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An autonomous portable platform for universal chemical synthesis

J. Sebastián Manzano, Wenduan Hou, Sergey S. Zalesskiy, Przemyslaw Frei, Hsin Wang, Philip J. Kitson and Leroy Cronin ✉

Robotic systems for synthetic chemistry are becoming more common, but they are expensive, fixed to a narrow set of reactions, and must be used within a complex laboratory environment. A portable system that could synthesize known molecules anywhere, on demand, and in a fully automated way, could revolutionize access to important molecules. Here we present a portable suitcase-sized chemical synthesis platform containing all the modules required for synthesis and purification. The system uses a chemical programming language coupled to a digital reactor generator to produce reactors and executable protocols based on text-based literature syntheses. Simultaneously, the platform generates a reaction pressure fingerprint, used to monitor processes within the reactors and remotely perform a protocol quality control. We demonstrate the system by synthesizing five small organic molecules, four oligopeptides and four oligonucleotides, in good yields and purities, with a total of 24,936 base steps executed over 329 h of platform runtime.

The synthesis of complex organic molecules requires a very high degree of manual labour from highly trained experts working in well-controlled laboratory environments[1–3]. Integrating automation into chemical laboratories can increase chemical accessibility, and replaces procedural ambiguities (for example, add dropwise, fast stirring, room temperature) with defined parameters, increasing the reliability of complex syntheses[4]. Current automated technologies typically focus on strictly circumscribed subsets of synthetic chemistry for discrete target molecule classes, resulting in different platforms for small-molecule synthesis[4–8] or solid-phase synthesis (SPS; for example oligopeptides[9], oligonucleotides[10] and oligosaccharides[11,12]). Although SPS systems can be applied to many small-molecule transformations, such systems require extensive method development[13,14] and remain based on only a small subset of practical chemistries. This means that most of the synthetic approaches already employed by chemists are neglected, and new synthetic routes must be designed and tested for even well-known compounds with established syntheses. Examples of small-molecule synthesis platforms that can perform a greater range of chemical processes are usually modular in nature and can require extensive reconfiguration to switch from one manufacturing process to another[15–20]. Coupled to this, these synthetic platforms are often infrastructure-intensive and are commonly laboratory-based. Compact universal platforms can be challenging to develop due to the laboratory infrastructure needed for different syntheses. A platform that could be compact and prepare any molecule on-demand, autonomously and on-site could increase the accessibility of important molecules across different fields.

Continuous multistep synthesis processes can be complex and technically challenging (using different equipment for each step), requiring reconfigurable systems to complete even relatively short protocols. One way to remove platform reconfiguration and miniaturize laboratory hardware is the use of bespoke, self-contained, modular reactors for multistep synthetic procedures such as three-dimensional (3D) printed reactors[21–23]. Even though the full synthetic route is enclosed within the reactors, manual execution is still needed, and the system must ideally be situated in a highly controlled and well-serviced laboratory.

In this Article we present the design, construction, and validation of a compact, universal, automated platform to execute multistep synthesis employing reusable 'module monolith' reactionware cartridges that are automatically generated from literature procedures using an intelligent software system based on the open-source universal chemical programming language standard, χDL (Fig. 1). This open standard has been designed to allow any chemical transformation to be precisely expressed and reliably run on any compatible robotic platform. The reaction procedures are automatically translated into the physical modules by using the unit synthetic operations described in the chemical code file (χDL). The physical modules are then automatically assembled into a single monolithic unit that contains all the infrastructure needed for the synthesis of the targeted molecule. The resulting monolith is fabricated and connected to the platform where all the synthetic operations take place. To ensure portability and autonomous operation, the platform was designed around a programmable manifold to control the vacuum/gas flow through the monolith, a liquid-handling system, and pressure sensors to control the unit operations needed to perform the synthetic sequences. To demonstrate wide applicability, the system was used for the multistep synthesis of phenelzine sulfate (an antidepressant drug[24]), isoniazid (an antibiotic drug for tuberculosis[25–27]), dihydralazine (an antihypertensive drug[28]), lomustine (an alkylating agent used in chemotherapeutic cancer treatments[29]) and umifenovir (an antiviral medication for the treatment of influenza[30]). The versatility of reactionware allowed us to use the same platform to perform iterative solid-phase syntheses (oligopeptides: VGSA, GFSVA, FVSGKA and SKVFGA; oligonucleotides: 5′-TACGAT, 5′-CTACGT, 5′-GCTACGAT and 5′-ATGCTACGGCTACGAT). These syntheses not only included the iterative process of coupling and deprotection of the respective monomers, but also the cleavage from the resin step and purification (typically performed manually in traditional synthesizers). This platform allows the miniaturization of a chemical manufacturing plant into a small-footprint (250 mm × 660 mm × 390 mm) synthesizer that only requires an

School of Chemistry, the University of Glasgow, University Avenue, Glasgow, UK. ✉e-mail: lee.cronin@glasgow.ac.uk

