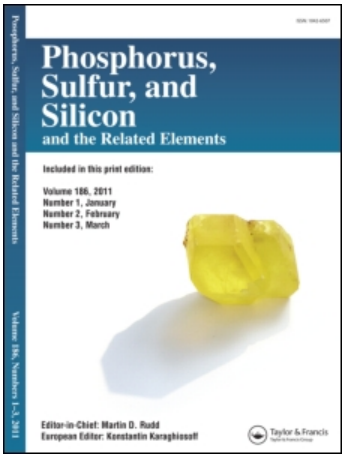

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A Facile and Efficient Synthesis of Polynuclear Heterocycles: Azolothienopyrimidines and Thienothiazolopyrimidines with Antimicrobial Activity

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A Facile and Efficient Synthesis of Polynuclear Heterocycles: Azolothienopyrimidines and Thienothiazolopyrimidines with Antimicrobial Activity

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*The research group I am a member of is interested in the preparation of thieno[2, 3-d]pyrimidine fused with different heterocycles compounds with potential biological activity. 2-Arylmethylene derivatives **4a–g** were prepared in one step by reacting 2-thioxothienopyrimidine derivatives **3a,b** with chloroacetic acid and the proper aldehyde. The ester **3a** and the acid **3b** were alkylated at different reaction conditions to produce the 2-alkylthio derivatives **5a–d**. Further alkylation of **5c** produced the N-3 alkylated product **6**. Compounds **5b**,**d** were cyclized in boiling acetic anhydride/pyridine to produce the thiazolothienopyrimidinone derivatives **7a**,**b**, respectively. Compounds **5a**,**c** reacted with hydrazine hydrate to give 2-hydrazinothienopyrimidines **8a**,**b** which could be used as precursors for triazolothienopyrimidines **9a**,**b** and pyrazolylthienopyrimidines **10a–c**,**13**. The purpose: Synthesis of thienopyrimidine derivatives which are highly biological active toward bacteria and fungi.*

Keywords aliphatic acids; antibacterial; antifungal; biological activity; mass spectra; NMR spectra; polynuclear; thienothiazolopyrimidines

INTRODUCTION

Fused pyrimidines continue to attract considerable attention of researchers in different countries because of their great practical usefulness, primarily, due to a very wide spectrum of their biological activities.[1–5] The pyrimidine ring is fused to various heterocycles to form compound with highly biological activities. Thienopyrimidine occupy a special position among these compounds. I hereby report the syntheses of new polynuclear heterocyclic thienopyrimidines, starting with 2-thioxo-[4,5]thieno[2,3-d]pyrimidin-4-one derivatives **3a**,**b**.

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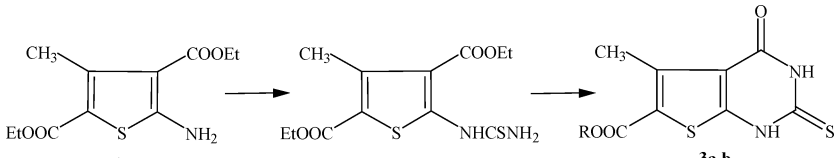
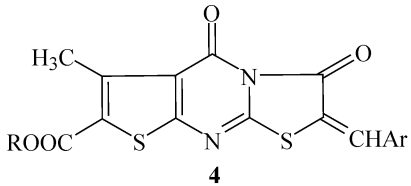
Thus heating under reflux 3,5-diethyl-2-amino-4-methyl-thiophene-3,5-dicarboxylate (**1**), prepared according to Karl Gewald method.[6]

Compound **1** was refluxed with potassium thiocyanate in dry dioxane in the presence of hydrochloric acid to give N-[3,5-diethoxycarbonyl-4-methylthien-2-yl]thiourea (**2**). Cyclization of compound **2** depends on the reaction conditions. Thus, it cyclized in acetic acid in the presence of sodium acetate to yield compound **3a**. The IR spectrum of **3a** (KBr) cm^{-1}: 3255(NH), 3107 (NH); 1691 (CO) and 1663 (CO); ^{1}H-NMR of **3a** (DMSO-d_6), as an example, showed signals at δ1.30 ppm (t, 3H, CH_3), 2.75 (s, 3H,CH_3), 4.35 (q, 2H, CH_2), 12.60 (br s, 1H, NH, D_2O exchangeable) and 13.55 (br s, 1H,NH, D_2O exchangeable), MS (m/z): 270.0 (M^+) 100%.

On the other hand when compound **2** was treated with 10% NaOH followed by acidification, it underwent cyclization and hydrolysis forming the free acid **3b**, in good yield. Its^{1}H-NMR spectrum showed no signal corresponding to ester and a signal of (OH) appeared, Experimental.



On heating under reflux a mixture of compound **3a**,**b**, chloroacetic acid and aromatic aldehyde in acetic acid and acetic anhydride in presence of anhydrous sodium acetate, it gave **4a–g** in good yield. Beside the correct values in elemental analyses, the spectral data of **4a–g** are in agreement with the assigned structure, Experimental.



