Multi-step Flow Synthesis of the Anthelmintic Drug Praziquantel

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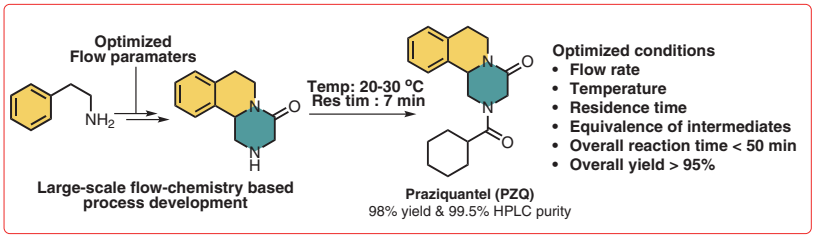

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Abstract Praziquantel (PZQ; Brand name: Biltricide) is categorized as an anthelminthic drug, and it is used for the treatment of Schistosomiasis and other parasitic infections. The World Health Organization (WHO) has classified it as one of the essential and emergency medicines needed across the globe. The price of PZQ formulated product depends on the associated method of preparation, along with cost of raw materials. A precise and reliable method for the preparation of PZQ using a flow-chemistry approach is described in this study using phenylethylamine as the starting material. The main objective of the present study is to identify a new economical route for the synthesis of PZQ that could decrease the production time drastically from days to minutes and be transferred to large-scale production. Simultaneously, the purity of the obtained intermediates in essential steps, as single or continuous process, determined by HPLC analysis were more than 90% pure. The continuous preparation process of PZQ in the current study was achieved in less time (ca. 3–4 h) than using conventional methods (ca. 3–4 days). Moreover, the required quantity of key intermediate dimethoxyethanamine is 40–50% less than in existing methods.

Key words Praziquantel, flow chemistry, optimization, continuous process, essential medicine

Praziquantel (PZQ) is a Biopharmaceutics Classification System II (BCS II) class of FDA approved drug used for treatment of Schistosomiasis, parasitic and other helminthic infections.[1] As per records of the World Health Organization, more than 1.5 billion cases of infection were reported in 2020 across the globe, and this number is expected to increase in the coming years.[2] The market value of antiparasitic drugs was estimated to be USD 7228 million in 2019, and its market growth is expected to expand another 5.2% between 2020 and 2027.[2] According to the DataIntelo analysis, PZQ was considered a major occupier compared to Oxamniquine and other antiparasitic agents in the Schistosomiasis market, which is a major prescription for the treatment of *S. haematobium* infections.[3] It is classified as part of the 'WHO list of emergency medicines', and is also being prescribed to treat infections in mammals such as Cystcercosis, Opisthorchiasis, Clonorchiaisis, Hydatid disease, tapeworm, and fluke infections.[4] PZQ is currently formulated in a tablet dosage form by most of the generic pharma industries in different dosages such as 50, 500, and 600 mg (adult/paediatric) and is age-dependent.[5] The oral dispersible tablets of PZQ as paediatric dosage for parasite infected infants and children are undergoing phase II trials.[6] The first veterinary use of PZQ was reported by Merck KGaA and Bayer AG companies in 1970s and patented in 1973 for human use.[7]

Chemically, PZQ is a class of tetrahydroisoquinolinone scaffold and is soluble in DMSO, ethyl alcohol, and chloroform. The use of flow-chemistry techniques have been demonstrated to produce a variety of quinoline,[8] tetrahydroquinoline,[9] tetrahydrosioquinoline,[10] and fused-tetrahydroquinolines using different flow reactors on milligram to multikilogram scales. The application of chemistry techniques to continuous-flow reactors enables the handling of a variety of chemical reactions such as C–C and C–N bond-formation, cycloisomerization, and 1,3-dipolar cycloaddition to afford desired heterocycles.[11] Based on the significance of flow-chemistry-based preparation methods of quinolines, the current research work was initially focused on achieving the synthesis of intermediates of PZQ and was further extended to produce PZQ anthelminthic drug. The

existing synthetic routes to PZQ (**1**) (Figure 1) involve a series of chemical processes and the utilization of expensive, harmful, and toxic chemical intermediates in harsh to optimal conditions.[12] Based on the use of phenylethylamine (**2**) as starting material, chemical reagents such as 2,2′-(benzylazanediyl)diacetic acid, (2-isocyanoethyl)benzene, 2,2-dimethoxyethan-1-amine, glycinoyl chloride HCl, 2-aminoethan-1-ol, 2-(1,3-dioxoisoindolin-2-yl)acetyl chloride and hydroxymethyl polystyrene as esters and intermediates (**2**–**7**) are used for the production of PZQ.[13] Similarly, praziquinamine (**8**, **9**) and isoquinoline carbonitrile analogues (**10**, **11**) under unique reaction conditions, also afforded PZQ.[14] Further, phenyl ethylamine intermediates, produced under individual processes, upon cyclization (**12**–**16**), yielded PZQ directly.[14b,15] The mono-N-substituted (**13**) and C1-substituted isoquinolines (**14**) and dual substituted isoquinolines (**15**, **16**) also produce PZQ.[13h,16] A bulk-scale preparation of PZQ (maximum enantiopurity >99%) was also achieved through ball milling, and mechanochemical aza-Henry approaches.[16b] Typically, batch processes need an excess amount of sulfuric acid and exothermic reactions need special attention and more precautions. Flow processes eliminate the hazards of open handling of corrosive reagents, and these reactors can control exotherm processes efficiently. The flow process has its own merit of new technology and smaller effluent footprint. A solid-phase synthesis of PZQ employing hydroxymethyl polystyrene as key intermediate was also developed.[17]