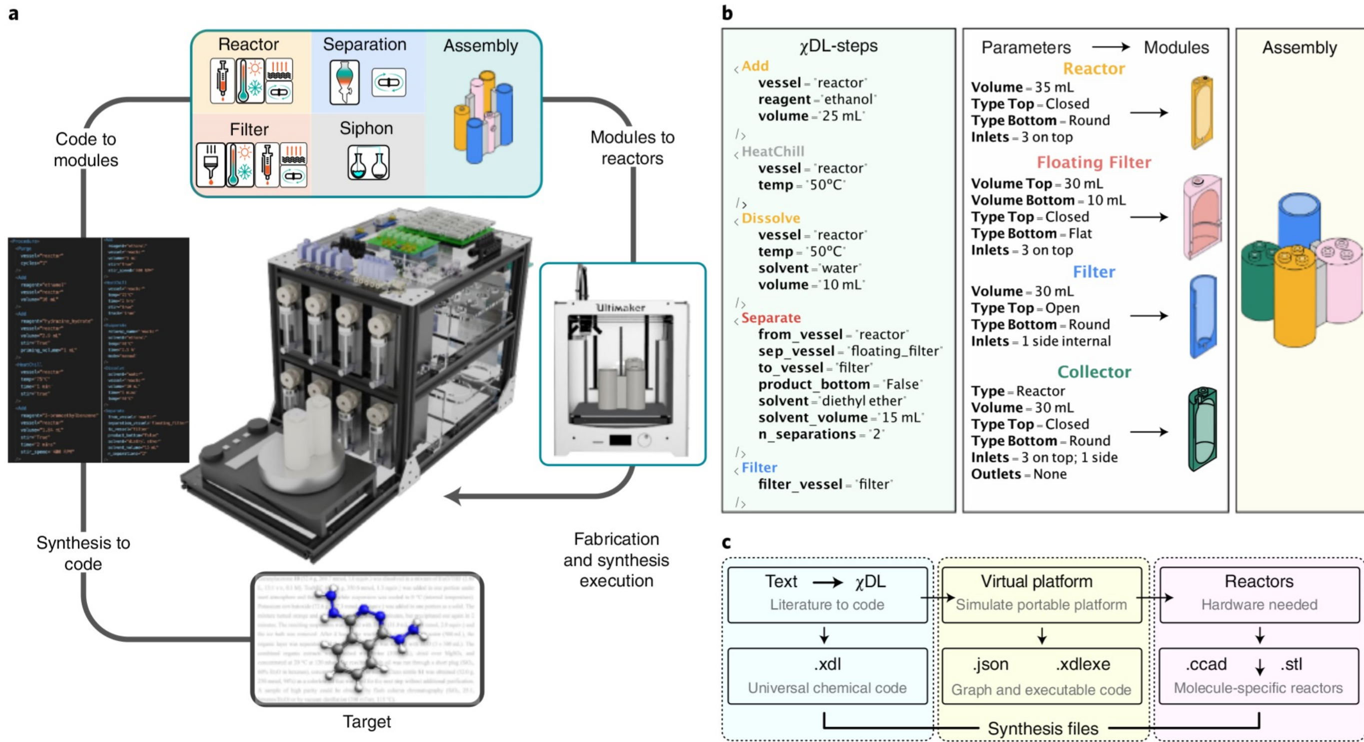


Fig. 1 | Schematic representation of any synthesis carried out in the compact/portable platform. a, Synthetic operations and variables are extracted from the literature procedure and converted into an executable chemical code (χDL). The operations and variables are used to generate single reactionware cartridges unique to the target molecule. The miniaturized laboratory hardware is manufactured and plugged into the platform for an automated execution of all synthetic steps. **b**, From the χDL steps, the reaction parameters are encoded into reactionware modules. Using the linearity of chemical processes, these modules can be assembled into a monolithic reactor that contains all the hardware required for the synthesis. **c**, All the necessary files for the automated synthesis of any molecule: .xdl, a universal chemical code for the synthesis of any molecule extracted from literature procedures; .json, a graph representation of the location, connectivity and capabilities of all the devices needed for the synthesis; .xdlexe, the portable platform executable code for the synthesis; .ccad, editable CAD designs of the reactors needed; .stl, a ready-to-print monolithic reactor containing all the chemical operations for the synthesis.

external supply of electricity, gas and coolant for operation anywhere. However, to operate at its minimal capacity (for example, in remote locations) without hindering the platform capabilities, an electricity supply is the sole requirement, and this, in principle, can be supplied as a portable source as well.

Results and discussion

Reactors design. The synthesis of any molecule consists of following a series of fixed consecutive steps (for example, add, filter, evaporate, heat) containing synthesis-specific parameters (for example, time, temperature, volume, mass and so on). Extracting these parameters from any literature protocol and combining them in the correct context results in a chemical code file (χDL file)[4]. Each χDL step expands into hardware-specific sub-steps, which define unit operations that can be directly executed. To carry out the synthetic protocols, a χDL implementation containing all the executable sub-steps was created. The software is composed of synthesis steps (common synthetic steps), utility steps (common low-level processes) and base steps (directly executable steps; Supplementary Tables 1–3).

Given that χDL inherently contains all synthetic steps (including parameters) for the preparation of any molecule, it can be used to define the required hardware that aligns with the sequential synthetic steps (Fig. 1a). Reactionware systems are composed of a series of discrete physical reactor modules that are designed to perform linear operations (that is, filtration, evaporation, reaction and separation) to prepare a targeted molecule. The design of these reactionware systems has previously been achieved by either manual CAD design[22,23] or by the use of specially created reactionware design software[21]. To fully automate the production of reactionware we have developed a cartridge generator software to produce prototypical reactionware systems based on the χDL description of the synthesis. The parameters of the physical modules can be extracted from the information embedded in the χDL file (Fig. 1b). Following the structural elements from ChemSCAD[21], the vessels' names in the χDL file are based on four basic designs (reactor, filter reactor, floating filter and double filter reactor). The program iterates through the χDL steps and, based on their physical operation, it will assign one of the basic designs to each operation. For example, a simplified χDL procedure for the synthesis of phenelzine sulfate is shown in Fig. 1b. In the first step, ethanol (25 ml) is added to 'reactor', which results in a reactor module with a volume of 25 ml. Next, the vessel is heated to 50 °C, not generating a new module. Water (10 ml) is then added to 'reactor', which will increase the volume of the already-made module to 35 ml. For a liquid–liquid extraction, the separate step specifies that the solution from 'reactor' is going to be extracted twice with diethyl ether (15 ml) through 'floating_filter' into a 'filter' reactor. This single operation will produce two new individual modules: a 'floating filter' reactor with a top volume of 30 ml (organic layer) and a bottom volume of 10 ml (aqueous layer), and a filter reactor with a volume of 30 ml, where the organic phase will be transferred. Finally, the product is precipitated, filtered and washed (see Supplementary Section 6.3 for the complete phenelzine sulfate synthesis). This last step adds a 'reactor' cartridge, from

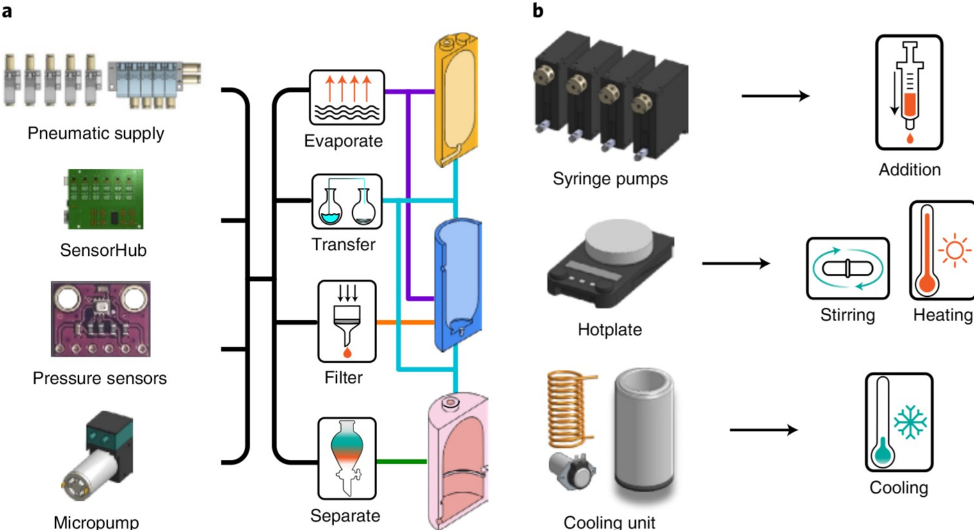


Fig. 2 | Summary of the implemented reaction and platform operations. a, Reaction operations: the synthesis operations are contained within the customized modules. To control the operations within the modules, a series of sequential steps involving the solenoid valves, pressure sensor and the micropump are executed. For example, to transfer a solution from one module to another: (i) the solenoids connected to the receiving module and following module are closed to cut off the inert gas supply, (ii) the vacuum is turned on in the receiving module, (iii) the pressure sensor is used to dynamically detect that the transfer is completed, (iv) the solenoids in the receiving flask and any other following module are turned on to refill the system with inert gas, (v) finally, the vacuum is turned off to refill the entire system with inert atmosphere. All the components are controlled from the custom-made SensorHub shield. **b**, Platform operations: generic operations needed for any chemical synthesis, including liquid handling of solvents and reagents, and heating and cooling the reactor.

where all filtrates are disposed to the proper waste through the liquid backbone. This single module is a standard reactor with a round bottom and a volume of 30 ml.