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a) R = C_2H_5, Ar = C_6H_5 **d)** R = H, Ar = C_6H_5
b) R = C_2H_5, Ar = $C_6H_4OCH_3$-p **e)** R = H, Ar = $C_6H_4OCH_3$
c) R = C_2H_5, Ar = C_6H_4Cl-p **f)** R = H, Ar = C_6H_4Cl-p
g) R = H, Ar = C_6H_4F-p

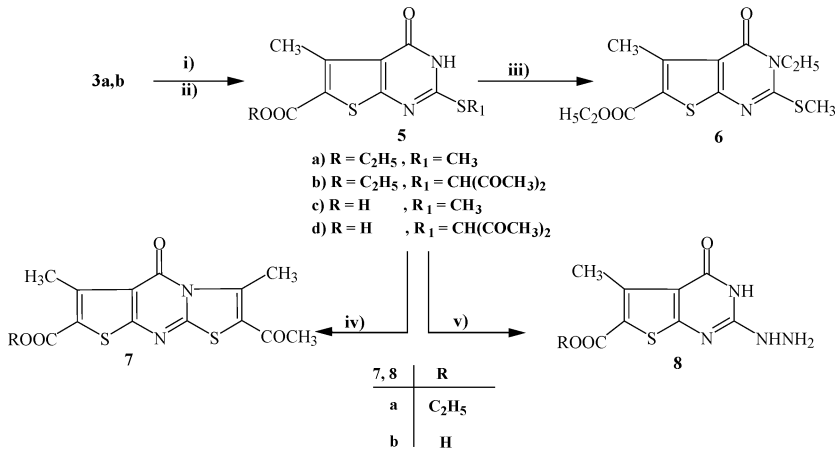
Methyl iodide and 3-chloropentane-2,4-dione were used to alkylate each of the ester **3a** in potassium carbonate solution and the

acid **3b** in ethanolic potassium hydroxide solution. The S-alkylation products could be formed as the 2-alkylthio-5-methyl-3H-thieno[2,3-d]pyrimidine-6-carboxylate **(5a,b)** and 6-carboxylic acid analogues **(5c,d)**, respectively. The IR spectra of **5a–d** (KBr) cm^{-1} showed: (NH) around 3150 and (2CO) around 1720, 1660; ^{1}H-NMR of **5a** (DMSO-d_6), as an example, showed signals at δ1.30 ppm (t, 3H, CH_3), 2.45 (s 3H, CH_3), 2.80 (s, 3H, CH_3), 4.30 (q, 2H, CH_2) and 12.90 (br s, 1H, NH, D_2O exchangeable); MS (m/z): 284.0 (M^+) 100%.

The 2-alkylthio derivative **5c** underwent further alkylation[7] on treatment with ethyl iodide in aqueous ethanolic potassium hydroxide solution to produce the N-3 alkylated product **6** in good yield (Scheme 1).

Heating **5b,d** in a mixture of acetic anhydride/pyridine, led to formation of the cyclic product **7a,b**. Beside the correct values in elemental analyses, the spectral data of **6** and **7a,b** are in agreement with the assigned structure, see experimental.

When **5a–c** reacted with hydrazine hydrate it gave the 2-hydrazino derivatives **8a,b**. The IR spectra of **8a,b** (KBr) cm^{-1} showed: [(NH_2), (NH)] around 3270; 3170 and (2CO) around 1690, 1660; ^{1}H-NMR of **8b** (DMSO-d_6), as an example, showed signals at δ2.75 ppm (s, 3H, CH_3), 5.00 (br, 2H, NH_2, D_2O exchangeable), 8.20 (br s, 1H, NH, D_2O exchange-able) and 12.90 (s, 1H, OH, D_2O exchangeable); MS (m/z): 240(M^+) 43%; 196 (M^+-COOH)100%, (Scheme 1).



SCHEME 1

The 2-hydrazinopyrimidine derivative **8b** used to prepare some new azolothienopyrimidines and pyrazolylthienopyrimidine

derivatives. Thus, heating under reflux, the 2-hydrazino **8b** with either formic acid or acetic acid yielded 5H-thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one derivatives **9a**,**b**. The IR spectra of **9a**,**b** (KBr) cm^{-1} showed: (OH) around 3430, (NH) around 3130 and (2CO)around1680, 1650; ^{1}H-NMR of **9a** (DMSO-d_6), as an example, showed signals at δg.45 ppm (s, 3H, CH_3), 6.75 (s, 1H, CH), 9.10 (s, 1H, NH, D_2O exchangeable) and 11.90 (1H, OH, D_2O exchangeable); MS (m/z): 250(M^+) 100%.

When equimolar amounts of **8b** and pentane-2,4-dione, 3-chloropentane-2,4-dione or triflouro-pentane-2,4-dione were heated under reflux in absolute ethanol, the 2-pyrazolylthieno[2,3-d]pyrimidinones **10a–c** were obtained in good yield.

Also, compound **8b** gave the arylhydrazone derivatives **11a**,**b**, when it was treated with the appropriate aldehyde in boiling dioxane in presence of catalytic amounts of piperidine. Trials to cyclize **11a**,**b** under different conditions had failed.

Heating under reflux compound **8b** with ethyl acetoacetate in absolute ethanol afforded the hydrazone derivative **12**, which could be cyclized by heating in ethanolic sodium ethoxide solution to give **13**. Also, compound **13** can be achieved directly from compound **8b** by heating with ethyl acetoacetate in ethanolic sodium ethoxide solution.

