Research Article

Synthesis and Biological Evaluation of 2-((2-Chlorophenyl) (6,7-Dihydrothieno [3,2-c]Pyridin-5(4H)- YL)Methyl)-4-Methylthiazole-5-CarboxylicAcid Derivatives

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ABSTRACT

During the course of our investigation in the field of carboxylic acid antithrombotic agents, we have identified and synthesized 2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-methylthiazole-5-carboxylicacid derivatives (5a-k), with good in vivo activity. These findings prompted us to prepare new 2-((2-chlorophenyl)(6,7-dihydrothieno [3,2-c]pyridin-5(4H)-yl)methyl)-4-methylthiazole-5-carboxylic acid derivatives (5a-k),were synthesized by reaction of 2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-methylthiazole-5-carboxylic acid with substituted halo anilines by using thionyl chloride and hydroxy benzotriazole in presence of triethylamine in Dichloromethane obtained the tile compounds. All the newly synthesized compounds were characterized by spectral methods. The title compounds were screened for in vitro antibacterial activity. Most of the compounds show moderate to good antimicrobial activity.

Keywords: Anti- bacterial activity, ethyl-2-chloro acetoacetate, thienopyridine, thiazole carboxylic acid, HOBT-$SOCl_2$, antifungal activity

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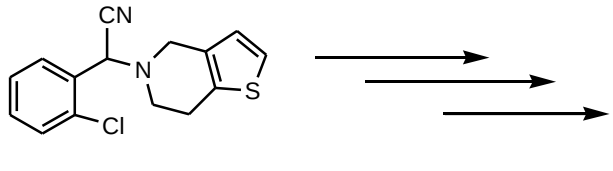
INTRODUCTION

Thienopyridines (4,5,6,7-tetrahydro thieno[3,2-c]pyridines) and their derivatives are important heterocyclic compounds that are widely distributed in nature. Many of the compounds containing tetrahydrothienopyridine skeleton are reported as antibacterial [1] non-peptide GPIIb/IIIa antagonists [2] platelet aggregators and antithrombotic agents[3]. The incorporation of benzylic or substituted benzylic groups on the nitrogen of the thienopyridine ring can bring an extensive modification in the biological activities of parent compound. Among the substitutions occurred at nitrogen of the thienopyridine moiety[4], the increased effect in the biological activity of the parent moiety affects the good antithrombotic activity in Ticlopidine and with more increased activity in Clopidogrel. Later on, the studies proved that the Prasugrel to be more efficient drug candidate than the existing Clopidogrel by making the structural modifications to the parent thienopyridine moiety. Hence, different substitutions at nitrogen of the biological activity of the new chemical entities (NCEs).

Thiazole and their derivatives have attracted continuing interest over the years because of their varied biological activities. [5]1,3-Thiazole nucleus containing compounds have exhibited a broad range of biological activities. [6-15]. Thiazole is five membered unsaturated heterocyclic moiety containing sulphur and nitrogen atoms as the main heterocyclic constituents. In continuation of our work towards the synthesis of new heterocyclic moieties on the phenyl system along with tetrahydrothieno pyridine nucleus in its structure .we explored to introduce the thiazole ring system on the second position of phenyl system. For this strategy, we are keen to use the one of the known intermediates for the functionalization of the thiazole mother skeleton. we found 2-

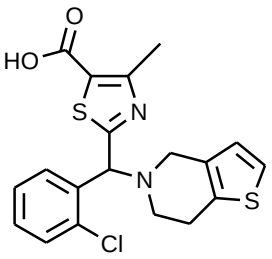
(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetonitrile**(1)** as an important intermediate for the preparation of thiazole moiety. For instance, the introduction of thiazole ring into the molecule of 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetonitrile **1** and also some of the derivatives of this substrate might afford the promising metabolically stable analogs. The nitrile function of compound **1** was transformed into thioamide**(2)** followed by ring construction using commercially available ethyl-2-chloro acetoacetate under reagent free conditions affords the thiazole skeleton ethyl 2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-methylthiazole-5-carboxylate**(3).**