From this process, the individual modules can be automatically assembled into a target-specific monolithic cartridge. The entire automated process produces five different files needed for the synthesis execution (Fig. 1c). The software-related files include a .xdl file (a universal chemical code, a platform-independent file extracted from literature procedures), a. json file containing a graph representation of the location, connectivity and capabilities of all the platform devices, and a .xdlexe file with all the executable unit operations to carry out the synthesis. Additionally to the software set-up, the automated synthesis protocol generates a .ccad, file (an editable CAD design of the reactor modules) and a .stl file of the first monolithic prototype ready to be manufactured. Finally, this monolith can then be fabricated and plugged into the platform for execution of the automated synthesis. To rapidly prototype the reactor designs, we 3D-printed polypropylene reactors; nonetheless, the final reactor design can be manufactured using different materials (for example, polyether ether ketone (PEEK) or glass) and methods (for example, injection moulding or glass blowing).

Platform specifications. Because all the reaction processes are part of the morphology of the reactionware monolith, the automated platform can be simplified to perform minimal operations to the monolith (that is, heat, cool, evaporate; Fig. 2). For liquid handling, a fluidic backbone consisting of eight Tricontinent C3000MP syringe pumps equipped with six-way distribution valves were used, giving the system a total of 32 inputs/outputs (two ports for each pair of pumps are used for inter-pump connections) for reagents, solvents, cartridges and waste disposal. This backbone has the ability to move a solution from any storage receptacle to any module input. Heating and stirring were accomplished by using a computer-controllable hotplate, along with a standard silicone oil bath, while for cooling, a thermal fluid was circulated through a copper coil (cooled in a dry ice/ethylene glycol mixture), allowing working temperatures of between about −13 °C and 120 °C (Supplementary Fig. 11).

To control the reaction operations within the reactionware vessels, we implemented a programmable manifold. The manifold consists of five solenoids dedicated for supplying nitrogen, and five solenoids for controlling the vacuum input/output (generated with a micropump). For monitoring and controlling the pressure within the system, a pressure sensor was added to one reactionware module (Supplementary Fig. 14). All the previous components are controlled with a custom-designed Arduino shield (Supplementary Fig. 13). This shield allows precise liquid manipulation within the monolith by operating the solenoids and micropump in the correct sequential order (Supplementary Fig. 15).

All the components were put together to maximize the capabilities of the platform, while minimizing the footprint (Fig. 3). The final portable synthesis platform consists of acrylic plates fixed to a metal framework (250 mm × 600 mm × 330 mm). The back acrylic plate contains all the power supply unit (PSU), two d.c.–d.c. convertors (24 V → 3.5 V and 24 V → 12.0 V), a micropump, a main gas inlet and an Ethernet switch for communications. The top-plate contains the gas/vacuum programmable manifold, the PumpHub (printed circuit board for syringe pump communication), SensorHub (custom-designed shield to control the programmable manifold and the sensor framework) and two serial-to-Ethernet convertors (for communication with the hotplate and the PumpHub). Finally, the pumps were allocated to the front side of the portable platform in two tiers, while behind the syringe pumps there was space for the reagent, solvent and waste bottles, with tailored acrylic shelves.

Multistep organic synthesis. To demonstrate the capabilities of the platform, we performed the automated synthesis of five different active pharmaceutical ingredients (APIs): dihydralazine (**2**), isoniazid (**3**), phenelzine sulfate (**5**), lomustine (**7**) and umifenovir (**13**). The digitization process starts with extracting the chemical operations from literature procedures into a χDL file. This file,

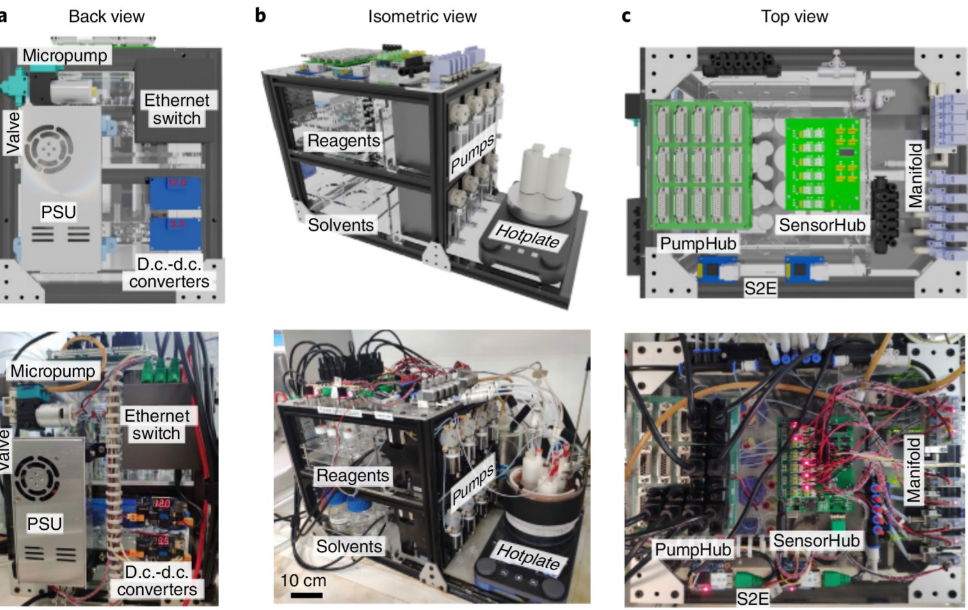


Fig. 3 | Physical implementation of the portable platform. a, Back view of the portable platform containing a micropump for liquid transfers within the cartridges, as well as evaporations; an Ethernet switch for communication; d.c.–d.c. converters for distributing power to the SensorHub and the serial-to-Ethernet converters; and a valve to control the input of inert gas into the platform. **b**, Isometric view of the portable platform showing the location of the hotplate for heating, stirring and cooling the reactors. Reagents and solvents are located behind the syringe pumps. **c**, Top view of the platform showing the location of the PumpHub (to control the liquid-handling robot), SensorHub along with the manifold for liquid handling within the monolith, and S2E (serial-to-Ethernet) convertors for Ethernet communication. The top row shows the design and location of the different hardware components. The bottom row shows physical examples of the compact automated platform.

