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Synthesis of some new S-glycosyl pyrimidine and condensed pyrimidine derivatives

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ABSTRACT

Mercaptopyrimidine (**4**) was synthesized by the reaction of isothiocyanate and acrylate (**1**). It was allowed to react with preacetylated sugar bromide and/or halomethylene derivatives to produce alkylated pyrimidines (**5**,**7a-d**). Hydrolysis of compound (**5**) produced compound (**6**). Interacyclization of compounds (**7a-d**) afforded thienopyrimidines (**8a-d**). Moreover oxidation of compound (**7b**) gave the corresponding thienopyrimidine dioxide (**9**). Cyanoethylation of compound (**4**) afforded compound (**10**) that reacted with hydrazine hydrate to give pyrazolopyrimidine (**11**). Oxidation of compound **4** afforded bisulphide (**12**). The cycloaddition product (**13**) was obtained by reaction of compound **4** with maleic anhydride. Pyrimidopyrimidine, pyrimidopyridazine and tetrazolopyriminde derivatives (**16-20**) were obtained by reaction of 4-chloropyrimidine (**15**) with thiourea, benzilhydrazone and sodium azide, respectively. *N*-alkylated pyrazolopyrimidine (**21**) was obtained by reaction of compound (**15**) with acetophenonehydrazone.

1. Introduction

Pyrimidines and heterocyclic annulated pyrimidines exhibit interesting biological activities as medicinal applications [1-3]. A variety of anticancer drugs made from pyrimidine derivatives have clinical use currently, the hydrazinopyrimidine-S-carbonitrile derivatives have antineoplastic activities [4]. Moreover, pyrimidines and condensed pyrimidines are important classes of heterocyclic compounds that exhibit broad spectrum of biological activities such as anticancer [5,6], anti-inflammatory, anti -allergic and analgesic activity [7-9]. In continuation of our efforts in this direction, we synthesized some new pyrimidine derivatives and condensed pyrimidine derivatives for biological evaluations.

2. Experimental

2.1. Instrumentation

Melting points are all uncorrected. The IR spectra (KBr) discs were recorded on a Perkin-Elmer 1650 spectrometer. ^{1}H NMR spectra was determined on Bruker Ac-300 MHz instrument. Chemical shifts are expressed as δ (ppm) relative to tetramethylsilane (TMS) as internal standard and DMSO-d_6 as solvent. The elemental analysis was carried by the Micro-analytical center, Cairo University.

2.2. Synthesis

2.2.1. Ethyl 2-(4-chlorophenyl) 1-4-mercapto-6-phenyl pyrimidine-5-carboxylate (4)

A solution of *p*-chlorobenzoylthiocyanate (**3**) (0.01 mol) (prepared by refluxing *p*-chlorobenzoyl chloride (0.01 mol) and ammonium isothiocyanate (0.01 mol) in dry acetone (20 mL) for 2 h.) was added to ethyl-3-amino-3- phenylacrylate (0.01 mol) (prepared by bubbling ammonia gas into ethylbenzoyl acetate (0.01 mol) for 3 h at room temperature) in dry acetone. The reaction mixture was refluxed for 4 h filtered off and cooled. The solid obtained was filtered off, dried and recrystallized from ethanol 95% to give yellow crystals, **4** (Scheme 1). Yield: 92%. M.p.: 210-212 °C. IR (KBr, ν, cm^{-1}): 3450-3350 (NH), 1725 (C=O, ester), 1200 (C=S). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.36 (t, 3H, CH_3CH$_2$), 4.39 (q, 2H, CH$_3$CH_2), 7.50-8.39 (m, 9H, Ar-H), 13.20 (br, 1H, SH). Anal. calcd. for $C_{19}H_{15}ClN_2O_2S$: C, 61.53; H, 4.08; N, 7.55; S, 8.65. Found: C, 61.49; H 3.98; N, 7.50; S, 8.59%.

2.2.2. 2-(Acetoxymethyl)-6-(2-(4-chlorophenyl)-5-(ethoxy carbonyl)-6-phenylpyrimidin-4-ylthio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (5)

A solution of compound **4** (0.01 mol) in aqueous potassium hydroxide (0.01 mol) in distilled water (10 mL) was added to a solution of 2,3,4,6-tetra-o-acetyl-β-D-glucopyranosyl bromide (0.01 mol) in acetone (30 mL). The reaction mixture was stirred for 4 h at room temperature. The mixture was evaporated under reduced pressure and the residue was washed with distilled water to remove the potassium bromide formed. The solid product was dried and recrystallized from ethanol affording pale gray crystals (Scheme 1). Yield: 35%. M.p.: 170-172 °C. IR (KBr, ν, cm^{-1}): 1745 (C=O, acetoxy groups), 1725 (C=O, ester), 1636 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.87, 1.92, 1.95 and 2.02 (4s, 12H, 4CH$_3$C=O), 1.37 (t, 3H, CH_3CH$_2$), 4.03 (m, 2H, H-5' and H-6''), 4.28 (m, 1H, H-6'), 4.38 (q, 2H, CH$_3$CH_2), 5.06 (t, 1H, H-4'), 5.61 (t, 1H, H-2'), 5.69 (t, 1H, H-3'), 6.21 (d, 1H, H-1'), 7.30-8.41 (m, 9H, Ar-H). Anal. calcd. for $C_{33}H_{33}ClN_2O_{11}S$: C, 56.53; H, 4.74; N, 4.00; S, 4.57. Found: C, 56.50; H, 4.69; N, 3.98; S, 4.52%.

