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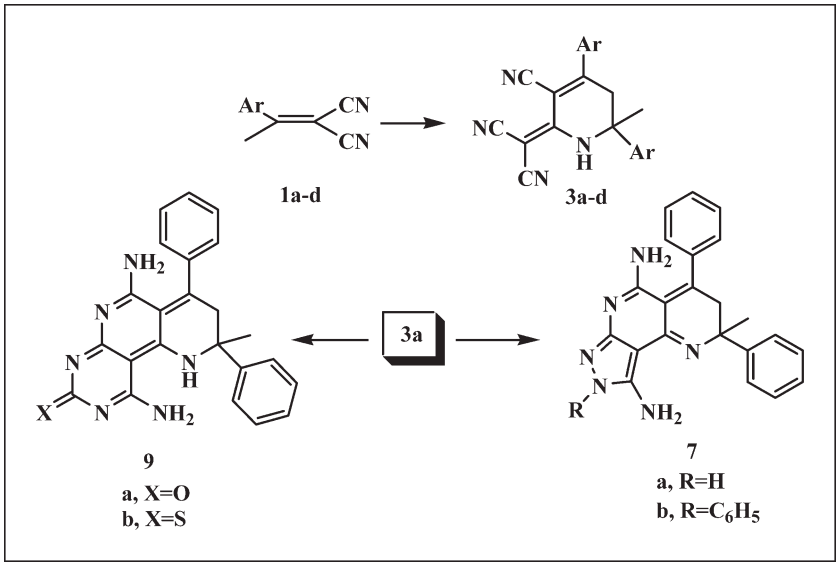

2-(1-Aryl-ethylidene)-malononitriles **1a-d** undergo self dimerization in ethanol catalyzed by sodium ethoxide to afford 2-[4,6-diaryl-3-cyano-6-methyl-5,6-dihydropyridin-2(1*H*)-ylidene]-malononitrile derivatives **3a-d,** respectively. The structure of the dimer was elucidated by X-ray crystallography and a plausible mechanism for its formation is depicted. Compound **3a** couples with arene diazonium salts **4a-d** to afford the hydrazo derivatives **5a-d**; and reacts with hydrazine hydrate and phenylhydrazine **6a,b** to afford the pyrazolo[3,4-h][1,6]naphthyridine derivatives**7a,b**; and with urea and thiourea **8a,b** to afford the pyrimido[4,5-h][1,6]naphthyridine derivatives **9a,b**, respectively.

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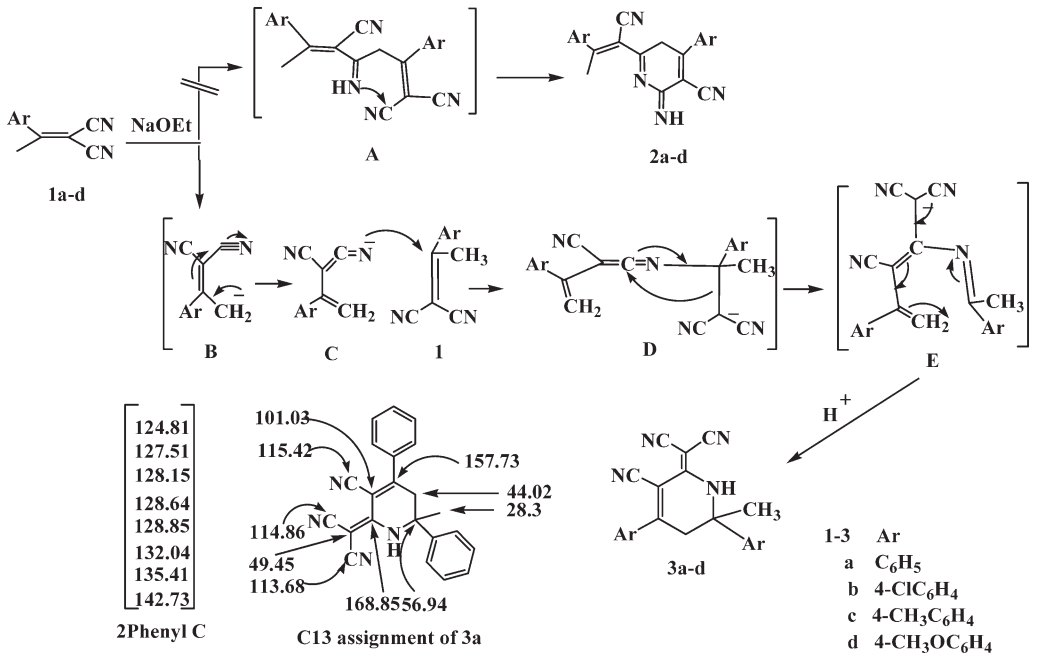
INTRODUCTION

