SYNTHESIS OF SOME NOVEL THIENO[3,2-\textit{d}]PYRIMIDINE DERIVATIVES OF PHARMACEUTICAL INTEREST

Hala M. Refat,1* Ahmed A. Fadda,2 Rasha E. El-Mekawy,3 and Aliaa M. Sleat2

1*Department of Chemistry, Faculty of Science, Suez Canal University, 45511 Al-Arish, Egypt, E-mail: hala7223530@hotmail.com
2Department of Chemistry, Faculty of Science, Mansoura University, ET-35516 Mansoura, Egypt
3Department of Petrochemicals, Egyptian Petroleum Research Institute, Nasr City, Cairo, Egypt

Abstract – New starting material, ethyl 6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-\textit{d}]pyrimidine-7-carboxylate (2) was prepared by Gewald reaction using \textit{N,N}-dimethylbarbituric acid. The reaction of compound 2 with phenyl isothiocyanate yields the non-isolable intermediate 3, which gave thiocarbamoyl derivative 4 upon treatment with dilute HCl. Also compound 2 react with carbon disulfide afforded carbamodithioic acid derivative 5, followed by addition of aniline to give the same product 4. On the other hand, when compound 4 refluxed in DMF and TEA afforded the thieno[2,3-\textit{d}:4,5-\textit{d}']dipyrimidine derivative 6. Moreover, treatment of 3 with \textalpha;-halo compounds in basic medium afforded the corresponding thiazol-2-ylidene derivatives (8a, 8b, 10), thiazolidin-2-ylidene derivative 12 and 1,3-thiazinan -2-ylidene derivative 15, respectively. Furthermore, the reaction of 2 with malononitrile and 2-cyano-3-phenylacrylamide afforded the corresponding pyrido[3',2':4,5]thieno[3,2-\textit{d}]pyrimidine derivatives 16 and 17, respectively. All the newly synthesized compounds were characterized by IR, \textit{\textsuperscript{1}H-NMR, \textsuperscript{13}C-NMR, mass spectra and elemental analyses.

INTRODUCTION

The derivatives of thieno[3,2-\textit{d}]pyrimidine have attracted strong interest due to their broad bioactivities, including antitumor,1-5 antimicrobial,6,7 anti-inflammatory8 and antiviral.9 On the other hand, aryl isothiocyanates have been used as synthetic intermediates to prepare biologically active heterocyclic compounds.10 The diversity of biological and physiological activities of sulfur heterocycles may be
attributed to the presence of N=C=S fragment, characteristic of thiazoles, thiazolines and thiazolidines.\textsuperscript{11} These are known to exhibit pesticidal,\textsuperscript{12} anticonvulsant,\textsuperscript{13} nematocidal,\textsuperscript{14} herbicidal,\textsuperscript{15} antiviral,\textsuperscript{16} fungicidal,\textsuperscript{17} bactericidal,\textsuperscript{18,19} antiprotozoal,\textsuperscript{20} and hypoglycemic activity.\textsuperscript{21} They are also act as chemotherapeutic agents.

In view of the above biological importance and in continuation of our studies on the chemistry of thiocarbamoyl and active methylene compounds,\textsuperscript{22-30} we aimed to the synthesis of novel heterocyclic compounds from readily obtainable thiocarbamoyl intermediates. We reported herein the synthesis of new thieno[3,2-d]pyrimidine incorporated thiazole or pyridine moiety that are important in medicinal chemistry programs.

**RESULT AND DISCUSSION**

The new starting, ethyl 6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (2) was obtained with high purity 99\% yield in the classic Gewald synthesis via the reaction of N,N-dimethylbarbituric acid, elemental sulfur and ethyl cyanoacetate in the presence of DMF and a catalytic amount of morpholine. Assignment of the product 2 was based on elemental and spectral analysis. The IR spectrum showed the absorption bands at 3436, 3350 cm\textsuperscript{-1} due to NH\textsubscript{2} group and 1708, 1679 cm\textsuperscript{-1} corresponding to three carbonyl groups. Its \textsuperscript{1}H-NMR spectrum revealed triplet signal at δ 3.00 ppm due to CH\textsubscript{3}, quartet signal at 3.71 ppm due to CH\textsubscript{2} and two singlet signals at 3.01 and 3.09 ppm due to two N-CH\textsubscript{3} protons. In addition to, a singlet signal at 4.64 ppm due to NH\textsubscript{2} proton. The mass spectrum gave a molecular ion peak at \textit{m/z} = 283 which matches with its molecular formula C\textsubscript{11}H\textsubscript{13}N\textsubscript{3}O\textsubscript{4}S.

Compound 2 reacted with phenyl isothiocyanate and potassium hydroxide in the presence of DMF at room temperature led to the formation of the non-isolable intermediate 3, which gave thiocarbamoyl derivative 4 upon treatment with dilute HCl. Assignment of 4, was based on an elemental analysis and spectral data. Its IR spectrum showed the absorption bands at 1709, 1698 cm\textsuperscript{-1} corresponding to three carbonyl groups and 1265 cm\textsuperscript{-1} due to C=S group. Its \textsuperscript{1}H-NMR spectrum revealed singlet signals at 11.17 and 11.68 ppm due to two NH protons. The mass spectrum gave a molecular ion peak at \textit{m/z} = 418 which matches with its molecular formula C\textsubscript{18}H\textsubscript{18}N\textsubscript{4}O\textsubscript{4}S\textsubscript{2}.

