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Development of green purification process for piperazine-type drugs: a case study of quetiapine process development

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A thorough study was conducted on the sequential synthesis route of quetiapine fumarate. In this process, a general approach was developed to enhance the quality of a key intermediate of quetiapine. This approach utilized ACD software to calculate the pH values of the intermediate and its impurities, and design distribution experiments according to the pK_a values. Subsequent experimental results demonstrated the feasibility of this strategy, wherein the precise pH control could effectively eliminate impurities and significantly improve the product's quality. Notably, this process could be carried out on the hundred-kilogram scale in the workshop. The multi-batch production has demonstrated the stability and great application value of this process.

Introduction

Green chemistry, commonly known as environmentally friendly chemistry, is dedicated to minimizing or eliminating negative effects on human health and the environment across the entire lifecycle of chemical products and processes, which not only promotes the progress of chemical science, but also has a profound impact on environmental protection, human health, economic development and social sustainable development.[1] In 1998, Paul Anastas and John Warner proposed the 12 principles of green chemistry, marking the formal establishment of green chemistry as an independent discipline.[2] These principles provided a clear framework for the chemical industry, academia, and policymakers.[3,4] In the process of chemical engineering design, the 12 principles play an increasingly significant role, which provide comprehensive guidance for chemical engineering design, helping to create more environmentally friendly, efficient and sustainable chemical processes and products.[3] By adhering to these principles, chemical engineering design can play a crucial role in reducing environmental pollution, lowering health risks, improving resource utilization and promoting sustainable development.[2,3a,5] This not only helps achieve environmental protection goals but also brings significant economic and social benefits. It is particularly important to follow the 12 principles of green chemistry in the pharmaceutical industry. This is because during the production of active pharmaceutical ingredient (API), it not only reduces pollution but also lowers costs, what's more, it helps to minimize the generation of impurities and harmful substances.[3a,6]

In the production, sales and usage stages of API, impurities is one of the most concerned issues, it has a significant impact on the quality and safety of the product.[7] During the production process of drugs, how to remove impurities, especially process impurities, has always been a research hotspot. At present, the methods for removing process impurities mainly fall into two categories: chemical methods and physical methods. Chemical impurity removal methods include: using chemical reagents to form precipitates for impurities, using redox reactions to transform impurities, removing acidic or alkaline impurities through acid–base neutralization reactions, and removing metal impurities through complexation reactions, *etc.*[8] Chemical impurity removal methods are often overlooked due to the possibility for introduction of new impurities, resulting in more physical methods being used for impurity removal during production. The main physical methods include using activated carbon adsorption for impurity removal, using crystallization and pulping based on the difference in solubility for impurity removal, and using extraction based on different solubilities in different solvents for impurity removal, *etc.*[9] However, these methods often lead to yield losses, higher costs, higher *E*-factors, and are inconsistent with the 12 principles of green chemistry.[3a] The ideal method of impurity removal would be able to precisely target and remove impurities without losing the product.

Piperazine is an important structural component in drugs. There are more than 50 marketed drugs that contain the piperazine motif (Fig. 1), such as aripiprazole, ciprofloxacin, bucinnazine, cetirizine, quetiapine, ziprasidone, and so on.[10] The main structural feature of piperazine-type drugs is that each of the N atom at both ends of piperazine is connected to a substituent. Meanwhile, these two substituents are often different from each other. Under such circumstances, when

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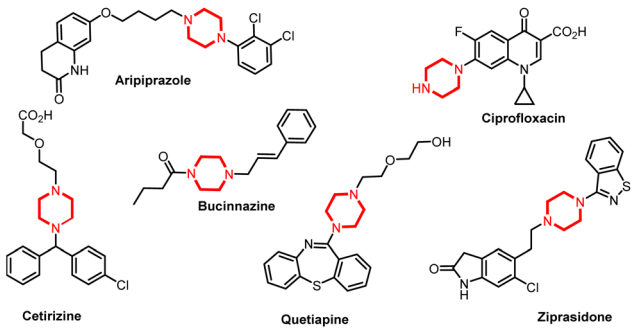
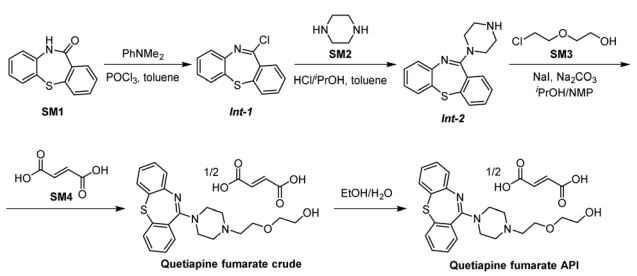