In another method, cyclohexanoyl chloride (**17**) was employed as initial substrate to react with 2,2′-iminodiacetonitrile, ethyl glycinate, and isoquinolin-1-ylmethanamine in the preparation of PZQ; however, their corresponding intermediates were needed to proceed via the pre- or post-cyclization process of praziquinamine (**9**).[16a,18] In brief, one of the complete synthetic routes to PZQ, shown in Scheme 1, is carried out by condensing 2-chloro-*N*-phenethylacetamide (**19**) (prepared by reaction of **2** and **18**) with 2,2-dimethoxyethanamine (**20**) *via* the formation of key coupled acetamide intermediate (**21**) required for cyclization to praziquinamine (**9**). Further reaction of praziquinamine (**9**) with cyclohexanoyl chloride (**17**) affords PZQ.[12,14d,15b] The deracemization process of PZQ analogues is initiated by a reaction of praziquinamine with various carbonyl chlorides under different flow-chemistry conditions, which are elaborated.[19] Most of the existing preparation routes to PZQ involve consumption of reagents that include hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, thionyl chloride, and hydrazine hydrate, which have to be carefully handled during synthesis. The cost of raw materials such as aminoacetaldehyde dimethylacetal is also very high and impacts the overall price of PZQ. Thus, flow chemistry is considered as an alternative and efficient method applied in synthetic organic chemistry for the manufacture of chemical intermediates as well as APIs.[20] General preparation methods of PZQ was reviewed by Adekiya et al.[20e] Flow-chemistry experiments are also dependent on flow reactors, length, pump, tube size, tube volume, scalability

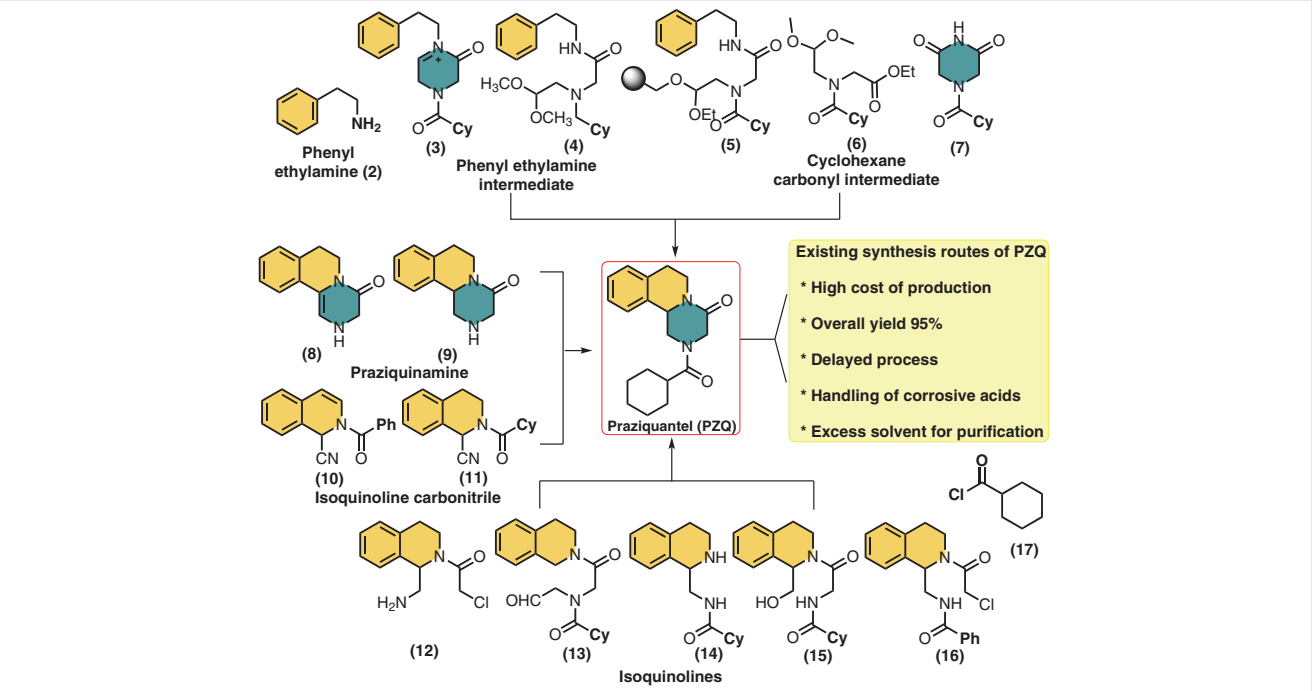
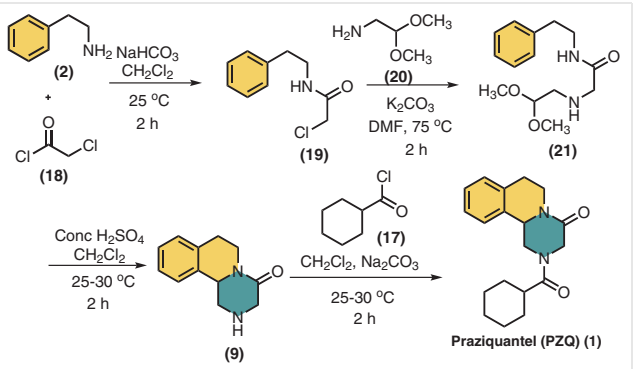