On the other hand, compound 2 reacted with carbon disulfide in DMF and potassium hydroxide, followed by addition dil HCl led to the corresponding carbamothioic acid derivative 5, which reacted with aniline gave the same product 4. The structure of compound 5 was established by the spectral data. The IR spectrum of compound 5 showed the absorption bands at 3391 cm\textsuperscript{-1} due to NH group, 1708, 1690 cm\textsuperscript{-1} corresponding to three carbonyl groups and 1278 cm\textsuperscript{-1} due to C=S group . Its \textsuperscript{1}H-NMR spectrum revealed a singlet signals at 2.70 and 12.95 ppm due to SH and NH protons. The mass spectrum gave a molecular ion peak at \textit{m/z} = 359 which matches with its molecular formula C\textsubscript{12}H\textsubscript{13}N\textsubscript{3}O\textsubscript{4}S\textsubscript{3}. 
Reflexing of 4 in the presence of DMF and a catalytic amount of TEA afforded 1,3-dimethyl-8-phenyl-7-thioxo-7,8-dihydrothieno[2,3-d:4,5-d']dipyrimidine-2,4,9(1H,3H,6H)-trione (6). The structure of 6 was characterized by the disappearance of ester group in its 1H-NMR spectrum and revealed two singlet signals at 3.01 and 3.09 ppm due to two N-CH₃ protons and a singlet signal at 11.98 ppm due to NH proton. Also, the product was confirmed by the mass spectrum, it showed the molecular ion peak at $m/z = 372$ in agreement with the molecular formula C₁₆H₁₂N₄O₃S₂.

Stirring of the intermediate 3 with chloroacetone or phenacyl bromide in a mixture of EtOH and DMF (2:1) at room temperature led to the formation of acyclic intermediates 7a and 7b. Structures 7a and 7b were established by spectral data. The IR spectra of compounds 7a and 7b showed the absorption band at 3325 cm⁻¹ due to NH group. Its ¹H-NMR spectra revealed singlet signals at 4.13 and 10.65 ppm due to CH₂ and NH protons. In addition, the mass spectra showed the molecular ion peaks at $m/z = 474$ (M⁺) and 536 (M⁺), respectively, which are in agreement with their molecular formulas.
Refluxing of compounds 7a and 7b in DMF and few drops of TEA led to the formation of thiazole-2-yridene derivatives 8a and 8b, respectively. Its $^1$H-NMR spectra revealed a singlet signals at 5.81 ppm due to C$_5$ of thiazole ring. Also, $^{13}$C-NMR spectra showed signal in region 96.6-98.7 ppm due to C$_5$ of thiazole ring. In addition, the mass spectra showed the molecular ion peaks at $m/z = 456$ (M$^+$) and 518 (M$^+$), respectively, which are in agreement with their molecular formulas.

Similarly, treatment of 3 with chloroacetonitrile in a mixture of EtOH and DMF (2:1) at room temperature gave acyclic thienopyrimidine derivative 9. The assignment of 9 was based on an elemental analysis and spectral data. Its IR spectrum showed the absorption bands at 3343 cm$^{-1}$ due to NH group, 2202 cm$^{-1}$ due to CN group and 1700, 1644 cm$^{-1}$ corresponding to three carbonyl groups. Its $^1$H-NMR spectrum revealed singlet signals at 4.25 and 10.65 ppm due to CH$_2$ and NH protons. $^{13}$C-NMR spectra showed signal at 117.8 ppm due to CN group. In addition, the mass spectra showed the molecular ion peaks at $m/z = 457$ (M$^+$), which matches with its molecular formula C$_{20}$H$_{19}$N$_5$O$_4$S$_2$.

Refluxing of 9 in DMF and TEA yielded ethyl 6-((4-amino-3-phenylothiazol-2(3H)-ylidene)amino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (10). The assignment of 10 was based on an elemental analysis and spectral data. Its IR spectrum showed the absence of a CN group and instead the presence of a new absorption band at 3444-3360 cm$^{-1}$ due to NH$_2$ group. Its $^1$H-NMR spectrum revealed singlet signals at 6.18 and 6.45 ppm due to NH$_2$ and C$_5$ of thiazole protons, respectively. In addition, the mass spectra showed the molecular ion peaks at $m/z = 457$ (M$^+$), which matches with its molecular formula C$_{20}$H$_{19}$N$_5$O$_4$S$_2$. 