Pyridines and pyrido-fused derivatives are important heterocyclic compounds that find many pharmaceutical and agrochemical applications [2–6]. In the last two decades, we have been involved in a program aiming to develop new simple routes for the synthesis of heterocyclic compounds of biological interest [7–18]. In the context of this program, some newly substituted pyridines and pyrido-fused heterocyclic derivatives were required for biological evaluation. 2-(1-Arylethylidene)-malononitrile derivatives **1a-d** seemed good candidates to fulfill this objective *via* their dimerization through the intermediate **A** to afford the pyridine-imine derivatives **2a-d** and then coupling of these expected pyridine derivatives (Scheme 1) with arene diazonium salts followed by cyclization of the products to afford pyrido[3,2-c]pyridazine derivatives.

RESULTS AND DISCUSSION

Thus 2-(1-phenyl-ethylidene)-malononitrile derivative **1a** (obtained from the condensation of acetophenone with malononitrile according to the literature method) [19] was refluxed in ethanol catalyzed by sodium ethoxide and we could isolate an analytically pure product with mp 202°C and in quantitative yield. The mass spectrum of this obtained product showed a molecular ion peak at $m/z = 336$; which points out to a dimer of **1a**. Theoretically different possible structures can be assumed for this dimmer, however, based on the spectral data it was thought that we have obtained the pyridine-imine derivative **2a** (Scheme 1). The ^{1}H NMR spectrum of this product revealed signals at δ 1.74 (s, 3H,) assignable to one methyl group, 3.33 (d, 1H; $J = 18.6$ Hz), 3.75 (d, 1H; $J = 18.6$ Hz) assignable to two chemically nonequivalent protons of a methylene group and

Scheme 1. Preparation of compounds **3a-d**.



aromatic multiplet (10H) at 7.29–7.56 beside an exchangeable singlet (1H) at δ 8.55 ppm assignable to NH. These ^{1}H NMR data seemed applicable to a structure like **2a**. However the ^{13}C NMR spectrum of this reaction product revealed 18 signals at δ_C = 28.3 (q); 44.02 (t); 49.45 (s), 56.94 (s); 101.03 (s); 113.68 (s); 114.86 (s); 115.42 (s); [124.81 (d), 127.51 (d), 128.15 (d), 128.64 (d), 128.85 (d), 132.04 (d), 135.41 (s), 142.73 (s) phenyl carbons], 157.73 (s), 168.85 (s). (*cf.* Scheme 1 and Experimental section). These ^{13}C NMR values are not completely applicable to structure **2a**.

Furthermore, when this product was allowed to couple with the diazotized aromatic amines **4a-d** (aniline, *p*-chloroaniline, *p*-toluidine and *p*-anisidine) it afforded highly colored hydrazo derivatives analyzed correctly as derivatives of **2a**; however, trials to cyclize these hydrazo derivatives into the expected pyrido[3,2-c]pyridazine derivatives failed under the different conditions reported to effect such cyclizations[14,20]. This behavior led us to the fact that the hydrazo group is not in the vicinity of the cyano group and the structure is not **2a**. Thus it was mandatory to have an X-ray crystallographic picture of this compound. Fortunately, we could obtain this X-ray [21,22] (Fig. 1). It shows clearly that the cyano groups are located far away from the hydrazo groups attached to the active methylene and that the methyl and one phenyl group are attached to the same carbon (C-2). The X-ray picture shows also that the structure appears with one molecule of ethyl acetate; the crystallization solvent. Thus structure **3a** was unambiguously established for this product (Scheme 1). All spectral and analytical data are now completely applicable to this structure and also those of the hydrazo derivatives **5a-d** (*cf.* Schemes 1 and 2 and the Experimental section).

