An efficient and safe process for the preparation of ticagrelor, a platelet aggregation inhibitor via resin-NO\textsubscript{2} catalyzed formation of triazole ring

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Abstract

An efficient, safe and improved process for the preparation of ticagrelor 1, a platelet aggregation inhibitor is described. Synthesis comprises the condensation of pyrimidine amine derivative 14 with cyclopentyl derivative 13 in ethylene glycol followed by construction of triazole compound 16 by diazotization of the obtained intermediate 15 with a green and safer reagent "Resin-NO\textsubscript{2}" in water and acetonitrile mixture. Condensation of 16 with cyclopropylamine derivative 10 followed by deprotection of compound 12 with hydrochloric acid in dichloromethane (DCM) furnished ticagrelor 1 with an overall yield of 65 % and purity of 99.78 % by HPLC. Each reaction stage was optimized independently to establish the scalable and plant friendly process. An efficient and a safe process for key intermediate 14 which involve nitration reaction has also been developed. Safety parameters were established by understanding the thermal events of the reaction by DSC analysis.

Keywords: Ticagrelor, Diazotization, Resin-NO\textsubscript{2}, Triazole, Nitration, Arterial thrombosis

Background

Establishing the safe chemical processes for manufacturing of active pharmaceutical ingredients and their intermediates in pharmaceutical/chemical industry is increasingly becoming important and challenging. Identification of critical process parameters by assessing the hazardous factors associated with material, reaction and operation that bring safety to the product and personnel involved in the production is very critical and important to grow and sustain in the business. Accidents can be avoided just by understanding the heat of reaction, kinetics, decomposition pattern of product mixture, addition pattern of reagents and reactants, mischarging of reactants and catalysts, agitation problems, proper temperature control, and etc. In this communication, we presented process development aspects of ticagrelor 1, a P2Y12 receptor antagonist (Jacobson and Boeynaems 2010) and a well-known dual ADP receptor inhibitor used in the treatment of arterial thrombosis (Springthorpe et al. 2007). This drug was invented by Astra Zeneca and approved by United state of food and drug administration (USFDA) during March 2012 for the prevention of thrombotic events such as stroke or heart attack in patients with acute coronary syndrome or myocardial infarction with ST elevation (Zhang et al. 2012). Through its direct and reversible mode of action, ticagrelor exhibits rapid onset and offset effects and thus more suitable for patients who are going to take surgery (Haberfeld 2010). In addition ticagrelor does not require metabolic activation (Van Giezen and Humphries 2005), indicating less variability related to genetic polymorphism (Huber et al. 2011).

The first synthetic approach reported (Hardern et al. 2003; Tadimeti and Chengzi 2011) for 1 is a multistep process (Scheme 1) and involve the reagents such as...
trifluoromethane sulfonyloxy acetic acid methyl ester in n-BuLi, isoamyl nitrite in bromoform, DIBAL-H in THF, and trifluoroacetic acid which are hazardous, toxic, flammable, pyrophoric and expensive. Further, the product formed by this method requires purification by column chromatography in order to control unacceptable amounts of critical and potential impurities formed in reaction and thus it is difficult to provide International conference on harmonization (ICH) grade material suitable for formulation and thus process is not feasible at industrial scale. Diazotization of 15 with sodium nitrite in mixture of acetic acid and water yielded substituted triazole compound 16 with the formation of critical impurity 27 (Fig. 1) along with other impurities which are difficult to remove from product 1. Further 16 was reacted with 10 in acetonitrile in presence of triethylamine to provide 12, followed by deprotection of the diketal group of 12 with aqueous hydrochloric acid (aq. HCl) in methanol (MeOH) to provide 1 (Scheme 2) with 18.0 % yield and 98.25 % purity by HPLC.

Another synthetic approach reported (Ulf et al. 2001) by Larsson and his team made extensive efforts towards
the convenient and efficient synthesis of 1. Few of the steps adopted are superior, improved and scalable over the first reported syntheses. The improved process involve condensation of pyrimidine amine 14 with 1-tartaric acid salt of 13 in ethanol in the presence of triethylamine at elevated temperature and high pressure (72 psi in autoclave) to provide 15.

The reaction conditions involved in this approach for 15 requires pressure reactor, high temperature and longer reaction time (40–45 h) which is unsafe to handle at commercial scale. Moreover the product formed by this process requires column chromatographic purification to control critical impurities formed in the reaction, thus makes the process unsuitable for large scale production.

