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Synthesis of some novel pyridine and naphthyridine derivatives

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ABSTRACT

2-[1-(Furan- or thiophen-2-yl)ethylidene)malononitriles (**1a**,**b**) undergo dimerization reactions in ethanol catalyzed by sodium ethoxide to afford 2-[4,6-di(furan- or thiophen-2-yl)-3-cyano-6-methyl-5,6-dihydropyridin-2(1*H*)-ylidene]malononitrile derivatives (**2a**,**b**), respectively. Compounds **2a** and **2b** couple with arene diazonium salts (**3a**-**c**) to afford the hydrazo derivatives (**4a**-**f**). They react also with hydrazines (**5a**,**b**) to afford the pyrazolo[3,4-*H*][1,6]naphthyridine derivatives (**6a**-**d**) and with urea derivatives (**7a**-**c**) to afford the pyrimido[4,5-*H*][1,6]naphthyridine derivatives (**8a**-**f**), respectively.

1. Introduction

Pyridines and pyrido-fused derivatives have attracted the attention of researchers due to their importance in pharmaceutical and agrochemical applications [1-8]. Naphthyridine derivatives are also interesting for their chemical reactivity, biological properties, and applications as they exhibit a wide spectrum of biological activity such as bactericidal, fungicidal, and carcenostatic [9-15]. They are also interesting ligands of the Werner-type σ-complexes with metal central atoms as well as EDA π-complexes [16]. Recently pyrazole derivatives were found to be potentially biologically active compounds [17-19].

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 [20-29]. In the context of this program we have recently reported novel syntheses of some naphthyridine derivatives [30,31]. In our previous work [31], we have reported that aryl ethylidene malononitrile derivatives undergo dimerization to afford 2-[4,6-diaryl-3-cyano-6-methyl-5,6-dihydropyridin-2(1*H*)-yli dene]malononitrile derivatives; the structure of which was elucidated by X-ray crystallography. We could also obtain some novel naphthyridine and fused naphthyridine derivatives from these dimers. It seemed interesting to see if the 2-furyl and 2-thienyl ethylidene malononitriles (**1a,b**) will undergo a similar dimerization and to explore the synthetic potential of the resulting pyridine derivatives (dimers) for the synthesis of some new naphthyridine derivatives carrying the 2-furyl or the 2-thienyl moieties, required for biological evaluation studies (Scheme 1).

2. 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.

2.1. The dimerization of 2-(1-aryl-ethylidene)malononitrile derivatives (1a,b), preparation of 2a,b

To a solution of each of **1a,b** (10 mmol) in absolute ethanol (15 mL) was added saturated sodium ethoxide solution (2 mL) (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 until just neutral. The precipitated solids were collected by filtration, washed with water, dried and recrystallized to afford **2a,b**.

2.1.1. 2-(3-Cyano-4,6-difuran-2-yl-6-methyl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (2a)

Color: Coffee brown powder. Yield: 2.46 g; 78 %. M.p.: 234-235 °C. IR (ν_{max}, cm^{-1}): 3335, 3265 (NH), 2200, 2216 (CN). MS (*m/z*): 316 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.72 (s, 3H, CH_3), 3.24 (d, 1H; *J*=17.1 Hz), 3.72 (d, 1H, *J*=17.1 Hz), 6.23-8.29 (m, 6H, furyl-H), 9.82 (s, 1H, D_2O exchangeable, NH). ^{13}C-NMR (δ, ppm): 27.35 (q), 45.92 (t), 51.54 (s), 54.17 (s), 104.81 (d), 105.93 (s), 110.31 (d), 111.75 (d), 112.64 (d), 113.78 (s),

