Novel synthetic methodology for the synthesis of Ticagrelor

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ABSTRACT

Ticagrelor is the first reversible P2Y\textsubscript{12} receptor antagonist blocking adenine diphosphate (ADP) induced platelet aggregation with rapid onset and offset of effect \cite{1} \cite{2}. A new methodology for the synthesis of Ticagrelor and its novel intermediates which is useful for the commercial synthesis of Ticagrelor.

Keywords: Ticagrelor, Antithrombotic agent

INTRODUCTION

Ticagrelor (1) acts as an adenosine uptake inhibitor, a platelet aggregation inhibitor, a P2Y\textsubscript{12} purinoceptor antagonist that belong to a novel class of compounds called cyclopentyltriazolopyrimidine inhibitors, and a coagulation inhibitor. It is the first reversible P2Y\textsubscript{12} inhibitor approved by FDA for the prevention of thrombotic events such as stroke or heart attack in patients with ACS or myocardial infarction with ST elevation. Through its direct and reversible mode of action, Ticagrelor exhibits rapid onset and offset of effects, making it more suitable for patients who are going to take surgery. In addition, unlike the thienopyridines, Ticagrelor does not require metabolic activation \cite{3}, indicating a less variability related to genetic polymorphisms \cite{4}. It is indicated for the treatment of thrombosis, angina, ischemic heart diseases, and coronary artery diseases \cite{5}. Ticagrelor is the first reversibly binding oral adenosine diphosphate (ADP) receptor antagonist, it selectively inhibits P2Y\textsubscript{12}, a key target receptor for ADP which blockade inhibits the action of platelets in the blood, reducing recurrent thrombotic events.

Being highly potent molecule and a molecule with very less side effect compared in its class the molecule become a classic example for the extensive study of synthesis. Although several synthetic procedures have been developed for Ticagrelor, still extensive study is undergoing on the molecule to find different synthetic approach to find best commercial route, which led us to develop an efficient and unprecedented synthetic method for Ticagrelor. We have previously reported a new synthetic approach for the synthesis of Ticagrelor \cite{6}, in continuation of our program on the study, herein we would like to report a novel synthetic methodology of Ticagrelor from the compound (2) as shown in the scheme-1, and it involves novel intermediates.

EXPERIMENTAL SECTION

The IR spectra were recorded using a Perkin-Elmer spectrum one FT-IR spectrometer instrument by using 1% potassium bromide pellet technique. The \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded in DMSO-\textsubscript{d}6 at 300 MHz & 75 MHz respectively on Bruker 300 MHz Advance NMR spectrometer using Tetramethylsilane as the internal standard. Mass spectra (MS) were recorded on Agilent 1100 Series LC-MSD-TRAP-SL instrument.
Reactions were monitored by thin layer chromatography on 0.2 mm silica gel 60 F254 (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent-grade chemicals are commercially available and were used without further purification.

The new synthetic methodology of Ticagrelor 1 involved novel intermediates, its synthesis started with the benzyl protection of (1R,2S)-2-(3,4-difluorophenyl)cyclopropanamine 2. Compound 2 can be synthesized as per the reported literature [2, 7, 8] & 4,6-dichloro-5-nitro-2-(prop-2-en-1-ylsulfanyl)pyrimidine compound 4 was synthesized as per the reported literature [6]. The benzyl protection of compound 2 was carried out by reductive amination reaction and obtained 3. Further 3 was subjected to reaction with 4,6-dichloro-5-nitro-2-(prop-2-en-1-ylsulfanyl)pyrimidine compound 4 in the presence of THF, DIPEA and obtained the desired compound 5. Then the compound 5 was condensed with compound 6 in the presence of Diisopropylethylamine and obtained 7. The compound 6 is prepared as per the reported literature [2, 8, 9]. Subsequently 7 was reduced using sodium dithionite in the presence of ammonia, MeOH and obtained 8. There are various reports in the literature for the reduction of nitro group like Palladium on Carbon [10, 11], Zinc [12, 13], Iron powders [14, 15], but the reduction reaction of compound 7 using sodium dithionite and ammonia gave better yield. The advantage of this reagent is that it is very cheap reagent compared to Palladium on carbon & Zinc, there was no emulsion formation observed like usually observed in the work up process of Zinc and Iron powder reactions and hence it is very easy in the operations of scale-up at plant level with quantitative yields. A sequence of steps such as reaction of compound 8 with NaNO2 in the presence of Acetic acid gives triazo compound 9 on further reaction with HCl leads to de-protected diol compound 10 and finally reduction using Palladium on Carbon in MeOH solvent followed by isolation from Ethylacetate and Hexanes provided the pure Ticagrelor (1).

