Al-Azhar Bull. Sci. Vol. 24, No. 1 (June.): pp. 17-32, 2013.

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF SOME NEW PYRIDINE-2(1*H*)-THIONES, NICOTINAMIDES ,THIENO[2,3-*B*]-PYRIDINES, PYRIDO[3',2':4,5]- THIENO[3,2-*D*]PYRIMIDINES AND PYRIDO[3',2':4,5]THIENO[3,2-*D*][1,2,3]- TRIAZINES CONTAINING ANTIPYRINE MOIETY.

ISMAIL. M. M. OTHMAN

Chemistry Department, Faculty of Science, Al-Azhar University at Assiut, Assiut 71524, Egypt

Abstract

N-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3-oxobutanamide (**1**) reacts with arylidinecyanothioacetamides **2a–c** in ethanol/piperidine solution under reflux to yield the pyridine-2(1*H*)-thiones **5a–c**. Compound **5a** reacts with α-haloketones **6a–e** to give the nicotinamide derivatives **7a–e**, which cyclized to thienopyridine derivatives **8a–e**. The reaction of compound **8a** with formamide, phenyl isothiocyanate and hydrazine hydrate afforded the pyridothienopyrimidine derivatives **9**, **11** and thienopyridine carbohydrazide derivative **12** respectively. Also, the reaction of **12** with phenyl isothiocyanate under reflux gave the thienopyridine derivative **14**. Condensation of **8b,c** with DMF-DMA afforded the corresponding 3-[(dimethylamino)methylene)-amino]thienopyridine derivatives **15a,b**, which cyclized into the pyridothienopyrimidine derivatives **16a,b**. Self coupling of compounds **8b,c** were occurred through their diazotization where, the corresponding pyridothienotriazine derivatives **17a,b** were obtained. Most of the target compounds were then evaluated for their antimicrobial and antifungal activities.

Keywords Antipyrine 3-oxobutanamide; pyridine-2(1*H*)-thiones; nicotinamides; thienopyridines; pyridothienopyrimidines; pyridothienotriazines; biological activity.

Introduction

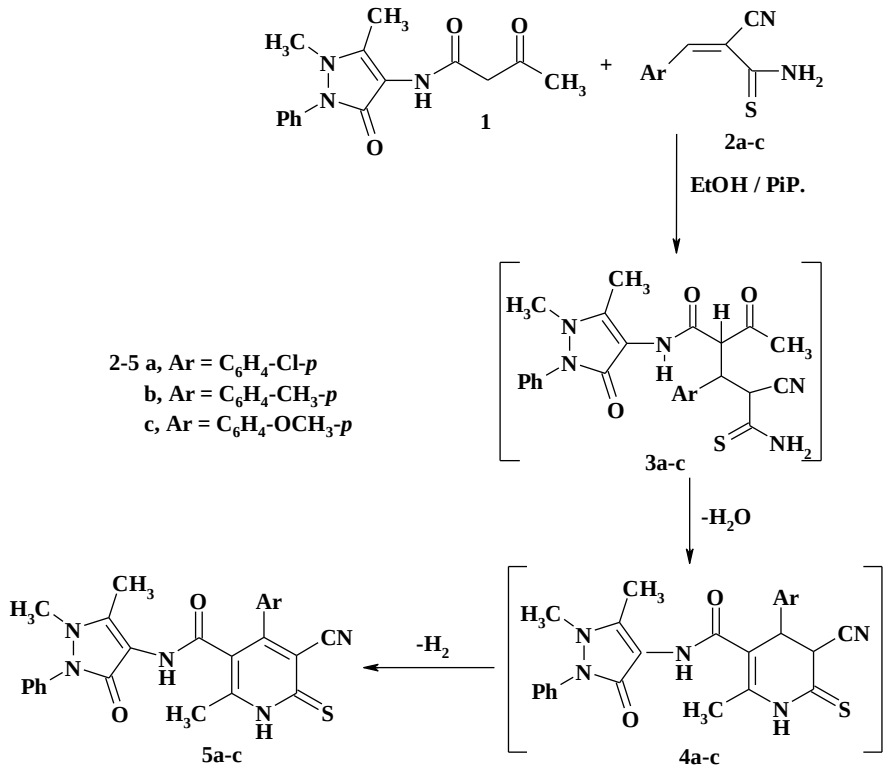
Since the antipyrine (AP) was first synthesized by Knorr[1] in 1883, there has been a continued interest in the studies of antipyrine derivatives (APDs). Up to now, broad properties of APDs have been investigated and reported in many fields. In bifunctional compounds, broad bioactivities of APDs as antitumor[2], antimicrobial[3], antiviral[4], analgesic, anti-inflammatory drugs[5], and anticancer activity[6] have been investigated. On the other hand, pyridine-2(*1H*)-thione compounds have gained considerable interest due to their importance as intermediates for the synthesis of the biologically active deazafolic acid and deaza amino protein ring system[7]. Moreover, pyridine carbonitriles were used as cardiotonic[8] and antiviral agents[9]. Furthermore, *S*-substituted thiopyridines possess neurotropic[10], cardiovascular[11], antimicrobial[12] activities and are used as adenosine receptor ligands[13]. Also, nicotinate derivatives have been reported to be used as agrochemical fungicides[14] and anticancer[15] agents.

Moreover, several thienopyridines have been synthesized and their pharmaceutical medicinal activities evaluated and used as anticoagulants[16], antiartherossclerotics[17] and gonaodotropin releasing hormone antagonists[18]. Also, thieno[2,3-*b*]pyridines possess a wide range of biological activities such as antiviral[9,19], antidiabetic[20], antimicrobial[12,21], antitumor[22] antiparasitic[23]. In addition, pyridothienopyrimidines have been reported to have antiallergic[24] antiprotozoal[25], antianaphylactic[26], and antimicrobial[12,27] activities. Moreover, pyridothienotriazines have been used as antiprotozoal[28] antitumor[29], antiangiogenic[30], and antimicrobial[11] agents and have been reported to inhibit NO and eicosanoid biosynthesis[31].

As a continuation of our program dealing with application of β-oxoanilide in the synthesis of pyridine derivatives[32,33] and fused pyridines[34]and in conjunction with this work we report here the results of our investigation on the synthesis of new nicotinamides, thieno[2,3-*b*]pyridines, pyridothienopyrimidines, and pyridothienotriazienes using pyridine-2(1*H*)-thiones containing antipyrine moiety. The newly synthesized compounds were evaluated as antimicrobial agents against gram positive, gram negative bacteria and fungi.