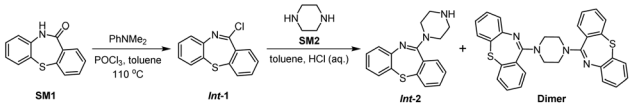
Fig. 1 Representative pharmaceuticals containing piperazine motif.

producing drugs using piperazine as the raw material, it is inevitable that the same part would be connected to the N atom. This is the root cause for the formation of dimer impurities in the production process of piperazine-based drugs. Therefore, how to reduce or inhibit the generation of dimeric impurities during the production process has always been a hot issue. By taking advantage of the slight difference between mono-substituted piperazine and di-substituted piperazine to control the formation of dimeric impurities, the consumption of materials can be reduced, making the impurity removal more convenient. This has positive significance for improving product quality, reducing waste emissions, and lowering production costs, and is in line with the principles of green chemistry.

By analysing the structures of mono-substituted and di-substituted piperazines, their pK_a may vary due to the different numbers of substituents and the dual effects of steric effect and induction effect. During the synthesis and purification of piperazine-based drugs, precise control of pK_a often leads to unexpected results.[11] However, in conventional acid–base extraction process; the determination of the pH range often relies on empirical pH screening. Here, we wish demonstrate a different strategy by using quetiapine fumarate as representative piperazine drug. This strategy first uses ACD software to predict the pK_a values of intermediate and dimer impurity, and then designs and implements pH-dependent experiments based on the predicted pK_a values, thereby quickly determining the optimal pH range for separating intermediate and dimer impurity. Meantime, this predictive framework is foreseeable not limited to quetiapine fumarate but is generalizable to other piperazine-containing drugs where similar dimer impurities arise.



Scheme 1 Sequential synthetic approaches for quetiapine fumarate.



Scheme 2 Reported synthetic route for ***Int*-2**.

At present, sequential synthesis is one of the routes for industrial production of quetiapine (Scheme 1).[12] However, this route also has many problems. These problems are also common problems in the production of piperidine-based drugs. Firstly, dimer impurity is bound to occur and is very difficult to remove. Secondly, during the process of removing dimer impurity, multiple crystallizations using ethanol are required, which will lead to the formation of solvate. Thirdly, ethanol will generate a small amount of ethyl impurity in subsequent reactions, which are extremely difficult to remove, increasing costs and actual consumption. These problems have led to the failure of traditional separation methods. To solve these problems, it is crucial to precisely separate mono-substituted and dis-substituted piperazines. Therefore, we hope to utilize pK_a and solubility during the production process to separate mono-substituted piperazine and avoid it recommended non-reaction to generate dimer impurity.

Results and discussion

The synthetic route of quetiapine fumarate was analysed firstly. In the synthesis of 11-(piperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine (***Int*-2**), the most significant impurity is the dimer impurity (Scheme 2), which is produced by the further reaction of ***Int*-2** with ***Int*-1**. For the dimer, there are two core issues. The first is how to reduce or inhibit its generation during the reaction process. Secondly, how to remove the dimer impurity that have already formed from the ***Int*-2**.

For question 1, the dimer impurity cannot be entirely eliminated from the process; it can only be minimized. The research indicated that the level of dimer is directly related to the amount of anhydrous piperazine (**SM2**), as shown in Table 1. Specifically, the content of dimer decreases as the equivalents of **SM2** increase. Notably, a significant reduction in dimer impurities occurs when the equivalents are increased from 2.0 to 2.5 (Table 1, entries 1 and 2). Further increases in the amount of **SM2** result in a decline gradually in dimer impurities (Table 1,

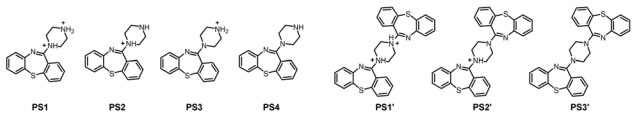
Table 1 The effect of SM2 equivalents on dimer[a,b]

Entry	**SM2** eq.	***Int*-2** %	Dimer %
1	2.0	91.11	8.28
2	2.5	95.88	3.84
3	3.0	96.49	3.16
4	4.0	97.48	2.24

[a] Reaction condition: **SM1** (1.0 equiv.), ***Int*-1** (1.0 equiv.), **SM2** (*X* equiv.), and toluene were added into a three-necked flask with stirring paddle, then heated to 110–115 °C for 4 h. [b] The content was determined by HPLC.

