Synthesis of 7-substituted pyrazolo[1,5-*a*]pyrimidine-3-carboxamides as potential non benzodiazepine hypnotics

Haider Behbehani,* Hamada Mohamed Ibrahim, and Saad Makhseed

Chemistry Department; Faculty of Science; Kuwait University; P.O. Box 5969; Safat; 13060-Kuwait
E-mail: hbehbehani@live.com

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.222

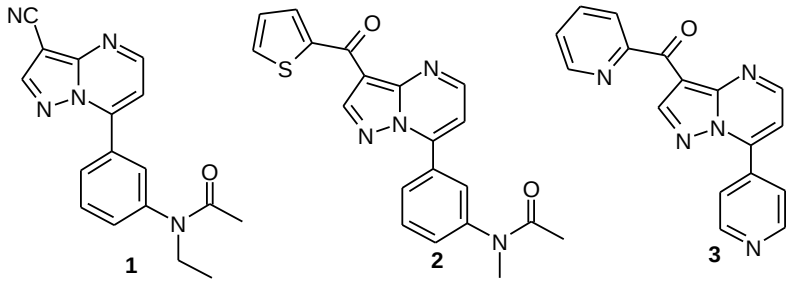
Abstract

A variety of new pyrazolo[1,5-*a*]pyrimidines has been prepared as potential drugs for the treatment of insomnia. The general synthetic route used for this purpose involves the condensation of substituted cyanoacetamides **5a-c**, prepared by reaction of cyanoacetic acid with amines in presence of acetic anhydride, with dimethylformamide dimethylacetal and subsequent treatment of the formed enamines **6** with hydrazine hydrate. This process affords the corresponding aminopyrazole carboxamides **9** that react with the enaminonitrile **12** to generate the targets. Structures of the substance prepared in these sequences were established by using spectroscopic methods, including ^{15}N HMBC and NOE difference experiments, as well as X-raycrystallographic analysis.

Keywords: Cyanoacetamides, aminopyrazoles, zaleplon analogs, pyrazolo[1,5-*a*] pyrimidines, arylhydrazonoisoxazole

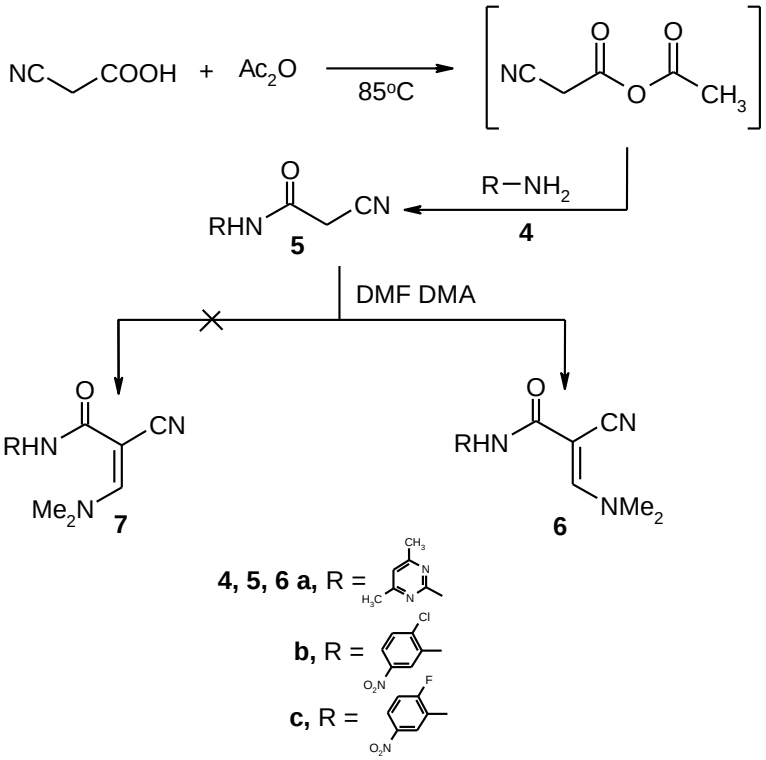
Introduction

Almost 40% of adults between ages 40-70 suffer from insomnia at least one time during their lives. The drug Zaleplon **1**[1-4] has been found to be efficient in the treatment of sleep disorder where difficulty in falling asleep is the primary issue. Unlike many other hypnotic drugs, this substance does not interfere with sleep architecture and can be administered for up to five weeks without the risk of dependence or rebound insomnia upon discontinuation. Indiplon **2**[1,5] has recently been released for use for the same purpose while the developments of ocinaplon **3**,[6] which is an anxiolytic drug in the pyrazolopyrimidine family of drugs, has been discontinued owing to liver complications observed in clinical trials. As a result, a need exists for the development of analogs of **1-3**. In the studies described in this publication, a new, simple and efficient route to 7-substituted pyrazolo[1,5-*a*]pyrimidine-3-carboxamides[7-10] that have structures related to **1-3** has been developed.



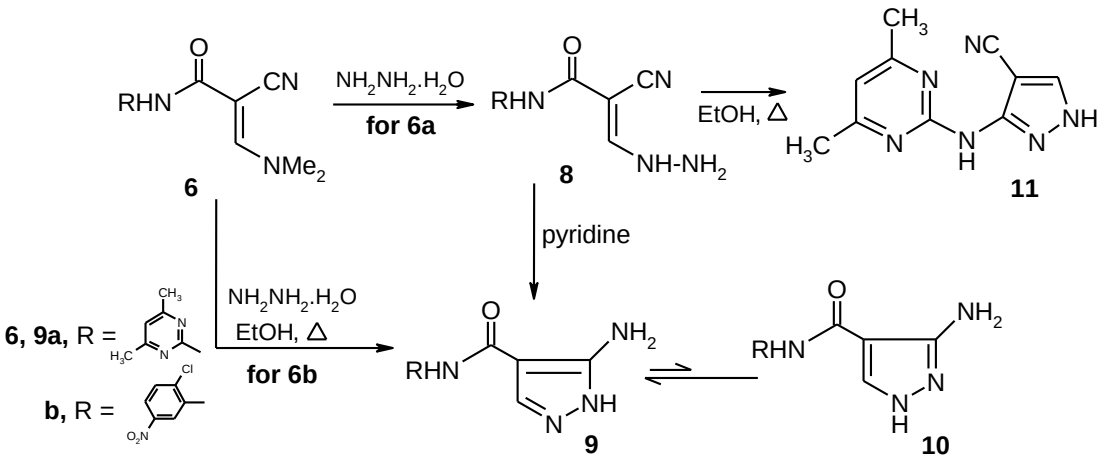
Results and Discussion

Preparation of the target compounds was initiated by reactions of amines **4a-c** with mixtures of acetic anhydride and cyanoacetic acid, following the recently published procedure.[7,11,12] This process affords the cyanoacetamides **5a-c** in 85-93% yields (Scheme 1). The products undergo reaction with dimethylformamide/dimethylacetal (DMF/DMA) to yield the corresponding enamines **6a-c**. Although this process has the potential of producing mixtures of the stereoisomeric enamines **6** and **7**, the fact that only the *E*-isomers **6** were generated has been demonstrated by using NOE experiments that showed that the vinyl protons were spatially proximate to the amide NH.



Scheme 1

An ethanol solution of the cyano-enamine **6a** and hydrazine hydrate at room temperature undergoes reaction to form the acyclic hydrazine derivative **8** (Scheme 2). When **8** was either stirred at 50 ºC or heated in pyridine solution, cyclization gradually took place *via* addition of hydrazine to the cyano group. This process generated pyrazole **9a**, which was shown by using ^{1}H NMR spectroscopy (*eg.*, ring CH at δ 8.1 ppm, singlet) to be the tautomeric form shown in Scheme 2. Stirring a solution of **6** in DMSO at reflux produces a mixture of **9a** and the tautomer **10** in a 2 to 1 ratio. Unexpectedly, stirring a solution of **8** in ethanol afforded the cyanopyrazole **11**. Consequently, it appeared that **9** was the kinetic product and **11** was the thermodynamic product. In contrast to **6a**, an ethanol solution of enamine **6b** reacted with hydrazine hydrate at reflux to give the amino pyrazole **9b** as a single product (Scheme 2).

