



Research Article

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## Synthesis of some novel thiazole derivatives

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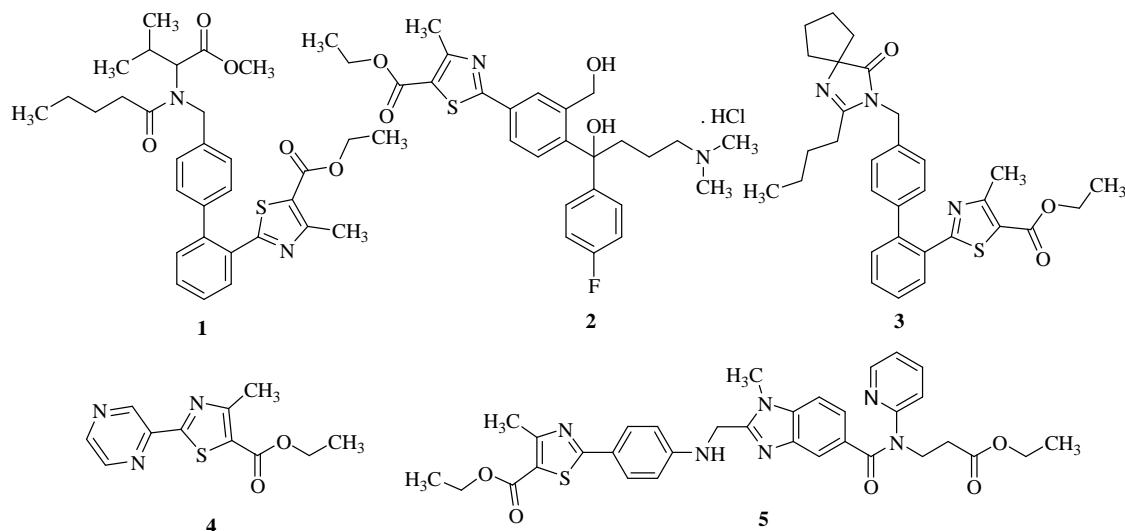
### ABSTRACT

Design, synthesis and characterization of novel series of thiazole derivatives are described.

**Keywords:** Synthesis, Thiazole, Characterization, Drugs

### INTRODUCTION

Thiazole derivatives have attracted enormous interest due to their diverse biological activities. Thiazole is a heterocyclic compound featuring both a nitrogen atom and sulfur atom as part of the aromatic five membered ring. Thiazoles have been reported to show pharmacological activities. Some of them are used as drugs[1]. The reported literature, thiazoles were possess antimicrobial[2-5], analgesic[6], anti-inflammatory[7], anti-convulsant[8], cardiotonic[9], anti-cancer[10,11], ant-tubercular[12] and anthelmintic[13] activities. Antimicrobial activities of some substituted thiazoles are well established because of its (S-C=N) toxophoric unit. Thiazoles have enhanced lipid solubility with hydrophilicity. Thiazoles are easily metabolized by routine biochemical reactions and are non-carcinogenic in nature [14].



Thiazoles are important class of heterocyclic compounds, found in many potent biologically active molecules such as sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral drug), Abafungin (antifungal drug) Bleomycine and Tiazofurin (antineoplastic drug). It has been noticed continuously over the year that interesting biological activities [15-17] were associated with thiazole derivatives. Recently the applications of thiazoles were found in drug development for the treatment of allergies[18], hypertension[19], nflammation[20], chizophrenia[21], bacterial[22], HIV infections[23], hypnotics[24] and more recently for the treatment of pain[25] as fibrinogen receptor antagonists with antithrombotic activity[26] and as new inhibitors of bacterial DNA gyrase B[27]. Based on the above biological importance we have synthesized of some novel thioazole derivatives.

As part of our research program in the development of new thiazole derivatives, preparation of thiazole derivative is undertaken. Herein, we described design, synthesis and characterization of thiazole derivatives **1-5**. All the synthesized derivatives were thoroughly characterized by spectral data.

