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Facile approach for the synthesis of rivaroxaban using alternate synthon: reaction, crystallization and isolation in single pot to achieve desired yield, quality and crystal form

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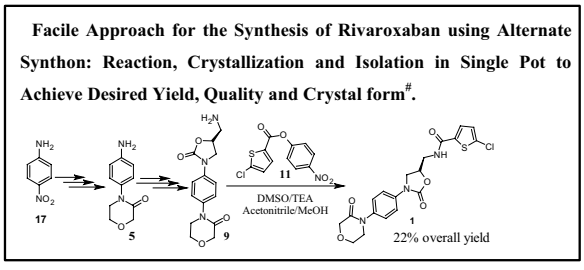
Abstract: An efficient and high yielding process for the production of impurity free rivaroxaban (**1**), an anti-coagulant agent using alternate synthon is reported. The key components of the process involve; synthesis of 4-(4-aminophenyl)-3-morpholinone (**5**) using easily available inexpensive nitro aniline (**17**), condensation of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one hydrochloride (**9**) with alternate synthon 4-nitrophenyl 5-chlorothiophene-2-carboxylate (**11**) in dimethylsulfoxide (DMSO) as a solvent and triethylamine as a base and isolation of the rivaroxaban (**1**) by designing the crystallization in same reaction pot using specific combination of acetonitrile and methanol as anti-solvents to obtain highly pure rivaroxaban (**1**) with desired ploymorphic form with an overall yield of around 22% (Calculated from **17**). The developed process avoids the use of hazardous chemicals, critical operations and tedious work-ups. Potential impurities arouse during the reaction at various stages and carry-over impurities from starting materials were controlled selectively by designing reaction conditions and tuning the crystallization parameters.

Graphical abstract:



Keywords: Rivaroxaban, Anti-coagulant drug, Polymorph, Crystallization, 4-Nitrophenyl 5-chlorothiophene-2-carboxylate

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Background

Rivaroxaban (**1**), chemically known as 5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide is an orally active direct factor Xa (FXa) inhibitor drug developed by Bayer and approved by United states Food and Drug Administration (USFDA) during July 2011 under the trade name of Xarelto [1, 2]. Rivaroxaban (**1**) used for the prevention and treatment of various thromboembolic diseases, in particular pulmonary embolism, deep venous thrombosis, myocardial infarction, angina pectoris, reocclusion and restenosis after angioplasty or aortocoronary bypass, cerebral stroke, transitory ischemic attacks, and peripheral arterial occlusive diseases [1–4].

Alexander and co-workers [3, 4] reported first synthesis of **1** using linear approach that involves condensation of morpholin-3-one (**2**) with fluoro nitrobenzene (**3**) using sodium hydride as a base in *N*-methylpyrrolidone (NMP) to get nitro morpholinone (**4**), nitro group of **4** was reduced using palladium on carbon (Pd–C) and hydrogen in tetrahydrofuran (THF) to achieve 4-(4-aminophenyl)-3-morpholinone (**5**) which was then condensed with 2-[(2*S*)-2-oxiranylmethyl]-1*H*-isoindole-1, 3(2*H*)-dione (**6**) in ethanol and water mixture to provide amino alcohol **7**. Cyclization of **7** using *N,N′*-carbonyldiimidazole (CDI) in presence of 4-dimethylaminopyridine (DMAP) in THF furnished 2-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindole-1,3(2*H*)-dione (**8**). Deprotection of **8** using methyl amine in ethanol followed by condensation of obtained **9** with 5-chlorothiophene-2-carbonyl chloride (**10**) in pyridine furnished rivaroxaban (**1**) with an overall yield of 4.5% starting from compound **2** (Scheme 1).

The disclosed process has several disadvantages such as: (a) use of highly pyrophoric reagent like sodium hydride, (b) excess loading of expensive key raw material **6** and CDI that generate excess amount of by-product imidazole and makes the process economically and environmentally inefficient, (c) repeated filtrations involved for the isolation of **7** decreases the production throughput, (d) use of highly flammable solvent like diethyl ether for washing the compound **7** and hazard and toxic solvent like pyridine for the reaction at API stage makes the process unsafe, (e) purification of **1**, **4**, **5** and **8** by column chromatography makes process lengthy and time consuming, (f) incomplete conversion of intermediates leads to formation of many process related impurities, and (g) low overall yield of 4.5% starting from compound **2** which makes process less viable for commercial production.

Rafecas et al. [5] disclosed process for the preparation of rivaroxaban (**1**) and intermediates thereof (Scheme 2) with an overall yield of 5.93 with 98.4% purity by HPLC. Silvo et al. in 2011 reported the purification of rivaroxaban (**1**) by solvent mediated crystallization process [6] using various solvents and/or solvent combinations to provide maximum of around 99.70% purity by HPLC with a loss of around 10–20% yield making the process expensive. Several other processes reported in the literature also suffer disadvantages similar to as described above and thus makes the process unsuitable for large scale production [7–19].

We hereby report an efficient, economic, scalable, impurity-free and production friendly process for the synthesis of rivaroxaban (**1**) which allows direct isolation of API from reaction mass without further purification complying with ICH quality [20] and desired polymorphic form [21, 22]. Rivaroxaban (**1**) was obtained from **17** in seven steps with an overall yield of 22% and purity of 99.85% by HPLC using commercially available and less expensive raw materials and reagents.

