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β-Oxoanilides in Heterocyclic Synthesis: Synthesis and Antimicrobial Activity of Pyridines, Pyrans, Pyrimidines and Azolo, Azinopyrimidines Incorporating Antipyrine Moiety

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ABSTRACT

Condensation of *β*-Oxoanilide **1** with active methylene derivatives **2a**,**b** afforded the pyridine derivative **5**, and with crotononitrile afforded the pyridine **8**. Compounds **9** and **11a-c** were obtained by reaction of **1** with malononitrile dimer and arylidinemalononitrile **10a-10c**. In contrast, when compound **1** reacted with ethoxymethylen malononitrile afforded the pyridine derivative **13**. On the other hand, treatment of **1** with anthranilic acid gave the quinoline derivative **14**. Also, reactions of **1** with isothiocyanate derivatives afforded compounds **16-18**. The reaction of **1** with chalcone derivative afforded the pyridine derivative **22**. Treatment of compound **1** with thiourea produced pyrimidine derivative **23**. Furthermore, compound **1** converted into pyrimidinethione **24a** and pyrimidinone **24b** on treatment with a mixture of aromatic aldehydes and thiourea or urea respectively. Reaction of **24a** with hydrazonyl halide, thiosemicarbazide and arylidinecyanothioacetamide afforded compounds **26**, **28** and **29**. Compound **29** was treated with chloroacetonitrile to afford compound **30**. Six compounds from the newly synthesized were screened for antibacterial and antifungal activity against bacteria *Staphylococcus aureus*, *Bacillus cereus* and *Klebsiella pneumonia* and fungi *Aspergillus flavus* and *Aspergillus ochraceous*, respectively. Some of the tested compounds showed significant antimicrobial activity. IR, ^{1}H NMR, mass spectral data, and elemental analysis elucidated the structures of all the newly synthesized compounds.

Keywords: *β*-Oxoanilides; Pyridines; Pyrans; Pyrimidines; Azolo; Azinopyrimidines

1. Introduction

β-Oxoanilides are valuable intermediates in synthetic organic chemistry [1-6]. In the last few years we and others reported a variety of synthesis of heteroaromatics that have been developed utilizing *β*-oxoanilides as readily obtainable compounds [7-9]. Due to the recent reported biological activities of the heterocyclic moieties mentioned here such as pyridine derivatives which posses antimicrobial [10], and fungicidal [11] activities. As well as, pyrimidine derivatives were reported to be showed antimicrobial [12], activity. On the other hand, pyrazolopyrimidines are widely used as antimicrobial [13], activity. In addition, antipyrine has attracted a great deal of interest due to its wide applications in the field of pharmaceuticals, so many of the heterocyclic compounds incorporating antipyrine moiety exhibited antimicrobial [14], activity. Incorporating antipyrine moiety with the mentioned newly synthesized heterocyclic derivative may be enhancement the biological activities of the synthesized compounds. In continuation to this work we report here the reactions of *β*-oxoanilide with some electrophilic and nucleophilic reagents to produce some new substituted azines moiety.

2. Results and Discussion

It has been found that condensation of *β*-oxoanilide derivative **1** [15] with malononitrile **2a** in ethanol containing a catalytic amount of piperidine furnished the novel pyridone derivative **5** in good yield. The structure of **5** was confirmed based on spectral data (IR, ^{1}H NMR and MS). So, the mass spectrum of compound **5** showed the molecular ion peak at m/z = 336 (22%, M + 1) and the base peak was found at m/z = 93 (100%) corresponding to C_5H_3NO ion. Formation of compound **5** was interpreted via intermediacy of condensation product **3** which cyclized to **4** followed by aromatized to the final

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product **5** (**Scheme 1**).

Similarly, reaction of **1** with cyanothioacetamide **2b** in ethanolic piperidine solution yielded the pyridinone derivative **5** not the expected pyridinethione derivative **7** under the same condition as literature [16]. Structure **5** formed via this route was established based on its elemental analysis and compatible spectral data (IR, ^{1}H NMR and MS). The product **5** formed via this route was assumed to formed by condensation of **1** with cyanothioacetamide to form the condensation product **6** which cyclized via loss of H_2S (detected by lead acetate paper) to give the adduct **4**. Rearrangement of compound **4** to the final product **5** (**Scheme 1**).

Also, the reaction of **1** with 3-aminocrotonitrile afforded the 6-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl-amino)-2,4-dimethylnicotinonitrile **8**, (**Scheme 1**). Compound **8** was confirmed based on the elemental analysis and spectral data.

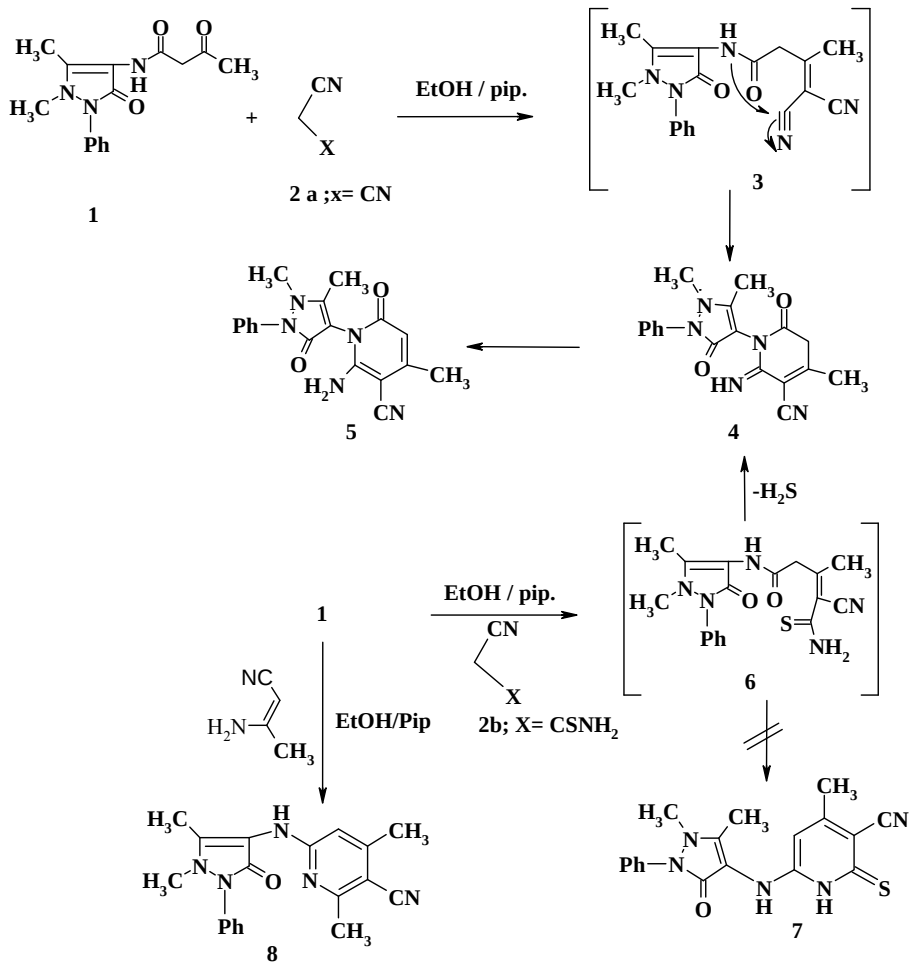
The behavior of **1** towards electrophilic reagents under an alkaline condition was investigated. Thus, the reaction of **1** with malononitrile dimer afforded the pyran derivative **9** which was established by spectral data (IR, ^{1}H NMR and ^{13}C NMR) (**Scheme 2**).

