A comprehensive literature review on Synthetic approaches of cardiovascular drugs such as Ticagrelor and Dronedarone

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Abstract:

Ticagrelor and Dronedarone hydrochloride are the cardiovascular drugs, Dronedarone hydrochloride is belongs to antiarrhythmic medications whereas Ticagrelor is used for treatment of Acute Coronary Symptom and Strokes. In this chapter/article, a comprehensive overview is discussed on synthetic approaches of Ticagrelor and Dronedarone hydrochloride based on literature references.

Dronedarone:

Dronedarone, approved by the Food and Drug Administration in 2009 for clinical use in atrial fibrillation (AF), is a structural analogue of the antiarrhythmic drug amiodarone, both belonging to Class III of antiarrhythmic medications. While amiodarone is a widely used antiarrhythmic agent, its clinical utility is hampered by the potential for toxicity. Prolonged usage of amiodarone may lead to various health issues, including thyroid disease, pulmonary fibrosis, and liver disease, which could be attributed to its high iodine content. In contrast, Dronedarone, a

relatively newer medication, offers a promising option for reducing hospitalizations in patients with cardiovascular diseases, especially those with paroxysmal or persistent atrial fibrillation (AF), in sinus rhythm (SR), or those anticipated to undergo cardioversion.[1]

Dronedarone is often regarded as the most suitable option for maintaining rhythm in patients with atrial fibrillation who do not have a history of heart disease, coronary artery disease, or hypertension, and who do not exhibit left ventricular hypertrophy.[2-5]

Dronedarone is a heterocyclic compound (figure 1) containing a benzofuran ring, and it shares structural similarities with Amiodarone, albeit with slight modifications. In this modification, the iodine group in amiodarone is substituted with a methane-sulfonyl group. This substitution was made with the aim of reducing the potential for adverse effects on non-target organs associated with amiodarone therapy. The replacement of iodine with the methane-sulfonyl group results in a reduction in the compound's lipophilicity, consequently lowering the risk of neurotoxicity and significantly shortening Dronedarone's half-life.[6-10] Dronedarone is characterized by its crystalline nature and has a melting point within the range of 149 to 153 degrees Celsius. Notably, Dronedarone appears to exhibit pharmacological activity across all four Vaughan-Williams antiarrhythmic classes.[11-13]

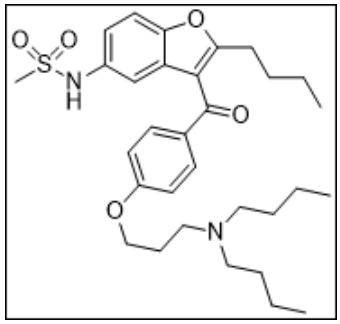
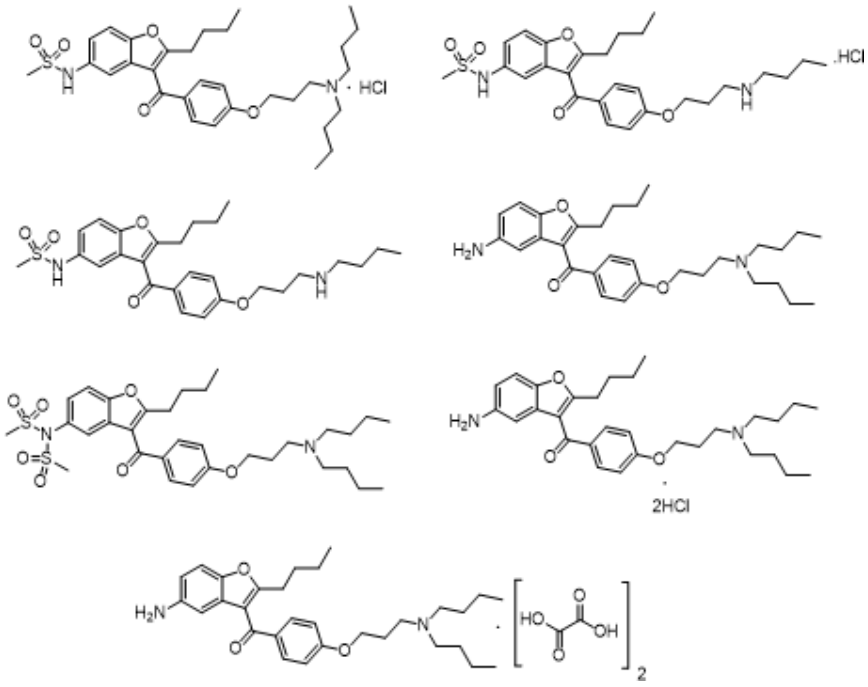


