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SYNTHESIS AND BIOLOGICAL ACTIVITY STUDIES OF 1-(2-(2-CHLOROPHENYL)-2-(6,7-DIHYDROTHIENO[3,2-c] PYRIDIN-5(4H)-YL) ETHYL) 5-METHYL-1H-1,2,3 TRIAZOLE-4-CARBOXYLIC ACID DERIVATIVES

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ABSTRACT

During the course of our investigation in the field of carboxylic acid antithrombotic agents, we have indentified and synthesized 1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylic acid **(6a-6p) ,**a carboxylic acid derivatives with good in vivo activity. These findings prompted us to prepare new derivatives 1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylic acid **(6a-6p),** in the hope of increasing activity and better understanding the influence of ester and amides.

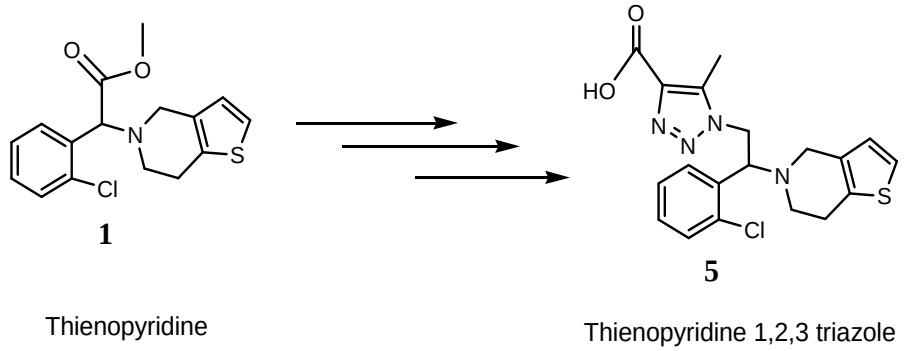
KEYWORDS: Antithrombotic activity, methylacetoacetate, thienopyridine, 1,2,3 triazoles, platelet aggregation.

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 tetrahydro thienopyridine 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).

Triazoles are heterocyclic compounds featuring five member ring of two carbon atoms and three nitrogen atoms as part of the aromatic five-membered ring. Triazole refers to either one. a pair of isomeric chemical compounds with molecular formula $C_2H_3N_3$.1,2,3-Triazoles are an important class of heterocyclic due to their wide range of applications as synthetic intermediates and pharmaceuticals.[5–8] Several therapeutically interesting 1,2,3-triazoles have been reported, including anti-HIV agents[9–12], antimicrobial compounds[13], β3-selective adrenergic receptor agonists[14], kinase inhibitors[15,16], other enzyme inhibitors[17,18], the β-lactam antibiotic tazobactam.[19]