Also, the reaction of **1** with arylidinemalononitrile **10a-10c** afforded the pyran moiety **11a-11c** or the hydroxy pyridines **12a-12c**. Structure **11** was confirmed for the reaction product on the basis of spectroscopic data. The ^{1}H NMR spectrum showed a singlet signal at δ 4.36 ppm for 4H-pyran, whereas structure **12** would be expected to show OH proton at down field.

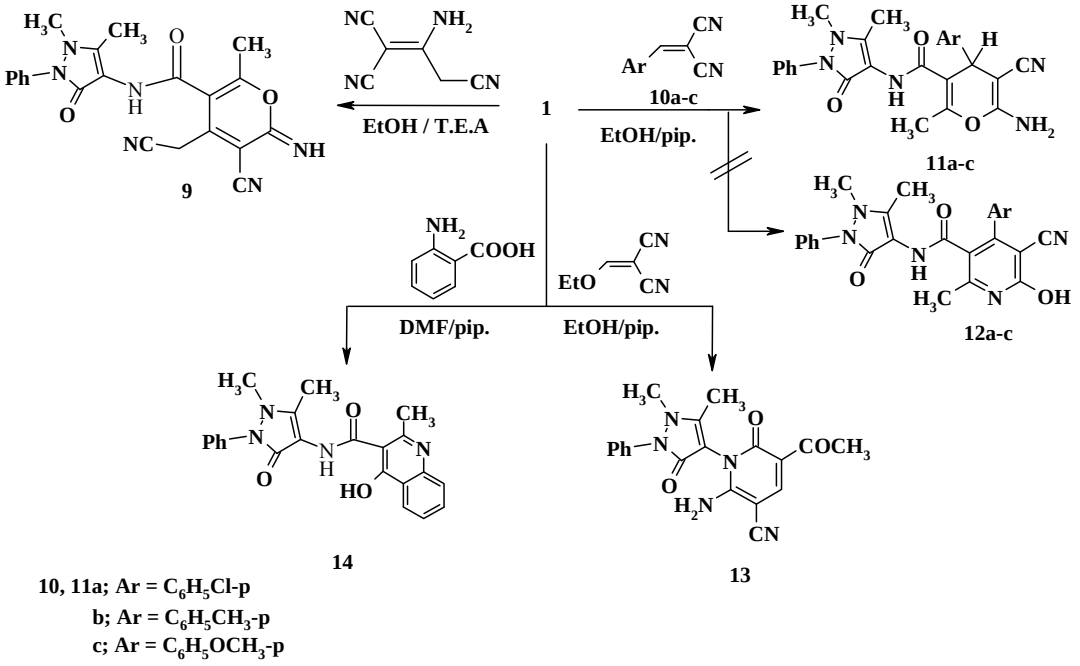
Further, β-oxoanilide **1** reacted with ethoxymethylene malononitrile to yield the pyridine derivative **13**.

On the other hand, treatment of **1** with anthranilic acid gave the quinoline derivative **14**. Establishing of the structure **14** by its elemental analysis and spectroscopic data (**Scheme 2**).

Reaction of β-oxoanilide **1** with ethoxycarbonylisothiocyanate **15a** (prepared *in situ*) in dry acetone afforded the adduct **16a**. Compound **16a** was established based on its elemental analysis and spectral data. The ^{1}H NMR spectrum of compound **16a** revealed the signals of OCH_2CH_3 protons at δ = 1.22 ppm as triplet, J = 7.2 Hz, and 4.15 as quartet, J = 7.2 Hz Compound **16a** was cyclized to the corresponding pyrimidinethione derivative



Scheme 1. Synthesis of compounds 5-8.



Scheme 2. Synthesis of compounds 9-14.

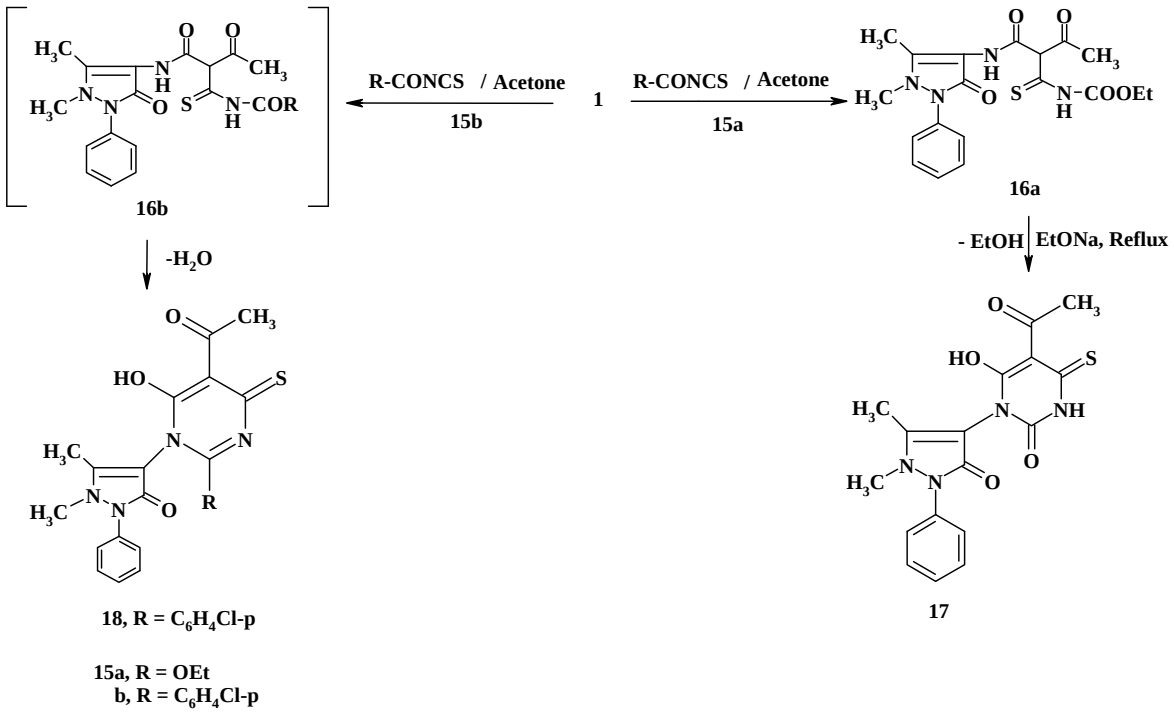
17 upon boiling in ethanolic sodium ethoxide solution. The ^{1}H NMR spectrum of compound **17** revealed the absence of any signals may be attributed to OCH_2CH_3 protons, and appearance only the signals assigned to $3CH_3$, NH, OH and aromatic protons.

