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A Facile Synthesis of New 3-(1-Methyl benzimidazol-2-yl) Pyrazolopyrimidine and Pyrimido[2, 1-b][1,3]benzothiazole Derivatives of Potential Biosignificant Interest

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Abstract A simple route for the synthesis of pyrazolo[1,5-a]pyrimidine derivatives was described through the reaction of readily accessible 4-(1-methyl benzimidazol-2-yl)-3-(methylthio)-1H-pyrazol-5-amine (3) with different reagents is described. Also 2-amino benzothiazole in N, N/-dimethyl formamide and anhydrous potassium carbonate reacted with 2-(1-methyl benzimidazol-2-yl)-3,3-bis(methylthio)acrylonitrile (2) to yield pyrimido[2,1-b]benzo-thiazole (21). The latter was further reacted with selected N-, O- and C- nucleophiles such as aryl amines, hetaryl amines, substituted phenols and compounds with an active methylene group. The in vitro antimicrobial activity of some synthesized compounds was examined. Most of the tested compounds proved to be active as antibacterial and antifungal agents.

Keywords 5-Aminopyrazole, Active Methylene and β-Arylacrylonitrile

1. Introduction

Pyrazolopyrimidine derivatives and related heteroaromatics are found to possess wide applications in medicine and agriculture. They are biologically interesting isomeric purine analogues and have importance properties as antimetabolites in purine biochemical reaction[1-3]. They exhibited diversified pharmacological activities like antitumor[4], antileukemio[5], tuberculostatic[6], antimicrobial activities [7], neuroleptic[8], CNS depressant[9], antihypertensive[10] and antileishmanial[11].

On the other hand, benzimidazole has been also found wide medicinal application as potent antihypertensive[12], antihistaminic[13], anticancer[14, 15] and anti-inflammatory [16] agents, as gastric Ulcer inhibitors[17] and for treatment of cardiovascular diseases[18]. In addition, several benzimidazole derivatives are useful in the textile industry as dying agents[19, 20]. Moreover, the pyrazole ring has shown to be the basic moiety for a number of dyes, drugs and agrochemicals[21-25]. As a part of our programmed[26, 27] amid at the synthesis of novel benzimidazole derivatives which could be useful for biological and pharmacological screening, we aimed to incorporate the benzimidazole moiety into the 4-position of pyrazolo[1,5-a]- pyrimidine ring system to thus obtain a new heterocyclic system which is expected to possess notable chemical and pharmacological activities. Also pyrimidine and iminopyrimidine and fused benzothiazole heterocycles are reported to be effective pharmacophores. Biological activities and various applications of benzothiazole compounds and compounds containing pyrimidine ring have stimulated considerable interest to explore the synthesis of new potential compounds in which pyrimidine ring is fused with another biologically active nucleus such as benzothiazole and benzimidazole through nitrogen atom. Very few references are available on the synthesis of pyrimido benzothiazole compounds. The synthesis of acidic derivatives of 4H-pyrimido [2,1-b]benzazole-4-ones by the condensation of 2-aminobenzo-thiazole, 2-amino benzooxazole and 2-amino-1-methyl benzimidazole independently with 2-aminofumarate and diethyl ethoxy methylene malonate and their anti-allergic activity were reported require the presence of steam of nitrogen gas, hance it was considered appropriate to devise a convenient route to synthesis of the these compounds. It is surmised that pyrimido[2,1-a][1,3]benzothiazole incorporating benzimidazole nucleus would exhibit interesting properties and pharmacological[28 and references cited in].

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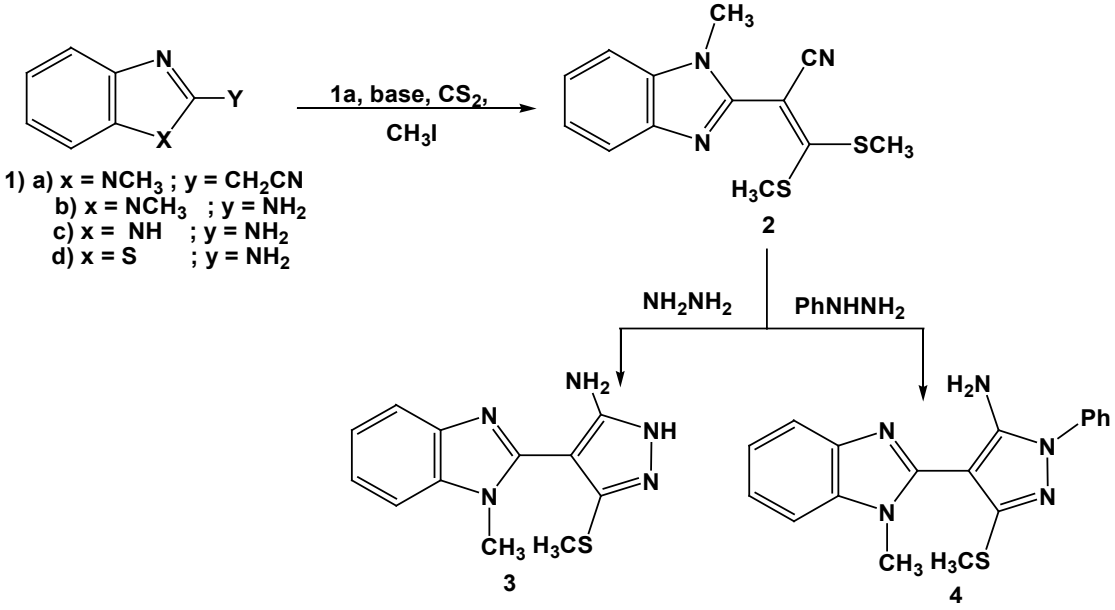
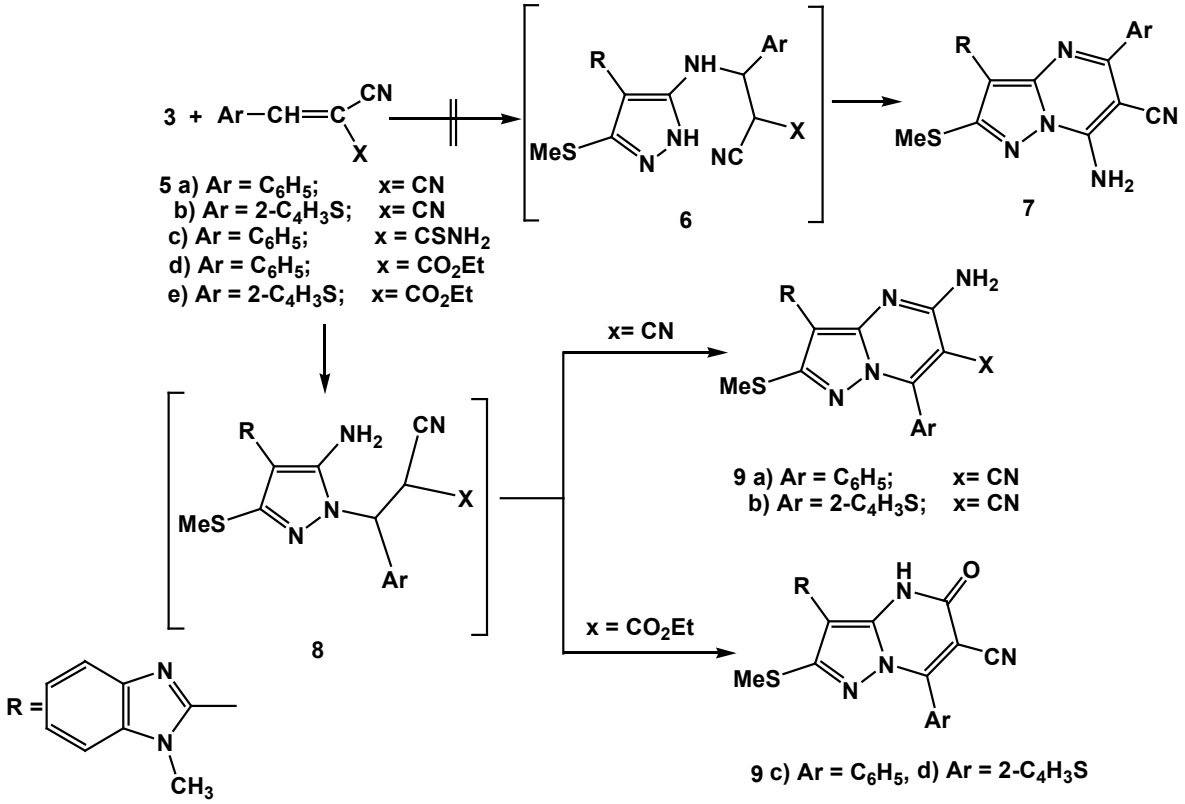
2. Results and Discussion

