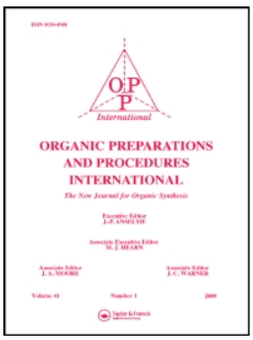


Taylor & Francis
Taylor & Francis Group

Organic Preparations and Procedures International

The New Journal for Organic Synthesis

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: http://www.tandfonline.com/loi/uopp20

An Improved Synthesis of Rivaroxaban

Shaixiao Tian, Bo Tang, Minzhong Zhang, Qingjiao Gao, Bo Chen, Qinghua Zhang & Guangyu Xu

To cite this article: Shaixiao Tian, Bo Tang, Minzhong Zhang, Qingjiao Gao, Bo Chen, Qinghua Zhang & Guangyu Xu (2017) An Improved Synthesis of Rivaroxaban, Organic Preparations and Procedures International, 49:2, 169-177

To link to this article: http://dx.doi.org/10.1080/00304948.2017.1291006

Published online: 20 Apr 2017.

Organic Preparations and Procedures International, 49:169–177, 2017

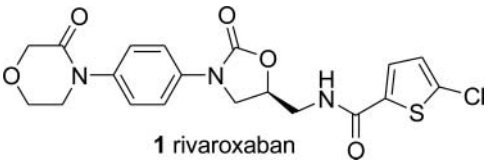
ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2017.1291006

An Improved Synthesis of Rivaroxaban

Shaixiao Tian,[1] Bo Tang,[1] Minzhong Zhang,[1] Qingjiao Gao,[2] Bo Chen,[2] Qinghua Zhang,[2] and Guangyu Xu[1]

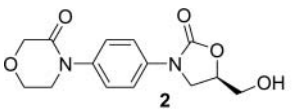
[1]Key Laboratory of Phytochemistry R&D of Hunan Province, College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, P. R. China
[2]Research and Development, Hunan Fangsheng Pharmaceuticals Limited, Changsha 410205, P. R. China

Rivaroxaban (**1**) is a novel, oral, selective direct inhibitor of factor Xa developed by Bayer Healthcare.[1,2] It has been approved by the EMEA and FDA for the prevention of venous thromboembolism in adult patients after total hip replacement or total knee replacement surgery.[3–6] Rivaroxaban is available on the market under the brand name *Xarelto*® in Europe and the US.

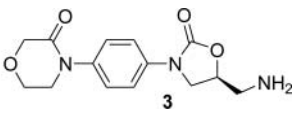


1 rivaroxaban

To date, several methods have been reported for the synthesis of rivaroxaban.[2,7–21] Most of them share the use of 5-*S*-hydroxymethyl or 5-*S*-aminomethyl oxazolidinones (**2** and **3** respectively) as key intermediates. However the 5-*S*-hydroxymethyl group must first be activated as its sulfonate ester, then displaced with excess ammonia in a sealed vessel[13] or substituted with potentially explosive NaN_3, followed by hydrogenation,[14,15] to generate the corresponding aminomethyl group of rivaroxaban. As result of these problems, additional approaches to the synthesis of 5-(*S*)-aminomethyl oxazolidinone **3** have been explored.[2,16–21]



