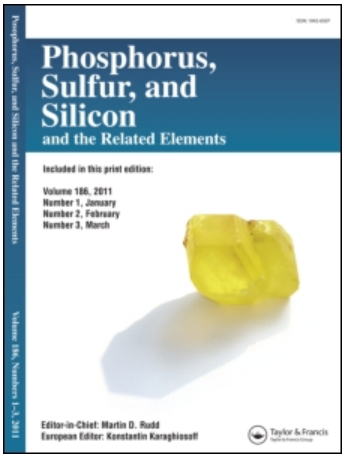

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Antimicrobial Activity of Thioxopyrimidines and Related Derivatives

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Synthesis and Antimicrobial Activity of Thioxopyrimidines and Related Derivatives

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*The interaction of thiourea with activated cyanoolefins under different reaction conditions were studied, in which a variety of thiopyrimidines (**8**, **9**, **12**, **18**, **20**, & **21**) and related derivatives (**10**, **11**, **14**, **16**, & **17**) were obtained respectively. Also, the reactions of thiopyrimidines (**8**, **9**) with different electrophilic and nucleophilic reagents were reported. IR, ^{1}H NMR, ^{13}C NMR and mass spectra for the newly synthesized compounds were studied. Most of the obtained compounds were screened against Gram-postive and Gram-negative bacteria and fungi, for which some of these derivatives gave promising results.*

Keywords Activated nitriles; antimicrobial activities; (1H-pyrazol-1-yl)pyrimidine; [(pyrimidin-2-yl)disulfanyl] pyrimidine; thiourea; thioxopyrimidines

INTRODUCTION

The importance of the pyrimidine nucleus is well established in the field of pharmaceutical chemistry and biochemistry.[1–3] The pyrimidine-2-thiol moiety is present in several compounds of biological and medicinal interest.[4–8]

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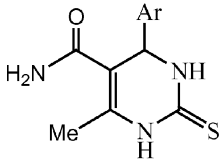
Pyrimidine-5-carboxamides of type (**1**) are reported to possess anticarcinogenic activity.[9] Antiinflammatory,[10,11] analgesic, and blood platelet aggregation inhibitory activity[12] was found in a number of derivatives. 1,4-Dihydropyrimidines (**2**) (Scheme 1) is useful as a platelet-activating factor antagonist.[13] Also, the 1,4-dihydropyrimidines have many biological activities. For example, they represent the largest and most studied class of organic calcium channel blockers widely used in the management of angina pectoris and hypertension as some 1,4-dihydropyrimidine (e.g., Nifedipine).[14]



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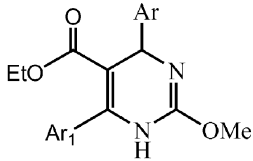


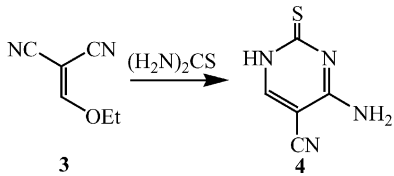
2

Ar = C_6H_4 .Het-4, Ar_1 = C_6H_4 .Cl-2

SCHEME 1

RESULTS AND DISCUSSION

The readily available cyanoolefins are a class of important organic synthones having exciting chemistry.[15–17] The obvious route to pyrimidine-5-carbonitriles is primary synthesis followed by the removal or modification of unwanted groups, e.g., ethoxymethylenemalononitrile (**3**) and thiourea give 4-amino-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (**4**),[18,19] (Scheme 2) which can be desulfurized, S-alkylated, N-acetylated, or hydrolyzed to 5-cyanocytosine without affecting the cyano group.

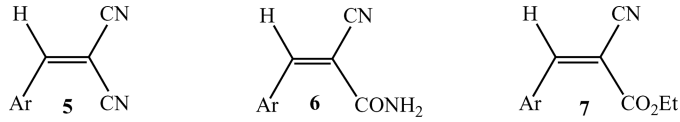


3 **4**

SCHEME 2

So, we felt it would be valuable to investigate the addition of thiourea to activated nitriles (**5–7**),[20,21] (Scheme 3) which was previously intensively investigated.[22–33]

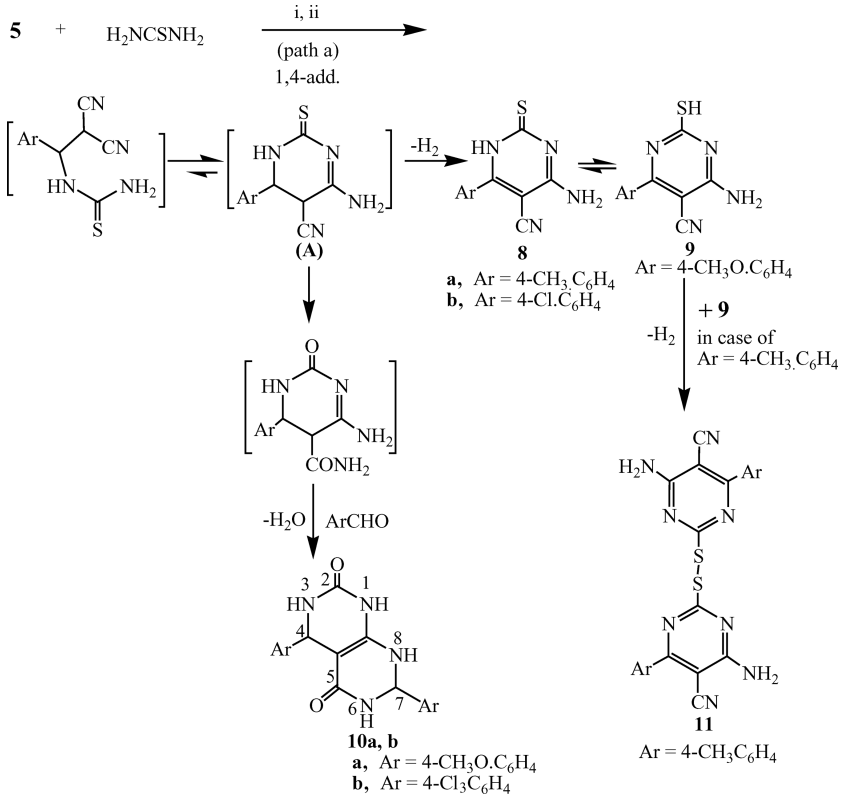
Thus, the piperidine-catalyzed addition of **5** with thiourea in boiling abs. ethanol gave two reaction products as 4-amino-1,2-dihydro-2-thioxo-6-(aryl)pyrimidine-5-carbonitrile (**8a**,**b**) and 4-amino-



a, Ar =$C_6H_4.OCH_3$-4; b, Ar = $C_6H_4.CH_3$-4; c, Ar =$C_6H_4.Cl$-4

SCHEME 3

2-mercapto-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile (**9**), respectively (Scheme 4).



SCHEME 4 Synthesis of **8a**,**b**,**9**, **10a**,**b** & **11** reagents and conditions: (i) piperidine, boiled EtOH, 4 h, 35–57% yield; (ii) Anh. K_2CO_3, boiled EtOH, 4 h 12–14% yield.

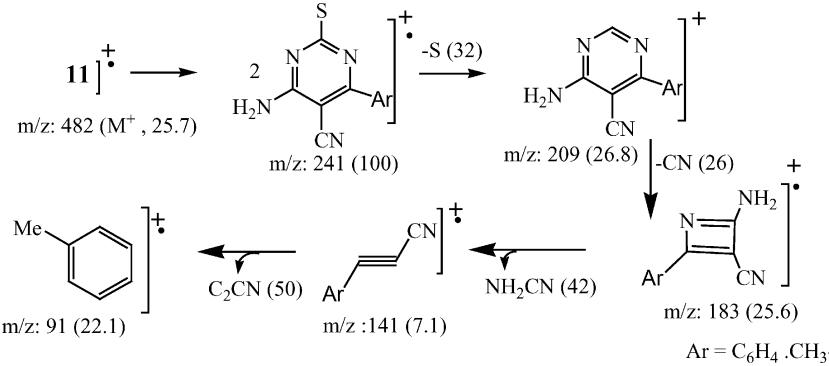
The structures of **8a**,**b** and **9** have been fully characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elementary analysis. In ^{1}H NMR spectra of **8** showed the signals of NH_2 at δ (ppm) = 7.909–8.361 (brs), NH as a singlet signal at δ (ppm) = 12.983–13.091, and ^{13}C NMR for **8a** showed δ_c(ppm) = CS at 180.464, while for compound **9**, ^{1}H NMR showed a

singlet signal at δ (ppm) = 3.572 (SH) and NH_2 protons at δ (ppm) = 7.987 (brs).

Treatment of **5a** with thiourea in the presence of boiled alcoholic K_2CO_3 solution gave a compound as 3,4,7,8-tetrahydro-4,7-bi (4-methoxyphenyl)pyrimido[4,5-d]pyrimidine-2,5(1*H*,6*H*)-dione (**10a**) (Scheme 4), while the treatment of **5b** with $(NH_2)_2CS/K_2CO_3$ under similar reaction conditions gave two reaction products as 3,4,7,8-tetrahydro-4,7-di(p-tolyl)-pyrimido[4,5-d]pyrimidine-2,5(1*H*,6*H*)-dione (**10b**) (Scheme 4) and 4-amino-6-(p-tolyl)-2-[2-(4-amino-5-cyano-6-(p-tolyl)pyrimidine-2-yl)disulfanyl]pyrimidine-5-carbonitrile (**11**) (Scheme 4).