On the other hand, reaction of **1** with *p*-chlorobenzoyl isothiocyanate **15b** in dry acetone furnished the pyrimidinethione derivative **18**. Establishing the pyrimidinethione derivative **18** based on its elemental analysis and spectral data (IR and ^{1}H NMR). (**Scheme 3**). The ^{1}H NMR spectrum of compound **18** revealed the absence of any signals may be attributed to OCH_2CH_3 protons. The formation of compound **18** in this reaction was assumed to proceed via addition of the methylene group in compound **1** to the isothiocyanate group in **15b** to give the nun-isolable adduct **16b**, which underwent cyclization with the loss of water molecule to give the final product pyrimidinethione derivative **18**.

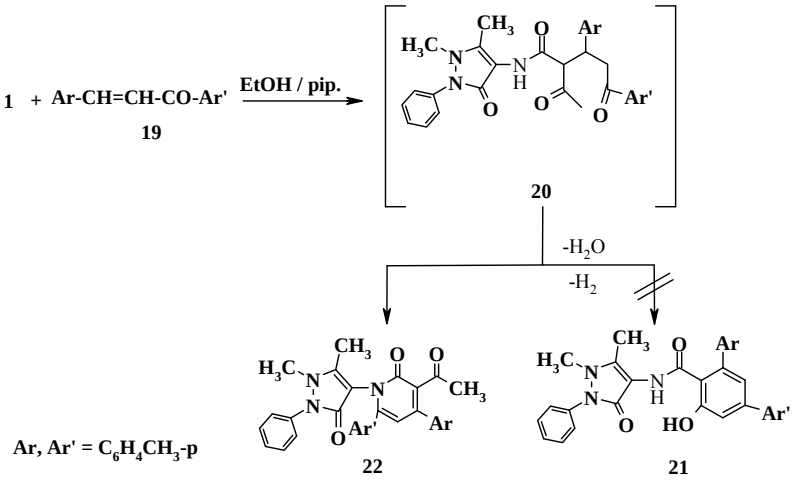
The reaction of *β*-oxoanilide **1** with the chalcone derivative **19** in ethanolic piperidine solution under reflux afforded a reaction product that could be formulated as the cyclized benzene derivative **21** as literature [17] or the pyridine derivative **22**. The structure **21** was ruled out according to the un-identical spectroscopic data for the structure. But the pyridine derivative **22** is considered the sole reaction product of the reaction based on its compatible spectroscopic data (IR, ^{1}H NMR, MS and ^{13}C NMR). Thus, ^{13}C NMR of the reaction product revealed a signal at 167.15, 188.33, 199.23 ppm assigned to three carbonyl function groups and five sp^3 signals at 10.91; 14.95; 20.60; 21.06; 36.00 ppm assigned to five CH_3 groups. We found that the two carbonyl group at 199.23, 188.33 ppm has high downfield and this high downfield is identical to acetyl carbonyl and carbonyl of pyridine ring not identified to the amidic carbonyl in structure **21** which may be assigned at rang 162.00 - 166.00 ppm. Also, the ^{1}H NMR spectrum of the reaction product revealed the presence of five singlet signals at δ = 1.63, 1.66, 2.26, 2.32, 2. 38, assigned for five CH_3 groups. Moreover, the IR spectrum of the reaction product indicated the presence of three absorption bands at ν = 1697, 1655, 1645 cm^{-1} which attributed to three carbonyl function groups. Also, the mass spectrum of the reaction product indicated the presence of the pyridinone ion peak at m/z = 91 (44%). From the above data we sure that the sole product is the pyridine derivative **22** (**Scheme 4**).

Treatment of **1** with thiourea afforded the pyrimidine derivative **23**. Establishing of compound **23** based on its elemental analysis and spectral data (IR and ^{1}H NMR), (**Scheme 5**).

The pyrimidinethione **24a** and pyrimidinone **24b** were synthesized by reacting of *β*-oxoanilide **1** with a mixture of aromatic aldehydes and thiourea or urea as one-pot three components. Thus, *β*-oxanilide **1** was reacted with a mixture of *p*-chlorobenzaldehyde and thiourea to form the pyrimidinethione derivative **24a** and with urea to form the pyrimidinone derivative **24b**. Establishing of structures **24a**, **24b** based on its spectroscopic data. The mass spectrum of pyrimidinethione **24a** showed a molecular ion peak at m/z = 467 (M^+) corresponding to the molecular formula $C_{23}H_{22}ClN_5O_2S$. Moreover, its ^{1}H NMR spectrum revealed the signals at δ = 5.44 (s, 1H,



Scheme 3. Synthesis of compounds 16a-18.

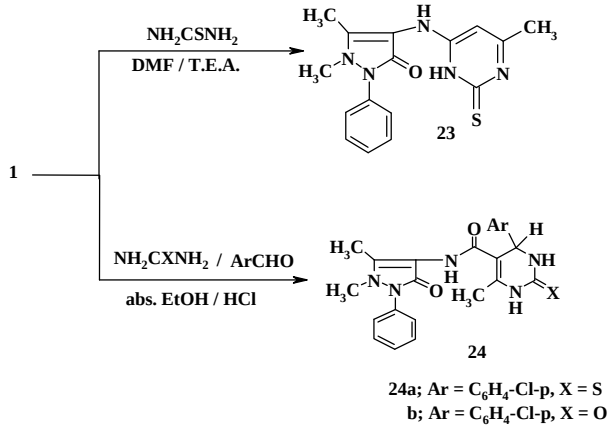


Scheme 4. Synthesis of compound 22.

