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SYNTHESIS OF SOME NOVEL BIS(PYRAZOLE), BIS(PYRIDINE) AND BIS(PYRAZOLO[5,1-*c*]-1,2,4-TRIAZINE DERIVATIVES

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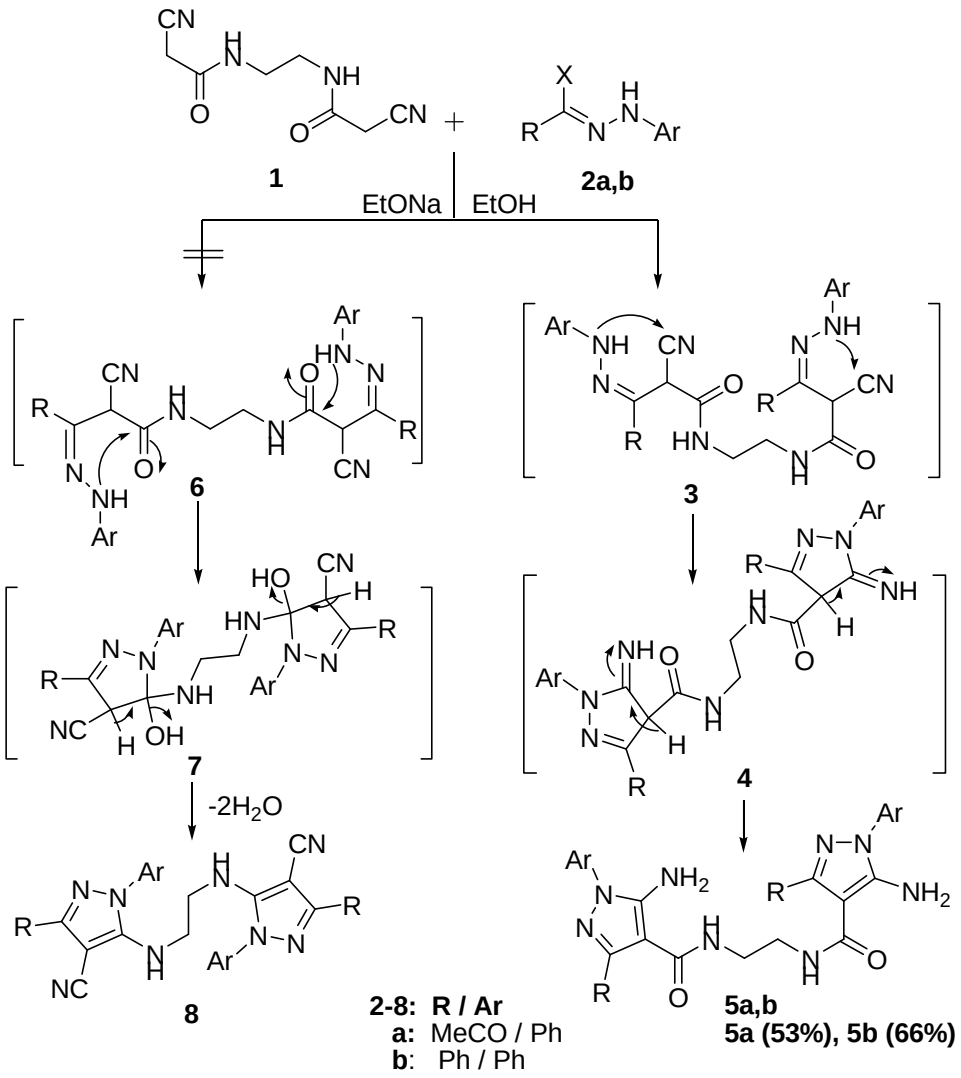
Abstract – Treatment of *N*,*N*'-(ethane-1,2-diyl)bis(cyanoacetamide) (**1**) with hydrazonoyl chlorides **2a,b** afforded bis(aminopyrazoles) **5a,b**. Heating of compound **1** with arylmethylenepropanedinitrile **9a-c** afforded bis(pyridine) derivatives **13a-c**. Also, compound **1** coupled smoothly with the arenediazonium salt generated from 3-chloroaniline or 5-amino-4-methyl-3-phenylpyrazole (**16**) to afford the corresponding hydrazones **15** or bis(pyrazolo[5,1-*c*]-1,2,4-triazine-3-carboxamide) **19**. Refluxing of compound **1** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in xylene afforded bis(2-cyano-3-(dimethylamino)-acrylamide) (**20**) which reacted with hydrazine hydrate to afford the novel bis(cyanoopyrazole) **23**.