Table 2 The distribution of ***Int*-2** and dimer in two phases under different pH conditions[a,b]

			Organic phase		Aqueous phase	
Entry	pH	Phenomenon	***Int*-2** %	Dimer %	***Int*-2** %	Dimer %
1	3.13	Turbid	Exist	Exist	Exist	n.d
2	2.45	Turbid	0.24	64.38	99.84	0.03
3	2.24	Clear	0.15	68.51	99.86	0.02
4	1.47	Clear	0.10	58.86	99.87	0.02
5	1.15	Clear	0.03	67.73	99.63	0.24
6	0.87	Clear	n.d	26.7%	98.53	1.36



[a] Reaction condition: slowly drip HCl (aq.) to the solution of ***Int*-2** that **SM2** has been removed to adjust to different pH values, test the content of ***Int*-2** and the dimer in organic phase and aqueous phase. [b] The content was determined by HPLC.

entries 3 and 4). Considering the overall costs, we ultimately decided to use 2.5 equivalents of **SM2**.

After obtaining a toluene solution of ***Int*-2** with increased purity, we consider how to remove the dimer that have already formed in the ***Int*-2**. By analysing the structures of ***Int*-2** and the dimer, the fact was discovered that both contain several nitrogen atoms with different basicity. Given structural differences, their pH should be different, which means that in a toluene-water solution, by adjusting pH values, one of substance would preferentially form a salt and enter the aqueous phase, while the other would remain in the organic phase.

With this hypothesis, computer ACD/labs software was used for simulating and evaluating the acidity and basicity of ***Int*-2** and the dimer impurities. The predicted pH value for ***Int*-2** was 8.4 ± 0.1, while that for the dimer impurities was 3.9 ± 0.7 (see the SI for the detailed calculation process), which strengthened our confidence in the hypothesis. This simulation shows that ***Int*-2** is more likely to form salts than dimer impurity. Based on the previous literature and this difference,[12b] we then designed and conducted small-scale experiments to verify the distribution of impurities in the aqueous and organic phases under different pH conditions according to above simulation (Table 2).

By adjusting the pH, we found that when the pH was 3.13 (Table 2, entry 1), the system became turbid and could not be separated into layers. It maybe that under these conditions, both **PS1** and **PS3** forms are present, but since **PS3** has low solubility in both aqueous and organic phases, which caused the system appears turbid. When the pH drops to 2.45, the system could separate into layers, but it requires a long period of standing (Table 2, entry 2). At this moment, the results of HPLC analysis showed that the vast majority (>99%) of ***Int*-2** was distributed in the aqueous phase. This indicated that ***Int*-2** preferentially forms a salt and transfers from the organic to the aqueous phase, whereas the dimer remains in the organic phase without forming a salt. As the pH further decreased to around 2.24 (entry 3), the system completely dissolved. Therefore, we speculate that ***Int*-2** mainly exists in the **PS1** form at this point, which has higher solubility, resulting in a clear solution. HPLC analysis of the organic and aqueous phases revealed that the aqueous phase contained almost exclusively the product, while the organic phase contained mostly dimer. Further reducing the pH to 1.15 and below would cause the dimer to form a salt and enter the aqueous phase significantly (entries 5 and 6). Thus, the pH of system should be controlled between 1.5 and 2.2 to allow ***Int*-2** to form a salt and dissolve in water while retaining the dimer in the organic phase. Simple extraction and separation can achieve precise impurity removal. The obtained ***Int*-2** aqueous solution does not require crystallization for separation as its quality fully meets requirements, allowing it to proceed directly to the next step in solution form.