2.1. Chemistry

Thus, it has been found that treatment of 2-(1-methyl benzimidazol-2-yl) 3,3-bis-(methylthio)acrylonitrile **(2)** with hydrazine hydrate and phenylhydrazine affords the target 5-aminopyrazole **(3)** and **(4)**, respectively. The structure of **(3)** was established and confirmed as the reaction product on the basis of their elemental analysis and spectral data (MS, IR and ^{1}H NMR and ^{13}C NMR). The analytical data for **(3)** revealed a molecular formula $C_{12}H_{13}N_5S$ (M^+= 259 *m/z*). The IR spectrum showed absorption bands in the region 3380 and 3230cm^{-1} for NH and NH_2, in addition to disappearance of cyano function signal. The ^{1}H NMR of **(3)** revealed a bands at δ= 2.64, 3.89, 5.85 and 13.2 ppm assignable to a SCH_3, N-CH_3, NH_2 and NH-pyrazole; respectively. ***(cf. Scheme 1)***



Scheme 1. Synthesis of 5-aminopyrazzole derivative 3 and 4



Scheme 2. Synthesis of pyrazolo[1,5-a]pyrimidine dervatives 9a-d

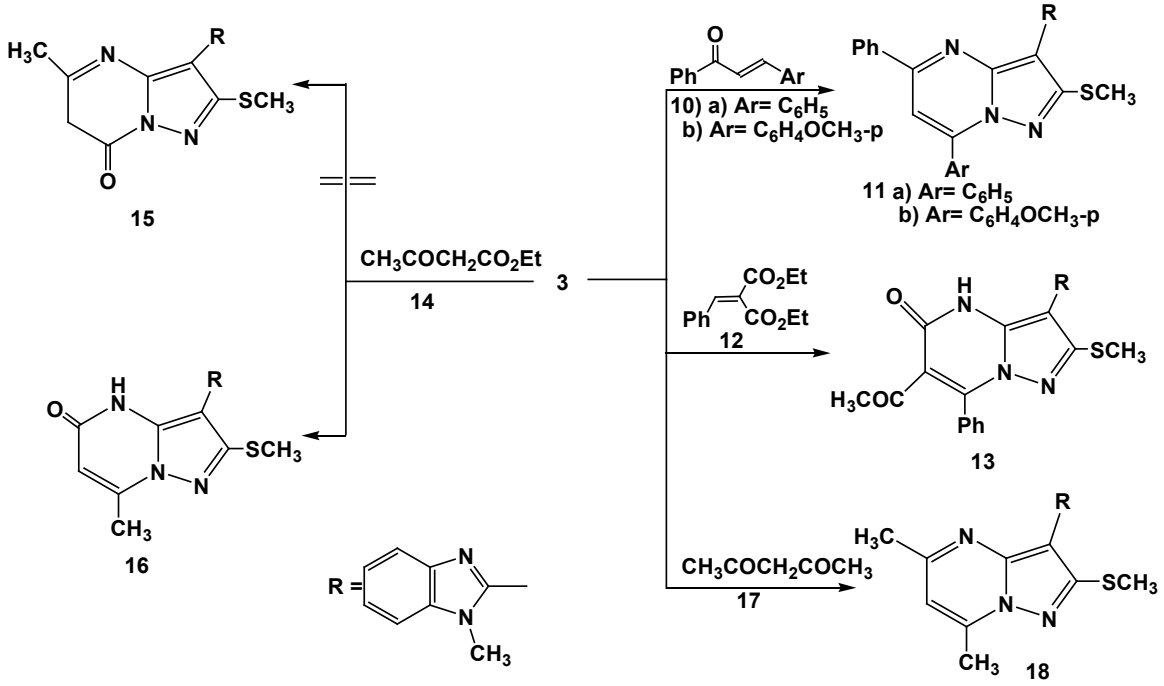
The reaction of aminopyrazole **(3)** with β-arylacrylonitrile derivatives is a matter of debate[29,30]. Although, later we[31] and other[32] gave reasonable rationalization of this controversy, we also would like to shed further light on the reaction of **(3)** with β-arylacrylonitirle derivatives. Thus, it has been found that **3** react with α-cyanocinnamonitiles **(5a)** afford a product of molecular formula $C_{22}H_{17}N_7S$ (M^+ = 411 *m/z*). Two theoretically possible isomeric structures were considerable **(7)** and **(9)**. Structure **(9a)** appears more likely than **(7)** based on the basis that the ring nitrogen is the most nucleophilic centre in the molecule. The proposed structure **(9a)** was supported by its independent synthesis from **(3)** and the 2-cyano-3-phenylprop-2-enethioamide **(5c)** via elimination of hydrogen sulfide. Also, compound **(3)** reacted with **(5d, e)** to afford **(9c, d)**, respectively. The structure of **(9c, d)** was incomplete agreement with their elemental analysis and spectral data ***(Scheme2)***.

