A Facile Synthesis and Heteroannulation of Thiazolopyrimidine and Related Heterocyclic Systems

A. A. Aly

Chemistry Department, Faculty of Science, Benha University, Benha, Egypt
E-mail:alymaboud@yahoo.com

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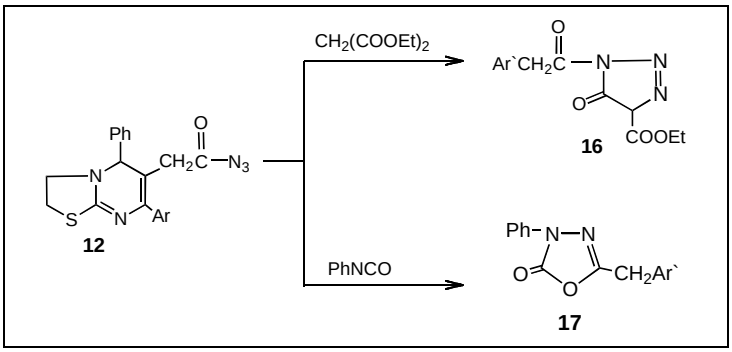

Reaction of pyrimidinylacetic acid **2** with different electrophilic and nucleophilic reagents gave annulated pyrimidine derivatives **3-11**, respectively. Compound **3** was transformed to pyrimidinylacetyl azide **12**, which upon heterocyclization with active methylene compounds, acidic and basic reagents furnished functionally substituted heteroaromatic compounds **13-21**, respectively. The antimicrobial activity of some synthesized compounds was investigated. The structures of the synthesized derivatives were elucidated by elemental and spectral analyses.

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INTRODUCTION

Pyrimidine derivatives and heterocyclic annulated pryimidine are well known in medicinal chemistry for their pronounced therapeutic applications [1-5] such as inhibitors of HIV-1 integrase, CNS stimulants, protein kinase inhibitors and anticancer drugs. Non-medicinal applications [6-10] include uses as herbicides, agricultural fungicides, growth promoters and UV absorbing molecules. One possible reason for their activity is the presence of pyrimidine base in thymine, cytosine and uracil which are essential building blocks of nucleic acids, DNA and RNA. Our studies [11-13] related to synthesis of annulated pyrimidines for testing as potential biodegradable agrochemical and antimicrobial agents by the functionalization and cyclization reactions of [4-(dibenzothien-2-yl)-2-mercapto-6-phenyl-1,6-dihydropyrimidin-5-yl]acetic acid (**2**) with different reagents.

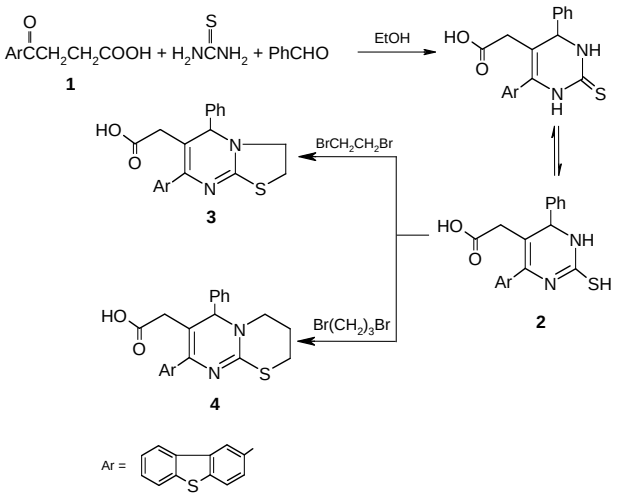
RESULTS AND DISCUSSION

The required starting material, [4-(dibenzothien-2-yl)-2-mercapto-6-phenyl-1,6-dihydropyrimidin-5-yl]acetic acid (**2**) was prepared from readily available 3-[(dibenzothien-2-oyl)]propanoic acid (**1**), thiourea and benzaldehyde in ethanolic solution containing anhydrous potassium carbonate. The structure of compound **2** was assigned on the basis of elemental analysis and compatible spectroscopic data. Thus, its IR spectrum showed characteristic absorption bands at 3410-3260 due to ν(OH, NH) and at 1695 cm^{-1} for νCO. The ^1H NMR ($CDCl_3$) spectrum showed signals at δ 2.95 ppm for methylene protons, singlet at 4.63 for methine proton, multiplet signals (12 H) for aromatic protons at (7.11-7.95) ppm, two broad singlets at (8.40-8.60) ppm for two NH and singlet at 10.61 ppm for OH, which disappeared upon addition of D_2O to the NMR sample. Also, the mass spectrum of **2** revealed a molecular ion peak at m/z = 430 which corresponding to molecular formula $C_{24}H_{18}N_2O_2S_2$.

