Organic Process Research & Development

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# Improved Process for Ranolazine: An Antianginal Agent†

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**ABSTRACT:** An improved process has been developed for the active pharmaceutical ingredient, ranolazine with 99.9% purity and 47% overall yield (including three chemical reactions and one recrystallization). Formation and control of all the possible impurities is described. All the solvents used in the process were recovered and reused. The unreacted piperazine is recovered as piperazine monophosphate monohydrate salt.

## 1. INTRODUCTION

Ranolazine (**1**) is a novel antianginal agent developed by Syntex[1−4] with the brand name Ranexa. Ranolazine is a new cardioselective and metabolism regulating antianginal drug. The mechanism of action is to inhibit the partial oxidation of fatty acid and modify the oxidation metabolism of heart fatty acid into the oxidation metabolism of glucose and, therefore, to reduce the oxygen consumption of the heart without causing any change of heart rate and blood pressure. It is reported that ranolazine can be used to treat myocardial infarction, congestive heart disease, angina, and arrhythmia, etc., and so far it is the one and only antianginal agent that will not cause any change in homodynamic, heart rate, or blood pressure.

A literature review revealed the presence of several different routes for the synthesis of ranolazine.[5,6] However, the reaction of piperazine derivative **6** and epoxy derivative **9** is the most practiced route (Scheme 1).[7−10] Synthesis of piperazine derivative **6** involves chloroacetylation of 2,6-dimethylaniline (**2**) with chloroacetyl chloride (**3**) followed by reaction with piperazine (**5**). Epoxy derivative **9** involves *O*-alkylation of 2-methoxyphenol (**7**) with epichlorohydrin (**8**). Nevertheless, the reported processes have some disadvantages. The literature search indicated that, the detailed impurity profile study was not reported for ranolazine. The maximum daily dosage of ranolazine is 2 g; therefore, known and unknown impurities must be shown below 0.05% in the final pharma.[11] In view of this stringent quality requirement, it is mandatory to study the detailed impurity profile to control the formation and to eliminate the impurities. To overcome the problems associated with the reported processes and to have a complete impurity profile study, we planned to study Scheme 1 in detail. Herein we report an improved and scalable process for the preparation of key starting material, piperazine derivative **6**, and ranolazine **1**. In addition to this, a detailed impurity profile study including conditions for the formation and control of impurities is discussed. A key starting material, epoxy derivative **9** utilized in the present work was synthesized according to the reported process.[5]

## 2. RESULTS AND DISCUSSION

**2.1. New Process Conditions for Chloroacetamide Derivative 4.** Chloroacetylation of 2,6-dimethylaniline (**2**) according to the process reported[5] using triethylamine in dichloromethane resulted in a grey colored solid in ∼80% yield and ∼95% purity. Another process was reported with 54% yield using 2 mol of 2,6-dimethylaniline (**3**) without use of any additional base,[12] which made the process more expensive. Xiao-lin et al.[9] reported a process with 94% yield using a mixture of toluene and water as a reaction medium, but the quality was not mentioned. In a recently published patent,[10] 82% yield and 99% purity were reported using 1.3 mol of sodium bicarbonate as a base and water as a reaction medium. Hence, to improve the yield and purity, we intended to optimize the key process parameters.

In this regard, different solvents, such as toluene, a mixture of toluene and water, dichloromethane, acetone, ethyl acetate, and a mixture of ethyl acetate and water, and different bases were screened at 0−5 °C. The experimental results indicated the optimum yield and purity obtained using dichloromethane and sodium carbonate (Table 1).

After selecting the solvent and base, another key process parameter, base mole ratio, was studied. On the basis of experimental results, a 0.5 mol ratio of sodium carbonate was found to be sufficient for the chloroacetylation reaction (Table 2). After completion of the reaction, water was added and the dichloromethane removed completely; then the precipitated solid was filtered.

During the initial experiments, we identified a new impurity at around 1.0%. On the basis of the LC−MS data, this impurity was identified as dichloro acetamide derivative **10** (Figure 1). The root cause for the formation of **10** was confirmed as the presence of dichloroacetyl chloride in the purchased chloroacetyl chloride. It was observed that the presence of 5% dichloroacetyl chloride in the chloroacetyl chloride leads to the

†Dr. Reddy's Communication no. IPDO IPM-00312.

