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Identification and Synthesis of Impurities Formed During Prasugrel Hydrochloride Preparation

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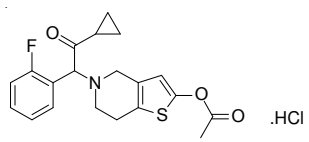
Prasugrel hydrochloride (**1**), an important platelet inhibitor is used for the reduction of thrombotic cardiovascular events. During laboratory optimization and later its bulk synthesis the formation of various impurities was observed. The impurities formed were monitored and their structures were tentatively assigned on the basis of their fragmentation patterns in LC-MS. Most of the impurities were synthesized and their assigned constitutions confirmed by co-injection in HPLC. We describe herein the formation, synthesis and characterization of these impurities. Present study will be of immense help to others to obtain chemically pure prasugrel hydrochloride.

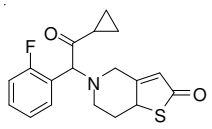
Key Words: Impurity profile, Prasugrel, Related substances.

INTRODUCTION

Prasugrel hydrochloride is designated chemically as 5-[1(RS)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxyethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-yl acetate hydrochloride (**1**). The literature synthesis[1,2] (**Scheme-I**) involves condensation of 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone (**2**) with 5,6,7,7a-tetrahydrothieno[3,2-c]pyridine -2(4*H*)-one hydrochloride (**3**) in the presence of base and acetonitrile gives 5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one (**4**), on treatment with acetic anhydride in presence of base and DMF affords prasugrel base (**5**) which on reaction with hydrochloric acid in presence of acetone gives prasugrel hydrochloride (**1**).



1 Prasugrel hydrochloride



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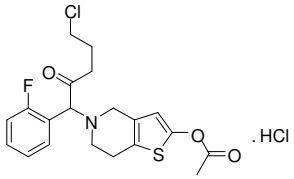

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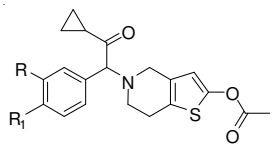
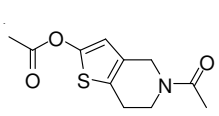


10 R = F, R_1 = H

13 R = H, R_1 = F



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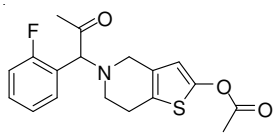

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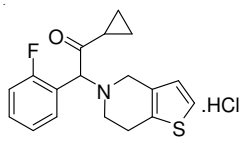

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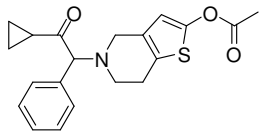

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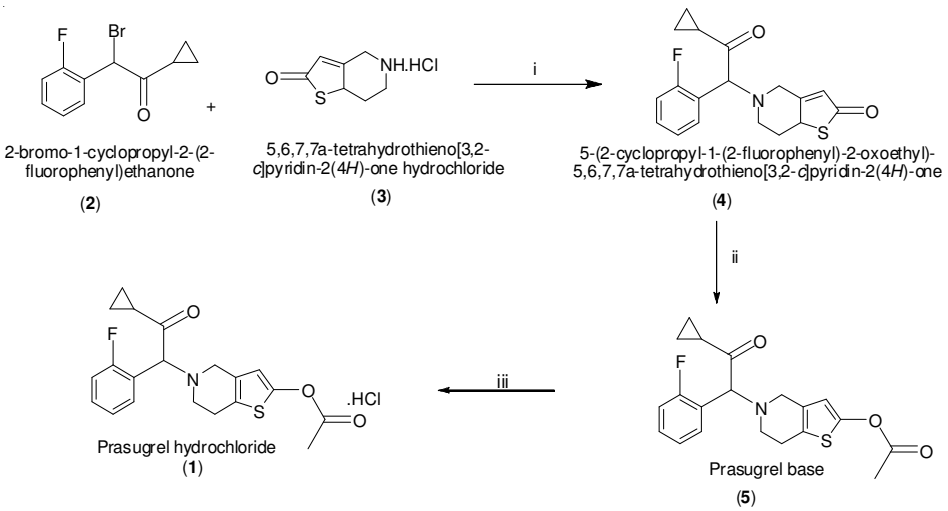
Fig. 1. Prasugrel hydrochloride (**1**), process related impurities

During laboratory optimization of prasugrel hydrochloride (**1**), many process related impurities were identified. The guidelines recommended by ICH state that the acceptable levels for a known and unknown compound (impurity) in the drug should be less than 0.15 and 0.10 %, respectively[3], also EMEA document state that the acceptable levels for a 3-fluro prasugrel and desacetyl prasugrel in the drug should be less than 0.20 %[4]. In order to meet the stringent regulatory requirements, the impurities present in the drug substances must be identified and characterized. Literature reports[5-7] include impurities formed due to either incomplete acetylation (*e.g.*, **4**) or during conversion of prasugrel hydrochloride (*e.g.*, **7**). However, no synthetic details have been reported. In this context, the present study described the identification, synthesis and characterization of impurities formed during prasugrel hydrochloride synthesis.