Scheme-1. Reagents and conditions: (a) Benzaldehyde, MeOH, NaBH₄; (b) DIPEA, THF, EtOAc, 30-35°C; (c) THF, DIPEA, 50-55°C; (d) MeOH, NH₃, Na₂S₂O₄, EtOAc, 40-45°C; (e) Toluene, NaNO₂, AcOH, Na₂CO₃ 10-15°C; (f) MeOH, HCl, 20-25°C; (g) MeOH, Pd-C, 40-45°C

Scheme-1. Synthesis of Ticagrelor (1)

In another alternate approach (Scheme-2) we have altered the reactions where the compound 6 was first reacted with dichloro-nitro compound 4 in the presence of TEA and obtained the condensed product 11, which was reduced with Zn and acetic acid reaction conditions, to get 12. The compound 12 was also prepared by direct reacting 6 with
compound 16 in presence of Na₂CO₃ and 1,4-Dioxane solvent. Then the obtained compound 12 was treated with NaNO₂ in the presence of Acetic acid to get 13, which was then condensed with 2 and obtained 14. Further the compound 14 was treated with HCl to get de-protected diol compound 15. This compound was reduced by hydrazine hydrate to get the desired Ticagrelor (1) as mentioned earlier.

Scheme-2. Reagents and conditions: (a) THF, TEA, (15), -10°C; (b) NaHCO₃, 1,4-Dioxane, 60-65°C, EtOAc, Hexanes; (c) Zn, MeOH, AcOH, 55°C; (d) Toluene, NaNO₂, AcOH, Na₂CO₃ 10-15°C; (e) THF, DIPEA, 40-45°C; (f) MeOH, HCl, Na₂CO₃, EtOAc, Hexanes, 5-10°C; (g) THF, EtOH, Hydrazine hydrate, NaI, EtOAc, Hexanes.

Compound 4 can be synthesized from Diethyl malonate as per the reported literature [6] Compound 16 was synthesized from 4 by reducing nitro group with Zinc acetic acid.

Scheme-3. Reagents and conditions: (a) Zn, AcOH, 55°C.

(1R,2S)-N-benzyl-2-(3, 4-difluorophenyl)cyclopropanamine (3)

(1R,2S)-2-(3,4-difluorophenyl)cyclopropanamine compound 2 (4 g) was dissolved in methanol (12 ml) at room temperature, benzaldehyde (2.5 g) was added to it and stirred for 120 minutes, Sodium borohydride (1.2 g) was
added to the above reaction mass in lot wise and stirred at room temperature for 3 hours, after completion of reaction, reaction mass was concentrated to get residue, water (40 ml) and ethyl acetate (40 ml) was added and layers were separated. Organic layer was concentrated to get 5 g of compound 3. 

\[ \text{HNMR(DMSO-d6, 300 MHz) (δ, ppm) 0.83-0.89 (m, 1H), 1.09-1.18 (m, 1H), 1.21 (s, 3H), 1.27-1.46 (m, 1H)\] 

2-((3a,7R,8R,9S,10aS)-3-(2-hydroxyethoxy)-5-(7-(N-benzyl-N-((1RS,2RS)-4-(7-(N-benzyl-N-((1RS,2RS)-2-(3,4-difluorophenyl)cyclopropyl)-5-nitropyrimidin-4-ylamino)-tетrahydro-2,2,2-dimethyl-3aH-cyclopenta[4,5-d] [1,3]dioxol-6-yloxy)ethanol (7)

Compound 7 (5 g) was dissolved in methanol (40 ml) and aqueous ammonia (6 ml) was added. The reaction mass temperature was raised to 40-45°C. Sodium dithionate (5 g) was added to reaction mixture in lot wise and stirred at room temperature for 3 hours, after completion of reaction water (15 ml) and Ethylacetate (30 ml) was added to it. Organic layer was separated and filtrate was concentrated to get residue, water (25 ml) and Ethylacetate (40 ml) was added to residue and layers were separated. Organic layer was concentrated to get residue, water (40 ml) and Ethylacetate (40 ml) was added to reaction mass, acetic acid (6.6 g) was diluted with toluene (12 ml) and slowly added to solid was filtered to get 6.5 gm crystalline HCl salt of compound 3.

