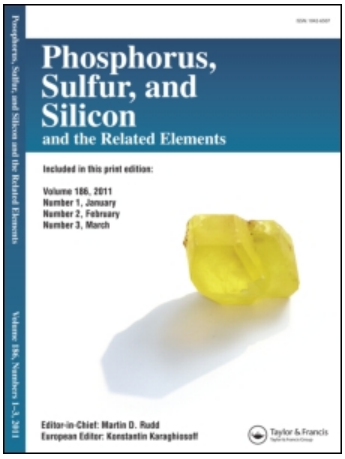

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A Novel Synthesis of Pyridine-2(1*H*)-thione, Pyrazolo[3,4-*b*]pyridine, Pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine, Thieno[2,3-*b*]pyrdine, and Pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine Derivatives Containing a Naphthyl Moiety

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A Novel Synthesis of Pyridine-2(1*H*)-thione, Pyrazolo[3,4-*b*]pyridine, Pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine, Thieno[2,3-*b*]pyrdine, and Pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine Derivatives Containing a Naphthyl Moiety

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6-Amino-4-naphthyl-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitriles ***3a,b*** *were synthesized from the reaction of naphthaldehydes* ***1a,b*** *and cyanothioacetamide (****2****). Compounds* ***3a,b*** *were taken as starting materials for the synthesis of pyrazolo[3,4-b]pyridine* ***7a,b****, and* ***8a****, Pyrido-[2′,3′:3,4]pyrazolo[1,5-a]pyrimidine* ***9a,b****; thieno[2,3-b]pyridine* ***16a–d****,* ***18a,b****,* ***21a–d****,* ***24a,b****, and* ***25a****; and pyrido[3,2:4,5]thieno[3,2-d]pyrimidine* ***17a,b*** *derivatives through their reactions with the corresponding reagents. All structures of the newly synthesized heterocyclic compounds were established on the basis of IR,* ^{1}H *NMR,* ^{13}C *NMR, mass spectra, and elemental analyses.*

Keywords Pyridine-2(1*H*)-thiones; pyrido[2′,3′:3,4]pyrazolo-[1,5-*a*]pyrimidine; pyrido[3,2:4,5]thieno[3,2-*d*]pyrimidine; thieno[2,3-*b*]pyridine

INTRODUCTION

Recently, many chemical structures containing a naphthyl moiety were reported to exhibit diverse biological and pharmaceutical activities such as anticonvulsant,[1] antimicrobial,[1,2] anticancer,[3,4] anti-allergic,[5] antiobesity,[6] and antidiabetic[6] agents. Moreover, 3,5-dicyanopyridines were reported to have antiproliferative activity on human cancer cell lines,[7] pyridine-3-carbonitriles were used as

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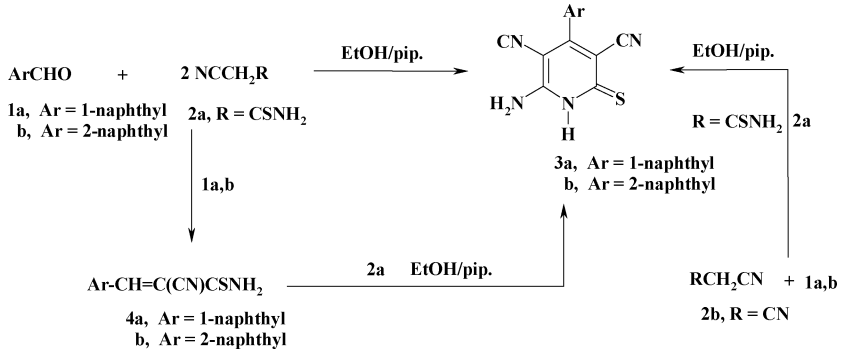
cardiotonic agents,[8,9] and pyridine-2(1*H*)-thiones were reported to have antiviral[10] activity. Furthermore, pyrazolo[3,4-*b*]-pyridines were used as antimalarial,[11] antiproliferative,[12] antimicrobial,[13] antiviral,[14] and inhibitors of cyclin-dependent kinases,[15] A1-adenosine receptor ligands.[16] On the other hand, thieno[2,3-*b*]pyridines were reported to have antimicrobial,[17] antiviral,[10,18] and anti-inflammatory[19] activities. Also pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines revealed anti-proliferative[20] activity. In addition, pyrido[3′,2′:4,5]thieno [3,2-*d*]-pyrimidines are used as anti-allergic,[21] antiprotozoals,[22] anti-anaphylactic,[23] and antimicrobial[17] agents. In view of these reports and as a continuation of our research program in the chemistry of pyridines,[24–33] we report the synthesis of additional new numbers of these derivatives that are required in medicinal chemistry programs.