containing the sequential synthesis operations, is then automatically converted into functional interconnected modules to form a molecule-specific monolith (Fig. 4). For the two-step reaction of dihydralazine (Fig. 4a), the cartridge consists of three different modules: module-1, a filter reactor for the synthesis and purification of **1**, module-2, a filter reactor for the precipitation of **2**, and module-3, a reactor with a round bottom designed for the collection and extraction of solvent waste. This two-step synthesis has 13 χDL steps compacted from 224 base steps, and a total runtime of ~24 h. For isoniazid (Fig. 4b), the cartridge consists of two different modules: module-1, a filter reactor for the synthesis and purification of **3**, and module-2, a reactor for the collection and extraction of solvent waste. This one-step synthesis has 15 χDL steps compacted from 121 base steps, and a total runtime of ~20 h. The monolith for phenelzine sulfate (Fig. 4c) comprises four different modules: module-1, a reactor for the synthesis **4**; module-2, a floating filter reactor for liquid–liquid extraction in the purification of **4**; module-3, a filter reactor for the synthesis and purification of **5**, and module-4, a standard reactor for the collection and extraction of waste. The two-step protocol consists of 28 χDL steps compacting a total of 279 base steps, and a total runtime of ~29 h. For lomustine, the monolith was composed of two different modules: module-1, a high-volume filter reactor, where the synthesis and purification of **6** and **7** take place, and module-2, a reactor for waste collection and extraction. The two-step procedure is composed of 23 χDL steps containing 159 base steps with a total runtime of ~30 h. These four small organic molecules (isoniazid, dyhydralazine, Nardil and lomustine) can be synthesized using the same platform set-up, with all the 15 reagents/solvents initially loaded. The only difference between syntheses would be the bespoke reactor, which is trivial to change. All the steps required 783 χDL base steps, with a total of 130 h of runtime. The four APIs were prepared in good purity along with similar yields compared to manual operation of the cartridges (Supplementary Table 15).

To demonstrate the robustness of the platform, umifenovir, an antiviral medication for the treatment of influenza (**13**) that has a six-step synthesis, was included as a target. The nature of the synthesis resulted in a three-module monolith: module-1, a filter reactor for the synthesis of **8**–**11**, module-2, a filter reactor for the synthesis of **12** and **13**, and module-3, a standard reactor used for the collection and extraction of solvent waste. Overall, the six-step protocol requires 96 χDL steps enclosing a total of 952 base steps, executed over 64 h of continuous platform operation.

One of the main features implemented in the platform is the dynamic use of a pressure sensor to control and monitor all the operations within the monolith. This allows not only to determine the start and end points of automated operations, but also profiling the reaction process itself. This 'fingerprint' can be used as a quality control to validate the reaction process progress, making sure the processes can proceed to completion. Figure 5 shows the pressure reaction profile for the synthesis of phenelzine sulfate, composed of 22 different synthesis steps (Fig. 5b), associated with a unique pressure profile (a portion of the overall fingerprint). For example, during purging, considering the length of the cartridge, the pressure drops to ~0.9 atm. In the first step, for the synthesis of **4**, vacuum pulses are applied to prevent over-pressurizing the reactor vessel and an undesired/early transfer to module-2. These vacuum pulses are short (~1 s every 30 s) and last for the entire reaction of hydrazine hydrate and 2-bromoethylbenzene. The reaction solution is then kept at 75 °C to evaporate the solvent using vacuum pulses (~4 s every 6 s). During the separation, diethyl ether is added to module-1 and transferred to module-2, where the separation happens. The diethyl ether solution, containing the product, is transferred to module-3, before continuing with evaporation.

To benchmark and validate the reaction protocols executed in the platform, phenelzine sulfate was chosen as the test reaction. The synthesis procedure is composed of 22 different χDL steps, each of them correlated with a unique pressure profile (Fig. 5b). To define

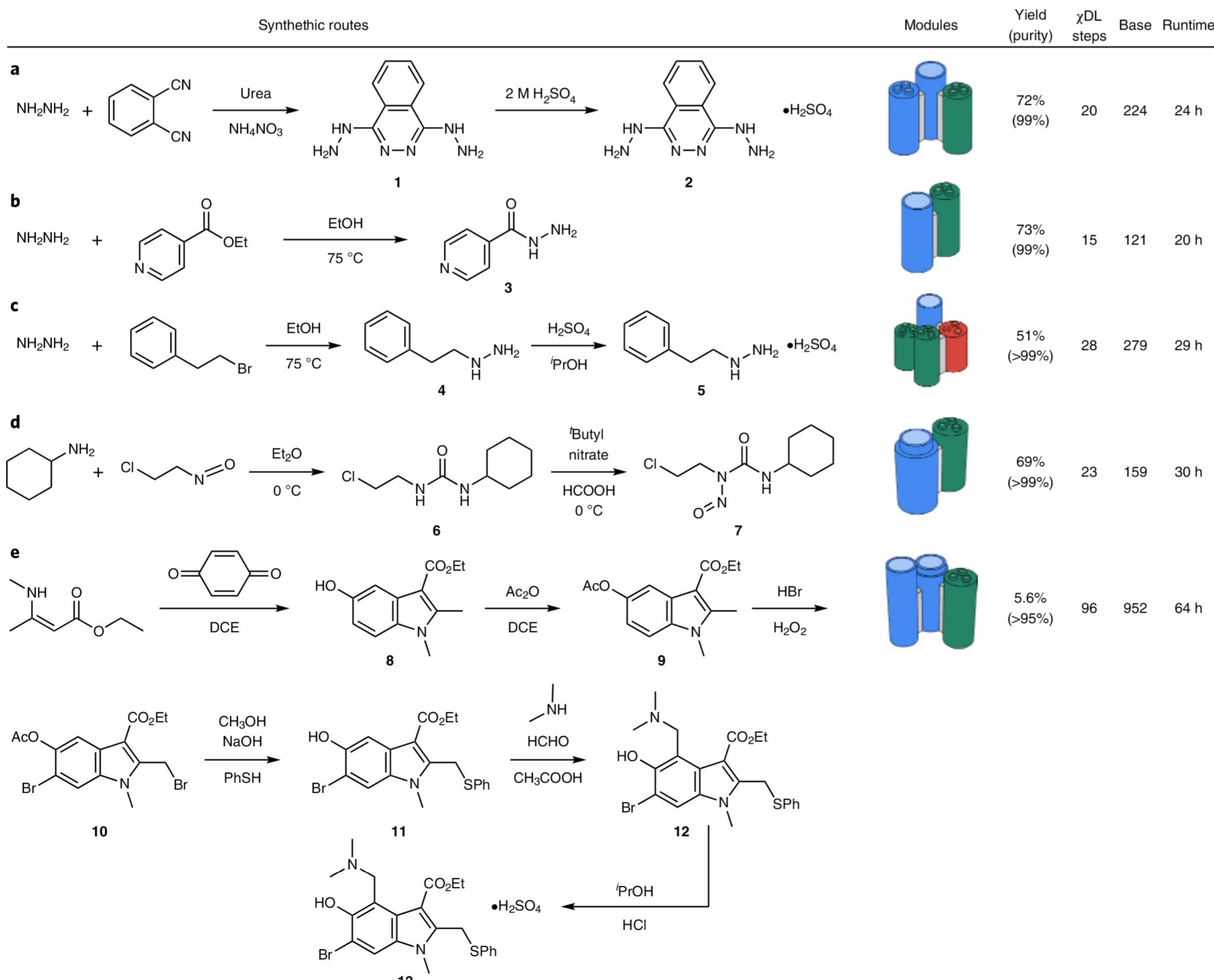


Fig. 4 | Synthetic schemes of five different APIs prepared using the platform. a–e, Synthetic routes for the synthesis of dihydralazine (**a**), isoniazid (**b**), phenelzine sulfate (**c**), lomustine (**d**) and umifenovir (**e**) with the respective monolithic cartridges used in the synthesis, yield (purity determined from HPLC), number of base steps executed, and runtime. All the monolithic cartridges are composed of three different modules, arranged in a different sequence depending on the target molecule: a filter reactor (blue) and a reactor (green) used for stirring, heating, filtering, and evaporating; and a floating filter module (red) used for liquid–liquid extractions. DCE, 1,2-dichloroethane.