Figure 1: Dronedarone

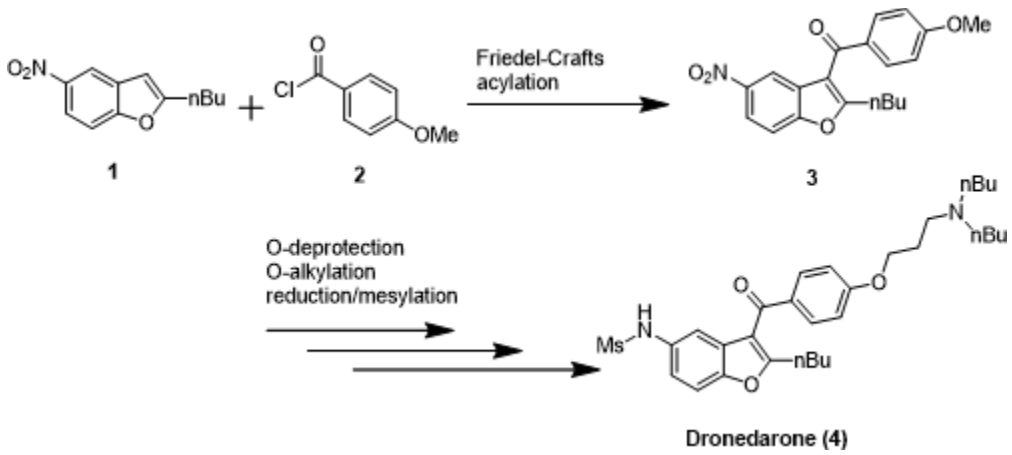
Dronedarone Hydrochloride is categorized as a Class antiarrhythmic medication utilized to reestablish the typical sinus rhythm in individuals who suffer from paroxysmal or persistent atrial fibrillation. It is chemically related to amiodarone, but its structure does not contain iodine components, which are linked to thyroid issues caused by amiodarone. The following are references for Dronedarone Hydrochloride API, as well as its pharmacopeial and non-pharmacopeial impurities, and stable isotopes.

Dronedarone Hydrochloride Impurities:

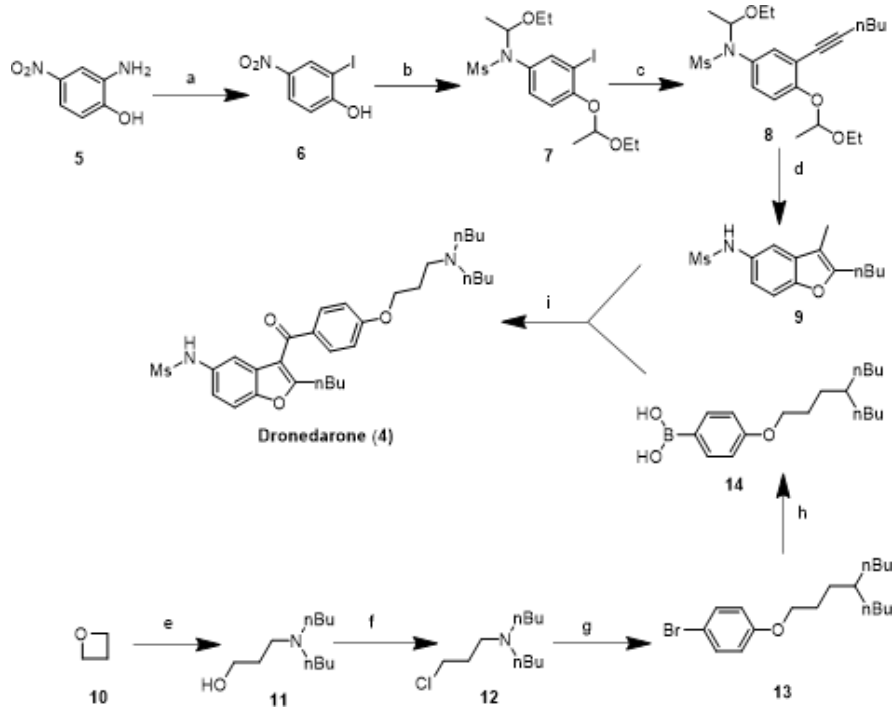


Literature reports:

The first synthesis of dronedarone was reported by Gubin et al.,[14] and this synthesis involved a linear process from 2-butyl-5- nitrobenzo[b] furan as a starting material (Chart 1).

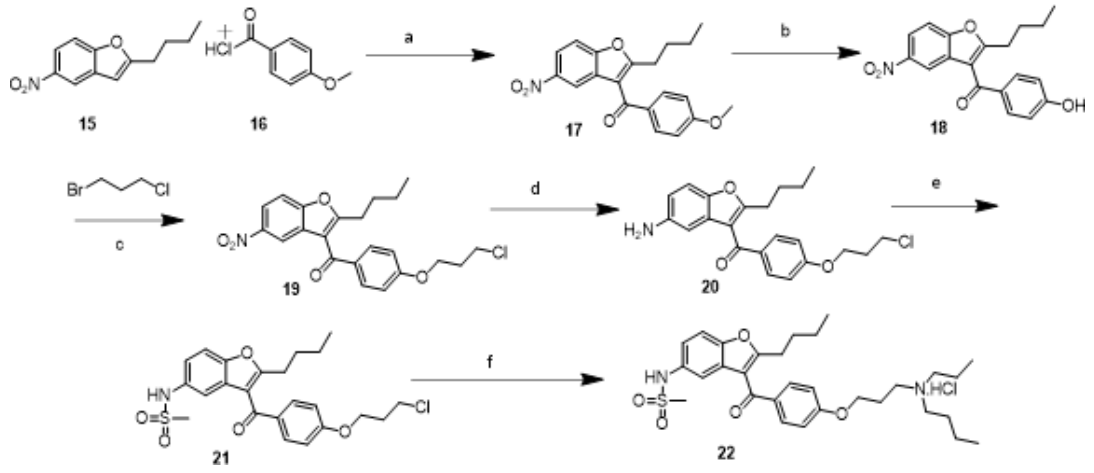


In the year of 2016 Takashi Okitsu *et. al.,*[15] were synthesized and reported Convergent Synthesis of Dronedarone, an Antiarrhythmic Agent. The primary stages of this procedure involve creating a benzofuran framework through iodocyclization and generating biaryl ketones via carbonylative Suzuki–Miyaura cross-coupling. This synthetic pathway, starting from 2-amino-4-nitrophenol, was accomplished in just eight steps, resulting in a total yield of 23%.