It is assumed that the ethoxide anion abstracts one proton from **1** to afford the anion **B**, which is electronically rearranged to the keteneimine **C**. This latter attacks another molecule of **1** at the C=C to afford **D**, which undergoes rearrangement with migration of the malonyl anion to the C=N to afford **E**. Such rearrangement in the keteneimine series are known in the literature [23]. The intermediate **E** undergoes cyclization and regains its lost proton to afford the final isolable product **3a**. The cyclization of alkylidenemalononitriles under Michael reaction conditions is reported also to afford pyridine derivatives [24].

The ethylidenemalononitrile derivatives **1b-d** (obtained from the condensation of the corresponding aryl methyl ketone with malononitrile according to literature method) [19] followed the same pathway under the same reaction conditions, and we could obtain the pyridine derivatives **3b-d**, respectively (Scheme 1). All analytical and spectral data are in complete agreement with their proposed structures (*cf.* Experimental).

It is worth to mention that this dimerization of **1** to give **3** could be catalyzed by aqueous NaOH in ethanol, aqueous Na_2CO_3 in ethanol, or NaOEt in ethanol. All these led to the same product in each case however the maximum yields and the cleanest products were achieved with NaOEt.

Although the obtained products are not the same which we expected, however these products were found

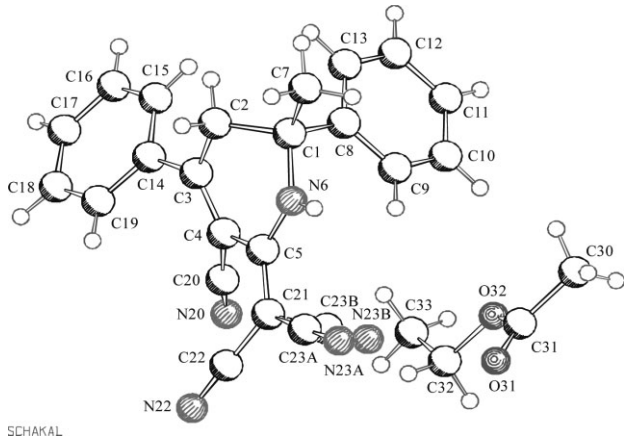


Figure 1. X-ray crystallographic structure of compound **3a** [21,22].

suitable also to fulfill our objective. Recently pyrazoles were found to be potentially biologically active compounds [25–27]. Also naphthyridine derivatives represent an important class of heterocyclic compounds due to their marked wide range of biological activities, such as anticonvulsant, antibacterial, anticancer, insecticidal, and fungicidal effects [28–31]. Thus, in continuation with our interest in naphthyridine synthesis [32], we describe here the synthesis of some novel fused naphthyridine derivatives.

Thus compound **3a** reacts with hydrazine hydrate and phenyl hydrazine **6a,b** to afford the pyrazolo-naphthyridine derivatives **7a,b**, respectively.

Compound **3a** reacts also with the urea derivatives **8a,b** to afford the pyrimido-naphthyridine derivatives **9a,b**, respectively. It is apparent that the hydrazines and ureas undergo cycloaddition to the two gem cyano groups with the aid of the labile hydrogen of the pyridine NH followed by further addition of the resulting NH_2 to the 5-cyano group.

The IR spectra of compounds **7a,b** and **9a,b** are all void of any cyano absorption bands at the region of υ_{max}= 1980–2240 cm^{-1}. All spectral and analytical data are in complete agreement with these structures (*cf.* Experimental).