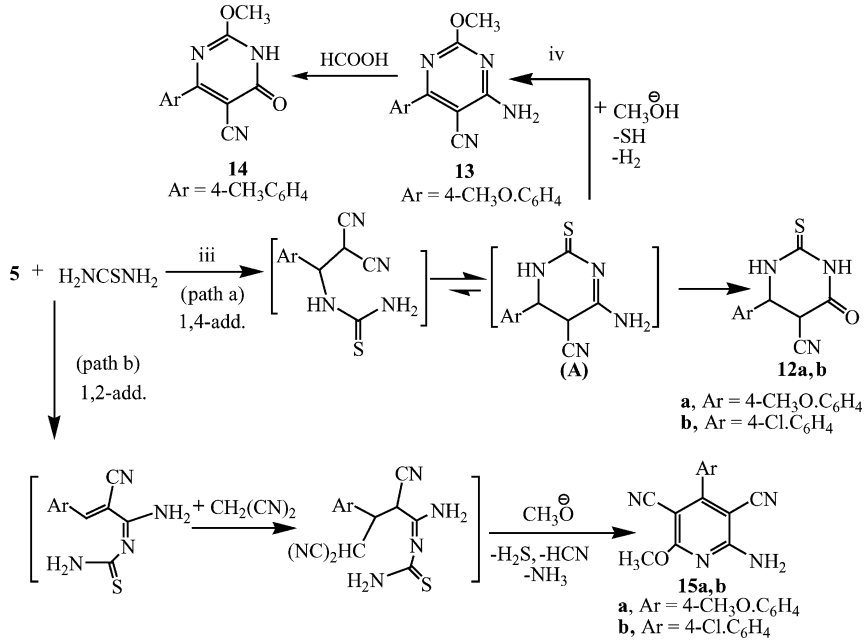
The establishment of structures **10** and **11** were based on its spectral analysis. The IR for compound **10** showed N-H at 3465–3268 and CONH at 1636–1634; ^{1}H NMR (δ ppm). For **10a**, 3.726 & 3.755 (2s, 6H, $2CH_3O$-Ar), 4.627 (br, s, 2H, H-4 & H-7) and singlet signals at 7.58, 7.963, 9.032, 9.847, 10.112, 10.964 (NH and enolic OH), the mass spectum gave molecular ion peak at m/z (%): 380 (M^+, 10.8) and a base peak at m/z 121 (100) with other peaks at 259 (14.9), 202 (18.9), 178 (19.8), 77 (14.8). For **10b**, the ^{1}H NMR showed absorption signals at 2.233, 2.321 (2s, 6H, $2CH_3$-Ar), 6.07 (t, 2H, H-4 & H-7, J = 5.1 Hz); and six absorption peaks at 7.327, 7.719, 7.972, 9.761, 10.043, 10.884 (NH & enolic OH); the mass spectrum showed a molecular ion peak at m/z (%): 343 (M^+, 30.5) and base peak at 105 (100) with other peaks at 288 (14.4), 243 (31.0), 186 (37.3), 262 (39.4). For compound **11**, the IR showed NH_2 at 3232.1 and 3144.7 and CN at 2218; ^{1}H NMR showed δ (ppm) at 2.302 (s, 6H, $2CH_3$-Ar) and 6.965 (br, s, 2H, NH_2), and the mass spectrum gave a molecular ion peak at m/z (%): 482 (25.7) and base peak at 241 (100) corresponding to $M^+/2$ with other peaks at 209 (26.8), 183 (25.6), 141 (7.1), 91 (22.1).

The spectrometric fragmentation of **11** supported the proposed structure (Scheme 5).



SCHEME 5 Spectrometric fragmentation pattern of compound **11**.

The base-catalyzed condensation of **5a** with thiourea in the presence of a methoxide ion under different reaction conditions have also been investigated, where 4-oxo-6-(4-methoxyphenyl)-2-thioxohexahydropyrimidine-5-carbonitr-ile (**12a**)[34] and 2-amino-6-methoxy-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (**15a**) were obtained (Scheme 6).



SCHEME 6 Synthesis of compounds 12–15 reagents and conditions. (iii) CH_3ONa, boiled MeOH, 4 h, 48–50% and 28–30% yield; (iv) excess CH_3ONa, boiled MeOH, 4 h 31% yield.

Similar to the behavior of **5a**, olefinic nitrile **5c** reacted with thiourea under the same reaction grounds in the presence of a methoxide ion and yielded 4-oxo-6-(4-chlorophenyl)-2-thioxohexahydropyrimidine-5-carbonitrile (**12b**) and 2-amino-4-(4-chlorophenyl)-6-methoxypyridine-3,5-dicarbonitrile (**15b**) (Scheme 6).

The refluxing of activated cyanoolefin **5a** with thiourea in the presence of an excess methoxide ion afforded 4-amino-5-cyano-2-methoxy-6-(4-methoxyphenyl)pyrimidine (**13**).

The treatment of **13** with formic acid under reflux afforded the corresponding 2-methoxy-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**14**) (Scheme 6).

The structures of **12–15** were established on the basis of spectral data. Thus, IR for **12** showed CO at 1748–1724; ^{1}H NMR for **12a** showed δ (ppm) at 5.479 (d, 1H, 5-H, J = 11.6 Hz), (5.746–5.621) (m, 1H, 6-H), 10.952, 10.632 (2s, 1H, 1H) and 12.336 (2s, 1H, 3-H). Compound **12b** showed signals at 5.034 (d, 1H, 5-H, J = 11.719 Hz) and 5.247 (d, 1H, H-6, J = 11.33 Hz) and four absorption signals at 10.198, 10.468, 11.796, & 11.907 (NH & enolic OH proton). Also, the mass spectrum for **12a**,**b** showed a very intense molecular ion peak at m/z (%) 269 (M^+, 100), & 265 ((M^+, 100), respectively. The ^{13}C NMR for **12a** showed δ_c (ppm) at 160.329 (CO) and 178.522 (CS).

For compound **13**, the IR showed the absence of υ C=O, its ^{1}H NMR showed δ (ppm) at 3.834 (s, 3H, H_3CO-pyrimidine) and 3.824 (s, 3H, H_3CO-Ar), and the mass spectrum showed a molecular ion peak at m/z (%); 257 (M^+, 100).

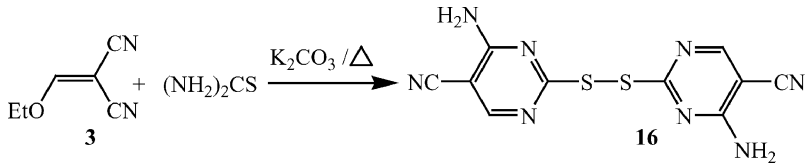
Also, for product **15a**, the ^{1}H NMR showed δ (ppm) at 3.828 (s, 3H, H_3CO-Ar) and 3.953 (s, 3H, H_3CO-py); the ^{13}C NMR showed signals at δ_c (ppm) 55.454 (C-CH_3O-Ar), 56.454 (C-CH_3O-py), 166.71 (C-2), 170.078 (C-6) and the mass spectrum showed a very intense molecular ion peak at m/z (%): 280 (M^+, 100). For compound **15b**, the ^{1}H NMR showed δ (ppm) at 3.985 (s, 3H, CH_3-O) and mass spectrum at m/z (%): 284 (100).

The formation of products **8–15** could be explained by the proposed mechanism (Schemes 4 and 6). The formation products 8–15 (Schemes 4 and 6) could be explained by initial Michael addition of thiourea to the activated double bond (path a 1,4-addition) followed by the cyclization to the intermediate [A], which hydrolyzed into the corresponding carboxamide (CN $\rightarrow$ $CONH_2$) and then reacted with a molecule of free aldehyde obtained from retro Michael addition[35] to give the product **10**. The previous intermediate may be oxidized into **8** and **9**, and two molecules of **9** joined together with the elimination of one molecule of hydrogen to give the product **11**.

Also, the intermediate [A] hydrolyzed into **12** or underwent the nucleophilic substitution of SH^- with MeO^- followed by aromatization to give **13**.

An alternative path b (1,2–addition) of thiourea to the cyano group was followed by the addition of a malononitrile molecule obtained from a retro Michael addition[35] to another molecule of cyano olefin, followed by a ring closure with the elimination of NH_3, HCN, and the substitution of SH^- by MeO^- to give the product **15**.[36]

The interaction of ethoxymethylenemalononitrile (**3**) with $(NH_2)_2CS$ in the presence of boiled alcoholic K_2CO_3 solution gave 4-amino-2-[2-(4-amino-5-cyanopyrimidine-2-yl)di-sulfanyl]pyrimidine-5-carbonitrile (**16**) (Scheme 7) instead of 4-amino-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile (**4**) previously obtained.[18,19]



SCHEME 7

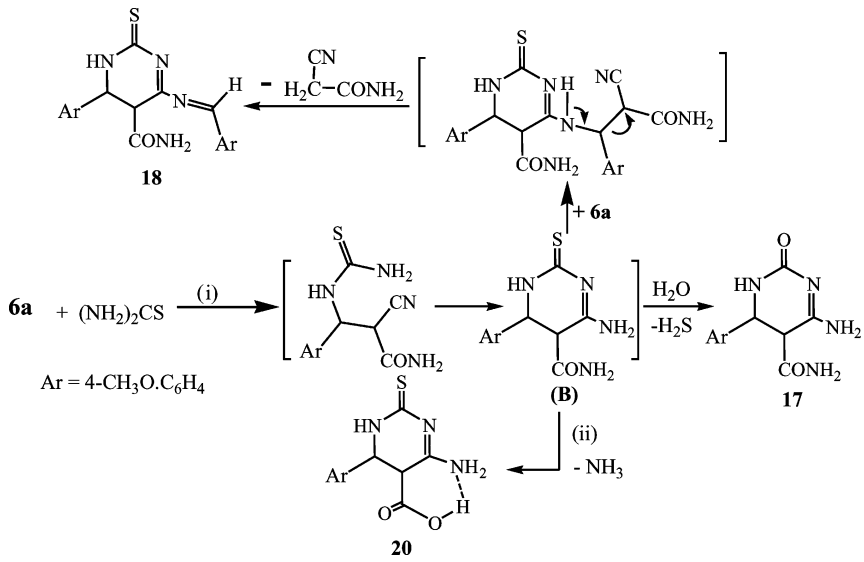
The ^{1}H NMR for **16** showed δ (ppm) at 8.252 (br, 4H, $2NH_2$ disappeared by D_2O) and 8.499 (s, 2H, H-6 & 6′), and the mass spectrum gave a molecular ion peak as an intense peak at m/z (%) 302 (92).