Scheme-I: Reagents and conditions: (i) K_2CO_3, acetonitrile, 0-5 ºC; (ii) K_2CO_3, acetic anhydride, DMF, 0-5 ºC, (iii) acetone, HCl, 40-45 ºC

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz Avance NMR spectrometer. The chemical shifts were reported ppm relative to either residual solvent or tetramethylsilane. The FT-IR spectra were recorded on Perkin-Elmer spectrum one FT-IR spectrometer and only prominent peaks are reported. Mass spectra were recorded on a Agilent 1100 series LC-MSD-TRAP-SL system. HPLC analysis was carried out on Waters Alliance 2487 or Waters Alliance 2695 systems. All the reagents used were of LR grade and used without further purification. All the anhydrous reactions were carried out under a nitrogen atmosphere. Silica gel (120-200 mesh) was used for column chromatography.

General experimental procedure

5-(2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one (4): To a suspension of 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride (10 g 52.17 mmol) (**3**) in acetonitrile (60 mL) was cool to 0-5 ºC, anhydrous potassium carbonate (14.45 g, 104.5 mmol) was added and charged 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone **2** (10.75 g, 41.8 mmol) at 0-5 ºC and the mixture was stirred for 4 h at 0-5 ºC. The salt was removed by filtration and then washed with acetonitrile (10 mL). The filtrate acetonitrile was removed by distillation under vacuum at 40-45 ºC to afford desacetyl prasugrel **4** as a brown oily liquid. The resulting oily crude was recrystallized from diisopropylether (100 mL) to afford desacetyl prasugrel **4** (4.0 g, 23.2 % yield, HPLC purity 95.82 %) as a off-white solid. IR (KBr, ν_{max}, cm^{-1}): 3053, 2968, 2812, 1700, 1640, 1584, 1486, 1440, 1397, 1384, 1222, 1171, 1076, 1055, 877, 845,761,645. ^1H NMR(DMSO-d_6): δ 7.37-7.44 (m, 1H), 7.37-7.44 (m, 1H), 7.24-7.30 (m, 1H), 7.24-7.30 (m, 1H), 6.22 (s, 1H), 4.86 (s, 1H), 4.42-4.48 (m, 1H), 3.94 (d, *J* = 12.0, 1H), 3.05 (d, *J* = 12.0, 1H), 2.96-3.00 (m, 1H), 2.36-2.42 (m, 1H), 2.24-2.32 (m, 2H), 1.62-1.67 (m, 1H), 0.83-0.93 (m, 4H). ^{13}C NMR : 206.72, 198.17, 170.11, 160.60 (d, *J* = 244.0), 131.36 (d, *J* = 3.8), 130.29 (d, *J* = 8.5), 125.40, 124.55 (d, *J* = 3.0), 121.08 (d, *J* = 14.8), 115.71 (d, *J* = 22.5), 70.95, 52.32, 50.50, 47.84, 33.71, 17.94, 11.18, 11.39. ESI-MS: m/z 332 ($[M + H]^+$, $C_{18}H_{18}NO_2SF$ calcd. (%) 332.1).

5-(5-Chloro-1-(2-fluorophenyl)-2-oxopentyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride (7): To a suspension of 5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one **4** (10 g, 30.17 mmol) in water (50 mL), hydrochloric acid (13.5 mL) was added and the mixture stirred for 0.5 h at 80-85 ºC. The pH was adjusted to 7.5 with 10 % NaOH solution at 25-30 ºC and extracted with toluene (2 × 50 mL) and the combined organic phases washed with water (2 × 20 mL), concentrated under reduced pressure afford desacetylchloro prasugrel **6** (6.2 g, 55.8 % yield) as a brown yellow liquid. Its mass (ESI-MS) displayed the required molecular ion peak at m/z 368 and the characteristic chlorine isotopic pattern.

To the residue (**6**), DMF (40 mL) was added and the mixture was stirred until clear solution was obtained. Cool the reaction mixture to 0-5 ºC, charged anhydrous potassium carbonate (5.24, 37.9 mmol) and slowly added acetic anhydride (3.45 g, 33.7 mmol) and maintain until the TLC revealed the completion of reaction. Charged toluene (100 mL) and water (100 mL). The clear biphasic system was stirred for 15 min and then the layers were separated. The aqueous phase was extracted with toluene (3 × 50 mL) and the combined organic phases washed with water (4 × 20 mL). The organic phase was distilled under vacuum and purified by silica column chromatography. Elution with 8-10 % ethyl acetate in hexane (v/v) afford pale yellow oily crude. The resulting crude was dissolved in acetone (60 mL) and slowly added conc. HCl (1.8 mL) at 25-30 ºC and stirred for 4 h. The obtained material was removed by filtration and washed with acetone (10 mL). The wet material was dried under vacuum at 40-45 ºC for 5 h to afford CATP hydrochloride impurity **7** (4.0 g, 57.8 % yield, HPLC purity 97.55 %) as a off-white solid. IR (KBr, ν_{max}, cm^{-1}) 2939, 1760, 1614, 1506, 1494, 1409, 1371, 1213, 1157, 1096, 1003, 881,768, 646. ^1H NMR (DMSO-d_6): δ 7.37-7.64 (m, 1H), 7.37-7.64 (m, 1H), 7.37-7.64 (m, 1H), 7.37-7.64 (m, 1H), 6.55 (s, 1H), 5.87 (br, s, 1H), 3.83 (br, s, 2H), 3.83 (br, s, 1H), 3.48-3.64 (m, 2H), 3.01 (br, s, 2H) 2.69-2.80 (m, 1H), 2.43 (br, 1H), 2.29 (s, 3H), 1.86-1.97 (m, 2H). ^{13}C NMR: 201.74, 167.73, 160.82 (d, *J* = 247.6), 149.71, 133.51, 131.83, 125.86, 124.33, 116.85 (d, *J* = 20.9), 112.02, 68.42, 49.52, 44.26, 25.94, 20.46. ESI-MS: m/z 410 ($[M + H]^+$, $C_{20}H_{21}NO_3SClF$ calcd. (%) 410.3).

