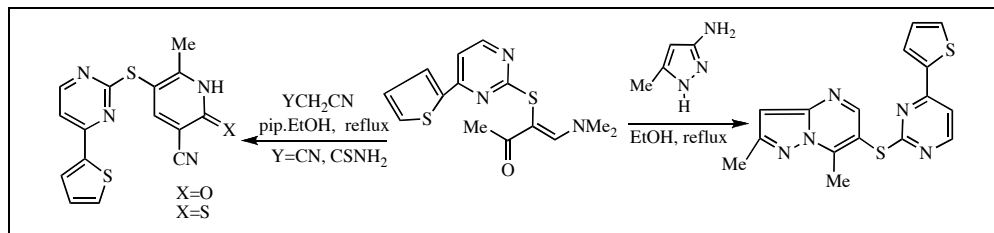


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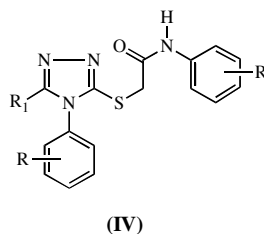
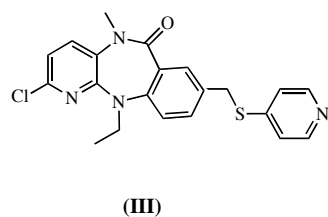
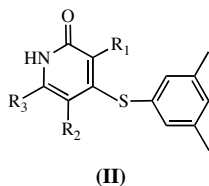
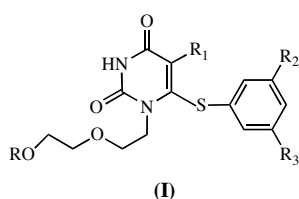


Derivatives of thiophene, thieno[2,3-*b*]pyridine, pyridine, isoxazol, pyrazolo[1,5-*a*]pyrimidine, pyridazine linked with *s*-pyrimidine derivative have been synthesized and tested for antimicrobial and antifungal activities. The structure of the newly synthesized compounds have been established on the basis of their analytical and spectral data.

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INTRODUCTION

Driven by increased demand for *anti*-HIV and antiviral drugs, the search for new heterocyclic compounds and novel methods of their synthesis is a major topic in contemporary synthesis. A variety of thiols have been synthesised and tested against non-nucleoside reverse transcriptase inhibitors (NNRTIs) resistant HIV infections. Among the numerous compounds showing such reactivity as 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (**I**) (HEPT), pyridinones (**II**), 8-heteroarylthiomethyldipyridodiazepinone (**III**) and tri-substituted triazoles (**IV**) [1-3].



In conjunction with previous interest in the synthesis of polyfunctionally substituted heterocycles with potential biological activities [4-7], it was interesting to study the

behaviour of pyrimidine-2(1*H*)-thione **1** which has been reported earlier from our laboratories [8] towards a variety of chemical reagents in applied to obtained a series of compounds where a sulfur atom links the pyrimidine with other heteroaromatic rings such as 2-aminothiophene, thieno[2,3-*b*]pyridine, pyridine, pyrazolo[1,5-*a*]pyrimidine and pyridazine derivatives (**V**) in the hope of obtaining compounds of potential anti HIV. The importance of the above compounds is due to their diverse pharmaceutical activities [9-12].

RESULTS AND DISCUSSION

The key intermediate of *S*-alkylated derivative **2** used in our experiments has been prepared in excellent yield by treatment of pyrimidine-2(1*H*)-thione **1** with α -chloroacetone in refluxing acetone containing anhydrous potassium carbonate. The structure of *S*-alkylated derivative **2** was established on the basis of its elemental analysis and spectral data. The mass spectrum of **2** revealed a molecular ion peak with m/z 250. The ^1H nmr of **2** revealed in addition to thiophene and pyrimidine rings protons, two singlet signals at δ_{H} 2.34 and 4.21 ppm due to corresponding methyl and methylene protons respectively. The ir spectrum of **2** revealed CO stretching bands at ν_{max} 1716 cm^{-1} . Moreover, ^{13}C nmr spectrum revealed highest frequency signal at δ_{C} 203.0 ppm assignable to the carbonyl carbon.

To study the behaviour of *S*-alkylated derivative **2** towards carbon nucleophiles in order to produce new polyfunctional substituted thiophene derivatives, where thiophene nucleus linked directly to a pyrimidine ring through, an *S*-linkage in hope of discovering compound of potential anti HIV agents. Therefore, 2-aminothiophene-

3-carbonitrile derivative **3** used in our experiments has been prepared according to Gawald's reaction [13] *in situ* via a one-step process by treatment of *S*-alkylated derivative **2** with malononitrile in refluxing ethanol and in the presence of elemental sulfur containing a catalytic amount of triethylamine to give a product that could be formulated as **3** or its isomers **4**. The mass spectrum of reaction product revealed a molecular ion peak with m/z at 330. However, the presence of methyl singlet at δ 2.12 ppm in the ^1H nmr spectrum indicate that methylene carbon in *S*-alkylated **2** is involved in the reaction which readily excluded the possibility of **4**. Moreover, the ir spectrum of **3** revealed the presence of amino stretching at ν_{max} 3421-3329 cm^{-1} in addition to cyano group stretching at ν_{max} 2201 cm^{-1} . The absence of carbonyl group absorption in the ir spectrum, indicates also that the carbonyl group is involved in the reaction.