Olefinic **6a** was allowed to react with thiourea in the presence of methanolic methoxide at r.t., which gave rise to three different reaction products, one assigned as 4-amino-1,2,5,6-tetrahydro-6-(4-methoxyphenyl)-2-oxopyrimidine-5-carboxamide (**17**), 4-(4-methoxybenzylidine)amino-1,2,5,6-tetrahydro-6-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxamide (**18**), and 3,5-dicyano-2,4-di(4-methoxyphenyl)-3,4,5,6-tetrahydro-6-oxopyridine-3-carboxamide (**19**).

The reaction seemed to proceed by the Michael addition of the thiourea anion to the activated double bond of **6a** followed by the cyclization of the adduct to give the nonisolated intermediate (**B**), which on hydrolysis gave **17** or when added to second mol of **6a** under the reaction conditions formed a acyclic adduct, which underwent a retro Michael addition to furnish the product **18**. The formation of **19** as a byproduct resulted from the dimerization of **6a** under the previous reaction conditions; a similar finding has been reported previously[37] (Schemes 8 and 9).

Refluxing a mixture of **6a** and thiourea in methanol-methoxide afforded 4-amino-1,2,5,6-tetrahydro-6-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxylic acid (**20**) as a solo product (Scheme 8).

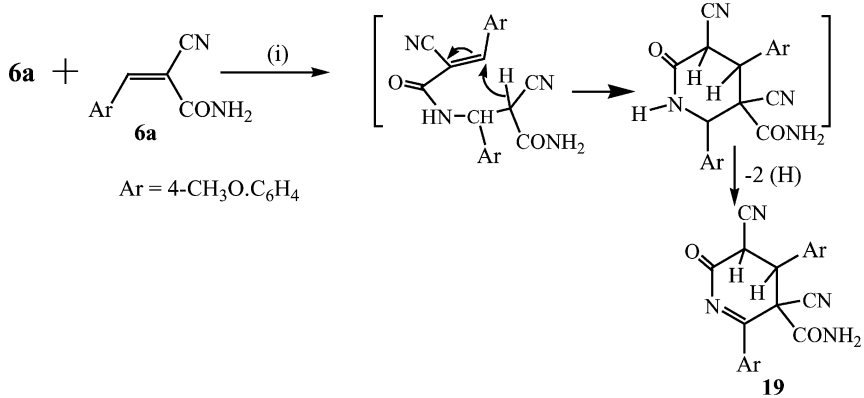
The structures of **17–20** are substantiated by IR, ^{1}H NMR, and mass spectra studies. For **18**, ^{1}H NMR showed δ (ppm) at 3.738, 3.767 (2s, 6H, $2OCH_3$), 5.205 (s, 1H, 5-H), 5.551 (s, 1H, 6-H), 6.135 (s, 1H, =CH-Ar), 9.553 (s, br, 3H, NH + NH_2). Ms for **17** and **18** gave a molecular ion peak at m/z (%): 262 (M^+, 88.9), 396 (M^+, 31.5), respectively. Also, the ^{1}H NMR for **19** showed absorption signals at δ (ppm) = 3.695, 3.775 (2s, 6H, $2CH_3O$-Ar), 4.818, 4.12 (2d, J = 2.734 Hz, 6-H + 5-H), and (8.35–8.616) (s, br, 2H, $CONH_2$). Its mass spectrum showed a molecular ion peak at m/z: 402 (M^+, 14.7) and a base peak 121 (100) with other peaks 360 (29.3), 294 (13.2), 242 (27.8), 201 (14.1), 162 (26.7), 134 (53.4), 77 (38.8). For **20**, IR (υ C=O at 1686) with a shoulder at 1704; ^{1}H NMR δ (ppm) = 4.296 (d, 1H, H-5, J = 12.89 Hz), 4.861 (d, 1H, H-6, J = 12.89 Hz), 5.217 (s, 1H, NH), 7.545 (s, 2H, NH_2), 8.797 (s, 1H, CO_2H), and mass



SCHEME 8 Synthesis of compounds **17**, **18**, and **20** and reagent and conditions, (i) Methanolic CH_3O^-, r.t. 48h (45 & 20) % yield for **17** and **18**; (ii) CH_3OH/CH_3O^-, refluxed methanol, 4h, 40% yield for compound **20**.

spectrum affords an additional support, which showed a molecular ion peak at (%) 279 (M^+, 1.35).

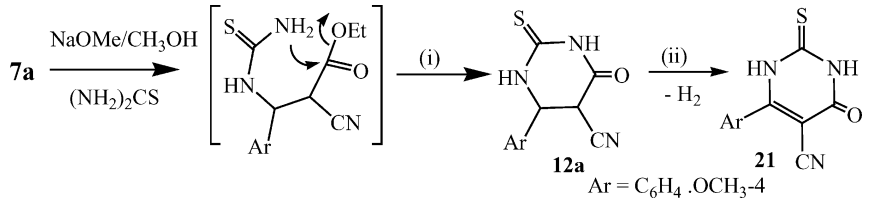
When **7a** was stirred with a methanolic methoxide solution containing thiourea at r.t., it gave 4-oxo-6-(4-methoxyphenyl)-2-thioxohexahydropyrimidine-5-carbonitrile (**12a**) previously obtained from **5a** and thiourea (identical IR, ^{1}H NMR, ^{13}C NMR, m.p., and mixed



SCHEME 9 The dimarization of **6a** reagent and conditions (i) CH_3OH/CH_3O^-, r.t., 48 h, 15% yield.

m.p.), while refluxing **7a** with thiourea in a methanolic solution containing sodium methoxide gave 4-oxo-2-thioxo-6-(4-methoxyphenyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**21**) besides **12a**.

It is assumed that the reaction involved the addition of an anionic form of thiourea to **7a** and a subsequent intramolecular attack at the carbonyl group of the ester to form the cyclized product **12a**, which underwent oxidation into **21** under the influence of olefinic nitrile upon reflux (Scheme 10).



SCHEME 10 (i) NaOMe/MeOH, r.t., 48 h, 50% yield; (ii) NaOMe/MeOH, boiled MeOH, 4 h, 77% yield.

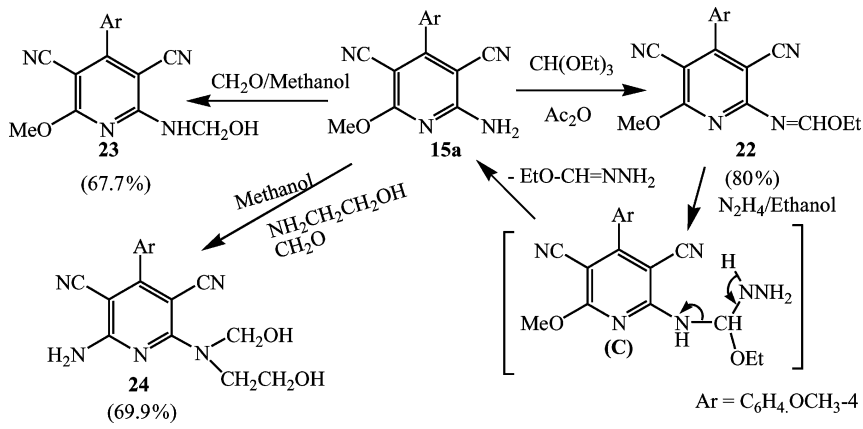
The structure of **21** is inferred from IR (υ C=O:1676.7); the ^{1}H NMR showed a signal at 13.099 (s, 1H, enolic OH), and its mass spectra added further support, which showed a molecular ion peak m/z (%): 259 (M^+, 100).

Compound **15a** reacted with $(EtO)_3CH/Ac_2O$ and gave 2-(E)-ethoxymethyleneamino-6-methoxy-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (**22**). The IR spectrum showed the disappearance of NH_2 bands and the appearance of CH=N at 3002.8; the ^{1}H NMR showed δ at 8.772 (s, 1H, N=CH), and its mass spectrum gave a molecular ion peak at m/z (%): 336 (M^+, 100).

When compound **22** was treated with hydrazine hydrate in well-stirred ethanol at r.t., it lead to the formation of a product, which was found to be identical in all respects (m.p., mixed m.p., and spectral data) with **15a** (Scheme 11).

The formation of **15a** from **22** was assumed to proceed via the addition of hydrazine as a nucleophile at a N=CH site to give the nonisolated intermediate (**C**) followed by the elimination of ethyl formatehydrazone (Scheme 11).

The treatment of **15a** with formaline solution in boiling methanol gave 2-(N-hydroxymethyl)amino-6-methoxy-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (**23**), while the treatment of **15a** with formaline solution in boiling methanol containing an equimolar ratio of ethanolamine gave a product, which was analyzed as 2-(N-hydroxymethyl,N-(β-hydroxyethyl))-amino-6-amino-4-(4-methoxyphenyl)-pyridine-3,5-dicarbonitrile (**24**) (Scheme 11).