Similarly, compound **3** reacted with chalcones **(10a, b)** and α-acetyl ethylcinnamate **(12)** to produce the pyrazolo[1,5-a]pyrimidine derivatives **(11a, b)** and **(13)**, respectively.

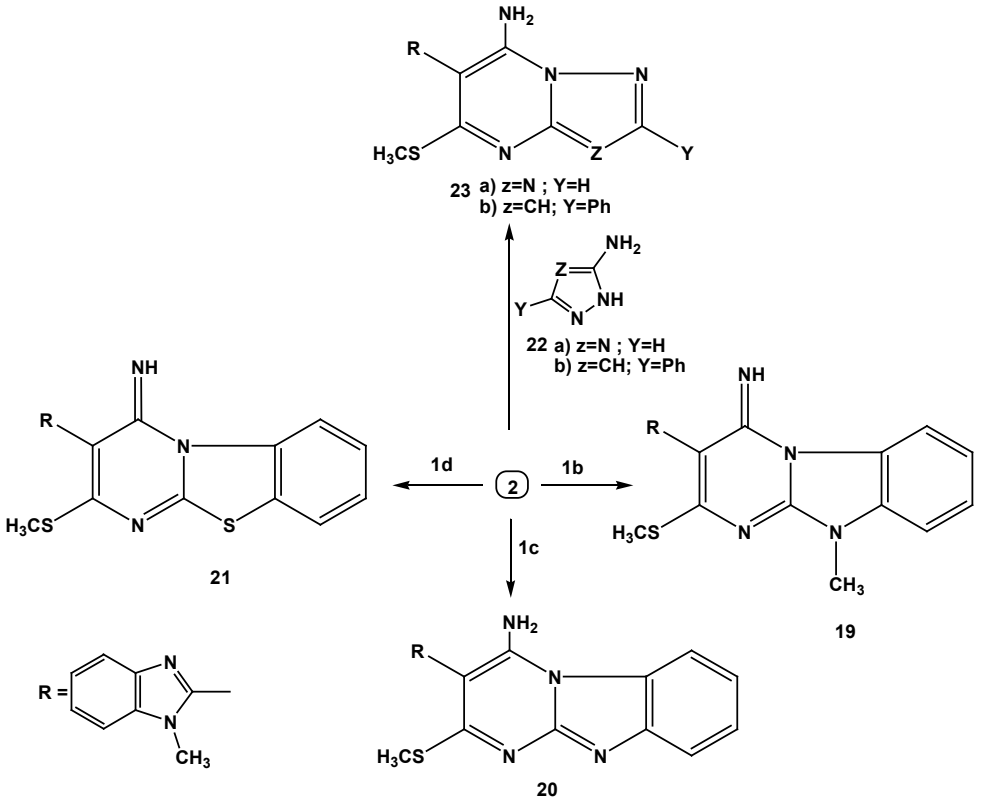
The ^{1}H NMR spectrum of **(13)** showed a two singlet signal at δ=2.51 and 2.62 ppm corresponding to acetyl and methylthio groups, respectively. Also, condensation of **(3)** with ethyl acetoacetate **(14)** afforded condensation product which may be formulated as **(15)** or isomeric **(16)**. Although structure **(15)** seemed more likely based on similarity to the well established of 5-aminopyrazoles toward β-keto ester[33] but isomeric **(16)** considered most likely based on ^{1}H NMR which revealed signals at δ=5.82 and 11.6 ppm for CH and NH-pyrimidine ring, respectively. If the product isomeric **(15),** one would expected a methylene group signal will appear at around 4.5 ppm, similar to that previously reported[34]. Also, pyrazole **(3)** condensed with acetylacetone **(17)** to yield the pyrazolo[1,5-a]pyrimidine derivative **(18)**. The structure of **(18)** was established based on the analytical data ***(scheme 3)***.

Also, a part of our programme at the synthesis of novel benzimidazole derivatives which could be useful for biological and pharmabiological screening, we now disclose the details of a successful synthetic approach to some new fused ring system with bridgehead nitrogen atom derived from benzimidazole and benzothiazole nucleus. A conceptually attractive entry to these compounds lies in the reactivity of readily accessible benzothiazole and benzimidazole derivatives which allow a fruitful one-step synthesis of polyheterocyclic ring via its reaction with **(2)**.

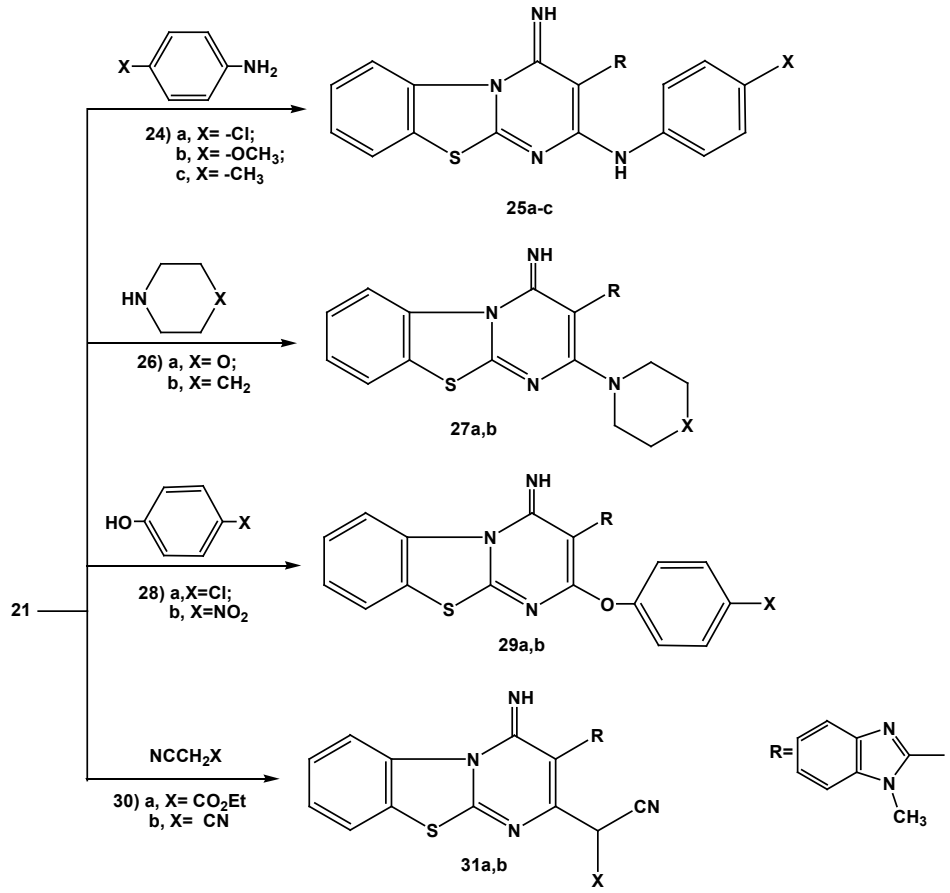
Refluxing of **(2)** with **(1b)** in N, N$^/$-dimethyl formamide and anhydrous potassium carbonate afforded the pyrimido[1,2-a]benzimidazole derivative **(19)**. The ^{1}H NMR spectrum of compound **(19)** revealed signal at δ=10.11 ppm assigned to =NH. Similarly, compound **(2)** reacted with **(1c,d),** 5-amino-1H-1,2,4-triazole **(22a)** and 5-amino-3-phenyl-1H-pyrazole **(22b)** to yield the pyrimido[1,2-a]benzimidazole (20),pyrimido[2,1-a][1,3]benzothiazole (21) 1,2,4-triazolo[2,3-a]pyrimidine (23a) and pyrazolo[1,5-a]pyrimidine (23b) derivatives, respectively. (Scheme4).