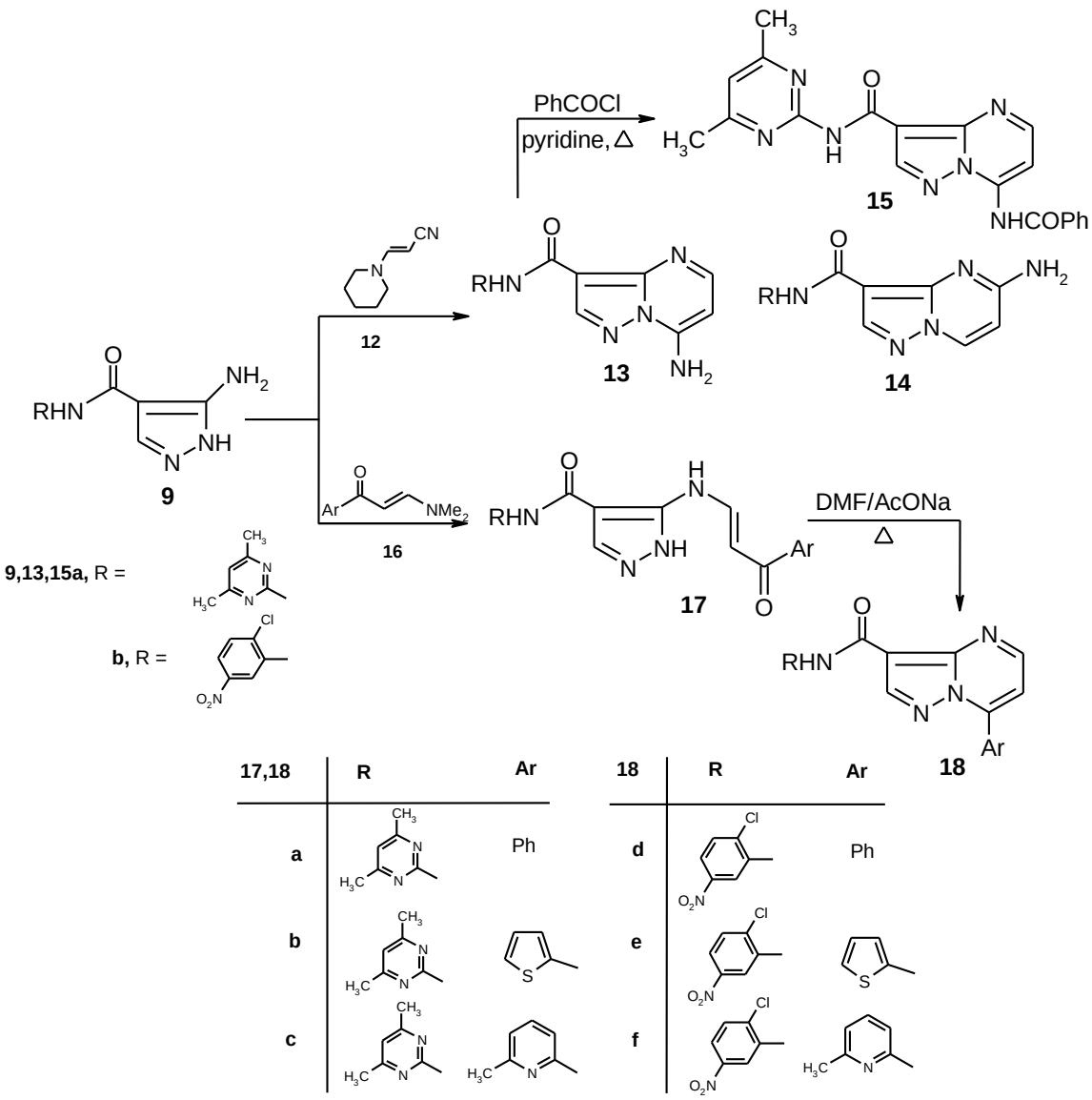


Scheme 2

Pyrazoles **9a,b** reacted smoothly with enaminonitrile **12** in pyridine to yield the aminopyrazolo[1,5-*a*]pyrimidines **13** and not the regioisomeric compounds **14**. Attempts to isolate the acyclic intermediate in these processes were not successful. ^{15}N HMBC analysis was used to demonstrate that the structures of **13** were those of 7-aminopyrazolo[1,5-*a*]pyrimidines.

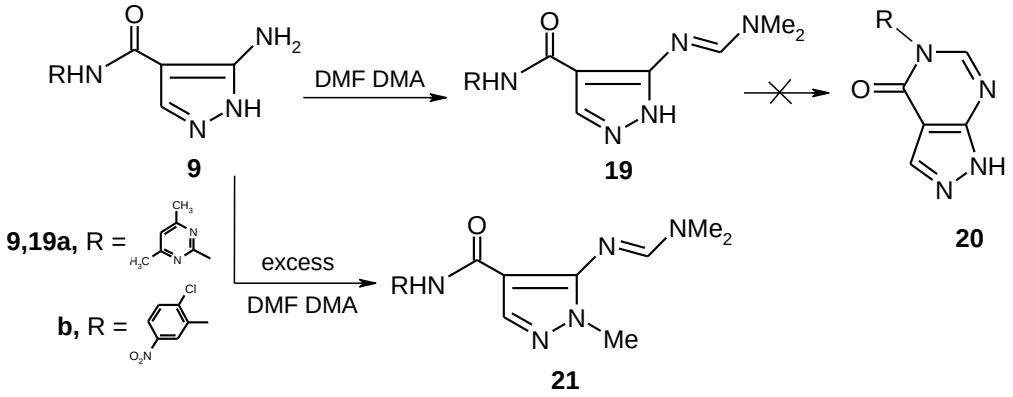
Specifically, the position of the amino group on C-7 was evidenced by ^{4}J coupling of the protons at δ 8.4 ppm with the sp^{3} bridged head nitrogen atom at δ 210.4 ppm. It is expected that if the regioisomeric structure **14** had been formed, protons of the amino group at δ 8.4 ppm would have been coupled only with N-4 at δ 224.2 ppm. In addition, **13** was observed to react with benzoyl chloride in pyridine to afford the benzoyl derivative **15**.

The reaction of pyrazoles **9** with the enaminones **16** led to formation of the acyclic products **17** that underwent cyclization to generate **18** upon stirring in DMF containing sodium acetate at reflux. It should be noted that the pyrazolo[1,5-*a*]pyrimidines **18** could be prepared directly from **9** and **16** by stirring in refluxing pyridine overnight (Scheme 3).



Scheme 3

Attempts to synthesize pyrazolo[3,4-*d*]pyrimidines **20** by the reactions of **9a,b** with dimethylformamide/dimethylacetal (DMF/DMA) failed and only the acyclic amidines **19** were formed. These substances did not cyclize to generate the corresponding pyrazolopyrimidines. Although, **19** may exist in 1*H*-3-amino forms, their existence in 1*H*-5-amino forms was established by analysis of ^{1}H NMR spectra that showed that H-3 is a singlet at δ 9.27. Reaction of **9b** with excess dimethylformamide/dimethylacetal affords the hydrazone **21** as a result of methylation of the pyrazole NH (Scheme 4).