We hereby report a scalable, efficient, safe, and impurity-free process for the synthesis of ticagrelor (1) which is suitable for commercial production.

**Results and discussion**

Process research and development of ticagrelor (1) presented in this article mainly focused on following four aspects: (a) to develop an efficient and high yielding process for the manufacture of one of the key intermediates 14 by establishing the safe critical process parameters for the nitration of 21 to achieve nitro compound 22, (b) to avoid high pressure reaction for condensation of 13 and 14, (c) to develop an alternative and safe diazotation process for preparing the triazole compound 16 using “Resin-NO₂” which is safe to handle, reduces the
formation of impurities and provide high reaction yield, and (d) to develop pure ticagrelor 1, which is free from potential impurities 26 and 27 without the use of column chromatography purifications. The details are presented here.

**Development of an improved and safe process for 14**

The thienopyrimidine 14 is one of the important building blocks required for the synthesis of ticagrelor (1). The literature processes (Scheme 3) for making 14 involves five steps wherein nitration and its reduction steps found to be critical and hazardous (Ulf et al. 2001; Khile et al. 2011). Reaction conditions used for nitration of 21 are found to be highly unsafe as we have observed several runaway kind of reaction during the initial experimentation in the laboratory. Further the reduction of obtained nitro compound 23 with Iron in the presence of acetic acid to yield 14 (Scheme 3, path A) posed serious operational problems as many of the reactions were again run away kind of nature with minor severity and lot of frothing. Filtration of unreacted iron and iron oxide with acetic acid was highly cumbersome as it took almost 2 days. The filtration of acetic acid in plant created irritant atmosphere and thus was not suitable. The reduction of diazo compound 25 to obtain amine 14 by hydrogenation in presence of Platinum catalyst on carbon according to path B (Scheme 3) though safe but the process was highly expensive and could not meet the economics.

For establishment of nitration of 21 we explored fuming nitric acid (alone) and fuming nitric acid along with acetic acid or sulfuric acid during feasibility experiments with precautionary temperature control during the addition or at the time of reaction progress but none of them worked out to be safe. We have then conducted DSC analysis for the nitration reaction to evaluate the safe reaction conditions. DSC analysis for the reaction mass was performed wherein mixture of fuming nitric acid and acetic acid was used as a nitrating agent. DSC

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**Scheme 3** Synthetic approaches for the preparation of compound 14
thermogram shows exotherm at around 83 °C with heat evolution of 272 J/g of sample which corresponds to the exothermic temperature rise of around 219 °C, i.e. if reaction mass is heated up to 83 °C then temperature of the reaction mass could go up to 302 °C (83 + 219 °C) [ΔT]. Since ΔT was more than 50 °C the reaction is considered to be highly exothermic and thus the reaction needs to be conducted below 33 °C (83 − 50 = 33 °C) to avoid safety issues due to high exotherm. During laboratory optimization it has also been noticed that the dilution of the reaction mass with acetic acid minimized the exotherm to some extent thus we decided to perform nitration using fuming nitric acid along with acetic acid (5.0 times with respect to wt. of 21) as the nitrating mixture at 0–5 °C. With these two critical reaction parameters we could perform the reaction safely during the commercial scale synthesis of 22 at 50 kg level. More importantly cooling/chilling unit of the plant should be efficient and it should not be allowed to break down during the reaction.

Further, the reduction of 23 has been developed with simple, inexpensive and mild reducing agent such as iron and catalytic quantity of ferric chloride [Fe/FeCl3] in presence of methanol at 50–55 °C (Gabriele et al. 2001). Reaction was smooth and went to completion within 3–4 h by HPLC. After completion of reaction, separation of the catalyst by filtration followed by acid–base workup of the filtrate provided amino compound 14 in 76 % yields and 99 % purity by HPLC (path C). Drastic change in the behavior of reaction and its filtration pattern was observed when Fe–FeCl3 was used as a reducing agent.

Preparation of ticagrelor 1
Condensation of 13 with 14 to provide compound 15
During development, nucleophilic aromatic substitution of 13 with 14 has been attempted in various solvents such as ethanol, toluene, acetonitrile, and monoethylene glycol along with different organic and inorganic bases. The experiments conducted with inorganic bases such as Na2CO3, NaHCO3, K2CO3, Cs2CO3 and Li2CO3 with or without catalysts at different temperatures did not proceed to form compound 15 in the reaction whereas use of selected organic bases such as triethylamine (TEA), N,N-dimethyl aniline (DMA), diisopropyl ethyl amine (DIPEA) provided encouraging results as presented in Table 1.