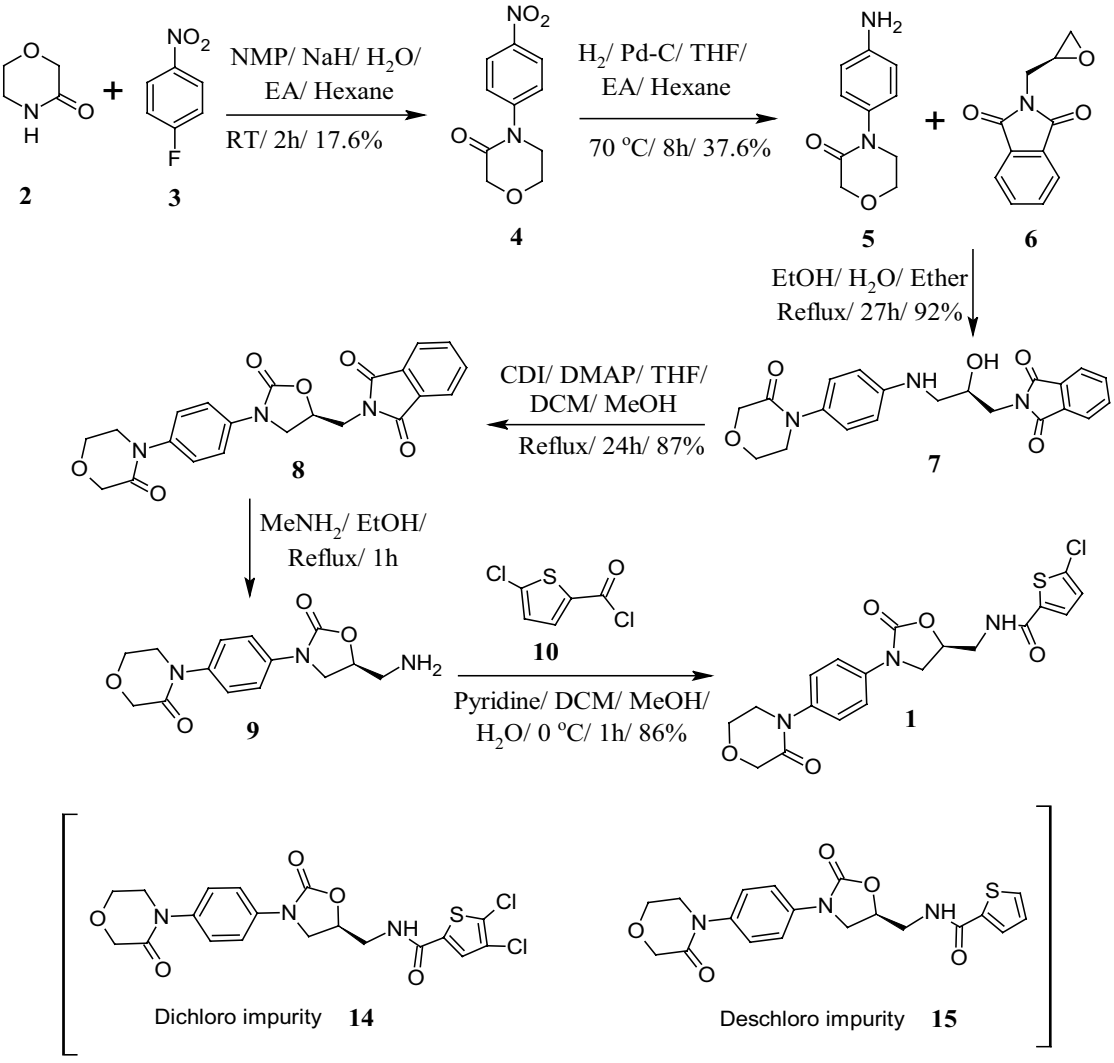
Results and discussion

Process research and development of rivaroxaban mainly focused on following three aspects: (a) to develop an improved and high yielding process for the manufacture of **9** starting from **17** without the use of column chromatographic purification and avoiding the hazardous and unsafe chemical reagents and solvents, (b) to develop an efficient process for the manufacture of **1** starting from **9** which reduces the formation of impurities and provide high reaction yield and (c) to achieve crystallization and isolation of **1** with ICH quality and desired polymorphic form (modification-I) [21] directly from reaction mass from the same pot without subjecting the crude to a further purification.

(a) Efficient process for the preparation of compound 9

Critical and cost-contributing intermediate **5** was prepared [23] using easily available inexpensive nitro aniline (**17**) as a starting material. Boric acid catalyzed condensation of **17** with 2-(2-chloroethoxy) acetic acid in toluene followed by cyclization of the obtained chloroamide **18** in sodium hydroxide in the presence of phase transfer catalyst *tetra*-butyl ammonium bromide (TBAB) provided nitro compound **19**. Catalytic reduction of **19** using Pd–C as catalyst and H_2 gas or ammonium formate as a source of hydrogen in methanol provided key intermediate **5** (Scheme 3). However, another key intermediate compound **6** was prepared as per the literature procedure with little process improvements.

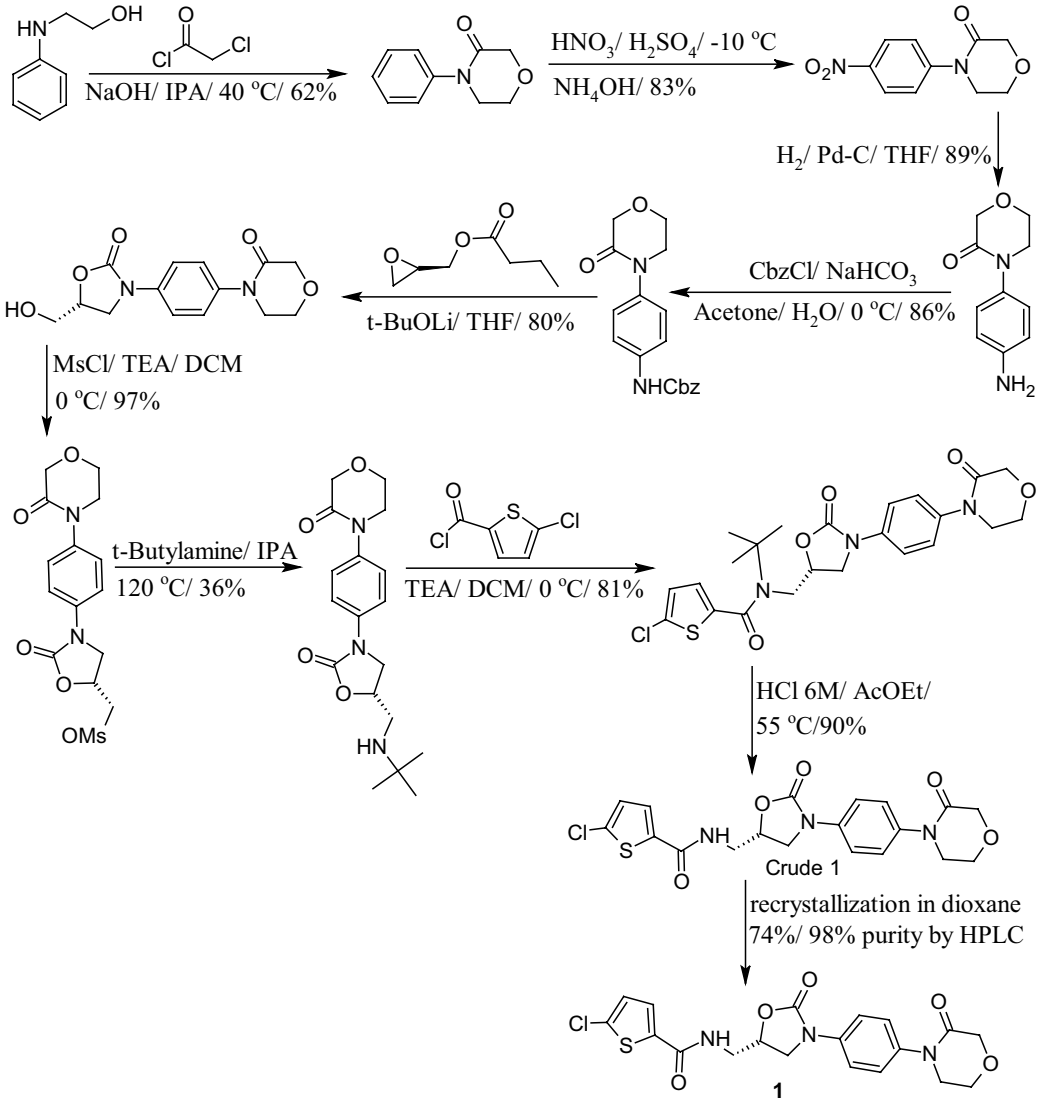
Preparation of amino alcohol **7** (Scheme 3) by nucleophilic attack of **5** on oxirane **6** has been attempted using various solvents. Among several solvents screened such as methanol, ethanol, IPA, DMF, DMSO, toluene, water, acetonitrile, ethyl acetate, THF and their mixtures, the mixture of IPA and water found to be the suitable solvent



