# New synthetic approach for preparation of Ticagrelor

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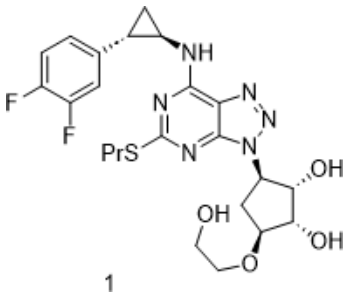
**Abstract:**

Ticagrelor is a platelet inhibitor with chemical name (1*S*, 2*S*, 3*R*, 5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl) cyclopropyl] amino}-5 (propylthio)-3*H*-[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 this article, we proposed new synthetic approach for manufacturing of Ticagrelor.

## Introduction:

The chemical Name of Ticagrelor is (1*S*, 2*S*, 3*R*, 5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl) cyclopropyl] amino}-5 (propylthio)-3*H*-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy) cyclopentane-1,2-diol. Ticagrelor is a platelet inhibitor and it works as antiplatelet medication. It helps to inhibit the blood clot.

Figure-1: Ticagrelor Structure.

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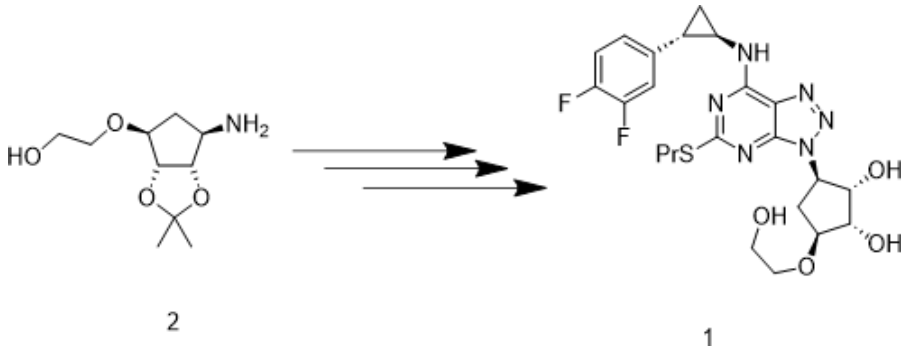
An effective process for manufacturing of Ticagrelor is mentioned by Vijayvittal T. mathad et. al. (ref-1), Venkat Rao et. al (ref-2) and Nitin et. al. As per above references the synthetic approach used by taking 2 as Key Starting Material.

Scheme-1:



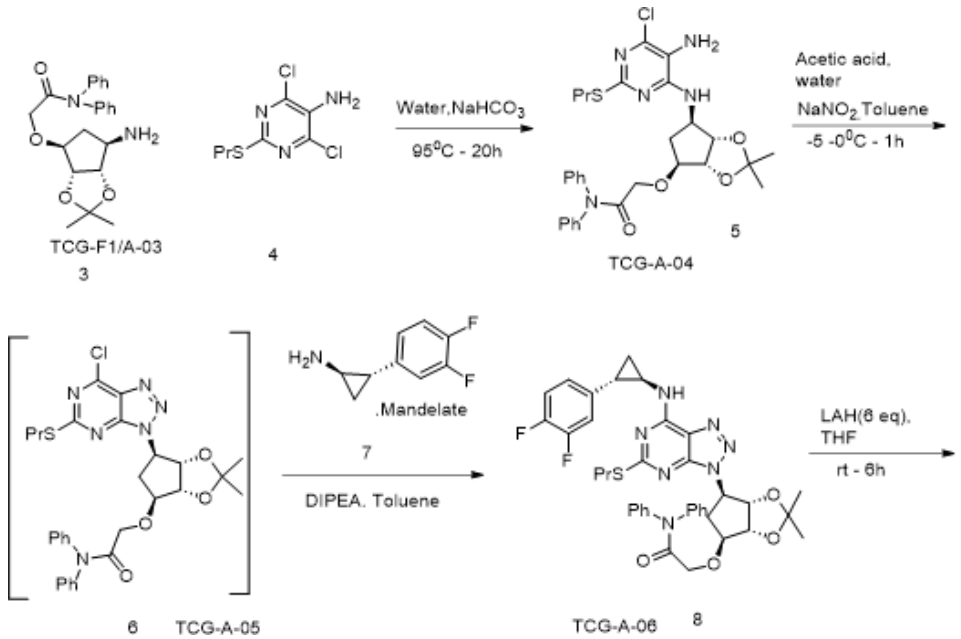
2 1

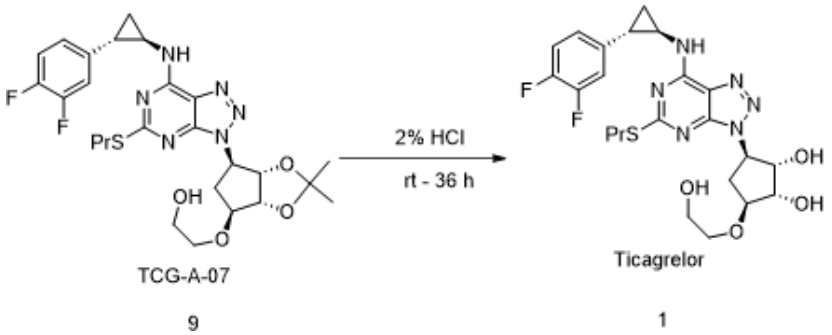
In this article, we discussed about the new synthetic approach for preparation of Ticagrelor by using alternate KSM instead of 2.