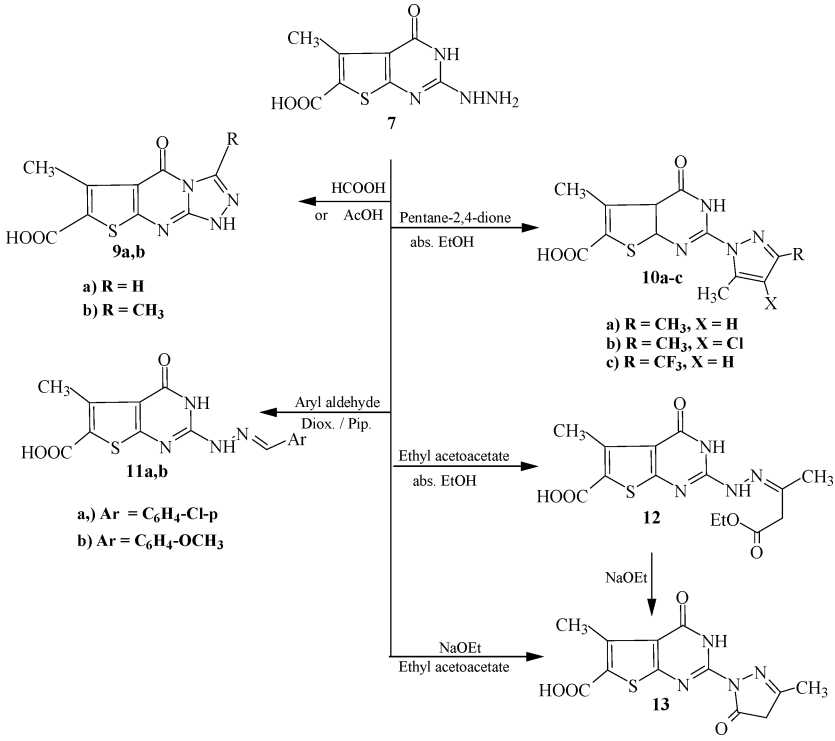
Beside the correct values in elemental analyses, the IR, ^{1}H-NMR and Mass spectra of **10a–c**, **11a**,**b** and **13** are in agreement with the assigned structure, see experimental, (Scheme 2).

BIOLOGICAL SCREENING

Measurement of Antimicrobial Activity Using Diffusion Disc Method

The prepared compounds were tested against one strain of gram +ve bacteria (*staphylococcus aureus* G^+), gram -ve bacteria (*Pseudomon as aeruginosa* G), Fungi (*Saccharomyces cereviseae*) and Fungi (*Candida albicans*). Whatman No. 1 filter paper disk of 5 mm diameter were sterilized by autoclaving for 15 min at 121°C. The sterile disks were impregnated with different compounds (600 μg/disk) Agar plates were surface inoculated uniformly from the broth culture of the tested microorganism.

The impregnated discs were placed on the medium suitably spaced apart, and the plates were incubated at 5°C for 1 h to permit good diffuse-ion and then transferred to an incubator at 37°C for 24 h for bacteria, at 28°C for 72 h for fungi.



SCHEME 2

After inoculation, the inhibition zones caused by the various compounds on the microorganism were examinant. The diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism.[8,9] The results of the preliminary screening test are listed in (Table I).

The antibacterial and antifungal activity of compounds **1**, **2**, **4c**, **4f**, **4g**, **6**, **7a**, **7b and 12** were tested. From the data obtained in Table I, it is clear that all above compounds were found to be highly active against *Candida albicans* (*fungus*), *Saccharomyces cereviseae*, *staphylococcus aureus* G^+ and *Pseudomonas aeruginosa* G^-.

EXPERIMENTAL

All melting points are uncorrected and were taken in open capillaries on a Gallen Kamp Apparatus. Microanalyses were carried out at the Microanalytical units, National Research Center and Faculty of Science, Cairo University. IR spectra were carried out at a FT/IR-300 E Jasco

TABLE I Data of Antimicrobial Activity Toward Some Products

Sample	Inhibition zone diameter (mm / mg sample)			
	Pseudomonas aerubinosa (G^-)	Staphylococcos aureus (G^+)	Saccharomyces cereviseae (Fungus)	Candida albicans (Fungus)
Control	0.0	0.0	0.0	0.0
1	14	12	13	14
2	12	13	11	12
4c	13	13	12	12
4f	14	15	14	14
4g	15	15	15	15
6	13	13	12	14
7a	14	13	13	13
7b	15	14	15	15
12	14	14	13	13

G : Gram reaction; Solvent : Chloroform and DMSO.

using KBr discs. ^{1}H-NMR spectra were measured in DMSO or $CDCl_3$, using JEOL-JNM-Ex270 NMR spectrometer. Signals were measured with reference to TMS as an internal standard. The Mass spectra were recorded on Finnigan SSQ 7000 spectrometer. All solid compounds were recrystallized to produce constant melting points. All the physical data is in Table I.

3,5-Diethyl-2-amino-4-methyl-thiophene-3,5-dicarboxylate (1)

Compound **1** was prepared according to Karl Gewald method.[6]

N-[3,5-Diethoxycarbonyl-4-methylthien-2-yl]thiourea (2)

A mixture of 1 (2.57g, 0.01 mole), potassium thiocyanate (0.97 g, 0.01 mole), and concentrated hydrochloric acid (30 ml) was refluxed in dioxane (30 ml) for five hours (the reaction was followed by TLC). The reaction mixture was cooled and poured into water. The deposited precipitate was filtered-off and recrystallized from dioxane to produce 2 as yellow crystals; IR spectrum (KBr) cm^{-1}: 3387, 3312 (NH_2), 3216 (NH), 1681 (CO) and 1648 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.35 (m, 6H, $2CH_3$), 2.75 (s, 3H, CH_3), 4.35 (m, 4H, $2CH_2$), 8.85 (br s, 2H, NH_2, D_2O exchangeable), and 11.75 (s, 1H,NH, D_2O exchangeable); MS (m/z): 316 (M^+) 100%.

Ethyl-5-methyl-4-oxo-2-thioxo-1H, 3H-thieno[2,3-d]pyrimidin-6-carboxylate (3a)

Compound **3a** was obtained by heating compound **2** (3.16g, 0.01 mole) under reflux in glacial acetic acid and anhydrous sodium acetate. Collect

the formed precipitate by filtration, wash with water, and recrystallize from dioxane to produce a colorless powder **3a**; IR spectrum(KBr) cm^{-1}: 3255(NH), 3107 (NH); 1691 (CO) and 1663 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.30 (t, 3H, CH_3), 2.75 (s, 3H,CH_3), 4.35 (q, 2H, CH_2), 12.60 (br s, 1H, NH, D_2O exchangeable), and 13.55 (br s, 1H,NH, D_2O exchangeable); MS (m/z): 270.0 (M^+) 100%.