SCHEME 11

The formation of **24** was assumed by the nucleophilic substitution of a methoxy group by the β-ethylamino group followed by N-hydroxymethylation by formaldehyde (Scheme 11).

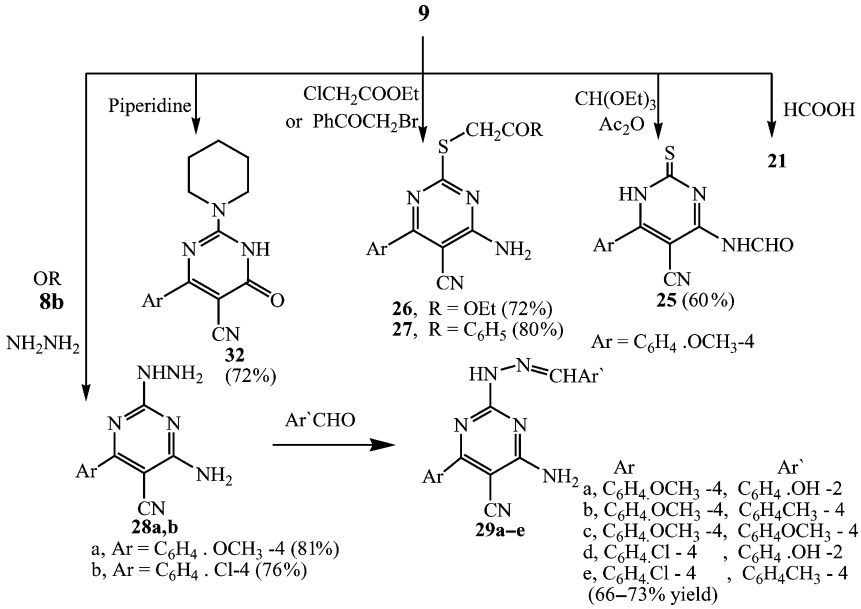
IR spectrum of **23** showed a broad strong absorption band at 3350 (OH, NH), and ^{1}H NMR δ (ppm) at 3.953 (s, 1H, OH), 4.877 (d, J = 6.4 Hz, C$\underline{H}_2$), 8.795 (s, br, 1H, NH); its mass spectrum gave a molecular ion peak at m/z (%) 310 (M^+, 12.1).

Also for compound **24**, IR [υNH_2 as a triplet at 3426, 3334, 3234],^{1}H NMR [δ (ppm) at 1.113 (t, J = 7Hz, 2H, $HOCH_2C\underline{H}_2N$), 3.543 (q, J = 7Hz, 2H, $NCH_2C\underline{H}_2OH$), 3.928 (s, 1H, OH), 4.006 (s, 1H, OH), 4.919 (d. J = 6Hz, NCH_2OH), 8.772 (s, br, 2H, NH_2)], its mass spectrum gave a molecular ion peak at m/z (%): 339 (M^+; 18) and a base peak at 309 (100) with other peaks 393 (80), 280 (72), 59 (42).

The treatment of **9** with boiling formic acid afforded the 4-oxo-2-thioxo-6-(4-methoxyphenyl)-1,2,3,4-tetrahydroprimidine-5-carbonitrile (**21**), (identical IR, ^{1}H NMR, mass, m.p., and mixed m.p.)

Also, the treatment of **9** with $CH(OEt)_3/Ac_2O$ under reflux gave the corresponding N-(5-cyano-2-thioxo-6-(4-methoxyphenyl)-1,2-dihydropyrimidin-4-yl)formamide (**25**) (Scheme 12). IR spectrum for **25** showed [υ CO at 1726.7 ^{1}H NMR gave δ at 9.255 (d, J = 4.688 Hz, 1H, HN-CHO), 11.565 (br, s, 2H, NH), and mass spectrum gave a molecular ion peak at m/z (%): 286 (12.8) together with a base peak at 241 (100).

Also, the condensation of **9** with ethyl chloroacetate and/or phenacyl bromide afforded the corresponding ethyl 2-(4-amino-5-cyano-6-(4-methoxyphenyl)pyrimidin-2-yl)thioacetate (**26**) and 4-amino-2-(2-benzoylmethylthio)-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile (**27**), respectively (Scheme 12).



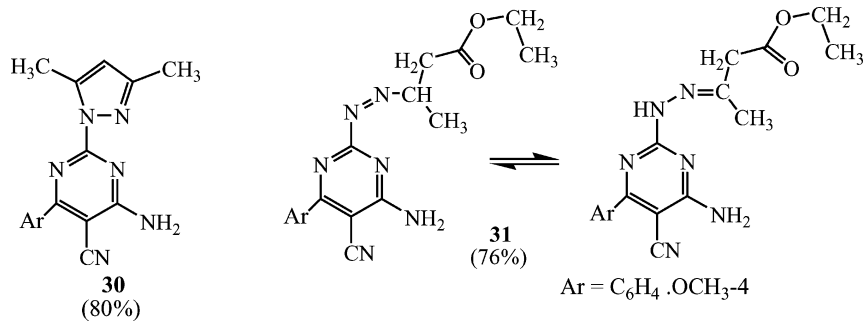
SCHEME 12

Spectral data for compounds **26** and **27** support the proposed structure, thus IR [υCO at 1742.7, 1690], ^{1}H NMR [δ (ppm) at 3.629 (s, 2H, CH_2S), 4.781 (s, 2H,CH_2S)], and its mass spectrum [m/z (%): 344 (M^+, 6.2), 271 (100), 225 (27.4) and 376 (M^+, 10.3), 343 (10.9), 271 (27.4), 105 (100), 77 (36.7)] respectively.

The condensation of **9** and **8b** with hydrazine hydrate gave products that were identified as 4-amino-6-aryl-2-hydrazinylpyrimidine-5-carbonitril (**28a**,**b**), respectively. Also, the condensation of **28a**,**b** with an equimolar ratio of aromatic aldehydes in refluxing n-butanol afforded the corresponding 4-amino-2-((Z)-2-arylidenehydrazinyl)-6-arylpyrimidine-5-carbonitrile **29a–e** (Scheme 12).

The condensation of 2-hydrazinylpyrimidine derivative (**28a**) with 1,3-dicarbonyl compounds, namely acetylacetone and ethyl acetoacetate in boiling ethanol containing a few drops of piperidine, gave 4-amino-6-(4-methoxyphenyl)-2-[(3,5-dimethyl)-1*H*-pyrazol-1-yl]pyrimidine-5-carbonitrile (**30**) and 4-amino-2-(2-ethoxycarbonylisopropylidenehydrazinyl)-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile (**31**), respectively (Scheme 13).

The ^{1}H NMR for **30** showed at δ (ppm) = 2.174 (s, 3H, CH_3), 2.603 (s, 3H, CH_3), and 6.137 (s, 1H, 4-H, pyrazole). Its mass spectrum gave a molecular ion peak as a base peak at m/z (%): 320 (M^+, 100). Also for



SCHEME 13

compound **31**, the IR showed υCO at 1732, ^{1}H NMR: δ (ppm) = 1.978 (s, 3H, CH_3C=), 3.297 (s, 2H, CH_2C=O), 7.4 (s, br, 2H, NH_2 cancelled by D_2O) 9.907 (s, 1H, NH cancelled by D_2O). Its mass spectrum gave m/z (%) at 368 (M^+, 5.08) and a base peak at 281 (100).

The condensation of **8** with piperidine afforded 1,6-dihydro-4-(4-methoxyphenyl)-6-oxo-2-(piperidin-1-yl)pyrimidine-5-carbonitrile (**32**) (Scheme 12). The ^{1}H NMR for **32** showed absorption signals in the form of a complex pattern at δ (ppm) = (1.506–1.591) (10 H, piperidine–H), its mass spectrum showed a molecular ion peak at m/z (%): 310 (M^+, 18.7). together with a base peak at 280 (M^+-CH_2O).

IR, ^{1}H NMR, ^{13}C NMR, and mass spectra for the newly synthesized pyrimidine derivatives were studied (Table I).

ANTIMICROBIAL ACTIVITIES

Some selected compounds were screened for their antimicrobial activity using *Bacillus subtilis* (**ATCC 7972**) (**BS**), *Staphylococcus aurous* (**NCTC 7447**) (**SA**) (Gram-positive), *Escherichia coli* (**NCTC 10416**) (**EC**), *Pseudomonas aeuroginosa* (**ATCC 10415**) (**PA**), **Candida albican** (**IMRU 3669**) (**CA**) (Gram-negative), and *Aspergillus niger* (**ATCC 6275**) (**AN**) (fungi) microorganisms. The activities of these compounds were tested using disc diffusion method.[38,39] The tested compound were dissolved in N,N-dimethylformamide (DMF) to get a solution of mg mL^{-1}. The inhibition zones were measured in millimeters at the end of incubation period of 48 h at 28°C. N,N-dimethylformamide showed no inhibition zones. The area of the zone of inhibition was measured using neomycin (30 mg) as a standard antibiotic.