## EXPERIMENTAL SECTION

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were measured in  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$  using 300 MHz, on a Bruker AVANCE-II 300 MHz FT NMR spectrometer; the chemical shifts ( $\delta_{\text{H}}$ ,  $\delta_{\text{C}}$ ) are reported in  $\delta$  ppm relative to TMS. The FT-IR spectra ( $\nu_{\text{max}}$  in  $\text{cm}^{-1}$ ) were recorded in the solid state as KBr dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70eV) was recorded on HP-5989A LC-MS spectrometer. Reaction monitoring was done by TLC (0.5 mm thickness) using silica gel-G coated Al-plates (Merck), mobile phase: Chloroform: Methanol (9:1) and Ethyl acetate: Hexane (6:4) and spots were visualized by exposing the dry plates in UV light (254.0 nm) or iodine vapors. Column chromatography was performed with silica gel 100 - 200 mesh. The melting points were determined by using the capillary method on POLMON (model MP-96) melting point apparatus and are uncorrected. The elemental analysis (C,H,N) of compounds was performed on Carlo Erba-1108 elemental analyzer. Their results were found to be in good agreement with the calculated values. The solvents and reagents were used without further purification.

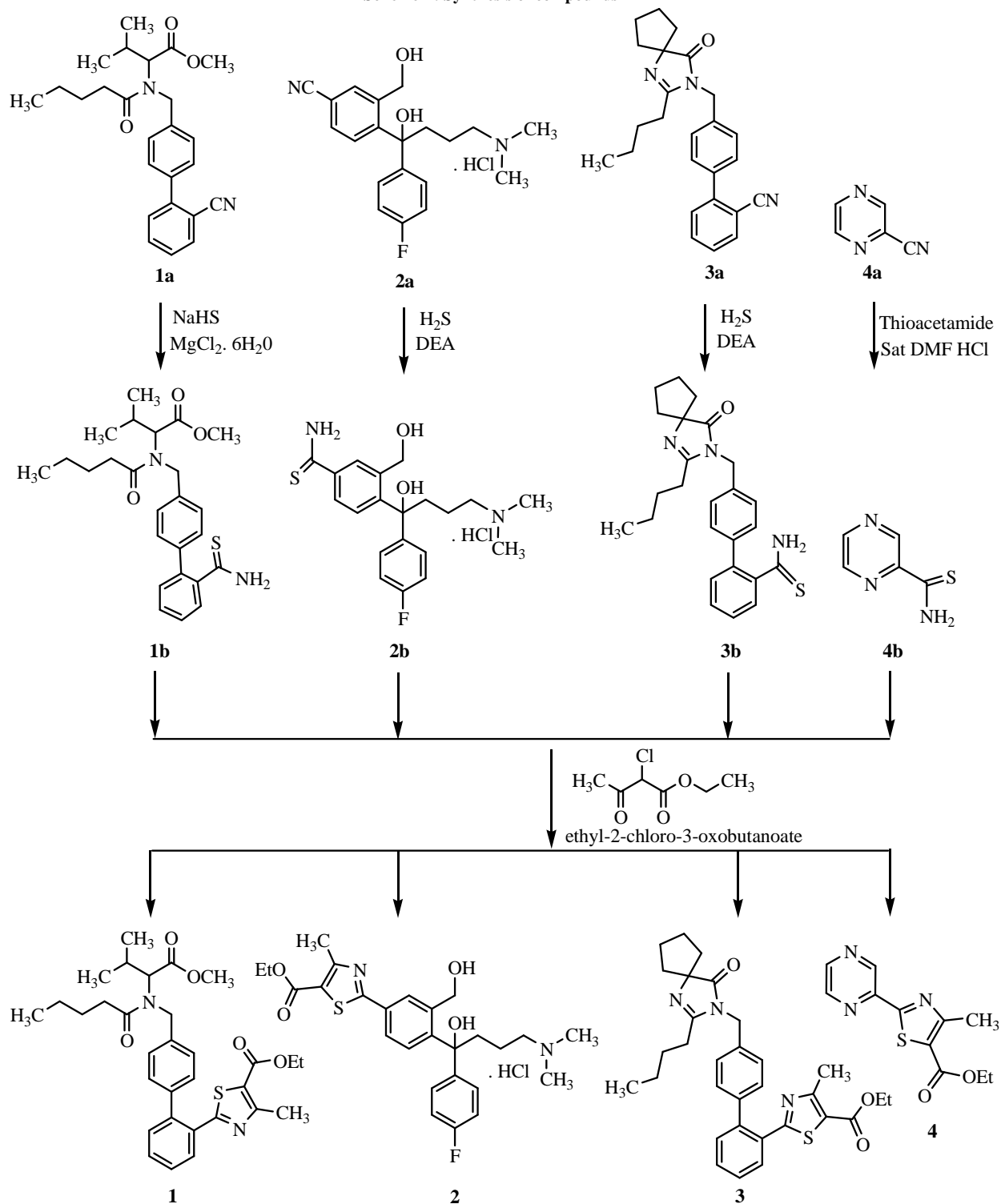
### Synthesis of ethyl 2-(4'-((N-(1-methoxy-3-methyl-1-oxobutan-2-yl) pentanamido) methyl) biphenyl-2-yl)-4-methylthiazole-5-carboxylate (**1**):

