A Flow Process Using Microreactors for the Preparation of a Quinolone Derivative as a Potent $5HT_{1B}$ Antagonist

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Dedicated to Prof. Gerry Pattenden, master synthesis chemist and friend

Abstract: This article describes the continuous flow synthesis of 6-methoxy-8-(4-methyl-1,4-diazepan-1-yl)-*N*-(4-morpholinophenyl)-4-oxo-1,4-dihydroquinoline-2-carboxamide, a potent $5HT_{1B}$ antagonist developed by AstraZeneca.

Key words: flow chemistry, solid-supported reagent, microreactor

Recently, following the development of various commercially available microreactor devices, flow chemistry is emerging as a useful laboratory synthesis tool.[1] When compared to the conventional batch-mode synthesis, these devices offer improved efficiency through telescoped reaction processes,[2] reduced solvent use and the production of less waste material.[3] Moreover, by incorporating solid-supported scavengers of by-products into the flow system, pure products can be obtained without the need for standard purification methods such as distillation, aqueous work-up or column chromatography.[4] It is also possible to operate these flow reactors at high pressures and temperature not readily accommodated by traditional batch-mode equipment, and, toxic or potentially hazardous reaction intermediates are readily contained within the device.[5] All these advantages make for safer handling of materials and improved downstream processing.

To demonstrate further the power of continuous-flow chemistry, we chose to prepare the quinolone derivative **1** (Figure 1), a potent $5HT_{1B}$ antagonist developed by AstraZeneca.[6] Several lines of evidence have suggested that the 5-HT_{1B} receptor is involved in psychopathologies, including migraine, pathological aggression and depression.[7] Recent studies have also shown that $5HT_{1B}$ antagonists stimulate release of 5-hydroxytryptamine, and ultimately result in fast antidepressant activity.[8]

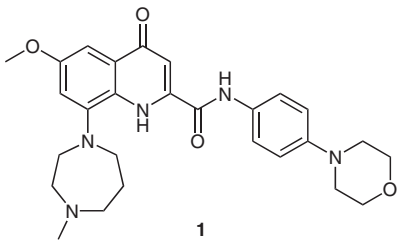

Figure 1 Target molecule

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In 2007, Horchler and coworkers published a seven-step synthesis of the target molecule **1** with an overall yield of 7%.[6] Our aim was to improve upon this yield and the efficiency of the synthesis by using flow chemistry. In this work we describe the development of a six-step flow sequence to **1** using the commercially available Vapourtec R2+/R4 reactor[9] in combination with the ThalesNano H-Cube flow hydrogenator (Figure 2).[10]

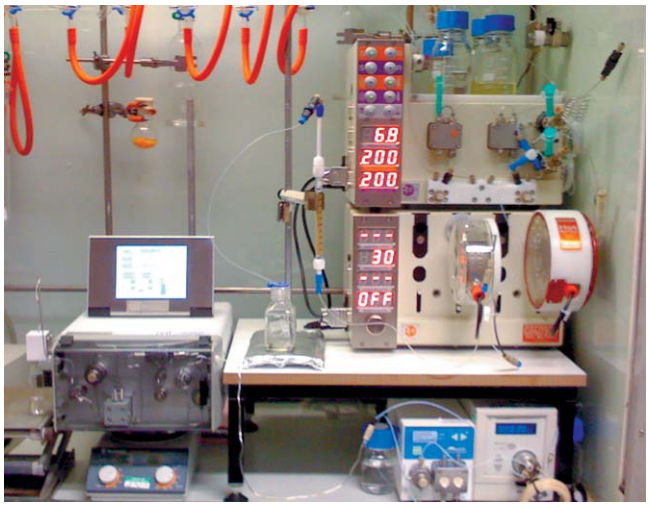
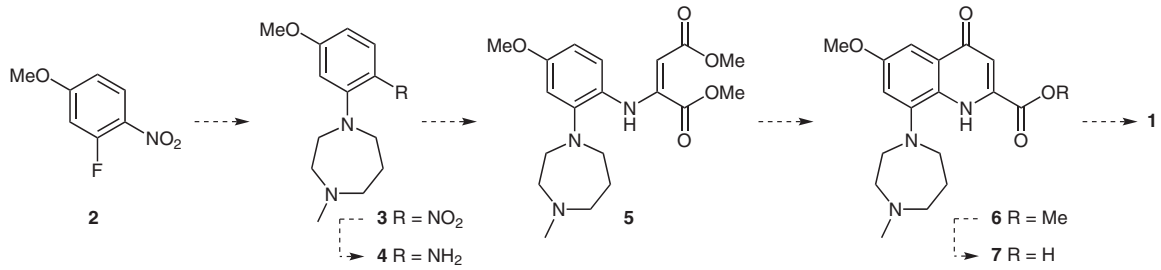