Schem 3. Reaction of 5-aminopyrazole (3) with chalcones (10a,b) and active methylene (14) and (17)



Schem 4. Synthesis of pyrimidobenzimidazole (19,20), pyrimidobemzothiazole (21) and triazolopyrimidine (23a) derivatives



Scheme 5. Reaction of pyrimidobenzothiazole derivative (21) with aniline ; phenol and cyanomethlylene derivatives

Compound **(21)** possess a replaceable active methylthio group at the 2-position, which is activated by the ring nitrogen atom and the electron withdrawing benzothiazole moiety. Compound **(21)** was reacted with the selected N-, O-, and C- nucleophiles like arylamines, hetaryl amines, substituted phenols and compounds have an active methylene group, respectively. On reaction of compound **(21)** with aniline derivatives **(24a-c)** in dimethyl formamide and catalyric amount of anhydrous potassium carobonate, afforded 4-imino-3-(1-methyl benzimidazol-2-yl)-2- (4/-chloroanilino/ 4/-methoxyanilino and 4/-methylanilino)-4H-pyrimido[2,1-b][1,3]-benzothiazoles **(25a-c)**, respectively. Under the same experimental conditions, compound **(21)** reacted independently with morphlino **(26a)** and piperdino **(26b)** to yield 4-imino-3-(1-methyl benzimidazol-2-yl)-2-(morphlino and piperdino)-4H-pyrimido[2,1-b][1,3]benzothiazoles **(27a,b)**, respectively. 4-imino-3-(1-methyl benzimidazol-2-yl)-2-(4/-chlorophenoxy and4/-nitrophenoxy)-4H-pyrimido[2,1-b]-[1,3]benzothiazoles **(29a,b)** were obtained by the condensation of **(21)** with phenol derivatives **(28a,b)**, respectively. Also compound **(21)** on reaction with, ethyl cyano-acetate and malononitrile **(30a,b)**, afforded compounds characterized on the basis of their analytical and spectral data as 4-imino-3-(1-methyl benzimidazol-2-yl)-2-(ethyl cyanoacetyl/ malononitrile)-4H-pyrimido[2,1-b][1,3]benzothiazoles **(31a,b)**, respect-tively. Compounds **(25a-c)**, **(27a,b)**, **(29a,b)** and **(31a,b)** show absorption bands in their IR spectra in the range of 3340- 3455cm^{-1} due to =NH stretching. ^{1}H NMR and mass spectral data are also in agreement with these structures **(Scheme 5).**

2.2. Antimicrobial Activity

The newly synthesized products **2, 4, 9a-c, 16, 18, 19, 21, 25a, 27a, 29a** and **31** were tested for their antimicrobial activities using three species of fungi, namely *Aspergillus niger AN*, *Aspergillus flavus AF* and *Fusarium moniliform FM*. The organisms were grown on a liquid schapexs media supplemented with the tested compounds and the growth were measured using the dry weight method[35].

2.2.1. Discussion of Stimulation

Aspergillus has a large chemical repertoire. Commodity products produced in Aspergillus cell "factories" include citric, gluconic, itaconic and kojic acid. The production of citric acid by using of Aspergillus niger back to Currie[36]. Citric acid is one of the most widely used food ingredients. It also has found use in the pharmaceutical and cosmetic industries as an acidulant and for aiding in the dissolution of active ingredients. Other technical applications of citric acid are as a hardener in adhesive and for retarding the setting of concrete[37]. Citric acid is a true bulk chemical with an estimated production approximating more than 1.6 billion kg each year[38]. Aspergillus niger also has found use in the industrial production of gluconic acid, which is used as an additive in certain metal cleaning applications, as well as for the therapy for calcium and iron deficiencies[39].

Also the newly synthesized products **2, 4, 9a-c, 16, 18, 19, 21, 25a, 27a, 29a** and **31** were investigated against four pathogenic representative microorganism *Staphylococcus aureus* and *Bacillus subtilis* (gram positive bacteria) and *Psuedomonas aeruginosa* and *Escherichia coli* (gram negative bacteria) using Ampicillin and streptomycine as standard drugs. Agar well-diffusion method[40] was used for studying the potential activities of these compounds. As shown in Table 2. the antimicrobial effect of the tested compounds was evaluated by measuring the zone diametera and their results were compared with those of well known drugs (standards).

Table 1. Antifungal activity 2, 4, 9a-c, 16, 18, 19, 21, 25a, 27a, 29a and 31a

	***Aspergillus niger* (AN)**	***Aspergillus flavus* (AF)**	***Fusarium moniliforn* (FM)**
Control / **Comp.**	*0.22*	*0.25*	*0.18*
2	0.41	0.34	0.17
3	0.43	0.33	0.16
4	0.39	0.29	0.14
9a	0.51	0.36	0.19
9b	0.56	0.38	0.28
9c	0.43	0.33	0.16
16	0.26	0.16	0.12
18	0.27	0.30	0.11
19	0.24	0.24	0.18
21	0.18	0.16	0.13
25a	0.12	0.18	0.14
27a	0.13	0.17	0.13
29a	0.35	0.29	0.18
31a	0.11	0.14	0.12

Key to symbols: 1) > 0.22, 0.25 and 0.18 indicate to stimulation. 2) < 0.22, 0.25 and 0.18 main that inhibition.