Scheme 1 Reported synthetic scheme for rivaroxaban (**1**) as per basic patent US 7576111.

for this reaction. It was noticed that oxirane **6** underwent degradation in other solvents except IPA–water resulting into unreacted **5** in the reaction. It was also noticed that excess use of oxirane **6** results into the formation of dimer impurity **16** (determined by LC–MS). Further, it has also been observed that oxirane **6** found to be stable in IPA–water mixture and thus reaction goes to completion with 1.05 mol equivalents of oxirane **6** at 80°C to provide **7** with negligible quantities of dimer **16**. The precipitated compound **7** was isolated by filtering and drying the product under vacuum at 60–65°C for 5–6 h with 95% yield and 97.0% purity by HPLC. During optimization, specific ratio of IPA and water (17:3) found to be optimum to provide excellent yield and quality of **7** (Table 1).

Amino alcohol **7** obtained was then treated with CDI to achieve oxazolidinone **8** without further purification. The reaction was explored in various solvents (toluene, THF, ethyl acetate, 2-Me-THF, DCM and acetonitrile) using different bases (K_2CO_3, Na_2CO_3, DIPEA, TEA and $NaHCO_3$). During screening experiments incomplete conversion of **7** was observed in various solvents and different bases after prolonged maintenance at various temperature conditions resulting into the formation of many side products. However, reaction in DCM in the presence of K_2CO_3 as a base at 25–30°C proceeded smoothly with a reduced amount of impurities (~0.5% by HPLC). Work-up involves the filtration of the reaction mass to separate inorganic solids, concentration of the DCM and purification of obtained residue in THF to furnish **8** as



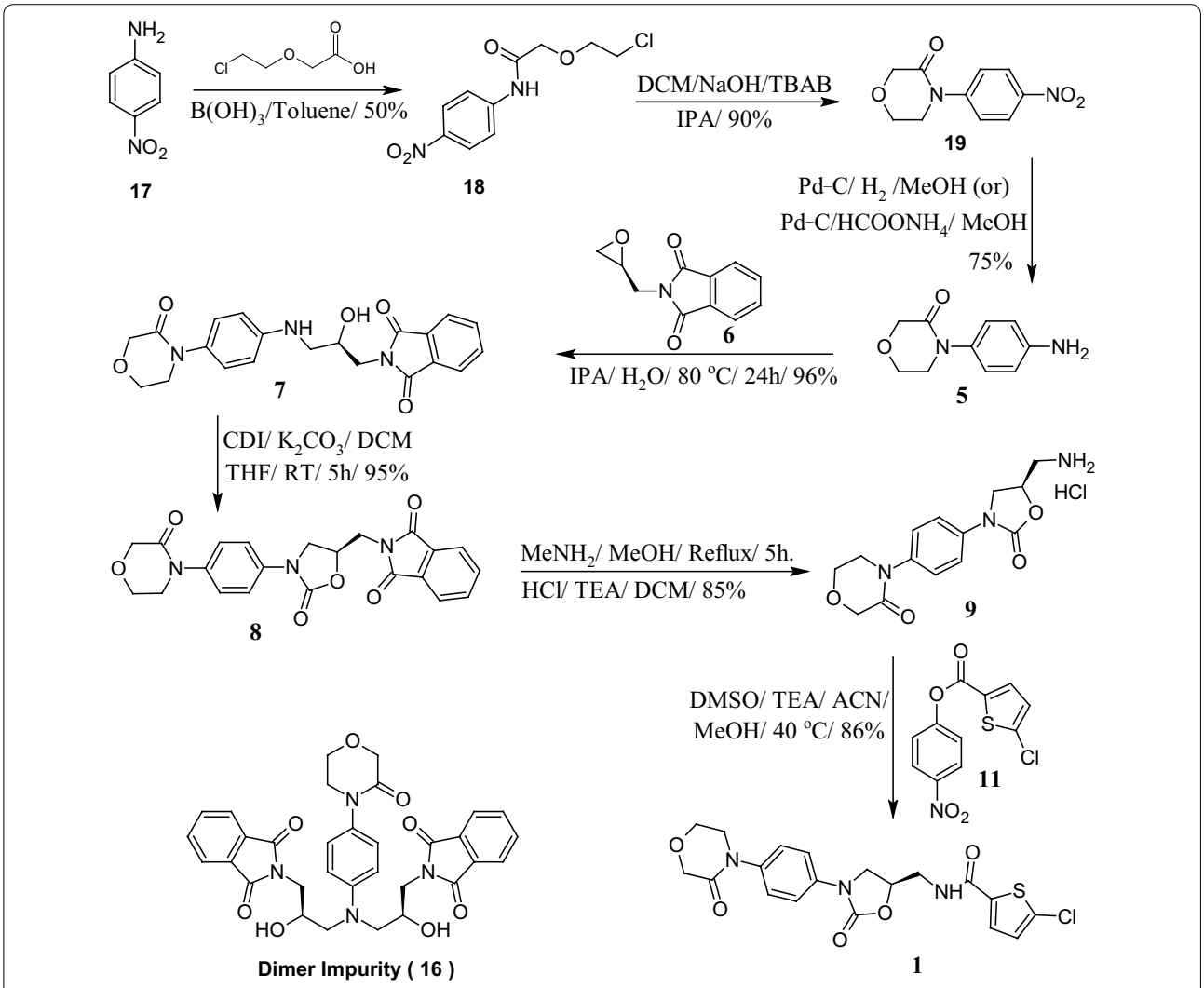
Scheme 2 Reported synthetic scheme for rivaroxaban (**1**) as per WO/2011 080341.