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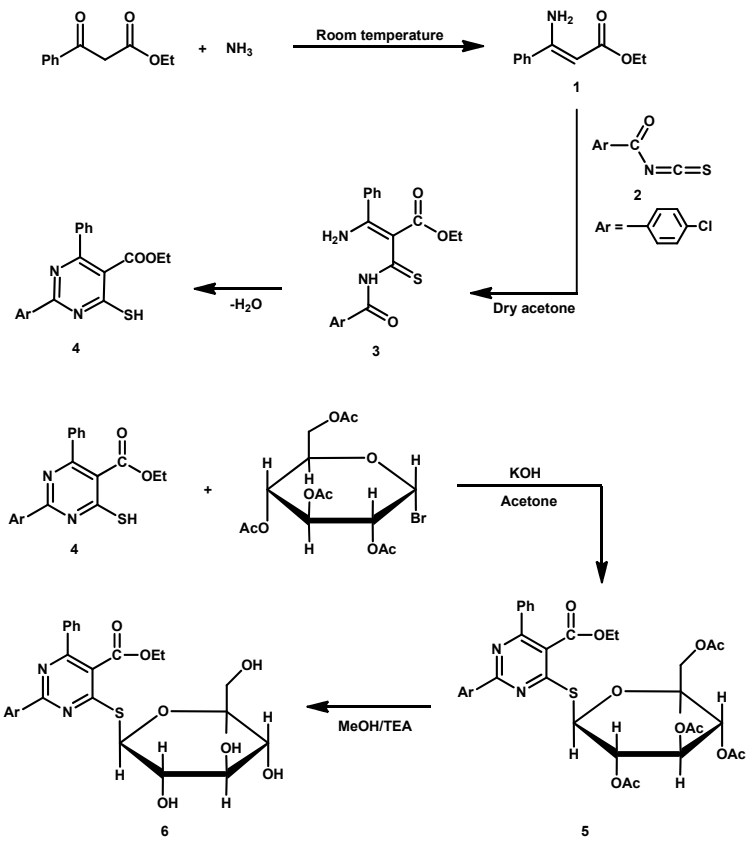


Scheme 1

2.2.3. Ethyl 2-(4-chlorophenyl)-4-phenyl-6-(3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yl thio) pyrimidine-5-carboxylate (6)

A mixture of compound **5** (0.01 mol) in methanol (30 mL), 1 mL of triethylamine (TEA) and few drops of water were stirred overnight at room temperature, the solvent was then removed under vacum, and the residue was washed with chloroform. The remaining residue was recrystallized from ethanol giving gray crystals (Scheme 1). Yield: 25%. M.p.: 180-182 °C. IR (KBr, ν, cm^{-1}): 3420-3395 (very broad band) (OH), 1735 (C=O, ester). ^{1}H NMR (300 MHz, DMSO-d_6/D_2O, δ, ppm): 1.40 (t, 3H, CH_3CH$_2$), 3.68 (m, 1H, H$_5$), 4.39 (q, 2H, CH$_3$CH_2), 4.48 (m, 2H, H$_{6'.6''}$), 5.02 (d, 1H, H-4'), 5.16 (d, 1H, H-2'), 5.44 (d, 1H, H$_{-3'}$), 5.61 (d, 1H, H$_{-1'}$), 4.40-8.41 (m, 9H, Ar-H). Anal. calcd. for $C_{25}H_{25}ClN_2O_7S$: C, 56.34; H, 4.73; N, 5.26; S, 6.02 Found: C, 56.29; H, 4.70; N, 5.27; S, 6.00%.

2.2.4. Synthesis of compounds 7a-d

A mixture of compound **4** (0.01 mol) and appropriate alkylating agent (benzyl chloride, ethyl bromoacetate, chloroacetamide and phenacyl bromide) and triethylamine (3 drops) in ethanol was refluxed for 30 min. The precipitate obtained upon cooling and dilution with water was collected and crystallized from suitable solvent (Scheme 2).

Ethyl 4-(benzylthio)-2-(4chlorophenyl)-6-phenyl pyrimidine-5-carboxylate (**7a**): A pale yellow crystal. Yield: 85%. M.p.: 110-112 °C. IR (KBr, ν, cm^{-1}): 1738 (C=O, ester). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.2 (t, 3H, CH_3 CH$_2$), 4.3 (q, 2H, CH$_3$CH_2), 4.7 (S, 2H, SCH$_2$), 7.0-8.4 (m, 14H, Ar-H). Anal. calcd. for $C_{26}H_{21}ClN_2O_2S$: C, 67.74; H, 4.59; N, 6.08; S, 6.96. Found: C, 67.69; H, 4.61; N, 6.12; S, 6.98%.

