HETEROCYCLES, Vol. 85, No. 9, 2012, pp. 2259 - 2268. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 4th June, 2012, Accepted, 6th July, 2012, Published online, 19th July, 2012
DOI: 10.3987/COM-12-12520

A FACILE AND CONVENIENT SYNTHESIS OF NOVEL PYRIDINE DERIVATIVES INCORPORATING ANTIPYRINE MOIETY AND INVESTIGATION OF THEIR ANTIMICROBIAL ACTIVITIES

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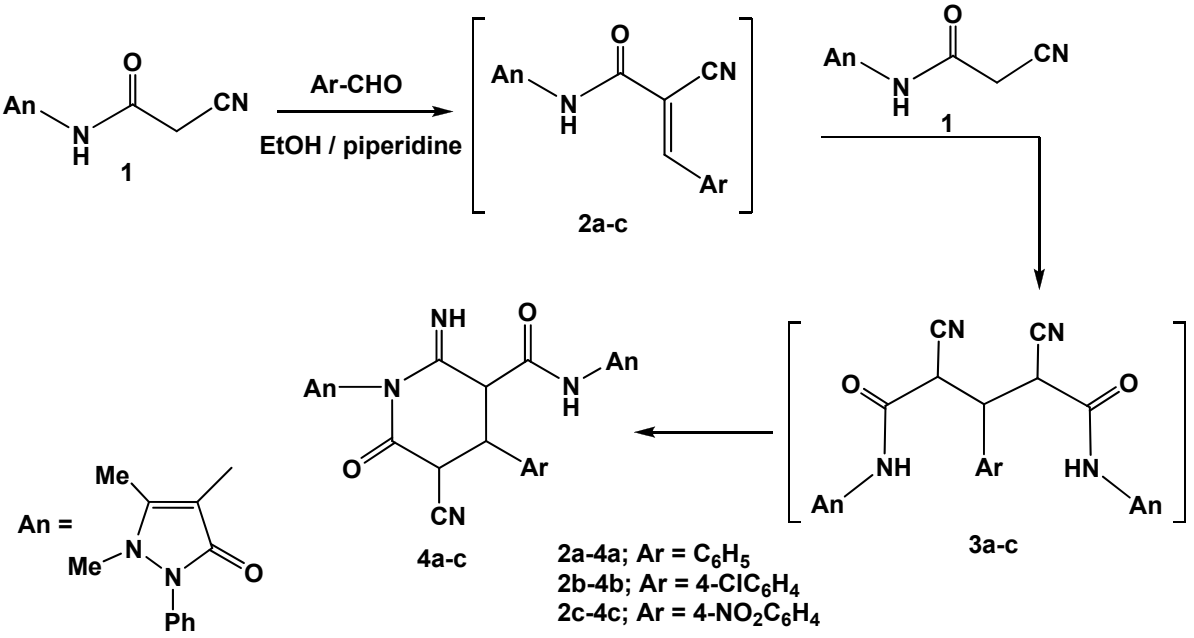
Abstract – A series of potentially bioactive piperidines and pyridines, pendant to antipyrine moiety, were synthesized and evaluated in vitro for their antimicrobial potential. Condensation of acetamide **1** with arylaldehydes in (2:1 molar ratio) gave hitherto unreported novel piperidine-3-carboxamide derivatives **4a-c**. Also, reaction of acetamide **1** with ethyl 2-cyano-3-(4-nitrophenyl)acrylate afforded unexpected piperidine-3-carboxamide **4c**. On the other hands, treatment of acetamide **1** with (arylmethylene)malononitriles **7a,b** afforded pyridine-3,5-dicarbonitrile derivatives **10a,b**. The structures of the synthesized products were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral techniques.

