Synthesis of Novel Fused Heterocycles Based on 6-Amino-4-phenyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile

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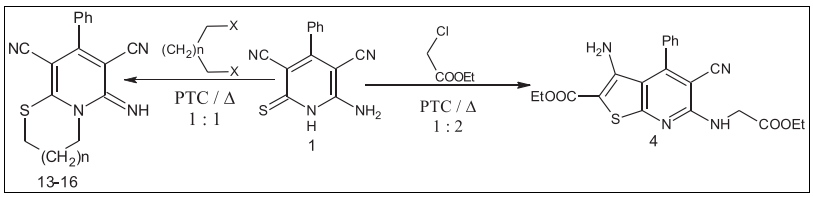

Under phase transfer catalysis conditions, 6-amino-4-phenyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1**) was allowed to react with halo compounds, acrylonitrile, chloroacetyl chloride, ethyl cyanoacetate, formamide, triethylorthoformate, or formic acid to give new derivatives of fused pyridines 2–22, respectively. Acetylation of compound **1** using acetic anhydride afforded product **23**, which in turn underwent intramolecular cyclization in pyridine to give the corresponding pyrido[2,3-*d*]pyrimidine **24**.

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INTRODUCTION

Fused heterocyclic containing pyrazolopyridine systems have been described associated with several biological and medicinal activities including anxiolytic [1], antiviral [2,3], antileishmanial [4], antimalarial [5], antiproliferative [6], antimicrobial [7–9], cardiovascular [10–12], and anti-inflammatory [13] profiles. In particular, thienopyridines have been reported to have biological activities [14], including antibacterial [15], anti-inflammatory [16], antiviral [17], antiparasitic [18,19], and immune-stimulating activities [20]. Others are useful as gonadotropin-releasing hormone antagonists [21] and as lipoxygenases inhibitors [22].

In view of the previous applications, we aim to use 6-amino-4-phenyl-2-thioxo-1, 2-dihydropyridine-3,5-dicarbonitrile (**1**) as building blocks for the synthesis of some new family of fused heterocyclic compounds incorporating pyridine moiety with the hope to possess better antimicrobial activity.

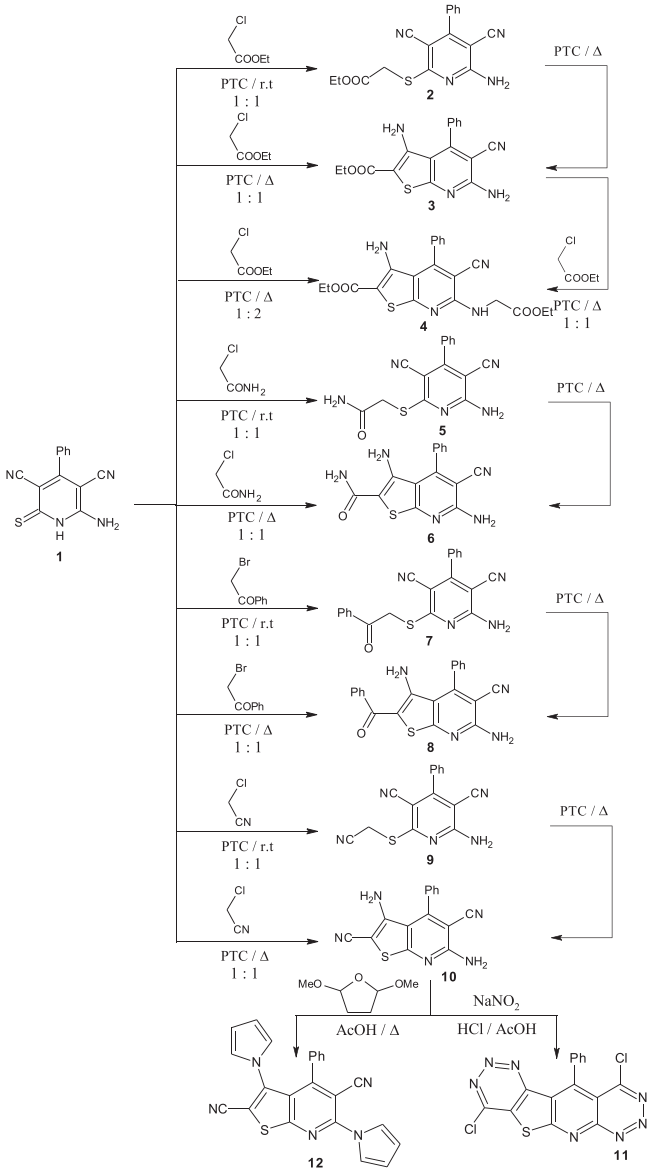
RESULTS AND DISCUSSIONS

The starting compound 6-amino-4-phenyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1**) was prepared by the reaction of benzaldehyde with cyanothioacetamide in 1:2 molar ratio in ethanol and piperidine as a catalyst [23].