Recently, bis(heterocycles) have received grate deal of attention, not only for being model compounds for main chain polymers,[1-6] but also because many biologically active natural and synthetic products have molecular symmetry.[7] On the other hand, the synthesis of combinatorial libraries of heterocyclic compounds permits the testing of the biological properties of a vast array of compounds. Routes to novel skeletons, which could be synthesized using combinatorial methods, are presently a major research objective. In continuation of our recent work aiming at the synthesis of bis(heterocyclic) systems,[8-12] it was found that compound **1**, is versatile and readily accessible building block for the synthesis of several new bis(pyrazole)-, bis(pyridine)- and bis(pyrazolo[5,1-*c*]-1,2,4-triazine) derivatives of expected biological potency.

Treatment of compound **1**[13] with hydrazonoyl chloride **2a**[14] in ethanolic sodium ethoxide solution at rt furnished a single product for which the two possible structures **5a** and **8a** can be envisaged (Scheme 1). However, elemental analyses and spectral data were in complete accordance with the bis(aminopyrazole)

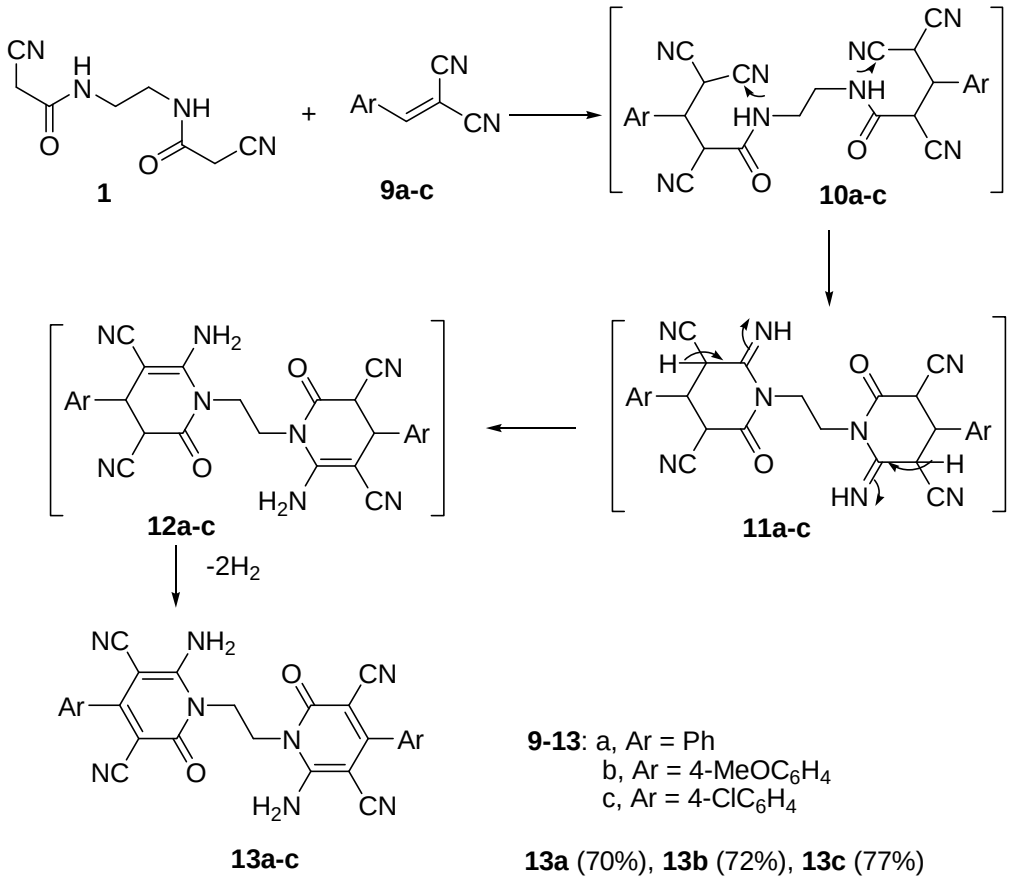
structure **5a**. The IR spectrum of **5a** showed absorption bands at 3439, 3315, 3261, 1675 and 1639 cm^{-1} due to amino, amide-NH and two carbonyl groups, respectively. Its ^1H NMR spectrum showed signals at δ 2.49, 3.37 and two D_2O-exchangeable signals at δ 6.83 and 9.65 due to CH_3, NCH_2, amino and imino protons, respectively in addition to an aromatic multiplet in the region δ 7.53-7.62. Prompted by the foregoing results and to generalize this finding I also studied the reaction of the acetamide **1** with other hydrazonoyl chloride **2b**[15] under the same experimental conditions and obtained the respective aminopyrazole derivative **5b**.



