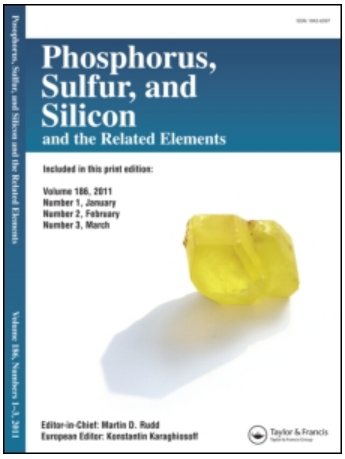

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Synthesis of Some Pyridothienopyrazolopyrimidopyrimidine and Mercaptomethylpyrazolopyrimidine Derivatives

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Synthesis of Some Pyridothienopyrazolopyrimidopyrimidine and Mercaptomethylpyrazolopyrimidine Derivatives

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Mercaptomethylpyrazolopyrimidine ***(2)*** *was synthesized and reacted with ethyl chloroacetate to afford ethyl pyrazolpyrimidinylmethylmercapto acetate* ***(3)****, which in turn was converted into the corresponding carbohydrazide* ***4****. Carbohydrazide* ***4*** *reacts with a variety of reagents to give different pyrazolopyrimidines* ***(5–12)****. Chloromethyl-pyrazolopyrimidine* ***(1)*** *reacts with chloropyridine to give compound* ***13****, which was subjected in a series of reactions to give new compounds* ***14–20****.*

Keywords Mercaptomethylpyrazolo-pyrimidine; pyrazolopyrimidine; reactions; synthesis; thienopyrazolopyrimidopyrimidin

INTRODUCTION

Pyrazole derivatives are an important class of compounds that possess biological and pharmacological activities.[1–8] They are used not only as potential inhibitors of HIV,[9] herbicides,[10] bactericides,[11] and analgesic drugs,[12] but they are also important and useful as starting materials for the synthesis of other fused heterocyclic pyrazolo[3,4-d]pyrimidine derivatives of considerable chemical and pharmacological importance such as purine analogs.[13,14] Several substituted pyrazolo[3,4-d]pyrimidine derivatives have xanthine oxidase inhibitor activity.[14,15]

We have previously reported that the synthesis of novel heterocyclic systems such as 3-(aryl or heteroaryl)azothieno[2,3-b]pyridines from 4,6-dimethylpyrazolo[2,3-b]pyridine-3-sulfonamide,[16] pyridopyrazolopyrimidine,[17] and pyrazolopyrimidines.[18,19] In continuation of our studies, we report here the synthesis of some new

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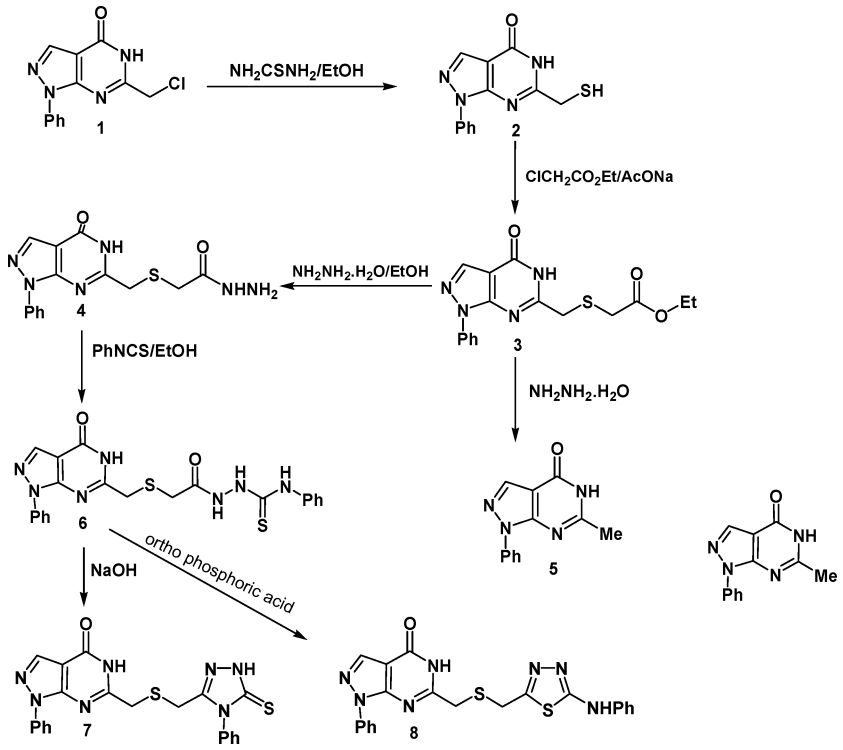
polynuclear heterocyclic compounds containing pyrazolopyrimidines fused with thienopyridine.

RESULTS AND DISCUSSION

6-Chloromethyl-1-phenylpyrazolo[3,4-d]pyrimidin-4(5H)-one (**1**) was synthesized and used for the synthesis of 6-mercaptomethyl-1-phenylpyrazolo[3,4-d]pyrimidin-4(5H)-one (**2**). When mercaptomethylpyrazolopyrimidine compound **2** was allowed to react with ethyl chloroacetate, ethyl (1-phenyl-4-oxopyrazolo[3,4-d]-pyrimidin-6-yl)-mercaptoacetate was formed (**3**). Hydrazinolysis of **3** using hydrazine hydrate in ethanol afforded the corresponding mercapto-(1-phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-yl)acetic hydrazide (**4**), which upon reaction with a variety of reagents gave a series of products discussed here (**5–12**), based on the conditions and reagent used. When the hydrazoninolysis was carried out under neat conditions, the ethyl mercaptoacetate group was eliminated to form 6-methyl-1-phenylpyrazolo[3,4-d]pyrimidin-4[5H]-one (**5**).[20] The structure of the resulting compound **5** was confirmed using spectral analyses, where its mass spectrum showed a peak at m/z = 226 as a molecular ion peak and as a base peak. Its ^{13}C NMR spectra showed signals at 20 for Me group, at 158 for C2 of pyrimidine, and at 160 for the CO group.