Under phase transfer catalysis (PTC) conditions using dioxane as the organic phase, potassium carbonate as the solid phase and tetrabutylammonium bromide as a catalyst, compound **1** was allowed to react at room temperature with halo compounds containing active methylene group, namely ethyl chloroacetate, chloroacetamide, phenacyl bromide, or chloroacetonitrileto give ethyl [(6-amino-3,5-dicyano-4-phenylpyridin-2-yl)thio]acetate (**2**), 2-[(6-amino-3,5-dicyano-4-phenylpyridin-2-yl)thio]acetamide (**5**), 2-amino-6-[(2-oxo-2-phenylethyl)thio]-4-phenyl-pyridine-3,5-dicarbonitrile (**7**), or 2-amino-6-[(cyanomethyl)thio]-4-phenylpyridine-3,5-dicarbonitrile (**9**), respectively. Compounds 2, 5, 7, and 9 underwent intramolecular cyclization on heating under similar PTC conditions to give ethyl 3,6-diamino-5-cyano-4-phenylthieno[2,3-*b*]pyridine-2-carboxylate (**3**), 3,6-diamino-5-cyano-4-phenylthieno[2,3-*b*] pyridine-2-carboxamide (**6**), 3,6-diamino-2-benzoyl-4-phenylthieno[2,3-*b*]pyridine-5-carbonitrile (**8**), or 3,6-diamino-4-phenylthieno[2,3-*b*]pyridine-2,5-dicarbonitrile (**10**), respectively. Compounds **3**, **6**, **8**, or **10** were synthesized directly in one step by heating compound **1** with ethyl chloroacetate, chloroacetamide, phenacyl bromide or chloroacetonitrile, respectively, under PTC conditions. Ethyl 3-amino-5-cyano-6-[(2-ethoxy-2-oxoethyl)-amino]-4-phenylthieno[2,3-*b*]pyridine-2-carboxylate **4** was obtained on heating compound **3** with ethyl chloroacetate under similar PTC conditions. Also, compound **4** was synthesized directly in one step by heating compound **1** with ethyl chloroacetate in 1:2 molar ratio (Scheme 2).

The IR spectra of compounds **2**, **5**, 7**,** and **9** showed the absence of absorption bands corresponding to C=S but exhibited new absorption bands at 2977–2926 cm^{-1} corresponding to aliphatic C–H and at 1719–1643 cm^{-1} corresponding to the C=O group. The ^{1}HNMR spectra of compounds **2**, **5**, **7**, and **9** revealed new singlet signals at 4.21–3.90 ppm corresponding to the S–CH_2 groups. In the case of compound **2,** a quartet signal at 4.19–4.12 ppm corresponding to the CH_2 ester and a triplet signal at 1.28–1.20 ppm corresponding to the CH_3 ester appeared. The ^{1}HNMR spectrum of compound **5** was characterized as a new broad signal at 3.80–3.60 ppm corresponding to

Scheme 1



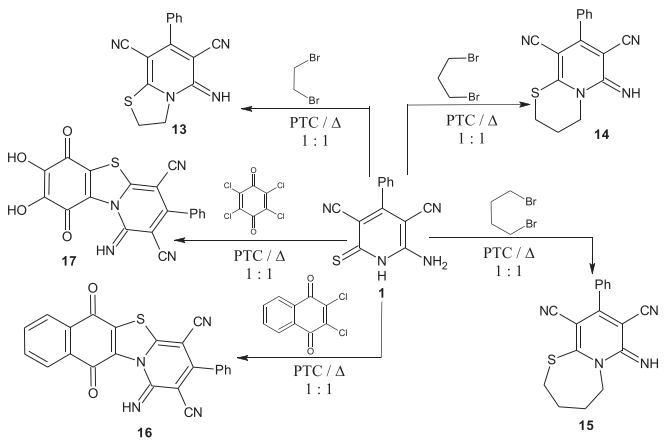
the NH_2 group. The IR spectra of compounds **3**, **6**, **8**, and **10** showed the absence of absorption bands corresponding to C=S but exhibited new absorption bands at 3487–3147 cm^{-1} corresponding to the NH_2 group. The ^{1}HNMR spectra of these compounds were consistent with the purposed structures. The IR and ^{1}HNMR spectra of compound **4** were consistent with the purposed structures. Moreover, the mass spectrum of compound **4** gave *m/z* 424 [M^+] (I_{rel} 87.07%), which corresponds to the molecular weight of the molecular formula $C_{21}H_{20}N_4O_4S$ of the assigned structure.

Diazotization of compound **10** using sodium nitrite and HCl/AcOH mixture gave 4,10-dichloro-11-phenyl[1,2,3] triazino-[5″,4″:5′,6′]pyrido[3′,2′:4,5]thieno[3,2-*d*][1,2,3]triazine (**11**). Compound **10** was allowed to react with 2,5-dimethoxytetrahydrofuran to give 4-phenyl-3,6-di(pyrrol-1-yl)-thieno[2,3-*b*]-pyridine-2,5-dicarbonitrile (**12**) (Scheme 1).

The IR spectrum of compound **12** showed the absence of the absorption bands corresponding to the NH_2 group. The ^{1}HNMR spectrum showed the absence of the signal corresponding to the NH_2 group but revealed new signals at 7.4–7.2, 6.3–5.9, and 5.5–5.2 ppm corresponding to the pyrrole protons.

Under similar PTC reaction conditions, compound **1** was cycloalkylated on heating with some dihalo reagents, namely 1,2-dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, 2,3-dichloro-1,4-naphthoquinone, or 2,3,5,6-tetrachloro-1,4-benzoquinone to give 5-imino-7-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo-[3,2-*a*]pyridine-6,8-dicarbonitrile (**13**), 6-imino-8-phenyl-3,4-dihydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]thiazine-7,9-dicarbonitrile (**14**), 7-imino-9-phenyl-2,3,4,5-tetrahydro-7*H*-pyrido[2,1-*b*] [1,3]thiazepine-8,10-dicarbonitrile (**15**), 4-imino-6,11-dioxo-2-phenyl-6,11-dihydro-4*H*-naphtho[2′,3′:4,5][1,3]thiazolo[3,2-*a*]pyridine-1,3-dicarbonitrile (**16**), and 7,8-dihydroxy-1-imino-6,9-dioxo-3-phenyl-6,9-dihydro-1*H*-pyrido[2,1-*b*] [1,3]-benzothiazole-2,4-dicarbonitrile (**17**), respectively (Scheme 2).

