Asian Journal of Chemistry; Vol. 32, No. 12 (2020), 3007-3011

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22881

Diversity and Oriented Synthesis of Clopidogrel Drug Derivatives

D. TEJESWARARAO

Department of Basic Science & Humanities, GMR Institute of Technology, GMR Nagar, Rajam-532127, India

Corresponding author: E-mail: tejeswararao.d@gmrit.edu.in

Received: 3 July 2020; *Accepted*: 20 August 2020; *Published online*: 7 December 2020; AJC-20131

An efficient synthetic route has been developed for the synthesis of new clopidogrel drug derivatives. Key step of this method is to replacement of mesyl protected alcohol group with various aliphatic amines in presence of base. Various clopidogrel drug derivatives have been prepared in good yields. All the new compounds were confirmed by spectral studies and mass analysis. The main advantage of the new synthetic route has low cost and is fit for industrial applications.

Keywords: Clopidogrel, Antithrombotic, Antiaggregant, Antiplatelet.

INTRODUCTION

As a new method for drug discovery and improvement, now a days cognizance on drug reprofiling as a way to become aware of new treatments for illnesses. In this approach, the actions of existing medicines [1], whose safety and pharmacokinetic outcomes in people have already been showed clinically and authorized for use, are tested comprehensively on the molecular stage and the consequences used for the improvement of latest drug treatments [2]. This process is based on the information that we still do not understand the underlying mechanisms of motion of many present drug treatments [3] and as such the mobile responses that supply upward thrust to their major consequences and aspect consequences are yet to be elucidated. To this extent, identity of the mechanisms underlying the side results of drugs gives a way for us to broaden safer tablets [4]. The outcomes can also be used for growing present pills to be used as drug treatments for the remedy of other sicknesses. Promoting this studies approach ought to offer breakthroughs in drug discovery and development [5].

To acquire this outcome, huge amounts of money had been invested to sell drug discovery and improvement [6]. Furthermore, to be able to increase the performance of drug discovery and improvement, principal pharmaceutical organizations have time and again merged with every other, and novel techniques for drug discovery, which includes genomic drug discovery [7], excessive throughput screening and combinatorial chemistry were installed. At the same time as it changed into consequently notion that the start of the 21 century might be heralded with the aid of an avalanche of new drugs coming onto the market, the quantity of medication reaching the marketplace has decreased year with the aid of year, which is because surprising facet consequences and bad pharmacokinetics [8-10] of ability drugs are being discovered at diverse degrees of scientific trials, accordingly rendering the medicine no longer healthy to be used on humans [11-13]. A big proportion of developable drugs (high safety and appropriate pharmacokinetics) [14,15] have simply already been discovered. However, a new strategy is required for drug discovery and improvement, which specializes in the use of present drug treatments; in other words, to rent a drug re-profiling method [16-19].

Palvix is a popular brand name for (*S*)-clopidogrel, is a powerful oral antiplatelet drug frequently utilized to work against coronary conduit, fringe vascular and cerebrovascular illness [20]. Clopidogrel bisulfate (Palvix), is the subsequent smash hit sedate on the planet, with worldwide deals of $9.1 billion in 2007 [21]. Clopidogrel is the best medicine to control heart diseases, particularly patients who suffer with heart diseases, contemporary stroke, or blood circulation ailment (peripheral vascular disease). It is commonly known as an anti-platelet drug and always improves blood flow rate steadily in internal organ parts. For severe heart attack and unstable angina (poor blood flow rate to heart), physicians may suggest this drug along with aspirin (pain killer). This combination maintains a uniform blood flow rate in vessels and stop blood clots.

In this work, different basic changes in clopidogrel have been done in order to discover a new manufactured subordinates with advanced exercises. A prolonged aliphatic chain is modified and the presentation of aliphatic amines by utilizing changing hydroxyl gathering, while at the same time protecting 6,7-dihydrothieno[3,2-*c*]pyridine as a structure.

