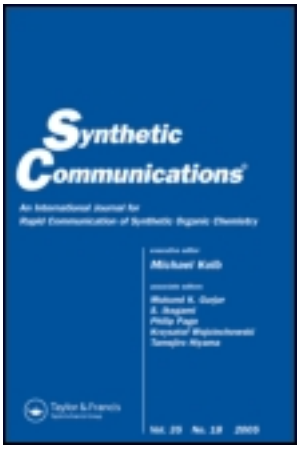

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SYNTHESIS AND CHARACTERIZATION OF IMPURITY B OF S-(+)-CLOPIDOGREL BISULFATE: AN ANTIPLATELET

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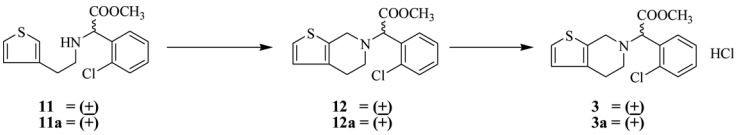
GRAPHICAL ABSTRACT



11 = (+)
11a = (+)

12 = (+)
12a = (+)

3 = (+)
3a = (+)

Abstract *S-(+)-Clopidogrel bisulfate [(S-(+)-methyl 2-(2-chlorophenyl)-2-(6, 7-dihydrothieno[3, 2-c]pyridin-5(4H)-yl)acetate bisulfate)] is a platelet aggregation inhibitor drug. S-(+)-Clopidogrel bisulfate is prepared by different synthetic approaches in the literature. In almost all the approaches the major impurities known in the literature (A, B, and C) are also listed in the U.S. pharmacopoeia. The control of these pharmaceutical impurities is currently a critical issue to the pharmaceutical industry. In this article, a description of these impurities and their origins in the S-(+)-clopidogrel bisulfate process are presented along with the preparation of impurity B.*

Keyword Antiplatelet; impurity B; S-(+)-clopidogrel bisulfate

INTRODUCTION

Clopidogrel bisulfate [S-(+)-methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno-[3,2-c]pyridin-5(4H)-yl)acetate bisulfate] **1**, is an oral, thienopyridine-class antiplatelet agent used to inhibit blood clots caused by coronary artery disease, peripheral vascular disease and cerebrovascular disease.[1,2] The drug works by irreversibly inhibiting a receptor called $P2Y_{12}$, an adenosine diphosphate ADP chemoreceptor.[3,4] Adverse effects include hemorrhage, severe neutropenia, and thrombotic thrombocytopenic purpura (TTP).

Clopidogrel bisulfate is a prodrug whose action may be related to an adenosine diphosphate (ADP) receptor on platelet cell membranes. The drug specifically and irreversibly inhibits the $P2Y_{12}$ subtype of the ADP receptor, which is important in

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aggregation of platelets and cross-linking by the protein fibrin.[3] The blockade of this receptor inhibits platelet aggregation by blocking activation of the glycoprotein IIb/IIIa pathway. The IIb/IIIa complex functions as a receptor mainly for fibrinogen and vitronectin but also for fibronectin and von Willebrand factor. Activation of this receptor complex is the "final common pathway" for platelet aggregation and is important in the cross-linking of platelets by fibrin. Platelet inhibition can be demonstrated 2 h after a single dose of oral clopidogrel bisulfate, but the onset of action is slow, so that a loading dose of 300–600 mg is usually administered.

Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs) or develop during formulation. The presence of these unwanted chemicals, even in small amounts, may influence the efficacy and safety of the pharmaceutical products. Impurity profiling (identification and quantification) is now receiving important critical attention from regulatory authorities. The different pharmacopoeias, such as the European Pharmacopoeia (EP), British Pharmacopoeia (BP), and the United States Pharmacopoeia (USP), are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations.

The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances,[5] products,[6] and residual solvents.[7] Impurity and API reference standards are in good demand for both regulatory authorities and pharmaceutical companies. A number of recent articles[8–10] have described a designed approach and guidance for isolating and identifying process-related impurities and degradation products using spectral and analytical techniques.

The important step in impurity profiling is the synthesis of the material (impurity standard) with the proposed structure. The synthesized material with the proposed structure is useful for analytical method development and validation.

There are many synthetic methods known in the literature for the synthesis of clopidogrel bisulfate.[11,12] Innovator route for the preparation of clopidogrel bisulfate[12] involves the formation of impurities A, B, and C.