Scheme 4

Further investigations showed that **5a-c** reacted with aryldiazonium chloride to yield arylhydrazones **22a-d** whose structures were established by using X-ray crystallography (Figure 1). The previous finding that 2-arylhydrazono-3-oxoalkanenitriles prefer to exist in *anti* conformations (*eg.*, **22**) rather than *syn.* Hydrogen bonded forms provides further support for the conclusion that stereoelectronic factors are more important than hydrogen bonding interactions in governing conformations in these systems.[13,14]

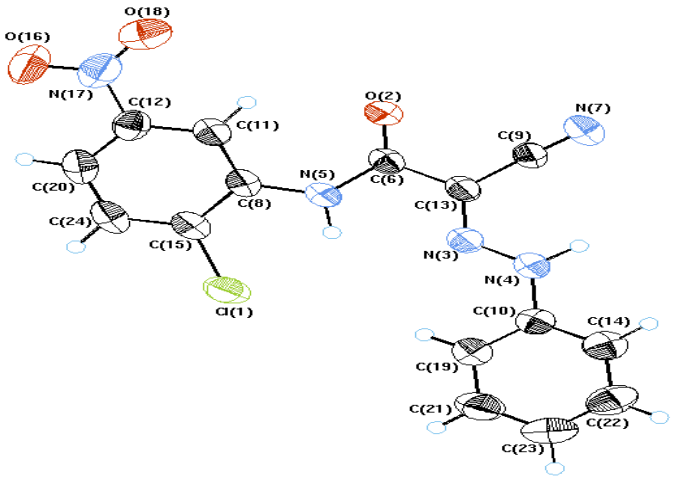
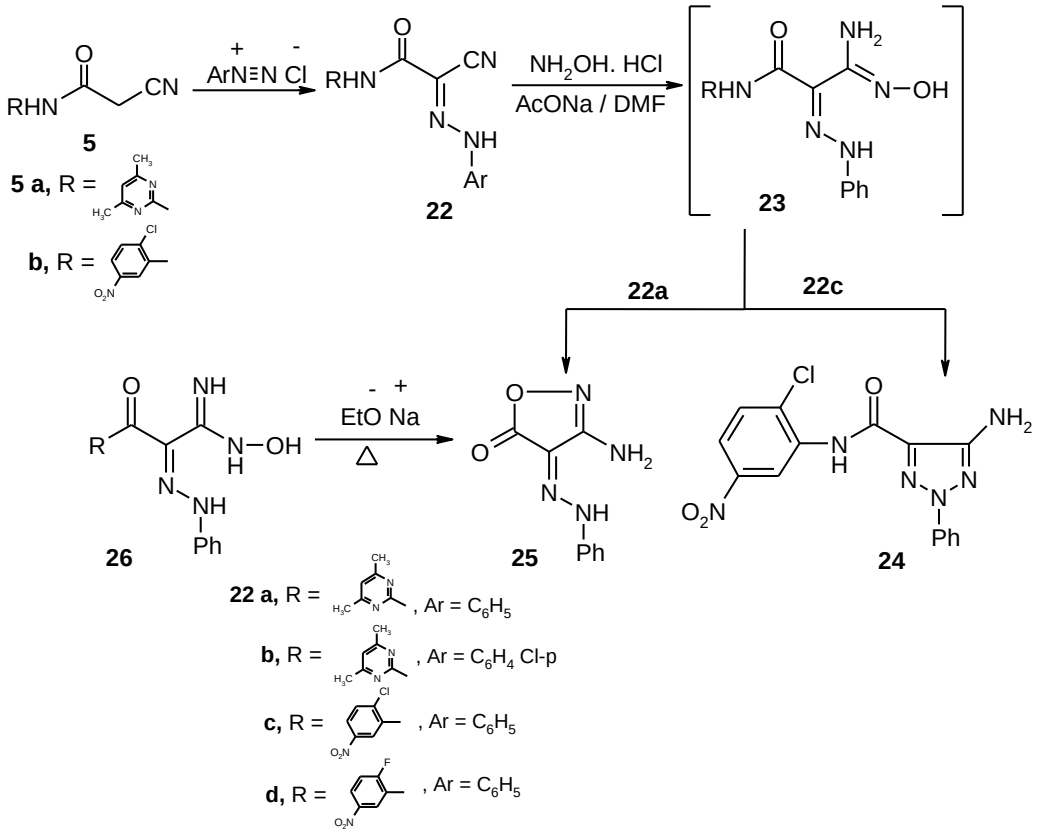


Figure 1. X-Ray crystallographic structure of **22c**.

The results of previous studies[7,15,16] demonstrated that the arylhydrazonitriles could be utilized as precursors for 1,2,3-triazoles, isoxazoles and pyrazoles. In the current effort, the possible utility of the arylhydrazones **22a-d** as precursors for the above mentioned heterocycles was explored. Thus, reaction of **22c** with hydroxylamine hydrochloride in refluxing DMF containing sodium acetate was observed to produce **24** *via* the amidoxime **23**. The structure of **24** was established on the basis of the results of NOE difference experiments. Specifically, irradiation of the amine hydrogen resonance at δ 6.21 ppm did not enhance the aryl hydrogen

signals at δ 7.41-8.91 ppm. On the other hand, reaction of **22a** with hydroxylamine hydrochloride in refluxing DMF in the presence of sodium acetate yielded the isoxazolone **25** *via* the amidoxime **23** through loss of an amine and not water. This same isooxazolone can be obtained *by* cyclization of the amidoxime **26**, which was previously prepared by Elnagdi *et al.*[17] by treatment with sodium ethoxide (Scheme 5).



Scheme 5

Conclusions

The results of the study described above have led to the development of a simple approach for synthesis of 5-aminopyrazole-4-carboxamides and methodology for the conversion of these compounds into pyrazolo[1,5-*a*]pyrimidines, substances that potentially interesting biological and medicinal properties. Furthermore, the observations made during this work showed that the reaction of hydrazine hydrate with enamines can afford cyanopyrazoles or aminopyrazoles, depending on the reaction conditions used.

Experimental Section

General. All melting points are reported uncorrected. IR spectra were recorded using KBr disks using a Perkin-Elmer System 2000 FT-IR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX 400, 400 MHz super-conducting NMR spectrometer on $CDCl_3$ or DMSO-d_6 solutions with TMS as internal standard. Chemical shifts are reported in ppm. Mass spectra were measured using a VG Autospec Q MS 3 and MS 9 (AEI) spectrometers with EI (70 EV). Microanalyses were performed on a LECO CHNS-932 Elemental Analyzer. The crystal structure was determined by using a X-ray instrument at the National Research Center, Dokki, Cairo.

General procedure for the preparation of 5a-c

A solution of cyanoacetic acid (10 mmol) in Ac_2O (10 mL) was heated on a water bath at 85 ºC for 10 min. Then, the appropriate starting materials **4a-c** were added to the reaction mixture and heating was continued at reflux for a further 15 min. The reaction mixture was cooled and poured onto cold water. The solid products **5a-c** were collected by filtration and crystallized from the appropriate solvent **.**

2-Cyano-*N*-(4,6-dimethylpyrimidin-2-yl)acetamide (5a). Recrystallized from acetic acid as creamy white crystals, 1.6 g (85%), mp 130 ºC; IR (KBr): 3221 (NH), 2259 (CN), 1680 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 6H, $2CH_3$), 4.30 (s, 2H, CH_2), 6.82 (s, 1H, pyrimidine H-5) and 9.74 ppm (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 23.73 ($2CH_3$), 28.88 (CH_2), 114.13 (CN), 116.12 (pyrimidine C-5), 156.23, 163.70 (Ar-C) and 168.75 ppm (CO); MS (EI): m/z (%) 192 (M^++1, 10.35), 190 (M^+, 42.80), 123 (100), 107 (18.25), 96 (23). Anal. Calcd. for $C_9H_{10}N_4O$ (190.21): C, 56.83; H, 5.30; N, 29.46. Found: C, 56.68; H, 5.42; N, 29.32.

***N*-(2-Chloro-5-nitrophenyl)-2-cyanoacetamide (5b).** Recrystallized from EtOH as creamy white crystals, 2.2 g (93%), mp 199-201 ºC; IR (KBr): 3292 (NH), 2256 (CN), 1677 cm^{-1} (CO); ^{1}H NMR (DMSO-*d6*): δ 4.10 (s, 2H, CH_2), 7.82 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.05 (d, *J* = 8.0 Hz, 1H, Ar-H), 8.70 (s, 1H, Ar-H) and 10.30 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d6): δ 26.62 (CH_2), 115.64 (CN), 119.49(CH), 120.90(CH), 130.90(CH),132.21(C), 135.27(C) ,146.30 (C) and 162.68 ppm (CO); MS (EI): m/z (%) 240 (M^++1, 12.9), 239 (M^+, 31.3), 204 (100), 172 (58.5), 126 (32.8). Anal. Calcd. for $C_9H_6ClN_3O_3$ (239.62): C, 45.11; H, 2.52; Cl, 14.80; N, 17.54. Found: C, 45.22; H, 2.46; Cl, 14.93; N, 17.59.

