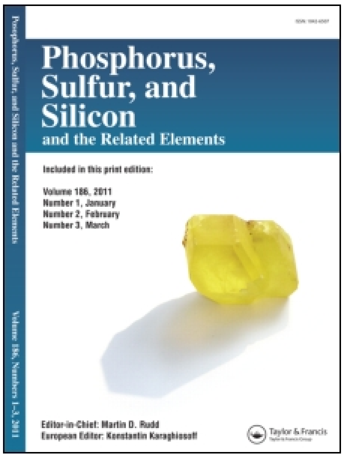

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Synthesis and Reactions of Some Novel Mercaptopyrimidine Derivatives for Biological Evaluation

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4-Mercapto-5-acetylpyrimidine derivative was used as a precursor for preparation of some novel thieno[2,3-d]pyrimidine, pyrazolo[2,3-d]pyrimidine, isothiazolo [5,4-d] pyrimidine, pyrrolo[4,5-d]pyrimidine, and pyrimidio[4,5-d]pyrimidine derivatives. Furthermore, some of the prepared products were revealed promising antimicrobial activities.

Keywords Isothiazolo[5,4-d]pyrimidine; pyrimidine; pyrimidio[4,5-d]pyrimidine; pyrrolo[4,5-d]pyrimidine; thieno[2,3-d]pyrimidine

INTRODUCTION

The synthesis of pyrimidine and condensed pyrimidines has attracted the attention of medicinal chemists because of their potential pharmacodynamic properties. Numerous publications describe the synthesis of condensed pyrimidines possessing a variety of pharmacological activities such as anticonvulsant,[1] anti-inflammatory,[2] bactericidal,[3] fungicidal,[4] and antifertility activities.[5] In conjunction with our previous work on the synthesis of pyrimidine thione derivatives for biological evaluations,[6–11] a series involving a simple pyrimidine thione moiety is described.

RESULTS AND DISCUSSION

The present study was directed to synthesis of several novel fused pyrimidines and pyrimidine derivatives by heteroannulation and

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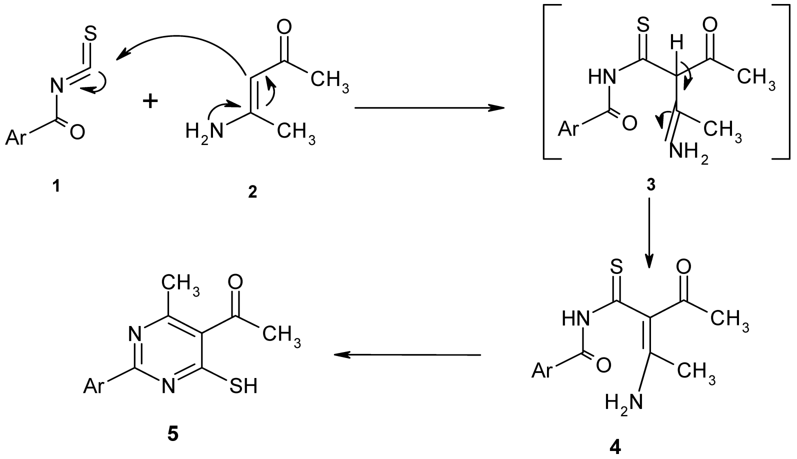


