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A Machine-Assisted Flow Synthesis of SR48692: A Probe for the Investigation of Neurotensin Receptor-1

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Abstract: Here we report the direct comparison of a conventional batch mode synthesis of Meclinertant (SR48692, **1**), a neurotensin receptor-1 antagonist, with its machine-assisted flow chemistry alternative. By using these enabling tools, combined with solid-supported reagents and scavengers, many process advantages were observed. Care, however, must be taken not to convert these techniques into expensive solutions to problems that do not exist.

Keywords: batch processes · flow chemistry · medicinal chemistry · organic chemistry · synthetic methods

Introduction

The discovery and development of new pharmaceutical substances is a major scientific priority for society. It involves multiple stages and can be an expensive process requiring the combined workings of scientists from many disciplines, spanning medicinal chemists to clinicians. Chemical synthesis is one of the most challenging aspects of this discovery process and manifests itself in nearly every stage of development. In the early phases of hit-to-lead and lead optimisation a quick and versatile synthetic route is needed for preparing a large number of compounds. Nevertheless, later on, molecules have to be made on larger scale for toxicology where there is the challenge of designing a scalable, reliable and robust process for clinical studies and eventual commercialisation.[1]

Over the years, chemists have improved tremendously many of the methods used in organic synthesis. For example, the development of transition-metal mediated transformations and asymmetric catalysis have expanded the range of molecules that can now be accessed. By way of contrast, the technology and many of the tools used to perform synthetic operations have remained more or less constant. Although batch-mode working is the most common manner of conducting reactions and subsequent downstream manipulations, there are many advantages in augmenting this with modern enabling technologies. Indeed, all components of a chemical process, such as reagent delivery, mixing, heating, analytical monitoring, quenching, work-up and finally purification can affect the overall success of the reaction and consequently all could benefit from improvement.

Recently, machine-assisted protocols have been influencing the way that molecules are being prepared.[2] In particular our group and others are addressing some of the recurring challenges that face organic synthesis by providing simpler and more efficient processing tools. In order to achieve this, we have been evaluating the utility of flow-based chemical synthesis. Under a dynamic flow regime mixing and heat transfer can be controlled more accurately[3] and the use of solid-phase reagents and catalysts can facilitate the purification as an in-line integrated process.[4] The importance of monitoring devices for learning and understanding these processes cannot be underestimated. Advanced systems are now available for detailed studies of each component of a reaction pathway.[5] Additionally the use of flow technologies has helped minimise tedious downstream processes (work-up, extraction and purification)[6] while gas-liquid flow reactors have changed the way we handle gases in the research environment.[7] Machines can assist in almost every aspect of the synthesis process and can even help in the integration of chemical synthesis and biological screening, which aids the discovery process.[8] Our group has special interest in using and developing these new methods to streamline the routes to new medicinal agents.[9] However, when developing new tools care must be taken to avoid creating technology for the sake of technology. To quote George M. Whitesides:[10]

> "*… the devices that have been developed have been elegantly imagined, immensely stimulating in their requirements for new methods of fabrication, and remarkable in their demonstrations of microtechnology and fluid physics, but they have not solved problems that are otherwise insoluble.*"

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Neurotensin (NT) is a neuropeptide which can be found in the nervous system and peripheral tissues. NT displays a wide range of biological effects and is considered a promising target for drug discovery.[11] It has important roles in the pathogenesis of Parkinson's disease.[12] Additionally, NT has been shown to be effective in inhibiting pro-proliferative and pro-survival signalling in colon, pancreatic and prostate cancer cells.[13] Recently, NT and its analogues have been investigated as potential radiosensitisers in prostate cancer cells.[14]

SR48692, Meclinertant (**1**), developed by Sanofi–Aventis, is a selective neurotensin probe (Figure 1). This non-peptide antagonist binds to the neurotensin receptor-1 (NTR-1; K_i = 2.6(±0.2) nM) and inhibits the downstream effects associated with this receptor stimulation, such as EGFR and Src activation.[15] To date however, only one poorly documented synthesis of SR48692 has been reported.[16]

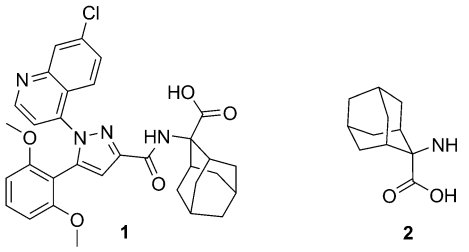


Figure 1. Chemical structure of Meclinertant (**1**) and amino acid **2**.

Our work began, therefore, with the development of a new procedure for the preparation of the amino acid (**2**), which was recently reported.[17] Here, we make a direct comparison of the reported synthesis of SR48692 (Meclinertant) and evaluate the advantages of machine-assisted flow procedures over the conventional batch processes. In particular, we report on how flow chemistry can assist in overcoming difficulties encountered in batch mode and also demonstrate that these new concepts can be telescoped together to provide even higher levels of efficiency throughout the synthesis of SR48692 (**1**).

Results and Discussion

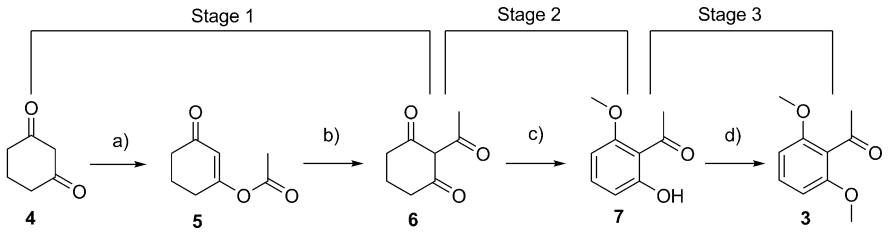
For the flow preparation of SR48692, it was decided to adopt an approach similar to that reported by Sanofi–Aventis.[16] It is important to emphasise here that this work was not undertaken as validation of the synthetic route but as the application of new tools to solving problems that chemists face in everyday chemical synthesis. The ultimate goal was therefore to evaluate how enabling technologies could be applied systematically to improve each step of this existing route.

The first general issue to address was the availability of appropriate starting materials. While it is true in general that starting from advanced commercially available compounds can accelerate a project, the cost, number of steps and the robustness of the selected chemistry at scale are also key criteria when taking a more holistic view. More importantly, having a reliable and cheap synthetic route to the starting material, can allow diversification and preparation of libraries of compounds when analogues are needed for evaluation. Flow chemistry is well suited to scaling processes to deliver quantities of building blocks, this is particularly effective when multiple reaction steps can be telescoped together into a single flow process.[6,9d,17,18]

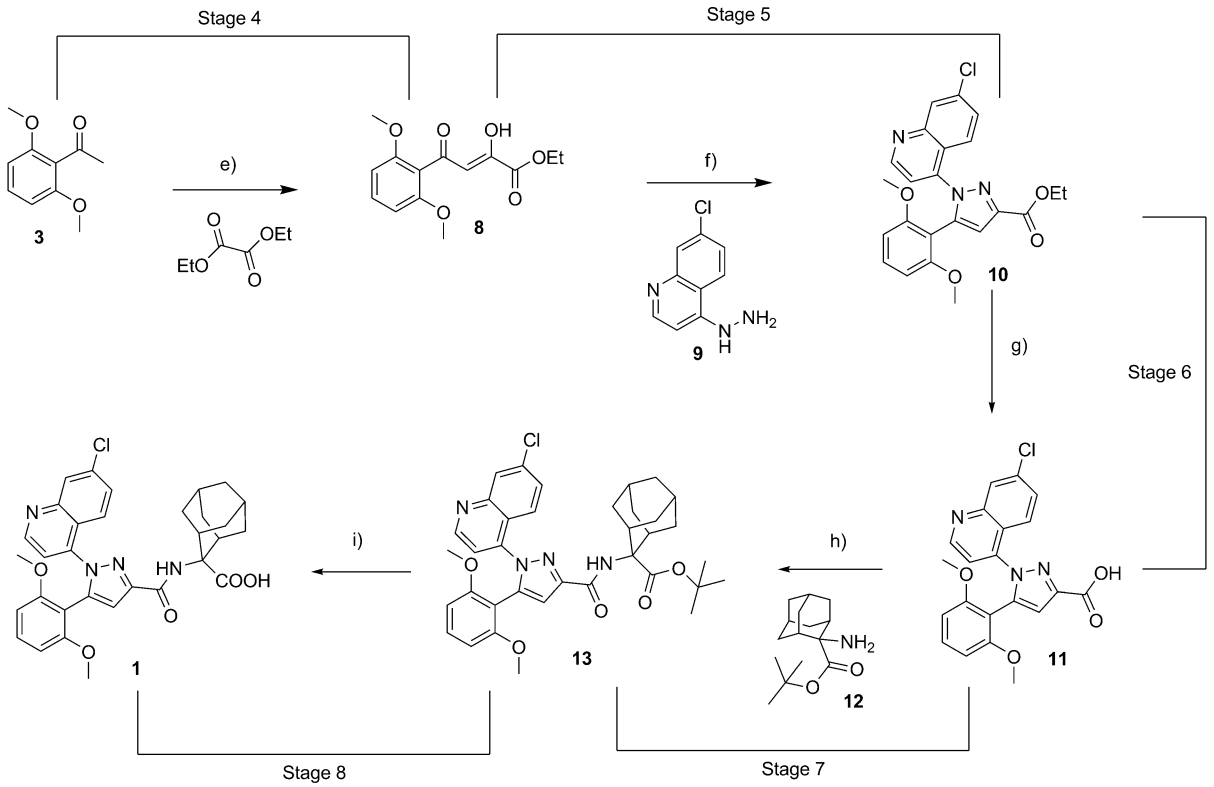
In terms of overall plan, we envisaged that ketone **3**, which is commercially available, could best be obtained from cheap starting materials using machine-assisted procedures (Scheme 1). The route commences with an O-acylation of cyclohexa-1,3-dione (**4**), which is subsequently converted to the triketone **6** via rearrangement. Iodine in MeOH effects oxidation to aromatise the triketone intermediate **6** to the monomethoxyacetophenone (**7**). A final methylation step using dimethyl carbonate and 1,2-dimethylimidazole furnishes the desired dimethoxy acetophenone (**3**). Not only was this route more cost effective than purchasing acetophenone **3** but it could also give the opportunity to diversify the phenolic substitution pattern for later analogue preparation.