Table 3 Comparison of the quality of ***Int*-2** before and after pH optimization

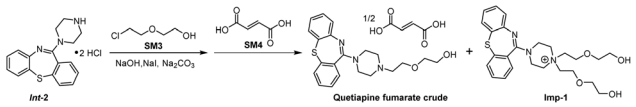
Entry	Process	***Int*-2** %	Dimer %	**SM1** %	Total impurity %
1	Earlier process	99.63	0.06	0.08	0.37
2	New method	99.70	N.D	0.01	0.30
3	New method	99.73	0.02	0.02	0.27
4	New method	99.72	0.03	0.01	0.28

Then, three batches of confirmation experiments were carried out (as shown in Table 3). After pH optimization, the dimer impurities in ***Int*-2** decreased from 0.06% to N.D to 0.03% (50%∼99% reduction), **SM1** decreased from 0.08% to 0.01%∼0.02% (75–88% reduction), and the total impurities decreased from 0.37% to 0.27% ∼0.30% (19–27% reduction). These results clearly indicate that this strategy was successful in effectively removing the dimer impurity and improving the overall purity of ***Int*-2**.

After the optimal process conditions for ***Int*-2** in hand, we then proceeded to optimize the crude product step. The most important impurity during the synthesis of the crude is the quaternary ammonium salt (**Imp-1**), which is generated through the reaction of quetiapine and **SM3**. Some experiments were conducted to obtain the optimal conditions for synthesizing quetiapine fumarate crude (Table 4). Firstly, temperature is an important parameter, and a low reaction temperature prevents the reaction from proceeding completely (entries 1–4). 0.2 equivalent TBAB is necessary, insufficient TBAB resulting in a decrease in the crude product yield to 80.1%. In addition, Na_2CO_3 requires 1.5 equivalent. Reducing the amount of Na_2CO_3 would result in the incomplete reaction of the ***Int*-2**.

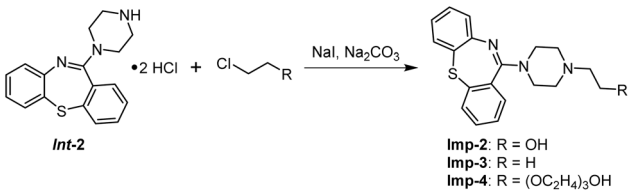
Meanwhile, the process-related impurities, **Imp-2**, **Imp-3** and **Imp-4**, are produced during the synthesis of quetiapine. **Imp-2** is formed by the reaction of ***Int*-2** with residual chloroethanol in the raw materials **SM3**, **Imp-3** is formed by the reaction of ***Int*-2** with residual chloroethane in **SM3**, and **Imp-4** is formed by the reaction of ***Int*-2** with residual 2-(2-(2-(2-chloroethoxy)ethoxy) ethoxy)eth-an-1-ol in **SM3**. These impurities, due to their high similarity to quetiapine, have an unsatisfactory removal rate

Table 4 Optimization of reaction conditions[a,b]



Entry	Temp °C	TBAB eq.	Na_2CO_3 eq.	Yield %	Quetiapine %	***Int*-2** %	**Imp-1** %
1	70	0.1	1.5	—	85.30	13.26	0.39
2	90	0.1	1.5	84.0	98.87	n.d	0.53
3	100	0.2	1.5	83.1	99.71	0.04	0.01
4	110	0.2	1.5	84.6	99.76	0.02	n.d
5	110	0.1	1.5	80.1	99.85	0.04	n.d
5	110	0.2	1.3	84.6	99.76	0.02	n.d
6	110	0.15	1.1	86.3	99.47	0.15	n.d

[a] Reaction condition: ***Int*-2** (1 equiv.), **SM3** (1 equiv.), Na_2CO_3 (X1 equiv.) and NaI (X2 equiv.) were heated at 110 ± 5 °C for 24 h, after completion, the mixture was cooled to 55 ± 5 °C. The reaction was then washed with water, followed by phase separation. The solvent was removed by rotary evaporation, and ethanol and fumaric acid were subsequently added. [b] The content was determined by HPLC.



Scheme 3 The general synthetic route of Imp-2, Imp-3 and Imp-4.