Received: January 26, 2012
Published: April 12, 2012

**Scheme 1. Reported Synthetic Scheme for Ranolazine**

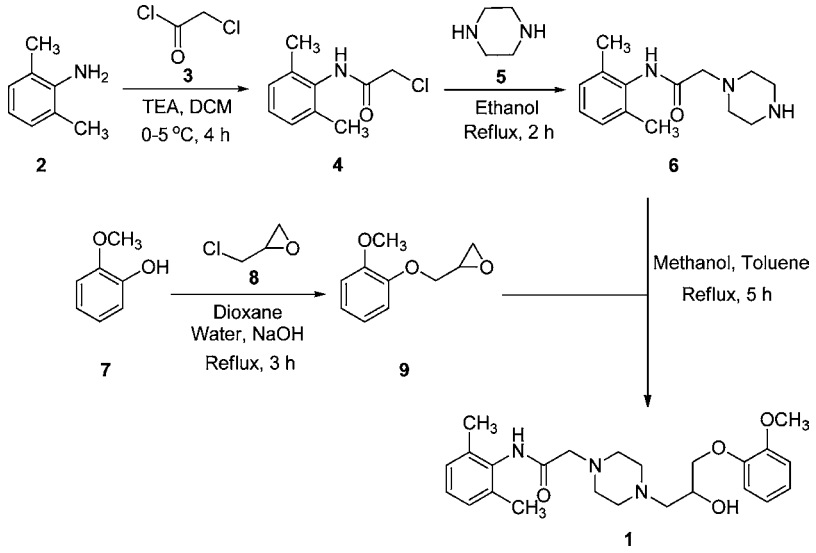



**Table 1. Solvent and Base Screening for Chloroacetylation of 2**

| entry | solvent | time (h) | base | purity (%) | 2 (%) | yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | toluene | 6 | $Na_2CO_3$ | 99.0 | 0.3 | 90 |
| 2 | mixture of toluene and water | 4 | $Na_2CO_3$ | 95.2 | 4.8 | 72 |
| 3 | acetone | 6 | $Na_2CO_3$ | 96.4 | 0.05 | 91 |
| 4 | dichloromethane | 5 | $Na_2CO_3$ | 99.5 | 0.02 | 97 |
| 5 | dichloromethane | 5 | TEA | 95.1 | 0.03 | 80 |
| 6 | mixture of ethyl acetate and water | 3 | $Na_2CO_3$ | 99.2 | 0.08 | 90 |
| 7 | ethyl acetate | 4 | $Na_2CO_3$ | 98.9 | 0.1 | 82 |
| 8 | water | 4 | $NaHCO_3$ | 98.6 | 0.1 | 80 |

[a]Isolated.

**Table 2. Optimization of Sodium Carbonate Mole Ratio for Chloroacetylation of 2**

| entry | sodium carbonate (m/r) | purity (%) | yield (%)[a] |
|---|---|---|---|
| 1 | 0.5 | 99.8 | 96 |
| 2 | 0.75 | 99.7 | 96 |
| 3 | 1.2 | 99.7 | 95 |
| 4 | 1.5 | 99.5 | 95 |

[a]Isolated.

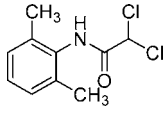


**Figure 1.** Dichloroacetamide derivative **10**.

formation of ~1.0% compound **10**. Hence, to avoid the formation of **10**, the content of dichloroacetyl chloride in the chloroacetyl chloride was controlled below 0.5%. With this stringent control, compound **10** was observed at below 0.1% level in the chloroacetamide derivative **4**.

Having redesigned the process conditions, our focus was shifted to the utilization of the recovered dichloromethane for the synthesis of compound **4**. The purity of recovered dichloromethane was found to be 99.9%. The use test experimental results showed that the recovered dichloromethane resulted in good yield and purity (Table 3).

**Table 3. Use Test Experiments of 4 with Recovered Dichloromethane**

| entry | purity (%) | yield (%)[a] | solvent recovery (%) |
|---|---|---|---|
| 1 | 99.7 | 97 | 75 |
| 2 | 99.8 | 97 | 70 |

[a]Isolated.

Therefore, the new process conditions, dichloromethane and 0.5 mol ratio of sodium carbonate, furnished compound **4** in 97% yield with 99.8% purity.

### 2.2. New Process Conditions for Piperazine Derivative 6.

Synthesis of piperazine derivative **6** involves *N*-alkylation of piperazine (**5**) with compound **4**. Most of the reported processes for the preparation of **6** involve the use of ethanol as a solvent and 3 mol of **5** with ~70% yield and without any quality data.[5,7−9] Bis alkylated product **11** (Figure 2) is a potential impurity, which forms during the *N*-alkylation of **5**. Foye et al.[12] reported a process to avoid the formation of bis alkylated product **11**; however, this process has more steps and a much lower overall yield (2.1%). Guillaume et al.[13] reported a process to control the formation of bis alkylated product **11** with 68% yield. In this process the formation of compound **11**

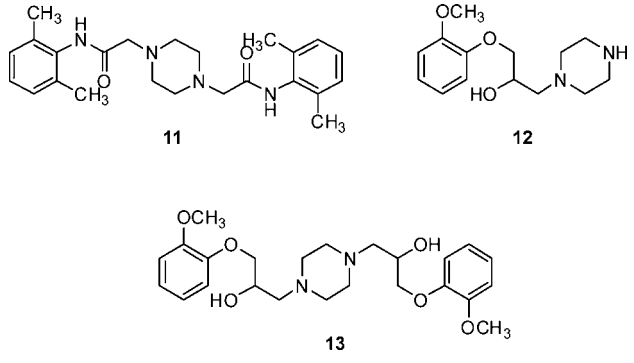



**Figure 2.** Structures of impurities **11**, **12**, and **13**.


dx.doi.org/10.1021/op300026r | Org. Process Res. Dev. 2012, 16, 748−754

was controlled up to 7% and was removed by the simple filtration. The fate of unreacted **5** in the next reaction is not discussed in the literature. In view of lower yields (~70%) and to study the impact of **5** on the quality of the next reaction, we wanted to study the process in detail.