**Results and discussion:**

As mentioned in the scheme-2, we attempted the new synthetic approach for making of Ticagrelor by using alternate key starting material 3. Coupling of 2 compound with 4 in presence of sodium bicarbonate reagent and water solvent. 4 is converted into 5 by using Acetic acid, sodium nitrite reagents and Toluene, water solvents. Further, 5 (in-situ intermediate) is coupled immediately with compound 6 to get 7. Reduction of compound 7 with LAH followed by Acetonide de-protection with HCl gives Ticagrelor.

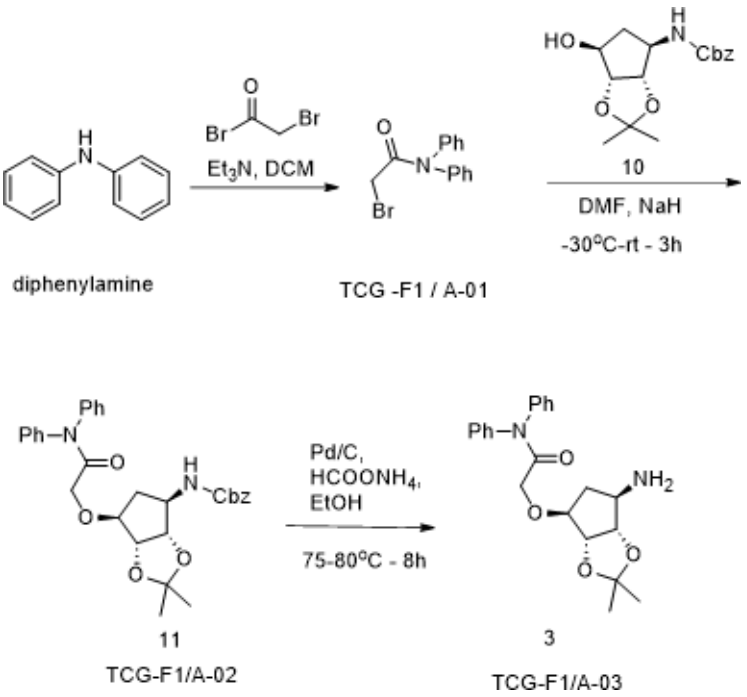
Scheme-2:






Synthesis of Alternate Key starting material for preparation of Ticagrelor is mentioned in the scheme-3 and it contains three steps. Staep-1 involves the coupling of diphenylamine with 2-bromoacetyl bromide gives 2-bromo-N,N-diphenylacetamide. Further it is coupled with compound 10 followed by de protection of Cbz group in presence of Pd/C gives alternate Key starting material (Compound 3).

Scheme-3:




**Conclusion:**

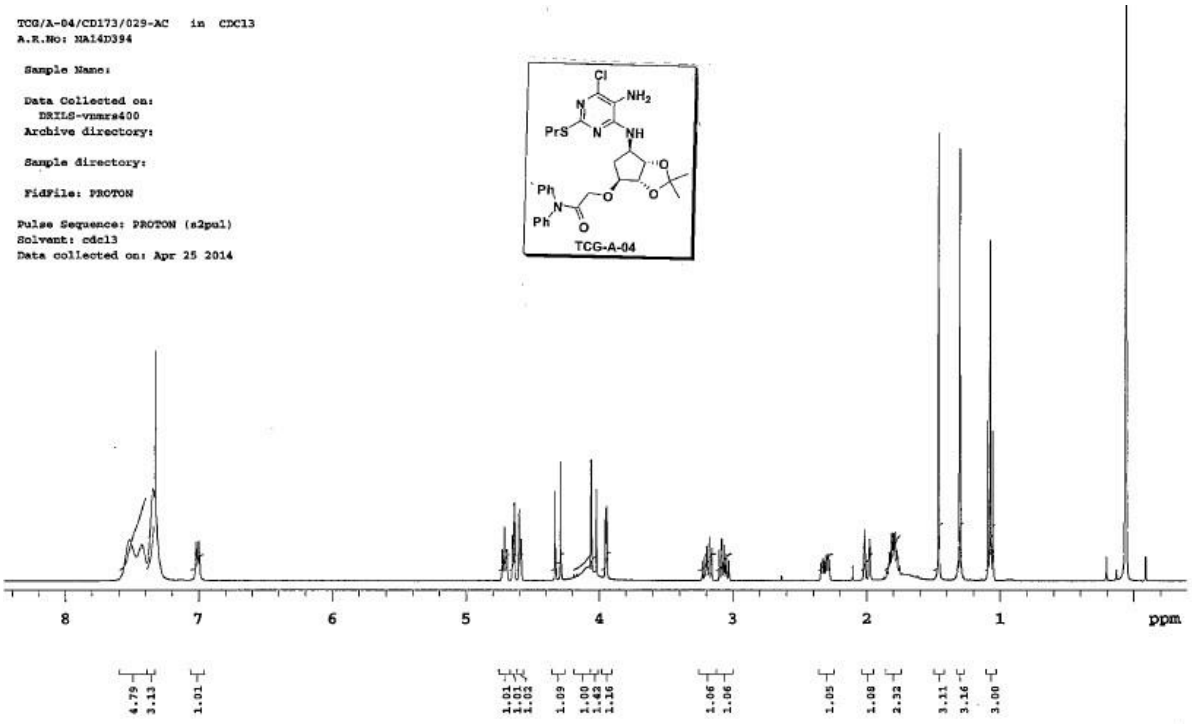
In conclusion, new synthetic approach is provided for preparation of Ticagrelor by using alternate Key starting material.