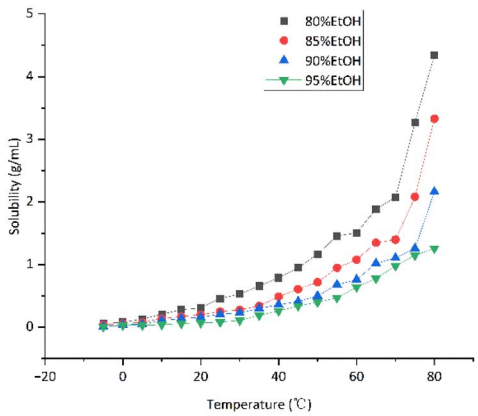


Fig. 2 The solubility curve of quetiapine fumarate.

during the crystallization process. These impurities could be controlled below the detection limit by regulating the content of impurities in **SM3** (Scheme 3).

Crystallization is an extremely important technique in the production of APIs. It not only enables the control of the crystal form of the API, but also effectively removes impurities, thereby further purifying the crude product and obtaining API of qualified quality. The crystallization process of the early quetiapine fumarate API required a large number of solvents, which not only generated a lot of waste but also seriously affected production capacity. To solve this problem, the solubility of the API was measured, and a temperature-solubility curve was obtained (Fig. 2). The curve shows that as the water concentration increases; the solubility of API also increases. Taking into account the production capacity, costs and API quality, 90% ethanol was ultimately selected as the crystallization solvent.

To prove the stability of this process, three batches of confirmation experiments were conducted. Firstly, **SM1** was used to synthesize ***Int*-1**, and then it directly reacted with **SM2** to afford ***Int*-2**. The quality of the ***Int*-2** shows that the improved strategy is effective. By adjusting the pH of the reaction solution, the dimer impurities can be effectively removed to a level of less than 0.10%.

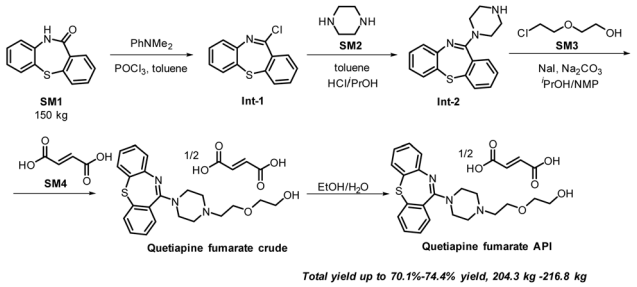
In order to further study the impact of the process optimization on the quality of subsequent intermediates and final products, we used the above three batches of ***Int*-2** to synthesize quetiapine fumarate crude according to the subsequent process. No dimer impurities were detected in quetiapine, and others impurities could be controlled well below the detection limit. The total yield up to 80.7%.

Then, the API was also obtained according to the production process. The quality of API shows the condition optimization was effective. Most of the known impurities in the API, such as dimer and **Imp-2**, were not detected (Table 5). The total impurity level was within 0.15%, and the yield of single-step crystallization reached 94.7%. Collectively, the total yield of the optimized process reached 76.4%.

Table 5 The quality of API after process optimization[a]

Batch	Quetiapine %	**Imp-1** %	Dimer %	Total impurity %	Yield %
1	99.88	n.d	n.d	0.12	73.3
2	99.86	n.d	n.d	0.14	74.6
3	99.89	n.d	n.d	0.11	73.1

[a] **SM1**, ***Int*-2**, **Imp-2**, **Imp-3** and **Imp-4** were not detected.



Scheme 4 Production on the hundred-kilogram scale of quetiapine fumarate.

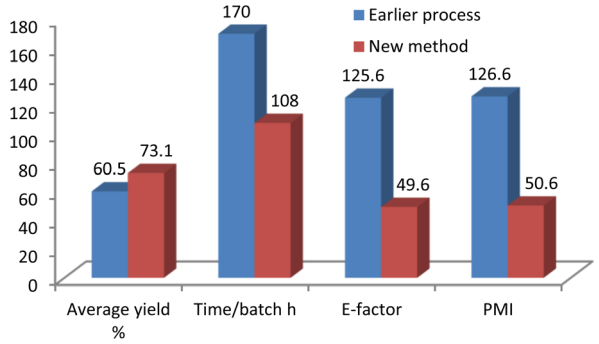


Fig. 3 Comparison of the earlier process & new method.

