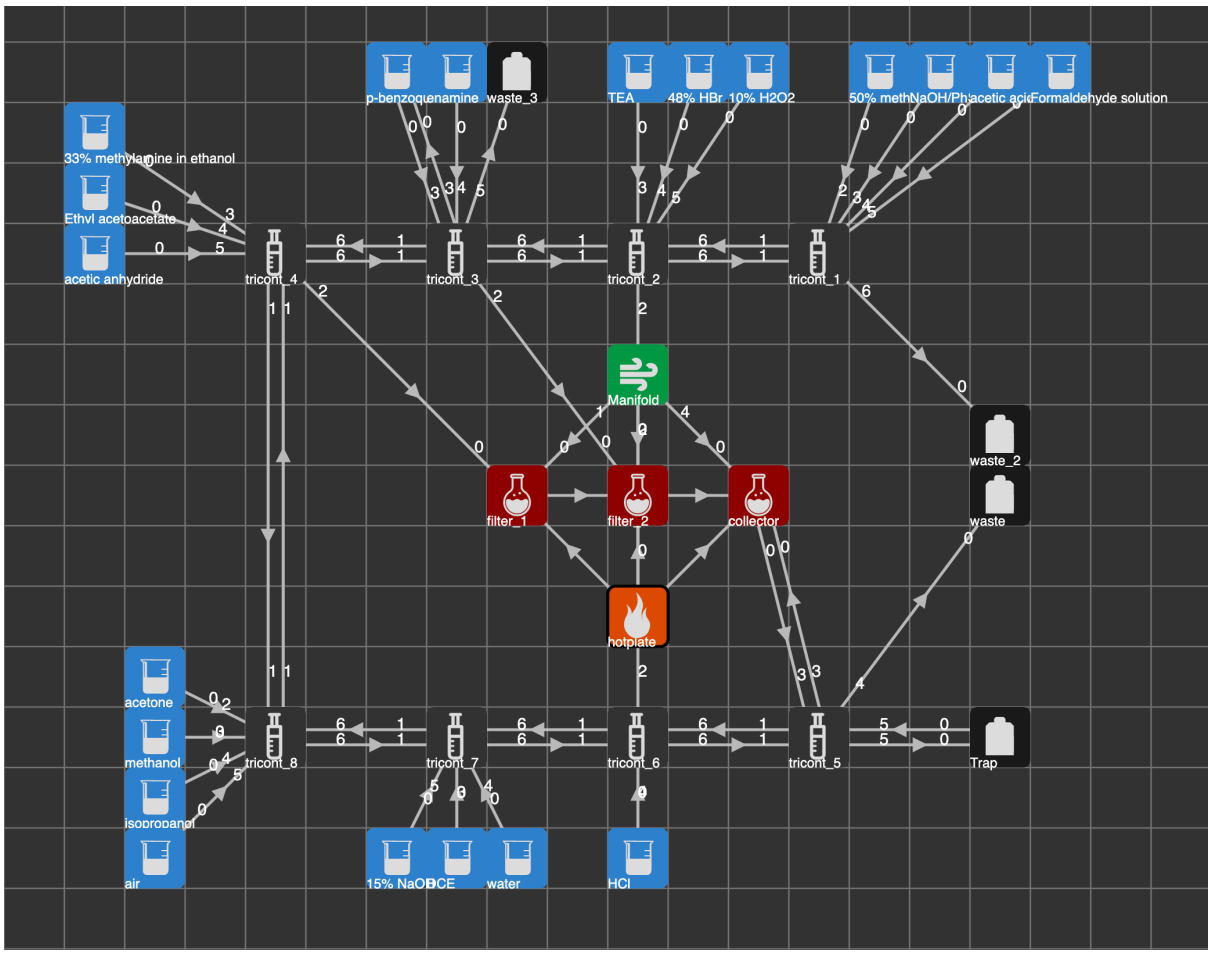


Figure S31. Graph describing all the physical elements and connections between them for the synthesis of Umifenovir

Pressure profile fingerprint

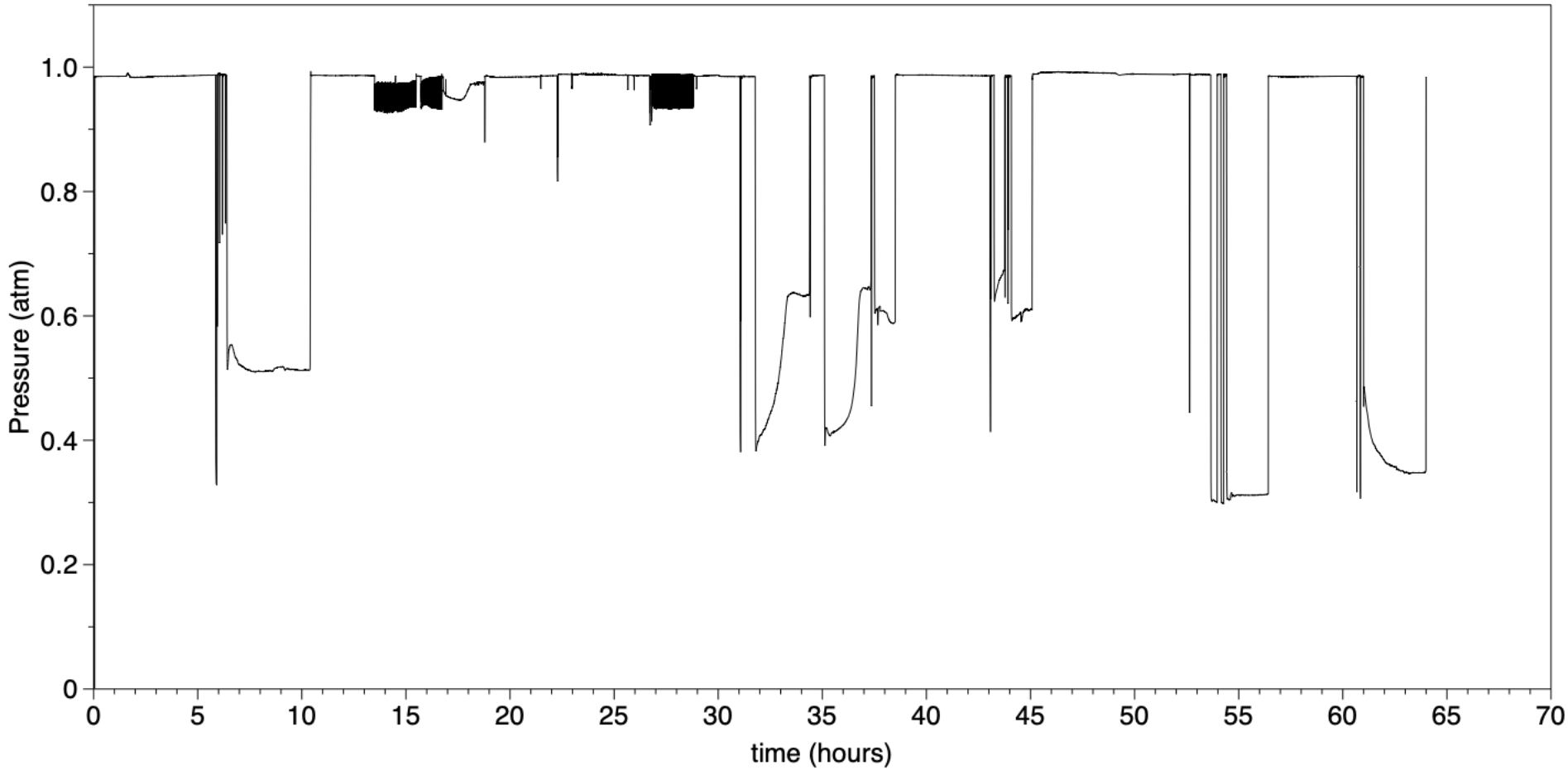
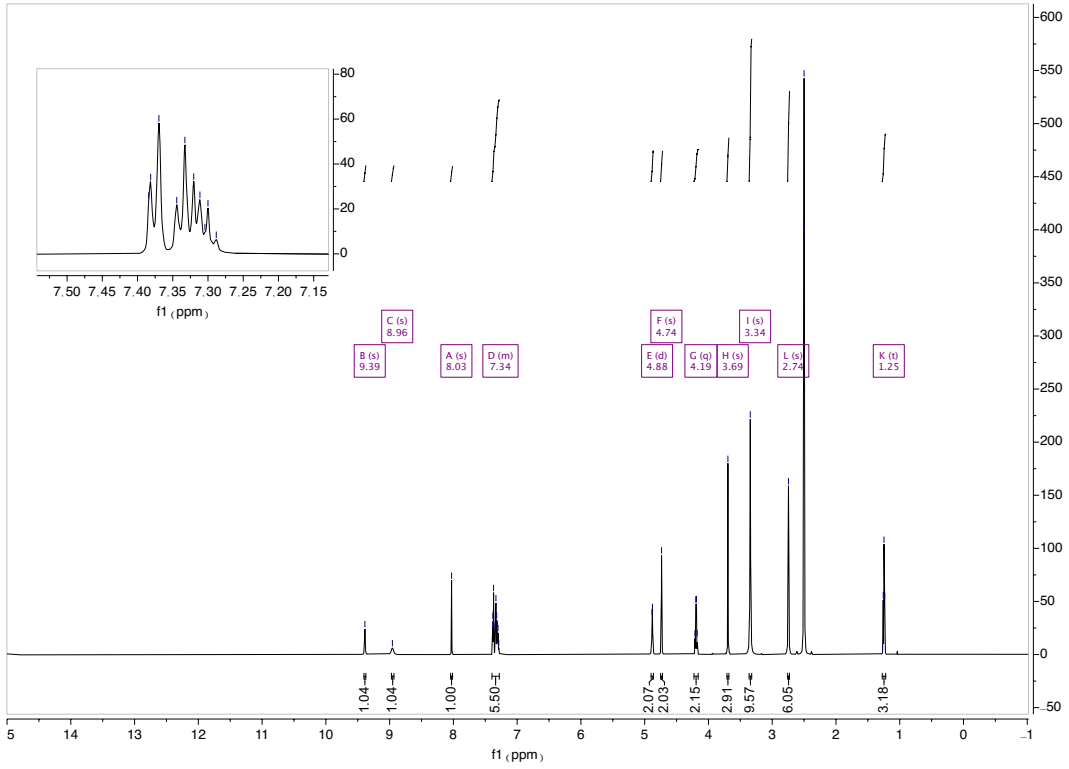
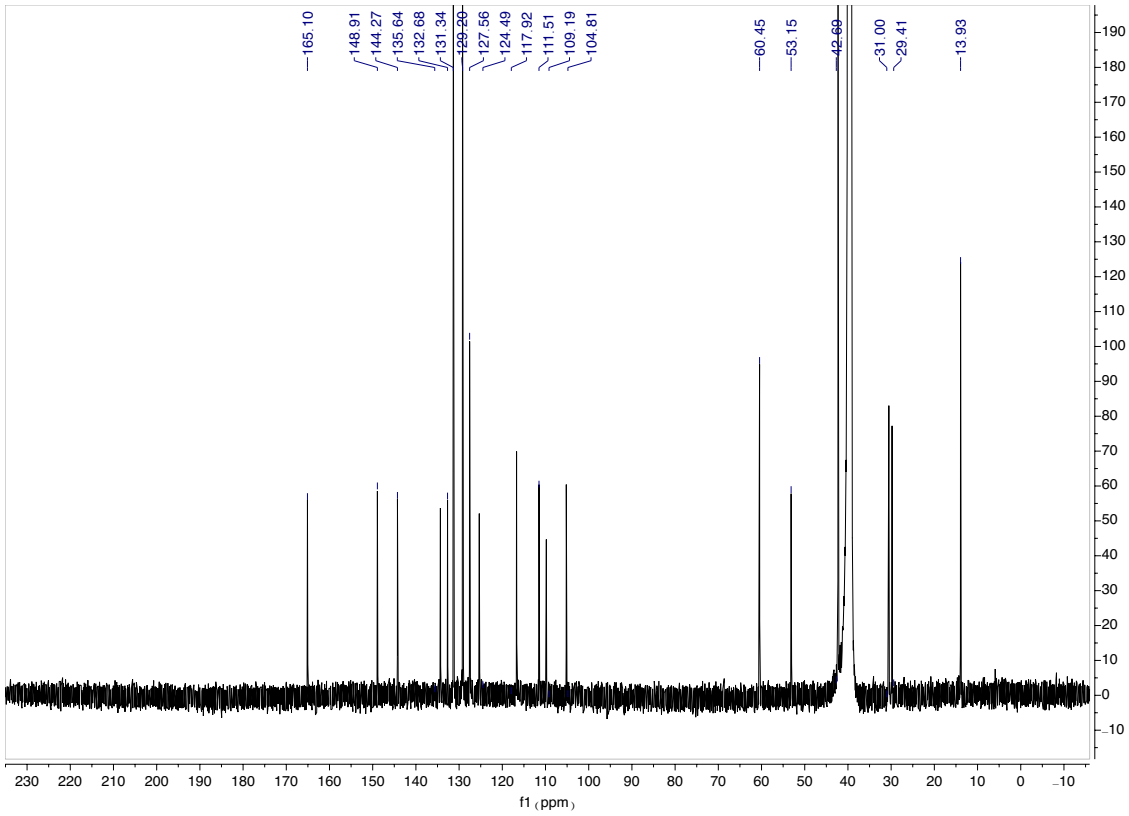


