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SYNTHESIS OF SOME NOVEL THIENO[3,2-*d*]PYRIMIDINE DERIVATIVES OF PHARMACEUTICAL INTEREST

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Abstract – New starting material, ethyl 6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,2-*d*]pyrimidine-7-carboxylate (**2**) was prepared by Gewald reaction using *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-*d*:4,5-*d*']dipyrimidine derivative **6**. Moreover, treatment of **3** with α-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-*d*]pyrimidine derivatives **16** and **17**, respectively. All the newly synthesized compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra and elemental analyses.

INTRODUCTION

The derivatives of thieno[3,2-*d*]pyrimidine have attracted strong interest due to their broad bioactivities, including antitumor,[1-5] antimicrobial,[6,7] anti-inflammatory[8] 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.[11] These are known to exhibit pesticidal,[12] anticonvulsant,[13] nematocidal,[14] herbicidal,[15] antiviral,[16] fungicidal,[17] bactericidal,[18,19] antiprotozoal,[20] and hypoglycemic activity.[21] They are also act as chemotherapeutic agents.

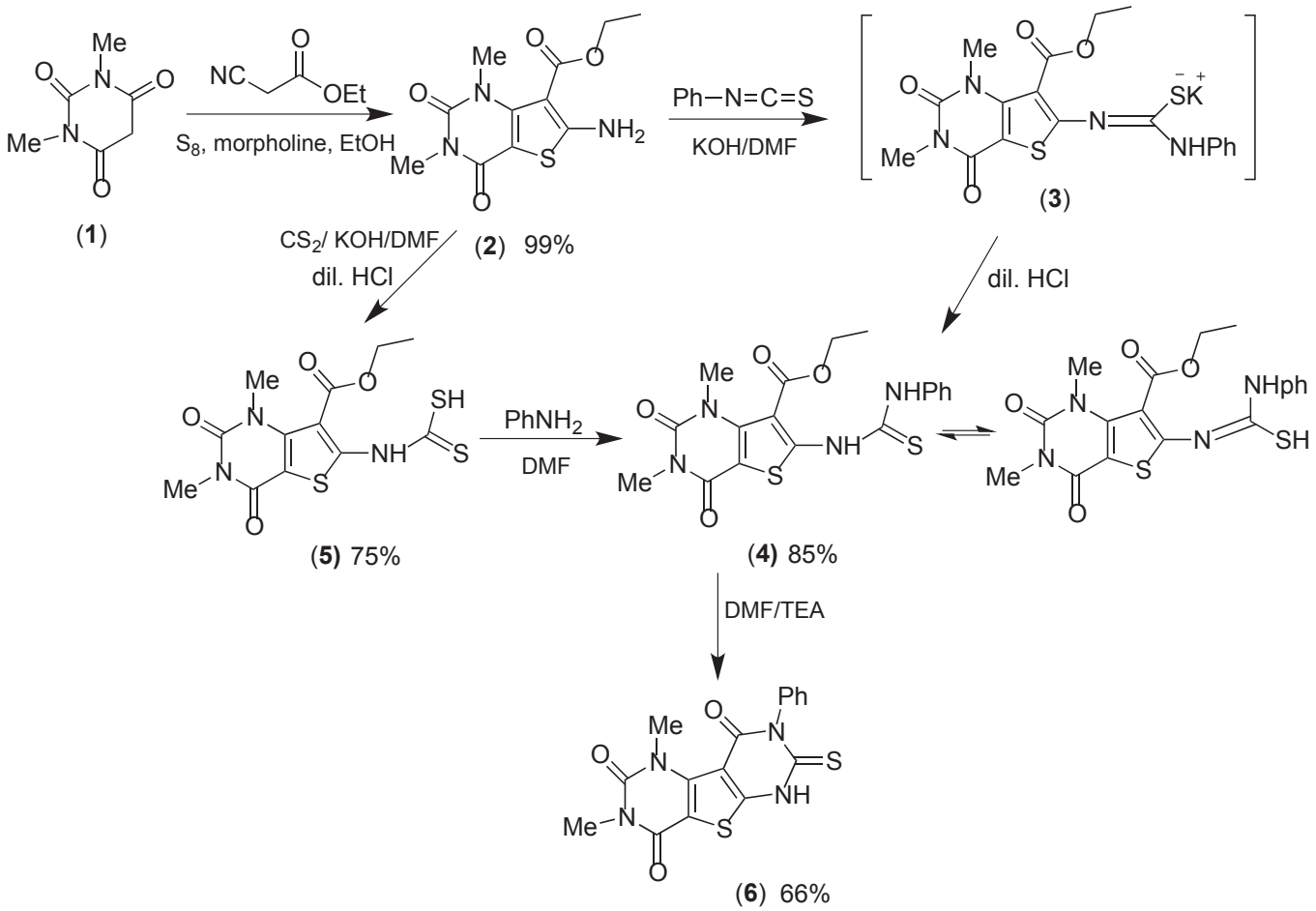
In view of the above biological importance and in continuation of our studies on the chemistry of thiocarbamoyl and active methylene compounds,[22-30] we aimed to the synthesis of novel heterocyclic compounds from readily obtainable thiocarbamoyl intermediates. We reported herein the synthesis of new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