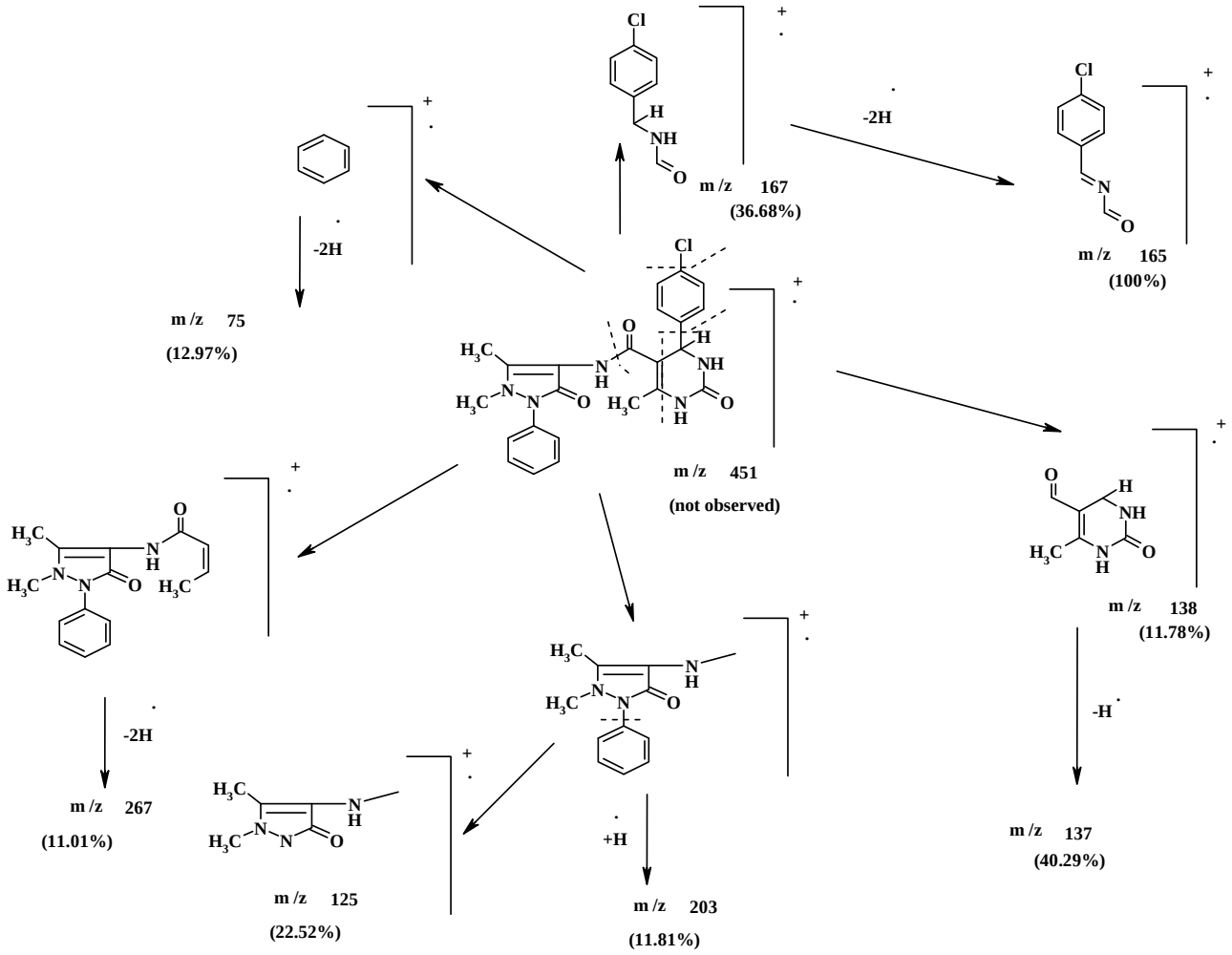
4H-pyrimidine), 9.26 (s, 1H, NH), 9.55 (s, 1H, NH), 9.84 (s, 1H, NH). On the other hand, the molecular ion peak of the structure **24b** was not observed [18,19] in its mass spectrum data due to the highly unstable M^+. The base peak was found at m/z = 165 (100%) corresponding to M^+ (451)-296 (**Sheet 1**). From the above data the structures **24a**, **24b** are correct structures for the reaction product (**Scheme 5**).

The pyrimidinethione derivative **24a** was used as starting material to obtain some fused azines [20]. Thus, it reacted with hydrazonylhalide derivative **25** in ethanol containing little amount of triethylamine to afforded the triazolopyrimidine derivative **26** or the isomeric structure **27**. We believe that the structure **26** is the correct one because it has the plane of symmetry than the structure **27** which has not this symmetry [21]. The structure **26** was established based on the compatible elemental analysis and spectroscopic data. The formation of **26** was assumed to proceed according to the mechanism described in scheme **6** as reported in literature [21].

Treatment of compound **24a** with thiosemicarbazide as binucleophlic reagent in ethanolic sodium ethoxide solution afforded the amino triazolopyrimidine derivative **28** by loss of H_2S.

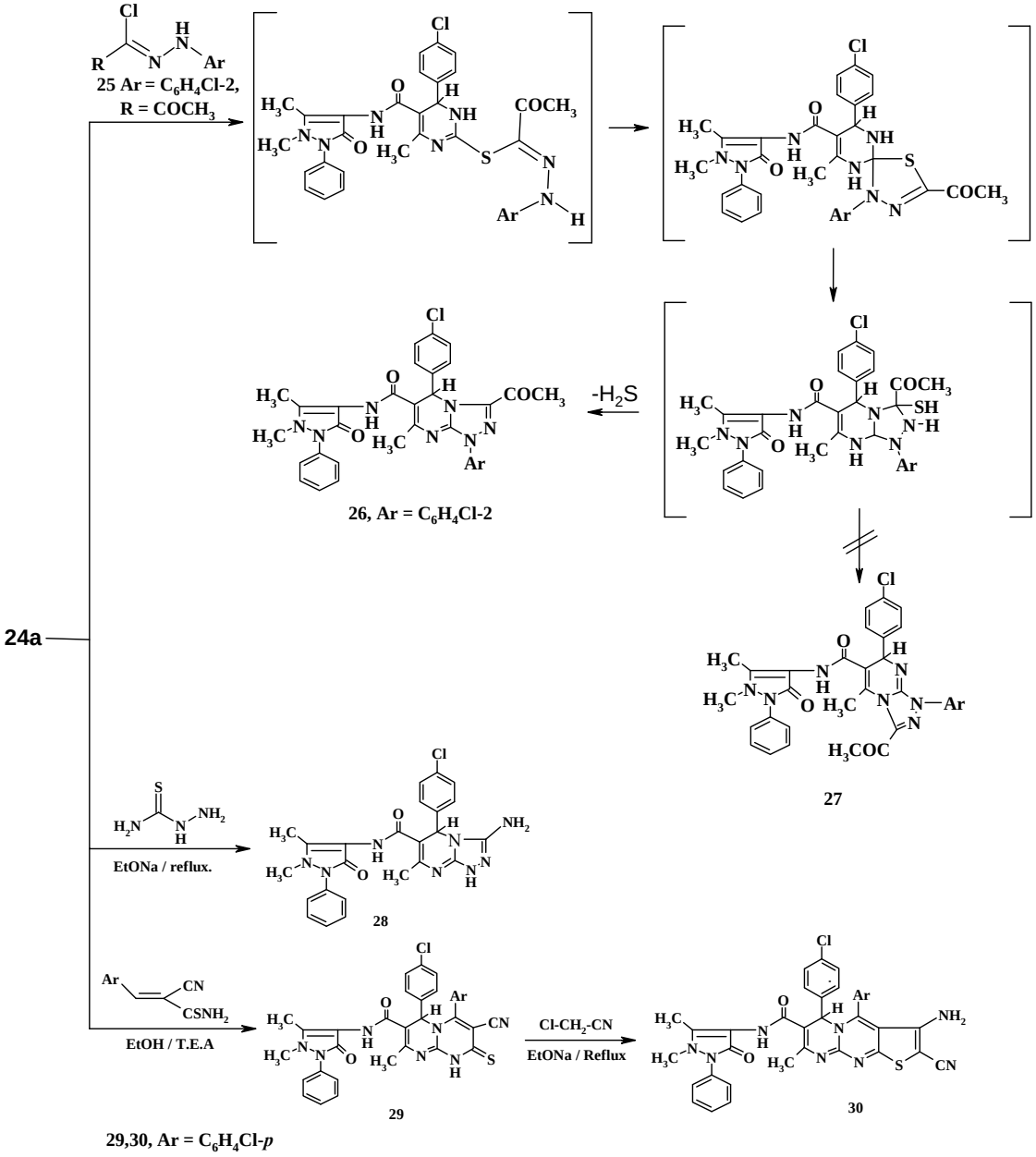


Scheme 5. Synthesis of compounds 23, 24a, 24b.