RESULTS AND DISCUSSION

The present work reports a possible route to the synthesis of 6-amino-3,5-dicyano-4-naphthylpyridine-2(1*H*)-thiones **3a**,**b** as starting materials. It has been found that 1-naphthaldehyde (**1a**) reacted with 2-cyanoethanethioamide (**2a**) in a 1:2 molar ratio in ethanolic piperidine solution under reflux to give the corresponding 6-amino-4-(1-naphthyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**3a**). The structure of **3a** was established via its elemental analysis, IR, and ^{1}H NMR spectra. The IR spectrum of **3a** revealed NH_2 and NH groups at 3450, 3356, and 3302 cm^{-1} and the CN group at 2214 cm^{-1}, while its ^{1}H NMR spectrum indicated signals at $\delta = 7.47$–8.08 (m, 7H, Ar-H), 8.12 (s, 2H, NH_2), and 13.13 (br, 1H, NH) (cf. Experimental Section and Scheme 1).



SCHEME 1

Similarly, 2-naphthaldehyde (**1b**) reacted with 2-cyanoethanethioamide (**2a**) in a 1:2 molar ratio under the same reaction

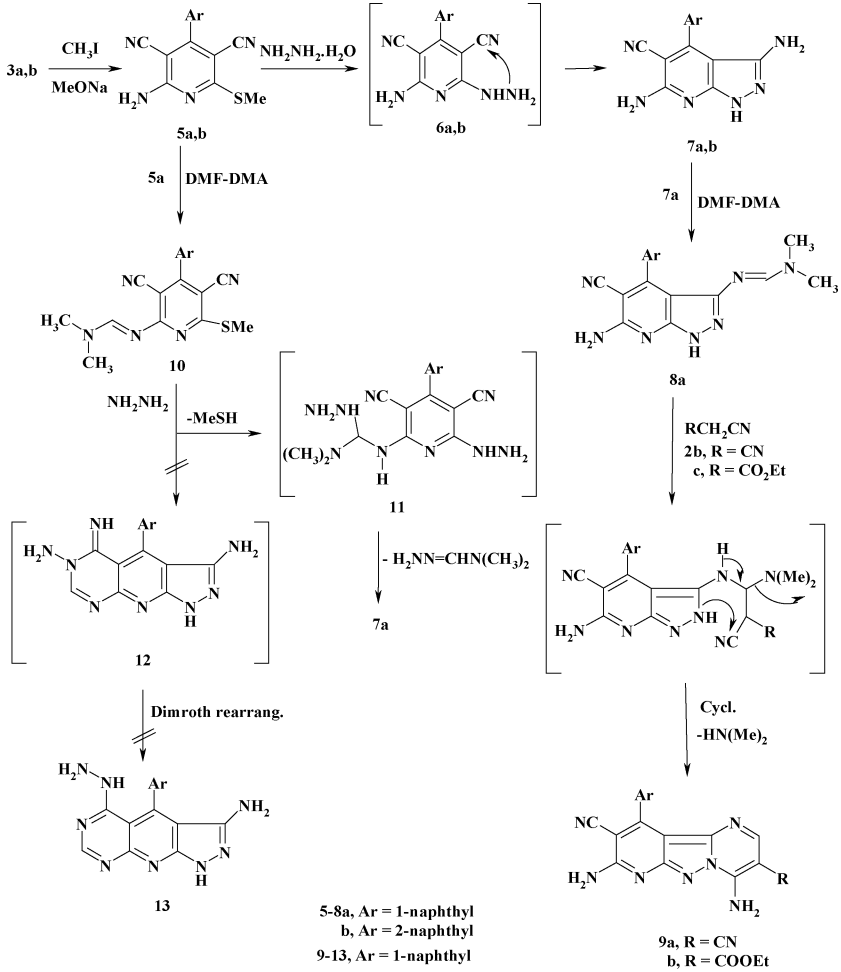
conditions to give the corresponding 6-amino-4-(2-naphthyl)-2-thioxo-1, 2-dihydropyridine-3,5-dicarbonitrile (**3b**). The structure of **3b** was established via its elemental analysis, IR spectra (cf. Experimental Section and Scheme 1).

The structure **3a**,**b** was elucidated via the synthesis by other routes. The reaction of **2a** with **1a**,**b** gave thiocarboxamidocinnamonitrile derivatives **4a**,**b**,[30] which further reacted with another molecule of **2a** to give **3a**,**b**. Condensation of malononitrile (**2b**) with **1a**,**b**, followed by the reaction with **2a**, afforded **3a**,**b**. Compounds **3a**,**b** that were prepared by these two routes were found completely identical in all aspects with **3a**,**b** , which were previously prepared (cf. Scheme 1).

It was found that compound **3a**,**b** reacted with methyl iodide to afford the corresponding 2-amino-6-(methylthio)-4-(naphthyl)pyridine-3,5-dicarbonitrile derivatives **5a**,**b**. Compound **5a** reacted with hydrazine hydrate to give a sulfur-free compound corresponding to 3,6-diamino-4-(1-naphthyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**7a**). The latter reaction product could be formed via the addition of a hydrazino group of **6a** to the nitrile function. The IR spectrum of **7a** showed the new amino group. Moreover, its mass spectrum gave m/e = 300, which corresponds to the molecular weight of compound **7a**. In the same manner compound **5b** reacted with hydrazine hydrate to give the corresponding 3,6-diamino-4-(2-naphthyl)-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**7b**). Compound **7b** could be confirmed based on the elemental analysis and spectral data as **7a** (cf. Experimental Section and Scheme 2).