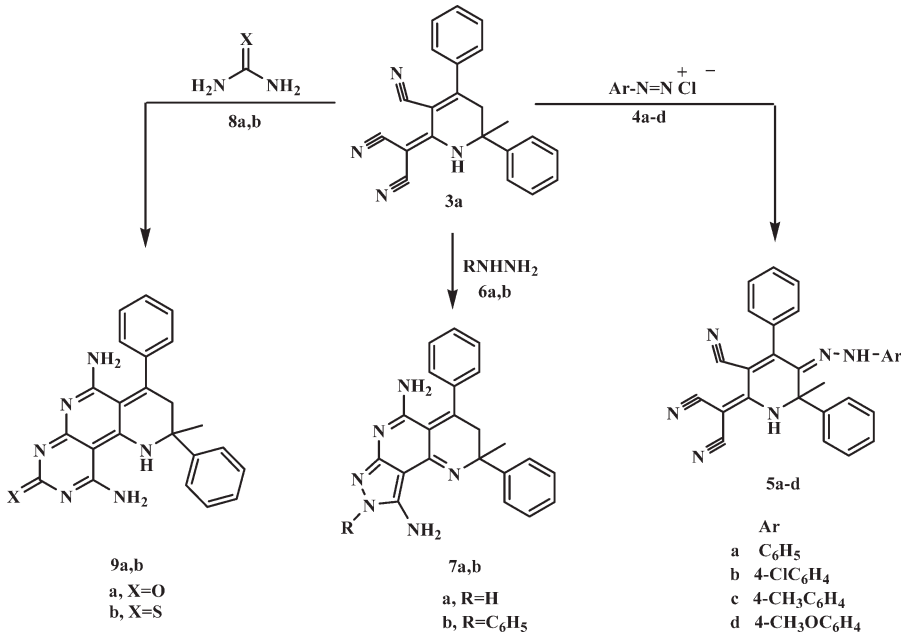
CONCLUSION

We could prepare some novel heterocyclic derivatives of biological interest. All the reactions were carried out using simple and clean eco-friendly synthetic methods. No heavy metals or hazardous solvents are involved: just ethanol, DMF, or water as solvents, sodium salts are used as a catalyst.

EXPERIMENTAL

Melting points were determined on an electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ (ppm) values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 eV). Elemental analyses were carried out by the Microanalytical Center at Cairo University. The X-ray crystallography was carried out in the Institute of Organic Chemistry, Technical University of Dresden, Germany.

Scheme 2. Preparation of compounds **5**, **7**, and **9**.



The dimerization of 2-(1-aryl-ethylidene)-malononitrile derivatives 1a-d: [Preparation of 3a-d]. To a solution of each of **1a-d** (10 mmol) in 15 mL of absolute ethanol was added 2 mL of saturated sodium ethoxide solution (obtained by dissolving 0.1 g of sodium metal in the least amount of absolute ethanol). The reaction mixture was refluxed on a water bath for 1 h, then left to cool to room temperature and poured on ice cold water and acidified with drops of conc. HCl till just neutral. The precipitated solids were collected by filtration, washed with water, dried, and recrystallized to afford **3a-d,** respectively.

2-(3-Cyano-6-methyl-4,6-diphenyl-5,6-dihydropyridin-2(1H)-ylidene)-malononitrile 3a. Yellow crystals; yield (3.26 g; 96%), mp: 201–203°C (EtOH/DMF). IR: υ_{max} (cm^{-1}) 3445 & 3260 (NH), 2213, 2214, 2217 (3CN). MS, m/z = 336 [M^+]; δ_H: 1.74 (s, 3H, CH_3), 3.33 (d, 1H; J = 18.6 Hz), 3.75 (d, 1H; J = 18.6 Hz), 7.29–7.56 (m, 10H, 2Ph), 8.55 (s, 1H D_2O exchangeable, NH). δ_C = 28.3 (q); 44.02 (t); 49.45 (s), 56.94 (s); 101.03 (s); 113.68 (s); 114.86 (s); 115.42 (s); [124.81 (d), 127.51 (d), 128.15 (d), 128.64 (d), 128.85 (d), 132.04 (d), 135.41 (s), 142.73 (s) phenyl carbons], 157.73 (s), 168.85 (s).