Sheet 1. Fragmentation pattern of compound 24b.

On the other hand, the pyrimidinethione **24a** was reacted with *p*-chlorobenzylidinecyanothioacetamide as example to the electrophilic reagents in ethanol containing a little amount of triethylamine under reflux to give the expected pyrimidopyrimidinthione derivative **29,** which reacted with one molecule of chloroacetonitrile in refluxing ethanolic sodium ethoxide solution to furnish the fused tricyclic pyrimidothienopyrimidine derivative **30**. Establishing the structure **30** based on its spectral data (**Scheme 6**).



Scheme 6. Synthesis of compounds 26-30.

3. Biological Activity

Seven compounds from the newly synthesized were screened *in vitro* for their antibacterial activities against Gram positive bacteria; *Staphylococcus aureus* and Bacillus cereus (G + ve), Gram negative bacteria; *Klebsiella pneumonia* (G − ve) and for their Antifungal activities against *Aspergillus flavus* and *Aspergillus ochraceous* by the agar diffusion technique [22]. 1 mg/ml solution in dimethylformamide (DMF) was used. The bacteria are maintained on nutrient agar. DMF showed no inhibition zones. The agar media were inoculated with different microorganism's culture tested after 24 hours of inoculated at 37˚C for bacteria and for antifungal tested after 72 hours of inoculated at 28˚C. The diameter of inhibition zone (mm) was measured. The data obtained is summarized in **Table 1**.

4. Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm^{-1}). The ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 at 200, 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX

Table 1. Antimicrobial activity of some of the newly synthesized compounds.

Compound no.	*Staphylococcus aureus* (G + ve)	*Bacillus cereus* (G + ve)	*Klebsiella pneumonia* (G − ve)	*Aspergillus flavus* (fungi)	*Aspergillus ochraceus* (fungi)
5	0.7	0.3	-	-	-
8	-	0.2	0.1	0.2	-
11a	1.4	0.3	0.8	-	
24a	0.9	1.3	0.4	-	-
26	1.4	-	0.6	-	-
29	1.0	0.7	0.9	0.4	0.4
DMF	-	-	-	-	-
Ciprofloxacin Flucoral	3	-	3	1.5	-

Inhibition Zone = 0.1 - 0.5 cm beyond control = + (slightly active); Inhibition Zone = 0.6 - 1.0 cm beyond control = + + (moderately active); Inhibition Zone = 1.1 - 1.5 cm beyond control = + + + (highly active); Inhibition Zone = 0.0 cm beyond control = − (inactive).

mass spectrometer at 70 ev. Elemental analysis were carried out by the Micro analytical Research Center, Faculty of Science, Cairo University, Assiut University and Al-azhar University, Faculty of Science, Department of Chemistry, Assiut Branch.

2-*Amino*-1-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-4-*methyl*-6-*oxo*-1,6-*dihydropyridine*-3-*carbonitrile* (5):

***General procedure*:**

Method A: A mixture of **1** (0.01 mole), malononitrile (**2a**) (0.01 mole) in ethanol (30 mL) was treated with a few drops of piperidine and refluxed for 12 hrs. The solid precipitate produced on cool was collected by filtration and recrystallized from the proper solvent to give **5**.

Method B: A mixture of **1** (0.01 mole), cyanothioacetamide (**2b**) (0.01 mole) and a few drops of piperidine, was refluxed in ethanol (30 mL) for 12 hrs. The obtained solid on cooling recrystallized from ethanol to give **5**.

It was obtained as green crystals from ethanol; yield 74%; mp. 193˚C; IR (KBr) ν cm^{-1} 3327, 3267 (NH_2), 3065 (CH-arom), 2934 (CH-aliph), 2193 (CN), 1654, 1635 (2C=O); ^{1}H NMR (DMSO-d_6) δ = 2.32 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 3.04 (s, 3H, NCH_3), 5.61 (s, 2H, NH_2), 7.24 - 7.87 (m, 6H, Ar-H + CH-pyridine), MS: m/z = 66 (32%), 93 (100%), 116 (43%), 148 (23%), 168 (31%), 183 (27%), 271 (26%), 299 (20%), 335 (30%) and 336 (22%) [M + 1]. Anal. Calc. For $C_{18}H_{17}N_5O_2$ (335.37): C, 64.47; H, 5.11; N, 20.88. Found: C, 64.73; H, 5.38; N, 20.63.

6-(1,5-*Dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*ylamino*)-2,4-*dimethylnicotinonitrile* (8):

To a solution of compound **1** (0.01 mole), 3-aminocrotonitrile (0.01 mole) in ethanol (30 mL) treated with a few drops of piperidine was heated under reflux for 12 hrs. Then cool, the solid product so formed was collected by filtration and recrystallized from dioxane as brown crystals; yield 70 %; mp. 187˚C; IR (KBr) ν cm^{-1} 3333 (NH), 3057 (CH-arom), 2923 (CH-aliph), 2193 (CN), 1655 (C=O); ^{1}H NMR (DMSO-d_6) δ = 2.17 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 3.04 (s, 3H, NCH_3), 7.09 - 7.78 (m, 6H, Ar-H + pyridine-H), 10.56 (s, 1H, NH), MS: m/z = 56 (47%), 77 (16%), 98 (100%), 120 (12%), 131 (3%), 161 (2%), 201 (5%), 213(4.9%), 280 (6%), 318 (3%) and 334 (3.62%) [M^{+1}]. Anal. Calc. For $C_{19}H_{19}N_5O$ (333.40): C, 68.45; H, 5.74; N, 21.01. Found: C, 68.72; H, 5.95; N, 21.22.

3-*Cyano*-4-(*cyanomethyl*)-*N*-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*imino*-6-*methyl*-2*H*-*pyran*-5-*carboxamide* (9):

A mixture of compound **1** (0.01 mole), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (0.01 mole) in ethanol (30 mL) was treated with a few drops of piperidine and heated under reflux for 18 hrs. Then cool, poured into crushed ice and acidified with dil. HCl. The product formed was collected by filtration and recrystallized from DMF/ ethanol as green crystal; yield 73%; mp. > 300˚C; IR (KBr) ν cm^{-1} 3373, 3181 (2NH), 3045 (CH-arom.), 2925 (CH-aliph), 2205, 2194 (2CN), 1666, 1635 (2CO), ^{1}H NMR (DMSO-d_6) δ = 2.14 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.02 (s, 3H, NCH_3), 3.97 (s, 2H, CH_2), 7.30 - 7.52 (m, 5H, Ar-H), 8.20 (s, 1H, NH), 10.01 (s, 1H, NH), ^{13}C NMR δ C = 17.70; 20.63; 24.84; 52.89; 112.38 (CN); 117.25 (CN); 122.42; 126.53; 126.53; 129.16; 129.16; 134.32; 134.32; 138.76; 146.0; 147.25; 147.25; 157.21; 157.21; 161.16 (CO); 180.45 (CO). Anal. Calc. For $C_{21}H_{18}N_6O_3$ (402.47): C, 62.68; H, 4.51; N, 20.88. Found: C, 62.89; H, 4.74; N, 20.65.