EXPERIMENTAL

All the required chemicals and solvents were procured from Aldrich and Lancaster and utilized without further purification. To monitor the reaction conditions, thin layer chromatography (SI-TLC) commercial silica gel sheets and silica gel F_{254} on Al (Aluminium) sheets Merck were used. An Agilent Resolutions Pro FT-IR spectrometer was used to identify the functional groups in the synthesized compounds using KBr pellets. Open capillary tubes were used to determine the melting points and are uncorrected. Waters Micromass Q-Tof micro instrument was used to record the mass spectra of these new clopidogrel drug derivatives. Bruker Avance III 600 NMR spectrometer was used to get the ^{1}H & ^{13}C NMR (DMSO and $CHCl_3$-d_6) spectra. Elemental analysis was done by using Perkin-Elmer 2400. Completion of all the reactions were checked by using silica gel SI-TLC plates (coated with SI-TLC grade silica gel, purchased from Merck). Here the detecting agents for thin layer chromatography were (i) iodine vapors (Iodine in silica gel mixture in iodine flask), (ii) PMA charing solution followed by heating at 150 ºC. Purification of mixture by column chromatography was performed over 60-120 particle size Merck silica and used 230-400 mesh size silica for flash chromatography.

Synthesis of (*S*)-1-phenylethane-1,2-diol (2): In nitrogen atmosphere, (*S*)-2-hydroxy-2-phenylacetic acid (**1**), (2 g, 13.15 mmol) was completely dissolved in THF (15 mL) in a dried two-necked flask. To this, added $BH_3{\cdot}Me_2S$ complex in THF at 0 ºC slowly by dropwise and then the reaction mixture was stirred for 30 min until the clear solution obtained. Formation of (*S*)-1-phenylethane-1,2-diol was confirmed by thin layer chromatography (SI-TLC), the reaction mixture was concentrated by rotary evaporation to afford a thick liquid. Before dilution with water, a solution of K_2CO_3 was added and the mixture was kept for 30 min under stirring. Pure distilled ethyl acetate was added to extract the reaction mixture from aqueous layer. Now the organic layer was dried over sodium sulphate. To isolate the pure compound by silica gel column the organic solvent hexane-ethyl acetate was evaporated at 40 ºC by rotary evaporator. 20% ethyl acetate in hexane was utilized to elute the pure white solid compound **2**. m.p.: 64 ºC; ^{1}H NMR ($CHCl_3$-d_6, 300 MHz) δ (ppm) 7.30 (m, 5H), 4.76 (dd, H, J_1 = 5.1 Hz, J_2 = 7.0 Hz), 3.84 (brs, 2H, OH), 3.69 (d, H, J = 5.0 Hz), 3.62 (d, H, J = 7.1 Hz); ^{13}C NMR ($CHCl_3$-D, 50 MHz) δ (ppm): 140.58, 128.55, 127.96, 126.18, 74.79, 68.05.

(*S*)-2-Hydroxy-2-phenylethyl 4-methylbenzenesulfonate (3): Under N_2 atmosphere, (*S*)-1-phenylethane-1,2-diol (**2**, 1 g, 1 equiv.) was completely liquefied in 18 mL CH_2Cl_2 in a dried two-necked flask. The reaction mixture was stirred at room temperature until compound **2** was completely disappeared on SI-TLC (thin layer chromatography). Formation of (*S*)-2-hydroxy-2-phenylethyl-4-methylbenzene sulfonate was confirmed by Si-TLC, the reaction mixture was concenterated by rotary evaporation at 20 ºC to afford a thick liquid. Before dilution with distilled water, a solution of NaCl was added and the mixture was kept for 25 min under stirring. Pure distilled ethyl acetate was added to extract the reaction mixture from the aqueous layer. Now the layer was dried over sodium Sulphate. To isolate the pure compound by silica gel column then by using RV the organic layer was removed at 35 ºC. About 20% ethyl acetate in hexane was utilized to elute a milky white solid compound **3** with 88% yield. m.p.: 67 ºC; ^{1}H NMR (300 MHz, $CHCl_3$-d_6) δ (ppm): 2.46 (s, 3H), 2.53-2.62(bs, 1H), 3.92-4.02 (m, H), 4.09-4.15 (m,H), 4.96 (dd, 1H, $J_{1,2}$ = 3.02, $J_{1,3}$ = 8.30, 7.23-7.36 (m,7H), 7.78 (d, 2H, J = 8.30); MS (ESI) *m/z* 292 $(M)^+$.

