Supplementary Information

CONCISE SYNTHESIS OF (±)-CLOPIDOGREL VIA INSERTION OF CO₂ AT THE BENZYLIC POSITION

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1. General information

Every reactions were carried out under the nitrogen atmosphere. Unless otherwise stated, all the chemicals and reagents were obtained commercially. Dry solvents were prepared by the standard procedures. Analytical Thin Layer Chromatography was done on pre-coated silica gel plates (Kieselgel 60F₂₅₄, Merck). Column chromatographic purifications were done with 230-400 Mesh Silica gel. NMR spectra were recorded in CDCl₃ on AV 200, AV 400 MHz Bruker NMR spectrometers. All chemical shifts are reported in ppm downfield to TMS and peak multiplicities are referred to as singlet (s), doublet (d), quartet (q), and multiplet (m). Elemental analyses were performed on an Elmentar-Vario-EL (Heraeus Company Ltd., Germany). IR spectra were recorded in CHCl₃ using Shimadzu FTIR-8400

spectrophotometer. LC-MS was carried out on Thermo Finnigan Surveyor MSQ LC-MS instrument.

2. EXPERIMENTAL SECTION

N-(2-chlorobenzyl)-2-(thiophen-2-yl)ethan-1-amine (5)

To a stirred solution of 2-chlorobenzaldehyde (3 g, 21.36 mmol) in CH₂Cl₂ (60 mL), was added 2-(thiophen-2-yl)ethan-1-amine (3.3 g, 25.63 mmol) in CH₂Cl₂ (15 mL) and anhyd. Na₂SO₄ at 25 °C. The reaction mixture was allowed to stir at the same temperature for 30 min. This was followed by the addition of MeOH (30 mL) and NaBH₄ (2 g, 53.4 mmol) at 0 °C and this mixture was allowed to stir for 30 min. It was then quenched with sat. NH₄Cl solution. The solvents were evaporated in rotavapour and the residue extracted with CH₂Cl₂ (3 x 60 mL). The combined organic layers were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give the crude benzylamine. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc/Et₃N (70:25:5) gave benzylamine **5** (4.9 g) as a yellow liquid.

Yield: 4.9 g, 92%; **IR** (CHCl₃, cm⁻¹): $\nu_{\max}$ 3440, 3331, 2912, 2826, 1471, 1441, 1049, 1037, 752, 696; **¹H NMR** (200 MHz, CDCl₃): δ 1.61 (br s, 1H), 2.84-2.98 (m, 2H), 2.99-3.11 (m, 2H), 3.89 (s, 2H), 6.78-6.85 (m, 1H), 6.86 - 6.96 (m, 1H), 7.11 (dd, J = 5.1, 1.1 Hz, 1H), 7.15 - 7.26 (m, 2H), 7.28 - 7.40 (m, 2H); **¹³C NMR** (50 MHz, CDCl₃): δ 30.4, 50.3, 50.9, 123.4, 124.9, 126.7, 128.1, 129.4, 129.9, 133.6, 137.5, 142.3; **Analysis:** C₁₃H₁₄ClNS required C, 62.02; H, 5.61; N, 5.56; S, 12.73; found: C, 61.89; H, 5.72; N, 5.71; S, 12.65%.

tert-Butyl-(N-2-chlorobenzyl)-(N'-2-(thiophen-2-yl)ethyl) carbamate (6)

To a solution of the benzyl amine **5**, (2.3 g, 9 mmol), triethylamine (1.38 mL, 9.93 mmol), and DMAP (0.6 g, 4.51 mmol) in dry CH₃CN (20 mL), was added (Boc)₂O (3.9 g, 18 mmol) in dry CH₃CN (10 mL) under nitrogen at 0 °C, and the mixture was allowed to warm to room

temperature and stirred for 7 h. The reaction mixture was then quenched with water and the solvent was evaporated and the crude product was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/EtOAc (95:5) gave carbamate **6** (2.7 g) as a colorless liquid.

Yield: 2.7 g, 85%; **IR** (CHCl₃, cm⁻¹): $\nu_{\max}$ 3019, 2981, 2839, 2400, 1698, 1612, 1585, 1368, 1216, 1035, 1167; **¹H NMR** (500 MHz, CDCl₃): δ 1.41 (brs, 4H), 1.49 (brs, 5H), 3.00 (brs, 1H), 3.07 (brs, 1H), 3.41 (brs, 1H), 3.49 (brs, 1H), 4.45 (brs, 1H), 4.55 (brs, 1H), 6.75 (brs, 1H), 6.89 (dd, J = 5.0, 3.5 Hz, 1H), 7.10 (d, J = 5.2 Hz, 1H), 7.16 - 7.29 (m, 3H), 7.33 (d, J = 7.6 Hz, 1H); **¹³C NMR** (125 MHz, CDCl₃): δ 28.4, 29.0, 47.6, 48.9, 49.1, 49.2, 76.7, 77.3, 80.0, 96.2, 123.7, 125.2, 126.9, 128.0, 128.3, 128.4, 129.1, 129.5, 133.0, 133.4, 135.7, 135.9, 141.1, 155.3, 155.6; **Analysis:** C₁₈H₂₂ClNO₂S required C, 61.44; H, 6.30; N, 3.98; S, 9.11; found: C, 61.26; H, 6.01; N, 3.79; S, 9.02%.