***Preparation of compounds* 11*a-c*:**

***General procedure*:**

A mixture of **1** (0.01 mole), arylidinemalononitriles **10a-c** (0.01 mole) in ethanol (30 mL) was treated with a few drops of piperidine and heated under reflux for 8 hrs.

The reaction mixture allowed to cool, poured into crushed ice and acidified with HCl. The solid product was filtered off and recrystallized from the proper solvent to give **11a-c**.

6-*Amino*-4-(4-*chlorophenyl*)-5-*cyano*-*N*-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*methyl*-4*H*-*pyran*-3-*carboxamide* (11*a*):

It was obtained as yellow crystals from ethanol; yield 88%; mp. 202˚C; IR (KBr) ν cm^{-1} 3423, 3333 (NH_2), 3212 (NH), 3053 (CH-arom.), 2926 (CH-aliph.), 2198 (CN), 1690, 1645 (2CO); ^{1}H NMR (DMSO-d_6) δ = 2.10 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 3.04 (s, 3H, NCH_3), 4.36 (s, 1H, 4H-pyran), 6.16 (s, 2H, NH_2), 7.25 - 7.53 (m, 9H, Ar-H), 11.15 (s, 1H, NH). MS: m/z = 68 (100%), 70 (89%), 84 (81%), 115 (83%), 178 (99.69%) and 472 (84%) [M^{-3}]. Anal. Calc. For $C_{25}H_{22}ClN_5O_3$ (475.94): Calcd: C, 63.09; H, 4.66; N, 14.71. Found: C, 63.29; H, 4.89; N, 14.97.

6-*Amino*-5-*cyano*-*N*-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-2-*methyl*-4-(4-*methylphenyl*)-4*H*-*pyran*-3-*carboxamide* (11*b*).

It was obtained as yellow crystals from ethanol; yield 85%; mp. 192˚C; IR (KBr) ν cm^{-1} 3318, 3283 (NH_2), 3161 (NH), 3050 (CH-arom), 2926 (CH-aliph), 2202 (CN), 1665, 1634 (2CO); ^{1}H NMR (DMSO-d_6) δ = 2.05 (s, 3H, CH_3), 2.13 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.16 (s, 3H, NCH_3), 4.16 (s, 1H, 4H-pyran), 6.66 (s, 2H, NH_2), 7.21 - 8.13 (m, 9H, Ar-H), 11.01 (s, 1H, NH). Anal. Calc. For $C_{26}H_{25}N_5O_3$ (455.52): C, 68.56; H, 5.53; N, 15.37. Found: C, 68.81; H, 5.76; N, 15.63.

6-*Amino*-5-*cyano*-*N*-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-4-(4-*methoxy*-*phenyl*)-2-*methyl*-4*H*-*pyran*-3-*carboxamide* (11*c*).

It was obtained as yellow crystals from ethanol; yield 87%; mp. 196˚C; IR (KBr) ν cm^{-1} 3313, 3275 (NH_2), 3161 (NH), 3049 (CH-arom), 2924 (CH-aliph), 2201 (CN), 1668, 1635 (2CO); ^{1}H NMR (DMSO-d_6) δ = 2.25 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.16 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 4.52 (s, 1H, 4H-pyran), 6.57 (s, 2H, NH_2), 7. 05 - 8.24 (m, 9H, Ar-H), 10.35 (s, 1H, NH). Anal. Calc. For $C_{26}H_{25}N_5O_4$ (471.52): C, 66.23; H, 5.34; N, 14.85. Found: C, 66.48; H, 5.61; N, 14.59.

5-*Acetyl*-2-*amino*-1-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-6-*oxo*-1,6-*dihydropyridine*-3-*carbonitrile* (13):

To a solution of **1** (0.01 mole) in ethanol (30 mL)/ piperdine (0.5 mL), ethoxymethylene malononitrile (0.01 mole) was added. The reaction mixture was refluxed for 15 hrs. Then left to stand, poured into cold water and acidified with HCl. The product formed was collected by filtration and recrystallized from ethanol to give (**13**; 66%) as brown crystals; mp. > 300˚C. IR (KBr) ν cm^{-1} 3421, 3400 (NH_2), 2923 (CH-aliph.), 2194 (CN), 1721, 1660, 1630 (3CO); ^{1}H NMR (DMSO-d_6) δ = 2.12 (s, 3H, CH_3), 2.14 (s, 3H, $COCH_3$), 3.02 (s, 3H, NCH_3), 5.59 (s, 2H, NH_2), 6.67 (s, 1H, CH-pyridine), 7.02 - 7.48 (m, 5H, Ar-H). Anal. Calc. For $C_{19}H_{17}N_5O_3$ (363.38): C, 62.80; H, 4.72; N, 19.27. Found: C, 62.55; H, 4.95; N, 19.54.

***N*-(1,5-*Dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-4-*hydroxy*-2-*methylquinoline*-3-*carboxamide* (14):**

To a solution of acetoacetanilide **1** (0.01 mole) in DMF (30 mL) containing a few drops of triethylamine, anthranilic acid (0.01 mole) was added. The reaction mixture was heated under reflux for 8 hrs. Then cool, poured into crushed ice and acidified with HCl. The solid product was collected by filtration and recrystallized from dioxane to give (**14**; 64%) as green crystals; mp. 196˚C; IR (KBr) ν cm^{-1} 3425 (OH), 3347 (NH), 3050 (CH-arom), 2924 (CH-aliph), 1670, 1648 (2C=O); ^{1}H NMR (DMSO-d_6) δ = 2.16 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.72 (s, 1H, NCH_3), 7.37 - 7.76 (m, 10H, Ar-H + OH), 10.23 (br, 1H, NH), MS: m/z = 56 (100%), 77 (78%), 102 (17%), 119(36%), 146 (24%), 166 (15%) and 387 (4.3 %) [M^+-1]. Anal. Calc. For $C_{22}H_{20}N_4O_3$ (388.43): C, 68.03; H, 5.19; N, 14.42. Found: C, 68.28; H, 5.45; N, 14.63.

***Ethyl*-2-{[(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)*amino*]*carbonyl*}-3-*oxobutanethiocarbamate* (16*a*):**

To a solution of compound 1 (0.01 mole) in dry acetone (30 mL), ethoxy carbonyl isothiocyanate 15a (prepared by reflux mixture of ethyl chloroformate (0.01 mol) and ammonium thiocyanate (0.01 mol) in dry acetone for 30 mins) was added. The reaction mixture was heated under reflux for 6 hrs. Then left to cool, the precipitate was collected by filtration and recrystallized from ethanol to give 16a, as white crystals; mp. 197˚C. IR (KBr) ν cm^{-1} 3254, 3212 (2NH), 2980 (CH-aliph), 1784, 1720, 1661, 1630 (4CO), 1H NMR (DMSO-d6), δ = 1.22 (t, J = 7.2 Hz, 3H, CH_3, CH_3CH_2O), 2.08 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.16 (s, 3H, NCH_3), 3.37 (s, 1H, CH), 4.15 (q, J = 7.2 Hz, 2H, CH_2, OCH_2CH_3), 7.30 - 7.55 (m, 5H, Ar-H), 10.55 (s, 1H, NH), 11.37 (s, 1H, NH). Anal. Calc. For $C_{19}H_{22}N_4O_5$ S (418.47): C, 54.53; H, 5.30; N, 13.39; S, 7.66. Found: C, 54.81; H, 5.56; N, 13.63; S, 7.50.