a standardized synthesis profile, and to account for batch differences, the pressure profiles of three different successful reactions were averaged to obtain a single pressure profile. For a new synthesis execution, a similarity score (Wasserstein distance) can be obtained by comparing it with the reaction standard. Performing this analysis over all the χDL steps results in a quality control vector. Figure 5c shows the vectors of successful and failed (nos. 1, 2, 5 and 7) reactions. At the end of each run, a quick analysis of the quality control vectors can identify failed steps. For example, the vector for the synthesis of phenelzine sulfate in reaction no. 1 suggests that step 16 (red square) differed from the standard notably. This step corresponds to the acid addition to precipitate phenelzine sulfate, which was corrected by manual addition of H_2SO_4/^{i}POH. However, because this addition happened in a different time in the reaction, step 17 was also flagged as failed. At the end of the reaction, and upon inspecting the platform, we realized the tubing connecting to the H_2SO_4/^{i}POH vessel was clogged. For reaction no. 2, the tubing was unclogged, but step 16 still showed a difference, probably due to poor backbone cleaning, which was corrected for the next syntheses. For reaction no. 5, even though the hardware operations were completed successfully, no product was obtained. However, the pressure profile differed from the standard enough to be flagged as failed. Finally, for reaction no. 7, the steps were scoring high (~160) overall, but the transfer from module-3 to module-4 during filtration showed an important deviation. This was due to a leak that developed during the reaction in the sensor case, resulting in an overall different signal profiling. This demonstrates that the generated pressure profile can be used, not only to control the operations within the monoliths, but, most importantly, to validate each executed step. Using this analysis, we found that a threshold of 140 (Wasserstein metric) can be used to perform a quality control remotely.

Solid-phase synthesis. Solid-phase synthesis is a process that involves reacting a molecule chemically bound to a solid support using selective protection/deprotection protocols. These

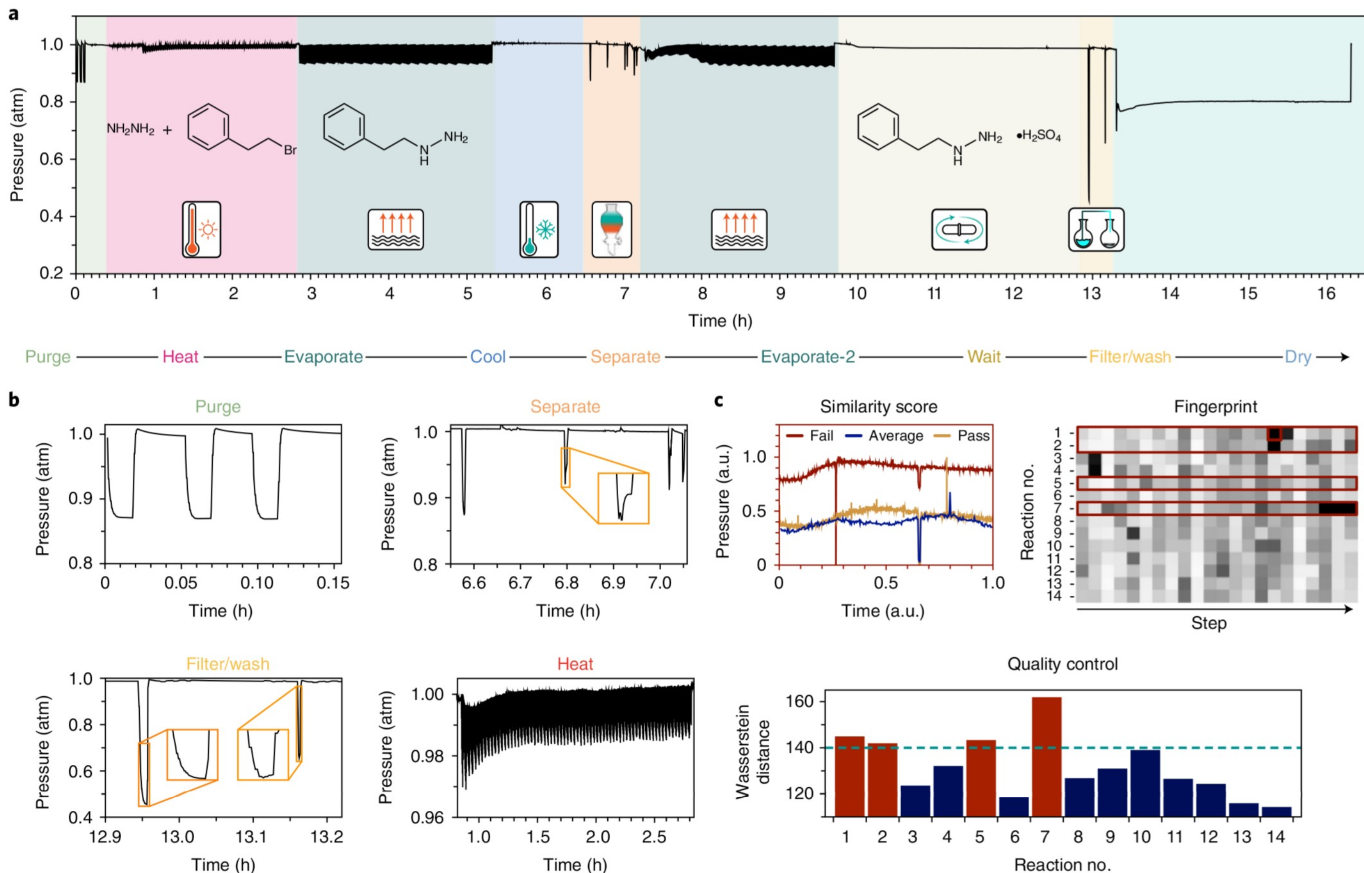
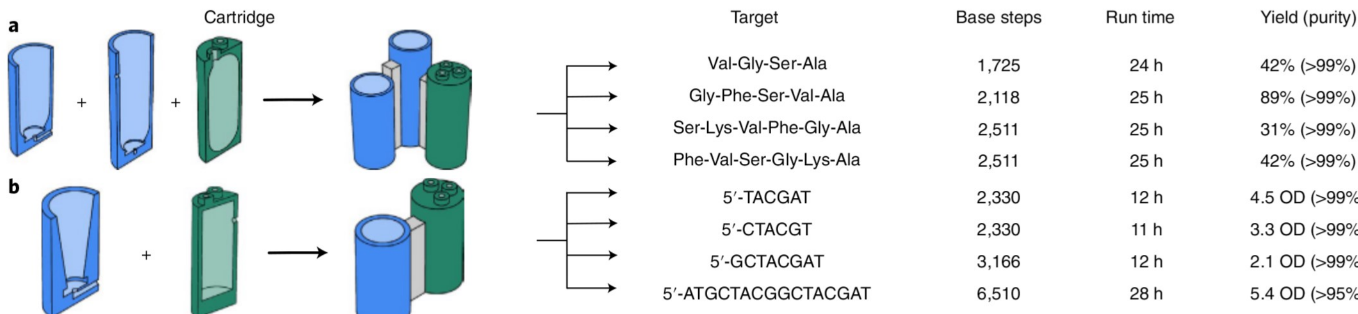