![Diagram of reaction scheme](image-url)
On the other hand, the intermediate 3 was treated with ethyl bromoacetate in a mixture of EtOH and DMF (2:1) at room temperature led to the formation of acyclic intermediate 11, followed by refluxing in DMF and a catalytic amount of TEA afforded the corresponding thiazolidin-2-ylidene derivative 12. Structure 12 was confirmed on the basis of its elemental and spectral data. The IR spectrum showed bands at 1727-1658 cm\(^{-1}\) due to four carbonyl groups. Its \(^1\)H-NMR spectrum revealed a singlet signal at 4.23 ppm due to C\(_5\) of thiazolidine ring. \(^13\)C-NMR spectra showed signal at 45.6 ppm due to C\(_5\) of thiazolidine ring. In addition, the mass spectra showed the molecular ion peaks at \(m/z = 458\) (M\(^+\)), which matches with its molecular formula C\(_{20}\)H\(_{18}\)N\(_4\)O\(_5\)S\(_2\).

\[
\text{Scheme 3}
\]

On the same manner, the intermediate 3 reacted with chloroacetyl chloride in stirring EtOH and DMF (2:1), a product 13 that analyzed for C\(_{20}\)H\(_{19}\)ClN\(_4\)O\(_5\)S\(_2\) was isolated in good yield. The acyclic structure 13 was established based on its IR spectrum that showed bands at 3340 and 1739-1691 cm\(^{-1}\) related to NH and four C=O function groups, respectively. Its \(^1\)H-NMR spectrum revealed two singlet signals at \(\delta 4.65\) and 10.67 ppm for CH\(_2\) and NH protons. The structure of compound 13 was confirmed by its mass spectrum which showed a peak at \(m/z = 494\) (M\(^+\)). Refluxing of compound 13 in DMF and a catalytic amount of TEA led to the formation of a product identical in all respects (mp, mixed mp, IR, \(^1\)H-NMR and \(^13\)C-NMR ) to compound 12 (Scheme 3). When the intermediate potassium salt 3 is stirred with methyl bromopropionate in a mixture of EtOH and DMF (2:1) at room temperature the corresponding acyclic intermediate 14 is exclusively isolated in good yield. The structure of 14 has been confirmed on the basis of elemental and spectral data. The IR spectrum exhibits bands at 3391 and 1710-1689 cm\(^{-1}\)
related to the NH and four C=O function groups, respectively. Its $^1$H-NMR spectrum revealed two triplet signals at δ 2.67 and 3.22 corresponding to two CH$_2$ and a singlet signal at 10.36 ppm due to NH proton. The correct structure of compound 14 was also confirmed by its mass spectrum which showed a peak at $m/z = 504$ (M$^+$).

![Scheme 4]

Also, refluxing of the acyclic intermediate 14 in DMF containing a catalytic amount of TEA gave the corresponding 1,3-thiazinan-2-ylidene derivative 15. The mass spectrum gave a molecular ion peak at $m/z = 472$ which matches with its molecular formula C$_{21}$H$_{20}$N$_4$O$_5$S$_2$ (Scheme 4).

Moreover, treatment of 2 with malononitrile in DMF and a catalytic amount of TEA afforded the corresponding pyrido[3′,2′:4,5]thieno[3,2-$d$]pyrimidine derivative 16. Structure 16 was confirmed on the basis of its elemental and spectral data. The IR spectrum showed bands at 3424-3317, 2209 and 1705, 1666 cm$^{-1}$ attributable to the NH$_2$, CN and two C=O functions, respectively. Its $^1$H-NMR spectrum revealed singlet signals at δ 6.14 and 10.83 ppm for NH$_2$ and NH protons, respectively. The structure of 16 was confirmed also by its mass spectrum which showed a peak at $m/z = 303$ (M$^+$).

![Scheme 5]
Furthermore, treatment of 2 with 2-cyano-3-phenylacrylamide in DMF and a catalytic amount of TEA afforded the corresponding pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine derivative 17. Structure 17 was confirmed on the basis of its elemental and spectral data. The IR spectrum showed bands at 3434-3380, 2210 and 1705-1678 cm⁻¹ attributable to the NH₂, CN and four C=O functions, respectively. Its ¹H-NMR spectrum revealed singlet signal at δ 7.20 ppm for CONH₂ proton. The structure of 17 was confirmed also by its mass spectrum which showed its molecular ion peak at m/z = 407 (M⁺) (Scheme 5).

In conclusion, the present study describes the synthesis of a series of novel thieno[3,2-d]pyrimidine derivatives containing pyrimidine, thiazole and pyridine moiety. This work has advantages of cheap starting materials, an excellent yield, mild reaction conditions and a simple experimental procedure. The compounds prepared are expected to be of pharmacological interest.

**EXPERIMENTAL**

Melting points were recorded on Gallenkamp electric melting point apparatus (Electronic Melting Point Apparatus, Great Britain, London) and are uncorrected. Precoated Merck silica gel 60F-254 plates were used for thin-layer chromatography (TLC) and the spots were detected under UV light (254 nm). The infrared spectra were obtained from potassium bromide triturate containing 0.5% of the product on Pye Unicam SP 1000 IR spectrophotometer (Thermoelectron Co. Egelsbach, Germany). The ¹H-NMR spectra were determined on Varian Gemini 400 MHz (Varian Co., Cairo university, Egypt), ¹³C-NMR = 100 MHz. Deuterated DMSO-d₆ and CDCl₃ was used as a solvents, tetramethylsilane (TMS) was used as an internal standard and chemical shifts were measured in δ ppm. Mass spectra were determined on a GC-MS.QP-100 EX Shimadzu (Japan). Elemental analyses were recorded on Perkin-Elmer 2400 Elemental analyzer at the Micro-analytical Center at Cairo University, Cairo, Egypt.