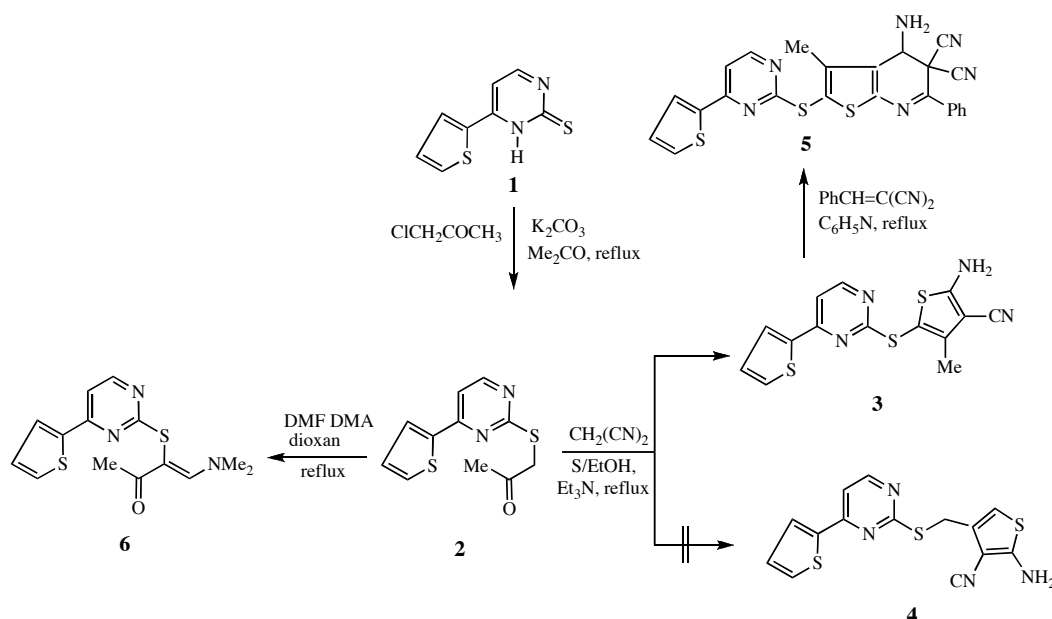
On the other hand, treatment of **3** with benzylidene-malononitrile in refluxing pyridine afforded 3,4-dihydrothieno[2,3-*b*]pyridine derivative **5** in good yield. The structure of latter compound was confirmed on the basis of elemental analysis and spectral data. The mass spectrum of **5** revealed a molecular ion peak with m/z 484. Compound **5** is assumed to proceed *via* initial Michael addition of the amino group in compound **3** to an activated double bond in benzylidenemalononitrile followed by cyclization to form adduct which did not aromatize by losing hydrogen cyanide (Scheme 1). Similar dihydrothieno[2,3-*b*]pyridine formations have been reported by us in Ref. [6].

Treatment of *S*-alkylated derivative **2** with dimethylformamide dimethylacetal (DMF/DMA) in dioxan under

reflux temperature gives the enaminone **6** in a good yield. The structure of enaminone was confirmed on the basis of elemental analysis and spectral data. The mass spectrum of compound **6** revealed a molecular ion peak with m/z 305. ^1H nmr revealed three upfield signals at δ_{H} 2.13, 3.14 and 3.16 ppm corresponding to methyl and two *N,N*-dimethylamino protons respectively in addition to the one signal downfield at δ_{H} 8.08 ppm corresponding to =CH proton (H-4) (*cf.* Scheme 1).

The reactivity of the enaminone **6** toward active methylene nitrile was investigated. Thus, treatment of **6** with malononitrile in the refluxing ethanol containing a catalytic amount of piperidine yielded a product that could be formulated as **7** or it is isomer **8**. The initial condensation product yield from the reaction **6** with malononitrile failed to react with elemental sulfur in a mixture of DMF/EtOH containing a catalytic amount of piperidine to obtain the thienopyridine derivative **9**, as is characteristic of azines with vicinal methyl and carbonitrile substituents [14]. The structure **8** was ruled out and the product assigned to be structure **7**. The formation of compound **7** is considered most likely based on its similarity to well established behaviour, which was assumed to proceed *via* initial Michael addition of active methylene reagent across double bond in enaminone **6** that cyclize and undergo Dirmoth type rearrangement followed by aromatisation *via* loss a hydrogen and dimethylamine molecules to yield the final product **7** [15]. In a similar manner, compound **6** reacted also with cyanothioacetamide in refluxing ethanol containing a catalytic amount of piperidine to give a high yield of crystalline product for which structure **10** was assigned on