Reagents and conditions: (a) $NaNO_2$, 30% H_2SO_4, DMSO, 0°C, 1 h; then KI, r.t., 12 h, 77%; (b) (i) $SnCl_2$, EtOH, 70°C, 15 h; (ii) MsCl, pyridine, CH_2Cl_2, r.t., 15 h; (iii) ethyl vinyl ether, PPTS, CH_2Cl_2, r.t., 24 h, 72% in 3 steps; (c) 1-hexyne, $PdCl_2$, Ph_3P, CuI, Et_3N, CH_3CN, r.t., 23 h, 95%; (d) (i) $I(coll)_2PF_6$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, r.t., 10 min;(ii) 10% HCl, THF, MeOH, 60°C, 30 min, 77% in 2 steps; (e) nBu_2NH, $LiBF_4$, CH_3CN, r.t., 4 h, 54%; (f) $SOCl_2$, $CHCl_3$, reflux, 1 h, 89%; (g) 4-bromophenol, Cs_2CO_3, NaI, CH_3CN, 65°C, 23 h, 92%; (h) nBuLi, THF, -78°C, 45 min; then $B(OiPr)_3$, r.t., 23 h; then sat. NH_4Cl aq., r.t., 30 min, 46%; (I)$PdCl_2(PPh_3)_2$, K_2CO_3, CO (1atm), anisole, 80°C, 23 h, 57%.

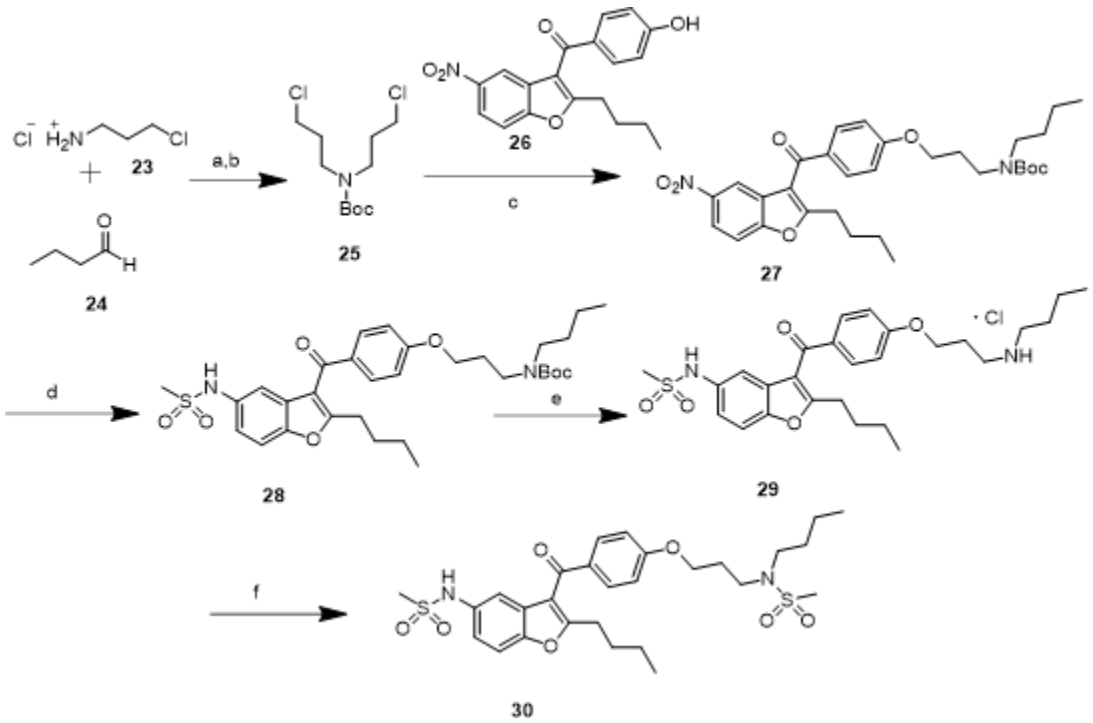
In the year of 2011, Saravanan Mohanarangam *et. al.,*[16] were synthesized and reported A Novel and Efficient Synthesis of Dronedarone Hydrochloride, an Antiarrhythmic Drug Substance, A new and effective method for synthesizing dronedarone hydrochloride, commencing with 2-n-butyl-5-nitrobenzofuran, is outlined. This approach utilizes gentle and specific reaction conditions, making it straightforward to carry out and well-suited for industrial purposes.