Fig. 5 | Fingerprinting and validation of phenelzine sulfate synthesis using the pressure profile. The reaction pressure profile elucidates all the different processes within the cartridge during the synthesis execution. **a**, The full pressure profile for the synthesis of phenelzine sulfate. The plot shows how the pressure changes depending on the physical operation (insets) that occurs within the monolith. **b**, The full pressure profile can be subsequently divided into χDL-step-specific profiles, showing different features depending on the ongoing process. **c**, Fingerprinting every step in the reaction process can be used to monitor and validate its execution. Comparing any ongoing procedure to a standard profile (an average of three successful reactions) and obtaining a similarity score (Wasserstein metric) for each executed step results in a quality control vector. This metric allows the determination of failed executions, and, upon inspection, a specific failed step can be identified (red squares in fingerprint). This analysis can be extended to the reaction profile to obtain an overall similarity metric, and a quality control analysis can be performed to determine successful syntheses (any protocol above the 140 metric will be marked as failed), without the use of expensive or complex equipment.

methods are commonly used for the synthesis of biological molecules (for example, oligopeptides[9], oligonucleotides[10] and oligosaccharides[11]) and polyolefins[5]. Considering it is an iterative process, the inherent abstraction of χDL can be used to implement a step-reaction class (solid-phase peptide synthesis, SPPS) containing all the necessary sub-steps to complete the sequence of the specified solid-phase synthesis based only on minimum parameters (sequence, scale and resin loading) to complete the desired sequence (Supplementary Fig. 5).

Based on all the steps needed for the oligopeptide synthesis, the monolithic cartridge for the SPPS synthesis consists of three modules: module-1, a filter reactor where the solid support is loaded and all the chemical operations (that is, deprotection, coupling, cleavage) take place; module-2, a filter reactor used for peptide precipitation; and module-3, a reactor cartridge to collect and remove solvent waste. The SPPS cycle finishes with a washing and drying step. To cleave the peptide from the solid support, with a -Fmoc protecting group, a freshly prepared solution of trifluoracetic acid (TFA) and scavenger reagents (triisopropylsilane, TIPS) was added to module-1. The solution was transferred to module-2, where diethyl ether was added to induce precipitation of the peptide. Because the synthetic protocol is the same, independent of the amino-acid sequence, the same monolith can be used for the synthesis of multiple oligopeptides. This protocol was used for the synthesis of VGSA, GFSVA, FVSGKA and SKVFGA. All the synthetic procedures were carried out using the same reactor without any detectable cross-contamination. The versatility offered by the software bound to the platform allowed us to execute the protocols with minimal change in between synthesis (only the oligopeptide sequence was different), which generated between 1,700 and 2,500 χDL base steps depending on the synthesized oligopeptide.

Similarly, oligonucleotides are commonly synthesized using solid-phase synthesis, for which a new step reaction was added (oligonucleotide solid-phase synthesis, OSPS). To ensure the solid support is completely submerged in the reagent solutions during the iterative process, a smaller cartridge (2 ml, inner diameter of 28 mm) with a cone-shaped interior (base, 8 mm; top, 25 mm) was designed. The final monolithic cartridge consisted of two modules: module-1, a filter reactor where all the chemical operations will take place; and module-2, a reactor module used for collecting and discarding filtrate waste. To cleave the synthesized oligonucleotide from the solid support, an ammonia solution is added to module-1, filtered to module-2, and the solution is heated to 55 °C for 12 h for the final heterocyclic base and phosphate deprotections. Finally, the solution



Target	Base steps	Run time	Yield (purity)
Val-Gly-Ser-Ala	1,725	24 h	42% (>99%)
Gly-Phe-Ser-Val-Ala	2,118	25 h	89% (>99%)
Ser-Lys-Val-Phe-Gly-Ala	2,511	25 h	31% (>99%)
Phe-Val-Ser-Gly-Lys-Ala	2,511	25 h	42% (>99%)
5′-TACGAT	2,330	12 h	4.5 OD (>99%)
5′-CTACGT	2,330	11 h	3.3 OD (>99%)
5′-GCTACGAT	3,166	12 h	2.1 OD (>99%)
5′-ATGCTACGGCTACGAT	6,510	28 h	5.4 OD (>95%)

Fig. 6 | Schematic representation of the oligopeptides and oligonucleotides synthesized in the platform. The syntheses are based on the solid-phase approach, where the iterative steps are executed until the desired oligopeptide (SPPS) or oligonucleotide (OSPS) sequences are obtained. The reactors can be reused without any cross-contamination. **a**, Oligopeptides prepared in the portable platform using a three-module cartridge system consisting of two filter reactors (blue) followed by a reactor module (green). The iterative coupling and cleavage of the oligopeptide from the solid support happen in module-1, precipitation of the final oligopeptide takes place in module-2, and module-3 is used to extract waste solvents from the system. **b**, Oligonucleotides sequences prepared in the portable platform. All the oligonucleotide sequences were prepared in the same monolithic cartridge consisting of two modules: module-1 a low-volume filter reactor (blue), where the iterative coupling and cleavage of the final oligonucleotide from the solid support take place, and module-2, a reactor (green) module, used to remove filtrates from the system. OD, optical density.

is transferred to the receiving flask, ready for further purification methods. This protocol was used for the synthesis of 5′-TACGAT, 5′-CTACGT, 5′-GCTACGAT and 5′-ATGCTACGGCTACGAT. All the oligonucleotides were synthesized using the same cartridge without any detectable cross-contamination, demonstrating the recyclability of these systems. Similarly to SPPS, one χDL step is needed (input the oligonucleotide sequence), resulting in outputs containing between 2,300 and 6,500 χDL base steps (Fig. 6).

In summary, we have shown a portable automated platform that can execute a wide variety of synthetic procedures that are mapped into a reactionware system. This platform, despite its small footprint, is capable of executing the synthesis of 13 different targets including the six-step synthesis of umifenovir and the solid-phase synthesis of oligopeptides and oligonucleotides (along with cleavage from the support). The synthetic steps are coded into the blueprint of the reactors, so switching between chemistries does not require any hardware reconfiguration of the platform (manual or automated), but just switching the reactor. Using pressure sensors to control and monitor the reaction progress, a reaction standard pressure profile can be obtained. Benchmarking the phenelzine sulfate synthesis in the portable platform suggested that a threshold of 140 (Wasserstein metric) can be used to remotely diagnose successful procedures without using expensive analytical techniques.