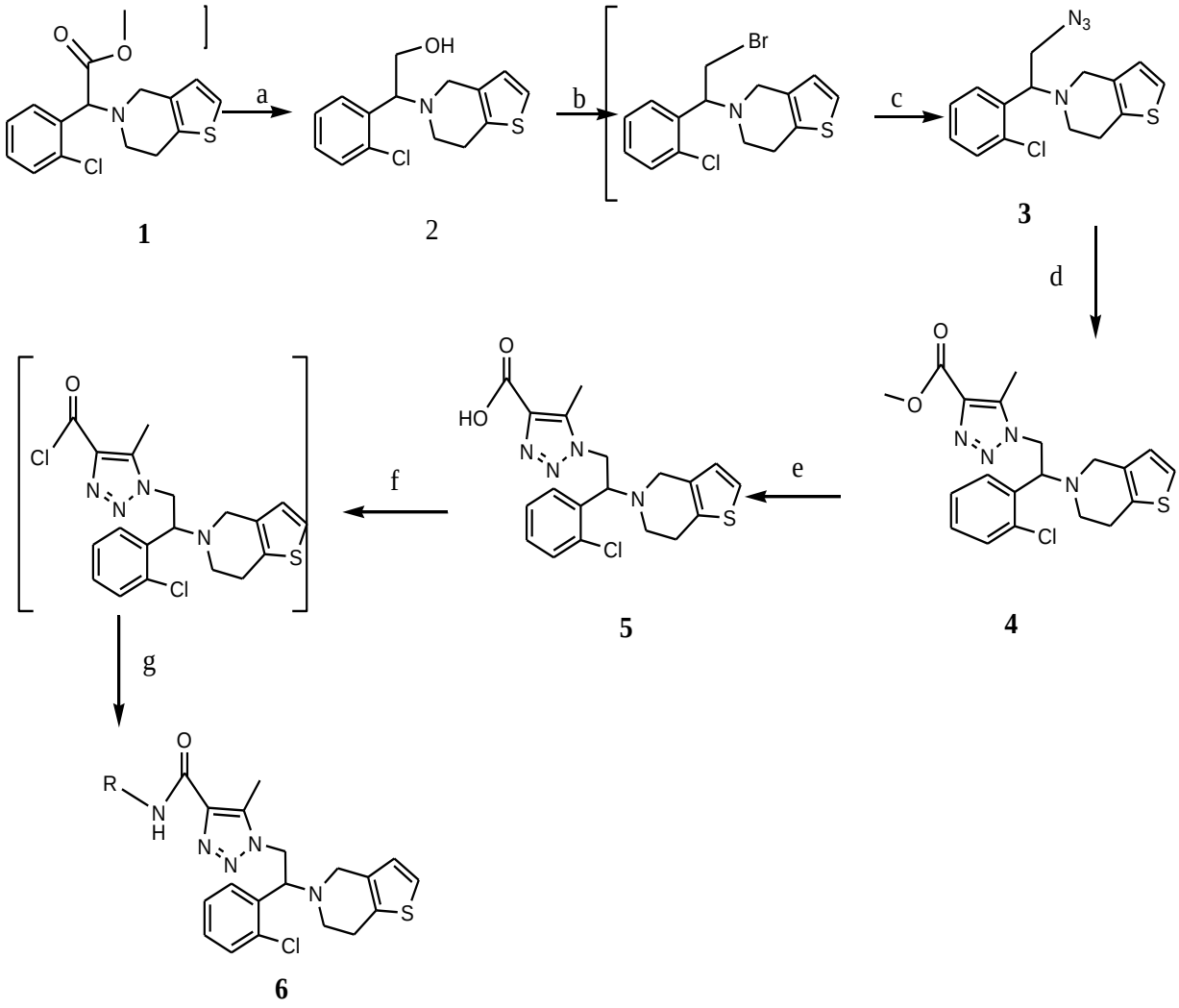
We started our journey towards the synthesis of new heterocyclic moieties having phenyl system along with tetra hydro thienopyridine nucleus. In continuation of our work towards the synthesis of new heterocyclic moieties on the phenyl system along with tetrahydro thieno pyridine nucleus in its structure we explored to introduce the 1,2,3 triazole 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 1,2,3 triazole mother skeleton. During our journey towards the synthesis of new molecules containing phenyl system along with tetrahydrothienopyridine nucleus we found methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate, **(1)** as an important intermediate for the preparation of triazole moiety. Thus we had targeted the synthesis of 1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylic acid **5** 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 methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate,, are the synthesis for the preparation of compounds **(6a-6p).**



1 **5**

Thienopyridine Thienopyridine 1,2,3 triazole

Scheme 1: Synthesis of title compounds triazole -4-carboxylic acid amides (6a–6p)



1 2 **3** **4** **5** **6**

R_1=Hal substituted 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, benzyl, 4-fluoro benzyl, 4-methoxy phenyl, 3-methoxy phenyl, 4-bromo phenyl

Reagents and Conditions

(a)$LiAlH_4$/THF RT (b)PBr_3/ACN (c) NaN3/DMSO 60°C (d) methyl acetate,K_2CO_3 /DMF (e)KOH/ACN (f) PCl_5/DCM / R_1-NH_2, MDC,reflux,

RESULTS AND DISCUSSIONS

The reaction sequence employed for the synthesis of title compounds is shown in(**Scheme-1**) Transformation of ester function of compound **1** to compound **2** reduced with lithium aluminium hydride obtained to alcohol without any impurity formation transformation of alcohol **2** to aryl azide **3** via aryl bromide intermediate quantitatively Functionalization of the bromide intermediate **3** to azide intermediate **3**could be achieved

using NaN_3 in DMF Reaction of azide compound **3** and commercially available cheap 1,3-dicarbonyl compounds such as methyl acetoacetate in the presence of K_2CO_3 as a base in DMSO medium at 60-65°C for 40-50 hr followed usual work up affords the 1,2,3 triazole skeleton methyl 1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate **(4).** Which is upon saponification affords 1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylic acid **5.** Reaction of compound **5** with PCl_5 addition at 0-5°C under nitrogen atmosphere followed by reflux maintenance for 3-4 hr affords the aryl chloride intermediate. The aryl chloride in situ converted into amide (**6a-p**) by solvent evaporation followed by addition of the corresponding amines in dichloromethane followed by usual work procedures affords the title compounds quantitatively) 1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide derivatives **6a-6p.**