Various solvents, such as water, toluene, *N*,*N*-dimethyl formamide, isopropyl alcohol, acetone, aqueous HCl, and methanol, were examined for the *N*-alkylation of **5**. Isopropyl alcohol, water, and acetone resulted in greater amounts of bis alkylated product **11**. Compared to the case for methanol, lower yields were observed in all other solvents (Table 4). Thus, methanol is an appropriate solvent for the *N*-alkylation of **5**.

**Table 4. Solvent Screening for Piperazine Derivative 6**

| entry | solvent | temp (°C) | time (h) | purity (%) | **11** (%) | yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | methanol | 60−65 | 2 | 99.5 | 0.1 | 76 |
| 2 | acetone | 50−55 | 2.5 | 98.7 | 0.4 | 71 |
| 3 | water | 60−65 | 2 | 98.9 | 0.9 | 66 |
| 4 | toluene | 60−65 | 2 | 98.8 | 0.2 | 71 |
| 5 | isopropyl alcohol | 60−65 | 4 | 96.6 | 2.9 | 56 |
| 6 | *N*,*N*-dimethyl formamide[b] | 60−65 | 1.5 | | | |
| 7 | aqueous HCl | 60−65 | 2.5 | 98.7 | 0.4 | 61 |

[a]Isolated. [b]Gummy solid observed.

Another important parameter, piperazine (**5**) mole ratio, was also studied in the methanol medium. On the basis of the results, it was observed that a minimum of 3 mol of **5** is required to minimize the formation of bis alkylated product **11** and more than 3 mol has no significant advantage (Table 5).

**Table 5. Study of Piperazine (5) Mole Ratio for *N*-Alkylation Reaction**

| entry | **5** (m/r) | purity (%) | yield (%)[a] | content of **11**(%) |
|---|---|---|---|---|
| 1 | 1.0 | 63.8 | 21 | 34.6 |
| 2 | 2.0 | 98.0 | 53 | 1.8 |
| 3 | 3.0 | 99.6 | 76 | 0.1 |
| 4 | 4.0 | 99.5 | 77 | 0.1 |

[a]Isolated.

We were able to improve the yield up to 76% with 99.6% purity by using methanol and 3 mol of **5** at reflux temperature. Around 0.3% of residual piperazine (**5**) was observed in the final isolated compound **6**. We identified that the piperazine present in compound **6** is reacting with epoxy derivative **9** and leading to the formation of impurities **12** and **13** in the next reaction (Figure 2).

To study the impact of piperazine (**5**) content on the formation of impurities **12** and **13**, experiments were conducted with piperazine derivative **6** having **5** at different levels (Figure 3). Experimental results indicate that the impurity **13** forms significantly in the next reaction (preparation of ranolazine). Recrystallization of ranolazine was tried in different solvents to wash out the impurity **13** to below the acceptable limit (0.05%). But we could not succeed, because of the similar solubility patterns of ranolazine **1** and impurity **13**. In view of this, the content of **5** must be controlled at below 0.05% in the piperazine derivative **6**.

Among the bis alkylated product **11** and unreacted piperazine (**5**), we focused on the control of **5**, because the

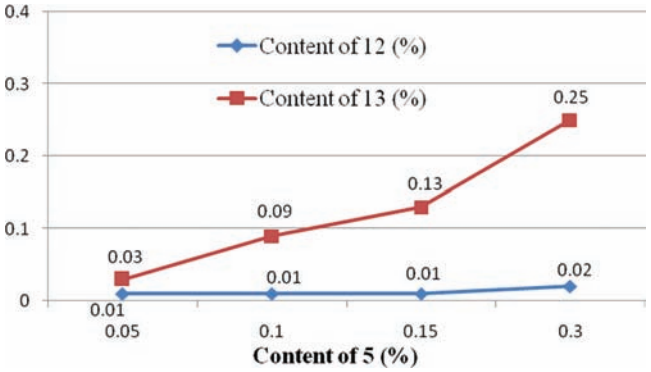



**Figure 3.** Impact of piperazine (**5**) content on the formation of **12** and **13**.

formation, control, and elimination of **11** were well studied and documented.[10,13] To reduce the piperazine content, compound **6** was converted into the hydrochloride salt and the phosphate salt followed by conversion into the free base. By converting into the hydrochloride salt, piperazine content was reduced to 0.02% from 0.5%, whereas converting into the phosphate salt, piperazine content was reduced to 0.008% from 0.5%. Therefore, converting into the phosphate salt is found to be the best option to reduce the piperazine content. On the basis of the solubility variation of piperazine phosphate salt and the phosphate salt of compound **6** in water, excess piperazine was recovered as piperazine monophosphate monohydrate from the aqueous layer by adjusting the aqueous layer pH to 5.0−5.5 with phosphoric acid. With this modification, the piperazine (**5**) content in compound **6** was reduced significantly (~0.01%). Three consecutive experiments were conducted with modified process conditions to check the quality of **6**. Experimental results are indicating that compound **6** is obtained with consistent yield and quality (Table 6).

**Table 6. Experimental Results of 6 Prepared by New Process Conditions[a]**

| entry | **6** (%) | **5** (%) | **4** (%) | **11** (%) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 99.7 | 0.01 | ND | 0.01 | 70 |
| 2 | 99.8 | 0.01 | ND | ND | 68 |
| 3 | 99.8 | 0.01 | ND | 0.03 | 71 |

[a]ND = Not detected. [b]Isolated.