The acetophenone derivative **3** is further elaborated in the total process by condensation with diethyl oxalate and combined with hydrazine to yield the pyrazole precursor **10**. Uniting compound **10** with the commercially available hydrazine **9** followed by hydrolysis of the pendant ester of **10** gave compound **11**. This material was directly coupled with the protected amino acid **12** to form SR48692 (Meclinertant, **1**) after deprotection (Scheme 2). Here we evaluate and discuss whether new technologies can have a positive impact on each of the steps of this synthesis of SR48692 when compared to the conventional batch route.

Stage 1: cyclohexadione acylation and development of a monolithic reactor: The route commenced with the O-acylation of diketone **4**. While the batch reaction can be performed on milligram-scale without difficulties, scaling up the



Scheme 1. Synthesis of acetophenone **3**. Reagents and conditions: a) acetyl chloride, DIPEA, toluene; b) DMAP (**M1**), toluene; c) iodine, methanol; d) DMI, DMC, methanol.

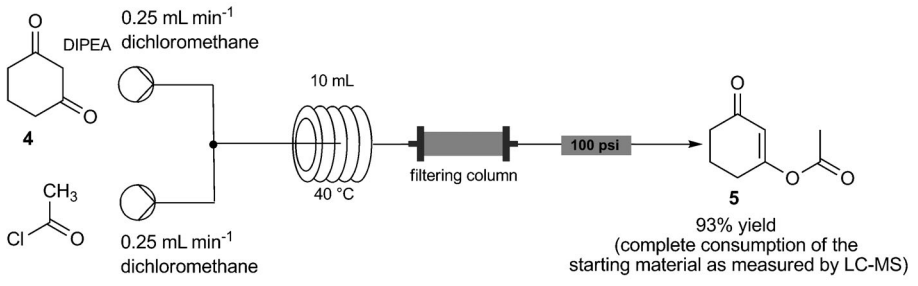


Scheme 2. Synthesis of Meclinertant (**1**). Reagents and conditions: e) NaOEt, ethanol; f) H_2SO_4, DMF; g) KOH, THF, H_2O; h) triphosgene, DIPEA, DCM; i) QP-SA, DCM

procedure past 50 mmol gives rise to a rapid increase of the reaction temperature, which is difficult to control and results in by-product formation. This required careful cooling along with the slow addition of the acetyl chloride to avoid reaction runaway and the formation of multiple side-products. Flow chemistry can therefore offer an immediate advantage. Simply introducing the diketone and the base solution from one pump, with the acetyl chloride solution delivered from a second pump at 0.25 mL min^{-1}, into a 10 mL reactor maintained at 40 °C controlled the exothermic process and resulted in *complete consumption of* **4** to give the O-acylated product **5** in high purity. This enabled us to prepare the product routinely on a 130 mmol scale after a simple aqueous acid wash (Scheme 3). The handling of exothermic reactions when conducting larger scale chemistry is a well-documented advantage of flow chemistry and proved to be beneficial in the chemistry used here.

The rearrangement of O-acylated diketone **5** to the triketone **6** is reported employing $AlCl_3$.[19] This Lewis acid is toxic and corrosive and the inevitable acid work-up is problematic when processing large amounts of material, especially due to the significant quantities of aluminum salts produced. Alternatively dimethylaminopyridine (DMAP) catalysed rearrangements of *O*-acyl to *C*-acyl derivatives have also been described in the literature.[20] However, most of these procedures require a prolonged reaction time of at least 12 h. Indeed, in our hands the batch reaction on 1 mmol scale using 20 mol % of soluble DMAP delivered full conversion, overnight, at ambient temperature. Interestingly, however, increasing the temperature to 120 °C led to completion reaction within 4 h on a 2 mmol scale.

We therefore speculated that a heterogeneous, supported DMAP catalyst could significantly improve this process. DMAP has well-known toxicity concerns so use of a poly-



Scheme 3. Synthesis of *O*-acyl derivative **5**.

mer-supported DMAP version would simultaneously address safety and recycling issues. Secondly, heating a large flask at 120 °C in batch mode can consume large amounts of energy. More importantly, less than ideal heat transfer in batch can lead to low conversions and by-product formation.

Initially therefore we investigated the use of commercially available polymer-supported DMAP under the batch conditions. As suspected, we discovered that increasing the amount of starting material prolonged the reaction times: starting from 100 mmol of *O*-acyl **5** derivative, complete consumption of the starting material was only possible after 5 days at 120 °C (using 3 mol % of PS-DMAP). This was likely due to the low accessibility of the functional sites within the polymer beads. We therefore saw this as an opportunity to use another enabling method to increase the substrate to catalyst interactions under a flowing regime. Our group has been involved for several years in the development of monolithic flow reactors for a number of synthesis applications. The use of monolithic reactors has been proven to expedite flow processes and overcome many synthetic problems, such as waste disposal and by-product formation.[21] A polymeric monolith is a single continuous piece of porous material prepared by precipitation polymerisation of monomers and a cross-linker within glass cartridges, in the presence of a porogenic mixture (Figure 2).[20]

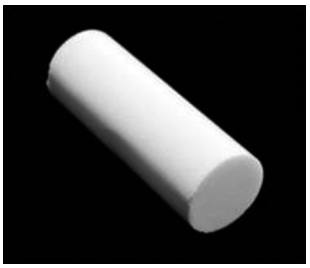
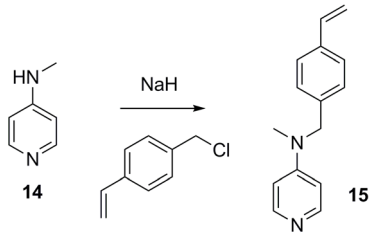


Figure 2. Photographic image of a monolithic polystyrene-based reactor.

Monolithic reactors are akin to macroporous resins and have a permanent porous structure that, unlike gel-type beads, are independent of the nature of the solvent. They can be made on existing flow chemistry equipment in a range of shapes and sizes.[22] Their porosity can be fine-tuned to allow optimum flow of solvents and reagents at reasonable pressures. As they are highly cross-linked, monolithic polymers do not exhibit swelling and shrinking with different solvents, and most importantly they operate through convection flow mode instead of diffusion, allowing molecules to interact with the functional sites more efficiently.[23] Another obvious advantage of monoliths compared to beads is the lack of solvent channelling, which can severely affect the efficiency of packed bed reactors when used in flow. Considering these potential gains, the generation of a monolithic reactor containing a DMAP catalyst was considered to be beneficial to our program. Preparation of the necessary monomer (**15**) was easily achieved through a simple one-pot reaction (Scheme 4). Using a mixture of divinylbenzene (15 % w/w), styrene (15 % w/w) and monomer (**15**; 10 % w/w) in the presence of dodecanol (60 % w/w) as



Scheme 4. Synthesis of monomer **15**.

porogen and aza-bis(cyclohexanecarbonitrile) (ACHC, 2 mol % excluding the porogen), a monolith with very good porosity and physical robustness was obtained which filled the glass reactor as a white amorphous polymeric structure (Figure 3). After flushing the polymer (to elute the porogen), the monolithic reactor was ready to use. The O-acylated substrate (**5**) was then passed through the heated reactor. Under optimised flow conditions, two grams (17.8 mmol) of the precursor (**5**) were processed through the monolithic reactor **M1** heated at 100 °C, delivering the solution of triketone **6** at a flow rate of 50 μL min^{-1} with a residence time of 20 min and in high purity (Scheme 5).

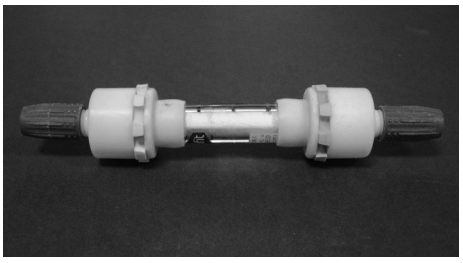
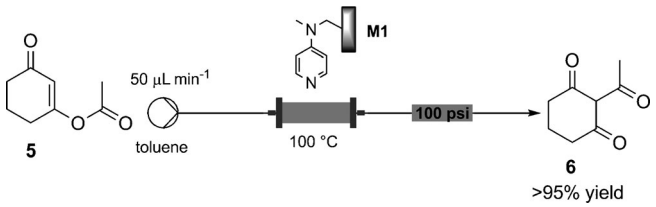


Figure 3. Monolith **M1** inside a glass column.



Scheme 5. Rearrangement step using the DMAP monolithic reactor in flow.

We were pleased to find that this small flow reactor with only 6.6 mm internal diameter and 5 cm length could be so productive. We argue that the improved heat transfer within a small mesofluidic reactor combined with accelerated mixing, and a high effective catalyst loading helped by con-

vection within the monolith, reduces the required reaction time to only 20 min.

To further examine the effect of the monolithic structure, we packed commercially available polymer-supported DMAP in a column of the same size and performed reactions at different temperatures and flow rates. In all cases the conversion was low (less than 30%) at temperatures below 80°C, even when applying very low flow rates. Increasing the temperature led to blockages of the system due to the excessive swelling of the polystyrene support. Attempts to reduce the density of the column packing by adding sand were unsuccessful. Overall the commercial product in our hands was far inferior to the monolithic material for this reaction.

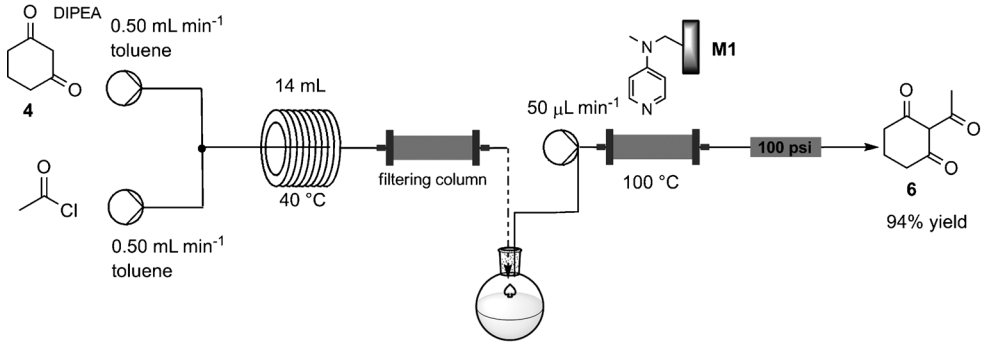
A further known advantage of flow processing compared to batch is the ease by which sequential reactions can be coupled together to generate multistep sequences.[24] Having found that the use of toluene as solvent is of particular importance for the rearrangement using the DMAP monolith, we were pleased to find that the O-acylation reaction could also be run in toluene. Therefore, the reactor output stream from the acylation step was filtered in-line to eliminate any solid particulates and directed into the glass column containing the DMAP monolith (**M1**). Collection and concentration of the final solution gave the triketone **6** as a telescoped product, in 94% yield on a 90 mmol scale (Scheme 6).