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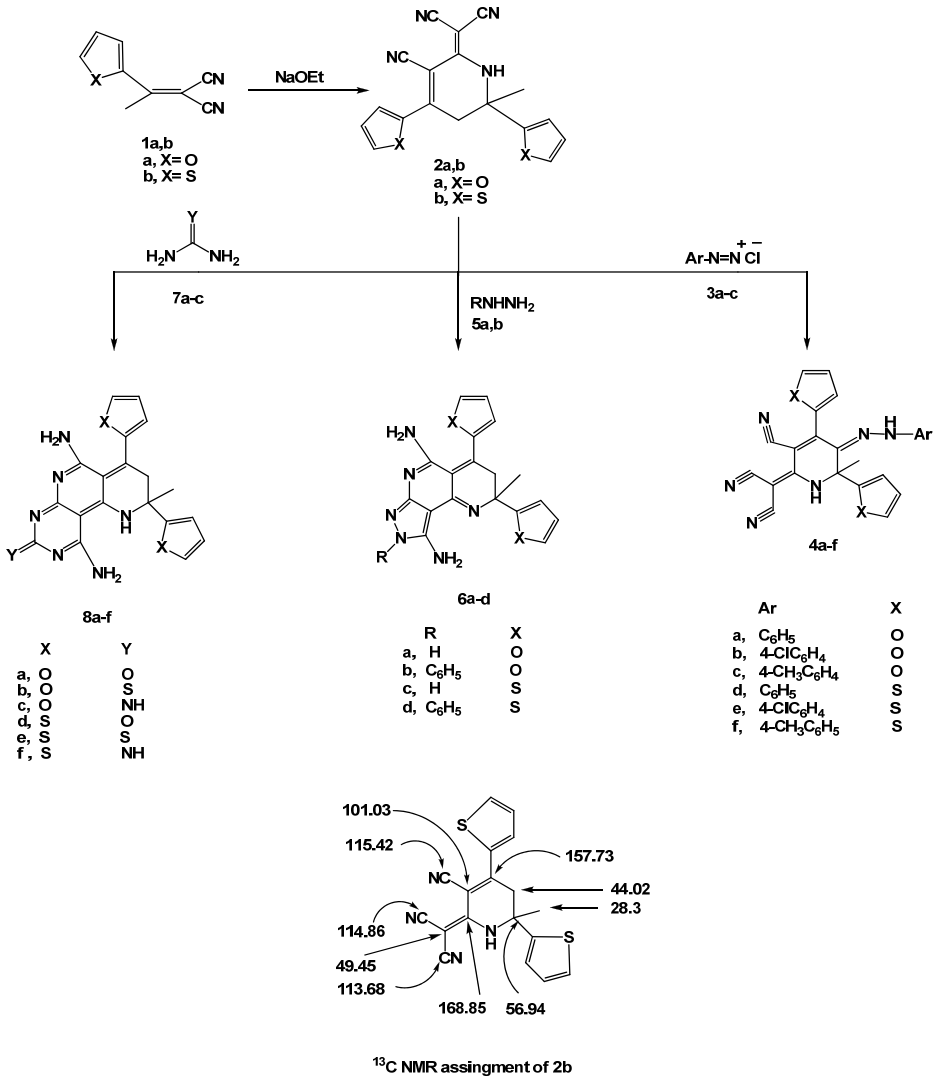

Scheme 1

114.85 (s), 116.52 (s), 140.65 (d), 145.14 (d), 155.41 (s), 157.73 (s), 157.76 (s), 186.35 (s). Anal. Calcd. for $C_{18}H_{12}N_4O_2$: C, 68.35; H, 3.82; N, 17.71. Found: C, 68.30; H, 3.87; N, 17.85.

2.1.2. 2-(3-Cyano-6-methyl-4,6-dithiophen-2-yl-5,6-dihydro pyridin-2(1H)-ylidene)malononitrile (2b)

Color: Coffee brown powder. Yield: 2.96 g; 85 %. M.p.: 221-223 ^{0}C. IR (ν_{max}, cm^{-1}): 3323, 3097 (NH), 2198, 2205 (CN). MS (*m/z*): 348 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.81 (s, 3H, CH_3), 3.44 (d, 1H, *J*=17.7 Hz), 3.93 (d, 1H; *J*=17.7 Hz), 6.93-8.25 (m, 6H, Thienyl H), 9.86 (s, 1H, D_2O exchangeable, NH). ^{13}C-NMR (δ, ppm): 28.3 (q), 44.02 (t), 49.45 (s), 56.94 (s), 101.03 (s), 113.68 (s), 114.86 (s), 115.42 (s), 121.59 (d), 124.23 (d), 124.83 (d), 125.68 (d), 126.42 (d), 127.86 (d), 129.42 (s), 136.65 (s), 157.73 (s), 168.55 (s). Anal. Calcd. for $C_{18}H_{12}N_4S_2$: C, 62.05; H, 3.47; N, 16.08; S, 18.40. Found: C, 62.10; H, 3.54; N, 16.20; S, 18.55.