Condensation of **7a** with one mole of Dimethylformamide-dimethylacetal (DMF-DMA) in dry dioxan afforded 6-amino-3-{[(*N*,*N*-dimethylamino)methylene]amino)}-1*H*-pyrazolo[3,4-*b*]pyridine derivative **8a** (cf. Scheme 2). The IR spectrum of **8a** showed the band at 3424, 3333, and 3216 cm^{-1}, which corresponds to the NH group at the pyrazole ring and NH_2 on the pyridine ring. Its ^1H NMR spectrum revealed signals at δ 3.09 (s, 3H, CH_3, $N(CH_3)_2$), 3.19 (s, 3H, CH_3, $N(CH_3)_2$), 7.32–7.63 (m, 7H, Ar—H), 8.04 (s, 2H, NH_2), 8.65 (s, 1H, N=CH), and 12.56 (s, 1H, NH). Further elucidation of the structure of **8a** was achieved via its reaction with active methylene compounds such as malononitrile (**2b**) and ethyl cyanoacetate (**2c**). Compound **8a** reacted with malononitrile (**2b**) to give the corresponding 4,8-diamino-10-(1-naphthyl)-pyrido[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-3,9-dicarbonitrile (**9a**). The IR spectrum of **9a** showed the new amino group on the pyrimidine ring in addition to the amino group on the pyridine ring.

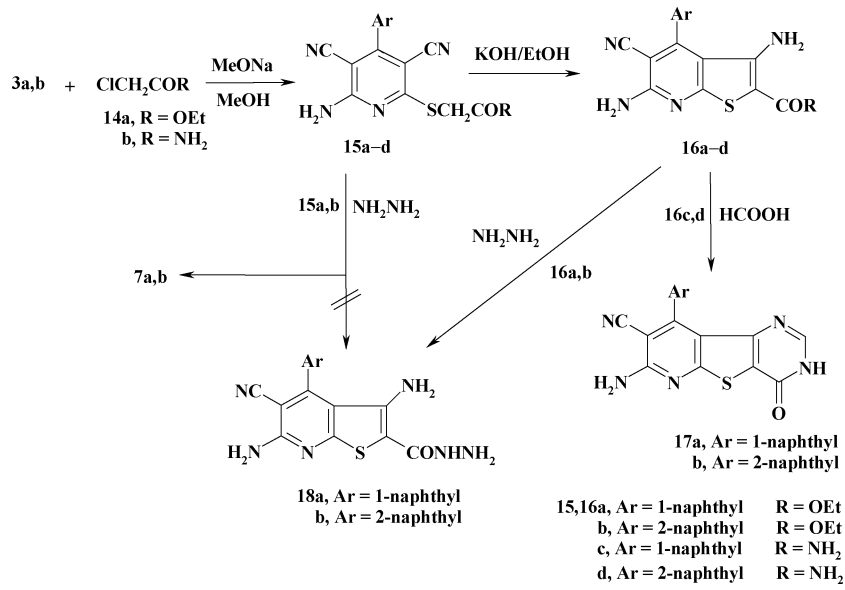
The ^1H NMR spectrum of **9a** showed the signals corresponding to the amino groups. Compound **8a** reacted with ethyl cyanoacetate (**2c**) to give the corresponding ethyl 4,8-diamino-9-cyano-10-(1-



SCHEME 2

naphthyl)Pyrido-[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**9b**). Compound **9b** was confirmed based on elemental analysis and spectral data.

It has been found that **5a** reacted with DMF-DMA to give the formamidine derivative **10**. Its IR spectrum showed the absence of the amino groups. The ^{1}H NMR spectrum of **10** revealed signals for $N(CH_3)_2$ and N=CH protons and the absence of any signal attributed to the NH_2 protons. The reaction of **10** with hydrazine hydrate did not give the expected product **13**, but gave compound **7a**. The formation of **7a** in this