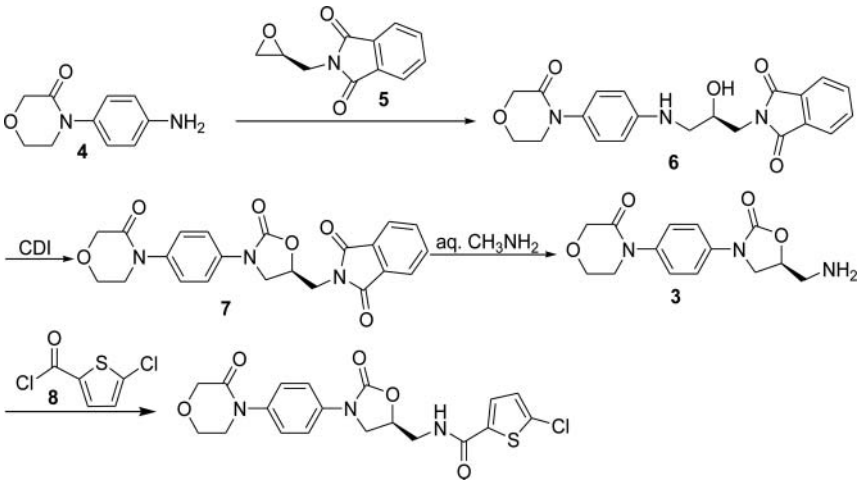
2



3

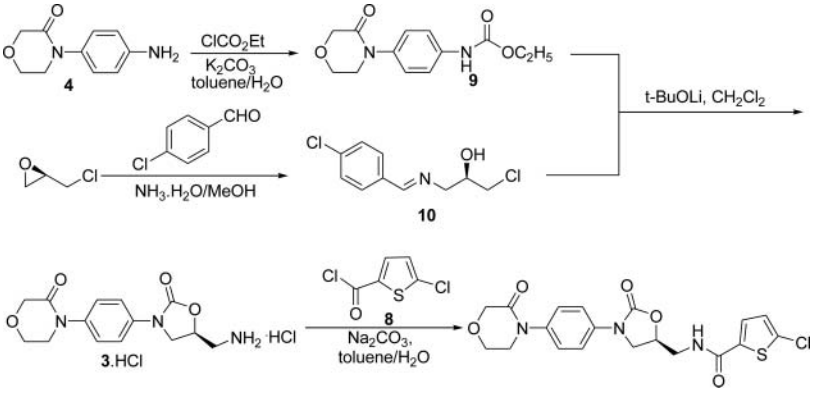
The synthesis of rivaroxaban *via* 5-*S*-aminomethyl oxazolidinone **3** was originally reported in patent WO 0147919 (*Scheme 1*).[2]

Received July 20, 2016; in final form October 19, 2016.
Address correspondence to Guangyu Xu, Key Laboratory of Phytochemistry R&D of Hunan Province, College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, P. R. China. E-mail: gyxu@hunnu.edu.cn



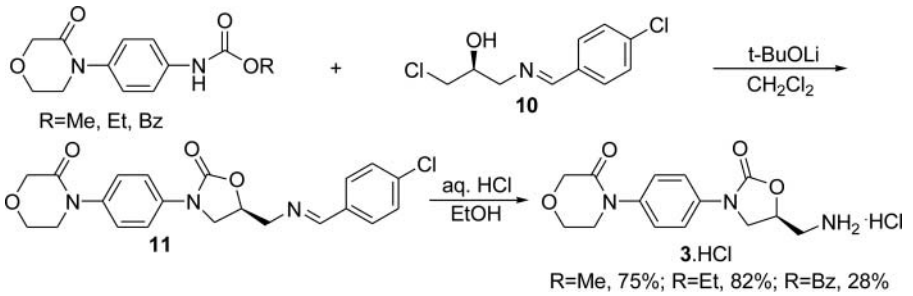
Scheme 1

Compound **6**, obtained by the reaction of **4** with **5** in an ethanol/water mixture, was treated with *N,N'*-carbonyldiimidazole (CDI) in the presence of a catalytic amount of dimethylaminopyridine (DMAP) in THF as solvent to afford compound **7**. Removal of the phthalimido protecting group of **7** by reaction with aqueous methylamine gave 5-(S)-aminomethyl oxazolidinone **3**, which was subsequently acylated with 5-chlorothiophene-2-carbonyl chloride (**8**) using pyridine as solvent and acid scavenger to afford rivaroxaban (**1**) with HPLC purity of 100% after column chromatography. Berwe[16] and Mali[17] and coworkers disclosed some optimization of reaction conditions described in the patent WO 0147919 to make this process suitable for scale-up in a commercial plant. Unfortunately, the difficulty in re-use of the phthalimide protecting group after hydrazinolysis or aminolysis makes this process less green and cheap. Several other routes have been reported on the synthesis of 5-(*S*)-aminomethyl oxazolidinone **3**; however, there are some drawbacks associated with the process described in these reports. These drawbacks include the use of tedious chromatography for purification,[18] use of potentially explosive[19] or flammable reagents during the reaction[20] and low yields of the intermediate and final product.[21] Therefore there is a need for an improved preparation of rivaroxaban suitable for industrial application.