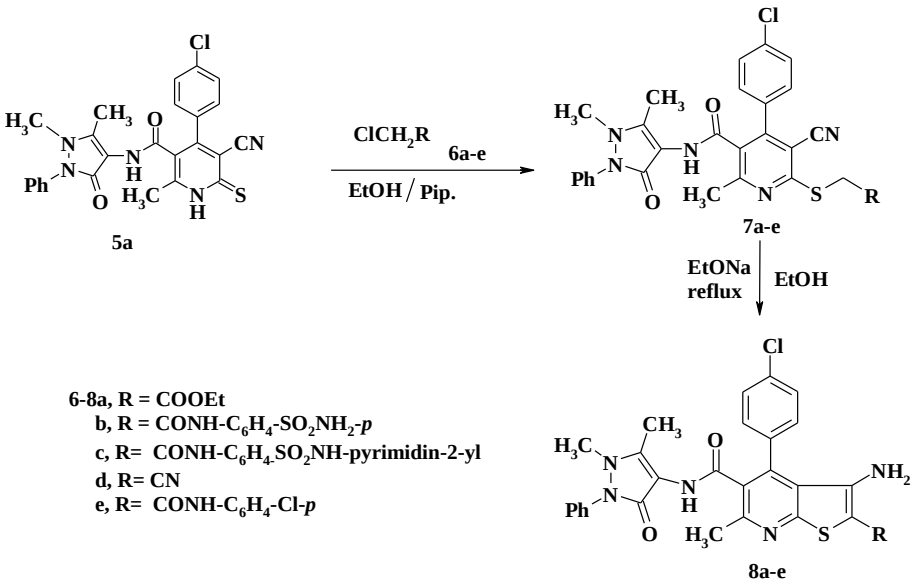
Results and Discussion

It has been found that *N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3-oxobutanamide **(1)**[35] easily reacted with arylidine cyanothioacetamide derivatives **2a–c** in refluxing ethanol containing few drops of piperdine to give the pyridine-2(1*H*) -thiones **5a–c**. Establishing the exact structure of the reaction products is based on the spectroscopic data. Thus, the ^{1}H NMR spectrum of compound **5a**, for example, revealed the presence of singlet signals at δ = 9.65, 10.59 ppm assigned to 2NH groups and the aromatic protons at δ 6.99-7.35 ppm. Also, ^{13}C NMR of the structure revealed signals at 13.55, 21.18, 38.87 ppm ($3CH_3$), 115.33 ppm (CN), 165.55, 168.27 ppm (2C=O), 185.21 ppm (C=S), in addition to the sp^2 carbon atoms as in the experimental section. The formation of compound **5a-c** is assumed to proceed via an initial addition of the active methylene moiety in **1** to the active double bond in **2a-c**, thus forming the acyclic Michael adduct **3a-c**, which then cyclized to **4a-c** by a loss of water molecule and aromatized by a loss of hydrogen molecule to the final product **5a-c** (Scheme1).



Scheme 1: synthesis of pyridine-2(1*H*)thiones

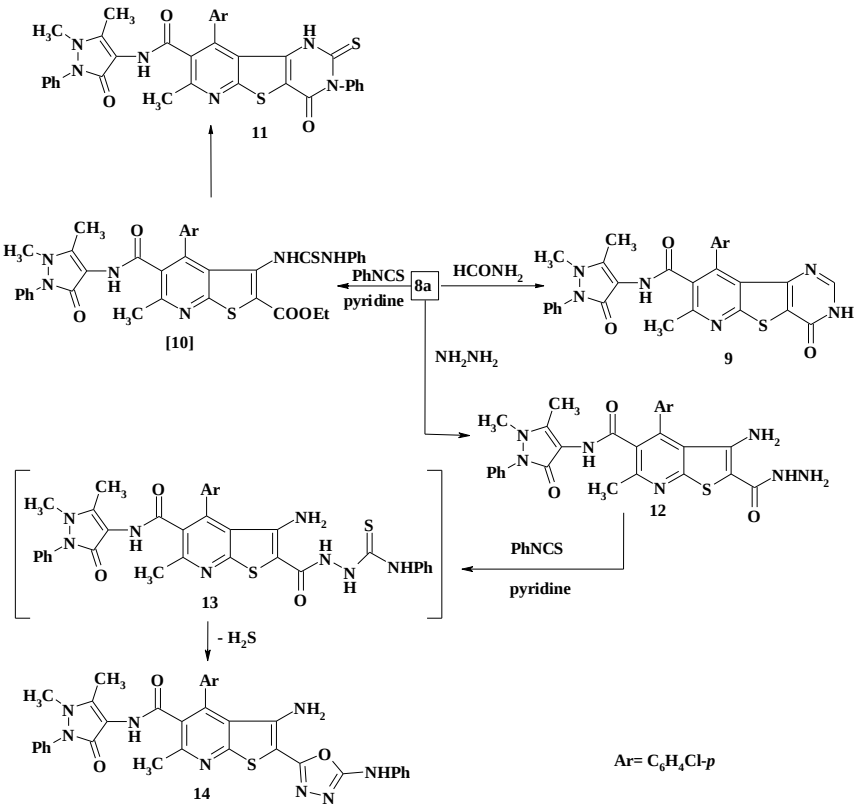
The reaction of pyridinethione derivative **5a** with α -haloketones **6a–e** in ethanol containing piperidine afforded the *S*-alkylnicotinamide derivatives **7a–e.** The structure of compounds **7a–e** has been confirmed as the correct one based on its spectral data and elemental analyses. Thus, the IR spectrum of compound **7a**, for example, indicated the presence of the absorption band of the CN functional group at υ 2217cm^{-1} and a carbonyl ester at υ 1715 cm^{-1}. The ^{1}H NMR spectrum of compound **7a** revealed a triplet signal at δ 1.24 ppm, J=7.2 Hz assigned to ester CH_3, quartet signal at δ 4.18 ppm, J =7.2 Hz assigned to CH_2 ester, SCH_2 protons at δ =5.48 ppm, in addition to the other protons assigned in compound **7a** and the disappearance of the proton of one NH (δ = 13.59 ppm in compound **5a**). The structures of **7a–e** were further elucidated via elemental analysis and their cyclization into the corresponding thieno[2,3-*b*]pyridine derivatives **8a–e** upon treatment with ethanolic sodium ethoxide under reflux. The structures of **8a–e** were confirmed based on elemental analysis and spectral data (Scheme 2 and Experimental data).



Scheme 2: synthesis of *S*-alkylnicotinates and thienopyridines

The IR spectrum of compound **8a** exhibited the disappearance of the absorption band due to the CN function group and the appearance of absorption band due to the NH_2 functional group at υ 3470, 3388 cm^{-1}. The ^1H NMR spectrum of compound **8a** revealed the disappearance of the protons assigned to the methylene group at δ = 5.48 ppm and revealed the presence of two protons as a singlet at δ = 6.25 ppm assignable to the NH_2 group beside the other protons in their proper positions.

Furthermore, treatment of compound **8a** with formamide solution under reflux gave the expected pyrido[3',2':4,5]thieno[3,2-*d*]-pyrimidine-8-carboxamide derivative **9** (Scheme 3). Structure **9** was confirmed on the basis of elemental analye and spectral data, Furthermore, treatment of compound **8a** with phenyl isothiocyanate in the presence of pyridine under reflux afforded the pyrido[3',2':4,5]thieno[3,2-*d*]-pyrimidine-8-carboxamide derivative **11** through the intermediate **10** which then cyclized via elimination of a molecule of ethanol to yield the aromatic final product **11.** The ^1H NMR spectrum of **11** revealed the absence of any signals may be attributed to ($CO_2C_2H_5$) and NH_2 protons, and appearance signals assigned to 2NH. Furthermore, the structure of compound **11** was supported by ^{13}C NMR spectrum (Scheme 3 and Experimental part).