X-ray crystallographic data [21,22]: Yellow crystals, $C_{22}H_{16}N_4{*}C_4H_8O_2$ (M_r = 424.49 g mol^{-1}), monoclinic, space group $P2_1/n$ (No. 14), a [Å] = 10.637(2), b [Å] = 19.286(4), c[Å] = 12.072(2), α[°] = 90.00, β[°] = 113.27(3), γ[°] = 90.00; V[Å^3] = 2282.8(9), Z = 4, D_{calc} = 1.235 g cm^{-3}, $F(000)$ = 896 e, $\mu(M_o\ K_\alpha)$ = 0.080 cm^{-1}; the final difference Fourier ρ = 0.45 (−0.39) e Å^{-3}.crystal size = 0.35 mm × 0.13 mm × 0.07 mm. Max. resolution [sin θ/λ_{max}] = 0.61 Å^{-1}/ 99.8%. Data were collected using a Bruker Nonius area detector at T[°C]=−75(2), with graphite monochromator with Mo Kα radiation (λ = 0.71073 Å) using the CCD data collection and SADABS absorption correction method; min. 85.1%; max 99.4%. Total No. of reflections are 57431, No. of independent reflections 4201 were counted with observed reflections 2726. No. of refined parameters 312/10 restrains. R_{av}= 0.099. The final R= 0.067 and $R_W{}^2$ = 0.177 with error of fit 1.048.

Anal. Calcd. for $C_{22}H_{16}N_4$ (336.39): C 78.55, H 4.79, N 16.66. Found: C 78.50, H 4.90, N 16.80.

2-[3-Cyano-4,6-bis-(4-chlorophenyl)-6-methyl-5,6-dihydropyridin-2(1H)-ylidene]-malononitrile 3b. Deep green powder; yield (3.93 g; 97%), mp: 158–160°C (EtOH). IR: υ_{max} (cm^{-1}) 3442 & 3230 (NH), 2211–2117 (3CN). δ_H: 1.72 (s, 3H, CH_3), 3.38 (d, 1H; J = 18.5 Hz), 3.74 (d, 1H; J = 18.5 Hz), 7.33–7.63 (m, 8H, Ar. H), 9.71 (s, 1H D_2O exchangeable, NH).

Anal. Calcd. for $C_{22}H_{14}\ Cl_2N_4$ (405.28): C 65.20, H 3.48, Cl 17.50, N 13.82. Found: C 65.35, H 3.55, Cl 17.80, N 13.90.

2-[3-Cyano-4,6-bis-(4-methylphenyl)-6-methyl-5,6-dihydropyridin-2(1H)-ylidene]- malononitrile 3c. Brown powder; yield (3.20 g; 88%), mp: 169–172°C (EtOH). IR: υ_{max} (cm^{-1}) 3442 & 3230 (NH), 2218–2224 (3CN). MS, m/z= 364 [M^+]; δ_H: 1.74 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.26 (d, 1H, J = 18.6 Hz), 3.36 (d, 1H; J = 18 Hz), 7.05–7.42 (m, 8H, Ar. H), 9.65 (s, 1H D_2O exchangeable, NH).

Anal. Calcd. for $C_{24}H_{20}N_4$ (364.44): C 79.10, H 5.53, N 15.37. Found C 79.25, H 5.55, N 15.60.

2-[3-Cyano-4,6-bis-(4-methoxyphenyl)-6-methyl-5,6-dihydropyridin-2(1H)-ylidene]-malononitrile 3d. Coffee brown powder; yield (3.72 g; 94%), mp: 181–183°C (EtOH). IR: υ_{max} (cm^{-1}) 3443 & 3232 (NH), 2215–2226 (3CN). MS, m/z= 397 [M^++1]; δ_H: 1.70 (s, 3H, CH_3), 3.29 (d, 1H, J = 18.6 Hz), 3.37 (s, 1H, J = 18.6 Hz), 3.65 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 7.24–7.44 (m, 8H, Ar. H), 9.66 (s, 1H D_2O exchangeable, NH).

Anal. Calcd. for $C_{24}H_{20}N_4O_2$ (396.44): C 72.71, H 5.08, N 14.13. Found: C 72.75, H 5.15, N 14.20.

Azo coupling of 3a with arene diazonium chloride derivatives 4a-d. Arene diazonium salts **4a-d** (0.01 mol) were freshly prepared by adding a solution of 0.01 mol of sodium nitrite in 5 mL H_2O to a cold solution of the hydrochloride (0.01 mol) of the respective aryl amine: (aniline, *p*-chloroaniline, *p*-toluidine, or *p*-anisidine, respectively, in 5 mL conc. HCl) with stirring. The resulting solutions of the aryl diazonium salts were added to a cold solution of **3a** (0.01 mol), in ethanol (35 mL) containing sodium acetate (2 g). The reaction mixture was stirred at room temperature for 1 h in each case and the solid products, so formed, were collected by filtration and recrystallized from ethanol/DMF.

