

# 3D Printed Polypropylene Continuous-Flow Column Reactors: Exploration of Reactor Utility in $S_NAr$ Addition Reactions and the Synthesis of Bicyclic and Tetracyclic Heterocycles

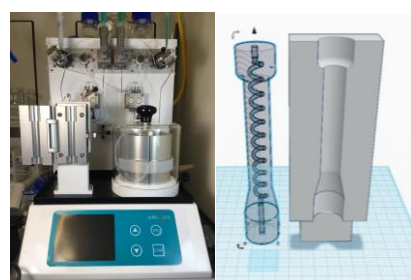
Zenobia X. Rao<sup>[a]</sup>, Bhaven Patel<sup>[a]</sup>, Alessandra Monaco<sup>[a]</sup>, Zi Jing Cao<sup>[a]</sup>, Marta Barniol-Xicota<sup>[b]</sup>, Enora Pichon<sup>[a]</sup>, Mark Ladlow<sup>[c]</sup>, Stephen T. Hilton\*<sup>[a]</sup>

**Abstract:** 3D printing has the potential to transform the way in which chemical reactions are carried out due to its low-cost, ease-of-use as a technology and its capacity to expedite the development of iteratively enhanced prototypes. In this present study, we developed a novel, low-cost polypropylene (PP) column reactor that was incorporated into an existing continuous-flow reactor for the synthesis of heterocycles. The utility and solvent resistance of the printed devices were explored in  $S_NAr$  reactions to produce substituted aniline derivatives and in the synthesis of bicyclic and tetracyclic heterocycles. Using this approach, a range of heterocyclic compounds were synthesised including the core structure of the natural product ( $\pm$ )- $\gamma$ -lycorane and the synthesis of structurally complex compounds based on the tetracyclic core of the Erythrina alkaloids.

3D-printing has undergone rapid development over the last decade, moving from the field of engineering through to a wide-range of scientific disciplines, due to its ease of use as a technology and the diminishing cost of 3D printers, with a wider range of materials that are now available.<sup>1</sup> It has become a novel manufacturing method used to fabricate low-cost bespoke objects with facile control of size and geometry with intricate internal structures with well-defined lengths and volumes.<sup>2</sup> There are a range of 3D printing technologies in use, but perhaps the one with the most widespread applicability is that based on Fused Deposition Modelling (FDM), which focuses on layer by layer printing of well-defined structural objects with accuracies as low as 50 microns.<sup>2</sup> Whilst most FDM printers use acrylonitrile butadiene styrene (ABS) or polylactic acid (PLA) as filament, these are not widely applicable to chemical synthesis. As such, recent reports have focussed on the printing of chemical reactors using polyamide or polypropylene, which is resistant to higher temperatures and compatible with a large range of solvents and chemicals but is often challenging to 3D print.<sup>3</sup> Reactions using such inert polymers have focussed on simple chemical reactions,

such as reductions or the formation of metal organic frameworks amongst others.<sup>4</sup> Whilst previously reported 3D printed reactors have been used for both batch and flow chemistry, their potential in flow-based reactions is clear, due to its widespread applicability in both research and industrial chemical processes as a result of the increased reproducibility, facile automation, improved safety and ease of transfer to large-scale production available in flow.<sup>5-7</sup> Despite its potential, flow-chemistry remains a challenge to research groups due to the costs of the machines themselves and the associated reactors. Current manufacturing technologies are highly expensive and allow for the production of microlitre-scale reactors in inert polymer or glass with a two-dimensional pattern of flow channels of millilitre-scale reactors in polymer and metal tubing, or glass chips with channels which cost in excess of \$2000 each.<sup>5-7</sup> As such, the integration of 3D printing with flow-chemistry's low-costs of raw material (PP -\$15/Kg) and ease of use as a technology in the development of iterative flow-reactor prototypes is an attractive prospect for synthetic chemistry.

As a result of the obvious potential advantages of linking flow-chemistry to 3D printing, we were interested in combining these two technologies via the 3D printing of low-cost column flow reactors that could be used with existing continuous flow devices, which would then be applicable to a range of chemical reactions. Herein, we now report on the results of our approach, which was realised using a Uniqis FlowSyn continuous flow reactor system with a 3D printed column designed to fit within the space of the existing column reactor segment as shown below (Figure 1).