RESULT AND DISSCUSION

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^{-1} due to NH_2 group and 1708, 1679 cm^{-1} corresponding to three carbonyl groups. Its ^{1}H-NMR spectrum revealed triplet signal at δ 3.00 ppm due to CH_3, quartet signal at 3.71 ppm due to CH_2 and two singlet signals at 3.01 and 3.09 ppm due to two *N*-CH_3 protons. In addition to, a singlet signal at 4.64 ppm due to NH_2 proton. The mass spectrum gave a molecular ion peak at *m/z* = 283 which matches with its molecular formula $C_{11}H_{13}N_3O_4S$.

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^{-1} corresponding to three carbonyl groups and 1265 cm^{-1} due to C=S group. Its ^{1}H-NMR spectrum revealed a singlet signals at 11.17 and 11.68 ppm due to two NH protons. The mass spectrum gave a molecular ion peak at *m/z* = 418 which matches with its molecular formula $C_{18}H_{18}N_4O_4S_2$.

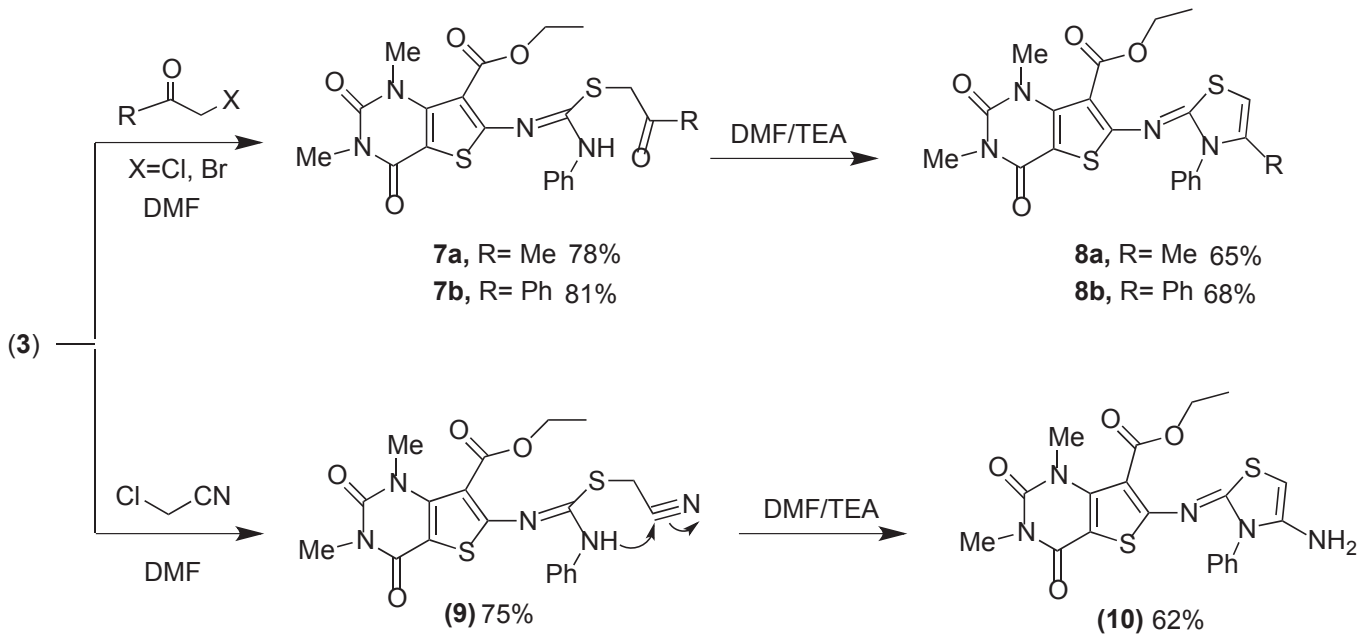
On the other hand, compound **2** reacted with carbon disulfide in DMF and potassium hydroxide, followed by addition dil HCl led to the corresponding carbamodithioic acid derivative **5**, which reacted with aniline gave the same product **4**. The structure of compound **5** was established by the spectral data. The IR spectrum of compound **5** showed the absorption bands at 3391 cm^{-1} due to NH group, 1708, 1690 cm^{-1} corresponding to three carbonyl groups and 1278 cm^{-1} due to C=S group . Its ^{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 *m/z* = 359 which matches with its molecular formula $C_{12}H_{13}N_3O_4S_3$.