5-Methyl-4-oxo-2-thioxo-1H, 3H-thieno[2,3-d]pyrimidin-6-carboxylic acid (3b)

Compound **3b** was obtained by boiling compound **2** (3.16g, 0.01 mole) in 10% NaOH solution [prepared by 10 g NaOH in 100ml water]. Allow to cool, acidify with conc. HCl, and collect the formed precipitate. Wash with water and recrystallize from dioxane to produce a colorless powder **3b**; IR spectrum(KBr) cm^{-1}: 3446(OH), 3128 (NH); 1713 (CO) and 1683 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.70 (s, 3H,CH_3) and 12.50 (br s, 1H,OH, D_2O exchangeable); MS (m/z): 242.0 (M^+) 100%.

General Method for Preparation 4a–g

A mixture of compound **3a** or **3b** (2.70 g or 2.42 g, 0.01 mole), chloroacetic acid (0.95 g, 0.01 mole), appropriate aromatic aldehyde (0.01 mole), and anhydrous sodium acetate (0.02 mole) was refluxed in (30 ml) of glacial acetic acid and (15 ml) of acetic anhydride for 5 h. The reaction mixture was cooled and poured into water. The deposited precipitate was filtered-off, and recrystallized from suitable solvent to produce **4a–g**.

Ethyl-3,5-Dioxo-6-methyl-2-(phenylmethylene)-thiazolo[3,2-a]thieno[2,3-d]pyrimi-dine-7-carboxylate (4a)

Compound **4a** was obtained by reaction of **3a** (2.70 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The product was recrystallized from dioxane to produce **4a** as pale yellow crystals; IR spectrum (KBr) cm^{-1}: 1770 (CO), 1720 (CO) and 1680 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.35 (t, 3H, CH_3), 2.85 (s, 3H, CH_3), 4.35 (q, 2H, CH_2), 7.50–7.70 (m, 5H, phenyl protons) and 8.10 (s, 1H, CH); MS (m/z): 398 (M^+) 100%.

Ethyl-3,5-Dioxo-6-methyl-2-(4-methoxyphenylmethylene)-thiazolo[3,2-a]thieno[2,3-d]pyrimidine-7-carboxylate (4b)

Compound **4b** was obtained by reaction of **3a** (2.70 g, 0.01 mole) and 4-methoxybenzaldehyde (1.36 g, 0.01 mole). The product was recrystallized from dioxane to produce **4b** orange crystals; IR spectrum (KBr) cm^{-1}: 1760 (CO), 1715 (CO), and 1675 (CO); MS (m/z): 428 (M^+) 100%.

Ethyl-3,5-Dioxo-6-methyl-2-(4-chlorophenylmethylene)-thiazolo[3,2-a]thieno[2,3-d]pyrimidine-7-carboxylate (4c)

Compound **4c** was obtained by reaction of **3a** (2.70 g, 0.01 mole) and 4-chlorobenz-aldehyde (1.40 g, 0.01 mole). The product was recrystallized from dioxane to produce **4c** as yellow crystals; IR spectrum (KBr) cm^{-1}: 1765 (CO), 1715 (CO) and 1685 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.40 (t, 3H, CH_3), 2.80 (s, 3H, CH_3), 4.25 (q, 2H, CH_2), 7.75 (d, 2H, aromatic protons), 7.85 (d, 2H, aromatic protons), and 8.00 (s, 1H, ethylenic proton); MS (m/z): 432, 434[M^+, (100%, 53.%)].

3,5-Dioxo-6-methyl-2-(phenylmethylene)-thiazolo[3,2-a]thieno[2,3-d]pyrimidine-7-carboxylic Acid (4d)

Compound **4d** was obtained by reaction of **3b** (2.42 g, 0.01 mole) and benzaldehyde (1.06 g, 0.01 mole). The product was recrystallized from dimethylformamide to produce **4d** as pale yellow crystals; IR spectrum (KBr) cm^{-1}: 3566(OH), 1765 (CO), 1715 (CO) and 1672 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.80 (s, 3H, CH_3), 7.50–7.65 (m, 5H, phenyl protons), 8.10 (s, 1H, CH), and 12.50 (s, 1H, OH, D_2O exchangeable); MS (m/z): 370 (M^+) 100%.

3,5-Dioxo-6-methyl-2-(4-methoxyphenylmethylene)-thiazolo[3,2-a]thieno[2,3-d]pyri-midine-7-carboxylic Acid (4e)

Compound **4e** was obtained by reaction of **3b** (2.42 g, 0.01 mole) and 4-methoxybenz-aldehyde (1.36 g, 0.01 mole). The product was recrystallized from dimethylformamide to produce **4e** orange crystals; IR spectrum (KBr) cm^{-1}: 3567(OH), 1762 (CO), 1715 (CO) and 1673 (CO); MS (m/z): 400(M^+) 100%.

3,5-Dioxo-6-methyl-2-(4-chlorophenylmethylene)-thiazolo[3,2-a]thieno[2,3-d]pyrim-idine-7-carboxylic Acid (4f)

Compound **4f** was obtained by reaction of **3b** (2.42 g, 0.01 mole) and 4-chlorobenz-aldehyde (1.40 g, 0.01 mole). The product was recrystallized from dimethylformamide to produce **4f** as yellow crystals; IR spectrum (KBr) cm^{-1}: 3550(OH), 1766 (CO), 1710 (CO) and 1676 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.85 (s, 3H, CH_3), 7.00 (d, 2H, aromatic protons), 7.30 (d, 2H, aromatic protons), 8.00 (s, 1H, ethylenic proton) and 11.85 (s, 1H, OH, D_2O exchangeable); MS (m/z): 404, 50, 406.50[M^+, (84%, 39.%)].