The antipyrine derivatives have been reported to possess diverse pharmacological activities such as antimicrobial,[1] antiviral,[2] antioxidant,[3] anticancer,[4] antipyretic,[5] analgesic and anti-inflammatory[6] activities. Also, several pyridine derivatives have been developed as pharmaceuticals compounds. They are reported as Calpains inhibitors,[7] Glycogen phosphorylase inhibitors,[8] cyclooxygenase (COX-2/COX-1) inhibitors,[9] HMG-CoA reductase inhibitors[10] and as anticancer agents.[11] Recently, it was reported that, piperidine linked to aminopyrimidines and aminotriazines have anti-HIV activities.[12] In view of the above mentioned findings, and in continuation of our previous work aimed at the synthesis of a variety of heterocyclic systems for biological and pharmacological evaluation,[13-20] we report in the

present work an efficient method for the synthesis of a series of pyridines and piperidines pendant to antipyrine moiety.

It was previously reported that 2-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)acetamide (**1**),[21] condensed with aromatic aldehydes in (1:1 molar ratio) to give arylmethylene derivatives.[21] On the other hand, in our study, acetamide **1** condensed with benzaldehyde in (2:1 molar ratio) to give the corresponding piperidine-3-carboxamide derivative **4a** *via* non-isolable intermediates **2a** and **3a** (Scheme 1). To account for the formation of this product **4a** we assumed that the reaction initially proceeds *via* elimination of water molecule to afford the non-isolable intermediate **2a** which reacted with another molecule of the acetamide **1** to give **3a**. Intramolecular cyclization of **3a** afforded the final product **4a** (Scheme 1).