When, carbohydrazide derivative **4** was reacted with phenyl isothiocyanate in refluxing ethanol, N-(mercapto-(1-phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-yl)-acetyl-N′-phenyl thiosemicarbazide (**6**) was produced. When thiosemicarbazide derivative **6** was heated in sodium hydroxide solution,[21] it underwent a ring closure accompanied by the elimination of water to afford (4-oxo-1-phenylpyrazolo-[3,4-d]pyrimidin-6-yl)-2,3-dihydro3-thioxo-4-phenyl-[1,2,4]triazol-5-yl)-dimethylthioether **7**. When the same above reaction was applied on the thiosemicarbazide derivative **6** using ortho phosphoric acid[22] instead of sodium hydroxide at 70–80°C on a steam bath, ring closure occurred accompanied by the elimination of water to give (4-oxo-1-phenylpyrazolo[3,4-d]pyrimidin-6-yl)-2–4-phenylamino[1,3,4]-thiadiazol-5-yl)-dimethylthioether (**8**) (Scheme 1).

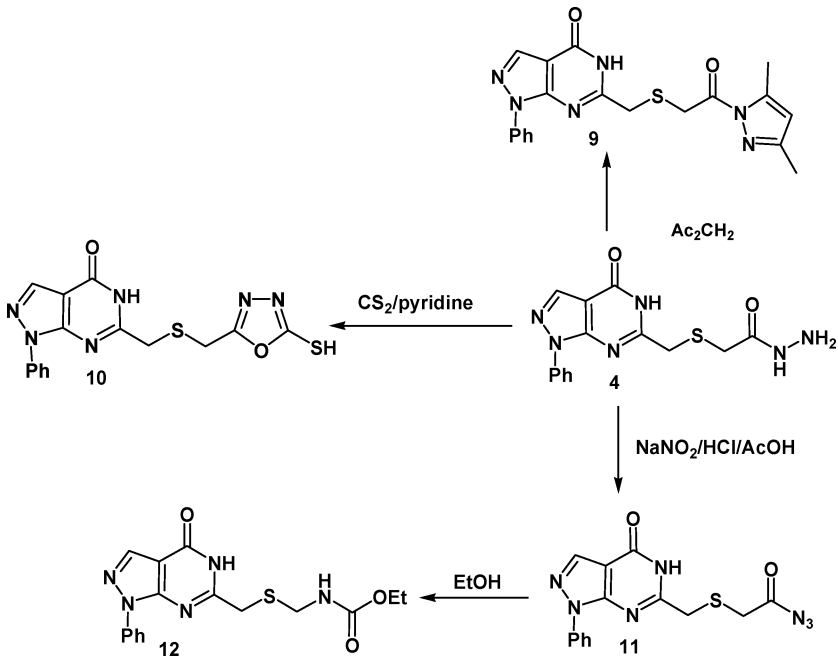
Alternatively, when compound **4** was allowed to react with acetyl acetone in refluxing ethanol, 1-(1-phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-yl)-mercaptoacetyl)-3,5-dimethyl-pyrazole (**9**) was synthesized. When carbohydrazide **4** was heated under reflux on a steam bath with carbon disulfide in pyridine, (4-oxo-1-phenylpyrazolo[3,4-d]pyrimidin-6-yl)-2-mercapto[1,3,4]-oxadiazol-5-yl)-dimethylthioether (**10**) was obtained. Upon treatment of carbohydrazide **4** with sodium nitrite at a low



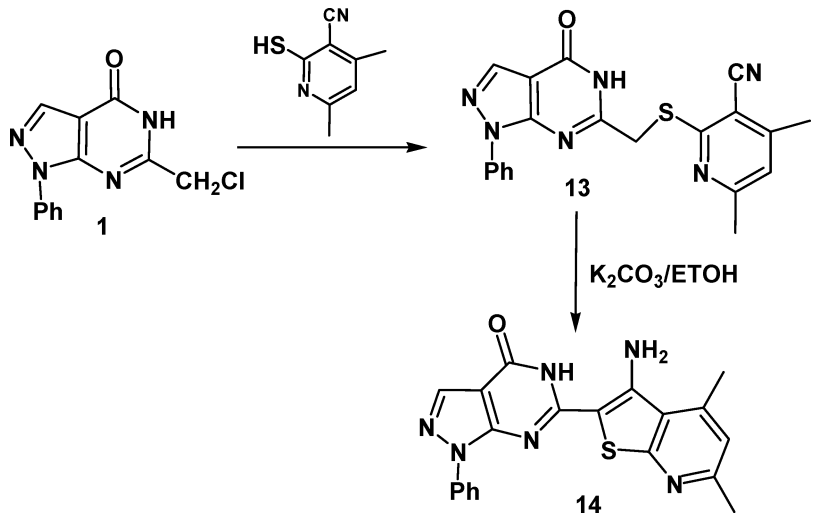
SCHEME 1

temperature in an acetic acid/HCl mixture, the corresponding 1-phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-methyl-mercaptoacetic azide (**11**) was obtained. Carboazide derivative **11** underwent a Curtis rearrangement when boiled in ethanol, yielding the corresponding ethyl N-(1-Phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-methylmercaptomethyl carbamate (**12**) (Scheme 2).