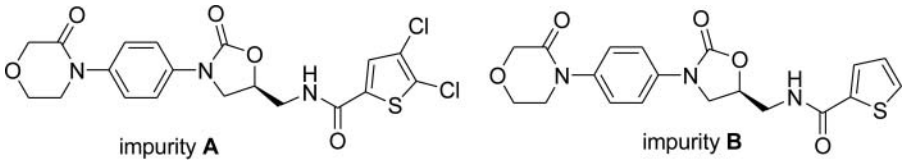
Scheme 2

The oxazolidinone ring is a crucial structural feature in many medicines, including linezolid, rivaroxaban, and cethromycin. Inspired by the process to prepare linezolid,[22,23] a similar protocol was adopted to building the oxazolidinone moiety of rivaroxaban. As shown in *Scheme 2*, commercially available **4** was reacted with ethyl chloroformate in a mixture of toluene and water using K_2CO_3 as acid scavenger to afford carbamate **9**. Carbamate **9** has poor solubility in water and toluene which leads to ready isolation through filtration. As it was reported that 4-chlorohydrin imine **10** was highly crystalline[23], it was selected as the second reaction partner for oxazolidinone formation. Accordingly the cyclization of carbamate **9** with chlorohydrin imine **10** proceeded in refluxing CH_2Cl_2 in the presence of lithium t-butoxide. The reaction was complete within 12 hours without the formation of significant impurities. However, isolation and purification of the desired imine **11** were problematic as it was prone to cleave to **3** during the work-up. To overcome this problem, the isolation of imine **11** from the reaction mixture was not carried out immediately when the reaction finished. The reaction mixture was acidified to pH 2–3 using a solution of aq. HCl and ethanol to precipitate **3** as the hydrochloride salt. It is noteworthy to mention that the reaction using benzyl carbamate and methyl carbamate gave the required product with 28% and 75% yields, respectively (*Scheme 3*).



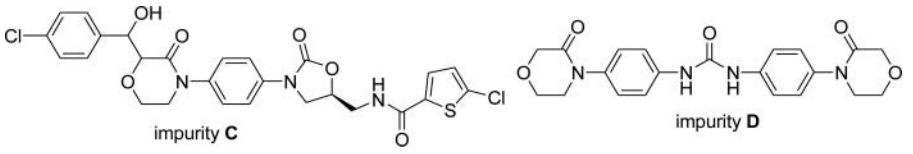
Scheme 3

Salt **3·HCl** was dissolved in water and subjected to acylation with 5-chlorothiophene-2-carbonyl chloride (prepared from 5-chlorothiophene-2-carboxylic acid **12**) in toluene using Na_2CO_3 according to the literature method.[16] Rivaroxaban **1** was precipitated out and recrystallized in good yield but also with the unexpected dichloro impurity **A** and deschloro impurity **B**. It is obvious that these two impurities are derived from the raw material 5-chlorothiophene-2-carboxylic acid, in which unreacted material and excess chlorination byproduct are present. We found that the source of these two impurities could be controlled in the starting material by choosing a different supplier.

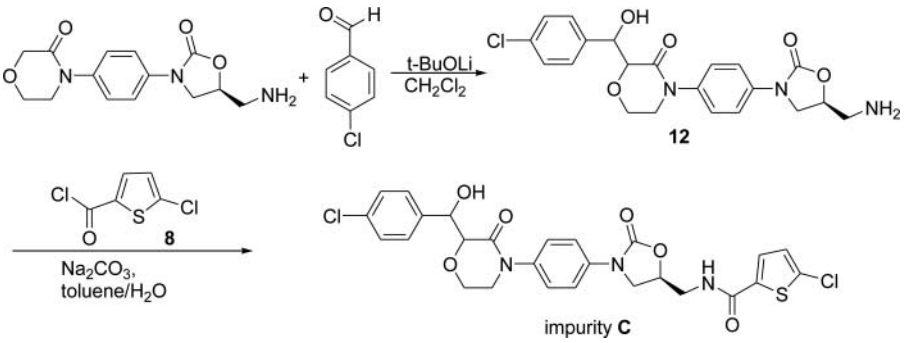


The synthetic route shown in *Scheme 2* has been used to manufacture several batches of the API Rivaroxaban. HPLC analysis indicated the presence of two new impurities at 0.15 and 0.20 area% in several batches of rivaroxaban, identified as 'impurity **C'** and 'impurity **D'**. Further work demonstrated that these two impurities were difficult to purge

during the final recrystallization and suggested that upstream control would be important. Impurities **C** and **D** were isolated from the mother liquor by silica gel column chromatography, and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS-ESI.



The impurity **C** was believed to arise from related impurities in the intermediate **3·HCl**. It is generally believed that there are small amounts of *p*-chlorobenzaldehyde in chlorohydrin imine **10**, where the carbonyl group could be attacked by the lithium salt of 4-aryl-3-morpholinone in the cyclization step to give 2-(1-hydroxyalkyl)-3-morpholinone **12** (*Scheme 4*). Similar nucleophilic attack on an aldehyde by a 3-morpholinone lithium salt[24] to form penultimate impurity **C** has been noted in the literature. After the amidation of **12** with 5-chlorothiophene-2-carbonyl chloride, the impurity **C** was found to be present at levels greater than 0.15% in the final product. Unfortunately, removal of *p*-chlorobenzaldehyde from imine **10** by slurry wash or recrystallization proved difficult; however, impurity **12** could be removed efficiently after the crude **3·HCl** was slurried with ethanol.



