Synthesis of Some Novel Thiazolo[3,2-a]pyrimidine and Pyrimido[2,1-b][1,3]thiazine Derivatives and their Antimicrobial Evaluation

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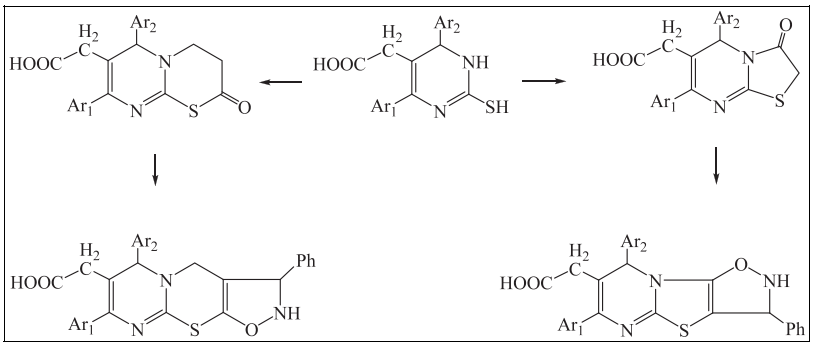


A 2-(2-Mercapto-4-(4-phenoxyphenyl)-6-(thiophen-2-yl)-1,6-dihydropyrimidin-5-yl) acetic acid was used as a reactive key precursor to design various pyrimidine derivatives such as thiazolo[3,2-a]pyrimidines and pyrimido[2,1-b][1,3]thiazines. The chemical structures of the newly synthesized products were confirmed by their elemental analyses and spectral data (IR, ^{1}H NMR, ^{13}C NMR, and mass spectra). The antibacterial and antifungal activities of some of the synthesized products were also evaluated, and it was found that compounds **3, 5, 9**, and **11** exhibited potent activity against tested microorganisms in comparison with standard drugs.

INTRODUCTION

In the recent years, pyrimidine derivatives gained great attention owing to their remarkable biological and pharmaceutical applications. They exhibited anticancer [1–5], antioxidant [6–8], antifungal [9,10], and antibacterial activities [11–14]. In addition, pyrimidine derivatives such as pyrazolo[1,5-a]pyrimidine, pyrido[2,3-d]pyrimidine, thieno[2,3-d]pyrimidines, pyrrolo[2,3-d]pyrimidines, and indolylpyrimidines showed potent antitumor [15–20], antitubercular [21], anti-inflammatory [22], and antidiabetic [23] activities. Furthermore, thiazolopyrimidine derivatives were considered as potent cytotoxic, analgesic, and antifungal agents [24–26]. On the basis of the reported observations and in continuation of our ongoing interest in the synthesis of biologically active molecules [27–30], the present work describes the synthesis of new series of thiazolo[3,2-a]pyrimidine and pyrimido[2,1-b][1,3] thiazine derivatives as well as the evaluation of their antibacterial and antifungal activities.

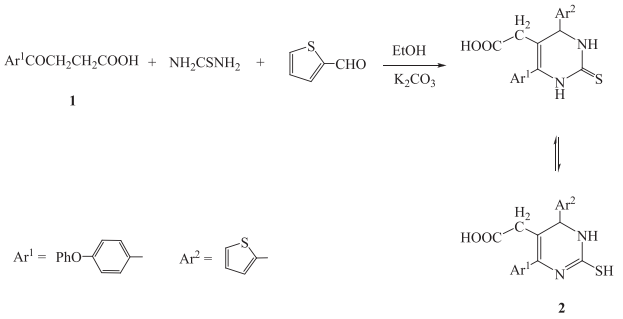
RESULTS AND DISCUSSION

Treatment of acid **1** (prepared from acylation of diphenyl ether by succinic anhydride under Fridel Crafts conditions [30]) with thiophen-2-carbaldehyde and thiourea in ethanol containing anhydrous potassium carbonate afforded 2-(2-mercapto-4-(4-phenoxyphenyl)-6-(thiophen-2-yl)-1,6-dihydropyrimidin-5-yl) acetic acid (2) (Scheme 1).

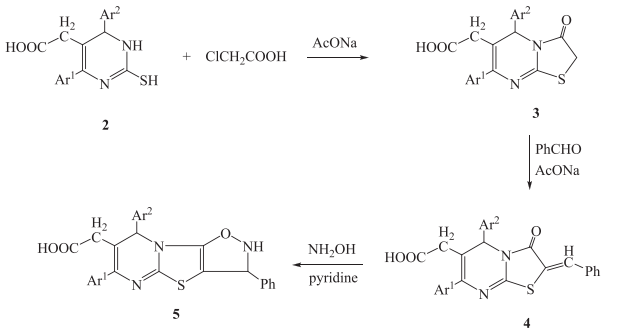
The structural formula of compound **2** was elucidated on the basis of its spectral data. IR spectrum exhibited absorption bands at 1690, 3415–3225, and 1690 cm^{-1} corresponding to NH, OH, and CO groups, respectively. On the other hand, ^{1}H NMR spectrum showed signals at 4.70, 7.53, and 12.33 ppm corresponding to protons of CH, NH, and OH, respectively.