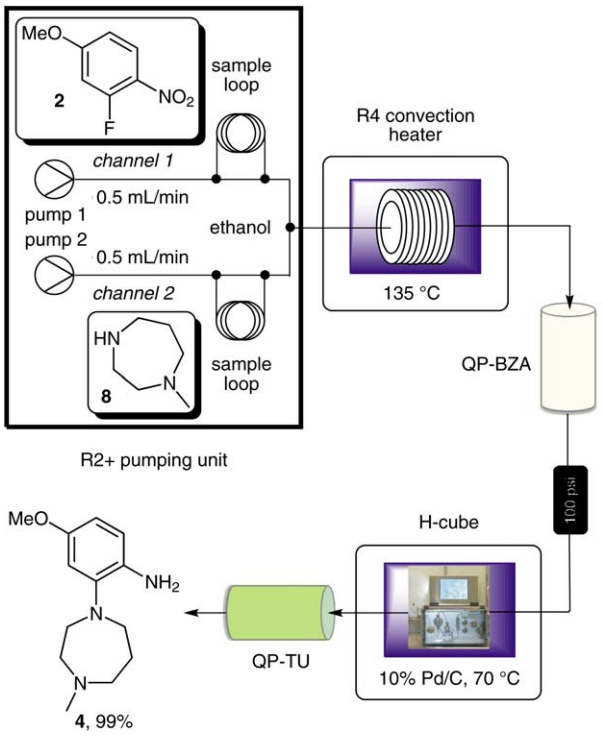
Figure 2 Vapourtec R2+/R4 flow system (right) and ThalesNano H-Cube hydrogenation reactor

To commence the synthesis (general route described in Scheme 1), solutions of the 3-fluoro-4-nitroanisole[11] (**2**; 0.5 M, 1 equiv) and 1-methylhomopiperizine (**8**; 0.5 M, 1 equiv) in ethanol were loaded into two identical PEEK sample loops (5 mL internal volume, 0.16 mm i.d.), the contents of which were then introduced to the main flow stream via a T-piece connector at 0.5 mL/min per channel (Scheme 2). The combined stream was then directed through a heated convection flow coil (CFC, 10 mL volume, 1 mm i.d. PFA[12]) attached via a glass jacket to the R4 unit (Scheme 2), which was maintained at 135 °C giving a residence time of 10 min. The existing flow stream from the CFC reactor was then directed into a glass column (10 mm bore × 100 mm length)[13] packed with Quadrapure-benzylamine (QP-BZA, 5 equiv)[14] to scavenge hydrofluoric acid generated during the S_NAr reaction.[15] The resultant stream of **3** (Scheme 1) was immediately subjected to continuous flow hydrogenation utilizing a ThalesNano



Scheme 1 A general scheme showing the intermediate structures for the synthesis of compound 1

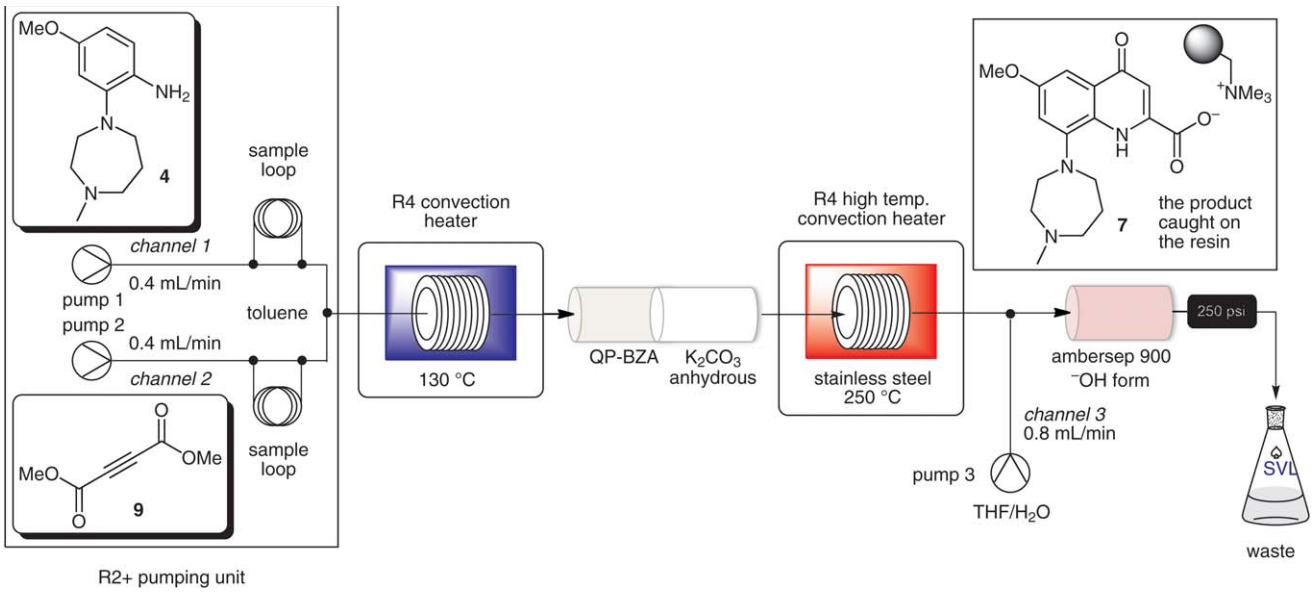
H-Cube® hydrogenation reactor,[16] which contained a cartridge of 10% palladium on charcoal as catalyst. In order to ensure complete reduction of the nitro functionality the system was run in maximum hydrogen generation mode. The outflow was connected to an additional glass column filled with Quadrapure thiourea (QP-TU, 5 equiv) to act as a metal scavenger removing any leached palladium and the desired product **4** was finally collected in essentially quantitative yield over approximately 25 minutes.