Scheme 2



The IR spectra of compounds **13–17** showed the absence of absorption bands corresponding to the C=S and NH_2 groups but exhibited new absorption bands at 2932–2928 cm^{-1} corresponding to aliphatic C–H, in the case of compounds **13–17** at 1675–1625 cm^{-1} corresponding to C=O, in the case of compounds **16** and **17**. Also, the IR spectrum of compound **17** exhibited new absorption bands at 3559 and 3447 cm^{-1} corresponding to two OH groups. The ^{1}HNMR spectra of compounds **13–17** showed the absence of the signal corresponding to the NH_2 group but revealed aliphatic cyclic protons signals at 4.15–1.60 ppm, in the case of compounds **13–17**, and aromatic proton signals at 7.8–7.0 ppm, in the case of compound **16**. The ^{1}HNMR spectrum of compound **17** showed new singlet signals at 3.5 ppm corresponding to two OH groups.

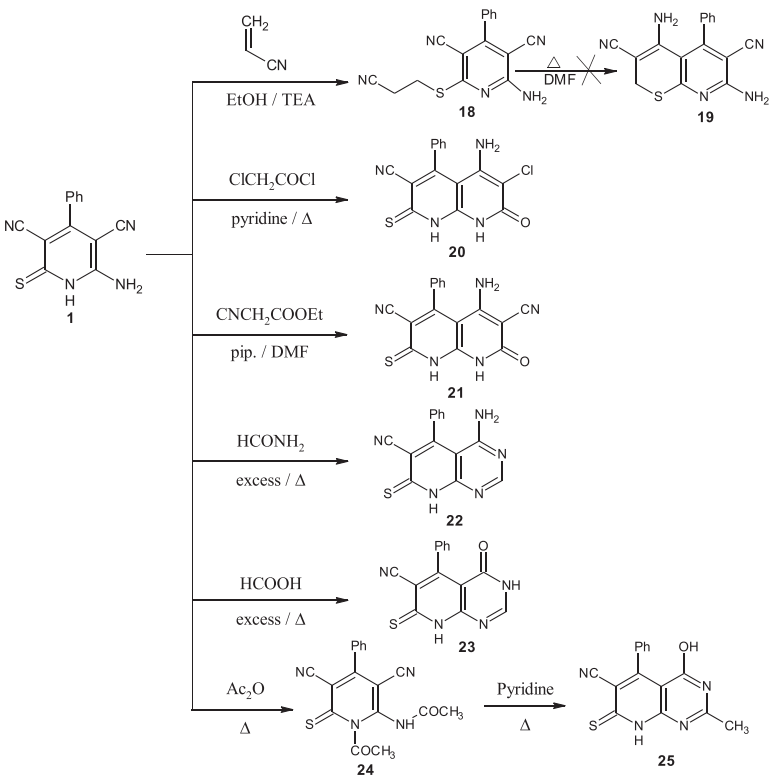
Compound **1** was allowed to react with acrylonitrile in ethanol and triethylamine as a catalyst to give 2-amino-6-[(2-cyanoethyl)thio]-4-phenylpyridine-3,5-dicarbonitrile **18**; however, the cyclized compound **19** was not obtained via heating compound **18** in DMF solution. In order to construct new derivatives of the interesting 1,8-naphthyridines [24], we have synthesized a new family of 1,8-naphthyridines via the reaction of compound **1** with chloroacetyl chloride or ethyl cyanoacetate to give the corresponding 1,8-naphthyridines **20** and **21**, respectively.

A new family of fused pyrido[2,3-*d*]pyrimidines was prepared via the reaction of compound **1** with formamide or formic acid to give the corresponding pyrido[2,3-*d*]pyrimidines **22** and **23**, respectively. The formation of compound **23** was assumed to proceed via the amide formation [25], followed by an intramolecular cyclization with formic acid to furnish the desired product (cf. Scheme 3). The acetylation of compound **1** using acetic anhydride afforded the diacetylated compound *N*-(1-acetyl-3,5-dicyano-4-phenyl-6-thioxo-1, 6-dihydropyridin-2-yl)acetamide **24,** which in turn underwent cyclization in pyridine followed by hydrolysis of an acetyl group to give 4-hydroxy-2-methyl-5-phenyl-7-thioxo-7,8-dihydropyrido[2,3-*d*]pyrimidine-6-carbonitrile **25** (cf. Scheme 3).

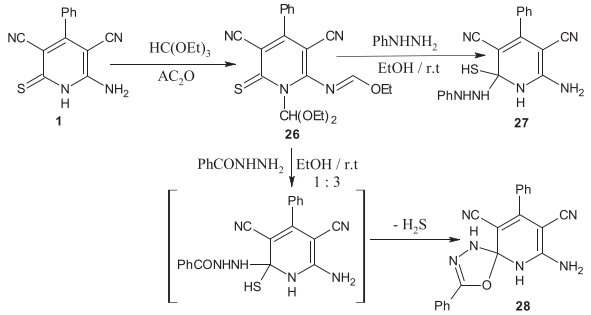
The IR spectrum of compound **25** showed the absence of absorption band corresponding to the C=O group but exhibited new absorption band at 3471 cm^{-1} corresponding to the OH group. The ^{1}HNMR spectrum showed the disappearance of the signal corresponding to one CH_3 group and revealed new broad signal at 4.3–3.7 ppm corresponding to the OH group.