Pyrimidine **2**, bearing adjacent SH and NH groups, was used as a reactive key precursor to construct a series of fused heterocycles that are expected to have antimicrobial activities. Thus, treatment of pyrimidine **2** with chloroacetic acid in acetic acid and acetic anhydride in the presence of sodium acetate furnished 2-(3-oxo-7-(4-phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5*H*-thiazolo[3,2-a]pyramidin-6-yl)acetic acid **(3)**. Condensation of the latter with benzaldehyde and sodium acetate resulted in the formation of 2-(2-benzylidene-3-oxo-7-(4-phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidin-6-yl) acetic acid **(4)**, which in turn reacted with hydroxylamine hydrochloride in pyridine to give thiazolo[3,2-a]pyrimidine **5** [31] (Scheme 2).

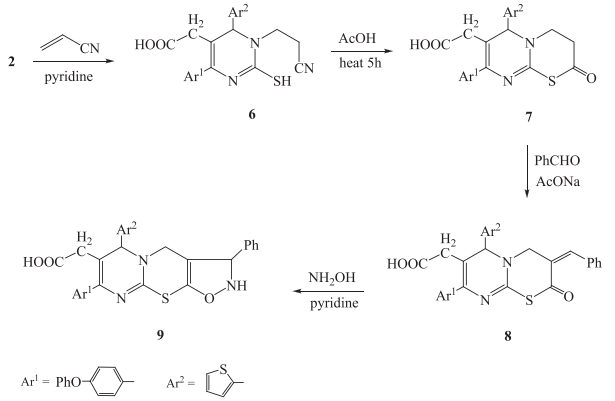
Scheme 1. Synthesis of 2-(2-mercapto-4-(4-phenoxyphenyl)-6-(thiophen-2-yl)-1,6-dihydro pyrimidin-5-yl) acetic acid **(2)**.



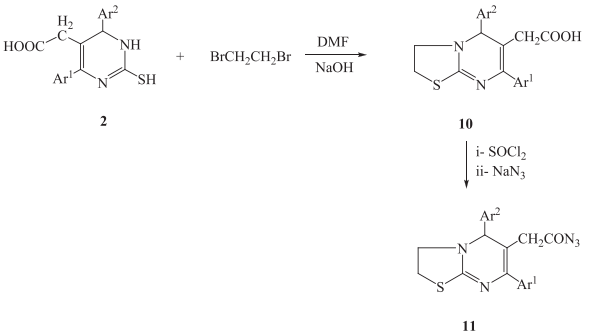
Scheme 2. Synthetic pathway of thiazolo[3,2-a]pyrimidine **5**.



Scheme 3. Synthetic pathway of 2-(8-(4-phenoxyphenyl)-3-phenyl-6-(thiophen-2-yl)-2,3-dihydro-4H,6H-isoxazolo[4,5-e]pyrimido[2,1-b][1,3] thiazin-7-yl) acetic acid **(9)**.



Scheme 4. Synthesis of thiazolo[3,2-a]pyrimidine derivatives **10, 11**.



On the other hand, pyrimidine **2** underwent Michael type addition upon treatment with acrylonitrile in pyridine to furnish pyrimidine derivative **6** [32]. IR spectrum of compound **6** displayed absorption bands at 3410–3270, 2620, 2207, and 1690 cm^{-1} corresponding to OH, SH, C≡N, and CO absorptions, respectively. Also, ^1H NMR spectrum revealed signals for methine and methylene protons at 4.50, 3.62, and 2.70 ppm, respectively. Cyclization of **6** with a mixture of acetic acid and hydrochloric acid afforded compound **7**. The tricyclic fused system 2-(8-(4-phenoxyphenyl)-3-phenyl-6-(thiophen-2-yl)-2,3-dihydro-4H,6H-isoxazolo[4,5-e]pyrimido[2,1-b][1,3]thiazin-7-yl) acetic acid **(9)** was synthesized *via* the condensation of **7** with benzaldehyde to give the benzylidene derivative **8** followed by the cyclization of **8** with hydroxylamine hydrochloride in pyridine (Scheme 3).

Treatment of pyrimidine **2** with 1,2-dibromoethane in dimethylformamide furnished 2-(7-(4-phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5H-thiazolo[3,2-a] pyrimidin-6-yl) acetic acid **(10)** (Scheme 4).