Impurities A and C are process impurities and were well controlled by maintaining proper reaction conditions. The main source for impurity B was a key raw material, that is, 2-substituted thiophene, along with traces amount of 3-substituted thiophene. The impurity B formation was controlled by controlling the impurity levels in that key raw material.

SOURCES OF IMPURITIES

Impurity A

During the synthesis of compound **1** [reaction of S-(+)-clopidogrel base with concentrated sulfuric acid], the ester group in the S-(+)-clopidogrel base hydrolyzed and afforded the formation of impurity A [S-(+)-2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetic acid hydrochloride], **2**.

Impurity B

According to the literature,[13] compound **1** was prepared by using 2-substitued thiophene as one of the key raw materials. It is well known that 3-substitued

thiophene was a major impurity during the synthesis of 2-substitued thiophene.[14] Commercially available 2-substitued thiophene contains about 0.5–1.0% of 3-substitued thiophene as an impurity. This 3-substituted thiophene also participates in the reaction during the synthesis of compound **1** and leads the formation of methyl 2-(2-chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridin-6(7H)-yl) acetate hydrochloride, **3**. Detailed synthesis of impurity B is discussed in the experimental section.

Impurity C

During the synthesis of compound **1**, concentrated sulfuric acid was used for bisulfate salt formation. Because of the high concentration of sulfuric acid, compound **1** undergoes racemization. Unwanted R-(−)-clopidogrel bisulfate remained as impurity **C, 4**, in the S-(+)-clopidogrel bisulfate **1**.

There is no synthetic approach available for impurity B in the literature. Out of these three impurities, synthesis of impurity B is critical. This impurity standard is not easily available to pharmaceutical industries. In the European pharmacopeia, impurity B was specified as racemic hydrochloride salt. In high-performance liquid chromatography (HPLC) analysis of clopidogrel bisulfate, **1** impurity B shows two peaks for both the isomers at different retention times. Sometimes this leads to confusion during interpretation of impurity B levels. To avoid such problems we prepared S-(+)-isomer of impurity B **(3a)** also. This made us provide a feasible synthetic approach for the synthesis of impurity B to cater the needs of the pharmaceutical industry as well as pharmacopeias.

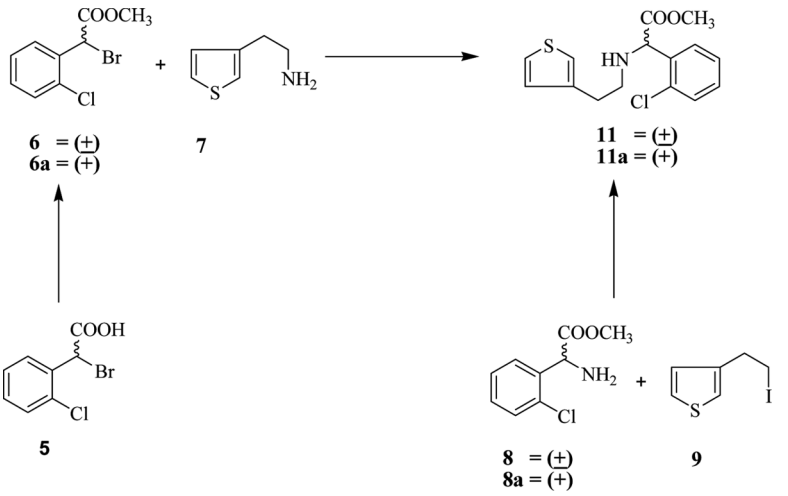
The present article describes a simple and facile synthesis for impurity B. This may serve as a standard for impurity profiling in drug development.

RESULTS AND DISCUSSION

The overall synthesis of impurity B proceeded through two routes. One was condensation of methyl 2-bromo-2-(2-chlorophenyl)acetate **6** with 2-(thiophen-3-yl)ethanamine **7** to afford compound **11**, which again underwent cyclization with formaldehyde, and resolution with a chiral agent followed by bisulfate formation afforded impurity B. In another way, direct condensation of methyl 2-bromo-2-(2-chlorophenyl)acetate **6** with 4,5,6,7-tetrahydrothieno[2,3-c]pyridine **10** followed by bisulfate formation afforded impurity B.