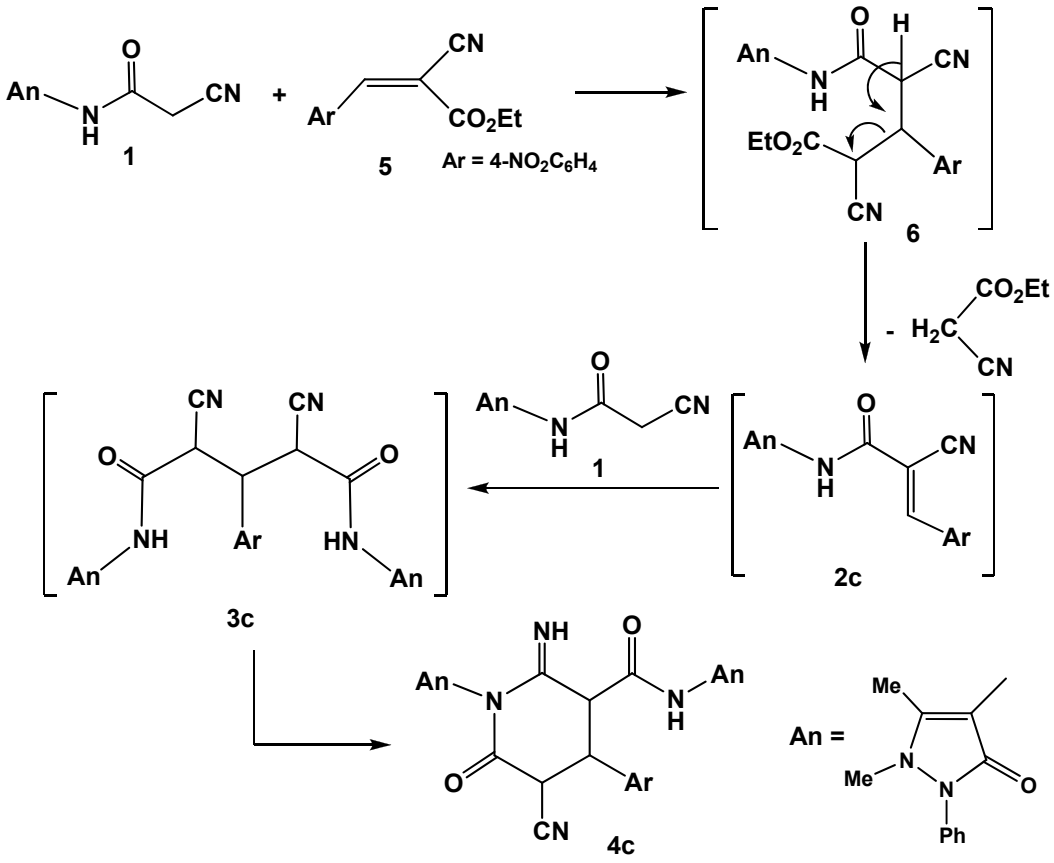


Scheme 1

The structure of the isolated product was inferred from its elemental analysis and spectral data [IR, ^{1}H NMR and ^{13}C NMR]. Its IR spectrum showed absorption bands at ν = 1670, 1701 (2 CO), 2251 (C≡N), 3323 and 3363 cm^{-1} (2 NH). Also, its ^{1}H NMR spectrum revealed doublet of doublet signal at δ 3.88 ppm (J = 10, 8 *Hz*) and another pair of doublets at δ 4.15 (J = 10 *Hz*), 5.0 ppm (J = 8 *Hz*) assignable to (3CH of piperidine ring). Also, two singlet signals (D_2O-exchangeable) were shown at δ 9.4 and 13.7 ppm assignable to (2NH) groups. Four singlet signals at δ 1.42, 2.33, 2.94 and 3.20 ppm due to four methyl protons, in addition to aromatic multiplet in the region δ 7.30-7.57 ppm were also revealed. The molecular ion peak at *m/z* = 628 confirmed the *bis* addition of acetamide **1**. Prompted by the foregoing results and to generalize this finding we also studied the reaction of the acetamide **1** with the aromatic aldehydes **2b,c** under the same experimental conditions and obtained the respective piperidine-3-carboxamide derivatives **4b,c**.

The structure of the isolated products **4b,c** was established on the basis of their elemental analyses and spectral data (see experimental part).

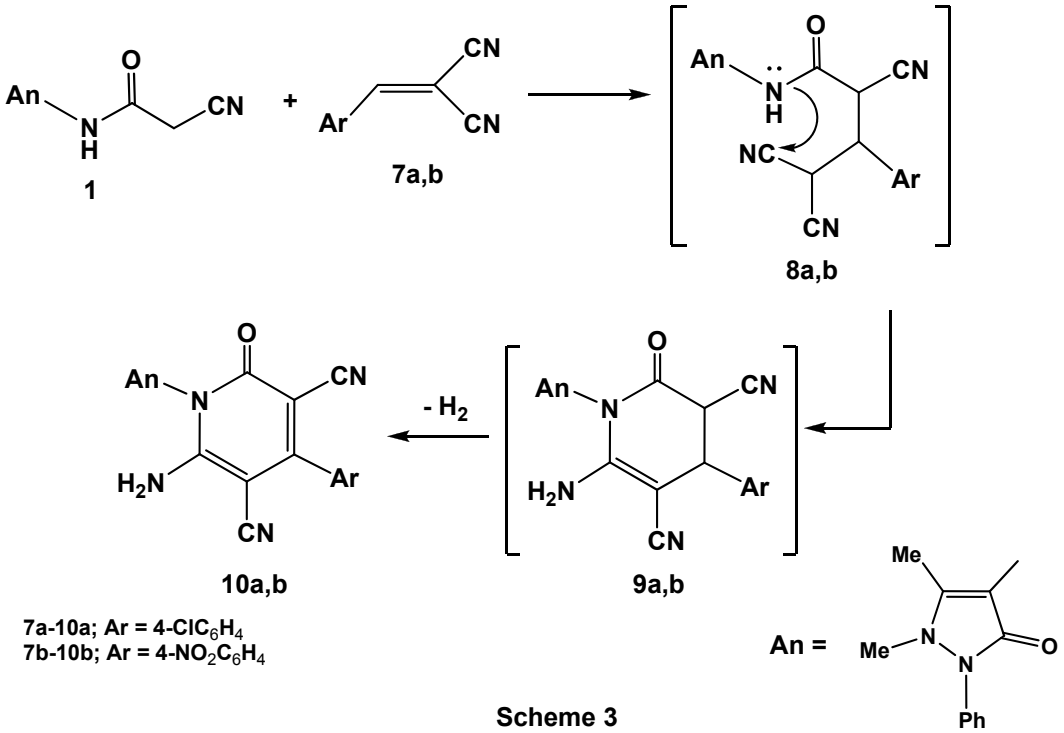
It was reported that, reaction of acetamide with ethyl 2-cyano-3-arylacrylate[22,23] afforded either aminopyridines[24,25] or pyridine-dicarbonitriles.[26] In our study, refluxing of an equimolar amounts of acetamide **1** with ethyl 2-cyano-3-(4-nitrophenyl)acrylate (**5**),[22,23] in EtOH, in the presence of catalytic amount of piperidine, gave astonishing the corresponding piperidine-3-carboxamide derivative **4c** (identical in all respects to sample obtained from the reaction between acetamide **1** and 4-nitrobenzaldehyde shown in Scheme 1). To account for the formation of this product we suggested that the acetamide **1** reacted with compound **5** to afford non-isolable intermediate **6**. Elimination of one molecule of ethyl cyanoacetate from intermediate **6** gave intermediate **2c**. Further reaction of the latter intermediate **2c** with another molecule of acetamide **1** gave the respective final product **4c** *via* intermediate **3c** (Scheme 2).