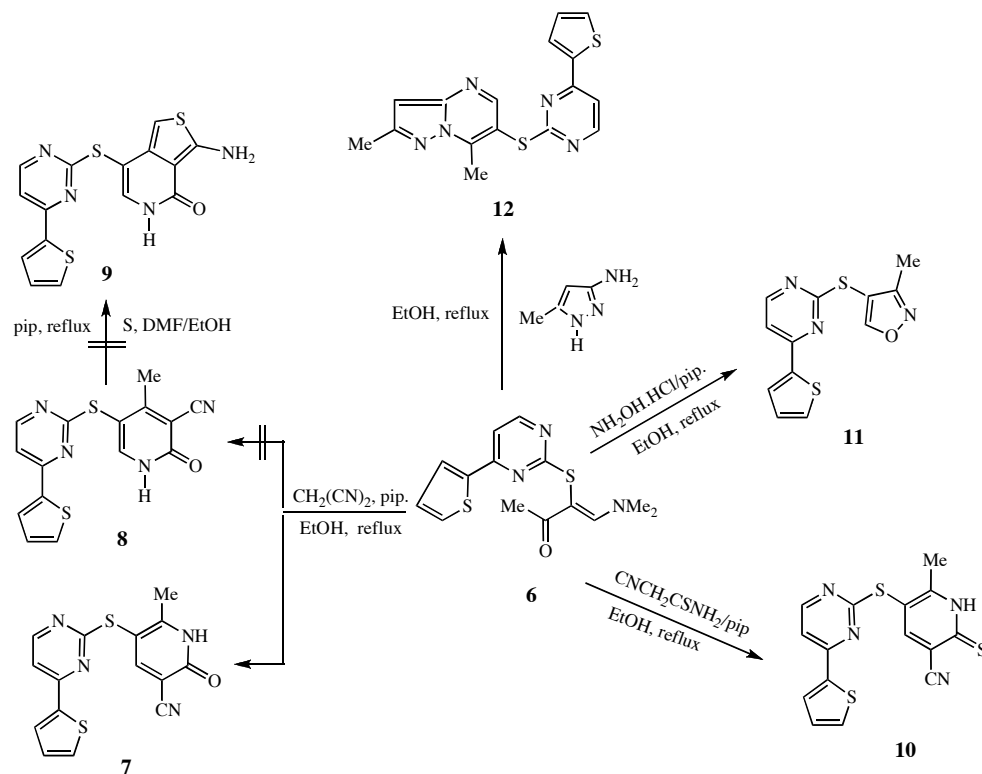
Scheme 1



the basis of its spectral data. Thus, the ir spectrum of the reaction product revealed NH and nitrile absorptions at $\nu_{\max}$ 3439 and 2197 cm^{-1} respectively (*cf.* Scheme 2).

attributed to the 3-H and other resonance at δ 8.46 ppm attributed to 5-H of pyrazolo[1,5-*a*]pyrimidine structure **12** (*cf.* Scheme 2).

Scheme 2



The reactivity of enaminone **6** towards nitrogen nucleophile was also investigated. Thus, treatment of **6** with hydroxylamine hydrochloride afforded isoxazole derivative **11**. The ^1H nmr spectrum revealed a singlet signal at δ_{H} 8.77 corresponding to H-5' of isoxazole [16]. Moreover, the ^{13}C nmr spectrum revealed highest frequency signals at δ_{C} 155 and δ_{C} 160 ppm corresponds to the carbons coupled with proton for isoxazole (C-5') and pyrimidine (C-6) systems. The formation of **11** is assumed to proceed *via* 1,2-addition at carbonyl group in compound **6** which readily undergoes intramolecular cyclization into isoxazole derivative **11** *via* loss of dimethylamine and a water molecule similar to that which recently has been reported from our laboratories [15].

The results described above prompted us to investigate the behaviour of compound **6** towards heterocyclic amine as potential procedures for fused heterocyclic system. Thus treatment of compound **6** with 3-amino-5-methyl-1H-pyrazole in refluxing ethanol afforded product of addition and elimination of both dimethylamine and water molecules (*cf.* Scheme 2), which is contrast to recent report [15]. ^1H nmr spectrum revealed two singlet signals at δ 6.59 ppm which integrates for one proton and

On the other hand, treatment of pyrimidine-2(1H)-thione derivative **1** with α -chloroacetic acid in refluxing ethanol and the presence of potassium hydroxide gave a yellow crystal of pyrimidin-2'-yl-thioethanoic acid derivative **13** in good yield. The structure of **13** was established on the basis of its elemental analysis and spectral data. Thus, the ^1H nmr spectrum of the isolated product exhibited two singlet signals at δ_{H} 4.03 ppm due to methylene protons and the other one at δ_{H} 12.77 ppm attributed to the OH proton. This signal underwent a facile hydrogen deuterium exchange upon addition of deuterium oxide. Moreover, the ^{13}C nmr spectrum of the reaction product characterized by two signals one at the δ_{C} 34.74 corresponding to methylene carbon and one at δ_{C} 171.2 corresponding to an acyl carbon. The hydroxyl group of **13** was easily transformed into hydrazide function. Thus, treatment of pyrimidin-2'-yl-thioethanoic acid derivative **13** with hydrazine hydrate in boiling ethanol gave yellow crystal of pyrimidin-2'-yl-thioacetohydrazide derivative **14** in good yield. The latter compound proves to be useful key intermediate in the synthesis of several heterocyclic nuclei.