Scheme 4

The structure of impurity **D** as bis[4-(3-oxo-4-morpholinyl)phenyl]urea was also confirmed by synthesis (*Scheme 5*), where impurity **D** was easily synthesized from 4-(4-aminophenyl)morpholin-3-one **4** with CDI and matched unambiguously with the fractionated sample of the impurity by ^{1}H NMR and HPLC retention time.

Scheme 5

This impurity is generated during the carbamate formation of **9**. The formation of impurity **D** is possible by the aminolysis of carbamate **9** with 4-(4-aminophenyl)morpholin-3-one under the given conditions. It was found that the use of an organic base, for example Et_3N or pyridine in CH_2Cl_2 or EtOAc, increased the formation of this impurity

drastically. When the reaction was carried out in a mixture of toluene and water using an inorganic base such as Na_2CO_3 or K_2CO_3, the amount of this impurity could be minimized to 0.35%. This impurity cannot be efficiently eliminated by recrystallization in the carbamation and the next cyclization step due to its high crystallizability. Fortunately, this impurity was almost insoluble in water, so we could remove it by filtration from **3·HCl** solution in water before the next amidation step.

In summary, we have developed a convenient synthesis of rivaroxaban in three steps from 4-(4-aminophenyl)morpholin-3-one with one additional step to prepare chiral intermediate chlorohydrin **10** (overall yield from **4** is 57.7%). Four impurities **A-D** of rivaroxaban were characterized by NMR and MS and their mode of formation during the preparation of rivaroxaban were also determined. In addition, the reaction sequences were optimized to afford low concentrations of these impurities to levels accepted by ICH guidelines.

Experimental Section

The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-*d*6 using Brücker 500 MHz NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The LC-MS and mass spectrum were recorded on a Waters XEVO LC-MS spectrometer. The melting points were determined by using the capillary method on an YRT-3 melting point apparatus, which are uncorrected. HPLC analysis was performed on a Shimadazu SPD-15C instrument with a UV detector using Agilent TC-C18 (250 mm × 4.6 mm, 5 μm) column. Mobile phase A: dissolve 0.79 g of ammonium bicarbonate in 1000 mL water and added 2.0 mL triethylamine, adjust the pH to 8.0 with formic acid. Mobile phase B: acetonitrile. Gradient: 0 min: 80% A, 20% B; 10 min: 80% A, 20% B; 18 min: 68% A, 32% B; 44 min: 34% A, 66% B; 50 min: 34% A, 66% B; 50.1 min: 80% A, 20% B; 60 min: 80% A, 20% B; UV detection at 250 nm; flow rate: 0.7 mL/min; Column oven temperature: 25°C. Chiral purity was estimated using Chiralcel OD-H (250 × 4.6 mm), 5μ column; mobile phase comprising a mixture of *n*-hexane, ethanol and trifluoroacetic acid in the ratio of 50:50:0.2 (v/v/v) respectively; flow rate 0.7 ml/min.; column temperature 35°C; wavelength 250 nm. The HPLC analysis data is reported in area % and is not adjusted to weight %. 4-(4-Aminophenyl)morpholin-3-one **4** was purchased from Taizhou World Pharm & Chem Co., Ltd.

Ethyl N-[4[(3-oxo-4-morpholinyl)phenyl]carbamate (9)

4-(4-Aminophenyl)morpholin-3-one (1.23 kg, 6.40 mol) and K_2CO_3 (1.07 kg, 7.74 mol) were suspended in 6.75 L toluene and 2.05 L water at 0–5°C. To the stirred suspension was slowly added a solution of ethyl chloroformate (0.91 kg, 8.39 mol) in 2.7 L toluene at the same temperature, then stirring was continued for 3 hr at room temperature. Subsequently, to the mixture was added 6.75 L water and it was stirred for 30 min. The precipitate was collected and washed with 1.5 L water. The crude solid was slurried with ethyl acetate (6.75 L) for 2 hr, collected and dried under vacuum to give **9** as a white solid (1.49 kg, 88%), mp. 190.3–193.1°C, with 99.2% purity by HPLC.