Heating of the latter with thionyl chloride followed by treatment with sodium azide resulted in the formation of the corresponding acid azide **11** that was used as a reactive key precursor for the preparation of compounds **12**–**15**, which are expected to be of biological importance. Thus, treatment of acid azide **11** with active methylene compounds namely, ethyl acetoacetate, ethyl cyanoacetate, malononitrile, and diethylmalonate in ethanol and sodium ethoxide afforded triazoles **12–15**, respectively (Scheme 5).

Antimicrobial activity. The antimicrobial activity of some of the synthesized compounds was evaluated against *Streptococcus sp* and *Bacillus subtilis* as Gram positive bacteria and *Escherichia coli* as Gram-negative bacteria. The compounds were also evaluated for their antifungal activity against *Aspergillus Niger* and *Candida Albican*. Streptomycin and ketoconazole were used as standard drugs to evaluate the potency of the tested compounds under the same conditions.

Agar diffusion method [33] was used for the determination of the preliminary antimicrobial activity and the results were recorded for each tested compound as the average diameter of inhibition zones (*d*) of bacterial or fungal growth around the disks in millimeters at concentration (100 mg/mL) in dimethyl sulfoxide. The observed data on the antimicrobial activity of the compounds and control drug are given in Table 1.

It has been observed from data depicted in Table 1 that, compared with standard drugs, most of the synthesized compounds showed varying degrees of

Scheme 5. Reaction of acid azide **11** with active methylene compounds.

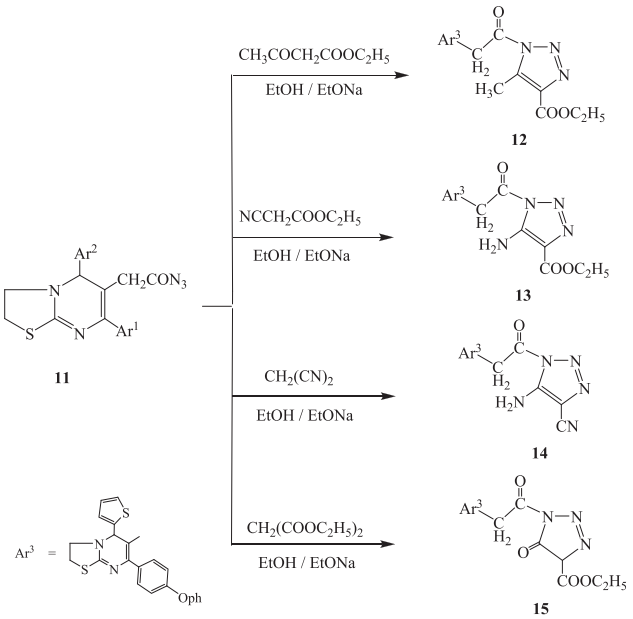


Table 1

Antimicrobial activity of compounds **2**–**13**.

Compds	*Streptococcus sp*	*Bacillus subtilis*	*Escherichia coli*	*Aspergillus Niger*	*Candida Albican*
2	++	+	+	+++	+
3	+++	+++	++	+	++
4	+	++	+	–	–
5	+++	++	+++	+++	++
6	++	+	–	+	–
7	++	++	+	+	–
8	+	–	++	–	+
9	++	+++	++	++	+
10	++	++	+++	+	–
12	+	+	++	+++	–
13	+++	++	++	++	+
S	+++	+++	+++		
K				+++	+++

Inhibition zone diameter: +++ (d > 12 mm, highly active); ++ (d = 9–12 mm, moderately active); + (d = 6–9 mm, slightly active); – (d ‹ 6 mm, inactive); S, Streptomycin; K, Ketoconazole.

inhibition against the tested microorganisms. Thus, compounds **3**, **5**, and **13** showed potent antibacterial activity against *Streptococcus sp*, while compounds **2**, **6**, **7**, **9**, and **10** showed moderate activity. Only compounds **2**, **5**, and **12** exhibited high activity against fungal strain *Aspergillus Niger*. On the other hand, all the tested compounds showed lower to no activity against *Candida Albican* except for compounds **3** and **5** that showed moderate activity. In addition, based on the results presented in Table 1, the synthesized products **3**, **5**, **9**, and **10** showed high antibacterial activity against *Bacillus subtilis and Escherichia coli*, while other compounds showed moderate and lower activity. From the previous results, it was observed that, the presence of thiazole and isoxazole moieties in compounds **3**, **5**, **9**, and **10** enhanced their antimicrobial activities.