Chloromethylpyrazoloprimidine (**1**) was reacted with 4,6-dimethyl-2-mercaptopyridin-3-carbonitrile in refluxed ethanol and in the presence of sodium acetate to afford 1-phenyl-6-(3-cyano-4,6-dimethylpyridin-2-ylmercaptomethyl)pyrazolo-[3,4-d]pyrimidin-4[5H]-one (**13**). Compound **13** was cyclized in refluxing ethanol in the presence of K_2CO_3 to give 1-phenyl-6-(3-amino-4,6-dimethyl-thieno[2,3-b]pyridin-2-yl)-1,5-dihydro-pyrazolo-[3,4-d]pyrimidin-4-one (**14**) (Scheme 3). The structures and formation of **13** and **14** were established by their spectral analyses, whereas the IR spectrum of compound **13** showed absorption bands at 2220 cm^{-1} for CN. The ^1H



SCHEME 2



SCHEME 3

NMR spectrum of compound **13** exhibited two singlets at 2.5 and 2.6 corresponding to $2CH_3$ and another broad singlet at 4.4 corresponding to the CH_2. IR spectra of compound **14** revealed the disappearance of the band corresponding to the CN group in the starting material and appearance of absorption band at 3480, 3400 cm^{-1} corresponding to the NH_2group. The ^1H NMR spectra of compound **14** showed the disappearance of the signal characteristic of CH_2 in the starting material. The mass spectrum of compound **14** showed a molecular ion peak at 288, which is in agreement with the expected structure.

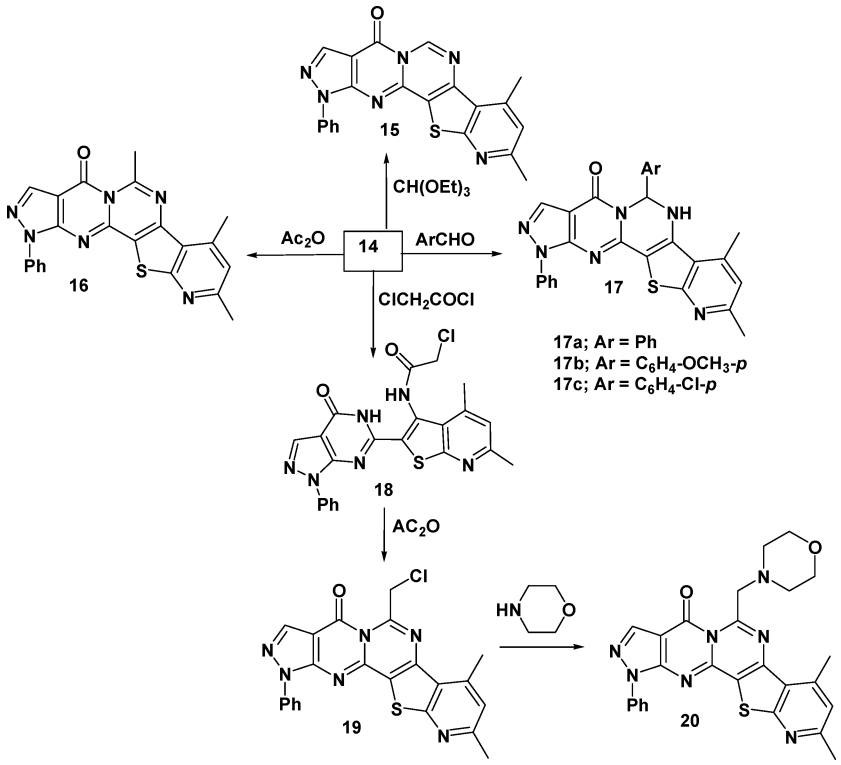
Compound **14** was used to synthesize fused polycyclic heterocyclic. It was condensed with triethyl orthoformate in the presence of acetic acid as catalyst to afford 1-phenyl-8,10-dimethylpyrido[2′,3′:2,3]thieno[4,5-e]pyrazolo[3′,4′:4,5]pyrimido[1,2-c]pyrimidin-4-one (**15**). The expected structure was established on the basis of elemental and spectral data. IR spectrum of **15** revealed the disappearance of bands characteristic of NH_2 and NH groups in the starting material. The mass spectrum of compound **15** showed a peak at m/z = 298 as a molecular ion peak.

When compound **14** was refluxed with acetic anhydride, acylation of the amino group occurred, followed by spontaneous dehydration to give 1-phenyl-6,8,10-trimethyl-pyrido[2′,3′:2,3]thieno[4,5-e]pyrazolo[3′,4′:-4,5]-pyrimido[1,2-c]pyrimidin-4-one (**16**). Formation of **16** was confirmed using spectral data. Its IR spectra revealed the disappearance of bands corresponding to the NH and NH_2 group in the starting material. Its ^1H NMR spectra revealed three singlets at 2.5, 2.9, and 3.2 for 3Me group, and its mass spectrum showed a molecular ion peak at 412 as a molecular ion beak and as base peak.

When compound **14** was allowed to react with aromatic aldehydes in the presence of piperidine as a catalyst, 1-phenyl-6-aryl-8,10-dmethylpyrido[2′,3′:2,3]thieno[4,5-e]-pyrazolo[3′,4′:4,5]pyrimido[1,2-c]pyrimidin-4-one (**17a–c**) were obtained in good yield. Formation of **17a–c** was established using spectral data. IR spectra of **17a,b** revealed the disappearance of bands characteristic for an amino group and showed absorption bands at 3320–3300 cm^{-1} for the NH group. ^1H NMR (DMSO-d_6) of compound **17b** showed the disappearance of a signal characteristic of the NH_2 group, three singlet signals, and revealed the appearance of new signal at 3.8 for OMe group. Mass spectrum of compound **17a** showed a peak at m/z = 474 as a molecular ion peak after elimination of the hydrogen molecule and aromatization of pyrimidine ring.