2-Cyano-*N*-(2-fluoro-5-nitrophenyl) acetamide (5c). Recrystallized from EtOH as white crystals, 1.9 g (89%), mp 168-170 ºC; IR (KBr): 3320 (NH), 2264 (CN), 1708 cm^{-1} (CO); ^{1}H NMR (DMSO-*d6*): δ 4.07 (s, 2H, CH_2), 7.59-8.94 (m, 3H, Ar-H), 10.61 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d6): δ 26.80(CH_2), 115.61 (CN), 116.86, 117.95, 121.00, 126.71,143.77,155.00, (Ar-C) and 162.66 ppm (CO); MS (EI): m/z (%) 224 (M^++1, 12.5), 223 (M^+, 73), 156 (100), 110 (58.6). Anal. Calcd. for $C_9H_6FN_3O_3$ (223.16): C, 48.44; H, 2.71; N, 18.83. Found: C, 48.26; H, 2.85; N, 18.79.

General procedure for the preparation of 6a-c

A mixture of 5**a-c** (10 mmol) and DMFDMA (1.2 g, 10 mmol) in EtOH (25 mL) was stirred at room temperature for 4h (for**6a**) or at reflux for 2 h (for **6b** and **6c**).The separated solid products formed on standing at room temperature were collected by filtration, washed by EtOH and rcrystallized from the appropriate solvent.

(*E*)-2-Cyano-3-(dimethylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)acrylamide (6a). Recrystall -ized from EtOH as creamy white crystals, 1.85 g (76 %), mp 164 °C; IR (KBr): 3399 (NH), 2194 (CN), 1691 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 6H, $2CH_3$), 3.26 (s, 3H, CH_3), 3.40 (s, 3H, CH_3), 6.75 (s, 1H, pyrimidine H-5), 7.93 (s, 1H, olefinic CH) and 8.28 ppm (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 23.93($2CH_3$), 38.63(CH_3), 47.81(CH_3), 71.64(C-2), 115.60(pyrimidine C-5), 119.24 (CN), 157.28 (C), 157.43 (olefinic CH), 162.63(C) and 168.13 ppm (CO); MS (EI): m/z (%) 246 (M^++1, 8.24), 245 (M^+, 41.5), 150(24.7), 123 (100). Anal. Calcd. for $C_{12}H_{15}N_5O$ (245.29): C, 58.76; H, 6.16; N, 28.55; Found: C, 58.65; H, 6.23; N, 28.59.

(*E*)-*N*-(2-Chloro-5-nitrophenyl)-2-cyano-3-(dimethylamino)acrylamide (6b). Recrystallized from EtOH/DMF as buff crystals, 2.45 g (83 %), mp 236 °C; IR (KBr): 3391, (NH), 2183 (CN), 1687 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$): δ 3.31 (s, 3H, CH_3), 3.44 (s, 3H, CH_3), 7.55 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.89 (d, *J* = 8.6 Hz, 1H, Ar-H) ,7.92 (s, 1H, olefinic CH), 8.43 (br, 1H, NH) and 9.37 ppm (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$): δ 38.81 (CH_3), 47.91 (CH_3), 71.30 (C-2), 115.80, 118.42, 118.97 (CN), 128.98, 129.49, 136.04, 147.08, 157.00 and 163.25 ppm (CO); MS (EI): m/z (%) 295 (M^++1, 4.1), 294 (M^+, 12.2), 123 (100). Anal. Calcd. for $C_{12}H_{11}ClN_4O_3$ (294.70): C, 48.91; H, 3.76; Cl, 12.03; N, 19.01. Found: C, 49.02; H, 3.66; Cl, 11.89; N, 19.15.

(*E*)-2-Cyano-3-(dimethylamino)-N--(2-fluoro-5-nitrophenyl)acrylamide (6c). Recrystallized from EtOH/dioxane as pale yellow crystals, 2.1 g (75 %), mp 148-150 °C; IR (KBr): 3259 (NH), 2186 (CN), 1679 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6): δ 3.25 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 7.54-8.7 (m, 3H, Ar-H),7.88 (s, 1H, olefinic CH) and 9.1 ppm (br, 1H, NH); MS (EI): m/z (%) 279 (M^++1, 4.3), 278 (M^+, 19.5), 123 (100). Anal. Calcd. for $C_{12}H_{11}FN_4O_3$ (278.24): C, 51.80; H, 3.98; N, 20.14. Found: C, 51.92; H, 4.06; N, 20.30.

(*E*)-2-Cyano-*N*-(4,6-dimethylpyrimidin-2-yl)-3-hydrazinylacrylamide (8). A solution of the enaminonitrile **6a** (2.45 g, 10 mmol) and hydrazine hydrate (80%, 0.65 ml) in EtOH (50 mL) stirred at reflux for 10 minand then cooled to room temperature Theformed solid was separated by filtration, washed with EtOH, and crystallized from the EtOH/dioxan mixture as white crystals, 1.85 g (80 %), mp 147 °C; IR (KBr): 3404, 3296, 3221, 3189 (NH_2 and 2NH), 2198 (CN), 1690 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 6H, $2CH_3$), 5.11 (br, 2H, NH_2), 6.87 (s, 1H, pyrimidine H-5), 7.72 (s, 1H, olefinic CH), 8.89 (br, 1H, NH) and 9.61 ppm (br, 1H, NH); ^{13}C NMR (pyridine-*d5*): δ 23.28 ($2CH_3$), 66.82,109.29, 114.64 (CN), 154.68, 158.65, 163.55, 167.32, and 167.57 ppm (carbons and CO); MS (EI): m/z (%) 233 (M^++1, 21.8), 232 (M^+, 100),124 (85.9), 123 (4835), 110 (90.3). Anal. Calcd. for $C_{10}H_{12}N_6O$ (232.25): C, 51.72; H, 5.21; N, 36.19; Found: C, 51.64; H, 5.32; N, 36.24.

5-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)-1*H*-pyrazole-4-carboxamide (9a). Method A. The crude reaction mixture of **8**, formed in the manner described above, was stirred at 50 °C for 4h.

Cooling to room temperature gave a precipitate which was separated by filtration, washed with EtOH and crystallized from EtOH/DMF to give white crystals.

Method B. A solution of **8** (1.1 g, 5 mmol) in pyridine (20 mL) was stirred at reflux for 3h and concentrated in vacuo to give a residue which was triturated with EtOH to afford solid. Separation by filtration gave a solid that was washed with EtOH and crystallized from EtOH/DMF to give white crystals, 0.85 g (73 %), mp 256 ºC; IR (KBr): 3454, 3343, 3273, 3129 (NH_2 and 2NH), 1663 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 6H, $2CH_3$), 5.95 (br, 2H, NH_2), 6.89 (s, 1H, pyrimidine H-5), 8.10 (s, 1H, pyrazole H-3), 10.12 (s, 1H, NH), and 11.87 ppm (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 23.87 ($2CH_3$), 98.15, 110.07, 116.11, 138.88, 157.99, 163.13 and 168.49 ppm (carbons and CO); MS (EI): m/z (%) 233 (M^++1, 15.6), 232 (M^+, 100),124 (72), 123 (63), 110 (68.7). Anal. Calcd. for $C_{10}H_{12}N_6O$ (232.25): C, 51.72; H, 5.21; N, 36.19; Found: C, 51.89; H, 5.36; N, 36.09.

General procedure for the preparation of 9b and 11

A mixture of the enaminonitrile **6a** (2.45 g, 10 mmol) and hydrazine hydrate (80%, 0.65 ml) in EtOH (40 mL) was stirred at reflux for 2h, concentrated in vacuo to one third of its volume, and cooled to room temperature. The crude solid which formed was collected by filtration, washed with water, and crystallized from the appropriate solvent.

5-Amino-*N*-(2-chloro-5-nitrophenyl)-1*H*-pyrazole-4-carboxamide (9b). Recrystallized from EtOH, 2.1 g (74 %), mp 229 oC; IR (KBr): 3442, 3404, 3347, 3256 (NH2 and 2NH), 1673 cm-1 (CO). 1H NMR (DMSO-d6): δ 6.08 (br, 2H, NH2), 7.81 (d, J = 8.6 Hz, 1H, Ar-H), 8.0-8.03 (m, 2H,1 Ar-H and pyrazole H-3), 8.65 (s, 1H, Ar-H), 9.44 (br, 1H, NH) and 11.97 ppm (br, 1H, NH); 13C NMR (DMSO-d6): δ 95.39, 120.08, 120.41, 130.60, 133.54, 136.28, 137.90, 146.21, 151.58 and 162.75 ppm (Ar-carbons and CO); MS (EI): m/z (%) 282 (M++1, 6.5), 281 (M+, 18), 110 (100). Anal. Calcd. for $C_{10}H_8ClN_5O_3$ (281.66): C, 42.64; H, 2.86; Cl, 12.59; N, 24.86; Found: C, 42.55; H, 2.92; Cl, 12.48; N, 24.89.