A solution of **1a** (5.0 g, 0.012 mol.), sodium hydrosulphide (2.77 g, 0.042 mol.), and magnesium chloride hexahydrate (2.67g, 0.012 mol) in dimethyl formamide (40.0 mL) stirred at ambient temperature up to **1a** disappeared in tlc. After completion of reaction, quenched with water (50 mL) at 25-35°C, the aqueous layer was extracted with dichloromethane (50 mL). The organic layer was distilled below 40°C under reduced pressure to obtain **1b** as oily residue. The oil residue was dissolved in isopropyl alcohol (25.0 mL) and ethyl-2-chloro-3-oxobutanoate (2.5 g, 0.015 mol.) at 25-30°C. The reaction mass heated to reflux temperature up to **1b** disappeared in tlc. The reaction mass was quenched with chilled water (100 mL), the aqueous layer was extracted with dichloromethane (50 mL). The organic layer was distilled below 50°C under reduced pressure to obtain residue, which was further purified by column chromatography (Silica gel 100 - 200 mesh) by using 3 % ethyl acetate in hexane as mobile phase to pure compound-**1** in 85% yield as white powder. Melting point: 84 to 87°C. IR (KBr,  $\text{cm}^{-1}$ ): 2958.90, 2874.03, 2360.95, 1732.13, 1701.27, 1647.26, 1458.23, 1369.50, 1330.93, 1095.60, and 767.69.  $^1\text{H}$ -NMR ( $\text{DMSO}-d_6$ ):  $\delta$  0.76 (d, 5H), 0.86 (m, 4H), 1.19 (m, 5H), 1.33 (q, 1H), 1.46 (m, 2H), 1.57 (t, 1H), 2.12 (m, 1H), 2.30 (m, 2H), 2.60 (d, 3H), 4.19 (q, 3H), 4.38 (m, 1H), 4.67 (m, 3H), 7.20 (m, 4H), 7.37 (t, 1H), 7.56 (m, 2H), 7.95 (t, 1H). MS ( $m/z$ ): 551 [M+H], Anal. Calcd for  $\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_5\text{S}$ : C, 67.61; H, 6.95; N, 5.09; O, 14.53; S, 5.82.