**Synthesis of ethyl 6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (2).** To a solution of compound 1 (1.56 g, 0.01 mol) in DMF (30 mL), ethyl cyanoacetate (1.13 g, 0.01 mol) and elemental sulfur in EtOH (15 mL) containing morpholine (4 drops), was refluxed for 6 h. The solid product was filtered off and recrystallized from EtOH-DMF to give compound 2; Shiny orange crystal; yield (2.80 g, 99%); mp 220-222 °C (EtOH-DMF (2:1)); IR (KBr): v/cm⁻¹ = 3436-3350 (NH₂), 1708-1679 (3C=O); ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 3.00 (t, 3H, J = 7.1 Hz, CH₂CH₃), 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 4.64 (s, 2H, NH₂); ¹³C-NMR (100 MHz , DMSO-d₆) δ (ppm): 18.9, 27.3, 30.2 , 67.4, 115.6, 123.7, 143.8, 151.7, 155.3, 163.5, 169.2; MS (EI, 70 eV) m/z = 283 (M⁺) Anal. Caled for C₁₁H₁₃N₃O₄S (283.30): C, 46.64; H, 4.63; N, 14.83; S, 11.32. Found: C, 46.71; H, 4.70; N, 14.92; S, 11.38.

**Synthesis of ethyl 1,3-dimethyl-2,4-dioxo-6-(3-phenylthioureido)-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (4).** Method (a): To a cold suspension of finely divided KOH (0.56 g, 0.01
mol) in dry DMF (15 mL) were added to compound 2 (2.83 g, 0.01 mol), followed by addition of phenyl isothiocyanate (1.5 mL, 0.01 mol). The mixture was stirred at room temperature for 12 h, and then poured into ice-cold water and then acidified with HCl (0.1 N) to a pH 3-4. The solid product was filtered off, washed with water and recrystallized from EtOH-DMF to give compound 4; Fin white crystal; yield (3.55 g, 85%); mp 153-155 °C (EtOH-DMF (2:1)); IR (KBr): v/cm⁻¹ = 3371, 3351 (2NH), 1709-1698 (3C=O), 1265 (C=S); ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 3.00 (t, 3H, J = 7.1 Hz, CH₂CH₃), 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 7.18-7.58 (m, 5H, Ar-H), 11.17 (s, 1H, NH, D₂O exchangeable), 11.68 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 18.5, 27.6, 30.5, 67.8, 115.3, 123.4, 126.0, 126.8, 127.6, 128.2, 128.9, 136.4, 143.2, 151.6, 155.3, 163.2, 169.3, 186.2; MS (EI, 70 eV) m/z = 418 (M⁺) Anal. Calcd for C₁₈H₁₈N₄O₄S₂ (418.49): C, 51.66; H, 4.34; N, 13.39; S, 15.32. Found: C, 51.72; H, 4.37; N, 13.47; S, 15.39. **Method (b):** A mixture of compound 5 (3.59 g, 0.01 mol) and aniline (0.91 mL, 0.01 mol) in DMF (10 mL) was heated under reflux for 6 h until the evolution of hydrogen sulfide was ceased. The reaction mixture was then allowed to cool and then poured to ice cooled water (100 mL). The solid products obtained was collected and recrystallized from EtOH-DMF to give as white crystal; yield 4 (65%).

**Synthesis of (7-(ethoxycarbonyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidin-6-yl)carbamodithioic acid (5).** To a cold suspension of finely divided KOH (0.56 g, 0.01 mol) in dry DMF (15 mL) were added to compound 2 (2.83 g, 0.01 mol), followed by addition of carbon disulfide (0.6 mL, 0.01 mol). The mixture was stirred at room temperature for 12 h, and then poured into ice-cold water and then acidified with HCl (0.1 N) to a pH 3-4. The solid product was filtered off, washed with water and recrystallized from EtOH-DMF to give compound 5; Gray powder; yield (2.69 g, 75%); mp 209-211 °C (EtOH-DMF (2:1)); IR (KBr): v/cm⁻¹ = 3391 (NH), 1708-1690 (3C=O), 1278 (C=S); ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 2.70 (s, 1H, SH), 3.00 (t, 3H, J = 7.1 Hz, CH₂CH₃), 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 12.95 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 18.2, 28.4, 30.5, 67.3, 115.3, 121.4, 144.6, 150.8, 155.6, 162.4, 170.5, 192.3; MS (EI, 70 eV) m/z = 359 (M⁺) Anal. Calcd for C₁₂H₁₃N₃O₄S₃ (359.43): C, 40.10; H, 3.65; N, 11.69; S, 26.76. Found: C, 40.00; H, 3.69; N, 11.77; S, 26.82.