Condensation of methyl 2-bromo-2-(2-chlorophenyl)acetate **6** with 2-(thiophen-3-yl)ethanamine **7** in the presence of a base afforded methyl 2-(2-(thiophen-3-yl)ethyl amino)-2-(2-chlorophenyl) acetate **11**. Compound **11** was also prepared by the condensation of methyl 2-amino-2-(2-chlorophenyl)acetate **8** with 3-(2-iodoethyl) thiophene **9**. The same synthesis was conducted with the S-(+)-isomer of methyl 2-bromo-2-(2-chlorophenyl)acetate **6a** and methyl 2-amino-2-(2-chlorophenyl)acetate **8a** for compound S-(+)-methyl 2-(2-(thiophen-3-yl)ethyl amino)-2--(2-chlorophenyl)acetate **11a** (Scheme 1).

Condensation of methyl 2-bromo-2-(2-chlorophenyl)acetate **6** with 4,5,6,7-tetrahydrothieno[2,3-c]pyridine **10** in the presence of a base afforded methyl 2-(2-chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridin-6(7H)-yl)acetate **12**. The same synthesis was conducted with S-(+)-methyl 2-bromo-2-(2-chlorophenyl) acetate **6a**.

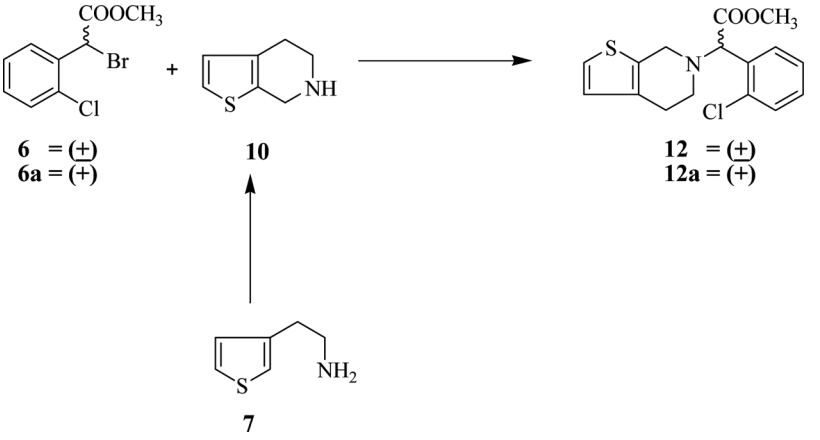


Scheme 1.

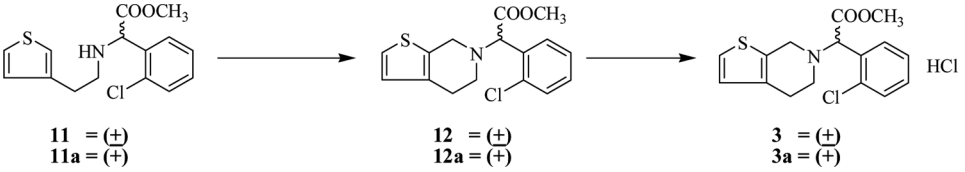
4,5,6,7-Tetrahydrothieno[2,3-c]pyridine **10** was prepared by the cyclization of 2-(thiophen-3-yl)ethanamine **7** with formaldehyde (Scheme 2).

Compound **3** was prepared by cyclization of 10 with 37% formaldehyde solution followed by hydrochloride salt formation. Compound **3a** was prepared in different methods. In one method compound **11a** was prepared from **11** by treatment with 1S-(+)-10-camphorsulfonic acid in acetone, which then proceeded to **12a** by cyclization in 37% formaldehyde solution. In another method compound **12** was prepared by the cyclzation in 37% formaldehyde solution, which then proceeded to **12a** by treatment with 1R-(−)-10-camphorsulfonic acid in acetone. Compound **12a** was converted to **3** in acetone with hydrochloric acid (Scheme 3).

In Schemes 1 and 2, condensation was attempted with methyl α-halo (2-chlorophenyl) acetate (halo = fluoro, chloro, bromo, iodo). The reaction proceeded well



Scheme 2.



11 = (±)
11a = (+)

12 = (±)
12a = (+)

3 = (±)
3a = (+)

Scheme 3.

with bromo moiety. In Scheme 3, resolution was attempted with S-(+) and R-(−) isomers of camphor sulfonic acid, tartaric acid and mandelic acid. Resolution of racemic mixture was achieved with S-(+)-camphor sulfonic acid. Methyl 2-bromo-2-(2-chlorophenyl) acetate **6** was prepared from α-bromo(2-chloro phenyl)acetic acid by the reported method.[13]

EXPERIMENTAL

Melting points were determined on a Buchi 540 melting-point apparatus and were uncorrected. Fourier transform–infrared (FT-IR) spectra were recorded as KBr pellet on a Nicolet 380 FT-IR instrument (model Thermo Electron Corporation Spectrum One). ^{1}H NMR spectra were recorded on a Varian 300-MHz spectrometer using $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) as solvents and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on an Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375 °C. All the organic extracts were dried over sodium sulfate after workup. Unless otherwise mentioned, all the solvents and reagents used were of commercial grade.