Thus we had targeted the synthesis of 2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-methylthiazole-5-carboxylicacid **4** and acid amide derivatives with an objective to study their biological activity. With this aim, we started to prepared the required pharmacophore using the known intermediates,2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c] pyridin-5(4H)-yl) acetonitrile are the synthesis for the preparation of compounds **(5a-5k)**



Thieno pyridineacetonitrile

1



Thiazole 5-caborxylic acid containing thienopyridine

4

MATERIAL AND METHODS

All solvents used were of commercial grade purchased from a qualified vendor. Melting point range reported was uncorrected and taken on a Polmon melting apparatus. The FT-IR spectra were recorded in the solid state as KBr dispersion using a Perkin–Elmer 1650 FT-IR spectrophotometer. Thin layer chromatography was performed on Merck precoated silicagel 60F254 plates using UV light as visualizing agent. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 and 100 MHz Gemini Varian spectrometer using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. The mass spectra were recorded on an Agilent 6310 Ion Trap.

Synthesis of 2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-methylthiazole-5-carbothioamide(2)

To a solution of the compound**1** (10.0 g, 0.024 moles) in Dimethyl form amide (100.0 mL), was added $NaSH.H_2O$ (4.5 g, 0.071 moles) the reaction mixture was for stirred over night at ambient temperature. The progress of the reaction mixture monitored using TLC. It was poured into water (200.0m). The product was filtered and washed the solid with water (20.0 mL) to remove the impurities. The obtained compound **2**The wet material suspended in water (50.0 mL) and adjusted to the 7–8 pH using dilute 1% aq. HCl solution to afford the title compound **2** as a cream colored solid. The wet compound was dried under reduced pressure at 25-30°C for 4-5 h. yield 80%, mp: 205–210°C, IR (KBr) cm−1; 1620 (C=S), 3371(NH2) 1HNMR (400 MHz $CDCl_3$,) 1.27 (t, 3H, CH_3), 1.72 (s, 2H, NH_2), δ 2.65-2.89 (m, 4H, 2 x CH_2), δ 3.60 (s, 2H, CH_2), δ 3.96 (s, 1H, CH), δ 6.71-7.5 (6H, ArH). :).^{13}C NMR (100 MHz, $CDCl_3$): ð, 50.85, 53.12, 73, 125.22, 127.82, 128.16, 128.88, 129.98, 130.01,130.82, 132.11, 133.32, 135.91, 138.05, 202.5. MS(m/z):323(M+I)

Synthesis of 2-((2-chlorophenyl) (6,7-dihydrothieno[3,2-c] pyridin-5(4H)-yl) methyl)-4-methylthiazole-5-carbothioamide (3)

To a solution of the compound**2**(10.0 g, 0.033 moles) in ethanol (100.0 mL), was added 2-chloro ethyl acetoacetate (22.0 mL, 0.156moles)(4.5 g, 0.071 moles) the

reaction mixture was for stirred over night at50-60°Cthe progress of the reaction mixture monitored using TLC. Reaction mixture is heterogeneous throughout the reaction time cycle). The product was filtered and washed the solid with chilled ethanol (20.0 mL). The wet material was recrystallized from ethanol and dried the compound at 50-60°C under reduced pressure for 3-4h.The obtained compound **3** yield 80%, mp: 105–110 °C, IR (KBr) cm−1;: 1710(C=O) 1HNMR (400 MHz $CDCl_3$,) :1.27 (t, 3H, CH_3), δ 2.69 (s, 3H, CH_3), 4.23 (q, , 2H, CH_2), 2.73–2.85 (m, 4H, 2 x CH), 3.63 (s, 2H,CH_2), 5.2 (s, 1H, CH), 6.78–7.5 (6H, ArH).^{13}C NMR (100 MHz, $CDCl_3$): ð 15.42,17.41, 25.63, 50.85, 53.12, 60.04, 61.86, 125.22, 127.82, 129.16, 129.88, 129.98, 130.01, 130.82, 132.11, 133.32, 134.91, 137.05, 159.42, 167.14, 168.16. MS (m/z):433 (M+1)).

