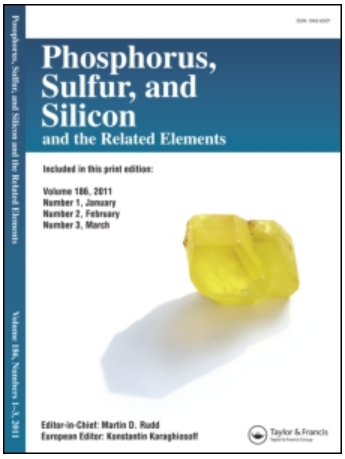

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Synthesis of Some New Pyrimidine Derivatives of Expected Antimicrobial Activity

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2-(2-Arylvinyl)-6-methyl-4-mercapto-5-acetylpyrimidine derivatives ***3***$_{a-d}$*, were synthesized form the reaction of the appropriate isothiocyanate derivatives* ***1*** *with α,β-unsaturated aminoketone* ***2****. Compound* ***3*** *was alkylated with methyl iodide, ethyl chloroacetate and/or bromosugar to afford* ***6****,* ***9****, and* ***22***$_{a-c}$ *respectively. Cyanoethylation of* ***3***$_b$ *afforded* ***6***$_b$ *which upon cyclization with hydrazine hydrate gave pyrazolopyrimidine* ***7****. Bromination of* ***6***$_b$ *gave dibromo compound* ***8****. Thieno[2,3-d]pyrimidines* ***10*** *and* ***12*** *were obtained by ring closure of the alkylated product* ***9*** *with TEA/EtOH and/or through cyclization of the hydrazide* ***11*** *with NaOEt/EtOH. While, Thieno[2,3-d]pyrimidine* ***14*** *was obtained directly by alkylation of* ***3***$_b$ *with chloroacetone in both TEA/EtOH and* Na_2CO_3 *solution. The cycloaddition products* ***15*** *and* ***16*** *were obtained by reaction of* ***3b*** *with diethylmaleate and /or maleic anhydride. Formation of 1,3,4-oxadiazole* ***17****, pyrazoles****18*** *and* ***19*** *where obtained by treating the hydrazide* ***11*** *with carbon disulphide, triethyl orthoformate and acetylacetone respectively. While, reaction of* ***11*** *with p-chlorobenzaldehyde resulted in the Schiff's base* ***20*** *which, cyclizes with thioglycolic acid to afford thiazolidone* ***21****. Hydrolysis of* ***22***$_{a-c}$ *in TEA/MeOH afforded the free sugar* ***23***$_{a-c}$.

The structures of all the new compounds were confirmed using IR, ^1H*, and* ^{13}C *NMR spectra and microanalysis. Selected members of the synthesized compound were screened for antimicrobial activity.*

Keywords Pyrazolopyrimidine; thieno[2,3-*d*]pyrimidines; thiazolidone and bromosugar

INTRODUCTION

The 5-substituted pyrimidines and their nucleoside derivatives have been the subject of many studies mainly due to their elevated antiviral

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and anticancer activities.[1,2] On the other hand, the functionality of the 6-position of pyrimidines showed important anti-HIV-1 activity[3,4] and antirubella virus activity.[5,6] A verity of anticancer drugs made from pyrimidine derivatives are currently in clinical use, as for example some of these compounds applied successfully for the treatment of several neoplastic diseases such as leukemia and testicular cancer, while the effect of anticancer drugs on solid tumors is weak. The hydrazinopyrimidine-S-carbonitrile derivatives have anti-tumoral activities.[7] Also, pyrimidine derivatives are very well known in medicinal chemistry for their therapeutic applications,[8,9] such as, analgesic,[10] antihypertensive,[11] antipyretic,[12] and anti-inflammatory[13] drugs. Also applications of pyrimidine compounds are extended to agriculture as a pesticides,[14] and plant growth regulators.[15]

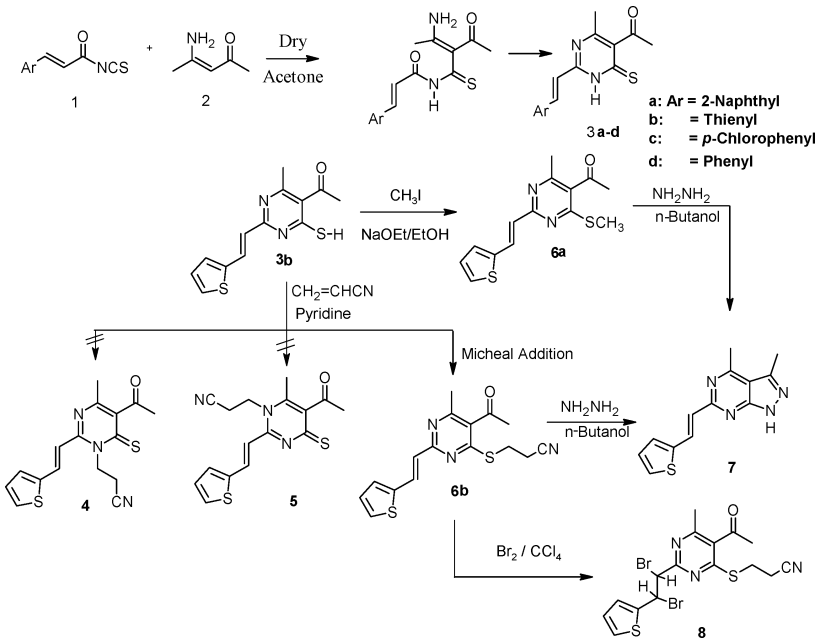
In view of the pharmacological importance of thienopyrimidine[16] and in continuation of our previous work on the synthesis of biologically active pyrimidines and thienopyrimidines, we aimed to obtain new compounds with some fused pyrimidine systems, which are expected to possess notable chemical and biological activities.

DISCUSSION

The synthesis of 5-acetyl-6-methyl-2-[(*E*)-2-(2-aryl)vinyl]pyrimidine-4-thiol **3a–d** has been achieved by the dehydrative cyclization of arylacryloyl isothiocyanate **1** with 4-aminopent-3-en-2-one (enaminone) **2** as reported[17,18] (Scheme 1).

In general, the ^{1}H NMR spectra of **3** exhibited two doublets at δ 6.89 and 7.79 ppm for the two trans ethylenic protons (α-H) and (β-H) with J = 15.9–16.0 Hz in addition to the signal of the thiol group at δ 14.02 ppm, respectively. The compounds **3c**,**d** known as in literature.[17,18] The irradiation of the doublet of doublet signal of thiophene protons for **3b** at δ 7.18 changes the signals at δ 7.54, 7.75 ppm to singlet signals with disappearance of the signal at 7.18 ppm and the irradiation of the signal at δ 7.54 ppm led to the disappearance of this signal with appearance of the two doublets at δ 7.28 and 7.75 ppm irradiation of the signal at δ 7.75 ppm changes the signals at δ 7.18, 7.54 ppm to two doublets with the disappearance of the signal at 7.75, and this in-turn confirmed the structure.

The alkylation of 5-acetyl-6-methyl-2-[(*E*)-2-(2-thienyl)vinyl] pyrimidine-4-thiol **3b** with methyl iodide in ethanolic ethoxide gave 5-acetyl-6-methyl-4-(methylthio)-2-[(*E*)-2-(2-thienyl)vinyl]pyrimidine **6a**, while, alkylation (cyanoethylation) with acrylonitrile in pyridine



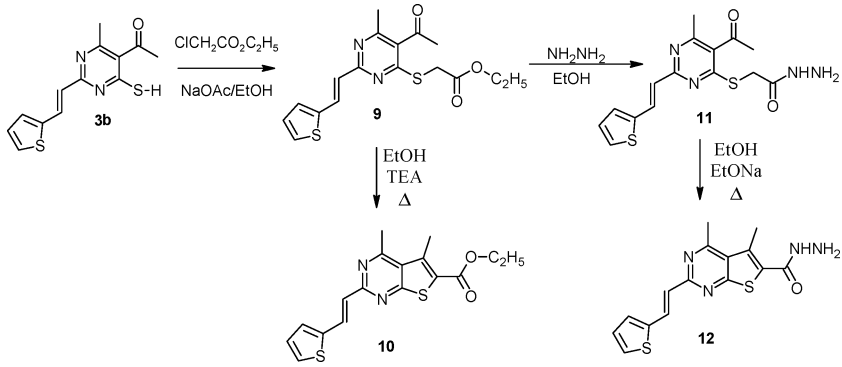
SCHEME 1

afforded Michael type adduct 5-acetyl-4-(2-propinonitrylthio)-6-methyl-2-[(*E*)-2-(2-thienyl)vinyl]pyrimidine **6b** and not the isomeric products **4** and **5**. An evidence in confirmation the structures of compounds **6a**,**b** is their conversion into pyrazolo[3,4-*d*]pyrimidine derivative **7** by reaction with hydrazine hydrate in *n*-butanol.[16,19] The IR spectra of **7** showed the disappearance of the carbonyl group of acetyl pyrimidine at 1688 cm^{-1} and also the disappearance of the (CN) group at 2370 cm^{-1}, and ^1H, ^{13}C NMR spectra indicated the disappearance of the two triplets of CH_2CH_2 of the compound **6b** at δ 3.01, 3.55 ppm and δ 17.6, 24.8 ppm, and also the disappearance of the signal of S-CH_3 methyl group of **6a** at δ 3.01 ppm, respectively (Scheme 1).