2.2. Azo coupling of 2a,b with arene diazonium chloride derivatives (3a-c)

Arene diazonium salts **3a-c** (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 or *p*-toluidine respectively, in 5 mL conc. HCl) with stirring. The resulting solutions of the aryl diazonium salts were added to a cold solution of **2a** or **2b** (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 to give **4a-f**.

2.2.1. 2-[3-Cyano-4,6-difuran-2-yl-6-methyl-5-(phenylhydra zono)-5,6-dihydro-1H-pyridin-2-ylidene]malononitrile (4a)

Color: Reddish brown powder. Yield: 3.73 g; 65 %. M.p.:224-225 ^{0}C. IR (ν_{max}, cm^{-1}): 3391, 3264 and 3122 (NH), 2207-2215 (CN). MS (*m/z*): 420 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.72 (s, 3H, CH_3), 6.21-8.26 (m, 11H, Ar. H), 9.54 (s, 1H, D_2O exchangeable, NH), 10.02 (s, 1H, D_2O exchangeable, hydrazone NH). ^{13}C-NMR (δ, ppm): 24.47 (q), 46.09 (s), 54.15 (s), 104.95 (d), 110.46 (d), 111.85 (d), 112.74 (d), 113.56 (s), 115.05 (s), 115.17 (d), 115.63 (s), 118.56 (d), 129.38 (d), 140.38 (d), 144.86 (d), 149.35 (s), 145.94 (s), 155.34 (s), 155.63 (s), 156.99 (s), 186.21 (s). Anal. Calcd. for $C_{24}H_{16}N_6O_2$: C, 68.56; H, 3.84; N, 19.99. Found: C, 68.60; H, 3.87; N, 20.18.

2.2.2. 2-{5-[(4-Chlorophenyl)-hydrazono]-3-cyano-4,6-difuran-2-yl-6-methyl-5,6-dihydro-1H-pyridin-2-ylidene} malononitrile (4b)

Color: Yellowish brown crystals. Yield: 2.63 g; 58 %. M.p.: 238-239 ^{0}C. IR ($\nu_{max,}$ cm^{-1}): 3338, 3290 and 3231 (NH), 2208-2217 (CN). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.98 (s, 3H, CH_3), 6.22-8.26 (m, 10H, Ar. H), 9.83 (s, 1H, D_2O exchangeable, NH), 10.07 (s, 1H, D_2O exchangeable, hydrazone NH). Anal. Calcd. for $C_{24}H_{15}ClN_6O_2$: C, 63.37; H, 3.32; N, 18.48. Found: C, 63.40; H, 3.38; N, 18.65.

2.2.3. 2-[3-Cyano-4,6-difuran-2-yl-6-methyl-5-(p-tolylhydrazono)-5,6-dihydro-1H-pyridin-2-ylidene]malononitrile (4c)

Color: Brown crystals. Yield: 2.86 g; 66 %. M.p.: 225-227 ^{0}C. IR (ν_{max}, cm^{-1}): 3336, 3291 and 3233 (NH), 2208-2216 (CN). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.93 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.26-8.33 (m, 10H, Ar. H), 9.65 (s, 1H, D_2O exchangeable, NH), 10.05 (s, 1H, D_2O exchangeable, hydrazone NH). Anal. Calcd. for $C_{25}H_{18}N_6O_2$: C, 69.11; H, 4.18; N, 19.34. Found: C, 69.25; H, 4.30; N, 19.54.

2.2.4. 2-[3-Cyano-6-methyl-5-(phenylhydrazono)-4,6-dithiophen-2-yl-5,6-dihydro-1H-pyridin-2-ylidene]malononitrile (4d)

Color: Reddish brown powder. Yield: 3.84 g; 85 %. M.p.: 229-231 ^{0}C. IR (ν_{max}, cm^{-1}): 3372, 3307 and 3251 (NH), 2207-2215 (CN). MS (*m/z*): 452 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.81 (s, 3H, CH_3), 6.45-7.24 (m, 11H, Ar. H), 9.51 (s, 1H, D_2O exchangeable, NH), 10.04 (s, 1H, D_2O exchangeable, hydrazone NH). Anal. Calcd. for $C_{24}H_{16}N_6S_2$: C, 63.70; H, 3.56; N, 18.57; S, 14.17. Found: C, 63.76; H, 3.70; N, 18.80; S, 14.35.