CONCLUSION

In conclusion, new derivatives of thiazolo[3,2-a] pyrimidine and pyrimido[2,1-b][1,3]thiazine were synthesized and evaluated for their antibacterial and antifungal activities. Compounds **3**, **5**, **9**, and **10** showed potent activity against tested microorganisms in comparison with Streptomycin and Ketoconazole.

EXPERIMENTAL

Melting points are uncorrected and FT-IR spectra were recorded on a JASCO FT-IR 660 Plus spectrometer. NMR spectra were recorded on a Bruker Avance 400 (400 MHz) using DMSO as a solvent. Mass spectra were obtained using a Shimadzu GCMS-QP 1000 EX mass spectrometer. The chemical reagents and solvents were purchased from Sigma-Aldrich. TLC was conducted on precoated silica gel polyester sheets (Kieselgel 60 F254, 0.20 mm, Merck).

4-Oxo-4-(4-phenoxyphenyl)butanoic acid (1). Compound **1** was prepared according to the published procedure [30].

Anhydrous aluminum chloride (0.015 mol) was added to a mixture of succinic anhydride (0.01 mol) and diphenyl ether (0.01 mol) in tetrachloroethane (15 mL) within 10 min with stirring in ice bath. The stirring was continued for 5 h, then left overnight and the reaction mixture was poured onto crushed ice/HCl. The product was treated with petroleum ether and the obtained solid was filtered off and crystallized from benzene. Yield: 68%; M.p. 173–5°C. IR spectrum (KBr, ν, cm^{-1}): 3430–3311 (OH), 1705–1720 (2CO); ^{1}H NMR (DMSO-d_6) δ: 12.10 (s, 1H, OH, exchangeable), 8.02–7.04 (m, 9H, Ar─H), 3.23 (t, 2H, *β* CH_2), 2.57 (t, 2H, α CH_2); ^{13}C NMR, 188.30, 175.24 (2CO), 155.22, 152.25, 128.20, 127.31, 126.70, 122.50, 119.35, 116.27 (aromatic carbons), 31.50, (*β* CH_2) 28.35 (α CH_2); Ms: m/z = 270 (M^{+}); *Anal*. Calcd. for $C_{16}H_{14}O_4$ (270.28): C, 71.10; H, 5.22%. Found: C, 71.03; H, 5.13%.

2-(2-Mercapto-4-(4-phenoxyphenyl)-6-(thiophen-2-yl)-1,6-dihydropyrimidin-5-yl) acetic acid (2). A mixture of acid 1 (0.01 mol), thiourea (0.01 mol), thiophen-2-carbaldehyde (0.01 mol), and potassium carbonate (0.01 mol) in ethanol (30 mL) was heated under reflux for 8 h. After cooling, the reaction mixture was poured into cold water and acidified with acetic acid. The separated solid was collected by filtration, dried and crystallized from ethanol. Yield: 71%; M.p. 196–8°C. IR spectrum (KBr, ν, cm^{-1}): 3435–3225 (OH, NH), 1703 (CO), 1305 (C═S); ^{1}H NMR (DMSO-d_6) δ: 12.33 (s, 1H, OH, exchangeable), 8.15–6.98 (m, 12H, Ar─H), 7.53 (s, 1H, NH, exchangeable), 4.70 (s, 1H, methine), 2.85 (s, 2H, CH_2); ^{13}C NMR, 173.27 (CO), 169.45 (CS), 153.14, 151.55, 133.57, 131.32, 128.67, 127.85, 127.37, 126.45, 125.50, 125.15, 123.28, 122.30, 121.52, 115.33 (aromatic carbons), 53.64 (CH), 32.45, (CH_2); Ms: m/z = 422 (M^{+}); *Anal*. Calcd. for $C_{22}H_{18}N_2O_3S_2$ (422.52): C, 62.54; H, 4.29; N, 6.63%. Found: C, 62.48; H, 4.21; N, 6.53%.

2-(3-Oxo-7-(4-phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl)acetic acid (3). Chloroacetic acid (0.01 mol) was added to a mixture of pyrimidine **2** (0.01 mol) and anhydrous sodium acetate (0.2 g) in glacial acetic acid (20 mL) and acetic anhydride (20 mL) and the reaction mixture was refluxed for 4 h. After cooling, the reaction mixture was poured into crushed ice and the precipitated solid was filtered and crystallized from dioxane. Yield: 67%; M.p. 212–4°C. IR spectrum (KBr, ν, cm^{-1}): 3420–3250 (OH), 1710–1688 (2CO); ^{1}H NMR (DMSO-d_6) δ: 11.82 (s, 1H, OH, exchangeable), 8.07–6.92 (m, 12H, Ar─H), 5.23 (s, 1H, methine), 3.25 (s, 2H, SCH_2), 2.91 (s, 2H, CH_2); ^{13}C NMR, 175.50, 171.68 (2CO), 155.26,154.57, 152.36, 133.57, 132.84, 130.05, 128.35, 127.22, 126.23, 125.64, 125.20, 123.30, 121.65, 121.17, 114.50 (aromatic carbons), 57.41 (CH), 33.50(CH_2), 32.32 (SCH_2); Ms: m/z = 462 (M^{+}); *Anal*. Calcd. for $C_{24}H_{18}N_2O_4S_2$ (462.54): C, 62.32; H, 3.92;N, 6.06%. Found: C, 62.25; H, 3.85; N, 5.98%.