Figure 1 Schematic representation of PZQ preparation methods using different key intermediates

and combination of multiple flow reactors. Moreover, the PZQ process requires corrosive reagents/acids, which are rate-limiting criteria in large-scale production. Similarly, the batch process for the synthesis of PZQ consists of multiple steps and this leads to an increase in the overall production time. Thus, based on the expertise and intent to fine-tune the PZQ synthesis, along with its intermediates, a continuous-flow chemistry method was developed that reduced production time and was amenable to large-scale manufacturing industries.

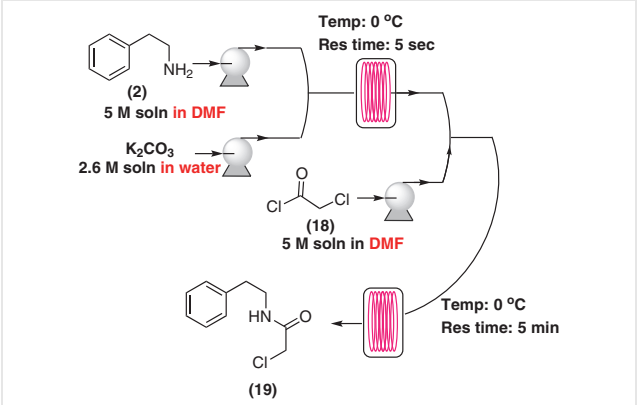


Scheme 1 A common efficient synthetic route to PZQ[13g,h]

The preparation of PZQ using flow-chemistry method development in continuous steps without isolation of intermediates is described herein, with the focus on reduction in overall production time. In comparison with the conventional batch process, this method utilizes minimal amounts of expensive reagents and gives good yields of intermediates along with the product. To reach the final production of PZQ, an integrated system of flow reactors/micro reactors are used to progress through a series of reactions in a multistep manner. The present method of PZQ synthesis is advantageous over existing routes as it does not require isolation from solid masses and product intermediates remain in the solution phase before passing directly into the next phase of the flow chemical reaction. The main aim of the present innovative method of PZQ process development is to minimize open handling, exposure of starting materials, reagents, intermediates and solvents to the environment and operator. Another objective of this research is to condense molar quantities of starting materials such as dimethylacetal and aminoacetaldehyde from 2 to 1.2 equivalents, which reduces the cost of production. It also curtails the solvent load, reduces waste and effluent generation, and has the potential to satisfy a green chemistry approach. Importantly, this method brings down the reaction time, and is considered as having fewer downstream processes, which ultimately increases the overall process efficiency and makes the process more economic. The microreactors provide accurate measures to the synthetic organic chemist such as regulation of concentration of reagents/chemical ingredients in chemical processes and temperature, monitoring of heat and mass transfer, and offers a high degree of reaction control towards selective product formation. The present flow chemistry process development of PZQ was carried out with a Vapourtec R series modular flow system, which consists of PFA (perfluoroalkoxy) coiled tubes, equipped with piston pump (0.20–50 mL/min at pressure up to 42 bar). The tube reactors are coiled with stainless steel, Teflon, and Hastelloy C, which has a profound heat- and mass-transfer that could be utilized for execution of the preparation of PZQ in scalable quantities. In another aspect, maintaining continuous-flow chemistry reactions in a sequential manner is not only advantageous but also integrates multi-reactor setups that perform their individual roles efficiently during the production of PZQ. For example, parameters such as reaction temperatures, length, and diameter of the reactor coils, heating/cooling systems, residence time, mixers, and in-line separation are crucial to each step involved in the synthesis of PZQ. Considering the flow-chemistry characteristics, and information on existing PZQ preparation methods, a continuous-flow-chemistry-based synthesis of PZQ is developed that, to our knowledge, has not been reported to date.