5-(2-Cyclopropyl-1-(3-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno [3,2-c]pyridin-2-yl acetate (10): To a suspension of 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride **3** (10 g, 52.17 mmol) in acetonitrile (60 mL) was cooled to 0-5 ºC, anhydrous potassium carbonate (14.4 g, 104.45 mmol) was added and charged 2-bromo-1-cyclopropyl-2-(3-fluorophenyl)ethanone) **8** (10.75 g, 41.7 mmol) at 0-5 ºC and the mixture was stirred for 4 h at 0-5 ºC. The salt was removed by filtration and then washed with acetonitrile (10 mL). The filtrate acetonitrile was removed by distillation under vacuum at 40-45 ºC to afford desacetyl 3-fluro prasugrel **9** (14 g) as a brown oily liquid. To the oily crude (14 g, 42.2 mmol), DMF (120 mL) was charged and stir until clear solution was obtained. The resulting solution was cooled to 0-5 ºC, anhydrous potassium carbonate (12.84 g, 92.9 mmol) was added and slowly added acetic anhydride (10.8 g, 105.60 mmol) at 0-5 ºC and then stirred for 1 h, when analytical TLC revealed the amount of des acetyl 3-fluro prasugrel 9 was below 2 %. The reaction mixture was cooled to 20-25 ºC then charged toluene (90 mL) and water (150 mL). The mixture was stirred for 15 min and then separated the layers. The aqueous layer was extracted with toluene (2 × 30 mL). The combined organic layer was washed with water (4 × 50 mL) and concentrated under vacuum at 40-45 ºC and purified by silica column chromatography using 10 % ethyl acetate in hexane (v/v) afforded 3-fluro prasugrel **10** as a off-white solid (5 g, 25.6 % yield, HPLC purity 98.82 %) IR (KBr, ν_{max}, cm^{-1}) : 3011, 2939, 2799, 1766, 1611, 1500, 1444, 1371, 1249, 1194, 1122, 894, 786, 685. ^{1}H NMR (DMSO-d_6): δ 7.41-7.49 (m, 1H) , 7.26-7.31 (m, 1H), 7.26-7.31 (m, 1H), 7.15-7.22 (m, 1H), 6.44 (s, 1H), 4.43 (1H), 3.43 (d, *J* = 14.7, 1H), 3.35 (d, *J* = 14.7, 1H), 2.68-2.77 (2H), 2.68-2.77 (2H), 2.45-2.48 (1H), 2.26 (s, 3H), 0.71-0.93 (m, 2H), 0.71-0.93 (m, 2H). ^{13}C NMR: 208.19, 167.82, 162.22 (d, *J* = 242.7), 148.71, 138.48 (d, *J* = 7.2), 130.66 (d, *J* = 8.1) 129.34, 125.45, 124.96, 115.41 (d, *J* = 21.7), 115.08 (d, *J* = 21.2), 112.42, 78.90, 50.21, 48.22, 24.40, 20.40, 17.49, 11.80, 11.15. ESI-MS: m/z 374 ([M + H]$^+$, $C_{20}H_{20}NO_3SF$, calcd. (%) 374.1).

5-(2-Cyclopropyl-1-(4-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate (13): Anhydous potassium carbonate (14.45 g, 104.58 mmol) was added to stirred suspension of 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride **3** (10 g, 52.17 mmol) in acetonitrile (60 mL) at 0-5 ºC and then charged 2-bromo-1-cyclopropyl-2-(4-fluorophenyl)ethanone **11** (12.7 g, 49.6 mmol) at 0-5 ºC and the mixture was stirred for 4 h at 0-5 ºC. The salt was removed by filtration and then washed with acetonitrile (10 mL). The filtrate acetonitrile was removed by distillation under vacuum at 40-45 ºC to afford desacetyl 4-fluro prasugrel **12** (14 g, 42.2 mmol) as a brown oily liquid. To the oily crude (14 g), DMF (120 mL) was charged and stir until clear solution was obtained. The resulting solution was cooled to 0-5 ºC, anhydrous potassium carbonate (12.84 g, 92.9 mmol) was added and slowly added acetic anhydride (10.8 g, 105.60 mmol) at 0-5 ºC and then stirred for 1 h, when analytical TLC revealed the amount of des acetyl 4-fluro prasugrel **12** was below 2 %. The reaction mixture was cooled to 20-25 ºC then charged toluene (90 mL) and water (150 mL). The mixture was stirred for 15 min and then separated the layers. The aqueous layer was extracted with toluene (2 × 30 mL). The combined organic layer was washed with water (4 × 50 mL) and concentrated under vacuum at 40-45 ºC and purified by silica column chromatography using 10 % ethylacetate in hexane (v/v) afford 4-fluoro prasugrel **13** as a off-white solid (5 g, 25.6 % yield, HPLC purity 98.97 %) IR (KBr, ν_{max}, cm^{-1}): 3009, 2942, 1761, 1602, 1435, 1373, 1221, 1200, 1158, 898, 832, 653. ^{1}H NMR (DMSO-d_6): δ 7.47-7.52 (dd, *J* = 5.7,8.7, 2H), 7.23 (t, *J* = 8.9, 2H), 6.43 (s, 1H), 4.39 (s, 1H), 3.36-3.42 (2H), 2.72 (s, 2H), 2.72 (s, 2H), 2.44- 2.48 (1H), 2.26 (s, 3H),0.70-0.91 (m, 2H), 0.70-0.91 (m, 2H). ^{13}C NMR : 208.47, 167.81, 161.89 (d, *J* = 243.3), 148.70, 131.84, 130.79 (d, *J* = 8.3), 129.39, 125.44, 115.59 (d, *J* = 21.2), 112.42, 78.61, 50.20, 48.20, 24.39, 20.40, 17.39, 11.66, 11.01. ESI-MS : m/z 374 ([M + H]$^+$, $C_{20}H_{20}NO_3SF$, calcd. (%) 374.2).