3-(4,6-Dimethylpyrimidin-2-ylamino)-1*H*-pyrazole-4-carbonitrile (11). Recrystallized from EtOH/dioxan, 1.75 g (82 %), mp 262-264 ºC; IR (KBr): 3273, 3162 (2NH), 2224 (CN), 1629 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 6H, $2CH_3$), 6.65 (s, 1H, pyrimidine H-5), 8.42 (br, 1H, NH), 9.63 (s, 1H, pyrazolyl H) and 13.16 ppm (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 23.25 ($2CH_3$), 86.11, 111.74, 114.31, 135.76, 149.25, 159.27 and 167.40 ppm (carbons and CO); MS (EI): m/z (%) 215 (M^++1, 27.5), 214 (M^+, 95), 213 (100). Anal. Calcd. for $C_{10}H_{10}N_6$ (214.23): C, 56.07; H, 4.71; N, 39.23; Found: C, 55.93; H, 4.82; N, 39.19.

General procedure for the preparation of 13a,b.

Mixtures of **9a,b**

(5 mmol), and enamine **12** (0.7 g, 5 mmol) in pyridine (20 mL) were stirred at reflux for 12 h, cooled to room temperature, and poured into ice cold water. The aqueous solution was acidified with hydrochloric acid (2N), forming a solid that was collected by filtration, washed with water and crystallized from the appropriate solvent.

7-Amino-*N*-(4,6-dimethylpyrimidin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (13a). Recrystallized from EtOH/DMF as buff crystals, 1.0 g (71%), mp above 300 ºC; IR (KBr): 3436, 3337, 3171 (NH_2 and NH), 1682 (CO), 1656 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ 2.37 (s, 6H, $2CH_3$), 6.34 (d, *J* = 5.6 Hz, 1H, H-6), 6.93 (s, 1H, pyrimidine H-5), 8.35 (d, 1H, *J* = 5.6 Hz, H-5), 8.39 (br, 2H, NH_2), 8.54 (s, 1H, pyrazole H-2) and 10.70 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 23.41 ($2CH_3$), 90.60, 102.81, 115.18, 1425.27, 147.00, 149.09, 151.21, 157.22, 158.50, 167.66 (Ar-C and CO); ^{15}N HMBC (DMSO-d_6): showed 6 δ at 79.4, 138.7, 210.4, 224.2, 260.3 and 265; MS (EI): m/z (%) 284 (M^++1, 5.6), 283 (M^+, 23.5),161 (100), 123 (7.5). Anal. Calcd. for $C_{13}H_{13}N_7O$ (283.29): C, 55.12; H, 4.63; N, 34.61. Found: C, 54.99; H, 4.69; N, 34.55.

7-Amino-*N*-(2-chloro-5-nitrophenyl)-pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (13b). Recrystallized from DMF as yellow crystals, 1.25 g (75 %), mp above 300 ºC; IR (KBr): 3409, 3269, 3201(NH_2 and NH), 1685 (CO), 1615 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ 6.39 (d, *J* = 5.4 Hz, 1H, H-6), 7.78 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.89 (d, *J* = 9.0 Hz, 1H, Ar-H), 8.09 (br, 2H, NH_2), 8.33 (d, *J* = 5.4 Hz, 1H, H-5), 8.55 (s, 1H, Ar-H), 9.46 (s, 1H, pyrazole H-2) and 10.92 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 91.01, 102.08, 114.64, 118.06, 128.07, 130.38, 136.78, 145.20, 146.51, 147.37, 149.20, 151.36, 160.66 (Ar-C and CO); MS (EI): m/z (%) 333 (M^++1, 2.75), 332 (M^+, 8.3), 161 (100), 133 (3.5). Anal. Calcd. for $C_{13}H_9ClN_6O_3$ (332.71): C, 46.93; H, 2.73; Cl, 10.66; N, 25.26. Found: C, 47.04; H, 2.79; Cl, 10.80; N, 25.32.

7-Benzamido-*N*-(4,6-dimethylpyrimidin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (15). A mixture of **13a** (0.7 g, 2.5 mmol), and benzoylchloride (0.4 g, 2.5 mmol) in pyridine (20 mL) was stirred at reflux for 3 h, cooled to room temperature and poured into ice cold water. The aqueous solution was acidified with hydrochloric acid (2N), forming a solid that was collected by filtration, washed with water and crystallized from EtOH/DMF to give pale brown crystals, 0.67 g (70%), 300 ºC; IR (KBr): 3368, 3281 (2 NH), 1707,1623 cm^{-1} (2 CO); ^{1}H NMR (DMSO-d_6): δ 2.41(s, 6H, $2CH_3$), 6.99 (s, 1H, pyrimidine H-5), 7.62 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.71 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.96 (d, *J* = 5.0 Hz, 1H, H-6), 8.06 (d, *J* = 8.0 Hz, 2H, Ar-H), 8.76 (s, 1H, pyrazole H-2), 8.86 (d, 1H, *J* = 5.0 Hz, H-5), 10.54 (s, 1H, NH) and 11.10 ppm (s, 1H, NH); MS (EI): m/z (%) 388 (M^++1, 9.0), 387 (M^+, 36.0), 360 (17.8), 265 (100), 105 (87.2), 77 (.38.5). Anal. Calcd. for $C_{20}H_{17}N_7O_2$ (387.40): C, 62.01; H, 4.42; N, 25.31. Found: C, 61.89; H, 4.54; N, 25.26.

General procedure for the preparation of 17a-c

Mixtures of **9a** (1.15 g, 5mmol) and enaminone **16a-c** (5 mmol) in pyridine (20 mL) were stirred at reflux for 5h, cooled to room temperature and poured into ice cold water. The aqueous solution was acidified with hydrochloric acid (2N) , forming asolid that was collected by filtration, washed with water and crystallized from the appropriate solvent.

(*E*)-*N*-(4,6-Dimethylpyrimidin-2-yl)-5-(3-oxo-3-phenylprop-1-enylamino)-1*H*-pyrazole-4-carboxamide (17a). Recrystallized from DMF as pale brown crystals, 1.3 g (70%), mp 267 ºC; IR (IR (KBr): 3335, 3173, 3145 (3 NH), 1672,1631 cm-1 (2 CO); 1H NMR (DMSO-d6) : δ 2.41(s, 6H, 2CH3), 6.21(d, J = 8.0 Hz, 1H, prop-1-enylamino H-2), 6.98 (s, 1H, pyrimidine H-5), 7.49-7.98 (m, 6H, Ar-H and prop-1-enylamino H-1), 8.63 (s, 1H, pyrazole H-3), 10.54 (s, 1H,

NH), 12.43 (d, *J* = 12.8 Hz, 1H, NH) and 12.95 ppm (s, 1H, NH); MS (EI): m/z (%) 363 (M^++1, 6.5), 362 (M^+, 21.0), 317 (28.5), 223 (14.8), 222 (100). Anal. Calcd. for $C_{19}H_{18}N_6O_2$ (362.39): C, 62.97; H, 5.01; N, 23.19. Found: C, 63.12; H, 4.95; N, 23.14.

(*E*)-*N*-(4,6-Dimethylpyrimidin-2-yl)-5-[3-oxo-3-(thiophen-2-yl)prop-1-enylamino]-1*H*-pyrazole-4-carboxamide (17b). Recrystallized from DMF as yellow crystals, 1.2 g (66%), 279 ºC; IR (KBr): 3308, 3149, 3109 (3 NH), 1671,1626 cm^{-1} (2 CO); ^{1}H NMR (DMSO-d_6): δ 2.41(s, 6H, $2CH_3$), 6.09 (d, *J* = 8.0 Hz, 1H, prop-1-enylamino H-2), 6.99 (s, 1H, pyrimidine H-5), 7.20-7.87 (m, 4H, Ar-H and prop-1-enylamino H-1), 8.61(s, 1H, pyrazole H-3), 10.53 (s, 1H, NH), 12.21 (d, *J* = 12.6 Hz, 1H, NH) and 12.93 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 94.53, 102.19, 115.60, 128.58, 129.96, 131.19, 132.97, 142.19, 146.18, 157.39, 161.13, 162.32, 167.60 and 182.70 ppm (Ar-C and 2CO); MS (EI): m/z (%) 369 (M^++1, 3.8), 368 (M^+, 16.0), 350 (14), 323 (19.5), 229 (10.3), 228 (100). Anal. Calcd. for $C_{17}H_{16}N_6O_2S$ (368.42): C, 55.42; H, 4.38; N, 22.81; S, 8.70. Found: C, 55.61; H, 4.42; N, 22.75; S, 8.59.