Data clearly indicates that the reaction performed with MEG as solvent, DIPEA as a base and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst provided very good reaction yield without applying the pressure (Table 1, entry 7). Further optimization to establish the mole ratios of 13 (with respect to 14) using monoethyl ene glycol (MEG) as solvent, DIPEA as base and DBU as a catalysts provided encouraging results at 120–125 °C (Table 2).

After complete optimization, three consecutive experiments were performed with optimized parameters to check the consistency of the results with 100 g input of compound 14 (Table 2, entry nos. 9–11). After completion of reaction, the reaction mass was diluted with water, extracted the contents into ethyl acetate, ethyl acetate layer was washed with water, brine and concentrated to obtain the residue. Crystallization of the residue in ethyl acetate and n-heptane provided crystalline compound 15 with around 80 % yield and 99.5 % purity by HPLC. Thus a suitable process avoiding the pressure reactor, higher temperature, longer reaction times (40–45 h) and purification of the product by column chromatography has been developed (Scheme 4). The structure of crystalline compound 15 was characterized by analytical and spectroscopic methods. As compound 15 was isolated as a solid for the first time in our hands, the PXRD analysis was performed on the dried solid to understand the crystal pattern or polymorphic form (Mathad et al. 2014).

Table 1  Screening experimental data for condensation of 13 and 14
| Solvent | Base    | Catalyst | Temp (°C) | Time (h) | Reaction yield (%) | Isolated yield (%) | HPLC purity |
|---------|---------|----------|-----------|----------|--------------------|--------------------|-------------|
| Ethanol | TEA     | –        | 75–78     | 30.0     | 62.5               | 28.25              | 68.00       |
| IPA     | DIPEA   | DBU      | 78–80     | 50.0     | 70.2               | 34.28              | 75.00       |
| Methanol| DIPEA   | DBU      | 61–65     | 52.0     | 12.0               | 45.71              | 15.00       |
| Toluene | TEA     | KI       | 108–111   | 31.0     | 11.5               | 48.97              | 15.00       |
| MEG     | DIPEA   | KI       | 120–125   | 6.0      | 83.5               | 72.00              | 99.51       |
| MEG     | DIPEA   | –        | 120–125   | 5.0      | 85.00              | 67.97              | 99.60       |
| MEG     | DIPEA   | DBU      | 120–125   | 5.0      | 85.5               | 77.14              | 99.65       |
| MEG     | TEA     | DBU      | 120–125   | 6.0      | 54.0               | 54.29              | 60.00       |
| ACN     | K2CO3   | –        | 80–85     | 30.0     | 25.0               | 60.00              | 30.00       |
| DMF     | K2CO3   | –        | 100–105   | 24.0     | 16.0               | 56.00              | 21.00       |
Further, the construction triazole ring on 15 to provide 16 comprises diazotization reaction followed by cyclization. The reported reactions for diazotization (NaNO₂–acetic acid) involve highly acidic conditions that are found to be not suitable as it leads to deprotection compound 15 and formation of other unknown impurities which are difficult to remove. The alternative diazotizing agents such as alkyl nitrite (isoamyl nitrite in bromoform) is not suitable for diazotization on an industrial scale, since they are expensive, decompose during storage, corrosive and requires exclusively organic medium (ether, acetonitrile, THF, etc.,). Diazonium salts obtained under classical conditions are potentially explosive substances and thus need a very safer mechanism to handle