Synthesis of 2((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl) methyl)-4-methylthiazole-5-carboxylic acid(4)

To a solution of the compound **3**(10.0 g, 0.024 moles) in acetonitrile (50.0 mL), was added KOH powder (2.0 g,0.37 moles) the reaction mixture was for reflux and maintained for 5-6h.The progress of the reaction mixture monitored using TLC. It was cooled to 25–30 °C. The product was filtered and washed the solid with acetonitrile (10.0 mL) to remove the impurities. The obtained product is in the form of potassium salt of compound **4**The potassium salt is dissolved in water (50.0 mL) and adjusted to the 4–5 pH using 5% acetic acid to afford the title product **4**as crude material. Recrystallized in acetonitrile (25.0 mL) affords compound **4** as white solid material. Off white solid, yield 80%, mp: 205–210 °C, IR (KBr) cm−1;: 1698 (C=O), 3600 (OH), ^{1}HNMR (400 MHz $CDCl_3$,) : ð 2.35 (s, 3H, CH3), 2.78–2.91 (m, 4H, 2 x CH), 3.60 (s, 2H,CH2), 5.1 (s, 1H, CH), 6.78–8.12 (6H, ArH).13C NMR (100 MHz, $CDCl_3$): ð 12.42, 25.63, 50.85, 53.12, 60.22, 125.22, 127.82, 129.16, 129.88, 129.98, 130.01, 130.82, 132.11, 133.32, 133.91, 138.05, 159.42, 167.14, 169.16.MS (m/z):405(M+1).

Synthesis of title compounds (5a–k2)-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-methylthiazole-5-carboxamide) (5a)

To a solution of the compound **4**(10.0 g, 0.01 moles) in dichloromethane (50.0 mL) and was added HOBT (0.31 g, 0.002moles) under nitrogen atmosphere. It was cooled the reaction mixture to -5°C to 0°Candwas added TEA (0.42 g, 0.004 moles) slowly into the reaction mixture at below -5°C. Then thionyl chloride added into the reaction mixture over a period of 30–40 minutes under nitrogen atmosphere at below -5°C. After completion of addition, the temperature was raised slowly to 10–15°C and maintained the reaction mixture at the same temperature for 2 h. Then water (5.0 mL) was added into the reaction mixture and stirred for 5 minutes and separated the organic layer (active ester layer). Charged the active ester layer into the RBF and substituted aniline (0.23 g, 0.002 moles) was taken into DCM (10.0 mL) and added the solution slowly over period of 30–40 minutes at 10–15°C. After completion of the addition the temperature of the reaction mixture was raised to 25–30 °C and maintained for 10–12 h at the same temperature. Progress of the reaction was monitored by using TLC, after completion of the reaction water (10.0 mL) was added into the reaction mixture, stirred for 10–15 minutes. Separated the organic layer and the organic layer was washed with 10% K_2CO_3 solution (5 mL) followed by water (5 mL) washing. Organic layer was dried over anhydrous sodium sulphate and solvent was removed completely under reduced pressure. Co-distillation of the solvent with diisopropyl ether (2 x 10 mL) followed by isolation in diisopropyl ether (5 mL) affords the title compound **5a** quantitatively. Pale brown solid, yield 70%.mp: 156–159 °C, IR (KBr)(cm-1): 1718 (C=O), 3400 (NH_2),^{1}H NMR (400 MHz, $CDCl_3$): ð 2.35 (s, 3H, CH_3), 2.78–2.80(m, 4H, 2 x CH_2), 3.53 (s, 2H, CH_2), 4.9 (s, 1H, CH), NH_2-8.5 (s,2H) 6.70–7.69 (6H, ArH).^{13}C NMR(100 MHz, $CDCl_3$): ð 12.62, 25.63, 50.58, 55.14, 116.2,124.82, 127.28,129.10, 129.38, 129.65, 130.00, 130.28, 132.01, 133.19,133.23, 137.52, 159.24, 161.91, 166.76. MS (m/z): 404 (M+l).

Employing the similar procedure as mentioned for 5a the remaining amides (5b-

k) were prepared in quantitatively.