Methyl 2-Bromo-2-(2-chlorophenyl)acetate (6)

Concentrated sulfuric acid (2.76 g, 28.14 mmol) was slowly added to a stirring solution of 2-bromo-2-(2-chlorophenyl) acetic acid **5** (50.0 g, 200.4 mmol) in methanol (250 mL) at room temperature. Reaction mass was refluxed for 3 h and then cooled to 45 °C. Methanol was completely distilled off under vacuum and the residue was dissolved in dichloromethane (200 mL) and washed with 10% sodium bicarbonate solution (50 mL) and water (2 × 100 mL). Dichloromethane was vacuum distilled to yield **6** as a yellowish oily residue. This residue was carried to the next stage as such (50.2 g, 95.07%); IR (KBr, cm^{-1}) 3009, 1758, 1572, 1439, 760, 684; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.6 (s, 3H), 5.0 (s, 1H), 7.3–7.6 (m, 4H); MS (ESI, m/z): 264.42 $[M+H]^+$. Anal. calcd. for $C_9H_8BrClO_2$ (263.52): C, 41.02; H, 3.06; O, 12.14%. Found: C, 41.12; H, 3.05; O, 12.15%.

S-(+) Methyl 2-Bromo-2-(2-chlorophenyl)acetate (6a)

This compound was prepared in a similar way to **6**, using S-(+)-2-bromo-2-(2-chlorophenyl) acetic acid (25.0 g, 100.2 mmol), as a light yellowish oily residue. This residue was carried to the next stage as such (24.3 g, 92.04%); MS (ESI, m/z): 264.62 $[M+H]^+$. Anal. calcd. for $C_9H_8BrClO_2$ (263.52): C, 41.02; H, 3.06; O, 12.14%. Found: C, 41.08; H, 3.09; O, 12.10%.

Methyl 2-(2-(Thiophen-3-yl)ethyl amino)-2-(2-chlorophenyl)acetate (11) from 6 and 7

Sodium bicarbonate (8.0 g, 94.85 mmol) and 2-(thiophen-3-yl) ethanamine **7** (24.13 g, 189.7 mmol) were added slowly to a stirring solution of methyl 2-bromo-2-(2-chlorophenyl) acetate **6** (50.0 g, 189.7 mmol) in methanol (180.0 mL) at below 10 °C. Mass was heated to reflux temperature for 2 h. After reaction completion, methanol was distilled off completely under vacuum, and water (200 mL) and dichloromethane (200 mL) were added. The dichloromethane layer was separated and washed with saturated sodium chloride solution (50 mL) and then with water (100 mL). Dichloromethane was distilled completely under vacuum to yield **11** as an off-white color oily residue (54.3 g, 92.4%); purity 99.48% (by HPLC); IR (KBr, cm^{-1}) 3463, 3071, 2912, 1741, 1485, 1462, 1232, 765; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.0 (t, $J = 7.8$ Hz, 2H), 3.1 (t, $J = 14.7$ Hz, 2H), 3.7 (s, 3H), 5.6 (s, 1H), 7.0 (d, $J = 6.3$ Hz, 1H), 7.3 (s, 1H), 7.5–7.7 (m, 4H); MS (ESI, m/z): 310.1 $[M + H]^+$. Anal. calcd. for $C_{15}H_{16}ClNO_2S$ (309.81): C, 58.15; H, 5.21; N, 4.52; S, 10.35; O, 10.33%. Found: C, 58.20; H, 5.25; N, 4.48; S, 10.31; O, 10.29%.

S-(+)-Methyl 2-(2-(Thiophen-3-yl)ethylamino)-2-(2-chlorophenyl)acetate (11a) from 6a and 7

This compound was prepared in a similar way to **11**, using S-(+)-methyl 2-bromo-2-(2-chlorophenyl) acetate, **6a** (25.0 g, 94.85 mmol), and 2-(thiophen-3-yl) ethanamine **7** (12.07 g, 94.85 mmol) as an off-white oily residue (27.0 g, 91.86%); purity 99.39% (by HPLC); SOR $[\alpha]D^{20} + 109.5$ (c 1.61, CH_3OH); MS (ESI, m/z): 310.28 $[M + H]^+$. Anal. calcd. for $C_{15}H_{16}ClNO_2S$ (309.81): C, 58.15; H, 5.21; N, 4.52; S, 10.35; O, 10.33%. Found: C, 58.18; H, 5.25; N, 4.55; S, 10.32; O, 10.30%.