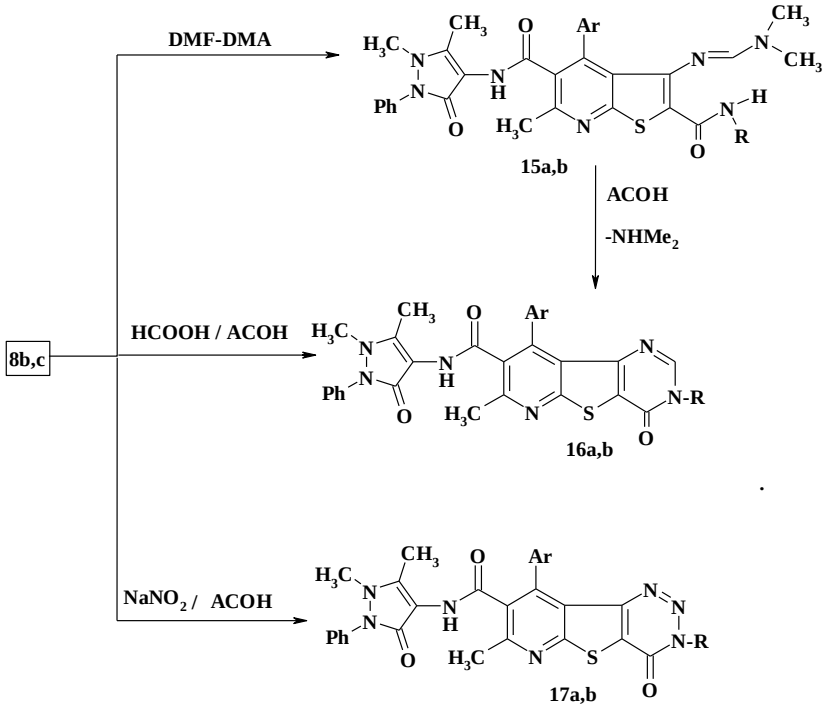


Scheme 3: synthesis of pyridothienopyrimidines

The reactivity of *β*-amino ester derivative **8a** toward some electrophilic reagents has been studied. Thus, the reaction of **8a** with hydrazine hydrate afforded 3-aminothieno [2,3-*b*]pyridine carbohydrazide derivative **12**. The structure of hydrazide **12** was compatible with the spectroscopic data (IR and ^{1}H NMR). Also, the reaction, of **12** with phenyl isothiocyanate in dry dioxane under reflux gave the corresponding 3-amino-2-(5-phenylamino-1,3,4-oxadiazol-2-yl)thieno[2,3-*b*] pyridine derivative **14** via the loss of one molecule of hydrogen sulfide[36] through the formation of the intermediate **13** as reported in literature[36] . The analytical and spectral data are in agreement with the proposed structure (Scheme 3 and Experimental part).

This work was extended to study the reactivity of the amino group in compounds **8b,c** as nucleophile. Thus, **8b** reacted with dimethylformamide-dimethylacetal (DMF-DMA) in dry dioxan to afford the corresponding 4-(4-chlorophen- yl)-N^5-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-3-{[(dimethylamino)methylene]amino}-6-methyl-N^2-(4-sulfamoyl-phenyl)thieno[2 ,3-*b*]pyridine-2,5-dicarboxamide (**15a**). ^{1}H NMR spectrum of **16a** revealed the new signals of N $(CH_3)_2$ at (δ = 3.64 ppm). In the same way **8c** condensed with DMF-DMA to give The corresponding 3-{[(dimethylamino)methylene]amino}thieno[2,3-

b]pyridine-2,5-dicarboxamide derivative **15b**. The structures of **15a,b** was inferred through elemental analysis, spectral data and chemical transformation. Cyclization of **15a,b** through boiling their solutions in glacial acetic acid afforded the corresponding pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxamide derivatives **16a,b** via dimethylamine elimination. The structures of **16a,b** were confirmed based on elemental analysis, spectral data and through synthesis *via* other route, by the reaction of **8b,c** with Conc. formic acid in Glacial acetic acid under reflux to give one and the same reaction products **16a,b**. Compounds **16a,b** prepared via this route were found completely identical in all aspects (mp., mixed mp. and tlc) with **16a,b** prepared from the cyclization of **15a,b** (cf. Scheme 4 and Experimental part).



Scheme 4: synthesis of pyridothienopyrimidines and triazines

Diazotization and self coupling of compounds **8b,c** afforded the corresponding pyrido[3',2':4,5]thieno[3,2-*d*][1,2,3]triazine benzene sulfonamide derivatives **17a,b**. ^{1}H NMR spectra of **17b**, for example, revealed the disappearance of the signal corresponding to NH_2 group. (cf. Scheme 4 and Experimental part).

Twelve compounds from the newly synthesized were screened in vitro for their antibacterial activity against Gram positive bacteria; Staphylococcus aureus and

Gram negative bacteria; Klebsiella pneumonia. Also, the antifungal activity against Aspergillus flavus and Aspergillus ochraceous was evaluated using the agar diffusion technique[37]. 1mg/ml solution in dimethylformamide (DMF) was used. The bacteria and fungi were grown on nutrient agar and Czapek's–Dox agar media, respectively. DMF as a negative control did not show 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.

Most of the synthesized compounds were found to possess various antimicrobial activities towards all the microorganisms used (Table 1). Compounds **8b** was found to possess highest antibacterial activity toward Staphylococcus aureus (G +ve), compound **17a** was found to be very active against aspergillus flavus. In addition, compounds **5a, 8a, 11** revealed a moderate activity against Staphylococcus aureus (G +ve). Compounds **7b, 11, 16a, 17a** showed a moderate activity against Klebsiella pneumonia (G -ve), compounds **5a, 8a, 9** and **15a** showed a moderate activity against aspergillus flavus. Moreover, compounds **7a, 7b, 9, 14, 16a, 17a** were found to have low activity against Staphylococcus aureus (G +ve), compounds **5a, 8a, 8b, 9, 12 and 15a** were found to be the low activity against Klebsiella pneumonia (G -ve). Whereas compounds **7a, 8b, 12, 16a** showed a low activity against aspergillus flavus and compounds **7b, 8b, 9, 11, 14** and **16a** showed a low activity against Aspergillus ochraceous.

Table1. Antimicrobial activity of some of the newly synthesized compounds.

Compound no.	Staphylococcus aureus (G +ve)	Klebsiella pneumonia (G -ve)	Aspergillus flavus (fungi)	Aspergillus Ochraceus (fungi)
5a	++	+	++	-
7a	+	-	+	-
7b	+	++	-	+
8a	++	+	++	-
8b	+++	+	+	+
9	+	+	++	+
11	++	+ +	-	+
12	-	+	+	-
14	+	-	-	+
15a	-	+	++	+
16a	+	++	+	-
17a	+	++	+++	-
Ciprofloxacin	++++	++++	-	-
Flucoral	-	-	++++	++++

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).

Experimental

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm^{-1}). The ^{1}H 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. 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.

Preparation of Compounds 5a–c: General Procedure

A mixture of compound **1** (0.01 mol) and arylidinecyanothioacetamide **2a–c** (0.01mol) in ethanol (30 mL) was treated with piperidine (0.5 mL) and heated under reflux for 7 h. The reaction mixture was then cooled by being poured into crushed ice and acidified with HCl. The solid product was collected and recrystallized from ethanol to give compounds **5a–c**.