Scheme 2

On the other hand, the behavior of (arylmethylene)malononitriles[27] towards acetamides was investigated and the reaction products were 2-oxopyridine-3,5-dicarbonitriles[21,28] or 6-imino-2-oxopyridine-3-carbonitriles.[29] Thus, refluxing of an equimolar amounts of acetamide **1** with

(arylmethylene)malononitriles[27] **7a,b**, under the same experimental conditions, afforded, in each case (1:1) cycloadduct (Scheme 3). The structure of the isolated cycloadducts was identified as 6-amino-4-aryl-2-oxo-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)pyridine-3,5-dicarbo nitriles **10a,b** (Scheme 3).



Scheme 3

The structure of compound **10** was established for the reaction product based on analytical and spectral data (see Experimental). The ^{1}H NMR spectra exhibited signal at δ 7.9-8.6 ppm (exchangeable with D_2O) due to NH_2 protons and did not revealed any signal assignable to NH protons. The pyridine structure **10** is assumed to be formed *via* an initial Micheal addition[30] adduct **8** followed by an intramolecular cyclization and subsequent oxidation of **9** to the final product **10** (Scheme 3).

ANTIMICROBIAL EVALUATION

The newly synthesized target compounds (**4a-c** and **10a,b**) were evaluated for their *in vitro* antibacterial activity against *Staphylococcus aureus* (SA) and *Bacillis subtilis* (BS) as examples of Gram-positive bacteria and *Pseudomonas aeruginosa* (PA) and *Escherichia coli* (EC) as examples of Gram-negative bacteria. They were also evaluated for their *in vitro* antifungal potential against *Aspergillus fumigatus* (AF), *Geotrichum candidum* (GC), *Candida albicans* (CA) and *Syncephalastrum racemosum* (SR) fungal strains. The organisms were tested against the activity of solutions of concentrations (5 mg/mL) and using inhibition zone diameter (IZD) in mm as criterion for the antimicrobial activity (agar diffusion well method). The fungicides *Itraconazole*, *Clotrimazole* and the bactericides *Penicillin G, Streptomycin* were

used as references to evaluate the potency of the tested compounds under the same conditions. The results are depicted in Table 1.

Table 1. Antibacterial and Antifungal Activities of the Synthesized Compounds 4a-c, 10a,b