Reagents and conditions: (a) DCM, $AlCl_3$, 25°C, 4 h, 88%; (b) Chlorobenzene, $AlCl_3$, 85°C, 4 h, 92%; (c) DMF, K_2CO_3, 25°C, 20 h, 88.8%; (d) IPA, 10% Pd-C, $HCOONH_4$, 50°C, 30 min,

94.2%; (e) DCM, $NaHCO_3$, 35°C, 6 h, 81%; (f) DMF, N,N-dibutylamine, 125°C, 4 h, EtOAc, 10% HCl in EtOAc, 25°C, 2 h, 63%.

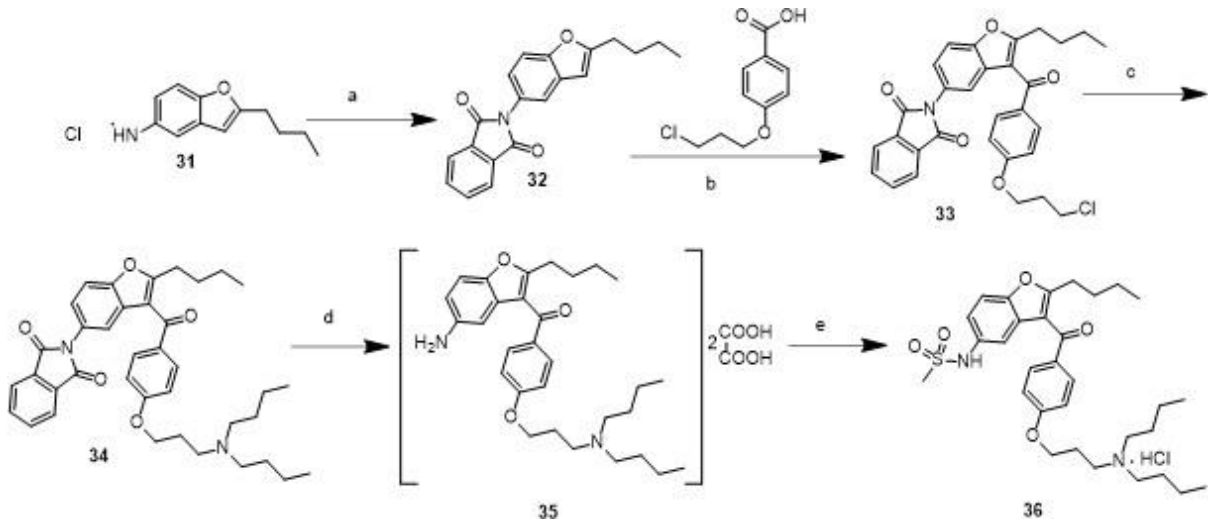
In the year of 2015, Maria J. Comin *et. al.*,[17] were synthesized and reported Synthesis and characterization of new related substances of the antiarrhythmic drug Dronedarone hydrochloride. During the process development of the antiarrhythmic drug Dronedarone Hydrochloride, two previously unidentified impurities, along with debutyl Dronedarone, were identified through LC–MS analysis. A successful synthetic method was devised for generating these potential impurities, leading to the creation of new reference standards for them. This paper delves into the synthesis and comprehensive characterization of these impurities. The availability of these impurity standards led to cost savings by enhancing process control measures.



Synthesis of process related monobutylated substances 8 and 13.

Reagents and Conditions: (a) i. MeOH, rt; ii. $NaBH_3CN$; (b) Boc_2O, CH_2Cl_2, 0°C, 93% (two steps); (c) K_2CO_3, KI, anhydrous DMF, 60°C, 67% ; (d) i. MeOH, H_2; (g) (45 psi), Pt.Cu/C, rt; ii. MsCl, THF, TEA, 0°C, 68% (two steps); (e) 4 M HCl.IPA, 0°C, rt; (f) MsCl, THF, TEA,0°C, 82% (two steps).

In the year of 2012, Raghvendra R. Hivarekar *et. al.*,[18] were synthesized and reported An Improved Scalable Route to Pure Dronedarone Hydrochloride. A highly efficient and scalable method for producing Dronedarone hydrochloride has been established. This synthesis involves the Friedel−Craft acylation of 2-(-2-butyl-1-benzofuran-5-yl)-1H-isoindole-1,3(2H)dione with 4-(3-chloropropoxy) benzoic acid, resulting in a high yield of pure product. Notably, this process employs Eaton's reagent instead of potentially hazardous and toxic metal halide catalysts like $AlCl_3$ or $SnCl_4$. To sum up, we have devised a resource-efficient, environmentally friendly, and high-yield method for producing dronedarone hydrochloride with minimal known and unknown impurities. This enhanced process has proven its effectiveness on a kilogram scale and is currently being implemented for large-scale commercial production of dronedarone hydrochloride.



Reagents and conditions: (a) phthalic anhydride, TEA, toluene, reflux 1.5 h; (b) P_2O_5-MsOH, 35 °C, 60 min; (c)di-n-butylamine, KI, TBAB, DMF, 85 °C, 14 h; (d) mono methylamine 40% aq soln, oxalic acid dihydrate, IPA, 75 °C, 60 min; (e) (i) $NaHCO_3$, DCM,CH_3SO_2Cl, TEA, toluene, -5 to 5 °C, 30 min, (ii) aq HCl, DCM.