4-(4-Chlorophenyl)-5-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (5a)

It was obtained as yellow crystals from ethanol; yield 86%; mp 180◦C;

IR (KBr) ν cm^{-1} 3345, 3212 (NH), 3053 (CH-arom.), 2926 (CH-aliph.), 2221 (CN), 1680, 1663 (2CO); ^{1}H NMR (DMSO-d_6) δ = 1.32 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.06 (s, 3H, NCH_3), 6.99-7.35 (m, 5H, Ar-H), 7.50, 7.67 (2d, 4H, Ar-H), 9.65 (s, 1H, NH) , 10.59 (s, 1H, NH). ^{13}C NMR DMSO-d_6) δ C = 13.55 (q); 21.18 (q); 38.87 (q); 103.22 (s); 110.49 (s); 115.33 (CN); 123.21 (s); 124.12 (d); 128.32 (d); 129.66 (d); 132.22 (d); 133.29 (s); 134.79 (s); 137.32 (d); 158.59 (d); 159.86 (s); 165.55 (CO); 168.27 (CO); 185.21 (CS). Anal. Calc. For $C_{25}H_{20}ClN_5O_2S$ (489.99): C, 61.28; H, 4.11.; Cl, 7.24; N, 14.29; S, 6.54%.Found: C, 61.50; H, 4.33; Cl, 7.45; N, 14.52; S, 6.77%.

5-Cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-methyl-6-thioxo-4-(4-methylphenyl)-1,6-dihydropyridine-3-carboxamide (5b)

It was obtained as yellow crystals from ethanol; yield 80%; m.p 182 °C; IR (KBr): υ cm^{-1} 3358, 3228 (2NH), 3047 (CH-arom.), 2925 (CH-aliph.), 2209 (CN), 1675, 1655 (2CO).^{1}H NMR (DMSO-d_6): δ = 1.60 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.17 (s, 3H, NCH_3), 6.98–7.21 (m, 5 H, Ar-H), 7.33, 7.50 (2d, 4H, Ar-H), 8.13 (s, 1H, NH) , 10.14 (s, 1H, NH). Anal. Calc. for $C_{26}H_{23}N_5O_2S$ (469.57): C, 66.51; H, 4.94; N, 14.91; S, 6.83%.Found: C, 66.74; H, 4.70; N, 14.67; S, 6.60%.

5-Cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-4-(4-methoxyphenyl)-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (5c)

It was obtained as yellow crystals from ethanol; yield 87 %; m.p. 177 °C; IR (KBr) ν cm^{-1} 3318, 3265 (2NH), 3047 (CH-arom.), 2928 (CH-aliph.), 2216 (CN), 1688, 1657 (2CO); ^{1}H NMR (DMSO-d_6) δ = 1.50 (s, 3H, CH_3), 1.64 (s, 3H, CH_3),

3.64 (s, 3H, NCH_3), 3.82 (s, 3H, OCH_3), 6. 97- 7.36 (m, 5H, Ar-H), 7.50, 7.79 (2d, 4H, Ar-H), 9.72 (s, 1H, NH), 10.43 (s, 1H, NH). Anal. Calc. for $C_{26}H_{23}N_5O_3S$ (485.57): C, 64.31; H, 4.77; N, 14.42; S, 6.60%.Found: C, 64.52; H, 4.96; N, 14.65; S, 6.83%.

Preparation of Compounds 7a–e: General Procedure

A mixture of compound **5a** (0.01 mol), halo compounds **6a–e** (0.01 mol), and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 3 h, then cooled, poured into crushed ice, and acidified with HCl. The precipitates formed were collected and recrystallized from the proper solvent to give **7a–**e.

Ethyl2-((4-(4-chlorophenyl)-3-cyano-5-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)carbamoyl)-6-methylpyridin-2-yl)thio)acetate (7a)

It was obtained as yellow crystals from ethanol; yield 82 %; m.p. 225 ^oC; IR (KBr) ν cm^{-1} 3326 (NH), 3060 (CH-arom.), 2923 (CH- aliph.), 2217 (CN), 1715, 1695, 1663 (3C=O); ^1H NMR (DMSO-d_6) δ = 1.24 (t, *J* = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 1.82 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.13 (s, 3H, NCH_3), 4.18 (q, *J* = 7.2 Hz, 2H, $O\underline{CH_2}CH_3$), 5.48 (s, 2H, SCH_2), 6.95- 7.54 (m, 9H, Ar-H), 9.19 (s, 1H, NH). Anal. Calc. for $C_{29}H_{26}ClN_5O_4S$ (576.08): C, 60.46; H, 4.55; Cl, 6.15N, 12.16; S, 5.57% .Found: C, 60.69; H, 4.77; Cl, 6.49; N, 12.37; S, 5.78 %

4-(4-Chlorophenyl)-5-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3- dihydro-1H-pyrazol-4-yl)-2-methyl-6-((2-oxo-2-((4-sulfamoylphenyl) amino) ethyl) thio)nicotinamide (7b)

It was obtained as yellow crystals from ethanol; yield 73 %; m.p. 242 ºC; IR (KBr) ν cm^{-1} 4420, 3375 (NH_2), 3363, 3181 (2NH), 3045 (CH-arom.), 2925 (CH-aliph.), 2221 (CN), 1695, 1676, 1655 (3CO), ^1H NMR (DMSO-d_6) δ = 1.65 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 2.46 (s, 3H, NCH_3), 4.45 (s, 2H, SCH_2), 6.94- 7.48 (m, 7H, Ar-H + NH_2), 7.60, 7.79 (2d, 4H, Ar-H), 7.81, 7.87 (2d, 4H, Ar-H), 9.72 (s, 1H, NH), 10.03 (s, 1H, NH). Anal. Calc. for $C_{33}H_{28}ClN_7O_5S_2$ (702.22): C, 56.45; H, 4.02; Cl, 5.05; N, 13.96; S, 9.13% .Found: C, 56.66; H, 4.24; Cl, 5.27; N, 13.73; S, 9.38%.

4-(4-Chlorophenyl)-5-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-methyl-6-((2-oxo-2-((4-(N-(pyrimidin-2-yl)sulfa-moyl)phenyl)amino)ethyl)thio)nicotinamide (7c)

It was obtained as yellow crystals from ethanol, yield 75%; mp 235◦C. IR (KBr): υ cm^{-1} 3453, 3375, 3241 (3NH), 3070 (CH-arom), 2920 (CH-aliph.), 2215 (CN), 1990, 1663, 1648 (3CO). ^1H NMR (DMSO-d_6) δ = 2.29 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.68 (s, 3H, NCH_3), 4.00 (s, 2H, SCH_2), 6.98- 8.04 (m, 17H, Ar-H+ NH), 9.92 (s, 1H, NH), 10.21 (s, 1H, NH). Anal. Calc. for $C_{37}H_{30}ClN_9O_5S_2$ (780.29). C, 56.95; H, 3.88; Cl, 4.54; N, 16.16; S, 8.22%.Found: C, 56.71; H, 3.65; Cl, 4.76; N, 16.37; S, 8.44%.

4-(4-Chlorophenyl)-5-cyano-6-((cyanomethyl)thio)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-methylnicotinamide (7d)

It was obtained as brown crystals from ethanol, yield 68%;mp 230◦C. IR (KBr): υ cm^{-1} 3225 (NH), 3057 (CH-arom), 2926 (CH-aliph.), 2220, 2203 (2CN), 1702, 1648 (2CO). ^{1}H NMR (DMSO-d_6) δ = 1.17 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.15 (s, 3H, NCH_3), 4.52 (s, 2H, SCH_2), 6.97- 7.37 (m, 5H, Ar-H), 7.55, 7.70 (2d, 4H, Ar-H), 9.26 (s, 1H, NH). Anal. Calc. for $C_{27}H_{21}ClN_6O_2S$ (529.02): C, 61.30; H, 4.00; Cl, 6.70; N, 15.89; S, 6.06 %.Found: C, 61.51; H, 4.23; Cl, 6.93; N, 15.57; S, 6.27%.