^{1}H NMR (500 MHz, DMSO) δ: 1.24 (t, 3H, J = 7.0 Hz), 3.66 (t, 2H, J = 5.0 Hz), 3.94 (t, 2H, J = 5.0 Hz), 4.10–4.16 (m, 2H), 4.16 (s, 2H), 7.26 (d, 1H, J = 9.0 Hz), 7.46 (d, 2H, J = 8.5 Hz), 9.70 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ: 14.96, 49.61, 60.65, 63.96, 68.19, 118.86, 126.43, 136.46, 137.99, 154.04, 166.36. MS *m/z* 264.05 $[M]^+$.

(S)-1-chloro-3-[(4-chloro-E-benzylidene)-amino]-propan-2-ol (10)

Compound **10** was synthesized from (*S*)-epichlorohydrin according to the reported procedure with minor modification.[22] To a solution of *p*-chlorobenzaldehyde (1.48 kg, 10.53 mol) in 6.0 L methanol was added 1.03 L aq. ammonia (28 wt%, 15.44 mol) in one portion, the resulting mixture was stirred for 20 min at room temperature then (*S*)-epichlorohydrin (986.0 g, 15.27 mol) was charged in single portion. The reaction mixture was stirred for 12 hr then heated to 40 °C and stirred for 2 hr. After cooling to room temperature, 9.0 L water was added and methanol was evaporated under vacuum below 45°C. The precipitate was filtered and slurried with 5.0 L petroleum ether. The solid was filtered and then dissolved in 5.0 L dichloromethane. The organic phase was separated and dried with anhydrous Na_2SO_4. The resultant filtrate containing compound **10** was used directly for the preparation of **3·HCl** without isolation.

^{1}H NMR (500 MHz, DMSO) δ: 3.57–3.62 (m, 2H), 3.70–3.73 (m, 2H), 3.91–3.97 (m, 1H), 5.28 (d, 1H, $J = 5.0$ Hz), 7.51 (d, 2H, $J = 8.5$ Hz), 7.77 (d, 2H, $J = 8.5$ Hz), 8.33 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ: 48.49, 64.08, 70.46, 129.21, 130.06, 135.34, 135.72, 161.81. MS *m/z* 231.90 $[M]^+$. mp. 70–72.1°C (lit.[25] 70–71°C).

4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one hydrochloride (3·HCl)

To a suspension of **9** (1.43 kg, 5.41 mol) in 2.25 L CH_2Cl_2 was added lithium *t*-butoxide (1.17 kg, 14.62 mol) at 5−10°C in three portions. After being stirred for 30 min at room temperature, the above solution containing compound **10** (~8.11 mol) was added over 30 min. The resulting solution was heated to reflux for 12 hr and then cooled to room temperature, 16.4 L ethanol was added and the pH of the solution was adjusted to 1.0–2.0 using concentrated HCl (1.6 L). The reaction mixture was stirred for 1.5 hr at room temperature and the resultant solid was filtered and washed with ethanol (1.6 × 2 L). The filtrate was stored for the reuse of *p*-chlorobenzaldehyde. The wet solid was charged into ethanol (11.0 L), heated to reflux, and stirred for 30 min. The resultant mixture was cooled to 25−30°C and stirred for 60 min. The product was filtered, washed with ethanol (1.1 × 2 L), and dried at 45°C under reduced pressure (400 mmHg) to afford 1.45 Kg (81.8%) of **3·HCl** as an off-white solid, mp. > 250°C (lit. [26] 210–220°C), with 99.4% purity by HPLC.

^{1}H NMR (500 MHz, DMSO) δ: 3.18–3.23 (m, 2H), 3.71 (t, 2H, $J = 5.0$ Hz), 3.92 (dd, 1H, $J_1 = 6.5$ Hz, $J_2 = 9.0$ Hz), 3.97 (t, 2H, $J = 5.0$ Hz), 4.19–4.22 (m, 3H), 4.95–5.00 (m, 1H), 7.42 (d, 2H, $J = 9.0$ Hz), 7.56 (d, 2H, $J = 9.0$ Hz), 8.41 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ: 41.98, 47.73, 49.48, 63.95, 68.21, 70.04, 119.01, 126.43, 136.78, 137.72, 154.10, 166.46. MS *m/z* 291 $[M\text{-}HCl]^+$.

To the filtrate containing *p*-chlorobenzaldehyde was added 25 L water, the organic phase was separated and washed with water (2.5 × 2 L). After drying (Na_2SO_4) and evaporation of the solvent, the residue was distilled under reduced pressure to give 0.77 kg of *p*-chlorobenzaldehyde (92–94°C/10 torr), which could be reused for the synthesis of compound **10**.