^1H NMR of **7** showed a signal at δ 2.46, 2.59 ppm for $2CH_3$ groups and presence of broad signal at δ 6.38 ppm characterized for NH group of pyrazzole ring.

Bromination of 5-acetyl-4-(2-propinonitrylthio)-6-methyl-2-[(*E*)-2-(2-thienyl)vinyl]pyrimidine **6b** in carbon tetrachloride gave 5-acetyl-2-[1,2-dibromo-2-(2-thienyl)ethyl]-4-(2-propinonitrylthio)-6-methylpyrimidine **8** (Scheme 1). The structure of **8** was confirmed from its ^1H

NMR spectra, which showed the presence of two doublet protons at δ 4.92 and 5.45 ppm and the disappearance of the olefinic protons at δ 6.89 and 7.89 ppm.



SCHEME 2

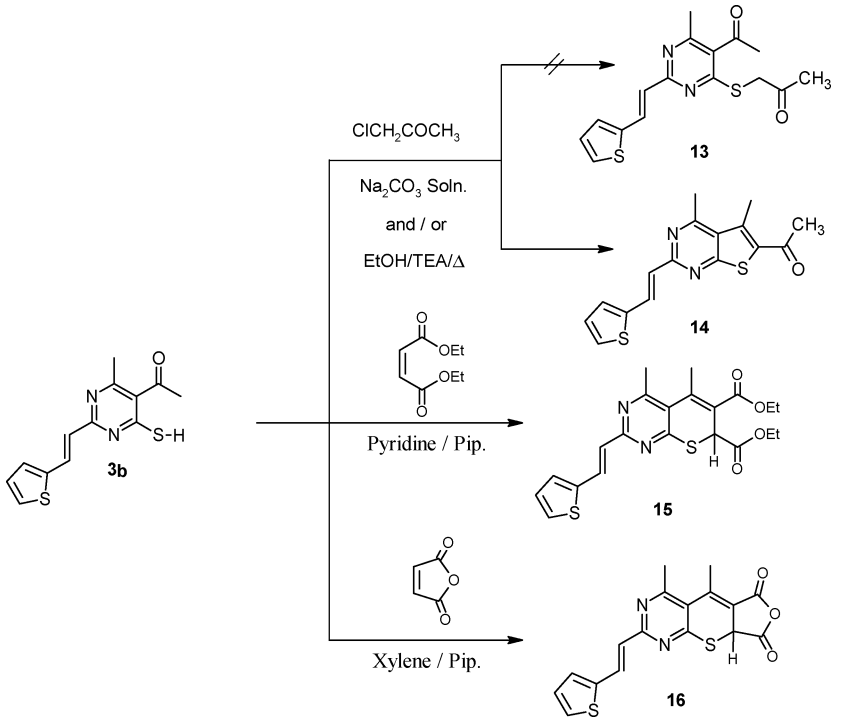
Alkylation of **3b** with ethyl chloroacetate under basic condition gave the carboethoxymethylated derivatives **9** (Scheme 2). The absorption bands in their IR spectra showed bands between 1737–1744 and 1685–1690 cm^{-1} indicating the presence of the ester carbonyl and C=O for acetyl at position-5, respectively. The ^1H NMR spectrum of **9** showed the presence of the ethyl group at δ 1.19 (t) and 4.12 (q) ppm. The ^{13}C NMR spectrum of **9** showed signals at δ 14.1, 22.6, 31.2, 32.3, and 60.9 ppm for the CH_3 (ester), CH_3 (acetyl) CH_3 in 6-position, CH_2S and CH_2O groups. The irradiation of the signal at δ 1.19 ppm changed the quartet at 4.12 ppm to singlet and the irradiation at δ 7.16 ppm changed the signals at 7.46 and 7.68 ppm to a singlet confirming the structure of **9**.

Heating compound **9** in ethanol and triethylamine gave the cyclized ethyl 4,5-dimethyl-2-[(*E*)-2-(2-thienyl)vinyl]thieno[2,3-*d*]pyrimidine-6-carboxylate **10**.

The IR of compound **10** shows the disappearance of the band at 1690 cm^{-1} characteristic to the C=O of the acetyl group in compound **9**, while the ^1H NMR spectrum of **10** showed the disappearance of the signal at δ 4.08 ppm which is characteristic to the CH_2S group. Reaction of **9** with hydrazine hydrate in boiling ethanol afforded the hydrazide **11**, which on heating under basic condition gave 4,5-dimethyl-2-[(*E*)-2-(2-thienyl)-vinyl]thieno[2,3-*d*]pyrimidine-6-carbohydrazide **12**. The structures of compounds **11** and **12** were confirmed by their IR and ^1H, ^{13}C NMR spectra.

Alkylation of **3b** with chloroacetone in sodium carbonate solution gave the thieno[2,3-*d*]pyrimidine **14** not the expected S-alkyl product

13, compound **14** was proved by refluxing **3b** with chloroacetone in presence of absolute ethanol and few drops of triethylamine, where, the same product was obtained (Scheme 3).



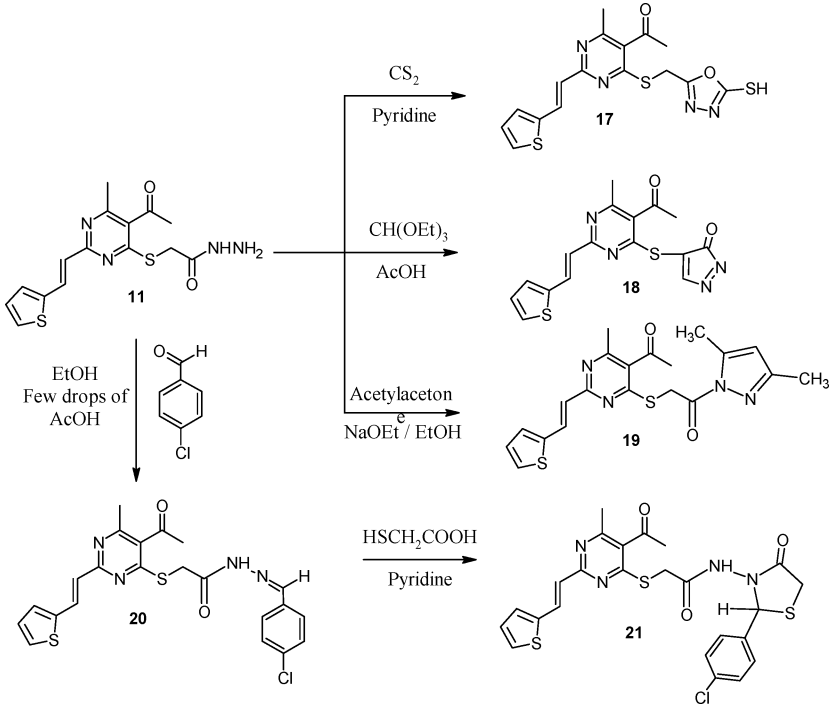
SCHEME 3

The ^{1}H NMR spectrum of **14** showed the presence of three methyl groups at δ 2.61, 2.86, and 2.91 ppm, and absence of SCH_2 group, respectively. The ^{13}C NMR spectrum of **14** showed signals at δ 16.3, 24.6, and 30.8 ppm for the $3CH_3$ groups.

Treatment of **3b** with diethyl maleate in pyridine and few drops of piperidine gave a product assigned the structure of diethyl 4,5-dimethyl-2-[(*E*)-2-(2-thienyl)vinyl]-7*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylate **15**. This cyclization has been proved by ^{1}H NMR spectrum, which exhibited two triplets at δ 1.20, 1.29 ppm and two quartets at 4.19, 4.23 ppm for two unsymmetrical ethyl groups and methinyl proton at δ 3.80 ppm. The IR spectrum gave a two carbonyl bands at 1735 and 1686 cm^{-1}. 4,5-Dimethyl-2-[(*E*)-2-(2-thienyl)vinyl]-6*H*-furo[3′,4′,5,6]thiopyrano[2,3-*d*]pyrimidine-6-(8a*H*)dione **16** was obtained by cycloaddition of compound **3b** with maleic anhydride in

refluxing xylene and few drops of piperidine. The ^{1}H NMR of **16** showed the presence of a singlet at δ 3.80 ppm for methinyl proton and two singlet signal at δ 2.56, 2.68 ppm for $2CH_3$ groups. The IR spectrum gave a broad band between 1810–1702 cm^{-1} characteristics for two anhydride carbonyl groups.