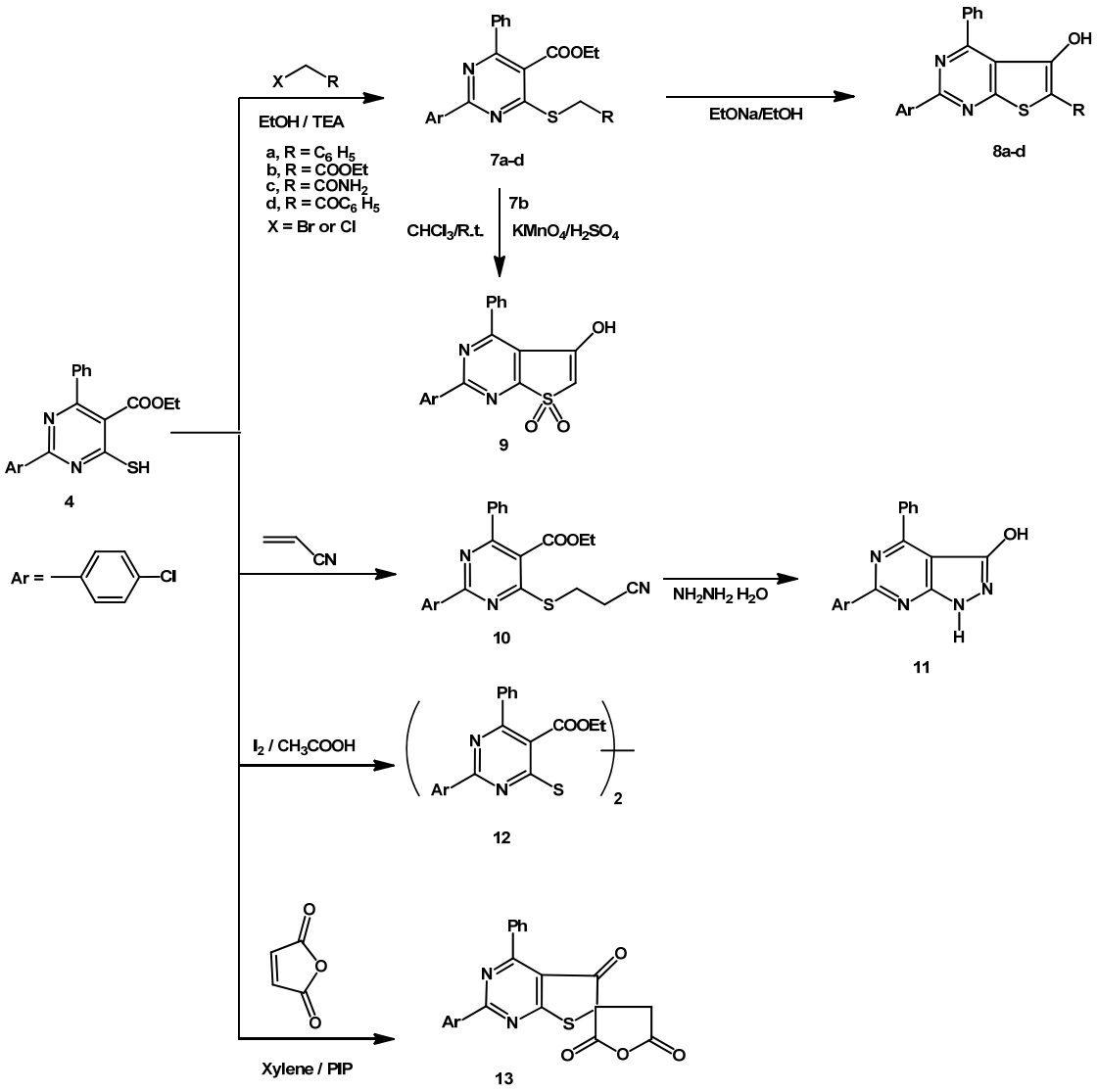
Ethyl 2-(4-Chlorophenyl)-4-(2-ethoxy-2-oxoethylthio)-6-phenylpyrimidine-5-carboxylate (**7b**): A pale yellow powder. Yield: 87%. M.p.: 120-122 °C. IR (KBr, ν, cm^{-1}): 1712 (C=O, ester), 1698 (C=O, ketonic). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.1 (t, 3H, CH_3CH$_2$), 1.3 (t, 3H, CH_3H$_2$), 3.2 (S, 2H, SCH$_2$), 4.2 (q, 2H, CH_3CH$_2$), 4.4 (q, 2H, CH$_3$CH_2), 7.2-8.2 (m, 9H, Ar-H). Anal. calcd. for $C_{23}H_2ClN_2O_4S$: C, 60.46; H, 4.63; N, 6.13; S, 7.02. Found: C, 60.44; H, 4.59; N, 6.11; S, 7.00%.