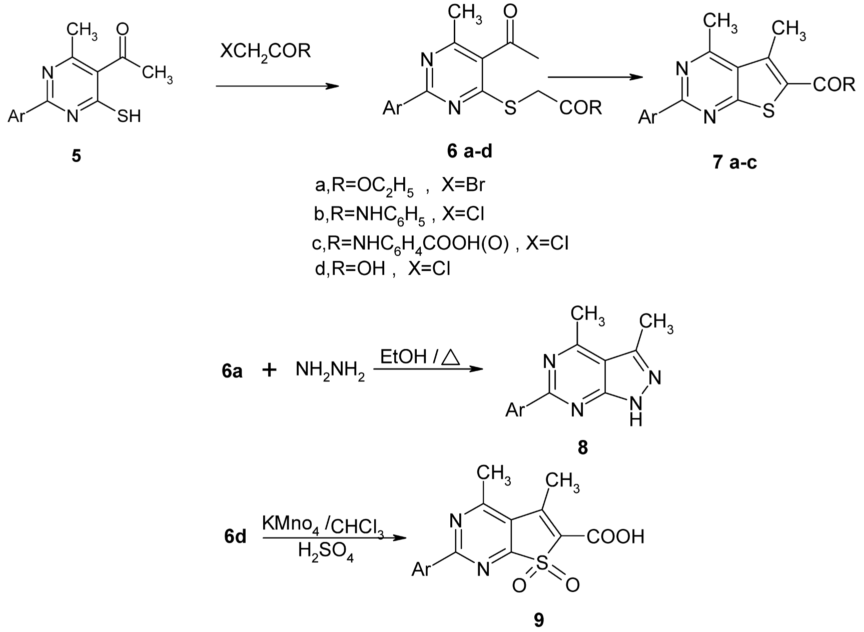
SCHEME 1

functionlization of 5-acetyl-4-mercaptopyrimidines.[12,13] Aroyl isothiocyanates are versatile building units that have been extensively utilized in organic synthesis.[14,15] Thus, the addition of nucleophilic enaminic carbon of β-enaminone **2** to the electrophilic carbon of isothiocynate **1**, afforded the open form **4**. Base induced cyclization of **4** using sodium hydroxide yielded 4-mercapto-5-acetylpyrimidine derivatives **5** (Scheme 1).

Compound **5** seemed to have suitably located functionality for further reactivity and heterocyclization. Thus, compound **5** was reacted with an activated halomethylene derivative in basic medium to give thienopyrimidine **7a-d** presumably via the alkylthio derivative **6a-d.** Compound **6a** reacted with hydrazine hydrate to produce the pyrazolopyrimidine **8**. Oxidation of compound **6d** with $KMnO_4$ in the presence of H_2SO_4 afforded thienopyrimidine dioxide **9**.

Qinoxazinyl thienopyrimidine **10** was the end product of the reaction of compound **7c** with Ac_2O followed by refluxing with formamide (Scheme 2, See Experimental).

When compound **5** was reacted with NaOCl in the presence of NH_4OH, the resulting sulfonation and intramolecular cyclization yielded isothiazolopyrimidine **11**. Cyanoethylation of compound **5** was also investigated. Thus, the addition of mercaptopyrimidine **5** to acrylonitril in the presence of triethyl amine gave 6-carboxamidomethylthienopyrimidine **12** through an intermediate Michael adduct. Oxidation of compound **5** using iodine gives disulphide **13**. The present study is also directed toward the functionlization