2-({5-Acetyl-6-methyl-2-[(*E*)-2-(2-thienyl)vinyl]pyrimidin-4-yl}thio)-acetylhydrazide **11** was reacted with carbon disulfide in pyridine to afford the corresponding 5-acetyl-4-{[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]thio}-6-methyl-2-[(*E*)-2-(2-thienyl)vinyl]pyrimidine **17**.[19] The IR spectrum of **17** showed bands at 2370, 1685 cm^{-1} for SH and CO stretching frequencies, and the ^{1}H NMR spectrum showed a signal at δ 2.45, 2.88, and 12.52 ppm for the CH_3, CH_3CO, and SH groups (Scheme 4).



SCHEME 4

Treatment of carbohydrazide **11** with triethyl orthoformate in acetic acid gave 5-acetyl-6-methyl-4[(3-oxo-pyrazol-4-yl)thio]-2-[(*E*)-2-(2-thienyl)vinyl]-pyrimidine **18**. The ^{1}H NMR spectrum of **18** showed signals at δ 2.48, 2.93, and 6.48 ppm for CH_3, CH_3CO, and pyrazole protons. ^{13}C NMR spectrum showed two carbon sp^3 and 14 lines sp^2

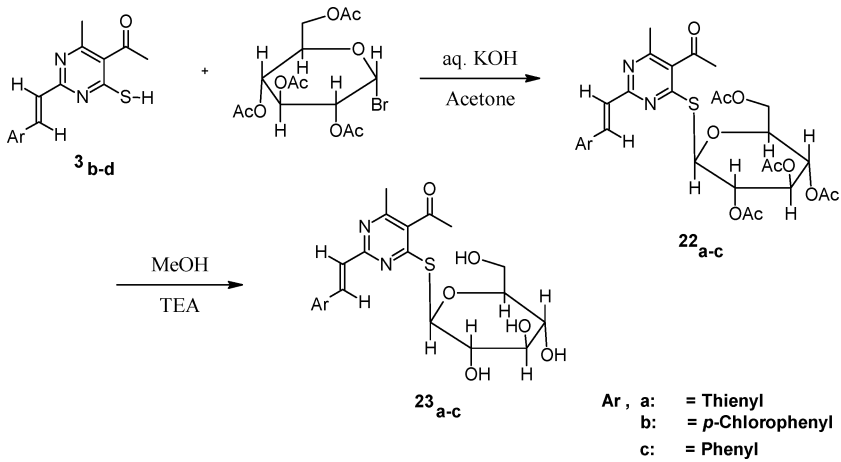
characterized all carbon atoms in the compound and two carbonyl groups. The IR spectrum showed the bands at 1711 and 1653 cm^{-1} indicated the presence of two carbonyl groups, respectively. Reaction of **11** with acetylacetone in ethanol and sodium ethoxide gave the corresponding 5-acetyl-(4-{[2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl]thio}-6-methyl-2-[(*E*)-2-(2-thienyl)vinyl]pyrimidine **19**[19] (Scheme 4). The absorption bands in its IR spectrum showed a broad band at 1684 cm^{-1} for 2C=O groups, with the disappearance of NH and NH_2 bands, while the ^{1}H NMR spectrum gave signals at δ 2.30, 2.61, 281, 3.12, and 3.91 ppm, which characterized for $4CH_3$ and CH_2S groups, respectively. Its ^{13}C NMR spectrum showed signals at δ 21.5, 32.1, 24.3, 30.2, and 51.5 ppm for four CH_3 and CH_2S groups.

When carbohydrazide **11** was reacted with *p*-chlorobenzaldehyde in ethanol in presence of few drops of acetic acid gave 2({5-acetyl-6-methyl-2-[(*E*)-2-(2-thienyl)-vinyl]pyrimidin-4-yl}thio-*N*′-[(1*Z*)-(4-chlorophenyl)-methylene]acetohydrazide **20**[19,20] (Scheme 4).

The absorption bands in its IR spectrum showed bands at 1719 and 1653 cm^{-1} indicating the presence of ketone C=O and amide C=O. The ^{1}H NMR spectrum of **22** showed the presence of signals at 2.71, 2.89, and 4.25 for 2 CH_3 and CH_2S beside two doublet signals at δ 7.32, 7.79 ppm with ($J = 9.8$ Hz) characteristic to *p*-chlorophenyl and at δ 8.79 and 12.01 ppm for CH=N and NH groups, respectively.

Heating compound **20** with thioglycolic acid in boiling pyridine gave 2({5-acetyl-6-methyl-2-[(*E*)-2-(2-thieyl)vinyl]pyrimidin-4-yl}thio)-*N*-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]acetamide **21**. The ^{1}H NMR spectrum of **21** showed the signals at δ 2.68, 2.86, 4.21, 4.32, 5.98 ppm characterized for $2CH_3$, CH_2S, SCHAr, $COCH_2S$ of (thiazolidine ring) and presence of two doublet for *p*-chlorophenyl at δ 7.35, 7.80 ppm with $J = 9.70$ Hz, with presence of singlet signal at δ 10.21 ppm for NH group, respectively (Scheme 4).

Reaction of **3b–d** with 2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranosylbromide in the presence of aqueous potassium hydroxide gave 5-acetyl-6-methyl-2[(*E*)-2-(2-aryl)vinyl]-4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-*D*-glucopyranosylthio)pyrimidine **22a–c**.[21,22] The structure of compounds **22a–c** was confirmed on the basis of their elemental analysis and spectral data, their IR spectra showed a broad band at 1765–1745 cm^{-1} for the acetoxy carbonyl groups in addition to absorption band at 1696 cm^{-1} due to the carbonyl of pyrimidine. Also, the ^{1}H NMR spectrum of **22a** showed the presence of singlet signals at δ 1.76, 1.96, 2.00, 2.02 ppm characteristic to the presence of four OAc, in addition to two methyl groups at δ 2.49, 2.58 ppm. In **24b** the IR spectrum showed a broad band at 1748 and 1698 cm^{-1} characteristic to the acetoxy carbonyl and the carbonyl in pyrimidine ring. Its ^{1}H NMR showed



SCHEME 5

four OAc in addition to two methyl groups in pyrimidine ring and two doublet for *p*-chlorophenyl at δ 7.51, 7.82 ppm with coupling constant ($J = 9.8$ Hz). The IR spectrum of **22c** showed bands at 1755–1728 cm^{-1} for acetoxy carbonyl in addition to a band at 1660 cm^{-1} for a carbonyl in pyrimidine ring. It's ^1H NMR showed a singlet signals at δ 1.84, 2.03, 2.04, 2.07, 2.47, and 2.57 ppm characteristic to four (OAc) and two (CH_3) groups, respectively.

In compound **22c**, the irradiation of signal at δ 3.99 ppm change the signals at δ 4.15 ppm to doublet of doublet and at δ 5.13 ppm to doublet, and irradiation the signal at δ 5.13 ppm change the signals at δ 3.99 and 5.41 ppm to doublet. Irradiation of the signal at δ 5.77 ppm changed the signal at δ 6.04 ppm into a singlet signal, also the irradiation of the signal at δ 5.41 ppm changed the signals at δ 5.13, 5.27 ppm into a doublet. The irradiation of signal at δ 6.04 ppm change the signal at δ 5.27 ppm into a doublet and disappears the signal at d 6.04 ppm, this assigned the position of sugar protons. The irradiation of signal at δ 8.01 ppm change the signal at δ 7.17 ppm to a singlet signal with disappearance of the signal at δ 7.17 ppm, which assigned the structure of trans ethylenic protons.^{13}C NMR of **22c** shows signals at δ 20.5, 20.6, 20.7, 22.7, 29.7, 31.6, 62.2, 68.4, 69.1, 74.1, 76.5, and 80.3 ppm characteristics to the sugar moiety and two methyl groups in pyrimidine ring. All sugar protons are irradiated by ^1H NMR spectrometer LA 400 MHz and illustrated in the experimental section. Hydrolysis of compounds **22a–c** in methanol in presence of triethylamine afforded the product 5-acetyl-6-methyl-2-[(*E*)-2-(aryl)vinyl]-4-(2′,3′,4′,6′-tetrahydroxy-β-*D*-glucopyranosylthiopyrimidine **23a–c**. The ^1H NMR of **23a–c** in ($DMSO/D_2O$) were carried out to prove the hydrolysis and are shown in the experimental section.