4-(4-Chlorophenyl)-6-((2-((4-chlorophenyl)amino)-2-oxoethyl)thio)-5-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-methylnicotinamide (7e)

It was obtained as yellow crystals from ethanol; yield 76 %; m.p. 245 ºC; IR (KBr) ν cm^{-1} 3345, 3253 (2NH), 3055 (CH-arom), 2923 (CH-aliph.), 2220 (CN), 1702, 1986, 1653 (3CO). ^{1}H NMR (DMSO-d_6) δ = 1.88 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.12 (s, 3H, NCH_3), 4.53 (s, 2H, SCH_2), 6.85- 7.87 (m, 14H, Ar-H+ NH), 9.51 (s, 1H, NH). Anal Calc. for $C_{33}H_{26}Cl_2N_6O_3S$ (657.58): C, 60.28; H, 3.99; Cl, 10.78; N, 12.78; S, 4.88%.Found: C, 60.50; H, 3.67; Cl, 10.57; N, 12.55; S, 4.65%.

Preparation of Compounds 8a–e: General Procedure

Solutions of each of **7a–e** (0.01) in ethanol and sodium ethoxide (0.01mol Na in 10 mL ethanol) were heated under reflux for 6 h, then left to stand at room temp., poured into cold water, and acidified with HCl. The product Formed was collected by filtration and recrystallized from the proper solvent to afford **8a–e.**

Ethyl 3-Amino-4-(4-chlorophenyl)-5-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)carbamoyl)-6-methylthieno[2,3-b]pyridine-2-carboxylate (8a)

It was obtained as pale yellow crystals from dioxane, yield 72%; mp 258 ◦C. IR (KBr): υ cm^{-1} 3470, 3388 (NH_2), 3185 (NH), 3070 (CH-arom), 2946 (CHaliph.), 1715, 1669, 1662 (3CO). ^{1}H NMR (DMSO-d_6) δ = 1.36 (t, J = 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 1.95 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.15 (s, 3H, NCH_3), 4.21 (q, J = 7.2 Hz, 2H, CH_2, $O\underline{CH_2}CH_3$), 6.25 (s, 2H, NH_2), 6.99 -7.73 (m, 9H, Ar- H), 9.70 (s, 1H, NH). Anal. Calc. for $C_{29}H_{26}ClN_5O_4S$ (576.08): C, 60.46; H, 4.55; Cl, 6.15; N, 12.16; S, 5.57%.Found: C, 60.69; H, 4.77; Cl, 6.36; N, 12.38; S, 5.79%.

3-Amino-4-(4-chlorophenyl)-N^5-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-6-methyl-N^2-(4-sulfamoylphenyl)thieno[2,3-b]pyridine-2,5-dicarboxamide(8b):

It was obtained as pale yellow crystals from ethanol, yield 62%; mp 290◦C. IR (KBr): υ cm^{-1} 4485, 4442, 3357, 3282 ($2NH_2$), 3224, 3213 (2NH), 3064 (CH-arom.), 2933 (CH-aliph.), 1696, 1685, 1660 (3CO). ^{1}H NMR (DMSO-d_6): δ = 1.30 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 3.12 (s, 3H, NCH_3), 6.54 (s, 2H, NH_2), 6.78- 7.93 (m, 15H, Ar-H + NH_2), 9.29 (s, 1H, NH), 10.35 (s, 1H, NH). Anal. Calc. for

$C_{33}H_{28}ClN_7O_5S_2$ (702.22): C, 56.45; H, 4.02; Cl, 5.05; N, 13.96; S, 9.13% .Found: C, 56.67; H, 4.25; Cl, 5.24; N, 13.71; S, 9.35%.

3-Amino-4-(4-chlorophenyl)-N^5-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-6-methyl-N2-(4-(N-(pyrimidin-2-yl)sulfamoyl)- phenyl) thieno[2,3-b]pyridine-2,5-dicarboxamide (8c):

It was obtained as pale yellow crystals from ethanol, yield 60%; mp 288◦C. IR (KBr): υ cm^{-1} 3421, 3345 (NH_2), 3274, 3233 (3NH), 3050 (CH-arom.), 2962 (CH-aliph.) 1688, 1660, 1652 (3CO). ^{1}H NMR (DMSO-d_6): δ = 1.04 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.08 (s, 3H, NCH3), 6.25 (s, 2H, NH_2), 6.95–7.85 (m, 17H, Ar-H + NH), 9.55 (s, 1H, NH), 10.22 (s, 1H, NH). Anal. Calc. for $C_{37}H_{30}ClN_9O_5S_2$ (780.29): C, 56.95; H, 3.88; Cl, 4.54; N, 16.16; S, 8.22% .Found: C, 56.72; H, 3.67; Cl, 4.76; N, 16.39; S, 8.43%.

3-Amino-4-(4-chlorophenyl)-2-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-6-methylthieno[2,3-b]pyridine-5-carboxamide (8d):

It was obtained as brown crystals from DMF/ethanol, yield 58%; mp 296 ◦C. IR (KBr): υ cm^{-1} 3332, 3256 (NH_2), 3175 (NH), 3063 (CH-arom.), 2945 (CH-aliph.), 2221 (CN), 1673, 1667 (2CO). ^{1}HNMR (DMSO-d_6): δ = 1.78 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.12 (s, 3H, NCH_3), 5.52 (s, 2H, NH_2), 6.75-7.35 (m, 6H, Ar-H+ NH), 7.55, 7.73 (2d, 4H, Ar-H). Anal. Calc. for $C_{27}H_{21}ClN_6O_2S$ (529.02): C, 61.30; H, 4.00; Cl, 4.79; N, 15.89; S, 6.06%.Found: C, 61.51; H, 4.22; Cl, 4.47; N, 15.58; S, 6.24%.

3-Amino-N^2,4-bis(4-chlorophenyl)-N^5-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-6-methylthieno[2,3-b]pyridine-2,5-dicarboxamide (8e)

It was obtained as brown crystals from DMF/ethanol, yield 64%; mp 293°C. IR (KBr): υ cm^{-1} 3452, 3385 (NH_2), 3266, 3228 (2NH), 3055 (CH-arom.), 2934 (CH-aliph.) 1692, 1677, 1663 (3CO). ^{1}H NMR (DMSO-d_6): δ = 1.02 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.49 (s, 3H, NCH_3), 6.98 - 7.99 (m, 15H, Ar-H+ NH_2), 9.85 (s, 1H, NH), 10.12 (s, 1H, NH). Anal. Calc. for $C_{33}H_{26}Cl_2N_6O_3S$ (657.58): C, 60.28; H, 3.99; Cl, 10.78; N, 12.78; S, 4.88%.Found: C, 60.52; H, 3.58; Cl, 10.53; N, 12.55; S, 4.64%**.**

9-(4-Chlorophenyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-7-methyl-4-oxo-3,4-dihydropyrido[3',2':4,5]thieno[3,2-d] pyrimidine-8-carboxamide (9)