Microorganisms	Compound Tested					Standard (30 µg / ml)	
	4a	**4b**	**4c**	**10a**	**10b**		
Fungi						**Itraconazole**	**Clotrimazole**
Aspergillus fumigatus	17.1 ± 0.05	12.2 ±0.08	15.2 ±0.07	16.2 ± 0.08	16.3 ± 0.02	28 ± 0.05	26 ± 0.1
Geotrichum candidum	15.3 ± 0.09	15.4 ± 0.50	14.7 ± 0.05	19.4 ± 0.5	15.2 ± 0.06	27 ± 0.1	23 ± 0.3
Candida albicans	12.4 ± 0.07	11.4 ±0.1	14.8 ± 0.08	13.4 ± 0.1	13.4 ± 0.09	26 ± 0.02	18 ± 0.1
Syncephalastrum racemosum	NA	NA	NA	NA	NA	22 ± 0.09	20 ± 0.2
Gram-Positive Bacteria						**Penicillin G**	**Streptomycin**
Staphylococcus aureus	19.3 ±0.2	13.5 ± 0.03	17.4 ± 0.02	22.4 ± 0.03	19.8 ± 0.04	29.48 ± 0.82	25 ± 0.2
Bacillis subtilis	18.6 ±0.40	12.9 ±0.10	19.1 ±0.03	23.5 ± 0.04	20.2 ± 0.03	32.56 ± 0.56	29 ± 0.4
Gram-Negative Bacteria						**Penicillin G**	**Streptomycin**
Pseudomonas aeruginosa	18 ± 0.10	11.4 ±0.05	13.7 ± 0.03	20.3 ± 0.3	14.8 ± 0.02	28.32 ± 0.10	24 ± 0.1
Escherichia coli	20 ± 0.3	13.4 ± 0.10	15.1 ±0.07	21.6 ± 0.03	18.7 ± 0.06	33.56 ± 0.78	25 ± 0.3

*NA: No activity, data are expressed in the form of mean ± SD

The results revealed that most of the tested compounds displayed variable inhibitory effects on the growth of the tested Gram-positive bacteria and Gram-negative bacteria strains and also against fungal strains. In general, most of the tested compounds revealed better activity against the Gram-positive bacteria rather than the Gram-negative bacteria and all compounds exhibited almost no activity against *Syncephalastrum racemosum*. Compounds **4a-c** and **10a,b** were found to have moderate inhibition activity, relative to the standard drugs *Itraconazole* and *Clatrimazole,* against *Aspergillus fumigates*, *Geotrichum candidum* and *Candida albicans*. Also, compounds **4a** and **10a** were found to be the most potent relative to the standard drugs, *Penicillin G* and *Streptomycin* against *Staphylococcus aureus*, *Bacillis subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli*. The structure antimicrobial activity relationship of the synthesized compounds revealed that the maximum activity was attained with compound **10a**, having pyridine nucleus with chloro substituent in the phenyl group. The results suggest that the new skeleton possessing

pyridine and antipyrine may provide valuable leads for synthesis and development of novel antibacterial agents.

Novel series of piperidines and pyridines bearing antipyrine moiety were synthesized and evaluated for their antimicrobial activities. Most of the newly synthesized products have promising activity against Gram-positive and Gram-positive bacteria.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a BRUKER VX-500 NMR spectrometer (Varian, Palo Alto, CA, USA). ^{1}H spectra were run at 500 MHz and ^{13}C spectra were run at 125 MHz in deuterated dimethylsulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. The biological evaluation of the products **4a-c** and **10a,b** were carried out in the Medical Mycology Laboratory of the Regional Center for Mycology and Biotechnology of Al-Azhar University, Cairo, Egypt. 2-cyano-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)acetamide (**1**),[21] ethyl 2-cyano-3-(4-nitrophenyl)acrylate (**5**)[22,23] and (arylmethylene)malononitriles **7a,b**,[27] were prepared as described in literature.

Reaction of acetamide 1 with aromatic aldehydes.

General Procedure:

To an ethanolic solution (10 mL) of acetamide **1** (0.54 g, 2 mmol) and the appropriate aromatic aldehydes (1 mmol) was added few drops of piperidine and the reaction mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure, and the residue was cooled, filtered off, washed with EtOH and purified by recrystallization from DMF/EtOH to afford **4a-c**.

5-Cyano-N,1-bis(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-imino-6-oxo-4-phenyl-piperidine-3-carboxamide (4a).