Compound **1** was allowed to react with triethylorthoformate using acetic anhydride as a catalyst to give 1-diethoxymethyl-6-[1-ethoxymethylideneamino]-4-phenyl-2-thioxo-1,2-dihydro-3,5-pyridinedicarbonitrile (**26**). The IR spectrum of compound **26** showed the absence of absorption bands corresponding to the NH_2 and NH groups but exhibited new absorption bands at 2926–2864 cm^{-1} corresponding to aliphatic C–H and at

Scheme 3



Scheme 4



1241 cm^{-1} corresponding to C–O–C. The ^{1}HNMR spectrum revealed a new quartet signal at 4.52–4.44 ppm corresponding to the =C–OCH_2 group, multiplet signal at 3.41–3.32 ppm corresponding to the $2CH_2$ groups, and multiplet signals at 1.43–1.35 ppm corresponding to the $3CH_3$ groups.

Compound **26** was treated at room temperature with phenyl hydrazine or benzohydrazide to give 6-amino-2-mercapto-4-phenyl-2-(2′-phenylhydrazino)-1,2-dihydropyridine-3,5-dicarbonitrile (**27**) and 7-amino-3,9-diphenyl-4-oxa-1,2,6-triazaspiro[4.5]deca-2,7,9-triene-8,10-dicarbonitrile (**28**), respectively. The IR spectra of compounds **27** and **28** showed the absence of absorption bands corresponding to aliphatic C–H but exhibited new absorption bands at 3461–3212 cm^{-1} corresponding to the NH_2 and NH groups. The ^{1}HNMR spectra of compounds **27** and **28** showed the absence of the signals corresponding to aliphatic protons but revealed new signals corresponding to NH_2 and NH groups (Scheme 4).

EXPERIMENTAL

All melting points are uncorrected and were recorded on Melt-Temp II melting point apparatus (USA). IR spectra were measured as KBr pellets on a Shimadzu DR-8001 spectrometer. ^{1}HNMR spectra were recorded in deuterated chloroform or dimethyl sulfoxide at 60 MHz on a Varian EM 360L and also at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference. Mass spectra analyses were performed on a Shimadzu GCMS-QP 1000 mass spectrometer at 70 eV. The elemental analyses were carried out on a Perkin-Elmer 240C. All compounds were checked for their purity on thin-layer chromatography plates.

Synthesis of compounds 2, 5, 7, and 9. ***General procedure.*** A mixture of compound **1** (0.001 mol, 0.252 g), the appropriate halo compound (0.001 mol), anhydrous potassium carbonate (3 g), a catalytic amount of tetrabutylammonium bromide, and dioxane (20 mL) was stirred for 2 h at r.t. The reaction mixture was filtered off, the filtrate was evaporated *in vacuo*, and the resulting product was washed with water and recrystallized from ethanol.

Ethyl [(6-amino-3,5-dicyano-4-phenylpyridin-2-yl)thio]acetate (2). Yield: 90%, mp 194°C; IR: 3356, 3218 (NH_2), 3054 ($CH_{arom.}$), 2977 ($CH_{aliph.}$), 2211 (CN), 1719 (C=O) cm^{-1}; ^{1}HNMR: 7.98 (s, 2H, NH_2), 7.6–7.4 (m, 5H, arom.), 4.21 (s, 2H, $–CH_2–$S), 4.19–4.12 (q, 2H, CH_{2ester}), 1.28–1.20 (t, 3H, CH_{3ester}). *Anal*. Calcd for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56; S, 9.48. Found: C, 60.18; H, 4.20; N, 16.32; S, 9.33.

2-[(6-Amino-3,5-dicyano-4-phenylpyridin-2-yl)-thio]acetamide (5). Yield: 68%, mp 231°C; IR: 3398, 3322, 3214 ($2NH_2$), 3060 ($CH_{arom.}$), 2928 ($CH_{aliph.}$), 2211 (CN), 1643 (C=O) cm^{-1}; ^{1}HNMR: 8.05 (s, 2H, NH_2), 7.79–7.28 (m, 5H, arom.), 3.9 (s, 2H, CH_2), 3.80–3.60 (br, 2H, $CONH_2$). *Anal*. Calcd for $C_{15}H_{11}N_5OS$: C, 58.24; H, 3.58; N, 22.64; S, 10.37. Found: C, 58.36; H, 3.49; N, 22.53; S, 10.22.

2-Amino-6-[(2-oxo-2-phenylethyl)thio]-4-phenylpyridine-3,5-dicarbonitrile (7). Yield: 65%, mp 292°C; IR: 3345, 3216 (NH_2), 3056 ($CH_{arom.}$), 2926 ($CH_{aliph.}$), 2210 (CN), 1676 (C=O) cm^{-1}; ^{1}HNMR: 8.2 (s, 2H, NH_2). 7.8–7.0 (m, 10H, arom.), 4.7 (s, 2H, CH_2). *Anal*. Calcd for $C_{21}H_{14}N_4OS$: C, 68.09; H, 3.81; N, 15.12; S, 8.66. Found: C, 68.15; H, 3.96; N, 15.03; S, 8.72.

2-Amino-6-[(cyanomethyl)thio]-4-phenylpyridine-3,5-dicarbonitrile (9). Yield: 75%, mp 214°C; IR: 3330, 3229 (NH_2), 3050 ($CH_{arom.}$), 2973 ($CH_{aliph.}$), 2205 (CN) cm^{-1}; ^{1}HNMR: 8.26 (s, 2H, NH_2), 7.65–7.42 (m, 5H, arom.), 4.3 (s, 2H, CH_2). *Anal*. Calcd for $C_{15}H_9N_5S$: C, 61.84; H, 3.11; N, 24.04; S, 11.01. Found: C, 61.91; H, 3.02; N, 4.10; S, 10.94.