**Figure 1.** A) Uniqis FlowSyn continuous flow reactor system showing the column heater block; B) Column reactor designed using Tinkercad software designed to fit the heating unit of the flow system.

Cognizant of the fact that any printed flow reactor device should be compatible with a wide range of synthetic chemistry and conditions, we elected to explore their utility in  $S_NAr$  reactions in the first instance, due to the harsh conditions associated with these reactions.<sup>8</sup> This key reaction has been utilized in the synthesis of commercial drugs such as zyprexa **1**,<sup>9</sup> zyvox **2**,<sup>10</sup>

[a] Miss, Z. Rao, Dr. A. Monaco, Dr B. Patel, Mr Z. Jing Cao, Miss E. Pichon, Dr. S.T., Hilton  
Department of Pharmaceutical and Biological Chemistry, UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX United Kingdom. E-mail: [s.hilton@ucl.ac.uk](mailto:s.hilton@ucl.ac.uk)  
<http://www.stephen-hilton.com>

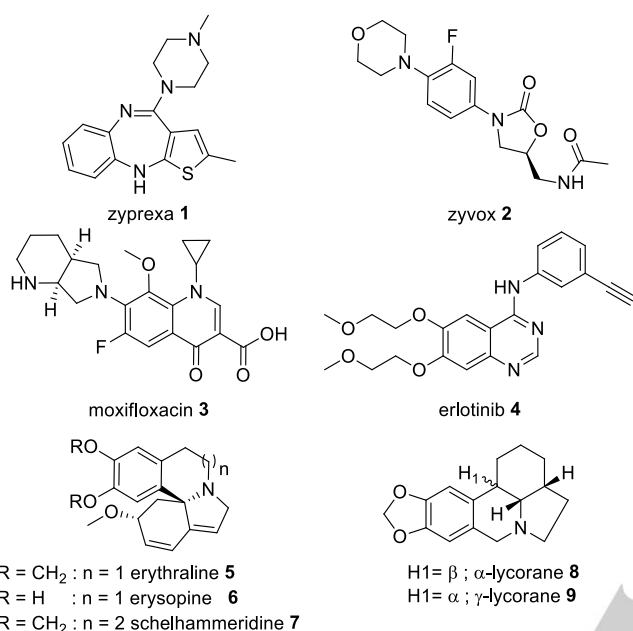
[b] Dr M. Barniol-Xicota, Laboratori de Química Farmacèutica, Facultat de Farmàcia, and Institute of Biomedicine (IBUB), Universitat de Barcelona, Av. Joan XXIII, s/n, Barcelona E-08028, Spain.

[c] Dr Mark Ladlow, Uniqis Ltd, 29 Station Road, Shepreth, Cambs, SG8 6GB, United Kingdom.

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moxifloxacin **3** and erlotinib **4**.<sup>11,12</sup> In addition, we were also interested in investigating their potential in the synthesis of bicyclic heterocycles and more complex structures based on the natural products erythratin **5-7** and lycorane **8, 9** as they would provide ready proof of principle of the utility of the reactors to a wider scope of synthetic chemistry (Figure 2).<sup>13-15</sup>



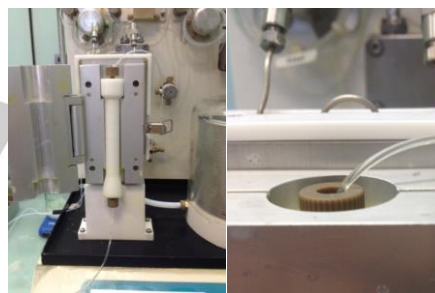
**Figure 2.** Selected synthetic targets for exploration of the scope of 3D printed polypropylene reactors.

In order to develop a reactor for use with the FlowSyn flow reactor system, the column reactor space was measured using Vernier callipers and an initial design realised using Tinkercad free online software (Autodesk) (Supplementary Information).<sup>16</sup> The reactor contained a central column, which would be in direct contact with the centre of the column reactor space and heated by the system, and as such, would not need expensive adaptation or further engineering (Figure 1). The solvent flow path for the reactor was designed as an internal spiral, which would facilitate prolonged contact with the outside hot surface of the column block to carry out chemical reactions as shown above (Figure 1). Once complete, the STL (surface tessalation language) file was exported into Cura software and the reactor printed on an Ultimaker2 3D printer in polypropylene (Supplementary Information).<sup>17</sup> The 3D printing of polypropylene proved challenging as there are scant reports of its use in the literature, nor the exact printing conditions.<sup>2,3</sup> Initial attempts failed due to poor adherence with the 3D printer build plate. Following experimentation, we found that printing directly onto an LDPE board, where the first layer could be directly melted into the solid surface enabled us to successfully print out the desired reactor (Figure 3 and Supplementary Information).<sup>2</sup>