5-Chlorothiophene-2-carbonyl chloride (8)

5-Chlorothiophene-2-carboxylic acid (0.75 kg, 4.61 mol) was suspended in 2.6 L toluene and heated to 80°C. Thionyl chloride (640 mL, 8.81 mol) was added dropwise over a

period of 20 min, and the reaction mixture was heated to 120°C and stirred for 2 hr at the same temperature. The reaction was monitored by TLC (charged one drop of reaction solution into 1 mL methanol) until gas evolution ceases. After removal of the excess thionyl chloride and toluene by evaporation under vacuum, the residue was dissolved in toluene (1.5 L) for the next step.

Rivaroxaban (1). 3·HCl

(1.40 kg, 4.27 mol) was dissolved in 4.85 L water and filtered, to the filtrate was added 6.0 L toluene and Na_2CO_3 (0.56 kg, 5.28 mol) at room temperature. The mixture was cooled to 8 to 12°C, the above solution of **9** in toluene was then added, and the reaction mixture was stirred for 2 hr at room temperature. After completion of reaction, 2.5 L acetone was added and the precipitated solid was filtered and washed with 2 mol/L aq. HCl (1.5 L). The wet solid was dried at 70°C under reduced pressure (400 mmHg) to afford 1.76 kg of the crude product **1** with 99.0% purity by HPLC. The crude product was charged into acetic acid (7.8 L) and heated to reflux for 15 min. The clear solution was cooled to 15°C and stirred for 2 hr, and the precipitated solid was filtered and washed with 1.5 L acetone. The wet solid was dried at 70°C under reduced pressure (400 mmHg) to furnish 1.49 kg (80.0%) of the final product, mp. 228.9–230.1°C (lit.[2] 232–233°C, lit.[25] 227.8–228.5°C), with 99.91% chemical purity and 99.93 chiral purity by chiral HPLC analysis. ^{1}H NMR (500 MHz, DMSO) δ: 3.61 (t, 2H, $J = 5.5$ Hz), 3.71 (t, 2H, $J = 5.5$ Hz,), 3.86 (dd, 1H, $J_1 = 6.0$ Hz, $J_2 = 9.0$ Hz), 3.97 (t, 2H, $J = 4.5$ Hz), 4.20 (t, 3H, $J = 6.5$ Hz), 4.83–4.86 (m, 1H), 7.20 (d, 1H $J = 4.0$ Hz), 7.41 (d, 2H, $J = 8.5$ Hz), 7.56 (d, 2H, $J = 9.0$ Hz), 7.69 (d, 1H, $J = 4.0$ Hz), 8.97 (t, 1H, $J = 5.5$ Hz); ^{13}C NMR (125 MHz, DMSO) δ: 42.69, 47.92, 49.49, 63.95, 68.20, 71.80, 118.83, 126.41, 128.61, 128.92, 133.73, 136.96, 137.56, 138.93, 154.57, 161.28, 166.43. MS *m/z* 436.0 $[M+H]^+$.

Isolation of Impurities C and D. The enriched mother liquor (12 ml) from two-fold recrystallization of Rivaroxaban was further purified on silica gel 60H (150 g), using a gradient elution system of ethyl acetate-methanol (40:1, 30:1, 25:1, 20:1, 15:1, 10:1, 8:1 volume ratio). The fractions 5–10 were subjected repeatedly to silica gel flash chromatography with ethyl acetate-methanol (40:1) as solvent to yield impurity **C**. The fractions 20–24 were also subjected repeatedly to silica gel flash chromatography with ethyl acetate-methanol (10:1) as solvent to yield impurity **D**.

Impurity C: mp. 232.3–233.9°C; ^{1}H NMR (500 MHz, DMSO): δ 3.61 (t, 3H, $J = 6.0$ Hz), 3.78–3.90 (m, 3H), 4.10 (t, 1H, $J = 5.0$ Hz), 4.19 (t, 1H, $J = 9.0$ Hz), 4.36 (d, 1H, $J = 2.0$ Hz), 4.81–4.86 (m, 1H), 5.22 (d, 1H, $J = 6.5$ Hz), 5.69 (d, 1H, $J = 6.5$ Hz), 7.24 (d, 1H, $J = 4.0$ Hz), 7.37–7.41 (m, 4H), 7.45 (d, 2H, $J = 8.5$ Hz), 7.57 (d, 2H, $J = 9.0$ Hz), 7.69 (d, 1H, $J = 4.0$ Hz), 8.97 (t, 1H, $J = 5.5$ Hz); ^{13}C NMR (125 MHz, DMSO): δ 42.62, 47.89, 49.78, 62.93, 71.71, 72.61, 81.23, 118.76, 126.25, 127.97, 128.50, 128.75, 128.84, 131.60, 133.60, 136.82, 138.85, 142.06, 154.49, 161.21, 167.13. MS *m/z* 598.02 $[M+Na]^+$.