Chloroacylation of compound **14** using chloroacetyl chloride and acylation of the amino group occurred to give the corresponding chloroacetylamino derivative **18**, which underwent elimination of

water when refluxed with acetic anhydride to afford 1-phenyl -6-chloromethyl-8,10-trimethyl-pyrido[2′,3′:2,3]thieno[4,5-e]pyrazolo [3′,4′:4,5]pyrimido-[1,2-c]pyrimidin-4-one (**19**). The IR spectrum of **18** showed absorption bands at 3450, 3200 cm^{-1} for two NH and at 1695 cm^{-1} for CO. ^1H NMR spectrum ($CDCl_3$) of compound **18** is in agreement with the expected structure. It showed signals at 2.9, 3.2 ppm for $2CH_3$ and CH_2. IR spectrum of compound **19** showed absorption bands at 1720 cm^{-1} for CO. ^1H NMR spectra (CF_3CO_2D) of compound **19** showed signals at δ 3.1(s, 3H, CH_3), 3.5(s, 3H, CH_3), 5.6(s, 2H, CH_2), and 7.6–8.9 (aromatic protons). The mass spectrum of compound **19** exhibited a peak at m/z = 446 and M^{+1} (447), and after elimination of chlorine atom at 412, and base beak at 398 for the structure **15** after elimination of CH_2Cl. Heating of chloromethylpyridothienopyrimidopyrimidine (**19**) with morpholine in ethanol produced 8,10-dimethyl-6-(N-methylmorphonyl)-1-phenylpyrido[2′,3′:2,3]-thieno[4,5-e]pyraolo-[3′,4′:4,5]pyrimido[1,2-c] pyrimidin-4-one (**20)** (Scheme 4). The structure of compound **20**



SCHEME 4

was confirmed using spectral analysis. ^{1}H NMR spectra ($CDCl_3$) of compound **20** showed beside the aromatic protons signals at 2.2 (s, CH_2), 2.8–3.8 (m, 8H, $4CH_2$). The mass spectrum showed a molecular ion peak at m/z = 499 corresponding to the expected structure and gave the base peak corresponding to the molecular weight of the expected structure after elimination of morpholinyl group.

EXPERIMENTAL

Melting points were determined on a Gallen-Kamp melting point apparatus and are uncorrected. IR spectra were recorded on a Pye-Unicam SP 3100 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer and in a suitable deuterated solvent using TMS as internal standard (chemical shifts in ppm). Mass spectra were measured on a Jeol-JMS 600 spectrometer. Elemental analyses were determined on Elementar Analyse system GmbH-VarioEL V.3 microanalyzer in the central lab of Assiut University.

6-Mercaptomethyl-1-phenylpyrazolo[3,4-d]pyrimidin-4(5H)-one (2)

A mixture of (**1**) (1.5 g, 5.75 mmol) and thiourea (1.3 g, 0.01 mol) in ethanol (25 mL) was refluxed for 5 h. The solid yellow product, which was obtained while hot, was filtered in dissolved sodium hydroxide (20 mL, 5%), then acidified with (0.01 N) HCl until acidic. The solid product was collected by filtration, dried under vacuum, and recrystallized from dioxan as yellow crystals in 50% yield, mp 250–252°C.

Anal. Calcd. for $C_{12}H_{10}N_4OS$ (258.30): C; 55.80; H, 3.90; N; 21.69; H; 3.87, S; 12.41%. Found: C; 55.55; H, 3.70; N; 21.62; S; 12.21%. IR: ν = 3250 cm^{-1} (NH), 1690 cm^{-1} (CO), 1590 cm^{-1} for C = N. ^{1}H NMR (DMSO-d_6):δ 4.8 (s, 2H, CH_2), 7.3–8.2 (m, 6H, 5Ar-H and CH pyrazole), 9.5 (s, 2H, NH, SH).

Ethyl (1-Phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-yl)-mercaptoacetate (3)

A mixture of **2** (1 g, 3.87 mmol), ethyl chloroacetate (0.47 mL, 3.87 mmol), and sod. acetate (0.7 g, 8.5 mmol) was refluxed in ethanol (20 mL) for 3 h then allowed cool. The solid product was filtered off and recrystallized from ethanol as yellowish crystals in 69% yield, mp 178–180°C.

Anal. Calcd. for $C_{16}H_{16}N_4O_3S$(344.39): C, 55.80; H, 4.68; N, 16.27; S, 9.31%. Found: C, 55.55; H, 4.45; N, 16.15; S, 9.19%. IR: $\nu = 3450$ cm^{-1} for NH, 1720, 1690 cm^{-1} for CO and at 1590 cm^{-1} for C=N. ^1H NMR(DMSO-d_6): $\delta = 1.1$ (s, 3H, CH_3), 3.8(q, 2H, CH_2), 3.6(s, 4H, $2CH_2$) and at 7.3–8.2 (m, 6H, 5Ar-H, CH pyrazole) and at 10.5 (s, 1H, NH).