### Synthesis of 1-(2-(4-(3-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxypropyl)-3-(hydroxymethyl) phenyl)-4-methylthiazol-5-yl) propan-1-one hydrochloride (**2**):

To a stirred solution of **2a** (5.0 g, 0.015 mol.), diethylamine (2.22 g, 0.030 mol.) in dimethyl formamide (25.0 mL) at room temperature and dried hydrogen sulphide gas was slowly purged in to the reaction mass up to **2a** disappeared in tlc. After completion of reaction mass quenched with chilled water (50 mL), the obtained solid was filtered dried under vacuum at 45-50°C to get **2b** as yellow solid. The **2b** was dissolved in isopropyl alcohol (25.0 mL) and ethyl-2-chloro-3-oxobutanoate (3.14 g, 0.019 mol.) at 25-30°C. The reaction mass heated to reflux and maintained up to **2b** disappeared in tlc. The reaction mass was quenched in to chilled water (100 mL), the obtained precipitated solid was filtered and recrystallized in acetone (50 mL), obtained solid was dried under vacuum at 40-45°C to provide compound-**2** as white solid, 90% yield. Melting point: 190 to 195°C (decomposed). IR (KBr,  $\text{cm}^{-1}$ ): 3464.27, 3259.81, 2951.19, 2596.27, 2480.54, 1705.13, 1600.97, 1508.38, 1323.21, 1265.35, 1087.89, 1014.89, 844.85, and 594.10.  $^1\text{H}$ -NMR ( $\text{DMSO}-d_6$ ):  $\delta$  1.30 (t, 3H), 1.65 (m, 2H), 2.21 (q, 2H), 2.67 (d, 9H), 2.98 (q, 3H), 4.05 (d, 1H), 4.30 (q, 2H), 4.54 (d, 1H), 5.21 (s, 1H), 5.96 (s, 1H), 7.12 (t, 2H), 7.28 (q, 2H), 7.79 (d, 1H), 7.91 (dd, 1H), 8.19 (s, 1H), 9.76 (bs, 1H). MS ( $m/z$ ): 487 [M+H], 522.5 (M + HCl); Anal. Calcd for  $\text{C}_{26}\text{H}_{32}\text{ClFN}_2\text{O}_4\text{S}$ : C, 59.70; H, 6.17; N, 5.36; O, 12.24; S, 6.13.

Scheme-1: Synthesis of compounds 1-4

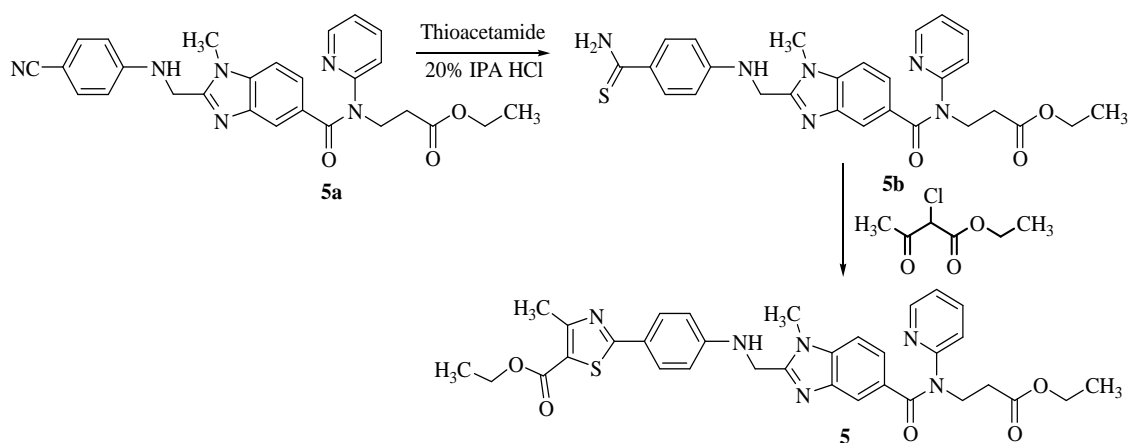


### Synthesis of N-(2-methyl-4-oxohexan-3-yl)-N-((2'-(4-methyl-5-propionylthiazol-2-yl) biphenyl-4-yl) methyl) pentanamide (3):