Ethyl 4-(2-amino-2-oxoethylthio)-2-(4-chlorophenyl)-6-phenylpyrimidine-5-carboxylate (**7c**): Yellow crystal. Yield: 75%. M.p.: 130-132 °C. IR (KBr, ν, cm^{-1}): 1725 (C=O, ester), 1649 (C=O, amide). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.3 (t, 3H, CH_3CH$_2$), 3.8 (S, 2H, SCH$_2$), 4.3 (q, 2H, CH$_3$CH_2), 6.8 (s, 2H, NH$_2$), 7.2-8.4 (m, 9H, Ar-H). Anal. calcd. for $C_{21}H_{18}ClN_3O_3S$: C, 58.94; H, 4.24; N, 9.82; S, 7.49. Found: C, 58.89; H, 4.21; N, 9.79; S, 7.44%.

Ethyl 2-(4-chlorophenyl)-4-(2-oxo-2-phenylethylthio)-6-phenylpyrimidine-5-carboxylate (**7d**): Yellow crystal. Yield: 80%. M.p.: 135-138 °C. IR (KBr, ν, cm^{-1}): 1712 (C=O, ketonic), 1698 (C=O, ester). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.3 (t, 3H, CH_3CH$_2$), 4.2 (q, 2H, CH_3CH$_2$), 4.6 (s, 2H, SCH$_2$), 7.0-8.4 (m, 14, Ar-H). Anal. calcd. for $C_{27}H_{21}ClN_2O_3S$: C, 66.32; H, 4.33; N, 5.73; S, 6.56. Found: C, 66.21; H, 4.19; N, 5.52, S, 6.41%.

2.2.5. Synthesis of compounds 8a-d

A mixture of appropriate pyrimidine (**7a-d**) (0.01 mol) and sodium ethoxide (0.01 mol) in ethanol (30 mL) was heated under reflux for 30 min. The precipitate formed after cooling and acidification with hydrochloric acid (3 mL, 60%) was collected and crystallized from suitable solvent (Scheme 2).



Scheme 2

2-(4-Chlorophenyl)-4,6-diphenylthieno [2,3-d] pyrimidin-5-ol (**8a**): A colorless crystals. Yield: 42%. M.p.: 220-222 °C. IR (KBr, ν, cm^{-1}): 3500 (OH), 1610 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.0-8.2 (m, 14H, Ar-H), 10.1 (s, 1H, OH). Anal. calcd. for $C_{24}H_{15}ClN_2OS$: C, 69.48; H, 3.64; N, 6.75; S, 7.73. Found: C, 69.49; H, 3.65; N, 6.76; S, 7.74%.

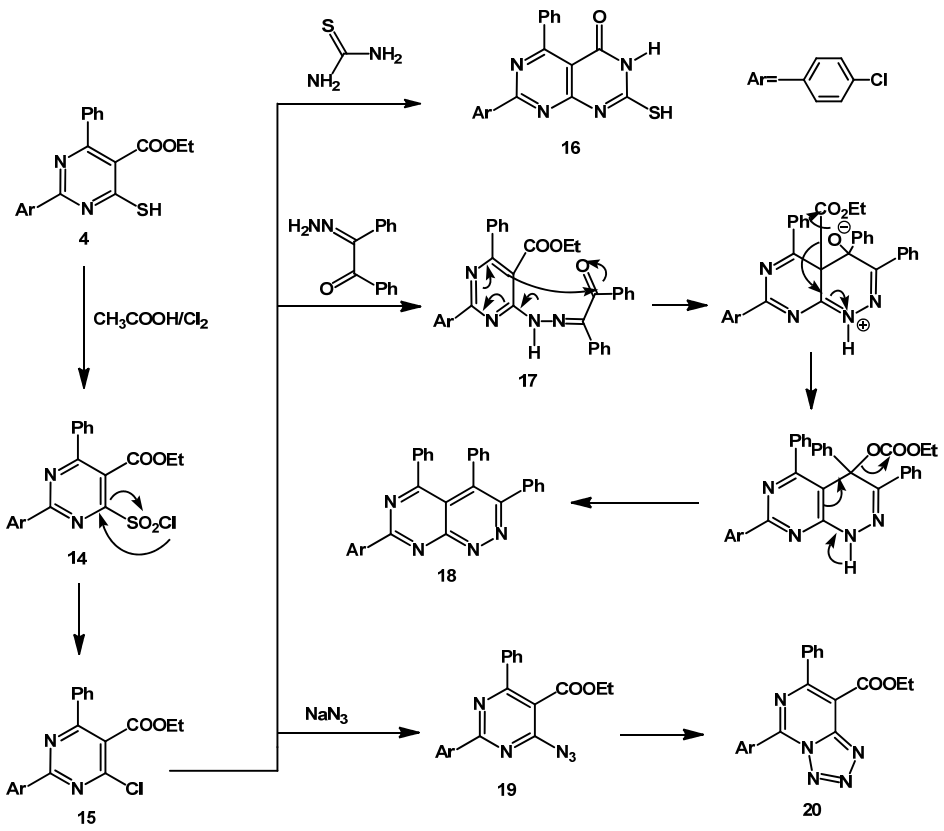
Ethyl 2-(4-chlorophenyl)-5-hydroxy-4-phenylthieno[2,3-d] pyrimidine-6-carboxyate (**8b**): Colorless crystals. Yield: 50%. M.p.: 210-212 °C. IR (KBr, ν, cm^{-1}): 3300-3200 (OH), 1725 (C=O, ester), 1692 (C=O, PH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.34 (t, 3H, CH_3CH_2), 4.21 (q, 2H, CH_3CH_2), 7.2-8.4 (m, 9H, Ar-H), 10.0 (s, 1H, OH). Anal. calcd. for $C_{21}H_{15}ClN_2O_3S$: C, 61.39; H, 3.68; N, 6.82; S, 7.80. Found: C, 61.35; H, 3.66; N, 6.80; S, 7.79%.