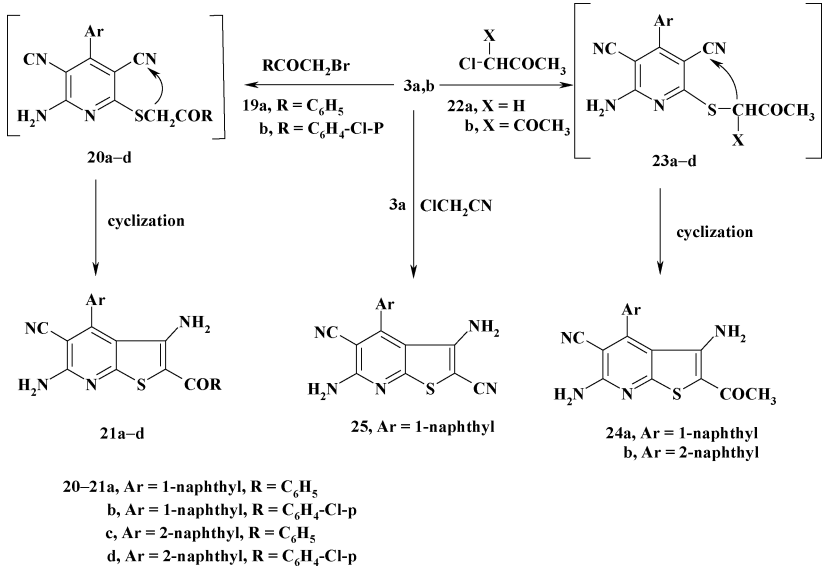
SCHEME 3

reaction is assumed to proceed via the first formation of the non-isolable hydrazino derivative **11**, which would then cyclize via an addition to the nitrile function at position-3 with the *N*,*N*-dimethylaminomethylene exchange of the hydrazino at position-6 under the applied reaction conditions leading to regeneration of the amino group[27,34] at that position, and hence the formation of **7a** (cf. Experimental Section and Scheme 2). The structure of **3a**,**b** was confirmed via the reaction of **3a**,**b** with halogenated compounds such as ethyl chloroacetate (**14a**) and chloroacetamide (**14b**) (cf. Scheme 3). Thus, it was found that compound **3a** reacted with ethyl chloroacetate (**14a**) in methanolic sodium methoxide solution to yield the corresponding ethyl [6-amino-3,5-dicyano-4-(1-naphthyl)pyridin-2-yl]thioacetate (**15a**) via dehydrochloronation. The structure of **15a** was confirmed by elemental analysis and spectral data. The IR spectrum of **15a** showed the presence of absorption bands due to CN, $NH_2$and ester CO functional groups (cf. Scheme 3 and Experimental Section). In a similar manner, compound **3a** reacted with **14b** to afford the corresponding 2-[6-amino-3,5-dicyano-4-(1-naphthyl)pyridin-2-yl]thioacetamide (**15c**). Compound **3b** reacted with each of **14a**,**b** to give the corresponding [6-amino-3,5-dicyano-4-(2-naphthyl)pyridin-2-yl]thio derivatives **15b**,**d**. The structures of **15a–d** were further elucidated via their cyclization to the corresponding thieno[2,3-*b*]pyridine derivatives **16a–d** upon boiling in

ethanolic potassium hydroxide solution. The structures of **16a–d** were inferred from analyses, spectral data, and chemical transformations. The IR spectra of compounds **16a–d** showed the presence of the absorption bands of the new NH_2 group (cf. Scheme 3 and Experimental Section).

Compounds **16c**,**d** reacted with formic acid to give the corresponding pyrido[2′, 3′:5,4]thieno[3,2-*d*]pyrimidine derivatives **17a**,**b**. The structure of compounds **17a**,**b** was confirmed from elemental analyses and spectral data. Reaction of compounds **15a**,**b** with hydrazine hydrate gave compounds **7a**,**b** and not the expected acid hydrazide products **18a**,**b**. Compounds **18a**,**b** were prepared via the reaction of **16a**,**b** with hydrazine hydrate. The elemental analyses, IR, ^{1}H NMR, ^{13}C NMR and mass spectra of **18a**,**b** were found in good agreement with the assigned structures. The mass spectrum of **18a** indicated the M^+ at m/z 374 (22.3%) and the base peak at m/z 343 (100%), which correspond to M^+ (374)–$NHNH_2$ (31) (cf. Scheme 3 and Experimental Section).

Furthermore, **3a** reacted with each of *ω*–bromoacetophenone derivatives **19a**,**b** in ethanol/piperidine solution under reflux to afford the corresponding thieno[2,3-*b*]pyridine derivatives **21a**,**b**, respectively (cf. Scheme 4). Compounds **21a**,**b** were formed via the non-isolable intermediates **20a**,**b**. The other analogue **3b** reacted with **19a**,**b** under the same reaction conditions to give the corresponding thieno[2,3-*b*]pyridine



SCHEME 4

derivatives **21c**,**d** through the non-isolable intermediates **20c**,**d**. Structures of **21a–d** were elucidated on the basis of IR, ^{1}H NMR and elemental analyses data (cf. Scheme 4 and Experimental Section).