The compound **4** appeared in the 1H NMR spectrum (400 MHz, $CDCl_3$), the signals observed at ð1.30 as triplet which is due to CH_3 of ester moiety of triazole ring (t, 3H, CH_3), a singlet appeared at ð 2.35 is due to the CH_3 of triazole ring (s, 3H, CH_3), adjacent methylene protons displayed between ð 2.73-2.85 (m, 4H, 2 x CH_2). Three singlet proton appeared at ð 3. 68 is allylic CH_2 of thienopyridine ring and another singlet appeared at ð 4.1 is due to benzylic CH,4.52 (s, 2H, CH_2 bridge benzylic). In the ^{13}C NMR (100 MHz, $CDC1_3$) spectrum the signals observed at ð 8.87 are signals of CH_3 of triazole ring, 14.29 (CH_3 ester), 21.63 (CH_2 pyridine ring), 50.26 (CH_2,allylic), 57.77 (CH_2 pyridine ring), 49.01 (benzylic CH), 52.91 (benzylic CH_2 60.75 (CH_2 ester), the compound**(4)** which is upon saponification gives1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylic acid **(5)**.The compound **(5)** In the^1H NMR (400 MHz, $CDCl_3$) spectrum the signals observed at ð 2.35 (s, 3H, CH3) is due to the methyl protons of the triazole ring system. Two adjacent methylene protons displayed between ð 2.79-2.82 (m, 4H, 2 x CH2). Three singlet protons appeared at ð 3.64 (s, 2H, CH_2) and ð 4.1 (s, 1H, CH) 4.52 (s, 2H, CH_2). In the ^{13}C NMR (100 MHz, CDCl3) spectrum the signals observed atð 8.32 are signals of CH_3 of triazole ring, 25.36 (CH_2 pyridine ring), 50.85 (CH_2, allylic),53.12 (CH_2 pyridine ring), 49 (benzylic CH).52.91 (bridge benzylic CH_2).

Finally the acid function further converted into amide **(6a–6p)** as per the synthetic path way the synthesis of target molecules using the commercially available, economically cheap starting materials to give different2-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-methylthiazole-5-carboxylic acid **(6a-6p).** The compound **6a** in the 1H NMR (400 MHz, CDCl3) spectrum, the signals observed at ð 2.35 (s,3H, CH3) is due to the methyl protons of the triazole ring system. Two adjacent methylene protons displayed between ð 2.78-2.83 (m, 4H, 2 x CH2). Three singlet protons appeared at ð3.50 (s, 2H, CH_2) and ð 5.52 (s, 1H, CH), 4.52 (s, 2H, CH_2)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, CDCl3) spectrum, the signals observed at ð 8.42 are signals of CH3 of triazole ring, 25.63 (CH_2 pyridine ring), 50.68 (CH_2, allylic), 52.95(CH_2 pyridine ring) 49 (benzylic CH).52.95 (bridge benzylic CH_2).

ANTIPLATELET ACTIVITY

Antiplatelet activity for all the new compounds **6a–p** was performed in vitro following Born's turbid metric methods available in the literature (Born, 1962). The potency of the new compounds was estimated and compared with Clopidogrel and the aggregation was induced by adenosine diphosphate (ADP; 0.3 mM). The test samples were pre incubated with platelets for 5 min at 37 LC. All the test compounds were dissolved in DMSO at 300 lg/mL concentration. All the tests were performed within 3 h after collection of blood. Corresponding solvents were used as blank controls for the corresponding tests. The antiplatelet aggregation potency is expressed as inhibition (%) which is calculated as follows:

Inhibition % = (A- B) /A X100

Where A and B were the absorbance values of the corresponding blank controls and test samples, respectively.

Among all the compounds **6a–p**, compound **6e** and **6k** showed significant platelet aggregation induced by ADP. It was observed that substituted triazoles showed good anti-platelet activity over the free triazoles **(6a).** Among all the substitutions occurred on the aryl ring, it was observed that substitution at the 4th position of the aromatic ring is more prominent than the substitution at other positions. We attempted to screen the antiplatelet activity of chloro and fluoro substituted series from the examples. It was showed that 4-chloro derivative **6e** to be prominent antiplatelet aggregate-tor among the other chloro substituted derivatives. It was also noticed that 2,3,4-trisubstituted derivative (**6k)** showed good antiplatelet activity over the other derivatives (Table 1). Substitution at the 3rd position of the phenyl ring showed poor antiplatelet activity (**6d**) over the other positions. It was also concluded that among the all substitution occurred on the aryl ring of amide derivatives, aromatic amides showed significant activity over the benzyl amides (**6l** and **6m)** Hence, all the compounds showed moderate to significant antiplatelet activity compared with Clopidogrel (Table 1).

In vitro antiplatelet aggregation activity studies

Preparation of platelet rich plasma

The citrated blood was used for the preparation of PRP collected from the healthy human volunteer and mixed

with 1.0 mL of 3.8% trisodium citrate and centrifuged at 180g for 10 min. The upper two-third fraction of plasma (PRP) was transferred to another centrifuge tube leaving behind lower one-third layer to avoid contamination with WBCs and RBCs. Platelet poor plasma (PPP) was obtained by the centrifugation of the remaining sample at 2500g for 10 min.