**Synthesis of 1,3-dimethyl-8-phenyl-7-thioxo-7,8-dihydrothieno[2,3-d:4,5-d′]dipyrimidine-2,4,9(1H,3H,6H)-trione (6).** A solution of compound 4 (4.18 g, 0.01 mol), in dry DMF (15 mL) and TEA (4 drops) was refluxed for 8 h. The reaction mixture was allowed to cool. The solid product was filtered off and recrystallized from EtOH-DMF to give compound 5; Brown crystal; yield (2.45 g, 66%); mp 234-236 °C (EtOH-DMF (2:1)); IR (KBr): v/cm⁻¹ = 3390 (NH), 1690 (3C=O), 1279 (C=S); ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 7.15-7.76 (m, 5H, Ar-H), 11.98 (s, 1H, 2HETEROCYCLES, Vol. 91, No. 12, 2015
NH, D₂O exchangeable); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 27.4, 30.5, 89.6, 115.8, 126.2, 126.9, 127.5, 128.4, 128.9, 136.2, 143.5, 151.4, 155.3, 162.8, 172.7, 186.5; MS (EI, 70 eV) m/z = 372 (M⁺) Anal. Caled for C₁₆H₁₂N₄O₃S₂ (372.42): C, 51.60; H, 3.25; N, 15.04; S, 17.22. Found: C, 51.68; H, 3.29; N, 15.11; S, 17.31.

**General procedure for compounds 7a, 7b, 9, 11, 13 and 14.** To a solution of compound 2 (2.83 g, 0.01 mol) in mixture of DMF/ EtOH (1:2) (20 mL) and phenyl isothiocyanate (1.5 mL, 0.01 mol) in the presence of KOH (0.56 g, 0.01 mol), was stirred overnight at room temperature to give non-isolable salt 3, followed by addition α-halo compounds such as chloroacetone (0.75 g, 0.01 mol) or phenacyl bromide (2.0 g, 0.01 mol) or chloroacetonitrile (0.70 g, 0.01 mol) or ethyl bromoacetate (1.15 mL, 0.01 mol) or chloroacetyl chloride (0.8 mL, 0.01 mol) or methyl bromopropionate (1.67 g, 0.01 mol), and stirred at room temperature for 12 h, and then poured into ice-cold water. The solid product was filtered off and recrystallized from EtOH-DMF to give compounds 7a, 7b, 9, 11, 13 and 14, respectively.

**Ethyl 1,3-dimethyl-2,4-dioxo-6-(((2-oxopropyl)thio)(phenylamino)methylene)amino)-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (7a).** Yellow powder; yield (3.69 g, 78%); mp 185-187 °C (EtOH-DMF (2:1)); IR (KBr): ν/cm⁻¹ = 3325 (NH), 1700-1658 (4C=O); ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 2.61 (s, 3H, CH₃), 3.00 (t, 3H, J = 7.1 Hz, CH₂CH₃), 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 4.13 (s, 2H, CH₂), 6.71-7.42 (m, 5H, Ar-H), 10.65 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 18.5, 24.2, 27.5, 30.3, 40.6, 67.3, 114.8, 121.4, 123.5, 128.6, 141.2, 143.6, 151.4, 155.3, 160.1, 161.5, 163.7, 178.5; MS (EI, 70 eV) m/z = 474 (M⁺) Anal. Caled for C₂₁H₂₂N₄O₅S₂ (474.55): C, 53.15; H, 4.67; N, 11.81; S, 13.51. Found: C, 53.24; H, 4.75; N, 11.74; S, 13.58.

**Ethyl 1,3-dimethyl-2,4-dioxo-6-(((2-oxo-2-phenylethyl)thio)(phenylamino)methylene)amino)-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (7b).** Buff powder; yield (4.34 g, 81%); mp 209-210 °C (EtOH-DMF (2:1)); IR (KBr): ν/cm⁻¹ = 3325 (NH), 1700-1654 (4C=O); ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 2.61 (s, 3H, CH₃), 3.00 (t, 3H, J = 7.1 Hz, CH₂CH₃), 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 4.13 (s, 2H, CH₂), 6.75-8.12 (m, 10H, Ar-H), 10.67 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 18.5, 24.2, 27.5, 30.3, 41.6, 67.3, 114.8, 121.4, 123.5, 128.6, 141.2, 143.6, 151.4, 155.3, 160.1, 161.5, 163.7, 178.5; MS (EI, 70 eV) m/z = 536 (M⁺) Anal. Caled for C₂₆H₂₄N₄O₅S₂ (474.55): C, 53.15; H, 4.67; N, 11.81; S, 13.51. Found: C, 53.24; H, 4.75; N, 11.74; S, 13.58.