To further verify the reliability, stability and application value of this strategy, we conducted production validation at the hundred-kilogram scale at Zhejiang Huahai Pharmaceutical Co. Ltd. A total of 6 batches ($n = 6$) of production on the hundred-kilogram scale were carried out (Scheme 4). Each batch uses 150 kg **SM1** to synthesis ***Int*-2** according to the process. The quality of the obtained ***Int*-2** aqueous solution was consistent with expectations, and the conversion rate of **SM1** could reach up to 99%, and the yield of ***Int*-2** could up to 95%. ***Int*-2** was then extracted with toluene, reacted directly with **SM3**, and subsequently with **SM4**, to yield crude quetiapine fumarate. The crude product was further purified using a 90% ethanol aqueous solution to obtain quetiapine fumarate. The purity of API was between 99.67% and 99.80% (RSD = 0.05%, SD = 0.05), that the exceptionally low RSD demonstrate excellent batch-to-batch consistency and confirm the robustness of the purification process. The yield was between 70.1% and 74.4% (SD = 1.46, RSD = 2.00%), that the low RSD values demonstrate good batch-to-batch reproducibility and confirm the stability of the synthetic process. The quality of API was tested thoroughly, and the results demonstrated that it meets the latest regulatory requirements. This demonstrates that this process effectively produces a stable, high-quality, and compliant product (see SI for the detail quality data of ***Int*-2** and API).

In order to confirm whether the optimized process meets the control requirements for impurities as stipulated by ICH M7, a total of 12 potential impurities were assessed, including genotoxic structural alert impurities (Table 6, entries 1–6) and *N*-nitrosamine impurities (Table 6, entries 7–12). For each impurity, the acceptable limit (ppm) was calculated based on the ICH M7 TTC principle (1.5 μg per day) or specific regulatory limits for nitrosamines, using a maximum daily dose of 0.80 g for quetiapine fumarate. All six batches of the API were tested, and none of the 12 impurities were detected (N.D.) in any batch. These results demonstrate that the API is fully compliant with ICH M7 requirements for both genotoxic and nitrosamine impurities.

Finally, a comparison was made between the new method and earlier process based on the average yield, *E*-factor, and batch time. Compared with the earlier process, the new method has significant benefits in terms of environmental protection and cost (Fig. 3). First, the average yield has increased from 60.5% to 73.1%, substantially reducing material costs. Second, the production time per batch has been reduced from 170 h to 108 h, effectively lowering the overall manufacturing cost of the API. More importantly, the *E*-factor has decreased significantly from 125.6 to 49.6, representing a 60.5% reduction in waste generation. The Process Mass Intensity (PMI) decreased from 126.6 to 50.6 (60.0% reduction), which shows a significant decrease in the total amount of materials used per unit product. Overall, the new method has shown significant improvements in terms of yield, efficiency, environmental friendliness and material utilization, which aligns well with the principles of green chemistry.

Table 6 Screening of genotoxic structural alert impurities and *N*-nitrosamine impurities

Entry	Name	Limit ppm	Results
1	2-(Phenylthio)aniline	1.88	N.D
2	1-Chloro-2-nitrobenzene	1.88	N.D
3	(2-Nitrophenyl)(phenyl)sulfane	1.88	N.D
4	Benzene	1.88	N.D
5	Acetaldehyde	10.00	N.D
6	1,1-Diethoxyethane	10.00	N.D
7	*N*,*N*-Diethylnitrous amide (NDEA)	0.03	N.D
8	*N*,*N*-Dimethylnitrous amide (NDMA)	0.12	N.D
9	11-(4-Nitrosopiperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine	0.43	N.D
10	2-(2-(4-Nitrosopiperazin-1-yl)ethoxy)ethan-1-ol	0.43	N.D
11	1-Nitrosopiperazine	0.43	N.D
12	1,4-Dinitrosopiperazine	0.43	N.D

Conclusions

In conclusion, an efficient synthetic route for quetiapine fumarate was developed. This process could obtain the key intermediate and API with high quality and yield through a simple post-processing procedure, which indicates that significant progress has been made in the green production of quetiapine fumarate. Especially when synthesizing ***Int*-2**, the precise removal of the dimer was achieved through pK_a and solubility. The production verification at the hundred-kilogram scale has demonstrated the reliability and stability of this process. Moreover, the method of separating intermediates and dimers through precise pH control could be expected to be extended to all piperazine-typed drugs as well as to these drugs containing secondary amine structures, which have the common problem that the intermediates or products are difficult to separate from the dimer.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Data will be made available on request.

Supplementary information (SI) is available. See DOI: https://doi.org/10.1039/d6ra00670a.

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