Methyl-2-((*tert*-butoxycarbonyl)(2-(thiophen-2-yl)ethyl)amino)-2-(2-chlorophenyl)acetate (7)

To a stirred solution of carbamate **6** (1.5 g, 4.3 mmol) in dry THF, was added *n*-BuLi (2.96 mL, 4.7 mmol) dropwise at -78 °C under N₂ atmosphere for 15 min. CO₂ (1 atm) gas was bubbled through the reaction mixture and allowed to stir for 3 h until it formed the pale yellow turbid solution. This was followed by the addition of NaHCO₃ (540 mg, 6.39 mmol) and MeI (1.5 g, 10.65 mmol) in DMF and stirred for further 3 h at 25 °C. The reaction mixture was quenched with sat. NH₄Cl solution and the solvent was evaporated under reduced pressure. The obtained crude mixture was extracted with EtOAc (3 × 15 mL) and washed with brine (3 × 10 mL). The combined organic extracts were dried over anhyd. Na₂SO₄ and concentrated. Silica gel column chromatographic purification of the crude

product using petroleum ether/EtOAc (90:10) as eluent gave α -amino ester **7** (1.13 g) as a colorless liquid.

Yield: 1.13 g, 65%; **IR** (CHCl_3 , cm^{-1}): ν_{max} 2977, 1751, 1696, 1398, 1367, 1304, 1251, 1214, 1169, 966, 756; **^1H NMR** (200 MHz, CDCl_3): δ 1.51 (s, 9H), 2.32-2.35 (m, 1H), 3.01-3.04 (m, 1H), 3.15-3.23 (m, 1H), 3.38-3.53 (m, 1H), 3.79 (s, 3H), 6.13 (brs, 1H), 6.52 (brs, 1H), 6.78-6.82 (m, 1H), 7.01 (d, $J = 4.9$ Hz, 1H), 7.22-7.35 (m, 3H), 7.43 - 7.48 (m, 1H); **^{13}C NMR** (50 MHz, CDCl_3): δ 28.3, 29.5, 47.6, 52.2, 60.0, 60.8, 80.5, 96.0, 123.2, 124.6, 126.6, 126.9, 130.0, 133.1, 135.4, 141.1, 154.4, 155.3, 170.8; **LCMS (ESI, m/z)**: Calculated for $\text{C}_{20}\text{H}_{24}\text{ClNO}_4\text{SNa}$ ($\text{M}+\text{Na}$) $^+$ 432.1, found 432.13; **Analysis**: $\text{C}_{20}\text{H}_{24}\text{ClNO}_4\text{S}$ required C, 55.49; H, 5.59; N, 3.24; S, 7.41; found: C, 55.38; H, 5.46; N, 3.15; S, 7.37%.

methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate ($\pm$)-

Clopidogrel (1)

To a solution of α -amino ester **7** (435 mg, 1.06 mmol) in dry CH_2Cl_2 was added trifluoroacetic acid (0.25 mL, 3.2 mmol) and kept under stirring for 4 h at room temperature. Subsequently, paraformaldehyde (38 mg, 1.3 mmol) was added to the above reaction mixture and allowed to stir for 24 h at room temperature. It was then quenched with sat. NaHCO_3 solution at 0 $^\circ\text{C}$ and further stirred for 10 min followed by organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic extracts were washed with water (2×10 mL) and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatographic purification of the crude product using petroleum ether/ EtOAc gave ($\pm$)-clopidogrel **1** (0.24 g) as a pale yellowish liquid.

Yield: 0.24 g, 70%; **IR** (CHCl_3 , cm^{-1}): ν_{max} 2977, 1741, 1654, 1434, 1203, 1167, 1042, 755; **^1H NMR** (200 MHz, CDCl_3): δ 2.88 (brs, 4H), 3.53 - 3.78 (m, 5H), 4.89 (s, 1H), 6.65 (d, $J = 5.2$ Hz, 1H), 7.04 (d, $J = 5.2$ Hz, 1H), 7.22 - 7.25 (m, 1H), 7.28 - 7.32 (m, 1H), 7.35 - 7.44 (m, 1H), 7.56 - 7.80 (m, 1H); **^{13}C NMR** (50 MHz, CDCl_3): δ 25.5, 48.3, 50.7, 52.1, 67.7,

76.4, 77.6, 96.2, 122.8, 125.2, 127.2, 129.4, 129.8, 130.0, 133.1, 133.8, 134.7, 171.0;

Analysis: $\text{C}_{16}\text{H}_{16}\text{ClNO}_2\text{S}$ required C, 59.72; H, 5.01; N, 4.35; S, 9.96; found: C, 59.61; H, 4.95; N, 4.15; S, 9.76%.

3. SPECTRA

Fig. 1: ¹H and ¹³C NMR spectra of N-substituted-2-chloro benzylamine **5**

Fig. 2: ¹H and ¹³C NMR spectra of Boc-carbamate 6

VV-CO2 #7-25 RT: 0.11-0.42 AV: 19 SB: 14 0.42-0.54 0.00-0.09 NL: 2.74E6
T: {0,0} + c ESI corona sid=40.00 det=1600.00 Full ms [100.00-1500.00]

Fig. 3: ^1H , ^{13}C NMR, IR and Mass spectra of α -aminoester **7**

Fig. 4: ¹H, ¹³C NMR spectra of (±)-clopidogrel (±)-1