All the solvents (methanol, dichloromethane, and cyclohexane) used in the process were recovered with 85%, 75%, and 80% yield, respectively, and reused in the preparation of piperazine derivative **6**.

### 2.3. Redesign of the Manufacturing Process for 1.

Preparation of ranolazine involves the reaction of piperazine derivative **6** and epoxy derivative **9** in the solvent medium. Xiao-lin et al.[9] prepared the ranolazine using a mixture of methanol and toluene. This process involves recrystallization of crude ranolazine from the mixture of ethanol and ether with 70% yield and without any quality data. Another process was reported using a single solvent, toluene,[10] but this process involves a laborious workup process, acid base treatment, product extraction with dichloromethane, and solvent evaporation followed by recrystallization from ethanol. Kluge and coworkers[5] reported a process using a mixture of methanol and toluene, and isopropyl alcohol, which also involves a cumbersome workup process including column chromatography


dx.doi.org/10.1021/op300026r | Org. Process Res. Dev. 2012, 16, 748−754

and conversion into ranolazine dihydrochloride salt followed by conversion into the ranolazine **1**. To overcome these problems and to make a simple and less expensive process, we intended to optimize the key parameters.

Different solvents were screened for the reaction of **6** and **9** (Table 7). Acetone, acetonitrile, and ethyl acetate gave better

**Table 7. Solvent Optimization for the Preparation of 1**

| entry | solvent | temp (°C) | time (h) | **1** (%) | **9** (%) | yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | acetone | 50−55 | 15 | 97.5 | 1.9 | 88 |
| 2 | tetrahydrofuran[b] | 65−70 | 12.5 | | | |
| 3 | acetonitrile | 80−85 | 8 | 98.0 | 1.0 | 88 |
| 4 | water | 95−100 | 7.5 | 73.0 | ND | 61 |
| 5 | ethyl acetate | 75−80 | 13.5 | 97.0 | 1.0 | 80 |
| 6 | methanol | 60−65 | 4.5 | 92.0 | 2.0 | 78 |
| 7 | isopropyl alcohol | 80−85 | 8.5 | 94.0 | 2.0 | 71 |
| 8 | *N*,*N*-dimethylformamide | 75−80 | 4.5 | 94.0 | 4.0 | 89 |

[a]Isolated. [b]50% reaction completed; therefore, solid not isolated.

results compared to other solvents. In view of cost and recoverability, acetonitrile is not preferable; compared to ethyl acetate, acetone furnished better yield. Hence, acetone was selected for the preparation of ranolazine **1**.

After selecting the suitable solvent, we studied the mole ratio of epoxy derivative **9**. Theoretically, one mole ratio of **9** is sufficient; however, the experimental results indicate that a 1.3 mol ratio of **9** is required to obtain the optimum yield and purity (Table 8).

**Table 8. Optimization of the Mole Ratio of 9 for the Preparation of 1**

| entry | **9** (m/r) | **1** (%) | **6** (%) | residual **9** (%) | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | 1.0 | 97.5 | 1.2 | 0.1 | 53 |
| 2 | 1.3 | 98.6 | 0.06 | 0.6 | 88 |
| 3 | 1.5 | 96.6 | 0.05 | 2.0 | 86 |

[a]Isolated.

It was observed that the reaction temperature plays a major role in the rate of reaction. At room temperature, the reaction was not completed after 40 h also, whereas, at the reflux temperature, the reaction was completed within 16 h. Hence, the reflux temperature was selected for the reaction of compounds **6** and **9**.

After studying the key process parameters, we paid attention to the workup process. It was observed that ranolazine is precipitating out from the reaction mixture at cold conditions. Hence, the reaction mass was subjected to cooling to 0−5 °C and the precipitated solid was separated by simple filtration to provide the ranolazine in 88% yield. The product obtained from the acetone medium showed 98.6% purity, 0.6% epoxy derivative **9**, and another impurity **14** also observed at a level of ∼0.1%. Clearly the formation of impurity **14** is from the presence of unreacted epichlorohydrin (**8**) in the epoxy derivative **9** (Scheme 2). To meet the quality requirement,[11] crude ranolazine needs to be purified. In this regard, the crude ranolazine was recrystallized from different solvents to improve the purity. The experimental results indicated that the mixture of methanol and acetone (1:4) is a suitable solvent medium for the purification of crude ranolazine (Table 9).

**Table 9. Solvent Optimization for Recrystallization of 1[a]**

| entry | solvent | **1** (%) | **9** (%) | **14** (%) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | acetone | 99.6 | 0.04 | 0.04 | 78 |
| 2 | methanol | 99.9 | ND | 0.01 | 50 |
| 3 | methanol and acetone (1:4) | 99.9 | ND | 0.02 | 75 |

[a]ND: Not detected. [b]Isolated.

After selecting the solvent, we studied other important process parameters: temperature and maintenance time for the recrystallization of **1**. However, better results were obtained at 0−5 °C and maintain the reaction mixture for 3.5 h.

**Table 10. Optimization of Temperature for Recrystallization of 1[a]**

| entry | temp (°C) | **1** (%) | **9** (%) | **14** (%) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | −10 to −5 | 99.8 | 0.02 | 0.03 | 79 |
| 2 | 0 to 5 | 99.9 | ND | 0.02 | 78 |
| 3 | 10 to 15 | 99.9 | ND | 0.01 | 68 |

[a]ND: Not detected. [b]Isolated.