Figure S32. Pressure profile for the synthesis of Umifenovir

[1]H NMR:

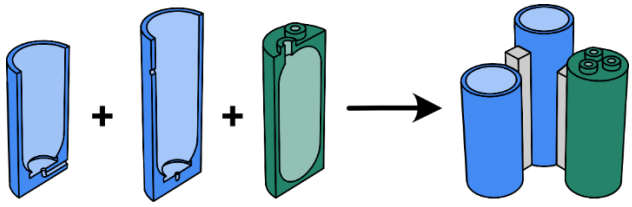


[13]C{[1]H} NMR:



7 Automated Oligopeptides synthesis

Synthesis cartridge



All oligopeptides were performed using the same reactionware system. The monolith is composed of a *filter rector* (blue), followed by another *filter reactor* (blue), and a *reactor* (green).

Synthesis description

All the different oligopeptides were synthesised using the same synthetic procedure. The following stock solutions were prepared manually before the synthesis.

- Fmoc-O-tert-butyl-L-serine (1.55 g, 4.0 mmol) in DMF (6.85 mL).
- Fmoc-L-glycine (1.24 g, 4.0 mmol) in DMF (7.15 mL).
- Fmoc-L-valine (1.38 g, 50.0 mmol) in DMF (7.00 mL).
- O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HBTU) (4.57 g, 12.05 mmol) in DMF (24.0 mL).
- Piperidine in DMF (100 mL, 20 % v/v, commercially available as a solution).
- N,N-Diisopropylethylamine (DIPEA) (4.13 mL, 32 mmol) in Nmethyl-2-pyrrolidone (7.89 mL).

The synthesis procedure was divided into the different reaction steps:

Swelling

Module-1 was manually charged with Fmoc-Ala-Wang resin (0.82 g, 0.50 mmol, 0.61 mmol/g). DMF (9 mL) was added to *module-1* and stirred for 1 h at room temperature to swell the Fmoc-Ala-Wang resin.

Deprotection

Then, a two stage deprotection was performed. Piperidine (9 mL, 20 % v/v in DMF) was added to *module-1* and the solution was stirred at room temperature for 3 min. The resin was filtered and the filtrate was transferred to the waste. Then, fresh piperidine (9 mL, 20 % v/v in DMF) was added to module-1 and the solution was stirred at room temperature for 12 min. The solution was drained and removed from the system into the waste.

Resin wash

DMF (9 mL) was added to *module-1*, and the reaction was stirred for 45 s before the solvent was drained and removed from the system. This washing cycle was repeated five times.

Coupling

To *module-1*, the appropriate amino acid solution (4 mL), HBTU (4 mL), and DIPEA (2 mL) were added sequentially. The reaction was stirred at room temperature for 1 h. Then the reagents were drained, and the resin was washed (DMF, 5 times, as *Resin wash*).

Repeating cycle

Then, *deprotection, resin wash, coupling and resin wash* were repeated for each amino acid. Then a final *deprotection* step is performed to remove the Fmoc group from the last amino acid coupled. The resin was washed with DCM (9 mL), following the same conditions as in the *resin wash* steps.

Cleavage

To cleave the peptide from the solid support, a cleavage mix was prepared by adding TFA (19 mL) to a mixing flask followed by the addition of TIPS (0.6 mL) and water (0.6 mL), while stirring. The cleavage solution was mixed using the syringe pump, by pumping and delivering the solution to the same flask 4 times. Cleavage solution (10 mL) was then added to *module-1*, and the reaction has been stirred at room temperature for 3 h. Diethyl ether (25 mL) was added to *module-2*, and then the solution (containing the cleaved peptide) was transferred from module-1 to *module-2*). The reactionware was then cooled to 0 ºC for 3 hrs to precipitate the product. The solution was filtered and washed 3 times with diethyl ether (5 mL). The filtrate solution was collected as a precaution if the precipitation method was not successful. The white solid was dissolved in acetonitrile (2 mL) and water (8 mL).