Stage 2: iodine oxidation: Iodine in MeOH has been successfully employed for the transformation of a number of different 2-acyl-1,3-cyclohexadiones, giving access to acetophenones in good yields.[25] This reaction was successfully reproduced in our laboratory on 1 mmol scale in batch mode. However, again upon scaling the reaction, a wide range of by-products, such as deacetylated anisole derivatives and iodinated products, were also formed. Here as before, flow chemistry presented an opportunity to circumvent these problems. The presence of these by-products on large scale can be attributed to the accumulation of hydroiodic acid. In flow, however, such an elevated concentration of hydroiodic acid in contact with the product or starting materials for an extended period is minimised.

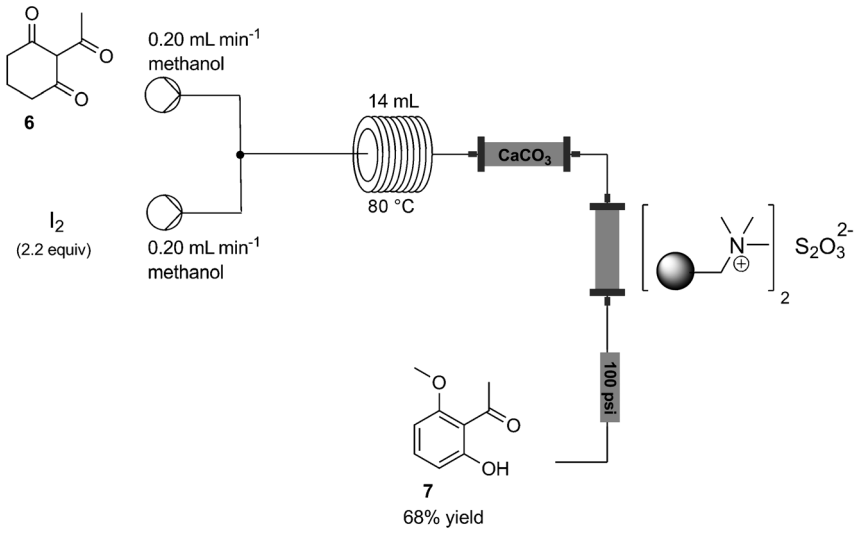
After screening various conditions, the final flow set-up used a stream of **6** in MeOH, which was combined with a MeOH solution of iodine, both delivered at a flow rate of 0.20 mL min^{-1}. The united stream was reacted thereafter in a tubular coil reactor (14 mL) at 80°C; the resulting solution was directed to a glass column packed with a mixture of calcium carbonate and sand to scavenge the hydroiodic acid formed. The sand in the column acted as a diluent, and reduced rapid increases in pressure due to an associated release of CO_2. The exiting flow stream from the calcium carbonate column was subsequently directed to another device packed with thiosulfate functional beads intermixed with Celite® to capture the excess iodine (Figure 4).[26]

Figure 4. Thiosulfate beads mixed with Celite® for the removal of excess iodine.

The final output stream was collected and concentrated in vacuo to obtain the monomethoxyacetophenone **7** in 68% yield and better than 99% purity (Scheme 7). This lower-than-ideal yield was thought to be a result of the interaction of the phenolic product (**7**) with the calcium carbonate, and hence material was retained on the column. Unfortunately, alternative strategies to remove the hydroiodic acid formed during the reaction proved more detrimental, leading to a further drop in yield. Nevertheless, the flow set-up still presented a genuine improvement compared to the batch process: the pure product was obtained with minimum down-



Scheme 6. Telescoped acylation and rearrangement in flow using the monolithic DMAP reactor **M1**.



Scheme 7. Iodine-mediated aromatisation of **7**.

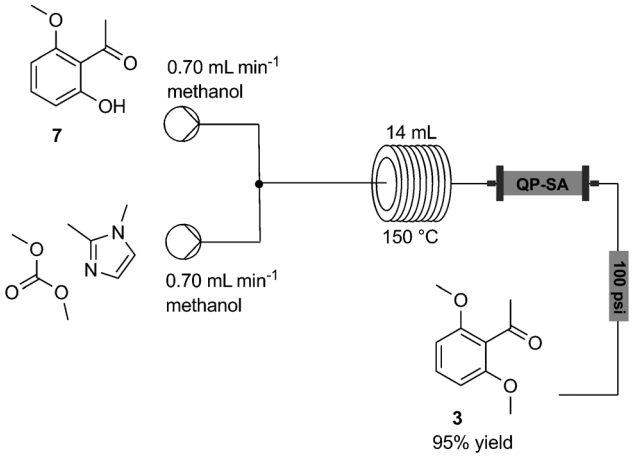
stream manipulations and no chromatography was required (unlike in the batch process).

Stage 3: methylation and reaction telescoping: Conventional methylation procedures usually rely on highly reactive and toxic reagents, such as methyl iodide. One way to avoid the high toxicity in vivo is to use less reactive reagents and to perform the required methylation at high temperatures. For example, the recently reported methylating mixture of dimethylcarbonate (DMC)[27] and 1,2-dimethylimidazole (DMI) is far less toxic to humans. DMC is considered a green solvent[28] and DMI is a poor nucleophile at ambient temperature.

A batch reaction for methylating the resorcinol-based starting material **7** using DMI/DMC was carried out at 120 °C in a high boiling solvent (DMF). Although this worked efficiently it obviously creates problems, not the least of which is the difficulty of removing it at a later stage. Again, a flow-derived process should be of immense help in circumventing this issue.[2] In a flow reactor we conveniently switched the solvent to MeOH and easily achieved a temperature of 150 °C by using a 250 psi back-pressure regulator. In laboratory scale synthesis, it is often argued that the same superheated conditions can be achieved using sealed reactors.

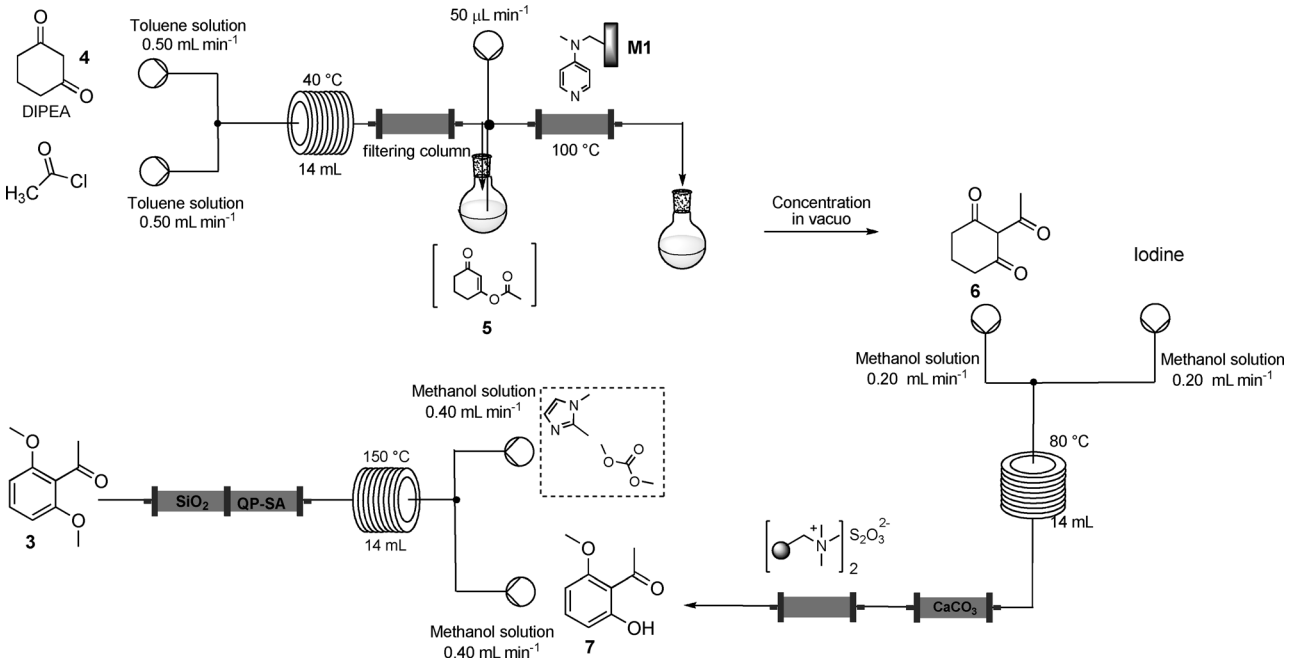
However, it should be noted that a pressurised flow reactor is essentially a monophasic closed system whereas a batch reactor possesses a headspace. In practice this means it is difficult to achieve 150 °C with MeOH in batch even using a 400 W microwave reactor when a reasonable headspace was provided to avoid extreme pressures.

When transferring this set-up to flow, a solution of acetophenone **7** in MeOH (flow rate 0.7 mL min^{-1}) and a solution of DMI in DMC (flow rate 0.7 mL min^{-1}) were combined in a T-piece and then directed to a perfluoroalkoxy polymer (PFA) tubular flow coil (14 mL) heated at 150 °C to obtain the methylated product (**3**) in quantitative yield (95 % isolated yield) after concentration and a trivial extraction procedure. Since DMC is unstable to strong acid and DMI can be retained by very strong acid media, an immobilised acid scavenger (QP-SA)[29] was incorporated to complete an in-line workup (Scheme 8). We were encouraged that MeOH proved to be effective in this reaction as this provided an opportunity for telescoping this and the previous aromatisation step. Following the procedure outlined earlier, the material (a solution of compound **6** in MeOH) from the aromatisation step was then directed into a second reactor where it was combined with the solution of DMC and DMI. Eventually, we were able to achieve a 63 % yield of ketone **3** over the last two steps, employing an overall flow rate of 0.80 mL min^{-1} for the final methylation step (Scheme 9).



Scheme 8. Methylation in flow using DMC/DMI.