Methyl 2-(2-(Thiophen-3-yl)ethyl amino)-2-(2-chlorophenyl)acetate (11) from 8 and 9

Triethyl amine (38.0 g, 375.69 mmol) and 3-(2-iodoethyl) thiophene **9** (71.55 g, 300.55 mmol) were added to a stirring solution of methyl 2-amino-2-(2-chlorophenyl) acetate **7** (50.0 g, 250.46 mmol) in acetonitrile (200.0 mL) at 25–30 °C and the mass was refluxed for 10–12 h. The reaction mass was completely distilled off under vacuum and the residue was dissolved in dichloromethane (100 mL). The dichloromethane layer was washed with water (100 mL) and distilled off under vacuum to yield **11** as an off-white oily residue (64.3 g, 82.86%); purity 99.56% (by HPLC); IR (KBr, cm^{-1}) 3463, 3071, 2912, 1745, 1521, 1452, 1232, 765; MS (ESI, m/z): 310.12 $[M + H]^+$. Anal. calcd. for $C_{15}H_{16}ClNO_2S$ (309.81): C, 58.15; H, 5.21; N, 4.52; S, 10.35; O, 10.33%. Found: C, 58.18; H, 5.22; N, 4.55; S, 10.34; O, 10.35%.

S-(+)-Methyl 2-(2-(Thiophen-3-yl)ethyl amino)-2-(2-chlorophenyl)acetate (11a) from 8a and 9

This compound was prepared in a similar way to **11**, using S-(+)-methyl 2-amino-2-(2-chlorophenyl)acetate **8a** (22.0 g, 110.20 mmol) and 3-(2-iodoethyl)thiophene **9** (31.48 g, 132.23 mmol) as an off-white oily residue (27.5 g, 80.68%); SOR

$[\alpha]D^{20} + 108.9$ (*c* 1.61, CH_3OH); IR (KBr, cm^{-1}) 3463, 3071, 2912, 1741, 1581, 1585, 1232, 765; MS (ESI, *m/z*): 310.22 $[M + H]^+$. Anal. calcd. for $C_{15}H_{16}ClNO_2S$ (309.81): C, 58.15; H, 5.21; N, 4.52; S, 10.35; O, 10.33%. Found: C, 58.10; H, 5.28; N, 4.59; S, 10.31; O, 10.39%.

4,5,6,7-Tetrahydrothieno[2,3-c]pyridine (10)

Concentrated hydrochloric acid (5 mL) added slowly to a solution of 2-(thiophen-3-yl) ethanamine **7** (100.0 g, 786.1 mmol) in 37% formaldehyde solution (500 mL) at 25–30 °C and the mass was heated at 80–85 °C for 30 min. The mass was cooled to room temperature, neutralized with sodium bicarbonate (24.5 gs), and extracted with dichloromethane (300 mL). The dichloromethane was washed with saturated sodium chloride solution (50 mL) and then with water (2×100 mL). Dichloromethane was distilled off completely under vacuum to yield **10** as a light yellow residue (101.6 g, 92.8%); purity 99.74% (by HPLC); IR (KBr, cm^{-1}) 2924, 2829, 1595, 1490, 1446, 1340; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.0 (s, 1H), 2.7–2.9 (m, 4H), 3.8 (s, 2H), 6.5 (s, 1H), 6.8 (s, 1H); MS (ESI, *m/z*): 139.48 $[M]^+$. Anal. calcd. for C_7H_9NS (139.22): C, 60.39; H, 6.52; N, 10.06; S, 23.03%. Found: C, 60.42; H, 6.55; N, 10.00; S, 23.01%.

Methyl 2-(2-Chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridin-6(7H)-yl)acetate (12) from 6 and 10

Water (150.0 mL) and potassium carbonate (72.37 g, 523.65 mmol) were added to a suspension of methyl 2-bromo-2-(2-chlorophenyl) acetate **6** (46.0 g, 174.55 mmol) in methanol (100.0 mL) and stirred for 10 min at 25 °C. 4,5,6,7-Tetrahydrothieno[2,3-c]pyridine **10** (24.3 g, 174.55 mmol) was added under stirring. Mass was maintained at 60–65 °C for 6 h and then water (150 mL) and dichloromethane (200 mL) were added at 25 °C. The dichloromethane layer was separated and washed with water. Dichloromethane was distilled off completely under reduced pressure to yield **11** as an off-white oily residue (46.17 g, 87.2%); purity 99.37% (by HPLC); IR (KBr, cm^{-1}) 3060, 2951, 1752, 1604, 1588, 1406, 1224, 771; MS (ESI, *m/z*): 322.33 $[M + H]^+$. Anal. calcd. for $C_{16}H_{16}ClNO_2S$ (321.82): C, 59.71; H, 5.01; N, 4.35; S, 9.96; O, 9.94%. Found: C, 59.69; H, 5.06; N, 4.32; S, 9.91; O, 9.98%.