2-(3-Cyano-6-methyl-4,6-diphenyl-5-(2-phenylhydrazono)-5,6-dihydropyridin-2(1H)-ylidene)-malononitrile 5a. Reddish brown powder; yield (3.78 g; 85 %), mp: 195–197°C (EtOH/DMF). IR: υ_{max} (cm^{-1}) 3372, 3307 and 3229 (NH), 2207–2215 (CN). MS, m/z = 441 [M^++1]; δ_H: 1.94 (s, 3H, CH_3), 6.89–7.54 (m, 15H, Ar. H), 9.51 (s, 1H D_2O exchangeable, NH), 10.02 (s, 1H, D_2O exchangeable, hydrazone NH).

Anal. Calcd. for $C_{28}H_{20}N_6$ (440.50): C 76.35, H 4.58, N 19.08. Found: C 76.40, H 4.55, N 19.05.

2-(5-(2-(4-Chlorophenyl)-hydrazono)-3-cyano-6-methyl-4,6-diphenyl-5,6-dihydropyridin-2(1H)-ylidene)-malononitrile 5b. Dark red crystals; yield (4 g; 86%), mp: 234–235°C (EtOH/ DMF). IR: υ_{max} (cm^{-1}) 3338, 3290, and 3231 (NH), 2208–2217 (CN). δ_H: 1.98 (s, 3H, CH_3), 6.49–7.72 (m, 14H, Ar. H), 9.63 (s, 1H D_2O exchangeable, NH), 10.07 (s, 1H, D_2O exchangeable, hydrazone NH).

Anal. Calcd. for $C_{28}H_{19}ClN_6$ (474.94): C 70.81, H 4.03, Cl 7.46, N 17.69. Found: C 70.85, H 4.13, Cl 7.56, N 17.60.

2-[3-Cyano-6-methyl-4,6-diphenyl-5-(2-(4-tolyl-hydrazono))-5,6-dihydropyridin-2(1H)-ylidene]-malononitrile 5c. Brown crystals; yield (3.77 g; 83%), mp: 225–227°C (EtOH/DMF). IR: υ_{max} (cm^{-1}) 3336, 3291, and 3233 (NH), 2205–2216 (CN). δ_H: 1.93 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.86–7.73 (m, 14H, Ar. H), 9.65 (s, 1H D_2O exchangeable, NH), 10.05 (s, 1H, D_2O exchangeable, hydrazone NH).

Anal. Calcd. for $C_{29}H_{22}N_6$ (454.53): C 76.63, H 4.88, N 18.49. Found: C 76.65, H 4.90, N 18.55.

2-[3-Cyano-6-methyl-4,6-diphenyl-5-(2-(4-methoxyphenyl)-hydrazono)-5,6-dihydropyridin-2(1H)-ylidene]-malononitrile 5d. Light brown crystals; yield (3.99 g; 85%), mp: 237–239°C (EtOH/DMF). IR: υ_{max} (cm^{-1}) 3335, 3292, and 3232 (NH), 2208 & 2219 (CN). δ_H: 1.89 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 6.95–7.50 (m, 14H, Ar. H), 9.66 (s, 1H D_2O exchangeable, NH), 10.02 (s, 1H, D_2O exchangeable, hydrazone NH).

Anal. Calcd. for $C_{29}H_{22}N_6O$ (470.52): C 74.03, H 4.71, N 17.86. Found: C 74.10, H 4.76, N 17.92.

The reaction of 3a with hydrazine hydrate and phenyl hydrazine 6a,b. To a solution of **3a** (0.01 mol) in ethanol (20 mL) was added 0.01 mol of either hydrazine hydrate **6a** or phenyl hydrazine **6b**. The reaction mixture was refluxed for 2h in each case, left overnight. The reaction mixture was then poured on ice cold water and acidified with dil. HCl till just neutral. The precipitated solids were filtered off and recrystallized from ethanol.