(*S*)-2-(4,5-Dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)-1-phenylethanol (4): Dissolved (*S*)-2-hydroxy-2-phenylethyl 4-methylbenzenesulfonate (**3**, 1 g, 3.42 mmol) and (4-7TDP·HCl) (596 mg, 3.43 mmol) in 15 mL of Et_3N and stirred the mixture for 4 h at 80 ºC. After product formation which was shown by SI-TLC, the reaction mixture was concentrated by rotary evaporation to afford a thick liquid. To this reaction, mixture was added in brine solution and kept for 20 min under stirring. Pure distilled ethyl acetate was added to extract the reaction mixture from the aqueous layer. Now the layer was dried over Na_2SO_4. To isolate the pure compound by silica gel column by using rotary evaporator, the organic layer was removed at 35 ºC. About 20% ethyl acetate in hexane was utilized to elute a milky white solid compound **4** with 90% yield. ^{1}H NMR (300 MHz, $CHCl_3$-d_6) δ (ppm): 2.57-2.71 (m, H), 2.74 (d, H, J = 3.78), 2.76-2.89 (m, H), 2.91-2.97 (m, 2H), 3.10-3.16 (m, H), 3.63 (d, H, J = 14.35), 3.85 (d, H, J = 14.35), 4.84 (dd, $J_{1,2}$ = 3.77, $J_{1,3}$ = 10.57), 6.75 (d, H, J = 4.53), 7.12 (d, H, J = 5.29), 7.23-7.48 (m, 5H); ^{13}C NMR ($CHCl_3$-D, 75 MHz) δ (ppm): 25.16; 29.61; 50.76; 52.80; 65.24; 69.15; 122.88; 125.09; 125.79; 127.48; 128.32; 133.12; 141.91; MS (ESI) *m/z* 260 $(M+H)^+$; HRMS calcd. for $C_{15}H_{18}NOS$: $(M+H)^+$ 260.1109; found: 260.1107.

1-((*S*)-2-(4,5-Dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)-1-phenylethyl)pyrrolidine-2-carboxamide (6a): Compound **5** was synthesized by adding mesyl chloride (MsCl) in diisopropylamine to a solution of compound **4** in methylene chloride at 0 ºC. Then continue the stirring the mixture at room temperature for 50 min. Then follow the standard work up process to isolate the compound **5**. L-Prolinamide dissolved in triethylamine was added to compound **5** and then refluxed this mixture at 80 ºC for 4 h. After successful completion of the reaction, the reaction mixture was concentrated by rotary evaporation to afford a thick liquid. Added brine solution to the reaction mixture was kept for 20 min under stirring. Pure distilled ethyl acetate was added to extract the reaction mixture from aqueous layer. Now the layer was dried over sodium sulphate. To isolate the pure compound by silica gel column by using rotary evaporator the organic layer was removed at 35 ºC. About 25% ethyl acetate in hexane was utilized to elute a milky white solid compound **6a** with 88% yield (**Scheme-I**). m.p.: 85-88 ºC; [α]$_D$ +14º (0.6c, CH$_3$OH); ^{1}H NMR (300 MHz, CHCl$_3$-D) δ (ppm): 2.70 (dd, 1H, $J_{1,2}$ = 4.53, $J_{1,3}$ = 12.84); 2.78-3.00 (m, 6H); 3.12-3.23 (m, 2H); 3.40 (t, 1H, J = 6.80); 3.50-3.61 (m, 2H); 3.82 (d, 1H, J = 14.35); 4.17 (dd, 1H, $J_{1,2}$ = 4.53, $J_{1,3}$ = 10.57); 4.57-4.67 (m, 1H); 5.46-5.60 (bs, 1H); 6.75 (d, H, J = 4.53); 7.10 (d, 1H, J = 4.53); 7.23-7.40 (m, 5H); 8.32-8.55 (bs, 2H); ^{13}C NMR (CHCl$_3$-d_6, 50 MHz) δ (ppm) 17.62, 24.24, 25.29, 27.46, 31.09, 50.95, 52.37, 52.78, 59.79, 61.08, 61.97, 122.78, 125.15, 127.65, 128.40, 133.21, 133.37, 138.18, 179.92; MS(ESI) *m/z* 356 (M+H)$^+$.

