SYNTHESIS OF NEW MERCAPTOPYRIMIDINES AND THIENOPYRIMIDINES

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Keywords: benzaldehyde, thiourea, ethyl cyanoacetate, α-halo carbonyl compounds.

2-Alkylmercapto- 4-Chloro-6-phenyl-pyrimidine-5-carbonitrile (**4a-c**) were synthesized and converted into 2-alkylmercapto 4-mercapto-6-phenyl-pyrimidine-5-carbonitriles (**7a-c**). Compounds (**7a-b**) were alkylated with halogenated compounds to afford compounds (**8a-g**). Compounds (**8a-g**) underwent Thorpe-Ziegler Cyclization to give thienopyrimidines (**9a-g**). 5-Amino-2-alkylmercapto-4-phenyl-thieno-[2,3-*d*]pyrimidine-6-carboxamide derivatives (**9a-f**) underwent cyclization reaction using triethyl orthoformate to afford pyrimido-thienopyrimidines (**10a-e**).

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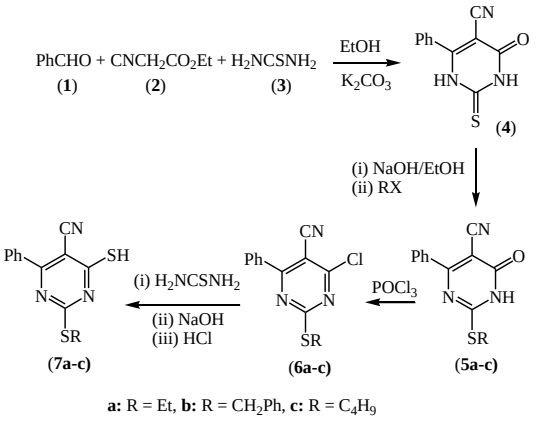
Introduction

The pyrimidine and thienopyrimidine derivatives have many biological activities, such as anticancer,[1] antiviral,[2] antitumor,[3] anti-inflammatory,[4] antimicrobial[5] and antimalarial.[6] Thieno[2,3-*d*]pyrimidine was first synthesized by Baker et al,[7] who reported that the action of methanolic ammonia on 2-formamido-3-carbomethoxythiophene gave a low yield (4%) of thieno[2,3-*d*]pyrimidin-4-one. Most of the methods for the preparation of this ring system have been achieved by ring closure of thiophene derivatives. In continuation of our program for the synthesis of heterocyclic compounds containing thienopyrimidine moiety,[8-17] in this paper we report the synthesis of new mercaptopyrimidine and thieno[2,3-*d*]pyrimidine derivatives from pyrimidine ring.

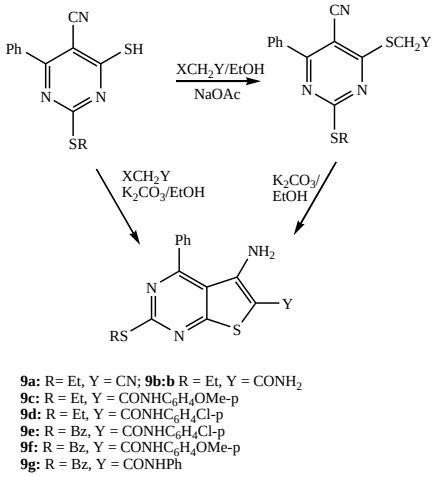
Result and Discussion

5-Cyano-4-oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine (**4**) was synthesized via multi components reaction (MCR) by one pot condensation reaction[18] of benzaldehyde (**1**), ethyl cyanoacetate (**2**) and thiourea (**3**) in refluxing ethanol in the presence of potassium carbonate. Refluxing (**4**) with sodium acetate in ethanol gave the sodium salt of (**4**) which reacts with alkyl halides to give 2-alkylmercapto-4-oxo-6-phenyl-pyrimidine-5-carbonitriles (**5a-c**). The carbonyl group in compound (**5a-c**) enolizes to hydroxyl group which it was displaced with a chlorine atom by reacting compound (**5**) with phosphorus oxychloride to give 2-alkylmercapto-4-chloro-6-phenyl-pyrimidine-5-carbonitriles (**6a-c**). Chlorine atom in compound (**6a-c**) is replaced by mercapto group on reacting it with thiourea in ethanol. Following it by treatment with sodium hydroxide solution and then acidification with dilute HCl gave 2-alkylmercapto-4-mercapto-6-phenyl-pyrimidine-5-carbonitriles (**7a-c**) (Scheme 1).