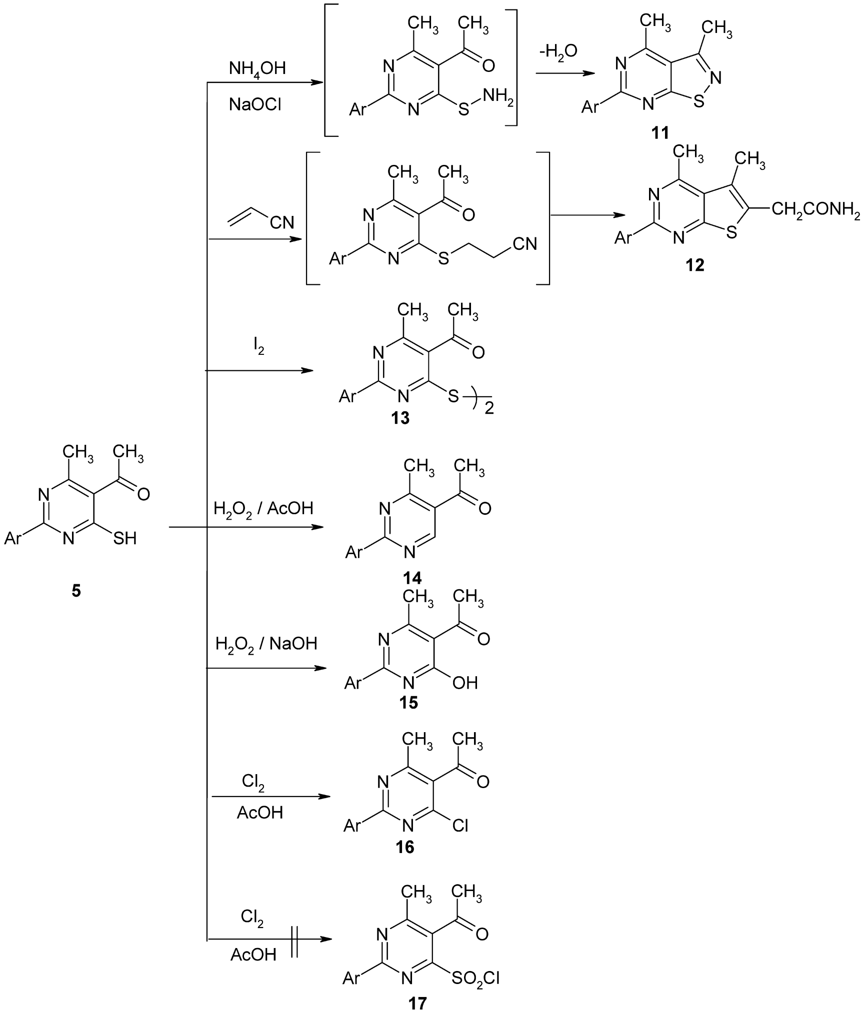


SCHEME 2

of compound **5** through the chemical transformation of the mercapto function. Thus, Treatment of mercaptopyrimidine **5** with H_2O_2 in acetic acid resulted in desulfurization and the formation of m-chlorophenyl-6-methyl-5-acetyl-pyrimidine **14**. Compound **5** underwent hydrolysis when reacted with hydrogen peroxide in basic medium producing 4-hydroxy pyrimidine **15** (Scheme 3).

The action of chlorine in acetic acid successfully converted mercaptopyrimidine **5** into chloropyrimidine **16** instead of the expected 4-pyrimidines sulphonyl chloride derivatives **17**. The conversion of such mercapto function to chloro functionality on a pyrimidine ring by chlorination in acetic medium is usually considered to proceed by rearrangment of the unstable sulphonyl chloride intermediate by an SN_1 mechanism (similar rearrangment for pyridine-2-sulphonyl chloride was proved) **16** (Scheme 4).

4-Chloro-5-acetylpyrimidine derivative **16** was fused with glycine, guanidium cyanide, and arylamines to afford pyrrolo[4,5-d]pyrimidine **18** pyrimido[4,5-d]pyrimidine **19** and arylaminopyrimidine **20a,b** derivatives, respectively.

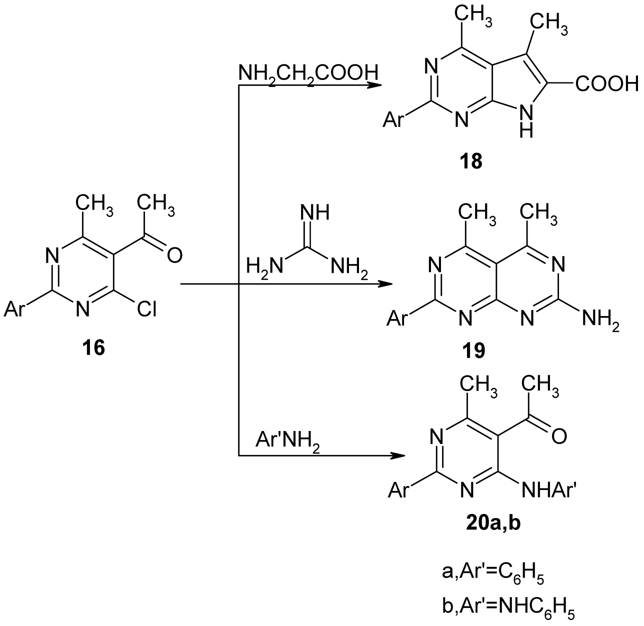


SCHEME 3

Biological Evaluation

Antimicrobial Activity of Some Newly Synthesized Compounds

The in vitro antimicrobial activity of the synthesized compounds was tested against several pathogenic representatives: *Escherichia coli, Bacillus subtilis, Candida albicans,* and *Aspergillus niger.* All microorganisms used were obtained from Chemistry of Natural and Microbial