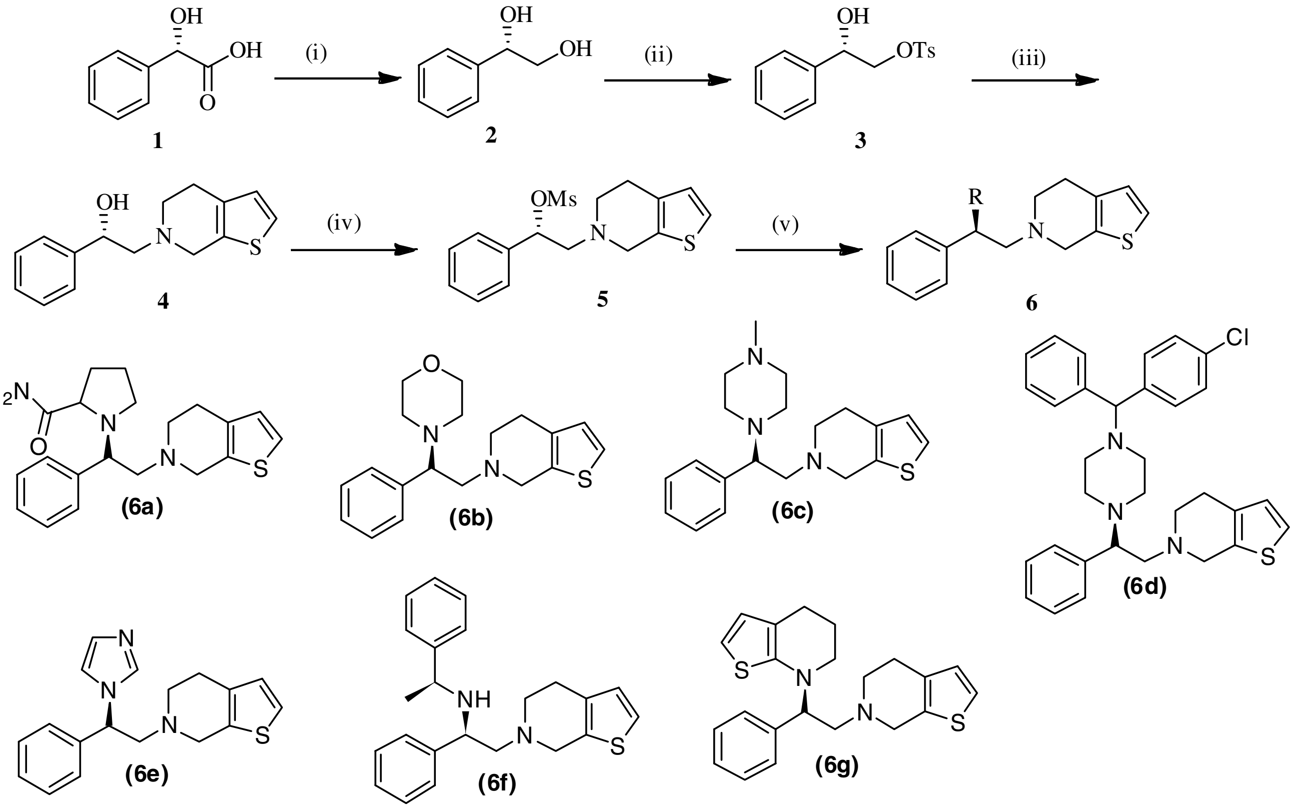
(*S*)-4-(2-(4,5-Dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)-1-phenylethyl)morpholine (6b): m.p.: 90-93 ºC; [α]$_D$ +19º (0.5c, CHCl$_3$); ^{1}H NMR (300 MHz, CHCl$_3$CHCl$_3$-d_6) δ (ppm): 2.34-2.47 (m, 2H), 2.48-2.59 (m, 2H), 2.73-2.87 (m, 5H), 3.11-3.16 (m, H), 3.53-3.66 (m, 7H), 6.63 (d, H, J = 5.33), 7.00 (d, H, J = 5.33), 7.23-7.32 (m, 5H); ^{13}C NMR (CHCl$_3$-D, 75 MHz) δ (ppm) 24.13, 29.67, 31.90, 50.79, 51.14, 52.95, 66.51, 67.99, 123.27, 125.13, 128.03, 128.52, 128.66, 128.77, 132.73; MS (ESI) *m/z* 329 (M+H)$^+$.