Scheme 1

Treatment of compound **1** with arylmethylenepropanedinitrile **9a-c**[16] furnished 1, 1'-(ethane-1,2-diyl)-bis(6-amino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) **13a-c** (Scheme 2). The IR spectrum of compound **13a**, taken as a typical example of the prepared series, revealed absorption bands at 1631, 2206, 3317 and 3392 cm^{-1} corresponding to carbonyl group, nitrile function and amino group, respectively. Its ^1H NMR spectrum showed signals at δ 3.13 and D_2O-exchangeable signals at δ 4.18 due

to NCH_2 and NH_2 protons, respectively, in addition to an aromatic multiplet in the region δ 7.44-7.53. Compounds **13a-c** are assumed to be formed *via* an initial Michael type adducts **10** followed by an intramolecular cyclization and dehydrogenation to the final products **13a-c** (Scheme 2).

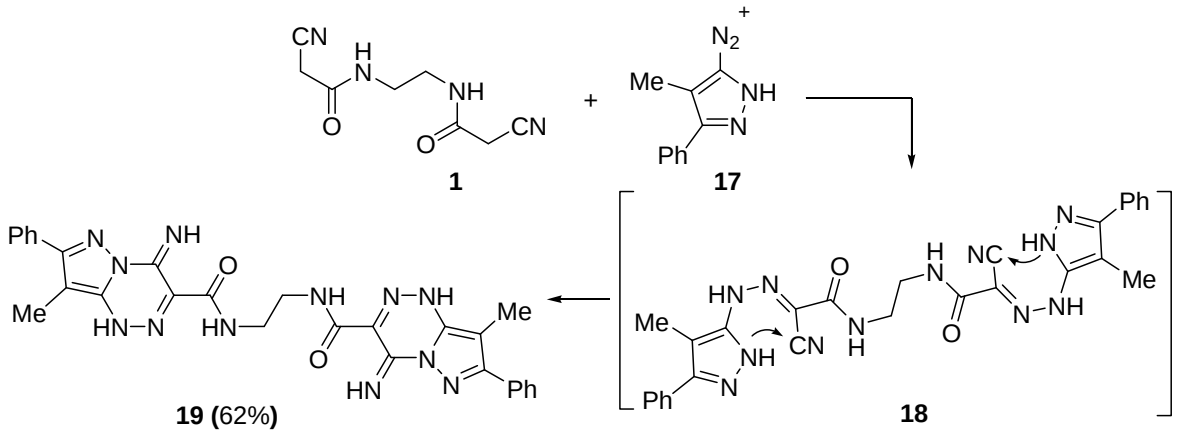


Scheme 2

Compound **1** coupled smoothly with the diazonium salt **14** generated from 3-chloroaniline in pyridine to afford *N*,*N*′-(ethane-1,2-diyl)bis[2-(*N*″-(4-chlorophenylhydrazonoyl)-2-cyanoacetamide] (**15**) (Scheme 3). The IR spectrum of **15** showed absorption bands at 1651 and 2222 cm^{-1} corresponding to carbonyl group and nitrile function, respectively. Its ^1H NMR spectrum showed signal at δ 3.39 due to NCH_2 and two D_2O-exchangeable signals at δ 8.65 and 14.39 due to two NH protons, in addition to an aromatic multiplet in the region δ 7.10-7.88.