Scheme 1

Refluxing 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(1*H*,3*H*,6*H*)-trione (**6**). The structure of 6 was characterized by the disappearance of ester group in its ^{1}H-NMR spectrum and revealed two singlet signals at 3.01 and 3.09 ppm due to two *N*-CH_3 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 $C_{16}H_{12}N_4O_3S_2$.

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 ^{1}H-NMR spectra revealed singlet signals at 4.13 and 10.65 ppm due to CH_2 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.



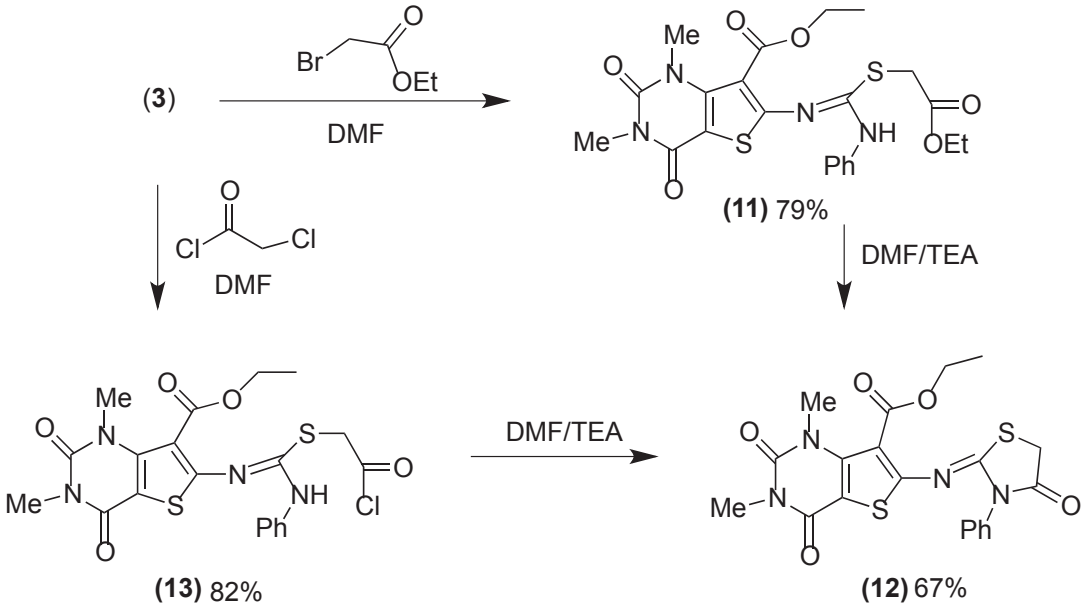
Scheme 2

Refluxing of compounds **7a** and **7b** in DMF and few drops of TEA led to the formation of thiazole-2-ylidene 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 $C_{20}H_{19}N_5O_4S_2$.