Stage 4: the Claisen condensation: The Claisen condensation reaction between acetophenone **3** and diethyl oxalyl ester is a straightforward process in batch. Simply stirring the two reagents in the presence of sodium ethoxide at room temperature for 3 h led to an isolated yield of around 60 % of the 1,3-dicarbonyl product (**8**). Screening a number of conditions under microwave irradiation indicated that the reaction could be driven to completion after just 30 min at 80 °C, using EtOH as the solvent. Superheating the reaction therefore in a flow reactor might provide a faster alternative to batch. However, the reaction set-up for the flow process



Scheme 9. Telescoped acylation and rearrangement in flow using the monolithic DMAP reactor.

proved initially troublesome due to blockages caused by precipitation of the product. It was noticed that with higher concentrations of sodium ethoxide solution this problem was amplified and at lower concentration the reaction failed to proceed to completion. It was therefore concluded that, from a process point of view, no immediate advantage could be gained by transferring this step to flow. Nevertheless, we saw this as an opportunity to evaluate an alternative back-pressure regulator designed within our group for handling of reaction slurries in flow (Figure 5).

This device consists of a stainless-steel tank, which is pressurised with a house nitrogen line to maintain up to 5 bar back-pressure in the flow system. It has been designed specifically to deal with the problem of solid accumulation in conventional spring-based back-pressure regulators and proved to be effective in handling thick slurries of **8** in flow (Figure 6). A detailed exploded diagram version of this device and explanation of the working mechanism are presented in the Supporting Information.

In order to transfer this key step to flow, a solution of acetophenone **3** and diethyl oxalyl ester in ethanol (flow rate 1.20 mL min^{-1}) was combined in a T-piece with a 1 M solution of sodium ethoxide in ethanol (flow rate 1.20 mL min^{-1}) and heated to 115 °C in a 52 mL PFA coil (1/8″ o.d.). This wider i.d. was essential to avoid blockage within the PFA reactor. The output from the reactor was attached to the pressure chamber, which was under 5 bar pressure, allowing the reaction to be run continuously *without any precipitation or blockage problems* (Scheme 10).

Stages 5 and 6: pyrazole core synthesis and hydrolysis: The reaction between the commercially available hydrazine **9** and the 1,3-dicarbonyl product (**8**) from the previous synthe-

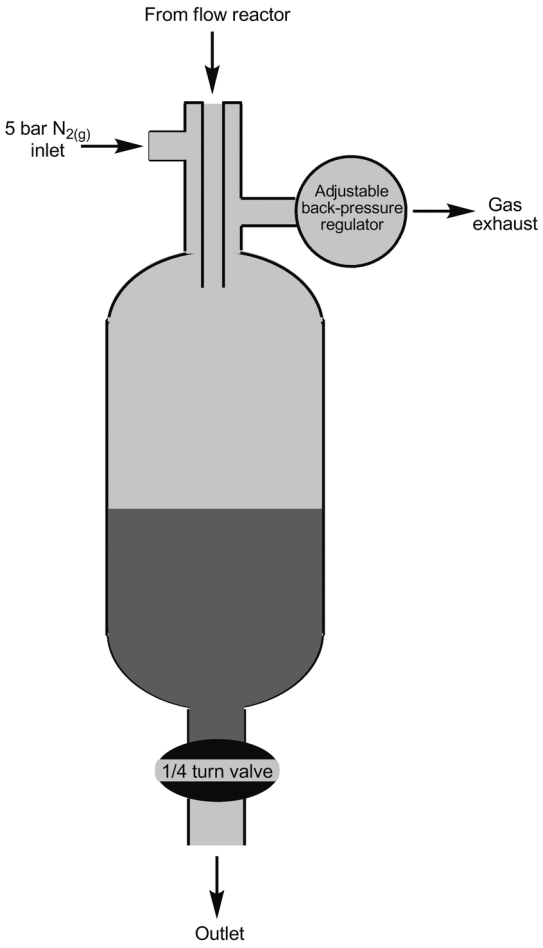


Figure 5. In-house designed back-pressure regulator for handling chemical slurries.

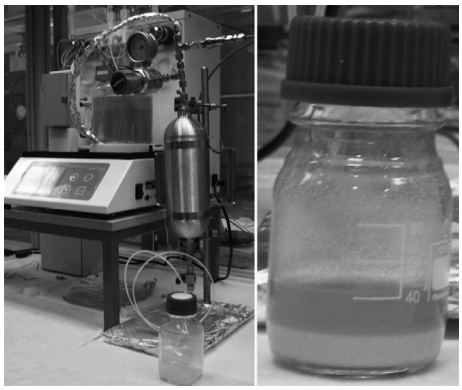
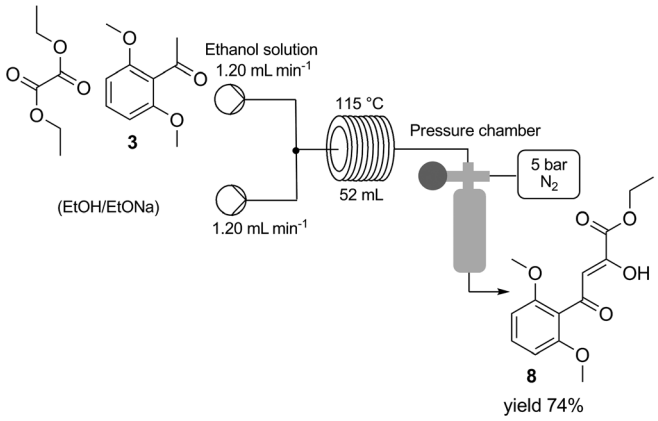


Figure 6. Uniqsis Flowsyn connected to our in-house "pressure chamber".



Scheme 10. Claisen rearrangement using the in-house "pressure chamber".

sis step was evaluated using microwave irradiation in batch. DMF proved to be the most effective solvent. The reaction went to completion under microwave conditions when heated to 140 °C for 2 h in the presence of sulfuric acid. Scaling the reaction up under batch conditions also proved successful, albeit with a drop in yield from 87 to 70 %. However, as stated above, there are problems associated with performing reactions in DMF at high temperatures in batch mode, especially considering the eventual scale-up process in a system with headspace. Again, here we considered the advantages that flow could provide over batch in terms of safety, reliability and robustness of the process. Under flow conditions, a mixture of hydrazine **9** and 1,3-dicarbonyl **8** in DMF were delivered to a T-piece to meet a solution of concentrated sulfuric acid in DMF. The mixture was then heated in a 52 mL PFA coil (1/8″ o.d.) at 140 °C. Collection, extraction and concentration of the output afforded the pyrazole ester **10** in a very good yield (89 %) and purity on a 3.58 mmol scale, without requiring the chromatography needed in the batch-mode process (Scheme 11). While in this example, at the scale that the reaction was performed (3.58 mmol), both batch and flow would be equally effective, when the work-up and purification steps are considered, the flow platform again proved to be advantageous.

We recently reported on a camera-controlled liquid–liquid extraction system to aid work-up following a flow synthesis.[6] An alternative solution to the problem of continuous liquid–liquid extraction is to use a universal membrane extraction device (Figure 7).[30] This allowed for a simple inte-

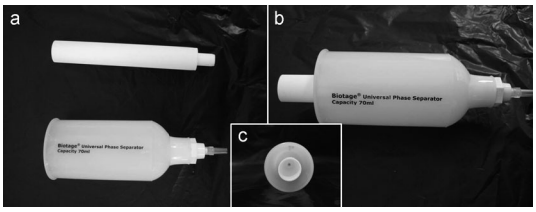
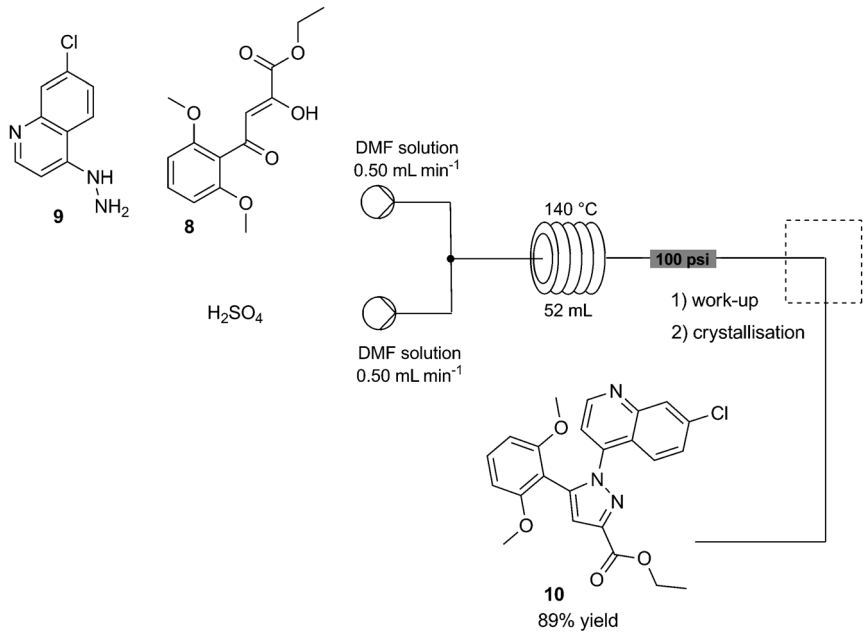


Figure 7. Biotage® universal phase separator; kit form: a) as supplied, and b) assembled.

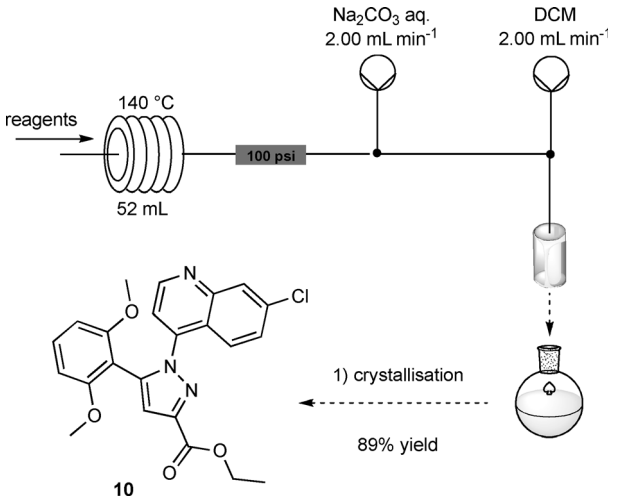
gration of the unit into the flow set-up to facilitate continuous work-up.