S-(+)-Methyl 2-(2-Chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridin-6(7H)-yl)acetate (12a) from 6a and 10

This compound was prepared in a similar way to **11**, using S-(+)-methyl 2-bromo-2-(2-chlorophenyl) acetate **6a** (23.0 g, 87.27 mmol) and 4,5,6,7-tetrahydrothieno[2,3-c]pyridine **10** (12.1 g, 86.91 mmol) as an off-white oily residue (23.9 g, 85.2%). Purity 99.55% (by HPLC); SOR $[\alpha]D^{20} + 52.58$ (*c* 1.61, CH_3OH); IR (KBr, cm^{-1}) 3060, 2951, 1752, 1604, 1588, 1406, 1224, 771; MS (ESI, *m/z*): 322.48 $[M + H]^+$. Anal. calcd. for $C_{16}H_{16}ClNO_2S$ (321.82): C, 59.71; H, 5.01; N, 4.35; S, 9.96; O, 9.94%. Found: C, 59.74; H, 5.04; N, 4.32; S, 9.90; O, 9.97%.

Methyl 2-(2-Chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridin-6(7H)-yl)acetate (12) from 11

Concentrated hydrochloric acid (0.85 g, 23.24 mmol) was added slowly to a suspension of methyl 2-(2-(thiophen-3-yl)ethyl amino)-2-(2-chlorophenyl)acetate **11** (36.0 g, 116.2 mmol) in 37% formaldehyde solution (288.0 mL) at 25 °C. The reaction mass was maintained at 50–55 °C for 3–4 h. Dichloromethane (100 mL) was added and the mass pH was adjusted to 7.0–7.5 with 10% sodium bicarbonate solution (64 mL). The dichloromethane layer was separated, washed with water (2 × 100 mL), and distilled off under reduced pressure to yield **11** as an off-white oily residue (34.7 g, 92.8%). Purity 99.72% (by HPLC); IR (KBr, cm^{-1}) 3060, 2951, 1750, 1604, 1588, 1406, 1224, 771; MS (ESI, m/z): 322.21 $[M]^+$. Anal. calcd. for $C_{16}H_{16}ClNO_2S$ (321.82): C, 59.71; H, 5.01; N, 4.35; S, 9.96; O, 9.94%. Found: C, 59.70; H, 5.06; N, 4.39; S, 9.92; O, 9.91%.

S-(+)-Methyl 2-(2-Chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridin-6(7H)-yl)acetate (12a) from 11a

This compound was prepared in a similar way to **11**, using S-(+)-methyl 2-(2-(thiophen-3-yl)ethyl amino)-2-(2-chlorophenyl)acetate **11a** (46.0 g, 148.47 mmol) as an off-white oily residue (44.6 g, 93.4%). Purity 99.88% (by HPLC); SOR $[\alpha]D^{20} + 53.01$ (*c* 1.61, CH_3OH); IR (KBr, cm^{-1}) 3060, 2951, 1752, 1604, 1588, 1452, 1224, 771; MS (ESI, m/z): 320.38 $[M\text{-}H]^+$. Anal. calcd. for $C_{16}H_{16}ClNO_2S$ (321.82): C, 59.71; H, 5.01; N, 4.35; S, 9.96; O, 9.94%. Found: C, 59.790; H, 5.02; N, 4.30; S, 10.01; O, 9.99%.