Ticagrelor

Ticagrelor is a platelet inhibitor[19-21] with chemical name (1S, 2S, 3R, 5S)-3-[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) cyclopentane-1,2-diol(Figure 1). Ticagrelor was first developed by Astra Zeneca company in 1999. Ticagrelor is a P2Y12 antagonist developed by Astra Zeneca under the trade name Brilinta which was approved by the FDA in 2011 for the prevention of platelet aggregation.

Ticagrelor (trade name Brilinta™ in the US, Brilique™ and Possia™ in the EU) is the world's leading drug for the treatment of acute coronary symptom and strokes, developed and marketed by AstraZeneca plc. The drug was approved for use in the European Union by the European Commission in 2010 and by the US Food and Drug Administration in 2011.

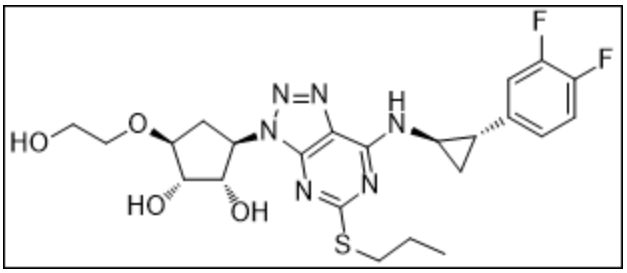
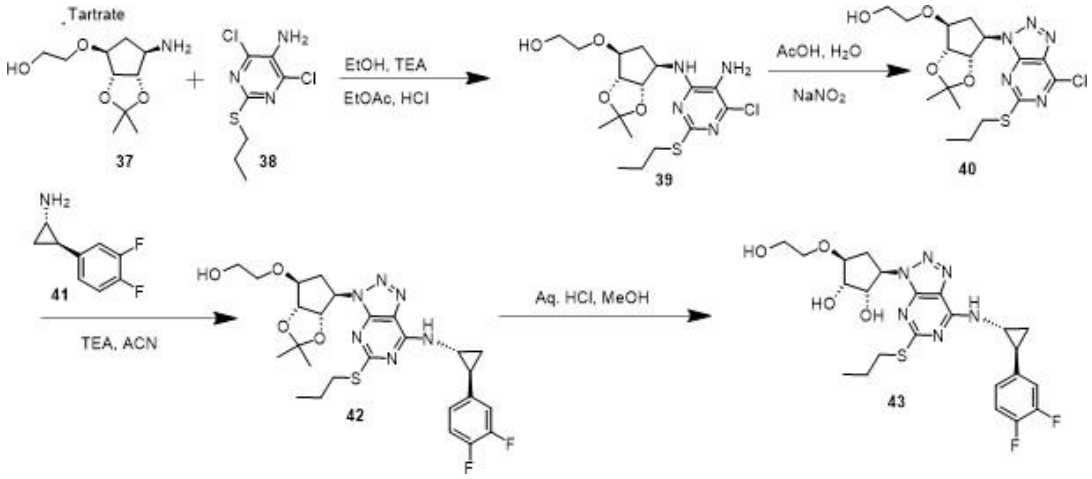


Figure 2: **Ticagrelor**

Mode of mechanism

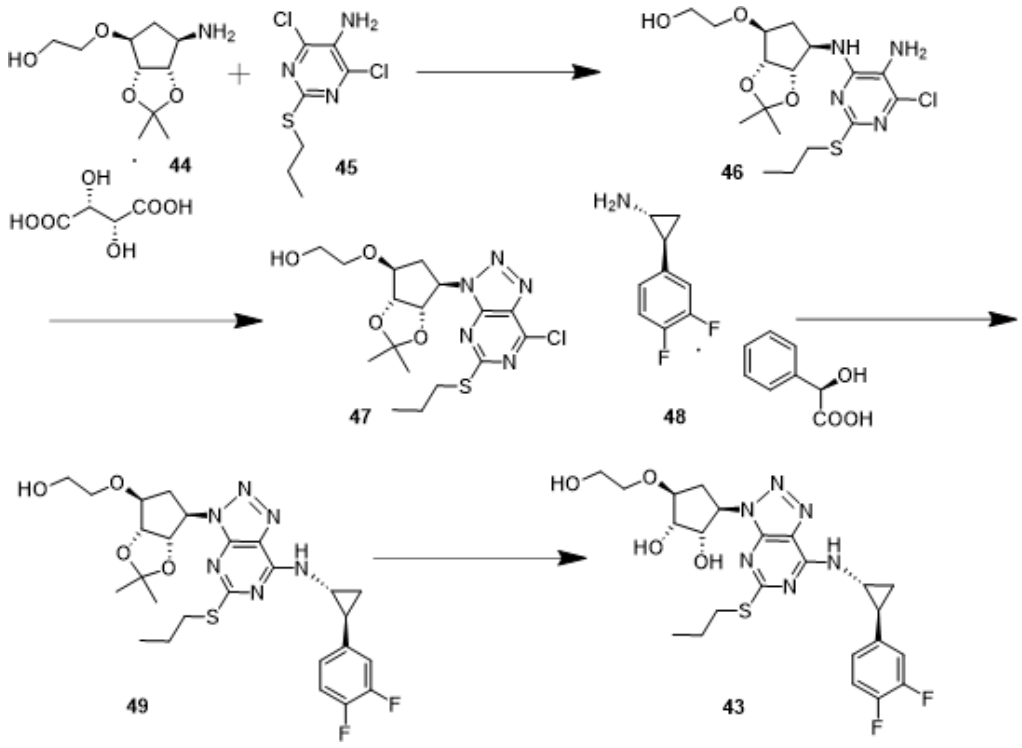
As a structural purine analogue, Ticagrelor antagonises adenosine diphosphate (ADP) activation of P2Y12 protein on the surface of thrombocytes. P2Y12 is a G-protein coupled receptor for ADP which is involved in the aggregation of platelets (simplified mechanism cf) and is commonly employed to reduce the risk of blood clotting in patients with cardiovascular diseases.