Scheme 2 Continuous flow synthesis of intermediate aniline **4**

After a solvent switch from ethanol to toluene, the aniline **4** (0.2 M, 1 equiv) and dimethyl acetylenedicarboxylate (**9**; 0.24 M, 1.2 equiv), also in toluene, were loaded into two PEEK sample loops (5 mL internal volume, 0.16 mm i.d.). A solvent flow rate of 0.4 mL/min per channel was used to introduce the two compounds and combine their channels at a standard T-piece mixer (Scheme 3). The reaction stream was then passed through a CFC (10 mL volume, 1 mm i.d. PFA), which was maintained at 130 °C, followed by in-line treatment with a column of QP-BZA (5 equiv) to sequester any residual dicarboxylate **9**. The stream of **5** was then directed through a column filled with anhydrous potassium carbonate (granular form, 2.5 g) to eliminate any traces of water carried forward from the hydrogenation reaction; the presence of water was significantly detrimental to the yield and purity of the following cyclisation reaction. The dried flow stream was then subjected to a high temperature cyclocondensation reaction in a stainless steel flow coil (11 mL volume, 1 mm i.d.), which was heated to 250 °C. As the operating temperature was much higher than the boiling point of the toluene, an in-line backpressure regulator (BPR) operating at 17.3 bar (250 psi) was fitted to the system. The residence time for the cyclisation reaction to furnish compound **6** was optimum at 13 min; longer times led to the decomposition of the quinolone intermediate, while shorter times gave incomplete conversion. The output stream from the stainless steel reactor was rapidly cooled to ambient temperature prior to being mixed with a third input of THF–H_2O (30:1) entering at 0.8 mL/min. The combined stream was then progressed through a glass resin packed column containing Ambersep 900 hydroxide form (2 equiv). The presence of the third stream was found necessary to promote efficient ester hydrolysis of **6** within the column. The resulting carboxylic acid **7** was immediately deprotonated and retained within the basic resin column.