5-*Acetyl*-1-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-6-*hydroxy*-4-*thioxo*-3,4-*dihydropyrimidin*-2(1*H*)-*one* (17):

To a solution of **16a** (0.01 mole) in ethanol, sodium ethoxide (0.01 mole) was added. The reaction mixture was refluxed for 12 hrs. Then left to stand, poured into cold water and acidified with HCl. The product formed was collected by filtration and recrystallized from ethanol to give (**17**; 68%) as brown crystals; mp. > 300˚C; IR (KBr) ν cm^{-1} 3485 (OH), 3357 (NH), 3060 (CH-arom), 2927 (CH-aliph), 1653, 1630 (3CO); ^{1}H NMR (DMSO-d_6) δ = 1.24 (s, 3H, CH_3), 2.18 (s, 3H, $COCH_3$), 2.71 (s,

3H, NCH_3), 7.07 - 7.50 (m, 5H, Ar-H), 9.62 (s, 1H, NH), 12.57 (s, 1H, OH). Anal. Calc. For $C_{17}H_{16}N_4O_4S$ (372.41): C, 54.83; H, 4.33; N, 15.04; S, 8.61. Found: C, 54.57; H, 4.61; N, 15.25; S, 8. 87.

4-(5-*Acetyl*-2-(4-*chlorophenyl*)-6-*hydroxy*-4-*thioxopyrimidin*-1(4*H*)-*yl*)-1,5-*dimethyl*-2-*phenyl*-1,2-*dihydro*-3*H*-*pyrazol*-3-*one* (18):

To solution of compound **1** (0.01 mole) in dry acetone (30 mL), *p*-chlorobenzoyl isothiocyanate (**15b**) (prepared by reflux a mixture of *p*-chlorobenzoyl chloride (0.01 mol) and ammonium thiocyanate (0.01 mol) in dry acetone for 30 mins) was added. The reaction mixture was heated under reflux for 6 hrs, then left to cool. The solid product formed was collected by filtration and recrystallized from ethanol; yield 62% as brown crystals; mp. 190˚C; IR (KBr) ν cm^{-1} 3441 (OH), 3060 (CH-arom), 2926 (CH-aliph), 1660, 1634 (2CO); ^{1}H NMR (DMSO-d_6), δ = 2.16 (s, 3H, CH_3), 2.71 (s, 3H, $COCH_3$), 3.11 (s, 3H, NCH_3), 7.07 - 7.93 (m, 9H, Ar-H), 12.52 (br, 1H, OH). Anal. Calc. For $C_{23}H_{19}ClN_4O_3S$ (466.95): C, 59.16; H, 4.10; N, 12.00; S, 6.87. Found: C, 59.43; H, 4.27; N, 12.24; S, 6.62.

3-*Acetyl*-1-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-4,6-*bis*(4-*methylphenyl)pyridin*-2(1*H*)-*one* (22).

A mixture of compound **1** (0.01 mole) and 1,3-bis (4-methylphenyl)prop-2-en-1-one (**19**) in ethanol (30 mL) containing a few drops of piperidine was heated under reflux for 6 hrs. The solid product formed after cooling was collected by filtration and recrystallized from ethanol to give (**22**; 87%) as white crystals; mp. 120˚C; IR (KBr) ν cm^{-1} 3060 (CH-arom), 2924 (CH-aliph), 1697, 1655, 1645 (3C=O); ^{1}H NMR (DMSO-d_6) δ = 1.63 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.10 - 8.02 (m, 13H, Ar-H), 9.34 (s, 1H, pyridine-H), MS: m/z = 57 (100%), 91 (44%), 149 (49%), 221 (77%), 306 (11%), 384 (5%) and 503 (4%) [M^+]. ^{13}C NMR δ C = 10.91; 14.95; 20.60; 21.06; 36.00; 120.85; 120.85; 120.85; 123.24; 123.24; 126.10; 127.47; 128.50; 128.70; 128.70; 128.70; 128.70; 129.17; 129.17; 129.17; 129.17; 129.41; 129.41; 131.89; 135.37; 140.34; 140.34; 143.65; 158.00; 167.15 (CO); 188.33 (CO); 199.23 (CO). Anal. Calc. For $C_{32}H_{29}N_3O_3$ (503.61): C, 76.32; H, 5.80; N, 8.34. Found: C, 76.58; H, 5.58; N, 8.59.

1,5-*Dimethyl*-4-[(6-*methyl*-2-*thioxo*-2,3-*dihydropyrimidin*-4-*yl*)*amino*]-2-*phenyl*-1,2-*dihydro*-3*H*-*pyrazol*-3-*one* (23):

To a solution of acetoacetanilide **1** (0.01 mole) in DMF (30 mL) containing a few drops of triethylamine, thiourea (0.01 mole) was added. The reaction mixture was heated under reflux for 8 hrs. Then cool, poured into crushed ice and acidified with HCl. The solid product was collected by filtration and recrystallized from DMF; yield 59 %; mp. > 300˚C; IR (KBr) ν cm^{-1} 3420, 3378 (2NH), 3053 (CH-arom), 2926 (CH-aliph), 1652 (C=O); ^{1}H NMR (DMSO-d_6) δ = 2.46 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 3.05 (s, 3H, NCH_3), 7.11 - 7.67 (m, 6H, Ar-H + pyrimidine-H), 9.67 (s, 1H, NH), 9.85 (s, 1H, NH). Anal. Calc. For $C_{16}H_{17}N_5OS$ (327.41): C, 58.70; H, 5.23; N, 21.39; S 9.79. Found: C 58.48; H, 5.51; N, 21.53; S, 9.65.

***Preparation of compounds* 24*a,b*:**

***General procedure*:**

To a solution of acetoacetanilide **1** (0.01 mole) in absolute ethanol (30 mL) and (1 mL) HCl. A mixture of aromatic aldehyde (0.01 mole) and thiourea or urea (0.01 mole) was added. The reaction mixture was refluxed for 9 hrs. The solid product was produced on hot was collected by filtration and recrystallized from the proper solvent to give **24a,b**.

4-(4-*Chlorophenyl*)-*N*-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-6-*methyl*-2-*thioxo*-1,2,3,4-*tetrahydropyrimidine*-5-*carboxamide* (24*a*):

It was obtained as pale yellow crystals from dioxane/ethanol; yield 79%; mp. 270˚C; IR (KBr) ν cm^{-1} 3388, 3189 (3NH), 3071 (CH-arom), 2925 (CH-aliph), 1646 (2C=O); ^{1}H NMR (DMSO-d_6) δ = 1.88 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.02 (s, 3H, NCH_3), 5.44 (s, 1H, 4H-pyrimidine), 7.34-7.58 (m, 9H, Ar-H), 9.26 (s, 1H, NH), 9.55 (s, 1H, NH), 9.84 (s, 1H, NH). MS: m/z = 61 (18%), 81 (100%), 94 (67%), 131 (78%), 158 (50%), 178 (40%), 187 (49%), 268 (38%), 290 (37%), 438 (36%) and 467 (40%) [M^+]. Anal. Calc. For $C_{23}H_{22}ClN_5O_2S$ (467.98): C, 59.03; H, 4.74; N, 14.97; S; 6.85. Found: C, 59.25; H, 4.97; N, 14.71; S; 6.58.