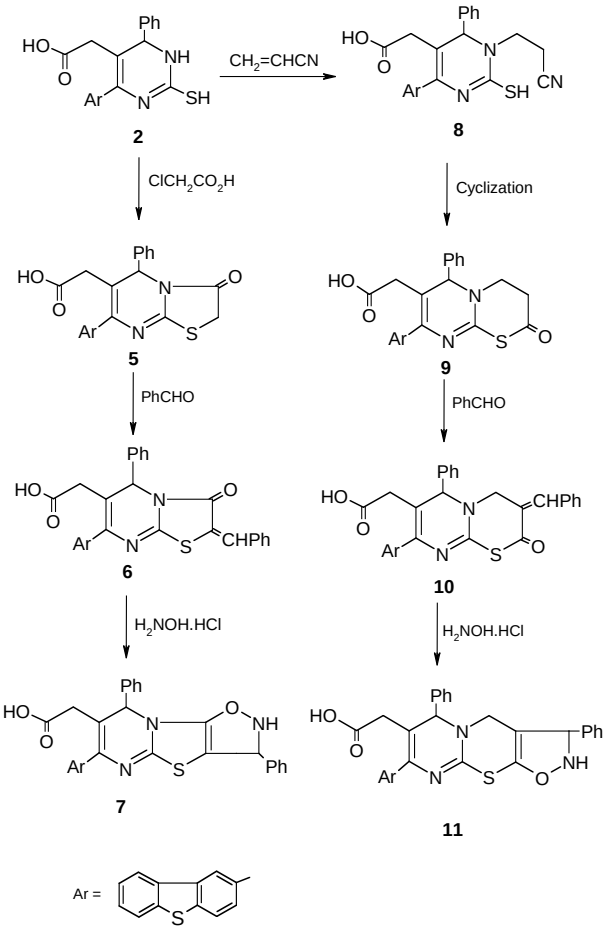
Pyrimidinylacetic acid **2** used as a versatile intermediate allowing access for preparation of a variety of multifunctionalized polyheterocycles, due to the presence of two adjacent reactive functional groups. Thus, the reaction of **2** with 1,2-dibromoethane afforded [7-(dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo-[3,2-*a*]pyrimidin-6-yl]acetic acid (**3**). While, the condensation of **2** with 1,3-dibromopropane yielded the corresponding pyrimido[2,1-*b*][1,3]thiazine derivative **4** (Scheme 1).

The preparative use of pyrimidinylacetic acid **2** was extended to prepare new annulated pyrimidine derivatives. Thus, the alkylation of **2** with chloroacetic acid in a mixture of glacial acetic acid/acetic anhydride containing anhydrous sodium acetate afforded [7-(dibenzothien-2-yl)-3-oxo-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]acetic acid **(5)**, which condensed with benzaldehyde to give the corresponding benzylidene derivative **6**, (Scheme 2).

Scheme 1



Scheme 2



Compound **6** underwent cyclization into isoxazolothiazolopyrimidine derivative **7** upon treatment with hydroxylamine hydrochloride in refluxing pyridine. Cyanoethylation of compound **2** with an equimolar amount of acrylonitrile in pyridine underwent a Michael-type addition to the activated double bond of the nitrile to afford the propionitrile derivative **8**, which underwent cyclization to pyrimidothiazine **9** by refluxing in a mixture of glacial acetic acid and hydrochloric acid (3:1). The condensation of compound **9** with benzaldehyde afforded [3-benzylidene-8-(dibenzothien-2-yl)-2-oxo-6-phenyl-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-7-yl]acetic acid (**10**), which reacted with hydroxylamine hydrochloride to give the cyclized tricyclic derivative **11**, (Scheme 2).

In recent years, there has been increasing interest in the synthesis of alkyl azide, this stems from its applicability for synthesis of polyfunctionally substituted heterocycles [14-16]. Thus, thiazolopyrimidinylacetyl azide **12** was synthesized following the reported method [17] by stirring equimolar amounts of [7-(dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*b*]pyrimidin-6-yl]acetyl chloride and aqueous sodium azide in dry acetone at 0-5 °C, (Scheme 3).

To increase the synthetic scope on the utility of the azide **12** as a building blocks for developing bioactive triazole [18], oxadiazole [19], quinazoline [20] derivatives. Accordingly, the cycloaddition reaction [21] of alkyl azide **12** with active methylene compounds (*viz* malononitrile, ethyl cyanoacetate, ethyl acetoacetate and diethyl malonate) afforded the triazole derivatives **13-16**, respectively (Scheme 3). While, the cycloaddition reaction of **12** with phenyl isocyanate in dry benzene yielded,5-{[7-(dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]-methyl}-3-phenyl-1-3,4-oxadiazol-2(3*H*)-one (**17**).