Thus, condensation of acetohydrazide derivative **14** *in situ* *via* one step with benzaldehyde and malononitrile in

refluxing ethanol containing pyridine as catalyst, in fact only a single product was obtained in 75% yield (*cf.* Scheme 3). Several structures seemed possible for this product. Thus, initial formation of adduct **16** (route a) would lead to pyridazine derivative **18**, while the formation of adduct **19** (route b) would lead to [1,3,4]triazole[1,5-*a*]pyridine derivative **21** [17]. The structure **21** was ruled out on the basis of the elemental analysis and spectral data. The mass spectrum revealed $m/z = 403$ ($M^+ - HCl$) corresponding to the molecular formula, $C_{20}H_{13}N_5S_2O$ like that **18**. However, the presence of the cyano absorption in the ir spectrum of the product at $\nu_{max} 2225\text{ cm}^{-1}$, indicates that cyano group was not involved in the reaction which readily excluded the possibility of **21** (route b). Also the ir spectrum revealed the higher frequency absorption for a cyclic carbonyl group stretching band at $\nu_{max} 1698\text{ cm}^{-1}$. If the reaction product is **21** (route b) one would expect the absence of cyano group and the amide carbonyl group stretching band absorbed at lower frequency than a cyclic carbonyl group [5,9]. Moreover, the 1H nmr spectrum revealed the presence of one D_2O exchangeable proton attributed to the NH function at $\delta 12.79$ ppm and not for NH_2 . The formation of pyridazine derivative **18** is assumed to proceed *via* initial condensation of benzaldehyde to amino group in compound **14** yield the intermediate **15**. The latter reacted with malononitrile *in situ* to give the final isolated product **18** through the intermediates **16** and **17** (*cf.* Scheme 3).

Biological Activity. The biological activities of some of the newly synthesized compounds were screened for antifungal activity against *Aspergillus niger*, *Penicillium digitatum* and *Fusarium* while the antibacterial activity was tested against *Bacillus subtilis* and *Escherichia coli*. Most of the test sample showed bacterial and fungicidal activity (Table 1).

EXPERIMENTAL

All melting points are uncorrected. The ir spectra (KBr) were recorded on a Perkin Elmer 2000 FT-IR spectrophotometer. 1H nmr and ^{13}C nmr spectra were recorded on a Bruker 400 MHz spectrometer in $DMSO-d_6$ as solvent using TMS as internal

standard, δ TMS = 0.00 ppm. Mass spectra were measured on

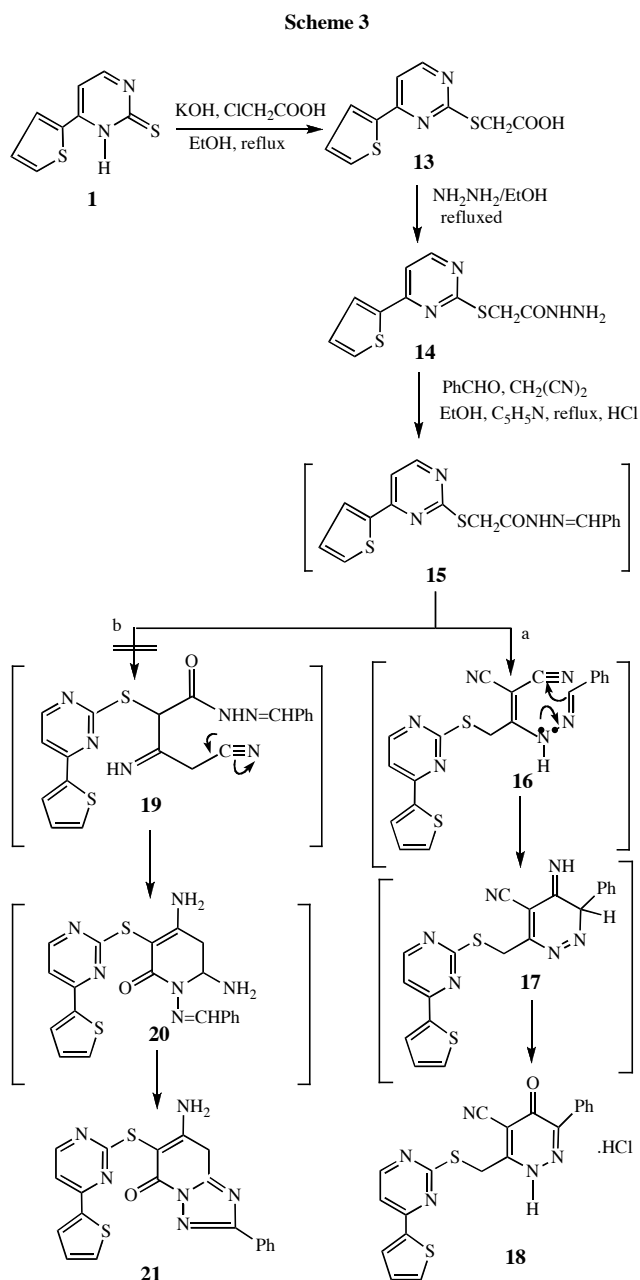


Table 1

In vitro antimicrobial and fungicidal activities [a] of some newly synthesized compounds [b-e].