TABLE I Antimicrobial Activity of Compounds 3b, 10, 15, 17, and 23a

Comp. No.	*S. aureus*	*S. lutea*	*B. subtilis*	*P. aeruginosa*	*K. peneumonie*	*E. coli*	*C. albicans*
3b	—	25	20	20	15	16	—
10	10	25	18	20	15	17	—
15	12	20	15	15	10	18	—
17	10	25	20	20	15	15	20
23a	—	—	—	—	—	—	—
Penicillin	15	17	20	13	14	15	—
Nystatin	—	—	—	—	—	—	15

Inhibition zones = mm; minimum inhibitory concentration = μg/ml.

The IR spectrum of **23a–c** showed the presence of a very broad band at 3400 cm^{-1} characterized for the hydroxyl groups of sugar moiety in addition to the carbonyl group of pyrimidine ring at 1689 cm^{-1}, respectively.

The results of the antimicrobial activity of compounds **3b**, **10,** and **15** showed interesting degrees of antibacterial activity. Penicillin was used as a reference to evaluate the potency of the tested compounds. Compounds **3b**, **10**, and **15** showed higher antibacterial activity than the standard drug (penicillin). Compound **23a** did not show any activity against the tested microorganisms, while, compound **17** showed higher activity against *C. albicans* than the standard drug (Nystatin), and was higher activity against Gram +ve, and Gram −ve bacteria. The results of biological activities encourage further work on such a ring system (Table 1).

EXPERIMENTAL

Melting points were determined with a melt temperature apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer model 1600 FTIR spectrometer as KBr discs. The ^{1}H and ^{13}C NMR spectra were determined with a JEOL-JNM-LA 400 and 100 MHz spectrometer. The chemical shifts are expressed on the δ (ppm) scale using TMS as an internal standard. Elemental analyses were determined on a Perkin-Elmer 240 (microanalysis).

5-Acetyl-6-methyl-2-[(*E*)-2-(2-aryl)vinyl]pyrimidine-4-thiol (3a–d)—General Procedure

A mixture of arylacryloyl isothiocyanate **1**[23] (10 mmol) and 4-aminopent-3-en-2-one (enaminone) **2** (1.98 ml, 20 mmol) in 20 ml dry

acetone was stirred for 3 h, then, an equivalent amount of sodium hydroxide solution (0.4 g/10.0 ml) was added. After the reaction was completed, neutralized with hydrochloric acid (6 ml, 30% soln.) to complete precipitation, the solid thus separated was collected by filtration, washed several times with water, dried, and recrystallized from ethanol.

5-Acetyl-6-methyl-2-[(E)-2-(2-naphthyl)vinyl]pyrimidine-4-thiol (3a)

Yellow powder (yield: 45%), m.p. 230–232°C. IR (KBr): 2371 (SH), 1690 (C=O), 1634 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 2.22$ (s, 3H, CH_3), 2.55 (s, 3H, CH_3CO), 7.30 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.58–8.19 (m, 7H, Ar-H), 8.12 (d, 1H, $J = 16.0$ Hz, $C{=}CH_\alpha$) and 13.2 (s, 1H, SH).^{13}C NMR (DMSO-d_6): $\delta = 21.6$, 30.2 (2 CH_3), 118.8, 123.1, 126.8, 127.4, 127.6, 128.4, 128.7, 130.0, 131.9, 132.8, 133.6, 135.7, 141.2, 154.9, (C=C and Ar-C), 156.8, 178.2, 202.1 (2 CN and C=S). Anal. Calcd. for $C_{19}H_{16}N_2OS$ (320.4): C, 71.22; H, 5.03; N, 8.74. Found: C, 71.03; H, 5.24; N, 8.81.

5-Acetyl-6-methyl-2-[(E)-2-(2-thienyl)vinyl]pyrimidine-4-thiol (3b)

Yellow powder (yield: 44%), m.p. 200–202°C. IR (KBr): 2369 (SH), 1686 (C=O) and 1624 (CN) cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 2.17$ (s, 3H, CH_3), 2.53 (s, 3H, CH_3CO), 6.91 (s, 1H, J =15.9 Hz, $HC{=}CH_\alpha$), 7.18 (dd, 1H, $J = 3.50$ Hz), 7.54 (d, 1H, $J = 3.5$ Hz), 7.75 (d, 1H, $J = 5.07$ Hz), 8.15 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$) and 11.36 (s, 1H, SH). The irradiation of the doublet of doublet signal of thiophene protons for **3b** at δ 7.18 changes the signals at δ 7.54, 7.75 ppm to a singlet signals with disappearance of the signal at 7.18 ppm and the irradiation of the signal at δ 7.54 ppm led to the disappearance of this signal with appearance of the two doublets at δ 7.28 and 7.75 ppm irradiation of the signal at δ 7.75 ppm changes the signals at δ 7.18, 7.54 ppm to two doublets with the disappearance of the signal at 7.75 as illustrated in the spectrum, and this intern confirmed the structure.^{13}C NMR (DMSO-d_6): $\delta = 21.5$ (CH_3), 30.3 (CH_3CO), 117.0, 128.6, 129.8, 132.3, 134.2, 135.4, 139.6, 154.7 (Ar-C), 165.4 (CN), 181.7 (C=O) and 202.1 (C=S). Anal. Calcd. for $C_{13}H_{12}N_2OS_2$ (276.3): C, 56.49; H, 4.38; N, 10.14. Found: C, 56.61; H, 4.37; N, 10.25.

5-Acetyl-6-methyl-4-(methylthio)-2-[(E)-2-(2-thienyl)vinyl] pyrimidine (6a)

A solution of compound **3b** (2.76 g, 10 mmol) and methyl iodide (1.4 g, 10 mmol) in ethanolic sodium ethoxide (0.23 g/20 ml ethanol), the reaction mixture was refluxed for 1 h, then allowed to cool and poured

into ice water. The solid product obtained after acidification with hydrochloric acid (6 ml, 30% soln.) was filtered off, washed with water, dried, recrystallization from ethanol to afford a colorless powder (yield: 80%) m.p. 90–92°C. ^{1}H NMR (DMSO-d_6): $\delta = 2.41$ (s, 3H, CH_3), 2.58 (s, 3H, CH_3CO), 3.01 (s, 3H, SCH_3), 6.91 (d, 1H, $J = 16.0$ Hz, HC=CH_α), 7.17 (dd, 1H, $J = 3.52$ Hz, thiophene-H), 7.50 (d, 1H, $J = 3.50$ Hz, thiophene-H), 7.68 (d, 1H, $J = 5.10$ Hz, thiophene-H), 8.14 (d, 1H, $J = 16.0$ Hz, H_βC=CH).^{13}C NMR (DMSO-d_6): $\delta = 22.2$, 25.3, 31.2 (3 CH_3), 124.2, 128.1, 129.0, 130.2, 132.1, 134.2, 140.8, 161.2, 162.0, 162.8, 179.8 (Ar-C, 2 C=N and C=O). Anal. Calcd. for $C_{14}H_{14}N_2OS_2$ (290.4): C, 57.90; H, 4.86; N, 9.65. Found: C, 58.01; H, 4.87; N, 9.75.

5-Acetyl-4-(2-propinonitrylthio)-6-methyl-2-[(E)-2-(2-thienyl)vinyl]pyrimidine (6b)

To a solution of compound **3c** (2.76 g, 10 mmol) in (20 ml) pyridine, acrylonitrile (0.53, 10 mmol) was added and the reaction mixture was stirred at room temperature for 2 h, then poured into ice water. The solid product obtained after acidification with hydrochloric acid (6 ml, 30% soln.), filtered off, washed with water, dried, and recrystallized from benzene to afford an orange powder (yield: 33%), m.p. 108–110°C. IR (KBr): 2370 (C≡N), 1687 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 2.41$ (s, 3H, CH_3), 2.59 (s, 3H, CH_3CO), 3.01 (t, 2H, $J = 6.60$ Hz, CH_2), 3.55 (t, 2H, $J = 6.60$ Hz, CH_2), 6.90 (d, 1H, $J = 16.0$ Hz, HC=CH_α), 7.17 (dd, 1H, $J = 3.51$ Hz, thiophene-H), 7.51 (d, 1H, $J = 3.60$ Hz, thiophene-H), 7.68 (d, 1H, $J = 5.08$ Hz, thiophene-H), 8.14 (d, 1H, $J = 16.0$ Hz, H_βC=CH). ^{13}C NMR (DMSO-d_6): $\delta = 17.6$, 22.3, 24.8, 31.2 (2 CH_3, 2 CH_2), 119.2 (C≡N), 125.0, 128.4, 128.5, 129.2, 130.4, 131.8, 140.2, 161.3, 161.8, 163.2, 202.0 (Ar-C, 2 C=N and C=O). Anal. Calcd. for $C_{16}H_{15}N_3OS_2$ (329.4): C, 58.33; H, 4.59; N, 12.76. Found: C, 58.50; H, 4.29; N, 12.82.