Hardware Graph

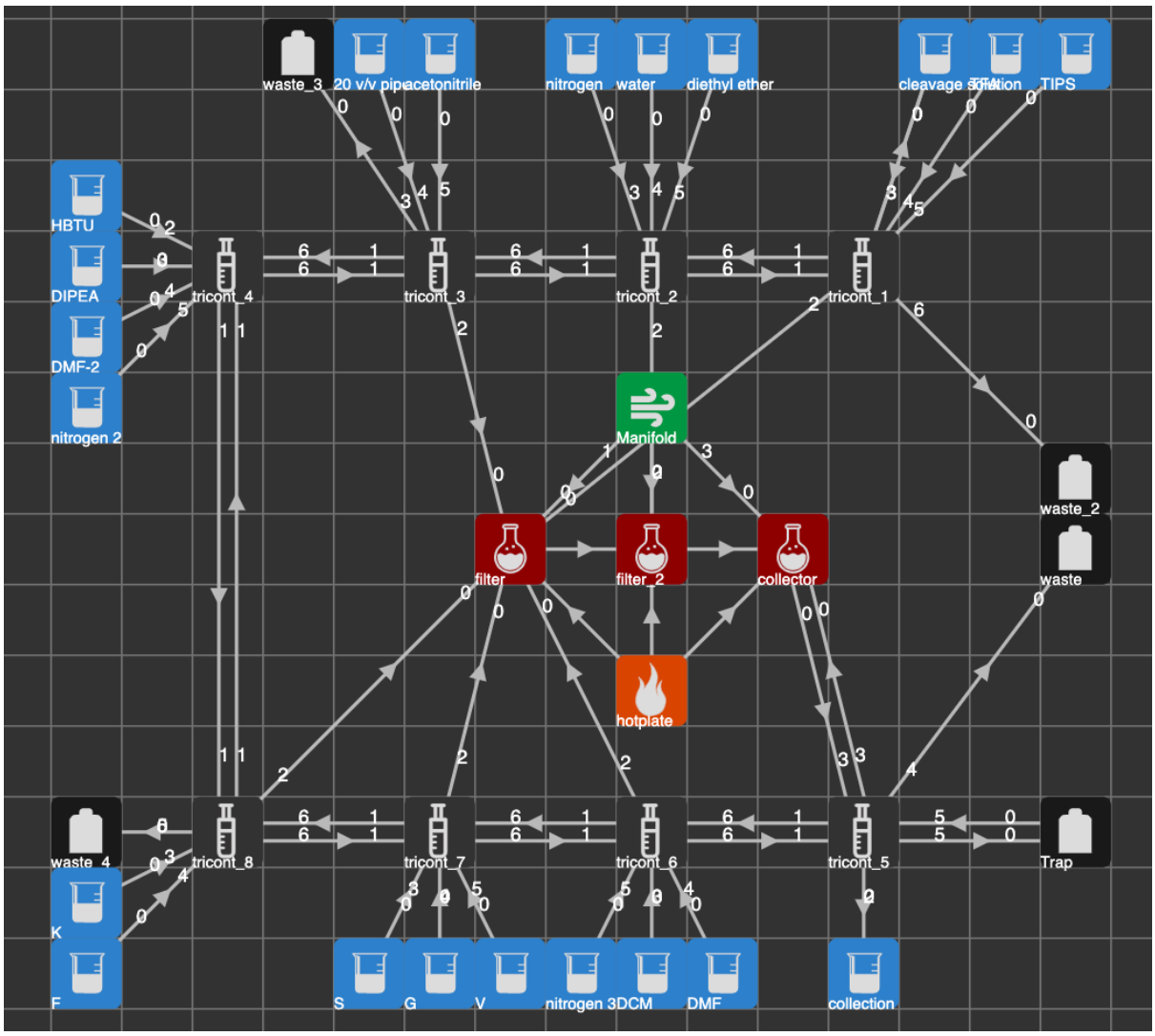
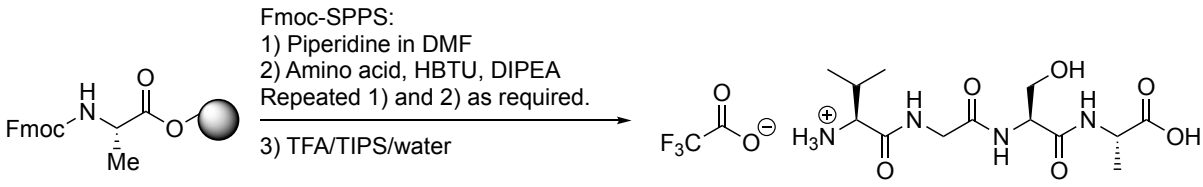


Figure S33. Graph describing all the physical elements and connections between them for the synthesis of oligopeptides

7.1 VGSA



1

XDL file

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      sequence="VGSA"
      resin_loading="0.61"
    />
  </Procedure>
</Synthesis>
```

Results

Yield = 42 %

Purity = > 99%

HPLC-UV/Vis retention time: 0.8 min, purity: > 99 % (at 214 nm).

ESI(M+H)$^+$: expected: 333.1769 Da, observed: 333.1751 Da

Pressure profile fingerprint

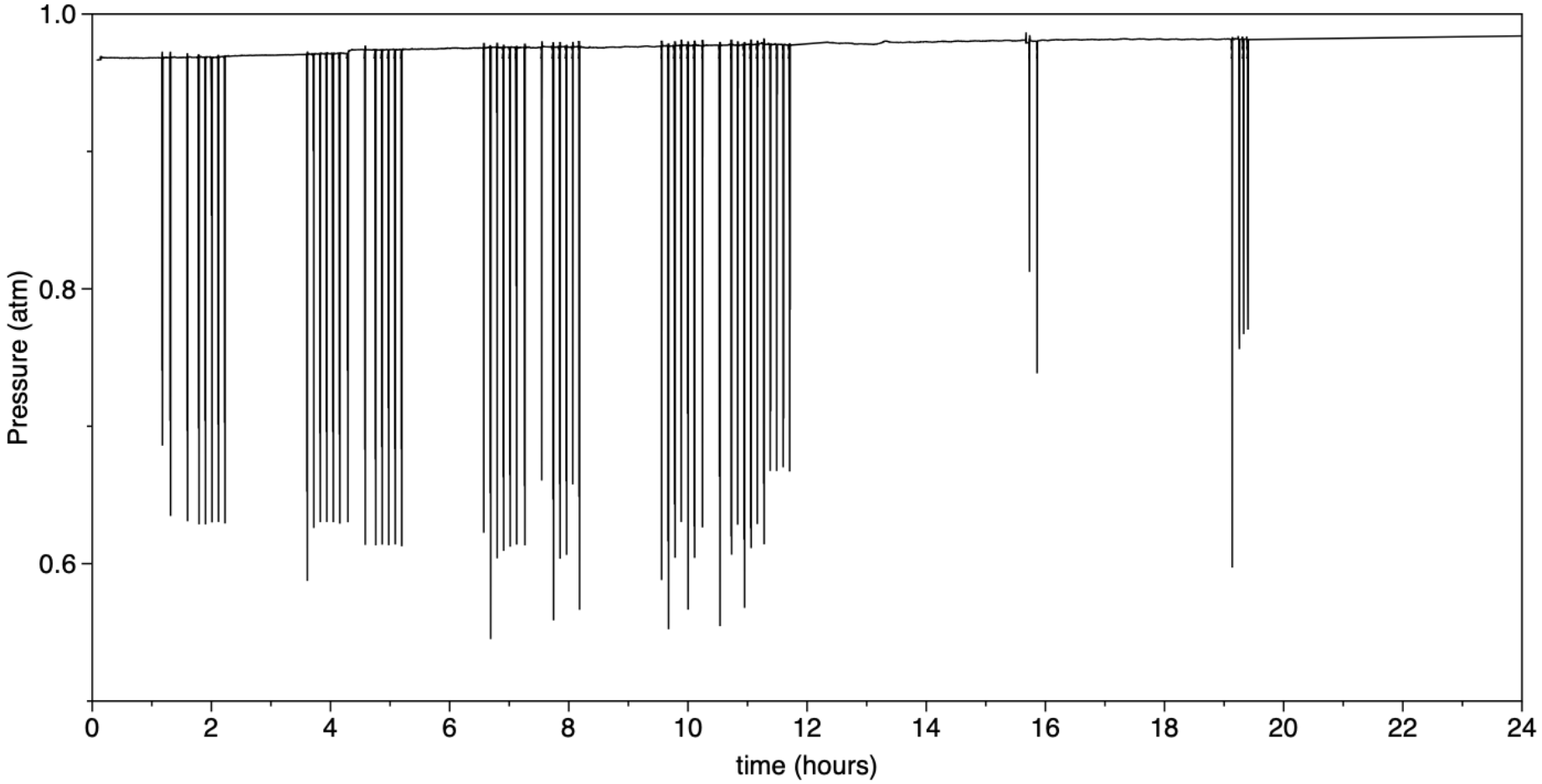
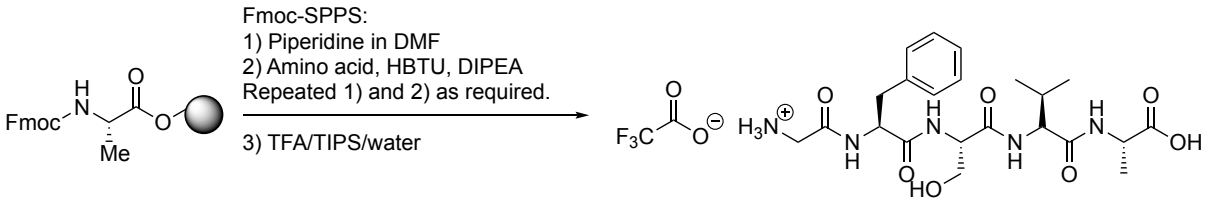


Figure S34. Pressure profile for the synthesis of VGSA

7.2 GFSVA



XDL file