SCHEME 4

Products Department, National Research Centre, Cairo, Egypt. Disc diffusion sensitivity test was done in the manner identical to that of Bauer et al.[17] Media for disc sensitivity tests were nutrient agar and Muller-Hinton agar (MHA), purchased from Difco, (USA). The nonsterile powder of the tested compounds was dissolved in sterile DMSO to yield 2 μg mL^{-1} passed through 0.2 μm membrane filter (Millipore Corp., USA). The filtrates were dispensed as 2 mL samples into sterile, small screw-capped vials and kept stored at −15°C. DMSO as a solvent showed no inhibition zones. The results were compared to Streptomycin as a reference drug.

The antimicrobial activity of some newly synthesized compounds **7b, 8, 9, 13, 18,** and **20b** were tested and the results are shown in Table I. Evaluation of the new compounds established that compounds **7, 9, 18,** and **20b** were slightly active against Gram positive and Gram negative bacteria. On the other hand, it was found that compounds **9** and **18** revealed activity against yeast more effectively than the other tested compounds while compounds **7, 8, 9, 18,** and **20b** revealed slight to strong antifungal activities. In particular, compound **9** revealed antifungal activity more effective than the other tested compounds and the reference drug.

TABLE I Antimicrobial Activity of Some Synthesized Compounds[a]

Tested compd. no. & stander	Disc diffusion test (mm) Microorganisms — Bacteria: Gram negative Escherichia coli	Bacteria: Gram positive Bacillus subtillis	Yeast Candida albicans	Fungi Aspergillus niger
Streptomycin[b]	+++	+++	+++	+
7b	+	+	−	++
8	+	−	−	+
9	+	+	++	+++
13	+	−	−	−
18	+	+	++	++
20b	+	+	−	+

[a] $\gamma = 2\ \mu$g/mL^{-1} in DMSO. [b] $\gamma = 25\ \mu$g/mL^{-1} in DMSO, Lot. 30730, Bioanalyse (Turkey). +++ highly sensitive (14–16 mm); ++ fairly sensitive (12–14 mm); + slightly sensitive (10–12 mm); and − not sensitive.

EXPERIMENTAL

All melting points are uncorrected and were measured using an Electrothermal IA 9100 apparatus. Analytical data were performed by Vario El Mentar apparatus, organic microanalysis section, National Research Centre. Their results were found to be in agreement with the calculated values (±0.5%). The IR spectra (KBr) were recorded on a Pye Unicam Sp-3–300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H spectra were run at 300 MHz in dimethylsulphoxide (DMSO-d$_6$). Chemical shifts are quoted in δ and were related to that of the solvents. The Mass spectra were recorded on a Shimadzu GCMS-QP-1000EX mass spectrometer at 70 ev. Microanalysis were carried out at the microanalytical unit, Cairo University (Cairo, Egypt).

Reagent—N-substituted Chloroacetamide

The synthesis of *N*-substituted chloroacetamide was accomplished according to the procedure of Widman by adding the appropriate aromatic amine to chloro acetylchloride.[18]

N-β-Amino-α-acetyl-1-thiocrotonyl-m-chlorobenzamid (4)

A mixture of m-chlorobenzoylchloride (0.01 mol), ammonium thiocyanate (0.015 mol) and β-enaminone (0.01 mol) in acetone (20 ml) was stirred for 1/2 h. The reaction mixture was poured onto ice water, filtered off, dried, and recrystallized from benzene to give red crystals of compound **4** in 78.3% yield; m.p. 150°C;. Anal. calcd. for $C_{13}H_{13}ClN_2O_2S$ (296.77): C, 52.61; H, 4.42; N, 9.44. Found C, 52.70; H, 4.43; N, 9.46.