In the year of 2015, Vijayavitthal T. Mathad *et. al.*,[22] were synthesized and reported An An efficient and safe process for the preparation of ticagrelor, a platelet aggregation inhibitor via resin- NO_2 catalyzed formation of triazole ring A more efficient and secure method for producing ticagrelor, a drug that inhibits platelet aggregation, is detailed in this description. The synthesis entails combining a pyrimidine amine derivative (referred to as **38**) with a cyclopentyl derivative (referred to as **37**) in ethylene glycol. Subsequently, the formation of the triazole compound **40** is achieved through the diazotization of intermediate **39**, utilizing the environmentally friendly "Resin-NO_2" reagent in a mixture of water and acetonitrile. The next steps involve condensing **40** with a cyclopropylamine derivative (known as **41**) and then deprotecting compound **42** using hydrochloric acid in dichloromethane (DCM) to produce ticagrelor **43**. This entire process results in a yield of 65% and a purity of 99.78%, as confirmed by HPLC analysis. Each reaction stage was optimized independently to ensure scalability and suitability for industrial-scale production. Additionally, a secure procedure for synthesizing key intermediate **38**, which involves a nitration reaction, has been developed. Safety protocols were established by analyzing the thermal characteristics of the reactions using DSC analysis.



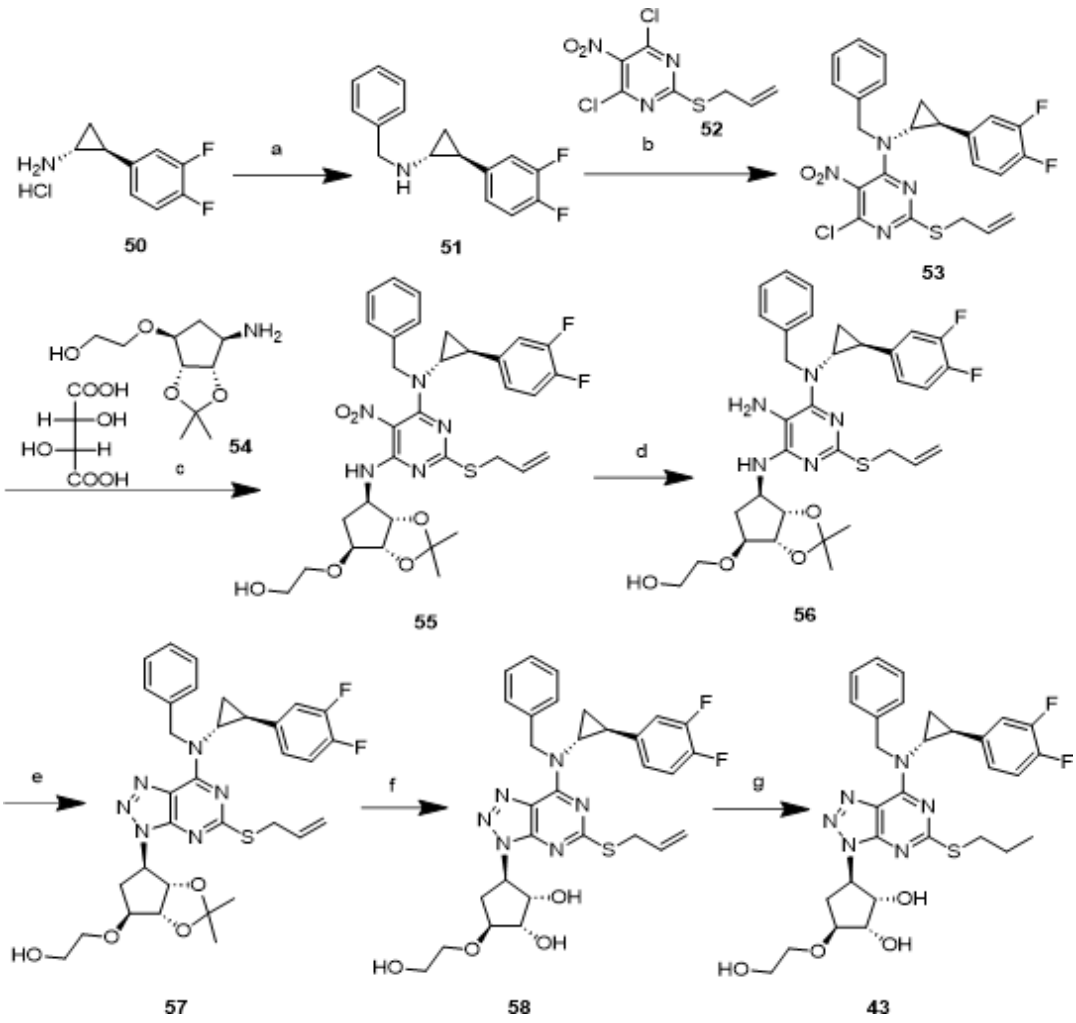
In the year of 2018, S. Venkat Rao *et. al.*,[23] were synthesized and reported 'Synthesis of high pure ticagrelor, an antiplatelet drug substance and its possible process related impurities'. A cost-efficient and resilient production method has been formulated for the N-alkylation of compounds **44** and **45**, employing readily accessible reagents and bases such as DBU and TEA, with ethanol serving as the solvent. The key advancement in this process is the attainment of high-purity pharmaceutical-grade Ticagrelor **43** by means of purification in a mixture of methanol and water.