a white crystalline solid with 99.8% purity by HPLC and 95% yield.

Synthesis of key intermediate **9** (Scheme 3) was then achieved by deprotection of **8** using 40% aqueous methyl amine solution in methanol at 60–65°C. After the reaction is completed the reaction mass was cooled gradually to 25–30°C and conc. HCl was added slowly to the mass to obtain HCl salt of **9** as white crystalline solid with 90% yield and 99.0% purity by HPLC. Many by-products and analogous impurities formed during the deprotection reaction were identified by LC–MS in reaction mass as well as in the isolated solid (Figure 1). Based on the understanding of impurities purification has been established by recrystallization using methanol and DCM to eliminate these impurities. Traces of these impurities if left behind at this stage will be carried forward with **9** to impact the purity of rivaroxaban (**1**) thus it is necessary to eliminate at this step. It was also experienced that these impurities were found to be difficult to remove from the product and ultimately require column chromatographic purifications. The data of the pilot batches along with the impurity details are presented in Table 2.

(b) Novel and efficient process for the preparation of rivaroxaban (1)

Our next objective was to establish the process for the condensation of pure **9** with 5-chlorothiophene-2-carboxylic acid or its derivatives to get rivaroxaban (**1**) with minimum



Scheme 3 Alternate and efficient synthesis of rivaroxaban (**1**).

Table 1 Impact of IPA–water ratio on nucleophilic substitution reaction between 5 and 6 to give 7

Expt. no.	Compd. 6 (mole. eq. w. r. to 5)	Volume w.r.to 5		Yield (%)	HPLC purity (%)	Content of 5 and 6	
		IPA	Water			5 (%)	6 (%)
1[a]	1.05	10	–	NI	62.00	12.00	10.0
2[b,c,d]	1.05	–	10	78.00	86.90	0.57	6.00
3[b,d]	1.05	9	1	90.00	94.38	1.70	2.00
4[b,d]	1.05	13.5	1.5	87.80	97.50	0.66	0.70
5	1.05	17	3	91.00	97.18	0.60	0.40

NI not isolated.

[a] Reaction not progressed.

[b] Reaction mass not stirrable.

[c] OXI (**6**) could not be removed in water.

[d] Thick reaction mass, unable to transfer from reaction flask to centrifuge.

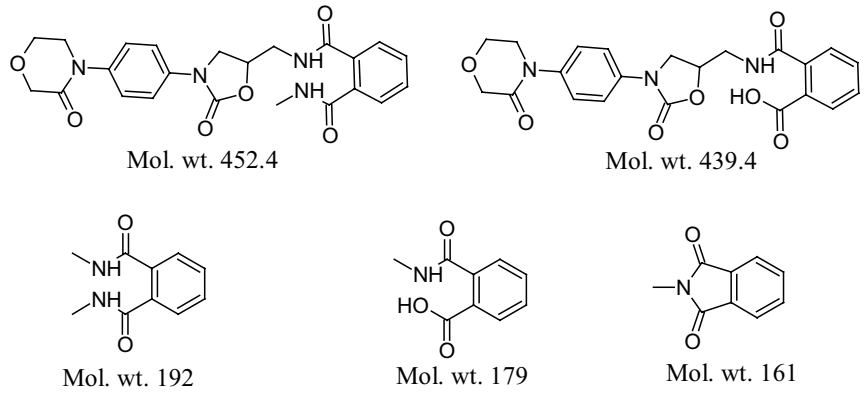


Figure 1 Identified impurities in the reaction mass of **9** by LC–MS. By-products and impurities formed during the deprotection of phthalimide group in **8** to form **9** by LC–MS in reaction mass as well as in the isolated solid of compound **9**.

Table 2 Yield and quality data of amine compound 9 from scale-up batches

No.	Comp 8 (kg)	$MeNH_2$ sol. (L)	MeOH (L)	Temp (°C)	Yield (%)	Quality details by HPLC (%)					
						9	**8**	**7**	**6**	**5**	**16**
1	2.88	2.93	28.8	60–65	87.5	99.76	ND	0.04	ND	ND	ND
2	2.87	2.92	28.7	60–65	86.0	99.80	ND	0.02	ND	ND	ND
3	2.90	2.95	29.0	60–65	85.0	99.86	0.01	0.02	ND	ND	ND

ND not detected.