Compound **26** showed the highest antibacterial activity (+++, the inhibition zone was between 12–15 mm), against **BS**, **SA**, **EC**,

TABLE I Spectral Data for the Newly Prepared Compounds

Compound	IR (ν_{max} cm^{-1})	^{1}HNMR/^{13}CNMR (δ ppm)/MS (m/z %)
8a	3405.8, 3345, 3233.6, 3163.9 (NH_2, NH), 2213.3 (CN), 1639.2 (C═N), 1392 (C═S)	2.386 (s, 3H, CH_3-Ar), 7.351, 7.570 (2d, J = 8.203 Hz, 4H, Ar-H), 7.909, 8.361 (2brs, 2H, NH_2), 12.983 (s, 1H, NH) 21.057, 68.275, 115.069, 128.792, 128.967, 142.16, 163.796, 180.464 242 (75.9), 241 (100), 209 (15.7), 184 (32.5), 140 (12.5), 118 (12.6), 91 (13.6), 65 (19.6)
8b	3471.3, 3329.8, 3226.3 (NH_2, NH), 2221.5 (CN), 1392 (C═S)	7.599, 7.826 (2d, 4H, Ar-H, J = 8.203 Hz), 8.112 (brs, 2H, NH_2), 13.091 (s, 1H, NH) 262 (85.2), 261 (100), 229 (24), 204 (40), 187 (12), 162 (14.5), 138 (22.4), 111 (14.3), 92 (17.6), 75 (34.4), 67 (29.3), 51 (29.6)
9	3434, 3333.4, 3229.5 (NH_2), 2218 (CN)	3.572 (s, 1H, SH), 3.831 (s, 3H, CH_3O-Ar), 7.057, 7.840 (2d, J = 8.984 Hz, 4H, Ar-H) and 7.987 (brs, 2H, NH_2)
10a	3465.3, 3268.9 (NH), 1634.3 (CONH)	3.726, 3.755 (2s, 6H, $2CH_3O$-Ar), 4.627 (br, s, 2H, H-4 & H-7), (6.907–6.948) (br, s, 4H, Ar-H), 7.05 & 7.18 (2d, 4H, Ar-H, J = 8.5 Hz), 7.58, 7.963, 9.032 (hump), 9.847 (broad), 10.112 (broad), 10.964 (NH and enolic OH protons) 380 (10.8), 121 (100), 259 (14.9), 202 (18.9), 178 (19.8), 77 (14.8)
10b	3460.5, 3404.1, 3326.1 (NH), 2986.2 , 2903.7 (CH), 1636.1 (CONH)	2.233 (s, 3H, CH_3-Ar), 2.321 (s, 3H, CH_3-Ar), 6.07 (t, 2H, H-4 & H-7, J = 5.1 Hz), 7.019 & 7.171 (2m, 8H, Ar-H), 7.327 & 7.719 & 7.972 & 9.761 & 10.043 & 10.884 (NH and enolic OH protons) 348 (30.5), 105 (100), 288 (14.4), 243 (31.0), 186 (37.3), 162 (39.4)
11	3232.1, 3144.7 (NH_2), 2218.6 (CN)	2.302 (s, 6H, $2CH_3$-Ar), 6.965 (br, s, 2H, NH_2), 7.049 (m, 8H, Ar-H) 482 (25.7), 241 (100), 209 (26.8), 184 (23.4), 183 (25.6), 142 (13.2), 141 (7.1), 140 (16.3), 91 (22.1), 65 (35.1)
12a	3431, 3137.9 (NH), 2267.4, (CN), 1724.1 (CO)	4.262 (s, 3H, OCH_3), 5.479 (d, J = 11.6 Hz, 1H, 5-H), (5.746–5.621) (m, 1H, 6-H), 7.869, 7.498 (2d, J = 8.2 Hz, 4H, Ar-H), 10.952 & 10.632 (2s, 1H, 1-H), 12.337, 12.336 (2s, 1H, 3-H) 39.667 (C-5), 40.669 (C-6), 55.189 (OCH_3), 114.128, 114.280 (C-3′, 5′), 114.575 (CN), 127.374 (C1′), 127.928, 129.096 (C2′, 6′), 159.806 (C4′), 160.329 (CO), 178.522 (CS) 261 (100), 186 (68.1), 178 (75.7), 158 (21.8), 134 (73.9), 121 (33.6), 89 (25.4), 77 (22.3), 51 (22.6)

(Continued on next page)

TABLE I Spectral Data for the Newly Prepared Compounds *(Continued)*

Compound	IR (ν_{max} cm^{-1})	^{1} HNMR/^{13}CNMR (δ ppm)/MS (m/z %)
12b	3302, 3162 (NH), 2940, 2902 (CH), 2245 (CN), 1748 (CO)	5.034 (d, 1H, H-5; J = 11.719 Hz), 5.247 (d, 1H, H-6; J = 11.328 Hz), 7.456 & 7.536 (2d, 4H, Ar-H, J = 8.594 Hz), 10.198, 10.468, 11.796, 11.907 (NH and enolic OH) 265 (100), M + 2 (39.37), 182 (55.37), 138 (38.47), 28.1 (36,93), 101 (9.76), 86 (7.14), 75 (16.04), 59 (20.76)
13		3.923 (s, 3H, CH_3O-Ar), 4.051 (s, 3H, CH_3O-pyrimidine), 7.352, 7.546 (2d, 4H, Ar-H, J = 9.0 Hz), 7.934 (br, s, 2H, NH_2)
14	3451.1 (NH), 3062.4 (C-H arom.), 2964 (C-H aliph.), 2214.8 (CN), 1673.4 (CO), 1603 (C═N)	3.834 (s, 3H, OCH_3-py), 3.824 (s, 3H, OCH_3-Ar), 7.100 & 7.625 (2d, 4H, Ar-H), 12.931, 13.081 (s, br, 2H, 2NH). 257 (M^+, 100), 200 (18.9), 199 (25.2), 134 (20.9), 63 (13.2)
15a	3424, 3330, 3234 (NH_2), 2942 (aliph. C-H), 2224, 2210 (CN)	3.828 (s, 3H, CH_3O-Ar), 3.953 (s, 3H, CH_3O-Py), 7.096 & 7.473 (2d, 4H, Ar-H; J = 8.985 Hz), 7.936 (s, br, 2H, NH_2) 55.454 (C-CH_3O-Ar), 56.454 (C-CH_3O-Py), 82.811 (C-3, C-5), 113.938 (C-3′, C-5′), 116.267 (2CN), 127.571 (C-2′, C-6′), 130.393 (C-1′), 161.885 (C-4′), 164.107 (C-4), 166.710 (C-2), 170.078 (C-6) 280 (100), 238 (2.8), 157 (2), 127 (2.3), 100 (2.9)
15b	3481, 3346, 3227.2 (NH_2), 2955 (aliph. C-H), 2217 (CN)	3.985 (s, 3H, CH_3O—), 7.544 & 7.654 (2d, 4H, Ar-H; J = 6.6 Hz) and at 7.967 (br, s, 2H, NH_2) 284 (100), M + 2 (33.4), 255 (24.2), 249 (42.2), 165 (12.7)
16	3421.6, 3308, 3205.6 (NH_2), 2224.4 (CN)	8.252 (br, 4H, $2NH_2$, disappeared by D_2O), 8.499 (s, 1H, 2H, 2H-6). 302 (92), 94 (100), 270 (8), 238 (45), 185 (20), 152 (64),119 (45), 93 (53), 66 (60)
17		262 (M^+, 88.9), 261 (100), 204 (33.2), 134 (19.2), 99 (20.7), 67 (40.4)
18	3372, 3172 (NH_2), 3075.2 (C-H arom.), 2932 (C-H aliph.), 1668.3 (CO)	3.738, 3.767 (2s, 6H, $2OCH_3$), 5.205 (s, 1H, 5-H), 5.551 (s, 1H, 6-H), 6.135 (s, 1H, =CH-Ar), 6.90, 6.972 (2d, J = 7 Hz, 4H, Ar-H), 7.237, 7.455 (2d, J = 7 Hz, 4H, Ar-H), 9.553 (s, br, 3H, NH + NH_2) 396 (31.51), 134 (100), 394 (47.8), 353 (41.3), 287 (90.7), 178 (38.5), 119 (33.1), 77 (57.6)

(Continued)