Preparation of 2-((2,2-Dimethoxyethyl)amino)-*N*-phenethylacetamide (21)

Our initial focus was the process development for the key starting material 2-chloro-*N*-phenethylacetamide (**19**) (Scheme 2). In this regard, 5.0 M solution of phenylethylamine (4.54 mL/min) in DMF and 2.6 M solution of K_2CO_3 (10.47 mL/min) in water were passed through the dosing pumps at 0 °C and 5 sec residence time and reacted with 5 M solution of chloroacetyl chloride (5.0 mL/min) in DMF (passed through another dosing pump). After screening the temperature, residence time and flow rates, optimal results of 97% yield were obtained at residence time of 5 min at a temperature of 5 °C and flow rates of 4.54 mL/min, 5.0 mL/min and 10.47 mL/min for phenylethylamine, chloroacetyl chloride and K_2CO_3, respectively, with 1:1.1:1.2 equivalent ratio (see Table 1).



Scheme 2 Flow-reaction-based preparation of 2-chloro-*N*-phenethylacetamide (**19**)

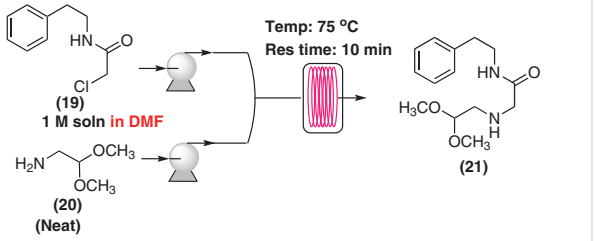
Table 1 Flow-Chemistry Parameters for the Preparation of 2-Chloro-*N*-phenethylacetamide (**19**)

Entry	Flow rate (mL/min)			**2**/**18**/K_2CO_3 (equiv)	Temp (°C)	Residence time (min)	HPLC purity (%)	Yield (%)
	2[a]	**18**[a]	K_2CO_3[b]					
	Temperature Study							
1	4.54	5.0	10.47	1:1.1:1.2	0	5.0	98.5	96
2	4.54	5.0	10.47	1:1.1:1.2	5	5.0	99.3	97
3	4.54	5.0	10.47	1:1.1:1.2	10	5.0	97.0	95
4	4.54	5.0	10.47	1:1.1:1.2	30	5.0	94.5	90
	Residence Time Study							
5	2.27	2.5	5.23	1:1.1:1.2	5	10.0	97.8	95
6	1.13	1.25	2.62	1:1.1:1.2	5	20.0	94.0	89
	Equivalence Study of Potassium Carbonate							
7	3.36	3.7	12.94	1:1.1:2.0	5	5.0	98.5	96
8	4.97	5.47	9.56	1:1.1:1.0	5	5.0	97.5	95

[a] 5.0 M in DMF.
[b] 2.6 M in H_2O.

The same transformation when performed with DCM as solvent proceeded well to produce the product **19** in 92% (see the Supporting Information). The obtained solution phase 2-chloro-*N*-phenethylacetamide (**19**) was pumped to a tube reactor and simultaneously 2,2-dimethoxyethan-1-amine (**20**) (1:1.0 to 1:2) was introduced by another pump at different flow rates (8.55–17.10 mL/min/0.72–2.89 mL/min) and variant temperatures (30–75 °C), and residence times (5–20 min) to identify ideal conditions required for achieving maximum yield and HPLC purity.

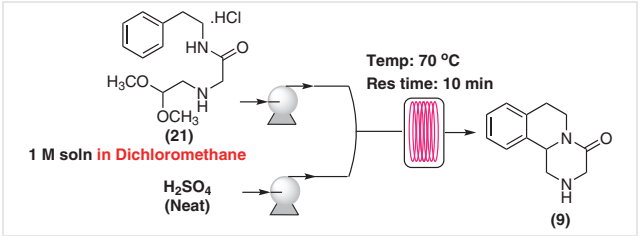
From the series of tested conditions, a flow rate of 8.55 mL/min for 2-chloro-*N*-phenethylacetamide (**19**) and 1.45 mL/min for 2,2-dimethoxyethan-1-amine (**20**) with 1:1.5 equivalent at 75 °C and 10 min residence time was found as preferential parameters to achieve 95% yield of 2-((2,2-dimethoxyethyl) amino)-*N*-phenethylacetamide (**21**) (Table 2; Scheme 3). The product was isolated in ethyl acetate, stirred, and the pH of the reaction mixture was adjusted to 1–2 with HCl solution at 10–15 °C. The solids were isolated by filtration, washed with ethyl acetate, and dried under vacuum at 600 mm of Hg vacuum to get solid **21** with 95% yield and 99% HPLC purity.



Scheme 3 Preparation of 2-((2,2-dimethoxyethyl)amino)-*N*-phenethylacetamide (**21**)

Preparation of Praziquinamine

A solution of 2-((2,2-dimethoxyethyl)amino)-*N*-phenethylacetamide (**21**) (1.0 M in water) and sulfuric acid (17.8 M) were passed through the dosing pumps in the tube reactor and used to study the ideal conditions required to obtain 99% purity with improved yield of praziquinamine (**9**) (Scheme 4).



Scheme 4 Flow-reaction-based preparation of praziquinamine (**9**)

It was observed that **21** and sulfuric acid under flow rates of 6.4 mL/min and 3.6 mL/min with 1:10 equivalents at 70 °C and 10 min residence time provided the product praziquinamine in optimal yields (Table 3). The eluting reaction mixture was then quenched with chilled water and 20% NaOH solution by maintaining pH between 8–9 and, finally, the product was extracted with dichloromethane and subjected to evaporation to yield praziquinamine **9** in 93% yield as a white powder.