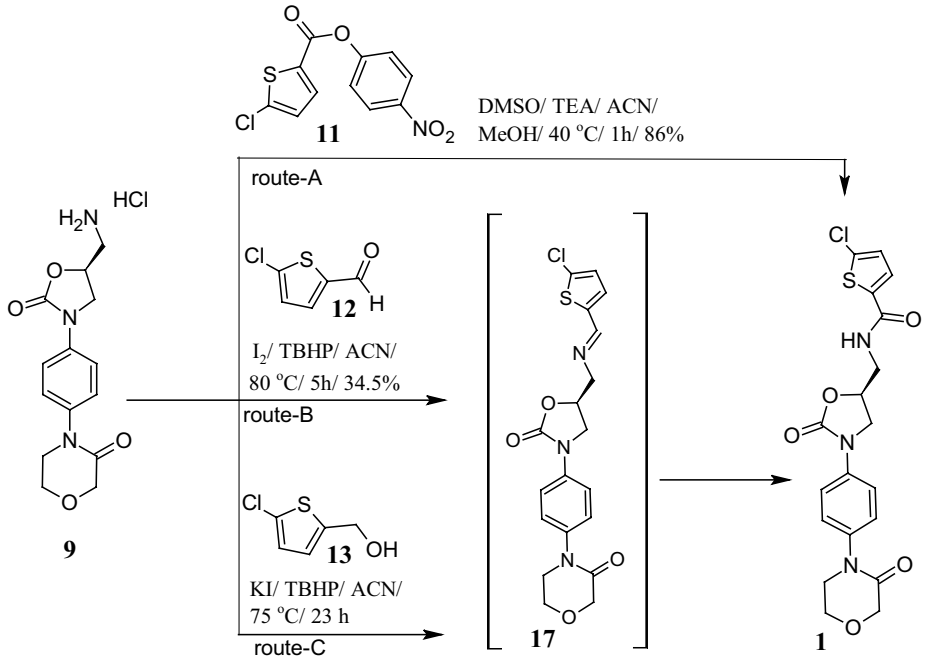
or no impurities in the reaction mass itself. We observed that reaction of **9** with 5-chlorothiophene-2-carbonyl chloride (**10**) as pre reported was incomplete leading to presence of unreacted starting material with few degraded impurities both in the reaction mass and isolated product **1**. To overcome the issue we identified three alternative synthons (Scheme 4) such as active ester **11**, aldehyde **12** and alcohol **13** as the counterpart to react with **9** instead of **10** to explore improved or efficient reaction profile. During the exploration of the experiments to check the feasibility of each of these options interesting results were noticed which are tabulated in Table 3.

Among the three synthons identified (**11**–**13**), active ester **11** as a substrate found to be the most promising synthon to react with **9** as the reaction underwent selectively and cleanly without formation of any impurities whereas in case of route-B and C, though oxidative amidation proceeded well via an imine intermediate (**17**, Scheme 4) but lead to the formation of many impurities with poor yields and hence discontinued. Thus route-A has been selected for further optimization.

Further, the situation was highly demanding to design the experiment for the synthesis of **1** which will directly yield ICH quality API from the reaction without any further purification of crude compound. In such a situation, the selection of suitable solvent and base was very important to achieve the target. Since the solubility of **1** is very low in most of the solvents except DMSO, DMF, NMP and acetic acid, we have selected DMSO and DMF as a reaction solvent for further screening based on the results of initial screen.

During the process optimization though the reaction of **9** with **11** progressed well with inorganic bases, filtration of the reaction mass to remove the inorganic base was not possible because the product is also precipitated out in the reaction mass as the reaction progresses. Alternatively, removing the inorganic base by adding water into the reaction mass and isolating the product found to possess several impurities which were difficult to remove even after repeated crystallizations. Thus we restricted our selection criteria to organic bases which are miscible with the selected solvents. Further, the solvents for the reaction were selected in which both organic base as well as rivaroxaban (**1**) is soluble.

Complete conversion **9** to **1** was observed when DMF or DMSO was used as a solvent in presence of triethylamine (TEA) as a base at 40°C. Though the reaction profile was same both in DMF and DMSO, we have chosen DMSO as it is a class-3 solvent whereas DMF is class-2 solvent. At the end of the reaction, the reaction mass was in a complete dissolved state and anti-solvent mediated crystallization shall be designed. Accordingly MeOH, IPA, ACN, ethyl acetate, acetone, THF, water, DIPE and their mixtures were tried as anti-solvents to



Scheme 4 Synthesis of **1** using coupling of different synthons **11**, **12** and **13** with **9**.

Table 3 Results obtained from different routes (A, B and C) for synthesis of 1

Route	Compd. 9 (g)	Substrate (mol. eq.)	Solvents	Time (h)	Temp (°C)	HPLC purity (%)		Yield (%)
						Reaction mass	Isolated solid	
A	10.0	11 (1.05)	DMSO	1.0	40	78.0	99.85	86.0
B	10.0	12 (1.20)	ACN	5.0	80	60.8	91.0	34.5
C	10.0	13 (1.50)	ACN	23.0	75	NA	67.17	NI

NA not analyzed, *NI* not isolated.

crystallize out the product with desired quality, yield and polymorph. The details of the same are summarized in Table 4.

When DMSO as solvent and methanol as anti-solvent are used the rivaroxaban **1** was precipitated out with a good yield but failed to eliminate dichloro impurity **14** and deschloro impurity **15**. When acetonitrile is used as an anti-solvent, impurities **14** and **15** were controlled well below 0.10% with good yield and purity of **1** (Scheme 1). Thus acetonitrile has been selected as an antisolvent for further optimization of the crystallization process. Alternatively source of these impurities (**14** and **15**) were further controlled in synthon **11**.

Mechanistically, the neucleophilic attack of amine **9** on active ester **11** was very facile because of the good leaving group (*p*-nitrophenol) on the electrophilic carbon of **11** that favored the progress of reaction without any side reaction. The by-product *p*-nitrophenol generated in the reaction was washed away with the mother liquors during the filtration. The content of *p*-nitrophenol in the pure **1** was measured using HPLC and found below 75 ppm in all the batches produced.

(c) Crystallization and isolation of 1 from the reaction pot

After the completion of reaction in DMSO at 40°C the temperature of the reaction mass was raised to 60°C and acetonitrile was added at same temperature and cooled gradually to 20–25°C to obtain the crystalline solid. The solid was filtered, washed with chilled acetonitrile and dried under vacuum to provide **1** with 75% yield and 99.8% purity with desired polymorph (Modification 1). Upon detailed analysis, it was learnt that the isolated solid was failed in residual solvent test by GC-HS with respect to acetonitrile content. The content of ACN by GC-HS was around 2,000 ppm against its acceptable limit of 410 ppm [20]. Different industrial techniques such as prolonged drying under vacuum, air tray drying, drying in RCVD (Rota Cone Vacuum Drier) at various

Table 4 Trend data of yield and impurity profile of 1 in different reaction solvents/anti-solvents