5-Acetyl-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate (14): To a suspension of 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride **3** (10 g, 52.17 mmol) in DMF (70 mL) was cooled to 0-5 ºC, anhydrous potassium carbonate (21.65 g, 156.7 mmol) was added and slowly added acetic anhydride (16 g, 156.7 mmol) at 0-5 ºC. The reaction mixture was stirred for 1 h at 0-5 ºC, analytical TLC revealed the completion of reaction. To the reaction mass ethyl acetate (100 mL) and water (60 mL) were charged and then stirred for 15 min. The layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with water (4 × 20 mL). The solvent was completely removed under vacuum at 45-50 ºC. The residue was purified by silica column chromatography using 10 % methanol in dichloromethane (v/v) to afford diacetyl prasugrel **14** (2.5 g, 20.03 % yield, HPLC purity 98.17 %). IR (KBr, ν_{max}, cm^{-1}): 3001, 2940, 1760, 1582, 1471, 1424, 1373, 1255, 1015, 882, 819, 641. ^{1}H NMR ($CDCl_3$): δ 6.38 (s, 1H), 4.56 (s, 1H), 4.44 (s, 1H), 3.90 (t, *J* = 5.7, 1H), 3.74 (t, *J* = 5.7, 1H), 2.81 (t, *J* = 5.7, 1H), 2.75 (t, *J* = 5.7, 1H), 2.29 (s, 3H), 2.18 (s, 3H). ^{13}C NMR : 169.30, 167.54, 149.86, 128.31, 124.57, 111.56, 45.97, 44.08, 24.90, 21.45, 20.56. ESI-MS: m/z 240 ([M + H]$^+$, $C_{11}H_{13}NO_3S$, calcd. (%) 240.0), m/z 262 (([M + Na]$^+$).

5-(1-(2-Fluorophenyl)-2-oxopropyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate (17): Anhydrous potassium carbonate (7.2 g, 52.11 mmol) was added to stirred suspension of 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride **3** (5 g, 26.1 mmol) in acetonitrile (30 mL) at 0-5 ºC and then charged 1-bromo-1-(2-fluorophenyl)propan-2-one **15** (5.73 g, 24.8 mmol) at 0-5 ºC and the mixture was stirred for 4 h at 0-5 ºC. The salt was removed by filtration and then washed with acetonitrile (5 mL). The filtrate acetonitrile was removed by distillation under vacuum at 40-45 ºC to afford desacetyl methyl keto prasugre **16** (4 g, 13.09 mmol) as a brown oily liquid. To the oily crude (4 g), DMF (30 mL) was charged and stirred until clear solution was obtained. The resulting solution was cooled to 0-5 ºC, anhydrous potassium carbonate (3.62 g, 26.2 mmol) was added and slowly added acetic anhydride (3.34 g, 32.7 mmol) at 0-5 ºC and then stirred for 1 h, when analytical TLC revealed the amount of desacetyl methyl keto prasugrel **16** was below 2 %. The reaction mixture was cooled to 20-25 ºC then charged toluene (45 mL) and water (150 mL). The mixture was stirred for 15 min and then

separated the layers. The aqueous layer was extracted with toluene (2 × 15 mL). The combined organic layer was washed with water (4 × 25 mL) and concentrated under vacuum at 40-45 ºC. The resulting residue was triturated with methanol (10 mL) for 1 h. The solid obtained was removed by filtration and washed with methanol (5 mL). The wet material was dried under vacuum to afford methyl keto prasugrel impurity **17** (1.0 g, 11.6 % yield, HPLC purity 89.82 %) as a pale yellow solid. IR (KBr, ν_{max}, cm^{-1}): 2954, 2844, 1759, 1613, 1488, 1372, 1217, 1134, 826, 760, 612. ^{1}H NMR (DMSO-d_6): δ 7.37-7.47 (m, 1H), 7.37-7.47 (m, 1H), 7.27 (d, *J* = 7.8, 1H), 7.22 (d, *J* = 3.0, 1H), 6.41 (s, 1H), 4.72 (s, 1H), 3.40 (s, 2H), 2.62-2.81 (m, 2H), 2.62-2.81 (m, 2H), 2.25 (s, 3H), 2.14 (s, 3H). ^{13}C NMR: 205.50, 167.77, 160.58 (d, *J* = 243.5), 148.66, 130.97 (d, *J* = 3.8), 130.19 (d, *J* = 8.5), 129.45, 125.30, 124.63 (d, *J* = 3.1), 121.53 (d, *J* = 14.5), 115.71 (d, *J* = 22.5), 112.29, 71.23, 49.60, 47.74, 26.82, 24.63, 20.37 ESI-MS: m/z 348 ([M + H]$^+$, $C_{18}H_{18}NO_3S$, calcd. (%) 348.1), m/z 370 ([M + Na]$^+$).