1-Phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-methylmercaptoacetic Hydrazide (4)

A mixture of compound **3** (0.9 g, 2.6 mmol) and hydrazine hydrate (99%, 0.5 mL, 10 mmol) was refluxed in ethanol (20 mL) for 3 h. The solid product obtained upon heating was collected, washed well with ethanol, and dried as white crystals in 34% yield, mp 238–240°C. Anal. Calcd. for ($C_{14}H_{14}N_6O_2S$ (330.37): C, 50.90; H; 4.27; N, 25.44; S, 9.71%. Found: C, 50.70; H; 4.12; N, 25.19; S, 9.47%. IR: $\nu = 3350$, 3300, 3100 cm^{-1} ($NHNH_2$), 1680 cm^{-1} for CO, 1590 Cm^{-1} (C=N). ^1H NMR (DMSO-d_6):$\delta = 3.2$(s, 2H, CH_2), 3.5(s, 2H, NH_2), 3.8(s, 2H, CH_2), 7.4–8.3(m, 7H, 5Ar-H, CH pyrazole and NH), 9.5 (s, 1H, NH).

6-Methyl-1-phenylpyrazolo[3,4-d]pyrimidin-4(5H)-one (5)

A mixture of compound **3** (5 mL, 0.10 mol) hydrazine hydrate was refluxed for 3 h under neat condition. The white precipitate that obtained upon heating was collected, mp > 300°C, yield (34%). Anal. Calcd. for $C_{12}H_{10}N_4O$ (226.24): C, 63.71; H, 4.46; N, 24.76%. Found: C; 63.92, H, 4.21; N, 24.73%. IR: $\nu = 3250$ cm^{-1} for NH,1650 cm^{-1} (CO), 1570 cm^{-1} (C=N). Mass spectrum m/z = (226, 100%), 211, 19% for (M^+-CH_3).

N-(1-phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-methylmercaptoacetyl)-N′-phenyl Thiosemicarbazide (6)

A mixture of 1-phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-methylmercaptoacetic hydrazide (**4**) (0.5 g, 1.5 mmol) and phenyl isothiocyanate (0.24 mL, 2 mmol) in ethanol (20 mL) was refluxed for 1 h. The solid product obtained upon heating was collected as white crystals in 84% yield, mp 208–210°C. Anal. Calcd. for ($C_{20}H_{19}N_7O_2S_2$,465.56): C, 54.18; H; 4.11; N, 21.06; S, 13.77%. Found: C, 53.98; H; 4.10; N, 21.77; S, 14.00%. IR: $\nu = 3350$, 3330, 3150 cm^{-1} (NH groups), 1690 for CO, 1600 (C=N). ^1H NMR (DMSO-d_6):$\delta = 3.1$, 3.8 (s, 4H, $2CH_2$), at 7.4–8.2 (m, 10H, Ar-H and CH pyrazole).

(4-Oxo-1-phenylpyrazolo-[3,4-d]pyrimidin-6-yl)-2,3-dihydro3-thioxo-4-phenyl-[1,2,4]triazol-5-yl)-dimethylthioether (7)

A sample of thiosemicarbazide derivative (**6**) (0.3 g, 0.9 mmol) in sodium hydroxide solution (0.4 g, 0.01 mol in 5 mL H_2O) was heated at 80°C for 6 h, then allowed to cool and was acidified using acetic acid. The solid product was collected and recrystallized from ethanol as white crystals in 47% yield, mp > 300°C. Anal. Calcd. for $C_{21}H_{17}N_7OS_2$ (447.53): C, 56.36; H, 3.83; N, 21.91; S, 14.33%. Found: C, 56.15; H, 3.57; N, 21.75; S, 14.12%. IR: $\nu = 3400$ cm^{-1} for NH, 1680 cm^{-1} (CO), 1580 cm^{-1} (C = N). ^1H NMR (DMSO-d_6):$\delta = 3.7$(s, 2H, CH_2), 3.8 (s, 2H, CH_2), 7.4–8.2 (m, 10H, Ar-H), 8.9 (s, 1H, CH pyrazole), 9.8, 11.0 (2s, 2H, 2NH).

(4-Oxo-1-phenylpyrazolo[3,4-d]pyrimidin-6-yl)-2-phenylamino[1,3,4]thiadiazol-5-yl)-dimethylthioether (8)

A sample of **6** (0.3 g, 0.9 mmol) in orthophosphoric acid (10 mL) was heated at 80°C for 6 h, then allowed to cool, and was neutralized with ammonium hydroxide solution. The solid product thus formed was collected and recrystallized from ethanol to give **8** as yellow crystals in 38% yield, mp 240–242°C. Anal. Calcd. for ($C_{22}H_{17}N_7OS$,44753): C, 56.36; H; 3.83; N; 21.91; S, 14.33%. Found: C, 56.23; H; 4.07, N, 22.17; S, 14.26%. IR: $\nu = 3350$, 3150 cm^{-1} for NH, 1680 cm^{-1} (CO), 1580 cm^{-1} (C = N). ^1H NMR (DMSO-d_6):$\delta = 3.9$ (s, 2H, CH_2), 4.1 (s, 2H, CH_2), 7.0–8.0 (m, 10H, Ar-H), 8.9 (s, 1H, CH pyrazole), 9.8, 10.5 (2s, 2H, 2NH).

1-(1-Phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-yl)-mercaptoacetyl-3,5-dimethyl-pyrazole (9)

A mixture of **4** (0.25 g, 0.75 mmol) and acetyl acetone (6 mL, 0.05 mol) in ethanol (15 mL) was refluxed for 6 h. The reaction mixture was allowed to cool, and the solid product was collected and recrystallized from ethanol to give **9** as yellow crystals in 41% yield, mp > 300°C. Anal. Calcd for $C_{19}H_{18}N_6O_2S$ (394.46): C, 57.85; H, 4.60; N, 21.31; S, 8.13%. Found: C, 57.50; H, 4.35; N, 21.10; S, 7.98%. IR: $\nu = 3400$ cm^{-1} (NH) 1720, 1690 cm^{-1} (CO), 1590 cm^{-1} (C=N). ^1H NMR (DMSO-d_6):$\delta = 2.1$ (s, 3H, CH_3), 2.5(s, 3H, CH_3), 3.9, 4.1(2s, 4H, $3CH_2$), at 6.0(s, 1H, CH), 7.0–8.0(m, 5H, 5Ar-H), 8.9(s, 1H, CH pyrazole), 9.2 (s, 1H, NH).