**Experimental Section:**

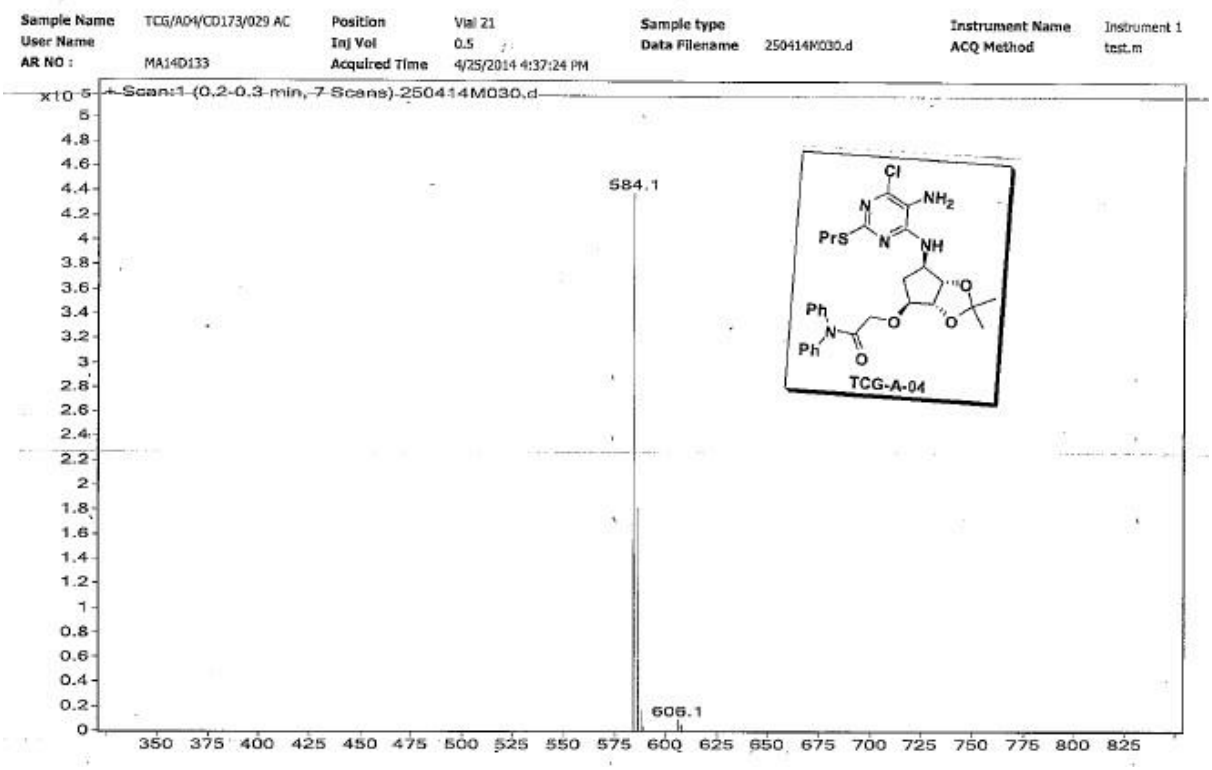
**Preparation of 5:**

In a RBF, charged compound 4 (6.5 g, 0.0272 moles), 3 (10.39 g, 0.0272 moles), water (19.5 mL) and $NaHCO_3$ (9.13 g, 0.1088 moles) at room temperature. Reaction mass was heated to 95-100°C and maintained for 20h. After the completion of the reaction (by TLC), the reaction mixture was cooled to room temperature and charged water (20 mL), Ethyl acetate (25 mL). The organic layer was separated and aqueous layer was extracted with Ethyl acetate (20 mL). The combined organic layer was washed with brine solution (2 X 25 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure (< 45$^{o}$C) to get crude. Crude product was purified by column chromatography (100-200 mesh silica gel) by eluting with 30 % Ethyl acetate and hexane to furnish **5** (9.2 g, 57.86 %) as a pale pink solid.