White powder, (0.28 g, 44%), mp 245 ^{o}C; IR (KBr) ν 3363, 3323 (2NH), 2251 (C≡N), 1701-1670 (4 C=O) cm^{1}; ^{1}H NMR (DMSO-d_6) δ 1.42 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.94 (s, 3H, N-CH_3), 3.20 (s, 3H, N-CH_3), 3.88 (dd, 1H, J = 10.0, 8.0 *Hz,* CH-piperidine), 4.15 (d, 1H, J = 10.0 *Hz*, CH-piperidine), 5.0 (d, 1H, J = 8.0 *Hz*, CH-piperidine), 7.30-7.57 (m, 15H, Ar-H), 9.40 (s, 1H, D_2O-exchangeable, NH), 13.7 (s, 1H, D_2O-exchangeable, NH); ^{13}C NMR (DMSO-d_6) δ 9.8 (CH_3), 10.4 (CH_3). 34.6 (N-CH_3), 35.8

(N-CH_3), 41.4, 42.9, 52.6, 107.1, 113.5, 123.3, 123.5, 126.1, 126.2, 128.3, 128.4, 128.6, 129.1, 129.3, 133.5, 135.1, 137.9, 142.3, 151.9, 152.1, 159.1, 161.4, 162.7, 166.9, 167.9; MS *m/z* (%) 628 (M^+, 10), 230 (10), 202 (14), 187 (18), 77 (100). Anal. Calcd for $C_{35}H_{32}N_8O_4$ (628.25): C, 66.87; H, 5.13; N, 17.82. Found: C, 66.77; H, 5.08; N, 16.93%.

4-(4-Chlorophenyl)-5-cyano-N,1-bis(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-imino-6-oxopiperidine-3-carboxamide (4b).

Yellow powder, (0.30 g, 46%), mp 230 ^oC; IR (KBr) ν 3287, 3198 (2NH), 2255 (C≡N), 1700-1670 (4 C=O) cm^1; ^1H NMR (DMSO-d_6) δ 1.50 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.97 (s, 3H, N-CH_3), 3.21 (s, 3H, N-CH_3), 3.95 (dd, 1H, *J* = 10.0, 8.0 *Hz*, CH-piperidine), 4.10 (d, 1H, *J* = 10.0 *Hz*, CH-piperidine), 5.03 (d, 1H, *J* = 8.0 *Hz*, CH-piperidine), 7.30-7.60 (m, 14H, Ar-H), 9.40 (s, 1H, D_2O-exchangeable, NH), 13.65 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%): 665 (M^++2, 4), 663 (M^+, 10), 624 (18), 460 (12), 202 (16), 187 (14), 111 (20), 77 (100). Anal. Calcd for $C_{35}H_{31}ClN_8O_4$ (663.22): C, 63.39; H, 4.71; N, 16.90. Found: C, 63.47; H, 4.78; N, 16.83%.

5-Cyano-N,1-bis(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-imino-4-(4-nitrophenyl)-6-oxopiperidine-3-carboxamide (4c).

Yellow powder, (0.32 g, 48%); mp 220 ^oC; IR (KBr) ν 3192, 3109 (2NH), 2255 (C≡N), 1690-1668 (4 C=O) cm^1; ^1H NMR (DMSO-d_6) δ 1.49 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.94 (s, 3H, N-CH_3), 3.21 (s, 3H, N-CH_3), 4.19 (dd, 1H, *J* = 10.0, 8.0 *Hz*, CH-piperidine), 5.03 (d, 1H, *J* = 10.0 *Hz*, CH-piperidine), 5.15 (d, 1H, *J* = 8.0 *Hz*, CH-piperidine), 7.29-7.59 (m, 10H, Ar-H), 7.77 (d, 2H, *J* = 8.0 *Hz*, Ar-H), 8.31 (d, 2H, *J* = 8.0 *Hz*, Ar-H), 9.49 (s, 1H, D_2O-exchangeable, NH), 13.71 (s, 1H, D_2O-exchangeable, NH); MS *m/z* (%) 673 (M^+, 10), 230 (16), 202 (21), 187 (12), 134 (10), 122 (14), 77 (100). Anal. Calcd for $C_{35}H_{31}N_9O_6$ (673.24): C, 62.40; H, 4.64; N, 18.71. Found: C, 62.47; H, 4.68; N, 18.63%.

Reactions of acetamide 1 with ethyl 2-cyano-3-(4-nitrophenyl)acrylate (5).