2.2.5. 2-{5-[(4-Chlorophenyl)-hydrazono]-3-cyano-6-methyl-4,6-dithiophen-2-yl-5,6-dihydro-1H-pyridin-2-ylidene} malononitrile (4e)

Color: Dark yellow crystals. Yield: 3.75 g; 77 %. M.p.: 234-235 ^{0}C. IR (ν_{max}, cm^{-1}): 3338, 3290 and 3231 (NH), 2209-2217 (CN). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.85 (s, 3H, CH_3), 6.42-7.24 (m, 10H, Ar. H), 9.63 (s, 1H, D_2O exchangeable, NH), 10.07 (s, 1H, D_2O exchangeable, hydrazone NH). ^{13}C-NMR (δ, ppm): 24.15 (q), 47.93 (s), 54.18 (s), 113.65 (s), 114.95 (s), 115.68 (s), 116.55 (d), 123.43 (d), 123.78 (s), 125.05 (d), 126.54 (d), 126.44 (d), 127.68 (d), 129.74 (d), 130.37 (d), 136.48 (s), 139.46 (s), 144.83 (s), 149.42 (s), 155.65 (s), 186.36 (s). Anal. Calcd. for $C_{24}H_{15}ClN_6S_2$: C, 59.19; H, 3.10; Cl, 7.28; N, 17.26; S, 13.17. Found: C, 59.30; H, 3.25; Cl, 7.18; N, 17.06; S, 13.32.

2.2.6. 2-[3-Cyano-6-methyl-4,6-dithiophen-2-yl-5-(p-tolyl hydrazono)-5,6-dihydro-1H-pyridin-2-ylidene]malononitrile (4f)

Color: Brown crystals. Yield: 2.70 g; 58 %. M.p.: 240-242 ^{0}C. IR (ν_{max}, cm^{-1}): 3336, 3291 and 3233 (NH), 2208-2216 (CN). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.87 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 6.30-7.23 (m, 10H, Ar. H), 9.65 (s, 1H, D_2O exchangeable, NH), 10.05 (s, 1H, D_2O exchangeable, hydrazone NH). Anal. Calcd. for $C_{25}H_{18}N_6S_2$: C, 64.35; H, 3.89; N, 18.01; S, 13.74. Found: C, 64.15; H, 3.92; N, 18.20; S, 13.82.

2.3. The reaction of (2a,b) with hydrazine hydrate and phenyl hydrazine (5a,b), preparation of 6a-d

To a solution of **2a** or **2b** (0.01 mol) in ethanol (20 mL) was added 0.01 mol of either hydrazine hydrate **5a** or phenyl hydrazine **5b**. The reaction mixture was refluxed for 2 h in each case, left overnight. The reaction mixture was then poured on ice cold water and acidified with dil. HCl until just neutral. The precipitated solids were filtered off and recrystallized from ethanol/DMF to afford **6a-d**.

2.3.1. 2,4-Difuran-2-yl-2-methyl-2,8-dihydro-3H-pyrazolo [3,4-H][1,6]naphthyridine-5,9-diamine (6a)

Color: Red crystals. Yield: 1.9 g; 55 %. M.p.: 290-292 ^{0}C. IR (ν_{max}, cm^{-1}): 3330, 3286-3231 (NH & NH_2). MS (*m/z*): 348 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.84 (s, 3H, CH_3), 3.32 (d, 1H; J=18.65 Hz), 3.45 (d, 1H; J=18.65 Hz), 6.60 (br. s, 2H, NH_2), 6.05-7.66 (m, 8H, Ar.H+NH_2), 13.55 (s, 1H, D_2O exchangeable, pyrazole NH). ^{13}C-NMR (δ, ppm): 27.23 (q), 45.9 (t), 52.79 (s), 93.45 (s), 105.03 (d), 110.14 (d), 111.46 (d), 112.82 (d), 113.69 (s), 131.94 (s), 140.49 (d), 145.26 (d), 154.38 (s), 156.82 (s), 155.41 (s), 157.77 (s), 162.14 (s), 164.49 (s). Anal. Calcd. for $C_{18}H_{16}N_6O_2$: C, 62.06; H, 4.63; N, 24.12. Found: C, 62.25; H, 4.80; N, 24.30.