The final flow experimental set-up was arranged in a way whereby the product stream of the reactor was further



Scheme 11. Knorr pyrazole condensation to obtain **10**.

merged, first with an aqueous stream of sodium carbonate and then at another T-piece with a stream of dichloromethane. The resulting biphasic output was dispensed into a semipermeable membrane, where the hydrophilic membrane allowed passage of the organic phase whilst retaining the aqueous washings, effecting a simple and direct liquid–liquid extraction (Scheme 12).

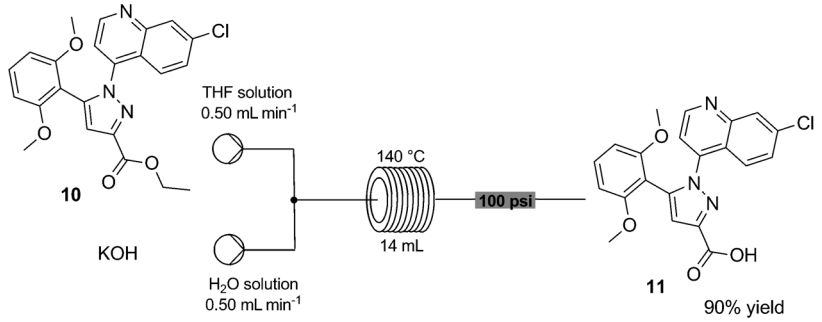


Scheme 12. Knorr pyrazole condensation to obtain **10**, and automated work-up using a semipermeable membrane system.

This proved to be a very efficient method of working-up this reaction sequence with minimal user intervention.

Attempts to telescope the extracted solution of ester **10** directly into a hydrolytic cleavage step were unsuccessful, possibly because of incompatibility of residual DMF with the hydrolysis conditions. The batch protocol proved to be a simple and efficient way to achieve hydrolysis. Indeed, refluxing a solution of pyrazole ester in THF/H_2O resulted in a 90% yield of the acid after just concentration and precipitation with HCl (3 M) aqueous solution. Although trivial, we envisaged this step could be run in flow where the efficient micro-mixing and heat transfer could provide a faster reaction and a safer system, especially when scaling up the process.

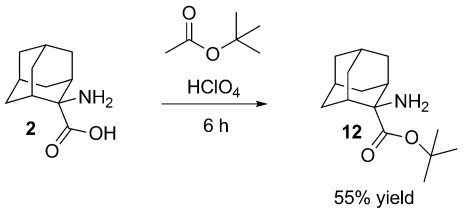
Indeed, the flow protocol allowed the reaction to reach completion after just 14 min, while the batch mode required much longer reaction times (1.5 h). We then established a flow procedure for the hydrolysis of the pyrazole ester by reacting it as a THF solution with 3 M aqueous KOH united via a T-piece (flow rate 0.50 mL min^{-1} for each pump). The mixture was progressed into a 14 mL PFA coil reactor maintained at 140 °C. The output stream was collected and the



Scheme 13. Hydrolysis step in flow.

THF was removed, in vacuo. Addition of 3 M aqueous HCl solution gave a precipitate of acid **11** at pH 3 which could be isolated by filtration in the normal way (Scheme 13).

Stage 7: synthesis of the protected amino acid and amide coupling: Our initial attempts to achieve the coupling between the carboxylic acid **11** and the amino acid **2** partner closely followed the route established by Sanofi–Aventis.[16] The pyrazole acid was activated as its acid chloride before introducing the adamantane amino acid **2** into a third stream. The first problem encountered when trying to translate this process into flow was the extremely poor solubility of amino acid **2**. Attempts to solubilise the amino acid in dichloromethane with an equivalent of DIPEA were unsuccessful. The amino acid could be solubilised in neat pyridine or DIPEA but using these solutions in flow resulted in poor conversions (45–47% as determined by LC-MS). Ultimately it was necessary to protect the amino acid as its *tert*-butyl ester to increase its solubility. The protection of the amino acid was performed in batch. We found this process to be low yielding (55% yield) but it provided sufficient quantities of the protected amino acid for us to proceed with the synthesis of SR48692 (Scheme 14). The insoluble nature of the adamantane amino acid starting material meant that transferring the protection process to flow was not practical.



Scheme 14. Protection of the amino acid **2**.

The final amide bond formation in batch is a well-studied transformation. To find the desired conditions various activating agents were investigated in a microwave reactor. The activated carbonyl which formed was quenched after the 30 min by addition of excess ethanol to allow simple analysis by LC-MS. Thionyl chloride, Ghosez reagent (1-chloro-

N,*N*,2-trimethyl-1-propenylamine), propylphosphonic anhydride (T3P) and 1,1′-carbonyldiimidazole (CDI) were all tested and found to be poor activators of the acid (0 to 36% conversion by LC-MS). More success was found using phosgene generated by the addition of catalytic pyridine to a dichloromethane solution of triphosgene (92% conversion by LC-MS after just 10 min at ambient temperature). The high toxicity and volatility of phosgene makes its direct use in chemical synthesis a potential challenge. It is generally preferable to generate phosgene in situ from other less hazardous reagents, such as triphosgene.[31]

The batch reaction was difficult to optimise. Triphosgene was activated with 2,6-lutidine to provide a controlled release of phosgene and then treated with the acid **11**; samples of the reaction mixture were followed by LC-MS and NMR analyses after quenching with ethanol. The protected amino acid **12** was added to obtain compound **13**. Despite our attempts to optimise these batch conditions, we were aware that the main drawback of this process was hazards associated with generation and handling of phosgene gas.

Recently Fuse et al. demonstrated that a safe and reliable process for this type of coupling could be made by containing the phosgene generated during reaction in a sealed fluidic system.[32] Inspired by this new protocol, a flow stream of triphosgene (0.037 M) in dichloromethane was combined with a second flow stream of DIPEA (0.01 M) in dichloromethane at a T-piece mixer (flow rate 0.2 mL min^{-1} per channel). The mixed solution was then passed through a 0.5 mL stainless steel heat exchanger at 100 °C to initiate nucleophilic decomposition of the triphosgene into phosgene. The solution then passed through a 2.5 mL stainless steel coil reactor to complete the formation of the acid chloride. A FlowIR™ inline infrared spectrometer[5b,c] was used to monitor the formation of phosgene without exposing the operator to this hazardous gas during analysis (Scheme 15).

A solution of pyrazole carboxylic acid **11** and DIPEA in dichloromethane was injected into the DIPEA/dichloromethane flow stream to react with the in situ generated phosgene yielding the corresponding acid chloride. Monitoring the reaction by infrared spectroscopy (observing a disappearance of the phosgene C–Cl stretch at 803 cm^{-1}, Figure 8) allowed an injection of a matching solution of the protected amino acid **12** to be timed to meet the plug of acid chloride as it travelled through the flow reactor. The combined reaction flow was directed into a 14 mL reactor coil, heated at 100 °C, undergoing amide coupling to afford **13**. The reactor output was collected into a flask containing

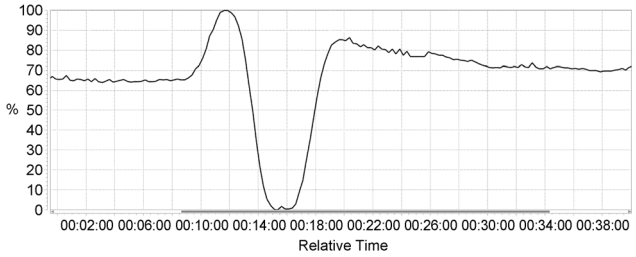
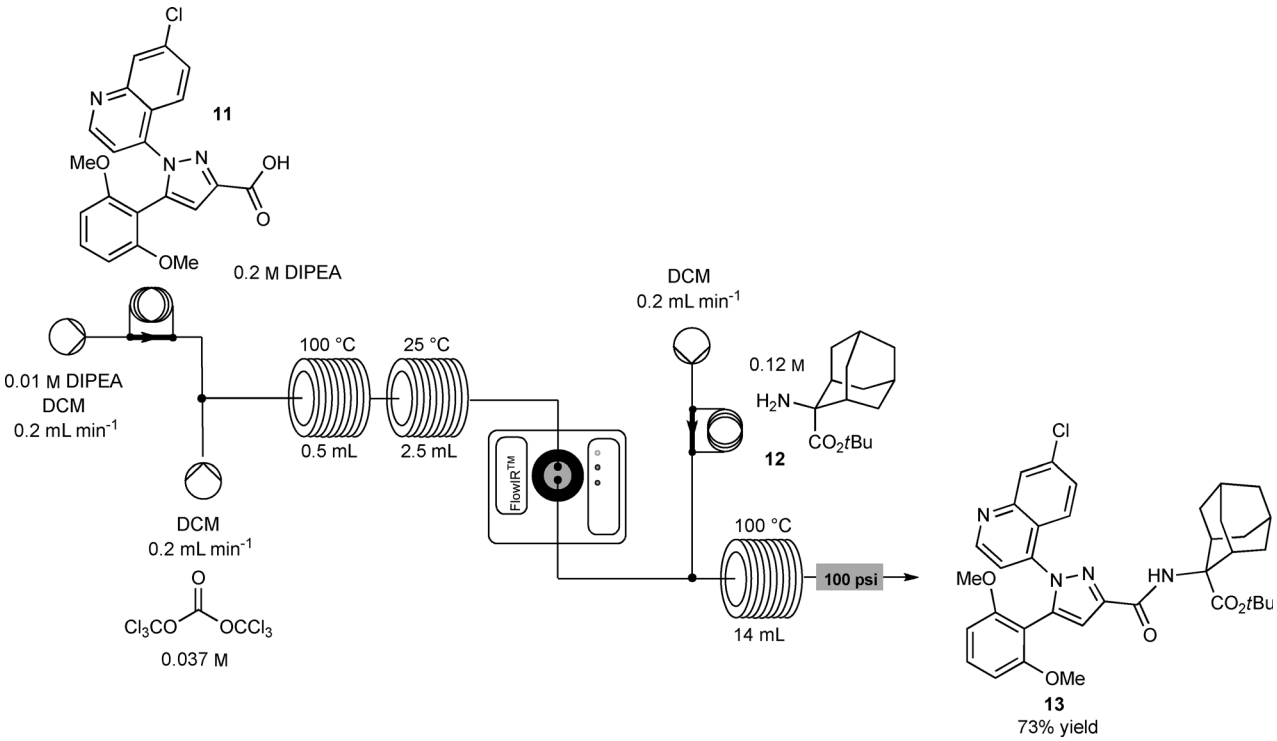


Figure 8. Trace showing the amount of phosgene (detected at 803 cm^{-1}) over time. The sharp drop in signal at 12 min clearly shows when the acid chloride **16** reaches the FlowIR detector.