Aggregometry

The antiplatelet aggregation studies were evaluated by a turbidimetric method based on ADP-induced (2.0 lM, 5 lL) platelet aggregation in human PRP. Platelet aggregation was studied at 37 LC using Born's method in a platelet aggregation module. A final concentration of ADP 2.0 lmol/L was used in a volume of 5 lL. The new compound 0.05 mL at different concentrations and normal saline were added to 0.45 mL PRP, respectively. After 5 min, ADP (2.0 lmol/L, 5 lL) was given. Maximal change in light transmission was assumed to represent maximal platelet aggregation. Platelet aggregation was measured and the maximal deflection was obtained after 5 min. The results were expressed as mean ± SEM and the means were compared using Student's t-test, p value is <0.05.

Table: 1 In vitro potency of compounds (6a-p) (n=6-8 experiments) in the inhibition of ADP induced platelet aggregation in human PRP

Compound	% of Inhibition of platelet aggregation
6a	**60±2**
6b	25±3
6c	20±1
6d	**17±2**
6e	**62±1**
6f	20±2
6g	24±4
6h	21±2
6i	18±1
6j	21±1
6k	**65±3**
6l	30±3
6m	30±1
6n	33±3
6o	30±3
6p	22±2
Clopidogrel	39±2

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)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethanol (2)

To a solution of the compound **1**(20.0 g, 0.62 moles) in Tetrahydrofuran (200.0 mL), was added slowly lithium aluminium hydride (4.65 g, 0.124 moles) at 0-5 in lot wise manner for 30 minutes raised the reaction mass to room temperature slowly heated to at reflux temperature. The progress of the reaction mixture monitored using TLC.After completion of the reaction, cooled the reaction mixture to 0-5°C, diluted the reaction mixture with ethyl acetate (230 mL) slowly over a period of 30-40 minutes. Then, added saturated NH_4Cl solution slowly into the reaction mixture. Maintained the stirring for 20-30 minutes, separated the organic layer. Organic layer was concentrated under reduced pressure to afford oily residue which was crystallized in the diisopropyl ether (115 mL) to result the title compound as cream colored solid. yield 80%, mp: 105–110 °C, IR (KBr) (cm'1):) 3453 (OH) (^{1}HNMR 400 MHz $CDCl_3$,) δ 2.65-2.89 (m, 4H, 2 x CH_2), δ 3.60 (s, 2H, CH_2), δ 4.0 (s, 1H, CH), δ 4.2 (s, 2H, CH_2 (OH),δ 6.71-7.5 (6H, ArH). :).^{13}C NMR (100 MHz, $CDCl_3$): ð, 25.43, 50.68, 53.11, 61.84, 63.12, 127.47, 127.55, 128.34, 128.78, 129.07, 130.02, 133.47, 133.96, 136.6,137.65, MS(m/z):294(M+1).

Synthesis of 5-(2-azido-1-(2-chlorophenyl)ethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine(3)

To a solution of the compound **2**(10.0 g, 0.034 moles) in acetonitrile (100.0 mL), was added . (10.1 g, 0.0371 moles) PBr_3 added slowly over a period of 30-40 minutes at 0-5°Cthe reaction mixture was for stirred over night at ambient temperature. The progress of the reaction mixture monitored using TLC. Product was precipitated during the reaction After completion of reaction, solvent was distilled off under reduced pressure to half of its total volume at below 35°C. Reaction mixture was diluted with ACN (50 mL) and cooled the reaction mixture to 0-5°C and added NaN_3 (6.7 g, 0.12 moles) slowly over a period of 30-40 minutes Then slowly raised the temperature to room temperature and maintained for overnight. Water (100 mL) was added to the reaction mixture to precipitate out the solid, followed by filtration and drying of the product at 60°C under reduced pressure affords the title compound Off-white colored solid yield 90%, mp: 123-125°C, IR (KBr) (cm'1):) :2095 (Azide) (400 MHz $CDCl_3$,) δ 2.8-3.7 (m, 4H, 2 x CH_2), δ 3.7. (s, 2H, CH_2), δ 4.28 (s, 2H, CH_2), 4.1 (s, 1H, CH) δ 6.76-7.74 (6H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.58, 49.41, 50.73, 52.76, 58.86, 124.88, 128.08, 128.40, 129.69, 129.85, 130.28, 130.72, 131.75, 132.90, 137.50, MS(m/z):319(M+1).

Synthesis of methyl 1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate(4)

To a solution of the compound **1**(10.0 g, 0.032 moles) dimethylsufloxide (100.0 mL), was added