(*S*)-6-(2-(4-Methylpiperazin-1-yl)-2-phenylethyl)-4,5,6,7-tetrahydrothieno[2,3-c] pyridine (6c): m.p.: 105-108 ºC; [α]$_D$ +24.4º (0.6c, CH$_3$OH); ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 2.14 (s, 3H); 2.36-2.50 (m, 2H), 2.55-2.59 (m, 2H), 2.72-2.90 (m, 5H), 3.14-3.16 (m, 1H), 3.53-3.66 (m, 7H), 6.63 (m, 1H), 7.05-7.15 (m, 3H), 7.25-7.35 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 24.24, 29.76, 30.89, 44.22, 50.88, 51.22, 52.56, 67.01, 67.98, 123.09, 124.93, 128.10, 128.02, 127.78, 128.07, 132.24; MS (ESI) *m/z* 342(M+H)$^+$; HRMS calcd. for $C_{20}H_{28}N_3S$: (M+H)$^+$ 342.1378 ; found: 342.1373.

6-((2*S*)-2-(4-((4-Chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2-phenylethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (6d): m.p.: 85-87 ºC; [α]$_D$ +57.2º (0.6c, CH$_3$OH); ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 2.65-2.85 (m, 4H), 2.73-2.80 (m, 4H), 3.15 (t, 2H), 3.33 (d, 2H), 3.44 (t, 2H), 4.14 (t, 1H), 4.20 (s, 2H), 5.14 (s, 1H), 4.65 (d, J = 3.23, 1H), 7.17 (m, 2H), 7.26 (m, 1H), 7.33 (d, 2H), 7.37 (m, 9H), 7.23-7.49 (m, 6H), 7.62-7.83 (m, 3H), 8.03 (s,1H), 9.64 (br, 2H); ^{13}C NMR (CDCl$_3$, 50 MHz) δ (ppm): 22.5, 40.5, 41.9, 46.5, 53.2, 54.6, 59.2, 84.5, 126.2, 128.2, 129.2, 129.3, 129.6, 131.8, 140.8, 142.7, 144.2, 149.5; MS (ESI) *m/z* 528(M+H)$^+$; HRMS calcd. for $C_{32}H_{34}N_3SCl$: (M+H)$^+$ 528.4564; found: 528.3356.

(*S*)-6-(2-(1*H*-Imidazol-1-yl)-2-phenylethyl)-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (6e): m.p.: 60-62 ºC; [α]$_D$ +50.2º (0.6c, CH$_3$OH); ^{1}H NMR (200 MHz, CHCl$_3$-D) δ (ppm): 2.62-2.85 (m, 5H), 3.01-3.16 (m, 2H), 3.94 (d, J = 3.23, 1H), 4.65 (d, J = 3.23, H), 4.52-4.63 (m, H), 6.13 (dd, H, $J_{1,2}$ = 4.51, $J_{1,3}$ = 10.63), 6.59 (d, H, J = 5.23), 7.12 (d, H), 7.26-7.49 (m, 6H), 7.62-7.83 (m, 3H); ^{13}C NMR (CHCl$_3$-d_6, 50 MHz) δ (ppm): 22.31, 57.80, 58.03, 62.41, 64.38, 112.41, 119.32, 120.06, 125.92, 128.09, 128.59, 128.84, 132.19, 144.63; MS (ESI) *m/z* 310(M+H)$^+$; HRMS calcd. for $C_{18}H_{20}N_3S$: (M+H)$^+$ 310.1378; found: 310.1373.

(*R*)-2-(4,5-Dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)-1-phenyl-*N*-((*S*)-1-phenylethyl)ethanamine (6f): m.p.: 101-103 ºC; [α]$_D$ +68.9º (0.5c, CHCl$_3$); ^{1}H NMR (200 MHz, CHCl$_3$-D):

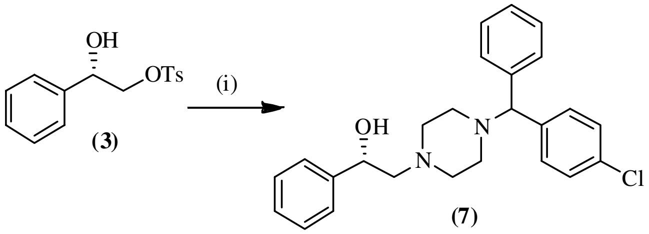


Scheme-I: Reagents and conditions: (i) BH$_3$.Me$_2$S, THF, 0 °C, RT; (ii) TsCl, Et$_3$N, tributyltin oxide, CH$_2$Cl$_2$, 0 °C, RT; (iii) 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine hydrochloride (4-7TDP·HCl), Et$_3$N, Reflux, 75-80 °C, 4 h; (iv) MsCl, diisopropyl amine, 0 °C, RT; (v) R-H, Et$_3$N, reflux, 75-80 °C, 50 min, 5 h