2-(allylthio)-N-benzyl-6-chloro-N-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)-5-nitropyrimidin-4-amine (5)

Compound 4 (2 g) was dissolved in Tetrahydrofuran (15 ml), mixture of Diisopropylethylamine (2.5 g) and compound 3 (1.8 g) dissolved in Tetrahydrofuran (15 ml) was slowly added to the above solution and stirred for 60 min. After completion of reaction water (15 ml) and Ethylacetate (30 ml) was added to it. Organic layer was separated and distilled out to get residue. Residue was purified by column chromatography to get 5 g of compound 5. 

\[ \text{HNMR(DMSO-d6, 300 MHz) (δ, ppm) 0.91-0.99 (m, 1H), 1.09-1.18 (m, 1H), 1.21 (s, 3H), 1.27-1.46 (m, 1H)\] 

2-((3aS,4R,6S,6aR)-4-6-(N-benzyl-N-((1R,2S)-2-(3,4-difluorophenyl)cyclopropyl)amino)-2-(allylthio)-5-nitropyrimidin-4-ylamino)-tетrahydro-2,2,2-dimethyl-3aH-cyclopenta[4,5-d] [1,3]dioxol-6-yloxy)ethanol (8)

Compound 8 (12 g) was dissolved in toluene (120 ml) and cooled to 0-5°C. Sodium nitrite (1.6 g) was dissolved in water (40 ml) and added to the reaction mass, acetic acid (6.6 g) was diluted with toluene (12 ml) and slowly added to the reaction mass. Reaction mass was maintained at 0-5°C for 60 min. After completion of reaction, water (60 ml) was added to it and pH was adjusted to 7.5 with sodium bicarbonate solution. Organic layer was separated and concentrated to get 12 g of compound 9.

(1S,2S,3S,5R)-3-2-hydroxyethoxy)-5-(7-(N-benzyl-N-((1R,2S)-2-(3,4-difluorophenyl) cyclopropyl)amino)-5-(allylthio)-3-(1,2,3)triazolo[4,5-d]pyrimidin-3-yl)cyclonentane-1,2-diol hydrochloride (10)

Compound 9 (12 g) was dissolved in methanol (18 ml) and cooled to 5-10°C. HCl (5.5 g) was added to reaction mass and temperature was raised to 20-25°C. After completion of reaction, reaction mass was cooled to 0-5°C and solid was filtered to get 6.5 gm crystalline HCl salt of compound 10. 

\[ \text{HNMR(DMSO-d6, 300 MHz) (δ, ppm) 1.42-1.65 (m, 2H), 1.98-1.08 (m, 1H), 2.25-2.35 (m, 1H), 2.55-2.68 (m, 2H)\]
(1S,2S,3R,5S)-3-{7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylsulfanyl)-3H-[1,2,3]triazolo[4,5-d][pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (Ticagrelor, 1)

Compound 10 (5 g) was dissolved in methanol (60 ml) and palladium on carbon (0.5 g) was added to it and hydrogenated at 6-8 Kg pressure of hydrogen at 40-45°C. Reaction mass was filtered and filtrate was concentrated and crystallized from ethyl acetate & hexane mixture (25ml: 25ml) to get 3.8 g of Ticagrelor.

2-((3aS,4R,6S,6aR)-4-((2-allylthio)-6-chloro-5-nitropyrimidin-4-ylamino)-tetrahydro-2,2-dimethyl-3aH-cyclopent[4,5]-d][1,3]dioxol-6-yl)ethanol (11)

Compound 4 (30 g) was dissolved in Tetrahydrofuran (150 ml) and cooled to -10°C, mixture of compound 6 (free base (24 g), Triethylamine (13 g dissolved in Tetrahydrofuran 150 ml) was slowly added to the above reaction mass at -10°C. Reaction temperature was raised to 20-25°C and stirred for 120 min. After completion of reaction water (120 ml) was added and layers were separated, aqueous layer was extracted with ethyl acetate (100 ml), organic layers were combined and concentrated to get 44g of compound 10. 1H NMR(DMSO-d6, 300 MHz) (δ, ppm) 1.29 (s, 3H), 1.45 (s, 3H). 1.91 (bd, 1H), 2.28-2.42 (dt, 1H), 3.58-3.62 (m, 1H), 3.67-3.83 (m, 5H), 3.97 (d, 1H), 4.53 (dd, 1H), 4.65 (dd, 1H), 4.72 (t, 2H), 5.14 (dd, 1H), 5.35-5.41 (dd, 1H), 5.93-5.99 (m, 1H), 8.65 (d, 1H); Mass (m/z) : 428 (M+1).