**Table 11. Optimization of Maintenance Time for Recrystallization of 1[a]**

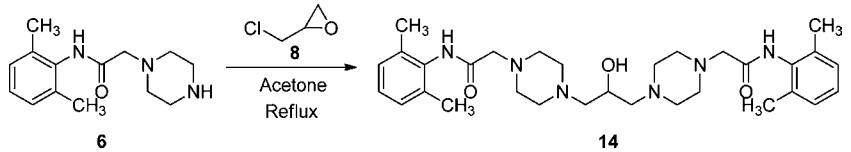
| entry | time (h) | **1** (%) | **9** (%) | **14** (%) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 1 | 99.8 | 0.01 | 0.02 | 75 |
| 2 | 2.5 | 99.9 | ND | 0.02 | 77 |
| 3 | 3.5 | 99.9 | ND | 0.01 | 78 |
| 4 | 9.5 | 99.9 | ND | 0.01 | 78 |

[a]ND: Not detected. [b]Isolated.

Having prepared highly pure ranolazine, the focus was shifted toward the utilization of the solvents used in the process. Acetone and a mixture of methanol and acetone were recovered by simple distillation, and reused in the process. It was observed that comparable results were obtained using the recovered solvents (Tables 12 and 13). The ratio of the recovered mixture of methanol and acetone was adjusted to 1:4 by the addition of required fresh solvent.

Finally, three consecutive experiments were carried out by implementing the newly designed process conditions (Scheme 3) to check the consistency of yield and quality (Table 14). These experimental results indicate that ranolazine is obtained consistently with 99.9% purity and 47% overall yield (including three chemical reactions and one recrystallization).

**Scheme 2. Synthetic Scheme for Impurity 14**




6 14


dx.doi.org/10.1021/op300026r | Org. Process Res. Dev. 2012, 16, 748−754

**Table 12. Experimental Results of 1 Using Recovered Acetone**

| entry | 1 (%) | residual 9 (%) | yield (%)[a] | purity (%)[b] | solvent recovery (%) |
|---|---|---|---|---|---|
| 1 | 99.9 | 0.01 | 75 | 99.7 | 75 |
| 2 | 99.9 | 0.01 | 73 | 99.7 | 78 |

[a]Isolated. [b]Purity of recovered acetone by GC.

**Table 13. Experimental Results of 1 Using a Recovered Mixture of Methanol and Acetone (1:4)**

| entry | 1 (%) | residual 9 (%) | yield (%)[a] | purity (%)[b] | solvent recovery (%) |
|---|---|---|---|---|---|
| 1 | 99.9 | 0.01 | 74 | 99.9 | 77 |
| 2 | 99.9 | 0.01 | 75 | 99.9 | 80 |

[a]Isolated. [b]Purity of recovered mixture of methanol and acetone by GC.

## 3. SUMMARY

Indeed, we have developed an improved and scalable process for the preparation of ranolazine with 99.9% purity and 47% overall yield (including three chemical reactions and one recrystallization). The root causes for the formation and control of all the possible impurities were discussed. The process mentioned in this article has certain advantages over the processes reported.

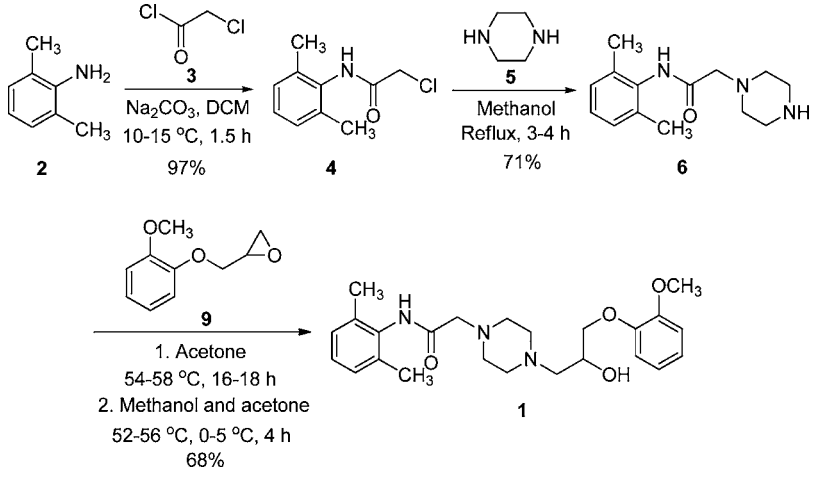
## 4. EXPERIMENTAL SECTION

A liquid chromatograph equipped with a variable wavelength UV detector and integrator was used in recording HPLC data. The $^1$H NMR and $^{13}$C NMR spectra were measured in $CDCl_3$ and DMSO-$d_6$ on Varian Gemini 400 MHz and Unity INOVA (Varian 500 MHz) FT NMR spectrometers, and the chemical shifts are reported in $\delta$ ppm relative to TMS ($\delta$ 0.0 ppm), $CDCl_3$ ($\delta$ 77.0 ppm) and DMSO-$d_6$ ($\delta$ 39.50 ppm). The FT IR spectra were recorded as KBr dispersions using a Perkin-Elmer 1650 FT IR spectrophotometer. Mass spectra (70 eV) were recorded on a HP-5989A LC−MS spectrometer. Solvents and reagents were used without further purification.