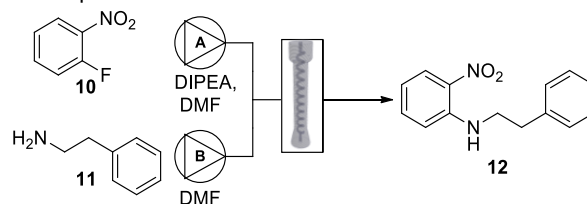
**Figure 3.** Illustration of the 3D printing of the column reactor directly onto an LDPE board to avoid shrinkage and adhesion to the build plate and the ease of production of up to six in one print.

Reactors were printed in groups of up to 6 in ~10 hours and each reactor had an average mass of 21 g with an internal coil diameter of 2 mm and a theoretical internal volume of 1.6 mL and a cost of less than \$0.50 per reactor. Columns were printed using 100% infill and a material flow rate of 110% in order to provide a contiguous sealed surface. Use of a lower material flow rate resulted in gaps in the print due to the tendency of polypropylene to contract once it had exited the nozzle. We next explored the reactors in the FlowSyn flow reactor system and their ability to be used for chemical reactions. Reactors were tapped out to provide a screw thread suitable for PEEK fittings as shown below (Figure 4).



**Figure 4.** Integration of the 3D Printed PP reactor into the column heating compartment of the FlowSyn flow reactor system using PEEK fittings.

We elected to explore S<sub>N</sub>Ar reactions with the 3D printed flow reactor in the first instance due to the relatively harsh synthetic conditions employed in the reaction to explore the limits of the 3D printed PP reactors using polar solvents and high temperatures to access compounds such as **1-4**.<sup>8-12</sup> We initially screened the reaction between 2-fluoronitrobenzene **10** and phenylethylamine **11** using DMF as solvent in order to develop optimised conditions (Scheme 1 and Table 1). Reactions were carried out using the FlowSyn flow reactor system and the percentage conversion of the reactions was determined from the <sup>1</sup>H NMR spectrum of the crude reaction mixture.<sup>18</sup>



**Scheme 1.** Reaction conditions selected for exploration of reactor utility.

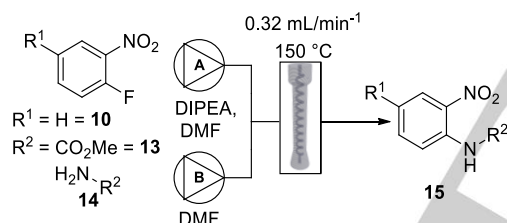
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**Table 1.** Screening of conditions for the  $S_NAr$  reaction between phenylethylamine **11** and 2-fluoronitrobenzene **10**.

Entry	Pump A Flow Rate [ml/min]	Pump B Flow Rate [ml/min]	Column Temperature [°C]	Conv./Isol. [%] <sup>[a]</sup>
1	1.00	0.65	100	21
2	0.50	0.32	100	36
3	0.16	0.16	150	66 (63)
4	0.13	0.08	150	55

[a] Determined by  $^1H$  NMR analysis of the crude reaction mixture.

Following reaction screening, it was clear that the printed reactors were able to withstand relatively harsh conditions (150 °C, Table 1, Entry 3) with good conversion to the addition product (66% conversion, 63% isolated) and a residence time of 5 minutes in the printed reactor. As a result of the fact that the reactor is held in the column unit of the flow reactor, it can be heated to a high temperature although it is worth noting that it required cooling prior to removal to avoid warping. With the optimised conditions in hand, we next carried out additional reactions with a range of amines and 2-fluoronitrobenzene **10** and methyl 4-fluoro-3-nitrobenzoate **13** (Scheme 2 and Table 2). Reactions were carried out at 150 °C using a flow rate of 0.16 mL/min for both the electrophile and DIPEA and 0.16 mL/min for the amine (Table 2).