$^{1}$H NMR Spectrum:



**Mass Spectrum:**



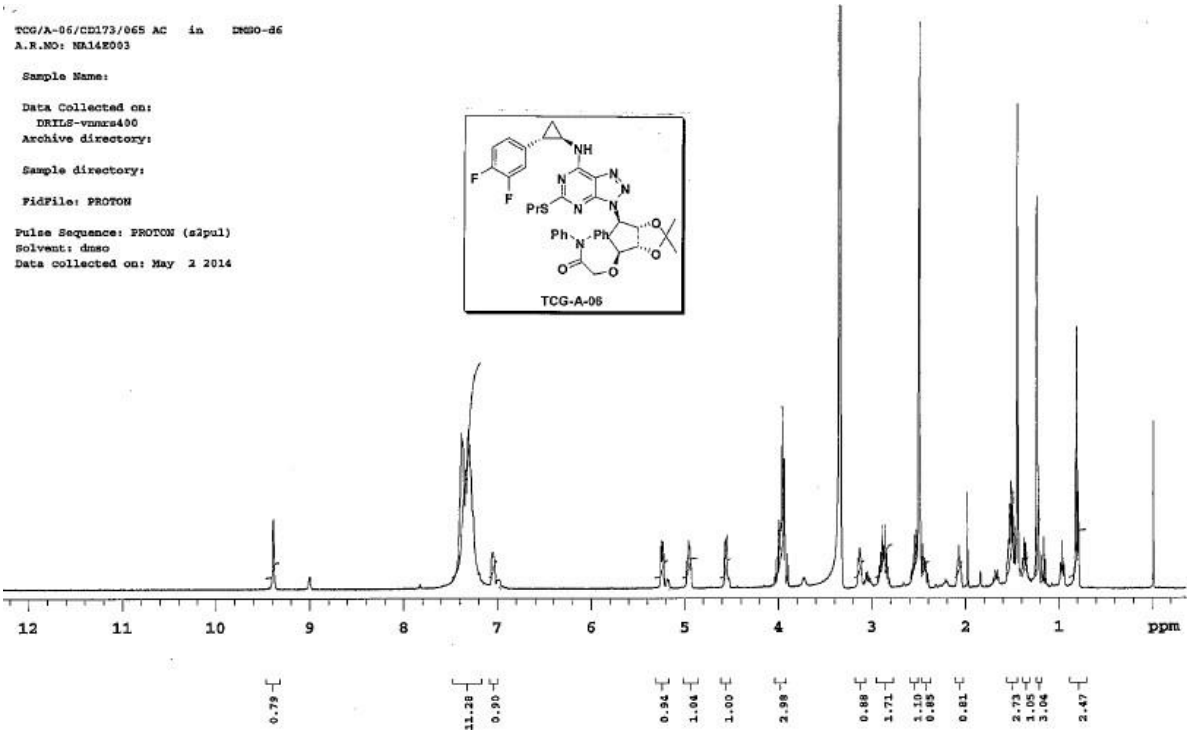

**Preparation of 8:**

In a RBF, charged **5** (6 g, 0.0102 moles), $CH_3COOH$ (30 mL) and Water (Lot-1) (6 mL) at room temperature. The resulting reaction mixture was cooled to -5 to 0 °C. Added $NaNO_2$ Solution (0.768g in 6 mL water) drop wise to the reaction mixture at -5 to $0^oC$ and maintained for 1 h. Temperature raised to 25 – 35 °C and stirred for 1 h. After the completion of the reaction (by TLC), the reaction mixture was diluted with Toluene (60 mL) and Layers were separated. Organic layer was washed with potassium carbonate solution (60 mL) and dried over anhydrous sodium sulfate. The above obtained organic layer (contained compound 6) was used for the next step.

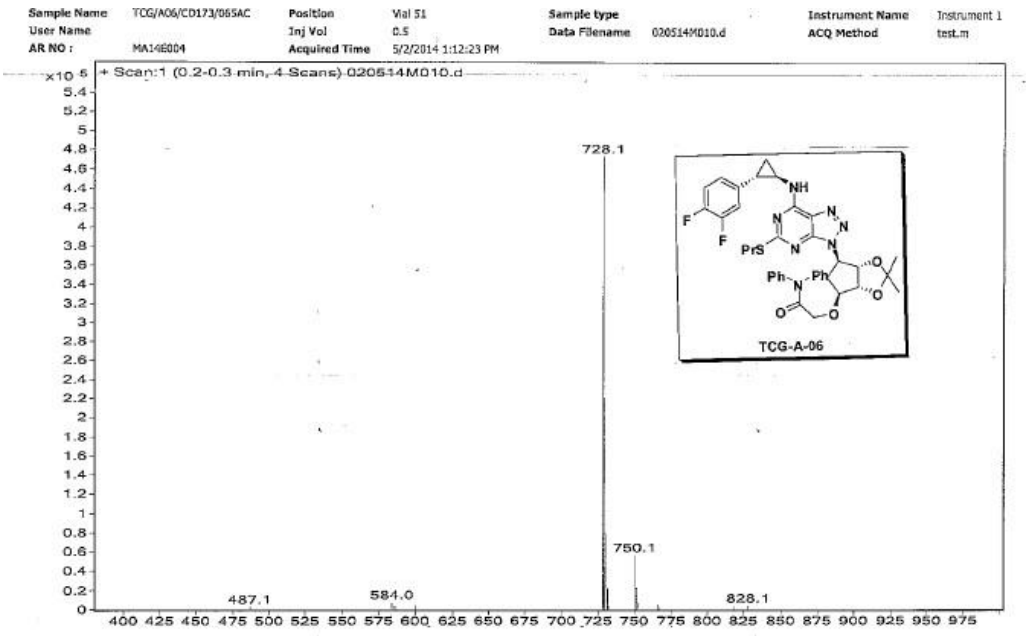
In a clean RBF, Charged **7** (3.25 g, 0.010 moles), Diisopropylethylamine (6.1 mL, 0.035 moles), and Toluene (60 mL) at room temperature under nitrogen atmosphere. The resulting reaction mixture stirred for 30 min. The above obtained organic layer (contained compound 6) was added drop wise to the reaction mixture at room temperature and stirred for 15 h. After the completion of the reaction, the reaction mixture was diluted with water (60 mL). The organic layer was separated and aqueous layer was extracted with Toluene (30 mL). The