A solution of compound **8a** (0.01 mol) in formamide (10 mL) was heated under reflux for 5 h, then allowed to cool and poured into cold water. The solid product was collected and crystallized from ethanol / dioxan to give **9** as green crystals, yield 61%; mp > 300◦C. IR (KBr): υ cm^{-1} 3396, 3312 (2NH), 3067 (CH-arom.), 2966 (CH-aliph.), 1680, 1655, 1635 (3CO). ^{1}H NMR (DMSO-d_6): δ = 1.58 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.02 (s, 3H, NCH_3), 6.80–7.32 (m, 5H, Ar-H), 7.34, 7.41 (2d, 4H,

Ar-H), 7.96 (s, 1H, CH-pyrimidine), 8.90 (s, 1H, NH), 9.44 (s, 1H, NH). Anal. Calc. for $C_{28}H_{21}ClN_6O_3S$ (557.03): C, 60.38; H, 3.80; Cl, 6.36; N, 15.09; S, 5.76%.Found: C, 60.62; H, 3.60; Cl, 6.57; N, 15.32; S, 5.97%**.**

9-(4-Chlorophenyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-7-methyl-4-oxo-3-phenyl-2-thioxo-1,2,3,4-tetrahydro-pyrido[3',2':4,5]thieno [3,2-d]pyrimidine-8-carboxamide (11)

To a solution of compound **8a** (0.01 mol) in pyridine 30 mL, phenyl isothiocyanate (0.01 mol) was added. The mixture was heated under reflux for 24 h. The solid product that formed after cooling was collected by filtration and recrystallized from dioxane to give **11** (55%) as brown crystals, mp > 300◦C. IR (KBr): υ cm^{-1} 3364, 3335 (2NH), 3066 (CH-arom.), 2947 (CH-aliph.), 1680, 1645 (2CO).^{1}H NMR (DMSO-d6): δ = 1.23 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 3.67 (s, 3H, NCH_3), 6.73–7.82 (m, 15H, Ar-H+ NH), 8.57 (s, 1H, NH). ^{13}C NMR DMSO-d_6) δ C = 14.05 (q); 20.32 (q); 33.56 (q); 103.42 (s); 121.42 (s); 123.26 (s) ; 124.51 (d); 127.62 (s); 128.01 (s) ; 128.43 (d); 129.48 (d); 129.82 (d); 129.98 (d); 130.31 (s);131.25 (d); 132.22 (s); 133.79 (s); 134.13 (s); 134.86 (s); 135.45 (s); 137.12 (s); 150.75 (s); 157.21 (s); 159.84 (s); 164.58(CO); 165.17(CO) ; 165.60 (CO); 180.13 (CS). Anal. Calc. for $C_{34}H_{25}ClN_6O_3S_2$ (665.20): C, 61.39; H, 3.79; Cl, 5.33; N, 12.63; S, 9.64%.Found: C, 61.63; H, 3.46; Cl, 5.56; N, 12.85; S, 9.88%**.**

3-Amino-4-(4-chlorophenyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(hydrazinecarbonyl)-6-methylthieno[2,3-b]pyridine-5-carboxamide (12)

To a solution of **8a** (0.01 mol) in ethanol (30 mL), hydrazine hydrate (2 mL) was added. The reaction mixture was heated under reflux for 5 h. The solid product that formed was collected by filtration and recrystallized from ethanol to give **12** as yellow crystals, yield 67%; mp 205◦C. IR (KBr): υ cm^{-1} 3480, 3388, 3325, 3265 ($2NH_2$), 3220, 3168 (2NH), 3060 (CH-arom.), 2954 (CH-aliph.), 1775, 1668, 1662 (3CO). ^{1}H NMR (DMSO-d_6): δ = 1.87 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.01 (s, 3H, NCH_3), 3.38 (s, 2H, NH_2), 5.13 (s, 2H, NH_2), 6.99 –7.32 (m, 5H, Ar-H), 7.42, 7.50 (2d, 4H, Ar-H), 8.96 (s, 1H, NH), 9.34 (s, 1H, NH). Anal. Calc. for $C_{27}H_{24}ClN_7O_3S$ (562.05): C, 57.70; H, 4.30; Cl, 6.31; N, 17.44; S, 5.70%.Found: C, 57.93; H, 4.54; Cl, 5.54; N, 17.67; S, 5.92%**.**

3-Amino-4-(4-chlorophenyl)- N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-6-methyl-2-[5-(phenylamino)-1,3,4-oxadiazol-2-yl]-thieno[2,3-b]pyridine-5-carboxamide (14)

To a solution of compound **12** (0.01 mol) in dry dioxane 30 mL, phenyl isothiocyanate (0.01 mol) was added. The mixture was heated under reflux for 15 h. The solid product that formed after cooling was collected by filtration and recrystallized from dioxane / ethanol to give **14** (60%) as brown crystals, mp > 300◦C. IR (KBr): υ cm^{-1} 3462, 3385 (NH_2), 3296, 3218 (2NH), 3055 (CH-arom.),

2946 (CH-aliph.), 1675, 1654 (2CO).^{1}H NMR (DMSO-d6): δ = 2.25 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.49 (s, 3H, NCH_3), 4.51 (s, 1H, NH), 5.02 (s, 1H, NH_2), 7.01–7.94 (m, 14H, Ar-H), 8.24 (s, 1H, NH). Anal. Calc. for $C_{34}H_{27}ClN_8O_3S$ (663.16): C, 61.58; H, 4.10; Cl, 5.35; N, 16.90; S, 4.84%.Found: C, 61.80; H, 4.33; Cl, 5.57; N, 16.67; S, 4.62%**.**

Preparation of Compounds 15a,b: General Procedure

A solution of the appropriate **8b,c** (0.01 mole) in dry dioxan (30 ml) and DMF-DMA (0.015 mole) was heated under reflux for 4 h. The reaction mixture was then cooled. The solid products so formed were filtered off and crystallized from dioxan to yield **15a, b.**

4-(4-Chlorophenyl)-N^5-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-(((dimethylamino)methylene)amino)-6-methyl-N^2-(4-sulfamoylphenyl)thieno[2,3-b]pyridine-2,5-dicarboxamide (15a)

It was obtained as brown crystals from dioxane, yield 68%; mp 238◦C. IR (KBr): υ cm^{-1} 4477, 3354 (NH_2), 3288, 3217 (2NH), 3060 (CH-arom.), 2926 (CH-aliph.), 1712, 1680, 1655 (3CO). ^{1}H NMR (DMSO-d_6): δ = 2.18 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.46 (s, 3H, NCH_3), 3.64 (s, 6H, $N(CH_3)_2$, 5.23 (s, 2H, NH_2), 6.71-7.88 (m, 14H, Ar-H + N=CH), 9.72 (s, 1H, NH) , 10.34 (s, 1H, NH). Anal. Calc. for $C_{36}H_{33}ClN_8O_5S_2$ (757.30): C, 57.10; H, 4.39; Cl, 4.68; N, 14.80; S, 8.47%.Found: C, 57.33; H, 4.62; Cl, 4.90; N, 14.57; S, 8.70%**.**

4-(4-Chlorophenyl)-N^5-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-3-(((dimethylamino)methylene)amino)-6-methyl-N^2-(4-(N-phenylsulfamoyl)phenyl) thieno[2,3-b]pyridine-2,5-dicarboxamide (15b)

It was obtained as brown crystals from dioxane, yield 69%; mp 218◦C. IR (KBr): υ cm^{-1} 3368, 3248, 3212 (3NH), 3056 (CH-arom.), 2922 (CH-aliph.) 1695, 1667, 1655 (3CO). ^{1}H NMR (DMSO-d_6): δ = 1.03 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.45 (s, 3H, NCH_3), 3.66 (s, 6H, $N(CH_3)_2$) 4.53 (s, 1H, NH), 6.72 (s, 1H, N=CH), 6.97–7.88 (m, 16H, Ar-H), 8.74 (s, 1H, NH) , 9.45 (s, 1H, NH). Anal. Calc. for $C_{40}H_{35}ClN_{10}O_5S_2$ (835.37): C, 57.51; H, 4.22; Cl, 4.24; N, 16.77; S, 7.68% .Found: C, 57.72; H, 4.44; Cl, 4.46; N, 16.98; S, 7.91%.