Scheme 15. In-line monitoring in the synthesis of protected SR4692 (**13**).

saturated ammonium chloride to quench the reaction. Simple extraction with EtOAc and filtration through a pad of silica gel provided the *tert*-butyl ester **13** in 85% yield. Although the flow system provided a contained environment for the phosgene, care must be taken to ensure the reactor safety before performing these reactions.

Stage 8: deprotection and synthesis of Meclinertant (SR48692, 1): Stirring a dichloromethane solution of the crude product **13** with Quadrapure sulfonic acid (QP-SA) removed the *tert*-butyl protecting group, overnight, to generate **1**. This batch reaction, aided by an immobilised reagent, proved to be versatile. Since this was the last step in the synthesis, it was not performed on a large scale. However, if this was an objective a column packed with commercial QP-SA could be used to transform readily the reaction to flow mode.

Conclusion

The initial aim of this work was to impartially investigate whether enabling methods could accelerate a multistep synthesis project of high complexity. Although a batch process had been defined previously, we have clearly demonstrated that new technologies can help chemists overcome many synthesis issues. Flow chemistry has mastered exothermic events and controlled superheating of solvents efficiently as well as streamlining the synthesis by allowing reaction telescoping. It has also helped circumvent problems arising due to back mixing and accumulation of by-products. Furthermore, utilising polymer-supported reagents has simplified the downstream processing of reaction streams and has significantly enhanced the safety of reactions. In-line monitoring aided the tracking of hazardous intermediates. In one instance in-line extraction and phase separation improved downstream processing. In summary, we believe these new technologies, if used correctly can be powerful tools but care must be taken not to convert them to expensive solutions to problems that do not exist.

Experimental Section

General experimental section: ^{1}H NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer with the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm, [D_6]DMSO = 2.50 ppm). ^{1}H resonances are reported to the nearest 0.01 ppm. ^{13}C NMR spectra were recorded on the same spectrometers with the central resonance of the solvent peak as the internal reference ($CDCl_3$ = 77.16 ppm, [D_6]DMSO = 39.52 ppm). All ^{13}C resonances are reported to the nearest 0.1 ppm. DEPT 135, COSY, HMQC, and HMBC experiments were used to aid structural determination and spectral assignment. The multiplicity of ^{1}H signals are indicated as: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, or combinations of thereof. Coupling constants (J) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant. Infrared spectra were recorded neat on a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Unless stated otherwise, reagents were obtained from commercial sources and were used without purification. Laboratory reagent grade EtOAc, petroleum ether 40–60, and dichloromethane were obtained from Fischer Scientific and distilled before use. Unless stated otherwise, heating was conducted using standard laboratory apparatus. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator. Melting points were performed on either a Stanford Research Systems MPA100 (OptiMelt) automated melting point system and are uncorrected. High resolution mass spectrometry (HRMS) was performed with a Waters Micromass LCT Premier™ spectrometer using time of flight with positive ESI, or conducted by Mr. Paul Skelton (Department of Chemistry, University of Cambridge) on a Bruker BioApex 47e FTICR spectrometer using positive ESI or EI at 70 eV to within a tolerance of 5 ppm of the theoretically calculated value. LC-MS analysis was performed on an Agilent HP 1100 series chromatography (Mercury Luna 3u C18 (2) column) attached to a Waters ZQ2000 mass spectrometer with ESCi ionisation source in ESI mode. Elution was carried out at a flow rate of 0.6 mL min^{-1} using a reverse phase gradient of acetonitrile and water containing 0.1% formic acid. Retention time (t_R) is given in min to the nearest 0.1 min and the m/z value is reported to the nearest mass unit (m.u.). X-ray crystal structures were determined by Dr. John Davies (Department of Chemistry, University of Cambridge). CIF numbers are reported as part of compound characterisation. Elemental analyses within a tolerance of ±0.3% of the theoretical values were determined by Mr. Alan Dickerson and Mrs. Patricia Irele in the microanalytical laboratories at the Department of Chemistry, University of Cambridge. Unless otherwise specified all the flow reactions were performed in a Uniqsis Flowsyn flow platform.[33]

3-Acetyloxy 2-cyclohexen-1-one (5): *Batch reaction*: To a solution of 1,3-cyclohexandione (**4**; 2.0 g, 17.8 mmol) and DIPEA (4 mL; 23 mmol) in anhydrous toluene (30 mL), acetyl chloride (1.4 mL; 19.6 mmol) was added dropwise over 2 min. The reaction was stirred for 2 h at RT before the salts formed were filtered off. The organic fraction was extracted with EtOAc and washed with aqueous HCl (1N). The organic layer was dried over sodium sulfate, filtered and concentrated to afford the product as a yellow oil (yield 2.45 g, 15.89 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.75 (s, 1H), 2.42 (t, 2H, J = 6.9 Hz), 2.30 (t, 2H, J = 6.9 Hz), 2.21 (s, 3H), 1.94 ppm (m, 2H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 199.55 (C), 169.82 (C), 167.30 (C), 117.34 (CH), 36.61 (CH_2), 28.22 (CH_2), 21.16 (CH_2), 21.14 ppm (CH_3); FT-IR (neat): 2954, 1768, 1669, 1640, 1363, 1182, 1115, 1007, 919, 878 cm^{-1}; LC-MS: t_R = 1.21 min, m/z [M+H] = 154.48; HRMS (ESI): m/z calcd for $C_8H_{11}O_3^+$: 155.1110; found 155.1111.

2-Acetyl 1,3-cyclohexandione (6): *Batch reaction*: To a solution of **5** was added PS-DMAP (0.5 g, 3 mmol) and the mixture was microwave irradiated for 3 h. The reaction mixture was then filtered to remove the PS-DMAP and the solution washed with aqueous HCl (2N) and saturated brine. The organic fraction obtained was dried over sodium sulfate, filtered and concentrated to obtain (**5**) as a red oil (yield 2.30 g, 14.9 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 15.75 (s, 1H), 2.65 (t, 2H, J = 6.9 Hz), 2.61 (s, 3H), 2.48 (t, 2H, J = 6.9 Hz), 1.97 ppm (m, 2H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 203.05 (C), 198.69 (C), 195.38 (C), 113.18 (C), 38.55 (CH_2), 33.21 (CH_2), 28.74 (CH_2), 18.98 ppm (CH_3); FT-IR (neat): 2953, 1660, 1550, 1410, 1351, 1188, 1007, 919, 841 cm^{-1}; LC-MS: t_R = 2.62 min, m/z [M+H] = 155.35; HRMS (ESI): m/z calcd for $C_8H_{11}O_3^+$: 155.0708; found 155.0705.

2′-Hydroxy-6′-methoxy-acetophenone (7): *Batch reaction*: Iodine (2 equiv, 6.8 g, 26.9 mmol) was added to a solution of (**6**; 2.0 g, 13 mmol) in MeOH (30 mL) and the reaction mixture was heated under microwave irradiation for 9 h. The mixture was then passed through calcium carbonate and a polymer supported sulfite resin mixed with Celite®. The organic fraction obtained was concentrated to obtain (**7**) as yellow needles (yield 1.75 g, 10.5 mmol, 80%). M.p. 55–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 13.23 (s, 1H), 7.32 (t, 1H, J = 8.9 Hz), 6.55 (d, 1H, J = 8.9 Hz), 6.34 (d, 1H, J = 8.9 Hz), 3.90 (s, 3H), 2.67 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 205.17 (C), 164.65 (C), 161.55 (C), 136.09 (CH), 111.32 (CH), 101.15 (CH), 55.86 (CH_3), 33.66 ppm (CH_3); FT-IR (neat): 2944, 1628, 1608, 1483,1367, 1325, 1211, 1180, 1035,

962, 838 (m), 786 cm^{-1}; LC-MS: $t_R = 4.51$ min, m/z $[M+H] = 167.37$; HRMS (ESI): m/z calcd for $C_9H_{11}O_3^+$: 167.0708; found 167.070.

2′,6′-Dimethoxyacetophenone (3): *Batch reaction*: A solution of (**7**; 1 mmol, 0.166 g) and 1,2-dimethylimidazole (1.04 mmol, 0.1 g) in dimethyl carbonate (0.8 mL)/MeOH (0.8 mL) was microwave irradiated for 1 h at 160 °C. The reaction mixture was then passed through a QP-SA scavenger and the solution obtained was concentrated to obtain (**3**) as a yellow solid (yield 0.183 g, 0.96 mmol, 96 %). *Telescoped flow reaction*: A solution of 1,3-cyclohexadione (**4**; 10.0 g, 89.0 mmol) and DIPEA (12.5 mL, 97.9 mmol), 1.1 equiv; flow rate 0.50 mL min^{-1}, pump A) in toluene (30 mL) and a solution of acetyl chloride (6.5 mL, 91.0 mmol, flow rate 0.50 mL min^{-1}, pump B) in toluene (30 mL) were combined at a T-piece and then delivered through a 14 mL CFC PFA (1/8″ o.d.) heated at 40 °C (~14 min residence time). A 100 psi back pressure regulator was placed after the reactor. After exiting the coil, the flow stream was dispensed onto a filter mat to remove any particulates and the eluent was collected in a storage flask. The resultant solution was pumped through the monolithic reactor **M1** heated to 100 °C (residence time 20 min, flow rate 50 μL min^{-1}). After exiting the CFC the flow stream was collected and the solution concentrated in vacuo to give the triketone (**6**; yield 12.8 g, 83.8 mmol, 94 %). A solution of the material obtained (2.50 g, 16.09 mmol) in MeOH (30 mL; flow rate 0.20 mL min^{-1}, pump A) and a solution of iodine (8.00 g, 32.00 mmol) in MeOH (30 mL; flow rate 0.20 mL min^{-1}, pump B) were pumped through a CFC PFA at 80 °C after mixing at a T-piece. A 100 psi back pressure regulator was placed after the reactor. The output stream was then directly delivered to a scavenger cartridge containing calcium carbonate, sand and polymer supported thiosulfate (5 g).[30] The resultant solution was delivered (flow rate 0.40 mL min^{-1}, pump A) at a T-piece to meet a solution of 1,2-dimethylimidazole (2.10 g, 13.06 mmol) in dimethyl carbonate (30 mL; flow rate 0.40 mL min^{-1}, pump B) and reacted in a PFA CFC heated to 150 °C (residence time 14 min). A 100 psi back pressure regulator was placed after the reactor. After exiting the CFC the flow stream was directed to a polymer-supported sulfonic acid (QP-SA) cartridge and then silica. The collection and concentration of the solution gave the title compound (**3**) as a yellow solid (yield 1.81 g, 10.00 mmol, 62 %). M.p. 67–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.26$ (t, 1H, $J = 8.7$ Hz,), 6.55 (d, 2H, $J = 8.7$ Hz), 3.80 (s, 6H), 2.47 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 202.77$ (C), 156.76 (C), 130.63 (CH), 104.02 (CH), 55.88 (CH_3), 32.33 ppm (CH_3); FT-IR (neat): 3000, 2943, 1696, 1590, 1471, 1434, 1358, 1282, 1249, 1107, 781, 759, 735 cm^{-1}; LC-MS: $t_R =$ 4.20 min, m/z $[M+H] = 181.37$; HRMS (ESI): m/z calcd for $C_{10}H_{13}O_3^+$: 181.0865; found 181.0857.