**[(2,6-Dimethylphenyl)aminocarbonylmethyl] Chloride (4).** Chloroacetyl chloride (6.72 kg, 59.5006 mol) was slowly added to a suspension of 2,6-dimethylaniline (6 kg, 49.5131 mol), dichloromethane (30 L), and sodium carbonate (2.62 kg, 24.7170 mol) at 10−15 °C. The resultant reaction mixture was stirred for 1.5 h at 10−15 °C. Water (60 L) was charged into the reaction mixture at 25−35 °C. Dichloromethane was distilled off completely below 45 °C under reduced pressure and cooled to 25−35 °C. The reaction mixture was stirred for 60 min at 25−35 °C, and then the solid was filtered and washed with water (12 L). The wet solid was dried under reduced pressure (400 mmHg) at 70 °C to furnish the 9.46 kg (97%) of the title compound with 99.8% purity by HPLC.[14] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.85 (s, 1H), 7.26−7.08 (m, 3H), 4.25 (s, 2H), 2.24 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.4, 135.4, 132.7, 128.4, 127.9, 42.8, 18.5, 18.3; IR (KBr, cm$^{-1}$): 3214, 3036, 2973, 1645, 1594, 1536, 1476; MS ($m/z$): 197.9 ($M^+$ + H); Mp: 146−148 °C; Anal. Calcd for $C_{10}H_{12}ClNO$ (197.66): C 60.76, H 6.12, N 7.09. Found: C 60.72, H 6.22, N 7.15.

**1-[(2,6-Dimethylphenyl)aminocarbonylmethyl]-piperazine (6).** Chloroacetamide derivative **4** (7 kg, 0.5059 mol), piperazine (9.14 kg, 1.5161 mol), and methanol (21 L) were charged into a reactor at 25−35 °C, stirred for 5−10 min, and then heated to reflux for 3−4 h. Methanol was distilled off completely below 65 °C under reduced pressure and cooled to 25−35 °C. Water (56 L) was added to the reaction mixture at 25−35 °C and stirred for 40 min. The unwanted solid (bis alkylated compound **11**) was filtered and washed with water (21 L). The resultant filtrate was charged into a reactor and the pH adjusted to 5.0−5.5 with 44% phosphoric acid solution (9.8 L) at room temperature. The reaction mixture was stirred for 30 min, and the piperazine monophosphate monohydrate salt was filtered. The filtrate was washed with water (7 L) and the pH adjusted to 10−11 with 20% aqueous sodium hydroxide solution (11.2 L). Dichloromethane (14 L) was charged and stirred for 5 min. Aqueous and organic layers were separated, and the product was extracted from the aqueous layer with dichloromethane (2 × 35 L). The total organic layers were combined, washed with water (21 L), and concentrated below 40 °C to 80% of the total volume. Cyclohexane (35 L) was charged and concentrated up to 70 °C. The resultant mass was stirred for 1.5 h at 25−35 °C, solid was filtered, washed with cyclohexane (100 mL), and dried at 50−55 °C under reduced pressure (400 mmHg) to afford 6.23 kg (71%) of the title compound with 99.8% purity by HPLC.[14] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.66 (s, 1H), 7.13−7.07 (m, 3H), 3.19 (s, 2H), 2.97 (t, $J$ = 4.8 Hz, 4H), 2.67 (t, $J$ = 4.8 Hz, 4H),

**Scheme 3. Synthetic Scheme for Ranolazine with New Process Conditions**





dx.doi.org/10.1021/op300026r | Org. Process Res. Dev. 2012, 16, 748−754

Table 14. Experimental Results of 1 Prepared by New Process Conditions[a]

| | | | | | | | | | residual solvents (ppm) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| entry | **1** (%) | **6** (%) | **9** (%) | **10** (%) | **11** (%) | **12** (%) | **13** (%) | **14** (%) | methanol | acetone | yield (%)[b] |
| 1 | 99.91 | 0.01 | 0.01 | ND | 0.02 | ND | 0.01 | 0.02 | 522 | 1164 | 46.8 |
| 2 | 99.90 | ND | 0.01 | ND | 0.02 | ND | 0.02 | 0.02 | 281 | 918 | 47.0 |
| 3 | 99.92 | 0.01 | 0.01 | ND | 0.01 | ND | 0.01 | 0.01 | 519 | 1570 | 47.1 |

[a]ND: Not detected. [b]Overall.

2.23 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.5, 135.0, 133.7, 128.3, 127.2, 62.4, 55.0, 46.3, 18.6; IR (KBr, cm$^{-1}$): 3337, 3298, 2949, 1677, 1595, 1500, 1479; MS ($m/z$): 248.1 ($M^+$ + H); Mp: 114−116 °C; Anal. Calcd for $C_{14}H_{21}N_3O$ (247.34): C 67.98, H 8.56, N 16.99. Found: C 67.88, H 8.62, N 16.87.