To a solution of **3a** (5.0 g, 0.012 mol.) in N, N-dimethyl formamide (25ml) and diethyl amine (1.94 g, 0.026 mol.), stirred at ambient temperature and dried hydrogen sulphide gas was slowly purged in to the reaction mass up to **3a** disappeared in tlc. After completion of starting material, quenched the reaction mass with chilled water (100 ml), the aqueous layer was extracted with ethyl acetate (100 mL). The organic layer was distilled below 45°C under reduced pressure to obtain **3b** as oily residue. The oil residue was dissolved in isopropyl alcohol (25.0 ml) and ethyl-2-chloro-3-oxobutanoate (2.67 g, 0.016 mol.) at 25-30°C. The reaction mass heated to reflux and maintained up to **3b** disappeared in tlc. The reaction mass was quenched in to chilled water (100 mL) and then extracted the

compound with dichloro methane (50 ML). The organic layer was distilled and degas below 50°C under reduced pressure to obtain residue, which was further purified by column chromatography (Silica gel 100 - 200 mesh) by using 5 % ethyl acetate in hexane as mobile phase by separated solid was recrystallized in hexane (100 mL), obtained solid was dried under vacuum at 45-50°C to provide compound-**3** in 85% yield as white powder. Melting point: 108 to 111°C. IR (KBr,  $\text{cm}^{-1}$ ): 3429.55, 2955.04, 2870.17, 2364.81, 2341.66, 1720.56, 1701.27, 1635.69, 1523.82, 1404.22, 1261.49, 1095.60, 810.13, and 767.69.  $^1\text{H-NMR}$  spectrum ( $\text{DMSO-d}_6$ ):  $\delta$  0.78 (t, 3H), 1.24 (q, 6H), 1.47 (q, 2H), 1.66 (d, 2H), 1.83 (d, 6H), 2.32 (t, 2H), 2.58 (s, 3H), 4.19 (q, 2H), 4.73 (s, 2H), 7.23 (q, 4H), 7.37 (q, 1H), 7.56 (m, 2H), 7.98 (q, 1H). MS ( $m/z$ ): 530 [ $\text{M} + \text{H}$ ]; Anal. Calcd for  $\text{C}_{31}\text{H}_{35}\text{N}_3\text{O}_3\text{S}$ : C, 70.29; H, 6.66; N, 7.93; O, 9.06; S, 6.05.

Scheme-2: Synthesis of compound 5



#### Synthesis of 1-(4-methyl-2-(pyrazin-2-yl) thiazol-5-yl) propan-1-one (**4**):

To a stirred solution of **4a** (5.0 g, 0.047 mol.) in saturated hydrochloride of N,N-dimethyl formamide (20ml) and thioacetamide (5.21 gm, 0.070 mole) was heated at 75-80°C. The reaction mixture was stirred up to **4a** disappeared in tlc. The reaction mass was quenched with water (50 mL) and then neutralized with 5% aqueous sodium hydroxide solution. The obtained solid was filtered dried under vacuum at 45-50°C to get **4b** as yellow solid. The **4b** was dissolved in isopropyl alcohol (25.0 mL) and ethyl-2-chloro-3-oxobutanoate (11.46 g, 0.069 mol.) at 25-30°C. The reaction mass heated to reflux and maintained up to **4b** disappeared in tlc. The reaction mass was quenched with chilled water (100 mL), the obtained precipitated solid was filtered and dried under vacuum at 40-45°C to provide compound-**4** as buff colored solid, 90% yield. Melting point: 100 to 103°C. IR (KBr,  $\text{cm}^{-1}$ ): 2985.91, 2360.95, 2341.66, 1975.17, 1708.99, 1527.67, 1400.37, 1373.36, 1311.64, 1261.49, 1099.46, 1010.73, 868.00, 825.56, and 759.98.  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  1.30 (t, 3H), 2.71 (s, 3H), 4.30 (q, 2H), 8.77 (dd, 2H), 9.30 (d, 1H). MS ( $m/z$ ): 250 [ $\text{M} + \text{H}$ ]; Anal. Calcd for  $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2\text{S}$ : C, 53.00; H, 4.45; N, 16.86; O, 12.84; S, 12.86.