2.3.2. 2,4-Difuran-2-yl-2-methyl-8-phenyl-2,8-dihydro-3H-pyrazolo[3,4-H][1,6]naphthyridine-5,9-diamine (6b)

Color: Deep green crystals. Yield: 2.63 g; 62 %. M.p.: > 300 ^{0}C. IR (ν_{max}, cm^{-1}): 3333-3285 (NH_2). MS (*m/z*): 424 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.76 (s, 3H, CH_3), 3.22 (d, 1H; J=18.65 Hz), 3.46 (d, 1H; J=18.5 Hz), 6.56 (br. s, 2H, NH_2), 6.03-7.58 (m, 13H, Ar.H+NH_2). Anal. Calcd. for $C_{24}H_{20}N_6O_2$: C, 67.91; H, 4.75; N, 19.80. Found: C, 67.97; H, 4.80; N, 20.08.

2.3.3. 2-Methyl-2,4-dithiophen-2-yl-2,8-dihydro-3H-pyrazolo [3,4-H][1,6]naphthyridine-5,9-diamine (6c)

Color: Deep orange crystals. Yield: 2.47 g; 65 %. M.p.: 231-232 ^{0}C. IR (ν_{max}, cm^{-1}): 3330, 3286-3231 (NH & NH_2). MS (*m/z*): 380 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.67 (s, 3H, CH_3), 3.44 (d, 1H; *J*=17.7 Hz), 3.93 (d, 1H; *J*=17.7 Hz), 6.69-7.05 (m, 8H, 2 Thioph+NH_2), 8.25 (br. s, 2H, NH_2), 9.86 (s, 1H, D_2O exchangeable, pyrazole NH). ^{13}C-NMR (δ, ppm): 29.47 (q), 44.01 (t), 54.89 (s), 94.35 (s), 114.94 (s), 121.99 (d), 124.09 (d), 124.87 (d), 125.26 (d), 126.38 (d), 127.82 (d), 129.41 (s), 136.17 (s), 137.14 (s), 137.29 (s), 147.77 (s), 157.52 (s), 158.45 (s). Anal. Calcd. for $C_{18}H_{16}N_6S_2$: C, 56.82; H, 4.24; N, 22.09; S, 16.85. Found: C, 56.90; H, 4.30; N, 22.35; S, 17.00.

2.3.4. 2-Methyl-8-phenyl-2,4-dithiophen-2-yl-2,8-dihydro-3H-pyrazolo[3,4-H][1,6]naphthyridine-5,9-diamine (6d)

Color: Brownish orange crystals. Yield: 3.24 g; 71 %. M.p.: 238-240 ^{0}C. IR (ν_{max}, cm^{-1}): 3323-3079 (NH_2). MS (*m/z*): 456 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.67 (s, 3H, CH_3), 3.44 (d, 1H; *J*=17.65 Hz), 3.93 (d, 1H; *J*=17.65 Hz), 6.64-7.15 (m, 13H, Ar.H+NH_2), 8.28 (br. s, 2H, NH_2). Anal. Calcd. for $C_{24}H_{20}N_6S_2$: C, 63.13; H, 4.42; N, 18.41; S, 14.05. Found: C, 63.00; H, 4.22; N, 18.55; S, 14.25.

2.4. The reaction of (2ab) with urea derivatives (7a-c), preparation of 8a-f

To a solution of **2a** or **2b** (0.01 mol) in ethanol (20 mL) was added 0.01 mol of urea **7a**, thiourea **7b** or guanidine nitrate **7c** followed by few drops (or the molar equivalent in case of 7c) 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 to afford **8a-f**.

2.4.1. 4,9-Diamino-6,8-difuran-2-yl-6-methyl-5, 6-dihydro-7H-pyrimido[4,5-H][5,10]naphthyridine-2-one (8a)

Color: Brown crystals. Yield: 2.93 g; 78 %. M.p.: 273-274 ^{0}C. IR (ν_{max}, cm^{-1}): 3332, 3289 and 3230 (NH & NH_2), 1667 (CO). MS (*m/z*): 376 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.74 (s, 3H, CH_3), 3.32 (d, 1H; *J*=17.6 Hz), 3.75 (d, 1H; *J*=17.6 Hz), 6.05-7.45 (m, 10H, Ar.H+2NH_2), 9.71 (s, 1H, D_2O exchangeable, NH). ^{13}C-NMR (δ, ppm): 27.23 (q), 46.90 (t), 52.54 (s), 88.09 (s), 104.79 (d), 110.23 (d), 111.76 (d), 112.74 (d), 123.58 (s), 144.25 (s), 140.62 (d), 145.13 (d), 155.37 (s), 157.63 (s), 158.76 (s), 167.21 (s), 167.23 (s), 172.32 (s), 194.35 (s). Anal. Calcd. for $C_{19}H_{16}N_6O_3$: C, 60.63; H, 4.28; N, 22.33. Found: C, 60.65; H, 4.35; N, 22.03.