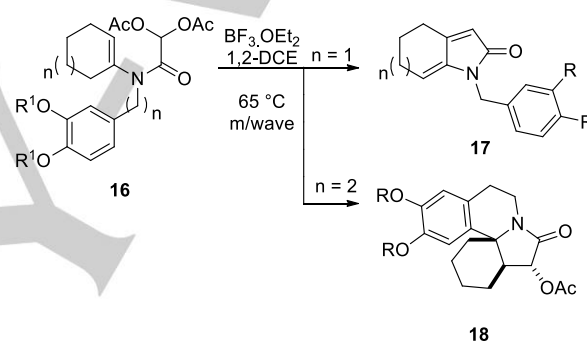
**Scheme 2.**  $S_NAr$  reaction between **10** and **13** and a range of amines.**Table 2.** Reaction of a range of amines and fluoronitrobenzenes under  $S_NAr$  reaction conditions with 3D printed polypropylene reactors.

Entry	Electrophile	Amine <sup>[a]</sup>	Product	Conv. [%] <sup>[b]</sup>
1	<b>10</b>	benzylamine	<b>15a</b>	47
2	<b>10</b>	4-chlorobenzylamine	<b>15b</b>	65
3	<b>10</b>	4-methoxybenzylamine	<b>15c</b>	57
4	<b>13</b>	phenylethylamine	<b>15d</b>	100
5	<b>13</b>	benzylamine	<b>15e</b>	100
6	<b>13</b>	4-chlorobenzylamine	<b>15f</b>	100
7	<b>13</b>	4-methoxybenzylamine	<b>15g</b>	97
8	<b>13</b>	aniline	<b>15h</b>	24
9	<b>13</b>	butylamine	<b>15i</b>	95
10	<b>13</b>	allylamine	<b>15j</b>	100

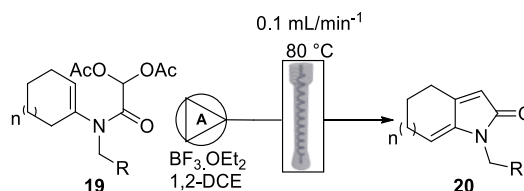
[a] Reactions were carried out at 150 °C and a flow rate of 0.16 mL/min for pumps A/ B. [b] Determined by  $^1H$  NMR analysis of the crude reaction mixture.

As outlined above, the reactors proved suitable for a range of reactions involving both 2-fluoronitrobenzene **10** and methyl 4-fluoro-3-nitrobenzoate **13** with good conversions to the  $S_NAr$  addition products **15a-15j** in all cases except that for the less reactive aniline (**15h**, Table 2, Entry 8). Pleasingly, the same column could be used up to five times for different reactions without loss of integrity. However, further continued use beyond this led to leakage of solvent around the PEEK fittings.

As a result of the successful demonstration of the applicability of the 3D printed polypropylene column reactors to withstand high temperatures and polar solvents such as DMF, we next elected to explore their utility in the synthesis of heterocycles related to the core of the Erythrina **5-7** and lycorane **8** and **9** family of natural products.<sup>13-15</sup> We have previously described an efficient approach to the core structures of these compounds and others using microwave accelerated synthesis of the bicyclic **17** and tetracyclic cores **18** from the acylal precursors **16** using 1,2-dichloroethane as the solvent and  $BF_3$  as the Lewis acid in an intramolecular acylal (IAC) cyclisation approach (Scheme 3).<sup>19-21</sup>

**Scheme 3.** Previous reported IAC approach to the bicyclic core of lycorane **17** and the tetracyclic core of the erythrina alkaloids **18**.

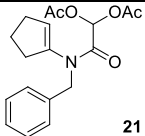
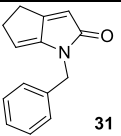
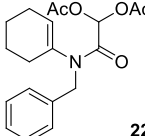
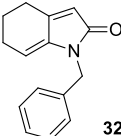
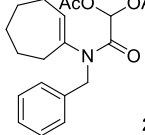
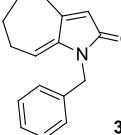
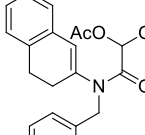
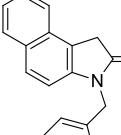
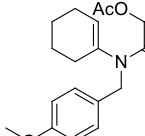
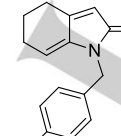
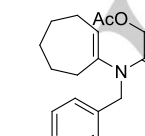
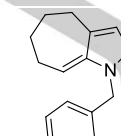
As such, we envisaged that the column reactors would prove suitable for the synthesis of complex heterocycles related to polycyclic natural products as our previously used microwave conditions could readily be translated into continuous flow via replication of the reaction conditions in the 3D printed flow reactor.<sup>21</sup> In the first instance, we decided to explore the synthesis of bicyclic heterocycles. Using the previously optimised conditions, where the IAC precursors were reacted with boron trifluoride at 65 °C in the microwave for 15 minutes,<sup>19-21</sup> IAC precursors were mixed with  $BF_3$  in 1,2-DCE and passed through the 3D printed flow reactor at a slightly elevated temperature of 80 °C at a flow rate of 0.1 mL/min giving a residence time of 16 minutes (1.6 mL internal volume), thus replicating the microwave conditions (Scheme 4).