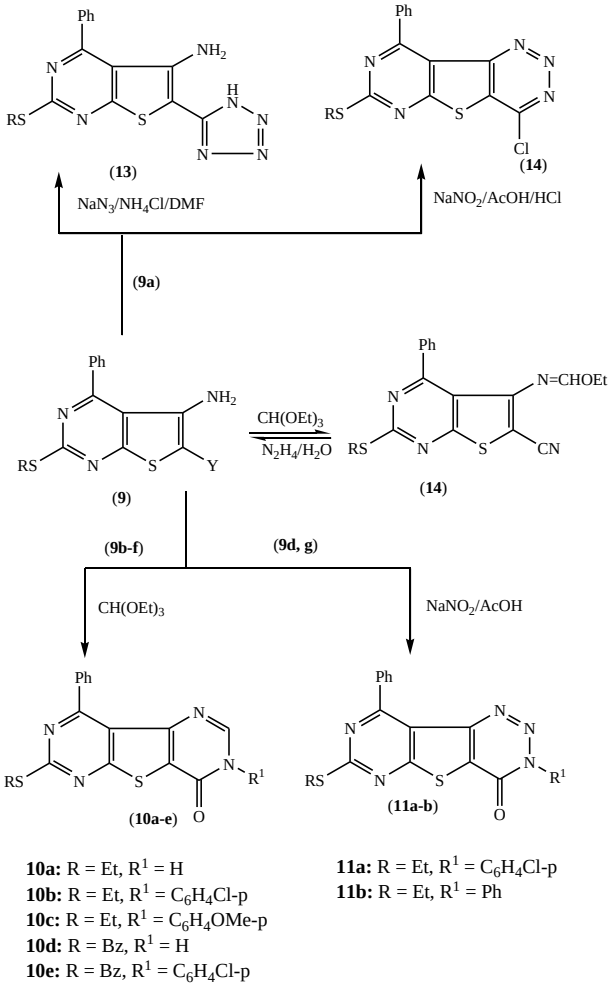
Scheme 1. Synthesis of 2-alkylmercapto-4-mercapto-6-phenyl-pyrimidine-5-carbonitriles.

Compound (**7a-b**) can be alkylated with α-halocarbonyl compounds in refluxed ethanol in the presence of sodium acetate to give alkylated mercaptopyrimidine derivatives (**8a-h**).



Scheme 2. Synthesis of thieno[2,3-*d*]pyrimidines.

Compounds (**8a-h**) upon refluxing with potassium carbonate in ethanol affording thieno[2,3-*d*]pyrimidine derivatives (**9a-h**). Compound (**9a-h**) can be prepared directly also from compound (**7a-b**) by refluxing it with α-halocarbonyl compounds in ethanol in the presence of potassium carbonate (Scheme 2).



Scheme 3. Synthesis of pyrimidothieno[2,3-*d*]pyrimidine derivatives.

Compounds (**9b-f**) were cyclized using triethyl orthoformate in the presence of catalytic amount of acetic acid affording pyrimidothieno[2,3-*d*]pyrimidine derivatives (**10a-e**). When compounds (**9d,g**) were treated with sodium nitrite in acetic acid, pyrimidothienotriazines (**11a,b**) were obtained. On the other hand, when compound (**9a**) was treated with sodium nitrite in acetic acid-HCl mixture, chloropyrimidothienotriazine (**12**) was obtained. Tetrazolyl thienopyrimidine (**13**) was obtained by treating compound (**9a**) with sodium azide in the presence of ammonium chloride in DMF. When compound (**9**) was refluxed with triethyl orthoformate in the presence of catalytic amount of acetic acid, 5-ethoxymethyleneamino-2-ethylmercapto-4-phenylthieno[2,3-*d*]pyrimidine-6-carbonitrile (**14**) was obtained which when treated with hydrazine hydrate in ethanol at refluxing temperature or even at room temperature, the C=N- underwent fission to afford compound (**9**) again (Scheme 3).

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr discs) with a Perkin-Elmer 1430 Spectrophotometer. ^{1}H NMR spectra were obtained on a BRUKER (400 MHz) spectrometer in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard, and chemical shifts are expressed as δ ppm. Mass spectra were obtained on a Jeol-JMS 600 spectrometer. Analytical data were obtained on Elementar Analyse system GmbH-VarioEL V.3 microanalyzer in the central lab of Assiut University. Compounds (**4,5a-c**) were prepared according to the literature procedure.[18,19]

2-(Alkylmercapto)-4-chloro-6-phenyl-5-pyrimidinecarbonitriles (6): General procedure

20 g of compound (**5b**) and 30 mL of $POCl_3$ was refluxed for 3 h. After cooling the solution was poured into a beaker containing 600 g of ice and was then neutralized using sodium carbonate. On stirring the solution for 30 min, a precipitate is formed. The crude precipitate was collected by filtration, washed several time with water, dried in air and recrystallized from ethanol.