3,4-Dimethyl-6-[(E)-2-(2-thienyl)vinyl]-1H-pyrazolo[3,4-d]pyrimidine (7)

A mixture of appropriate S-alkylated derivatives **6a,b** (10 mmol) and hydrazine hydrate 98% (0.2 ml, 40 mmol) in n-butanol (10 ml) was heated under reflux for 3 h. The precipitate obtained upon cooling was collected, dried and recrystallized from ethanol to afford a pale yellow powder (yield: 56%) m.p. 228–229°C. ^{1}H NMR (DMSO-d_6): $\delta = 2.46$ (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 6.38 (br, 1H, NH), 6.91 (d, 1H, $J = 16.0$ Hz, HC=CH_α), 7.17 (dd, 1H, $J = 3.52$ Hz, thiophene-H), 7.50 (d, 1H, $J = 3.50$ Hz, thiophene-H), 7.68 (d, 1H, $J = 5.10$ Hz, thiophene-H), 8.14 (d, 1H, $J = 16.0$ Hz, H_βC=CH). ^{13}C NMR (DMSO-d_6): $\delta = 20.8$, 31.0 (2 CH_3), 125.0, 128.4, 128.5, 129.2, 130.4, 131.8, 140.1, 161.3, 161.8, 163.1,

166.8 (Ar-C and 3 C=N). Anal. Calcd. for $C_{13}H_{12}N_4S$ (256.3): C, 60.91; H, 4.72; N, 21.86. Found: C, 61.03; H, 4.80; N, 21.7.

5-Acetyl-2-[1,2-dibromo-2-(2-thienyl)ethyl]-4-(2-propinonitrylthio)-6-methylpyrimidine (8)

To a stirred suspension of compound **6b** (3.29 g, 10 mmol) in (20 ml) carbon tetrachloride, bromine (1.6 g, 10 mmol) in (10 ml) carbon tetrachloride was added dropwise at room temperature during 30 min. After complete addition, the stirring was continued for 3 h, the solid thus separated was collected, dried, and recrystallized from ethanol to give a pale yellow powder (yield: 60%), m.p. 120–123°C (dec.). ^{1}H NMR (DMSO-d_6): $\delta = 2.41$ (s, 3H, CH_3), 2.58 (s, 3H, CH_3CO), 3.01 (t, 2H, $J =$ 6.60 Hz, CH_2), 3.55 (t, 2H, $J = 6.60$ Hz, CH_2), 4.91 (d, 1H, $J = 12.6$ Hz, CHBr), 5.45 (d, 1H, $J = 12.7$ Hz, CHBr), 7.17 (dd, 1H, $J = 3.51$ Hz, thiophene-H), 7.51 (d, 1H, $J = 3.50$ Hz, thiophene-H), 7.68 (d, 1H, $J =$ 5.10 Hz, thiophene-H).^{13}C NMR (DMSO-d_6): $\delta = 17.6$, 22.3, 24.8, 31.2, 36.2, 38.8 (2 CH_3, 2 CH_2, 2 CHBr), 119.2 (C≡N), 125.0, 128.5, 129.2, 131.8, 140.2, 161.3, 161.8, 162.1, 202.0 (Ar-C, 2 C=N and C=S). Anal. Calcd. for $C_{16}H_{15}Br_2N_3OS_2$ (489.2): C, 39.28; H, 3.09; N, 8.59. Found: C, 39.40; H, 3.12; N, 8.54.

Ethyl (5-acetyl-6-methyl-2-[(E)-2-(aryl)vinyl]pyrimidin-4-ylthio)acetate (9)

A mixture of thiol derivative **3b** (10 mmol), sodium acetate (1.00 g, 12 mmol) and ethyl chloroacetate (1.22 g, 10 mmol) in ethanol (20 ml) was heated under reflux for 2 h, then allowed to cool, poured into water. The precipitate formed was collected, washed with water, dried, and recrystallized from petroleum ether 60–80. A pale yellow powder (yield: 36%) m.p. 90–92°C. IR (KBr): 1744, 1690 (2 C=O) and 1623 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): $\delta = 1.19$ (t, 3H, $J = 7.03$ Hz, CH_3), 2.45 (s, 3H, CH_3), 2.60 (s, 3H, CH_3CO), 4.08 (s, 2H, CH_2S), 4.12 (q, 2H, $J =$ 7.03 Hz, CH_2), 6.84 (d, 1H, $J = 16.0$ Hz, $H_\beta C$=CH), 7.16 (dd, 1H, $J =$ 3.50 Hz, thiophene-H), 7.46 (d, 1H, $J = 3.50$ Hz, thiophene-H), 7.68 (d, 1H, $J = 5.07$ Hz, thiophene-H), 8.08 (d, 1H, $J = 16.0$ Hz, HC=CH_α). ^{13}C NMR (DMSO-d_6): $\delta = 14.1$, 22.6, 31.2, 32.3, 60.9 (3 CH_3, CH_2S and OCH_2), 125.0, 128.3, 128.5, 128.6, 131.9, 140.2, 161.6, 161.8, 164.3, 168.6, 201.6 (Ar-C, 2 C=N and 2C=O). Anal. Calcd. for $C_{17}H_{18}N_2O_3S_2$ (362.5): C, 56.33; H, 5.01; N, 7.73. Found: C, 56.52; H, 4.95; N, 7.82.

Ethyl 4,5-dimethyl-2-[(E)-2-(2-thienyl)vinyl]thieno[2,3-d]pyrimidine-6-carboxylate (10)

To a solution of compound **9** (3.62 g, 10 mmol) in ethanol, a few drops of triethylamine was added and then heated under reflux for 1 h, cooled,

and poured into ice water. The solid product formed was filtered off, dried, and recrystallized from ethanol to afford a yellow crystals (yield: 50%) m.p. 296–297°C. IR (KBr): 1703 (C=O), 1621 (C=N) and 1180 (C–O) cm^{-1}.^{1}H NMR (DMSO-d_6): $\delta = 1.18$ (t, 3H, $J = 7.03$ Hz, CH_3), 2.91 (s, 3H, CH_3), 2.94 (s, 3H, CH_3), 4.19 (q, 2H, $J = 7.03$ Hz, CH_2), 6.84 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.17 (dd, 1H, $J = 3.50$ Hz, thiophene-H), 7.46 (d, 1H, $J = 3.5$ Hz, thiophene-H), 7.68 (d, 1H, $J = 3.51$ Hz, thiophene-H), 8.09 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$).^{13}C NMR (DMSO-d_6): $\delta = 14.8$, 22.7, 23.8, 52.9 (3 CH_3 and OCH_2), 125.4, 125.9, 127.9, 128.1, 128.3, 130.1, 131.0, 139.4, 140.5, 159.9, 163.7, 164.7, 167.1 (Ar-C, 2 C=N and C=O). Anal. Calcd. for $C_{17}H_{16}N_2O_2S_2$ (344.4): C, 59.28; H, 4.68; N, 8.13. Found: C, 59.26; H, 4.86; N, 8.50.

2-({5-Acetyl-6-methyl-2-[(E)-2-(2-thienyl)vinyl]pyrimidin-4-yl}thio)acetohydrazide (11)

To a solution of compound **9** (3.62 g, 10 mmol) hydrazine hydrate 98% (1.3 ml/40 mmol) was added and the reaction mixture was refluxed for 1 h, then allowed to cool. The solid product was filtered off and recrystallized from ethanol to give a colorless crystals (yield: 42%) m.p. 210–212°C. IR (KBr): 3400 (NH), 1710, 1695 (2 C=O), 1621 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6): $\delta = 2.41$ (s, 3H, CH_3), 2.91 (s, 3H, CH_3CO), 3.42 (br, 2H, NH_2), 3.98 (s, 2H, CH_2S), 6.83 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.17 (dd, 1H, $J = 3.50$ Hz, thiophene-H), 7.46 (d, 1H, $J = 3.51$ Hz, thiophene-H), 7.68 (d, 1H, $J = 5.08$ Hz, thiophene-H), 8.08 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$), 9.08 (br, 1H, NH).^{13}C NMR (DMSO-d_6): $\delta = 15.1$, 23.8, 52.7 ($2CH_3$ and CH_2S), 125.4, 125.9, 127.9, 128.1, 128.4, 130.1, 131.0, 139.4, 140.5, 163.7, 164.7, 167.2 (Ar-C, 2 C=N and 2 C=O). Anal. Calcd. for $C_{15}H_{16}N_4O_2S_2$ (348.4): C, 51.70; H, 4.63; N, 16.08. Found: C, 52.61; H, 4.58; N, 16.12.