Compounds **3a**,**b** reacted with chloroacetone (**22a**) in methanolic sodium methoxide solution at room temperature to afford the corresponding thieno[2,3-*b*]pyridine derivatives **24a**,**b** through the non-isolable intermediates **23a**,**b**. The reaction seemed to proceed through dehydrochlorination to give the non-isolable intermediates **23a**,**b**, which underwent cyclization *via* addition of the methine or a methylene group to the nitrile function. Elemental analyses and spectral data were the basis of which the structures of **24a**,**b** were established. Moreover, compounds **24a**,**b** were authenticated via the reaction of each of **3a**,**b** with α-chloroacetylacetone (**22b**) via the intermediacy of each of the non-isolable **23c,d**. The non-isolable intermediates **23c,d** are assumed to be cyclized to give the corresponding non-isolable 3-imino derivatives that hydrolyzed readily with liberation of one molecule of acetic acid under the applied reaction conditions to afford the final isolable **24a**,**b**. On the other hand, compound **3a** reacted with chloroacetonitrile to give the corresponding thieno[2,3-*b*]pyridine derivative **25**. Its structure was confirmed on the basis of elemental analysis and spectral data (cf. Scheme 4 and Experimental data).

EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra from KBr discs were recorded on a Bruker Vector 22 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were determined in DMSO-d_6 and $CDCl_3$ at 300 MHz on a Varian Mercury VX spectrometer using TMS as an internal standared. Chemical shifts are expressed as δ or ppm. Mass spectra were recorded on a GCMS-QP 1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

Compounds **4a**,**b**[30] were prepared according to the literature procedure.

Synthesis of 6-Amino-4-(naphthyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitriles 3a,b:

General Procedures

Method A

An equimolecular amount of arylidine **4a**,**b** (0.238 g, 1.0 mmole), cyanoethanethioamide (**2a**) (0.1 g, 1.0 mmole) and piperidine (0.5 mL)

TABLE I Elemental Analyses of the Newly Synthesized Compounds

Compound No.	Solvent of Cry. Yield %	Color M.P., °C	Mol. Formula Mol. wt	% Analysis Calcd./ Found				
				C	H	N	S	Cl
3a	Ethanol	Yellow	$C_{17}H_{10}N_4S$	67.54	3.31	18.54	10.59	—
	65	294–296	302	67.30	3.30	18.40	10.50	—
3b	Ethanol	Yellow	$C_{17}H_{10}N_4S$	67.54	3.31	18.54	10.59	—
	60	276–278	302	67.40	3.20	18.30	10.40	—
5a	Ethanol	Yellow	$C_{18}H_{12}N_4S$	68.35	3.79	17.72	10.12	—
	55	264–268	316	68.30	3.60	17.60	10.20	—
5b	Ethanol	White	$C_{18}H_{12}N_4S$	68.35	3.79	17.72	10.12	—
	68	254–256	316	68.20	3.70	17.60	10.10	—
7a	Ethanol	Yellow	$C_{17}H_{12}N_6$	67.54	4.67	27.80	—	—
	65	296–298	300	67.40	4.50	27.70	—	—
7b	Ethanol	Yellow	$C_{17}H_{12}N_6$	67.54	4.67	27.80	—	—
	75	278–280	300	67.30	4.50	27.60	—	—
8a	Dioxane	Yellow	$C_{20}H_{17}N_7$	67.61	4.79	27.61	—	—
	67	308	355	67.50	4.70	27.60	—	—
9a	Ethanol	Red	$C_{21}H_{12}N_8$	67.02	3.19	29.70	—	—
	70	354–356	376	67.10	3.10	29.70	—	—
9b	Acetic acid	Yellow	$C_{21}H_{12}N_8$	65.25	4.02	23.17	—	—
	64	320	423	65.20	3.90	23.10	—	—
10	Dioxane	Yellow	$C_{21}H_{17}N_5S$	67.92	4.58	18.87	8.63	—
	70	284–286	371	67.80	4.50	18.70	8.50	—
15a	Ethanol	Yellow	$C_{21}H_{16}N_4O_2S$	64.94	4.12	14.43	8.24	—
	60	202–204	388	64.80	4.10	14.30	8.20	—
15b	Ethanol	Yellow	$C_{21}H_{16}N_4O_2S$	64.94	4.12	14.43	8.24	—
	65	210	388	64.70	4.10	14.20	8.10	—
15c	Ethanol	Yellow	$C_{19}H_{13}N_5OS$	63.51	3.62	19.49	8.91	—
	64	264	359	63.40	3.50	19.30	8.80	—
15d	Ethanol	Yellow	$C_{19}H_{13}N_5OS$	63.51	3.62	19.49	8.91	—
	55	220	359	63.30	3.50	19.30	8.80	—
16a	Ethanol	White	$C_{21}H_{16}N_4O_2S$	64.94	4.12	14.43	8.24	—
	68	310–312	388	64.70	4.00	14.20	8.20	—
16b	Ethanol	Yellow	$C_{21}H_{16}N_4O_2S$	64.94	4.12	14.43	8.24	—
	55	>300	388	64.70	4.10	14.20	8.10	—
16c	Ethanol	Yellow	$C_{19}H_{13}N_5OS$	63.51	3.62	19.49	8.91	—
	64	310	359	63.40	3.50	19.30	8.80	—
16d	Ethanol	Yellow	$C_{19}H_{13}N_5OS$	63.51	3.62	19.49	8.91	—
	54	272–274	359	63.40	3.40	19.40	8.80	—
17a	Ethanol	Yellow	$C_{20}H_{11}N_5OS$	65.04	2.98	18.97	8.67	—
	70	200	369	65.10	2.80	18.80	8.60	—
17b	Ethanol	Yellow	$C_{20}H_{11}N_5OS$	65.04	2.98	18.97	8.67	—
	50	>300	369	64.90	2.90	18.80	8.60	—
18a	Ethanol	Yellow	$C_{19}H_{14}N_6OS$	60.96	3.74	22.46	8.56	—
	65	278	374	60.80	3.60	22.40	8.40	—
18b	Ethanol	Yellow	$C_{19}H_{14}N_6OS$	60.96	3.74	22.46	8.56	—
	60	200	374	60.80	3.60	22.30	8.40	—