This method is based on the following key components: graph, which describes the location and connectivity of all the platform's physical components, and the reactionware monolith, a set of reactor modules connected sequentially containing all the necessary hardware for the chemical operations to obtain the targeted molecule. The bespoke reactors were reused multiple times (>20) during the development of the platform and validation syntheses, with no sign of degradation, and no notable effect in the synthesis yield (Supplementary Fig. 44). As a result of a fully digitized process, the system runs using a versionable executable code that is capable of executing all the abstract explicit operations in the chemical programming language. Finally, the platform is designed to be used with minimal requirements, such as electricity and inert gas supply, and coolant. However, at its minimal capacity, it only requires an electricity supply, which, in principle, can be supplied as a portable source.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-022-01016-w.

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Methods

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

Characterization. NMR measurements were performed with a 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 parts per million (ppm), calibrated for the (residual) NMR solvent signal.

HPLC analysis was performed on a Thermo Dionex Ultimate 3000 system 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 instrument 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 was set at 4,500 V, the end plate offset at −500 V, the nebulizer at 1.6 bar, dry gas at 8.0 l min^{-1}, funnel 1 radiofrequency (RF) at 400 V_{pp}, funnel 2 RF at 400 V_{pp}, isCID energy at 0 eV, hexapole RF at 100 V_{pp}, ion energy at 5.0 eV, low mass at 50 *m*/*z*, collision energy at 5 eV, collision cell RF at 200 V_{pp}, transfer time at 63.5 μs, and the pre-pulse storage time at 1.0 μs. The mass range was set to 50–2,000 *m*/*z* for small molecules and oligopeptides, and 500–5,000 *m*/*z* for oligonucleotides. Data were analysed using the Bruker DataAnalysis v4.1 software suite.

3D printing. The 3D printing reactionware vessels were processed using a Ultimaker 2+. Polypropylene (PP) filament was purchased from Barnes Plastic Welding Equipment. All prints were performed on a 12-mm PP sheet as a replacement of the standard glass bed provided by Ultimaker. This is a necessary requirement to achieve good adhesion of the first PP layer. The main 3D printer settings were as follows: bed temperature, off (that is, 0 °C); nozzle temperature, 260 °C; speed, 15 mm s^{-1}. Sensor cases were 3D-printed using a Connex 500 printer from Stratasys using Fullcure 720 translucent resin for the major body of the printed parts. Once the print was finished, the supports were scraped manually before washing thoroughly using a water-jet cleaning station (Quill Vogue Polyjet). The parts were then placed in a 0.1 M NaOH(aq.) bath for 30 min. Finally, the parts were again washed thoroughly in the cleaning station.

Platform liquid-handling and pneumatic system. For solvents/reagents handling, eight C3000MP syringe pumps equipped with 12.5-ml syringes were used. Polytetrafluoroethylene (PTFE) plastic tubing with an outer diameter of 1/16 in was used and connected using standard HPLC low-pressure PTFE connectors and PEEK manifolds (Kinesis). The pneumatic system is formed of five 3/2 V114A-6LU SMC solenoids dedicated for supplying nitrogen, and five 2/2 LVM11-6C solenoids for controlling the vacuum input/output. For vacuum, a compact diaphragm pump (TopsFlo TF30A-B) was used. 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 vapours coming from the reaction mixtures.

Automated isoniazid synthesis. 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 °C and kept at this temperature for 4 h. The solution was cooled to 40 °C and stirred for 30 min 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 °C for 20 min. The solution was then cooled to 8 °C and stirred for 30 min. Finally, the solution was filtered and dried for 10 h under vacuum. Isoniazid was obtained as a white solid (2.0 g, 73% yield)

Automated dihydrilazine synthesis. The monolith was preloaded with 1,4-dicyanobenzene (1.28 g, 10 mmol) and urea (3.65 g, 61 mmol). The system was purged with nitrogen three times. Hydrazine hydrate (3.65 ml, 75 mmol) was added to module-1 while stirring. The monolith was heated to 100 °C and kept at this temperature for 3 h. The reactionware was cooled to 30 °C and water (10 ml) was added to module-1. The solution was filtered and washed with water (10 ml) twice, then 2 M H_2SO_4 (12.5 ml) was added to module-1 over 10 min while stirring at 500 r.p.m. The monolith was heated to 100 °C for 1 h. The solution was hot-filtered, then cooled to 30 °C. The precipitate formed was filtered off and washed twice with 5 ml of water. Dihydralazine sulfate (2.1 g, 72% yield) was obtained as a yellow solid after drying under vacuum for 10 h.

Automated phenelzine sulfate synthesis. The reactor was purged with nitrogen three times. Ethanol (10 ml) and hydrazine hydrate (2.9 ml, 60 mmol) were added to module-1. The solution was heated to 75 °C, and 2-bromoethylbenzene (1.84 ml, 10 mmol) was added to module-1 over 2 min. Ethanol (5 ml) was added to module-1, and the system was kept at 75 °C for 2 h while applying vacuum pulses of 1 s every 60 s. The solution was cooled to 40 °C and a vacuum was applied to module-1 for 2.5 h 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. A vacuum was applied to module-3 to evaporate diethyl ether, for 2.5 h, while heating to 35 °C. 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 min, and the solution was stirred for 2 h. Hexane (5 ml) was added to module-3 and stirred for 30 min. 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 (1.2 g, 51% yield) after drying for 10 h.

Automated synthesis of lomustine. The reactor was purged with nitrogen three times. Diethyl ether (20 ml) and 2-chloroethyl isocyanate (1.05 ml, 10 mmol) were added to module-1. The solution was cooled to 5 °C, and cyclohexylamine (0.5 M, 20 ml, 10 mmol) was added over 5 min. The solution was stirred for 3 h, filtered and washed with diethyl ether twice (5 ml). The obtained solid was dried for 1 h under vacuum. Formic acid (18 ml) was added to module-1, and the solution was cooled to 5 °C, followed by adding *t*-butyl nitrate (1.8 ml, 13.5 mmol). The solution was stirred for 2 h at 0 → 25 °C. Water (36 ml) was added to module-1, and the solution was stirred for an extra 1 h. 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 h to yield **5** (1.6 g, 69% yield)