Refluxing of **9** in DMF and TEA yielded ethyl 6-((4-amino-3-phenylthiazol-2(3*H*)-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 $C_{20}H_{19}N_5O_4S_2$.

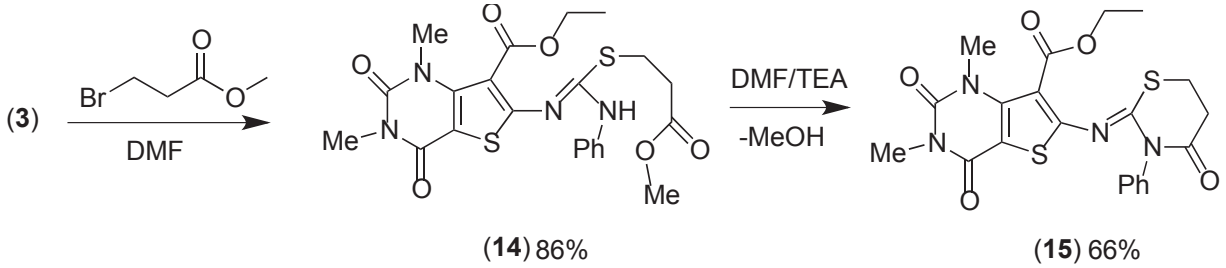
On the other hand, the intermediate **3** was treated with ethyl bromoacetate in a mixture of EtOH and DMF (2:1) at room temperature led to the formation of acyclic intermediate **11**, followed by refluxing in DMF and a catalytic amount of TEA afforded the corresponding thiazolidin-2-ylidene derivative **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 $C_{20}H_{18}N_4O_5S_2$.



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 $C_{20}H_{19}ClN_4O_5S_2$ 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 δ 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}