4-(4-*Chlorophenyl*)-*N*-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-6-*methyl*-2-*oxo*-1,2,3,4-*tetrahydropyrimidine*-5-*carboxamide* (24*b*):

It was obtained as yellow crystals from dioxane/ethanol; yield 82 %; mp. 184˚C; IR (KBr) ν cm^{-1} 3447, 3275 (3NH), 3049 (CH-arom), 2924 (CH-aliph), 1667, 1647, 1630 (3C=O); ^{1}H NMR (DMSO-d_6) δ = 1.87 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 3.01 (s, 3H, NCH_3), 5.45 (s, 1H, 4H-pyrimidine), 7.30 - 7.58 (m, 9H, Ar-H), 9.34 (s, 1H, NH), 9.61 (s, 1H, NH), 10.03 (s, 1H, NH). MS: m/z = 75 (12.97%), 125 (22.52%), 137 (40%), 138 (11.78%), 165 (100%), 267 (11%). Anal. Calc. For $C_{23}H_{22}ClN_5O_3$ (451.92): C, 61.13; H, 4.91; N, 15.50. Found: C, 61.35; H, 4.66; N, 15.77.

3-*Acetyl*-5-(4-*chlorophenyl*)-1-(2-*chlorophenyl*)-7-*methyl*-*N*-(1,5-*dimethyl*-2-*phenyl*-3-*oxo*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-1,5-*dihydro*-[1,2,4]*triazolo*[4,3-*a*]*pyrimidine*-6-*carboxamide* (26):

A mixture of compound **24a** (0.01 mole), *N*-(2-chlorophenyl)-2-oxopropane hydrazonoyl chloride (**25**) in ethanol (30 mL) was treated with a few drops of triethylamine and heated under reflux for 8 hrs. Then cool,

poured into crushed ice and acidified with HCl. The solid product was collected and recrystallized from ethanol to give (**26**; 74 %) as green crystals; mp. 183˚C; IR (KBr) ν cm^{-1} 3421 (NH), 3066 (CH-arom), 2927 (CH-aliph), 1721, 1680, 1647 (3C=O); ^{1}H NMR (DMSO-d_6) δ = 2.39 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.48 (s, 3H, $COCH_3$), 3.19 (s, 3H, NCH_3), 5.21 (s,1H, 5H-pyrimidine), 7.35 - 7.84 (m, 13H, Ar-H), 9.56 (s, 1H, NH). Anal. Calc. For $C_{32}H_{27}Cl_2N_7O_3$ (628.52): C, 61.15; H, 4.33; N, 15.60. Found: C, 61.36; H, 4.61; N, 15.82.

3-*Amino*-5-(4-*chlorophenyl*)-*N*-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-7-*methyl*-1,5-*dihydro*[1,2,4]*triazolo*[4,3-*a*]*pyrimidine*-6-*carboxamide* (28).

A mixture of **24a** (0.01 mole), and thiosemicarbazide (0.01 mole) in ethanol containing sodium ethoxide (0.01 mole) was refluxed for 24 hrs. Then left to cool, poured into cold water and acidified with HCl. The product formed was collected by filtration and recrystallized from ethanol to give (**28**; 67%) as brown crystals; mp. 205˚C. IR (KBr) ν cm^{-1} 3408, 3320 (NH_2), 3234, 3198 (2NH), 3085 (CH-arom), 2925 (CH-aliph.), 1660, 1652 (2CO); ^{1}H NMR (DMSO-d_6) δ = 1.97 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.00 (s, 3H, NCH_3), 5.32 (s, 1H, 5H-pyrimidine), 7.05 - 8.02 (m, 11H, Ar-H + NH_2), 9.60 (s, 1H, NH), 11.44 (s, 1H, NH). Anal. Calc. For $C_{24}H_{23}ClN_8O_2$ (490.96): C, 58.72; H, 4.72; N, 22.82. Found: C, 58.94; H, 4.95; N, 22.60.

4,6-*Bis*-(4-*Chlorophenyl*)-3-*cyano*-*N*-(1,5-*dimethyl*-3-*oxo*-2-*phenyl*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-8-*methyl*-2-*thioxo*-1,6-*dihydro*-2*H*-*pyrimido*[1,2-*a*]*pyrimidine*-7-*carboxamide* (29):

A mixture of compound **24a** (0.01 mole), *p*-chloroarylidinecyanothioacetamide **16b** (0.01 mole) in ethanol (30 mL) was treated with a few drops of triethylamine and heated under reflux for 8 hrs. Then cool, poured into crushed ice and acidified with HCl. The solid product was collected and recrystallized from ethanol to give (**29**, 70%) as yellow crystals; mp. 183˚C; IR (KBr) ν cm^{-1} 3389, 3201 (2NH), 3070 (CH-arom.), 2921 (CH-aliph.), 2214 (CN), 1648, 1630 (2C=O); ^{1}H NMR (DMSO-d_6) δ = 2.44 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.02 (s, 3H, NCH_3), 5.42 (s, 1H, 6H-pyrimidine), 7.05 - 7.84 (m, 13H, Ar-H), 9.59 (s, 1H, NH), 9.96 (s, 1H, NH). Anal. Calc. For $C_{33}H_{25}Cl_2N_7O_2S$ (654.58): C, 60.55; H, 3.85; N, 14.98; S, 4.90. Found: C, 60.77; H, 3.68; N, 14.76; S, 4.66.

3-*Amino*-4,6-*bis*(4-*chlorophenyl*)-2-*cyano*-*N*-(1,5-*dimethyl*-2-*phenyl*-3-*oxo*-2,3-*dihydro*-1*H*-*pyrazol*-4-*yl*)-8-*methyl*-6*H*-*pyrimido*[1,2-*a*]-*thieno*[2,3-*d*]*pyrimidine*-7-*carboxamide* (30):

To a solution of **29** (0.01 mole) in ethanol, *α*-chloroacetonitrile (0.01 mole) and sodium ethoxide (0.01 mole) were added. The reaction mixture was refluxed for 24 hrs. Then left to stand, poured into cold water and acidified with HCl. The product formed was collected by filtration and recrystallized from ethanol to give (**30**; 60%) as green crystals; mp. 295˚C; IR (KBr) ν cm^{-1} 3430, 3355 (NH_2), 3200 (NH), 3065 (CH-arom.), 2925 (CH-aliph.), 2200 (CN), 1664, 1640 (2CO); ^{1}H NMR (DMSO-d_6), δ = 1.70 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 3.03 (s, 3H, NCH_3), 5.42 (s, 1H, 6H-pyrimidine), 6.61 (s, 2H, NH_2), 7.11 - 8.12 (m, 13H, Ar-H), 9.45 (s, 1H, NH). Anal. Calc. For $C_{35}H_{26}Cl_2N_8O_2S$ (693.62): C, 60.61; H, 3.78; N, 16.15; S, 4.62. Found: C, 60.80; H, 3.57; N, 16.38; S, 4.86.

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