(Continued on next page)

TABLE I Elemental Analyses of the Newly Synthesized Compounds *(Continued)*

Compound No.	Solvent of Cry. Yield %	Color M.P., °C	Mol. Formula Mol. wt	% Analysis Calcd./ Found C	H	N	S	Cl
21a	Ethanol	Yellow	$C_{25}H_{16}N_4OS$	71.42	3.80	13.33	7.61	—
	65	322–324	420	71.20	3.70	13.20	7.50	—
21b	Ethanol	Yellow	$C_{25}H_{15}N_4OSC$	66.00	3.30	12.32	7.04	7.8
	55	344–346	454.5	65.90	3.20	12.30	6.80	7.8
21c	Ethanol	Orange	$C_{25}H_{16}N_4OS$	71.42	3.80	13.33	7.61	—
	60	318–320	420	71.20	3.70	13.20	7.50	—
21d	Ethanol	Orange	$C_{25}H_{15}N_4OSC$	66.00	3.30	12.32	7.04	7.8
	68	330–332	454.5	66.10	3.20	12.30	6.80	7.8
24a	Ethanol	Yellow	$C_{20}H_{14}N_4OS$	67.03	3.91	15.64	8.94	—
	55	320–322	358	67.10	4.10	15.50	8.80	—
24b	Ethanol	Yellow	$C_{20}H_{14}N_4OS$	67.03	3.91	15.64	8.94	—
	65	318	358	67.10	4.10	15.50	8.80	—
25	DMF	Green	$C_{19}H_{11}N_5S$	66.86	3.23	20.53	9.38	—
	68	286	341	66.70	3.20	20.40	9.30	—

in ethanol (30 mL) was heated under reflux for 5 h. The excess of the ethanol was evaporated by vacuum. The solid obtained was collected by filtration and crystallized from ethanol to give **3a**,**b**, respectively (cf. Tables I and II).

Method B

A mixture of 1- or 2-naphthalaldehyde (**1a**,**b**) (0.156 g, 1.0 mmole), cyanoethanethioamide (**2a**) (0.2 g, 2.0 mmole), and piperdine (0.5 mL) in ethanol (30 mL) was heated under reflux for 5 h. The excess of the ethanol was evaporated by vacuum. The solid obtained was collected by filtration and crystallized from ethanol to give **3a**,**b**, respectively (cf. Tables I and II).

Method C

A mixture of 1- or 2-naphthalaldehyde (**1a**,**b**) (0.156 g, 1.0 mmole), cyanoethanethioamide (**2a**) (0.1 g, 1 mmole), malononitrile (**2b**) (0.066 g, 1.0 mmole), and piperdine (0.5 mL) in ethanol (30 mL) was heated under reflux for 5 h. The excess of ethanol was evaporated by vacuum. The solids obtained were collected by filtration and crystallized from ethanol to give **3a**,**b**, respectively (cf. Tables I and II).