TABLE I Spectral Data for the Newly Prepared Compounds *(Continued)*

Compound	IR (ν_{max} cm^{-1})	^{1} HNMR/^{13}CNMR (δ ppm)/MS (m/z %)
19	3240.5 (NH_2), 2215 (CN), 1663.4 (CO)	3.695 (s, 3H, OCH_3), 3.775 (s, 3H, OCH_3), 4.818, 4.12 (2d, J = 2.734 Hz, 6-H + 5-H), 7.515, 7.122, 6.995, 6.87 (4d, 8H, Ar H), (8.35–8.616) (s, br, 2H, $CONH_2$) 402 (M^+, 14.7), 121 (100), 360 (29.3), 294 (13.2), 242 (27.8), 201 (14.1), 162 (26.7), 134 (53.4), 77 (38.8)
20	3454, 3350 (NH_2), 1704, 1686 (CO)	3.746 (s, 3H, OCH_3), 4.296 (d, 1H, H-5, J = 12.89 Hz), 4.861 (d, 1H, H-6, J = 12.89 Hz), 5.217 (s, 1H, NH), three set of multiples at (6.922–7.424) (m, 4H, Ar-H), 7.545 (s, 2H, NH_2), 8.797 (s, 1H, CO_2H) 279 (M^+, 1.35), 268 (7.7), 211 (24.79), 196 (29.62), 161 (9.16), 149 (12.47), 135 (6.75), 97 (10.08), 85 (15.21), 71 (23.1), 45 (100)
21	3470.9 (NH), 2212.1 (CN), 1676.7, (CO)	3.843 (s, 3H, OCH_3), 7.103 & 7.651 (2d, J = 9.0 Hz, 4H, Ar-H), 13.099 (s, 1H, OH) 259 (M^+, 100), 231 (19.7), 201 (27), 158 (16.2), 134 (63.5), 91 (13.8), 63 (13.8)
22	3002.8 (C-H arom.), 2966.2 (C-H aliph.) 2226.2 (CN)	1.352 (t, J = 7.0 Hz, 3H, CH_3), 3.848 (s, 3H, OCH_3), 4.088 (s, 3H, OCH_3); 4.424 (q, J = 7.0 Hz, 2H, CH_2) 7.147, 7.565 (2d, J = 8.6 Hz, 4H, Ar-H), 8.772 (s, 1H, N=CH) 336 (M^+, 100), 280 (98.40), 249 (24.9), 195 (12.0), 114 (11.3)
23	Strong broad at 3350 (OH & NH), 2214 (CN)	3.836 (s, 3H, OCH_3-Ar), 3.953 (s, 1H, OH), 4.010 (s, 3H, OCH_3-Py), 4.877 (d, J = 6.4 Hz, $C\underline{H_2}$), 7.112, 7.499 (2d, J = 8.59, 4H, Ar-H), 8.795 (s, br, 1H, NH). 310 (M^+, 12.1), 309 (13.2), 292 (100), 280 (83.8), 195 (20), 152 (18.2), 114 (16.2), 63 (13.2)
24	3426, 3334, 3234 (NH_2), 2944 (CH-aliph.), 2212 (CN)	1.113 (t, J = 7 Hz, 2H, $HOCH_2\underline{CH_2}N$), 3.543 (q, J = 7 Hz, 2H, $NCH_2\underline{CH_2}OH$), 3.83 (s, 3H, OCH_3), 3.928 (s, 1H, OH), 4.006 (s, 1H, OH), 4.919 (d. J = 6Hz, NCH_2OH), 7.104, 7.484 (2d, J = 8.6 Hz, 4H, Ar-H), 8.772 (s, br, 2H, NH_2) 339 (M^+; 18), M-1 (68), 309 (100), 293 (80), 280 (72), 59(42)
25	3329, 3228 (NH), 2219.4 (CN), 1726.7 (CO)	3.826 (s, 3H, OCH_3), 7.089, 7.889 (2d, J = 9.0 Hz, 4H, Ar-H), 9.255 (d, J = 4.688 Hz, 1H, HN-CHO), 11.565 (br, s, 2H, NH).

(Continued on next page)

TABLE I Spectral Data for the Newly Prepared Compounds *(Continued)*

Compound	IR (ν_{max} cm^{-1})	^{1}HNMR/^{13}CNMR (δ ppm)/MS (m/z %)
		286 (12.8), 241 (100), 257 (64.2), 199 (41.7), 157 (11.2), 92 (11.4), 64 (20)
26	3354.8, 3327, 3150.7 (NH_2), 2217.1 (CN), 1742.7 (CO)	2.074 (s, 3H, CH_3), 3.629 (s, 2H, CH_2S), 3.838 (s, 3H, OCH_3), 4.01 (s, $\underline{CH_2}CH_3$) (7.071–7.893) (m, 6H, Ar-H + NH_2) 344 (M^+, 6.2), 271 (100), 225 (27.4)
27	3354, 3164 (NH_2), 2222 (CN), 1690 (CO), 1666 (C═N)	3.777 (s, 3H, OCH_3), 4.781 (s, 2H, CH_2); 6.868, 7.559 (2d, J = 8.5 Hz, 4H-ArH), (7.634-8.061) (m, 7H, Ar-H + NH_2) 376 (M^+, 10.3), 343 (10.9), 271 (27.4), 105 (100), 77 (36.7)
28a	3454.2, 3301.8, 3238.3 (NH_2), 3153.4 (NH), 2193.7 (CN)	3.809 (s, 3H, OCH_3); 4.375 (s, 2H, NH_2), 7.039 (d, J = 8.985, 4H, ArH), 7.834, 8.661 (2s, br, 3H, NH_2+ NH) 256 (M^+, 100), 227 (26), 225 (30), 184 (10)
28b	3414, 3342 (NH_2), 3250 (NH), 2214 (CN)	260 (M^+, 100), M + 2 (34.4), 231 (42.2), 230 (16.1), 204 (15.91), 138 (14.4), 67 (16.1)
29a	3475, 3372 (NH_2), 3298 (NH), 2200 (CN)	360 (M^+, 25.43), 343 (20.15), 241 (100), 240 (61.29), 225 (27.35), 200 (28.39), 199 (28.52), 157 (15.37), 134 (24.02), 119 (42.89), 105 (38), 91 (70.17), 77 (60.34)
29b	3470, 3350, 3294 (NH_2), 3148 (NH), 2202 (CN)	2.335 (s, 3H, CH_3), 3.848 (s, 3H, OCH_3), 7.092–7.246 (2d, J = 8.4 Hz, 4H, Ar-H), 7.42 (s, br, 2H, NH_2, cancelled by D_2O) 7.566, 7.867 (2d, J = 8.7 Hz, 4H, Ar-H), 8.167 (s, 1H, N = CH), 11.29 (s, br, 1H, NH, cancelled by D_2O) 358 (M^+, 8), 276 (16), 241 (100) 199 (28), 134 (16), 117 (44), 91 (68), 65 (40)
29c	3476, 3290 (NH_2), 3112 (NH), 2196 (CN)	3.795 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.100, 7.083 (2d, J = 8.7 Hz, 4H, Ar-H), 7.394 (s, br, 2H, NH_2 cancelled by D_2O), 7.631, 7.856 (2d, J = 8.4 Hz, 4H, Ar-H), 8.14 (s, 1H, N=CH), 11.227 (s, br, 1H, NH, cancelled by D_2O) 374 (M^+, 3.36), 241 (100), 199 (27.3), 157 (12.84), 133 (37.4), 91(35), 77 (44.74)
29d	3402 (br), 3254 (NH_2, NH), 2210 (CN)	6.881 (m, 4H, Ar-H), 7.244 (hump, 2H, NH_2), (7.629–7.885) (m, 4H, Ar-H), 8.413 (s, 1H, N=CH), 11.052, (11.702–11.903) (br signals, OH + NH)
29e	3470, 3346, 3292 (NH_2), 3158 (NH), 2206 (CN)	2.32 (s, 3H, CH_3), 7.232, 7.547 (2d, J = 8.203 Hz, 4H, Ar-H), 7.610, 7.843 (2d, J = 8.6 Hz, 4H, Ar-H), 8.155 (s, 1H, N=CH), 7.598 (s, br, 2H, NH_2), 11.434 (s, br, 1H, NH)

(Continued)

TABLE I Spectral Data for the Newly Prepared Compounds *(Continued)*

Compound	IR(ν_{max} cm^{-1})	^{1} HNMR/^{13}CNMR (δ ppm)/MS (m/z %)
		362 (4.89), M + 2 (2.21), 271 (4.4), 245 (100), 229 (2.56), 205 (11), 203 (24.74), 162 (2.12), 138 (4.6), 91 (6.18)
30	3477.4, 3274.1 (NH_2), 3140.9, 2208.7 (CN), 1649.1 (C═N)	2.174 (s, 3H, CH_3), 2.603 (s, 3H, CH_3), 3.842 (s, 3H, OCH_3), 6.137 (s, 1H, 4-H, pyrazole), 7.117, 7.944 (2d, J = 9 Hz, 4H, Ar-H), 7.922–7.965 (s, br, 2H, NH_2)
		320 (100), 305 (21.4), 278 (11.8), 225 (11.7), 121 (10.2), 95 (11.7)
31	3484, 3294, 3152 (NH_2, NH), 2202 (CN), 1732 (CO)	1.202 (t, J = 5.1 Hz, 3H, CH_3), 1.978 (s, 3H, CH_3C=), 3.297 (s, 2H, CH_2C=O), 3.835 (s, 3H, OCH_3), 4.118 (q, J = 5.1 Hz, $\underline{CH_2}CH_3$), 7.008, 7.819 (2d, J = 8.7 Hz, 4H, Ar-H), 7.4 (s, br, 2H, NH_2 cancelled by D_2O) 9.907 (s, 1H, NH cancelled by D_2O)
		368 (5.08), 281 (100), 353 (2.51), 322 (12.74), 254 (9.56), 225 (18.91), 183 (10.86), 158 (7.42), 134 (10.11), 77 (5.86), 68 (10)
32	3258.6 (NH), 2947.9, 28471 (C-H aliph.), 229.8 (CN), 1730.8 (CO)	(1.506–1.591) (complex pattern, 10 H, piperidine–H), 3.812 (s, 3H, OCH_3), 7.041, 7.816 (2d, J = 8.6 Hz, 4H, Ar-H), 7.131 (s, br, 1H, NH)
		310 (18.7), 180 (100), 309 (89.2), 294 (30.2), 281 (26.3), 266 (39), 254 (42.8), 226 (37.0), 225 (38.5), 183 (10.7), 84 (81.3)

and **PA**, while compound **12a** showed the same effect against **BS**, **SA**, and **PA**, and compound **24** gave the same effect against **BS** and **SA**. Compound **26** showed moderate inhibition (++, inhibition zone ≈ 8–12 mm) against **CA** and **AN**, while compounds **17**, **18**, **27**, **29a**, and **30** showed moderate inhibition against **BS**, **SA**, **EC**, and **PA**, compound **8** gave a moderate effect against **BS**, and **SA**, Compound **24** gave a moderate effect against **EC**, and **PA**, compound **12a** also gave a moderate effect against **EC**. The remaining tested compounds showed weak (+) to poor (−) activities against all the tested microorganisms.

It was observed that the compounds containing pyridine nucleus substituted by two carbonitriles (3,5-) and two amino groups (2,6-) (compound **24**) that contained a pyrimidine moiety with poly functional substituted groups (compounds **12a**, **26**) showed a promising effect against most of the tested microorganisms (Table II).