1-Cyclopropyl-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4*H*)-yl)-2-(2-fluorophenyl)ethanone hydrochloride (19): To a suspension of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride **18** (20 g, 113.86 mmol) in acetonitrile (120 mL) was cooled to 0-5 ºC, anhydrous potassium carbonate (31.4 g, 227.2 mmol) was added and charged 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone) **2** (23.4 g, 91.0 mmol) at 0-5 ºC and the mixture was stirred for 4 h at 0-5 ºC. The salt was removed by filtration and then washed with acetonitrile (40 mL). The filtrate acetonitrile was removed by distillation under vacuum at 40-45 ºC. The resulting crude was dissolved in acetone (200 mL) and slowly added 10 % ethanolic HCl (20 mL) at 25-30 ºC and stirred for 1 h. The obtained material was removed by filtration and washed with acetone (30 mL). The wet material was dried under vacuum at 40-45 ºC for 5 h to afford thiophene impurity **19** (14 g, 34.8 % yield, HPLC purity 99.30 %) as a off-white solid. IR (KBr, ν_{max}, cm^{-1}): 3430, 3094, 2937, 1708, 1611, 1492, 1458, 1417, 1383, 1236, 773, 614, 598. ^{1}H NMR (DMSO-d_6): δ 10.5-11.5 (br, 1H) 7.58-7.63 (m, 1H), 7.58-7.63 (m, 1H), 7.38-7.50(m, 1H), 7.38-7.50 (m, 1H), 6.88 (s, 1H), 6.09 (1H), 4.0-4.28 (2H), 3.11 (br, 2H), 1.97 (br, 1H), 0.88-1.07 (m, 2H), 0.88-1.07 (m, 2H). ^{13}C NMR: 201.73, 160.95 (d, *J* = 248.0), 133.45 (d, *J* = 8.1), 132.65, 131.47, 128.06, 125.68 (d, *J* = 3.3), 125.41, 124.95, 116.69 (d, *J* = 21.5), 115.72, 68.81, 49.95, 47.51, 21.97, 12.69, 12.34, ESI-MS: m/z 316 ([M + H]$^+$, $C_{18}H_{18}NO_3S$, calcd. (%) 316.1).

5-(2-Cyclopropyl-2-oxo-1-phenylethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate (22): Anhydous potassium carbonate (14.4 g, 104.6 mmol) was added to stirred suspension of 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride **3** (10 g, 52.17 mmol) in acetonitrile (30 mL) at 0-5 ºC and then charged 2-bromo-1-cyclopropyl-2-phenylethanone **20** (11.25 g, 47.0 mmol) at 0-5 ºC and the mixture was stirred for 4 h at 0-5 ºC. The salt was removed by filtration and then washed with acetonitrile (5 mL). The filtrate acetonitrile was removed by distillation under vacuum at 40-45 ºC to afford desacetylfluoro prasugrel **21** (14 g, 44.7 mmol) as a brown oily liquid. To the oily crude (14 g), DMF (60 mL) was charged and stirred until clear solution was obtained. The resulting solution was cooled to 0-5 ºC, anhydrous potassium carbonate (11.68 g, 84.5 mmol) was added and slowly added acetic anhydride (11.4 g, 111.8 mmol) at 0-5 ºC and then stirred for 1 h, when analytical TLC revealed the amount of des acetylfluoro prasugrel **21** was below 2 %. The reaction mixture was cooled to 20-25 ºC then charged toluene (90 mL) and water (150 mL). The mixture was stirred for 15 min and then separated the layers. The aqueous layer was extracted with toluene (2 × 30 mL). The combined organic layer was washed with water (4 × 50 mL) and concentrated under vacuum at 40-45 ºC. The resulting residue was triturated with methanol (10 mL) for 1 h. The solid obtained was removed by filtration and washed with methanol (5 mL). The wet material was dried under vacuum to afford desfluoro prasugrel impurity **22** (3 g, 16.21 % yield, HPLC purity 93.65 %) as a off-white solid. IR (KBr, ν_{max}, cm^{-1}): 3086, 2989, 1754, 1584, 1495, 1455, 1417, 1369, 1217, 1193, 888, 832, 822, 761, 714, 698, 665. ^{1}H NMR (DMSO-d_6): δ 7.32-7.47 (m, 2H), 7.32-7.47 (m, 2H), 7.32-7.47(m, 1H), 6.43 (s, 1H), 4.33 (s, 1H), 3.33-3.38 (2H), 2.72 (s, 2H), 2.72 (s, 2H), 2.46-2.48 (1H), 2.26 (s, 3H), 0.68-.91 (m, 2H), 0.68-.91 (m, 2H). ^{13}C NMR: 208.61, 167.84, 148.70, 135.69, 129.46, 128.80, 128.76, 128.20, 125.49, 112.43, 79.86, 50.34, 48.32, 24.44, 20.42, 17.31, 11.62, 11.03. ESI-MS: m/z 356 ([M + H]$^+$, $C_{20}H_{21}NO_3S$, calcd. (%) 356.2).