3,5-Dioxo-6-methyl-2-(4-triflurophenylmethylene)-thiazolo[3,2-a]thieno[2,3-d]pyri-midine-7-carboxylic Acid (4g)

Compound **4g** was obtained by reaction of **3b** (2.42 g, 0.01 mole) and 4-trifluorobenzaldehyde (1.86 g, 0.01 mole). The product was recrystallized from dimethylformamide to produce **4f** as yellow crystals; IR spectrum (KBr) cm^{-1}: 3450(OH), 1760 (CO), 1700 (CO) and 1670 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.85 (s, 3H, CH_3), 7.60 (d, 2H, aromatic protons), 7.70 (d, 2H, aromatic protons), 8.05 (s, 1H, ethylenic proton), and 12.00 (s, 1H, OH, D_2O exchangeable); MS (m/z): 438%.

General Method for Preparation 5a,b

A mixture of **3a** (2.70 g, 0.01 mole) and potassium carbonate (1.38 g, 0.01 mole) in pure acetone was heated for 30 min, then allowed to cool to room temperature, and the proper halo compound (0.013 mole) was added. The mixture was heated under reflux for 5 h, then cooled and poured into water. The solid product was filtered-off and recrystallized from appropriate solvent to produce **5a**,**b**.

Ethyl-5-Methyl-2-methylthio-3H-thieno[2,3-d]pyrimidine-6-carboxylate (5a)

Compound **5a** was obtained by reaction of **3a** and methyl iodide (1.72 g, 0.013 moles). The compound was recrystallized from dioxane to produce **5a** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3157 (NH); 1717 (CO) and 1667 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.30 (t, 3H, CH_3), 2.45 (s 3H,CH_3), 2.80 (s, 3H, CH_3), 4.30 (q, 2H, CH_2) and 12.90 (br s, 1H, NH, D_2O exchangeable); MS (m/z): 284.0 (M^+) 100%.

Ethyl-2-(Diacetylmethylthio)-5-methyl-3H-4-oxo-thieno[2,3-d]pyrimidine-6-carboxy-late (5b)

Compound **5b** was obtained by reaction of **3a** and 3-chloropentane-2,4-dione (1.34 g, 0.012 moles). The compound was recrystallized from dioxane to produce **5b** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3444 (broad NH and OH), 1717 (CO) and 1663 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.30 (t, 3H, CH_3), 2.35 (s, 6H, $2CH_3$), 2.80 (s, 3H, CH_3), 4.30 (q, 2H, CH_2), 4.75 (s, 1H, CH) and 8.00 (br s, 1H, NH, D_2O exchangeable); MS (m/z): 368 (M^+) 100%.

General Method for Preparation 5c,d

To a warmed ethanolic potassium hydroxide solution [prepared by dissolving potassium hydroxide (0.56 g, 0.01 mole) in ethanol (50 ml)] was

added compound **3b** (2.42 g, 0.01 mole), heated for 30 min; the mixture was allowed to cool to room temperature, and the proper halo compound (0.013 mole) was added. The mixture was heated under reflux for 5 h, then cooled and poured into water. The solid product was filtered-off and recrystallized from the appropriate solvent to produce **5c**,**d**.

5-Methyl-2-methylthio-3H-4-oxo-thieno[2,3-d]pyrimidine-6-Carboxylic acid (5c)

Compound **5c** was obtained by reaction of **3b** and methyl iodide (1.72 g, 0.013 mole). The compound was recrystallized from dioxane to produce **5c** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3448 (NH); 1717 (CO) and 1654 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.80 (s, 3H, CH_3), 3.65 (s, 3H,CH_3), and 12.90 (s, 1H, OH, D_2O exchangeable); MS (m/z): 209.0 (M^+-SMe) 100%.

2-(Diacetylmethylthio)-5-methyl-3H-4-oxo-thieno[2,3-d]pyrimidine—6-carboxylic acid (5d)

Compound **5d** was obtained by reaction of **3b** and 3-chloropentane-2,4-dione (1.34 g, 0.012 moles). The compound was recrystallized from dioxane to produce **5d** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3355 (broad NH and OH), 1704 (CO) and 1655 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.35 (s, 6H, $2CH_3$), 2.75 (s, 3H, CH_3), 4.35 (s, 1H, CH), 7.45 (s, 1H, NH, D_2O exchangeable) and 13.00 (br s, 1H, OH, D_2O exchangeable); MS (m/z): 340 (M^+) 58%, 322 (M^+-18)100%.

Ethyl-3-Ethyl-2-methylthio-5-methyl-4-oxo-thieno[2,3-d]pyrimidine-6-carboxylate (6)

To a warmed ethanolic potassium hydroxide solution (prepared by dissolving (0.56 g, 0.01 mole) in 50 ml ethanol) was added compound **5c** (2.56 g, 0.01 mole). Heating was continued for 30 min and the mixture was allowed to cool and the proper ethyl iodide (1.86g, 0.012 mole) was added. The mixture was heated under reflux for 4 h, and then cooled at room temperature, poured into cold water. The solid so-precipitate was filtered-off, washed with water, and recrystallized from the appropriate solvent to give **6** as colorless crystals; IR spectrum (KBr) cm^{-1}: 1715 (CO) and 1672 (CO); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.35 (m, 6H, $2CH_3$), 2.60 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 4.15 (q, 2H, CH_2), 4.35 (q, 2H, CH_2), MS (m/z): 312 (M^+) 100%.

General Procedure for Preparation of 7a,b

A solution of compound **5b** or **5d** (0.01 mole) in (10 ml) acetic anhydride and (20 ml) of pyridine was heated under reflux for 5 h. The reaction

mixture was cooled, the deposited precipitate was filtered-off and recrystallized from dioxane to give **7a**,**b** as yellow crystals.