2-(4-Chlorophenyl)-5-hydroxy-4-phenylthieno[2,3-d] pyrimidine-6-carboxyate (**8c**): Colorless crystals. Yield: 65%. M.p.: 240-242 °C. IR (KBr, ν, cm^{-1}): 3500-3100 (OH, NH_2), 1665 (C=O, amide). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.42 (br, 2H, NH_2), 7.56-8.12 (m, 9H, Ar-H), 10.2 (s, 1H, OH). Anal. calcd. for $C_{19}H_{12}ClN_3O_2S$: C, 59.76; H, 3.17; N, 11.00; S, 8.40. Found: C, 59.74; H, 3.09; N, 11.04; S, 8.39%.

(2-(4-Chlorophenyl)-5-hydroxy-4-phenylthieno[2,3-d] pyrimidine-6-yl)(Phenyl) methanone (**8d**): Pale yellow crystals. Yield: 50%. M.p.: 215-218 °C. IR (KBr, ν, cm^{-1}): 3400 (OH), 1720 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6,δ ppm): 7.21-8.70 (m, 14H, Ar-H), 10.2 (s, 1H, OH). Anal. calcd. For $C_{25}H_{15}ClN_2O_2S$: C, 67.79; H, 3.41; N, 6.32; S, 7.24. Found: C, 67.71; H, 3.39; N, 6.31; S, 7.22%.

2.2.6. 6-(4-Chlorophenyl)-3-hydroxy-4-phenylthieno[2,3-d] pyrimidine dioxide (9)

Potassium permanganate (0.01 mol) was added in portions to a solution of compound **7b** (0.01 mol) in chloroform (20 mL) and concentrated H_2SO_4 (1 mL) [10]. The reaction mixture was left at room temperature overnight, then ethanol (10 mL) was added and filtered off. The precipitate obtained was collected by filtration, dried and recrystallized from ethanol yield a colorless crystals (Scheme 2). Yield: 25%. M.p.: 120-122 °C. IR (KBr, ν, cm^{-1}): 3500 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.23 (s, 1H, thiophene proton), 8.28-8.70 (m, 9H, Ar-H), 11.52 (br, 1H, OH). Anal. calcd. for $C_{18}H_{11}ClN_2O_3S$: C, 58.30; H, 2.99; N, 7.55; S, 5.65. Found: C, 58.29; H, 2.10; N, 7.53; S, 8.66%.



Scheme 3

2.2.7. Ethyl 2-(4-chlorophenyl)-4-((2-cyanoethyl)thio)-6-phenylpyrimidine-5-carboxylate (10)

A mixture of compound **4** (0.01 mol) and acrylonitrile (0.01 mol) and triethylamine (4 drops) in ethanol (20 mL) was heated under reflux for 2 h. After cooling the precipitate was collected and crystallized from ethanol to give white crystal (Scheme 2). Yield: 40%. M.p.: 118-120 °C. IR (KBr, ν, cm^{-1}): 2220 (C≡N), 1725 (C=O, ester). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.3 (t, 3H, CH_3CH$_2$), 4.2 (q, 2H, CH$_3$CH_2), 4.6 (m, 4H, 2CH$_2$), 7.2-8.2 (m, 9H, Ar-H). Anal. calcd. for $C_{22}H_{18}ClN_3O_2S$: C, 62.33; H, 4.28; N, 9.91. Found: C, 62.40; H, 4.23; N, 9.90.

2.2.8. 6-(4-Chlorophenyl)-4-(cyanomethylthio)-6-phenyl pyrimidine-5-carboxylate (11)

A mixture of compound **10** (0.01 mol) and hydrazine hydrate (0.01 mol) in *n*-butanol (20 mL) was refluxed for 2 h. The precipitate obtained upon cooling was collected and crystallized from butanol to give colorless crystal (Scheme 2). Yield: 60%. M.p.: 230-232 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.61 (br, 1H, NH), 7.2-8.38 (m, 9H, Ar-H), 10.91 (br, 1H, OH). Anal. calcd. for $C_{17}H_{11}ClN_4O$: C, 63.26; H, 3.44; N, 17.36. Found: C, 63.24; H, 3.45; N, 17.34%.