Compound	<i>Bacillus Subtilis</i>	<i>Escherichia coli</i>	<i>Penicillium digitatum</i>	<i>Aspergillus niger</i>	<i>Fusarium</i>
2	- ^[b]	-	-	5.0 ^[c]	10.0
6	-	-	-	-	-
7	-	-	-	-	-
10	-	-	-	-	10.0
11	-	-	5.0	-	-
12	-	10.0	-	10.0 ^[d]	5.0
13	-	-	7.5 ^[d]	-	-
14	-	-	-	-	-
18	15.0	10.0	12.0 ^[e]	15.0 ^[e]	10.0

[a] Diameter (in mm) of growth inhibition zones; [b] no activity; [c] little activity; [d] moderate activity; [e] maximum activity.

GC/MS VS Autospec Q. Microanalyses were performed on a CHNS-LECO 932 analyzer. Abbreviation: Me₂CO = acetone, EtOH = ethanol, Et₃N = triethylamine, DMF = *N,N*-dimethylformamide, DMSO-d₆ = dimethyl-d₆-sulfoxide, TMS = tetramethylsilane, DMF/DMA = *N,N*-dimethylformamide dimethylacetal.

1-[4'-(2"-Thienyl)pyrimidin-2'-ylthio]propan-2-one (2). A mixture of **1** (1.94 g, 10 mmoles) potassium carbonate anhydrous (1.38 g, 10 mmoles) and chloroacetone (0.79 g, 10 mmoles) in Me₂CO (20 mL) was refluxed for 2 hours. The solvent was then evaporated under reduced pressure. The solid product, so formed, was collected by filtration and recrystallized from EtOH as light brown crystal, 2.0 g (73%), mp. 80-82 °C; ir. ν 1716 (CO) cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.34 (s, 3H, CH₃), 4.21 (s, 2H, CH₂), 7.23 (t, 1H, *J*=3Hz, thiophene proton), 7.65 (d, 1H, *J*=3Hz, thiophene proton), 7.84 (d, 1H, *J*=4 Hz, thiophene proton), 8.03 (d, 1H, *J*=5Hz, H-5' pyrimidine proton), 8.56 ppm (d, 1H, *J*=5 Hz, H-6' pyrimidine proton); ¹³C nmr (DMSO-d₆): δ 20.0 (CH₃), 42.0 (CH₂), 112.1 (C-5'), 130.0, 130.5, 132.9 (thiophene carbons), 140.1 (C-2"), 159.1 (C-4'), 159.6 (C-6'), 171.1 (C-2'), 203.0 (CO) ppm; ms: *m/z* 250 (M⁺). *Anal.* Calcd. for C₁₁H₁₀N₂OS₂ (250.21): C, 52.80; H, 4.03; N, 11.20; S, 25.62. Found: C, 52.89; H, 4.02; N, 11.24; S, 25.68.

2-Amino-4-methyl-5-[4'-(2"-thienyl)pyrimidin-2'-ylthio]-thiophene-3-carbonitrile (3). A mixture of **2** (2.50 g, 10 mmoles) malononitrile (0.66 g, 10 mmoles) and elemental sulfur (0.32 g, 10 mmoles) in EtOH (20 mL) containing Et₃N was refluxed for 3 hours. The reaction mixture was left to cool at room temperature, then poured onto ice cold water. The solid product, so formed, was collected by filtration and recrystallized from a EtOH as brown crystal, 2.0 g (79%), mp. 130-132 °C; ir. ν 3431-3329 NH₂, 2201 (CN) cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.12 (s, 3H, CH₃), 4.37 (br.s, 2H, NH₂, D₂O exchangeable), 7.17 (m, 1H, thiophene proton), 7.55 (m, 1H, thiophene proton), 7.71 (m, 1H, thiophene proton), 7.89 (d, 1H, *J*=5 Hz, H-5' pyrimidine proton), 8.47 ppm (d, 1H, *J*=5 Hz, H-6' pyrimidine proton); ms: *m/z* 330 (M⁺). *Anal.* Calcd. for C₁₄H₁₀N₄S₃ (330.45): C, 50.91; H, 3.05; N, 16.97. Found: C, 51.02; H, 3.04; N, 17.03.