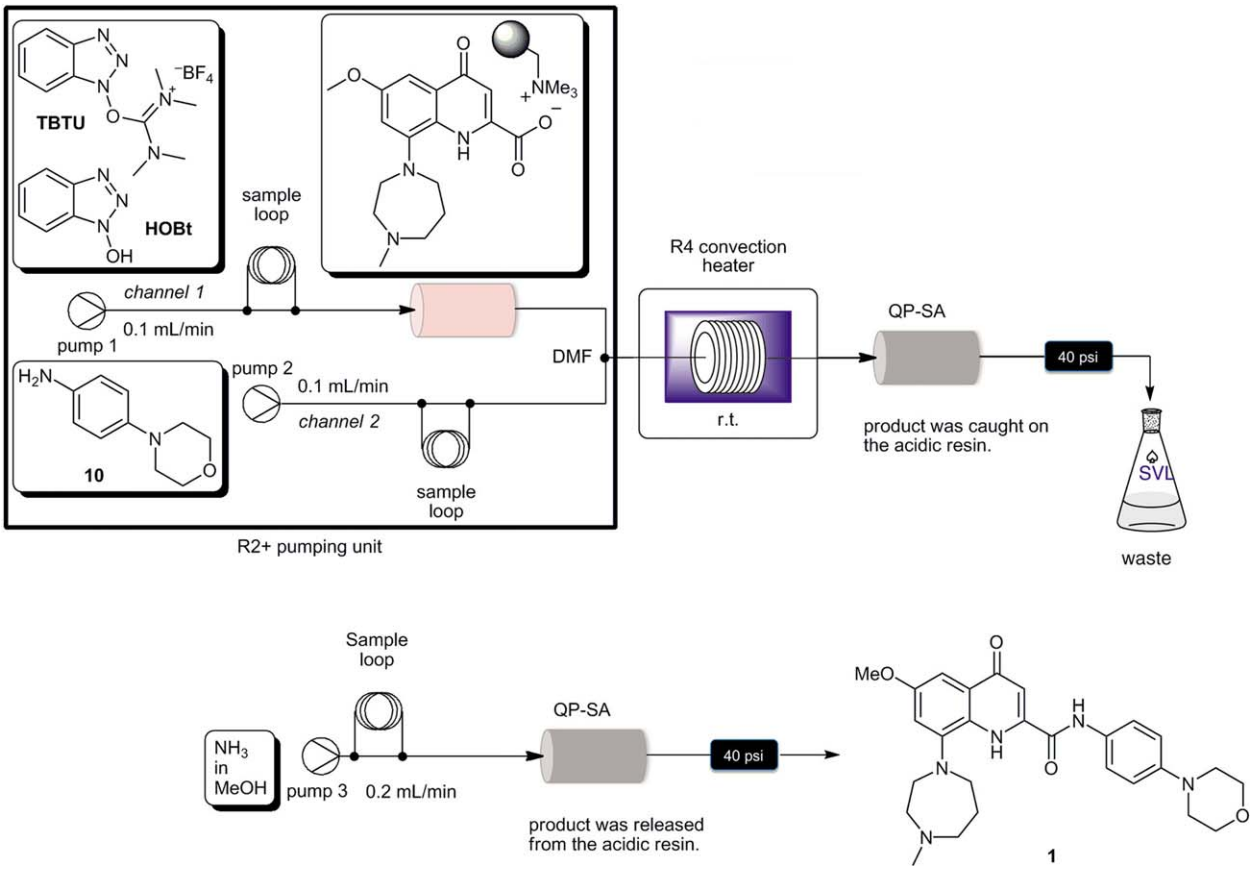
The final step of the synthesis involved an amide coupling reaction and featured a 'catch and release' purification.[17] Firstly, a solution of *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU; 0.5 M, 5 mL, 2.5 equiv) and 1-hydroxybenzotriazole (HOBt; 0.5 M, 5 mL, 2.5 equiv) in DMF was pumped through the column containing the Ambersep 900 at 0.1 mL/min (Scheme 4). This stream both activated and released the carboxylic acid generated in the last step of the previous reaction. The output stream from this step containing the newly generated activated ester was coupled directly with a second stream of 4-morpholinoaniline in DMF (0.24 M, 1.2 equiv), which was pumped from a 5 mL sample loop at 0.1 mL/min. The ensuing flow stream next entered a CFC (10 mL volume, 1 mm i.d.), which was maintained at ambient temperature giving a residence time of 50 min. The incubated reaction mixture was then passed through a glass column loaded with Quadrapure-sulfonic acid (QP-SA, 5 equiv) that trapped the desired product onto the resin and aided in concentrating the sample for subsequent displacement. Finally, the product was released by passing a solution of NH_3 in MeOH (2.0 M, 5 equiv) through the



Scheme 3 Continuous-flow synthesis of the quiniline carboxylic acid intermediate

column, completing this 'catch and release' purification. The solution was simply concentrated in vacuo, and the crude product **1** was recrystallised from MeOH to obtain an 18% overall yield in better than 98% purity.

In summary, the continuous flow synthesis of the quinolone derivative **1** was completed using a combination of flow microreactors, while incorporating polymer-supported reagents and scavengers to aid reaction telescoping and purification. The result is very encouraging, as it clearly demonstrates that multi-step sequences can be incorporated into flow chemistry platforms leading to polyfunctional molecules of biological interest.



Scheme 4 Amide coupling reaction

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(10) ThalesNano H-Cube hydrogenation reactor is available from ThalesNano Nanotechnology Inc, Hungary. Website: http://www.thalesnano.com.

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(12) PFA (Perfluoroalkoxy tubing).

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(14) Quadrapure benzylamine (QP-BZA), Quadrapure sulfonic Acid (QP-SA), Quadrapure thiourea (QP-TU) are high-loading scavengers commercially available from Reaxa. Website: http://www.reaxa.com.

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