| Compd. 14 (g) | Compd. 13 (mol. eq) | Base    | Catalyst | Temp (°C) | Reaction yield (%) | Isolated yield (%) | HPLC purity (%) |
|---------------|---------------------|---------|----------|-----------|-------------------|-------------------|-----------------|
| 10.0          | 1.00                | DIPEA   | DBU      | 120–125   | 85.15             | 59.40             | 99.03           |
| 10.0          | 0.90                | DIPEA   | DBU      | 120–125   | 82.30             | 54.25             | 95.11           |
| 10.0          | 1.05                | DIPEA   | DBU      | 120–125   | 87.95             | 69.85             | 99.38           |
| 10.0          | 1.10                | DIPEA   | DBU      | 100–105   | 88.65             | 67.14             | 98.38           |
| 10.0          | 1.20                | DIPEA   | DBU      | 120–125   | 94.50             | 73.14             | 99.31           |
| 25.0          | 1.10                | DIPEA   | KI       | 120–125   | 91.85             | 73.00             | 99.51           |
| 10.0          | 1.10                | DIPEA   | –        | 120–125   | 89.45             | 67.97             | 99.60           |
| 10.0          | 1.10                | DIPEA   | –        | 135–140   | 92.20             | 72.00             | 99.30           |
| 100.0         | 1.10                | DIPEA   | KI       | 120–125   | 94.90             | 79.95             | 99.37           |
| 100.0         | 1.10                | DIPEA   | DBU      | 120–125   | 95.05             | 80.81             | 99.35           |
| 100.0         | 1.10                | DIPEA   | DBU      | 120–125   | 94.65             | 79.96             | 99.57           |

All the reactions are performed in MEG. 10 volumes of MEG was used w. r. to compound 13 provided favourable results.
in the plant scale. Diazotization using cation exchange resin along with mild acidic reagent such as P-toluene sulphoniacid (TsOH) with sodium nitrite in acetonitrile and water mixture releases brown fumes of gaseous nitrogen oxide which is again not safe in the production environment (Filimonov et al. 2008; Gorlushko et al. 2008; Lee et al. 2010; Moon et al. 2010). While exploring safer means of conducting this reaction, we have identified and introduced the anion exchange resin (Resin NO$_2^-$) saturated with nitrite ions from sodium nitrite successfully as diazotization reagent (Trusova et al. 2011) for synthesis of stable 16. Resin-NO$_2$ was found to be an industrially feasible, safe and green reagent for the diazotization of 15. The resin NO$_2^-$ was prepared by treating readily available Amberlyst A26 hydroxide form (Aldrich) with sodium nitrite solution in water. The suspension was filtered, washed with water till the filtrate solution shows neutral pH. The ion exchange capacity of the reagent was measured by potentiometer and found to be around 2.6–3.6 mmol of NO$_2^-$/g. The reagent was also found to be stable for at least 1 month in moist state. The diazotization process comprises a very simple and friendly operation; the compound 15 was stirred with Resin-NO$_2^-$ in water and acetonitrile (1:1) mixture in presence of TsOH for 20–30 min. After completion of the reaction, resin was separated by filtration followed by water washing. Compound 16 was extracted from filtrate layer into DCM and then DCM layer was washed with NaHCO$_3$ solution and concentrated to yield compound 16 as thick syrup which was directly used for next reaction without further purifications. The resin obtained was recovered by treating it with sodium hydroxide (NaOH) solution to yield hydroxyl resin and it can be recycled further for diazotization by converting it to nitrite resin using the above process. Thus, a green and safe approach for diazotization of 15, which produces no toxic gases and can be performed in water acetonitrile mixture at room temperature, is developed.

The next step of the process includes nucleophilic substitution of 16 with 10 to provide protected ticagrelor 12. During development, reaction of 16 with 10 has been explored with various solvents in presence of selected bases at different temperature range. Among those combinations, reaction conducted in acetonitrile in presence of anhydrous K$_2$CO$_3$ at 25–30 °C for 2–3 h provided 12 as an oil with 98 % yield and 93 % purity by HPLC. The reaction with organic bases such as TEA and DIPEA though found good but taken longer reaction time (12–15 h) for the completion. The deprotection of ketal group on 12 was explored in various solvent like methanol, ethanol and DCM in presence of acidic reagents like acetic acid, trifluoro acetic acid andaq. HCl. Trifluoroacetic acid reported for this reaction by earlier investigators was avoided as it was unsafe to handle in the production environment. Further, we have avoided the combination of methanol and aqueous HCl, wherein formation of potential genotoxic impurity, methyl chloride (CH$_3$Cl) was observed at trace level in the product. It was also observed that the reaction mass exposed to strong acidic condition for longer time, generated degradation impurity (15,25,3R,5S)-3-[7-amino-5-(propylthio)-3H-[1,2,3] triazole-[4,5-d][pyramid -in-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol impurity (27) both in methanol and ethanol. When reaction was performed in DCM andaq. HCl (biphasic condition), reaction was proceeded smoothly in 2–3 h with reduced amount of impurities (less than 0.05 % by HPLC) due to less contact time of the product with acid. Hence, DCM has been selected as a reaction medium and aq. HCl as an acid source.