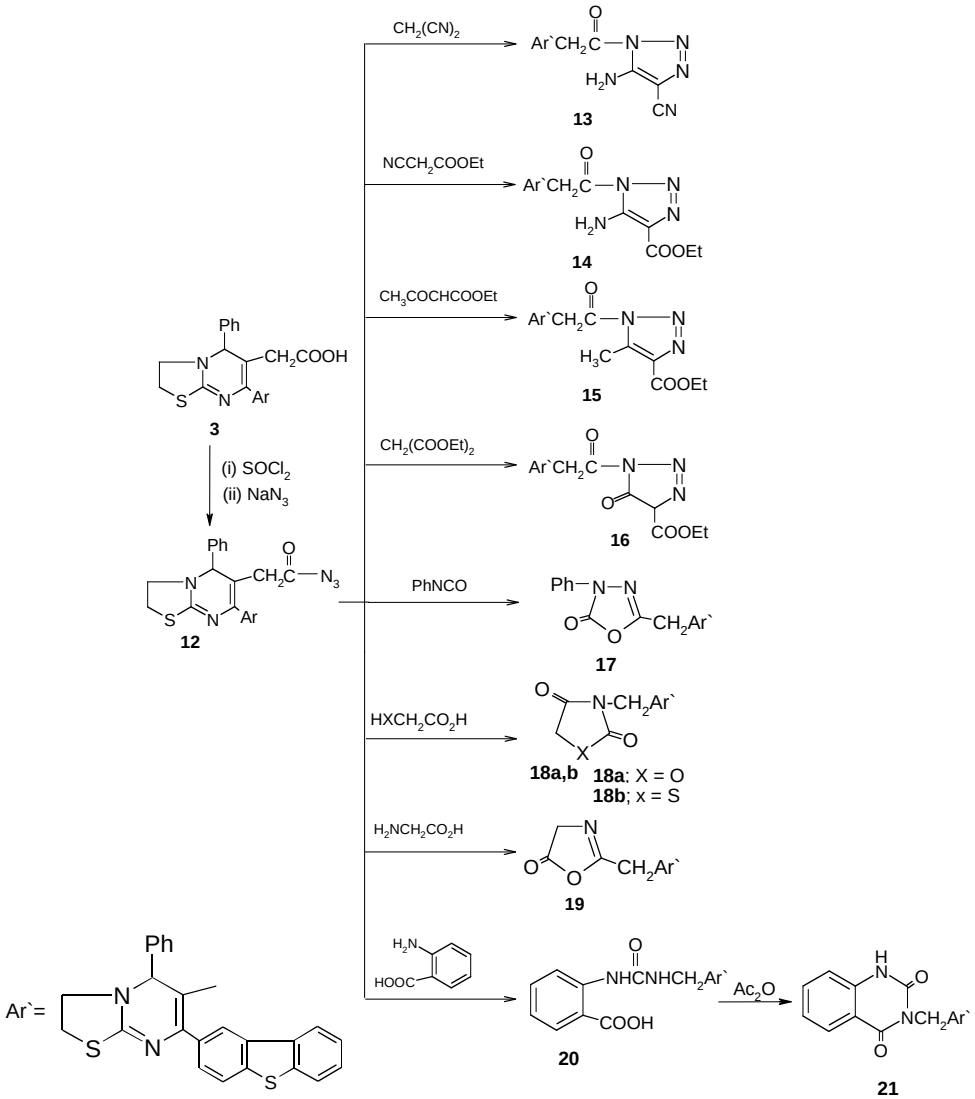
Additionally, the reaction of azide **12** with glycolic acid and/or thioglycolic acid in boiling dry benzene afforded oxazolidine-2,4-dione and thiazolidine-2,4-dione **18a,b**, respectively, *via* Curtius rearrangement followed by 1,2-dipolar addition and cyclization to give the desired product. Moreover, azide **12** was shown to decompose through azido-displacement pathway upon treatment with glycine in dry toluene containing catalytic amount of piperidine to give 2-{[7-(dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]-methyl}oxazol-5(4*H*)-one (**19**).

Finally, the reaction of azide **12** with anthranilic acid afforded disubstituted urea **20**, which easily cyclized by boiling in acetic anhydride to give the quinazoline derivative **21**, (Scheme 3*)*.

The structures of the synthesized compounds were assigned on the basis of elemental analysis and spectral data (*cf.* experimental).

Antimicrobial activity. The antimicrobial activity of the synthesized compounds was tested *in vitro* using the hole plate and filter paper disc methods [22]. All compounds were tested for activity against Gram-positive

Scheme 3



and Gram-negative bacteria using streptomycin as a reference standard drug. Based on the previous preliminary test, the tested compounds were dissolved in 10 % acetone (v/v), and the selected concentrations are (500, 250, 125 μg/mL). A qualitative screen was performed on all compounds, while quantitative assays were done on active compounds only. The results are summarized in Table I. The results obtained from microbiological screening of the synthesized compounds showed highly antibacterial and moderate antifungal activities comparable to that of streptomycin, the reference drug used.