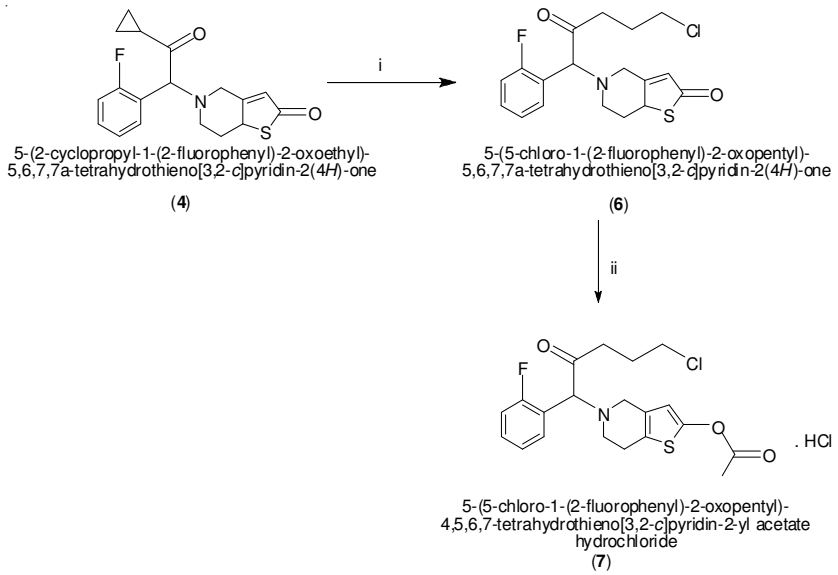
RESULTS AND DISCUSSION

Desacetyl prasugrel (**4**), a possible contaminant in prasugrel hydrochloride that can be formed by incomplete acetylation of desacetyl prasugrel or may be deacetylation of prasugrel base. The desacetyl prasugrel impurity (**4**) was synthesized by condensation of (**2**) with 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride (**3**) in the presence of base and acetonitrile[8] (**Scheme-I**).

During hydrochloride conversion of prasugrel (**5**), formation of 0.3-0.5 % of the chloro prasugrel (**7**) is observed, the level is reduced to less than 0.1 % during its isolation and purification. The CATP impurity (**7**) was prepared by reaction of HCl/water with (**4**) and the desacetyl chloro prasugrel formed (**6**) was acetylated with acetic anhydride in the presence of DMF and potassium carbonate, followed by purification by column chromatography and further treatment with conc. hydrochloric acid in the presence of acetone (**Scheme-II**).

In some of commercial samples, 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone (**2**) was found to be contaminated with traces of 2-bromo-1-cyclopropyl-2-(3-fluorophenyl)-ethanone (**8**), although the amount of contamination of the fluoro analogue (**10**) in prasugrel hydrochloride (**1**) was never more than 0.2 %[4]. The fluoro analogue of prasugrel[9] (**10**) was synthesized from 2-bromo-1-cyclopropyl-2-(3-fluorophenyl)-ethanone (**8**) following the reaction sequence used to synthesize (**5**), followed by purification by column chromatography (**Scheme-III**).

In some of commercial samples, 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone (**2**) was found to be contaminated with traces of 2-bromo-1-cyclopropyl-2-(4-fluorophenyl)-ethanone (**11**), although the amount of contamination of the fluoro analogue (**13**) in prasugrel hydrochloride (**1**) was never more than 0.15 %[4]. The fluoro analogue of prasugrel[9] (**13**) was synthesized from 2-bromo-1-cyclopropyl-2-(4-fluorophenyl)-

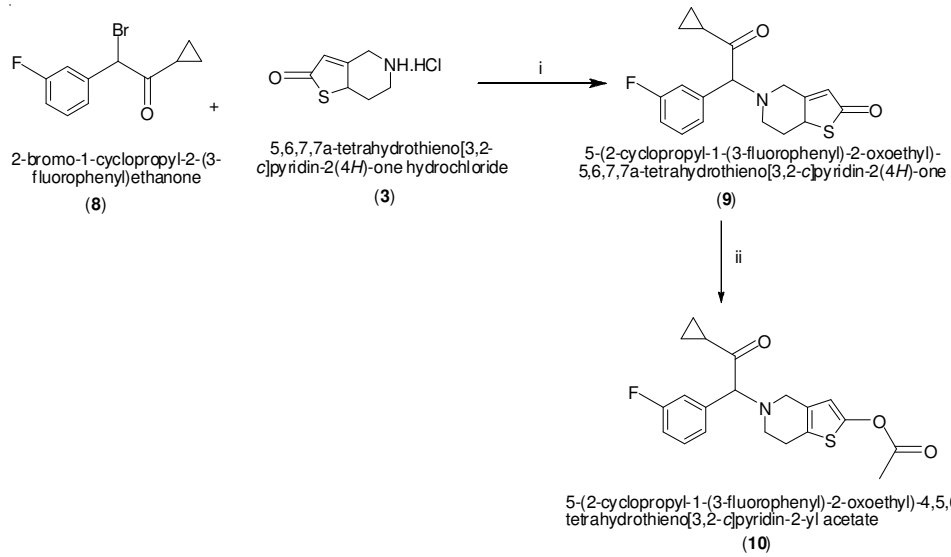


5-(2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one (**4**)

5-(5-chloro-1-(2-fluorophenyl)-2-oxopentyl)-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one (**6**)

5-(5-chloro-1-(2-fluorophenyl)-2-oxopentyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate hydrochloride (**7**)

Scheme-II: Reagents and conditions: (i) HCl, water, 80-85 ºC; (ii) (a) K_2CO_3, acetic anhydride, DMF, 0-5 ºC; (b) column chromotography; (c) acetone, conc. HCl