Scheme 3

In a similar manner, compound **1** coupled smoothly with the diazonium salt **17** generated from 5-amino-4-methyl-3-phenylpyrazole (**16**) in pyridine, at room temperature to afford a single product identified as *N*,*N*′-(ethane-1,2-diyl)bis(4-imino-8-methyl-7-phenyl-1,4-dihydropyrazolo[5,1-*c*]-1,2,4-triazine-3-carboxamide) (**19**) (Scheme 4).



Scheme 4

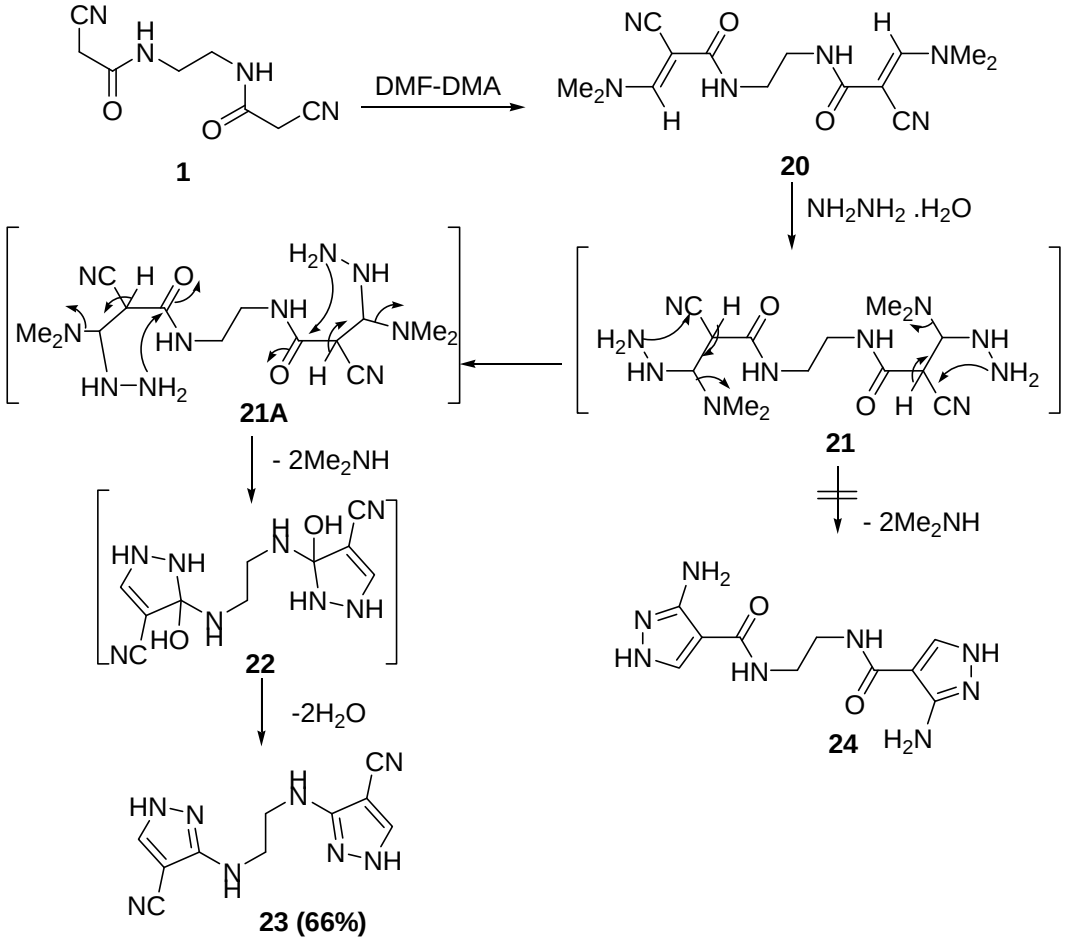
The IR spectrum of **19** revealed the absence of a band corresponding to nitrile function. Its ^{1}H NMR spectrum showed signals at δ 2.48, 3.59 due to CH_3 and NCH_2 protons, and three D_2O-exchangeable signals at δ 9.01, 9.12 and 9.2 due to three NH protons, in addition to aromatic multiplet in the region 7.30-7.89.