After completion of the reaction, the reaction mass was cooled to 10 °C and adjusted the pH of the contents to 9–11 with NaOH solution followed by distillation of DCM below 40 °C to provide the oily syrup. The syrup was then diluted with water, extracted from ethyl acetate, and ethyl acetate layer was concentrated to provide product 1 as syrup. The syrup was then recrystallized in neat acetonitrile to furnish 1 as a white crystalline solid with an overall yield of 63 % and HPLC purity of 99.85 % (Scheme 4; Table 3). The potential O-acetyl ticagrelor impurity 26 formed during the work-up was found below 0.10 % and degraded impurity 27 below 0.05 % by HPLC. The impurity profile data of three consecutive batches was provided in Table 3.

**Conclusion**

In conclusion, simple, efficient, production friendly and environment friendly green chemistry approach process for the synthesis of ticagrelor that is substantially free from potential impurities 26 and 27.

**Experimental section**

Melting points were determined on Analab melting point apparatus, in open capillary tubes and are uncorrected. The $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Varian Gemini 400 MHz FT NMR spectrometer. Chemical shifts were reported in parts per million (ppm) using tetramethylsilane as internal standard and are given in δ units. The solvents used for NMR spectra were deuterated chlorofrom and deuterated dimethylsulfoxide unless otherwise stated. Infared spectra were taken on Perkin Elmer Spectrum 100 in potassium bromide pallets unless otherwise stated. Elemental analyses were performed on a Hosli CH-Analyzer and the results were within ±0.3 % of the calculated values. High-resolution mass spectra were obtained with a Shimadzu GC–MS QP mass spectrometer with
Table 3 Monitoring the elimination of impurities in downstream process for 1

| Sample station (for HPLC analysis) | Impurities and their content by HPLC (%) | 1  | 12 | 16 | 26 | 27 | SMUI |
|-----------------------------------|----------------------------------------|----|----|----|----|----|------|
| Crude                             | ND                                     | 99.25 | ND | ND | 0.32 | 0.01 | 0.06 |
| Acetonitrile purification         | ND                                     | 99.74 | ND | ND | 0.05 | 0.01 | 0.06 |
| Crude                             | ND                                     | 98.70 | 0.07 | ND | 0.30 | 0.06 | 0.14 |
| Acetonitrile purification         | ND                                     | 99.60 | ND | ND | 0.05 | 0.01 | 0.05 |
| Crude                             | ND                                     | 99.44 | ND | ND | 0.29 | 0.02 | 0.03 |
| Acetonitrile purification         | ND                                     | 99.78 | ND | ND | 0.04 | ND | 0.03 |

ND not detected

an ionization potential of 70 eV. All the reaction were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60F254 (Merck) plates using UV light (254 and 366 nm) or High performance liquid chromatography (HPLC) on Agilent Technologies 1200 series for detection. Gas chromatography on Agilent Technologies 7893B with head space was used for analyzing the residual solvents. Common reagent-grade chemicals are either commercially available and were used without further purification or were prepared by standard literature procedures.

2-[[3aR,4S,6R,6aS]-6-[[5-amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino]-2,2-dimethyltetrahydro-3H-cyclopenta[d][1,3]dioxol-4-yl]oxy]-1-ethanol, (15)

To a stirred solution of 14 (1.0 kg, 4.19 mol) in ethylene glycol 5.0 L with 13 (1.69 kg, 4.61 mol) was added DBU (50.0 g), followed by addition of DIPEA (2.43 kg, 18.85 mol) at 25–30 °C. The reaction temperature was slowly raised to 120–125 °C and maintained for 4–5 h. After completion of reaction (by HPLC), reaction mass was cooled to 25–30 °C and diluted with water (20 L). The pH of reaction mass was adjusted to 4–5 with aqueous hydrochloric acid and product was extracted with ethyl acetate (15 L). The ethyl acetate layer was separated, washed with water (10 L) and 15 % (w/v) sodium chloride solution (10 L). Collected ethyl acetate layer was concentrated under reduced pressure at 50–55 °C to provide thick syrup (1.6 kg). The syrup was dissolved in ethyl acetate (1 L) stirred, heated at 50 °C, followed by addition of n-heptane (20 L) at 50 °C and maintained for 30 min. The resulting isolated suspensions was gradually cooled, chilled at 0–5 °C, maintained for 30–40 min; obtained solid was filtered, washed with n-heptane (1 L), suck dried and dried at 50–55 °C to afford 15 as white crystalline solid. Yield: 1.41 kg, (80.53 %). Purity by HPLC: 99.51 %. M.P: 108–112 °C. IR (KBr, cm⁻¹): 3441.88, 3379.74, 3346.07, 2935.63, 1643.23, 1570.57, 1373.35, 1115.91, 1050.31, 951.55, and 763.48. PXRD (2θ°): 5.36, 6.65, 10.53, 13.39, 18.21, 22.54, 24.18. The spectral data of compound 15 prepared by our process was found to be in agreement with the reported data (Tadimeti and Chengzi 2011).