2-bromo-1-cyclopropyl-2-(3-fluorophenyl)ethanone (**8**)

5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one hydrochloride (**3**)

5-(2-cyclopropyl-1-(3-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one (**9**)

5-(2-cyclopropyl-1-(3-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate (**10**)

Scheme-III: Reagents and conditions: (i) K_2CO_3, acetonitrile, 0-5 ºC; (ii) (a) K_2CO_3, acetic anhydride, DMF, 0-5 ºC; (b) column chromotography

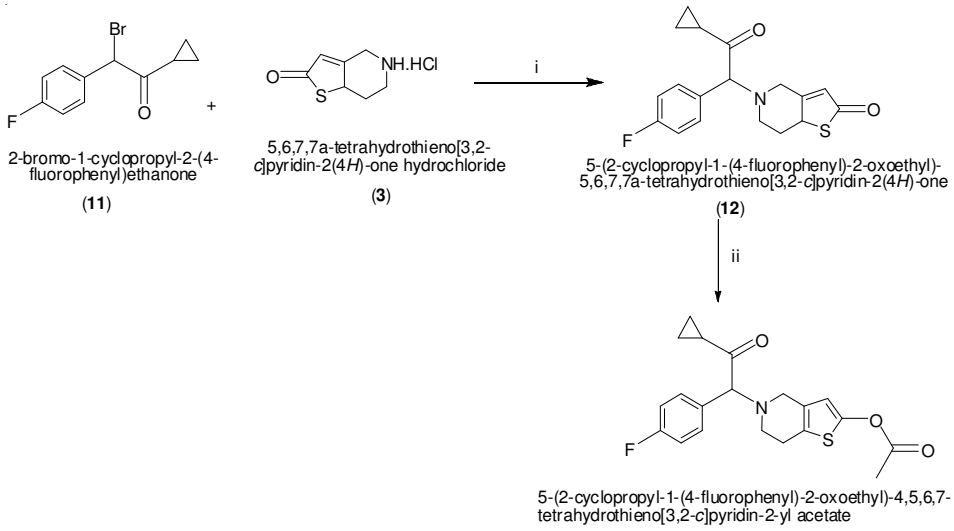
ethanone (**11**) following the reaction sequence used to synthesize (**5**), followed by purification by column chromatography (**Scheme-IV**).

During the acetylation reaction there is always the probability of diacetylation due to presence of excess 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride (**3**), hence the diacetyl thieno pyridine (**14**) was synthesized by acetylation of thienopyridine (**3**) with acetic anhydride, followed by purification by column chromatography (**Scheme-V**).

In some of commercial samples, 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone (**2**) was founded to be contaminated with traces of 1-bromo-1-(2-fluorophenyl)propan-2-one (**15**), although the amount of contamination of methylketo impurity[9] (**17**) in prasugrel hydrochloride (**1**) was never more than 0.15 %[3]. Methylketo impurity (**17**) was synthesized from 1-bromo-1-(2-fluorophenyl)propan-2-one (**15**) following the reaction sequence used to synthesize **5** (**Scheme-VI**).

In some of the commercial samples, 5,6,7,7a-tetrahydrothieno[3,2-c]pyridin-2(4*H*)-one hydrochloride (**3**) was found to be contaminated with traces of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (**18**), although the amount of contamination of thiophene impurity (**19**) in prasugrel hydrochloride (**1**) was never more than 0.15 %[3]. Thiophene impurity (**19**) was synthesized from 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (**18**) by alkylation with 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone (**2**) in presence of potassium carbonate and acetonitrile followed by treatment with etahnolic HCl in the presence of acetone (**Scheme-VII**).

In some of the commercial samples, 2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone (**2**) was found to be contaminated with traces of 2-bromo-1-cyclopropyl-2-phenylethanone (**20**), although the amount of contamination of the desfluoro analogue (**22**) in prasugrel hydrochloride (**1**) was never more than 0.15 %[3]. The desfluoro analogue of prasugrel (**22**) was synthesized from 2-bromo-1-cyclopropyl-2-phenylethanone (**20**) following the reaction sequence used to synthesize **5** (**Scheme-VIII**).



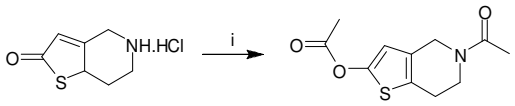
2-bromo-1-cyclopropyl-2-(4-fluorophenyl)ethanone (**11**)

5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one hydrochloride (**3**)

5-(2-cyclopropyl-1-(4-fluorophenyl)-2-oxoethyl)-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one (**12**)

5-(2-cyclopropyl-1-(4-fluorophenyl)-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate (**13**)