Anal. Calcd. for $C_{26}H_{23}Cl_2N_3O_6S$: C, 54.17; H, 4.02; N, 7.29. Found: C, 54.08; H, 4.09; N, 7.14.

Impurity D: mp. > 250°C; ^{1}H NMR (500 MHz, DMSO): δ 3.69 (d, 4H, $J = 4.5$ Hz), 3.96 (t, 4H, $J = 4.5$ Hz), 4.18 (s, 4H), 7.28 (d, 4H, $J = 8.5$ Hz), 7.47 (d, 4H, $J = 9.0$ Hz), 8.80 (s, 2H); ^{13}C NMR (125 MHz, DMSO): δ 49.64, 63.98, 68.20, 118.90, 126.51, 136.07, 138.42, 152.98, 166.37. MS *m/z* 411.16 $[M+H]^+$.

Synthesis of Impurities A, B and D. Impurities **A** and **B** were synthesized from the desired thiophenecarbonyl chloride with **3·HCl** according to the procedure described for **1**.

Impurity A: mp. 194.3–197.7°C; ^{1}H NMR (500 MHz, DMSO): δ 3.60 (t, 2H, J = 5.5 Hz), 3.70 (t, 2H, J = 5.0 Hz), 3.87 (dd, 2H, J_1 = 4.0 Hz, J_2 = 9.0 Hz), 3.96 (t, 2H, J = 4.5 Hz), 4.19 (t, 3H, J = 8.0 Hz), 4.82–4.87 (m, 1H), 7.15 (dd, 1H, J_1 = 4.0 Hz, J_2 = 5.0 Hz), 7.40 (d, 2H, J = 9.0 Hz), 7.55 (d, 2H, J = 9.0 Hz), 7.76–7.79 (m, 2H), 8.87 (t, 1H, J = 6.0 Hz); ^{13}C NMR (125 MHz, DMSO): δ 42.68, 47.95, 49.49, 63.96, 68.21, 71.85, 118.83, 126.44, 128.44, 128.99, 131.61, 136.99, 137.54, 139.81, 154.62, 162.27, 166.44. MS *m/z* 402.0 $[M+H]^+$.

Impurity B: mp. 202.3–205.2°C; ^{1}H NMR (500 MHz, DMSO): δ 3.62 (t, 2H, J = 5.5 Hz), 3.71 (t, 2H, J = 5.0 Hz), 3.83 (dd, 1H, J_1 = 6.5 Hz, J_2 = 9.0 Hz), 3.96 (t, 2H, J = 4.5 Hz), 4.16–4.20 (m, 3H), 4.81–4.86 (m, 1H), 7.40 (d, 2H, J = 9.0 Hz), 7.55 (d, 2H, J = 9.0 Hz), 7.86 (s, 1H), 9.07 (t, 1H, J = 6.0 Hz); ^{13}C NMR (125 MHz, DMSO): δ 42.77, 47.89, 49.50, 63.97, 68.22, 71.76, 118.81, 123.80, 126.43, 128.26, 129.06, 136.97, 137.16, 137.56, 154.56, 160.45, 166.46. MS *m/z* 470.0 $[M+H]^+$.

Synthesis of 1,3-bis[4-(3-oxomorpholin-4-yl)phenyl]urea (impurity D). To a solution of 4-(4-aminophenyl)morpholin-3-one (4.04 g, 21 mmol) in 20 mL DMF were added triethylamine (1.01g, 10 mmol) and CDI (1.62g, 10 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at same temperature overnight before poured into water. The precipitant was filtered, washed with water and then washed with acetone. The resultant solid was dried at 60°C for 2 hr to get the title compound (2.65g, 64.6%), an off-white powder. The ^{1}H NMR and mp. are in accordance with impurity **D** separated from rivaroxaban.

Acknowledgments

This work was supported by Changsha Administration of Science & Technology (k1508012-11).