2-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-ylmethyl)-phenyl-2-yl]-4-methylhiazole-5-carboxylicAcid phenyl amide (5b)

Pale yellow solid, yield 75%, mp: 120–123°C, IR (KBr) (cm-1): 1680 (C=O), 3350 (NH) ^{1}HNMR (400 MHz, $CDC1_3$): ð 2.41 (s, 3H, CH_3), 2.83–2.91 (m, 4H, 2 x CH_2, pyridine ring), 3.61 (s, 2H,CH_2allylic pyridine ring), 5.0 (s, 1H, CH), NH-7.5 (s,1H),6.61–7.8 (11H, ArH).^{13}C NMR (100 MHz, $CDC1_3$): ð 15.33, 25.4,2, 50.70, 53.09 ,56, 114, 120.31, 124.85, 125.31, 127.40, 128.11, 128.84, 129.42, 129.79, 129.88, 130.02, 130.85, 131.75, 133.33, 133.70, 137.28,137.41, 160.04, 162.9, 166.66. MS (m/z): 480.1 (M+l).

2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-N-(2chlorophenyl)-4-methylthiazole-5-carboxamide (5c)

Brown yellow solid, yield 75%, mp: 159–161 °C, IR (KBr) (cm-1): 1667 (C=O), 3453 (NH)783 (C–Cl)^{1}HNMR (400 MHz, $CDCl_3$): ð 2.41 (s, 3H, CH_3), 2.83–2.91 (m, 4H, 2 x CH2, pyridine ring), 3.61 (s, 2H,CH_2allylic pyridine ring), 5.0 (s, 1H, CH), NH-7.5 (s,1H) 6.61–7.8 (11H, ArH).^{13}C NMR(100 MHz, $CDCl_3$): ð 15.73, 25.62, 51.70, 54.09, 56, 114, 121.31, 124.85, 125.31, 127.40, 128.14, 128.81, 129.32, 129.78, 129.79, 130.02, 130.85, 131.75, 133.33, 133.70, 137.28, 137.41, 161.9,162.04, 166.66. MS (m/z): 514. (M+l).

2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-N-(3-chlorophenyl)-4-methylthiazole-5-carboxamide (5d)

Off white solid ,yield 65%, mp: 180–183 °C, IR (KBr) (cm-1): 1667 (C=O), 3453 (NH),1H783 (C–Cl)^{1}HNMR (400 MHz, , $CDC1_3$): ð 2.41 (s, 3H, CH_3), 2.7–2.91 (m, 4H, 2 x CH2, pyridine ring), 3.65 (s, 2H,CH2allylic pyridine ring), 5.1 (s, 1H, CH), NH-7.5 (s,1H) 6.67–7.8 (10H, ArH).^{13}C NMR (100 MHz, $CDC1_3$): ð 15.33, 25.42, 50.70, 53.09, 56, 114, 120.31, 124.85, 125.31, 127.40, 128.84, 128.11, 129.42, 129.79, 129.88, 130.02, 130.85, 131.75, 133.33, 133.70, 137.41, 137.28, 162.9, 160.04, 166.66. MS (m/z): 514. (M+l).

2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-N-(4chlorophenyl)4-methylthiazole-5-carboxamide (5e)

Yellow solid, yield 62%, mp: 150–153 °C, IR (KBr) (cm-1): 1638 (C=O),825 (C–Cl)^{1}HNMR (400 MHz, , $CDC1_3$): ð 2.41 (s, 3H, CH_3), 2.83–2.91 (m, 4H, 2 x CH2, pyridine ring), 3.61 (s, 2H,CH2allylic pyridine ring), 5.0 (s, 1H, CH), NH-7.6 (s,1H) 6.61–7.8 (10H, ArH).^{13}C NMR (100 MHz, $CDC1_3$): ð 15.33, 25.42, 50.70, 53.09, 56, 114, 120.31, 124.85, 125.31, 127.40, 128.11, 128.84, 129.42, 129.79, 129.88, 130.02, 130.85, 131.75, 133.33, 133.70, 137.28, 137.41, 160.04, 162.9, 166.7 MS (m/z): 514. (M+l).