TABLE II Spectral Data of the Newly Synthesized Compounds

Compound No.	Spectral data, IR (cm^{-1}), ^1H NHR, ^{13}C NMR and MS
3a	IR: 3450, 3356, 3302 (NH_2 and NH) and 2214 (CN); ^1H NMR: (DMSO-d_6)δ 7.47–8.08 (m, 7H, Ar-H), 8.12 (s, 2H, NH_2, and 13.13 (br., 1H, NH); ^{13}C NMR (DMSO-d_6)δ 82.94, 103.82, 114.15, 116.05, 124.36, 125.31, 125.79, 126.55, 127.24, 128.41, 129.15, 130.0, 132.04, 132.87, 154.43, 158.02 and 179.25.
3b	IR: 3442, 3365, 3308 (NH_2 and NH) and 2216 (CN).
5a	IR: 3315, 3193 (NH_2) and 2215 (CN); ^1H NMR: (DMSO-d_6)δ 2.75 (s, 3H, SCH_3), 7.38–7.88 (m, 7H, Ar-H), 8.11 (s, 2H, NH_2).
5b	IR: 3320, 3195 (NH_2) and 2214 (CN).
7a	IR: 3473, 3354, 3300, 3155 (two $NH_2$and NH) and 2213 (CN); ^1H NMR: (DMSO-d_6)δ 6.54 (s, 2H, NH_2), 7.42–7.75 (m, 7H, Ar-H), 8.24 (s, 2H, NH_2) and 12.18 (s, 1H, NH); MS: m/z 300 (33%), 301 (100%).
7b	IR: 3460, 3355, 3306, 3150 (two NH_2 and NH) and 2215(CN); ^1H NMR: (DMSO-d_6)δ 6.79 (s, 2H, NH_2), 7.60–8.08 (m, 7H, Ar-H), 8.14 (s, 2H, NH_2) and 11.91 (s, 1H, NH).
8	IR: 3424, 3333 and 3216 (NH_2 and NH) and 2214 (CN); ^1H NMR: (DMSO-d_6)δ 3.09 (s, 3H, CH_3, $N(CH_3)_2$), 3.19 (s, 3H, CH_3, $N(CH_3)_2$), 7.32–7.63 (m, 7H, Ar-H), 8.04 (s, 2H, NH_2), 8.65 (s, 1H, N=CH) and 12.56 (s, 1H, NH); ^{13}C NMR (DMSO-d_6)δ 32.39, 34.37, 105.13, 117.49, 124.79, 125.22, 125, 64, 126.14, 126.82, 127.79, 128.50, 129.85, 130.92, 132.55, 150.19, 152.40, 153.04, 155.94, 156.01 and 162.47.
9a	IR: 3427, 3391, 3310, 3289 (two NH_2), 2214 (CN); ^1H NMR: (DMSO-d_6)δ 8.04–8.96 (m, 7H, Ar-H), 9.01 (s, 2H, NH_2), 9.66 (s, 1H, N=CH) and 9.98 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6)δ 78.86, 100.46, 101.93, 114.78, 116.68, 118.49, 118.80, 125.15, 125.92, 128.19, 129.28, 130.18, 131.87, 132.81, 144.08, 148.78, 152.64, 159.40 and 164.42.
9b	IR: 3400, 3336, 3273, 3235, (two NH_2); 2218 (CN) and 1694 (ester CO); ^1H NMR: (DMSO-d_6)δ 1.23–1.27 (t, J = 7.5 Hz, 3H, $CH_2\underline{CH_3}$), 4.26–4.28 (q, J = 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 7.39–8.13 (m, 9H, Ar-H and NH_2), 8.38 (s, 2H, NH_2) and 8.83 (s, 1H, CH).
10	IR: 2221 (CN); ^1H NMR: (DMSO-d_6)δ 2.82 (s, 3H, SCH_3), 3.06 (s, 3H, CH_3, $N(CH_3)_2$), 3.11 (s, 3H, CH_3, $N(CH_3)_2$), 7.42–7.83 (m, 7H, Ar-H) and 8.55 (s, 1H, N=CH).
15a	IR: 3479, 3325 (NH_2), 2214 (CN) and 1743 (ester CO).
15b	IR: 3475, 3320, (NH_2), 2218 (CN), and 1745 (ester CO); ^1H NMR: (DMSO-d_6)δ 1.21–1.26 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 4.13–4.20 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 4.22 (s, 2H, SCH_2), 7.61–8.09 (m, 7H, Ar-H), and 8.15 (s, 2H, NH_2).
15c	IR: 3450, 3417, 3294, 3178 (two NH_2), 2217 (CN) and 1651 (amidic CO).
15d	IR: 3452, 3402, 3332, 3224 (two NH_2), 2214(CN) and 1643 (amidic CO).
16a	IR: 3478, 3367, 3294, 3198 (two NH_2), 2218 (CN) and 1690 (CO-ester with H-bond).
16b	IR: 3400, 3356, 3273, 3178 (two NH_2), 2216 (CN) and 1694 (CO-ester with H-bond); MS: m/z 388 (53.2%), 316 (100%).

(Continued on next page)