combined organic layer was washed with brine solution (6 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure (< 45$^{o}$C) to get crude. Crude product was purified by column chromatography (60-120 mesh silica gel) by eluting with 80 % EtOAc-hexane to furnish Compound **8** (4.9 g, 65.5 %) as an off-white solid.

$^{1}$H NMR Spectrum:




**Mass Spectrum:**



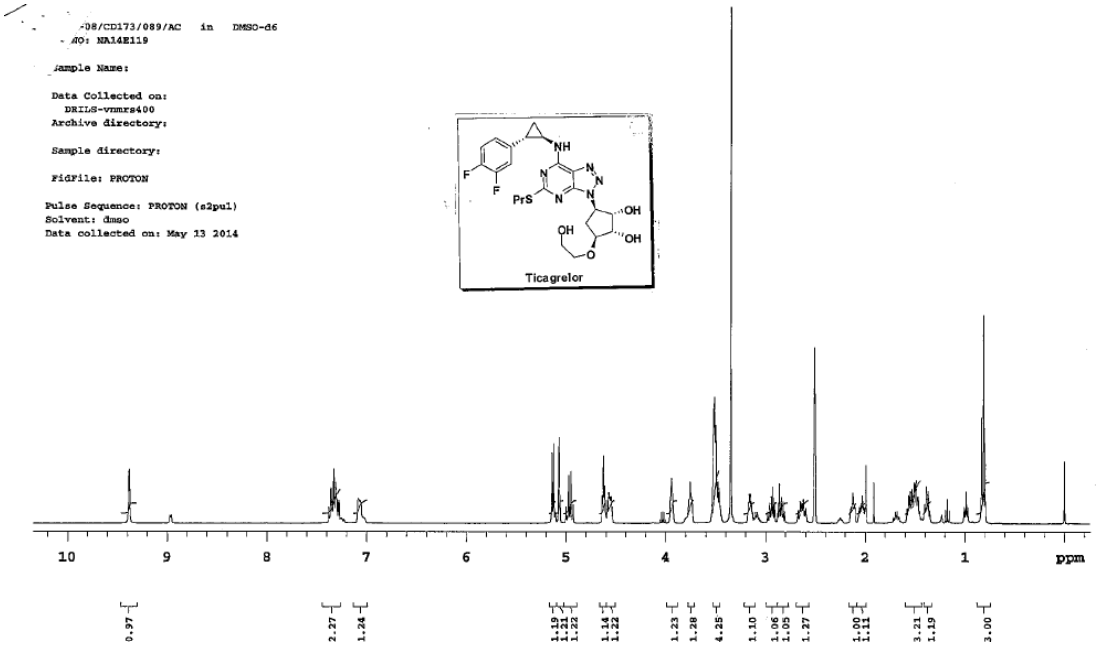
**Preparation of 1 (Ticagrelor):**

In a RBF, charged **8** (3 g, 0.004 moles) and THF (90 mL) at room temperature under nitrogen atmosphere. The resulting reaction mixture was cooled to 0 to 5 °C. Lithium Aluminium Hydride ($LiAlH_4$) (0.940 g, 0.0247 moles) was added lot wise to the reaction mixture at 0 to 5$^oC$ and maintained for 1 h. The resulting reaction mixture was allowed to reach 25 – 35 °C and stirred for 5 h. After completion of the reaction (by TLC), added ice cold water (100mL) and extracted with Ethyl acetate (30 mL) and dried over anhydrous sodium sulfate. Organic layer (contained compound 9) was used for the next step.