2-(Ethylmercapto)-4-chloro-6-phenyl-5-pyrimidinecarbonitrile (6a)

This compound was obtained as white crystals (75 %). m.p. 64-66 °C. IR (KBr): 3047 (C-H aromatic), 2925 (C-H aliphatic), 2227 (C-N), 1640 (C=O), 694 (C–Cl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (t 3H, CH_3), 3.39 (q, 2H, CH_2), 7.45, 7.89 (2m, 5H, ArH). MS *m\z* 275.6. Anal. Calcd. for $C_{13}H_{10}ClN_3S$; C, 56.62; H, 3.66; Cl, 12.86; N, 15.24; S, 11.63 %; Found: C, 56.44; H, 3.44; Cl, 13.05; N, 15.06; S, 11.80 %.

2-(Benzylmercapto)-4-chloro-6-phenyl-5-pyrimidine-carbonitrile (6b)

This compound was obtained as white crystals (75 %). m.p. 78-80 °C. IR (KBr): 3047 (C-H aromatic), 2954 (C-H aliphatic), 2223 (C-N), 820 (C–Cl) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 4.48, (s, 2H, CH_2), 7.25-7.9 (m, 5H, Ar-H). Anal. Calcd. for $C_{18}H_{12}ClN_3S$: C, 64.00; H, 3.58; Cl, 10.49; N, 12.44; S 9.49 %; Found: C, 63.82; H, 3.70; Cl, 10.64; N, 12.28; S 9.29 %.

2-(Butylmercapto)-4-chloro-6-phenyl-5-pyrimidinecarbonitrile (6c)

This compound was obtained as white crystals (83 %). m.p. 58-60 °C. IR (KBr) 3069 (C-H aromatic), 2956 (C-H aliphatic), 2223 (C-N), 816 (C–Cl) cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.95 (t, 3H, CH_3), 1.45, 1.8 (2m, 4H, $2CH_2$), 3.5 (t, 2H, CH_2), 7.45, 7.9 (2m, 5H, Ar-H). Anal. Calcd. for: $C_{15}H_{14}ClN_3S$: C, 59.30; H, 4.64; Cl, 11.67; N, 13.83; S, 10.55 %; Found: C, 59.18; H, 4.50; Cl, 11.80; N, 14.03; S, 10.70 %.

2-(Alkylmercapto)-4-mercapto-6-phenyl-5-pyrimidinecarbonitriles (7): General procedure

0.01 Mole of compound (**6**) and 0.02 mole of thiourea was refluxed in 100 mL ethanol for 6 h. On cooling, a yellow precipitate is formed. It was filtered, washed with ethanol, dissolved in 10 % NaOH solution and reprecipitated with dilute HCl. The crude precipitate is collected by filtration, washed several time with water, dried in air and recrystalized from ethanol\dioxane mixture.

2-(Ethylmercapto)-4-mercapto-6-phenyl-5-pyrimidinecarbonitrile (7a)

This compound was obtained as yellow crystals (63 %). m.p. 178-180 °C. IR (KBr): 3047 (C-H aromatic), 2984 (C-H aliphatic), 2216 (C-N), 1255(C=S) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 1.3(t, 3H, CH_3), 3.1 (q, 2H, CH_2), 7.7 (s, 1H, NH), 8.3-7.9 (s, 5H, ArH). Anal. Calcd. for $C_{13}H_{11}N_3S_2$: C, 57.12; H, 4.06; N, 15.37; S 23.46 %; Found: C, 57.00; H, 3.98; N, 15.52; S 23.61 %.

2-(Benzylmercapto)-4-mercapto-6-phenyl-5-pyrimidinecarbonitrile (7b)

The crude product was recrystalized from ethanol as yellow crystals (65 %). m.p. 184-186 °C. IR (KBr): 3114 (C-H aromatic), 2969 (C-H aliphatic), 2223 (C-N) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 2.7 (s, 1H, SH), 4.0 (s, 2H, CH_2, 7, 25, 7.42, 7.7, 8.3 (4m, 10H, Ar-H). MS *m\z* 335.6. Anal. Calcd. for $C_{18}H_{13}N_3S_2$: C 64.45; H; 3.91; N, 12.53; S, 19.12 %; Found: C 64.45; H; 3.91; N, 12.53; S, 19.12 %.

2-(Butylmercapto)-4-mercapto-6-phenyl-5-pyrimidinecarbonitrile (7c)

The crude product recrystalized from ethanol as yellow crystals (66 %). m.p. 182-184 °C. IR (KBr): 3115 (C-H aromatic), 2953 (C-H aliphatic), 2220 (C-N), 1250 (C=S) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 0.93 (t, 3H, CH_3), 1.46-1.60 (m, 4H, $2CH_2$), 2.83-2.95 (m, 2H, CH_2), 2.75 (s, 1H, SH, 7, 25, 8.33 (2m, 5H, Ar-H). Anal. Calcd. for $C_{15}H_{15}N_3S_2$: C, 59.77; H, 5.02; N, 13.94; S, 21.27 %; Found: C, 59.92; H, 4.88; N, 14.10; S, 21.08 %.