Treatment of compound **1** with *N*,*N*-dimethylformamide-dimethylacetal (DMF-DMA) in refluxing xylene afforded *N*,*N*′-(ethane-1,2-diyl)bis[2-cyano-3-(dimethylamino)acrylamide] (**20**). The ^{1}H NMR spectrum of compound **20** showed signals at δ 3.19, 3.22, 3.33, 7.19 and 7.68 due to *N*,*N*–dimethylamino, NCH_2, C=*CH*-N and amide-*NH* protons, respectively. When compound **20** was treated with hydrazine hydrate in refluxing EtOH, the novel 3,3'-(ethane-1,2-diyl)bis(azanediyl)bis(1*H*-pyrazole-4-carbonitrile) (**23**) was produced (Scheme 5). The IR spectrum of the isolated product showed absorption bands at 3314 and 2217 cm^{-1} characteristic for NH and nitrile function, respectively. Its ^{1}H NMR spectrum showed signals at δ 3.35, 8.40, 10.2 and 11.0 corresponding to NCH_2, CH and two D_2O-exchangeable signals corresponding to two NH protons. The foregoing spectral data supported the proposed structure **23** and ruled out the other possible pyrazole structure **24** (Scheme 5).

In conclusion, the reactivity of *N*,*N*′-(ethane-1,2-diyl)bis(cyanoacetamide) (**1**) was investigated as a versatile and readily accessible building block for the synthesis of new bis(heterocycles) of biological and pharmaceutical importance.

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 Varian Mercury VX-300 NMR spectrometer.



Scheme 5

^{1}H spectra were run at 300 MHz and ^{13}C spectra were run at 75.46 MHz in deuterated dimethyl sulfoxide (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. *N, N'*-(Ethane-1,2-diyl)bis[cyanoacetamide] (**1**),[13] hydrazonoyl halides **2a**,[14] **2b**,[15] arylmethylenepropanedinitrile **9a-c**[16] and 5-amino-4-methyl-3-phenyl- pyrazole (**16**)[17] were prepared following the literature procedure.

Reaction of N, N'-(Ethane-1,2-diyl)bis(cyanoacetamide)(1) with hydrazonoyl halides.

General procedure:

Compound **1** (0.194 g, 1 mmol) was added to an ethanolic sodium ethoxide solution [prepared from sodium metal (46 mg, 2 mmol) and absolute EtOH (20 mL)] with stirring. After stirring the resulting

solution for 15 min., the appropriate hydrazonoyl halide **2a,b** (2 mmol) was added portionwise and the reaction mixture was stirred further for 12 h at rt. The solid product that formed was filtered off, washed with water and dried. Recrystallization from the proper solvent afforded the corresponding bis(pyrazole) derivatives **5a,b**.

N,N'-(Ethane-1,2-diyl)bis(3-acetyl-5-amino-1-phenyl-1H-pyrazole-4-carboxamide)(5a). Yield (53%), mp > 300 °C (DMF); IR (KBr) ν 1639 (C=O), 1675 (C=O), 3261 and 3315 (NH_2), 3439 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.49 (s, 6H, $2CH_3$), 3.37 (s, 4H, $2NCH_2$), 6.83 (s, 4H, D_2O-exchangeable $2NH_2$), 7.53-7.62 (m, 10H, Ar-H), 9.65 (s, 2H, D_2O-exchangeable 2NH); MS *m/z* (%) 271 (6.91), 258 (1.47), 257 ($M^+/2$, 2.64). Anal. Calcd for $C_{26}H_{26}N_8O_4$: C, 60.69; H, 5.09; N, 21.78. Found: C, 60.61; H, 5.02; N, 21.72%.

N, N'-(Ethane-1,2-diyl)bis(5-amino-1,3-diphenyl-1H-pyrazole-4-carboxamide) (5b).

Yield (66%), mp > 300 °C (DMF); IR (KBr) ν 1632 (C=O), 3055 (NH), 3314 and 3422 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.20 (s, 4H, $2NCH_2$), 6.29 (s, 4H, D_2O-exchangeable $2NH_2$), 7.18-7.62 (m, 20H, Ar-H), 9.57 (s, 2H, D_2O-exchangeable 2NH). Anal. Calcd for $C_{34}H_{30}N_8O_2$: C, 70.09; H, 5.19; N, 19.23. Found: C, 70.01; H, 5.24; N, 19.25%.