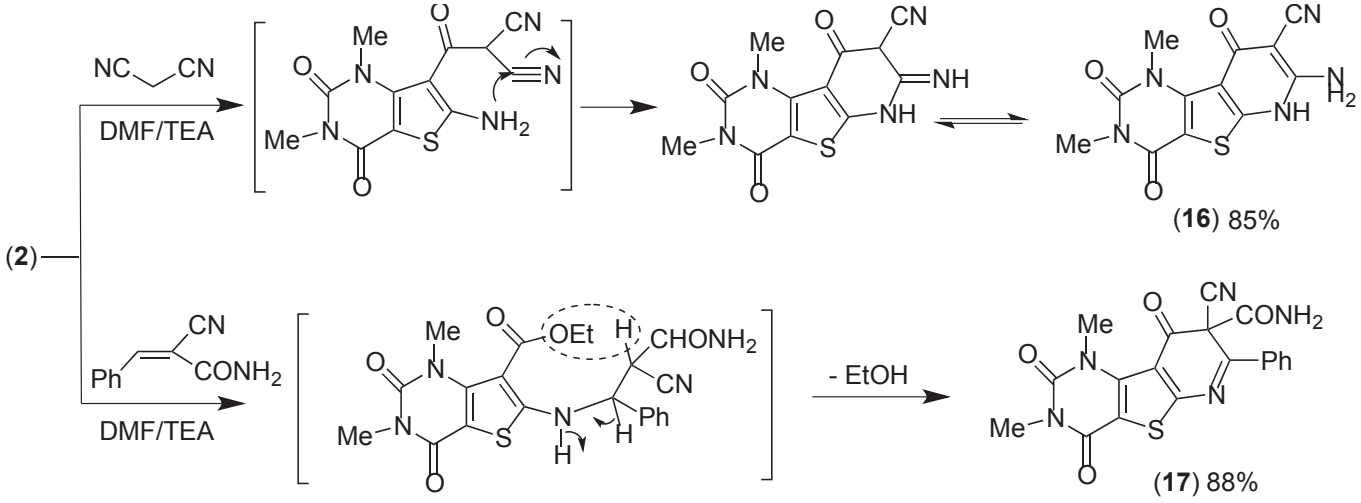
related to the NH and four C=O function groups, respectively. Its ^{1}H-NMR spectrum revealed two triplet signals at δ 2.67 and 3.22 corresponding to two CH_2 and a singlet signal at 10.36 ppm due to NH proton. The correct structure of compound **14** was also confirmed by its mass spectrum which showed 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 $C_{21}H_{20}N_4O_5S_2$ (**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 NH_2, CN and four C=O functions, respectively. Its ^{1}H-NMR spectrum revealed singlet signal at δ 7.20 ppm for $CONH_2$ 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 ^{1}H-NMR spectra were determined on Varian Gemini 400 MHz (Varian Co., Cairo university, Egypt), ^{13}C-NMR = 100 MHz. Deuterated DMSO-d_6 and $CDCl_3$ 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): *ν*/cm^{-1} = 3436-3350 (NH_2), 1708-1679 (3C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.00 (t, 3H, *J* = 7. 1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3), 3.71 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 4.64 (s, 2H, NH_2); ^{13}C-NMR (100 MHz , DMSO-d_6) 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. Calcd for* $C_{11}H_{13}N_3O_4S$ (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): ν/cm^{-1} = 3371, 3351 (2NH), 1709-1698 (3C=O), 1265 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.00 (t, 3H, J = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, N-CH_3), 3.09 (s, 3H, N-CH_3), 3.71 (q, 2H, J = 7.1 Hz, $\underline{CH_2}CH_3$), 7.18-7.58 (m, 5H, Ar-H), 11.17 (s, 1H, NH, D_2O exchangeable), 11.68 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6) 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* $C_{18}H_{18}N_4O_4S_2$ (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): ν/cm^{-1} = 3391 (NH), 1708-1690 (3C=O), 1278 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.70 (s, 1H, SH), 3.00 (t, 3H, J = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, N-CH_3), 3.09 (s, 3H, N-CH_3), 3.71 (q, 2H, J = 7.1 Hz, $\underline{CH_2}CH_3$), 12.95 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6) 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* $C_{12}H_{13}N_3O_4S_3$ (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(1*H*,3*H*,6*H*)-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): ν/cm^{-1} = 3390 (NH), 1690 (3C=O), 1279 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.01 (s, 3H, N-CH_3), 3.09 (s, 3H, N-CH_3), 7.15-7.76 (m, 5H, Ar-H), 11.98 (s, 1H,

NH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6) 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. Calcd for* $C_{16}H_{12}N_4O_3S_2$ (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); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.61 (s, 3H, CH_3), 3.00 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3), 3.71 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 4.13 (s, 2H, CH_2), 6.71-7.42 (m, 5H, Ar-H), 10.65 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6) 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* = 474 (M^+) *Anal. Calcd for* $C_{21}H_{22}N_4O_5S_2$ (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); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.00 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3), 3.71 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 4.63 (s, 2H, CH_2), 6.75-8.12 (m, 10H, Ar-H), 10.67 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (100 MHz , DMSO-d_6) 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. Calcd for* $C_{26}H_{24}N_4O_5S_2$ (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.

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); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.00 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3),

3.71 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 4.25 (s, 2H, CH_2), 6.74-7.31 (m, 5H, Ar-H), 10.65 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (100 MHz , DMSO-d_6) 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* $C_{20}H_{19}N_5O_4S_2$ (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); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm: 2.87 (t, 3H, *J* = 6.8 Hz, $CH_2\underline{CH_3}$), 3.00 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3), 3.71 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 3.85 (q, 2H, *J* = 6.8 Hz, $\underline{CH_2}CH_3$), 4.18 (s, 2H, CH_2), 6.74-7.67 (m, 5H, Ar-H), 10.65 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (100 MHz , DMSO-d_6) 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* $C_{22}H_{24}N_4O_6S_2$ (504.58): C, 52.37; H, 4.79; N, 11.10; S, 12.71. 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); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.00 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3), 3.71 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 4.65 (s, 2H, CH_2), 6.71-7.42 (m, 5H, Ar-H), 10.67 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (100 MHz , DMSO-d_6) δ (ppm): 18.4, 27.7, 30.5, 41.6, 67.8, 114.2, 121.2, 122.4, 123.5, 129.3, 140.1, 143.1, 151.8, 155.6, 160.3, 161.6, 163.6, 174.4; MS (EI, 70 eV) *m/z* = 494 (M^+) *Anal. Calcd for* $C_{20}H_{19}ClN_4O_5S_2$ (494.97): C, 48.53; H, 3.87; N, 11.32; S, 12.95. Found: C, 48.57; H, 3.90; N, 11.36, S, 13.00.