methylacetoacetate(2.0 g, 0.064 moles) then added K_2CO_3(30 g, 0.224 moles (the reaction mixture was for stirred over night at ambient temperature. The progress of the reaction mixture monitored using TLC.. Reaction mixture was heated at 60-65°C for 24 hr. Progress of the reaction mixture monitored using TLC). After completion of the TLC, cooled the reaction mixture to 25-30°C it was cooled to 0-5°C, water (180 mL) was added slowly drop wise to precipitate out the solid material. Adjusted the pH of the reaction mixture to 7-8 using 5% diluted HCl and stirred for 30-40 minutes. It was filted and washed the with water. Then solid was dissolved in dichloromethane (100 mL) and separated water layer, evaporate the solvent under reduced pressure affords the compound 4 as a semisolid. The residue was dissolved in diisopropylether (54 mL) and adjusted the pH of the suspension to 1-2 using methanolic HCl at 0-5°C to afford the title compound (**4)**, as off white colored solid material. The product was dried under reduced pressure for 4-5 hr at below 60°C. Yield 85% M.R. 80-85° Off-white colored solid IR (KBr) (1731 (C=O) cm'1):) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), δ 2.76-3.68(m, 4H, 2 x CH_2), δ 3.8. (s, 2H, CH_2) , δ 4.26 (q, 2H, OCH2) δ 3.68 (s, 3H, CH_3), δ 4.10 (s, 1H, CH), δ 4.52 (s, 2H, CH_2), δ 6.76-7.84 (6H, ArH).^{13}C NMR (100 MHz, $CDCl_3$): δ 8.87, 14.29, δ 21.36, 49.01, 50.26, 57.77, 60.75, 125.06, 125.48, 126.65, 128.25, 128.58, 129.77, 130.36, 131.27, 131.67, 136.81, 138.16, 138.67. 161.62 MS(m/z):417(M+1).

Synthesis of 1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxylic acid(5)

To a solution of the compound **4**(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 5-6–4 h.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 **5** 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 **5** as crude material. Cream colored solid recrystallized in acetonitrile (25.0 mL) affords compound **5** as white solid material., yield 75% M.R.115-120° c IR (KBr) (c 1631 (C=O), 3480 (OH)^{1}HNMR (400MHz, DMSO-d_6) : δ 2.35 (s, 3H, CH_3), δ 2.79-2.82 (brs, 4H, 2 x CH_2), δ 3.54 (s, 2H, CH_2), δ 3.74 (s, 2H, CH_2), δ 4.52 (s, 2H, CH_2), δ 4.1 (s, 1H, CH). δ 6.79-7.44 (6H, ArH)^{13}C NMR (100MHz, DMSO-d_6): δ 8.79, 25.39, 49.46, 50.61, 52.91, 123.21, 125.76, 128.23, 128.48, 129.21, 129.27, 130.52, 132.73, 133.25, 134.19, 136.75, 138.11, 153.44, 168.94. MS(m/z):403 (M+1).

Synthesis of title compounds (7a-7p)1 -(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide(6a)

To a solution of the compound **5**(5.0 g, 0.012 moles) in carbonterachloride (50.0 mL) and pyridine (0.6. g, 0.006moles was added under nitrogen atmosphere. It was cooled the reaction mixture to -5 °C to 0 °C and was added slowly PCl_5 (5 g, 0.025 moles) slowly into the reaction mixture at below5 °C. Stirred the reaction mixture over a period of 30–40 minutes under nitrogen atmosphere at below 5 °C. Slowly heated the reaction to reflux temperature for 2 h. Progress of the reaction was monitored by using TLC, after completion of the reaction). Concentrated under reduced pressure. cooled to 10 then diluted with chloroform 50 ml and passed ammonia gas/substituted anilines(0.04moles) into the reaction mixture until pH of the reaction mixture will became 9-10. After completion of the reaction mixture was further diluted with $CHCl_3$ (10 mL) and filtered the undissolved salts. Then organic layer wash washed with dilute HCl (5%) (2x10 mL) followed by washing with saturated $NaHCO_3$ solution (2x 10 mL). Finally, washed the organic layer with water (2x10 mL). Organic layer was dried over anhydrous Na_2SO_4 and removed the solvent completely under reduced pressure. Solid was isolated from ether and dried under reduce pressure for 4-6 hr at 60°C affords the title compound off white colored solid Yield50% M.R: 125-128°C IR (KBr) (cm^{-1}) 1622 (C=O), 3340 (NH_2) ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), δ 2.78-2.83 (m, 4H, 2 x CH_2), δ 3.50 (s, 2H, CH_2), δ 3.74 (s, 2H, CH_2), δ 5.51 (s, 1H, CH_2), 4.52 (s, 2H, CH_2), δ 6.79-7.45 (6H,ArH), δ 7.70 (s, 2H, NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ 8.42, 25.46, 49.27, 50.67, 52.95, 61.29, 123.27, 125.90, 128.29, 128.45, 128.52, 129.25, 133.32, 134.46, 136.57, 138.81, 143.43,160.4, 162.29 MS (m/z) 402. (M+1). Employing the similar experimental procedures the remaining derivatives from **6b-6p** have been prepared. The following are the characteristic data of the compounds **6b-6p**.