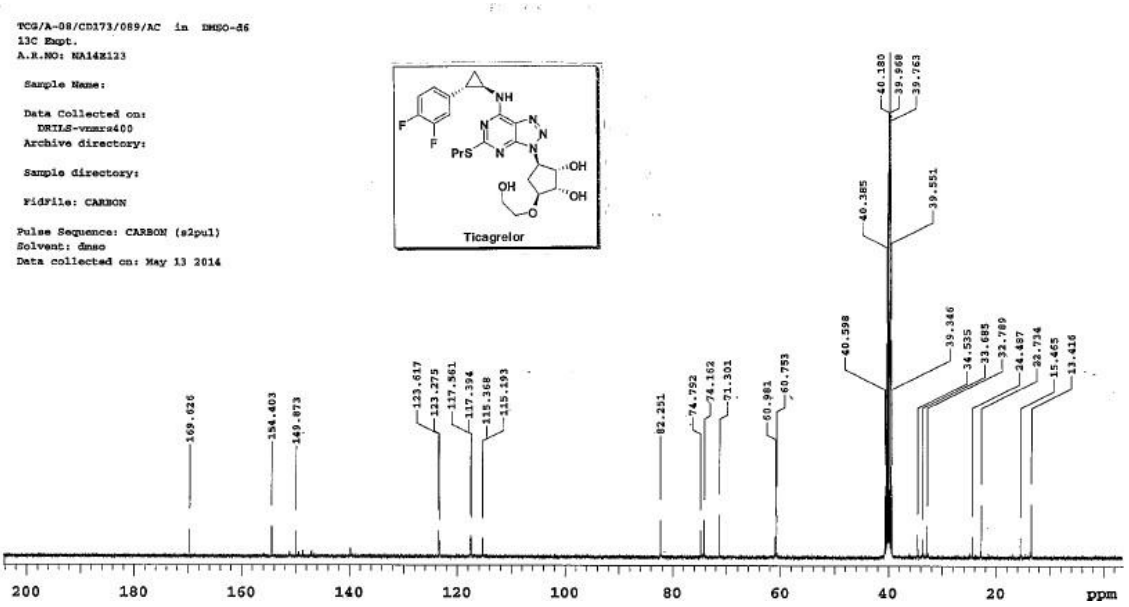
In a RBF, Charged Organic layer (contained compound 9) (110 ml, equivalent to 8), 2%HCl (75 mL) at room temperature and stirred for 36 h. After the completion of the reaction by TLC, the reaction mixture was diluted with EtOAc (50 mL). Organic layer was separated, washed with brine solution (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure (< 45$^oC$) to get crude. The obtained crude material was dissolved in Ethyl acetate (12 mL) and added Hexane (50 mL) stirred for 2 h. Solid product was filtered to furnish crude **Ticagrelor** (wet wt: 2 g, HPLC purity: 88.27 %) as a pale brown solid.

The obtained wet product was dissolved in Ethyl acetate (12 mL), filtered through celite bed, and concentrated under reduced pressure (< 45$^oC$) to get Ticagrelor (1.69 g, HPLC purity: 88.16 %) as a off-white solid. Obtained product was purified by column chromatography (60-120 mesh silica gel) by eluting with 5 % MeOH-DCM to furnish **Ticagrelor (1)** (1 g, 50.64 %) as an off-white solid.

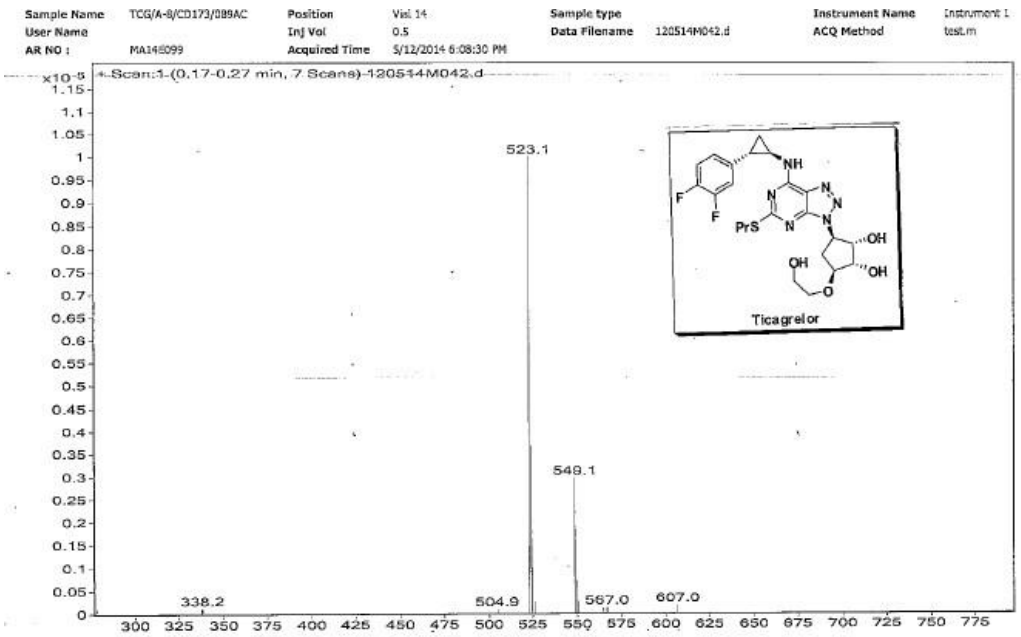
$^1H$ NMR Spectrum:



13C NMR Spectrum:




Mass Spectrum:




**Preparation of 11:**

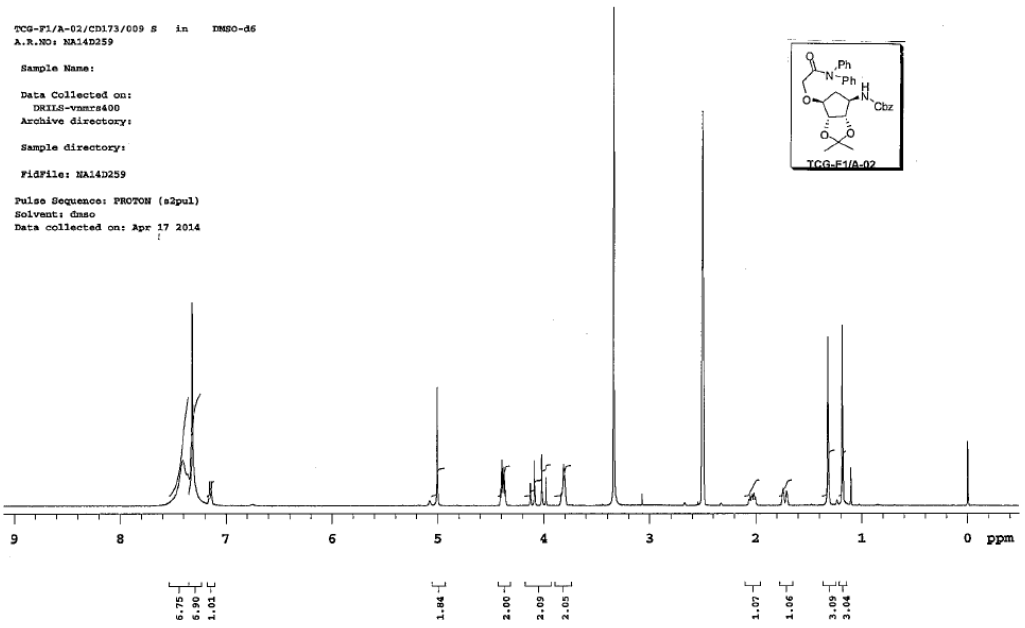
In a RBF equipped with condenser, *N*,*N*-Diphenyl amine (25 g, 0.147 moles) and dichloromethane (lot-1) (350 mL) were charged at RT. The resulting reaction mixture was cooled to 0 - 5 °C and stirred for 15 min. Bromo acetyl bromide (38.72 mL, 0.443 moles) dissolved dichloromethane (lot-2) was added drop wise to the reaction mixture at 0 - 5$^{o}$C for

35 min. The resulting reaction mixture was allowed to reach 25 – 35 °C and stirred for 16 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted with dichloromethane (250 mL) and washed with 0.5 N HCl (3X 150 mL) and sat NaCl solution (100 mL). The resulted organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure (< 45$^{o}$C) to get crude. The crude material was diluted with mixture of Hexane & MeOH (250 mL & 100 mL) and stirred for 30 min, filtered the solid and washed with Hexane (25 mL) to furnish 2-bromo-N,N-diphenylacetamide (23 g, 53.64 %) as a pale brown solid.

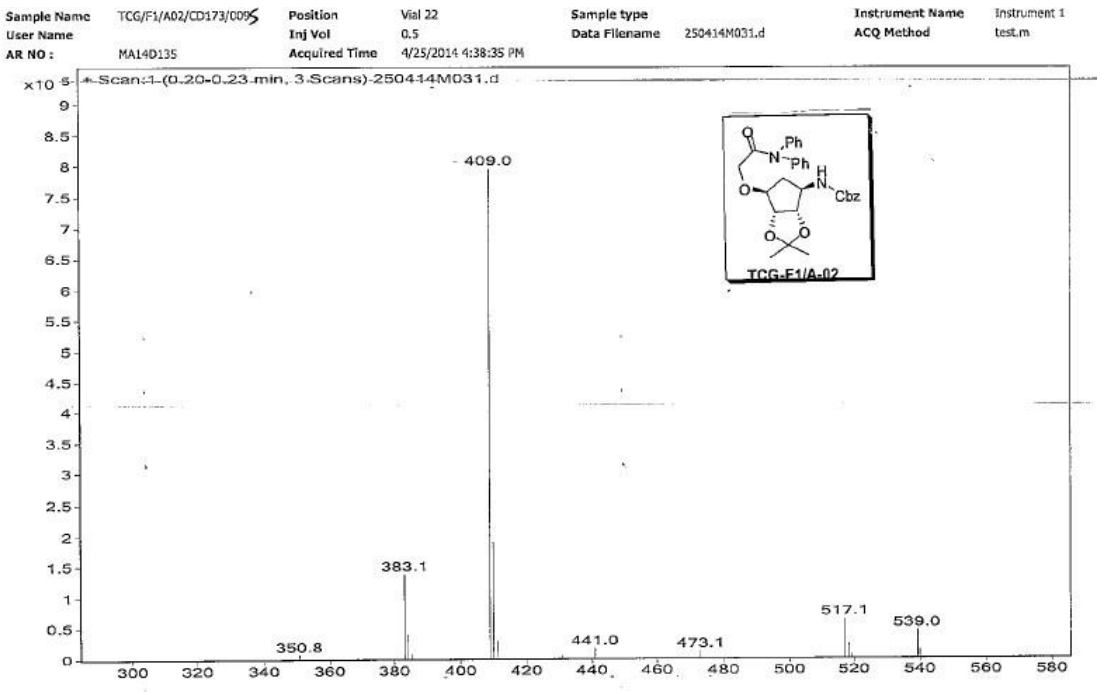
Sodium hydride (60% dispersion in oil) (1.71 g, 0.071 moles) & DMF (10 mL) were charged under nitrogen atmosphere. The resulting reaction mixture was cooled to -30 °C. Compound 10 (20 g, 0.065 moles) dissolved DMF (lot-2) (40 mL) was added drop wise to the reaction mixture at -30$^{o}$C for 45 min. Added 2-bromo-N,N-diphenylacetamide (23 g) in DMF solution to the reaction mass at -30$^{o}$C. The resulting reaction mixture was allowed to reach 25 – 35 °C and stirred for 3 h.