Table 2 Flow Chemistry Parameters in Preparation of 2-((2,2-Dimethoxyethyl)amino)-*N*-phenethylacetamide (**21**)

Entry	Flow rate (mL/min)		**19**/**20** (equiv)	Temp (°C)	Residence time (min)	HPLC purity (%)	Yield (%)
	19[a]	**20**[b]					
	Temperature Study						
1	8.55	1.45	1:1.5	85	10.0	99.0	94.0
2	8.55	1.45	1:1.5	75	10.0	99.0	95.0
3	8.55	1.45	1:1.5	50	10.0	96.0	92.0
4	8.55	1.45	1:1.5	30	10.0	80.5	73.0
	Residence Time Study						
5	17.10	2.89	1:1.5	75	5.0	97.8	94.0
6	4.28	0.72	1:1.5	75	20.0	98.9	94.0
	Equivalence Study of Dimethoxyethan-1-amine						
7	8.98	1.01	(1:1.0)	75	10.0	92.5	90.0
8	8.16	1.84	(1:2)	75	10.0	99.0	94.0

[a] 1.0 M in DMF.
[b] 8.86 M.

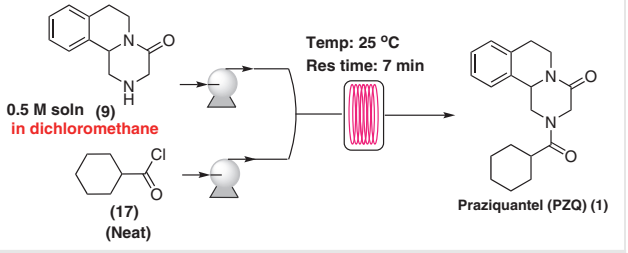
Table 3 Flow-Chemistry Parameters in Preparation of Praziquinamine (**9**)

Entry	Flow rate (mL/min)		**21**/H_2SO_4 (conc.) (equiv)	Temp (°C)	Residence time (min)	HPLC purity (%)	Yield (%)
	21[a]	H_2SO_4 (conc.)[b]					
	Temperature Study						
1	6.4	3.6	1:10	80	10.0	97.0	82.0
2	6.4	3.6	1:10	70	10.0	98.5	93.0
3	6.4	3.6	1:10	50	10.0	96.0	80.0
4	6.4	3.6	1:10	30	10.0	70.5	63.0
	Residence Time Study						
5	12.8	7.19	1:10	75	5.0	95.80	81.0
6	3.2	1.8	1:10	75	20.0	96.90	83.0
	Equivalence Study of Sulfuric Acid						
7	6.9	3.1	1:8	75	10.0	95.0	80.0
8	5.42	4.57	1:15	75	10.0	98.0	83.5

[a] 1.0 M in H_2O.
[b] 17.8 M in H_2O.

Preparation of PZQ

Praziquinamine (**9**) (0.5 M solution in DCM) premixed with triethylamine (1.3 equiv) and cyclohexanecarbonyl chloride (7.3 M) were continuously introduced to the flow reactor through dosing pumps under different parameters of temperature and residence time. After a series of experiments, 1:1.1 equivalents of praziquinamine (**9**) and cyclohexanoyl chloride (**17**) with 13.28 mL/min and 1.0 mL/min at 7 min residence time and 25 °C (Table 4) was found as preferential conditions to achieve the best yield (98%) of PZQ with 99% HPLC purity (Scheme 5).



Scheme 5 Flow-Reaction-Based Preparation of PZQ (**1**)

Table 4 Flow-Chemistry Parameters in Preparation of PZQ

Entry	Flow rate (mL/min)		**9**/**17** (equiv)	Temp. (°C)	Residence time (min)	HPLC purity (%)	Yield (%)
	9[a]	**17**					
	Temperature Study						
1	13.28	1.0	1:1.1	10	7.0	87.0	78.0
2	13.28	1.0	1:1.1	25	7.0	99.0	97.0
3	13.28	1.0	1:1.1	50	7.0	95.0	96.0
4	13.28	1.0	1:1.1	80	7.0	92.5	93.0
	Residence Time Study						
5	18.6	1.4	1:1.1	25	5.0	95.8	95.0
6	4.65	0.35	1:1.1	25	20.0	97.9	96.0
	Equivalence Study of Cyclohexane Carbonyl Chloride						
7	13.54	0.74	1:0.8	25	7.0	92.5	90.0
8	12.95	1.33	1:1.5	25	7.0	99.0	97.0