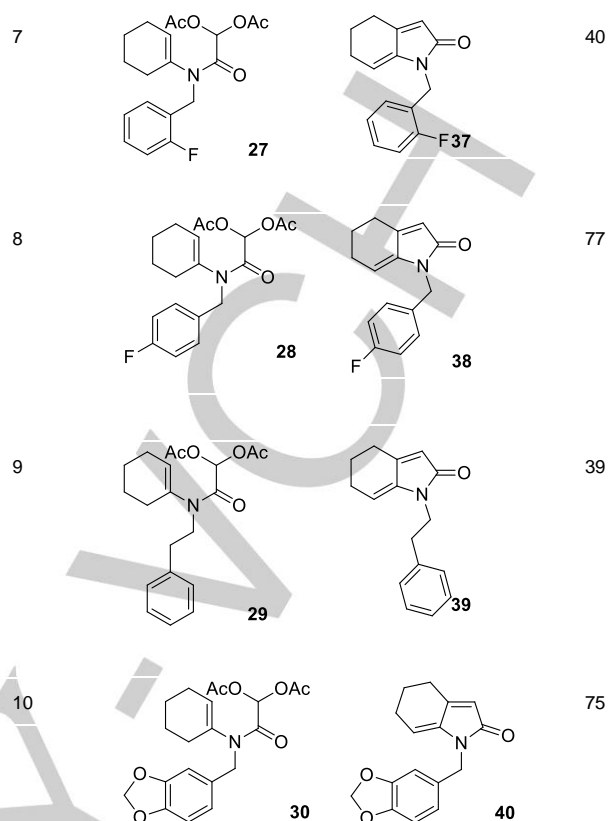
**Scheme 4.** IAC reaction using the 3D printed flow reactor.

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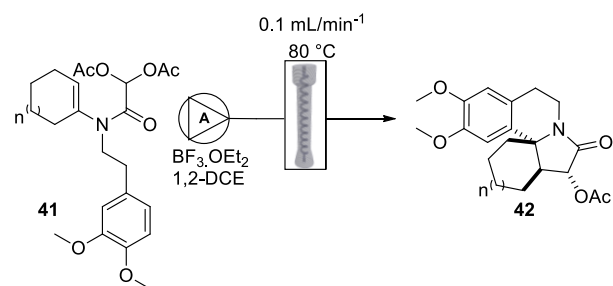
Cyclisation precursors were dissolved in anhydrous DCE and  $\text{BF}_3 \cdot \text{OEt}_2$  (5 equiv) was added, whereupon the solutions were subsequently passed through a pre-warmed ( $80^\circ\text{C}$ ) PP reactor with a flow rate of  $0.1\text{ mL/min}$  using a single pump. Compounds synthesised in this manner are shown below (Table 3).

**Table 3.** IAC cyclisation to synthesise bicyclic heterocycles using the 3D printed polypropylene reactor.

Entry	Cyclisation Precursor	Product	Isolated Yield [%]
1			34
2			51
3			70
4			43
5			61
6			47

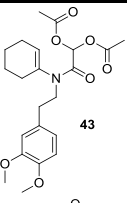
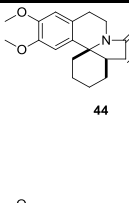
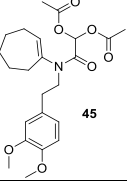
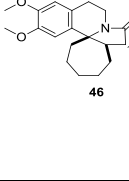