Ethyl 3-amino-5-cyano-6-[(2-ethoxy-2-oxoethyl)amino]-4-phenylthieno[2,3-b]-pyridine-2-carboxylate (4). *Method A.* A mixture of compound **1** (0.001 mol, 0.252 g), ethyl chloroacetate (0.002 mol, 0.22 mL), anhydrous potassium carbonate (3 g), a catalytic amount of tetrabutylammonium bromide, and dioxane (20 mL) was stirred for 1 h at r.t. The reaction mixture was further stirred for 2 h at 60–70°C and treated as previously mentioned.

Method B. A mixture of compound **3** (0.001 mol, 0.338 g), ethyl chloroacetate (0.001 mol, 0.11 mL), anhydrous potassium carbonate (3 g), a catalytic amount of tetrabutylammonium bromide, and dioxane (20 mL) was stirred for 1 h at r.t. The reaction mixture was further stirred for 2 h at 60–70°C, then filtered off, and the filtrate was evaporated *in vacuo*, and the resulting product was washed with water and crystallized from ethanol.

Yield: 80%, mp 235°C; IR: 3488, 3406, 3352 (NH_2, NH), 3051 ($CH_{arom.}$), 2978 ($CH_{aliph.}$), 2211 (CN), 1732 (C=O), 1667 (C=O) cm^{-1}; ^{1}HNMR: 7.98 (s, 1H, NH), 7.64–7.46 (m, 5H, arom.), 5.49 (s, 2H, NH_2), 4.25–4.14

(m, 6H, $2CH_{2ester}+CH_2$–N), 1.27–1.20 (t, 6H, $2CH_{3ester}$). Mass spectrum, *m/z* (%): 424 (M^+, 87.09), 338 (97.33), 291 (100). *Anal.* Calcd for $C_{21}H_{20}N_4O_4S$: C, 59.42; H, 4.75; N, 13.20; S, 7.55. Found: C, 59.31; H, 4.62; N, 13.34; S, 7.39.

Synthesis of compounds 3, 6, 8, and 10. ***Method A.*** A mixture of compound **1** (0.001 mol, 0.252 g), the appropriate halo compound, anhydrous potassium carbonate (3 g), a catalytic amount of tetrabutylammonium bromide, and dioxane (20 mL) was stirred for 1 h at r.t. The reaction mixture was further stirred for a period of time at 60–70°C, then filtered off, and the filtrate was evaporated *in vacuo*, and the resulting product was washed with water and crystallized from ethanol or dioxane.

Method B. To a solution of the appropriate compounds **2**, **5**, **7**, or **9** (0.001 mol) in dioxane (20 mL), anhydrous potassium carbonate (3 g) and a catalytic amount of tetrabutylammonium bromide were added. The reaction mixture was stirred for 2 h at 60–70°C and then filtered off. The filtrate was evaporated *in vacuo*, and the resulting product was washed with water and crystallized from ethanol.

Ethyl 3,6-diamino-5-cyano-4-phenylthieno[2,3-b]pyridine-2-carboxylate (3). Yield: 90%, mp 278°C; IR: 3487, 3359, 3291, 3147 ($2NH_2$), 3050 ($CH_{arom.}$), 2983 ($CH_{aliph.}$), 2210 (CN), 1677 (C=O) cm^{-1}; ^{1}HNMR: 7.66–7.5 (m, 7H, arom.+NH_2), 5.49 (s, 2H, NH_2), 4.24–4.13 (q, 2H, CH_{2ester}), 1.27–1.20 (t, 3H, $CH_{3\ ester}$). *Anal*. Calcd for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56; S, 9.48. Found: C, 60.18; H, 4.25; N, 16.60; S, 9.33.

3,6-Diamino-5-cyano-4-phenylthieno[2,3-b]pyridine-2-carboxamide (6). Yield: 60%, mp 269°C; IR: 3458, 3346, 3204 ($3NH_2$), 3050 ($CH_{arom.}$), 2217 (CN), 1640 (C=O) cm^{-1}; ^{1}HNMR: 7.6–7.4 (m, 5H, arom.), 6.5 (s, 2H, NH_2-exchanged by D_2O), 6.2 (s, 2H, NH_2-exchanged by D_2O), 5.4 (s, 2H, NH_2-exchanged by D_2O). *Anal.* Calcd for $C_{15}H_{11}N_5OS$: C, 58.24, H, 3.58; N, 22.64; S, 10.37. Found: C, 58.13; H, 3.66; N, 22.73; S, 10.29.

3,6-Diamino-2-benzoyl-4-phenylthieno[2,3-b]pyridine-5-carbonitrile (8). Yield: 72%, mp >300°C; IR: 3471, 3345, 3211 ($2NH_2$), 3067 ($CH_{arom.}$), 2209 (CN), 1678 (C=O) cm^{-1}; ^{1}HNMR: 7.9 (s, 2H, NH_2), 7.6–7.4 (m, 10H, arom.), 5.2 (s, 2H, NH_2). *Anal.* Calcd for $C_{21}H_{14}N_4OS$: C, 68.09, H, 3.81; N, 15.12; S, 8.66. Found: C, 68.02; H, 3.89; N, 15.21; S, 8.75.

3,6-Diamino-4-phenylthieno[2,3-b]pyridine-2,5-dicarbonitrile (10). Yield: 91%, mp 286°C; IR: 3414, 3338, 3232 ($2NH_2$), 3050 ($CH_{arom.}$), 2189 (CN) cm^{-1}; ^{1}HNMR: 7.66–7.56 (m, 7H, arom.+NH_2), 5.28 (s, 2H, NH_2). *Anal.* Calcd for $C_{15}H_9N_5S$: C, 61.84, H, 3.11; N, 24.04; S, 11.01. Found: C, 61.77; H, 3.21; N, 24.11; S, 24.11.