2.2.9. Diethyl 6,6'-disulfanediyl bis(2-(4-chlorophenyl)-4-phenylpyrimidine-5-carboxylate (12)

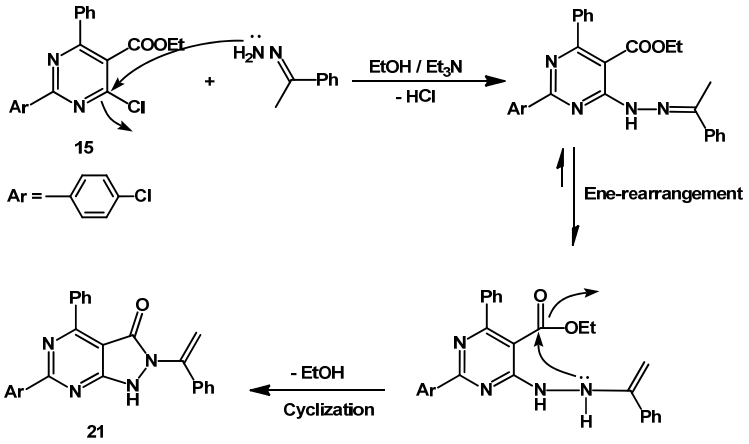
Iodine (0.01 mol) was added to a suspension solution of compound **4** (0.01 mol) in acetic acid (20 mL) and stirred for 4 h. The white solid that obtained was filtered off and recrystallized from benzene afforded a colourless crystals (Scheme 2). Yield: 52%. M.p.: 140-142 °C. IR (KBr, ν, cm^{-1}): 1710 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.4 (t, 6H, 2CH_3CH$_2$), 4.49 (q, 4H, 2CH$_3$CH_2), 7.34-8.05 (m, 18H, Ar-H). Anal. calcd. for $C_{38}H_{28}Cl_2N_4O_4S_2$: C, 61.70; H, 3.82; N, 7.57; S, 8.67. Found: C, 61.69; H, 3.84; N, 7.56; S, 8.65%.

2.2.10. 2'-(4-Chlorophenyl)-4'-phenyl-2H,5'H-spiro[furan-3,6'-thieno[2,3-d] pyrimidine]-2,5,5'(4H)-trione (13)

A mixture of compound **4** (0.01 mol), maleic anhydride (0.01 mol) and few drops of piperidine (PIP) in (20 mL) xylene was refluxed for 16 h. The solid product that obtained after cooling was collected by filtration, dried and recrystallized from toluene to afford pale gray crystals (Scheme 2). Yield: 35%. M.p.: 260-262 °C. IR (KBr, ν, cm^{-1}): 1810-1702 (br), (2C=O) anhydride and (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.82 (s, 2H, CH$_2$), 7.38-7.98 (m, 9H, Ar-H). Anal. calcd. for $C_{21}H_{11}ClN_2O_4S$: C, 59.65; H, 2.62; N, 6.63; S, 7.58. Found: C, 59.67; H, 2.61; N, 6.60; S, 7.56%.

2.2.11. Ethyl 4-chloro-2-(4-chlorophenyl)-6-phenyl pyridimine-5-carboxylate (15)

Chlorine gas was bubbled through a suspension of compound **4** (0.01 mol) in acetic acid (20 mL, 25%) for about 4 h [11]. The resulting product was collected by filtration, washed with water, dried and recrystallized from benzene as a colorless crystal (Scheme 3). Yield: 75%. M.p.: 100-102 °C. IR (KBr, ν, cm^{-1}): 1725 (C=O, ester), 1620 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.3 (t, 3H, CH_3CH$_2$), 4.40 (q, 2H, CH$_3$CH_2), 7.2-8.0 (m, 9H, Ar-H). Anal. calcd. for $C_{19}H_{14}Cl_2N_2O_2$: C, 61.14; H, 3.78; N, 7.51. Found: C, 61.10; H, 3.77; N, 7.50%.



Scheme 4

2.2.12. 7-(4-Chlorophenyl)-2-mercapto-5-phenylpyrimido [4,5-d] pyrimidin-4 (3H)-one (16)

A mixture of compound **15** (0.01 mol) and thiourea (0.01 mol) in ethanol (30 mL) in the presence of triethylamine (3 drops) was refluxed for 3 h. The solid that separated after cooling and pouring into water was collected by filtration and recrystallized from ethanol to give brown crystals (Scheme 3). Yield: 65%. M.p.: 220-222 °C. IR (KBr, ν, cm^{-1}): 3440 (NH), 1665 (C=O), 1080 (SH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.20-8.98 (m, 10H, Ar-H + NH proton), 12.2 (s, 1H, SH). Anal. calcd. for $C_{18}H_{11}ClN_4OS$: C, 58.94; H, 3.02; N, 15.27; S, 8.74. Found: C, 58.90; H, 3.00; N, 15.29; S, 8.70.