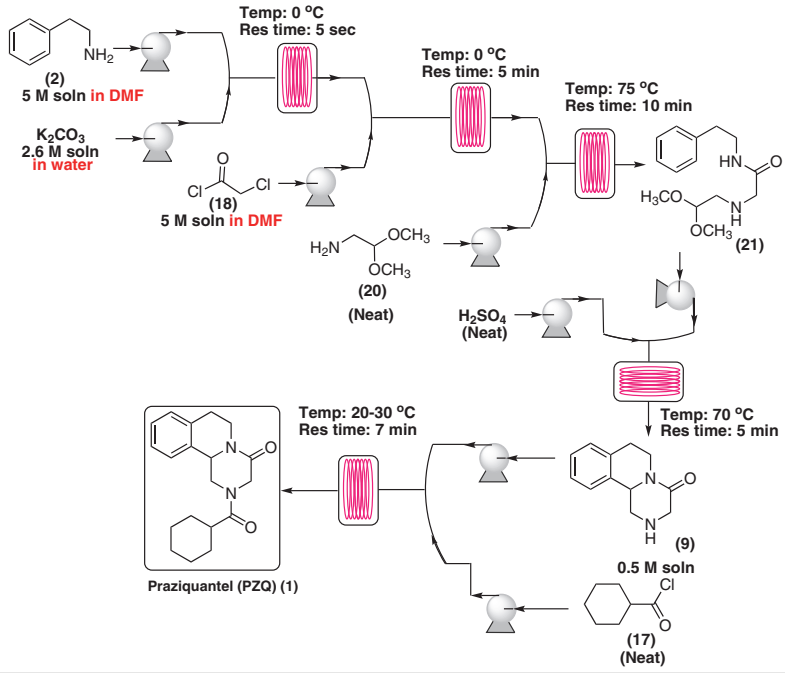
[a] 0.5 M in DCM.
[b] 7.3 M.

Preparation of PZQ in Large-Scale Continuous Process

As per the optimized flow-reaction conditions of key intermediates and PZQ, the whole process was investigated to achieve PZQ in an in-situ manner in continuous mode. 2-Phenylethanamine (**2**) (5.0 M in DMF), at a flow rate of 4.54 mL/min and 2.6 M potassium carbonate (at flow rate of 10.47 mL/min) were introduced to a tube reactor at 0 °C and 5 sec residence time, and 5 M chloroacetyl chloride (**18**) (with a flow rate of 5.0 mL/min) in DMF was continuously introduced to the same tube reactor at 0 °C with 5 min residence time. 2,2-Dimethoxyethan-1-amine (**20**) (8.86 M) was introduced at 1.45 mL/min through another dosage pump connected to the output of the previous process at 10 min residence time and 75 °C and the eluting mixture was then extracted using ethyl acetate. The pH of the ethyl acetate solution was adjusted to 1–2 with HCl while maintaining the temperature at 10–15 °C and the obtained solid was filtered. A 1 M solution of crude filtered product **21** in water at a flow rate of 6.4 mL/min and 17.8 M sulfuric acid were continuously pumped to the tube reactor in 1:10 equivalent manner at 5 min residence time and 70 °C to form praziquinamine (**9**). Upon completion, the reaction was quenched with chilled water and the pH was adjusted to 8–9 with 20% NaOH solution. The resultant product was dissolved in dichloromethane and 1.3 equivalent of triethylamine was added to the solution to get 0.5 M concentration. Then 1:1.1 equivalents of 0.5 M praziquinamine solution and 7.3 M neat cyclohexanoyl chloride (**17**) solutions at a flow rate of 13.28 mL/min and 1.0 mL/min were introduced to the tube reactor at a residence time of 7 min and 25 °C. The reaction was then quenched with water, the organic layer was separated, and sodium sulfate was added to remove the water before distillation. This flow reaction process provided a dry weight of 242 g PZQ with 95% yield with 99.5% HPLC purity (Scheme 6).

A few drawbacks in the known processes[12b,14d,21] are the use of solvents such as chloroform, which is a class 2 solvent and is suspected to cause cancer, and is not environment friendly. In addition, use of two or more equivalents of aminoacetaldehyde dimethylacetal, an expensive raw material, with one equivalent being consumed in the reaction and the second equivalent being lost as waste, can affect the cost at commercial-scale production. The reported state-of-the-art processes are batch process and with large energy consumption. The process described here for the preparation of Praziquantel employs the use of a flow reactor with a smaller footprint, is energy efficient, and requires fewer equivalents of reagents. Furthermore, optionally, all steps can be carried out in a telescoped manner, making the process more economical.

In conclusion, a new continuous-flow chemistry method for the preparation of PZQ and its intermediates has been demonstrated. Optimization of temperature, residence time, reactor volume, equivalents, flow rate, and solvents has been carried out to achieve the maximum yield with high purity on a large scale. Thus, flow chemistry continues to attract industries focusing on process development of APIs and intermediates and opens a wide range of applications in the future.



Scheme 6 The continuous-flow-chemistry-based synthesis of PZQ

The ^{1}H and ^{13}C NMR analysis of the obtained intermediates and PZQ from the current flow-chemistry-derived preparation was carried out with a 400 MHz Bruker instrument using DMSO-d_6 as solvent. The FTIR and UV analyses were conducted with a Thermo Nicolet iS10 instrument and a Shimadzu UV-1800 double-beam spectrophotometer. All flow-chemistry reactions were carried out with a Vapourtec R series modular flow system equipped with multiple dosing pumps and perfuoroalkoxy (PFA) coiled tubes.