Ethyl 4-(2,6-dimethoxyphenyl)-2,4-dioxobutanoate (8): *Batch reaction*: A solution of 2′,6′-dimethoxy-acetophenone (**3**; 0.90 g, 4.90 mmol), diethyl oxalate (1.344 mL, 9.8 mmol, 2 equiv) and a solution of sodium ethoxide (1 M, 10 mL, 10 mmol) in ethanol (8 mL) was microwave irradiated for 25 min at 80 °C. Hydrochloric acid (1 M, 10 mL) was then added until the pH reached 2. The product (**8**) crystallised, overnight, as an off-white solid (yield 1.10 g, 3.93 mmol, 80 %). *Flow reaction*: A solution of 2′,6′-dimethoxy-acetophenone (**3**; 2.252 g, 12.36 mmol) and diethyl oxalate (3.328 mL, 24.7 mmol, 2 equiv) in ethanol (50 mL; flow rate 1.30 mL min^{-1}, pump A) and a solution of sodium ethoxide (1 M; flow rate 1.30 mL min^{-1}, pump B) were reacted in a 52 mL (1/8″ o.d.) PFA reactor at 140 °C after combining at a T-piece (20 min residence time). A pressure chamber was placed at the output of the reactor (5 bar). After exiting the reactor, the solution was collected and hydrochloric acid (1 M, 10 mL) was added until the pH reached 2. The product (**4**) crystallised, overnight, as an off-white solid (yield 2.559 g, 9.14 mmol, 74 %). M.p. 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta = 7.32$ (t, 1H, $J =$ 8.4 Hz), 6.59 (s, 1H), 6.57 (d, 2H, $J = 8.4$ Hz), 4.33 (q, 2H, $J = 7.1$ Hz), 3.79 (s, 6H), 1.35 ppm (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta = 195.8$ (C), 163.8 (C), 162.5 (C), 157.9 (C), 132.3 (CH), 117.0 (C), 106.4 (CH), 104.2 (CH), 62.4 (CH_2), 56.1 (CH_3), 14.1 ppm (CH_3); FT-IR (neat): 1735, 1620, 15486, 1475, 1257 cm^{-1}; LC-MS: $t_R = 4.19$ min, m/z $[M+Na]^+$: 302.83; HRMS (ESI): m/z calcd for $C_{14}H_{16}O_6Na^+$: 303.0845; found 303.0847; microanalysis: calculated (found) for $C_{14}H_{16}O_6$: C 59.99 % (59.99 %), H 5.52 % (5.75 %).

Ethyl 1-(7-chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3-carboxylate (10): *Batch reaction*: A solution of ethyl 4-(2,6-dimethoxyphenyl)-2,4-dioxobutanoate (**8**; 0.14 g, 0.50 mmol) and 1-(7-chloroquinolin-4-yl)hydrazine (**9**; 0.12 g, 0.65 mmol, 1.3 equiv) in dimethylformamide (3 mL) was microwave irradiated at 140 °C for 3 h. Sodium hydrogencarbonate (2 g) was added and the mixture stirred until no more evolution of gas was observed. The mixture was added to water (10 mL) and extracted with dichloromethane (4 × 15 mL). The organic fractions collected were dried over sodium sulfate, filtered and concentrated, in vacuo. The oil obtained was stirred with hexane (10 mL), overnight, to afford a solid which was recrystallised from ethanol/hexane to furnish the product as yellow crystals (yield 0.18 g, 0.43 mmol, 87 %). *Flow reaction*: A solution of ethyl 4-(2,6-dimethoxyphenyl)-2,4-dioxobutanoate (**8**; 1.12 g, 4.0 mmol) and 1-(7-chloroquinolin-4-yl)hydrazine (**9**; 0.926 g, 1.2 equiv, 4.8 mmol) in dimethylformamide (10 mL; flow rate 0.50 mL min^{-1}, pump A) and a solution of sulfuric acid (1.2 mL) in dimethylformamide (10 mL; flow rate 0.50 mL min^{-1}, pump B) were reacted in a 52 mL (1/8″ o.d.) PFA reactor at 140 °C after combining at a T-piece (52 min residence time). A 100 psi back pressure regulator was placed after the reactor. The exiting stream was combined with an aqueous sodium hydrogencarbonate solution (2.00 mL min^{-1}). The quenched solution was then directly merged at a T-piece with a stream of dichloromethane (2.00 mL min^{-1}) and the output delivered into a Biotage® universal phase separator, where the organic solution was separated from the aqueous (two Biotage® universal phase separators were used alternately to allow processing of volumes greater than the individual separator capacity of 70 mL). The organic solution was dried over sodium sulfate, filtered and concentrated, in vacuo. The oil obtained was stirred with hexane (20 mL), overnight, to afford a solid which was recrystallised from ethanol/hexane (1:1, v/v) to furnish the product (**10**) as yellow crystals (yield 1.58 g, 3.58 mmol, 89 %). M.p. 147–149 °C; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): $\delta = 8.91$ (d, 1H, $J = 4.5$ Hz), 8.17 (d, 1H, $J = 1.8$ Hz), 7.72 (dd, 1H, $J = 9.0$, 1.8 Hz), 7.68 (d, 1H, $J = 9.0$ Hz), 7.26 (t, 1H, $J =$ 8.4 Hz), 7.23 (d, 1H, $J = 4.5$ Hz), 7.04 (s, 1H), 6.54 (d, 2H, $J = 8.4$ Hz), 4.35 (q, 2H, $J = 7.1$ Hz, H-1′), 3.40 (s, 6H), 1.33 ppm (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): $\delta = 161.4$ (C), 157.5 (C), 151.7 (CH), 149.1 (C), 144.5 (C), 143.3 (C), 139.2 (C), 134.8 (C), 132.0 (CH), 128.1 (CH), 127.7 (CH), 125.7 (CH), 122.1 (CH), 118.3 (C), 111.6 (CH), 105.4 (C), 104.0 (CH), 60.6 (CH_2), 55.4 (CH_3), 14.2 ppm (CH_3); FT-IR (neat): 1719, 1590, 1476, 1434, 1232 cm^{-1}; LC-MS: $t_R = 5.10$ min, m/z $[M+H]^+$: 437.93; HRMS (ESI): m/z calcd for $C_{23}H_{21}N_3O_4Cl^+$: 438.1221, found 438.1219; microanalysis: calculated (found) for $C_{23}H_{20}N_3O_4Cl$: C 63.09 % (62.80 %), H 4.60 % (4.62 %), N 9.60 % (9.53 %).

1-(7-Chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3-carboxylic acid (11): *Batch reaction*: A solution of ethyl 1-(7-chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3-carboxylate (**10**; 0.438 g, 1.0 mmol) in THF (5 mL) was microwave irradiated in the presence of KOH aqueous solution (3 M, 5 mL) for 2 h at 120 °C. The solution obtained was concentrated in vacuo and the mixture was filtered to eliminate any presence of solid. The solution obtained was then acidified to pH 2–3 with concentrated hydrochloric acid (6 M) in an ice water-bath. The solid obtained was filtered to afford the product as a yellow solid (yield 0.370 g, 0.90 mmol, 90 %). *Flow reaction*: A solution of ethyl 1-(7-chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3-carboxylate (**10**; 0.876 g, 2.0 mmol) in THF (10 mL; flow rate 0.25 mL min^{-1}pump A) and a solution of KOH (0.56 g, 10 mmol) in water (10 mL; flow rate 0.25 mL min^{-1}, pump B) were reacted in a 14 mL PFA reactor at 120 °C after combining at a T-piece (28 min residence time). A 100 psi back pressure regulator was placed after the reactor. The solution obtained was concentrated in vacuo and the obtained mixture was filtered to eliminate any presence of solid. The solution obtained was then acidified to pH 2–3 with concentrated hydrochloric acid (6 M) in an ice water-bath. The solid obtained was filtered to afford the product (**11**) as a yellow solid (yield 0.75 g, 1.84 mmol, 92 %). M.p. >255 °C decomposition; ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): $\delta = 13.08$ (s, 1H), 8.89 (d, 1H, $J = 4.6$ Hz), 8.16 (d, 1H, $J = 1.9$ Hz), 7.73 (d, 1H, $J = 9.0$ Hz), 7.70 (dd, 1H, $J = 9.0$, 1.9 Hz), 7.26 (t, 1H, $J = 8.4$ Hz), 7.20 (d, 1H, $J = 4.6$ Hz), 6.99 (s, 1H), 6.54 (d, 2H, $J = 8.5$ Hz), 3.39 ppm (s, 6H); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): $\delta = 162.9$ (C), 157.5 (C), 151.6 (CH), 149.1 (C), 145.4

(C), 143.3 (C), 138.9 (C), 134.7 (C), 131.8 (CH), 128.0 (CH), 127.7 (CH), 125.9 (CH), 122.1 (C), 118.1 (CH), 111.7 (CH), 105.6 (C), 104.0 (CH), 55.3 ppm (CH_3); FT-IR (neat): 1687, 1575, 1479, 1456, 1434 cm^{-1}; LC-MS: $t_R = 4.35$ min, m/z $[M+H]^+$: 410.25; HRMS (ESI): m/z calcd for $C_{21}H_{17}N_3O_4Cl^+$: 410.0908; found 410.0904; microanalysis calculated (found) for $C_{12}H_{16}N_3O_4Cl$: C 61.54 (61.30%), H 3.94% (4.00%), N 10.25% (10.17%).