2-(2-Benzylidene-3-oxo-7-(4-phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl)acetic acid (4). A mixture of **3** (0.01 mol), benzaldehyde (0.01 mol), and sodium acetate (0.5 g) in glacial acetic acid (30 mL) was heated under reflux for 5 h. The reaction mixture was cooled, poured onto crushed ice and the precipitated solid was filtered and crystallized from ethanol to give acid **4**.

Yield: 76%; M.p. 224–6°C. IR spectrum (KBr, ν, cm^{-1}): 3430–3210 (OH), 1695–1678 (2CO); ^{1}H NMR (DMSO-d_6) δ: 12.13 (s, 1H, OH, exchangeable), 8.21–6.86 (m, 18H, Ar─H and CH═C), 4.75 (s, 1H, methine), 2.87 (s, 2H, CH_2); ^{13}C NMR, 177.42, 172.26 (2CO), 155.33, 153.37, 152.36, 140.20, 135.64, 133.41, 132.17, 129.77, 129.53, 128.10, 127.30, 127.13, 126.45, 125.86, 122.38, 121.55, 121.36, 116.23, 114.85 (aromatic carbons and CH═C), 62.75 (CH), 31.50 (CH_2); Ms: m/z = 550 (M^{+}); *Anal*. Calcd. for $C_{31}H_{22}N_2O_4S_2$ (550.65): C, 67.62; H, 4.03; N, 5.09%. Found: C, 67.54; H, 3.88; N, 4.98%.

2-(6-(4-Phenoxyphenyl)-3-phenyl-8-(thiophen-2-yl)-2,3-dihydro-8H-isoxazolo[5′,4′:4,5]thiazolo[3,2-a]pyrimidin-7-yl) acetic acid (5). Hydroxylamine hydrochloride (0.01 mol) was added to compound **4** (0.01 mol) in pyridine (30 mL), the mixture was refluxed for 6 h. After cooling, the reaction mixture was poured onto crushed ice/HCl. The separated solid was filtered, washed, dried, and recrystallized from benzene to give compound **5**.

Yield: 82%; M.p. 193–5°C. IR spectrum (KBr, ν, cm^{-1}): 3430–3205 (OH, NH), 1690 (CO); ^{1}H NMR (DMSO-d_6) δ: 12.28 (s, 1H, OH, exchangeable), 10.35 (s, 1H, NH, exchangeable), 8.11–7.02 (m, 17H, Ar─H), 4.96, 4.51 (s, 2H, 2 methine), 2.92 (s, 2H, CH_2); ^{13}C NMR, 174.60 (CO), 156.33, 155.15, 154.46, 153.43, 143.31, 136.25, 132.30, 131.50, 130.15, 129.50, 128.41, 127.63, 127.41, 125.45, 123.22, 122.54, 121.69, 120.58, 118.46, 118.25, 115.70 (aromatic carbons and C═C), 61.73, 60.52 (2 CH), 33.65 (CH_2); Ms: m/z = 565 (M^{+}), 566 (M^{+1}); *Anal*. Calcd. for $C_{31}H_{23}N_3O_4S_2$ (565.66): C, 65.82; H, 4.10; N, 7.43%. Found: C, 67.76; H, 4.05; N, 7.35%.

2-(1-(2-Cyanoethyl)-2-mercapto-4-(4-phenoxyphenyl)-6-(thiophen-2-yl)-1,6-dihydropyrimidin-5-yl)acetic acid (6). A mixture of equimolar amounts of pyrimidine derivative **2** and acrylonitrile (0.01 mol) in pyridine (30 mL) was heated under reflux for 5 h. The reaction mixture was poured onto crushed ice. The solid product was filtered, washed, dried, and recrystallized from ethanol.