```
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      resin_loading="0.40"
    />
  </Procedure>
</Synthesis>
```

Results

Yield = 89 %

Purity = > 99%

HPLC-UV/Vis retention time: 1.8 min, purity: > 99 % (at 214 nm).

ESI(M+H)$^+$: expected: 480.2453 Da, observed: 480.2875 Da

Pressure profile fingerprint

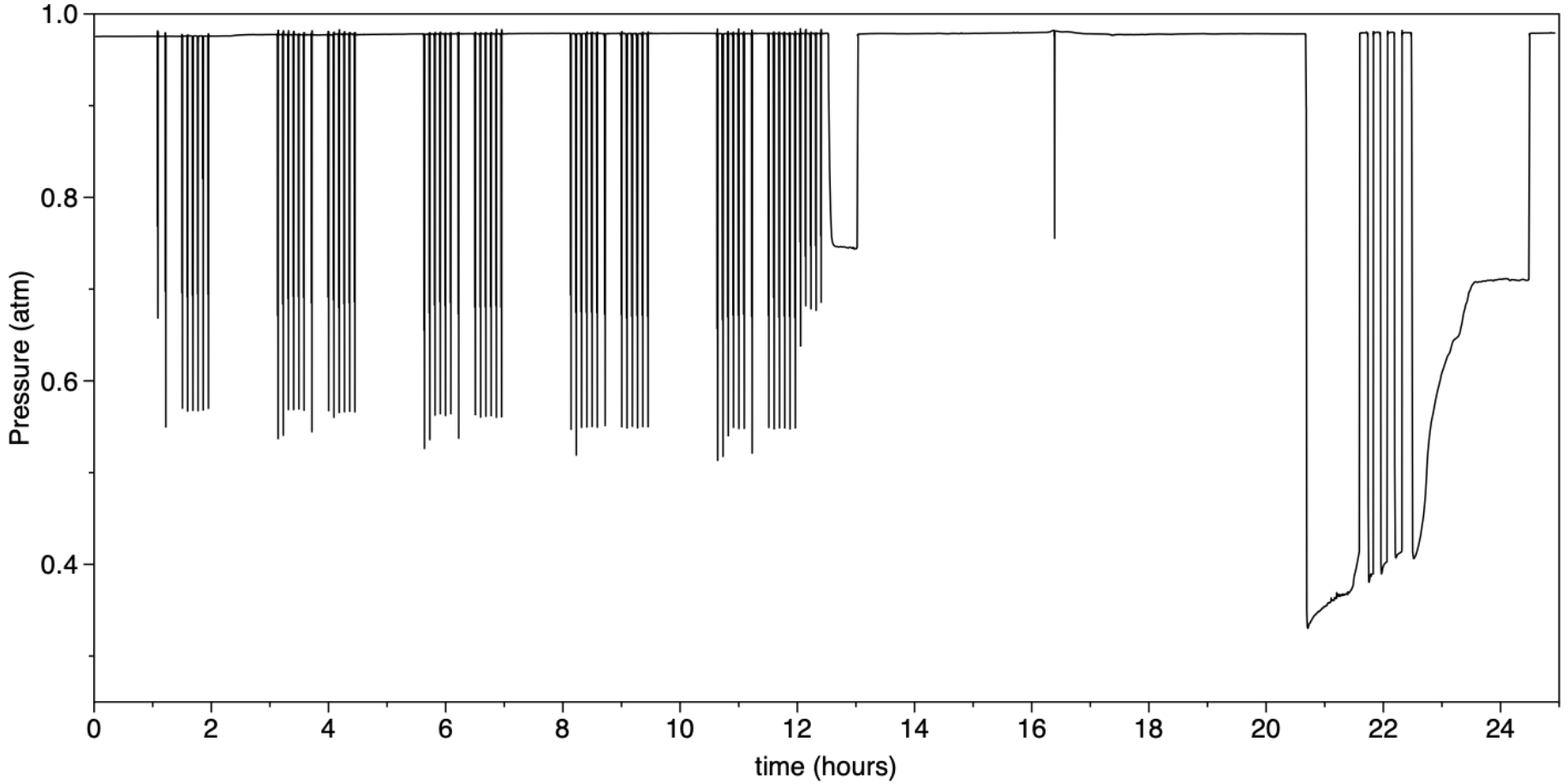
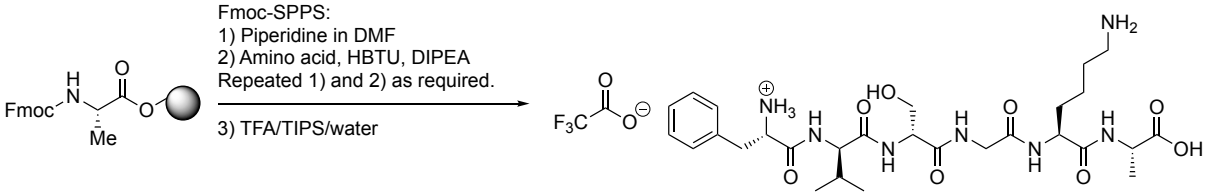


Figure S35. Pressure profile for the synthesis of GFSVA

7.3 FVSGKA



XDL file

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      resin_loading="0.40"
    />
  </Procedure>
</Synthesis>
```

Results

Yield = 31 %

Purity = > 99%

HPLC-UV/Vis retention time: 10.6 min, purity: > 99 % (at 214 nm).

ESI(M+H)$^+$: expected: 608.3403 Da, observed: 608.3903 Da

Pressure profile fingerprint

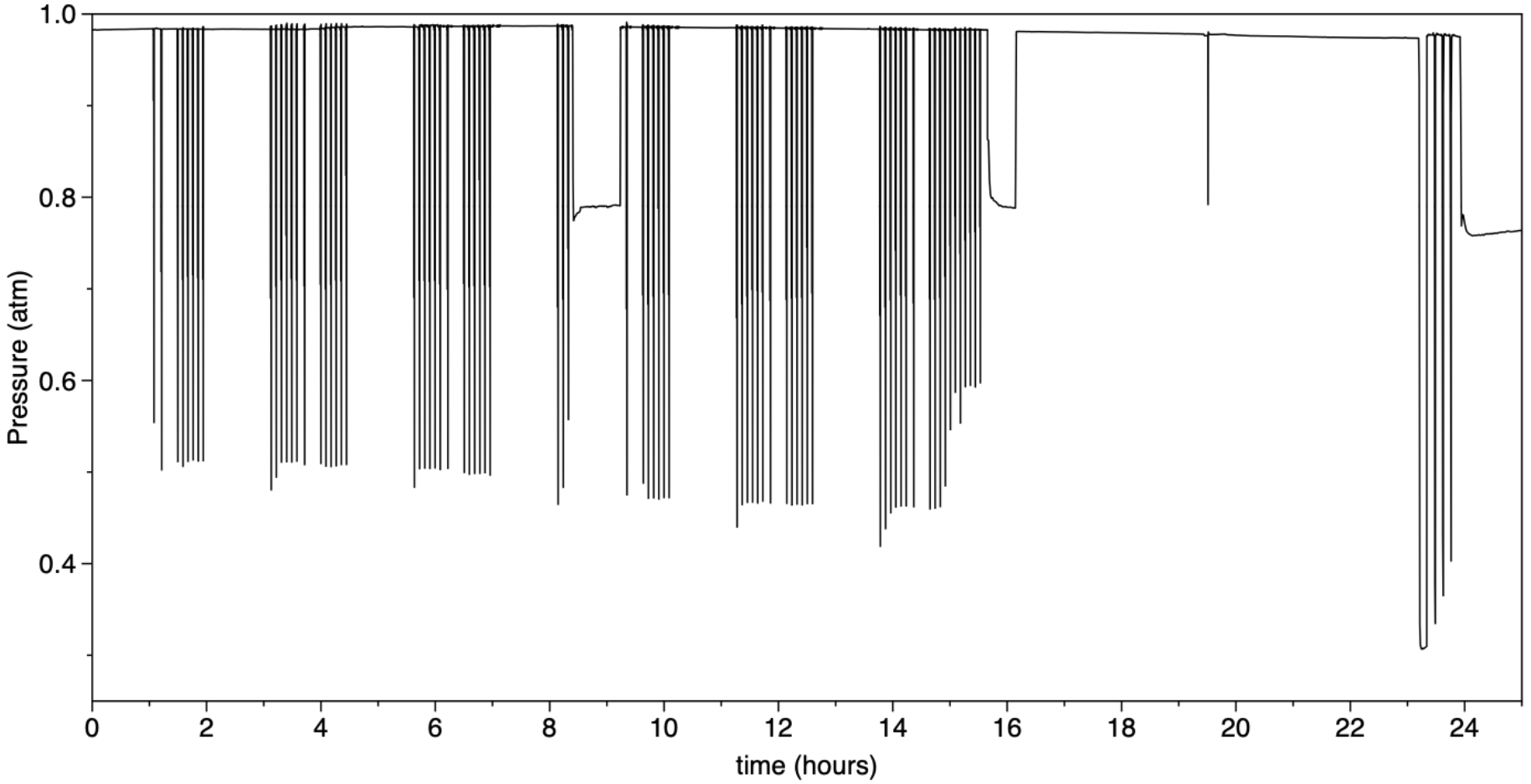
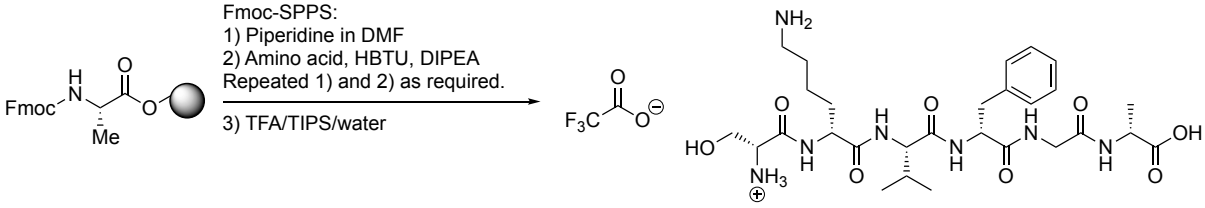


Figure S36. Pressure profile for the synthesis of FVSGKA. The flat line at ca. 8.2 h was due to a solvent bottle that finished, so no solvent was added during the washing. Since no solvent was transferred to *module-2*, no transferred was detected and the system halted until it was manually resumed.

7.4 SKVFGA



XDL file

```
<Synthesis>
  <Procedure>
    <SPPS
      mmol="0.5"
      sequence=" SKVFGA"
      resin_loading="0.40"
    />
  </Procedure>
</Synthesis>
```

Results

Yield = 42 %

Purity = > 99%

HPLC-UV/Vis retention time: 1.8 min, purity: > 99 % (at 254 nm).