To a solution of ethyl 2-cyano-3-(4-nitrophenyl)acrylate (**5**) (1 mmol) in EtOH (10 mL) was added an eqimolar amount of the acetamide **1** (0.27 g, 1 mmol), and few drops of piperidine and the reaction mixture was heated for 3 h. The solid product that obtained was collected by filtration, washed with EtOH and then crystallized from DMF to afford product **4c** (50%) which was identical in all respects to sample obtained from the reaction between acetamide **1** and 4-nitrobenzaldehyde.

Reaction of acetamide 1 with (arylmethylene)malononitriles 7a,b.

General procedure.

To a solution of the appropriate (arylmethylene)malononitriles **7a,b** (1 mmol) in EtOH (10 mL) was added an equimolar amount of the acetamide **1** (0.27 g, 1 mmol), and few drops of piperidine and the reaction mixture was heated under reflux for 2 h. The solid product that formed was collected by filtration, washed with EtOH and then crystallized from DMF/EtOH to give **10a,b**.

6-Amino-4-(4-chlorophenyl)-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (10a).

White powder, (0.32 g, 70%), mp > 300 ^{o}C; IR (KBr) ν 3280, 3194 (NH_2), 2240, 2213 (2 C≡N), 1667, 1672 (2 C=O) cm^{1}; ^{1}H NMR (DMSO-d_6) δ 2.16 (s, 3H, CH_3), 3.28 (s, 3H, N-CH_3), 7.41-7.69 (m, 9H, Ar-H), 8.6 (s, 2H, D_2O-exchangeable, NH_2); ^{13}C NMR (DMSO-d_6) δ 10.2 (CH_3), 34.9 (N-CH_3), 74.7, 87.4, 100.4, 115.5, 116.1, 124.8, 127.1, 128.8, 129.2, 129.9, 133.4, 134.3, 135.2, 153.8, 157.7, 158.6, 159.5, 160.5; MS *m/z* (%) 458 (M^++2, 4), 456 (M^+, 10), 269 (40), 111 (30), 77 (100). Anal. Calcd for $C_{24}H_{17}ClN_6O_2$ (456.11): C, 63.09; H, 3.75; N, 18.39. Found: C, 63.16; H, 3.88; N, 18.19%.

6-Amino-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (10b).

Yellow powder, (0.35 g, 75%), mp 265 ^{o}C; IR (KBr) ν 3383, 3161 (NH_2), 2240, 2215 (2 C≡N), 1663, 1676 (2 C=O) cm^{1}; ^{1}H NMR (DMSO-d_6) δ 2.18 (s, 3H, CH_3), 3.28 (s, 3H, N-CH_3), 7.40-8.50 (m, 9H, Ar-H), 7.9 (s, 2H, D_2O-exchangeable, NH_2); ^{13}C NMR (DMSO-d_6) δ 10.2 (CH_3), 34.9 (N-CH_3), 74.7, 87.3, 100.4, 115.4, 115.8, 123.8, 124.8, 127.2, 129.2, 129.7, 134.3, 140.9, 148.5, 153.8, 157.7, 158.4, 159.4, 162.3; MS *m/z* (%) 467 (M^+, 10), 281 (10), 122 (14), 77 (100). Anal. Calcd for $C_{24}H_{17}N_7O_4$ (467.13): C, 61.67; H, 3.67; N, 20.98. Found: C, 61.76; H, 3.58; N, 21.09%.

ANTIMICROBIAL ACTIVITY TEST

Agar diffusion well method to determine the antimicrobial activity

The microorganism inoculums were uniformly spread using sterile cotton swab on a sterile Petri dish Malt extract agar (for fungi) and nutrient agar (for bacteria). One hundred μL of each sample was added to each well (10 mm diameter holes cut in the agar gel, 20 mm apart from one another). The systems were incubated for 24-48 h at 37 °C (for bacteria) and at 28 °C (for fungi). After incubation, the microorganism's growth was observed. Inhibition of the bacterial and fungal growth were measured as IZD in mm. Tests were performed in triplicate.[31]

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