Table 2. Antibacterial activity 2, 3, 9a,c, 16, 18, 19, 21, 25a, 27a, 29a and 31a

	Gram positive bacteria		*Gram negative bacteria*	
Compound	***S. aureus***	***B. sssubtilis***	***P. aeruginosa***	***E. coli***
Ampiclline	+++	++	++	+++
Streptomycine	+++	+++	+++	+++
2	+			+
3	++		+	++
9a	++			+
9c		+		+
16	+		+	+
18	+		+	++
19	++	+		++
21	+	+	++	++
25a	++		+	++
27a	++	++	+	++
29a	++	+	+	++
31a	++	+	+	++

Key to symbols: *Inactive = - (inhibition zone < 6mm); slightly active = + (inhibition zone 6-9mm); moderately active = ++ (inhibition zone 9-12mm) and highly active = +++ (inhibition zone > 12mm).*

3. Experimental

Melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were determined in DMSO-*d6* at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70Ev. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

2-(1-Methyl benzimidazol-2-yl)-3,3-bis(methylthio)acrylonitrile (2)

To solution of sodium hydride (0.45 mole) in benzene (150ml), a solution of 1-methyl benzimidazol-2-yl acetonitrile **(1a)** (0.2 mole), carbon disulphide (0.2 mole) in dry dimethylformamide (100 ml) was added in portions during 1 hr. The reaction mixture was kept under stirring for 3hrs. followed by addition of methyliodide (0.4 mole) in portions with cooling. The reaction mixture was allowed to stand at room temperature for 5h. and then refluxed for addition 4h. After cooling, it was poured onto ice/water, the resulting solid was collected by filtration and finally recrystallisted from DMF to afford (72% yield) of compound **2**. mp 220°C; IR υ_{max}/ cm^{-1} (KBr) 2176 (CN), 1615 (C=N); ^{1}H NMR (DMSO-d_6) δ= 2.58(s, 3H, SCH_3), 2.65(s, 3H, SCH_3), 3.9(s, 3H, NCH_3), 7.15-7.78(m,4H, Ar-H). ^{13}C-NMR 17.3, 31.2(SCH_3, NCH_3), 118.2(CN), 122, 116.3, 132.6, 138.5, 141.2(benzimidazole carbons), 83, 171.1(C=C) M/S: m/z 275(M^+, 62.8. (Found: C, 56.63, H; 4.65; N, 15.12; S, 23.43. $C_{13}H_{13}N_3S_2$ require C, 56.70; H, 4.76; N, 15.26; S, 23.28%)

4-(1-Methyl benzimidazol-2-yl)-3-(methylthio)-1*H*-pyrazol-5-amine (3)

A solution of 2-(1-methyl benzimidazol-2-yl) 3,3-bis(methylthio)acrylonitrile **2** (0.1 mol) in absolute ethanol (150ml) was treated with hydrazine hydrate (0.12 mol). The reaction mixture was refluxed for about 4-6h. (TLC control). After evaporation of the solvent, the solid product was collected by filtration and recrystallised from ethanol/DMF to afford (79%, yield) of **3**, mp 260°C; IR υ_{max}/ cm^{-1} (KBr) 3275, 3172 (NH and NH_2), 1627(C=N); ^{1}H NMR (DMSO-d_6) δ= 2.64(s, 3H, SCH_3), 3.89(s, 3H, NCH_3) 5.85(br, 2H, D_2O exchangeable NH_2), 7.35-7.76(m,4H, Ar-H), 13.2(s, 1H, NH). ^{13}C-NMR 14.8, 31.9(SCH_3, NCH_3), 122, 116.3, 132.6, 138.5, 152.2(benzimidazole C), 104, 139.1, 150.2(pyrazole C) M/S: m/z 259(M^+, 86.19),. (Found: C, 55.32;H, 4.1; N, 27.2; S, 12.24. $C_{12}H_{13}N_5S$. requires C, 55.58; H, 5.05; N, 27.01; S, 12.36%).

4-(1-Methyl-1*H*-benzo[d]imidazol-2-yl)-3-(methylthio) -1-phenyl-1H-pyrazol-5-amine (4)

A mixture of **2** (0.02 mol), phenylhydrazine (0.02 mol) and 0.1 ml of triethylamine was refluxed in 50 ml of absolute ethanol for 3-5h (TLC control). The solvent was evaporated *in vacuo*. The remaining solid was triturated with methanol. The solid product was collected by filtration and finally recrystallization from ethanol/DMF solvent to afford (68%, yield) of compound **4**, mp. 270-271°C; IR υ_{max}/cm^{-1} (KBr) 3430, 3285, (NH_2), 1635(C=N); ^{1}H NMR (DMSO-d_6) δ= 2.62(s, 3H, SCH_3), 3.98(s, 3H, NCH_3) 5.72(br, 2H, D_2O exchangeable NH_2), 7.31-7.75(m, 8H, Ar-H). (Found: C, 64.41; H, 5.13; N, 20.82; S, 9.52. $C_{18}H_{17}N_5S$ requires C, 64.45; H, 5.11; N, 20.88; S, 9.56%).

Reaction of 5-aminopyrazole (3) with cinnamonitriles (5a-e), chalcones (10a,b) and α-acetyl ethylcinnamate (12).

General procedure

A suspension of **3** (0.01 mol) and the appropriate cinnamonitriles **5a-e**, chalcones **(10a,b)** and/or α-acetyl ethylcinnamate **(12)** (0.01 mol) in absolute ethanol was treated with piperidine (1 ml). The reaction mixture was refluxed for 3-5h. (TLC control), the solvent was then evaporated *in vacuo*. The remaining solid was triturated with ice water and acidified with concentrated HCl. The product was collected by filteration and finally recrystallised from the appropriate solvent to afford the corresponding 5-aminpyrazolo[1,5-a]pyrimidine derivatives **(9a-d), (11a,b)** and **(13)**, respectively.

2-Amino-8-(1-methyl benzimidazol-2-yl)-7-(methylthio)-4-phenylpyrazolo[1,5-a]-pyrimidine-3-carbonitrile (9a): Yield, 70%; mp. 345°C, IR υ_{max} / cm^{-1} (KBr) 3337, 3285(NH_2), 2208(CN), 1631(C=N); ^1H NMR (DMSO-d_6) δ=2.63(s, 3H, SCH_3), 3.97(s, 3H, NCH_3) 4.1(br, 2H, D_2O exchangeable NH_2), 7.31-7.75(m, 9H, Ar-H). ^{13}C-NMR 116.9(CN); 14.8, 31.7(SCH_3, NCH_3), 123, 115.8, 134.6, 138.7, 153.2-(benzimidazole C), 87, 166.4, 168.4 (pyrimidine C); 104, 136.1, 135.2(pyrazole C), 126.2, 129.3, 128.1, 136.2 (C_6H_5 C). M/S: m/z 411(M^+, 18.4). (Found: C, 64.2; H, 4.11; N, 23.77; S, 7.67.$C_{22}H_{17}N_7S$ requires C, 64.22; H, 4.17; N, 23.83; S, 7.79%).