ESI(M+H)$^+$: expected: 608.3402 Da, observed: 608.3819 Da

Pressure profile fingerprint

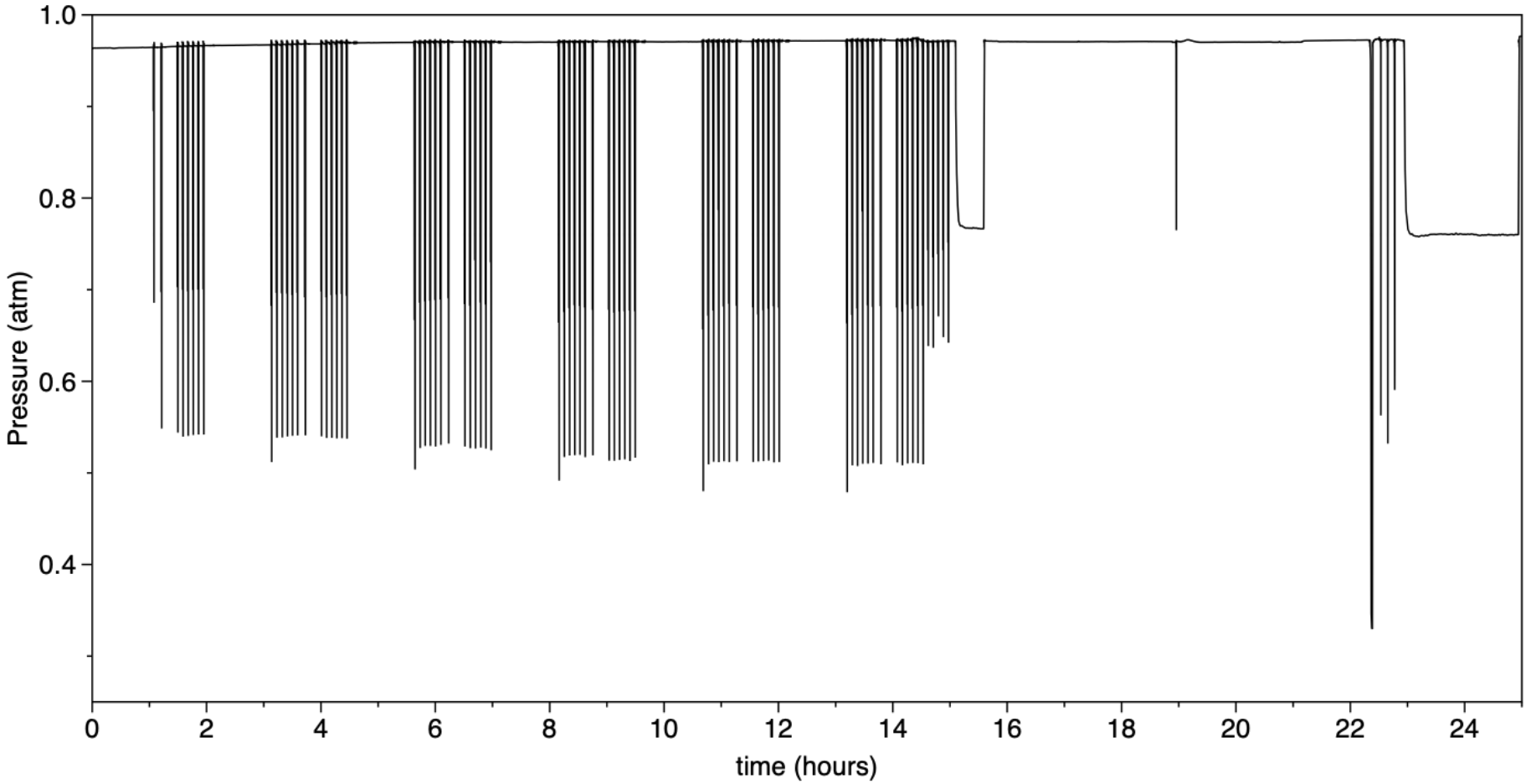
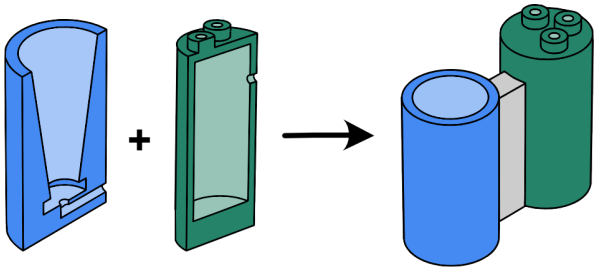


Figure S37. Pressure profile for the synthesis of SKVFGA

8 Automated Oligonucleotides Synthesis

Synthesis cartridge



All oligonucleotides were performed using the same reactionware system. The monolith is composed of a *filter rector* (blue, *module-1*), and a *reactor* (green, *module-2*). All the synthetic operations were carried out in *module-1*, while *module-2* was used for solvent/waste extraction.

Synthesis description

All the phosphoramidites, 0.5 M 5-Ethylthio-1H-tetrazole in anhydrous acetonitrile (ETT), THF/pyridine/acetic anhydride (CapA), 10% Methylimidazole in THF (CapB), and 0.1 M Iodine solution were purchased from Linktech and used without any further purification. Anhydrous acetonitrile (ACN, extra dry) was purchased from Fisher and used without any further purification. Ammoniuim hydroxide was purchased from Fisher and used without any further purification.

All the different oligopeptides were synthesised using the same synthetic procedure. The following stock solutions were prepared manually before the synthesis.

- iBu-dG-CE Phosphoramidite (1.0 g, 1.2 mmol) in anhydrous acetonitrile (11.90 mL)
- Bz-dA-CE Phosphoramidite (1.0 g, 1.2 mmol) in anhydrous acetonitrile (11.6 mL)
- Bz-dC-CE Phosphoramidite (1.0 g, 1.2 mmol) in anhydrous acetonitrile (12.0 mL)
- dT-CE Phosphoramidite (1.0 g, 1.34 mmol) in anhydrous acetonitrile (13.4 mL)

Module-1 was manually charged with CPG (Controlled Pore Glass resin, 10 µmol). The cartridge was purged with Argon (three cycles), and the resin was washed with dry acetonitrile (2.5 mL) twice. The synthesis procedure was divided into the different reaction steps:

Deprotection

A three stage deprotection was performed. 3% Trichloroacetic acid in dichloromethane (2 mL) was added to *module-1* and the solution was bubbled with argon (by applying vacuum pulses of 0.1 seconds every 10 seconds to *module*-1) at room temperature for 5 mins. Solution was drained and removed from the system.

Resin wash

Anhydrous acetonitrile (2.5 mL) was added to *module-1*, and the reaction was bubbled with argon (by applying vacuum pulses of 0.1 seconds every 10 seconds to *module*-1) at room temperature for 5 mins. The solution was drained and removed from the system. This washing cycle was repeated twice.

The deprotection and resin wash cycle was repeated three times. At the end of the last washing cycle the solid was dried under vacuum for 1 min.

Coupling

To *module-1*, ETT (1.5 mL) was added to wet the resin with activator. The solution was drained and removed from the system. ETT (1 mL) and the appropriate nucleobase solution (1 mL) were added to the same syringe, and let it mix for 2 mins. After that, the solution was added to *module-1*, and was bubbled with argon for 8 mins. The solution was drained, and it was removed from the system, and the resin was washed (anhydrous ACN, 3 times, as *Resin wash*).

Oxidation

To *module-1*, 0.1 M Iodine solution (2.0 mL) was added, and the solution was bubbled with argon for 5 mins. The solution was drained, and it was removed from the system, and the resin was washed (anhydrous ACN, 3 times, as *Resin wash*)

Capping

CapA (1.5 mL) and CapB (1.5 mL) were mixed in the syringe for 30 seconds before the addition to *module-1*. The solution was bubbled for 5 mins. The solution was drained and removed from the system, and the resin was washed (anhydrous ACN, 3 times, as *Resin wash*)

Repeat!

Then, *deprotection, resin wash, coupling, resin wash, oxidation, resin wash, capping and resin wash* were repeated for each nucleotide. Then a final *deprotection* step is performed. The resin was washed two more times with ACN (2.5 mL).

Cleavage and deprotection

To cleave the oligonucleotide from the solid support ammonium hydroxide solution (5 mL) was added to *module-1*, and the reaction was stirred at 55 C for 12 h. The solution containing the targeted oligonucleotide was filtered and the resin was washed with ammonium hydroxide (2.5 mL). The solution was transferred from *module*-2 to a collection vial for further purifications.

OPC purification

Acetonitrile (5 mL) of was carefully passed through an Oligonucleotide Purification Cartridge* (OPC), followed by 5 mL of 2M triethylammonium acetate (TEAA) buffer. The eluate was discarded. Aqueous solution of the crude oligonucleotide (1.5 mL) was then passed through the cartridge at a rate of approximately 1 drop per second. The eluate was collected and passed through the cartridge another three times. Following the final collection, the eluate was discarded. 15 mL of 0.1M TEAA buffer was then carefully passed through the cartridge and the eluate discarded. 1.2 mL of a mixture of water and acetonitrile at 1:1 ratio (by volume), was then passed dropwise through the cartridge, to elute the purified oligonucleotide.