4,5-Dimethyl-2-[(E)-2-(2-thienyl)vinyl]thieno[2,3-d]pyrimidine-6-carbohydrazide (12)

To a solution of compound **11** (3.48 g, 10 mmol) in ethanol (20 ml), sodium ethoxide (0.23 g/10 ml ethanol) was added and the solution was heated under reflux for 1 h, cooled, poured into water, neutralized with hydrochloric acid (6 ml, 30% soln.). The solid product formed was collected by filtration, washed with water and recrystallized from ethanol affording a colorless powder (yield: 63%) m.p. 240–241°C. IR (KBr): 3420 (NH), 1676 (C=O) cm^{-1}.^{1}H NMR (DMSO-d_6): $\delta = 2.90$ (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 3.76 (br, 2H, NH_2), 6.83 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.17 (dd, 1H, $J = 3.50$ Hz, thiophene-H), 7.46 (d, 1H, $J = 3.50$ Hz, thiophene-H), 7.68 (d, 1H, $J = 5.09$ Hz, thiophene-H), 8.09 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$), 12.1 (br, 1H, NH). Anal. Calcd. for

$C_{15}H_{14}N_4OS_2$ (330.4): C, 54.52; H, 4.27; N, 16.96. Found: C, 54.59; H, 4.32; N, 16.86.

6-Acetyl-4,5-dimethyl-2-[(E)-2-(2-thienyl)vinyl]thieno[2,3-d]pyramidine (14)

Method A. A mixture of compound **3c** (2.76 g, 10 mmol) in aqueous sodium carbonate (10 ml, 10% soln.) and chloroacetone (1.10 g, 12 mmol) was stirred for 3 h at room temperature and neutralized with hydrochloric acid (6 ml, 30% soln.). The solid product formed was collected by filtration, washed with water and recrystallized from ethanol affording a pale yellow crystals (yield: 45%) m.p. 253–255°C.

Method B. A mixture of compound **3c** (2.76 g, 10 mmol) and chloroacetone (1.10 g, 12 mmol) in ethanol (20 ml) and few drops of triethylamine was allowed to reflux for 1 h after that, the reaction mixture was cooled. The solid precipitated filtered off, washed with water and recrystallized from ethanol to afford pale yellow crystals (yield: 35%) m.p. 254–256°C.

IR (KBr): 1671 (C=O), 1622 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6): $\delta =$ 2.61 (s, 3H, CH_3), 2.86 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 6.92 (d, 1H, $J =$ 16.0 Hz, $H_\beta C{=}CH$), 7.12 (dd, 1H, $J = 3.50$ Hz, thiophene-H), 7.46 (d, 1H, $J = 3.50$ Hz, thiophene-H), 7.61 (d, 1H, $J = 5.08$ Hz, thiophene-H), 8.10 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$).^{13}C NMR (DMSO-d_6): $\delta = 16.3$, 24.6, 30.8 ($3CH_3$), 125.7, 128.0, 128.3, 128.4, 129.7, 131.2, 134.5, 137.5, 140.6, 160.2, 165.3, 167.3, 192.6 (Ar-C, 2 C=N and C=O). Anal. Calcd. for $C_{16}H_{14}N_2OS_2$ (314.4): C, 61.12; H, 4.49; N, 8.91. Found: C, 61.18; H, 4.38; N, 9.01.

Diethyl 4,5-dimethyl-2-[(E)-2-(2-thienyl)vinyl]-7H-thiopyrano[2,3-d]pyramid-ine-6,7-dicarboxylate (15)

A mixture of compound **3b** (2.76, 10 mmol), diethyl maleate (1.70 g, 10 mmol) in pyridine (20 ml) and few drops of piperidine was reflux for 6 h, poured into ice water, then the pH was adjusted to 7 with hydrochloric acid. The solid separated was filtered off, washed with water, and recrystallized from benzene affording pale yellow crystals (yield: 45%) m.p. 240–241°C. IR (KBr): 1735 (C=O) ester, 1686 (C=O) conjugated ester, 1623 (C=N), 1155 (C–O) cm^{-1}.^{1}H NMR (DMSO-d_6): $\delta = 1.20$ (t, 3H, $J = 7.03$ Hz, CH_3), 1.29 (t, 3H, $J = 7.03$ Hz, CH_3), 2.46 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.80 (s, 1H, methinyl-H), 4.19 (q, 2H, $J = 7.03$ Hz, CH_2), 4.23 (q, 2H, $J = 7.03$ Hz, OCH_2), 6.92 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.12 (dd, 1H, $J = 3.50$ Hz, thiophene-H), 7.46 (d, 1H, $J =$ 3.50 Hz, thiophene-H), 7.61 (d, 1H, $J = 5.08$ Hz, thiophene-H), 8.10 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$). Anal. Calcd. for $C_{21}H_{22}N_2O_4S_2$ (430.5): C, 58.58; H, 5.15; N, 6.51. Found: C, 58.50; H, 5.18; N, 6.61.

4,5-Dimethyl-2-[(E)-2-(2-thienyl)vinyl]-6H-furo [3′,4′,5,6]thiopyrano-[2,3-d]pyrimidine-6,8-(8$_\alpha$H)-dione (16)

A mixture of compound **3c** (2.76 g, 10 mmol), maleic anhydride (0.9 g, 10 mmol) and few drops of piperidine in (20 ml) xylene was reflux for 16 h, the solid product that obtained after cooling was collected by filtration, dried and recrystallized from benzene to afford a pale yellow crystals (yield: 42%) m.p. 260–262°C. IR (KBr): 1810–1702 (br), (2C=O) anhydride, 1602 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6): $\delta = 2.56$ (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.81(s, 1H, methinyl-H), 6.92 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.12 (dd, 1H, $J = 3.50$ Hz, thiophene-H), 7.46 (d, 1H, $J =$ 3.50 Hz, thiophene-H), 7.61 (d, 1H, J =5.08 Hz, thiophene-H), 8.14 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$). Anal. Calcd. for $C_{17}H_{12}N_2O_3S_2$ (356.4): C, 57.29; H, 3.39; N, 7.86. Found: C, 57.38; H, 3.48; N, 7.92.

5-Acetyl-4-[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]thio-6-methyl-2-[(E)-2-(2-thienyl)vinyl]pyrimidine (17)

To a solution of compound **11** (3.48 g, 10 mmol) in pyridine (20 ml), carbon disulfide (1 ml) was added and the reaction mixture heated under reflux for 12 h, cooled, poured into ice-water, then the pH was adjusted to 7 with hydrochloric acid, the solid separated was filtered off, washed with water, dried and recrystallized with methanol to give a pale brown powder (yield: 46%), m.p. 118–120°C. IR (KBr): 2370 (SH), 1685 (C=O), 1623 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6): $\delta = 2.45$ (s, 3H, CH_3), 2.88 (s, 3H, $COCH_3$), 4.36 (s, 2H, SCH_2), 6.94 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.13 (dd, 1H, $J = 3.50$ Hz, thiophene-H), 7.52 (d, 1H, $J = 3.50$ Hz, thiophene-H), 7.65 (d, 1H, $J = 5.08$ Hz, thiophene-H), 8.19 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$), 12.52 (s, 1H, SH). Anal. Calcd. for $C_{16}H_{14}N_4O_2S_3$ (390.5): C, 49.21; H, 3.61; N, 14.35. Found: C, 49.28; H, 3.68; N, 14.50.

5-Acetyl-6-methyl-4-[(3-oxo-pyrazol-4-yl)thio]-2-[(E)-2-(2-thienyl)vinyl]pyrimidine (18)

A mixture of compound **11** (3.48 g, 10 mmol) and triethyl orthoformate (1.40 g, 10 mmol) in acetic acid (20 ml) was refluxed for 3 h, then allowed to cool, and poured into water. The solid product formed was collected by filtration, washed, dried, and recrystallized from ethanol affording pale yellow crystals (yield 56%) m.p. 120–122°C. IR (KBr): 1711 (C=O), 1653 (C=O) cm^{-1} (for pyrazolone ring).^{1}H NMR (DMSO-d_6): $\delta = 2.48$ (s, 3H, CH_3), 2.93 (s, 3H, CH_3CO), 6.48 (s, 1H, pyrazol-H), 6.94 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.13 (dd, 1H, $J = 3.50$ Hz, thiophene-H), 7.52 (d, 1H, $J = 3.50$ Hz, thiophene-H), 7.65 (d, 1H, $J =$ 5.08 Hz, thiophene-H), 8.19 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$).^{13}C NMR

(DMSO-d_6): δ = 21.5, 30.2 (2 CH_3), 117.0, 118.3, 128.5, 128.6, 129.8, 132.3, 134.2, 135.4, 139.1, 139.6, 154.7, 165.4, 178.4, 181.7 (Ar-C, 2 C=N and 2C=O). Anal. Calcd. for $C_{16}H_{12}N_4O_2S_2$ (356.4): C, 53.92; H, 3.39; N, 15.72. Found: C, 54.01; H, 3.48; N, 15.89.