2-Amino-8-(1-methyl benzimidazol-2-yl)-7-(methylthio)-4-(thieno-2-yl)pyrazolo-[1,5-a]pyrimidine-3-carbonitrile (9b): Yield, 68%; mp. 350°C, IR υ_{max} / cm^{-1} (KBr) 3263, 3203(NH_2), 2191(CN), 1628(C=N); ^1H NMR (DMSO-d_6) δ=2.63(s, 3H, SCH_3), 3.97(s, 3H, NCH_3) 4(brs, 2H, D_2O exchangeable NH_2), 7.31-7.75(m, 7H, Ar-H). (Found: C, 57.45; H, 3.35; N, 23.43; S, 15.36.$C_{20}H_{15}N_7S_2$ requires C, 57.54; H, 3.62; N, 23.48; S, 15.36%).

3-cyano-8-(1-methyl benzimidazol-2-yl)-7-(methylthio)-4-phenylpyra-zolo[1,5-a]-pyrimidine-2-(1H)-one (9c): Yield, 63%; mp. 280°C, IR υ_{max} / cm^{-1} (KBr) 3333, 3170(NH), 2196(CN), 1668(C=O), 1631(C=N); ^1H NMR (DMSO-d_6) δ=2.64(s, 3H, SCH_3), 3.98(s, 3H, NCH_3) 5.91(s, 1H, D_2O exchangeable NH), 7.31-7.75(m, 9H, Ar-H); M/S: m/z 413(M^++1, 5.9), 412(M^+, 32.3). (Found: C, 66.10; H, 3.82; N, 20.23; S, 7.71. $C_{22}H_{16}N_6SO$ requires C, 66.06; H, 3.91; N, 20.37; S, 7.77%).

3-cyano-8-(1-methyl benzimidazol-2-yl)-7-(methylthio)-4-(thieno-2-yl)-pyrazolo-[1,5-a]pyrimidine-2-(1H)-one (9d): Yield, 68%; mp. 180°C, IR υ_{max} / cm^{-1} (KBr) 3343, 3274 (NH), 2186(CN), 1658(C=O), 1628(C=N); ^1H NMR (DMSO-d_6) δ= 2.63(s, 3H, SCH_3), 3.99(s, 3H, NCH_3) 6.1(s, 1H, D_2O exchangeable NH), 7.31-7.75(m, 7H, Ar-H). (Found: C, 57.31; H, 3.34; N, 20.10; S, 15.21. $C_{20}H_{14}N_6S_2O$ requires C, 57.40; H, 3.37; N, 20.08; S, 15.32%).

8-(1-methyl benzimidazol-2-yl)-7-(methylthio)-2,4-diphenylpyrazolo[1,5-a]pyr-imidine (11a): Yield, 62%; mp. 215°C, IR υ_{max} / cm^{-1} (KBr), 1635(C=N); ^1H NMR (DMSO-d_6) δ=2.63(s, 3H, SCH_3), 3.99(s, 3H, NCH_3), 7.19-7.97(m, 14H, Ar-H) 8.38(s, 1H, pyrimidine), M/S: m/z 448(M^++1, 8.9), 447(M^+, 63.1). (Found: C, 72.48; H, 4.65; N, 15.67; S, 7.12. $C_{27}H_{21}N_5S$ requires C, 72.46; H, 4.73; N, 15.65; S, 7.16%).

8-(1methyl benzimidazol-2-yl)-4-(4-methoxyphenyl)-7-(methylthio)-2-phenylpyr-azolo[1,5-a]pyrimidine (11b): Yield, 58%; mp. 238°C, IR υ_{max} / cm^{-1} (KBr), 1635(C=N); ^1H NMR (DMSO-d_6) δ =2.6(s, 3H, SCH_3), 3.97(s, 3H, NCH_3) 4.1(s, 3H, CH_3), 7.31-7.98(m, 13H, Ar-H), 8.35(s, 1H, pyrimidine). (Found: C, 70.52; H, 4.81; N, 14.66; S, 6.74. $C_{28}H_{23}N_5SO$ requires C, 70.42; H, 4.85; N, 14.67; S, 6.71%).

3-Acetyl-8-(1methyl benzimidazol-2-yl)-7-(methylthio)-4-phenylpyrazolo[1,5-a]-pyrimidin-2(1H)-one (13): Yield, 53%; mp. 264°C, IR υ_{max} / cm^{-1} (KBr), 1685, 1660(C=O), 1635(C=N); ^1H NMR (DMSO-d_6) δ= 2.51(s, 3H, $COCH_3$), 2.62(s, 3H, SCH_3), 3.97(s, 3H, NCH_3), 7.23-8.08(9H, m), 8.45(s, 1H, pyrimidine), M/S: m/z 429(M^+, 53.2). (Found: C, 64.31, H, 4.50; N, 16.23; S, 7.45. $C_{23}H_{19}N_5SO_2$ requires C, 64.32; H, 4.46; N, 16.31, S, 7.46%).

8-(1-methyl benzimidazol-2-yl)-4-methyl-7-(methylthio) pyrazolo[1,5-a]pyrimi-din-2-(1H)-one (16) and 8-(1-methyl benzimidazol-2-yl)-2,4-dimethyl)-7-(methylthio) pyrazolo[1,5-a]pyrimidine (18).

General procedure

A solution of **3** (0.01mol) in acetic acide (30 ml)was treated with ethyl acetoacetate **(14)** and acetylacetone **(17)** (0.01 mol). The solution was refluxed for 3h and the obtained product was recrystallized from ethanol to give **16** and **18**, respectively.

Compound (16): Yield, 67%; mp. 270°C, IR υ_{max} / cm^{-1} (KBr) 3500, 3330(NH), 1660(C=O) 1635(C=N); ^1H NMR (DMSO-d_6) δ = 2.35(s, 3H, CH_3), 2.61(s, 3H, SCH_3), 3.98(s, 3H, NCH_3) 6.1(s, 1H, D_2O exchangeable NH), 7.31-7.85(m, 4H, Ar-H), 8.76(s, 1H, pyrimidine), M/S: m/z 325(M^+, 83.3). (Found: C, 59.12; H, 4.62; N, 21.51; S, 9.89. $C_{16}H_{15}N_5SO$ requires C, 59.06; H, 4.65; N, 21.52; S, 9.85%).