2,4-Alkylmercapto-6-phenyl-pyrimidine-5-carbonitriles (8a-g): General procedure

Compound (**5**) (0.01 mole), sodium acetate (0.02 mole) and appropriate α-halogenated compound (0.01 mole) in 50 mL ethanol was refluxed for 1 h and allowed to cool. The solid product was filtered off, washed with water and ethanol, dried in air and recrystallized from ethanol.

4-(Cyanomethylthio)-2-(ethylthio)-6-phenylpyrimidine-5-carbonitrile (8a)

Yield 88.5 %. m.p. 136-138 °C. IR (KBr): 3037 (C-H aromatic), 2983 (C-H aliphatic), 2244 (C-N), 2215 (C-N) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.3 (q, 2H, CH_2), 4.3, (s, 2H, CH_2) and 7.5, 7.9 (2m, 5H, ArH). Anal. Calcd. for $C_{15}H_{12}N_4S_2$: C, 57.67; H, 3.87; N, 17.93; S, 20.53 %; Found: C, 57.83; H, 3.71; N, 17.73; S, 20.64 %.

2-(5-Cyano-2-(ethylthio)-6-phenylpyrimidin-4-ylthio)acetamide (8b)

Yield 66.5 %. m.p. 170-172 °C. IR (KBr): 3377, 3195 (NH_2), 3043 (C-H aromatic), 2967(C-H aliphatic), 2215 (C-N), 1645 (C=O) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.25 (q, 2H, CH_2), 4.1, (s, 2H, CH_2), 6.95 (s, 2H, NH_2) and 7.5, 7.9 (2m, 5H, ArH). Anal. Calcd. for $C_{15}H_{14}N_4OS_2$: C, 54.52; H, 4.27; N, 16.96; S, 19.41 %; Found: C, 54.37; H, 4.09; N, 16.74; S, 19.29 %.

2-(5-Cyano-2-(ethylmercapto)-6-phenylpyrimidin-4-ylthio)-N-(4-methoxy phenyl)acetamide (8c)

Yield 62 %. m.p. 148-150 °C. IR (KBr): 3279(N-H), 3047 (C-H aromatic), 2957 (C-H aliphatic), 2215 (C-N), 1659 (C=O) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.28 (q, 2H, CH_2), 3.72 (s, 3H, CH_3), 4.2(s, 2H, CH_2), 6.9-7.9 (m, 9H, Ar-H) and 9.1 (s, 1H, NH). MS *m\z* 436.22. Anal. Calcd. for $C_{22}H_{20}N_4O_2S_2$: C, 60.53; H, 4.62; N, 12.83; S, 14.69 %; Found: C, 60.68; H, 4.82; N, 13.00; S, 14.54 %.

N-(4-chlorophenyl)-2-(5-cyano-2-(ethylmercapto)-6-phenylpyrimidin-4-ylthio)acetamide (8d)

Yield 47 %. m.p. 158-160 °C. IR (KBr): 3297(N-H), 3058 (C-H aromatic), 2985 (C-H aliphatic), 2214 (C-N), 1662 (C=O) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ= 1.38 (t, 3H, CH_3), 3.05(q, 2H, CH_2), 4.23(s, 2H, CH_2), 7.23-8.34 (m, 9H, Ar-H) and 9.50 (s, 1H, NH). MS *m\z* 440.26. Anal. Calcd. for $C_{21}H_{17}ClN_4OS_2$: C 57.20; H, 3.89; Cl, 8.04; N, 12.71; S, 14.54 %; Found: C, 57.02; H, 4.02; Cl, 7.86; N, 12.91; S, 14.44 %.

2-(2-(Benzylmercapto)-5-cyano-6-phenylpyrimidin-4-ylthio)-N-(4-chloro phenyl)acetamide (8e)

Yield 63 %. m.p. 182-184 °C. IR (KBr): 3296(N-H), 3061 (C-H aromatic), 2924 (C-H aliphatic), 2215 (C-N), 1661 (C=O) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 4.00 (s, 2H, CH_2), 4.23 (s, 2H, CH_2), 7.25-8.36 (m, 14H, Ar-H) and 9.50 (s, 1H, NH); MS *m\z* 502. Anal. Calcd. for $C_{26}H_{19}ClN_4OS_2$: C, 62.08; H, 3.81; Cl, 7.05; N, 11.14; S, 12.75 %; Found: C, 61.92; H, 4.00; Cl, 6.90; N, 10.98; S, 12.92 %.