TABLE II Antimicrobial Activity of Some Newly Synthesized Compounds. −ve (no activity); +ve (when inhibition zone up to 8 mm); ++ve (when inhibition zone was between 8–12 mm); +++ve (when inhibition zone was between 12–15 mm); ++++ve (when inhibition zone was over 15 mm); −MIC 50 mg/mL.

	Gram-positive		Gram-negative			Fungi
Compound	BS	SA	EC	PA	CA	AN
8a	−ve	−ve	−ve	−ve	−ve	−ve
9	++ve	++ve	−ve	−ve	−ve	−ve
12a	+++ve	+++ve	++ve	+++ve	+ve	+ve
15a	+ve	+ve	+ve	+ve	−ve	−ve
15b	+ve	+ve	+	+ve	+ve	−ve
17	++ve	++ve	++ve	++ve	−ve	−ve
18	++ve	++ve	++ve	++ve	−ve	−ve
19	+ve	+ve	+ve	+ve	−ve	−ve
21	+ve	+ve	+ve	+ve	+ve	−ve
22	+ve	+ve	+ve	+ve	−ve	−ve
24	+++ve	+++ve	++ve	++ve	−ve	−ve
26	+++ve	+++ve	+++ve	+++ve	++ve	++ve
27	++ve	++ve	++ve	++ve	+ve	−ve
29a	++ve	++ve	++ve	++ve	−ve	−ve
30	++ve	++ve	++ve	++ve	−ve	−ve
Neomycin	++++ve	++++ve	+++ve	+++ve	−ve	−ve

EXPERIMENTAL SECTION

Melting points were measured using the melting point apparatus (Stuart Scientific Co., UK), and remained uncorrected. The IR spectra were recorded on a Shimadzu IR 440 spectrophotometer (Shimadzu, Japan) in KBr. ^{1}H and ^{13}C NMR spectra were recoded on a Varian Gemini 200 NMR spectrometer at 200 and 50 MHz with a chemical shift calculated from deuterated solvent residues. Microanalytical data (Table II) were obtained from the Microanalytical Unit of the Cairo University (Cairo, Egypt).

4-Amino-1,2-dihydro-2-thioxo-6-arylpyrimidine-5-carbonitrile (8a, b) 4-Amino-2-mercapto-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile (9)

A solution of thiourea (760 mg, 10 mmol) in ethanol (15 mL) containing three drops of piperidine and the corresponding benzylidenemalononitrile (**5**) (10 mmol) dissolved in ethanol (15 mL), were successively

added, and the reaction mixture was refluxed for 4 h. The reaction mixture was precipitated with dil. HCl; the solid product so formed was collected by filtration, washed several times by water, and then recrystallized from the appropriate solvent (Table III).

3,4,7,8-Tetrahydro-4,7-bis(4-methoxyphenyl)pyrimido[4,5-d]-pyrimidine-2,5(*1H, 6H*)-dione (10a), 3,4,7,8-Tetrahydro-4,7-bi-(p-tolyl)pyrimido[4,5-d]-pyrimidine-2,5*(1H, 6H)*-Dione (10b), 4-Amino-6-(p-tolyl)-2-[2-(4-amino-5-cyano-6-(p-tolyl))pyrimidin-2-yl)-disulfanyl]pyrimidine-5-carbonitrile (11) and 4-Amino-2- [2-(4-amino-5-cyanopyrimidin-2-yl) disulfanyl]-pyrimidine-5-carbonitrile (16)

To a solution of respective benzylidenemalononitrile (**5**) or ethoxymethylenemalononitrile (**3**) (10 mmol) in (10 mL) absolute ethanol and (760 mg, 10 mmol) of thiourea in ethanol (10 mL) containing anhydrous K_2CO_3 (1.380 g, 10 mmol) were added. The reaction mixture was refluxed for 4 h. The potassium salt, which precipitated during the reaction, was collected. The crude salt was stirred in water at 80°C; stirring was continued until a clear solution was obtained. After cooling, the solution was acidified with dil. HCl; the solid product so formed was collected by filtration, washed several times by water, and then recrystallized from the appropriate solvent (Table III). In the case of **5b**, the reaction product was a mixture of **10b** and **11** and was separated by gas–liquid chromatography.

4-Oxo-6-(4-methoxyphenyl)-2-thioxohexahydropyrimidine-5-carbonitrile (12a), 2-Amino-6-methoxy-4-(4-methoxyphenyl)-pyridine-3,5-dicarbonitrile (15a), and 4-Oxo-6(4-chlorophenyl)-2-thioxohexahydroprimidine-5-carbonitrile (12b) and 2-Amino-4-(4-chlorophenyl)-6-methoxypyridine-3,5-dicarbonitrile (15b)

To a solution of sodium (230 mg, 10 mmol) in methanol (50 mL), thiourea (760 mg, 10 mmol) was added. When it became dissolved, (10 mmol) of the corresponding benzylidenemalononitrile (**5**) dissolved in methanol was added. The resulting mixture was refluxed for 4 h. The reaction mixture was poured onto ice water and neutralized by dil. hydrochloric acid (10%); the solid product so formed was collected by filtration, washed several times with water, and then recrystallized from the appropriate solvent (Table III).

TABLE III Physical and Analytical Data for the Newly Prepared Compounds

Compound	M.P.°C (solvent)	Color (yield %)	M. formula (m. wt.)	Calcd/(found) C	H	N
8a	.265–267 (D)	Colorless (57)	$C_{12}H_{10}N_4S$ (242.23)	59.48 (59.38)	4.16 (4.08)	23.12 (23.03)
8b	268–270 (D)	Colorless (53)	$C_{11}H_7ClN_4S$ (262.72)	50.29 (50.18)	2.69 (2.53)	21.33 (21.25)
9	258–260 (DMF)	Colorless (35)	$C_{12}H_{10}N_4OS$ (258.23)	55.80 (55.79)	3.90 (3.74)	21.69 (21.57)
10a	206–208 (Et)	Brown (12)	$C_{20}H_{20}N_4O_4$ (380.40)	63.15 (62.96)	5.30 (5.18)	14.73 (14.56)
10b	Mixed 230–234 (Et)	Yellow (14)	$C_{20}H_{20}N_4O_2$ (348.40)	68.95 (68.84)	5.79 (5.67)	16.08 (16.08)
11	Mixed 230–234 (Et)	Yellow (14)	$C_{24}H_{18}N_8S_2$ (482.58)	59.73 (59.67)	3.76 (3.63)	23.22 (23.11)
12a	226–228* (Et)	Yellow (50)	$C_{12}H_{11}N_3O_2S$ (261.30)	55.16 (54.98)	4.24 (4.28)	16.08 (15.30)
12b	216–218 (B)	Yellow (48)	$C_{11}H_8ClN_3OS$ (265.72)	49.72 (49.28)	3.03 (2.96)	15.81 (15.04)
13	250–252 (E/B)	Colorless (31)	$C_{13}H_{12}N_4O_2$ (256.26)	60.93 (60.84)	4.72 (4.61)	21.86 (21.72)
14	268–270 (GAA)	Yellow (92)	$C_{13}H_{11}N_3O_3$ (257.24)	60.70 (60.61)	4.31 (4.22)	16.33 (16.22)
15a	280–282** (D)	Colorless (30)	$C_{15}H_{12}N_4O_2$ (280.28)	64.28 (64.17)	4.32 (4.23)	19.99 (19.86)
15b	282–284 (D)	Colorless (28)	$C_{14}H_9ClN_4O$ (284.7)	59.06 (58.92)	3.19 (3.02)	19.68 (19.53)
16	314–316 (DMF)	Yellow (53)	$C_{10}H_6N_8S_2$ (302.40)	39.73 (39.62)	2.00 (1.91)	37.06 (36.93)
17	Mixed 248–252 (Et)	Colorless (45)	$C_{12}H_{14}N_4O_3$ (262.26)	54.96 (54.82)	5.38 (5.18)	21.36 (21.12)
18	Mixed 248–252 (Et)	Colorless (20)	$C_{20}H_{20}N_4O_3S$ (396.46)	60.59 (60.42)	5.08 (4.98)	14.13 (14.6)
19	272–174 (DMF)	Green (15)	$C_{22}H_{18}N_4O_4$ (402.40)	65.66 (65.58)	4.51 (4.43)	13.92 (13.81)
20	252–254 (D)	Colorless (40)	$C_{12}H_{13}N_3O_3S$ (279.31)	51.60 (51.49)	4.69 (4.53)	15.04 (14.92)
21	280–282 (Et)	Colorless (77)	$C_{12}H_9N_3O_2S$ (259.28)	55.59 (55.49)	3.50 (3.39)	16.21 (16.15)
22	188–190 (B)	Colorless (80)	$C_{18}H_{16}N_4O_3$ (336.12)	64.28 (64.18)	4.79 (4.70)	16.66 (16.58)
23	184–186 (Et)	Colorless (67.7)	$C_{16}H_{14}N_4O_3$ (310.31)	61.93 (61.82)	4.55 (4.47)	18.06 (17.94)
24	178–180 (Et)	Colorless (69.9)	$C_{17}H_{17}N_5O_3$ (339.35)	60.17 (60.8)	5.05 (4.96)	20.64 (20.58)
25	226–228 (D)	Colorless (60)	$C_{13}H_{10}N_4O_2S$ (286.31)	54.54 (54.43)	3.52 (3.51)	19.57 (19.48)

(Continued on next page)

TABLE III Physical and Analytical Data for the Newly Prepared Compounds *(Continued)*