2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-N-(2,3dichlorophenyl)-4-methylthiazole-5-carboxamide (5f)

Off white solid ,yield 65%, mp: 170–173 °C, IR (KBr) (cm-1): 1667 (C=O), 3453 (NH),1H789 (C–Cl)^{1}HNMR (400 MHz, $CDC1_3$): ð 2.45 (s, 3H, CH_3), 2.83–2.91 (m, 4H, 2 x CH2, pyridine ring), 3.63 (s, 2H,CH_2allylic pyridine ring), 5.2 (s, 1H, CH), NH-7.6 (s,1H) NH-7.8 (s,1H) 6.68–7.7 (9H, ArH).^{13}C NMR (100 MHz, , $CDC1_3$): ð 15.4, 25.62, 50.70, 53.09, 56, 114, 121.31, 124.85, 125.31, 127.40, 128.11, 128.84, 129.42, 129.79, 129.88, 130.02, 130.85, 131.75, 133.33, 133.70, 137.61, 137.28, 160.9, 162.04, 166.66. MS (m/z): 549 (M+l).

2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-N-(3,4dichloro phenyl) -4-methylthiazole-5-carboxamide (5g)

Cream colored solid, yield 70%, mp: 161–164 °C, IR (KBr) (cm-1): 1643 (C=O), 3304 (NH),789 (C–Cl))^{1}HNMR (400 MHz, $CDC1_3$): ð 2.41 (s, 3H, CH_3), 2.83–2.91 (m, 4H, 2 x CH2, pyridine ring), 3.61 (s, 2H,CH_2allylic pyridine ring), 5.2 (s, 1H, CH), NH-7.7 (s,1H) 6.61–7.8 (9H, ArH).^{13}C NMR(100 MHz, $CDC1_3$): ð 15.33, 25.42, 50.70, 53.09, 56, 114, 122.31, 124.85, 125.31, 127.40, 128.11, 128.84, 129.42, 129.79, 129.88, 130.02, 130.85, 131.75, 133.33, 133.70, 137.28, 137.41, 160.04, 162.9, 166.66. MS (m/z): 549 (M+l).

2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-N-(2-fluorophenyl)-4-methylthiazole-5-carboxamide (5h)

Off white coloured solid, yield 65% , mp: 118–121 °C, IR (KBr) (cm-1): 1656 (C=O),

3451(NH), 769 (C–F)^{1}HNMR (400 MHz, $CDC1_3$): ð 2.41 (s, 3H, CH_3), 2.78–2.91 (m, 4H, 2 x CH2, pyridine ring), 3.61 (s, 2H,CH_2allylic pyridine ring), 5.0 (s, 1H, CH), NH-7.5 (s,1H), 6.7–7.8 (11H, ArH).^{13}C NMR(100 MHz, $CDC1_3$): ð 15.33, 25.42, 50.70, 53.09, 56, 119, 120.31, 124.85, 125.31, 127.40, 128.11, 128.42, 128.84 129.79, 129.88, 130.02, 130.85, 131.75, 133.33, 133.70, 137.41, 160.04,162.9, 166.17, 167.66. MS (m/z): 498 (M+l).

2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-N-(4-fluorophenyl)-4-methylthiazole-5-carboxamide (5i)

Off white solid, yield 70%, mp: 146–149 °C, IR (KBr) (cm-1): 1653 (C=O), 3423 (NH),1H, 839 (C–F) ^{1}HNMR (400 MHz, $CDC1_3$): ð 2.41 (s, 3H, CH_3), 2.83–2.91 (m, 4H, 2 x CH2, pyridine ring), 3.61 (s, 2H,CH2allylic pyridine ring), 5.2 (s, 1H, CH), NH-7.6 (s,1H) 6.61–7.7 (11H, ArH).^{13}C NMR(100 MHz, $CDC1_3$): ð 15.33, 25.42, 50.70, 53.09,56, 116, 120.31, 124.85, 125.31, 127.40, 128.11, 128.84, 129.42, 129.79, 129.88, 130.02, 130.85, 131.75, 133.33, 133.70, 137.28, 160.04, 163.9, 164.2, 166.66.MS (m/z): 498.1 (M+l).