4,10-Dichloro-11-phenyl[1,2,3]triazino[5″,4″:5′,6′]pyrido[3′,2′:4,5]-thieno[3,2-d]-[1,2,3]triazine (11). To a chilled solution of compound **10** (0.001 mol, 0.291 g) in a mixture of acetic acid (10 mL) and concentrated hydrochloric acid (7 mL), a sodium nitrite solution 10% (2 mL) was added with stirring for 5 min. The stirring was continued at 5°C for 3 h. The formed precipitate was collected by filtration and crystallized from dioxane as yellow crystals, 0.2 g (52% yield), mp 224°C; IR: 3060 ($CH_{arom.}$) cm^{-1}; ^{1}HNMR: 7.5–7.0 (m, 5H, arom.). *Anal.* Calcd for $C_{15}H_5Cl_2N_7S$: C, 46.65, H, 1.30; N, 25.39; S, 8.30. Found: C, 46.72; H, 1.42; N, 25.48; S, 8.25.

4-Phenyl-3,6-di-1H-pyrrol-1-ylthieno[2,3-b]-pyridine-2,5-dicarbonitrile (12). A mixture of compound **10** (0.001 mol, 0.291 g) and 2,5-dimethoxytetrahydrofuran (0.002 mol, 0.26 mL) in 20 mL of glacial acetic acid was heated under reflux for 4 h and left to cool. The precipitated crystals were collected by filtration and crystallized from dioxane as pale yellow crystals, 0.22 g (57% yield), mp 224°C; IR: 3070 ($CH_{arom.}$), 2220 (CN) cm^{-1}; ^{1}HNMR: 7.4–7.2 (d, 4H, 2 =CH–N–CH=), 7.0–6.6 (m, 5H, arom.), 6.3–5.9 (t, 2H, =CH–CH=), 5.5–5.2 (t, 2H, =CH–CH=). *Anal.* Calcd for $C_{23}H_{13}N_5S$: C, 70.57, H, 3.35; N, 17.89; S, 8.19. Found: C, 70.45; H, 3.46; N, 17.97; S, 8.21.

Synthesis of compounds 13–17. ***General procedure.*** A mixture of compound **1** (0.001 mol, 0.252 g, 0.001 mol) of the appropriate halo compound, anhydrous potassium carbonate (3 g), a catalytic amount of tetrabutylammonium bromide, and dioxane (20 mL) was stirred for 1 h at r.t. The reaction mixture was further stirred for a period of time at 60–70°C, then filtered off, and the filtrate was evaporated *in vacuo*. The resulting product was washed with water, dried, and crystallized from ethanol.

5-Imino-7-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (13). Yield: 61%, mp >300°C (decomp.); IR: 3328 (NH), 3056 ($CH_{arom.}$), 2928 ($CH_{aliph.}$), 2212 (CN) cm^{-1}; ^{1}HNMR: 7.50 (s, 1H, NH), 7.30–7.00 (m, 5H, arom.), 4.15–3.80 (t, 2H, CH_2–N), 3.50–3.25 (t, 2H, CH_2–S). *Anal.* Calcd for $C_{15}H_{10}N_4S$: C, 64.73, H, 3.62; N, 20.13; S, 11.52. Found: C, 64.62; H, 3.73; N, 20.24; S, 11.45.

6-Imino-8-phenyl-3,4-dihydro-2H,6H-pyrido[2,1-b][1,3]thiazine-7,9-dicarbonitrile (14). Yield: 86%, mp 155°C; IR: 3353 (NH), 3050 ($CH_{arom.}$), 2929 ($CH_{aliph.}$), 2210 (2CN) cm^{-1}; ^{1}HNMR: 7.5 (s, 1H, NH), 7.4–7.0 (m, 5H, arom.), 3.4–3.0 (t, 2H, CH_2–N), 3.0–2.8 (t, 2H, CH_2–S), 2.3–2.0 (m, 2H, CH_2). *Anal.* Calcd for $C_{16}H_{12}N_4S$: C, 65.73, H, 4.14; N, 19.16; S, 10.97. Found: C, 65.64; H, 4.05; N, 19.21; S, 11.05.

7-Imino-9-phenyl-2,3,4,5-tetrahydro-7H-pyrido[2,1-b][1,3]thiazepine-8,10-dicarbonitrile (15). Yield: 57%, mp 140°C; IR: 3342 (NH), 3061 ($CH_{arom.}$), 2932 ($CH_{aliph.}$), 2208 (CN) cm^{-1}; ^{1}HNMR: 7.50 (s, 1H, NH), 7.30–6.90 (m, 5H, arom.), 3.85–3.50 (t, 2H, CH_2–N), 3.40–3.00 (t, 2H, CH_2–S), 2.10–1.60 (m, 4H, CH_2–CH_2). *Anal.* Calcd for $C_{17}H_{14}N_4S$: C, 66.64, H, 4.61; N, 18.29; S, 10.47. Found: C, 66.61; H, 4.69; N, 18.37; S, 10.39.

4-Imino-6,11-dioxo-2-phenyl-6,11-dihydro-4H-naphtho[2′,3′:4,5][1,3]thiazolo-[3,2-a]pyridine-1,3-dicarbonitrile (16). Yield: 81%, mp 274°C; IR: 3442 (NH), 3070 ($CH_{arom.}$), 2210 (CN), 1675 (C=O) cm^{-1}; ^{1}HNMR: 7.8–7.0 (m, 10H,

arom.+NH). *Anal.* Calcd for $C_{23}H_{10}N_4O_2S$: C, 67.97; H, 2.48; N, 13.79; S, 7.89. Found: C, 67.92; H, 2.39; N, 13.85; S, 7.93.