2-(2-(Benzylmercapto)-5-cyano-6-phenylpyrimidin-4-ylthio)-N-(4-methoxy phenyl)acetamide (8f)

Yield 67 %. m.p. 172-174 °C. IR (KBr): 3288 (N-H), 3061 (C-H aromatic), 2924 (C-H aliphatic), 2212 (C-N), 1662 (C=O) cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ = 3.6 (s, 3H, CH_3) 4.00 (s, 2H, CH_2), 4.23 (s, 2H, CH_2), 6.9-8.36 (m, 14H, Ar-H) and 9.50 (s, 1H, NH). MS *m\z* 498.29. Anal. Calcd. for $C_{27}H_{22}N_4O_2S_2$: C, 65.04; H, 4.45; N, 11.24; S, 12.86 %; Found: C, 64.88; H, 4.60; N, 11.02; S, 13.02 %.

2-(5-Cyano-2-(ethylmercapto)-6-phenylpyrimidin-4-ylthio)-N-phenylacetamide (8g)

Yield 62 %. m.p. 160-162 ºC. IR(KBr): 3276 (N-H), 3037 (C-H aromatic), 2943 (C-H aliphatic), 2214 (C-N), 1664 (C=O). Anal. Calcd. for $C_{21}H_{18}N_4OS_2$: C, 62.05; H, 4.46; N, 13.78; S, 15.77 %; Found: C, 62.18; H, 4.27; N, 13.57; S, 15.51 %.

5-Amino-2-ethylmercapto-4-phenyl-6-subistituted thieno[2,3-d]pyrimidines (9a-g): General procedure

Compound (**7**) (0.01 mole), potassium carbonate (0.02 mole) and α-halocarbonyl compounds like chloroacetamide, chloloacetonitrile, ethyl chloroacetate, and p-chloro chloroacetanilide (0.011 mole) in 50 mL ethanol was refluxed for 3 h. The solid product was filtered off, washed with water and ethanol and dried in air.

5-Amino-2-ethylmercapto-4-phenyl-thieno[2,3-*d*]pyrimidine-6-carbonitrile (9a)

The compound was obtained as pale yellow crystals (65 %). m.p. 198-200 ºC. IR (KBr): 3464, 3331 (NH_2), 3227 (N-H tautomer), 3047 (C-H aromatic), 2978 (C-H aliphatic), 2202 (C-N). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.4 (t, 3H, CH_3), 3.2 (q, 2H, CH_2), 4.58 (s, 2H, NH_2), 7.52 (s, 5H, Ar-H). ^{13}C NMR ($CDCl_3$) δ = 171.16, 169.82, 162.75, 148.5, 136, 130.9, 129.17, 128.72, 114.93, 114.74, 25.7, 14.36. MS *m\z* 312. Anal. Alcd. for $C_{15}H_{12}N_4S_2$: C, 57.67; H, 3.87; N, 17.93; S, 20.52 %; Found: C, 57.82; H, 4.06; N, 18.08; S, 19.32 %.

5-Amino-2-ethylmercapto-4-phenyl-thieno[2,3-*d*]pyrimidine-6-carbamide (9b)

The compound was obtained as pale yellow crystals (62 %). m.p. 174-176 ºC. IR (KBr): 3475, 3429 (NH_2), 3327, 3208 (NH_2), 3047 (C-H aromatic), 2965 (C-H aliphatic), 1667 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.4 (t, 3H, CH_3), 3.2(q, 2H, CH_2), 5.35 (s, 2H, NH_2), 6 (s, 2H, NH_2), 7.4-7.6 (m, 5H aromatic). ^{13}C NMR ($CDCl_3$) δ = 170.19, 168, 167.13, 163.07, 146.46, 136.36, 130.58, 128.98, 128.76, 117.31, 94.32, 25.66, 14.44; MS *m\z* 329.8. Anal. Calcd. for $C_{15}H_{14}N_4OS_2$: C, 54.53; H, 4.27; N, 16.96; S 19.41 %; Found: C, 54.70; H, 4.19; N, 17.14; S 19.50 %.

5-Amino-2-ethylmercapto-4-phenyl-N-(p-methoxy-phenyl)-thieno[2,3-*d*]pyrimidine-6-carbamide (9c)

The compound is obtained as yellow crystals (40 %). m.p. 158-160 ºC. IR (KBr): 3472, 3409 (NH_2), 3303 (N-H), 3046 (C-H aromatic), 2969 (C-H aliphatic), 1635 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.4 (t, 3H, CH_3), 3.25 (q, 2H, CH_2), 3.7 (s, 3H, CH_3), 6.3 (s, 2H, NH_2), 6.9, 7.6 (2d, 4H, Ar-H), 7.5, 8.2 (2m, 5H, ArH) 8.9 (s, 1H, NH); MS *m\z* 436.18. Anal. Calcd. for $C_{22}H_{20}N_4O_2S_2$: C, 60.53; H, 4.62; N, 12.83; S, 14.69 %; Found: C, 60.19; H, 4.21; N, 12.65; S, 14.52 %.