5-Acetyl-(4-{[2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxo-ethyl] thio}-6-methyl-2-[(E)-2-(2-thienyl)vinyl]pyrimidine (19)

To a mixture of compound **11** (3.48, 10 mmol) and acetylacetone (1 ml, 10 mmol) in ethanol (20 ml), sodium ethoxide solution was added (0.23 g, 10 ml ethanol) and the reaction mixture was heated under reflux for 3 h., cooled, diluted with water and acidified with hydrochloric acid (6 ml, 30% solution). The solid that separated was filtered off, dried and recrystallized from ethanol affording orange crystals (yield: 30%) m.p. 268–269°C. IR (KBr): 1684 (br) (2C=O), 1611 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6): δ = 2.30 (s, 3H, CH_3), 2.61 (s, 3H, CH_3CO), 2.81 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 3.91 (s, 2H, SCH_2), 6.94 (d, 1H, J = 16.0 Hz, $H_\beta C$=CH), 7.13 (dd, 1H, J = 3.50 Hz, thiophene-H), 7.52 (d, 1H, J = 3.50 Hz, thiophene-H), 7.65 (d, 1H, J = 5.08 Hz, thiophene-H), 8.19 (d, 1H, J = 16.0 Hz, HC=CH_α).^{13}C NMR (DMSO-d_6): δ = 21.5, 32.1, 24.3, 30.2 (4 CH_3), 51.5 (SCH_2), 117.1, 118.3, 128.6, 128.7, 129.9, 132.2, 132.6, 134.2, 135.4, 139.1, 139.6, 154.7, 165.5, 178.4, 181.8 (Ar-C, 3 C=N and 2 C=O). Anal. Calcd. for $C_{20}H_{20}N_4O_2S_2$ (412.5): C, 58.23; H, 4.89; N, 13.58. Found: C, 58.52; H, 4.80; N, 13.59.

2-(5-Acetyl-6-methyl-2-[(E)-2-(2-thienyl)vinyl]pyrimidin-4-ylthio)-N′-[(1Z)-(4-chlorophenyl)methylene]acetohydrazide (20)

A mixture of compound **11** (3.48 g, 10 mmol), *p*-chlorobenzaldehyde (1.40 g, 10 mmol) in ethanol (20 ml) and acetic acid (1 ml) was refluxed for 3 h. The solid product formed after cooling was collected by filtration washed with water, dried, and recrystallized from ethanol affording a colorless powder (yield: 72%) m.p. 279–280°C. IR (KBr): 3158 (NH), 1719 (C=O), 1653 (C=O) amide, 1625 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6): δ = 2.71 (s, 3H, CH_3), 2.89 (s, 3H, CH_3CO), 4.25 (s, 2H, SCH_2), 6.94 (d, 1H, J = 16.0 Hz, $H_\beta C$=CH), 7.13 (dd, 1H, J = 3.50 Hz, thiophene-H), 7.32 (d, 2H, J = 9.80 Hz, Ar-H), 7.52 (d, 1H, J = 3.50 Hz, thiophene-H), 7.65 (d, 1H, J = 5.08 Hz, thiophene-H), 7.79 (d, 2H, J = 9.80 Hz, Ar-H), 8.19 (d, 1H, J = 16.0 Hz, HC=CH_α), 8.79 (s, 1H, N=CH), 12.01 (s, 1H, NH). Anal. Calcd. for $C_{22}H_{19}ClN_4O_2S_2$ (470.9): C, 56.10; H, 4.07; N, 11.90. Found: C, 56.28; H, 4.18; N, 12.01.

2-[(5)-Acetyl-6-methyl-2-[(E)-2-(2-thienyl)vinyl]pyrimidin-4-yl)thio]-N-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]acetamide (21)

A mixture of compound **2**0 (4.70 g, 10 mmol) and thioglycolic acid (0.70 ml, 10 mmol) in pyridine (20 ml) was heated under reflux for 12 h, cooled, poured into ice-water, then the pH was adjusted to 7 with hydrochloric acid, the solid separated was filtered off, washed with water, dried and recrystallized with ethanol affording gray crystals (yield: 41%) m.p. 280–281°C. IR (KBr): 3210 (NH), 1698, 1685, and 1653 (3 C=O) cm^{-1}.^{1}H NMR (DMSO-d_6): $\delta = 2.68$ (s, 3H, CH_3), 2.86 (s, 3H, CH_3CO), 4.21 (s, 2H, SCH_2), 4.32 (s, 1H, SCHAr), 5.98 ($COCH_2S$, thiazolidine ring), 6.94 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.13 (dd, 1H, $J =$ 3.50 Hz, thiophene-H), 7.35 (d, 2H, $J = 7.90$ Hz, Ar-H), 7.52 (d, 1H, $J =$ 3.50 Hz, thiophene-H), 7.55 (d, 1H, $J = 5.08$ Hz, thiophene-H), 7.80 (d, 2H, $J = 7.90$ Hz, Ar-H), 8.19 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$), 10.21 (s, 1H, NH). Anal. Calcd. for $C_{24}H_{21}ClN_4O_3S_3$ (545.1): C, 52.88; H, 3.88; N, 10.28. Found: C, 52.78; H, 3.89; N, 10.59.

5-Acetyl-6-methyl-2-[(E)-2-(2-aryl)vinyl]-4-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)pyrimidine (22a–c)—General Procedure

To a solution of compound **3b** and **3c,d**[17] (10 mmol) in aqueous potassium hydroxide (0.56 g, 10 mmol) in distilled water (10 ml) was added a solution of 2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl bromide (4.11 g, 10 mmol) in acetone (30 ml). The reaction mixture was stirred for 4 h at room temperature until the starting material was consumed (TLC). 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.

5-Acetyl-6-methyl-2-[(E)-2-(2-thienyl)vinyl]-4-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)pyrimidine (22a)

Pale gray crystals (yield: 20%) m.p. 115–117°C. IR (KBr): 1745, 1696, 1663 (C=O) cm^{-1} for acetyl and ketone groups, 1626 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6): $\delta = 1.76$, 1.96, 2.00, 2.02 (4s, 12H, 4 $OCOCH_3$), 2.49 (s, 3H, CH_3), 2.58 (s, 3H, $COCH_3$, pyrimidine), 3.88 (m, 1H, $H_{-5'}$), 4.17 (m, 2H, $H_{-6',6''}$), 4.95 (t, 1H, $J = 9.00$ Hz, $H_{-4'}$), 5.11 (t, 1H, $J = 9.0$ Hz, $H_{-2'}$), 5.60 (t, 1H, $J = 9.0$ Hz, $H_{-3'}$), 6.23 (d, 1H, $J = 12.0$ Hz, $H_{-1'}$), 6.94 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.13 (dd, 1H, $J = 3.50$ Hz, thiophene-H), 7.52 (d, 1H, $J = 3.50$ Hz, thiophene-H), 7.65 (d, 1H, $J = 5.08$ Hz, thiophene-H), 8.19 (d, 1H, $J =$ 16.0 Hz, $HC{=}CH_\alpha$). Anal. Calcd. for

$C_{27}H_{30}N_4O_{10}S_2$ (606.6): C, 53.45; H, 4.98; N, 4.62. Found: C, 53.56; H, 4.96; N, 4.68.

5-Acetyl-6-methyl-2-[(E)-2-(2-chlorophenyl)vinyl]-4-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)pyrimidine (22b)

A pale brown powder (yield: 25%) m.p. 102–104°C. IR (KBr): 1748 (br), 1698 (C=O) cm^{-1} for acetyl and ketone groups, 1635 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6): δ = 1.76, 1.96, 2.01, 2.03 (4s, 12H, 4 $OCOCH_3$), 2.48 (s, 3H, CH_3), 2.59 (s, 3H, $COCH_3$), 4.02 (m, 2H, $H_{-6',6''}$), 4.17 (m, 1H, $H_{-5'}$), 4.97 (t, 1H, J = 9.0 Hz, $H_{-4'}$), 5.13 (t, 1H, J = 9.0 Hz, $H_{-2'}$), 5.64 (t, 1H, J = 9.0 Hz, $H_{-3'}$), 6.28 (d, 1H, J = 12.0 Hz, $H_{-1'}$), 7.31 (d, 1H, J = 16.0 Hz, HC=CH_α), 7.51 (d, 2H, J = 9.8 Hz, Ar-H), 7.82 (d, 2H, J = 9.8 Hz, Ar-H), 8.15 (d, 1H, J = 16.0 Hz, H_βC=CH). Anal. Calcd. for $C_{29}H_{31}ClN_2O_{10}S$ (635.1): C, 54.84; H, 4.92; N, 4.41. Found: C, 55.00; H, 4.89; N, 4.52.