Expt. no.	Reaction solvent	Base	Anti solvents	Yield (%)	HPLC purity (%)	Impurity profile by HPLC (%)				
						9	14	15	NP	11
1	DCM	TEA	–	NI	35.9	41	0.09	0.20	13.3	1.05
2	DMF	K_2CO_3	Water	60	98.84	0.56	0.02	0.10	0.16	0.12
3	DMF	TEA	Methanol	30	99.65	0.01	0.14	0.09	0.09	ND
4	DMF	TEA	Ethyl acetate	NI	99.62	0.07	0.14	0.08	0.02	ND
5	DMF	TEA	THF	20.0	99.70	0.07	0.05	0.08	0.02	ND
6	DMSO	TEA	Methanol	90.0	99.12	ND	0.14	0.22	0.14	ND
7	DMSO	TEA	IPA	NI	98.7	0.20	0.10	0.2	0.23	ND
8	DMSO	TEA	Acetic acid/water	75.0	97.1	0.04	0.13	0.10	1.78	ND
9	DMSO	TEA	Water	75.0	98.6	0.43	0.18	0.11	0.12	0.02
10	DMSO	TEA	Acetonitrile	69.1	99.85	0.01	0.06	0.03	0.01	0.02
11	DMSO	TEA	Acetonitrile	75.0	99.86	ND	0.07	0.02	0.02	ND
12	DMSO	DBU	Acetonitrile	75.1	99.70	ND	0.13	0.05	0.02	ND

NP Nitrophenol, *NI* not isolated, *ND* not detected.

temperatures, intermittent milling of the crystals followed by drying were tested to remove the acetonitrile content but none of these techniques were successful.

Observations of the crystallization process were thoroughly investigated to understand theory of nucleation and crystal growth in the reaction flask to overcome the issue of high residual content in the crystals. Detailed observation of the process provided the following insight on the crystallization viz., (1) *Solution* Reaction mass at 60°C to provide the clear solution indicating that the product is in the soluble state, (2) *Saturation* Acetonitrile was added as anti-solvent at 60°C to achieve the saturated solution, (3) *Super saturation* The saturated solution was gradually cooled to 20–25°C to achieve super saturation which lead to nucleation and crystal growth. It was presumed that the nucleation and growth of crystals are occurring under acetonitrile environment. As the concentration of acetonitrile was more than that of DMSO which could get trapped into the crystal lattice during the primary nucleation and continued to do so as the crystal growth continues. Thus, we envisaged that if we limit the contact of acetonitrile during nucleation step by reducing its volume and/or by introducing the third anti solvent during crystal formation/nucleation process, the entrance of solvent into the crystal lattice may be arrested. Accordingly, different set of solvents were screened as a third solvent along with acetonitrile. As per our assumption, methanol has given an excellent result in controlling the residual solvent content as a third solvent among the many screened. Further the ratio of first anti solvent (ACN) and second anti solvent (methanol) played a tremendous impact on the quality and yield (Table 5).

Table 5 HPLC trend data, yield, and acetonitrile content by GC in 1

Expt. no.	DMSO (Vol[a])	ACN (Vol[a])	MeOH (Vol[a])	Yield (%)	Content by HPLC (%)					ACN content by GC (ppm)
					1	14	15	NP	11	
1	5	10	–	69.1	99.85	0.06	0.03	0.02	ND	1,980
2	3	8	–	75	99.86	0.07	0.02	0.02	ND	753
3	4	10	–	71	99.51	ND	0.14	ND	ND	NA
4	4	6	4	71	99.51	0.15	0.03	ND	ND	580
5	4	4	6	75.0	99.56	0.06	ND	ND	ND	256
6	4	6	4	75.1	99.72	0.12	ND	0.02	ND	NA
7	4	6	9	80.2	99.68	0.05	ND	0.05	ND	337
8	4	4	6	87	99.79	0.04	0.03	0.03	ND	424
9	4	4	4	–	99.55	0.06	ND	0.01	ND	371
10	4	2	6	–	99.68	0.05	0.04	ND	ND	283
11	6	2	6	86.4	99.81	0.04	ND	0.04	ND	110
12	6	2	6	84.2	99.84	0.03	0.02	ND	ND	135

ND not detected, *NA* not analyzed.

[a] Volumes used with respect to wt of **9**.

Based on the data the solvent and anti-solvents ratio of 6:2:6 volumes of DMSO:ACN:MeOH was finalized (entry 11 and 12, Table 5) to achieve robust process to provide **1** with yield of 86% and purity of 99.8% by HPLC. The acetonitrile content was achieved below 300 ppm (GC-HS) in the final product. The trend data of content of impurities by HPLC and residual solvent content by GC-HS from pilot batches is provided in Table 6.

Further, to measure the extent of greenness of newly developed process, we have calculated process mass intensity (PMI), e-factor and atom economy (calculated for last four stages) using the standard calculations provided in ACS guideline [24] and compared with the originator's process. The details are provided in Table 7.

Conclusion

An efficient, economic, and production friendly process for the preparation of highly pure rivaroxaban via alternate synthon (**11**) is described. Reaction and isolation by crystallization have been designed in the same pot avoiding the work-up which normally involve extraction, distillation, separations etc., to provide the rivaroxaban (**1**) meeting the ICH quality and desired polymorphic form with an overall yield of 22% is starting from nitro aniline (**17**) over seven stages.

Experimental

All reagents, solvents, and processing aids are commercial products and were used as received. For reactions run of pilot scale, glass line reactors having variable rate agitation, a −10 to 150°C jacket temperature range were used for the reaction. ^{1}H NMR spectra was recorded in DMSO-D_6 and D_2O using Varian Gemini 400 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. Related substance purity and residual solvent content in solid were monitored by high performance liquid chromatography (HPLC) on Agilent Technologies 1200 series. The gas chromatography on Agilent Technologies 7683B with head space was used for analyzing the residual solvents.

HPLC method for calculating the chemical purity, chiral purity and assay

Related substances, assay and chiral purity of rivaroxaban (**1**) were estimated by a gradient HPLC analysis method developed at Megafine.