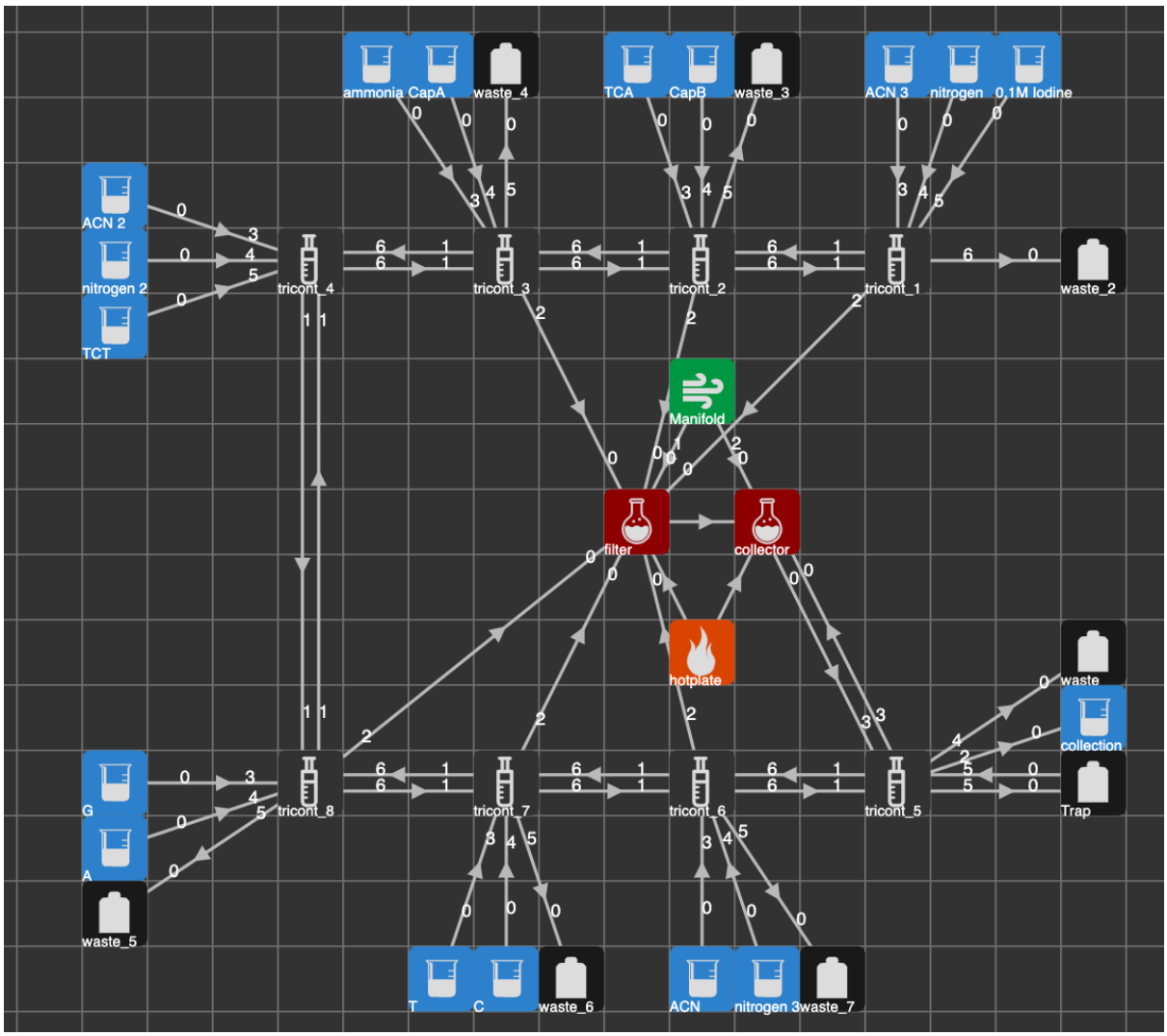


Figure S38. Graph describing all the physical elements and connections between them for the synthesis of oligopeptides

8.1 5’-TACGAT

XDL file

```
<Synthesis>
  <Procedure>
    <OSPS
      mmol="0.01"
      sequence="TACGAT"
      resin_loading="0.35"
    />
  </Procedure>
</Synthesis>
```

Results

OD yield: 4.5

ESI:

Species	Expected	Observed
$(M+H)^{+}$	1789.3426	1789.1365
$(M+H)^{2+}$	894.6713	894.0672
$(M+H)^{3+}$	596.4475	595.7106

Pressure profile fingerprint

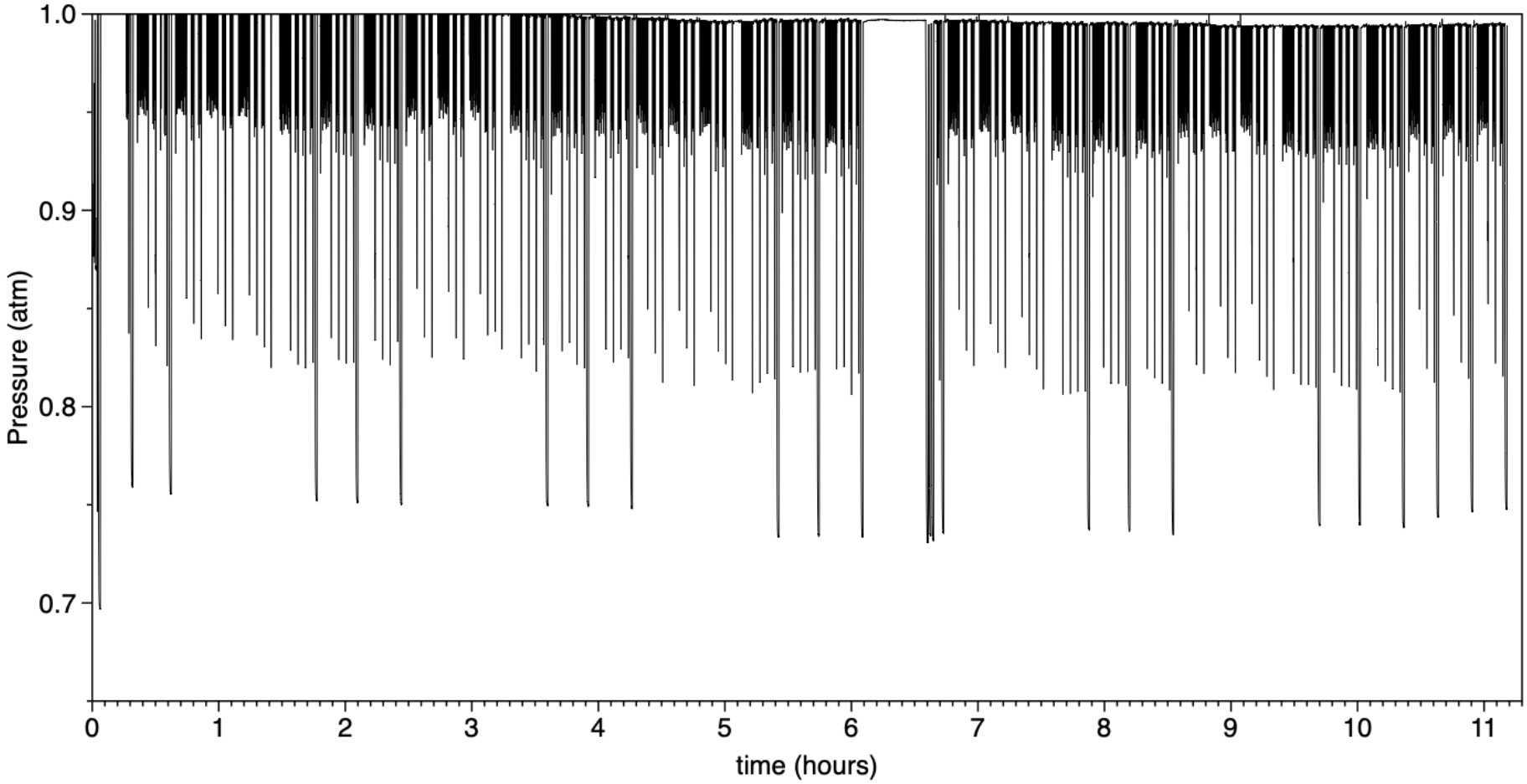


Figure S39. Pressure profile for the synthesis of 5'-TACGAT. The flat line around 6.3 h was due to a programmed pause to sample the solid support. After it, the system restarted with a purge.

8.2 5’-CTACGT

XDL file

```
<Synthesis>
  <Procedure>
    <OSPS
      mmol="0.01"
      sequence="CTACGT"
      resin_loading="0.35"
    />
  </Procedure>
</Synthesis>
```

Results

OD yield: 3.3

ESI:

Species	Expected	Observed
$(M+H)^{+}$	1765.3314	1765.1159
$(M+H)^{2+}$	882.6657	882.0574
$(M+H)^{3+}$	588.4438	587.7046

Pressure profile fingerprint

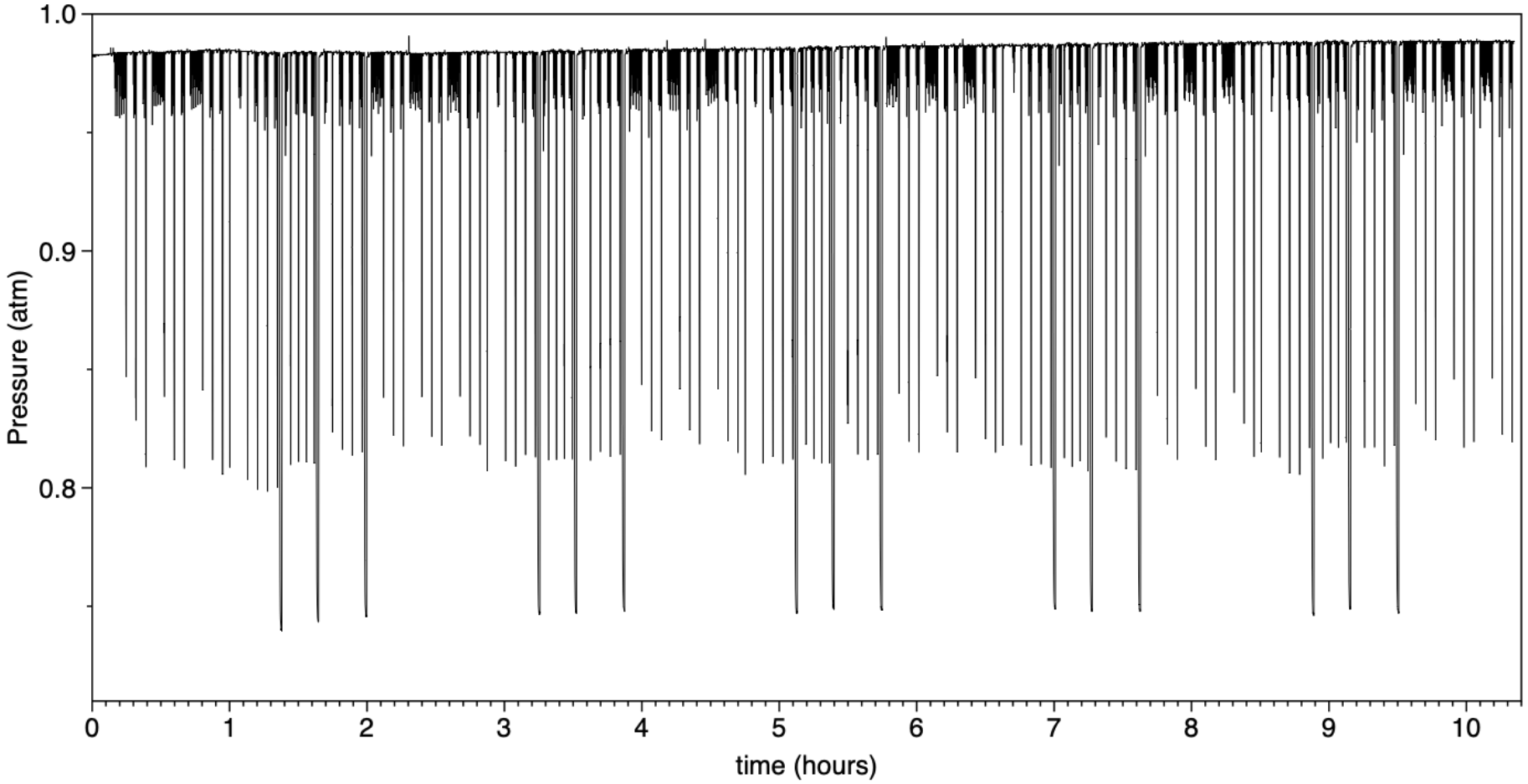


Figure S40. Pressure profile for the synthesis of 5'- CTACGT

8.3 5’-GCTACGT

XDL file

```
<Synthesis>
  <Procedure>
    <OSPS
      mmol="0.01"
      sequence="GCTACGT"
      resin_loading="0.35"
    />
  </Procedure>
</Synthesis
```