5-Amino-N-(4-chlorophenyl)-2-(ethylmercapto)-4-phenyl-thieno[2,3-*d*]pyrimidine-6-carboxamide (9d)

The compound is obtained as orange crystals (50 %). m.p. 188-190 ºC. IR (KBr): 3485,3460 (NH_2), 3292 (N-H), 3046 (C-H aromatic), 2924 (C-H aliphatic), 1636 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, 3H, CH_3), 1.5 (s, 1H, NH), 3.2 (q, 2H, CH_2), 6 (s, 2H, NH_2), 7.2-7.5 (m, 9H, ArH). ^{13}C NMR ($CDCl_3$) δ = 170.46, 163.52, 163.09, 146.8, 136.2, 130.69, 129.54, 129.07, 128.76, 121.86, 117.4, 94.76, 25.71, 14.43. MS *m\z* 440. Anal. Calcd. for $C_{21}H_{17}ClN_4OS_2$: C, 57.20; H, 3.89; Cl, 8.04; N 12.71; S, 14.54 %; Foubd: C, 56.98; H, 4.10; Cl, 7.90; N 12.58; S, 14.70 %.

5-Amino-2-benzylmercapto–4-phenyl-N-(p-chlorophenyl)-thieno[2,3-*d*]pyrimidine-6-carbamide (9e)

The compound is obtained as orange crystals (53 %). m.p. 176-178 ºC. IR (KBr): 3475, 3406 (NH_2), 3313 (N-H), 3046 (C-H aromatic), 2994 (C-H aliphatic), 1643 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.2 (s, 2H, CH_2), 6.5 (s, 2H, NH_2), 7.2-7.7 (m, 14H, ArH), 10.9 (s, 1H, NH). MS *m\z* 502. Anal. Calcd. for $C_{26}H_{19}ClN_4OS_2$: C, 62.08; H, 3.81; Cl, 7.05; N, 11.14; S, 12.75 %; Found: C, 61.90; H, 4.02; Cl, 6.88; N, 10.96; S, 12.92 %.

5-Amino-2-benzylmercapto–4-phenyl-N-(p-methoxyphenyl)-thieno-[2,3-*d*]pyrimidine-6-carbamide (9f)

The compound is obtained as orange crystals (53 %). m.p. 164-166 ºC; IR (KBr): 3466, 3410 (NH_2), 3309 (N-H), 3030 (C-H aromatic), 2945 (C-H aliphatic), 1638 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.6 (s, 3H, CH_3), 4.1 (s, 2H, CH_2), 6.45 (s, 2H, NH_2), 6.8-7.7 (m, 14H, ArH), 11.0 (s, 1H, NH). MS *m\z* 436.18. Anal. Calcd. for $C_{27}H_{22}N_4O_2S_2$: C, 65.04; H, 4.45; N, 11.24; S, 12.86 %; Found: C, 64.88; H, 4.65; N, 11.04; S, 13.02 %.

5-Amino-2-(ethylmercapto)-N,4-diphenylthieno[2,3-*d*]pyrimidine-6-carboxamide (9g)

The crude product was recrystalized from acetic acid to yield yellow crystals (53 %). m.p. 88-90 ºC. IR (KBr): 3603, 3479 (NH_2), 3321 (N-H), 3035 (C-H aromatic), 2955 (C-H aliphatic), 1636 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.45 (t, 3H, CH_3), 3.3 (q, 2H, CH_2), 7.15 (d, 2H, NH_2), 7.35 (m, 10H, 2ArH) and 7.55 (d, 1H, NH). MS *m\z* 405.75. Anal. Calcd. for $C_{21}H_{18}N_4OS_2$: C, 62.05; H, 4.46; N, 13.78; S, 15.77 %; Found: C, 61.83; H, 4.13; N, 13.53; S, 15.58 %.

2-Alkylmercapto-8-oxo-4-phenyl-7-subistitutedpyrimido [4',5':4,5]- thieno[2,3-*d*]pyrimidines (10a-d): General procedure:

Compound (**9**) (0.01 mole), 20 mL of triethyl orthoformate and few drops of glacial acetic acid was refluxed for 2 h. White crystals were formed during the reflux. After cooling the crystals were filtered, washed with ethanol and then dried in air.