(4-Oxo-1-phenylpyrazolo[3,4-d]pyrimidin-6-yl)-2-mercapto-[1,3,4]oxadiazol-5-yl)-dimethylthioether (10)

A mixture of **4** (0.25 g, 0.75 mmol) and carbon disulfide (1 mL) in pyridine (10 mL) was refluxed on a water bath for 15 h then allowed to cool. The solid product was collected and recrystallized from ethanol to give **10** as yellow crystals in 21% yield, mp 280°C. Anal. Calcd for $C_{15}H_{12}N_6O_2S_2$ (372.43): C, 48.38; H, 3.25; N, 22.57; S, 17.22%. Found: C, 48.21; H, 3.05; N, 22.45; S, 17.01%. IR: $\nu = 3450$ cm^{-1} (NH), 1680 cm^{-1} (CO), 1590 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6): $\delta = 3.5$ (s, 1H, SH), 3.8 (s, 2H, CH_2), at 4.2 (s, 2H, CH_2), at 7.4–8.3 (m, 5H, Ar-H), 8.9 (s, 1H, CH pyrazole) and 9.8 (s, 1H, NH).

1-Phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-methylmercaptoacetic azide (11)

To an ice cooled solution of carbohydrazide **4** (0.25 g, 0.75 mmol) in an acetic acid (5 mL)/HCl (1 mL) mixture, sodium nitrite solution (0.14 g, 20 mmol in 3mL H_2O) was added dropwise with stirring. After the addition was finished, the stirring was continued for an additional 2 h at room temperature. The solid product was collected, washed with water several times, and collected as pale green crystals in 44% yield, mp 120–122°C decomposed. Anal. Calcd. For $C_{14}H_{11}N_7O_2S$ (341.35): C, 49.26; H; 3.25; N, 28.72; S, 9.39%. Found: C, 49.01; H; 3.05 N, 28.45; S, 8.98%. IR: ν =3100 (NH), 2100 cm^{-1} (N_3), 1715, 1690, cm^{-1} (2CO). ^{1}H NMR ($CDCl_3$): $\delta = 3.8$ (s, 2H, CH_2), at 4.1 (s, 2H, CH_2), at 7.4–8.3 (m, 5H, Ar-H), 9.0 (s, 1H, CH pyrazole) and 10.5 (s, 1H, NH).

Ethyl-N-(1-phenyl-4-oxopyrazolo[3,4-d]pyrimidin-6-methylmercaptomethyl Carbamate (12)

A sample of compound (**11**) (0.25 g, 0.73 mmol) in absolute ethanol (10 mL) was refluxed for 3 h, then was allowed to cool and was poured into cold water. The solid product was collected, dried, and recrystallized from pet. ether (60–80°C) to give **12** as white crystals in 50% yield, mp 198–200°C. Anal. Calcd. for $C_{16}H_{17}N_5O_3S$ (359.40): C, 53.48; H, 4.77; N, 19.49; S, 8.91%. Found: C, 53.23; H, 4.56; N, 39.10; S, 8.75%. IR: $\nu =$ 3350 cm^{-1} (NH), 1720, 1680 cm^{-1} (CO), 1590 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6):$\delta = 1.2$ (t, 3H, CH_3), 3.2 (s, 2H, CH_2), 4 (q, 2H, OCH_2), at 4.3 (s, 2H, CH_2), 7.3–8.2(m, 5H, Ar-H), 9.0(s, 1H, CH pyrazole) and 9.3, 11.0 (2s, 2H, 2NH).

1-Phenyl-6-(3-cyano-4,6-dimethylpyridin-2-ylmercapto-methyl)pyrazolo[3,4-d]pyrimidin-4[5H]-one (13)

A mixture of 2-chloromethyl-7-phenylpyrazolo[3,4-d]pyrimidin-4(3H)-one (**1**) (1.3 g, 4.7 mmol), 3-cyano-4,6-dimethylpyridine-2(1H)-thione (0.77 g, 4.7 mmol), and sodium acetate (0.82 g, 10 mmol) in ethanol (20 mL) was refluxed for 3 h. The solid product obtained upon heating was collected and recrystallized from ethanol as pale green crystals in 55% yield, mp 260–262°C. Anal. Calcd. for $C_{20}H_{16}N_6OS$ (388.45): C, 61.84; H, 4.15; N, 21.63; S, 8.25%. Found: C, 61.60; H, 4.01; N, 21.43; S, 8.05%. IR: $\nu = 3250$ cm^{-1} (NH), 2200 cm^{-1} (CN), 2950 cm^{-1} (CH aliphatic), 1725 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6): $\delta = 2.5$, 2.65 (2s, 6H, $2CH_3$), 4.7 (s, 2H, CH_2), 6.9 (s, 1H, CH pyridine), 7.2–8.2 (m, 5H, Ar-H), 9.0 (s, 1H, CH pyrazole), 9.5(s, 1H, NH).