In accordance with ICH guidelines, stringent purity standards have been met, ensuring that all known and unknown impurities are maintained below the threshold of not more than 0.10%. This achievement is coupled with an outstanding yield of 75% and a remarkable product quality of 99.9%.

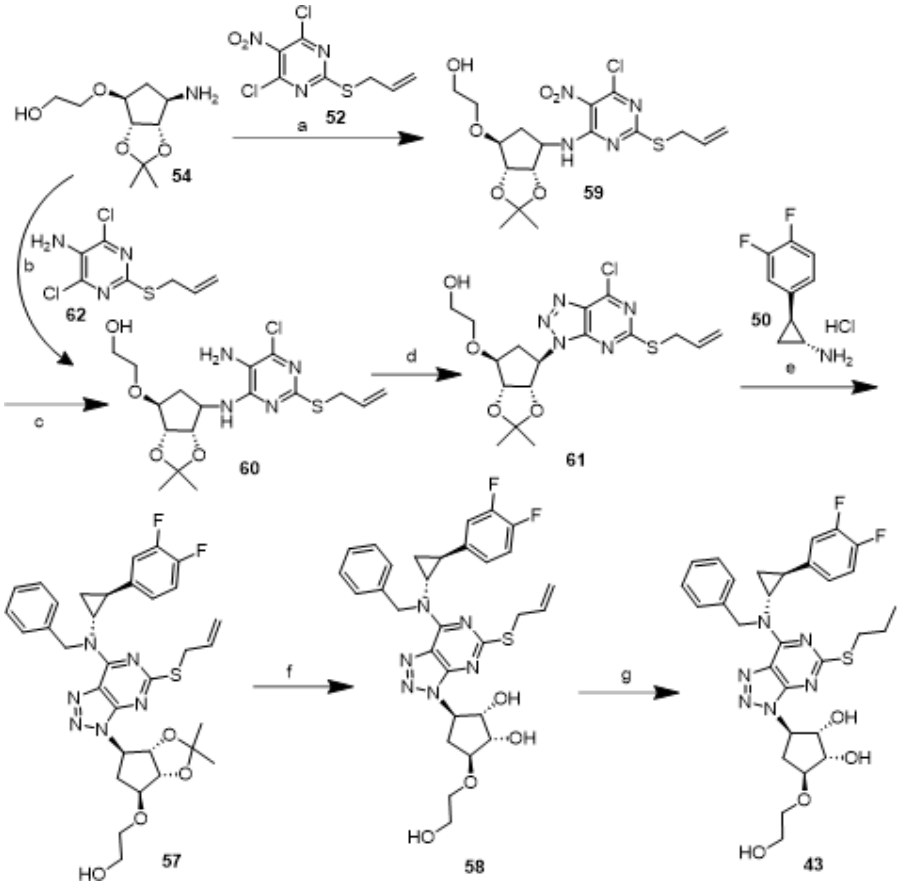


Reagents and solvents: (a) Ethanol, TEA and DBU (b) ethyl acetate $NaNO_2$/Acetic acid (c) Sodium Carbonate (d) Methanol and dil. HCl

In the year of 2016, Nitin A. Shimpi *et. al.*,[24] were synthesized and reported 'Novel synthetic methodology for the synthesis of Ticagrelor'. Ticagrelor stands out as the inaugural reversible P2Y12 receptor antagonist, effectively inhibiting platelet aggregation induced by adenine diphosphate (ADP) with a swift onset and cessation of its effects. A novel synthesis methodology has been devised for Ticagrelor and its intermediate compounds, facilitating the commercial production of Ticagrelor **43**.