**Ethyl 6-((((cyanomethyl)thio)(phenylamino)methylene)amino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (9).** Green powder; yield (3.42 g, 75%); mp 230-232 °C (EtOH-DMF (2:1)); IR (KBr): ν/cm⁻¹ = 3343 (NH), 2202 (CN), 1700-1644 (3C=O); ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 3.00 (t, 3H, J = 7.1 Hz, CH₂CH₃), 4.63 (s, 2H, CH₂), 6.75-8.12 (m, 10H, Ar-H), 10.67 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 18.4, 27.6, 30.1, 40.6, 67.3, 114.6, 120.8, 122.2, 123.3, 127.6, 128.5, 129.4, 135.0, 138.2, 140.1, 143.7, 151.4, 155.7, 160.2, 161.4, 163.2, 187.0; MS (EI, 70 eV) m/z = 536 (M⁺) Anal. Caled for C₂₆H₂₄NaO₅S₂ (536.62): C, 58.19; H, 4.51; N, 10.44; S, 11.95. Found: C, 58.09; H, 4.58; N, 10.51; S, 12.01.
3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 4.25 (s, 2H, CH₂), 6.74-7.31 (m, 5H, Ar-H), 10.65 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 16.5, 18.8, 27.7, 30.3, 67.6, 114.3, 117.8, 120.6, 122.1, 123.4, 129.3, 140.3, 143.6, 151.6, 155.7, 160.1, 161.2, 163.4; MS (EI, 70 eV) m/z = 457 (M⁺)  

Anal. Calcd for C₂₀H₁₉N₅O₄S₂ (457.52): C, 52.50; H, 4.19; N, 15.31; S, 14.01. Found: C, 52.59; H, 4.27; N, 15.37; S, 14.06.

**Ethyl 6-(((2-ethoxy-2-oxoethyl)thio)(phenylamino)methylene)amino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (11).** Buff powder; yield (3.98 g, 79%); mp 220-222 °C (EtOH-DMF (2:1)); IR (KBr): ν/cm⁻¹ = 3341 (NH), 1700-1690 (4C=O); ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 3.00 (t, 3H, J = 6.8 Hz, CH₂CH₃), 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 3.85 (q, 2H, J = 6.8 Hz, CH₂CH₃), 4.18 (s, 2H, CH₂), 6.74-7.67 (m, 5H, Ar-H), 10.65 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 18.2, 18.9, 27.4, 30.2, 40.6, 66.8, 67.5, 114.8, 121.4, 122.3, 123.3 129.4, 138.6, 143.4, 151.2, 155.6, 160.1, 161.4, 163.7, 168.9; MS (EI, 70 eV) m/z = 504 (M⁺)  

Anal. Calcd for C₂₂H₂₄N₄O₆S₂ (504.58): C, 52.37; H, 4.79; N, 11.10; S, 12.75. Found: C, 52.45; H, 4.86; N, 11.13; S, 12.75.

**Ethyl 6-(((2-chloro-2-oxoethyl)thio)(phenylamino)methylene)amino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (13).** Yellow crystal; yield (4.05 g, 82%); mp 199-200 °C (EtOH-DMF (2:1)); IR (KBr): ν/cm⁻¹ = 3340 (NH), 1739-1691 (4C=O); ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 4.65 (s, 2H, CH₂), 6.71-7.42 (m, 5H, Ar-H), 10.67 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 18.4, 27.7, 30.5, 41.6, 67.8, 114.2, 121.2, 122.4, 123.5, 129.3, 130.1, 143.1, 151.8, 155.6, 160.3, 161.6, 174.4; MS (EI, 70 eV) m/z = 494 (M⁺)  


**Ethyl 6-(((3-methoxy-3-oxopropyl)thio)(phenylamino)methylene)amino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (14).** Pink powder; yield (4.33 g, 86%); mp 202-204 °C (EtOH-DMF (2:1)); IR (KBr): ν/cm⁻¹ = 3391 (NH), 1710-1689 (4C=O); ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 3.22 (t, 2H, J = 7.5 Hz, CH₂), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 3.87 (s, 3H, CH₃), 7.01-7.56 (m, 5H, Ar-H), 10.36 (s, 1H, NH, D₂O exchangeable); ¹³C-NMR (100 MHz, DMSO-d₆) δ (ppm): 18.3, 27.6, 30.5, 38.5, 42.4, 56.4, 67.4, 114.3, 121.4, 122.9, 123.7, 129.5, 140.6, 143.7, 151.8, 155.2, 160.3, 161.4, 163.6, 170.5; MS (EI, 70 eV) m/z = 504 (M⁺)  

Anal. Calcd for C₂₂H₂₄N₄O₆S₂ (504.58): C, 52.37; H, 4.79; N, 11.10; S, 12.75. Found: C, 52.41; H, 4.84; N, 11.17; S, 12.74.

**General procedure for synthesis compounds 8a, 8b, 10, 12 and 15.** A solution of compound 7a (4.74 g,
or 7b (5.36 g, 0.01 mol) or 9 (4.57 g, 0.01 mol) or 11 (5.04 g, 0.01 mol) or 13 (4.94 g, 0.01 mol) or 14 (5.04 g, 0.01 mol) in DMF (30 mL) and in the presence of TEA (4 drops), was refluxed for 4 h. The reaction mixture was poured onto crushed ice. The obtained solid product was collected by filtration, dried and crystallized from EtOH/DMF to give compounds 8a, 8b, 10, 12 and 15, respectively.