Ethyl-2-Acetyl-3,6-dimethyl-5-oxo-thiazolo[3,2-a]thieno[2,3-d]pyrimidin-7-carboxyl-ate (7a)

Compound **7a** was obtained by heating of **5b** (3. 68 g, 0.01 mole) with (10 ml) acetic anhydride and (20 ml) of pyridine; IR spectrum (KBr) cm^{-1}: 1740 (CO), 1694 (CO) and 1668 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.30 (t, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 4.30 (q, 2H, CH_2); MS (m/z): 350 (M^+) 100%.

2-Acetyl-3,6-dimethyl-5-oxo-thiazolo[3,2-a]-thieno[2,3-d]pyrimidin-7-carboxylic acid (7b)

Compound **7b** was obtained by heating of **5d** (3.40 g, 0.01 mole) with (10 ml) acetic anhydride and (20 ml) of pyridine; IR spectrum (KBr) cm^{-1}: 3446(OH), 1716 (CO), 1683 (CO) and 1663 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.60 (s, 3H, CH_3), 2.85 (s, 3H, CH_3) 3.15 (s, 3H, CH_3) and 12.95(1H, OH, D_2O exchangeable); MS (m/z): 322(M^+) 100%.

General Procedure for Preparation of 8a,b

A mixture of **5a** or **5c** (0.01 mole) and hydrazine hydrate (99–100%) (7 ml, 0.03 mole) in dioxane and ethanol was heated under reflux for 5 h. The reaction mixture was cooled and filtered-off and recrystallized from proper solvent to produce **8a**,**b** as colorless crystals

Ethyl-2-Hydrazino-5-methyl-3H-4-oxo-thieno[2,3-d]pyrimidine-6-carboxylate (8a)

Compound **8a** was obtained by reaction of 5a (2.84 g, 0.01 mole) and hydrazine hydrate. The product recrystallized from dioxane; IR spectrum (KBr) cm^{-1}: 3341; 3178 [(NH_2), (NH)]; 1707 (CO) and 1667 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 1.35 (t, 3H, CH_3), 2.80 (s, 3H, CH_3), 4.40 (q, 2H, CH_2), 4.60 (br, 2H, NH_2, D_2O exchangeable), and 8.20 (br s, 1H, NH, D_2O exchangeable); MS (m/z): 268 (M^+) 100%.

2-Hydrazino-5-methyl-3H-4-oxo-thieno[2,3-d]pyrimidine-6-Carboxylic Acid (8b)

Compound **8b** was obtained by reaction of **5c** (2.56 g, 0.01 mole) and hydrazine hydrate. The product recrystallized from dimethylformamide; IR spectrum (KBr) cm^{-1}: 3270; 3177 [(NH_2), (NH)]; 1690 (CO) and 1660 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.75 (s, 3H, CH_3), 5.00 (br, 2H, NH_2, D_2O exchangeable), 8.20 (br s, 1H, NH, D_2O exchange-able),

and 12.90 (s, 1H, OH, D_2O exchangeable); MS (m/z): 240(M^+) 43%; 196 (M^+-COOH)100%.

General Procedure for Preparation of 9a,b

A mixture of **7b** (2.40 g, 0.01 mole) and aliphatic acid was heated under reflux for 6 h. The reaction mixture was allowed to cool to room temperature and poured into water. The solid product so precipitated was filtered off and recrystallized from dioxane to produce **9a**,**b** as colorless crystals.

6-Methyl-1H-5-oxo-thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-7-Carboxylic Acid (9a)

Compound **9a** was obtained by heating compound **7b** and formic acid (30 ml) with a catalytic amount of concentrated hydrochloric acid; IR spectrum (KBr) cm^{-1}: 3430(OH), 3138 (NH), 1686 (OH) and 1654 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.45 (s, 3H, CH_3), 6.75 (s, 1H, CH), 9.10 (s, 1H, NH, D_2O exchangeable), and 11.90 (1H, OH, D_2O exchangeable); MS (m/z): 250(M^+) 100%.

3,6-Dimethyl-1H-5-oxo-thieno[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-7-Carboxylic acid (9b)

Compound **9b** was obtained by heating compound **7b** and glacial acetic acid (30 ml), IR spectrum (KBr) cm^{-1}: 3420(OH), 3115 (NH), 1681 (CO) and 1651 (CO), ^{1}H-NMR (DMSO-d_6) δ ppm: 1.90 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 9.95 (s, 1H, NH, D_2O exchangeable), and 11.55 (1H, OH, D_2O exchangeable); MS (m/z): 264(M^+) 100%.

General procedure for preparation of 10a–c

A mixture of compound **7b** (2.40 g, 0.01 mole) and the appropriate β-diketone (0.01 mole) was heated under reflux in absolute ethanol (30 ml) for 5 h. The reaction mixture was allowed to cool to room temperature. The precipitate solid was collected by filtration, dried and recrystallized from dioxane to produce **10a–c**.

2(3,5-Dimethyl-pyrazol-1-yl)-5-methyl-3H-4-oxo-thieno[2,3-d]pyrimidin-6-Carboxy-lic Acid (10a)

Compound **10a** was obtained by heating compound **7b** and pentane-2,4-dione (1.00 g, 0.01 mole). The product was recrystallized from dioxane to produce 10a as pale yellow crystals; IR spectrum (KBr) cm^{-1}: 3435(OH), 3130 (NH), 1688 (CO) and 1655 (CO); ^{1}H-NMR

(DMSO-d_6) δ ppm: 2.25 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 6.30 (s, 1H, CH), 6.65 (s, 1H, NH, D_2O exchangeable), and 11.90 (brs, 1H, OH, D_2O exchangeable); MS (m/z): 304 (M^+) 100%.