#### Synthesis of ethyl 2-(4-((5-((3-ethoxy-3-oxopropyl)(pyridin-2-yl)carbamoyl)-1-methyl-1H-benzo[d]imidazol-2-yl)methyl amino)phenyl)-4-methylthiazole-5-carboxylate (**5**)

To a stirred solution of **5a** (5.0 g, 0.010 mol.) in 20% isopropyl alcohol hydrochloride (15ml) dilute with isopropyl alcohol (25ml) and thioacetamide (1.48 gm, 0.020 mole) was heated at 75-80°C. The reaction mixture was stirred up to **5a** disappeared in tlc. The reaction mass was quenched with water (50 mL) and then neutralized with 5% aqueous sodium hydroxide solution the obtained solid was filtered dried under vacuum at 45-50°C to get **5b** as yellow colored solid. The **5b** was dissolved in isopropyl alcohol (25.0 ml) and ethyl-2-chloro-3-oxobutanoate (3.4 g, 0.020 mol.) at 25-30°C. The reaction mass heated to reflux and maintained up to **5b** disappeared in tlc. The reaction mass was quenched with chilled water (100 mL), the obtained precipitated solid was filtered and recrystallized in ethanol (50 mL), obtained solid was dried under vacuum at 45-50°C to provide compound-**5** as off white solid, 85% yield. Melting point: 152 to 155°C. IR (KBr,  $\text{cm}^{-1}$ ): 3398.69, 2982.05, 2360.95, 1701.27, 1608.69, 1435.09, 1323.21, 1265.35, 1184.33, 1095.60, 817.85, and 748.41.  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ):  $\delta$  1.11 (t, 3H), 1.28 (t, 3H), 2.62 (s, 3H), 2.67 (t, 2H), 3.76 (s, 3H), 3.96 (q, 2H), 4.24 (m, 4H), 4.60 (d, 2H), 6.81 (d, 2H), 6.88 (d, 1H), 7.05 (t, 1H), 7.13 (m, 2H), 7.40 (d, 1H), 7.46 (s, 1H), 7.54 (m, 1H), 7.72 (d, 2H), 8.38 (m, 1H). MS ( $m/z$ ): 627 [ $\text{M} + \text{H}$ ]; Anal. Calcd for  $\text{C}_{33}\text{H}_{34}\text{N}_6\text{O}_5\text{S}$ : C, 63.24; H, 5.47; N, 13.41; O, 12.76; S, 5.12.

## RESULTS AND DISCUSSION

Reaction of compound **1a** with sodium hydrogen sulfide in the presence of magnesium chloride hexahydrate and subsequent condensation with ethyl-2-chloro-3-oxobutanoate furnished compound **1**. The structural assignment of **1**

based on its IR, NMR and Mass spectral data. In the Mass spectrum of **1** the highest peak at  $m/z$  551 (M+H) corresponds to molecular ion. In the IR spectrum (KBr) 2958.90 aliphatic C-H, 1701.27 ester carbonyl, 1647.26 t-amide carbonyl, 1095.60 C-O-C in ester,  $^1\text{H-NMR}$  shows characteristic peaks corresponding to thiazole ethyl ester at 1.30 (t, 3H), 2.71 (s, 3H), 4.30 (q, 2H).

Reaction of compound **2a** with hydrogen sulfide in the presence of diethylamine and subsequent condensation with ethyl-2-chloro-3-oxobutanoate furnished compound **2**. The structural assignment of **2** based on its IR, NMR and Mass spectral data. In the Mass spectrum of **2** the highest peak at  $m/z$  487 (M+H) corresponds to molecular ion. In the IR spectrum (KBr) 3259.81 and 1087.89 alcoholic -OH, 2951.19 aliphatic -CH, 2596.27 t-amine, 1705.13 ester carbonyl,  $^1\text{H-NMR}$  shows characteristic peaks corresponding to thiazole ethyl ester at 1.30 (t, 3H), 2.67 (s, 3H), 4.30 (q, 2H).