**Ethyl 1,3-dimethyl-6-((4-methyl-3-phenylthiazol-2(3H)-ylidene)amino)-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (8a).** Brown powder; yield (2.96 g, 65%); mp > 300 °C (EtOH-DMF (2:1)); IR (KBr): ν/cm⁻¹ = 1700-1658 (3C=O), 1606 (C=N); ¹H-NMR (400 MHz, DMSO- _d_6) δ (ppm): 2.56 (s, 3H, CH₃), 3.00 (t, 3H, J = 7.1 Hz, CH₂CH₃), 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 5.81 (s, 1H, C₅ of thiazole ring), 6.95-7.64 (m, 5H, Ar-H); ¹³C-NMR (100 MHz, DMSO- _d_6) δ (ppm): 18.4, 21.3, 27.6, 30.5, 67.5, 96.6, 114.7, 121.6, 122.8, 123.9, 129.8, 141.3, 143.5, 146.7, 151.3, 155.7, 160.3, 161.6, 163.6; MS (EI, 70 eV) m/z = 456 (M⁺) Anal. Calcd for C₂₁H₂₀N₄O₄S₂ (456.54): C, 55.25; H, 4.42; N, 12.27; S, 14.04. Found: C, 55.30; H, 4.48; N, 12.32; S, 14.10.

**Ethyl 6-((3,4-diphenylthiazol-2(3H)-ylidene)amino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (8b).** Brown powder; yield (3.52 g, 68%); mp > 300 °C (EtOH-DMF (2:1)); IR (KBr): ν/cm⁻¹ = 1700-1654 (4C=O), 1635 (C=N); ¹H-NMR (400 MHz, DMSO- _d_6) δ (ppm): 3.00 (t, 3H, J = 7.1 Hz, CH₂CH₃), 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃), 6.43 (s, 1H, C₅ of thiazole ring), 7.35-7.87 (m, 10H, Ar-H); ¹³C-NMR (100 MHz, DMSO- _d_6) δ (ppm): 18.5, 27.7, 30.5, 67.6, 98.7, 114.7, 120.4, 122.8, 123.4, 127.4, 128.6, 129.5, 130.4, 136.5, 138.7, 143.6, 146.6, 151.2, 155.8, 160.5, 161.3, 163.5; MS (EI, 70 eV) m/z = 518 (M⁺) Anal. Calcd for C₂₆H₂₂N₄O₄S₂ (518.61): C, 60.22; H, 4.28; N, 10.80; S, 12.36. Found: C, 60.29; H, 4.35; N, 10.84; S, 12.41.

**Ethyl 6-((4-amino-3-phenylthiazol-2(3H)-ylidene)amino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (10).** Brown powder; yield (2.83 g, 62%); mp > 300 °C (EtOH-DMF (2:1)); IR (KBr): ν/cm⁻¹ = 3444-3360 (NH₂), 1700-1657 (3C=O); ¹H-NMR (400 MHz, DMSO- _d_6) δ (ppm): 3.00 (t, 3H, J = 7.1 Hz, CH₂CH₃), 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.17 (q, 2H, J = 7.1 Hz, CH₂CH₃), 6.18 (s, 2H, NH₂, D₂O exchangeable), 6.45 (s, 1H, C₅ of thiazole ring), 7.02-7.48 (m, 5H, Ar-H); ¹³C-NMR (100 MHz, DMSO- _d_6) δ (ppm): 18.5, 27.7, 30.5, 67.6, 98.7, 114.7, 120.4, 122.8, 123.4, 127.4, 128.6, 129.5, 130.4, 136.5, 138.7, 143.6, 146.6, 151.2, 155.8, 160.5, 161.3, 163.5; MS (EI, 70 eV) m/z = 457 (M⁺) Anal. Calcd for C₂₀H₁₉N₅O₄S₂ (457.52): C, 52.50; H, 4.19; N, 15.31; S, 14.01. Found: C, 52.58; H, 4.29; N, 15.38; S, 14.05.

**Ethyl 1,3-dimethyl-2,4-dioxo-6-((4-oxo-3-phenylthiazolidin-2-ylidene)amino)-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (12).** Yellowish brown powder; yield (3.06 g, 67%); mp > 300 °C (EtOH-DMF (2:1)); IR (KBr): ν/cm⁻¹ = 1727-1658 (4C=O), 1623 (C=N); ¹H-NMR (400 MHz, DMSO- _d_6) δ (ppm): 3.00 (t, 3H, J = 7.1 Hz, CH₂CH₃), 3.01 (s, 3H, N-CH₃), 3.09 (s, 3H, N-CH₃), 3.71 (q, 2H, J = 7.1 Hz, CH₂CH₃).
CH$_2$CH$_3$), 4.23 (s, 2H, C$_5$ of thiazolidine ring), 7.05-7.75 (m, 5H, Ar-H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ (ppm): 18.1, 27.5, 30.3, 45.6, 67.2, 114.4, 123.2 126.5, 127.4, 128.9, 138.2, 143.5, 151.4, 155.5, 160.7, 161.8, 163.8, 173.5; MS (EI, 70 eV) m/z = 458 (M$^+$) Anal. Caled for C$_{20}$H$_{18}$N$_4$O$_5$S$_2$ (458.51): C, 52.39; H, 3.96; N, 12.22, S, 13.98. Found: C, 52.48; H, 4.02; N, 12.30, S, 14.04.