2(3,5-Dimethyl-4-chloropyrazol-1-yl)-5-methyl-3H-4-oxo-thieno[2,3-d]pyrimidin-6-carboxylic Acid (10b)

Compound **10b** was obtained by heating compound **7b** and 3-chloropentane-2,4-dione (1.34 g, 0.01 mole). The product was recrystallized from dioxane to produce **10b** as orange crystals; IR spectrum (KBr) cm^{-1}: 3440(OH), 3120 (NH), 1683 (CO) and 1655 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm:, 2.35 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 10.20 (s, 1H, NH, D_2O exchangeable)and 11.45 (brs, 1H, OH, D_2O exchangeable); MS (m/z): 340, 342[M^+, (84%, 39.%)].

2(3-Trifluoro,5-methyl-pyrazol-1-yl)-5-methyl-3H-4-oxo-thieno[2,3-d]pyrimidin-6-carboxylic Acid (10c)

Compound **10c** was obtained by heating compound **7b** and 1,1,1-trifluoro-2,4-pentandione (1.54 g, 0.01 mole). The precipitated solid was collected by filtration, dried and recrystallized from dioxane to produce **10c**, as pale yellow crystals,; IR spectrum (KBr) cm^{-1}: IR spectrum (KBr) cm^{-1}: 3445(OH), 3130 (NH), 1689 (CO) and 1658 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.30 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 6.70 (s, 1H, CH), 9.15 (s, 1H, NH, D_2O exchangeable)and 14.00 (brs, 1H, OH, D_2O exchangeable); MS (m/z): 360 [M^+, (84%, 39.%)].

General Procedure for Preparation of 11a,b

A mixture of compound **7b** (2.40 g, 0.01 mole), and the appropriate aromatic aldehyde (0.01 mole), dioxane (30 ml), and a catalytic amount of piperidine was heated under reflux for 6 h. The reaction mixture was allowed to cool to room temperature, and then it was poured into water. The formed precipitate was filtered-off, washed with water, dried and recrystallized from dimethylformamide to produce **11a**,**b**.

2-(4-Chlorophenylmethylenehydrazone)-5-methyl-3H-4-oxo-thieno[2,3-d]pyrimidin-6-carboxylic acid (11a)

Compound **11a** was obtained by heating compound **7b** and 4-chlorobenzaldehyde (1.40 g, 0.01 mole). The product was recrystallized from dimethylformamide to produce **11a** as yellow crystals; IR spectrum (KBr) cm^{-1}: 3475 (OH), 3180 (NH), 3135 (NH) 1685 (CO) and 1665 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.85 (s, 3H, CH_3), 7.50 (d, 2H, aromatic protons), 8.00 (t, 3H, aromatic protons + CH), 11.25 (br s, 1H, NH, D_2O exchangeable), 12.00 (br s, 1H, NH, D_2O exchangeable), and

12.90 (brs, 1H, OH, D_2O exchangeable); MS (m/z): 362, 264 [M^+, (100%, 24.%)].

2-(4-Methoxyphenylmethylenehydrazone)–5-methyl-3H-4-oxo-thieno[2,3-d]pyrami-din-6-carboxylic Acid (11b)

Compound **11b** was obtained by heating compound **7b** and 4-methoxybenzaldehyde (1.36 g, 0.01 moles). The product was recrystallized from dimethylformamide to produce **11b** as yellow crystals; IR spectrum (KBr) cm^{-1}: 3440 (OH), 3135 (NH), 3125 (NH) 1690 (CO) and 1675 (CO); ^{1}H-NMR (DMSO-d_6) δ ppm: 2.80 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 6.95 (d, 2H, aromatic protons), 7.95 (d, 2H, aromatic protons), 8.05 (s, 1H, CH), 8.80 (br s, 1H, NH, D_2O exchangeable), and 11.85 (brs, 1H, OH, D_2O exchangeable); MS (m/z): 358 (M^+) 100%.

2-Ethylacetoacetatehydrazon-3H-4-oxo-thieno[2,3-d]pyrimidin-6-carboxylic Acid (12)

A mixture of compound **7b** (2.40 g, 0.01 mole) and ethyl acetoacetate (1.30 g, 0.01 mole) was heated under reflux in absolute ethanol for 5 h. The reaction mixture was allowed to cool to room temperature. The precipitate so-formed was collected by filtration, dried, and recrystallized from ethanol to produce **12** as colorless crystals; IR spectrum (KBr) cm^{-1}: 3421 (broad OH and NH), 1716 (CO), 1676 (CO) and 1652 (CO); ^{1}H-NMR ($CDCl_3$) δ ppm: 1.25 (m, 3H, CH_3), 2.00 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 3.40 (s, 2H, CH_2), 4.10 (q, 3H, CH_2+ NH, D_2O exchangeable), 10.75 (brs, 1H, NH, D_2O exchangeable), and 10.80 (brs, 1H, OH, D_2O exchangeable); MS (m/z): 352(M^+) 100%.

5-Methyl-2-(3-methyl-5-oxo-4H-pyrazol-1-yl)-3H-4-oxo-thieno[2,3-d]pyrimidin-6-Carboxylic Acid (13)

Method A. A solution of compound **7b** (2.40 g, 0.01 mole) and ethyl acetoacetate (1.30 g, 0.01 mole) in sodium ethoxide solution (prepared by dissolving sodium metal (0.23 g, 0.01 mole) in absolute ethanol (30 ml)) was heated under reflux for 5 h. The reaction mixture was allowed to cool to room temperature, poured into water, and neutralized by dilute acetic acid solution. The solid product so precipitated was filtered off, dried and recrystallized from dimethylformamide to produce **13** as colorless crystals.