Results

OD yield: 2.13

ESI:

Species	Expected	Observed
$(M+H)^{+}$	2094.3839	-
$(M+H)^{2+}$	1047.1919	1046.6069
$(M+H)^{3+}$	698.1280	697.4006
$(M+H)^{4+}$	523.5960	

Pressure profile fingerprint

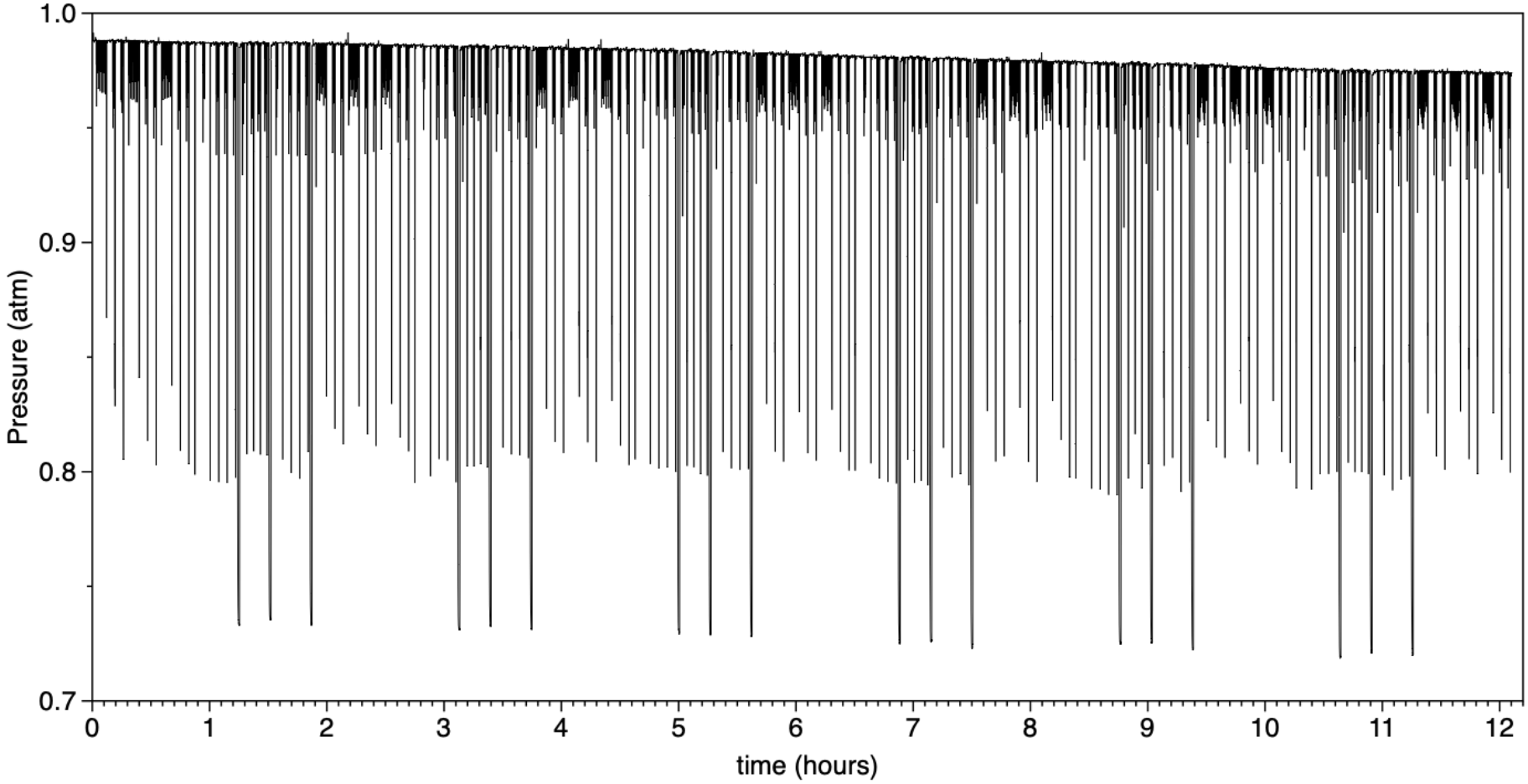


Figure S41. Pressure profile for the synthesis of 5'- GCTACGT

8.4 5’-ATGCTACGGCTACGAT

XDL file

```
<Synthesis>
  <Procedure>
    <OSPS
      mmol="0.01"
      sequence="ATGCTACGGCTACGAT"
      resin_loading="0.47"
    />
  </Procedure>
</Synthesis
```

Results

OD yield: 5.37

ESI:

Species	Expected	Observed
$(M+H)^{+}$	4877.8466	-
$(M+H)^{2+}$	2438.9233	-
$(M+H)^{3+}$	1625.9489	1625.7477
$(M+H)^{4+}$	1219.4617	1219.0606
$(M+H)^{5+}$	975.56932	975.0482
$(M+H)^{6+}$	812.9744	812.3735
$(M+H)^{7+}$	696.8352	696.1772
$(M+H)^{8+}$	609.7308	609.0304
$(M+H)^{9+}$	541.9830	541.2490

Pressure profile fingerprint

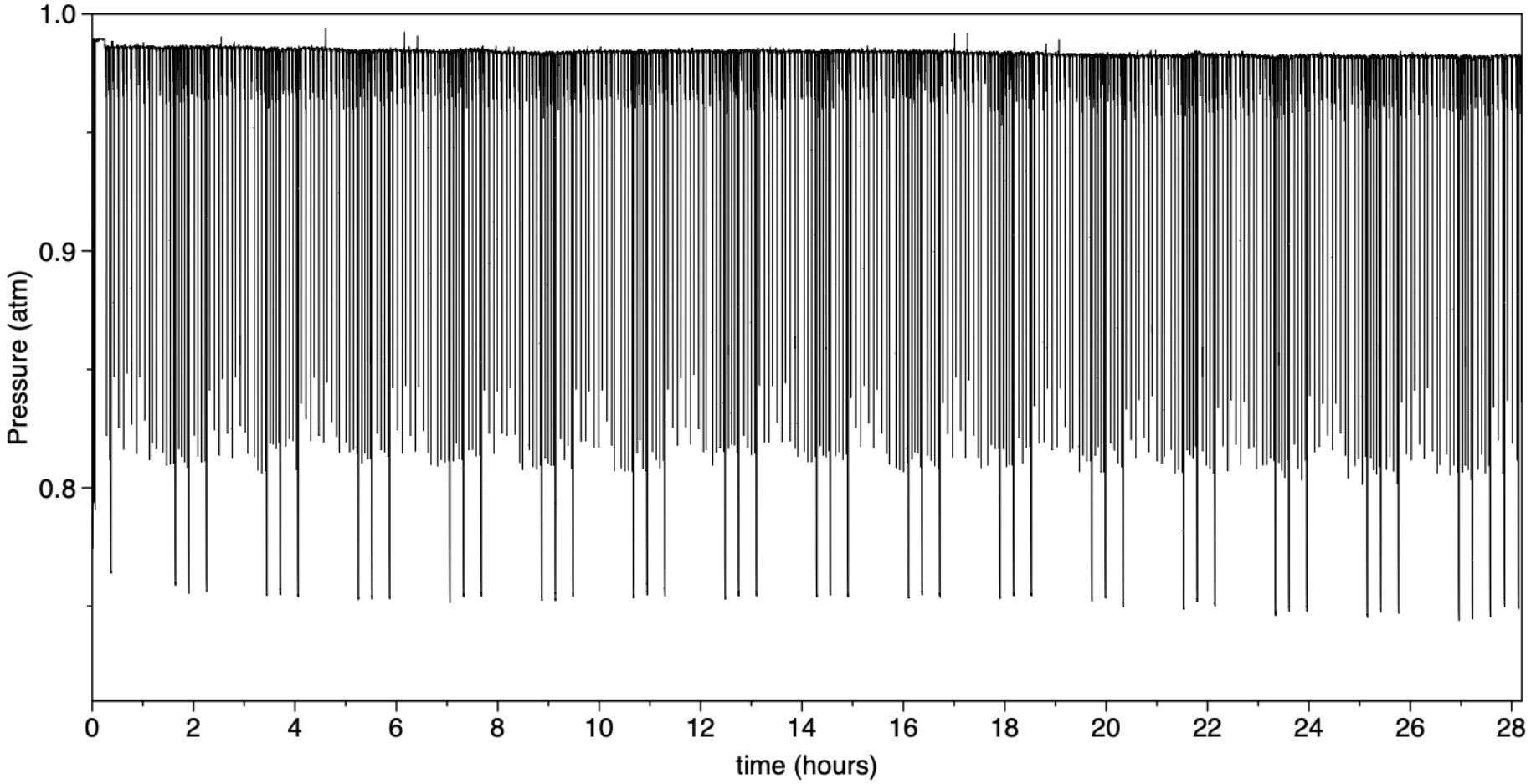


Figure S42. Pressure profile for the synthesis of 5'- ATGCTACGGCTACGAT

9 Manual vs Automated syntheses

Table S15. Yield comparison between manual and automated synthesis

Compound	Manual synthesis (yield)	Automated synthesis (yield)
Phenelzine sulfate	1.2 g (51%)	1.2 g (51%)
Isoniazid	2.0 g (73%)	2.0 g (73%)
Dihydralazine sulfate	2.1 g (72%)	2.1 g (72%)
Lomustine	1.6 g (69%)	1.6 g (69%)
Umifenovir	1.3 g (10%)	0.75 g (5.6%)