Synthesis of 1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-N-phenyl-1H-1,2,3-triazole-4-carboxamide (6b):Yield 65% M.R 105-110°C: Off white colored solid IR (KBr) (cm-1): 1682(C=O), 3368 (NH) MS (m/z): 520.2 (M+1) 1H NMR (400 MHz, CDCl3): δ 2.24(s, 3H, CH3), 2.80-2.90 (m, 4H, 2 x CH2),), δ 3.74(s, 2H, CH2), δ 3.63(s, 3H, OCH3), δ 4.2 (s, 2H, CH2) δ 4.6 (s, 1H, CH)) δ 6.7-7.7(11H, ArH), δ 9.14 (s, 1H, NH) 13C NMR (100 MHz, CDCl3): δ 8.42, 25.6 50.4,51.86, 53.46, 121.73, 122.65, 124.29, 125.82,127.69,127.84, 128.21, 128.38, 129.09, 130.69,130.47, 131.26, 134. 63, 135.63,137.2,137.2, 136.9, 146.0 , 161.82, 163.7 MS (m/z 478 (M+1):

Synthesis of N-(2-chlorophenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide**(7c)** Yield: 60% M.R.: 133-138°COff white colored solid IR (KBr) (cm^{-1}): 1683 (C=O), 3349 (NH) ^{1}H NMR (400 MHz, $CDCl_3$)): δ 2.24(s, 3H, CH_3), 2.80-2.90 (m, 4H, 2 x CH_2),), δ

3.64(s, 2H, CH_2), δ 3.73(s, 3H, OCH_3), δ 4.2 (s, 2H, CH_2) δ 4.6 (s, 1H, CH)) δ 6.7-7.7(10H, ArH), δ 9.14 (s, 1H, NH) ^{13}C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.94, 51.86, 53.46, 119.98, 121.73, 122.65, 125.29, 127.82,128.69,127.84, 128.21, 128.38, 129.09, 130.69,130.47, 131.26, 134. 63, 137.2,137.2, 138.9, 146.54 , 161.82, 163.7 MS (m/z) : 511 (M+1)).

Synthesis of N-(3-chlorophenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide**(6d)** Yield: 61% M.R.: 112-116°C Cream colored solid IR (KBr) (cm^{-1}): 1686 (C=O), 3374 (NH) ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28(s, 3H, CH_3), 2.82-2.93 (m, 4H, 2 x CH_2),), δ 3.65 (s, 2H, CH_2), δ 3.78(s, 3H, OCH_3), δ 4.1. (s, 2H, CH_2) δ 4.6 (s, 1H, CH)) δ 6.6-7.6(10H, ArH), δ 9.14 (s, 1H, NH) ^{13}C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.94, 51.86, 53.46, 118.98, 121.73, 122.65, 125.29, 127.82,128.69,127.84, 128.21, 128.38, 129.09, 130.69,130.47, 131.26, 134..63, 137.2,138.2, 139.9, 145.54 , 161.82, 163.7 MS (m/z) : 511 (M+1))

Synthesis of N-(4-chlorophenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide**(6e)** Cream colored solid Yield: 58% M.R.: 152-158°C IR (KBr) (cm^{-1}): 1681 (C=O), 3371 (NH) ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28(s, 3H, CH_3), 2.82-2.93 (m, 4H, 2 x CH_2),), δ 3.65 (s, 2H, CH_2), δ 3.78(s, 3H, OCH_3), δ 4.1. (s, 2H, CH_2) δ 4.6 (s, 1H, CH)) δ 6.67.8(10H, ArH), δ 9.14 (s, 1H, NH) ^{13}C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.94, 51.86, 53.46, 118.98, 121.73, 122.65, 125.29, 127.82,128.69,127.84, 128.21, 128.38, 129.09, 130.69,130.47, 131.26, 134..63, 137.2,138.2, 139.9, 145.54 , 161.82, 163.7 MS (m/z) : 511 (M+1)

Synthesis of N-(2,3dichlorophenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide**(6f)** Cream colored solid Yield: 48%M.R.: 138-142°C IR (KBr) (cm^{-1}): 1688 (C=O), 3346 (NH^{1}H NMR (400 MHz, $CDCl_3$ δ 2.28(s, 3H, CH_3), 2.82-2.93 (m, 4H, 2 x CH_2),), δ 3.65 (s, 2H, CH_2), δ 3.78(s, 3H, OCH_3), δ 4.1. (s, 2H, CH_2) δ 4.6 (s, 1H, CH)) δ 6.7-7.7(9H, ArH), δ 9.14 (s, 1H, NH) ^{13}C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.94, 51.86, 53.46, 118.98, 121.73, 122.65, 125.29, 127.82,128.69,127.84, 128.21, 128.38, 129.09, 130.69,130.47, 131.26, 134..63, 137.2,138.2, 139.9, 145.54 , 161.82, 163.7 MS (m/z) : 546 (M+1).