2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-N-(2,5-difluorophenyl)-4-methylthiazole-5-carboxamide (5j)

Off white coloured solid, yield 72%, mp :163–166 °C, IR (KBr) (cm-1): 1659 (C=O), 3449(NH), 879 (C–F)^{1}H NMR (400 MHz, $CDC1_3$): ð 2.41 (s, 3H, CH_3), 2.83–2.91 (m, 4H, 2 x CH_2, pyridine ring), 3.61 (s, 2H,CH_2allylic pyridine ring), 5.0 (s, 1H, CH), NH-7.9 (s,1H) 6.61–7.6(9H, ArH).^{13}C NMR(100MHz, $CDC1_3$): ð 15.33, 25.52, 51.70, 53.09, 56, 114,118, 124.85, 125.31, 127.40, 128.11, 128.84, 129.42, 129.79, 129.88, 130.02, 130.85, 131.75, 133.33, 133.70, 137.41, 159.16, 160.04, 160.17, 162.9, 167.66.MS (m/z): 516(M+l).

2-((2-chlorophen(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-methyl)-N-(2,3,4-triflurophenyl)-4-methyl thiazole-5-carboxamide 5k)

Off white coloured solid, yield 80% , mp: 128–131 ° C, IR (KBr) (cm-1): 1654 (C=O), 3421(NH),894 (C–F) ^{1}HNMR (400 MHz, $CDC1_3$): ð 2.41 (s, 3H, CH_3), 2.83–2.91 (m, 4H, 2 x CH_2, pyridine ring), 3.63 (s, 2H,CH_2allylic pyridine ring), 5.1 (s, 1H, CH),NH-8 (s,1H) 6.61–7.6 (8H, ArH).^{13}C NMR (100 MHz, $CDC1_3$): ð 15.33, 25.42, 50.70, 53.09,56, 114, 127.40, 122.85, 128.84, 128.11, 129.42, 129.79, 129.88, 130.02, 130.85, 131.75, 133.33, 133.70, 137.41, 143,14, 157, 160.04, 162.9, 166.66.MS (m/z): 534. (M+1).

Antimicrobial Activity

The synthesized compounds **5a–5k** were screened for their in vitro antimicrobial activity against the standard strains B. subtilis, S. aureus (Gram-positive) and E. coli, K. pneumonia (Gram-negative) by the disk diffusion method [16,17]. Disks measuring 6 mm in diameter were punched from whatman no.1 filter paper. Batches of 100 disks were dispensed to each screw-caped bottle and sterilized by dry heat at 145^{o}C for one hour. The test compounds were prepared with 100 µg/mL and 200 µg/mL concentration in dimethyl sulfoxide (DMSO). Disks of each concentration were placed in nutrient agar medium inoculated with fresh bacteria strains separately. Chloramphenicol was used as positive controls and DMSO was used as negative control. The incubation was carried out at37^{o}C for 24 h. The diameter of the zone of growth inhibition around each well was measured after incubation using Verniercalliper.

The compounds were screened for their antifungal activity against F. solani, C. lunata and A. niger in DMSO by disc diffusion method under standard conditions using Sabourad Dextrose Agar medium as described by NCCLS[18]. Sterile filter paper discs (6 mm diameter) containing specific amount of anti-fungal agent (100 µg for the synthesized compounds) were placed on the surface of an agar plate inoculated with the standardized suspension of microorganisms tested. The plates were incubated at 37^{o}C for 2 days for evaluating antifungal activity. The diameters of inhibition zones (in mm) were measured. Ketoconazole was used as positive control.

RESULTS AND DISCUSSION

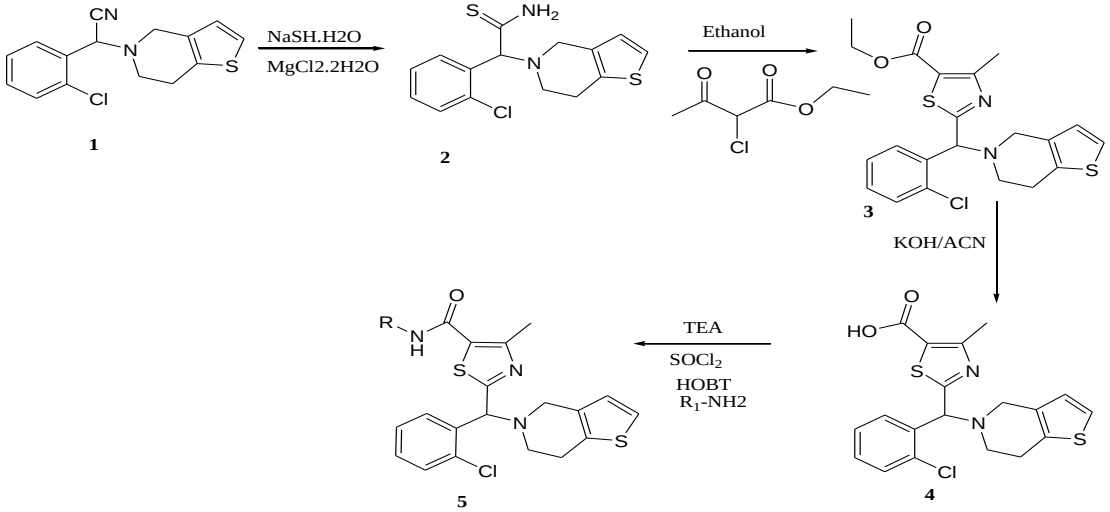
The reaction sequence employed for the synthesis of title compounds is shown in(**Scheme-1**). The nitrile function of compound **1** was transformed into thioamide**(2)** followed by ring construction