10 Validation

Phenelzine sulfate synthesis was chosen as a test procedure to corroborate if the generated pressure profiles can be used to validate and to understand if/when a process fails. To do this we repeated the Phenelzine sulfate synthesis 17 times (using the same cartridge) and used three of the successful reactions to create an average profile of a successful reaction (**Figure S43**). We compared the remaining reactions to the standard created by using the Wasserstein Distance.

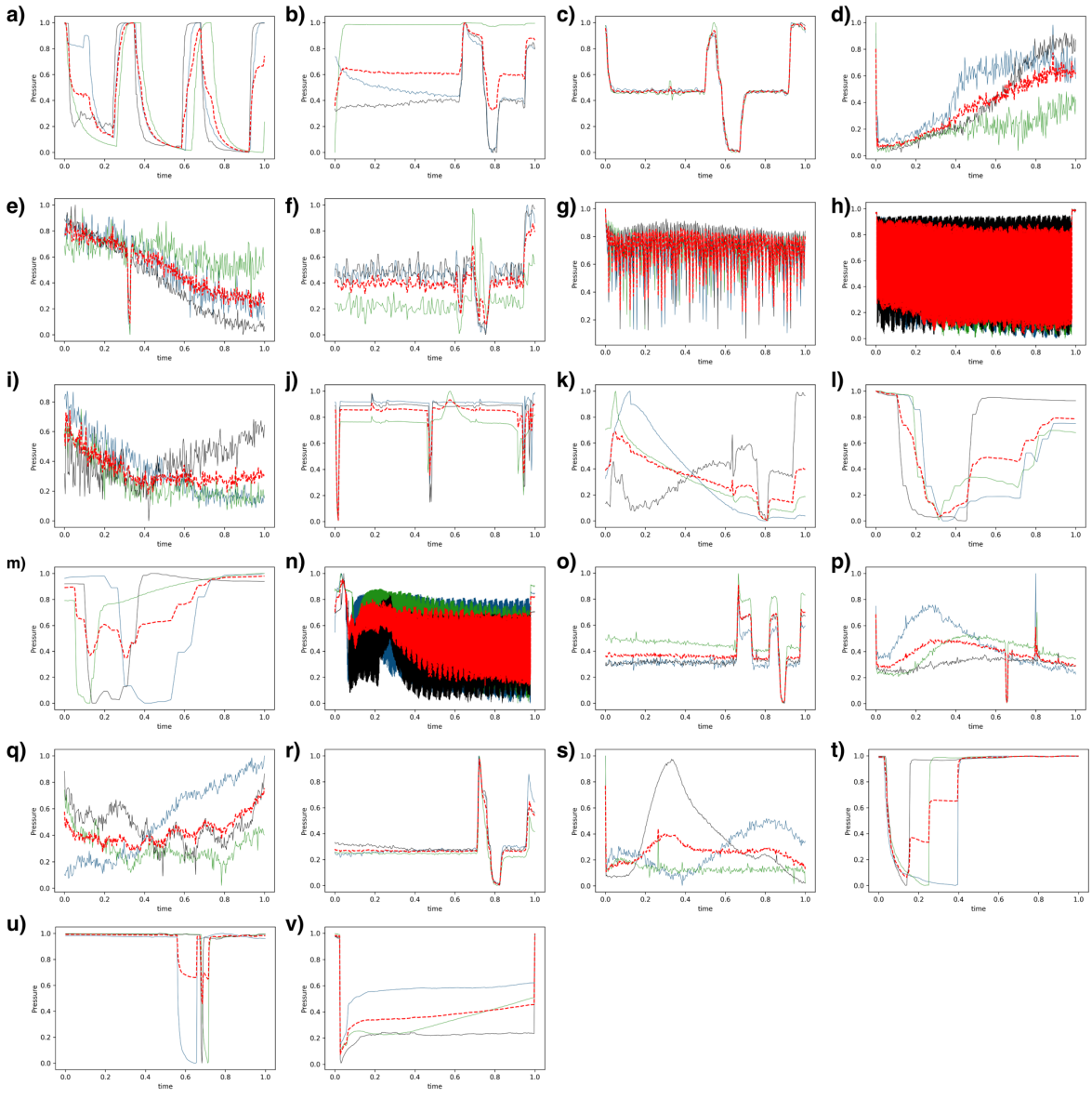


Figure S43. χDL steps pressure profile for the synthesis of Phenelzine sulfate. Blue, black and green traces represent three different successful synthesis, while the red trace represents the average. The χDL steps are: a) Purge, b) Add, c) Add, d) HeatChillToTemp, e) Add, f) Add, g) HeatChill, h) Evaporate, i) HeatChillToTemp, j) Separate, k) Add, l) Transfer, m) Transfer, n) Evaporate, o) Add, p) Add, q) Wait, r) Add, s) Stir, t) Filter, u) WashSolid, v) Dry

Running the synthesis gives a *log* file with all the χDL step durations with the respective time stamp. By using the χDL file (that contains all the synthesis steps) in combination with the step duration file results in step pressure profiles with the exact time stamps in which the XDL step started and ended.

Once having the specific step pressure profile, these profiles are normalized in both axes to account for any shift in between synthesis. The normalized pressure plots can now be compared to the standard profiles (treated the same way), and a quantitative measure can be obtained (Wasserstein Distance).

The reactions were executed using the same 3D printed reactionware cartridges to test their recyclability. After every reaction, the cartridge was washed with methanol, ethanol, water and acetone. The average yield across 17 different reactions was not affected by the reusability of the monolith, resulting in an average yield of 71 ± 4 % (**Figure S44**). During the recyclability and validation process, it was identified that the step that was prone for failure was the acid addition to precipitate Phenelzine sulfate. This step caused not only syringe clogging if the proper washes are not included, but also, a slower addition improved original yield of 52% to 71%.

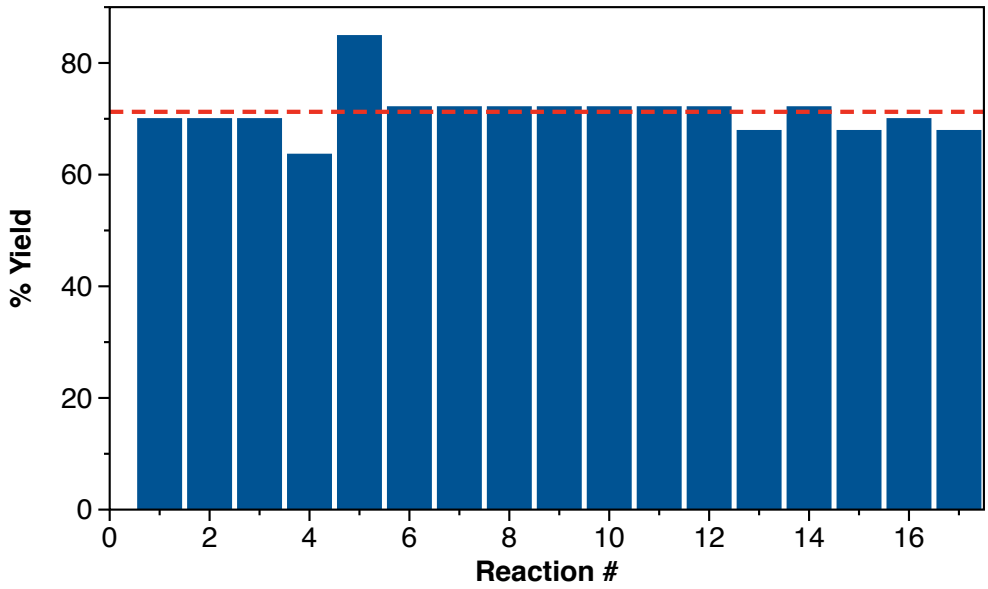


Figure S44. Phenelzine sulfate % yield across the validation reactions. The average yield is 71% ± 4 across 17 different reactions. This demonstrates the reusability and recyclability if the final designs.

11 References

1 *XDL documentation*, <http://xdl-standard.com/> (2021).

2 Mehr, S. H. M., Craven, M., Leonov, A. I., Keenan, G. & Cronin, L. A universal system for digitization and automatic execution of the chemical synthesis literature. *Science* **370**, 101-108, (2020).

3 Hou, W. *et al.* Automatic Generation of 3D-Printed Reactionware for Chemical Synthesis Digitization using ChemSCAD. *ACS Cent Sci* **7**, 212-218, (2021).

4 Grizou, J., Points, L. J., Sharma, A. & Cronin, L. A curious formulation robot enables the discovery of a novel protocell behavior. *Sci Adv* **6**, eaay4237, (2020).

5 Angelone, D. *et al.* Convergence of multiple synthetic paradigms in a universally programmable chemical synthesis machine. *Nat Chem* **13**, 63-69, (2021).