Synthesis of N-(3,4dichlorophenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide**(6g)** Off white colored solid Yield: 56% M.R.: 133-135°C IR (KBr) (cm^{-1}): 1688 (C=O), 3364 (NH) ^{1}H NMR (400 MHz, $CDCl_3$):): δ 2.28(s, 3H, CH_3), 2.82-2.93 (m, 4H, 2 x CH_2),), δ 3.65 (s, 2H, CH_2), δ 3.78(s, 3H, OCH_3), δ 4.1. (s, 2H, CH_2) 4.6 (s, 1H, CH) δ 6.7-7.7(9H, ArH), δ 9.14 (s, 1H, NH) ^{13}C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.94, 51.86, 53.46, 118.98, 121.73, 12265, 125.29, 127.82,128.69,127.84, 128.21, 128.38, 129.09, 130.69,130.47, 131.26, 134.24, 134..63, 138.64,139.9, 145.54 , 161.82, 163.7 MS (m/z) : 546 (M+1).

Synthesis of N-(2-fluorophenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide**(6h)** Cream colored solid Yield: 68% M.R.: 122-124°C IR (KBr) (cm^{-1}): 1690 (C=O), 3379 (NH) ^{1}H NMR (400 MHz, $CDCl_3$): 2.29(s, 3H, CH_3), 2.84-2.92 (m, 4H, 2 x CH_2),), δ 3.68 (s, 2H, CH_2), δ 3.73(s, 3H, OCH_3), δ 4.3. (s, 2H, CH_2) δ 4.4 (s, 1H, CH) δ 6.7-7.7(10H, ArH), δ 9.10 (s, 1H, NH) ^{13}C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.94, 51.86, 53.46, 118.98, 121.73, 12265, 125.29, 127.84, 128.21, 128.38, 129.09, 130.69,130.47, 131.26, 134.24, 136.63, 138.64,139.9, 145.54 ,157.27, 159.27,162.82, 164.7 MS (m/z) : 496 (M+1).

Synthesis of N-(4-fluorophenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide(6i) Off white colored solid Yield: 63% M.R.: 122-126°CIR (KBr) (cm^{-1}): 1681 (C=O), 3374 (NH) ^{1}H NMR (400 MHz, $CDCl_3$): 2.29(s, 3H, CH_3), 2.84-2.92 (m, 4H, 2 x CH_2),), δ 3.65 (s, 2H, CH_2), δ 3.68 (s, 3H, OCH_3), δ 4.4. (s, 2H, CH_2) δ 4.1 (s, 1H, CH) δ 6.8-7.5(10H, ArH), δ 9.10 (s, 1H, NH) ^{13}C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.74, 50.86, 53.26, 119.98, 121.73, 12265, 125.29, 127.84, 128.21, 128.38, 129.09, 130.47, 131.26, 131.99, 134.24, 136.63, 138.64,139.9, 145.54 ,157.27, 158.27,159.82, 163.7 MS (m/z) : 496 (M+1).

Synthesis of N-(2,5difluorophenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide**(6j)** Cream colored solidYield: 62% M.R: 157-163°CIR (KBr) (cm^{-1}): 1694 (C=O), 3376 (NH) ^{1}H NMR (400 MHz, CDCl δ 2.29(s, 3H, CH_3), 2.84-2.90 (m, 4H, 2 x CH_2),), δ 3.67 (s, 2H, CH_2), δ 3.65 (s, 3H, OCH_3), δ 4.2 (s, 1H, CH) 4.4. (s, 2H, CH_2) δ 6.8-7.8(10H, ArH), δ 9.13 (s, 1H, NH) ^{13}C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.74, 50.86, 53.26, 119.2 122.73, 124.65, 125.29, 127.84, 128.21, 128.38, 129.09, 130.47, 131.26, 131.99, 134.24, 136.63, 138.64,139.9, 145.54 ,157.27, 158.27,159.82, 162.7 MS (m/z): 514.2 (M+1).

Synthesis of N-(2,3,4,triifluorophenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide(6k) White solid Yield70% M.R.: 155-156°CIR (KBr) (cm^{-1}): 1698 (C=O), 3373 (NH) ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29(s, 3H, CH3), 2.84-2.90 (m, 4H, 2 x CH2),), δ 3.67 (s, 2H, CH2), δ 3.65 (s, 3H, OCH3), δ 4.6. (s, 2H, CH_2) δ 4.2 (s, 1H, CH))δ 6.77-7.6(8H, ArH), δ 9.1 (s, 1H, NH) ^{13}C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.74, 50.86, 53.26, 119.45, 122.73, 124.65, 124.68, 125.29, 127.84, 128.21, 128.38, 129.09, 130.47, 131.26, 131.99, 134.24, 136.63, 138.64,139.9, 141.54 ,151.2, 159.82, 162.7 MS (m/z): 532 (M+1).

Synthesis of N-benzyl-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide(6l): Cream colored solid Yield: 50% M.R.: 108-114°C IR (KBr) (cm^{-1}): 1660 (C=O), 3419 (NH) ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH3), 2.80-2.95 (m, 4H, 2 x CH2),), δ 3.77 (s, 2H, CH2), δ 4.4. (s, 2H, CH_2) δ 4.0 (s, 1H, CH) 4.1. (s, 2H, CH_2)δ 6.77-7. 7 (11H, ArH), δ 9.01 (s, 1H, NH) ^{13}C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.74, 50.86, 53.26, 120.32, 122.73, 124.65, 124.68, 125.29, 127.84, 128.21, 128.38, 129.09, 129.27, 130.47, 131.26, 131.99, ,134.24, 136.63, 138.64, 138.92, 141.54 ,159.72, 159.82, 163.7 MS (m/z): 492. (M+1).