1-Phenyl-6-(3-amino-4,6-dimethylthieno[2,3-b]pyridin-2-yl)-1, 5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one (14)

A sample of 1-phenyl-6-(3-cyano-4,6-dimethylpyridin-2-ylmercaptomethyl)-pyrazolo-[3,4-d]pyrimidin-4[5H]-one (0.47 g, 1.2 mmol) and potassium carbonate (0.39 g, 2.8 mmol) in ethanol (20 mL) was refluxed for 3 h. The solid product thus obtained upon heating was filtered off, washed with water several times, and recrystallized from dioxan to give **14** as greenish yellow crystals, mp >300°C, yield (80%). Anal. Calcd. for $C_{20}H_{16}N_6OS$ (388.45): C, 61.84; H, 4.15; N, 21.63; S, 8.25%. Found: C, 62.04; H, 4.01; N, 21.45; S, 8.02%. IR: $\nu = 3400$–3480 cm^{-1} (NH, NH_2), 1690 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6): $\delta = 2.7$, 2.8(2s, 6H, $2CH_3$), 5.9 (s, 2H, NH_2), 6.9 (s, 1H, CH-pyridine), 7.2–8.3 (m, 5H, Ar-H), 8.9 (s, 1H, CH pyrazole) and 9.7 (s, 1H, NH).

1-Phenyl-8,10-dimethyl-pyrido[2′,3′:2,3]thieno[4, 5-e]pyrazolo[3′,4′:4,5]pyrimido-[1,2-c]pyrimidin-4-one (15)

A sample of compound (**14**) (0.3 g, 0.77 mmol), triethyl orthoformate (1 mL), and few drops of acetic acid were refluxed for 2 h. The solid product obtained upon heating was collected and recrystallized from acetic acid to give **15** as green crystals in 66% yield, mp >300°C. Anal. Calcd. for $C_{21}H_{14}N_6OS$ (398.45): C, 63.30; H, 3.54; N, 21.09; S, 8.05%. Found: C, 63.10; H, 3.30; N, 20.98; S, 7.95%. IR: $\nu = 3030$ cm^{-1} (CH aromatic), 1720 cm^{-1}(CO), 1600 cm^{-1}(C = N). ^{1}H NMR (CF_3CO_2D): 2.8, 3.1 (2s, 6H, $2CH_3$), 7.1 (s, 1H, CH-pyridine), 7.2–8.2 (m, 6H, aromatic and

CH-pyrimidine) and at 8.7 (s, 1H, pyrazole). Mass spectrum: m/z = (398, 38%) for M^+, (397,100%) for (M^+-1).

1-Phenyl-6,8,10-trimethylpyrido[2′,3′:2,3]thieno[4,5-e]pyrazolo-[3′,4′:4,5]pyrimido-[1,2-c]pyrimidin-4-one (16)

A sample of **14** (0.3 g, 0.77 mmol) in acetic anhydride (5 mL) was refluxed for 4 h. The solid product obtained upon heating was collected and recrystallized from dioxan to give **16** as green crystals in 48% yield, mp 290–292°C. Anal. Calcd. for $C_{22}H_{16}N_6OS$(412.48): C, 64.06; H, 3.91; N, 20.37; S, 7.77%. Found: C, 63.95; H, 3.69; N, 20.16; S, 7.53%. IR: ν = 2900 cm^{-1}(CH aliphatic), 1720 cm^{-1}(CO), 1600 cm^{-1}(C=N). ^{1}HNMR (CF_3CO_2D): δ = 2.7, 2.9, 3.2 (3s, 9H, $3CH_3$), 7.2 (s, 1H, CH-pyridine), 7.2–8.2 (m, 5H, CH-aromatic), 8.9 (s, 1H, CH-pyrazole). Mass spectrum m/z = 412(M^+, 100%).

1-Phenyl-6-aryl-8,10-dmethylpyrido[2′,3′:2,3]thieno[4, 5-e]pyrazolo-[3′,4′:4,5]pyrimido[1,2-c]pyrimidin-4-one (17a–c)

General Procedure

To a mixture of **14** (0.3 g, 0.77 mmol), benzaldehyde(3 mL, 29.7 mmol) and a few drops of piperidine were fused gently for 20 min, then ethanol (20 mL) was added and then refluxed for additional 2 h. The solid precipitate obtained on hot was collected and recrystalized as yellow crystals, mp >300°C, yield (58%). Anal. Calcd. for $C_{27}H_{20}N_6OS$ (476.56): C, 68.05; H, 4.23; N, 17.63;S, 6.73%. Found: C, 68.10; H, 4.45; N, 17.40; S, 6.56%. IR: ν = 3300 cm^{-1} for NH, 1670 cm^{-1} (CO), 1580 cm^{-1} (C=N)). ^{1}H NMR (CF_3CO_2D):δ = 3.0, 3.3 (2s, 6H, $2CH_3$), 7.1 (s, 1H, CH-pyridimidin), 7.2 (s, 1H, CH-pyridine), 7.3–8.1 (m, 10H, aromatic protons), 9.0 (s, 1H, CH pyrazole).

1-Phenyl-6-p-methoxyphenyl-8,10-dmethyl-pyrido[2′,3′:-2,3]-thieno[4,5-e]-pyrazolo[3′,4′:4,5]pyrimido[1,2-c]pyrimidin-4-one (17b)

Prepared as in the previous method from **14** (0.2 g, 0.51 mmol) and anisaldehyde (0.3 mL, 2.4 mmol), as yellow crystals in 48% yield, mp < 300°C. Anal. Calcd. for $C_{28}H_{22}N_6O_2S$ (506.59): C, 66.39; H, 4.38; N, 16.59; S, 6.33%. Found: C, 66.30; H, 4.17; N, 16.46; S, 6.09%. IR: ν = 3320 cm^{-1} for NH, 1670 cm^{-1} (CO), 1580 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6):δ = 2.7 (s, 3H, CH_3), 2.8 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 6.8 (a, 1H, CH-pyrimidine), 6.9 (s, 1H, CH-pyridine), 7.1–8.3 (m, 9H, Ar-H), 8.5 (s, 1H, CH pyrazole) and 9.5 (s, 1H, NH).