In conclusion, the described method seems to be very useful for the synthesis of annulated pyrimidine derivatives of potentially biologically active compounds using the readily available pyrimidinylacetic acid.

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 298 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 200 MHz instrument using TMS as internal reference with chemical shifts expressed as δ ppm. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 instrument (70 eV El mode). ^{13}C NMR values of phenyl and dibenzothiophene groups for compounds **3-21** are the same as in compound **2** with δ ± 0.1-0.5 ppm.

[4-(Dibenzothien-2-yl)-2-mercapto-6-phenyl-1,6-dihydropyrimidin-5-yl]acetic acid (2). A mixture of 3-[(dibenzothien-2-oyl)]propanoic acid (**1**), (5.7 g, 20 mmol), thiourea (1.6 g, 20 mmol), benzaldehyde (2.1 mL, 20 mmol) and K_2CO_3 (2.8 g, 20 mmol) in ethanol (60 mL) was refluxed for 10 h. The reaction mixture was cooled and the solid obtained was dissolved in hot water. The filtrate was neutralized with acetic acid to give solid product which was recrystallized from ethanol to give **2**. Yield,

Table I

The antimicrobial activity of the tested compounds.

Compound No	*Staphylococcus aureus*		*Bacillus cereus*		*Escherichia coli*		*Pseudomon aurignosa*		*Aspergillus niger*		*Penicillium italicum*	
	A	**MIC**	**A**	**MIC**	**A**	**MIC**	**A**	**MIC**	**A**	**MIC**	**A**	**MIC**
2	+	250	+	500	++	250	+	250	+	500	-	-
3	+	500	++	250	+	250	+	125	+	125	-	-
5	++	250	+	250	+++	500	++	250	++	250	-	-
7	+++	250	+++	250	++	125	+	250	-	-	+	125
9	++	250	+++	500	++	125	++	125	-	-	-	-
10	++	250	+	250	++	250	+	125	+	250	-	-
11	+++	500	++	250	++	125	++	500	+	250	-	-
13	++	250	+++	125	+++	250	+	250	+	250	++	125
15	++	125	++	250	++	250	+	250	-	-	-	-
16	+++	250	++	250	++	250	++	125	-	-	+	125
17	++	125	++	125	+++	250	+++	250	+	125	+	500
18b	++	125	++	500	++	250	+	125	-	-	-	-
19	++	250	++	125	+	250	+	125	++	250	+	125
21	++	250	+++	500	++	250	+	125	+	125	+	500
Streptomycin	++	250	++	125	++	125	+++	125	+	125	+	500

A = Antimicrobial activity of tested compounds; MIC = Minimum inhibitory concentration; -, inactive; + > 5mm, slightly active; ++ > 7 mm, moderately active; +++ > 9 mm, highly active

5.4 g (63%); mp 221-3 °C; IR: ν = 3410-3260 (multiple bands OH, NH), 1695 (CO), 1265 cm^{-1} (CS); ^1H NMR ($CDCl_3$): δ = 2.95 (s, 2H, CH_2), 4.63 (s, 1H, methine), 7.11-7.95 (m, 12H, ArH), 8.40-8.60 (br s, 2H, 2NH, exchangeable), 10.61 (s, 1H, OH, exchangeable); Ms: m/z = 430 (M^+): ^{13}C NMR: δ=26.8 (CH_2),59.3(C-6),108.3(C-5), 136.3(C-4), 160.3(CO), 167.2(CS); 115.2, 115.8, 117.3, 118.2, 121.4, 126.3(C-of phenyl ring); 120.2, 120.8, 121.6, 122.2, 124.4, 124.9, 130.2, 130.9, 136.2, 137.1, 140.2, 141.3(C-of dibenzothiophene ring); *Anal*. Calcd for $C_{24}H_{18}N_2O_2S_2$ (430.54): C, 66.95; H, 4.21; N, 6.51 %. Found: C, 66.80; H, 4.11; N, 6.71%.

[7-(Dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo-[3,2-*a*]pyrimidin-6-yl]acetic acid (3). 1,2-Dibromoethane (1.9 mL, 10 mmol) in DMF (20 mL) was added dropwise to a stirred solution containing compound **2** (4.3 g, 10 mmol) and sodium hydroxide (0.07 g in 10 mL H_2O). The reaction mixture was refluxed for 2 h then stirred at room temperature for an additional 2 h. The solid product that formed was collected by filtration, washed with water and triturated with ethanol to give colorless product which recrystallized from ethanol to give **3**. Yield, 3.4 g (74 %); mp 163-5 °C; IR: ν = 3390-3170 (OH), 1695 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.71-2.85 (m, 4H, $2CH_2$ of thiazole), 3.96 (s, 2H, CH_2), 4.71 (s, 1H, methine), 7.51-8.21 (m, 12H, ArH), 10.80 (s, 1H, OH, exchangeable); ^{13}C NMR: δ=21.6(C-2), 28.1(CH_2), 56.2(C-3), 62.7(C-5), 125.1(C-6), 138.2(C-7), 163.4(CO), 176.2(C-8a); *Anal*. Calcd for $C_{26}H_{20}N_2O_2S_2$ (456.58): C, 68.39; H, 4.42; N, 6.14%. Found: C, 68.53; H, 4.51; N, 6.26%.