(*E*)-*N*-(4,6-Dimethylpyrimidin-2-yl)-5-[3-(6-methylpyridin-2-yl)3-oxoprop-1-enylamino]-1*H*-pyrazole-4-carboxamide (17c). Recrystallized from DMF as pale yellow crystals, 1.35 g (73%), 299 ºC; IR (KBr): 3336, 3266, 3143 (3 NH), 1673,1631 cm^{-1} (2 CO); ^{1}H NMR (DMSO-d_6): δ 2.41(s, 6H, $2CH_3$), 2.56 (s, 3H, CH_3), 6.73 (d, *J* = 8.0 Hz, 1H, prop-1-enylamino H-2), 7.00 (s, 1H, pyrimidine H-5), 7.42-7.96 (m, 4H, Ar-H and prop-1-enylamino H-1), 8.62(s, 1H, pyrazole H-3), 10.55 (s, 1H, NH), 12.43 (d, *J* = 12.4 Hz, 1H, NH) and 12.97 ppm (s, 1H, NH); MS (EI): m/z (%) 378 (M^++1, 3.2), 377 (M^+, 12.4), 332 (24.4), 236 (11.3), 237 (100). Anal. Calcd. for $C_{19}H_{19}N_7O_2$ (377.41): C, 60.47; H, 5.07; N, 25.98. Found: C, 60.33; H, 4.98; N, 26.04.

General procedure for the preparation of 18a-f

Mixtures of **9a,b** (5mmol) and enaminone **16a-c** (5 mmol) in pyridine (20 mL) were stirred at reflux overnight, or refluxing **13a-c** (5 mmol) in DMF containing anhydrous sodium acetate (1g) for 6 h. The reaction mixtures were cooled to room temperature and poured onto ice cold water. The aqueous solution was acidified with hydrochloric acid (2N), forming a solid that was collected by filtration, washed with water and crystallized from the appropriate solvent.

***N*-(4,6-Dimethylpyrimidin-2-yl)-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (18a).** Recrystallized from DMF as buff crystals, 1.4 g (81%), mp 270 ºC; IR (KBr): 3278 (NH), 1696 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 6H, $2CH_3$), 6.79 (s, 1H, pyrimidine H-5), 7.14 (d, *J* = 5.0 Hz, 1H, H-6), 7.60-8.07 (m, 5H, Ar-H), 7.80 (d, 1H, *J* = 5.0 Hz, H-5), 8.82 (s, 1H, pyrazole H-2) and 10.67 ppm (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 24.15 ($2CH_3$), 106.04, 108.70, 115.64, 128.90, 129.52, 129.89, 131.87, 146.99, 147.47, 148.52, 151.10, 157.81, 159.30, 168.27 (Ar-C and CO); MS (EI): m/z (%) 345 (M^++1, 3.8), 344 (M^+, 12.5), 317 (27.3), 223 (13.4), 222 (100). Anal. Calcd. for $C_{19}H_{16}N_6O$ (344.38): C, 66.27; H, 4.68; N, 24.40. Found: C, 66.21; H, 4.75; N, 24.42.

***N*-(4,6-Dimethylpyrimidin-2-yl)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (18b).** Recrystallized from DMF as yellow crystals, 1.5 g (86 %), mp above 300 ºC; IR (KBr): 3249 (NH), 1690 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 6H, $2CH_3$), 6.80 (s, 1H, pyrimidine H-

5), 7.33 (t, *J* = 6.0 Hz, 1H, thiophene H), 7.44 (d, *J* = 4.8 Hz, 1H, H-6), 7.84 (d, *J* = 6.0 Hz, 1H, thiophene H), 8.44 (d, *J* = 6.0 Hz, 1H, thiophene H), 8.75 (d, 1H, *J* = 4.8 Hz, H-5), 8.91 (s, 1H, pyrazole H-2) and 10.70 ppm (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 24.12 ($2CH_3$), 104.97, 105.86, 115.59, 128.12, 130.40, 132.86, 134.12, 141.64, 147.03, 147.11, 150.20, 157.75, 159.33, 168.26 (Ar-C and CO); MS (EI): m/z (%) 351 (M^++1, 4.5), 350 (M^+, 17.25), 323 (27.2), 229 (12.8), 228 (100). Anal. Calcd. for $C_{17}H_{14}N_6OS$ (350.40): C, 58.27; H, 4.03; N, 23.98; S, 9.15. Found: C, 58.32; H, 3.98; N, 23.80; S, 9.06.

***N*-(4,6-Dimethylpyrimidin-2-yl)-7-(6-methylpyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (18c).** Recrystallized from DMF as pale yellow crystals, 1.4 g (77 %), mp above 300 ºC; IR (KBr): 3270 (NH), 1691 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 2.53 (s, 6H, $2CH_3$), 2.70 (s, 3H, CH_3), 6.80 (s, 1H, pyrimidine H-5), 7.39 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.87 (t, *J* = 7.8 Hz, 1H, Ar-H), 8.00 (d, *J* = 4.8 Hz, 1H, H-6), 7.88-8.92 (m, 3H, 1 Ar-H, H-5 and pyrazole H-2) and 10.74 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 24.12 ($2CH_3$), 24.69 (CH_3), 105.89, 109.26, 115.64, 123.81, 125.93, 137.05, 146.04, 146.42, 147.22, 147.29, 151.17, 157.72, 159.31, 159.32, 168.30 (Ar-C and CO); MS (EI): m/z (%) 360 (M^++1, 3.0 %), 359 (M^+, 9.5 %), 332 (31.7), 238 (13.4), 237 (100). Anal. Calcd. for $C_{19}H_{17}N_7O$ (359.39): C, 63.50; H, 4.77; N, 27.28. Found: C, 63.59; H, 4.64; N, 27.32.

***N*-(2-Chloro-5-nitrophenyl)-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (18d).** Recrystallized from DMF as creamy white crystals, 1.35 g (69 %), mp above 300 ºC; IR (KBr): 3270 (NH), 1674 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6) at 110 ºC: δ 7.54-7.67 (m, 4H, Ar-H), 7.85 (d, *J* = 9.0 Hz, 1H, Ar-H), 7.97 (d, *J* = 9.0 Hz, 1H, Ar-H), 8.18-8.98 (m, 4H, H-6, H-5 and 2 Ar-H), 9.45 (s, 1H, pyrazole H-2) and 10.78 ppm (s, 1H, NH); ^{13}C NMR (TFA-*d*): δ 104.98, 112.18, 123.36, 125.36, 129.21, 132.21, 133.10, 133.61, 135.61,138.48, 138.60, 144.89, 148.72, 148.93, 150.03, 161.84 and 163.94 (Ar-C and CO); MS (EI): m/z (%) 394 (M^++1, 1.2) 393 (M^+, 5.2), 223 (16.9), 222 (100). Anal. Calcd. for $C_{19}H_{12}ClN_5O_3$ (393.79): C, 57.95; H, 3.07; Cl, 9.00; N, 17.78. Found: C, 58.06; H, 3.12; Cl, 8.85; N, 17.88.

***N*-(2-Chloro-5-nitrophenyl)-7-(thiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (18e).** Recrystallized from DMF as pale yellow crystals, 1.2 g (60 %), mp above 300 ºC; IR (KBr): 3265 (NH), 1674 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6) at 110 ºC: δ 7.42-8.91 (m, 8H, 6 Ar-H, H-6 and H-5), 9.46 (s, 1H, pyrazole H-2) and 10.78 ppm (s, 1H, NH); ^{13}C NMR (TFA-*d*): δ 104.06, 106.89, 123.52, 125.45, 130.57, 133.03, 133.71, 135.69, 138.81, 143.97, 144.37, 145.64, 147.66, 149.07, 149.81, 153.54, and 163.56 (Ar-C and CO); MS (EI): m/z (%) 400 (M^++1, 6.0), 399 (M^+, 23.5), 227 (49.5), 228 (100), 200 (18.9). Anal. Calcd. for $C_{17}H_{10}ClN_5O_3S$ (399.82): C, 51.07; H, 2.52; Cl, 8.87; N, 17.52; S, 8.02. Found: C, 50.94; H, 2.60; Cl, 9.00 ; N, 17.66; S, 8.11.