Resin NO₃⁻ To a stirred solution of sodium nitrite (0.6 kg) in water was added Amberlyst A26 hydroxide form (1.0 kg). The reaction mass was stirred for 25–30 min at 25–30 °C. Resin was filtered and washed with water (3 × 2 L) till the pH of filtrate shows 7–8 and sucked dried the material for 10–15 min to provide resin NO₃⁻ as brown granules. Yield: 0.95 kg, (95 %); Ion exchange capacity: 2.6–3.6 mmol of NO₃⁻/g.

2-[[3aR,4S,6R,6aS]-6-[[7-chloro-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d] pyrimidin-3-y1]-2,2-dimethyltetrahydro-3H-cyclopenta[d][1,3]dioxol-4-yl]oxy]-1-ethanol (16)

To a stirred solution of TsOH (0.68 kg, 3.58 mol) in water (5 L) was added resin nitrite (2.0 kg) and reaction mass was stirred for 10–15 min followed by addition of 15 (1.0 kg, 2.38 mol) in acetonitrile (5 L). The reaction mass was stirred for 20–30 min at 25–30 °C. Upon completion of reaction by TLC, resin was removed by filtration and washed with DCM (10 L). The mother liquor was combined and diluted with water (10 L). The DCM layer was separated, washed with water (10 L) followed by 15 % (w/v) sodium chloride solution and evaporated under reduced pressure at 35–40 °C to provide 16 as thick syrup. Yield: 1.01 kg, (98.42 %). HPLC purity: 92.0 %. The spectral data of compound 16 prepared by our process were found to be in agreement with the reported data (Tadimeti and Chengzi 2011).

2-[[3aR,4S,6R,6aS]-6-[[1R,2S]-2-(3,4-difluorophenyl)-cyclopropyl]amino]-5(propylthio)-3H-[1,2,3]triazolo[4,5-d] pyrimidin-3-y1]-2,2-dimethyltetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-yl]oxy]-1-ethanol (12)

To a stirred solution of 16 (1.0 kg, 2.32 mol) in acetonitrile (7 L) was added 10 (0.709 kg, 2.2 mol) and anhydrous K₂CO₃ (0.640 kg, 4.64 mol) and stirred at 25–30 °C for 2–3 h. After completion of the reaction by HPLC, reaction mass was diluted with water (10 L) and extracted.
with DCM (10 + 5 L). DCM layer was separated, washed with water (10 L) followed by 15 % (w/v) sodium chloride solution (10 L) and concentrated under reduced pressure at 35–40 °C to provide 12 as thick brownish syrup. Yield: 1.25 kg, (95.52 %). HPLC purity: 93.0 %. The spectral data of compound 12 prepared by our process were found to be in agreement with the reported data (Tadimeti and Chengzi 2011).

\[(15,25,3R,5S)-3\text{-[7-[[1R,2S]-2-(3,4-Difluorophenyl) cyclopropyl]amino]-5-(propylthio)-3H-[1,2,3]-triazolo[4,5-d] pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol (ticagrelor, 1)}\]