[8-(Dibenzothien-2-yl)-6-phenyl-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-7-yl]acetic acid (4). 1,3-Dibromopropane (1 mL, 5 mmol) in DMF (20 mL) was added dropwise to a stirred solution containing compound **2** (2.2 g, 5 mmol) and sodium hydroxide (0.07 g in H_2O, 10 mL). The reaction mixture was refluxed for 3 h then stirred at room temperature for an additional 2 h. The solid product that formed was collected by filtration, washed with water and triturated with ethanol to give colorless product, which recrystallized from ethanol to give **4**. Yield 1.6 g (67 %); mp 183-5 °C. IR: ν = 3385-3180 (OH), 1690 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.65-2.93 (m, 6H, $3CH_2$ of thiazine), 3.93 (s, 2H, CH_2), 4.13 (s, 1H, methine), 7.29-8.11 (m, 12H, ArH), 10.71 (s, 1H, OH, exchangeable); *Anal*. Calcd for $C_{27}H_{22}N_2O_2S_2$ (470.61): C, 68.91; H, 4.71; N, 5.95%. Found: C, 68.80; H, 4.91; N, 5.83%.

[7-(Dibenzothien-2-yl)-3-oxo-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]acetic acid (5). A mixture of compound **2** (4.3 g, 10 mmol), chloroacetic acid (0.95 g, 10 mmol) and anhydrous sodium acetate (2.0 g) was refluxed in a mixture of glacial acetic acid (30 mL) and acetic anhydride (20 mL) for 4 h. The reaction mixture was cooled and poured onto crushed ice (50 g). The solid that formed was collected by filtration and recrystallized from benzene to give **5**. Yield, 3.5 g (75 %); mp 201-3 °C; IR: ν = 3380-3210 (OH), 1690-1685 cm^{-1} (CO); ^1H NMR ($CDCl_3$); δ = 2.85 (s, 2H, CH_2 of thiazole), 3.11 (s, 2H, CH_2), 4.12 (s, 1H, methine), 7.15-7.85 (m, 12H, ArH), 10.65 (s, 1H, OH, exchangeable); *Anal*. Calcd for $C_{26}H_{18}N_2O_3S_2$ (470.56): C, 66.36; H, 3.86; N, 5.95%. Found: C, 66.50; H, 3.97; N, 5.81%.

[2-Benzylidene-7-(dibenzothien-2-yl)-3-oxo-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]acetic acid (6). A mixture of compound **5** (4.7, 10 mmol) and benzaldehyde (1.1 mL, 10 mmol) in glacial acetic acid (25 mL) containing anhydrous sodium acetate (1 g) was refluxed for 6 h. The reaction mixture left to cool then poured onto crushed ice (30 g) and the solid that formed was recrystallized from dioxane to give **6**. Yield, 3.8 g (68%); mp 230-2 °C; IR: ν = 3405-3190 (OH), 1690-1680 cm^{-1} (CO); MS: m/z = 558 (M^+); *Anal*. Calcd for $C_{33}H_{22}N_2O_3S_2$ (558.67): C, 70.95; H, 3.97; N, 5.01%. Found: C, 70.81; H, 3.82; N, 5.15%.

[6-(Dibenzothien-2-yl)-3,8-diphenyl-2,3-dihydro-8*H*-isoxazolo[5',4':4,5]thiazolo[2,3-*a*]pyrimidin-7-yl]acetic acid (7). A mixture of compound **6** (2.2 g, 4 mmol) and hydroxylamine hydrochloride (0.28 g, 4 mmol) was refluxed in pyridine (25 mL) for 6 h. The reaction mixture was cooled then poured onto ice-HCl (30 g, 10 mL) and the solid that formed was collected by filtration and recrystallized from dioxane to give **7**. Yield, 1.5g (66 %); mp 213-5 °C; IR: ν = 3395-3185 (multiple bands, OH, NH), 1685 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.76 (s, 2H, CH_2), 4.11-4.30 (br s, 2H, 2CH, two methine), 7.35-8.12 (m,

17H, ArH), 9.12 (s, 1H, NH, exchangeable), 10.90 (s, 1H, OH, exchangeable); ^{13}C NMR: δ=28.3(CH_2), 59.6(C-4), 62.6(C-9), 78.8(C-8a), 114.2(C-5), 137.3(C-6), 160.1(C-7a), 162.2(C-2a), 165.2(CO); 119.1, 119.9, 120.2, 120.9, 123.2, 125.1(C-of phenyl ring of oxazole); *Anal.* Calcd for $C_{33}H_{23}N_3O_3S_2$ (573.69): C, 69.09; H, 4.04; N, 7.32%. Found: C, 69.22; H, 4.21; N, 7.16%.