***N*-(2-Chloro-5-nitrophenyl)-7-(6-methylpyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (18f).** Recrystallized from DMF as creamy white crystals, 1.35 g (69 %), mp 297-299 ºC; IR (KBr): 3280 (NH), 1695 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6) at 110 ºC: δ 2.66 (s, 3H, CH_3), 7.56-9.06 (m, 8H, 6 Ar-H, H-6 and H-5), 9.48 (s, 1H, pyrazole H-2) and 10.83 ppm (s, 1H, NH); ^{13}C NMR (TFA-*d*): δ 22.05 (CH_3), 108.37, 113.16, 119.99, 123.14, 126.56, 132.95, 133.30, 134.80, 137.04, 137.36, 144.04, 148.94, 149.22, 149.79, 150.24, 155.71, 158.41 and 163.57 (Ar-C and CO); MS (EI): m/z (%) 47

B09 (M^++1, 1.3), 408 (M^+, 4.5), 238 (14.5), 237 (100). Anal. Calcd. for $C_{19}H_{13}ClN_6O_3$ (408.81): C, 55.82; H, 3.21; Cl, 8.67; N, 20.56. Found: C, 55.75; H, 3.32; Cl, 8.80; N, 20.49.

General procedure for the preparation of 19 and 21

A mixture of **9b** (1.4 g, 5 mmol) and DMFDMA (0.6 g, 5 mmol) in case of **19** or (1.3 g, 11 mmol) in case of **21**, in DMF (20 mL) was stirred at reflux for 6h, cooled to room temperature and poured onto ice cold water. The formed crude solid was collected by filtration, washed with water and crystallized from the appropriate solvent.

(*E*)-*N*-(2-Chloro-5-nitrophenyl)-5-[(dimethylamino)methyleneamino]-1*H*-pyrazolo-4-carboxamide (19). Recrystallized from EtOH as yellow crystals,.25 g (75 %), mp 237 °C; IR (KBr): 3426, 3213 (2NH), 1669 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6): δ 3.08 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 7.80 (d, *J* = 8.8 Hz, 1H, Ar-H), 7.92 (d, *J* = 8.8 Hz, 1H, Ar-H), 8.12 (s, 1H, Ar-H), 8.28 (s, 1H, imino CH), 9.27 (s, 1H, pyrazole H-3) 10.77 (br, 1H, NH) and 12.71 ppm (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 34.66 (CH_3), 40.34 (CH_3), 106.63, 116.49, 118.37, 128.61, 130.24, 133.04, 136.43, 146.35, 155.32, 156.09 and 161.75 ppm (carbons and CO); MS (EI): m/z (%) 337 (M^++1, 7.8), 336 (M^+, 25.0), 256 (20.8), 210 (12.4), 165 (100) 120 (24.6). Anal. Calcd. for $C_{13}H_{13}ClN_6O_3$ (336.74): C, 46.37; H, 3.89; Cl, 10.53; N, 24.96. Found: C, 46.44; H, 3.78; Cl, 10.66; N, 25.06.

(*E*)-*N*-(2-Chloro-5-nitrophenyl)-5-[(dimethylamino)methyleneamino]-1-methyl-1*H*-pyrazolo-4-carboxamide (21). Recrystallized from EtOH/DMF as yellow crystals, 1.6 g (92 %), mp 234 °C; IR (KBr): 3121 (NH), 1691 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6): δ 3.13 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 7.53 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.86-7.90 (m, 2H, Ar-H), 8.26 (s, 1H, imino CH), 9.38 (s, 1H, pyrazole H-3) and 10.65 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 35.25 (CH_3), 39.38 (CH_3), 40.99 (CH_3), 108.39, 118.09, 118.30, 129.49, 129.80, 134.75, 136.89, 146.96, 154.93, 156.25 and 162.00 ppm (carbons and CO); MS (EI): m/z (%) 351 (M^++1, 6.5), 350 (M^+, 21.0), 179 (100), 134 (36.4). Anal. Calcd. for $C_{14}H_{15}ClN_6O_3$ (350.77): C, 47.94; H, 4.31; Cl, 10.11; N, 23.96. Found: C, 48.10; H, 4.36; Cl, 9.98; N, 24.03.

General procedure for the preparation of 22a-d

A cold solution of the aryldiazonium salts (10 mmol) was prepared by adding a solution of sodium nitrite (1.4 g dissolved in 10 mL water) to a cold solution of arylamine hydrochloride (10 mmol in 6 mL, 6M HCl) with stirring. The resulting solution of aryldiazonium salts were then added to a cold solution of 3-oxoalkanonitriles **5a-c** in ethanol (50 mL) in the presence of sodium acetate trihydrate (4.2 g, 30 mmol). The mixture was stirred at room temperature for 1 h and the solid was collected by filtration, washed with water and crystallized from the appropriate solvent.

***(E)*-2-Cyano-*N*-(4,6-dimethylpyrimidin-2-yl)-2-(2-phenylhydrazono)acetamide (22a).** Recrystallized from EtOH as yellow crystals, 2.45 g (83 %), mp 2202 °C; IR (KBr): 3376, 3186 (2 NH), 2218 (CN), 1700 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 3.37 (s, 6H, $2CH_3$), 7.00 (s, 1H, pyrimidine H-5), 7.12 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.37 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.65 (d, *J* = 8.0 Hz, 2H, Ar-H), 10.23 (s, 1H, NH) and 11.96 ppm (s, 1H, NH); MS (EI): m/z (%) 295 (M^++1,14.3), 294 (M^+,

87.9), 189 (68.4), 188 (53), 150 (100), 123 (19.5). Anal. Calcd. for $C_{15}H_{14}N_6O$ (294.32): C, 61.22; H, 4.79; N, 28.55. Found: C, 61.40; H, 4.65; N, 28.42.

***(E)*-2-[2-(4-Chlorophenyl)hydrazono]-2-cyano-*N*-(4,6-dimethylpyrimidin-2-yl)acetamide (22b).** Recrystallized from EtOH as yellow crystals, 2.6 g (79 %), mp 224 °C; IR (KBr): 3393, 3177 (2 NH), 2214 (CN), 1693 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 3.36 (s, 6H, $2CH_3$), 7.00 (s, 1H, pyrimidine H-5), 7.39 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.63 (d, *J* = 8.8 Hz, 2H, Ar-H), 10.12 (s, 1H, NH) and 13.04 ppm (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 23.86 ($2CH_3$), 108.37, 111.79, 117.08 (CN), 118.75, 129.24, 129.79, 141.79, 156.90, 160.07 and 168.87 ppm (Ar-C and CO); MS (EI): m/z (%) 330 (M^++2, 22.4), 329 (M^++1,13.7), 328 (M^+, 67.5), 189 (48.6), 188 (62.8), 150 (100), 123 (21.2). Anal. Calcd. for $C_{15}H_{13}ClN_6O$ (328.76): C, 54.80; H, 3.99; Cl, 10.78; N, 25.56. Found: C, 54.65; H, 4.11; Cl, 10.93; N, 25.37.

(*E*)-*N*-(2-Chloro-5-nitrophenyl)-2-cyano-2-(2-phenylhydrazono)acetamide (22c). Recrystallized from EtOH/DMF as orange crystals, 3.0 g (89 %), mp 268-270 °C; IR (KBr): 3359, 3227 (2 NH), 2212 (CN), 1675 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 7.14(t, *J* = 8.0 Hz, 1H, Ar-H), 7.39 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.57 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.82 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.00 (d, *J* = 7.6 Hz, 1H, Ar-H), 8.85 (s, 1H, Ar-H), 9.68 (s, 1H, NH) and 12.31 ppm (br, 1H, NH); ^{13}C NMR (DMSO-d_6): 106.07, 110.82, 116.09 (CN), 117.72, 120.33, 124.87, 129.42, 130.60, 132.01, 135.14, 141.77, 146.43 and 159.62 ppm (Ar-C and CO); MS (EI): m/z (%) 345 (M^++2, 28.6), 344 (M^++1,15.3), 343 (M^+, 97.2), 172 (100), 143 (24.6). Anal. Calcd. for $C_{15}H_{10}ClN_5O_3$ (343.73): C, 52.42; H, 2.93; Cl, 10.31; N, 20.37. Found: C, 52.54; H, 3.04; Cl, 10.24; N, 20.48.