Preparation of 2-((2,2-Dimethoxyethyl)amino)-*N*-phenethylacetamide (21)

2-Phenylethanamine (**2**; 100 g) was dissolved in DMF to make 1650 mL of solution (5.0 M in DMF) at a flow rate of 4.54 mL/min, and 1383 g of potassium carbonate was dissolved in water to make 3850 mL of solution (2.6 M in water), at a flow rate of 10.47 mL/min in the tube reactor at 0 °C and 5 sec residence time, and chloroacetyl chloride (**18**; 100 g) diluted to 1770 mL with DMF (5.0 M in DMF) at flow rate of 5.0 mL/min was continuously introduced in a tube reactor of 100 mL volume. The residence time in the reactor was 5 min at *T*=0 °C. The reaction was then quenched with TEA (207 mL) and water (100 mL). The reaction mixture was diluted with DMF (100 mL) and water (50 mL) to make 1.0 M solution of 2-chloro-*N*-phenethylacetamide (**19**). The solution was further pumped into the next tube reactor with a flow rate of 8.55 mL/min along with 2,2-dimethoxyethan-1-amine (**20**) through another pump at a flow rate of 1.45 mL/min at 75 °C and residence time of 10 min. Reaction conversion was recorded and confirmed by HPLC analysis. After completion of the reaction, EtOAc and water were added to the reaction mixture, stirred for 10 min and the layers were separated. The organic layers were combined, washed with water, and concentrated below 50 °C at 600 mm of Hg vacuum. The residue was dissolved in EtOAc, stirred, and the pH of reaction mixture was adjusted to 1–2 with HCl solution at 10–15 °C. The solids were isolated by filtration, washed with EtOAc, and dried under vacuum at 45 °C to yield title compound as white powder. Dry wt = 237.3 g, Yield = 95% and HPLC purity 99%.

2-Chloro-*N*-phenethylacetamide (19)

White powder; mp 66–67 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.31 (s, 1 H), 7.18–7.31 (m, 5 H), 4.03 (s, 2 H), 3.32–3.28 (m, 2 H), 2.74–2.71 (t, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.81, 139.18, 128.64, 128.35, 126.17, 42.63, 40.55, 34.84.

ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{10}H_{12}ClNO^+$: 198; found: 198.0.

2-((Dimethoxymethyl)amino)-*N*-phenethylacetamide (21)

Mp 153–154 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.22 (s, 1 H), 8.82 (t, *J* = 5.5 Hz, 1 H), 7.32–7.18 (m, 5 H), 4.76 (t, *J* = 5.4 Hz, 1 H), 3.68 (s, 2 H), 3.38–3.34 (m, 4 H), 3.32 (s, 6 H), 3.06 (d, *J* = 4.8 Hz, 2 H), 2.74 (t, *J* = 7.3 Hz, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.77, 139.10, 128.67, 128.36, 126.21, 99.69, 54.17, 47.65, 47.36, 40.22, 34.84.

ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{13}H_{20}N_2O_3^+$: 267; found: 267.0.

Preparation of Praziquinamine (9)

2-((2,2-Dimethoxyethyl)amino)-*N*-phenethylacetamide (**21**; 100 g) was dissolved in water to make 330 mL of 1.0 M solution at flow rate of 6.4 mL/min, and sulfuric acid (17.8 M neat) at a flow rate of 3.6 mL/min in equivalent amounts of 1:10 were continuously introduced in a tube reactor of 100 mL. The residence time in the reactor was 5 min at *T*=70 °C. Conversion of reaction was confirmed by TLC. The reaction was quenched in chilled water and the pH of the reaction mass

was adjusted to 8–9 with 20% NaOH solution at 0–25 °C. Dichloromethane was added to the reaction mixture and stirred at RT for 30 min. Layers were separated and the aqueous layer was back-extracted with dichloromethane. The combined organic layers were concentrated under vacuum to yield the title compound as a white solid powder.

Dry wt: 62 g, Purity: 99.1%, Yield: 93.0%. Mp 116–118 °C.

^{1}H NMR (400 MHz, MeOD): δ = 7.27–7.15 (m, 5 H), 4.80–4.73 (m, 1 H), 4.67–4.59 (m, 1 H), 3.71 (dd, *J* = 12.9, 4.0 Hz, 1 H), 3.41–3.24 (m, 2 H), 2.78–2.70 (m, 3 H), 2.62 (dd, *J* = 12.8, 10.3 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.71, 134.99, 134.51, 128.96, 126.36, 125.07, 55.92, 49.52, 49.17, 37.80, 28.39.

ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{12}H_{14}N_2O^+$: 203; found: 203.0.

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.287; H, 6.93; N, 13.86. Found: C, 69.14; H, 6.853; N, 13.26.