2-*m*-Chlorophenyl-6-methyl-4-mercapto-5-acetylpyrimidine (5)

A solution of **4** (0.01 mol) in sodium hydroxide solution (0.01 mol) was stirred at room temperature for 1/2 h., the yellow crystals obtained upon acidification using HCl (0.01 mol) was collected by filtration and crystallized from ethanol into yellow crystals of **5** in 56.1% yield; m.p. 280°C; IR spectrum (KBr, ν, cm^{-1}): 1670 (CO), 1010 (SH); ^1H NMR spectrum (DMSO-d_6, δ ppm): 2.7 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 7.4–8.0 (m, 4H, Ar'Hs), 10.74 (s, 1H, SH); MS *m/z* (%): 278 (M^+, 10.93). Anal. calcd. for $C_{13}H_{11}ClN_2OS$ (278.76).: C, 56.10; H, 3.98; N, 10.05. Found C, 56.11; H, 3.99; N, 10.07.

2-*m*-Chlorophenyl-4-carboxymethylthio-6-methyl-5-acetyl pyrimidine (6a) and 4-Carboethoxymethylthio-6-methyl-5-acetylpyrimidine (6d)

A mixture of **5** (0.01 mol), chloroacetic acid and/or ethyl bromo acetate and sodium carbonate (0.02 mol) was stirred at room temperature for 1 h, the colorless precipitate obtained upon acidification with HCl (0.01 mol) was collected by filtration and crystallized from ethanol into colorless crystals of **6a** and **6d**.

6a: in 71.4% yield; m.p. 160°C; IR spectrum (KBr, ν, cm^{-1}): 1711(CO ester), 1650 (CO acetyl); Anal. calcd. for $C_{17}H_{17}ClN_2O_3S$ (364.85): C, 55.97; H, 4.70; N, 7.68. Found C, 56.03; H, 4.71; N, 7.69.

6d: in 58.7% yield; m.p. 120°C; IR spectrum (KBr, ν, cm^{-1}): 3449 (OH), 1711(CO acidic), 1650 (CO acetyl), Anal. calcd. for $C_{15}H_{13}ClN_2O_3S$ (336.79): C, 53.49; H, 3.89; N, 8.32. Found C, 53.57; H, 3.90; N, 8.33.

Ethyl-2-*m*-chlorophenyl-4,5-dimethylthieno[2,3-d]pyrimidine-6-carboxylate (7a)

A mixture of compound **6a** (0.01 mol) and few drops of triethyl amine in ethanol (15 ml) was heated under reflux for 1 h. After cooling, the precipitate was collected and crystallized from acetone into colorless crystals of **7a** in 49.8% yield; m.p. 170–175°C; IR spectrum (KBr, ν, cm^{-1}): 1677 (CO); ^1H NMR spectrum (DMSO-d_6, δ ppm): 1.45 (t, 3H,

CH_3), 2.9 (s, 3H, CH_3), 2.99 (s, 3H, CH_3), 4.43 (q, 2H, CH_2), 7.2–8.4 (m, 4H, Ar'Hs); Anal. calcd. for $C_{17}H_{15}ClN_2O_2S$ (346.83): C, 58.87; H, 4.36; N, 8.08. Found C, 58.95; H, 4.37; N, 8.09.

2-*m*-chlorophenyl-4,5-dimethylthieno[2,3-d]pyrimidine-6-carboxanilide (7b)

A mixture of compound **5** (0.01 mol) N-phenylchloroacetamide (0.01 mol) and sodium ethoxide (0.01 mol) was refluxed for 2 h., the precipitate obtained upon cooling was collected and crystallized from acetone into colorless crystals of **7b** in 59.7% yield; m.p. 280°C; IR spectrum (KBr, ν, cm^{-1}): 3461 (NH), 1641(CO); ^1H NMR spectrum (DMSO-d_6, δ ppm): 2.8 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 6.8–7.6 (m, 9H, ArH's), 10.62 (s, 1H, NH); MS *m/z* (%): 393 (M^+, 25.33). Anal. calcd. for $C_{21}H_{16}ClN_3OS$ (393.89): C, 64.04; H, 4.09; N,10.67. Found C, 64.11; H, 4.10; N, 10.69.