7,8-Dihydroxy-1-imino-6,9-dioxo-3-phenyl-6,9-dihydro-1H-pyrido[2,1-b][1,3]-benzothiazole-2,4-dicarbonitrile (17). Yield: 89%, mp 279°C; IR: 3559, 3447 (2OH), 3215 (NH), 3066 ($CH_{arom.}$), 2213 (2CN), 1629 (2C=O) cm^{-1}; ^{1}HNMR: 7.7–7.0 (m, 6H, arom.+NH), 3.5 (s, 2H, 2OH). *Anal*. Calcd for $C_{19}H_8N_4O_4S$: C, 58.76; H, 2.08; N, 14.43; S, 8.26. Found: C, 58.72; H, 1.98; N, 14.51; S, 8.32.

2-Amino-6-[(2-cyanoethyl)thio]-4-phenylpyridine-3,5-dicarbonitrile (18). A mixture of compound **1** (0.00125 mol, 0.315 g), acrylonitrile (0.00125 mol, 0.066 g), triethylamine as a catalyst, and ethanol (20 mL) was refluxed for 3 h. After cooling, the separated crystals were collected by filtration and recrystallized from ethanol to yield **18** (0.23 g, 69%); mp 208°C (ethanol); IR: 3432, 3310 (NH_2), 3016 ($CH_{arom.}$), 2917 ($CH_{aliph.}$), 2218 (CN) cm^{-1}; ^{1}HNMR: 8.16 (s, 2H, NH_2), 7.59–7.58 (m, 5H, arom.), 3.54–3.46 (t, 2H, CH_2CN), 3.09–3.00 (t, 2H, CH_2–S). *Anal.* Calcd for $C_{16}H_{11}N_5S$: C, 62.93; H, 3.63; N, 22.93; S, 10.50. Found: C, 62.84; H, 3.75; N, 22.84; S, 10.42.

5-Amino-6-chloro-7-oxo-4-phenyl-2-thioxo-1,2,7,8-tetrahydro-1,8-naphthyridine-3-carbonitrile (20). To a solution of compound **1** (0.001 mol, 0.252 g) in pyridine (15 mL), chloroacetyl chloride (0.001 mol, 0.11 g) was added dropwise with stirring at room temperature for 30 min and then refluxed for 6 h. The reaction mixture was left to cool, poured onto ice cold water, and neutralized by HCl. The obtained solid product was filtered, washed with water, and recrystallized from ethanol to yield **20** (0.24 g, 85%); mp 226°C; IR: 3434, 3337, 3227 (NH_2, 2NH), 3050 ($CH_{arom.}$), 2215 (CN), 1714 (C=O), 1541 (C=S), 700 (C–Cl) cm^{-1}; ^{1}HNMR: 7.6–6.8 (m, 7H, arom.+2NH), 4.9–4.3 (br, 2H, NH_2). *Anal*. Calcd for $C_{15}H_9ClN_4OS$: C, 54.80; H, 2.76; N, 17.04; S, 9.75. Found: C, 54.72; H, 2.81; N, 17.11; S, 9.63.

4-Amino-2-oxo-5-phenyl-7-thioxo-1,2,7,8-tetrahydro-1,8-naphthyridine-3,6-dicarbonitrile (21). A mixture of compound **1** (0.001 mol, 0.252 g), ethyl cyanoacetate (0.001 mol, 0.11 g), DMF (10 mL), and piperidine (0.5 mL) was heated under reflux for about 3 h. The reaction mixture was left to cool and poured onto ice cold water. The medium was acidified with two drops of HCl. The solid product was filtered and crystallized from dioxane to yield **21** (0.21 g, 77%); mp 244°C; IR: 3401, 3324, 3197 (NH_2, 2NH), 2220 (CN), 1646 (C=O), 1562 (C=S) cm^{-1}; ^{1}HNMR: 7.6 (s, 1H, NH), 7.5–7.0 (m, 8H, arom.+NH+NH_2). *Anal.* Calcd for $C_{16}H_9N_5OS$: C, 60.18; H, 2.84; N, 21.93; S, 10.04. Found: C, 60.27; H, 2.76; N, 21.80; S, 10.10.

4-Amino-5-phenyl-7-thioxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (22). A mixture of compound **1** (0.001 mol, 0.252 g) and excess of formamide (10 mL) was heated under reflux for 30 min. The reaction mixture was left to cool and poured onto ice cold water. The obtained solid product was filtered, washed with water, and crystallized from ethanol to yield **22** (0.11 g, 45%); mp 210°C; IR: 3456, 3372, 3162 (NH_2, NH), 3050 ($CH_{arom.}$), 2220 (CN), 1565 (C=S) cm^{-1}; ^{1}HNMR: 8.0 (s, 1H, N=CH), 7.8 (s, 1H, NH), 7.4–6.7 (m, 5H, arom.), 6.0 (s, 2H, NH_2). *Anal.* Calcd for $C_{14}H_9N_5S$: C, 60.20, H, 3.25; N, 25.07; S, 11.48. Found: C, 60.11; H, 3.32; N, 25.12; S, 11.36.

4-Oxo-5-phenyl-7-thioxo-3,4,7,8-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (23). A mixture of compound **1** (0.001 mol, 0.252 g) and excess of formic acid (10 mL) was heated under reflux for 23 h. The reaction mixture was left to cool. The obtained crystals were filtered and recrystallized from ethanol to yield **23** (0.13 g, 54%); mp 260°C; IR: 3378 (NH), 3203 (NH), 3040 ($CH_{arom.}$), 2212 (CN), 1655 (C=O), 1530 (C=S) cm^{-1}; ^{1}HNMR: 7.6–7.2 (m, 7H, arom.+2NH), 6.4 (s, 1H, =CH–). *Anal*. Calcd for $C_{14}H_8N_4OS$: C, 59.99; H, 2.88; N, 19.99; S, 11.44. Found: C, 60.06; H, 2.72; N, 19.84; S, 11.57.