Synthesis of N-(4-fluorobenzyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide(6m) Off white colored solid Yield: 64% M.R.: 120-122°C IR (KBr) (cm^{-1}): 1651 (C=O), 3412 (NH) ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH3), 2.80-2.93 (m, 4H, 2 x CH2),), δ 3.77 (s, 2H, CH2), δ 4.4. (s, 2H, CH_2) δ 4.0 (s, 1H, CH) 4.2. (s, 2H, CH_2)δ 6.73-7. 7 (10H, ArH), δ 9.01 (s, 1H, NH). . 13C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.74, 50.86, 53.26, 55.76, 121.73, 122.65, 122.68, 125.29, 127.84, 128.21, 128.38, 129.09, 129.27, 130.47, 131.26, 131.89, 141.54 ,134.04, 136.63, 138.74, 138.92, , 158.72, 159.72, 163.7 MS (m/z): 510 (M+1).

Synthesis of N-(4-methoxy phenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide (6n) Beige colored solid Yield: 50% M.R.: 165-169°C IR (KBr) (cm^{-1}): 1633 (C=O), 3204 (NH)^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.80-2.93 (m, 4H, 2 x CH_2),), δ 3.77 (s, 2H, CH_2), δ 3.78 (s, 3H, OCH_3), δ 4.4. (s, 2H, CH_2) δ 4.0 (s, 1H, CH)), δ 6.73-7. 7 (10H, ArH), δ 9.01 (s, 1H, NH). . ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.42, 25.59, 49.74, 50.86, 53.26, 61.76, 121.73, 122.65, 122.68, 125.29, 127.84, 128.21, 128.38, 129.09, 129.27, 130.47, 131.26, 131.89, 141.54 ,134.04, 136.63, 138.74, 138.92, 158.72, 159.72, 163.7 MS (m/z): 508. (M+1).

Synthesis of N-(3-methoxy phenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide(6o) Yield: 48% M.R.: 98-104°C IR (KBr) (cm^{-1}): 1681 (C=O), 3374 (NH)^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H, CH3), 2.81-2.95 (m, 4H, 2 x CH2),), δ 3.77 (s, 2H, CH2), δ 3.78 (s, 3H, OCH3), δ 4.4. (s, 2H, CH2) δ 4.4 (s, 1H, CH)), δ 6.73-7. 7 (10H, ArH), δ 9.1 (s, 1H, NH). 13C NMR (100 MHz, CDCl3): δ 8.42, 25.59, 49.74, 50.86, 53.26, , 61.76, 121.73, 122.65, 122.68, 125.29, 127.84, 128.21, 128.38, 129.09, 129.27, 130.47, 131.26, 131.89, 141.54 ,134.04, 136.63, 138.74, 138.92, , 158.72, 159.72, 163.7 MS (m/z): 508. (M+1).

Synthesis of N-(4-bromophenyl)-1-(2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)ethyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide(6p) Cream colored solid Yield: 40% M.R. 157-163°C IR (KBr) (cm^{-1}): 1681 (C=O), 3371 (NH) ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), δ 2.78-2.93 (m, 4H, 2 x CH_2), δ 3.62 (s, 2H, CH_2), δ 4.0 (s, 1H, CH), δ 4.2 (s, 2H, CH_2), δ 6.73-7. 67 (10H, ArH), δ 9.01 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.40, 25.48, 49.66, 50.73, 53.13, 55.73, 121.28, 122.25, 125.18, 127.58, 128.14, 128.36, 128.97, 129.22, 130.38, 131.51, 131.97, 133.42, 133.82, 136.88, 138.48, 138.70,152.26, 161.03, 163 MS (m/z): 556 (M+1).

APPLICATIONS

All synthesized compounds were screened for antiplatelet activity noticed that 2,3,4-trisubstituted derivative **(6k, (6k,6a**) showed good antiplatelet activity over the other derivatives (Table 1). Substitution at the 3rd position of the phenyl ring showed poor antiplatelet activity **(6d**) over the other positions. Hence, all the compounds showed moderate to significant antiplatelet activity compared with Clopidogrel (Table1).

CONCLUSION

We have successfully synthesized of sixteen new triazole -4-carboxylic acid amide derivatives**(6a–6p)** via (**5**) in good yields. From the results and discussions made above it may be concluded that:The substituted derivatives should be used in future drug designing. Introduction of other heterocyclic moieties may also bring improved inhibitory activity. All the compounds showed moderate to significant platelet aggregation inhibitor activity.

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