As can be seen above, all IAC cyclisation precursors gave good yields of the cyclised products (34–77%) using the 3D printed polypropylene reactors. Yields were comparable to the previously reported microwave conditions and were also comparable in terms of reaction time albeit at a slightly elevated temperature.<sup>21</sup> Compound **40** was obtained in excellent yield and represents an important intermediate in the synthesis of the lycorane family of compounds.<sup>21</sup> With the synthesis of bicyclic heterocycles in hand, we next elected to explore the synthesis of compounds related to the tetracyclic core of the Erythrina alkaloid family. As per the conditions used previously in the synthesis of bicyclic heterocycles, the IAC tetracyclic precursor **41** was dissolved in anhydrous DCE and  $\text{BF}_3 \cdot \text{OEt}_2$  (5 equiv) added and the reaction mixture passed through the 3D printed reactor at a flow rate of  $0.1\text{ mL/min}$  using a single pump (Scheme 5, Table 4).<sup>19</sup>



**Scheme 5.** IAC reaction to access tetracyclic heterocycles related to the erythrin core.

**Table 4.** IAC cyclisation to synthesise tetracyclic heterocycles using the 3D printed polypropylene reactor.

Entry	Cyclisation precursor	Product	Yield [%]
1			45
2			54

We have previously demonstrated that this Lewis acid mediated domino cyclisation process, which facilitates the simultaneous formation of the B and C ring of the erythrina core **43** leads to the formation of a single diastereoisomer of the product **44**.<sup>19</sup> Pleasingly, upon cyclisation, the tetracyclic products **44** and **46** were also obtained as single diastereoisomers in excellent yields which were comparable to reactions carried out in the microwave.<sup>19</sup> As such they represent a facile approach to the scalable synthesis of complex heterocycles using the 3D printed polypropylene reactors.

In conclusion, we have designed, developed and 3D printed a low-cost custom-made polypropylene column reactor that was fitted in an existing FlowSyn continuous flow reactor system. We demonstrated that it is resistant to solvents such as DMF and dichloroethane and that it is capable of being used in  $S_NAr$  reactions as well as to access substituted bicyclic heterocycles and complex tetracycles related to natural products. As such, it represents an excellent demonstration of the potential of developing and using bespoke low-cost 3D printed reactors in synthetic chemistry. Further studies on additional reactors are currently under way in our laboratory and will be reported in due course.

## Acknowledgements

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**Keywords:** 3D-printing, continuous-flow, reactionware, polypropylene, heterocycles.

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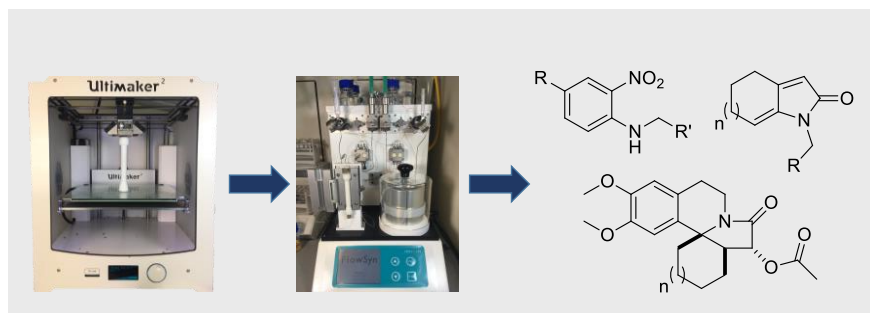
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Zenobia Rao<sup>[a]</sup>, Bhaven Pate<sup>[a]</sup>,  
Alessandra Monaco<sup>[a]</sup>, Zi Jing Cao<sup>[a]</sup>,  
Marta Barniol-Xicota<sup>[b]</sup>, Enora Pichon<sup>[a]</sup>,  
Mark Ladlow<sup>[c]</sup>, Stephen T.  
Hilton<sup>\*[a]</sup> Author(s), Corresponding  
Author(s)\*

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**3D Printed Polypropylene Continuous-  
Flow Column Reactors: Exploration of  
Reactor Utility in S<sub>N</sub>Ar Addition  
Reactions and the Synthesis of  
Bicyclic and Tetracyclic Heterocycles**

Low-cost inert polypropylene (PP) continuous flow reactors were designed and 3D printed for use in a FlowSyn continuous flow reactor. Reactor utility was explored in reactions ranging from S<sub>N</sub>Ar addition reactions through to formation of complex heterocycles. It was shown that they are an inexpensive source of reactors for continuous flow, facilitating the synthesis of a range of heterocycles.