5-Acetyl-6-methyl-2-[(E)-2-(phenyl)vinyl]-4-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosylthio)pyrimidine (22c)

Colorless crystals (yield: 25%) m.p. 132–133°C. IR (KBr): 1755–1728 (br), 1660 (C=O) cm^{-1} for acetyl groups, 1636 (C=N) cm^{-1}.^{1}H NMR ($CDCl_3$): δ = 1.89, 2.03, 2.04, 2.07 (4s, 12H, 4 $OCOCH_3$), 2.47 (s, 3H, CH_3), 2.57 (s, 3H, $COCH_3$), 3.99 (m, 1H, $H_{-5'}$), 4.15-4.20 (m, 2H, $H_{-6',6''}$), 5.13 (t, 1H, J = 9.0 Hz, $H_{-4'}$), 5.27 (t, 1H, J = 9.0 Hz, $H_{-2'}$), 5.41 (t, 1H, J = 9.0 Hz, $H_{-3'}$), 6.04 (d, 1H, J = 10.5 Hz, $H_{-1'}$), 7.17 (d, 1H, J = 16.0 Hz, HC=CH_α), 7.38–7.65 (m, 5H, Ar-H), 8.01 (d, 1H, J = 16.0 Hz, H_βC=CH). Irradiation of signal at δ 3.99 ppm change the signals at δ 4.15 ppm to doublet of doublet and at δ 5.13 ppm to doublet, and irradiation of the signal at δ 5.13 ppm change the signals at δ 3.99 and 5.41 ppm to doublet. Irradiation of the signal at δ 5.77 ppm changed the signal at δ 6.04 ppm into a singlet signal, also the irradiation of the signal at δ 5.41 ppm changed the signals at δ 5.13, 5.27 ppm into a doublet. The irradiation of signal at δ 6.04 ppm change the signal at δ 5.27 ppm into a doublet and disappear the signal at d 6.04 ppm, this assigned the position of sugar protons. The irradiation of signal at δ 8.01 ppm change the signal at δ 7.17 ppm to a singlet signal with disappear the signal at δ 7.17 ppm, which assigned the structure of trans ethylenic protons.^{13}C NMR ($CDCl_3$): δ = 20.5, 20.6, 20.7, 22.7, 29.7, 31.6, 62.2, 68.4, 69.1, 74.1, 76.5 (6 CH_3 and sugar carbon), 80.3, 126.6, 127.8, 128.2, 128.9, 129.6, 130.2, 135.5, 139.7, 162.1, 162.2, 162.9, 169.3, 169.4, 170.1, 170.5, 201.5 (Ar-C, 2 C=N and 5 C=O). Anal. Calcd. for $C_{29}H_{32}N_2O_{10}S$ (600.6): C, 57.99; H, 5.37; N, 4.66. Found: C, 58.02; H, 5.48; N, 4.68.

5-Acetyl-6-methyl-2-[(*E*)-2-(aryl)vinyl]-4-(2′,3′,4′,6′-tetrahydroxy-β-*D*-glucopyranosylthio)pyrimidine (23a–c)—General Procedure

A mixture of compound **22a–c** (10 mmol) in methanol (30 ml), 1 ml of triethylamine and few drops of water were stirred overnight at room temperature under nitrogen gas, the solvent was then removed under vacuo, and the residue was washed with chloroform to extract unreacted materials. The remaining residue was recrystallized from ethanol.

5-Acetyl-6-methyl-2-[(E)-2-(2-thienyl)vinyl]-4-(2′,3′,4′,6′-tetrahydr-oxy-β-D-glucopyranosylthio)pyrimidine (23a)

Gray crystals (yield: 36%) m.p. 140–142°C. IR (KBr): 3400 (very broad band) (OH), 1689 (C=O), 1623 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6/D_2O): $\delta = 2.49$ (s, 3H, CH_3), 2.57 (s, 3H, $COCH_3$), 4.00 (m, 1H, $H_{-5'}$), 5.02 (m, 2H, $H_{-6',6''}$), 5.32 (d, 1H, $J = 5.40$ Hz, $H_{-4'}$), 5.43 (d, 1H, $J = 4.80$ Hz, $H_{-2'}$), 5.58 (d, 1H, $J = 6.30$ Hz, $H_{-3'}$), 5.62 (d, 1H, $J = 9.90$ Hz, $H_{-1'}$), 6.63 (d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$), 7.13 (dd, 1H, $J = 3.50$ Hz, thiophene-H), 7.47 (d, 1H, $J = 3.50$ Hz, thiophene-H), 7.63 (d, 1H, $J = 5.08$ Hz, thiophene-H), 8.06 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$). Anal. Calcd. for $C_{19}H_{22}N_2O_6S_2$ (438.5): C, 52.04; H, 5.06; N, 6.39. Found: C, 51.99; H, 5.14; N, 6.41.

5-Acetyl-6-methyl-2-[(E)-2-(4-chlorophenyl)vinyl]-4-(2′,3′,4′,6′-tetrahydr-oxy-β-D-glucopyranosylthio)pyrimidine (23b)

A pale brown powder (yield: 25%), m.p. 103–104°C. IR (KBr): 3400 (very broad band) for (OH), 1685 (C=O) and 1620 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6/D_2O): $\delta = 2.49$ (s, 3H, CH_3), 2.58 (s, 3H, $COCH_3$), 3.68 (m, 1H, $H_{-5'}$), 4.48 (m, 2H, $H_{-6',6''}$), 5.02 (d, 1H, $J = 5.40$ Hz, $H_{-4'}$), 5.16 (d, 1H, $J = 4.80$ Hz, $H_{-2'}$), 5.44 (d, 1H, $J = 6.30$ Hz, $H_{-3'}$), 5.61 (d, 1H, $J = 9.80$ Hz, $H_{-1'}$), 7.20 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$), 7.47 (d, 2H, $J = 8.40$ Hz, Ar-H), 7.79 (d, 2H, $J = 8.40$ Hz, Ar-H), 7.98 (d, 1H, $J = 16.0$ Hz, $H\beta C{=}CH$). Anal. Calcd. for $C_{21}H_{23}ClN_2O_6S$ (466.94): C, 54.02; H, 4.96; N, 6.00. Found: C, 54.31; H, 5.01; N, 6.11.

5-Acetyl-6-methyl-2-[(E)-2-(phenyl)vinyl]-4-(2′,3′,4′,6′-tetrahydroxy-β-D-glucopyranosylthio)pyrimidine (23c)

White crystals (yield: 20%) m.p. 120–122°C. IR (KBr): 3379 (very broad band) (OH), 1685 (C=O) and 1636 (C=N) cm^{-1}.^{1}H NMR (DMSO-d_6/D_2O): $\delta = 2.46$ (s, 3H, CH_3), 2.58 (s, 3H, CH_3CO), 3.67 (m, 1H, $H_{-5'}$), 4.45 (m, 2H, $H_{-6',6''}$), 5.02 (d, 1H, $J = 5.40$ Hz, $H_{-4'}$), 5.17 (d, 1H, $J = 4.80$ Hz, $H_{-2'}$), 5.45 (d, 1H, $J = 6.40$ Hz, $H_{-3'}$), 5.62 (d, 1H, $J = 9.90$ Hz, $H_{-1'}$), 7.23 (d, 1H, $J = 16.0$ Hz, $HC{=}CH_\alpha$), 7.41–7.74 (m, 5H, Ar-H), 8.00

(d, 1H, $J = 16.0$ Hz, $H_\beta C{=}CH$). Anal. Calcd. for $C_{21}H_{24}N_2O_6S$ (432.5): C, 58.32; H, 5.59; N, 6.48. Found: C, 58.01; H, 5.6; N, 6.56.

ANTIMICROBIAL ACTIVITY

The antimicrobial activities of some newly synthesized compounds were screened for their antibacterial and antifungal activity against six species of bacteria and one fungi, namely *Staphylococcus aureus*, *Sarcina lutea, Bacillus subtilis* as Gramm +ve, *Pseudomonas aeruginosa*, *Klebseilla pneumonie*, *Escherichia coli* as Gram –ve, and *Candida albicans* as Fungi, using a cup plate agar diffusion method.[24] The tested compounds were dissolved in DMF to get a solution of 1 mg/mL concentration. The inhibition zones were measured in (mm) at the end of an incubation period of 48 h at 37°C. Dimethylformamide showed no inhibition zones. The fungi cultures were maintained on dextrose agar medium. Penicillin and Nystatin were used as reference.

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