Ethyl 1,3-dimethyl-2,4-dioxo-6-((4-oxo-3-phenyl-1,3-thiazinan-2-ylidene)amino)-1,2,3,4-tetrahydrothieno[3,2-d]pyrimidine-7-carboxylate (15). Brown powder; yield (3.11 g, 66%); mp 216-218 °C (DMF-EtOH (1:2)); IR (KBr): ν/cm$^{-1}$ = 2853-2923 (CH aliphatic), 1710, 1645 (4C=O); $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 2.88 (t, 2H, J = 7.5 Hz, CH$_2$), 3.00 (t, 3H, J = 7.1 Hz, CH$_2$CH$_3$), 3.01 (s, 3H, N-CH$_3$), 3.09 (s, 3H, N-CH$_3$), 3.26 (t, 2H, J = 7.5 Hz, CH$_2$), 3.71 (q, 2H, J = 7.1 Hz, CH$_2$CH$_3$), 7.01-7.56 (m, 5H, Ar-H); $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ (ppm): 18.6, 27.5, 30.4, 36.8, 39.7, 67.7, 114.6, 123.5, 124.6, 127.6, 128.7, 139.4, 143.2, 151.6, 155.5, 160.2, 161.3, 163.3, 172.6; MS (EI, 70 eV) m/z = 472 (M$^+$) Anal. Caled for C$_{21}$H$_{20}$N$_4$O$_5$S$_2$ (472.53): C, 53.38; H, 4.27; N, 11.86; S, 13.57. Found: C, 53.42; H, 4.33; N, 11.93; S, 13.62.

General procedure for synthesis compounds 16 and 17. A solution of compound 2 (2.83 g, 0.01 mol) in DMF (15 mL) and malononitrile (0.66 g, 0.01 mol) or 2-cyano-3-phenylacrylamide (1.72 g, 0.01 mol) in the presence of TEA (4 drops), was refluxed for 4 h. The reaction mixture was allowed. The obtained solid product was collected by filtration, dried and crystallized from EtOH/DMF to give compounds 16 and 17, respectively.

7-Amino-1,3-dimethyl-2,4,9-trioxo-1,2,3,4,6,9-hexahydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carbonitrile (16). Yellowish brown powder; yield (2.57 g, 85%); mp > 300 °C (DMF-EtOH (1:2)); IR (KBr): ν/cm$^{-1}$ = 3424-3317 (NH$_2$), 2209 (CN), 1705, 1666 (2C=O); $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 3.01 (s, 3H, N-CH$_3$), 3.09 (s, 3H, N-CH$_3$), 6.14 (s, 2H, NH$_2$, D$_2$O exchangeable), 10.83 (s, 1H, NH, D$_2$O exchangeable); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 28.6, 30.5, 64.8, 114.5, 117.3, 139.5, 144.6, 151.4, 155.8, 165.4, 168.5, 172.5; MS (EI, 70 eV) m/z = 303 (M$^+$) Anal. Caled for C$_{12}$H$_9$N$_5$O$_3$S (303.30): C, 47.52; H, 2.99; N, 23.09; S, 10.57. Found: C, 47.60; H, 3.04; N, 23.15; S, 10.61.

8-Cyano-1,3-dimethyl-2,4,9-trioxo-7-phenyl-1,2,3,4,8,9-hexahydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-8-carboxamide (17). Deep brown powder; yield (3.58 g, 88%); mp > 300 °C (DMF-EtOH (1:2)); IR (KBr): ν/cm$^{-1}$ = 3434-3380 (NH$_2$), 2210 (CN), 1705, 1666 (2C=O); $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 3.00 (s, 3H, N-CH$_3$), 3.09 (s, 3H, N-CH$_3$), 7.20 (s, 2H, CONH$_2$, D$_2$O exchangeable), 7.37-8.05 (m, 5H, Ar-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (ppm): 28.7, 30.1, 60.4, 114.5, 117.6, 127.4, 128.6, 131.2, 132.5, 133.8, 144.3, 151.3, 155.8, 163.4, 164.6, 172.4, 178.6; MS (EI, 70 eV) m/z = 407 (M$^+$) Anal. Caled for C$_{19}$H$_{13}$N$_5$O$_4$S (407.40): C, 56.02; H, 3.22; N, 17.19; S, 7.87. Found: C, 56.10; H, 3.25; N, 17.25; S, 7.92.
ACKNOWLEDGEMENTS

This study was supported by Chemistry Department, Faculty of Science, Mansoura University, Egypt.

REFERENCES