Reaction of compound **3a** with hydrogen sulfide in the presence of diethyl amine and subsequent condensation with ethyl-2-chloro-3-oxobutanoate furnished compound **3**. The structural assignment of **3** based on its IR, NMR and Mass spectral data. In the Mass spectrum of **3** the highest peak at  $m/z$  530 (M+H) corresponds to molecular ion. In the IR spectrum (KBr) 2955.04 aliphatic -CH, 1701.27 ester carbonyl, 1635.69 t-amide -CO, 1261.49 aromatic C-N, 1095.60 C-O-C in ester, 767.69 di substituted benzene,  $^1\text{H-NMR}$  shows characteristic peaks corresponding to thiazole ethyl ester 1.24 (t, 3H), 2.88 (s, 3H), 4.19 (q, 2H).

Reaction of compound **4a** with thioacetamide in the presence of saturated hydrochloride of dimethyl formamide and subsequent condensation with ethyl-2-chloro-3-oxobutanoate furnished compound **4**. The structural assignment of **4** based on its IR, NMR and Mass spectral data. In the Mass spectrum of **4** the highest peak at  $m/z$  250 (M+H) corresponds to molecular ion. In the IR spectrum (KBr) 2985.91 aliphatic -CH, 1708.99 ester carbonyl, 1099.46 C-O-C in ester, 759.98 C-S-C in ring  $^1\text{H-NMR}$  shows characteristic peaks corresponding to thiazole ethyl ester at 1.30 (t, 3H), 2.67 (s, 3H), 4.30 (q, 2H).

Reaction of compound **5a** with thioacetamide in the presence of 20% isopropyl alcohol hydrochloride and subsequent condensation with ethyl-2-chloro-3-oxobutanoate furnished compound **5**. The structural assignment of **5** based on its IR, NMR and Mass spectral data. In the Mass spectrum of **5** the highest peak at  $m/z$  627 (M+H) corresponds to molecular ion. In the IR spectrum (KBr) 3398.69 aromatic -NH, 2982.05 aliphatic -CH, 1701.27 ester carbonyl, 1608.68 pyridine derivative, 1095.60 C-O-C in ester,  $^1\text{H-NMR}$  shows characteristic peaks corresponding to thiazole ethyl ester at 1.28 (t, 3H), 2.62 (s, 3H), 4.24 (q, 2H).

## CONCLUSION

In conclusion, we have developed a facile method for the synthesis of new class of thiazole derivatives by utilizing well known chemical reactions. All the synthesized derivatives were well characterized by using Mass, NMR and IR spectral data.

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## REFERENCES

- [1] NS Mahajan; SR Pattana; RL Jadhav; NV Pimpodhar; AM Manikrao, *Int. J. Chem. Sci.*, **2008**,6(2),800-806.
- [2] RV Ragavan; V Vijayakumar; NS Kumari, *Eur. J. Med. Chem.*, **2010**,45(3),1173-1180.
- [3] E-ST Ali; AM El Kazak, *Eur. J. Chem.*, **2010**,1(1),6-11.
- [4] P. Karegoudar; MS Karthikeyan; DJ Prasad; M Mahalinga; BS Holla; NS Kumari, *Eur. J. Med. Chem.*, **2008**,43,261-267.
- [5] P Vicini; A Geronkiaki; M Incerti; F Zani; J Dearden; M Hewitt, *Bioorg. Med. Chem.*, **2008**,16,3714-3724.
- [6] KM Basavaraja; B Somasekhar; S appalaraju, *Ind. J. Heterocycl. Chem.* **2008**,18,69-72.
- [7] T Karabasanagouda; AV Adhikari; D Ramgopal; G Parameshwarappa, *Ind. J. Chem.*, **2008**, 47B,144-152.
- [8] MAK Amine; DE Abdel Rahman. YA El-Eryani, *Bioorg. Med. Chem.*, **2008**,16,5377-5388.
- [9] A Andreani; M Rambaldi; A Leoni; A Locatelli; R Bossa; M Chiericozzi; I Galatulas; G Salvatore, *Eur. J. Med. Chem.*, **1996**,31,383-387.
- [10] B Jiang; X-H Gu, *Bioorg. Med. Chem.*, **2000**,8,363-371.
- [11] TF Abbs; F Reji; SKC Devi; KK Thomas; KG Sreejalekshmi; SL Manju; M Francis; SK Philip; A Bharathan; KN Rajasekharan, *Ind. J. Chem.*, **2008**,47B,1145-1150.