Synthesis of 1,1'-(ethane-1,2-diyl)bis[6-amino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile] 13a-c.

General procedure:

To a solution of the appropriate arylmethylenepropanedinitrile **9a-c** (2 mmol) in EtOH (20 mL) was added compound **1** (0.194 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 a proper solvent to afford the corresponding bis(pyridine) derivative**s 13a-c**.

1,1'-(Ethane-1,2-diyl)bis(6-amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile)(13a). Yield (70%), mp > 300 °C (DMF); IR (KBr) ν 3392 and 3317 (NH_2), 2206 (C≡N), 1631 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.13 (s, 4H, $2NCH_2$), 4.18 (s, 4H, D_2O-exchangeable 2 NH_2), 7.44-7.53 (m, 10H, Ar-H); ^{13}C NMR (DMSO-d_6) δ 43.92, 76.92, 83.28, 117.15, 117.49, 127.79, 128.40, 129.72, 135.34, 158.02, 159.33, 160.39. Anal. Calcd for $C_{28}H_{18}N_8O_2$: C, 67.46; H, 3.64; N, 22.48. Found: C, 67.41; H, 3.60; N, 22.51%.

1,1'-(Ethane-1,2-diyl)bis(6-amino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile) (13b). Yield (72%), mp > 300 °C (DMF); IR (KBr) ν 3333 and 3179 (NH_2), 2214 (C≡N), 1651 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.02 (s, 4H, $2NCH_2$), 3.83 (s, 6H, $2OCH_3$), 4.21 (s, 4H, D_2O- exchangeable 2 NH_2), 7.06 (d, 4H, ArH's, J = 8.7 Hz), 7.4 (d, 4H, ArH's, J = 8.7 Hz). Anal. Calcd for $C_{30}H_{22}N_8O_4$: C, 64.51; H, 3.97; N, 20.06. Found: C, 64.57; H, 3.92; N, 20.10%.

1,1'-(Ethane-1,2-diyl)bis(6-amino-4-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile)

(13c). Yield (77%), mp > 300 °C (DMF); IR (KBr) ν 3333 and 3179 (NH_2), 2214 (C≡N), 1636 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.01 (s, 4H, $2NCH_2$), 4.17 (s, 4H, D_2O-exchangeable 2 NH_2), 7.48 (d, 4H, ArH's, J = 8.4 Hz), 7.62 (d, 4H, ArH's, J = 8.4 Hz); ^{13}C NMR (DMSO-d_6) δ 43.92, 76.93, 89.16, 117.03, 117.39, 128.59, 129.80, 134.19, 134.57, 157.97, 158.09, 160.28. Anal. Calcd for $C_{28}H_{16}N_8Cl_2O_2$: C, 59.27; H, 2.84; N, 19.75. Found: 59.32; H, 2.80; N, 19.70%.

Synthesis of N,N'-(ethane-1,2-diyl)]bis[2-(N''-(4-chlorophenylhydrazonoyl)-2-cyanoacetamide] (15) and N,N'-(ethane-1,2-diyl)bis(4-imino-8-methyl-7-phenyl-1,4-dihydropyrazolo[5,1-c]-1,2,4-triazine-3-carboxamide)(19).

General procedure.

To a cold solution of the compound **1** (0.194 g, 1 mmol) in pyridine (20 mL) was added the appropriate diazonium salt generated from 3-chloroaniline or 5-amino-4-methyl-3-phenylpyrazole (**16**) [prepared by diazotizing the appropriate amine (2 mmol) in hydrochloric acid (6M, 1.2 mL) with sodium nitrite solution (0.138 g, 2 mmol) in water (1.0 mL)]. The addition was carried out portionwise with stirring at 0-5 ºC over a period of 30 min. After complete addition, the reaction mixture was stirred for further 4 h, then kept in an ice chest for 12 h, and finally diluted with water. The precipitated solid was collected by filtration, washed with water, dried and finally recrystallized from a proper solvent to afford the corresponding products **15** and **19**, respectively.