2-Ethylmercapto-8-oxo-4-phenyl-(7H)-pyrimido[4',5':4,5]thieno[2,3-*d*]pyrimidine (10a)

The compound was obtained as white crystals (77 %). m.p. 278-280 °C. IR (KBr): 3431(N-H), 3030 (C-H aromatic), 2967 (C-H aliphatic), 1679 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.0 (q, 2H, CH_2), 7.3, 7.5 (2m, 5H, Ar-H), , 7.65 (s, 1H, CH pyrimidine), 9.5 (s, 1H, NH). MS *m\z* 339.5. Anal. Calcd. for $C_{16}H_{12}N_4OS_2$: C, 56.45; H, 3.55; N, 16.46; S, 18.84 %; Found: C, 56.60; H, 3.74; N, 16.62; S, 19.04 %.

2-Ethylmercapto-8-oxo-4-phenyl-7(p-chlorophenyl)pyrimido[4',5':4,5]thieno[2,3-*d*]pyrimidine (10b)

The compound was obtained as white crystals (68 %). m.p. 220-222 °C. IR (KBr): 3075 (C-H aromatic), 2929 (C-H aliphatic), 1689 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.0 (q, 2H, CH_2), 7.3, 7.5, 7.65 (3m, 9H, Ar-H), 8.9 (s, 1H, CH pyrimidine). MS *m\z* 450. Anal. Calcd. for $C_{22}H_{15}ClN_4OS_2$: C, 58.60; H, 3.35; Cl, 7.86; N, 12.42; S, 14.22 %; Found: C, 58.38; H, 3. 05; Cl, 8.04; N, 12.60; S, 14.00 %.

2-Ethylmercapto-8-oxo-4-phenyl-7(methoxyphenyl)pyrimido[4',5':4,5]-thieno[2,3-*d*]pyrimidine (10c)

The compound was obtained as white crystals (68 %). m.p. 164-166 °C; IR (KBr): 3035 (C-H aromatic), 2976 (C-H aliphatic), 1682 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.0 (q, 2H, CH_2), 3.7 (s, 3H, O-CH_3), 6.8, 7.2, 7.5, 7.65 (3m, 9H, Ar-H), 8.8 (s, 1H, CH pyrimidine). MS *m\z* 446. Anal. Calcd. for $C_{23}H_{18}N_4O_2S_2$: C 61.87, H; 4.06; N, 12.55; S, 14.36 %; Found: C 62.04, H; 3.90; N, 12.70; S, 14.50 %.

2-Benzylmercapto-8-oxo-4-phenyl-(7H)-pyrimido[4',5':4,5]-thieno[2,3-*d*]pyrimidine (10d)

The compound was obtained as white crystals (77 %). m.p. 244-246 °C. IR: 3136 (N-H), 3024 (C-H aromatic), 2953 (C-H aliphatic) and 1671 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.6 (s, 2H, CH_2), 7.3-7.95 (m, 10H, 2ArH), 7.9 (d, 1H, CH pyrimidine) and 8.1 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{14}N_4OS_2$ (402.50): C, 62.67; H, 3.51; N, 13.92; S, 15.93 %; Found: C, 62.48; H, 3.19; N, 13.67; S, 15.67 %.

2-Benzylmercapto-8-oxo-4-phenyl-7(p-chlorophenyl)pyrimido[4',5':-4,5]thieno[2,3-*d*]pyrimidine (10e)

The compound was obtained as white crystals (95 %). m.p. 168-170 °C; IR (KBr): 3075 (C-H aromatic), 2929 (C-H aliphatic) and 1689 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.05 (s, 2H, CH_2), 7.3-7.7 (m, 14H, Ar-H), 9.2 (s, 1H, CH pyrimidine); MS *m\z* 511.9. Anal. Calcd. for $C_{27}H_{17}ClN_4OS_2$: C, 63.21; H, 3.34; Cl, 6.91; N, 10.92; S, 12.50 %; Found: C, 63.08; H, 3.02; Cl, 6.75; N, 10.74; S, 12.32%.

7-Ethylmercapto-9-phenyl-4-oxo-3-substituted pyrimido[5',4':4,5]thieno[3,2-d]triazines (11a,b): General procedure

Sodium nitrite solution (7 g, 0.1 mol) in water (10 mL) was added drop wise to a solution of (**9d,g**) (0.01 mol) in ice cooled acetic acid with stirring in five min. Then the solution was allowed to stand for 10 h. The solid product was filtered off, dried and recrystalized from ethanol.

7-Ethylmercapto-3,9-diphenyl-4-oxopyrimido[5',4':4,5]thieno[3,2-*d*]triazine (11a)

The compound was obtained as white crystals (95 %). m.p. 190-192 °C. IR (KBr): 3053 (C-H aromatic), 2968 (C-H aliphatic) and 1693 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.55 (t, 3H, CH_3), 3.4 (q, 2H, CH_2) and 7.55-7.7 (m, 10H, 2ArH). Anal. Calcd. for $C_{21}H_{15}N_5OS_2$: C, 60.41; H, 3.62; N, 16.77; S, 15.36 %; Found: C, 60.17; H, 3.34; N, 16.53; S, 15.18 %.