***tert*-Butyl 2-aminoadamantane-2-carboxylate (12)**: *Batch reaction*: $HClO_4$ (0.09 mL, 70% aqueous solution) was added dropwise to a sealed solution of (**2**; 0.150 g, 0.65 mmol) in *tert*-butyl acetate (5.4 mL) cooled to 0°C. The reaction was stirred at RT for 6 h and then quenched slowly at 0°C with NaOH solution (1N) until the pH reached 9–10. The mixture was extracted with EtOAc (4×50 mL) and washed with brine. After being dried with sodium sulfate, the solution was filtered and concentrated to give the product as an off-white solid (yield 0.090 g, 0.36 mmol, 55%). M.p. 101–103°C; ^{1}H NMR (500 MHz, [D$_6$]DMSO, 25°C): $\delta = 3.32$ (s, 2H), 2.40 (d, 2H, $J = 12.1$ Hz), 1.91 (s, 2H), 1.72 (m, 2H), 1.67 (m, 4H), 1.60 (m, 2H), 1.40–1.42 ppm (m, 11H); ^{13}C NMR (125 MHz, [D$_6$]DMSO, 25°C): $\delta = 176.1$ (C), 78.8 (C), 61.0 (C), 37.3 (CH_2), 34.6 (CH_2), 33.5 (CH), 31.4 (CH_2), 27.5 (CH), 26.7 (CH), 26.3 ppm (CH_3); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta = 2.22$ (2H, d, $J = 12.4$ Hz), 2.03 (2H, s), 1.71–1.78 (6H, m), 1.66 (2H, m) 1.54 (2H, d, $J = 12.4$ Hz), 1.46 (9H, s), 1.43 ppm (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta = 176.1$ (C), 80.1 (C), 62.0 (C), 37.9 (CH_2), 35.3 (CH_2), 34.3 (CH), 32.1 (CH_2), 28.1 (CH), 27.3 (CH), 27.0 ppm (CH_3); FT-IR (neat): 2901, 2851, 1710, 1450, 1365 cm^{-1}; LC-MS: $t_R = 3.44$ min, $[M+Na]^+$: 252.36; HRMS (ESI): m/z calcd for $C_{15}H_{26}O_2N^+$: 252.1964; found 252.1952; microanalysis: calculated (found) for $C_{15}H_{25}O_2N$: C 71.37% (71.67%), H 10.05% (10.02%), N 5.69% (5.57%); the structure was unambiguously confirmed by single X-ray crystallography; space group $P2_1/c$: $a = 10.501$, $b = 10.882$, $c = 12.101$ Å; $\alpha = 90.0$, $\beta = 92.0$, $\gamma = 90.0$°.

***tert*-Butyl 2-[1-(7-chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3-carboxamido]adamantane-2-carboxylate (13)**: *Batch reaction* : 1-(7-Chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3-carboxylic acid (**11**; 22 mg, 54 μmol), DIPEA (49 mg, 0.38 mmol) and 2,6-lutidine (58 mg, 5.4 μmol) were dissolved in dichloromethane (1 mL) and stirred at RT. A solution of triphosgene (17 mg, 57 μmol) in dichloromethane (1 mL) was added dropwise to the stirred reaction at RT. The reaction was allowed to mature at RT for 10 min before adding *tert*-butyl 2-aminoadamantane-2-carboxylate (**12**; 15 mg, 60 μmol) and stirring at RT for 18 h. Saturated ammonium chloride (2 mL) was added to quench the reaction. The organic fraction was separated and the dichloromethane removed, in vacuo. The residue obtained was suspended in EtOAc (5 mL) and filtered through a pad of silica to provide the title compound as yellow crystals (30 mg, 0.07 mmol, 86% yield). *Flow Reaction*: A solution of DIPEA (13 mg, 9.9 μmol) in dichloromethane (10 mL, 0.2 mL min^{-1} pump A) was combined with a solution of triphosgene (**16**; 110 mg, 370 μmol) in dichloromethane (10 mL, 0.2 mL min^{-1} pump B) combined at a T-piece mixer and flowed through a 500 μL stainless steel reactor at 100°C (1.25 min residence time) and then another 2.5 mL stainless steel reactor at 25°C (6.25 min residence time) before flowing into a Mettler-Toledo FlowIR™ (50 μL flow cell). A 100 psi back pressure regulator was placed after the reactor. 1-(7-Chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3-carboxylic acid (**7**; 41 mg, 0.10 mmol) was dissolved in a solution of DIPEA (0.2 M) in dichloromethane (1 mL) and introduced to flow stream A through a 1 mL injection loop. The flow reaction was monitored at 803 cm^{-1} to observe the consumption of phosgene by **7** and coordinate the introduction of the coupling partner. A solution of *tert*-butyl-2-aminoadamantane-2-carboxylate (**12**; 30 mg, 0.12 mmol) in dichloromethane (1 mL) was introduced into a flowing stream of dichloromethane (0.25 mL min^{-1}, pump C) through a 1 mL injection loop to coincide, at a T-piece mixer, with the plug of acid chloride from the reaction of flow streams A and B. The combined reaction mixture then flowed through a 14 mL PFA reactor at 100°C (23.33 min retention time) before exiting the flow reactor through a 100 psi back pressure regulator and into a flask of saturated ammonium chloride (20 mL). The organic fraction was separated and the dichloromethane removed, in vacuo. The residue obtained was suspended in EtOAc (5 mL) and filtered through a pad of silica to provide the title compound (**1**) as yellow crystals after crystallisation from dichloromethane/hexane (yield 47 mg, 0.07 mmol, 73%). M.p. 230–234°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta = 8.76$ (d, 1H, $J = 4.6$ Hz), 8.13 (d, 1H, $J = 2.1$ Hz), 7.95 (d, 1H, $J = 9.0$ Hz), 7.48 (dd, 1H, $J = 9.1$, 2.2 Hz), 7.21 (t, 1H, $J = 8.4$ Hz), 7.10 (s, br, 1H), 7.07 (s, 1H), 7.04 (d, 1H, $J = 4.6$ Hz), 6.39 (d, 2H, $J = 8.4$ Hz), 3.38 (s, 6H), 2.66 (m, 2H), 2.20–2.09 (m, 2H), 2.09–2.00 (m, 2H), 1.84–1.61 (m, 8H), 1.51 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta = 171.63$ (C), 160.55 (C), 158.00 (C), 151.01 (CH), 150.16 (C), 148.59 (C), 144.48 (C), 139.40 (C), 135.96 (C), 131.58 (CH), 128.44 (CH), 128.09 (CH), 126.34 (CH), 122.89 (C), 117.52 (CH), 110.66 (CH), 106.85 (C), 103.79 (CH), 80.87 (C), 64.06 (C), 55.41 (CH_3), 38.03 (CH_2), 34.17 (CH_2), 33.39 (CH_2), 32.95 (CH), 28.20 (CH), 27.13 (CH), 26.84 ppm (CH_3); FT-IR (neat): 2914, 1731, 1685, 1589, 1532, 1473, 1430, 1364.9 (w), 1290, 1252, 115, 1101, 1057, 1006, 951, 908, 881, 851, 835, 818, 781.9, 731.0, 682.0 cm^{-1}; LC-MS: $t_R = 5.96$ min, m/z $[M+H]^+$: 644.08; HRMS (ESI): m/z calcd for $C_{36}H_{40}N_4O_5Cl^+$: 643.2687; found 643.2693; the structure was unambiguously confirmed by single X-ray crystallography; space group $P2_1/n$: $a = 10.541$, $b = 19.462$, $c = 15.486$ Å; $\alpha = 90.0$, $\beta = 90.5$, $\gamma = 90.0$°.

2-[1-(7-Chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3-carboxamido]adamantane-2-carboxylic acid (1): Polymer-supported sulfonic acid (QP-SA; 0.6 g, 2.4 mmol) was added to a solution of *tert*-butyl 2-[1-(7-chloroquinolin-4-yl)-5-(2,6-dimethoxyphenyl)-1*H*-pyrazole-3-carboxamido]adamantane-2-carboxylate (**13**; 30 mg, 0.05 mmol) in dichloromethane and the reaction was stirred at RT for 18 h. The QP-SA was filtered off and the filtrate concentrated in vacuo to provide the title compound as white crystals (yield 25 mg, 0.04 mmol, 86%). M.p. 219–222°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): $\delta = 8.91$ (d, 1H, $J = 4.6$ Hz), 8.15 (d, 1H, $J = 2.1$ Hz), 7.78 (d, 1H, $J = 9.1$ Hz), 7.68 (dd, 1H, $J = 2.1$, 9.1 Hz), 7.28 (d, 1H, $J = 4.7$ Hz), 7.24 (t, 1H, $J = 8.5$ Hz), 7.91 (s, 1H), 6.52 (d, 2H, $J = 8.5$ Hz), 3.42 (s, 6H), 2.64–2.56 (m, 2H), 2.17–2.05 (m, 2H), 2.04–1.92 (m, 2H), 1.82–1.71 (m, 2H), 1.71–1.61 (m, 4H), 1.61–1.50 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): $\delta = 173.3$(C), 159.9 (C), 157.5 (C), 157.5 (C), 151.8 (CH), 149.1 (C), 143.4 (C), 139.2 (C), 134.8 (C), 131.9 (CH), 128.0 (CH), 127.7 (CH), 125.9 (CH), 122.2 (C), 118.6 (CH), 109.6 (CH), 105.8 (C), 104.0 (CH), 55.4 (CH_3), 55.3 (C), 37.4 (CH_2), 33.6 (CH_2), 32.8 (CH_2), 31.9 (CH), 26.5 (CH), 26.2 ppm (CH); FT-IR (neat): 3405, 2922, 1728, 1674, 1591, 1527, 1474, 1433, 1379, 1357, 1288, 1251, 1206, 1101, 1077, 1031, 1006, 957, 882, 865, 823, 779, 725, 682 cm^{-1}; LC-MS: $t_R = 5.29$ min, m/z $[M+H]^+$: 587.46; HRMS (ESI): m/z calcd for $C_{32}H_{32}N_4O_5Cl^+$: 587.2061, found 587.2053; the structure was unambiguously confirmed by single X-ray crystallography; space group $P\bar{1}$: $a = 10.249$, $b = 11.718$, $c = 12.634$ Å; $\alpha = 76.6$, $\beta = 72.9$, $\gamma = 76.4$°.

CCDC-919687 (**12**), 919688 (**13**) and 919686 (**1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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