4-{[2-*m*-chlorophenyl-4,5-dimethylthieno[2,3-d]pyrimidine-6-carbonyl]-amine}-benzoic acid (7c)

A mixture of compound **5** (0.01 mol), N-O-carboxyphenyl chloroacetamide (0.01 mol), and sodium ethoxide (0.01 mol) was refluxed for 2 h., the precipitate obtained upon cooling was collected and crystallized from acetone into colorless crystals of **7c** in 55.3% yield; m.p. 290°C; MS *m/z* (%): 438 (M^+, 21.76). Anal. calcd. for $C_{22}H_{16}ClN_3O_3S$ (437.9): C, 60.34; H, 3.68; N, 9.60. Found C, 64.11; H, 4.10; N, 10.69.

Pyrazolo[2,3-d]pyrimidine (8)

A mixture of **6a** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol into (20 ml) was heated under reflux for 3 h., after cooling the colorless precipitate was collected and crystallized from ethanol.

Colorless crystals of **8** in 45.4% yield; m.p. 180°C; IR spectrum (KBr, ν, cm^{-1}): 3444 (NH); MS *m/z* (%): 258 (M^+, 35.45). Anal. calcd. for $C_{13}H_{11}ClN_4$ (258.71): C, 60.35; H, 4.29; N, 21.66. Found C, 60.45; H, 4.30; N, 21.70.

Ethyl-2-*m*-chlorophenyl-4,5-dimethylthieno[2,3-d] pyrimidine7,7-dioxide-6-carboxylate (9)

A solution of **6d** (0.01 mol) in chloroform (10 ml) and sulphuric acid (2 ml, 98%) was cooled to 0° and then potassium permanganate (0.1 mol) was added slowly in Portions. The solution was set aside at room temperature, made alkaline, decolorized with acetone, and extracted with chloroform. After evaporation to dryness the residue was crystallized from ethanol as colorless crystals **9** in 40% yield; m.p. 180–181°C; IR spectrum (KBr, ν, cm^{-1}): 3449 (OH), 1654 (CO), 1160 (SO_2); MS *m/z* (%): 351 (M^+, 11.06). Anal. calcd. for $C_{15}H_{11}ClN_2O_4S$ (350.78): C, 51.36; H, 3.16; N, 7.99. Found C, 51.43; H, 3.17; N, 8.00.

2-*m*-chlorophenyl-6-qunoxazinyl-4,5-dimethylthieno [2,3-d] pyrimidine (10)

A mixture of compound **7c** (0.01 mol), and acetic anhydride (5 ml) sodium acetate (0.01 mol) in acetic acid (20 ml) was heated under reflux for 3 h. The solid obtained upon concentration was collected and refluxed with formamide for 5 hours the solid obtained crystallized from benzene into colorless crystals of **10** in 42.2% yield; m.p. 300°C; IR spectrum (KBr, ν, cm^{-1}): 1653 (CO), 3421 (NH); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.8 (s, 3H, CH_3), 2.9 (s, 3H, CH_3), 7.6–8.3 (m, 8H, ArH's), 8.46 (s, 1H, NH). MS *m/z* (%): 421 (M^+, 9.91). Anal. calcd. for $C_{22}H_{17}ClN_4OS$ (420.92): C, 62.78; H, 4.07; N, 13.31. Found C, 62.84; H, 4.08; N, 13.33.