[1-(2-Cyanoethyl)-4-(dibenzothien-2-yl)-2-mercapto-6-phenyl-1,6-dihydropyrimidin-5-yl]acetic acid (8). A mixture of compound **2** (4.3 g, 10 mmol) and acrylonitrile (0.74 mL, 14 mmol) in pyridine (30 mL) was refluxed for 6 h. The colourless solid which formed after concentration and cooling was recrystallized from ethanol to give **8**. Yield 3.6 g (74 %); mp 216-8 °C; IR: ν = 3375-3190 (OH), 2510 (SH), 2210 (CN), 1685 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 2.22 (t, 2H, CH_2), 2.86 (s, 2H, CH_2), 3.3 (t, 2H, CH_2CN), 4.35 (s, 1H, methine), 7.14-7.95 (13H, ArH and SH), 10.76 (s, 1H, OH, exchangeable); MS: m/z = 483 (M^+); *Anal.* Calcd for $C_{27}H_{21}N_3O_2S_2$ (483.61): C, 67.06; H, 4.38; N, 8.69%. Found: C, 67.18; H, 4.50; N, 8.73%.

[8-(Dibenzothien-2-yl)-2-oxo-6-phenyl-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-7-yl]acetic acid (9). Compound **8** (2 g) in a mixture of glacial acetic acid (30 mL) and hydrochloric acid (10 mL) was refluxed for 5 h. The reaction mixture was concentrated by evaporation under reduced pressure. The solid that formed was collected by filtration, washed with water and recrsytallized from dioxane to give **9**. Yield 1.4g (69%); mp 195-7°C; IR: ν = 3390-3200 (OH), 1695-1690 cm^{-1} (CO);^{1}H NMR ($CDCl_3$): δ = 2.81 (s, 2H, CH_2), 2.90-3.1 (m, 4H, 2CH_2 of thiazine), 4.13 (s, 1H, methine), 7.51-8.13 (m, 12H, ArH), 10.76 (s, 1H, OH, exchangeable); MS: m/z = 484 (M^+); *Anal.* Calcd for $C_{27}H_{20}N_2O_3S_2$ (484.59): C, 66.92; H, 4.16; N, 5.78%. Found: C, 66.79; H, 4.01; N, 5.57%.

[3-Benzylidene-8-(dibenzothien-2-yl)-2-oxo-6-phenyl-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-7-yl]acetic acid (10). A mixture of compound **9** (4.8 g, 10 mmol) and benzaldehyde (1.1 mL, 10 mmol) in glacial acetic acid (30 mL) containing anhydrous sodium acetate (1.5 g) was refluxed for 6 h. The reaction mixture was cooled, poured onto crushed ice (30 g) and the solid formed was recrystallized from ethanol to give **10**. Yield 3.8g (66%); mp 230-2°C; IR: ν = 3410-3180 (OH), 1690-1680 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 2.90 (s, 2H, CH_2), 3.70 (s, 2H, CH_2 of thiazine), 4.20 (s, 1H, methine), 7.13-8.11 (m, 18H, ArH and benzylic proton), 10.50 (s, 1H, OH, exchangeable); *Anal.* Calcd for $C_{34}H_{24}N_2O_3S_2$ (572.70): C, 71.31; H, 4.22; N, 4.89%. Found: C, 71.50; H, 4.32; N, 4.96%.

[8-(Dibenzothien-2-yl)-3,6-diphenyl-2,3-dihydro-4*H*,6*H*-isoxazolo[4,5-*e*]pyrimido[2,1-*b*][1,3]thiazin-7-yl]acetic acid (11). A mixture of compound **10** (2.3 g, 4 mmol) and hydroxylamine hydrochloride (0.28 g, 4 mmol) in pyridine (30 mL) was refluxed for 6 h. The reaction mixture was cooled, then poured onto crushed ice (40 g) and the solid product was collected by filtration and recrystallized from DMF to give **11**. Yield, 1.7 g (69%); mp 207-9 °C; IR: ν = 3390-3180 (multiple bands, OH, NH), 1690 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ = 2.91 (s, 2H, CH_2), 3.60 (s, 2H, CH_2 of thiazine), 4.15-4.30 (br s, 2H, two methine), 9.55 (br s, 1H, NH, exchangeable); 10.75 (s, 1H, OH, exchangeable); *Anal.* Calcd for $C_{34}H_{25}N_3O_3S_2$ (587.71): C, 69.48; H, 4.29; N, 7.15%. Found: C, 69.61; H, 4.40; N, 7.31%.