- [12] CS Magdum; PL Ladda, SK Mohite, *Int. J. Chem. Sci.*, **2008**,6(3),1600-1605.
- [13] KP Bhusari; PB Khedekar; SN Umathe; RH Bahekar; RRA Raghu, *Ind. J. Heterocycl. Chem.*, **2000**,9,275-278.
- [14] K Taori; VJ Paul; H Luesch, *J. Am.Chem. Soc.*, **2008**,130,1806-1807.
- [15] N Siddiqui; MF Arshad; W Ahsan; MS Alam, *Int. J. of Pharmaceutical Sciences and Drug Research.*, **2009**,1(3),136-143.
- [16] J Quiroga; P Hernandez; B Insuasty; R Abonia; J Cobo; A Sanchez; M Nogueras; JN Low, *J. Chem. Soc. Perkin Trans-I.*, **2002**,4,555-559.
- [17] I Hutehrnson; SA Jennings; BR Vishnuvajjala; AD Westwell; MFG Stevens, *J. Med. Chem.* **2002**,45,744-747.
- [18] KD Hargrave; FK Hess; JT Oliver, *J. Med. Chem.*, **1983**,26,1158-1163.
- [19] WC Patt; HW Hamilton; MD Taylor; ML Ryan; Jr. DG Taylor; CJC Connolly; AM Doherty; SR Klutehko; L Sirear; BA Steinbaugh; BL Batley; CA Panichaud; ST Rapundalo; BM Michniewicz; SCJ Olson, *J. Med. Chem.*, **1992**,35,2562-2572.
- [20] RN Sharma; FP Xavier; KK Vasu; SC Chaturvedi; SS Pancholi, *J. Enz. Inhib. Med. Chem.*, **2009**,24,890-897.
- [21] JC Jaen; LD Wise; BW Caprathe; H Teele; S Bergmeter; CC Humblet; TG Heffner; LT Meltzner; TA Pugsley, *J. Med. Chem.* **1996**,33,311-317.
- [22] K Tsuji; H Ishikawa, *Bioorg. Med. Chem. Lett.*, **1994**,4,1601-1606.
- [23] FW Bell; AS Cantrell; M Hogberg; SR Jaskunas; NG Johansson; CL Jordon; MD Kintek; P Land; C Sahlberg; RJ Ternansky; RT Vasileff; L Vrang; SL West; H Zhang; XX Zhou, *J. Med. Chem.*, **1995**,38,4929-4936.
- [24] N Brgene; G Capan; NS Gunay; S Ozkirmli; M Gungor; S Ozbey; F Kendi, *Arch. Pharma. Med. Chem.*, **1999**,332,343-347.
- [25] JS Carter; S Kramer; JJ Talley; T Penning; P Collins; MJ Graneto; K Selbert; C Loboldt; J Masferrer; B Zwettel, *Bioorg. Med. Chem. Lett.*, **1999**,9,1171-1174.
- [26] A Badore; MF Bordes; P De Cointet; P Savi; A Bernat; A Lale; M Petitou; JP Maffrand; JM Herbert, *J. Med. Chem.*, **1997**,40,3393-3401.
- [27] J Rudolph; H Theis; R Hanke; R Endermann; L Johannsen; FU Geschke, *J. Med. Chem.*, **2001**,44,619-626.