2-*m*-chlorophenyl-4,5-dimethylisothiazolo[5,4-d] pyrimidine (11)

A solution of sodium hypochloride (125 ml, 5%) was added dropwise over a period of 20 min to a stirred solution of pyrimidine **5** (0.01 mol) in aqueous sodium hydroxide solution (90 ml, 3.3%), and ammonium hydroxide (90 ml, 3.3%) at room temperature. The solid obtained was collected, washed with water and then crystallized from ethanol to give colorless crystals of **11** in 40.8% yield; m.p. 120°C; IR spectrum (KBr, ν, cm^{-1}): 1654 (C=N); MS *m/z* (%): 275 (M^+, 38.77). Anal. calcd. for $C_{13}H_{10}ClN_3S$ (275.02): C, 56.72; H, 3.66; N, 15.27. Found C, 56.61; H, 3.61; N, 15.21.

6-carboxamidomethylthienopyrimidine 12

A mixture of **1** (0.01 mol), acrylonitrile (0.01 mol) and triethyl amine (3 drops) in ethanol (10 ml) was heated under reflux for 1 h. After cooling the precipitate was collected and crystallized from ethanol to give colorless crystals of **12** in 65% yield; m.p. 89–90°C; IR spectrum (KBr, ν, cm^{-1}): 3369 (NH), 1649 (CO); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.24 (s, 3H, CH_3), 2.55 (s,3H,CH_3), 3.8(s, 2H,CH_2), 6.5 (s, 2H,NH_2), 7.5–8.1 (m, 4H,ArH's). MS *m/z* (%): 331 (M^+, 9.67). Anal. calcd. for $C_{16}H_{14}ClN_3OS$ (331.82): C, 57.92; H, 4.25; N, 12.66. Found C, 58.00; H, 4.26; N, 12.69.

Bis[2-*m*-chlorophenyl-6-methyl-5-acetylpyrimidyl] disulfide 13

Iodine (0.01 mol) was added to a solution of **5** (0.01 mol) in acetic acid (20 ml) and left at room temperature for 1/2 h. The resulting yellowish precipitate was collected by filtration, washed with water, and crystallized from ethanol into yellowish crystals of **13** in 12.23% yield; m.p. 150°C; IR spectrum (KBr, ν, cm^{-1}): 1655.3 (CO); MS *m/z* (%): 554 (M$^+$, 46.07). Anal. calcd. for $C_{26}H_{20}Cl_2N_4O_2S_2$ (554.04): C, 56.31; H, 3.64; N, 10.11. Found C, 56.22; H, 3.63; N, 10.09.

2-*m*-Chlorophenyl-6-methyl-5-acetylpyrimidine 14

A mixture of compound **5** (0.01 mol), hydrogen peroxide (60 ml, 30%) and acetic acid (20 ml) was shaken for 5 min, an exothermic reaction occurred (the temperature rise to 60°C). The solution was heated gently tell boiling for 3 min, after cooling in ice water and scratching the solid produced was recrystallized from ethanol to give colorless crystals of **14** in 44.4% yield; m.p. 180°C; IR spectrum (KBr, ν, cm^{-1}): 1699 (CO); Anal. calcd. for $C_{15}H_{12}N_6$ (276.30): C, 63.40; H, 4.51; N, 11.38. Found C, 63.29; H, 4.49; N, 11.36.

2-*m*-chlorophenyl-6-methyl-5-acetylpyrimidine-4-one 15

A mixture of compound **5** (0.01 mol) hydrogen peroxide (60 ml, 30%) and sodium hydroxide (0.01 mol) was shaken for 5 min, the flask content was allowed to stand at room temperature for 1/2 h., the colorless precipitate obtained upon acidification with HCl (0.1 mol) was collected and crystallized from ethanol into colorless crystals of **15** in 42.1% yield; m.p. 170.°C; IR spectrum (KBr, ν, cm^{-1}): 1699 (CO), 3445 (OH); ^{1}H NMR spectrum (DMSO-d$_6$, δ ppm): 2.2 (s, 3H, CH_3), 2.3 (s,3H,CH_3), 7.4–8 (m, 4H, ArH's), 13.19 (s, 1H,OH). Anal. calcd. for $C_{13}H_{11}ClN_2O_2$ (262.05): C, 59.53; H, 4.23; N, 10.69. Found C, 59.44; H, 4.22; N, 10.66.