7-Ethylmercapto-9-phenyl-3(4-chlorophenyl)-4-oxopyrimido-[5',4':4,5]thieno[3,2-*d*]triazine (11b)

The compound was obtained as white crystals (77 %). m.p. 218-220 °C. IR (KBr): 3092 (C-H aromatic), 2952 (C-H aliphatic) and 1691 (C=O) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, 3H, CH_3), 3.3 (q, 2H, CH_2) and 7.35-8.05 (m, 9H, ArH). Anal. Calcd. for $C_{21}H_{14}ClN_5OS_2$: C, 55.81; H, 3.12; Cl, 7.84; N, 15.50; S, 14.19 %, Found: C, 55.68; H, 2.98; Cl, 7.53; N, 15.23; S, 14.07 %.

4-Chloro-7-ethylmercapto-9-phenylpyrimido [5',4':4,5]thieno[3,2-*d*]triazine (12)

To compound (**9a**) (1.3 g, 0.005 mol), dissolved in a mixture of acetic acid (10 mL) and concentrated HCl (7 mL), a 10 % sodium nitrite solution (4 mL, 0.006 mol) was added with stirring during 5 min. The stirring was continued at 5 °C for 3 h. The precipitate was collected and crystallized from ethanol to yield white plates of (**12**) (62.5 %). m.p. 180–181°C. IR (KBr): 3093 (C-H aromatic), 2950 (C-H aliphatic) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 1.45(t, 3H ,CH_3), 3.3(q,2H,CH_2), 7.5-8(m, 5H-ArH). ^{13}C NMR ($CDCl_3$) δ = 175.26, 172, 165.87, 153.05, 151.48, 135.27, 132, 130.51, 128.78, 128.31, 115.56, 26.12, 14.27. MS *m/z* 359.5. Anal. Calcd. for $C_{15}H_{10}ClN_5S_2$: C, 50.07; H, 2.80; Cl, 9.85; N 19.46; S, 17.82 %; Found: C, 49.90; H, 3.00; Cl, 10.04; N 19.62; S, 19.02%.

5-Amino-2-ethylmercapto-4-phenyl-6-(1H-tetrazol-5-yl)thieno-[2,3-*d*]pyrimidine (13)

A mixture of compound (**9a**) (1.25 g, 0.004 mol), sodium azide (0.4 g, 0.006 mol), and ammonium chloride (0.32 g, 0.006 mol) in DMF (15 mL) was heated on a water bath for 5 h. The reaction was allowed to cool, diluted with water, and acidified with dilute acetic acid. The solid product was collected and crystallized from ethanol to yield yellow crystals (65 %). m.p. 236–240 °C. IR (KBr): 3469, 3352 (NH_2), 3142 (N-H), 3063 (C-H aromatic) and 2984 (C-H aliphatic) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.4 (t, 3H, CH_3), 3.2 (q, 2H, CH_2), 6.0 (s, 3H, NH, NH_2) and 7.6-7.7 (m, 5H, ArH). MS *m/z* 353.5. Anal. Calcd. for $C_{15}H_{13}N_7S_2$: C, 50.69; H, 3.69; N, 27.58; S, 18.04 %; Found: C, 50.49; H, 3.52; N, 27.57; S, 17.94 %.

5-Ethoxymethyleneamino-2-ethylmercapto-4-phenylthieno[2,3-*d*]pyrimidine-6-carbonitrile (14)

Compound (**9a**) (1 g, 0.004 mol) in triethyl orthoformate (10 mL) was heated under reflux for 3 h in the presence of acetic acid and then left to cool. The solid product was collected and crystallized from ethanol to yield yellow crystals (67 %). m.p. 112 – 114 ºC. IR (KBr): 3073 (C-H aromatic), 2978 (C-H aliphatic) and 2207 (C-N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.25, 1.45 (2t, 6H, $2CH_3$), 3.3, 4.25 (2q, 4H, $2CH_2$), 7.5-7.6 (m, 5H, ArH) and 8.1 (s, 1H, CH); MS *m/z* 368. Anal. Calcd. for $C_{18}H_{16}N_4OS_2$: C, 58.67; H, 4.38; N, 15.20; S, 17.40 %; Found: C, 58.54; H, 4.19; N, 14.96; S, 17.27 %.

Acknowledgements

We thank Prof. Dr. Ahmed Abdo Geies Vice-President and Professor of Organic Chemistry Assiut University.

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Received: 01.09.2015
Accepted: 18.10.2015.