4-Amino-3-methyl-6-phenyl-2-[4'-(2"-thienyl)pyrimidin-2'-ylthio]thieno[2,3-*b*]pyridine-5,5-(4*H*)dicarbonitrile (5). A mixture of **3** (3.30 g, 10 mmoles) and benzylidinemalononitrile (1.54 g, 10 mmoles) in pyridine (20 mL) was refluxed for 3 hours. The reaction was poured onto ice-cold water and acidified with 10% HCl. The solid product, so formed, was collected by filtration and recrystallized from EtOH as brown crystal, 3.33 g (69 %), mp. 220-222 °C; ir. ν 3435 (NH₂), 2204 (2CN) cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.11 (s, 3H, CH₃), 4.11 (s, 1H, H-4), 7.22-8.66 (m, 12H, aromatic protons & NH₂); ¹³C nmr (DMSO-d₆): δ 15.1 (CH₃), 29.2 (C-5), 37.7 (C-4), 113.5 (C-5'), 114.3 & 115.2 (2CN), 119.6 (C-2), 130.2, 130.6, 130.7, 131.5, 132.8, 133.4, 135.5 (phenyl & thiophene carbons), 141.8, 142.8 (C-3 & C-3a), 142.0 (C-2"), 154.0 (C-7a), 159.3, 159.8 (C-4' & C-6'), 162.6 (C-6), 171.6 (C-2') ppm; ms: *m/z* 484 (M⁺). *Anal.* Calcd. for C₂₄H₁₆N₆S₃ (484.17): C, 59.48; H, 3.32; N, 17.34. Found: C, 59.85; H, 3.35; N, 17.46.

4-(*N,N*-Dimethylamino)-3-[4'-(2"-thienyl)pyrimidin-2'-ylthio]-3-buten-2-one (6). A solution of **2** (2.50 g, 10 mmoles) in dioxan (20 mL) was treated with DMF DMA (1.33 g, 10 mmoles) and refluxed for 5 hours. The solvent was then evaporated under reduced pressure. The solid product, so formed, was collected by filtration and recrystallized from EtOH as yellow crystal, 2.62 g (86%), mp. 105-107 °C; ir: ν

1642 (CO) cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.18 (s, 3H, CH₃), 3.14 (s, 3H, NCH₃), 3.16 (s, 3H, NCH₃), 7.22 (t, 1H, *J*=3Hz, thiophene proton), 7.64 (d, 1H, *J*=3Hz, thiophene proton), 7.83 (d, 1H, *J*=4 Hz, thiophene proton), 8.00 ppm (d, 1H, *J*=5 Hz, H-5', pyrimidine proton), 8.08 (s, 1H, H-4), 8.57 ppm (d, 1H, *J*=5 Hz, H-6' pyrimidine-proton); ¹³C nmr (DMSO-d₆): δ 27.4 (CH₃), 41.3 (2NCH₃), 112.1 (C-5' pyrimidine carbon), 128.5 (C-3), 129.8, 130.1, 130.9 (thiophene carbons), 132.7 (C-4), 142.5 (C-2"), 159.2, 159.5. (C-4' & C-6'), 173.8 (C-2'), 195.6 (CO) ppm; ms: *m/z* 305 (M⁺). *Anal.* Calcd. for C₁₄H₁₅N₃S₂O (305.42): C, 55.05; H, 4.95; N, 13.75. Found: C, 54.83; H, 4.79; N, 13.88.

6-Methyl-2-oxo-5-[4'-(2"-hienyl)pyrimidin-2'-ylthio]1,2-dihydropyridine-3-carbonitrile (7). A mixture of **6** (3.05, 10 mmoles) and malononitrile (0.66 g, 10 mmoles) in EtOH (20 mL), containing piperidine was refluxed for 1 hour. The solvent was evaporated under reduced pressure. The solid product, so formed, was collected by filtration and recrystallized from EtOH as yellow crystal, 2.67 g (82 %), mp. 195-197 °C; ir. ν 3425-3185 (NH), 2208 (CN), 1641 (amide CO) cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.39 (s, 3H, CH₃), 7.22 (t, 1H, *J*=4 Hz, thiophene proton), 7.60 (m, 1H, thiophene proton), 7.75 (m, 1H, thiophene proton), 7.92 (d, 1H, *J*=5 Hz, H-5' pyrimidine proton), 8.00 (br.s, 1H, NH, D₂O exchangeable), 8.22 (s, 1H, H-4), 8.68 ppm (d, 1H, *J*=5 Hz, H-6' pyrimidine proton); ¹³C nmr (DMSO-d₆): δ 19.8 (CH₃), 101.7 (C-3), 105.2 (C-5), 112.7 (C-5'), 116.9 (CN), 130.1, 130.2, 133.2, 142.0 (thiophene carbons), 156.7 (C-4), 159.2 (C-6), 159.8, 160.0 (C-6' & C-4'), 161.3 (amide CO), 170.7 (C-2') ppm. *Anal.* Calcd. for C₁₅H₁₀N₄OS₂ (326.39): C, 55.19; H, 3.08; N, 17.16; S, 19.64. Found: C, 55.01; H, 3.08; N, 17.37; S, 19.46.