(a) Related substances and assay of rivaroxaban were estimated using Zorbax SB-CN, (250 × 4.6 mm ID), 5 µ column; mobile phase A comprising a mixture of phosphate buffer (0.01 m potassium dihydrogen orthophosphate, 0.005 m 1-heptane sulphonic acid sodium salt, triethylamine, and adjust the pH 6.7 using orthophosphoric acid). Mobile phase B comprising a mixture of acetonitrile/water in the ratio 80:20 (v/v); gradient elution: time (min)/A (v/v): B (v/v), $T_{0.0}$/80:20, $T_{5.0}$/75:25, $T_{25.0}$/50:50, $T_{38.0}$/50:50, $T_{42.0}$/80:20, $T_{50.0}$/80:20; flow rate 1.5 ml/min column temperature 35°C wavelength 240 nm. The observed retention time of rivaroxaban under these chromatographic conditions is about 16.0 min.

(b) Chiral purity was estimated using Chiralpak IE (250 × 4.6 mm ID), 5 µ column; mobile phase comprising a mixture of *n*-Hexane, ethanol, methanol, THF and ammonia in the ratio of 35:35:15:15:0.1 (v/v/v/v/v) respectively; flow rate 1.0 ml/min.; column temperature 35°C; wavelength 240 nm. The observed retention time of (*S*)-rivaroxaban is about 11.7 min and (*R*)-rivaroxaban is about 10 min.

Table 6 Trend data of residual solvent, HPLC purity and yield of three pilot batches

Sr. no.	Solvent content by GC-HS in ppm			HPLC purity (%)					Yield (%)
	DMSO	Acetonitrile	Methanol	1	9	11	14	15	
1	1,068	238	352	99.81	0.01	ND	0.02	ND	85.2
2	991	226	368	99.81	0.01	ND	0.03	ND	85.3
3	969	241	407	99.83	0.01	ND	0.02	ND	85.9

ND not detected.

Table 7 PMI, e-factor, and atom economy of the developed process

Process	Theoretical PMI	Actual PMI	Aqueous PMI	Solvent PMI	e-factor	Atom economy
Megafine process	4.13	7.40	2.04	76.6	85.13	37.97
U.S. Pat. 7,576,111	2.24	28.14	25.0	415.3	455.95	44.91

By-products and impurities formed during the deprotection of phthalimide group in **8** to form **9** by LC–MS in reaction mass as well as in the isolated solid of compound **9**.

GC method for calculating residual solvent content

(a) Residual solvents content was estimated using DB-624, 60 m, 0.25 mm ID, 1.4 μ film thickness fused silica capillary column; detector temperature 280°C; injector temperature 250°C; split ratio 10:1; column flow 0.8 ml/min; nitrogen used as carrier gas; head space conditions: oven temperature 90°C; loop temperature 115°C; Transfer line temperature 120°C. The observed elution order of solvents is methanol, isopropyl alcohol, acetonitrile, dichloromethane, and tetrahydrofuran at RT 9.1, 13.5, 13.9, 14.4 and 18.1, respectively.

(b) DMSO was estimated by using HP-5, 30 m, 0.53 mm ID, 5.0 μ film thickness, Fused silica capillary column; detector temperature 280°C; injector temperature 250°C; split ratio 3:1; column flow 4 psi (at constant pressure).; nitrogen used as carrier gas; The observed retention time of DMSO is 5.5 min.

Preparation of 2-(2-chloroethoxy)-N-(4-nitrophenyl) acetamide (18)

A solution of boric acid (13 g, 0.21 mol) and 4-nitroaniline (**17**, 50 g, 0.36 mol) in toluene (500 mL) were heated to 110–115°C to remove the water by azeotropic distillation. To this solution 2-(2-chloroethoxy)-acetic acid (50 g, 0.36 mol) was added at 50–60°C and reheated to 110–115°C for 18 h. Reaction mass was cooled and filtered. Filtrate was concentrated to get residue, residue was recrystallized using isopropyl alcohol (300 mL) to afford yellow solid of compound **18**. Yield: 47 g (50.0%). M.P.: 101–104°C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.38 (s, 1H), 8.22 (d, 2H), 7.91 (d, 2H), 4.22 (s, 2H), 3.82 (s, 4H). Chemical purity by HPLC: 98.5%.

Preparation of 4-(4-nitophenyl)-3-morpholinone (19)

A solution of 2-(2-chloroethoxy)-*N*-(4-nitrophenyl) acetamide (**18**, 50 g, 0.19 mol), TBAB (3.5 g) and sodium hydroxide (12 g, 0.3 mol) in dichloromethane (500 mL) was stirred at 25–35°C for 3 h. After completion of reaction organic layer was washed with water (150 mL), organic layer was distilled out to provide residue which was crystallized in isopropyl alcohol (85 mL) to obtain yellow solid of compound **19**. Yield: 37.8 g (90.0%). M.P.: 148–152°C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.27 (d, 2H), 7.77 (d, 2H), 4.27 (s, 2H), 4.0 (t, 2H, 3.86 (t, 2H). Chemical purity by HPLC: 99.5%.

Preparation of 4-(4-aminophenyl) morpholin-3-one (5)

A solution of 4-(4-nitophenyl)-3-morpholinone (**19**, 100 g, 0.45 mol) with Pd–C (10% w/v, 50% wet, 2 g) and ammonium formate (170 g) in methanol (1,000 mL) was heated to 55–60°C for 90 min, upon completion of reaction catalyst was filtered, filtrate was cooled to 5–10°C to precipitate compound **5**, which was filtered and recrystallized in water to get white solid of compound **5**. Yield: 65.0 g (75.0%). M.P.: 169–172°C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.94 (d, 2H), 6.54 (d, 2H), 5.15 (d, 2H), 4.27 (s, 2H), 3.90 (t, 2H), 3.56 (t, 2H). Purity by HPLC: 99.9%. Chemical purity by HPLC: 99.9%.

Preparation of 2-[(2R)-2-hydroxy-3-{[4-(3-oxomorpholin-4-yl) phenyl]amino}propyl]-1H-isoindole-1,3(2H)-dione (7)

A suspension of 4-(4-aminophenyl)morpholin-3-one (**5**, 100 g, 0.52 mol) and 2-[(2*S*)-oxiran-2-ylmethyl]-1*H*-isoindole-1,3(2*H*)-dione (**6**, 116.2 g, 0.57 mol) in isopropyl alcohol (1,700 mL) and water (300 mL) was refluxed for 24 h. After completion of reaction (by HPLC), reaction mass was cooled to 25–30°C, precipitated solid **7** was filtered, washed with isopropyl alcohol (100 mL) and dried the solid under vacuum (650–700 mm/Hg) at 50–55°C for 6 h to afford **7** as light yellow to off white colored solid. Yield: 196.8 g (96.0%). MS *m*/*z*: 395.9 ($M^+ + 1$). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.98–3.04 (m, 1H), 3.13–3.19 (m, 1H), 3.68–3.57 (m, 4H), 4.02–3.91 (m, 3H), 4.13 (s, 2H), 5.16 (d, $J = 5.2$ Hz, 1H), 5.65 (t, $J = 6.4$ Hz, 1H), 6.61 (d, $J = 8.8$ Hz, 2H), 7.01 (d, $J = 8.8$ Hz, 2H), 7.82–7.88 (m, 4H). Purity by HPLC: 97.50%. Chemical purity by HPLC: 97.5%.