2.2.13. 7-(4-Chlorophenyl)-3,4,5-triphenylpyrimido[4,5-c] pyridazine (18)

A mixture of compound **15** (0.01 mol) and benzilmonohydrazone (0.01 mol) in ethanol (30 mL) in presence of TEA (3 drops) was refluxed for 2 h. The solid that separated after cooling and pouring into water was collected by filtration and crystallized from ethanol to give yellow crystals (Scheme 3). Yield: 60%. M.p.: 200-202 °C. ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 7.21-8.41 (m, 19H, Ar-H). Anal. calcd. for $C_{30}H_{19}ClN_4$: C, 76.51; H, 4.07; N, 11.90. Found: C, 76.50; H, 4.02; N, 11.89%.

2.2.14. Ethyl 5-(4-chlorophenyl)-7-phenyltetrazolo [1,5-c] pyrimidine-8-carboxylate (20)

A mixture of compound **15** (0.01 mol) and sodium azide (0.01 mol) in ethanol (30 mL) was refluxed for 4 h. The solid that separated after cooling and pouring into water was collected by filtration and crystallized from ethanol to give yellow crystals (Scheme 3). Yield: 60%. M.p.: 280-282 °C. IR (KBr, ν, cm^{-1}): 1690 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.4 (t, 3H, CH_3CH_2), 4.40 (q, 2H, CH_3CH_2), 7.10-8.12 (m, 9H, Ar-H). Anal. calcd. for $C_{19}H_{14}ClN_5O_2$: C, 60.09; H, 3.72; N, 18.44. Found: C, 60.02; H, 3.71; N, 18.45%.

2.2.15. 6-(4-Chlorophenyl)-4-phenyl-2-(1-phenylvinyl)-1H-pyrazolo[3,4-d]pyrimidin-3 (2H)-one (21)

A mixture of compound **15** (0.01 mol) and acetophenonehydrazone (0.01 mL) and a drops of TEA in ethanol (20 mL) was refluxed for 6 h. The reaction mixture was cooled, neutralized by hydrochloric acid poured into ice water, filtered off, dried and recrystallized from ethanol to give a yellow crystal (Scheme 4). Yield: 65%. M.p.: 190-192 °C. IR (KBr, ν, cm^{-1}): 3440 (NH), 1675 (C=O). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 4.0 (s, H, NH), 4.61 (s, 2H, $=CH_2$), 7.14-7.79 (m, 14H, Ar-H). Anal. calcd. for $C_{25}H_{17}ClN_4O$: C, 70.67; H, 4.03; N, 13.19. Found: C, 70.65; H, 4.01; N, 13.15%.

3. Results and discussion

The present work involves the synthesis of some new pyrimidine and condensed pyrimidine derivatives. Ethyl 2-(4-chlorophenyl)1-4-mercapto-6-phenylpyrimidine-5-carboxylate (**4**) which was readily synthesized by the interaction of isothiocyanate (**2**) with unsaturated amino ester (**1**) presumably via the non-isolable acyclic compound **3** that undergo intramolecular cyclodehydration affording the ethyl 2-(4-chlorophenyl)1-4-mercapto-6-phenylpyrimidine-5-carboxylate (**4**) (Scheme 1).

In an attempt to prepare nucleoside derivatives from the reaction of ethyl 2-(4-chlorophenyl)1-4-mercapto-6-phenylpyrimidine-5-carboxylate (**4**) and 2,3,4,6-tetra-O-acetyl-α-D-glycopyranosyl bromide in the presence of aqueous potassium hydroxide led to the formation of S-glycosyl derivative **5**. The formation of compound **5** is proved by the disappearance of ν(SH) in IR spectra and appearance of signals at δ 1.87, 1.92, 1.95, 2.02 ppm due to the four methyl of the acetyl groups . Hydrolysis of compound **5** using triethylamine in methanol afforded the deacylated compound **6** which showed in IR spectra the disappearance of the acetyl groups and appearance of bands at 3420-3395 cm^{-1} for resulting of free hydroxyl groups.

The synthetic strategy toward thienopyrimidine is based on bulding a thiophene ring into a pyrimidine ring with two ortho substituents one electrophilic (C=O) and one potentially nucleophilic (SH) by its reaction with halomethylene to form a thiophene ring with appropriate functionalities. This result is usually achieved in one operation by a series of constitutive reactions, alkylation followed by ring closure at the electrophilic center and subsequent aromatization (**8a-d**).

Thus, when ethyl 2-(4-chlorophenyl) 1-4-mercapto-6-phenylpyrimidine-5-carboxylate (**4**) was allowed to react with activated halomethylene compounds (benzyl chloride, ethyl bromoacetate, chloroacetamide and/or phenacyl bromide) afforded the corresponding 4-alkylthiopyrimidine derivatives (**7a-d**) which converted to thienopyrimidine (**8a-d**) upon refluxing in basic medium.