α (ppm) 1.34 (d, 3H, $J = 6.80$), 2.33 (dd, 1H, $J_{1,2} = 3.21$, $J_{1,3} = 12.27$), 2.52-2.73 (m, 3H), 2.76-2.97 (m, 2H), 3.30-3.39 (m, 2H), 3.41-3.50 (m, 2H), 6.61 (d, 1H, $J = 5.10$), 7.04 (d, 1H, $J = 5.10$), 7.09 (d, 2H, $J = 6.61$), 7.15-7.34 (m, 8H); ^{13}C NMR ($CHCl_3$-d_6, 50 MHz) δ (ppm): 24.33, 25.49, 29.70, 50.70, 52.86, 54.75, 56.52, 122.45, 125.19, 126.45, 126.77, 127.21, 128.29, 128.37, 133.31, 133.81; MS (ESI) *m/z* 363 (M+H)$^+$; HRMS calcd. for $C_{23}H_{27}N_2S$: (M+H)$^+$ 363.1895; found: 363.1893.

(*S*)-6-(2-(5,6-Dihydrothieno[2,3-*b*]pyridin-7(4*H*)-yl)-2-phenylethyl)-4,5,6,7-tetrahydrotheno[2,3-*c*]pyridine (6g): ^{1}H NMR (500 MHz, $CHCl_3$-D) δ (ppm): 2.70-2.83 (m, 7H), 2.88 (dd, 2H, $J_{1,2} = 5.94$, $J_{1,3} = 13.86$), 3.16 (dd, $J_{1,2} = 5.94$, $J_{1,3} = 12.87$); 3.53-3.70 (m, 4H), 3.85 (t, 1H, $J = 5.93$), 6.61 (dd, 2H, $J_{1,2} = 4.95$, $J_{1,3} = 9.90$), 6.97(dd, 2H, $J_{1,2} = 4.95$, $J_{1,3} = 10.89$), 7.19-7.37 (m, 5H); ^{13}C NMR ($CHCl_3$-d_6, 75 MHz) δ (ppm): 25.17, 25.77, 29.65, 47.95, 50.58, 51.10, 53.47, 60.92, 66.91, 122.38, 122.41, 125.20, 125.32, 127.17, 128.15, 128.39, 133.29, 133.35, 133.78, 134.09, 140.15; MS (ESI) *m/z* 381(M+H)$^+$; HRMS calcd. for $C_{22}H_{25}N_2S_2$: (M+H)$^+$ 381.1381; found: 381.1380.

Synthesis of (1*S*)-2-(4-((4-chlorophenyl)(phenyl)methyl)-piperazin-1-yl)-1-phenylethanol (7): Dissolved (*S*)-2-hydroxy-2-phenylethyl 4-methylbenzenesulfonate (**3**, 1 g, 3.42 mmol) and 1-((4-chlorophenyl)(phenyl)methyl)piperazine (665 mg, 3.43 mmol) in 15 mL of triethylamine and stirred the solution for 4 h at 85 ºC. Subsequently the product formation which was shown by SI-TLC, the reaction mixture was concentrated by rotary evaporation to afford a thick liquid. To this thick liquid added water (10 mL) and kept under stirring for 20 min and added pure distilled EtOAc (3 × 100 mL) to extract product from aqueous layer. The organic layer was washed with water (4 × 75 mL) and with saturated brine (50 mL), dried by adding $MgSO_4$. To isolate the pure composite by silica gel column the organic solvent, ethyl acetate was vaporized by RV. About 20% ethyl acetate in hexane was utilized to elute a yellow solid compound **7** with 85% yield (**Scheme-II**). ^{1}H NMR (300 MHz, $CHCl_3$-D) δ (ppm): 1.79-1.98 (bs, 2H), 2.68-2.86 (bs, H), 3.09-3.25 (bs, H), 3.25-3.75 (m, 5H), 4.76 (dd, 3H, $J_{1,2} = 3.02$, $J_{1,3} = 8.30$), 7.21-7.36 (m, 14H); ^{13}C NMR ($CHCl_3$-d_6, 75 MHz) δ (ppm): 40.84, 53.64, 126.35,127.55, 128.95, 129.05, 129.58, 132.05, 140.55, 143.06; MS (ESI) *m/z* 407(M+H)$^+$.