Compound (18): Yield, 53%; mp. 280°C, IR υ_{max} / cm^{-1} (KBr) 1635(C=N); ^1H NMR (DMSO-d_6) δ= 2.1(s, 3H, CH_3), 2.35(s, 3H, CH_3), 2.61(s, 3H, SCH_3), 3.98(s, 3H, NCH_3), 7.23-7.95(m, 4H, Ar-H), 8.46(s, 1H, pyrimidine). (Found: C, 63.13; H, 5.28; N, 21.66; S, 9.89. $C_{17}H_{17}N_5S$ requires C, 63.13; H, 5.3; N, 21.66; S, 9.91%).

4-Imino-2-methylthio-3-(1-methyl benzimidazol-2-yl)-4*H*-pyrimido[1,2-a]benz-imidazole (19); 4-Amino-2-methylthio-3-(1-methyl benzimidazol-2-yl)-4*H*-pyr-imido[1,2-a]benzimidazole (20); 4-Imino-2-methylthio-3-(1-methyl benzimidazol-2-yl)-4*H*-pyrimido[2,1-b]benzothiazole (21) 4-Amino-2-methylthio-3-(1-methyl benzimidazol-2-yl)-1,2,4-triazolo[2,3-a]pyrimidine (23a) and 4-Amino-2-methyl-thio-3-(1-methyl benzimidazol-2-yl)-7-phenyl pyrazolo[1,5-a]pyrimidine (23b), respectively.

General procedure

A suspension of **(2)** (0.01 mol) and the appropriate 2-amino benzimidazole derivatives **(1b,c)** and 2-amino benzothiazole **(1d)**, 5-amino-1H-1,2,4-triazole **(22a)** and 5-amino-3-phenyl-1H-pyrazole **(22b)** (0.01 mol) in 15 ml of N, N/-dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 4-6 hours. The reaction mixture was refluxed for 3-5h. (TLC control), the solvent was then evaporated *in vacuo*. The remaining solid was coold to room temperature and triturated with ice cold water. The product was collected by filtration, washed with water several times and finally recrystallized from the appropriate solvent to afford the corresponding pure **(19-21)** and **(23a,b)** derivatives, respectively

Compound (19): Yield, 67%; mp. 282°C, IR υ_{max} / cm^{-1} (KBr) 3400, 3335(NH), (C=N); ^1H NMR (DMSO-d_6) δ =2.65 (s, 3H, SCH_3), 3.96(s, 3H, NCH_3), 3.98(s, 3H, NCH_3), 7.21-7.98(m, 8H, Ar-H), 9.68(s, 1H, D_2O exchangeable =NH), M/S: m/z 375(M^++1,3.9), 374(M^+,72.2). (Found: C, 64.12; H, 4.83; N, 22.51; S, 8.59. $C_{20}H_{18}N_6S$ requires C, 64.15; H, 4.84; N, 22.44; S, 8.56%).

Compound (20): Yield, 63%; mp. 310°C, IR υ_{max}/ cm^{-1} (KBr) 3320, 3180 (NH_2), 1630 (C=N); ^1H NMR (DMSO-d_6) δ = 2.65 (s, 3H, SCH_3), 3.96(s, 3H, NCH_3), 7.21-8.19(m, 10H, Ar-H) M/S: m/z 360(M^+, 79.6). (Found: C, 63.11; H, 4.45, N, 23.29; S, 8.78. $C_{19}H_{16}N_6S$ requires C, 63.31; H, 4.48; N, 23.32; S, 8.89%).

Compound (21): Yield, 57%; mp. 256°C, IR υ_{max}/ cm^{-1} (KBr) 3350, 3335(NH), (C=N); ^1H NMR (DMSO-d_6) δ =2.63 (s, 3H, SCH_3), 3.99(s, 3H, NCH_3), 7.23-7.96(m, 8H, Ar-H), 9.65(s, 1H, D_2O exchangeable =NH). (Found: C, 64.43; H, 4.10; N, 18.62; S, 17. $C_{19}H_{15}N_5S_2$ requires C, 60.45; H, 4.01; N, 18.55; S, 16.99%).

Compound (23a): Yield, 72%; mp. 270-2°C, IR υ_{max} / cm^{-1} (KBr) 3218(NH_2), 1620(C=N); ^1H NMR (DMSO-d_6) δ = 2.64 (s, 3H, SCH_3), 3.97(s, 3H, NCH_3), 7.21-8.12(m, 6H, Ar-H), 8.8(s, 1H, triazole) M/S: m/z 312(M^++1, 9.6), 311(M^+, 54.2). (Found: C, 54.10; H, 4.12; N, 31.46; S, 10.4. $C_{14}H_{13}N_7S$ requires C, 54.01; H, 4.21; N, 31.49; S, 10.30%).

Compound (23b): Yield, 58%; mp.298°C, IR υ_{max}/ cm^{-1} (KBr) 3200, 3190 (NH_2), 1628 (C=N); ^1H NMR (DMSO-d_6) δ = 2.6 (s, 3H, SCH_3), 3.99(s, 3H, NCH_3), 7.23-8.23(m, 12H, Ar-H). (Found: C, 65.23; H, 4.7; N, 21.59; S, 8.23. $C_{21}H_{18}N_6S$ requires C, 65.27; H, 4.69; N, 21.75; S, 8.3%).

2-Substituted-4-imino-3-(1-methyl benzimidazol-2-yl)-4*H*-pyrimido[2,1-b][1,3]-benzothiazoles (25a-c; 27a,b; 29a,b and **31a,b)**.

A suspension of **(21)** (0.01 mol) and independently, the appropriate aromatic amines, hetaryl amines, substituted phenols or compounds containing active methylene group (0.01 mol) in 15 ml of N, N/-dimethyl formamide and anhydrous potassium carbonate (10mg) was refluxed for 4-6 hours. The reaction mixture was refluxed for 3-5h. (TLC control), the solvent was then evaporated *in vacuo*. The remaining solid was coold to room temperature and triturated with ice cold water. The product was collected by filtration, washed with water several times and finally recrystallized from the appropriate solvent to afford the corresponding pure **(25a-c)**, **(27a,b)**, **(29a.b)** and **(31a,b)** derivatives, respectively

2-(4/-Chloroanilino)-4-imino-3-(1-methyl benzimidazol-2-yl)-4*H*-pyrimido[2,1-b]-[1,3]benzothiazole (25a): Yield, 46%; mp.199°C, IR υ_{max} / cm^{-1} (KBr) 3380, 3335, (NH), 1635 (C=N); ^1H NMR (DMSO-d_6) δ = 3.99(s, 3H, NCH_3), 4.35(brs, 1H, D_2O exchangeable NH), 9.97(brs, 1H, D_2O exchangeable =NH),7.21-7.98(12H, m), M/S: m/z 457(M^++1, 15.5), 456(M^+, 48). (Found: C, 63.06; H, 3.71; N, 18.42; S, 7.10, Cl, 7.74. $C_{24}H_{17}N_6SCl$ requires C, 63.08; H, 3.75; N, 18.39; S, 7.02, Cl, 7.76%).