Preparation of Praziquantel (1)

A solution of praziquinamine (**9**; 100 g) and TEA (89.6 mL, 1.3 equiv) were added to make 989 mL solution in dichloromethane (0.5 M), and cyclohexanecarbonyl chloride (**17**) (7.3 M neat) in equivalent amounts of 1:1.1, were continuously introduced in a flow reactor of 100 mL and pumped with flow rate of 13.28 mL/min and 1.0 mL/min, respectively. The residence time in the reactor was 7 min at *T*=25 °C. The conversion of the reaction was recorded and confirmed by HPLC analysis. The reaction was quenched in water and extracted in dichloromethane. The organic layer was separated and washed with sodium carbonate solution. The organic layer was distilled below 50 °C at 600 mm of Hg vacuum and the solids were stirred in a methanol/water mixture, filtered, and dried in a vacuum oven to yield Praziquantel as a white powder.

Dry wt: 150 g. Yield: 97%. HPLC Purity: >99%. Mp 135–136 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.33–7.19 (m, 4 H), 4.96 (d, *J* = 7.1 Hz, 1 H), 4.80 (m, 1 H), 4.56–4.49 (m, 1 H), 4.43 (m, 1 H), 3.73 (d, *J* = 17.8 Hz, 1 H), 3.35 (m, 1 H), 2.94–2.75 (m, 4 H), 1.82–1.57 (m, 5 H), 1.42–1.14 (m, 5 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 173.9, 164.7, 164.1, 135.1, 133.2, 129.0, 127.1, 126.5, 125.9, 125.3, 54.8, 53.9, 48.4, 48.0, 45.6, 44.4, 42.1, 38.6, 38.2, 29.2, 28.1, 25.5, 24.9.

ESI-MS: *m*/*z* [M + 1]$^+$ calcd for $C_{19}H_{24}N_2O_2^+$: 313; found: 313.2.

Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 72.98; H, 7.682; N, 8.962. Found: C, 71.46; H, 7.789; N, 9.020.

IR: 2929.7 (aromatic C-), 2852.5 (alkyl C-H), 1661.0, 1627.8 (ketone group C=O), 1445.5, 1421.4 (aromatic C=C), 1357.8 (CH_2), 1299.9 (C-O) and 1211.2 (C-N) cm^{-1}. Data matched the benchmark regions of the Praziquantel.

X-ray diffraction pattern of Praziquantel was recorded with a Shimadzu XRD-6000 Copper Kα (wavelength 1.54060 Å).

Differential scanning colorimetry analysis of Praziquantel with a DSC Thermoanalyser (50–200 °C at 20.0 °C/min) showed a melting pattern of 144.29–148.18 °C. The resulting spectra is included in the Supporting information.

Continuous Preparation of Praziquantel

2-Phenylethanamine (**2**; 100 g) dissolved in 1650 mL DMF (5.0 M in DMF) at a flow rate of 4.54 mL/min and chloroacetyl chloride (**18**; 100 g) diluted up to 1770 mL with DMF (5.0 M in DMF) at a flow rate of 5.0 mL/min were continuously introduced in a tube reactor of 100 mL volume along with potassium carbonate (2.6 M in water), at a flow rate of 10.47 mL/min. The residence time in the reactor was 5 min at *T*=0 °C. 2,2-Dimethoxyethan-1-amine (**20**; 8.55 M) was introduced through another pump at flow rate of 1.45 mL/min at 75 °C and residence time of 10 min. After completion of collection, EtOAc and water were added, the reaction mixture was stirred for 10 min, and layers were separated. Organic layers were combined, washed with water, and concentrated under vacuum. The residue was dissolved in EtOAc, stirred, and the pH of reaction mixture was adjusted to 1–2 with HCl solution at 10–15 °C. The solids were isolated by filtration and then taken in water to make 1 M solution at flow rate of 6.4 mL/min and sulfuric acid (17.8 M neat) at flow rate of 3.6 mL/min in equivalent amounts of 1:10 eq were continuously introduced in a tube reactor of 100 mL. The residence time in the reactor was 5 min at T=70 °C. Conversion of the reaction was confirmed by TLC. The reaction mixture was quenched in chilled H_2O and the pH of the reaction mass was adjusted to 8–9 with 20% NaOH solution at 0–25 °C. Dichloromethane was added and the mixture was stirred at room temperature for 30 min. The organic layer was taken to the next stage as a solution of praziquinamine (**9**) and TEA (1.3 equiv) was added to make a solution in dichloromethane (0.5 M). The solution of **9** and cyclohexanoyl chloride (**17**) (7.3 M neat) in equivalent amounts of 1:1.1, were continuously introduced in a flow reactor of 100 mL and pumped with flow rate of 13.28 mL/min and 1.0 mL/min, respectively. The residence time in the reactor was 7 min at *T* = 25 °C. The conversion of the reaction was recorded and confirmed by HPLC. The reaction was quenched in water, the mixture was extracted in dichloromethane, and the organic layer was separated and washed with sodium carbonate solution. The organic layer was distilled below 50 °C at 600 mm of Hg of vacuum and the solids were stirred in a methanol-water mixture, filtered, and dried in a vacuum oven to yield Praziquantel. Dry wt: 245 g. Percentage yield: 95%, HPLC Purity: 99.5%.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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