The progress of the reaction was monitored by TLC. After the completion of the reaction, reaction mixture was cooled to 0°C and quenched with ice cold water (200 mL) and extracted with Ethyl acetate (3 X 150 mL). The combined organic layer was washed with water (3 X 100 mL), brine (100 mL) and dried over anhydrous sodium sulfate. Organic layer was concentrated under reduced pressure (< 45$^{o}$C) to get crude product. The obtained crude was diluted with MTBE (150 mL) and stirred for overnight at rt. The solid material was filtered and dried to furnish **compound 11** (17 g, 50.57 %) as a white solid.

1H NMR Spectrum:



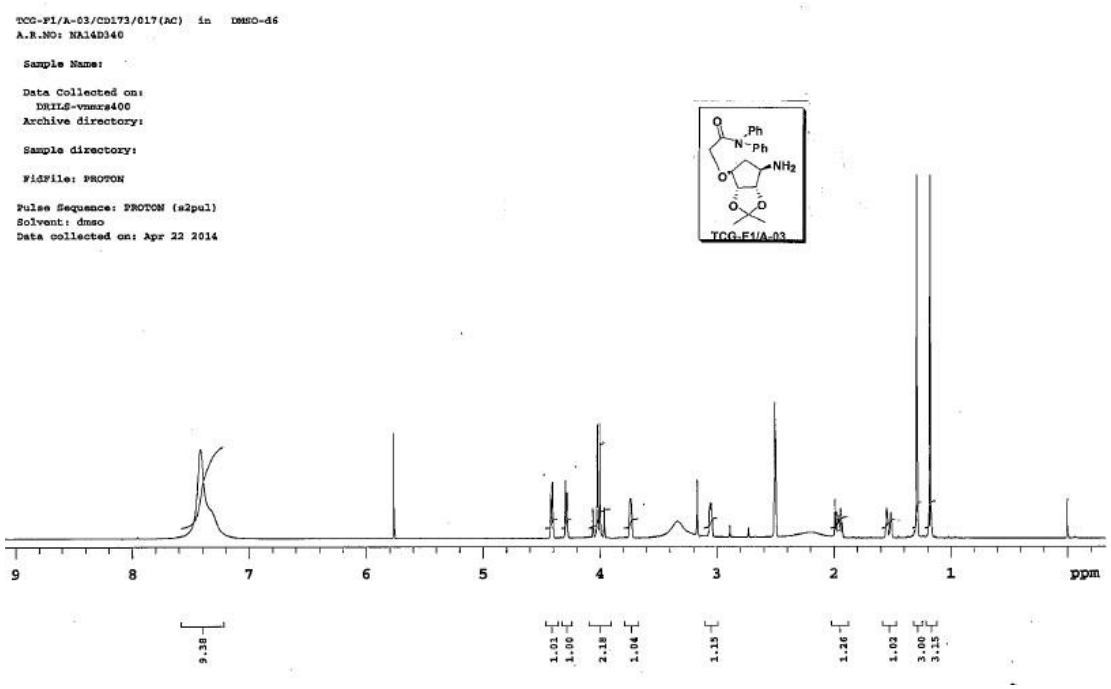
Mass Spectrum:




**Preparation of 3:**

In a RBF, **compound 11** (15 g, 0.029 moles), EtOH (300 mL), 10% Pd/C(1.5 g), and Ammonium formate (5.49 g, 0.057 moles) were charged at room temperature under nitrogen atmosphere. Then the reaction mixture was heated to 75- 80$^{o}$C and stirred for 8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to 25-35 °C. Reaction mixture was filtered through celite bed (30 g) and washed thoroughly with ethyl acetate (100 mL). The resulting filtrate was concentrated under reduced pressure (< 45 °C) to get crude product. The resulting crude product was diluted with EtOH (120 mL) L(+) Tartaric acid(4.88 g) was charged in the reaction mixture and triturated with MTBE (300 mL) (Gummy nature product formation observed) MTBE layer was decanted, crude product was diluted with MTBE (100 mL), stirred for 12 h at room temperature. The solid material was filtered. (Gummy nature observed during drying) Once again crude product was diluted with MTBE (150 mL) & aqueous $NaHCO_3$ (200 mL) and extracted with Ethyl acetate (100 mL). Organic layer was concentrated under reduced pressure (< 45$^{o}$C) to get crude product. The obtained crude was diluted with hexane (150 mL) and Ethyl acetate (20 mL) and stirred for 1 h at 25 – 35$^{o}$C. The solid material was filtered to furnish **compound 3** (7 g).

1H NMR Spectrum:

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