2.4.2. 4,9-Diamino-6,8-difuran-2-yl-6-methyl-5, 6-dihydro-7H-pyrimido[4,5-H][5,10]naphthyridine-2-thione (8b)

Color: Brown crystals. Yield: 3.68 g; 94 %. M.p.: 203-205 ^{0}C. IR (ν_{max}, cm^{-1}): 3335, 3291 and 3232 (NH & NH_2). MS (*m/z*): 392 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.75 (s, 3H, CH_3), 3.31 (d, 1H; *J*=17.32 Hz), 3.64 (d, 1H; *J*=17.32 Hz), 6.08-7.50 (m, 10H, Ar.H+2NH_2), 9.74 (s, 1H D_2O exchangeable, NH). Anal. Calcd. for $C_{19}H_{16}N_6O_2S$: C, 58.15; H, 4.11; N, 21.42; S, 8.17. Found: C, 58.05; H, 4.15; N, 21.55; S, 8.25.

2.4.3. 6,8-Difuran-2-yl-2-imino-6-methyl-5,6-dihydro-7H-pyrimido[4,5-H][5,10]naphthyridine-4,9-diamine (8c)

Color: Dark yellow crystals. Yield: 2.93 g; 78 %. M.p.: > 300 ^{0}C. IR (ν_{max}, cm^{-1}): 3435, 3321 and 3237 (NH & NH_2). MS (*m/z*): 375 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): (s, 3H, CH_3), 3.34 (d, 1H; *J*=17.30 Hz), 3.64 (d, 1H; *J*=17.30 Hz), 6.04-7.42 (m, 10H, Ar.H+2NH_2), 9.66 (s, 1H, D_2O exchangeable, NH), 9.89 (s, 1H, D_2O exchangeable, NH). ^{13}C-NMR (δ, ppm): 27.17 (q), 46.97 (t), 52.55 (s), 88.12 (s), 104.85 (d), 110.33 (d), 111.87 (d), 112.78 (d), 123.37 (s), 144.32 (s), 140.68 (d), 145.18 (d), 155.42 (s), 157.78 (s), 158.89 (s), 164.48 (s), 165.34 (s), 167.17 (s), 168.35 (s). Anal. Calcd. for $C_{19}H_{17}N_7O_2$: C, 60.79; H, 4.56; N, 26.12. Found: C, 60.86; H, 4.50; N, 26.32.

2.4.4. 4,9-Diamino-6-methyl-6,8-dithiophen-2-yl-5, 6-dihydro-7H-pyrimido[4,5-H][5,10]naphthyridine-2-one (8d)

Color: Greenish crystals. Yield: 3.92 g; 96 %. M.p.: 293-294 ^{0}C. IR (ν_{max}, cm^{-1}): 3335, 3292 and 3233 (NH & NH_2), 1665 (CO). MS (*m/z*): 408 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.76 (s, 3H, CH_3), 3.35 (d, 1H; J=17.62 Hz), 3.73 (d, 1H; J=17.62 Hz), 6.55-7.25 (m, 10H, Ar.H+2NH_2), 9.73 (s, 1H, D_2O exchangeable, NH). Anal. Calcd. for $C_{19}H_{16}N_6OS_2$: C, 55.86; H, 3.95; N, 20.57; S, 15.70. Found: C, 55.89; H, 4.05; N, 20.76; S, 15.80.

2.4.5. 4,9-Diamino-6-methyl-6,8-dithiophen-2-yl-5, 6-dihydro-7H-pyrimido[4,5-H][5,10]naphthyridine-2-thione (8e)

Color: Yellowish brown crystals. Yield: 3.99 g; 94 %. M.p.: 233-235 ^{0}C. IR (ν_{max}, cm^{-1}): 3470, 3372 and 3101 (NH & NH_2). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.81 (s, 3H, CH_3), 3.34 (d, 1H; *J*=17.45 Hz), 3.68 (d, 1H; *J*=17.45 Hz), 5.52 (s, 2H, D_2O exch., NH_2), 6.94-8.25 (m, 8H, Ar.H + NH_2), 9.85 (s, 1H, D_2O exchangeable, NH). ^{13}C-NMR (δ, ppm): 29.35 (q), 52.01 (t), 54.4 (s), 91.24 (s), 134.94 (s), 120.56 (s), 123.4 (d), 125.07 (d), 126.4 (d), 126.55 (d), 127.78 (d), 129.91 (d), 136.19 (s), 137.3 (s), 148.98 (s), 159.28 (s), 181.01 (s). Anal. Calcd. for $C_{19}H_{16}N_6S_3$: C, 53.75; H, 3.80; N, 19.79; S, 22.66. Found: C, 53.82; H, 3.85; N, 19.90; S, 22.60.