Scheme-II: Reagents and conditions: 1-((4-chlorophenyl)(phenyl)methyl)-piperazine hydrochloride, Et_3N, Reflux, 75-80 °C, 4 h

RESULTS AND DISCUSSION

As shown in **Scheme-I**, the designed synthetic route began with reduction of commercially available (+)-(*S*)-mandelic acid (**1**) with borane-dimethyl sulfide afforded the corresponding (*S*)-1-phenylethane-1,2-diol (**2**). Compound **2** was confirmed by spectral data showing characteristic peaks and its ESI-MS showed 292(M)$^+$ further confirming the structure. The selective primary tosyl-protection of compound **3** was synthesized by treatment of *p*-toluenesulfonic acid (pTSA) in presence of tributyltin oxide and triethylamine with compound **2**, which was confirmed by ^{1}H NMR and ESI-MS spectra.

Compound **4** was synthesized by nucleophilic substitution of compound (*S*)-2-hydroxy-2-phenylethyl-4-methylbenzenesulfonate by 4-7TDP·HCl in presence of triethylamine. Both compounds **3** and 4-7TDP·HCl were dissolved in triethyl amine. To isolate compound **4**, different work up processes was followed, where addition of water to reaction mixture gave 75% yield, whereas addition ice to reaction mixture gave 90% of yield. Compound **5** was synthesized by adding methanesulfonyl chloride to a solution of (*S*)-2-(4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)-1-phenylethanol in anhydrous pyridine and diisopropylamine at 0 ºC. After standard workup procedure, compound **5** was separated from reaction mixture by using column chromatography on silica gel.

Finally, the synthetic approach for 1-((S)-2-(4,5-dihydrothieno[2,3-*c*]pyridin-6(7*H*)-yl)-1-phenylethyl)pyrrolidine-2-carboxamide from compound **5** and L-proline. Herein, the reaction mechanism involves nucleophilic substitution S_N^2. To isolated the expected compound added ice and CH_2Cl_2 to the reaction mixture. By using column chromatography separated compound **6a**. To investigate the best conditions for this reaction, various other bases *viz.* K_2CO_3, pyridine, NaOH, KOH, $Ba(OH)_2$ were also investigated.

The molecular structures of the quinazoline compounds were identified by FTIR, 1H NMR, Carbon-13 NMR, ESI-MS and elemental analysis. The peak at 2900-3055 cm^{-1} in IR spectrum confirmed the presence of carbon hydrogen bond, peak at 1590-1560 cm^{-1} evidenced the presence of alkene (C=C) bond and 1214 cm^{-1} stretching showed the presence of C-N bond. All compounds exhibit the same peak at 1214 cm^{-1} which evidenced the presence of tertiary amine functional group. Absorption band in the range between 3600-3100 cm^{-1} indicated the presence of -$CONH_2$ in compound **6a**. In the same way, remaining compounds were confirmed by ^{1}H & ^{13}C NMR and mass analyses. Singlet at δ 2.14 ppm indicates the presence of -CH_3, which evidenced the formation of compound **6c**. Compound **6e** was confirmed by the the strong signal 310 (ESI-Ms) in mass spectra. Appearance of 363 in the mass spectra and exhibited doublet at δ 1.33 ppm of -CH_3 and respective peaks in ^{13}C NMR confirmed the formation of compound **6f**.

Compound **7** was synthesized *via* the nucleophilic substitution of -OTs group with 1-((4-chlorophenyl)(phenyl)methyl)-piperazine hydrochloride in excess of triethylamine at 80 ºC.