Yield: 67%; M.p. 210–12°C. IR spectrum (KBr, ν, cm^{-1}): 3410–3270 (OH), 2620 (SH) 2207 (C≡N), 1690 (CO); ^{1}H NMR ($CDCl_3$) δ: 10.36 (s, 1H, OH, exchangeable), 7.46-6.62 (m, 13H, Ar-H + SH exchangeable), 4.18 (s, 1H, methine), 3.87 (t, 3H, CH_2), 2.11 (s, 2H, CH_2), 3.33 (t, 2H, CH_2);^{13}C NMR, 175.50 (CO), 157.35, 153.15, 152.23, 148.50, 133.11, 132.30, 131.28, 128.15, 127.30, 126.55, 122.24, 121.43, 120.58, 118.46,118.32, 115.30 (aromatic carbons and CN), 58.50 (CH), 42.20, 33.65, 20.34(3 CH_2); Ms: m/z = 475 (M^{+}), 566 (M^{+1}); *Anal*. Calcd. for $C_{25}H_{21}N_3O_3S_2$ (475.58): C, 63.14; H, 4.45; N, 8.84%. Found: C, 63.04; H, 4.32; N, 7.72%.

2-(2-Oxo-8-(4-phenoxyphenyl)-6-(thiophen-2-yl)-3,4-dihydro-2H,6H-pyrimido[2,1-b][1,3]thiazin-7-yl)acetic acid (7). Glacial acetic acid (20 mL) and hydrochloric acid (10 mL) were added to compound **6** (0.01 mol) and all was heated under reflux for 5 h. The precipitate that formed after concentration and cooling was filtered, washed, dried, and recrystallized from ethanol.

Yield: 65%; M.p. 202–4°C. IR spectrum (KBr, ν, cm^{-1}): 3410–3270 (OH), 1705–1690 (2 CO); ^{1}H NMR (DMSO-d_6) δ: 12.82 (s, 1H, OH, exchangeable), 8.17–7.05 (m, 12H, Ar─H), 4.83 (s, 1H, methine), 3.65 (t, 2H, CH_2), 2.97 (s, 2H, CH_2), 2.73 (t, 2H, CH_2); ^{13}C NMR, 184.57, 178.24 (2 CO), 158.45, 155.17, 153.58, 136.72, 133.35, 131.13, 129.30, 128.62, 126.76, 126.43, 123.24, 121.50, 118.60, 118.43, 114.50 (aromatic carbons), 65.38 (CH), 47.22, 43.50, 32.65(3 CH_2); Ms: m/z = 476 (M^{+}); *Anal*. Calcd. for $C_{25}H_{20}N_2O_4S_2$ (476.57): C, 63.01; H, 4.23; N, 5.88%. Found: C, 62.87; H, 4.15; N, 5.79%.

2-(3-Benzylidene-2-oxo-8-(4-phenoxyphenyl)-6-(thiophen-2-yl)-3,4-dihydro-2H,6H-pyrimido[2,1-b][1,3]thiazin-7-yl)acetic acid (8). A mixture of derivative **7** (0.01 mol), benzaldehyde (0.01 mol), and sodium acetate (0.5 g) in glacial acetic acid (30 mL) was heated under reflux for 5 h. The reaction mixture was cooled, poured onto crushed ice and the precipitated solid was filtered and crystallized from ethanol to give compound **8**.

Yield: 72% M.p. 230–2°C. IR spectrum (KBr, ν, cm^{-1}): 3430–3215 (OH), 1695–1685 (2CO); ^{1}H NMR (DMSO-d_6) δ: 10.65 (s, 1H, OH, exchangeable), 8.39-7.10 (m, 18H, Ar─H and CH═C), 4.35 (s, 1H, methine), 3.10 (s, 2H, CH_2), 2.88 (s, 2H, CH_2); ^{13}C NMR, 182.50, 174.42 (2 CO), 156.80, 155.37, 153.42, 152.50, 142.30, 138.50, 135.65, 132.50, 131.58, 131.20, 128.90, 128.36, 127.50, 126.30, 124.58, 122.55, 122.20, 118.37, 117.50, 115.53, 114.80 (aromatic carbons), 63.35 (CH), 52.50, 33.25(2 CH_2); Ms: m/z = 564 (M^{+}); *Anal*. Calcd. for $C_{32}H_{24}N_2O_4S_2$ (564.67): C, 68.07; H, 4.28; N, 4.96%. Found: C, 67.88; H, 4.12; N, 4.85%.

2-(8-(4-Phenoxyphenyl)-3-phenyl-6-(thiophen-2-yl)-2,3-dihydro-4H,6H-isoxazolo[4,5-e]pyrimido[2,1-b][1,3]thiazin-7-yl)acetic acid (9). Hydroxylamine hydrochloride (0.01 mol) was added to compound **8** (0.01 mol) in pyridine (30 mL), the mixture was refluxed for 6 h. After cooling, the reaction mixture was poured onto crushed ice/HCl. The separated solid was filtered, washed, dried, and recrystallized from dioxane.