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); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.67 (t, 2H, *J* = 7.5 Hz, CH_2), 3.00 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3), 3.22 (t, 2H, *J* = 7.5 Hz, CH_2), 3.71 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 3.87 (s, 3H, CH_3), 7.01-7.56 (m, 5H, Ar-H), 10.36 (s, 1H, NH, D_2O exchangeable); ^{13}C-NMR (100 MHz, DMSO-d_6) 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* $C_{22}H_{24}N_4O_6S_2$ (504.58): C, 52.37; H, 4.79; N, 11.10; S, 12.71. 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,

0.01 mol) 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(3*H*)-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): *v*/cm^{-1} = 1700-1658 (3C=O), 1606 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 2.56 (s, 3H, CH_3), 3.00 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3), 3.71 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 5.81 (s, 1H, C_5 of thiazole ring), 6.95-7.64 (m, 5H, Ar-H); ^{13}C-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* $C_{21}H_{20}N_4O_4S_2$ (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(3*H*)-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): *v*/cm^{-1} = 1700-1654 (4C=O), 1635 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.00 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3), 3.71 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 6.43 (s, 1H, C_5 of thiazole ring), 7.35-7.87 (m, 10H, Ar-H); ^{13}C-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* $C_{26}H_{22}N_4O_4S_2$ (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(3*H*)-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): *v*/cm^{-1} = 3444-3360 (NH_2), 1700-1657 (3C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.00 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3), 3.71 (q, 2H, *J* = 7.1 Hz, $\underline{CH_2}CH_3$), 6.18 (s, 2H, NH_2, D_2O exchangeable), 6.45 (s, 1H, C_5 of thiazole ring), 7.02-7.48 (m, 5H, Ar-H); ^{13}C-NMR (100 MHz , DMSO-d_6) δ (ppm): 18.5, 27.4, 30.5, 67.8, 97.5, 114.5, 121.2, 122.8, 123.7, 128.5, 138.4, 143.8, 151.3, 155.9, 160.3, 161.4, 163.6; MS (EI, 70 eV) *m/z* = 457 (M^+) *Anal. Calcd for* $C_{20}H_{19}N_5O_4S_2$ (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): *v*/cm^{-1} =1727-1658 (4C=O), 1623 (C=N);); ^{1}H-NMR (400 MHz, DMSO-d_6) δ (ppm): 3.00 (t, 3H, *J* = 7.1 Hz, $CH_2\underline{CH_3}$), 3.01 (s, 3H, *N*-CH_3), 3.09 (s, 3H, *N*-CH_3), 3.71 (q, 2H, *J* = 7.1 Hz,

$\underline{CH_2}CH_3$), 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. Calcd for* $C_{20}H_{18}N_4O_5S_2$ (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-tetrahydro-thieno[3,2-*d*]pyrimidine-7-carboxylate (15). Brown powder; yield (3.11 g, 66%); mp 216-218 °C (DMF-EtOH (1:2)); IR (KBr): *v*/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, $CH_2\underline{CH_3}$), 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, $\underline{CH_2}CH_3$), 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. Calcd for* $C_{21}H_{20}N_4O_5S_2$ (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): *v*/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_2O exchangeable), 10.83 (s, 1H, NH, D_2O 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. Calcd for* $C_{12}H_9N_5O_3S$ (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): *v*/cm^{-1} = 3434-3380 (NH_2), 2210 (CN), 1705- 1678 (4C=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_2O 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. Calcd for* $C_{19}H_{13}N_5O_4S$ (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.

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