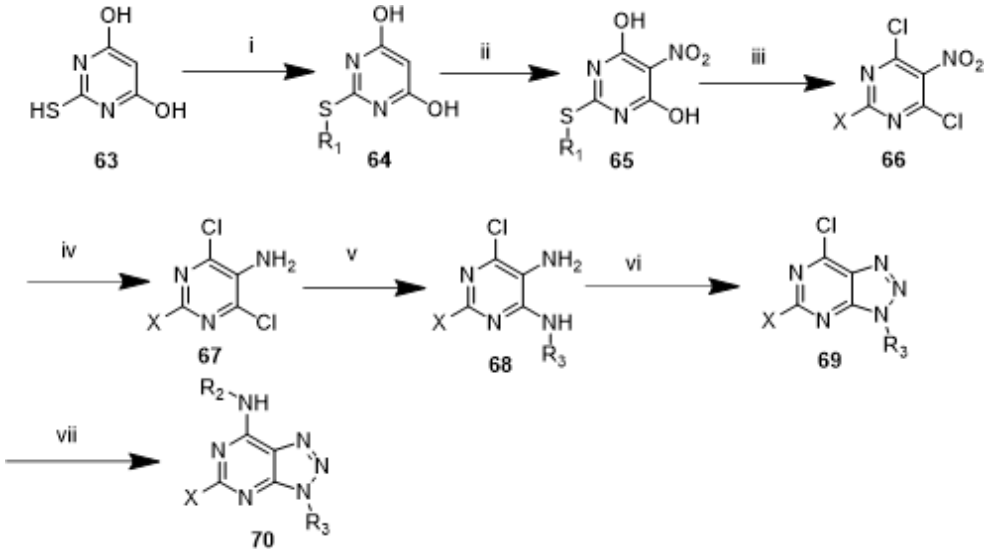
Reagents and conditions: a) Benzaldehyde, MeOH, $NaBH_4$; b)DIPEA, THF, EtOAc, 30-35°C; c) THF, DIPEA, 50-55°C; d) MeOH, NH_3, $Na_2S_2O_4$, EtOAc, 40-45°C; e) Toluene, $NaNO_2$, AcOH, Na_2CO_3, 10-15°C; f) MeOH, HCl, 20-25°C; g) MeOH, Pd-C, 40-45°C

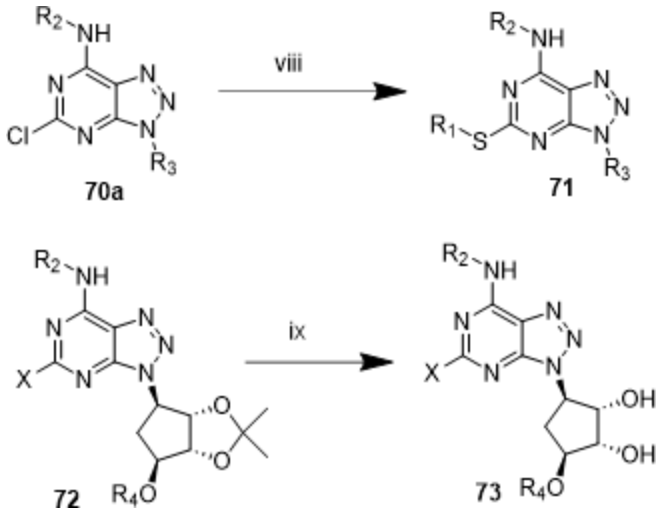


Reagents and conditions: a) THF, TEA, -10°C; b)$NaHCO_3$, 1,4-dioxane, 60-65°C, EtOAc, Hexane c) Zn, MeOH, AcOH, 55°C; d) Toluene, $NaNO_2$, AcOH, Na_2CO_3, 10-15°C ; e) THF, DIPEA, 40-45°C; f) MeOH, HCl, Na_2CO_3, EtOAc, Hexanes, 5-10°C; g) THF, EtOH, Hydrazine hydrate, $NaIO_4$, EtOAc, Hexanes.

In the year of 2020, Bernard Pirotte *et. al.*,[25] were synthesized and reported 'Synthesis of ticagrelor analogues belonging to 1,2,3-triazolo[4,5-d]pyrimidines and study of their antiplatelet

and antibacterial activity'. Based on recent observations indicating that ticagrelor, an antiplatelet agent, and one of its metabolites exhibit bactericidal effects against gram-positive bacteria, a series of structurally related 1,2,3-triazolo[4,5-d]pyrimidines were synthesized and investigated as potential agents with dual roles in antiplatelet and antibacterial activities. The objective was to explore the possibility of separating these two biological properties and to identify new 1,2,3-triazolo[4,5-d]pyrimidines that display antiplatelet effects while lacking in vitro antibacterial activity. The newly synthesized compounds included known metabolites of Ticagrelor as well as simplified analogs with similar structures. Some of these compounds demonstrated antiplatelet activity while no longer exhibiting antibacterial effects, providing evidence that the two activities may not be inherently linked.





Synthesis of Ticagrelor Analogues Belonging to 1,2,3-Triazolo[4,5-d]pyrimidines.

Reagents and conditions: (i) R_1X, KOH, water, 80°C, sealed tube, 2 h; (ii) nitric acid, acetic acid, 0°C to r.t., 1 h; (iii) $POCl_3$, 2,6-lutidine, 0-80°C, 2 h; (iv) iron powder, acetic acid, methanol, r.t., 2 h; (v) R_3NH_2, methanol, 110°C, sealed tube, 1 h; (vi) $NaNO_2$, acetic acid, 0°C to r.t., 2 h; (vii) R_2NH_2, TEA, acetonitrile, 80°C, 1-4 h; (viii) R_1SH, K_2CO_3, acetonitrile, 60-110°C, 3 h; (ix) HCl, methanol, r.t., 30 min.

Conclusion:

In conclusion, a comprehensive study on synthetic approaches for Ticagrelor and Dronedarone hydrochloride are provided in this article.

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