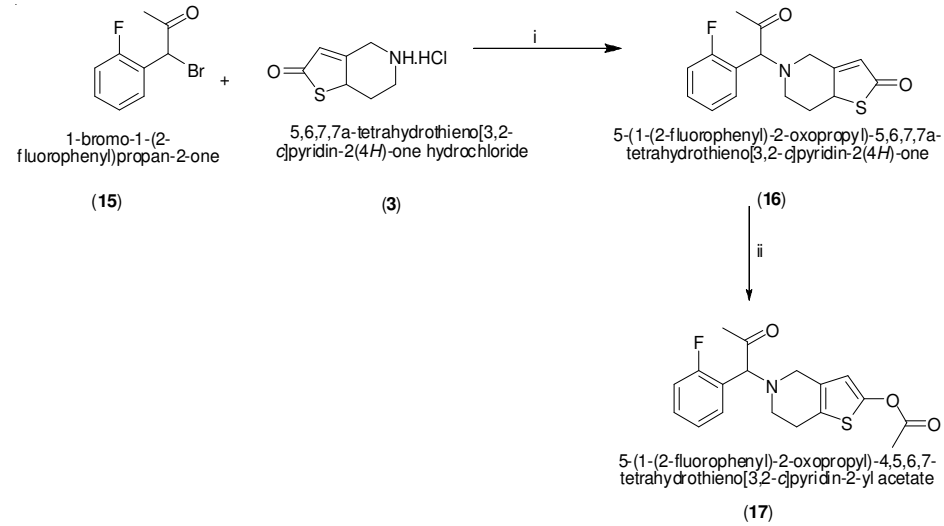
Scheme-IV: Reagents and conditions: (i) K_2CO_3, acetonitrile, 0-5 ºC; (ii) K_2CO_3, acetic anhydride, DMF, 0-5 ºC; (b) column chromotography



5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one hydrochloride (**3**)

5-acetyl-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate (**14**)

Scheme-V: Reagents and conditions: (i) (a) K_2CO_3, acetic anhydride, DMF, 0-5 ºC; (b) column chromotography



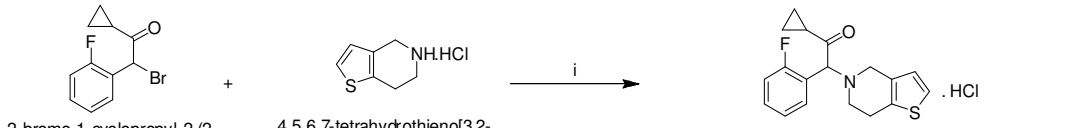
1-bromo-1-(2-fluorophenyl)propan-2-one (**15**)

5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one hydrochloride (**3**)

5-(1-(2-fluorophenyl)-2-oxopropyl)-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one (**16**)

5-(1-(2-fluorophenyl)-2-oxopropyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate (**17**)

Scheme-VI: Reagents and conditions: (i) K_2CO_3, acetonitrile, 0-5 ºC; (ii) K_2CO_3, acetic anhydride, DMF, 0-5 ºC



2-bromo-1-cyclopropyl-2-(2-fluorophenyl)ethanone (**2**)

4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride (**18**)

1-cyclopropyl-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)-2-(2-fluorophenyl)ethanone hydrochloride (**19**)

Scheme-VII: Reagents and conditions: (i) (a) K_2CO_3, acetonitrile, 0-5 ºC; (b) ethanolic HCl, acetone, 35-40 ºC

Conclusion

For better knowledge of the synthetic path way of an active pharmaceutical ingredient (API) it is mandatory to identify all the impurities formed/anticipated. In this context we have synthesized and characterized different potential process related impurities of prasugrel hydrochloride.

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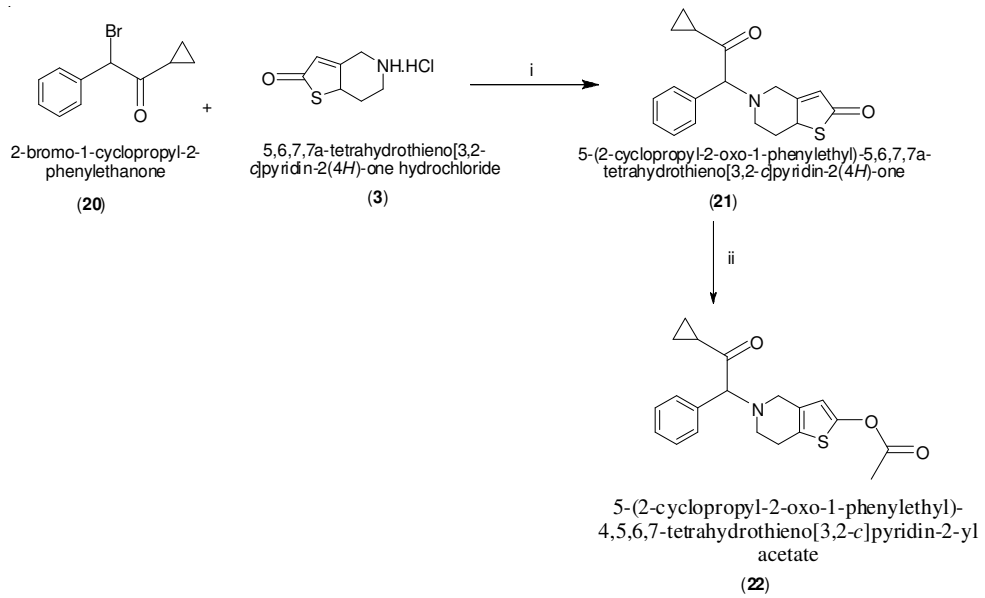

2-bromo-1-cyclopropyl-2-phenylethanone (**20**)

5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one hydrochloride (**3**)

5-(2-cyclopropyl-2-oxo-1-phenylethyl)-5,6,7,7a-tetrahydrothieno[3,2-*c*]pyridin-2(4*H*)-one (**21**)

5-(2-cyclopropyl-2-oxo-1-phenylethyl)-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate (**22**)

Scheme-VIII: Reagents and conditions: (i) K_2CO_3, acetonitrile, 0-5 ºC; (ii) K_2CO_3, acetic anhydride, DMF, 0-5 ºC

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