**(±)-*N*-(2,6-Dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazine Acetamide (Ranolazine).** Acetone (25 L), epoxy derivative **9** (4.75 kg, 26.3596 mol), and piperazine derivative **6** (5 kg, 20.2151 mol) were charged into a reactor and then heated to 54−58 °C for 16−18 h. The reaction mixture was cooled to 0−5 °C and stirred for 3−4 h. The precipitated solid was filtered and washed with chilled acetone (5 L). The resultant wet solid was charged into a mixture of acetone (28 L) and methanol (7 L), and heated to 52−56 °C for 45 min. The reaction mixture was cooled slowly to 0−5 °C and stirred for 4 h. The precipitated solid was filtered, washed with chilled acetone (5 L), and dried at 70−75 °C under reduced pressure (400 mmHg) to afford 5.9 kg (68%) of the title compound **1** with 99.92% purity by HPLC.[14] Residual solvents: methanol, 519 ppm; acetone, 1570; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 9.13 (s, 1H), 7.06 (s, 3H), 6.98−6.85 (m, 4H), 4.77 (s, 1H), 3.95 (d, $J$ = 7.2 Hz, 2H), 3.93−3.83 (m, 1H), 3.75 (s, 3H), 3.10 (s, 2H), 2.51−2.37 (m, 10H), 2.08 (s, 6H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 167.9, 149.2, 148.3, 135.0, 134.9, 127.6, 126.3, 120.9, 120.7, 113.6, 112.3, 71.9, 66.6, 61.4, 61.1, 55.5, 53.3, 53.1, 18.2; IR (KBr, cm$^{-1}$): 3330, 3002, 2955, 2936, 1686, 1592, 1506, 1495, 1253, 1224; MS ($m/z$): 428 ($M^+$ + H); Mp: 120−121.5 °C; Anal. Calcd for $C_{24}H_{33}N_3O_4$ (427.54): C 67.42, H 7.78, N 9.83. Found: C 67.62, H 7.47, N 9.68.

**2,2-Dichloro-*N*-(2,6-dimethylphenyl)acetamide (10).** Dichloroacetyl chloride (14.6 g, 0.0990 mol) was slowly added to a suspension of 2,6-dimethylaniline (10 g, 0.0825 mol) and sodium carbonate (8.8 g, 0.0830 mol) in dichloromethane (50 mL) at 10−15 °C. The resulted reaction mixture was stirred for 1.5 h at 10−15 °C. Water (100 mL) was charged into the reaction mixture at 25−35 °C, and the dichloromethane was distilled off completely below 45 °C under reduced pressure. Then the reaction mixture was cooled to 25−35 °C for 60 min, and the solid was removed by filtration and washed with water (20 mL). The wet solid was charged into *n*-hexane (50 mL) and stirred for 30 min at 25−35 °C. The solid was filtered, washed with *n*-hexane (10 mL), and dried under reduced pressure at 70 °C under reduced pressure (400 mmHg) to provide 15 g (78%) of the title compound **10** with 99.7% purity by HPLC.[14] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.72 (s, 1H), 7.18−7.09 (m, 3H), 6.07 (s, 1H), 2.26 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 162.6, 135.6, 131.7, 128.5, 128.2, 66.8, 18.0; IR (KBr, cm$^{-1}$): 3245, 3039, 2925, 1676, 1593, 1541, 1470; MS ($m/z$): 232 ($M^-$ − H); Mp: 169−171 °C; Anal. Calcd for $C_{10}H_{11}Cl_2NO$ (232.11): C 51.75, H 4.78, N 6.03. Found: C 51.92, H 4.90, N 6.15.

**1,4-Bis[(2,6-dimethylphenyl)aminocarbonylmethyl]-piperazine (11).** To a solution of **4** (10 g, 0.0506 mol) in methanol (30 mL) was charged piperazine (**5**, 4.4 g, 0.0511), and the reaction mixture was heated to reflux and stirred for 3 h. The reaction mixture was cooled to 25−35 °C and stirred for 60 min. The precipitated solid was filtered and washed with methanol (10 mL). Wet solid was dried at 55 °C under reduced pressure (400 mmHg) to afford 10 g (48%) of the title compound **11** with 99.0% purity by HPLC.[14] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.56 (s, 2H), 7.14−7.07 (m, 6H), 3.25 (s, 4H), 2.82 (s, 8H), 2.24 (s, 12 H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.1, 134.9, 133.5, 128.4, 127.3, 61.7, 54.0, 18.7; IR (KBr, cm$^{-1}$): 3303, 3007, 2962, 2943, 1682, 1500, 1465, 1438; MS ($m/z$): 409 ($M^+$ + H); Mp: 98−102 °C; Anal. Calcd for $C_{24}H_{32}N_4O_2$ (408.54): C 70.56, H 7.90, N 13.71. Found: C 70.66, H 7.76, N 13.84.

**1-[3-(2-Methoxyphenoxy)-2-hydroxypropyl]piperazine (12).** To a solution of piperazine (19.2 g, 0.2229 mol) in methanol (50 mL) was slowly added epoxy derivative **9** (10 g, 0.0555) at 0−5 °C. The resulting reaction mixture was stirred for 3 h at 0−5 °C and then poured into water (40 mL), and the product was extracted with dichloromethane (5 × 10 mL). Acetic acid (6.5 mL) and water (40 mL) were charged into the dichloromethane layer and stirred for 10 min. Aqueous ammonia (10 mL) was charged into the aqueous layer, and product was extracted with dichloromethane (5 × 10 mL). The dichloromethane was distilled off completely under reduced pressure (400 mmHg) below 50 °C to obtain 8.8 g (59%) of the title compound **12** with 98.4% purity by HPLC.[14] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.96−6.85 (m, 4H), 4.14−4.10 (m, 1H), 4.02−3.94 (m, 2H), 3.83 (s, 3H), 3.09−3.03 (m, 2H), 2.93−2.51 (m, 8H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 149.7, 148.4, 121.7, 120.9, 114.4, 111.9, 72.4, 65.7, 60.6, 55.8, 54.7, 46.0; IR (KBr, cm$^{-1}$): 3408, 3009, 2942, 1593, 1505, 1470, 1253, 1223; MS ($m/z$): 267 ($M^+$ + H); Anal. Calcd for $C_{14}H_{22}N_2O_3$ (266.34): C 63.13, H 8.33, N 10.52. Found: C 63.25, H 8.21, N 10.76.