Automated synthesis of umifenovir. $ZnCl_2$ (160 mg) was preloaded to module-1. A solution of *p*-benzoquinone (7 ml, 3.32 g in 13 ml of 1,2-dichloroethane (DCE)) was added to module-2. The monolith was cooled to 6 °C for 30 min, then enamine (4.9 ml) was added to module-2 within 10 min. The monolith was heated to 75 °C and kept at this temperature for 2 h and stirred at 200 r.p.m. The monolith was cooled to 30 °C. The solution was stirred at 200 r.p.m. for 1 h. Finally, the solution was filtered and dried under vacuum for 1 h to obtain a grey-yellow solid. DCE (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. The DCE was then evaporated at 60 °C for 2 h under vacuum pulses (4 s vacuum, 6 s waiting). Methanol (8 ml) was added to module-1, and evaporated first at 60 °C for 1 h under vacuum pulses (4 s vacuum, 6 s waiting), and then at 60 °C under vacuum for 2 h. After evaporation, methanol (4 ml) was added to module-1, and the solution was cooled to 25 °C, the 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 once with 50% methanol (4 ml). Finally, the grey solid was dried under vacuum for 3 h. DCE (10 ml) was added to module-2, and the solution was stirred at 200 r.p.m. for 30 min to dissolve umifenovir-B. Then, 48% HBr (2.8 ml) was added to module-1, and the monolith was heated to 70 °C. 10% H_2O_2 (9 ml) was added within 30 min, and the reaction was stirred at 70 °C for 2 h. DCE was evaporated at 60 °C using vacuum pulses (3 s vacuum, 6 s waiting). The monolith was then cooled to 30 °C, and it was stirred at this temperature for 1 h. 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 min. This process was repeated twice. Finally, the white-red solid was dried under vacuum for 1 h. 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. The reaction mixture was stirred at room temperature for 2 h. Acetic acid (3 ml) was then 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 for 1 h. A solution containing 40% dimethylamine (2.4 ml), acetic acid (10 ml) and 37% formaldehyde (1.4 ml) was pre-prepared. A 7-ml volume of this solution was added to module-2 containing umifenovir-D. The reaction mixture was heated to 65 °C and stirred at this temperature for 3 h. Water (5 ml) was added to module-1, then 15% NaOH (35 ml) was added to module-2, and the monolith was cooled to 6 °C for 30 min. Once cooled, the solution in module-2 was transferred to module-3 and it was stirred for 30 min. Finally, the solution was filtered, washed with water (15 ml) and dried under vacuum for 2 h to obtain a pale yellow solid. Isopropanol (5 ml) was added to module-2 containing umifenovir-E, and the monolith was heated to 70 °C. Once at this temperature, concentrated HCl (1 ml) was added to module-2 within 5 min. The reaction mixture was stirred at this temperature for 30 min, before it was cooled to 30 °C, turning off the heating. The solution was then stirred for 30 min and then filtered and washed with isopropanol (3 ml). Finally, the white-yellow solid was dried under vacuum for 3 h (0.75 g, 5.6% overall yield).

Automated SPPS synthesis. This general procedure was used for the synthesis of all oligopeptides, by using the amino acids required for the desired sequence. The 3D-printed reactor was manually charged with Fmoc-Ala-Wang resin (0.82 g, 0.50 mmol, 0.61 mmol g^{-1}). *N*,*N*-dimethylformamide (DMF; 9 ml) was added to module-1 and stirred for 1 h at room temperature to swell the Fmoc-Ala-Wang resin. A two-stage deprotection was then performed. Piperidine (9 ml, 20% vol/vol in DMF) was added to module-1 and the solution was stirred at room temperature for 3 min. The resin was filtered, and fresh piperidine (9 ml, 20% vol/vol 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. 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. To module-1, the appropriate amino-acid solution (4 ml),

(2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU; 4 ml) and *N*,*N*-diisopropylethylamine (DIPEA; 2 ml) were added sequentially. The reaction was stirred at room temperature for 1 h. The reagents were drained, and the resin was washed (DMF, five times, as resin wash). The deprotection, resin wash, coupling and resin wash were repeated for each amino acid. A final deprotection step was performed to remove the Fmoc group from the last amino acid coupled. The resin was washed with dichloromethane (9 ml). 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 four times. Cleavage solution (10 ml) was then added to module-1, and the reaction was stirred at room temperature for 3 h. Diethyl ether (25 ml) was added to module-2, then the solution (containing the cleaved peptide) was transferred from module-1 to module-2. The reactionware was then cooled to 0 °C for 3 h to precipitate the product. The solution was filtered and washed three 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). The obtained solution was freeze-dried to obtain a white solid, which was further analysed by HPLC. Full details are provided in Supplementary Section 7.

Automated oligonucleotides synthesis. This general procedure was used for the synthesis of all oligopeptides, by using the amino acids required for the desired sequence. 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. 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 s every 10 s to module-1) at room temperature for 5 min. The solution was drained and removed from the system. Anhydrous acetonitrile (ACN, 2.5 ml) was added to module-1, and the reaction was bubbled with argon (by applying vacuum pulses of 0.1 s every 10 s to module-1) at room temperature for 5 min. 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. To module-1, 5-ethylthio-1*H*-tetrazole (1.5 ml) was added to wet the resin with activator. The solution was drained and removed from the system. 5-Ethylthio-1*H*-tetrazole (1 ml) and the appropriate nucleobase solution (1 ml) were added to the same syringe, and allowed to mix for 2 min. After that, the solution was added to module-1, and was bubbled with argon for 8 min. The solution was drained and removed from the system, and the resin was washed (anhydrous ACN, three times). To module-1, 0.1 M iodine solution (2.0 ml) was added, and the solution was bubbled with argon for 5 min. The solution was drained, then removed from the system, and the resin was washed (anhydrous ACN, three times). CapA (1.5 ml) and CapB (1.5 ml) were mixed in the syringe for 30 s before addition to module-1. The solution was bubbled for 5 min. The solution was drained and removed from the system, and the resin was washed (anhydrous ACN, three times). The deprotection, resin wash, coupling, resin wash, oxidation, resin wash, capping and resin wash were repeated for each nucleotide. A final deprotection step was performed. The resin was washed two more times with ACN (2.5 ml). 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. To purify further the oligonucleotide, acetonitrile (5 ml) was carefully passed through an oligonucleotide purification cartridge (OPC), followed by 5 ml of 2 M triethylammonium acetate buffer. The eluate was discarded. Am aqueous solution of the crude oligonucleotide (1.5 ml) was then passed through the cartridge at a rate of ~1 drop per second. The eluate was collected and passed through the cartridge another three times. Following the final collection, the eluate was discarded. A 15-ml volume of 0.1 M triethylammonium acetate buffer was then carefully passed through the cartridge and the eluate discarded. A 1.2-ml volume of a mixture of water and acetonitrile (1:1 ratio, by volume) was then passed dropwise through the cartridge to elute the purified oligonucleotide.

Data availability

The Supplementary Information includes full details to reproduce this work. This consists of full details to reproduce the electronic and mechanical construction of the platform. The XDL files (.xdl), along with the respective graph (.json) and 3D reactor design (.stl), and full analytical data are provided, including our pneumatic fingerprint for the reactions, at https://doi.org/10.5281/zenodo.5248762.

Code availability

Code is available from https://doi.org/10.5281/zenodo.5248762.

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Author contributions

L.C. invented the concept and devised the project and the digitization approach, with help from J.S.M., S.S.Z. and P.J.K. S.S.Z. developed the initial system design and built the first prototype together with J.S.M. W.H. carried out reactionware synthetic routes for the small organic molecules, and P.F. and H.W. helped with method development for the synthesis of oligopeptides and oligonucleotides. J.S.M. carried out all the automated synthesis and developed the necessary code for the platform. J.S.M. and P.J.K. wrote the paper, with help from L.C.

Competing interests

The work described here has been filed as a patent GB 2213747.5 filed by the University of Glasgow.

Additional information

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Correspondence and requests for materials should be addressed to Leroy Cronin.

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