Preparation of 2-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]-1,3-oxazolidin-5-yl} methyl)-1H-isoindole-1,3(2H)-dione (8)

N–*N*-carbonyldiimidazole (CDI) (61.5 g, 0.38 mol) was added to a suspension of **7** (100 g, 0.25 mol) and potassium carbonate (34.5 g, 0.25 mol) in dichloromethane (1,000 mL) at 25–30°C. Reaction mixture was maintained at 25–30°C for 5–6 h until completion of the reaction (by HPLC). Inorganic solid was filtered and washed with dichloromethane (200 mL). Filtrate was collected and concentrated to obtain the residue. The residue was further slurried in tetrahydrofuran (500 mL) at 50–55°C and cooled to 25–30°C, filtered the solid, washed the solid with tetrahydrofuran (50 mL) to furnish **8** as light yellow to off white solid. Yield: 101.1 g (95.0%). MS *m*/*z*: 422.0 ($M^+ + 1$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.75–3.72 (t, $J = 5.2$, 4.8 Hz, 2H), 4.0 (dt, 2H), 4.04 (t, 2H), 4.17 (dt, 2H), 4.33 (s, 2H), 5.02 (m, 1H), 7.35–7.32 (d, $J = 12$ Hz, 2H), 7.57–7.55 (d, $J = 9.2$ Hz, 2H), 7.77–7.74 (dd, 2H), 7.89–7.78 (dd, 2H). Purity by HPLC: 99.80%. Chemical purity by HPLC: 99.80%.

Preparation of 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl] phenyl}morpholin-3-one hydrochloride (9)

40% Methylamine solution (102 mL) was added to the solution of **8** (100 g, 0.23 mol) in methanol (1,000 mL)

at 25–30°C. Reaction mass was stirred at 60–65°C for 4–6 h (completion of reaction monitored by HPLC). Reaction mass was cooled to 25–30°C, pH of reaction mass was adjusted to 1–2 using concentrated hydrochloric acid, precipitated solid was filtered, and washed with methanol (100 mL) to obtain crude **9**. The obtained crude **9** was dissolved in mixture of methanol (800 mL) and dichloromethane (300 mL) by adjusting the pH 8–9 of reaction using triethylamine at 25–30°C to achieve clear solution. Reaction mass was acidified to pH 2–3 using concentrated hydrochloric acid to precipitate **9**. Precipitated solid was filtered, washed with methanol (150 mL) and dried to furnish pure **9** as white solid. Yield: 65.5 g (85.0%). MS *m*/*z*: 292.2 ($M^+ + 1$). ^{1}H NMR (D_2O, 400 MHz): δ 3.49 (d, 2H), 3.81–3.78 (t, $J = 5.2$, 4.8 Hz, 2H), 3.97 (q, 1H), 4.11–4.08 (t, $J = 4.8$, 5.2 Hz, 2H), 4.40–4.36 (t, $J = 9.2$, 6.8 Hz, 3H), 5.13 (m, 1H), 7.42–7.40 (d, $J = 8.8$ Hz, 2H), 7.61–7.58 (d, $J = 8.8$ Hz, 2H). Purity by HPLC: 99.80%. Chemical purity by HPLC: 99.80%.

Preparation of 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]-1,3-oxazolidin-5-yl}methyl) thiophene-2-carboxamide (1) as per route-A

4-Nitrophenyl 5-chlorothiophene-2-carboxylate (**11**, 95 g, 0.33 mol) was added to a solution of **9** (100 g, 0.30 mol) and triethylamine (46.2 g, 0.45 mol) in DMSO (600 mL) at 35–40°C. After completion of reaction (by HPLC) acetonitrile (200 mL) was added to the reaction mixture at 35–40°C. Reaction mixture was further heated up to 65°C, methanol (600 mL) was added to the reaction mixture at 60–65°C. Reaction mixture was cooled to 25–30°C, the obtained solid was filtered, washed with methanol (100 mL), and dried under vacuum (700 mm/Hg) for 4–5 h at 50–55°C to get pure rivaroxaban (**1**) as white to off white solid. Yield: 114.3 g (86.0%). MS *m*/*z*: 436.0 ($M^+ + 1$). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.61–3.59 (t, $J = 5.6$ Hz, 2H), 3.72–3.69 (t, $J = 5.2$, 4.8 Hz, 2H), 3.86–3.82 (q, 1H), 3.97–3.95 (t, $J = 4.8$, 5.6 Hz, 2H), 4.21 (s, 2H), 4.16 (t, 1H), 4.87 (m, 1H), 7.2 (d, 1H), 7.42–7.38 (d, 2H), 7.57–7.53 (d, 2H), 7.69 (d, 1H), 8.99–8.96 (t, $J = 4$, 6 Hz, 1H). ^{3}C NMR (DMSO-d_6, 400 MHz): δ 166.01, 160.85, 154.13, 138.48, 137.05, 136.51, 133.35, 128.46, 128.15, 125.95, 118.31, 71.38, 67.75, 63.50, 49.03, 47.44, 42.24. Elemental analysis: C, 52.5; H, 4.14; N, 9.65; S, 7.33. Purity by HPLC: 99.80%. Chiral purity by HPLC: 99.95%. Chemical purity by HPLC: 99.80%. Chiral purity by HPLC: 99.95%.

Residual solvent by GC HS (ppm)

Methanol: 407, isopropyl alcohol: not detected, dichloromethane: not detected, tetrahydrofuran: not detected, acetonitrile: 120, DMSO: 510, triethylamine: 20.

Author's contributions

All authors read and approved the final manuscript.

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The authors declare that they have on competing interests.

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