using commercially available ethyl-2-chloro acetoacetate under reagent free conditions affords the thiazole skeleton ethyl 2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-methylthiazole-5-carboxylate**(3).**

The compound **3**appeared in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$), the signals observed at ð1.25 as triplet which is due to CH_3 of ester moiety of thiazole ring (t, *J*=7.2 Hz, 3H, CH_3), asinglet appeared at ð 2.69 is due to the CH_3 of thiazole ring (s, 3H, CH_3), adjacent methyleneprotons displayed between ð 2.73-2.85 (m, 4H, 2 x CH_2). Another singlet proton appeared atð 3.6 is allylic CH_2 of thienopyridine ring and another singlet appeared at ð 5.2 is due tobenzylic CH. A quartet appeared at ð 4.23 (q, J=7.2 Hz, 2H, OCH_2) is due to the ester CH_2protons. In the ^{13}C NMR (100 MHz, $CDC1_3$) spectrum the signals observed at ð 15.42 are signals of CH_3 of thiazole ring, 17.41 (CH_3 ester), 25.63 (CH_2 pyridine ring), 50.81 (CH_2,allylic), 53.12 (CH_2 pyridine ring), 61.04 (benzylic CH), 61.86 (CH_2 ester), the compound**(3)** which is upon saponification gives 2-[4-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-ylmethyl)-biphenyl-2-yl]-4-methyl-thiazole-5-carboxylicacid**(4)**.The compound **(4)** In the^{1}H NMR (400 MHz, $CDCl_3$) spectrum the signals observed at ð 2.35 (s, 3H, CH3) is due to the methyl protons of the thiazole ring system. Two adjacent methylene protons displayed between ð 2.78-2.91 (m, 4H, 2 x CH_2). Two singlet protons appeared at ð 3.60 (s, 2H, CH_2) andð 5.1 (s, 1H, CH). In the ^{13}C NMR (100 MHz, $CDCl_3$) spectrum the signals observed atð 15.32 are signals of CH_3 of thiazole ring, 25.36 (CH_2 pyridine ring), 50.85 (CH_2, allylic),53.12 (CH_2 pyridine ring), 51 (benzylic CH).

Finally the acid function further converted into amide **(5a–k)** as per the synthetic path way the synthesis of target molecules using the commercially available, economically cheap starting materials to give different 2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-methylthiazole-5-carboxylic acid (5a-k). The compound **5a** in the ^{1}H NMR (400 MHz, $CDCl_3$) spectrum, the signals observed at ð 2.35 (s,3H, CH_3) is due to the methyl protons of the thiazole ring system. Two adjacent methylene protons displayed between ð 2.78-2.93 (m, 4H, 2 x CH_2). Two singlet protons appeared at ð3.50 (s, 2H, CH_2) and ð 5.1 (s, 1H, CH) are due to the methylene protons of the pyridine ring and benzylic protons respectively. Aromatic protons resonated between ð 6.79**–**7.69(6H, ArH).In the ^{13}C NMR (100 MHz, $CDCl_3$) spectrum, the signals observed at ð 15.42are signals of CH_3 of thiazole ring, 25.63 (CH_2 pyridine ring), 50.68 (CH_2, allylic), 53.14(CH_2 pyridine ring).