Compound	M.P.°C (solvent)	Color (yield%)	M. formula (m. wt.)	Calcd/(found) C	H	N
26	180–182 (Et)	Yellow (72)	$C_{16}H_{16}N_4O_3S$ (344.39)	55.80 (55.69)	4.68 (4.56)	16.27 (16.18)
27	174–176 (Et)	Colorless (80)	$C_{20}H_{16}N_4O_2S$ (376.43)	63.81 (63.72)	4.28 (4.21)	14.88 (14.79)
28a	280–282 (D)	Colorless (81)	$C_{12}H_{12}N_6O$ (256.26)	56.24 (56.16)	4.72 (4.64)	32.79 (32.79)
28b	258–260 (D)	Colorless (76)	$C_{11}H_9ClN_6$ (260.68)	50.68 (50.79)	3.48 (3.41)	32.24 (32.17)
29a	216–218 (Et)	Colorless (68)	$C_{19}H_{16}N_6O_2$ (360.37)	63.32 (63.22)	4.48 (4.41)	23.32 (23.21)
29b	218–220 (Et)	Colorless (69)	$C_{20}H_{18}N_6O$ (358.40)	67.02 (66.93)	5.06 (4.96)	23.45 (23.38)
29c	234–236 (Et/B)	Yellow (73)	$C_{20}H_{18}N_6O_2$ (374.40)	64.16 (64.8)	4.85 (4.78)	22.45 (22.35)
29d	246–248 (Et)	Colorless (70)	$C_{18}H_{13}ClN_6O$ (364.79)	59.27 (59.18)	3.59 (3.49)	23.04 (22.96)
29e	230–232 (Et)	Colorless (66)	$C_{19}H_{15}ClN_6$ (362.82)	62.90 (62.87)	4.17 (4.9)	23.16 (23.7)
30	255–256 (Et/B)	Colorless (80)	$C_{17}H_{16}N_6O$ (320.35)	63.74 (63.66)	5.03 (4.96)	26.23 (26.13)
31	160–161 (Et)	Yellow (76)	$C_{18}H_{20}N_6O_3$ (368.39)	58.69 (58.59)	5.47 (5.41)	22.81 (22.69)
32	260–262 (Et/B)	Colorless (72)	$C_{17}H_{18}N_4O_2$ (310.35)	65.79 (65.66)	5.85 (5.78)	18.05 (17.96)

*(lit.[34] m.p. 231–232).

**(lit.[37] m.p. 279–280).

B, Benzene; D, Dioxan; DMF, Dimethylformamide; Et, Etanol; GAA, Glacial acetic acid.

2-Methoxy-5-cyano-4-amino-6-(4-methoxyphenyl)-pyrimidine (13)

To a solution of sodium (230 mg, 10 mmol) in methanol (30 mL), thiourea (380 mg, 5 mmol) was added. When it became dissolved, (920 mg, 5 mmol) of p-methoybenzylidenemalononitrile (**5a**) dissolved in methanol (10 mL) were added. The resulting mixture was refluxed for 4 h. The reaction mixture was poured onto ice water and neutralized by dil. hydrochloric acid (15%) up to pH 6; the solid product so formed was collected by filtration and washed several times by water (Table III).

6-Amino-1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxamide (17), 6-(4-Methoxybenzylidine) amino-1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxamide (18), and 3,5-Di-cyano-4,6-di(4-methoxyphenyl)-2,3,4,5-tetrahydropyridine-2-one (19)

Thiourea (760 mg, 10 mmol) and (E)-3-(4-methoxyphenyl)-2-cyanopropenamide (**6a**) (2.02 g, 10 mmol) were added to a solution of sodium methoxide (230 mg, 10 mmol) in dry methanol (40 mL). The mixture was stirred at r.t. for 48 h, and the solvent was removed in vacuo. By the addition of water (60 mL) and then adicified with 10% hydrochloric acid, a precipitate was formed that was collected and washed with water. The product thus obtained was boiled with ethanol and filtered. The remaining solid was recrystallized from DMF to give **19**. The boiled ethanol gave a solid, which was separated by gas–liquid chromatography into **17** and **18** (Table III).

6-Amino-1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-2-thioxopyrimidine-5-carboxylic acid (20)

Thiourea (760 mg, 10 mmol) and (E)-3-(4-methoxyphenyl)-2-cyanopropenamide **(6a)** (2.02 g, 10 mmol) were added to a solution of sodium methoxide (230 mg, 10 mmol) in dry methanol (40 mL). The mixture was refluxed for 4 h. The reaction mixture was poured onto ice water and acidification with (10%) hydrochloric acid; a precipitate was formed that was collected and washed with water (Table III).

5-Cyano-4-oxo-6-(4-methoxyphenyl)-2-thioxotetrahydro-pyrimidine (21)

Method A

To a solution of sodium (230 mg, 10 mmol) in methanol (50 mL), thiourea (760 mg, 10 mmol) was added. When it became dissolved, (2.31 g, 10 mmol) of ethyl p-methoybenzylidenecyanoacetate (**7a**) was added the resulting mixture was refluxed for 4 h. The reaction mixture was poured onto ice water and neutralized by dil. hydrochloric acid (10%) the solid product so formed was collected by filtration and washed several times by water (Table III).

Method B for Compound 21 and 14

A mixture of **8** or **13** (1 mmol) and formic acid (10 mL) was refluxed for 3 h; the solvent was evaporated in vacuo, and the solid so obtained

was washed by dil. ethanol; the obtained solid was recrystallized from a suitable solvent.

(E)-Ethoxymethyleneamino-6-methoxy-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (22) and N-(5-Cyano-2-thioxo-6-(4-methoxyphenyl)-1,2-di-Hydropyrimidin-4-yl)formamide (25)

A mixture of **13a** or **8** (1 mmol), triethylorthoformate (148 mg, 1 mmol), and acetic anhydride (10 mL) was refluxed for 3–5 h then cooled, and the solid product was collected by filtration, washed by pet. ether, and recrystallized from an appropriate solvent (Table III).

2-(N-Hydroxymethyl)amino-6-methoxy-4-(4-methoxyphenylpyridine-3,5-di-carbonitrile (23)

A mixture of **13a** (280 mg, 1 mmol) and formaline solution (1 mL) in ethanol (10 mL) was refluxed for 2 h; the solid product was collected by filtration and washed by dil. ethanol (Table III).

2-(N-Hydroxymethyl,N-(β-hydroxyethyl))amino-6-amino-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (24)

A mixture of **13a** (560 mg, 2 mmol), formaline solution (1 mL), and ethanolamine (122 mg, 2 mmol) in ethanol (10 mL) was refluxed for 2 h; the solid product was collected by filtration and washed by dil. ethanol (Table III).

2-(4-Amino-5-cyano-6-(4-methoxyphenyl)pyrimidin-2-yl)thioethylacetate (26)

A solution of 4-amino-2-mercapto-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile (**8**) (258 mg, 1 mmol), ethyl chloroacetate (122 mg, 1 mmol), and 2 drops of sodium methoxide were added. The mixture was refluxed for 3 h in dioxane (30 mL). The reaction mixture was poured onto ice water and neutralized by dil. hydrochloric acid (10%); the solid product so formed was collected by filtration and washed several times by water (Table III).

2-(2-Benzoylmethylthio)-4-amino-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile (27)

A solution of 4-amino-2-mercapto-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile (**8**) (516 mg, 2 mmol) and phenacylbromide (384 mg

2 mmol). The mixture was refluxed for 1 h in ethanol (30 mL); the solid product so formed was collected by filtration and washed by dil. ethanol (Table III).

4-Amino-6-(4-methoxyphenyl)-2-hydrazinylpyrimidine-5-carbonitrile (28a) and 4-Amino-6-(4-chlorophenyl)-2-hydrazinylpyrimidine-5-carbonitrile (28b)

A suspension of **8** or **9b** (10 mmol) and hydrazine hydrate (320 mg, 10 mmol) in n-butanol (30 mL) was refluxed for 3 h. The solvent was evaporated in vacuo; the residue was triturated with dil. ethanol and the solid, which separated, was filtered off (Table III).

2-((Z)-2-Arylidenehydrazinyl)-4-amino-6-(aryl)pyrimidine-5-carbonitrile 29a–e

A mixture of **28a**,**b** (1 mmol) and aromatic aldehyde (1 mmol) in n-butanol (10 mL) was refluxed for 30 min. The solvent was evaporated in vacuo; the solid product was collected by filtration, washed by dil. ethanol, and recrystallized from an appropriate solvent (Table III).

4-Amino-6-(4-methoxyphenyl)-2-[(3,5-dimethyl)-*1H*-pyrazol-1-yl)pyrimidine-5-carbonitrile (30) and 2-(2-Ethoxycarbonylisopropylidenehydrazinyl)-4-amino-6-(4-methoxyphenyl)pyrimidine-5-carbonitrile (31)

A suspension of 4-amino-6-(4-methoxyphenyl)-2-hydrazinylpyrimidine-5-carbonitril (**28a**) (256 mg, 1 mmol), acetyl acetone and/or ethyl aceto-acetate (1 mmol) in ethanol (30 mL) and 2 drops of piperidine was added. The mixture was refluxed for 3 h; the solid obtained was collected by filtration, washed by dil. ethanol, and recrystallized from a suitable solvent (Table III).

1,6-Dihydro-4-(4-methoxyphenyl)-6-oxo-2-(piperidin-1-yl)-pyrimidine-5-carbonitrile (32)

A suspension of 4-amino-2-mercapto-6-(4-methoxyphenyl)-pyrimidine-5-carbonitrile (**8**) (516 mg, 2 mmol) and piperidine (168 mg, 2 mmol) was refluxed in ethanol (30 mL) for 3 h. The solid obtained was collected by filtration and washed by dil. ethanol (Table III).

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