2-*m*-chlorophenyl-4-chloro-6-methyl-5-acetylpyrimidine 16

Chlorine gas was bubbled through a suspension of 5 (5g) in acetic acid (50 ml, 25%) for about 2 h at 10°C, the resulting precipitate was collected by filtration washed with water, dried and crystallized from acetone into colorless crystals of **16** in 74.6% yield; m.p. 100°C; IR spectrum (KBr, ν, cm^{-1}): 3382, 3280 (NH_2), and 2220 (CN) 1672 (CO); Anal. calcd. for $C_{13}H_{10}Cl_2N_2O$ (281.14): C, 55.54; H, 3.59; N, 9.96. Found C, 55.71; H, 3.60; N, 10.00.

Pyrrolopyrimidine 18

A solution of compound **17** (0.01 mol) and glycine (0.01 mol) in DMF (20 ml) was heated under reflux for 2 h; the resulting colorless crystals was collected by filtration and crystallized from ethanol to give colorless crystals of pyrrolopyrimidine **18** in 35.7% yield; m.p. 185°C; IR spectrum (KBr, ν, cm^{-1}): 3594 (OH), 3444 (NH), 1648 (CO); MS *m/z* (%): 302 (M$^+$, 8.28). Anal. calcd. for $C_{15}H_{12}ClN_3O_2$ (301.73): C, 59.71; H, 4.01; N, 13.93. Found C, 59.71; H, 4.02; N, 13.91.

7-Amino-2-*m*-chlorophenyl-4,5-dimethylpyrimidio[4,5-d] pyrimidine 19

A mixture of **17** (0.01 ml) and guanidinum cyanate (0.01 mol) was fused on oil bath at 170°C, for 2 h., the solid mass obtained upon air cooling was refluxed with ethanol, the precipitate obtained upon cooling was collected and crystallized from ethanol into colorless crystals of **19** in 40.8% yield; m.p. 130°C; IR spectrum (KBr, ν, cm^{-1}): 3366, 3179 (NH_2); MS *m/z* (%): 286 (M$^+$, 29.10). Anal. calcd. for $C_{14}H_{12}ClN_5$ (285.74): C, 58.85; H, 4.23; N, 24.51. Found C, 58.93; H, 4.24; N, 24.56.

4-Arylamino-2-*m*-chlorophenyl-6-methyl-5-acetylpyrimidine 20a

A solution of **17** (0.01 mol) and appropriate aromatic amine (0.01 mol) (aniline, p-toludine and/or anthranilic acid) in DMF (20 ml) was refluxed for 2 h. The resulting colorless precipitate was collected by filtration and crystallized from ethanol to colorless crystals of **20a** in 63.3% yield; m.p. 150°C; IR spectrum (KBr, ν, cm^{-1}): 3455 (NH),1661 (CO); ^{1}H NMR spectrum (DMSO-d$_6$, δ ppm): 2.7 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 7.1–8 (m, 8H, ArH's), 10.3 (s, 1H, NH). MS *m/z* (%): 337 (M$^+$, 9.28). Anal. calcd. for $C_{19}H_{16}ClN_3O$ (337.81): C, 67.56; H, 4.77; N, 12.44. Found C, 67.61; H, 4.71; N, 12.41.

2-*m*-chlorophenyl-6-methyl-4(2-phenylhydrazino)-5-acetylpyrimidine 20b

A mixture of compound **17** (0.01 mol) and phenylhydrazine (0.01 mol) in ethanol (20 ml) was heated under reflux for 2 h. The resulting precipitate was collected by filtration was recrystallized from ethanol into colorless crystals of **20b** in 48.5% yield; m.p. 180°C; IR spectrum (KBr, ν, cm^{-1}): 3455 (NH), 1661(CO); Anal. calcd. for $C_{19}H_{17}ClN_4O$ (352.82): C, 64.68; H, 4.86; N, 15.88. Found C, 64.71; H, 4.81; N, 15.91.

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