N-(1-Acetyl-3,5-dicyano-4-phenyl-6-thioxo-1,6-dihydropyridin-2-yl)acetamide (24). A solution of compound **1** (0.001 mol, 0.252 g) in acetic anhydride (20 mL) was heated under reflux for 4 h. The reaction mixture was left to cool and poured onto ice cold water. The obtained solid product was filtered, washed with water, and recrystallized from ethanol to yield **24** (0.21 g, 73%); mp 276°C; IR: 3210 (NH), 3056 ($CH_{arom.}$), 2964 ($CH_{aliph.}$), 2231 (2CN), 1705 (2C=O), 1579 (C=S) cm^{-1}; ^{1}HNMR: 11.34 (s, 1H, NH), 7.67–7.60 (m, 5H, arom.), 2.23 (s, 3H, CH_3), 2.16 (s, 3H, CH_3). *Anal.* Calcd for $C_{17}H_{12}N_4O_2S$: C, 60.70; H, 3.60; N, 16.66; S, 9.53. Found: C, 60.61; H, 3.49; N, 16.58; S, 9.42.

4-Hydroxy-2-methyl-5-phenyl-7-thioxo-7,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (25). A solution of compound **24** (0.001 mol, 0.336 g) in pyridine (15 mL) was heated under reflux for 2 h. The reaction mixture was left to cool and poured onto ice cold water. The medium was acidified with HCl. The solid product was filtered, crystallized from ethanol, and then recrystallized from dioxane to yield **25** (0.14 g, 46%); mp 168°C; IR: 3471 (OH), 3381 (NH), 3051 ($CH_{arom.}$), 2931 ($CH_{aliph.}$), 2208 (CN), 1537 (C=S) cm^{-1}; ^{1}HNMR: 8.2 (s, 1H, NH), 7.2–6.9 (m, 5H, arom.), 4.3–3.7 (br, 1H, OH), 2.4 (s, 3H, CH_3). *Anal*. Calcd for $C_{15}H_{10}N_4OS$: C, 61.21; H, 3.42; N, 19.04; S, 10.89. Found: C, 61.28; H, 3.35; N, 19.12; S, 10.96.

1-Diethoxymethyl-6-[1-ethoxymethylideneamino]-4-phenyl-2-thioxo-1,2-dihydro-pyridine-3,5-dicarbonitrile (26). A mixture of compound **1** (0.005 mol, 1.26 g), triethylorthoformate (15 mL), and acetic anhydride (2 drops) was refluxed for 8 h. The reaction mixture was left to cool. The solid product was filtered and recrystallized from ethanol to afford **26** (0.76 g, 43%); mp 145°C; IR: 2926, 2864 (CH_{aliph}), 2220 (2CN), 1521 (C=S), 1241 (C–O) cm^{-1}; ^{1}HNMR: 8.81 (s, 1H, N=CH), 7.64–7.62 (m, 6H, arom.+CH–N), 4.52–4.44 (q, 2H, =C–OCH_2), 3.41–3.32 (m,

4H, $2OCH_2$), 1.43–1.35 (m, 9H, $3CH_3$). *Anal*. Calcd for $C_{21}H_{22}N_4O_3S$: C, 61.44; H, 5.40; N, 13.65; S, 7.81. Found: C, 61.53; H, 5.52; N, 13.73; S, 7.89.

6-Amino-2-mercapto-4-phenyl-2-(2-phenylhydrazino)-1,2-dihydropyridine-3,5-dicarbonitrile (27) and 7-amino-3,9-diphenyl-4-oxa-1,2,6-triazaspiro[4.5]deca-2,7,9-triene-8,10-dicarbonitrile (28). *General procedure.* To a mixture of compound **26** (0.001 mol, 0.41 g), phenyl hydrazine, or benzohydrazide (0.003 mol) in ethanol (20 mL), TEA (2 drops) was added. The reaction mixture was stirred for 4 h at r.t. The product that formed was collected by filtration and then crystallized from ethanol.

6-Amino-2-mercapto-4-phenyl-2-(2-phenylhydrazino)-1,2-dihydropyridine-3,5-dicarbonitrile (27). Yield: 53%, mp 233°C; IR: 3459, 3320, 3212 (NH_2, NH), 3073 ($CH_{arom.}$), 2553 (SH), 2208 (CN) cm^{-1}; ^{1}HNMR: 10.1 (s, 1H, NH), 8.5 (s, 1H, NH), 7.4–6.7 (m, 10H, arom.), 5.9 (s, 2H, NH_2), 4.3 (s, 1H, NH), 2.4 (s, 1H, SH). *Anal*. Calcd for $C_{19}H_{16}N_6S$: C, 63.31, H, 4.47; N, 23.32; S, 8.90. Found: C, 63.45; H, 4.42; N, 23.40; S, 8.88.

7-Amino-3,9-diphenyl-4-oxa-1,2,6-triazaspiro[4.5]deca-2,7,9-triene-8,10-dicarbonitrile (28). Yield: 40%, mp 244°C; IR: 3459, 3326, 3215 (NH_2, NH), 3072 ($CH_{arom.}$), 2214 (CN) cm^{-1}; ^{1}HNMR: 7.5 (s, 2H, NH_2), 7.4–7.0 (m, 10H, arom.), 4.3 (s, 1H, NH). *Anal.* Calcd for $C_{20}H_{14}N_6O$: C, 67.79; H, 3.98; N, 23.72. Found: C, 67.61; H, 4.07; N, 23.63.

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