6-Methyl-5-[4'-(2"-thienyl)pyrimidin-2'-ylthio]-2-thioxo-1,2-dihydropyridine-3-carbonitrile (10). A mixture of **6** (3.05 g, 10 mmoles) and cyanothioacetamide (1.00 g, 10 mmoles) in EtOH (20 mL) containing piperidine was refluxed for 1 hour. The solvent was evaporated under reduced pressure. The solid product, so formed, was collected by filtration and recrystallized from EtOH as green crystal, 2.59 g (76%), mp. 240-242 °C; ir. ν 3439-3365 (NH), 2197 (CN) cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.45 (s, 3H, CH₃), 7.22 (t, 1H, *J*=4 Hz, thiophene proton), 7.75 (m, 1H, thiophene proton), 7.88 (m, 1H, thiophene proton), 8.02 (d, 1H, *J*=5 Hz, H-5' pyrimidine proton), 8.26 (s, 1H, H-4), 8.68 (d, 1H, *J*=5 Hz, H-6' pyrimidine proton), 14.60 ppm (br.s, 1H, NH, D₂O exchangeable); ¹³C nmr (DMSO-d₆): δ 19.3 (CH₃), 112.7 (C-5'), 113.3 (C-3), 115.4 (C-5), 117.2 (CN), 129.9, 130.5, 133.0, 141.8 (thiophene carbons), 151.8 (C-4), 159.6, 159.9 (C-6' & C-4'), 160.2 (C-2), 169.7 (C-6), 179.6 (C-2') ppm. *Anal.* Calcd. for C₁₅H₁₀N₄S₃ (342.46): C, 52.60; H, 2.94; N, 16.36. Found: C, 52.47; H, 3.14; N, 16.12.

2-(3'-Methylisoxazo-4'-ylthio)-4-(2"-thienyl)pyrimidine (11). A mixture of **6** (3.05 g, 10 mmoles) and hydroxylamine hydrochloride (0.69 g, 10 mmoles) in EtOH (20 mL) was refluxed for 1 hour. The reaction mixture was left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from EtOH as brown crystal, 1.89 g (69 %), mp. 80-82°C; ¹H nmr (DMSO-d₆): δ 2.18 (s, 3H, CH₃), 7.24 (t, 1H, *J*=4Hz, thiophene proton), 7.75 (m, 1H, thiophene proton), 7.86 (m, 1H, thiophene proton), 8.09 (d, 1H, *J*=5 Hz, H-5 pyrimidine proton), 8.63 (d, 1H, *J*=5 Hz, H-6 pyrimidine proton), 8.77 ppm (s, 1H, H-5'); ¹³C nmr (DMSO-d₆): δ 19.6 (CH₃), 102.0 (C-4'), 112.7 (C-5), 129.9, 130.6, 133.1, 141.7 (thiophene carbons), 154.5 (C-3'), 155.4 (C-5'), 159.6,

159.9 (C-4 & C-6); 173.8 (C-2) ppm. *Anal.* Calcd. for $C_{12}H_9N_3S_2O$ (275.37): C, 52.34; H, 3.29; N, 15.26. Found: C, 52.37; H, 3.37; N, 15.03.

2,7-Dimethyl-6-[4'-(2"-thienyl)pyrimidin-2'-ylthio]pyrazolo[1,5-a]pyrimidine (12). A solution of **6** (3.05 g, 10 mmoles) in EtOH (20 mL) was treated with 3-amino-5-methyl-1H-pyrazole (0.97 g, 10 mmoles). The reaction mixture was refluxed for 3 hours and left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from EtOH as brown crystal, 2.43 g (72 %), mp. 143-145 °C; 1H nmr (DMSO- d_6): δ 2.46 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 6.59 (s, 1H, H-3), 7.15 (m, 1H, thiophene proton), 7.65 (m, 1H, thiophene proton), 7.75 (m, 1H, thiophene proton), 7.93 (d, 1H, $J=4$ Hz, H-5' pyrimidine proton), 8.46 (s, 1H, H-5), 8.50 ppm (d, 1H, $J=4$ Hz, H-6' pyrimidine proton); ^{13}C nmr (DMSO- d_6): 15.4 (CH_3), 16.2 (CH_3), 97.5 (C-3), 112.6 (C-5'), 129.8, 130.4, 132.9, 141.7 (thiophene carbons), 149.6 (C-2), 149.2 (C-6), 151.6 (C-5), 154.7 (C-3a), 156.1 (C-7), 159.5, 159.8 (C-4' & C-6'), 170.5 (C-2') ppm. *Anal.* Calcd for $C_{16}H_{13}N_5S_2$ (339.43): C, 56.61; H, 3.86; N, 20.63. Found: C, 56.54; H, 3.75; N, 20.68.