To a stirred solution of 12 (1.0 kg, 1.77 mol) in DCM (7 L), was added aqueous hydrochloric acid (5 L) and the resultant reaction mass was stirred for 2–3 h. Upon completion of reaction by HPLC, the pH of reaction mass was adjusted to 9–11 with aqueous NaOH solution (~2.4 L). The DCM layer was concentrated under reduced pressure to provide oil. The oil was diluted with water (12 L) and extracted in ethyl acetate (200 cm³). The ethyl acetate layer was washed with 2 % (v/v) sodium chloride solution (2 × 7.08–7.07 (d, 1H), 5.16–5.14 (d, 1H), 5.09–5.08 (d, 1H), 4.99–4.52 (t, 1H), 4.56–4.51 (q, 1H), 4.13–4.10 (t, 2H), 3.93–3.91 (t, 1H), 3.78–3.75 (t, 1H), 3.70–3.62 (m, 2H), 3.17–3.13 (q, 1H), 2.96–2.89 (q, 1H), 2.87–2.80 (q, 1H), 2.67–2.59 (q, 1H), 2.14–2.09 (m, 1H), 2.02–1.98 (t, 4H), 1.55–1.46 (m, 3H), 1.39–1.36 (t, 1H), 0.83–0.79 (t, 3H). 13C NMR (DMSO-\(d_6\)): δ 170.45, 169.22, 168.35, 155.44, 154.00, 150.73, 149.43, 149.09, 148.30, 146.68, 139.37, 123.23, 122.87, 117.16, 114.95, 81.80, 74.34, 73.78, 66.86 (CH₂), 63.37 (CH₂), 60.70, 35.74, 34.14, 33.09 (CH₂), 32.36 (CH₂), 24.09, 24.09, 22.36 (CH₂), 20.76, 16.59 (CH₂), 15.05 (CH₂), 13.01 (CH₃).

\[(15,25,3R,5S)-3\text{-[7-amino-5-(propylthio)-3H-[1,2,3]-triazolo[4,5-d] pyrimidin-3-yl]-5-(2 hydroxyethoxy)-1,2-cyclopentanediol (27)}\]

To a stirred solution of 16 (10.0 g, 0.025 mol) in tetrahydrofuran (100 cm³) was added ammonium hydroxide (100 cm³) and stirred at 25–30 °C for 7–8 h. After completion the reaction by TLC, reaction mass was filtered, washed with tetrahydrofuran (10 cm³), and dried under vacuum to provide 27 as white crystalline solid. Yield: 7.95 g, (83.68 %). HPLC purity: 98.2 %. M.P: 175.8–176.9 °C. IR (KBr, cm⁻¹): 3413.4, 3178.2, 2961.9, 1665.7, 1571.0, 1321.5, 1121.1. MS \(m/z\) (%): 371.2 [M + 1] (100). 1H NMR (DMSO-\(d_6\)): δ 8.41 (bs, OH), 8.06 (bs, OH), 5.36 (bs, NH₂), 4.99–4.92 (d, 1H), 4.64 (bs, OH), 4.59–4.55 (q, 1H), 3.94–3.93 (d, 1H), 3.76–3.73 (t, 1H), 3.51–3.45 (q, 4H), 3.13–3.01 (m, 2H), 2.65–2.57 (m, 1H), 2.08–2.01 (m, 1H), 1.72–1.65 (q, 2H), 1.59 (s, 1H), 1.00–0.96 (t, 3H). 13C NMR (DMSO-\(d_6\)): δ 169.08, 155.14, 149.66, 122.86, 81.82, 74.19, 73.72, 70.82 (CH₂), 60.86, 60.28 (CH₂), 33.10 (CH₂), 32.14 (CH₂), 25.22, 22.44 (CH₂), 13.30 (CH₃).

**Sodium salt of thiobarbutaric acid (19)**

Sodium methoxide (70.94 g, 1.31 mol) was added to stirred and hot solution of thiourea (17, 100.0 g, 1.31 mol) and dimethyl malonate (18, 208.26 g, 1.57 mol) in methanol (200 cm³) at 50–55 °C and maintained for 3–4 h. Upon completion of reaction, the reaction mass was cooled to 0–5 °C and maintained for 30–45 min. The product obtained was filtered, washed with pre-chilled methanol (25 cm³) and dried under vacuum at 35–40 °C to offer sodium salt of 19 as white crystalline solid. Yield: 190.0 g, (88.0 %). HPLC purity: 99.7 %. The spectral data of compound 19 prepared by our process were found to be in agreement with the reported data (Tadimeti and Chengzi 2011).

**2-(propylthio)pyrimidine-4,6-diol (21)**

To a stirred solution of NaOH (59.83 g, 1.50 mol) in water (300 cm³) was added 18 (100.0 g, 0.59 mol) and propyl bromide (20, 88.29 g, 0.72 mol). The reaction mass was heated at 50–55 °C and maintained for 4–5 h. After
completion of reaction by TLC, the reaction mass was diluted with water (300 cm$^3$) and acidified with aqueous hydrochloric acid till pH 0.5–1.5. The contents were stirred for 60–90 min and the solid obtained was filtered, washed with water (100 cm$^3$) and dried under vacuum at 55–60 °C for 4–5 h to provide 21 as white crystalline solid. Yield: 105.0 g, (80.0 %). HPLC purity: 97.5 %. The spectral data of compound 21 prepared by our process were found to be in agreement with the reported data (Tadimeti and Chengzi 2011).