S-(+)-Methyl 2-(2-(Thiophen-3-yl)ethyl amino)-2-(2-chlorophenyl)acetate (11a) from 11

1S-(+)-10-Camphorsulfonic acid (24.0 g, 103.29 mmol) was added at room temperature to a solution of methyl 2-(2-(thiophen-3-yl)ethyl amino)-2-(2-chlorophenyl) acetate **11** (32.0 g, 103.29 mmol) in acetone (50.0 mL). The mass was maintained under stirring at 25–30 °C for 5 h, filtered, and washed with acetone (10 mL). Wet material was refluxed three times in a mixture of acetone (84.0 mL) and methyl ethyl ketone (52.0 mL). The resulting wet material was charged to a stirring solution of dichloromethane (50 mL) and water (30 mL) and the mass pH was adjusted to 8–8.5 with 10% sodium bicarbonate solution (35 mL). The dichloromethane layer was separated and washed with water (2 × 50 mL). The dichloromethane was distilled off completely at reduced pressure to yield **11a** as an almost white residue (12.4 g, 38.7%); purity 99.57% (by HPLC); SOR $[\alpha]D^{20} + 110.42$ (*c* 1.61, CH_3OH); IR (KBr, cm^{-1}) 3463, 3071, 2912, 1741, 1485, 1462, 1232, 765; MS (ESI, m/z): 310.34 $[M + H]^+$. Anal. calcd. for $C_{15}H_{16}ClNO_2S$ (309.81): C, 58.15; H, 5.21; N, 4.52; S, 10.35; O, 10.33%; Found: C, 58.12; H, 5.26; N, 4.59; S, 10.38; O, 10.35%.

S-(+)-Methyl 2-(2-Chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridin-6(7H)-yl)acetate (12a) from 12

To a stirring solution of methyl 2-(2-chlorophenyl)-2-(4,5-dihydrothieno-[2,3-c]pyridin-6(7H)-yl) acetate **12** (40.0 g, 124.29 mmol) in acetone (140.0 mL),

1R-(−)-10-camphorsulfonic acid (23.1 g, 99.43 mmol) was added, and the mixture was stirred at 30–35 °C for 20–24 h. The separated material was filtered and washed with acetone (10 mL). The wet material was charged into a dichloromethane (100 mL) and water (100 mL) mixture and the mass pH was adjusted to 7.5–8.0 with 10% sodium bicarbonate solution (46 mL). The dichloromethane layer was separated and washed with water (2 × 60 mL). Dichloromethane was distilled off completely at reduced pressure to yield **12a** as an almost white residue (12.4 g, 38.7%); purity 99.90% (by HPLC); SOR $[\alpha]D^{20} + 52.58$ (*c* 1.61, CH_3OH); IR (KBr, cm^{-1}) 3060, 2912, 1740, 1604, 1480, 1224, 771; MS (ESI, *m/z*): 322.34 $[M + H]^+$. Anal. calcd. for $C_{15}H_{16}ClNO_2S$ (321.82): C, 59.71; H, 5.01; N, 4.35; S, 9.96; O, 9.94%. Found: C, 59.78; H, 5.02; N, 4.34; S, 9.98; O, 9.95%.

Methyl 2-(2-Chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridine-6(7H)-yl)acetate Hydrochloride (3) from 12

Concentrated hydrochloric acid (13.4 g) was added slowly to a stirring solution of methyl 2-(2-chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridin-6(7H)-yl) acetate **12** (40.0 g, 124.29 mmol) in acetone (200.0 mL) at 25 °C and stirred for 10–12 h. It was filtered, washed with chilled acetone (10 mL), and dried at 40–45 °C under reduced pressure to yield **3** (32.8 g, 73.7%) as an off-white crystalline solid; purity 99.90% (by HPLC); assay 99.50% (by HPLC); IR (KBr, cm^{-1}) 3060, 2963, 1752, 1604, 1588, 1480, 1326, 1224, 771; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.9 (t, $J = 3.3$ Hz, 2H), 3.3 (t, $J = 2.9$ Hz, 2H), 3.7 (s, 3H), 4.3 (s, 2H), 5.4 (s, 1H), 6.9 (d, $J = 5.1$ Hz, 1H), 7.4–7.6 (m, 4H), 7.8 (d, $J = 3.2$ Hz, 1H); ^{13}CNMR (300 MHz, DMSO-d_6): δ 22.7, 48.1, 49.2, 53.3, 64.20, 65.2, 125.0, 126.7, 127.3, 128.1, 128.8, 130.3, 131.7, 132.0, 134.18, 167.4; MS (ESI, *m/z*): 322.2 $[M + H]^+$. Anal. calcd. for $C_{16}H_{17}Cl_2NO_2S$ (358.28): C, 53.64; H, 4.78; N, 3.91; S, 8.95; O, 8.93%. Found: C, 53.60; H, 4.76; N, 3.98; S, 8.92; O, 8.92%.