Crystallographic analysis for 22c

Crystals were mounted on a glass fiber. All measurements were performed on an ENRAF NONIUS FR 590. The data were collected at 25 °C using the ω scanning technique to a maximum of a 2θ of 24.108 °. The structure was solved by direct methods using SIR 92 and refined by full-matrix least squares. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located geometrically and were refined isotropically.

Crystal data

$C_{15}H_{10}ClN_5O_3$, M_r = 343.730, monoclinic, a = 12.6511 (4)Å, b = 8.2357 (3)Å, c = 16.9705 (8)Å, V = 1532.88 (10)Å^3, α = γ = 90.00 °, β = 12. (18) x 10^{1}°, space group: $P2_1/c$, D_x = 1.489 Mg m^{-3} reflection 9737 measured, θ_{max} = 27.50 °, ωR factor = 0.075. Figure 1 illustrates the structure as determined. Full data can be obtained on request from the CCDC.[18]

(*E*)-2-Cyano-*N*-(2-fluoro-5-nitrophenyl)-2-(2-phenylhydrazono)acetamide (22d). Recrystallized from EtOH / Ddioxan as yellow crystals, 2.8 g (85 %), mp 235 °C; IR (KBr): 3389, 3233 (2 NH), 2214 (CN), 1682 cm^{-1} (CO); ^{1}H NMR (DMSO-d_6): δ 7.16 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.41 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.61-8.63 (m, 5H, Ar-H), 10.05 (s, 1H, NH) and 12.20 ppm (s, 1H, NH); ^{13}C NMR (DMSO-d_6): 106.45, 111.11, 116.32 (CN), 117.24, 121.36, 122.39, 124.74, 126.38, 129.29, 141.92, 143.69, 157.58 and 160.06 ppm (Ar-C and CO); MS (EI): m/z (%) 328

(M^++1, 22.5), 327 (M^+, 100), 172 (26.5), 156 (43), 143 (39.3). Anal. Calcd. for $C_{15}H_{10}FN_5O_3$ (327.28): C, 55.05; H, 3.08; N, 21.40. Found: C, 54.89; H, 2.99; N, 21.52.

General method for the preparation of 24 and 25

A mixture of arylhydrazononitriles **22a,c** (5 mmol), and hydroxylamine hydrochloride (0.5 g, 7.5 mmol) was stirred at reflux in DMF (20 mL) in presence of anhydrous sodium acetate (1 g) for 5 h. Then, the reaction mixture was a cooled to room temperature and poured onto ice cold water. The formed solid was collected by filtration washed with water and crystallized from EtOH/DMF mixture as pale brown crystals.

5-Amino-*N*-(2-chloro-5-nitrophenyl)-2-phenyl-2*H*-1,2,3-triazole-4-carboxamide (24). Yield: 1.2 g (68 %); mp: 193-195 °C; IR (KBr): 3436, 3374, 3164 (NH_2 and NH), 1684 cm^{-1} (CO); ^{1}H MNR (DMSO-d_6): δ 6.21 (s, 2H, NH_2), 7.41-8.91 (m, 8H, Ar-H), 9.89 (s, 1H, NH); MS (EI): m/z (%) 360 (M^++2, 68.3), 359 (M^++1, 55.8), 368 (M^+, 86.8), 323 (47.2), 187 (100), 180 (38.1), 77 (87). Anal. Calcd for $C_{15}H_{11}ClN_6O_3$ (358.75): C, 50.22; H, 3.09; Cl, 9.88; N, 23.43. Found: C, 50.38; H, 2.89; Cl, 9.74; N, 23.60.

(*E*)-3-Amino-4-(2-phenylhydrazono)-4*H*-isoxazol-5-one (25). Yield: 0.7 g (70%); mp: 198 °C; IR (KBr): 3420, 3294, 3221 (NH2 and NH), 1711 cm^{-1} (CO); ^{1}H MNR (DMSO-d_6): δ 6.40 (s, 2H, NH_2), 7.19 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.40 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.60 (d, *J* = 8.0 Hz, 2H, Ar-H),12.41 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): 115.91, 116.36, 125.40, 129.30, 141.79, 159.05 and 162.37 ppm (Ar and CO); MS (EI): m/z (%) 205 (M^++1, 16.3), 204 (M^+, 93.9), 186 (16.3), 91 (100). Anal. Calcd. for $C_9H_8N_4O_2$ (204.19): C, 52.94; H, 3.95; N, 27.67. Found: C, 53.06; H, 3.86; N, 27.52.

Note: The biological activities of the new zaleplon analogues prepared in this study are now under investigation and the results will be the subject of a further communication.

Acknowledgements

The support for this work was from University of Kuwait through research grant (SC03/07). The facilities of Analab/SAF (GS01/01), (GS01/05) and (GS01/03) are gratefully acknowledged. The authors are grateful to Prof. Dr. M. H. Elnagdi for his support and for reading the manuscript in its original form.

References

1. Petroski, R. E.; Pomeroy, J. E.; Das, R.; Bowman, H.; Yang, W.; Chen, A. P.; Foster, A. C. *J. Pharmacol. Exp. Ther.* **2006,** *317*, 369.
2. George, C. F. P. *Lancet* **2001**, *358*, 1623.
3. Drover, D.; Lemmens, H.; Naidu,S.; Cevallos, W.; Darwish, M.; Stanski, D. *Clinical*

Therapeutics **2000**, *22*, 1443.
4. Weitzel, K. W.; Wickman, J. M.; Augustin, S. G.; Strom, J. G. *Clinical Therapeutics* **2000**, *22*, 1254.
5. Ming, L.; Wei-Si, G.; Li-Rong, W.; Bo, Q. *Jiegou Huaxue* **2006**, *25*, 108.
6. Mirza, N. R.; Rodgers, R. J.; Mathiasen, L. S. *J. Pharmacol. Exp. Ther.* **2006,** *316*, 1291.
7. Ibrahim, H. M.; Makhseed, S.; Abdel-Motaleb, R. M.; Makhloof, A. A.; Elnagdi, M. H. *Heterocycles* **2007**, *71*, 1951.
8. Khalil, K. D.; Al-Matar, H. M.; Al-Dorri, D. M.; Elnagdi, M. H. *Tetrahedron* **2009**, *65*, 9421.
9. McFadden, H.G.; Huppatz, J.L.; Halladay, P.K. *Austral. J. Chem.* **1993**, *46*, 873.
10. Jianguo, S.; Peiyu, W.; Ming, Z.; Qi, Z. *Yangzhou, Daxue Xuebao, Ziran Kexueban* **1998,** *1***,** 17.
11. Abdel-Motaleb, R. M.; Makhloof, A. A.; Ibrahim, H. M.; Elnagdi, M. H. *J. Heterocycl. Chem*. **2007**, *44*, 109.
12. Slatt, J.; Romero, I.; Bergman, J. *Synthesis* **2004**, 2760.
13. Aziz, S. I.; Anwar, H. F.; Felita, D. H.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2007**, *44*, 725.
14. Kenawi, I. M.; Elnagdi, M. H. *Spectrochim. Acta Molecul. Biomolecul. Spectroscopy* **2006,** *65A*, 805.
15. Ghozlan, S. A. S.; Abdelhamid, I. A.; Ibrahim, H. M.; Elnagdi, M. H. *Arkivoc* **2006**, (*xv*), 53.
16. Al-Matar, H.M.; Riyadh, S.M.; Elnagdi, M. H., *Arkivoc* **2007**,(xiii), 53.
17. Elnagdi, M. H.; Elmoghayer, M. R. H.; Hafez, E. A. A.; Alnima, H. H. *J. Org. Chem.* **1975**, *40*, 2604.
18. Crystal data for **22c** (ref. CCDC 759425) can be obtained on request from the director, Cambridge Crystallographic Data Center, 12 Union Road, Cambrige CB2 1EW, UK.