2.4.6. 6,8-Dithiophen-2-yl-2-imino-6-methyl-5,6-dihydro-7H-pyrimido[4,5-H][5,10]naphthyridine-4,9-diamine (8f)

Color: Yellowish brown crystals. Yield: 3.6 g; 89 %. M.p.: > 300 ^{0}C. IR (ν_{max}, cm^{-1}): 3432, 3327 and 3242 (NH & NH_2). MS (*m/z*): 407 [M$^+$]. ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.75 (s, 3H, CH_3), 3.36 (d, 1H; *J*=17.42 Hz), 3.74 (d, 1H; *J*=17.42 Hz), 6.58-7.25 (m, 10H, Ar.H+2NH_2), 9.78 (s, 1H, D_2O exchangeable, NH), 9.92 (s, 1H, D_2O exchangeable, NH). Anal. Calcd. for $C_{19}H_{17}N_7S_2$: C, 56.00; H, 4.20; N, 24.06; S, 15.74. Found: C, 56.05; H, 4.28; N, 24.00; S, 15.95.

3. Results and discussion

The 2-(1-fur-2-yl- or thien-2-yl-ethylidene)malononitriles derivatives (**1a**,**b**) (obtained from the condensation of 2-acetylfuran and 2-acetylthiophene, respectively, with malononitrile) were refluxed in ethanolic sodium ethoxide [32]. The mass spectra of the obtained products showed molecular ion peaks at *m/z* = 316 and 348, respectively, which points out that a dimerization process of both **1a** and **1b** took place. The spectral data of the dimers (**2a**,**b**) were found very similar to that of 2-[4,6-diphenyl-3-cyano-6-methyl-5,6-dihydropyridin-2(1*H*)-ylidene] malononitrile derivatives described earlier by us whose structure was confirmed by X-ray crystallographic analysis [31]. Thus the ^{1}H NMR spectrum of **2a** and **2b** revealed a singlet at 1.70 ppm assignable to one methyl group, doublets at 3.24 and 3.70 ppm assignable to two chemically nonequivalent protons of a methylene group, a multiplet at 6.10-7.52 ppm due to the three furan or thiophene protons and an exchangeable singlet at 9.55 ppm assignable to NH. Furthermore the ^{13}C NMR spectrum of **2a** revealed the requisite 18 signals (Scheme 1). Thus the NMR data are completely compatible to the assigned structures **2a** and **2b**.

The methylene group in compounds **2a** and **2b** were found to be active enough to couple with the diazotized aromatic amines **3a-c** (aniline, *p*-chloroaniline and *p*-toluidine) to afford highly colored products. Analytical and spectral data were in complete agreement with the hydrazo structures **4a-f** which were assigned to these products (Scheme 1). It is worth mentioning that this dimerization of **1** to give **2** could also be catalyzed by aqueous NaOH in ethanol, aqueous Na_2CO_3 in ethanol or NaOEt in ethanol however the maximum yields and the cleanest products were achieved with NaOEt.

Compounds **2a,b** were next reacted with hydrazine hydrate and phenyl hydrazine **5a,b** to afford the pyrazolo-naphthyridine derivatives **6a-d**, respectively. Compounds **2a,b** were reacted also with urea derivatives **7a-c** to afford the pyrimido-naphthyridine derivatives **8a-f**, 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 **6a-d** and **8a-f** did not reveal any cyano absorption bands at the region of 1985-2245 cm^{-1}. All spectral and analytical data are in complete agreement with these structures.

4. Conclusion

We have prepared some novel difur-2-yl- and dithien-2-yl-dihydropyridin-2(1*H*)-ylidene)malononitrile, pyrazolonaphthyridines and pyrimidonaphthyridines derivatives of potential biological interest. All the reactions were carried out using simple and clean eco-friendly synthetic methods. No heavy metals or hazardous solvents were involved, ethanol, acetic acid or water were used as solvents and sodium salts were used as catalysts.

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