Yield: 75% M.p. 217–9°C. IR spectrum (KBr, ν, cm^{-1}): 3450–3160 (OH, NH), 1685 (CO); ^{1}H NMR (DMSO-d_6) δ: 11.36 (s, 1H, OH, exchangeable), 9.82 (s, 1H, NH), 8.26–7.08 (m, 17H, Ar─H), 4.62, 4.23(2s, 2H, 2 methine), 3.88 (s, 2H, CH_2), 2.90 (s, 2H, CH_2); ^{13}C NMR, 176.41 (CO), 158.62, 154.27, 152.23, 148.75, 141.20, 136.80, 133.52, 132.37, 129.50, 128.79, 127.46, 127.20, 126.15, 123.64, 122.30, 121.22, 117.68, 117.53, 115.13 (aromatic carbons), 66.32, 57.33 (2 CH), 37.58, 33.30 (2 CH_2); Ms: m/z = 579 (M^{+}); *Anal*. Calcd. for $C_{32}H_{25}N_3O_4S_2$ (579.69): C, 66.30; H, 4.35; N, 7.25%. Found: C, 66.17; H, 4.28; N, 7.11%.

2-(7-(4-Phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl)acetic acid (10). To stirred solution of acid **2** (0.01 mol) in sodium hydroxide (0.1 g in 10 mL water), 1,2-dibromoethane (0.01 mol in 20 mL DMF) was added dropwise. The mixture was heated for 2 h under reflux and stirred at room temperature for another 2 h. The precipitated solid was filtered and washed with water, dried and crystallized from ethanol to form compound **10**.

Yield: 78%; M.p. 212–4°C. IR spectrum (KBr, ν, cm^{-1}): 3430–3220 (OH), 1705 (CO); ^{1}H NMR (DMSO-d_6) δ: 10.86 (s, 1H, OH, exchangeable), 7.78–7.01 (m, 12H, Ar–H), 4.73 (s, 1H, methine), 2.93 (t, 2H, CH_2), 2.44 (t, 2H, CH_2), 2.43 (s, 2H, CH_2); ^{13}C NMR, 174.30 (CO), 158.64, 154.56, 153.18, 132.70, 129.44, 128.31, 127.86, 127.71, 126.62, 123.50, 122.27, 119.20, 118.45, 118.38, 115.14 (aromatic carbons), 47.32, 31.50, 29.75 (3 CH_2); Ms: m/z = 448 (M^{+}); *Anal*. Calcd. for $C_{24}H_{20}N_2O_3S_2$ (448.56): C, 64.27; H, 4.49; N, 6.25%. Found: C, 64.11; H, 4.37; N, 6.18%.

2-(7-(4-Phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5H-thiazolo[3,2-a] pyrimidin-6-yl)acetyl azide (11). A solution of sodium azide (0.01 mol) in water (2 mL) was added dropwise to the acid chloride [prepared from heating of acid **2** with thionylchloride under reflux for 2 h] (0.01 mol) in acetone (20 mL) at 0°C. The reaction mixture was stirred for 2 h at room temperature then poured onto crushed ice and the precipitated acid azide was filtered. Yield: 68%; M.p. 132–4°C (decomposed). IR spectrum (KBr, ν, cm^{-1}): 2210 (CON_3), 1690 (CO).

General procedures for synthesis of 12–15. A solution of acid azide **11** (0.01 mol) in absolute ethanol (20 mL) was added to a cold solution of active methylene compounds namely ethyl acetoacetate, ethyl cyanoacetate, malononitrile, and diethyl malonate in ethanol (20 mL) containing sodium ethoxide. The reaction mixture was stirred for 15 h and the solvent was evaporated under vacuum and poured onto crushed ice. The formed solid was filtered, dried, and crystallized from proper solvent.

Ethyl-5-methyl-1-(2-(7-(4-phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl)acetyl)-1H-1,2,3-triazole-4-carboxylate (12). Yield: 84% (benzene); M.p. 186–8°C. IR spectrum (KBr, ν, cm^{-1}): 1730, 1678 (2CO), 1615 (C═N); ^{1}H NMR (DMSO-d_6) δ: 7.83–6.96 (m, 12H, Ar─H), 5.26 (s, 1H, methine), 4.32 (q, 2H, CH_2CH_3), 3.82 (t, 2H, CH_2), 3.10 (t, 2H, CH_2), 2.95 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.15 (t, 3H, CH_2CH_3); ^{13}C NMR, 171.35, 167.5 (2 CO), 156.12, 154.35, 150.72, 136.68, 132.30, 131.22, 128.25, 128.05, 127.50, 127.28, 126.40, 123.36, 122.27, 120.25, 117.20, 115.14, 114.50 (aromatic carbons), 61.25 (OCH_2) 48.50, 33.20, 27.75 (3 CH_2), 15.60, 14.35 (2 CH_3); Ms: m/z = 585 ($M^{\cdot+}$); *Anal*. Calcd. for $C_{30}H_{27}N_5O_4S_2$ (585.70): C, 61.52; H, 4.65; N, 11.96%. Found: C, 61.37; H, 4.54; N, 11.82%.