Preparation of Compounds 16a,b: General Procedure
Method A: Cyclization of 15a,b:

A solution of the appropriate formamidine derivatives **15a,b** (0.01 mole) in glacial acetic acid (30 ml) was heated under reflux for 6 h. The reaction mixture was then cooled. The solid products so formed were filtered off and crystallized from ethanol /dioxane to yield **16a, b.**

Method B: Reaction of 8b,c with Concentrated formic acid:

A solution of the appropriate **8b,c** (0.01 mole) in glacial acetic acid (30 ml) was treated with anhydrous formic acid (5 ml) and then heated under reflux for 6 h. The

reaction mixture was then cooled. The solid products so formed were filtered off and crystallized from ethanol / dioxane to yield **16a, b.**

9-(4-Chlorophenyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-7-methyl-4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydropyrido- [3',2':4,5]thieno[3,2-d] pyrimidine-8-carboxamide (16a)

It was obtained as brown crystals, yield 58%; mp 302◦C. IR (KBr): υ cm^{-1} 4385, 3317 (NH_2), 3268 (NH), 3055 (CH-arom.), 2923 (CH-aliph.), 1715, 1674, 1654 (3CO). ^{1}H NMR (DMSO-d_6): δ = 1.72 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.14 (s, 3H, NCH_3), 5.25 (s, 2H, NH_2), 7.02- 7.94 (m, 14H, Ar-H + CH-pyrimidine), 10.48 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ C = 11.63 (q); 20.77 (q); 29.35 (q); 104.78 (s); 120.15 (d); 122.38 (s) ; 125.32 (d); 126.95 (s); 128.47 (s) ; 128.83 (d); 129.22 (d); 129.68 (d); 130.02 (d); 133.52 (s);133.96 (s); 135.42 (s); 136.18 (s); 136.84 (s); 141.23 (s); 141.87 (s); 145.25 (s); 148.65 (s); 150.12 (s); 157.51 (s); 158.44 (s); 162.88 (CO); 165.49 (CO) ; 168.40 (CO). Anal. Calc. for $C_{34}H_{26}ClN_7O_5S_2$ (712.21): C, 57.34; H, 3.68; Cl, 4.98; N, 13.77; S, 9.00%.Found: C, 57.58; H, 3.89; Cl, 4.74; N, 13.55; S, 9.22%**.**

9-(4-Chlorophenyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-7-methyl-4-oxo-3-(4-(N-(pyrimidin-4-yl)sulfamoyl)phenyl) -3,4-dihydropyrido[3',2':4,5]thieno[3,2-d]pyrimidine-8-carboxamide (16b)

It was obtained as brown crystals, yield 62%; mp 310◦C. IR (KBr): υ cm^{-1} 3337, 3276 (2NH), 3070 (CH-arom.), 2944 (CH-aliph.) 1697, 1671, 1652 (3CO). ^{1}H NMR (DMSO-d_6): δ = 1.05 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 3.10 (s, 3H, NCH_3), 4.64 (s, 1H, NH), 7.01–7.85 (m, 17H, Ar-H+ CH-pyrimidine), 9.86 (s, 1H, NH). Anal. Calc. for $C_{38}H_{28}ClN_9O_5S_2$ (790.29): C, 57.75; H, 3.57; Cl, 4.49; N, 15.95; S, 8.11% .Found: C, 57.96; H, 3.36; Cl, 4.73; N, 15.70; S, 8.33%.

Preparation of Compounds 17a,b: General Procedure

A solution of the appropriate **8c, b** (0.01 mole) in glacial acetic acid (30 ml) was treated with cold solution of sodium nitrite (1 g in 2 mL water) and the reaction mixtures were stirred in ice-chest for 2 hours. The solid products so formed were filtered off and crystallized from the proper solvent to yield **17a,b**.

9-(4-Chlorophenyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-7-methyl-4-oxo-3-(4-sulfamoylphenyl)-3,4-dihydro- pyrido[3',2':4,5]thieno[3,2-d][1,2,3]triazine-8-carboxamide (17a)

It was obtained brown crystals from dioxane, yield 70 %; mp > 300°C. IR (KBr): υ cm^{-1} 4428, 3384 (NH_2), 3257 (NH), 3064 (CH-arom.), 2933 (CH-aliph.) 1691, 1671, 1665 (3CO). ^{1}H NMR (DMSO-d_6): δ = 1.86 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 3.14 (s, 3H, NCH_3), 6.92- 7.91 (m, 15H, Ar-H + NH_2), 9.87 (s, 1H, NH). Anal. Calc. for $C_{33}H_{25}ClN_8O_5S_2$ (713.20): C, 55.58; H, 3.53; Cl, 4.97; N, 15.71; S, 8.99% .Found: C, 55.80; H, 3.76; Cl, 4.65; N, 15.93; S, 8.68%.

9-(4-Chlorophenyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-7-methyl-4-oxo-3-(4-(N-(pyrimidin-4-yl)sulfamoyl)phenyl)-3,4-dihydropyrido[3',2':4,5]thieno[3,2-d][1,2,3]triazine-8-carboxamide (17b)

It was obtained as brown crystals from dioxane, yield 68%; mp > 300°C. IR (KBr): υ cm^{-1} 3377, 3246 (2NH), 3055 (CH-arom.), 2923 (CH-aliph.) 1692, 1670, 1655 (3CO). ^{1}H NMR (DMSO-d_6): δ = 1.12 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.05 (s, 3H, NCH3), 6.89–7.87 (m, 17H, Ar-H + NH), 10.05 (s, 1H, NH). Anal. Calc. for $C_{37}H_{27}ClN_{10}O_5S_2$ (791.27): C, 56.16; H, 3.44; Cl, 4.48; N, 17.70; S, 8.10% .Found: C, 56.39; H, 3.68; Cl, 4.72; N, 17.94; S, 8.32%