2-[4'-(2"-Thienyl)pyrimidin-2'-ylthio]ethanoic acid (13). A solution of **1** (1.94 g, 10 mmoles) and potassium hydroxide (0.56 g, 10 mmoles) in EtOH (20 mL) was treated with chloroacetic acid (0.94 g, 10 mmoles). The reaction mixture was refluxed for 2 hours and left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from EtOH as yellow crystal, 1.78 g (71 %), mp. 201-203 °C; ir.v 3500-3360 (OH), 1698 (CO) cm^{-1} ; 1H nmr (DMSO- d_6): δ 4.03 (s, 2H, CH_2), 7.25 (m, 1H, thiophene proton), 7.67 (m, 1H, thiophene proton), 7.82 (m, 1H, thiophene proton), 7.89 (d, 1H, $J=4$ Hz, H-5' pyrimidine proton), 8.60 (d, 1H, $J=4$ Hz, H-6' pyrimidine proton), 12.77 ppm (br.s, 1H, OH, D_2O exchangeable); ^{13}C nmr (DMSO- d_6): δ 34.74 (CH_2), 112.1 (C-5'), 130.3, 130.6, 133.0 (thiophene carbons), 142.1 (C-2'), 159.2, 159.6 (C-4' & C-6'), 171.0 (C-2'), 171.2 (CO) ppm. *Anal.* Calcd for $C_{10}H_8N_2S_2O_2$ (252.18): C, 47.62; H, 3.20; N, 11.11. Found: C, 47.54; H, 3.33; N, 11.15.

2-[4'-(2"-Thienyl)pyrimidin-2'-ylthio]acetohydrazide (14). A solution of **13** (2.52 g, 10 mmoles) in EtOH (20 mL) was treated with hydrazine hydrate (0.50 g, 10 mmoles). The reaction mixture was refluxed for 1 hour and left to cool at room temperature. The solid product, so formed, was collected by filtration and recrystallized from EtOH as yellow crystal, 1.99 g (75 %), mp. 201-212 °C; ir.v 3195-3319 (NH & NH_2), 1618 (amide CO) cm^{-1} ; 1H nmr (DMSO- d_6): δ 1.59 (br.s, 2H, NH_2 , D_2O exchangeable), 3.87 (s, 2H, CH_2), 7.23 (t, 1H, $J=4$ Hz, thiophene proton), 7.28 (br.s, 1H, NH, D_2O exchangeable), 7.49 (m, 1H, thiophene proton), 7.64 (m, 1H, thiophene proton), 7.86 (d, 1H, $J=5$ Hz, H-5' pyrimidine proton), 8.51 ppm (d, 1H, $J=5$ Hz, H-6' pyrimidine proton). *Anal.* Calcd for $C_{10}H_{10}N_4S_2O$ (266.21): C, 45.11; H, 3.78; N, 21.04. Found: C, 45.11; H, 3.92; N, 20.99.

4-Oxo-3-phenyl-6-[4'-(2"-thienyl)pyrimidin-2'-ylthio-methyl]-1,4-dihydropyridazine-5-carbonitrile hydrochloride (18). A mixture of **14** (2.66 g, 10 mmoles), benzaldehyde (1.06 g, 10 mmoles) and malononitrile (0.66 g, 10 mmoles) in EtOH (20 mL) containing pyridine (3 mL) was refluxed for 3 hours. The reaction was allowed to cool at room temperature, then poured onto ice-cold water and neutralized with 10% HCl. The solid product, so formed, was collected by filtration and recrystallized from a mixture of EtOH/DMF (2:1) as pale brown

crystal, 3.29 g (75 %), mp. 173-174 °C; ir. v 3408 (NH), 2225 (CN), 1698 (CO) cm^{-1} ; 1H nmr (DMSO- d_6): δ 3.98 (s, 2H, CH_2), 7.22 (t, 1H, $J=4$ Hz, thiophene proton), 7.59-7.66 (m, 5H, phenyl protons), 7.67 (m, 1H, thiophene proton), 7.85 (m, 1H, thiophene proton), 8.05 (d, 1H, $J=5$ Hz, H-5' pyrimidine proton), 8.58 (d, 1H, $J=5$ Hz, H-6' pyrimidine proton), 12.79 ppm (br.s, 1H, NH, D_2O exchangeable); ^{13}C nmr (DMSO- d_6): δ 34.2 (CH_2), 82.6 (C-5), 112.1 (C-5'), 115.2 (CN), 136.6 (C-3), 130.0, 130.5, 130.6, 131.5, 132.3, 132.9, 135.4, 142.1 (phenyl & thiophene carbons), 159.2, 159.5 (C-4' & C-6'), 162.6 (C-6), 171.0 (C-2'), 171.2 (CO) ppm; ms:m/z 403 (M^+ -HCl). *Anal.* Calcd. for $C_{20}H_{14}N_5S_2OCl$ (439.94): C, 54.60; H, 3.20; N, 15.91. Found: C, 54.75; H, 3.34; N, 15.80.

Biological Testing. The newly synthesized compounds were tested against the specified microorganism, using 400 $\mu g/mL$ (w/v) solutions in sterile dimethyl- d_6 -sulfoxide (DMSO). A solution of the tested compound (0.1 mL) was poured aseptically in a well of 6 mm diameter made by a Cork borer in the nutrient agar medium for bacterial test and Sabourand agar for fungal test. After placing the same volume in wells of all tested microorganism, nutrient agar plates were incubated at 37 °C for 24 hours and Sabourand dextrose agar plates were incubated at 25 °C for 48 hours. The diameter of zones inhibition was measured in millimeters and the results are shown in Table 1. The least concentration, which showed inhibitory effect on any specific microorganism, was considered as the minimum inhibitory concentration (MIC) which was determined using streptomycin (50 $\mu g/mL$) as the references.

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