Ethyl-5-amino-1-(2-(7-(4-phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl)acetyl)-1H-1,2,3-triazole-4-carboxylate (13). Yield: 81% (benzene); M.p. 213–5°C. IR spectrum (KBr, ν, cm^{-1}): 3325, 3195 (NH_2), 1722, 1680 (2CO); ^{1}H NMR (DMSO-d_6) δ: 9.10 (s, 2H, NH_2, exchangeable), 8.78-7.62 (m, 12H, Ar-H), 4.96 (s, 1H, methine), 4.34 (q, 2H, CH_2CH_3), 3.61 (t, 2H, CH_2), 3.23 (t, 2H, CH_2), 2.98 (s, 2H, CH_2), 1.33 (t, 3H, CH_2CH_3); ^{13}C NMR, 173.25, 170.30 (2 CO), 153.80, 151.65, 147.20, 133.25, 132.37, 131.38, 129.30, 128.45, 127.90, 127.75, 126.40, 123.25, 122.50, 121.36, 118.15, 115.60, 114.10 (aromatic carbons), 63.50 (OCH_2) 45.25, 32.30, 28.68 (3 CH_2), 15.20 (CH_3); MS: m/z = 586 ($M^{\cdot+}$); *Anal*. Calcd. for $C_{29}H_{26}N_6O_4S_2$ (586.69): C, 59.37; H, 4.47; N, 14.32%. Found: C, 59.45; H, 4.51; N, 14.40%.

5-Amino-1-(2-(7-(4-phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl)acetyl)-1H-1,2,3-triazole-4-carbonitrile (14). Yield: 83% (benzene); M.p. 224–6°C. IR spectrum (KBr, ν, cm^{-1}): 3335, 3250 (NH_2), 2216 (C≡N), 1677 (CO); ^{1}H NMR (DMSO-d_6) δ: 7.56-6.99 (m, 12H, Ar─H), 6.50 (s, 2H, NH_2, exchangeable), 4.85 (s, 1H, methine), 3.18 (t, 2H, CH_2), 2.91 (t, 2H, CH_2), 2.40 (s, 2H, CH_2); ^{13}C NMR, 169.50 (CO), 155.30, 152.25, 148.12, 133.26, 131.60, 131.42, 129.30, 128.20, 127.40, 127.25, 123.50, 123.22, 122.75, 121.50, 118.10, 117.50, 115.37, 114.45 (aromatic carbons and C≡N), 47.25, 36.50, 27.30 (3 CH_2); MS: m/z = 539 ($M^{\cdot+}$); *Anal*. Calcd. for $C_{27}H_{21}N_7O_2S_2$ (539.63): C, 60.10; H, 3.92; N, 18.17%. Found: C, 59.92; H, 3.80; N, 18.09%.

Ethyl-5-oxo-1-(2-(7-(4-phenoxyphenyl)-5-(thiophen-2-yl)-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl)acetyl)-4,5-dihydro-1H-1,2,3-triazole-4-carboxylate (15). Yield: 86% (dioxane); M.p. 205–7°C. IR spectrum (KBr, ν, cm^{-1}): 1735–1673 (3CO); ^{1}H NMR (DMSO-d_6) δ: 8.07–6.96 (m, 12H, Ar─H), 4.85 (s, 1H, methine), 4.13 (q, 2H, CH_2CH_3), 3.72 (t, 2H, CH_2), 3.15 (t, 2H, CH_2), 2.83 (s, 2H, CH_2), 0.98 (t, 3H, CH_2CH_3); ^{13}C NMR, 174.58, 172.17, 168.26 (3 CO), 157.52, 152.34, 148.60, 132.80, 132.55, 131.20, 128.64, 128.45, 127.60, 126.23, 123.40, 121.70, 121.42, 118.30, 114.32, 112.50 (aromatic carbons), 65.40 (OCH_2), 44.40, 35.20, 27.85 (3 CH_2), 15.36 (CH_3); MS: m/z = 587 ($M^{\cdot+}$); *Anal*. Calcd. for $C_{29}H_{25}N_5O_5S_2$ (587.67): C, 59.27; H, 4.29; N, 11.92%. Found: C, 59.08; H, 4.18; N, 11.83%.

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