2-((3aS,4R,6S,6aR)-4-((2-allylthio)-5-amino-6-chloropyrimidin-4-ylamino)-tetrahydro-2,2-dimethyl-3aH-cyclopent[4,5]-d][1,3]dioxol-6-yl)ethanol (12)

To a compound 16 (5 g), free base of compound 6 (5 g) and Sodium carbonate (1.8 gm) was added followed by 1,4-dioxane (50 ml) and heated up to 60-65°C. After completion of reaction water (100 ml) and Ethylacetate (70 ml) was added and layers were separated, organic layer was washed with Sodium chloride solution and then concentrated under vacuum to get residue, hexanes was added to residue at 50-55° and gradually cooled to room temperature and stirred for overnight to get 7g of compound 12. 1H NMR(DMSO-d6, 300 MHz) (δ, ppm) 1.28 (s, 3H), 1.44 (s, 3H), 1.91 (bd, 1H), 2.24-2.42 (dt, 1H), 3.58-3.62 (m,1H), 3.67-3.83 (m, 5H), 3.95 (d, 1H), 4.52-4.58 (m, 2H), 4.60 (t, 1H), 5.05 (dd, 1H), 5.27-5.33 (dd, 1H), 5.10 (bs, 2H), 5.93-6.04 (m, 1H), 6.28 (d, 1H); Mass (m/z) : 417 (M+1).

2-((3aS,4R,6S,6aR)-4-((2-allylthio)-5-amino-6-chloropyrimidin-4-ylamino)-tetrahydro-2,2-dimethyl-3aH-cyclopent[4,5]-d][1,3]dioxol-6-yl)ethanol (13)

To a solution of Zinc dust (30 g), methanol (10 ml) and water (60 ml), acetic acid (33 g) was added and heated up to 55°C. Compound 11 (20 g; which was dissolved in methanol 80 ml) was added slowly to the reaction mass, and stirred for 30 min. After completion of reaction, filtered through hyflo-bed and washed methanol (30 ml) and filtrate was concentrated, product was extracted with Ethylacetate (100 ml), Ethylacetate layer was dried on Sodium sulfate (10 g) and concentrated to get 16 g of compound.

2-((3aS,4R,6S,6aR)-4-((2-allylthio)-7-chloro-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (Ticagrelor, 1)

Compound 5 (5 g) was dissolved in Tetrahydrofuran (150 ml) and cooled to -10°C, mixture of compound 6 (24 g), Triethylamine (13 g dissolved in Tetrahydrofuran 150 ml) was slowly added to the above reaction mass at -10°C. Reaction temperature was raised to 20-25°C and stirred for 120 min. After completion of reaction water (120 ml) was added and layers were separated, aqueous layer was extracted with ethyl acetate(150 ml), organic layers were combined and concentrated to get 44g of compound 11. 1H NMR(DMSO-d6, 300 MHz) (δ, ppm) 1.29 (s, 3H), 1.45 (s, 3H), 1.91 (bd, 1H), 2.28-2.42 (m, 1H), 2.49 (bs, 1H), 3.63-3.68 (m, 1H), 3.72-3.85 (m, 5H), 3.97 (d, 1H), 4.53 (dd, 1H), 4.65 (dd, 1H), 4.72 (t, 2H), 5.14 (dd, 1H), 5.35-5.41 (dd, 1H), 5.93-5.99 (m, 1H), 8.65 (d, 1H); Mass (m/z) : 447 (M+1).
Early stage. The advantage of this route is that the cost of the product is competitive to the other routes reported so far. The regulated market. This novel route of Ticagrelor synthesis will help the industry to enter the regulated market, because of patents which prevent the industry from manufacturing and supplying drug substances or drug products to the market. Organic layer was separated and concentrated to get residue. The yield at each stage is quantitative.

Ticagrelor (15), which remains a challenging area, despite impressive progress in organic synthesis. The development of alternate route is useful for the pharmaceutical industry when there is a restriction of reported literature routes. The aim of present work is to provide a new synthetic methodology for the synthesis of bioactive target compound Ticagrelor (1). The methodology is useful for industrial scale up as the reagents and chemicals are cheaper and easily available.

RESULTS AND DISCUSSION

The present work is to provide new synthetic methodology for the synthesis of bioactive target compound Ticagrelor (1), which remains a challenging area, despite impressive progress in organic synthesis. The development of alternate route is useful to the pharmaceutical industry when there is a restriction of reported literature routes. The methodology is helpful for the industry to enter to the regulated market at the early stage. The advantage of this route is that the cost of the product is competitive to the other routes reported so far, as it provides easy access to the market.

CONCLUSION

In summary, we have demonstrated a novel synthetic methodology for the synthesis of Ticagrelor using scheme-1 & scheme-2. The methodology is useful for industrial scale up as the reagents and chemicals are cheaper and easily available.

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