Scheme 1: Synthesis of title compounds thiazole-5-carboxylic acid amides (5a–5K)



R_1=substituted halo anilines

Where R=H, phenyl, 2-chloro phenyl,3-chlro phenyl, 4-chloro phenyl,2,3-dichloro phenyl, 3,4-dichloro phenyl, 2-fluoro phenyl, 4-fluoro phenyl, 2,5-difluoro phenyl, 2,3,4-trifluoro phenyl

BIOLOGICAL ACTIVITY

Antimicrobial Activity

All the newly prepared compounds **(5a–k)** were screened for the antibacterial activities done by the paper disc method. Organisms used: Escherichia coli and K. pneumonia.(Gram-negative), Staphylo-coccusaureous and B.subtilis (gram-positive).To evaluate the activity of the synthesized compounds, the zone of inhibition was determined. The in vitro antimicrobial screening results of tested compounds are listed in (**Table 1 and 2**).

The antibacterial screening data showed that almost all the compounds **5a–k** is active and showing moderate to good antibacterial activity. among the screened compounds **5c**, **5f, 5i** and **5k** in which respectively showed high activity against all the micro-organism employed. The activities of these compounds are almost equal to the standards the remaining compounds showed moderate to good antibacterial activity.

Table 1: Antibacterial screening results of the compounds 5a–5k (Zone diameter of growth inhibition in mm

(Gram positive) Conc. µg/ml					**(Gram negative) Conc. µg/ml**			
	S. aureous		B. subtilis		E. coli		K. Pneumonia	
Compd	100	200	100	200	100	200	100	200
5a	26	30	24	27	25	29	23	26
5b	24	27	23	13	14	2	25	10
5c	**33**	**36**	**37**	**39**	**39**	**44**	**34**	**37**
5d	23	20	19	22	25	11	11	16
5e	14	15	16	17	14	11	18	11
5f	**36**	**39**	**34**	**37**	**31**	**34**	**29**	**33**
5g	23	25	26	15	19	20	15	11
5h	23	32	23	21	18	22	26	10
5i	**32**	**34**	**33**	**30**	**33**	**39**	**33**	**39**
5j	20	22	26	13	35	23	26	28
5k	**38**	**43**	**37**	**41**	**36**	**40**	**37**	**39**
Chloramphenicol	35	39	38	41	40	44	42	45

Table 2: Antifungal screening results of the compounds 5a–5k (Zone diameter of growth inhibition in mm

		F. solani		**C.lunata**		**A. niger**	
Compound	**Conc. µg/ml**	100	200	100	200	100	200
5a		16	19	17	20	15	18
5b		19	21	22	24	17	21
5c		17	16	23	19	15	16
5d		9	10	13	11	6	7
5e		**24**	**27**	**23**	**25**	**20**	**24**
5f		25	21	34	18	13	17
5g		17	20	18	22	16	21
5h		17	19	18	23	18	21
5i		**23**	**25**	**25**	**23**	**23**	**25**
5j		16	20	15	17	16	19
5k		21	18	20	23	17	18
Ketoconazole		**38**	**42**	**38**	**42**	**38**	**42**

The result of antifungal activity revealed that all the tested compounds show moderate to good antifungal activity as compared to the standard drug ketoconazole. Compound **5e(**R =4-chloro), and**5i** (R =4-fluoro –) exhibited good activities against all the fungal species. However compounds **5e,**is inactive against

bacterial strain but showed good antifungal activity. Thus, it is concluded that compounds with **R = 2-chloro, 2,3 dichloro,4-fluoro and 2,3,5 trifluoro**– show good to excellent antibacterial activity

CONCLUSION

We have successfully synthesized of eleven new thiazole-5-carboxylic acid amide derivatives**(5a–k)** via (**2**) in good yields. The structures of all the compounds were confirmed by their spectral data. All the newly synthesized compounds were screened for their MIC and zone of inhibition against four strains of bacteria. Amongst the compounds screened, most of the compounds **5c, 5f, 5i, 5k** have shown moderate to good antibacterial The antimicrobial activity results make them interesting lead molecules for further synthetic and biological evaluation. Further studies are in progress to acquire more information regarding structure activity relationship.

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