ACKNOWLEDGEMENTS

The author thanks GMR Institute of Technology, Rajam and Indian Institute of Chemical Technology, Hyderabad, India for supporting the research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. S.P. Lee, B.F. O'Dowd and S.R. George, *Life Sci.*, **74**, 173 (2003); https://doi.org/10.1016/j.lfs.2003.09.028
2. S. Terrillon and M. Bouvier, *EMBO Rep.*, **5**, 30 (2004); https://doi.org/10.1038/sj.embor.7400052
3. J.M. Rodriguez-Frade, A.J. Vila-Coro, A.M. de Ana, J.P. Albar, C. Martinez-A and M. Mellado, *Proc. Natl. Acad. Sci. USA*, **96**, 3628 (1999); https://doi.org/10.1073/pnas.96.7.3628
4. S. Angers, A. Salahpour, E. Joly, S. Hilairet, D. Chelsky, M. Dennis and M. Bouvier, *Proc. Natl. Acad. Sci. USA*, **97**, 3684 (2000); https://doi.org/10.1073/pnas.060590697
5. A. Cornea, J.A. Janovick, G. Maya-Nunez and P.M. Conn, *J. Biol. Chem.*, **276**, 2153 (2001); https://doi.org/10.1074/jbc.M007850200
6. T. Wurch, A. Matsumoto and P.J. Pauwels, *FEBS Lett.*, **507**, 109 (2001); https://doi.org/10.1016/S0014-5793(01)02969-6
7. R.C. Patel, U. Kumar, C. Lamb, J.S. Eid, M. Rocheville, M. Grant, A. Rani, T. Hazlett, S.C. Patel, E. Gratton and Y.C. Patel, *Proc. Natl. Acad. Sci. USA*, **99**, 3294 (2002); https://doi.org/10.1073/pnas.042705099
8. M. Hunzicker Dunn, G. Barisas, J. Song and D.A. Roess, *J. Biol. Chem.*, **278**, 42744 (2003); https://doi.org/10.1074/jbc.M306133200
9. D.A. Roess and S.M. Smith, *Biol. Reprod.*, **69**, 1765 (2003); https://doi.org/10.1095/biolreprod.103.018846
10. S. Gines, J. Hillion, M. Torvinen, S. Le Crom, V. Casado, E.I. Canela, S. Rondin, J.Y. Lew, S. Watson, M. Zoli, L.F. Agnati, P. Verniera, C. Lluis, S. Ferre, K. Fuxe and R. Franco, *Proc. Natl. Acad. Sci. USA*, **97**, 8606 (2000); https://doi.org/10.1073/pnas.150241097
11. M.C. Overton and K.J. Blumer, *Curr. Biol.*, **10**, 341 (2000); https://doi.org/10.1016/S0960-9822(00)00386-9
12. M.A. Ayoub, C. Couturier, E. Lucas-Meunier, S. Angers, P. Fossier, M. Bouvier and R. Jockers, *J. Biol. Chem.*, **277**, 21522 (2002); https://doi.org/10.1074/jbc.M200729200
13. H. Issafras, S. Angers, S. Bulenger, C. Blanpain, M. Parmentier, C. Labbe-Jullie, M. Bouvier and S. Marullo, *J. Biol. Chem.*, **277**, 34666 (2002); https://doi.org/10.1074/jbc.M202386200
14. G.J. Babcock, M. Farzan and J. Sodroski, *J. Biol. Chem.*, **278**, 3378 (2003); https://doi.org/10.1074/jbc.M210140200
15. S. Terrillon, T. Durroux, B. Mouillac, A. Breit, M.A. Ayoub, M. Taulan, R. Jockers, C. Barberis and M. Bouvier, *Mol. Endocrinol.*, **17**, 677 (2003); https://doi.org/10.1210/me.2002-0222
16. F. Trettel, S. Di Bartolomeo, C. Lauro, M. Catalano, M.T. Ciotti and C. Limatola, *J. Biol. Chem.*, **278**, 40980 (2003); https://doi.org/10.1074/jbc.M306815200
17. K. Simons and R. Ehehalt, *J. Clin. Invest.*, **110**, 597 (2002); https://doi.org/10.1172/JCI0216390
18. K. Simons and E. Ikonen, *Nature*, **387**, 569 (1997); https://doi.org/10.1038/42408
19. L.J. Pike, *J. Lipid Res.*, **44**, 655 (2003); https://doi.org/10.1194/jlr.R200021-JLR200
20. O. Cunningham, A. Andolfo, M.L. Santovito, L. Iuzzolino, F. Blasi and N. Sidenius, *EMBO J.*, **22**, 5994 (2003); https://doi.org/10.1093/emboj/cdg588
21. B. Jarvis and K. Simpson, *Drugs*, **60**, 347 (2000); https://doi.org/10.2165/00003495-200060020-00012