[7-(Dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo-[3,2-*a*]pyrimidin-6-yl]acetyl azide (12). A saturated solution of sodium azide (0.78 g, 12 mmol) in H_2O (2 mL) was added dropwise to a stirred solution of thiazolopyrimidinylacetyl chloride (5.79, 12 mmol) in dry acetone (30 mL) at 0-5 °C then the mixture was stirred for further 1 h at room temperature. The reaction mixture was added to crushed ice (40 g) and the precipitated product was collected by filtration to give the acid azide **12**.Yield, 3.8 g (65%); mp 117-9 °C (with decomposition); IR: ν = 2215 (CON_3), 1680 cm^{-1} (CO).

General procedure for the preparation of triazole derivatives (13-16). A cold solution of compound **12** (0.96 g, 2 mmol) in absolute ethanol (25 mL) was added to a cold solution of active methylene compounds (2 mmol) (*viz* malononitrile, ethyl cyanoacetate, ethyl acetoacetate and diethyl malonate) in ethanolic sodium ethoxide solution (prepared from sodium 1.66 g in absolute ethanol 20 mL). The reaction mixture was stirred at room temperature overnight then the solvent was evaporated under vacuum. The concentrated ethanol solution was poured onto crushed ice (50 g) and the solid obtained was collected by filtration and recrystallized to give the compounds **13-16**.

5-Amino-1-{2-[7-(dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]acetyl}-1*H*-1,2,3-triazole-4-carbonitrile (13). Yield, 0.73g (66%) (benzene); mp 195-7 °C; IR: ν = 3350, 3280 (NH_2), 2220 (CN), 1680 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 2.71-2.95 (m, 4H, 2CH_2 of thiazole), 3.95 (s, 2H, CH_2), 4.51 (s, 1H, methine), 5.85 (br s, 2H, NH_2), 7.51-8.25 (m, 12H, ArH); *Anal.* Calcd for $C_{29}H_{21}N_7OS_2$ (547.66): C, 63.60; H, 3.86; N, 17.90%. Found: C, 63.72; H, 3.95; N, 17.79%.

Ethyl 5-amino-1-{2-[7-(dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]acetyl}-1*H*-1,2,3-triazole-4-carboxylate (14). Yield, 0.74g (62%) (xylene); mp 226-8 °C; IR: ν = 3340, 3270 (NH_2), 1725, 1680 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 1.40 (t, 3H, CH_3), 2.65-2.95 (m, 4H, 2CH_2 of thiazole), 3.75 (s, 2H, CH_2), 4.12 (q, 2H, CH_2), 4.65 (s, 1H, methine), 5.91 (br s, 2H, NH_2), 7.61-8.23 (m, 12H, ArH); *Anal.* Calcd for $C_{31}H_{26}N_6O_3S_2$ (594.71): C, 62.61; H, 4.41; N, 14.13%. Found: C, 62.49; H, 4.63; N, 14.25%.

Ethyl 1-{2-[7-(dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]acetyl}-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (15). Yield, 0.73 (61%) (xylene); mp 240-2 °C; IR: ν = 1725, 1680 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 1.40 (t, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.85-2.95 (m, 4H, 2CH_2 of thiazole), 3.50 (s, 2H,CH_2), 4.20 (q, 2H, CH_2), 4.25 (s, 1H, methine), 7.23-8.31 (m, 12H, ArH); *Anal.* Calcd for $C_{32}H_{27}N_5O_3S_2$ (593.72): C, 64.74; H, 4.58; N, 11.80 %. Found: C, 64.85; H, 4.67; N, 11.96%.

Ethyl 1-{2-[7-(dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]acetyl}-5-oxo-4,5-dihydro-1*H*-1,2,3-triazole-4-carboxylate (16). Yield, 0.68g (57%) (toluene); mp 217-9 °C; IR: ν = 1730 (CO of ester), 1685-1680 cm^{-1} (CO of amide); ^{1}H NMR ($CDCl_3$): δ = 1.3 (t, 3H, CH_3), 2.71-2.90 (m, 4H, 2CH_2 of thiazole), 3.62 (s, 2H, CH_2), 4.11 (q, 2H, CH_2), 4.35, 4.51 (2s, 2H, two methines), 7.15-8.11 (m, 12H, ArH); *Anal.* Calcd for $C_{31}H_{25}N_5O_4S_2$ (595.69): C, 62.51; H, 4.23; N, 11.76%. Found: C, 62.65; H, 4.34; N, 11.85%.

5-{[7-(Dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]methyl}-3-phenyl-1,3,4-oxadiazol-2(3*H*)-one (17). A mixture of compound **12** (0.96 g, 2 mmol) and phenyl isocyanate (3 mL) in dry benzene (40 mL) was heated under reflux for 5 h. The solid that separated after concentration and cooling was recrystallized from benzene to give **17**. Yield, 0.76 g (69%); mp 201-3 °C; IR: ν = 1725 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 2.63-2.85(m, 4H, 2CH_2 of thiazole), 3.42 (s, 2H, CH_2), 4.35 (s, 1H, methine), 7.37-8.13(m,

17H, ArH); *Anal.* Calcd for $C_{33}H_{24}N_4O_2S_2$ (572.70): C, 69.21; H, 4.22; N, 9.78%. Found: C, 69.11; H, 4.10; N, 9.86%.