2-Methyl-2,4-diphenyl-3,8-dihydro-2H-pyrazolo[3,4-h][1,6] naphthyridine-5,9-diamine 7a. Yellow crystals; yield (2.9 g; 80%), mp: 120–122°C (EtOH). IR: υ_{max} (cm^{-1}) 3330, 3286–3231 (NH & NH_2). MS, m/z = 368 [M^+]; δ_H: 1.89 (s, 3H, CH_3), 3.32 (d, 1H; J = 18.65 Hz), 3.45 (d, 1H; J = 18.65 Hz), 6.60 (br. s, 4H, $2NH_2$), 7.15–7.56 (m, 10H, 2Ph), 11.65 (s, 1H D_2O exchangeable, NH).

Anal. Calcd. for $C_{22}H_{20}N_6$ (368.43): C 71.72, H 5.47, N 22.81. Found: C 71.75, H 5.52, N 22.87.

2-Methyl-2,4,8-triphenyl-3,8-dihydro-2H-pyrazolo[3,4-h][1,6] naphthyridine-5,9-diamine 7b. Yellow crystals; yield (3.46 g; 78%), mp: 128–129°C (EtOH). IR: υ_{max} (cm^{-1}) 3333, 3285 (NH_2). MS, m/z = 444 [M^+]; δ_H: 1.76 (s, 3H, CH_3), 3.22 (d, 1H; J = 18.65 Hz), 3.46 (d, 1H; J = 18.65 Hz), 6.56 (br. s, 4H, $2NH_2$), 6.75–7.55 (m, 15H, 3Ph).

Anal. Calcd. for $C_{28}H_{24}N_6$ (444.53): C 75.65, H 5.44, N 18.91. Found: C 75.68, H 5.50, N 19.03.

The reaction of 3a with urea and thiourea 8a,b. To a solution of **3a** (0.01 mol) in ethanol (20 mL) was added 0.01 mol of either urea **8a** or thiourea **8b** followed by few drops of triethylamine. The reaction mixture was refluxed for 2 h in each case and then left to cool overnight. The precipitated solids were collected by filtration and recrystallized from ethanol/DMF.

5,10-Diamino-2-methyl-2,4-diphenyl-2,3-dihydropyrimido[4,5-h][1,6]naphthyridin-8(1H)-one 9a. Yellow crystals; yield (3 g; 78%), mp: 147–149°C (EtOH/DMF). IR: υ_{max} (cm^{-1}) 3332, 3289, and 3230 (NH & NH_2), 1667 (CO). MS, m/z = 395 [M^+-1]. δ_H: 1.74 (s, 3H, CH_3), 3.32 (d, 1H; J = 18.3 Hz), 3.75 (d, 1H; J = 18.3 Hz), 7.29–7.57 (m, 14H, 2Ph+$2NH_2$), 9.71 (s, 1H D_2O exchangeable, NH).

Anal. Calcd. for $C_{23}H_{20}N_6O$ (396.44): C 69.68, H 5.08, N 21.20. Found: C 69.65, H 5.10, N 21.28.

5,10-Diamino-2-methyl-2,4-diphenyl-2,3-dihydropyrimido[4,5-h][1,6]naphthyridine-8(1H)-thione 9b. Dark yellow crystals; yield (3.2 g; 78%), mp: 160–162°C (EtOH/DMF). IR: υ_{max} (cm^{-1}) 3335, 3291, and 3232 (NH & NH_2). MS, m/z = 412 [M^+]. δ_H: 1.75 (s, 3H, CH_3), 3.31 (d, 1H; J = 18.32 Hz), 3.64 (d, 1H; J = 18.32 Hz), 7.28–7.58 (m, 14H, 2Ph+$2NH_2$), 9.66 (s, 1H D_2O exchangeable, NH).

Anal. Calcd. for $C_{23}H_{20}N_6S$ (412.51): C 66.97, H 4.89, N 20.37, S 7.77. Found: C 67.05, H 4.95, N 20.42, S 7.92.

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[21] Crystallographic data (excluding structure factors) for the structure **2a** reported in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-744590. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 441223/336–033; e-mail: deposit@ccdc.cam.ac.uk.

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