S-(+)-Methyl 2-(2-Chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridine-6(7H)-yl)acetate Hydrochloride (3a) from 12a

This compound was prepared in a similar way to **3**, using S-(+)-methyl 2-(2-chlorophenyl)-2-(4,5-dihydrothieno[2,3-c]pyridin-6(7H)-yl) acetate **12a** (20.0 g, 62.14 mmol) as an off-white crystalline solid (16.6 g, 74.6%). Purity 99.94% (by HPLC); SOR $[\alpha]D^{20} + 50.06$ (*c* 1.61, CH_3OH); purity 99.94% (by HPLC); assay 99.64% (by HPLC); IR (KBr, cm^{-1}) 3060, 2951, 1752, 1604, 1588, 1461, 1326, 1224, 771; MS (ESI, *m/z*): 321.38 $[M]^+$. Anal. calcd. for $C_{16}H_{17}Cl_2NO_2S$

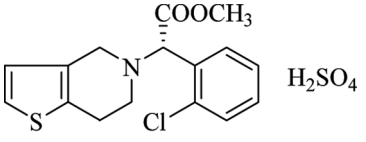


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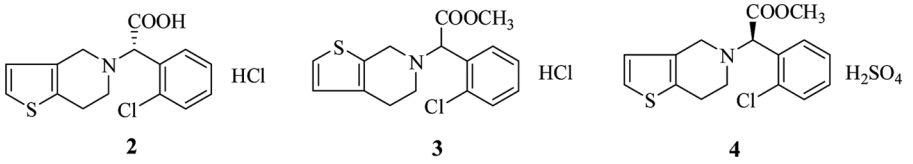
Figure 1.



2 3 4

Figure 2.

(358.28): C, 53.64; H, 4.78; N, 3.91; S, 8.95; O, 8.93%. Found: C, 53.69; H, 4.71; N, 3.95; S, 8.90; O, 8.99%.

REFERENCES

1. Randall, M. D.; Neil, K. E. *Disease Management*, 2nd ed.; Pharmaceutical Press: London, 2004.
2. Simon, T.; Verstuyft, C.; Mary-Krause, M.; Quteineh, L.; Drouet, E.; Méneveau, N.; Steg, P. G.; Ferrières, J. *N. Eng. J. Med.* **2009**, *360*(4), 363.
3. Savi, P.; Zachayus, J. L.; Delesque-Touchard, N. *PNAS* **2006**, *103*(29), 11069.
4. Ho, P. M.; Maddox, T. M.; Wang, L.; Fihn, S. D.; Jesse, R. L.; Peterson, E. D.; Rumsfeld, J. S. *JAMA* **2009**, *301*(9), 937.
5. International Conferences on Harmonization. *Federal Register* **2000**, 65(140), 45085.
6. International Conferences on Harmonization. *Federal Register* **2000**, 65(139), 44791.
7. International Conferences on Harmonization. *Federal Register* **1997**, 62(247), 67377.
8. Alsante, K. M.; Hatajik, T. D.; Lohr, L. L.; Sharp, T. R. *Am. Pharm. Rev.* **2001**, *4*, 70.
9. Lohr, L. L.; Sharp, T. R.; Alsante, K. M.; Hatajik, T. D. *Am. Pharm. Rev.* **2001**, *4*, 55.
10. Winger, B. E.; Kemp, C. A. J. *Am. Pharm. Rev.* **2001**.
11. (a) Wang, L.; Shen, J.; Tang, Y.; Chen, Y.; Wang, W.; Cai, Z.; Du, Z. *Org. Process. Res. Dev.* **2007**, *11*, 487; (b) Xianhua, P.; Haifang, M.; Xihong, L. *Jingxi Huagong* **2006**, *23*(12), 1221; (c) Bousquet, A.; Calet, S.; Heymes, A. U.S. Patent 5, 132, 435, 1992; (d) Bousquet, A.; Musolino, A. U.S. Patent 5, 036, 156, 1991.
12. (a) Alian Badore, R.; Daniel Frehel, T. U.S. Patent 4,874,265, 1989; (b) Aubert, D.; Ferrand, C. FR 2,530,247 B1, 1984; (c) Castro, B.; Dormoy, J.; Previero, A. U.S. Patent 6,080,875, 2000.
13. Marcel Descamps, L.; Joel Radisson, T. U.S. Patent 5,204,469, 1993.
14. (a) Blicke, F. F.; Burckhalter, J. H. *J. Am. Chem. Soc.* **1942**, *64*(3), 477; (b) Kenneth, J. B.; Scott, C. B.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*(15), 4323.