N,N'-(Ethane-1,2-diyl)bis[2-(N''-(4-chlorophenylhydrazonoyl)-2-cyanoacetamide] (15). Yield (66%), mp 270 °C (DMF); IR (KBr) ν 3356 (NH), 3074 (NH), 2222 (C≡N), 1651 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.39 (s, 4H, $2NCH_2$), 7.10-7.88 (m, 8H, Ar-H), 8.65 (s, 2H, D_2O-exchangeable 2NH), 14.39 (s, 2H, D_2O-exchangeable 2NH); MS *m/z* (%) 473 (14.1), 472 (30.6), 470 (M^+-1, 30.5), 248 (14.5), 112 (8.4), 111 (64.5). Anal. Calcd for $C_{20}H_{16}Cl_2N_8O_2$: C, 50.97; H, 3.42; N, 23.78. Found: C, 50.93; H, 3.47; N, 23.72%.

N,N'-(Ethane-1,2-diyl)bis(4-imino-8-methyl-7-phenyl-1,4-dihydropyrazolo[5,1-c]-1,2,4-triazine-3-carboxamide)(19). Yield (62%), mp 283 °C (DMF); IR (KBr) ν 3306 (NH), 3209 (NH), 1659 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.48 (s, 6H, $2CH_3$,), 3.59 (s, 4H, $2NCH_2$), 7.30 (m, 2H), 7.47 (m, 4H), 7.89 (d, 4H), 9.01 (s, 2H, D_2O-exchangeable 2NH), 9.12 (s, 2H, D_2O-exchangeable 2NH), 9.20 (s, 2H, D_2O-exchangeable 2NH). Anal. Calcd for $C_{28}H_{26}N_{12}O_2$: C, 59.78; H, 4.66; N, 29.88. Found: C, 59.72; H, 4.63; N, 29.83%.

Reaction of N,N'-(ethane-1,2-diyl)bis(cyanoacetamide) (1) with DMF-DMA.

A mixture of the compound **1** (1.94 g, 10 mmol) and *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) (2.66 ml, 20 mmol) in dry xylene (30 mL) was refluxed for 3 h, then left to cool to rt. The yellow precipitated product was filtered off, washed with petroleum ether and dried. Crystallization from EtOH/ DMF gave *N,N'*-(ethane-1,2-diyl)bis[2-cyano-3-(dimethylamino)acrylamide] (**20**) in 54 % yield,

mp 224 °C; IR (KBr) ν 3348 (NH), 2195 (C≡N), 1655 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.19 (s, 6H, $2CH_3$), 3.22 (s, 6H, $2CH_3$,), 3.33 (s, 4H, $2NCH_2$), 7.19 (s, 2H, 2CH), 7.68 (s, 2H, D_2O-exchangeable 2NH); ^{13}C NMR (DMSO-d_6) δ 37.90, 46.69, 69.90, 119.49, 155.86, 164.81. Anal. Calcd for $C_{14}H_{20}N_6O_2$: C, 55.25; H, 6.62; N, 27.61. Found: C, 55.20; H, 6.67; N, 27.57%.

Reaction of N,N'-(ethane-1,2-diyl)bis[2-cyano-3-(dimethylamino)acrylamide] (20) with hydrazine hydrate.

To a solution of the compound **20** (0.30 g, 1 mmol) in EtOH (20 mL), hydrazine hydrate (80%, 0.2 mL, 2 mmol) was added and the reaction mixture was refluxed for 4 h, then left to cool. The solid product so formed was filtered off, washed with EtOH and dried. Recrystallized from DMF afforded 3,3'-(ethane-1,2-diylbis(azanediyl)bis[1*H*-pyrazole-4-carbonitrile] (**23**), yield (66%), mp > 300 °C; IR (KBr) ν 3314 (NH), 2217 (C≡N) cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.35 (s, 4H, $2NCH_2$), 8.40 (s, 2H, 2CH), 10.2 (s, 2H, D_2O-exchangeable 2NH), 11.0 (s, 2H, D_2O-exchangeable 2NH). Anal. Calcd for $C_{10}H_{10}N_8$: C, 49.58; H, 4.16; N, 46.26. Found: C, 49.52; H, 4.20; N, 46.21%.

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