1-Phenyl-6-p-chlorophenyl-8,10-dmethyl-pyrido[2′,3′:-2,3]-thieno[4,5-e]pyrazolo-[3′,4′:4,5]-pyrimido[1,2-c]pyrimi-din-4-one (17c)

As previously described, this compound was prepared from **14** (0.3 g, 0.77 mmol) and *p*-chlorbenzaldehyde (0.4 g, 2.8 mmol) in yield (40%), mp >300°C. Anal. Calcd. for $C_{27}H_{19}ClN_6OS$ (511.01): C, 63.46; H; 3.75; Cl, 6.94; N, 16.45; S, 6.27%. Found: C, 63.23; H, 3.55; Cl, 6.77; N, 16.25; S, 6.07%. IR: $\nu = 3300$ cm^{-1} (NH), 1710cm^{-1} for (CO). ^{1}H NMR (DMSO-d_6):$\delta = 2.7$ (s, 3H, CH_3), 2.9(s, 3H, CH_3), 6.9 (s, 2H, CH-pyrimidine, CH-pyridine), 7.3–8 (am, 9H, Ar-H), 8.9 (s, 1H, CH-pyrazole), 9.7 (s, 1H, NH).

1-Phenyl-6-(3-N-chloroacetylamino-4,6 di methylthieno (2,3-b)pyridine-2-yl)pyrazole[3,4-d]pyrimidin-4(3H)-one (18)

A mixture of **14** (1 g, 2.5 mmol) and chloroacetylchlorid (1 mL, 0.01 mol) were refluxed at 80°C for 2 h, and then was allowed to cool and was neutralized using Na_2CO_3 (10%) solution. The solid product thus formed was collected and recrystallized from EtOH/$CHCl_3$ mixture to give **18** as yellow crystals in 76% yield, mp > 300°C. Anal. Calcd. For: $C_{22}H_{17}ClN_6O_2S$ (464.94): C, 56.83; H, 3.69; Cl, 7.63; N, 18.08; S, 6.90%. Found: C; 56.68; H, 3.45; Cl, 7.43; N, 17.97; S, 6.65%. IR: $\nu = 3450$, 3200 cm^{-1} (2NH), 2900 cm^{-1} (CH aliphatic), 1695, 1660 cm^{-1} (2CO), 1560 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$):$\delta = 2.6$–2.9 (2s, 6H, 2CH_3), 3.8(s, 1H, CH_2), 6.9–7.7 (m, 6H, Ar-H and CH pyridine), 8.9 (s, 1H, CH pyazole), 9.2, 10.3 (2s, 2H, 2NH).

1-Phenyl-6-chloromethyl-8,10-trimethylpyrido-[2′,3′:2,3]thieno[4,5-e]pyrazolo-[3′,4′:4,5]pyrimido-[1,2-c]pyrimidin-4-one (19)

A sample of **18** (2.1 g, 5.4 mmol) in acetic anhydride (20 mL) was refluxed for 20 min after cooling the reaction mixture. The solid product obtained was collected and recrystallized from dioxan to give **19** as yellowish crystals, mp 178–180°C, yield (69%). Anal. Calcd. for $C_{22}H_{15}N_6OSCl$ (446.91): C, 59.13; H, 3.38; Cl, 7.93; N, 18.80; S, 7.17%. Found: C, 59.01; H, 3.15; Cl, 8.14; N, 18.60; S, 7.01%. IR: $\nu = 2990$ cm^{-1} (CH aliphatic), 1720 cm^{-1} (CO), 1610 cm^{-1} (C = N). ^{1}H-NMR (CF_3CO_2D): $\delta = 3.1$(s, 3H, CH_3), 3.5 (s, 3H, CH_3), 5.6 (s, 2H, CH_2), 7.1(s, 1H, CH pyridine), 7.6–8.9 (m, 6H, Ar-H, CH pyrazole).

8,10-Dimethyl-6-(N-methylmorphonyl)-1-phenylpyrido-[2′,3′:2,3] thieno[4,5-e]-pyrazolo[3′,4′:4,5]pyrimido-[1,2-c]pyrimidin-4-one (20)

A mixture of **19** (0.25 g, 0.55 mmol) and morpholine (0.5 mL, 5.6 mmol) was fused for 15 min then refluxed in ethanol for 3 h. The reaction mixture was allowed to cool, and the solid product that formed was collected and recrystallized from ethanol to give **20** as pale green crystals in 47% yield, mp > 300°C. Anal. Calcd. for $C_{26}H_{23}N_7O_2S$ (497.58): C, 62.76; H, 4.66; N, 19.70; S, 6.44%. Found: C, 62.57; H, 4.47; N, 19.45; S, 6.20%. IR: $\nu = 2950$ cm^{-1} (CH aliphatic), 1690 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): $\delta = 2.5$, 2.7(2s, 6H, $2CH_3$), 2.3, 3.3 (2m, 8H, $4CH_2$), 3.9 (s, 2H, CH_2), 6.9 (s, 1H, CH pyridine), 7.3–7.8 (m, 5H, 5Ar), 8.9 (s, 1H, CH pyrazole). Mass spectrum m/z = 497 (M^+, 5%), 412 (M^+-$(CH_2)_4NO$, 100%), (86, 48.5%) for $(CH_2)_4NO^+$.

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