**1-{4-[2-Hydroxy-3-(2-methoxyphenoxy)propyl]-piperazin-1-yl}-3-(2-methoxyphenoxy)propan-2-ol (13).** To a solution of epoxy derivative **9** (10 g, 0.0555 mol) in methanol (30 mL) was charged piperazine (4.8 g, 0.0557 mol), and the reaction mixture was heated to reflux for 3 h. The reaction mixture was cooled to 25−35 °C and stirred for 60 min. The precipitated solid was filtered and washed with methanol (5 mL). The wet solid was charged into methanol (25 mL), heated to reflux, and stirred for 30 min. The resultant reaction mixture was cooled to 25−35 °C and stirred for 60 min. The solid precipitate was filtered, washed with methanol (5 mL), and dried at 65 °C under reduced pressure (400 mmHg) to afford 13.6 g (55%) of the title compound **13** with 98.5% purity by HPLC.[14] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.97−6.87 (m, 8H), 4.15−4.10 (m, 2H), 4.0 (d, $J$ = 4.8 Hz, 4H), 3.85 (s, 6H), 2.69−2.52 (m, 8H), 2.57 (d, $J$ = 5.2 Hz, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 149.9, 148.3, 121.9,


dx.doi.org/10.1021/op300026r | Org. Process Res. Dev. 2012, 16, 748−754

120.9, 114.7, 112.0, 72.3, 65.8, 60.5, 55.9, 53.4; IR (KBr, $cm^{-1}$): 3003, 2933, 1589, 1505, 1250, 1223; MS ($m/z$): 447 ($M^+ + H$); Mp: 172−176 °C; Anal. Calcd for $C_{24}H_{34}N_2O_6$ (446.54): C 64.55, H 7.67, N 6.27. Found: C 64.35, H 7.60, N 6.36.

**1,3-Bis{4-[(2,6-dimethylphenyl)aminocarbonylmethyl]-piperazin-1-yl}propan-2-ol (14).** Compound **6** (12 g, 0.0485 mol), epichlorohydrin (6.5 g, 0.0702 mol), and acetone (120 mL) were charge into a round-bottom flask, and then the reaction mixture was heated to reflux for 15 h. The reaction mixture was concentrated below 55 °C under reduced pressure, and acetone (40 mL) was charged at 25−35 °C. The solid was filtered after stirring for 60 min at 25−35 °C. The wet solid was charged into isopropyl alcohol (20 mL) and heated to reflux for 15 min. The clear solution was cooled to 10−15 °C for 45 min, and the precipitated solid was collected by filtration. The wet solid was dried at 65 °C under reduced pressure (400 mmHg) to furnish 12 g (45%) of the title compound **14** with 98.8% purity by HPLC.[14] $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.13 (s, 2H), 7.06 (s, 6H), 4.20 (s, 1H), 3.80−3.77 (m, 1H), 3.11 (s, 4H), 2.56−2.50 (m, 16H), 2.35 (d, $J$ = 12.8 Hz, 2H), 2.25 (d, $J$ = 12.8 Hz, 2H), 2.13 (s, 12H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 168.4, 135.0, 133.6, 128.3, 127.2, 64.5, 62.4, 61.7, 53.8, 18.6; IR (KBr, $cm^{-1}$): 3394, 3262, 3023, 2937, 2815, 1662, 1593, 1524, 1475, 1303, 1162; MS ($m/z$): 551 ($M^+ + H$); Mp: 175−178 °C; Anal. Calcd for $C_{31}H_{46}N_6O_3$ (550.74): C 67.61, H 8.42, N 15.26. Found: C 67.58, H 8.55, N 15.31.

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We thank the management of Dr. Reddy's Laboratories Ltd. for supporting this work. Cooperation from the colleagues of analytical research & development and process research & development is highly appreciated.

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(14) HPLC method: Symmetry shield RP-18, 250 mm × 4.6 mm, 5 $\mu$m; flow: 1 mL/min; eluent A: buffer and acetonitrile in the ratio of 90:10 (v/v); eluent B: buffer and acetonitrile in the ratio of 45:55 (v/v); Buffer preparation: Dissolve 1.38 g of $NaH_2PO_4{\cdot}H_2O$ in 1000 mL of water and add 1.0 mL of triethylamine, then adjust the pH to 7.3 with orthophosphoric acid; Gradient: 0 min: 65% A, 35% B; 12 min: 65% A, 35% B; 25 min: 30% A, 70% B; 30 min: 20% A, 80% B; 42 min: 20% A, 80% B; 45 min: 65% A, 35% B; 55 min: 65% A, 35% B. UV detection at 223 nm.