4-Imino-3-(1-methyl benzimidazol-2-yl)- 2-(4/-methoxyanilino)-4H-pyrimido[2,1-b][1,3]benzothiazoles (25b): Yield, 47%; mp.214°C, IR υ_{max} / cm^{-1} (KBr) 3375, 3330, (NH), 1630 (C=N); ^1H NMR (DMSO-d_6) δ = 3.71(s, 3H, OCH_3), 3.97(s, 3H, NCH_3), 4.41(brs, 1H, D_2O exchangeable NH), 9.98(brs, 1H, D_2O exchangeable =NH),7.21-7.98(12H, m). (Found: C, 66.32; H, 4.47; N, 18.46; S, 7.04. $C_{25}H_{20}N_6SO$ requires C, 66.35; H, 4.45; N, 18.52; S, 7.08%).

4-Imino-3-(1-methyl benzimidazol-2-yl)-2-(4/-methylanilino)-4*H*-pyrimido[2,1-b][1,3]benzothiazoles (25c): Yield, 46%; mp.195°C, IR υ_{max} / cm^{-1} (KBr) 3385, 3340, (NH), 1635 (C=N); ^1H NMR (DMSO-d_6) δ = 2.34(s, 3H, CH_3), 3.98(s, 3H, NCH_3), 4.21(brs, 1H, D_2O exchangeable NH), 9.98(brs, 1H, D_2O exchangeable =NH),7.25-7.86(12H, m). (Found: C, 68.76; H, 4.63; N, 19.32; S, 7.24.$C_{25}H_{20}N_6S$ requires C, 68.79; H, 4.62; N, 19.25; S, 7.34%).

4-Imino-3-(1-methyl benzimidazol-2-yl)-2-(morpholino)-4*H*-pyrimido[2,1-b]-[1,3]benzothiazoles (27a): Yield, 44%; mp.208°C, IR υ_{max} / cm^{-1} (KBr) 3380, 3300, (NH), 1635 (C=N); ^1H NMR (DMSO-d_6) δ = 3.8(t, 4H, 2 –N-CH_2), 4.1(t, 4H, 2–OCH_2), 3.99(s, 3H, NCH_3), 9.95(brs, 1H, D_2O exchangeable =NH),7.25-7.86(8H, m), M/S: m/z 417(M^++1, 15.2), 416(M^+, 51.2). (Found: C, 63.53; H, 4.84; N, 20.23; S, 7.64.$C_{22}H_{20}N_6SO$ requires C, 63.44; H, 4.84; N, 20.18; S, 7.7%).

4-Imino-3-(1-methyl benzimidazol-2-yl)-2-(piperidino)-4*H*-pyrimido[2,1-b][1,3]-benzothiazoles (27b): Yield, 41%; mp.192°C, IR υ_{max} / cm^{-1} (KBr) 3330, 3310, (NH), 1635 (C=N); ^1H NMR (DMSO-d_6) δ = 1.6(m, 6H, $3CH_2$), 2.6(t, 4H, $2NCH_2$), 3.97(s, 3H, NCH_3), 9.92(brs, 1H, D_2O exchangeable =NH),7.25-7.86(8H, m). (Found: C, 66.54; H, 5.21; N, 20.18; S, 7.64.$C_{23}H_{22}N_6S$ requires C, 66.64; H, 5.35; N, 20.27; S, 7.73%).

2-(4/-Chlorophenoxy)-4-imino-3-(1-methyl benzimidazol-2-yl)-4*H*-pyrimido[2,1-b][1,3]benzothiazole (29a): Yield, 52%; mp.178°C (dec.), IR υ_{max} / cm^{-1} (KBr) 3314, (NH), 1630 (C=N); ^1H NMR (DMSO-d_6) δ = 3.98(s, 3H, NCH_3), 9.95(brs, 1H, D_2O exchangeable =NH),7.25-7.83(12H, m), M/S: m/z 458(M^++1, 13.3), 457(M^+, 36.3). (Found: C, 62.83; H, 3.54; N, 15.19; S, 6.95, Cl, 7.67. $C_{24}H_{16}N_5SClO$ requires C, 62.95; H, 3.52; N, 15.29; S, 7, Cl, 7.74%).

4-Imino-3-(1-methyl benzimidazol-2-yl)-2-(4/-nitrophenoxy)-4*H*-pyrimido[2,1-b]-[1,3]benzothiazoles (29b): Yield, 52%; mp.156°C (dec.), IR υ_{max} / cm^{-1} (KBr) 3310, (NH), 1633 (C=N); ^1H NMR (DMSO-d_6) δ = 3.99(s, 3H, NCH_3), 9.96(brs, 1H, D_2O exchangeable =NH),7.25-7.83(12H, m). (Found: C, 61.51; H, 3.24; N, 17.79; S, 6.74.$C_{24}H_{16}N_6SO_3$ requires C, 61.53; H, 3.44; N, 17.94; S, 6.84%).

2-(Ethyl cyanoacetyl)-4-imino-3-(1-methyl benzimidazol-2-yl)-4*H*-pyrimido[2,1-b][1,3]benzothiazole (31a): Yield, 59%; mp.281°C (dec.), IR υ_{max} / cm^{-1} (KBr) 3380, 3300, (NH), 2203 (CN), 1705 (CO), 1635 (C=N); ^1H NMR (DMSO-d_6) δ = 1.3(t, 3H, CH_3), 3.96(s, 3H, NCH_3), 4.01 (s, 1H, CH), 4.14(q, 2H, CH_2), 9.93(brs, 1H, D_2O exchangeable =NH),7.25-7.86(8H, m), M/S: m/z 442(M^+, 47.1). (Found: C, 62.33; H, 4.11; N, 18.91, S, 7.22. $C_{23}H_{18}N_6SO_2$ requires C, 62.43; H, 4.1; N, 18.99; S, 7.25%).

4-Imino-3-(1-methyl benzimidazol-2-yl)-2-(malononitrile)-4*H*-pyrimido[2,1-b]-[1,3]benzothiazole (31b): Yield, 62%; mp.243°C (dec.), IR υ_{max} / cm^{-1} (KBr) 3320, 3305, (NH), 2203, 2198 (CN), 1628 (C=N); ^1H NMR (DMSO-d_6) δ = 3.96(s, 3H, NCH_3), 4.23 (s, 1H, CH), 9.99(brs, 1H, D_2O exchangeable =NH),7.25-7.86(8H, m). (Found: C, 63.76; H,

3.33; N, 24.71; S, 8.13. $C_{21}H_{13}N_7S$ requires C, 63.78; H, 3.31; N, 24.8; S, 8.11%).

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