5-Nitro-2-(propylthio)pyrimidine-4,6-diol (22)

To a pre chilled (0–5 °C) solution of acetic acid (500 cm$^3$) was added fuming nitric acid (83.89 g, 1.33 mol) and stirred for 10–15 min. Compound 21 (100.0 g; 0.54 mol) was added lot wise (five equal lots) below 5 °C to the above nitrating mixture and maintained at 0–5 °C for 45–60. After completion of reaction by TLC, the reaction mass was diluted with water (500 cm$^3$) and stirred for 45–60 min. The obtained solid was filtered, washed with water (300 cm$^3$) and dried under vacuum at 55–60 °C for 4–5 h to afford 22 as crystalline pale yellow solid. Yield: 95.0 g, (80.0 %). HPLC purity: 98.4 %. The spectral data of compound 22 prepared by our process were found to be in agreement with the reported data (Tadimeti and Chengzi 2011).

4,6-Dichloro-5-nitro-2-(propylthio)pyrimidine (23)

To a pre cooled (0–5 °C) mixture of 22 (100.0 g, 0.43 mol) and phosphorus oxy chloride (238.71 g, 1.55 mol) was added N,N-dimethyl aniline (104.8 g, 0.86 mol). The mixture was heated at 100–110 °C and maintained for 60–90 min. After completion of reaction by TLC the reaction mass was cooled at 25–30 °C and then quenched over chilled water (1.5 L). The product was extracted in DCM (2 × 500 cm$^3$) and the DCM layer was washed with 10 % (w/v) sodium bicarbonate solution (500 cm$^3$) followed by 15 % (w/v) sodium chloride solution (500 cm$^3$). Concentration of DCM under reduced pressure at 35–40 °C furnished 23 as brownish oil. Yield: 111.0 g, (95.73 %). HPLC purity: 97.80 %. The spectral data of compound 23 prepared by our process were found to be in agreement with the reported data (Tadimeti and Chengzi 2011).

4,6-Dichloro-5-amino-2-(propylthio)pyrimidine (14)

To a stirred solution of 23 (100.0 g, 0.37 mol) in methanol (800 cm$^3$) was added iron powder (116.62 g, 2.08 mol) and the contents were heated up to 35–40 °C. Ferric chloride (13.0 g, 0.08 mol) solution in water (130 cm$^3$) was added to the above mixture and heated at 50–55 °C for 3–4 h. Upon completion of reaction by TLC, the reaction mass was cooled to 25–30 °C and iron was removed by filtration. The collected filtrate was concentrated under reduced pressure to yield oil which was diluted with water (500 cm$^3$), basified with ammonium hydroxide and extracted with DCM (500 cm$^3$). DCM layer was washed with 10 % (w/v) EDTA solution (500 cm$^3$) followed by 15 % (w/v) sodium chloride solution (500 cm$^3$) and evaporated at 35–40 °C under reduced pressure to provide 14 as crude oil. The crude oil was diluted with di-isopropyl ether (500 cm$^3$) and pH of the solution was adjusted to 0.5–1.5 using concentrated hydrochloric acid (50 cm$^3$). Diisopropyl ether layer was separated, washed with water (2 × 500 cm$^3$) and evaporated under reduced pressure at 45–50 °C to offer 14 as brownish thick oil. Yield: 72.0 g, (81.07 %). HPLC purity: 99.60 %. IR (NaCl, cm$^{-1}$): 3473.83, 2964.84, 1608.13, 1502.57, 1493.74. MS m/z (%): 238.1 [M$^+$ + 1] (100). 1HNMR (CDCl$_3$): δ 4.19 (bs, NH$_3$), 3.08–3.05 (t, 2H) 1.77–1.67 (m, 2H), 1.03–1.00 (t, 3H), 1$^{13}$C NMR (CDCl$_3$): δ 158.25, 145.06, 143.06, 131.39, 33.20 (CH$_2$), 22.24 (CH$_2$), 13.29 (CH$_3$).
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