References

1. Li, J.J.; in: , Knorr, Pyrazole Synthesis, 331, Springer, **2006** Berlin, Heidelberg, New York.
2. Nishio, M.; Matsuda, M.; Ohyanagi, F.; Sato, Y.; Okumura, S.; Tabata, D.; Morikawa, A.; Nakagawa, K.; Horai, T., *Lung Cancer*. **2005**, 49, 245.
3. Bondock, S.; Rabie, R.; Etman, H .A.; Fadda, A.A., *Eur. J. Med. Chem*., **2008,** 43 , 2122.
4. Madiha, M. A.; Rania, A.; Moataz, H.; Samira, S.; Sanaa, B., *Eur. J. Pharmacol.*, **2007**, 569, 222.
5. Sherif, A. F.; Rostom, A.; El-Ashmawy, I.M.; Abd El Razik, H. A.; Badr, M. H.; Ashour,H. M. A., *Bioorg. Med. Chem.* **2009**, 17, 882.
6. Sondhi, S. M.; Singhal, N.; Verma, R. P.; Arora, S. K.; Dastidar, S. G., *Indian J. Chem., Sect .B*, **2001**, 40, 113.
7. Gangiee, A.; Devraj, R.; Lin, F., *J.Heterocycl. Chem.*, **1991**, 28, 1747.
8. Krauze, A.; Vitolina, R.; Garaliene, V.; Stile, L.; Klusa, V.; Dubrus,G., *Eur J Med Chem***.,** **2005,** 40, 1163.
9. Attaby, F. A.; Ali, M. A.; Elghandour, A. H. H.; Ibrahem,Y. M., *Phosphorus Sulfur Silicon*, **2006,** 181, 1.
10. Krauze, A.; Germame, S.; Eberlins, O.; Sturms, I.; Klusa, V.; and Duburs, G., *Eur. J. Med. Chem.*, **1999,** 34**,** 301.
11. Krause, A.; Baumane, L.; Sile, L.; Vilums, M.; Cernova, L.; Vitolina, R.; Duburs, G.; and Stradinˇs, J., *Chem. Heterocycl. Compd.*, **2004,** 40 (7)**,** 876.
12. Gad-Elkareem, M. A. M.; Abdel-Fattah, A. M. and Elneairy, M. A. A., *J. Sulfur Chem*., **2011,** 32**,** 273.
13. Rosentreter, U.; Kraemer, T.; Vaupel, A.; Huebsch, W.; Diedrichs, N.; Krahn, T.; Dembowsky, K.; and Stasch, P. J. PCT Int. *Appl*. WO, 02 70, 485, **2002**; *Chem. Abstr.*, **2002**, 137**,** 216880g.
14. Croshy, D. G.; Emerson, R.W.; Miller, T. C.; Peterson, D. P.; and Sharap, L. P. PCT Int. *Appl.*WO 01 19, 185, **2001**; *Chem. Abstr.*, **2001**, 134, 218309.
15. Krislin B.; and Andreas, H., *Bioorg. Med. Chem. Lett.*, **2002**, 12(3)**,** 411.
16. Bridson, P. K.; Davis, R. A.; .Renner, L. S., *J. Heterocycl. Chem*., **1985**, 22, 753.
17. Saito, Y.; Yasushi, M.; Sakoshita, M.; Toyda, K.; Shibazalti, T.; *Eur. Patent Appl.*, 535548, **1993**; *Chem. Abstr*., **1993**, 119, 117112e.
18. Furuya, S.; Choh, N.; Suzuki, N.; Imada, T.; PCT Int. Appl. WO 000 00 493. *Chem. Abst.*, **2000**, 132, 64179.

19. Attaby, F. A.; Elghandour, A. H. H.; Ali, M. A.; and Ibrahem, Y. M., *Phosphorous, Sulfur, and Silicon*, **2007**, 182**,** 695.
20. Bahekar, R. H.; Jain, M. R.; Jadav, P. A.; Prajapati, V. M.; Patel, D. N.; Gupta, A. A.; Sharma, A.; Tom, R.; Bandyopadhya, D.; Modi, H.; and Patel,vP. R.; *Bioorg. Med. Chem.*, **2007**, 15, 782.
21. Hussein, A. M.; Abu-Shanab, F. A.; and Ishak, E. A.; *Phosphorous, Sulfur, and Silicon*, **2000**, 159**,** 55.
22. Hayakawa, I.; Shioya, R.; Agatsuma, T.; Furukawa, H.; and Sugano, Y.; *Bioorg. Med. Chem. Lett.*, **2004**, 14**,** 3411.
23. Bernardino, A. M. R.; daS. Pinheiro, L. C.; Rodrigues, C. R.; Loureiro, N. I.; Castro, H. C.; Lanfredi-Rangel, A.; Sabtini-Lopes, J.; Borges, J. C.; Carvalho, J. M.; Romeiro, G. A.; Ferreira, V. F.; Fruguphetti, I. C. P. P.; and Vannier-Santos, M. A., *Bioorg. Med. Chem.*, **2006**, 14**,** 5765.
24. Quintela, J. M.; Peinador, C.; Veiga, C.; Gonzales, L.; Botana, L. M.; Alfonso, A.; and Riguera, R., *Bioorg. Med. Chem.*, **1998**, 6**,** 1911.
25. Quintela, J. M.; Peinador, C.; Gonzales, L.; Iglesias, R.; Parama, A.; Alvares, F.; Sanmartin, M. L.; and Riguera, R., *Eur. J. Med. Chem.*, **2003**, 38**,** 265.
26. Wagner, G.; Leistner, S.; Vieweg, H.; Krasselt, U.; and Prantz, J., *Pharmazie*, **1993**, 48**,** 342.
27. Abdel-Rahman, E. A.; Bakhite, E. A.; Al-Taifi, E. A., *J. Chin. Chem. Soc*., **2002**, 49, 223.
28. Param´a, A.; Iglesias, R.; A´ lvarez, F.; Lerio, J. M.; Quntela, J. M.; Peinador, C.; Gonza´lez, L.; Riguera, R.; and Sanmart´ın, M. L., *Dis. Aquat. Organ.*, **2004**, 62**,** 97.
29. Paronikyan, E. G.; Noravyan, A. S.; Akopyan, Sh. F.; Arsenyan, F. G.; Stepanyan, G. M.; and Garibdzhanyan, B. T., *Pharma. Chem. J.*, **2006**, 40 (6)**,** 3.
30. Martınez-Poveda, B.; Munoz-Chapuli, R.; Rodrıguez-Nieto, S.; Quintela, J. M.; Fernandez, A.; Medina, M. ; and Quesada, A. R., *Mol. Cancer Ther.*, **2007**, 6(10)**,** 2675.
31. Quintela, J. M.; Peinador, C.; Gonz´alez, I. M.; Riguera, R.; Rioja, I.; Terencio, M. C.; Ubeda, A.; and Alcaraz, M. J., *J. Med. Chem.*, **1999**, 42(22)**,** 4720.
32. Hussein, A. M.; Gad-Elkareem, M. A. M.; El-adasy A. M.; and Othman, I. M. M., *Organic Chemistry and Indian Journal*, **2008**, 4 (3), 178.
33. Hussein, A. M.; Gad-Elkareem, M. A. M.; El-adasy, A. M.; Othman I. M. M,; and Khames, A., *Inter. J. Org. Chem.*, **2012**, 2, 341.
34. Hussein, A. M.; Gad-Elkareem, M. A. M.; El-adasy A. M.; and Othman, I. M. M., phosphorus, *sulfur and silicon*, **2009**, 184, 2263.
35. Abdel Rahman, A. A. H.; Ahmed, A. H. A.; and Ramiz, M. M. M., *Chem. Heterocycl. Compd*, **2010**, 46 (1), 72.
36. Elneairy, M. A. A.; Gad-Elkareem, M. A. M. and Abdel-Fattah, A. M., *phosphorus, sulfur and silicon*, **2006**, 181, 1451.
37. National Committee for Clinical Laboratory Standards, "Performance Standards for Antimicrobial Disk Suscepti bility Tests," Approved Standard NCCLS. M2-A5, 13, 24, NCCLS, Villanova, **1993**.