Oxidative cyclization of compound **7b** using potassium permengenate in acidic medium afforded thienopyrimidine dioxide (**9**). While, alkylation of ethyl 2-(4-chlorophenyl) 1-4-

mercapto-6-phenylpyrimidine-5-carboxylate (**4**) with acrylonitrile in pyrimidine afforded 4-cyanoethylmercapto pyrimidine derivative (**10**) which proved its structure by reaction with hydrazine hydrate [12] giving pyrazolo-pyrimidine (**11**).The IR spectra of compound **11** showed the disappearance of the (C=O) group and the (CN) group. ^{1}H NMR of compound **11** showed a signal at δ 6.41 ppm characterized for NH group of pyrazole ring. Oxidation of ethyl 2-(4-chlorophenyl) 1-4-mercapto-6-phenylpyrimidine-5-carboxy-late (**4**) using iodine in acetic acid [13] gives disulphide (**12**). Spiro compound **13** was also obtained by addition of compound **4** to maleic anhydride in refluxing xylene and few drops of piperdine (Scheme 2).

Reaction of compound **4** with chlorine gas in acetic acid [14,15] gave chloropyrimidine (**15**). The conversion of compound **4** into compound **15** may be proceed through the formation of pyrimidine-4-sulphonyl chloride (**14**) which liberated sulfurdioxide to give compound **15** which reacted with thiourea affording the pyrimidopyrimidine (**16**), while the condensation of compound **15** with benzilmonohydrazone gave the corresponding pyrimidopyridazine (**18**) via the initial formation of non-isolated open form (**17**) that underwent intramolecular cyclocondensation [16-18]. The reaction of compound **15** with sodium azide gave the corresponding tetrazolopyrimidine (**20**) presumably via the formation of azide form (**19**). The structure of compound **20** was proved by the disappearance of azido group in IR spectrum (Scheme 3).

Finally, synthesis of 6-(4-chlorophenyl)-4-phenyl-2-(1-phenylvinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-3(2*H*)-one (**21**) was achieved by refluxing chloropyrimidine (**15**) with acetophenonehydrazone in ethanol in the presence of TEA (Scheme 4). The reaction may be proceeding via the formation of acyclic intermediate, followed by Ene-rearrangement then ring cyclization as shown in the following mechanism.

References

[1]. Padmaja, A.; Payani, T.; Diunneswra Reddy, G.; Padmavahi, V. *Eur. J. Med. Chem*. **2009**, *44*, 4557-4566.
[2]. Sondhi, S. M.; Singh, N.; Johar, M.; Kumar, B. *Bioorg. Med. Chem*. **2005**, *13*, 6158-6166.
[3]. Sondhi, S. M.; Jain, S.; Dinodia, M.; Shukla, R.; Raghubir, R. *Bioorg. Med. Chem*. **2007**, *15*, 3334-3344.
[4]. Gary, R.; Gupta, S. P.; Gao, H.; Babu, M. S.; Debnath, A. K.; Hansch, C. *Chem. Rev*. **1999**, *99*, 3525-3601.
[5]. Amr, A. E.; Mohamed, A. M.; Mohamed, S. F.; Abdel-Hafez, N. A.; Hamman, A. G. *Bioorg. Med. Chem*. **2006**, *14*, 5481-5488.
[6]. Ghorab, M. M.; Regab, F. A.; Alqasoumi, S. I.; Alafeefy, A. M.; Aboulmagd, S. A. *Eur. J. Med. Chem*. **2010**, *45*, 171-178.
[7]. Breoutt, G. A.; Pease, J. E.; PCT. Int. Appl. Wo 2000012485. Chem. Abstr. 2000, 132, 194385.
[8]. Zhikareva, G. P.; Mostafanova, L. I.; Evstratova, M. I.; Polukhina, I. M.; Pushkina, T. V.; Pershin, G. N.; Yakhantov, L. N.; *Khim. -Farm. Zh.* **1982**, *16*, 183-185.
[9]. Assy, M. G.; Ouf, N. H.; Fikry, R. M. *Polish J. Chem*. **1995**, *69*, 892-895.
[10]. Assy, M. G.; Hassamine, G. A. *Phosphorus sulfur* **1995**, *102*, 95-102.
[11]. Assy, M. G. *Sulfur Lett.* **1990**, *11*, 75-80.
[12]. Drobinca, K.; Augustin, J.; Patai, S. 22 Edn., Wiley and Sons; New York 1977.
[13]. El-Dean, A. M. K.; Abdel-Moneam, M. E. *J. Chinese Chem. Soc*. **2002**, *49*, 1057-1060.
[14]. El-Dean, A. M. K.; Abdel-Moneam, M. E. *Phosphorus sulfur* **2002**, *177*, 2745-2751.
[15]. El-Bahaie, S.; Assy, M. G.; Ibrahim, Y. A. *Sulfur Lett.* **1989**, *9*, 201-208.
[16]. Cumha, S.; Bastos, R. M.; Silva, P. De O.; Nobre, C.; Giselle, A.; Vencato, I.; Lariucci, G.; Napolitano, H. B.; deOiveria, C. A.; Kato, L.; daSilva, C. C. *Moatsh. Furchem*. **2007**, 138, 111-119.
[17]. Assy, M. G.; El-Bahaie, S.; Ibrahim, M. R.; Ibrahim, Y. A. *Indian J. Chem. Soc. B* **1996**, *35(6)*, 598-601.
[18]. Amisworth, G.; Yanes, R. G. *J. Am. Chem. Soc*. **1953**, *75*, 4915-4922.