Method B. A solution of compound **12** (3.52 g, 0.01 mole) was heated under reflux with sodium ethoxide solution (prepared by dissolving sodium metal (0.23 g, 0.01 mole) in absolute ethanol (30 ml)) for 5 h. The reaction mixture was allowed to cool to room temperature then poured into water and neutralized by dilute acetic acid solution.

TABLE II Physical Data for the Products 1–13

Comp. no.	m.p.°C	Yield %	M.F. (M.wt.)	Elemental analyses (calcd./ found) %C	%H	%N
1	103–105	80	$C_{11}H_{15}NO_4S$	51.35	5.83	5.44
			257.31	51.80	5.50	5.40
2	200–202	75	$C_{12}H_{16}N_2O_4S_2$	45.55	5.09	8.85
			316.40	45.40	5.00	8.75
3a	240–242	80	$C_{10}H_{10}N_2O_3S_2$	44.43	3.72	10.36
			270.34	44.40	3.70	10.30
3b	288–290	75	$C_8H_6N_2O_3S_2$	39.66	2.49	11.56
			242.28	39.50	2.45	11.55
4a	260–262	73	$C_{19}H_{14}N_2O_4S_2$	57.27	3.54	7.03
			398.46	57.20	3.50	7.03
4b	275–277	70	$C_{20}H_{16}N_2O_5S_2$	56.06	3.76	14.96
			428.49	56.00	3.75	14.85
4c	265–267	75	$C_{19}H_{13}ClN_2O_4S_2$	52.71	3.02	6.47
			432.91	52.71	3.02	6.47
4d	312–314	65	$C_{17}H_{10}N_2O_4S_2$	55.12	2.72	7.56
			370.41	55.10	2.72	7.55
4e	319–321	60	$C_{18}H_{12}N_2O_5S_2$	53.99	3.02	6.99
			400.43	53.90	3.00	6.95
4f	325–327	65	$C_{17}H_9ClN_2O_4S_2$	50.43	2.24	6.91
			404.85	50.43	2.20	6.88
4g	354–356	65	$C_{18}H_9FN_2O_4S_2$	49.31	2.06	6.39
			438.41	49.25	2.06	6.35
5a	275–277	85	$C_{11}H_{12}N_2O_3S_2$	46.46	4.25	9.85
			284.36	46.40	4.25	9.83
5b	255–257	80	$C_{15}H_{16}N_2O_5S_2$	48.90	4.37	7.60
			368.43	48.85	4.37	7.55
5c	300–302	80	$C_9H_8N_2O_3S_2$	42.17	3.14	10.93
			256.31	42.10	3.14	10.90
5d	285–287	75	$C_{13}H_{12}N_2O_5S_2$	45.87	3.55	8.23
			340.38	45.86	3.54	8.20
6	268–270	80	$C_{13}H_{16}N_2O_3S_2$	49.98	5.16	8.96
			312.42	49.96	5.10	8.94
7a	278–280	75	$C_{10}H_{12}N_4O_3S$	44.76	4.50	20.88
			268.30	44.74	4.47	20.85
7b	290–292	70	$C_8H_8N_4O_3S$	39.99	3.35	23.32
			240.24	39.95	3.34	23.30
8a	219–221	80	$C_{15}H_{14}N_2O_4S_2$	51.41	4.02	7.99
			350.42	51.41	4.00	7.96
8b	330–332	70	$C_{13}H_{10}N_2O_4S_2$	48.43	3.13	8.70
			322.37	48.40	3.10	8.65
9a	263–265	85	$C_9H_6N_4O_3S$	43.19	2.42	22.39
			250.24	43.15	2.42	22.39
9b	300–302	80	$C_{10}H_8N_4O_3S$	45.45	3.05	21.20
			264.27	45.40	3.00	21.20

(Continued on next page)

TABLE II Physical Data for the Products 1–13 (*Continued*)

Comp. no.	m.p.°C	Yield %	M.F. (M.wt.)	Elemental analyses (calcd./ found) %C	%H	%N
10a	340–342	75	$C_{13}H_{14}N_4O_3S$	51.00	4.60	18.28
			306.34	51.00	4.55	18.25
10b	300–302	75	$C_{13}H_{13}ClN_4O_3S$	45.81	3.84	16.44
			340.79	45.80	3.84	16.40
10c	310–312	70	$C_{13}H_{11}F_3N_4O_3S$	43.33	3.07	15.55
			360.31	43.33	3.05	15.50
11a	305–307	75	$C_{15}H_{11}ClN_4O_3S$	49.66	3.05	15.44
			362.79	49.62	3.05	15.42
11b	315–317	80	$C_{16}H_{14}N_4O_4S$	53.62	3.93	15.63
			358.38	53.60	3.90	15.60
12	230–232	85	$C_{14}H_{16}N_4O_5S$	47.72	4.57	15.90
			352.37	47.70	4.50	15.90
13	302–304	60	$C_{12}H_{10}N_4O_4S$	47.06	3.29	18.30
			306.30	47.00	3.25	18.30

The precipitate so-formed was collected by filtration, dried and recrystallized from dimethylformamide to produce **13** as colorless crystals. IR spectrum (KBr) cm^{-1}: 3446 (OH) 1685 (CO), 1665 (CO) and 1654 (CO). .^{1}H-NMR (DMSO-d_6) δ ppm: 2.65 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 4.00 (s, 2H, CH_2), and 12.50 (brs, 1H, OH, D_2O exchangeable); MS (m/z): 306(M^+) 100%.

CONCLUSIONS

This work is concerned with the synthesis and reactions of thieno[2,3-d]pyrimidone with functional and bifunctional groups to give pyrazolothieno, thiazolothieno, and triazolo thieno[2,3-d]pyrimidine derivatives. Those reactions carrying out transformation, which in one or two steps added a new heterocyclic ring to the molecules

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