References

1. S. Roehrig, A. Straub, J. Pohlmann, T. Lampe, J. Pernerstorfer, K.-H. Schlemmer, P. Reinemer, and E. Perzborn, *J. Med. Chem.*, **48**, 5900 (2005).
2. A. Straub, T. Lampe, J. Pohlmann, S. Roehrig, E. Perzborn, K.-H. Schlemmer, and J. Pernerstorfer, PCT Int. Appl. WO 0147919 A1, 2001; *Chem. Abstr.*, **148**, 285176 (2008).
3. K. Mann, K. Brummel, and S. Butenas, *J. Thromb. Haemostasis*, **1**, 1504 (2003).
4. W. Mueck, S. Schwers, and J. Stampfuss, *Thromb. J.*, **11**, 10 (2013).
5. R. Bauersachs, S. Berkowitz, H. Buller, H. Decousus, A. Gallus, A. Lensing, F. Misselwitz, M. Prins, G. Raskob, A. Segers, P. Verhamme, P. Wells, G. Agnelli, H. Bounameaux, A. Cohen, B. Davidson, F. Piovella, and S. Schellong, *New Engl. J. Med.*, **363**, 2499 (2010).
6. B. Biemond, E. Perzborn, P. Friederich, M. Levi, U. Buetehorn, and H. Büller, *Thromb. Haemostasis*, **97**, 471 (2007).
7. C. Thomas, PCT Int. Appl. WO 2004060887 A1, 2004; *Chem. Abstr.*, **141**, 106454 (2004).
8. C. Gerdes, E. Perzborn, J. Pohlmann, S. Roehrig, A. Straub, C. Thomas, A. Tuch, and K.-H. Schlemmer, PCT Int. Appl. WO 2004101557 A1, 2004; *Chem. Abstr.*, **142**, 6516 (2004).
9. P. Bodhuri, and G. Weeratunga, PCT Int. Appl. WO 2010124385 A1, 2010; *Chem. Abstr.*, **153**, 555212 (2010).

10. D. Rao, P. Reddy, and B. Reddy, PCT Int. Appl. WO 2013046211 A1, 2013; *Chem. Abstr.*, **158**, 534951 (2013).

11. P. Singh, M. Hashmi, Y. Sachdeva, and C. Khanduri, PCT Int. Appl. WO 2013156936 A1, 2013; *Chem. Abstr.*, **159**, 639217 (2013).

12. A. Kumar, U. Rameshchandra, T. Mansukhlal, and V. Kanaksinh, PCT Int. Appl. WO 2015026761 A1, 2015; *Chem. Abstr.*, **162**, 353221 (2015).

13. D. Rao, and B. Reddy, PCT Int. Appl. WO 2013105100 A1, 2013; *Chem. Abstr.*, **159**, 260152 (2013).

14. J. Rafecas, A. Comely, A. Ferrali, C. Amela Cortés, and M. Pastó Aguilà, PCT Int. Appl. WO 2011080341 A1, 2011; *Chem. Abstr.*, **155**, 152534 (2011).

15. S. Maroju, P. Kumar, R. Maroju, G. Velupula, A. Haq, and T. Prasad, *J. Appl. Chem. (Lumami, India)*, **3**, 2573 (2014).

16. M. Berwe, C. Thomas, J. Rehse, and D. Grotjohann, PCT Int. Appl. WO 2005068456 A1, 2004; *Chem. Abstr.*, **143**, 172902 (2005).

17. A. Mali, D. Deshmukh, D. Joshi, H. Lad, P. Patel, V. Medhane, and V. Mathad, *Sustain. Chem. Process*, **3**, 11 (2015).

18. J. Yuan, K. Liu, L. Li, Y. Yuan, X. Liu, and Y. Li, *Molecules*, **19**, 14999 (2014).

19. C. Li, Y. Liu, Y. Zhang, and X. Zhang, *J. Chem. Res.*, **35**, 400 (2011).

20. V. Reddy, V. Rao, and D. Reddy, IN 2012CH03375 A, 2012; *Chem. Abstr.*, **163**, 427412 (2014).

21. C. Masse, PCT Int. Appl. WO 2009023233 A1, 2009; *Chem. Abstr.*, **150**, 237590 (2009).

22. R. Imbordino, W. Perrault, and M. Reeder, PCT Int. Appl. WO 2007116284 A1, 2007; *Chem. Abstr.*, **147**, 469356 (2007).

23. W. Perrault, J. Keeler, W. Snyder, C. Clark, M. Reeder, R. Imbordino, R. Anderson, N. Ghazal, S. Secreast, B. Pearlman, in *Scalable Green Chemistry*, edited by S. Koenig, CRC Press: Boca Raton, 2013; pp 157–166.

24. A. Dobrev, L. Nechev, and C. Ivanov, *Liebigs Ann. Chem.*, 815 (1989).

25. A. Halama, R. Krulis, O. Dammer, and S. Kalasek, PCT Int. Appl. WO 2013120465 A1, 2013; *Chem. Abstr.*, **159**, 399302 (2013).

26. H. Sturm, and K. Knepper, PCT Int. Appl. WO 2012140061 A1, 2012; *Chem. Abstr.*, **157**, 634380 (2012).