3-{[7-(Dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]methyl}oxazolidine-2,4(3*H*,5*H*)-dione (18a) and 3-{[7-(dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]methyl}thiazolidine-2,4(3*H*,5*H*)-dione (18b). A solution of **12** (0.96 g, 2 mmol) in dry benzene (30 mL), containing piperidine (1 mL), glycolic acid and/or thioglycolic acid (3 mmol) was heated under reflux temperature for 2 h. The solvent was evaporated under reduced pressure and the residue was redissolved in ether (40 mL). The solution was washed with 10% sodium carbonate (3 x 25 mL) and water (40 mL), dried over anhydrous Na_2SO_4. Evaporation of the dried etheral layer under vacuum gave the compounds **18a,b**.

18a; Yield, 0.71g (71%) (ethanol); mp 214-6 °C; IR: ν = 1710 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.80-2.95 (m, 4H, $2CH_2$ of thiazole), 3.40, 3.60 (2s, 4H, $2CH_2$), 4.31 (s, 1H, methine), 7.23-8.13 (m, 12H, ArH); *Anal.* Calcd for $C_{28}H_{21}N_3O_3S_2$ (511.62): C, 65.73; H, 4.14; N, 8.21%. Found: C, 65.52; H, 4.10; N, 8.09%.

18b; Yield, 0.84g (76%) (ethanol); mp 230-2 °C; IR: ν = 1705 cm^{-1} (CO); MS: m/z = 527 (M^+); *Anal.* Calcd for $C_{28}H_{21}N_3O_2S_3$ (527.68): C, 63.73; H, 4.01; N, 7.96%. Found: C, 63.84; H, 4.18; N, 7.83%.

2-{[7-(Dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-a]pyrimidin-6-yl]methyl}oxazol-5(4H)-one (19). A mixture of **12** (0.96 g, 2 mmol) and glycine (0.15 g, 2 mmol) in dry toluene (30 mL) containing piperidine (1 mL) was heated under reflux for 7 h. The solid that separated after concentration and cooling was recrystallized from toluene to give **19**. Yield, 0.73g (73%); mp 223-5 °C; IR: ν = 1726 (CO), 1610 cm^{-1} (C=N); ^1H NMR ($CDCl_3$): δ = 2.70-2.81 (m, 4H, $2CH_2$ of thiazole), 3.71, 3.92 (2s, 4H, $2CH_2$), 4.57 (s, 1H, methine), 7.63-8.25 (m, 12H, ArH); *Anal.* Calcd for $C_{28}H_{21}N_3O_2S_2$ (495.62): C, 67.85; H, 4.27; N, 8.48%. Found: C, 67.76; H, 4.10; N, 8.31%.

1-{[7-(Dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]methyl}-3-*o*-tolylurea (20). A mixture of compound **12** (0.96 g, 2 mmol) and anthranilic acid (0.27 g, 2 mmol) in dry benzene (30 mL) was refluxed for 30 min, the reaction mixture was allowed to cool and the solid which precipitated after cooling, was collected by filtration, dried and recrystallized from benzene to give **20**.Yield, 1.0 g (84%); mp 242-4 °C; IR: ν = 3460-3260 (OH, NH), 1690-1680 cm^{-1} (CO); MS: m/z = 590 (M^+); *Anal.* Calcd for $C_{33}H_{26}N_4O_3S_2$ (590.72): C, 67.10; H, 4.44; N, 9.48%. Found: C, 67.23; H, 4.53; N, 9.61%.

3-{[7-(Dibenzothien-2-yl)-5-phenyl-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl]methyl}quinazoline-2,4(1*H*,3*H*)-dione (21). A solution of **20** (1 g) in acetic anhydride (10 mL) was refluxed for 1 h. The reaction mixture was cooled, poured onto crushed ice (50 g) and the precipitated product was collected by filtration and recrystallized from *n*-butanol to give **21**. Yield, 0.61 g (63%); mp 196-8 °C; IR:ν = 3210 (NH), 1680-1670 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.72-2.93 (m, 4H, $2CH_2$ of thiazole), 3.95 (s, 2H, CH_2), 4.45 (s, 1H, methine), 7.61-8.13 (m, 16H, ArH), 9.22 (br s, 1H, NH, exchangeable);

Anal. Calcd for $C_{33}H_{24}N_4O_2S_2$ (572.70): C, 69.21; H, 4.22; N, 9.78%. Found: C, 69.35; H, 4.37; N, 9.86%.

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