TABLE II Spectral Data of the Newly Synthesized Compounds *(Continued)*

Compound No.	Spectral data, IR (cm^{-1}), ^1H NHR& ^{13}C NMR and MS
16c	IR: 3479, 3425, 3379, 3325, 3325, 3209 (three NH_2), 2214 (CN) and 1635 (amidic-CO with H-bond).
16d	IR: 3490, 3402, 3332, 3224 (three NH_2), 2214 (CN) and 1643 (amidic-CO); ^1H NMR: (DMSO-d_6)δ 5.58 (s, 2H, NH_2), 6.97 (s, 2H, NH_2), 7.33 (s, 2H, NH_2) and 7.57–8.12 (m, 7H, Ar-H).
17a	IR: 3490, 3332, 3200 (NH_2 and NH), 2214 (CN) and 1658 (CO); ^1H NMR: (DMSO-d_6)δ 7.55–7.67 (m, 7H, Ar-H), 8.05 (s, 2H, NH_2), 8.11 (s, 1H, CH) and 8.14 (s, 1H, NH).
17b	IR: 3495, 3336, 3204 (NH_2 and NH), 2214 (CN) and 1651(CO).
18a	IR: 3463, 3402, 3301, 3186 (three NH_2 and NH), 2214 (CN) and 1630(CO); ^1H NMR: (DMSO-d_6)δ 4.32 (br, 2H, NH2), 5.24 (br, 2H, NH_2), 7.36–7.74 (m, 7H, A-rH), 8.19 (s, 2H, NH_2) and 8.84 (s, 1H, NH); ^{13}C NMR: (DMSO-d_6)δ 90.66, 115.46, 124.34, 125.42, 126.44, 126.75, 127.48, 128.50, 129.89, 130.86, 132.81, 145.42, 145.70, 150.10, 158.41, 188.71.
18b	IR: 34643, 3400, 3309, 3196 (three NH_2 and NH), 2214 (CN) and 1635(CO).
21a	IR: 3467, 3334, 3220, 3178 (two NH_2), 2214 (CN) and 1650 (CO); ^1H NMR: (DMSO-d_6)δ 5.55 (br, 2H, NH_2), 6.68–7.47 (m, 14H, A-rH and NH_2); ^{13}C NMR: (DMSO-d_6)δ 91.58, 99.65, 113.34, 114.99, 124.18, 125.60, 126.40, 126.81, 128.27, 129.52, 130.22, 132.98, 140.78, 150.64, 152.00, 159.24, 166.17, 183.09 and 187.50; MS: m/z 420 (100%), 77 (48.1%).
21b	IR: 3467, 3334, 3220, 3178 (two NH_2), 2219 (CN) and 1650 (CO).
21c	IR: 3467, 3334, 3220, 3178 (two NH_2), 2217(CN) and 1654 (CO).
21d	IR: 3467, 3334, 3220, 3178 (two NH_2), 2214(CN) and 1656 (CO); ^1H NMR: (DMSO-d_6)δ 6.75 (br, 2H, NH_2), 7.56–8.17 (m, 11H, Ar-H) and 8.21 (s, 2H, NH_2).
24a	IR: 3437, 3324, 3210, 3188 (two NH_2), 2218(CN) and 1646 (CO with H-bond); ^1H NMR: (DMSO-d_6)δ 2.21 (s, 3H, CH_3), 5.95 (br, 2H, NH_2), 7.38–8.12 (m, 7H, Ar-H) and 8.21 (s, 2H, NH_2).
24b	IR: 3447, 3354, 3230, 3198 (two NH_2), 2216(CN) and 1643 (CO With H-bond).
25	IR: 3464, 3229, 3221, 3163 (two NH_2), 2193 (CN); ^1H NMR: (DMSO-d_6)δ 4.96 (s, 2H, NH_2), 7.40–8.13 (m, 7H, Ar-H) and 8.23 (s, 2H, NH_2).

Synthesis of 2-Amino-6-(methylthio)-4-(naphthyl)pyridine-3,5-dicarbonitriles 5a, b

A solution of each of **3a**,**b** (0.302 g, 1.0 mmole) and methyl iodide (0.213 mL, 1.5 mmole) in sodium methoxide (prepared from 0.01 mol sodium metal in 30 mL of methanol) was heated under reflux for 2 h and then cooled, poured onto ice-cold water, and acidified with hydrochloric acid. The solid products were collected by filtration, washed with water, and crystallized from ethanol to give **5a**,**b**, respectively (cf. Tables I and II).

Reactions with Hydrazine Hydrate: General Procedure

A solution of the appropriate **5a, b** or **10** (0.316 or 0.371 g, 1.0 mmole) in hydrazine hydrate (15 mL) and ethanol (20 mL) was heated under reflux for 5 h. The solid products formed were collected by filtration and crystallized from the proper solvent to give **7a**,**b** and **7a**, respectively (cf. Tables I and II).

Reactions of 5a and/or 7a with DMF-DMA

A mixture of the appropriate **5a** or **7a** (0.316 or 0.3 g, 1.0 mmole) and DMF-DMA (1.692 mg, 1.2 mmole) in dry dioxane (30 mL) was heated under reflux for 3 h. The solids obtained after cooling were collected by filtration and crystallized from dioxane to give **10** and **8a**, respectively (cf. Tables I and II).

Synthesis of 4,8-Diamino-10-(1-naphthyl)pyrido[2′,3′:3,4]-pyrazolo[1,5-*a*]pyrimidine-3,9-dicarbonitrile (9a) and Ethyl 4,8-Diamino-9-cyano-10-(1-naphthyl)pyrido[2′,3′:3,4]pyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (9b)

A mixture of compound **8a** (0.355 g, 1.0 mmole) and either malononitrile (**2b**) or ethyl cyanoacetate (**2c**) (0.066 g or 0.113 ml, 1.0 mmole) in ethanol (30 mL) containing 0.5 mL of triethylamine, as a catalyst, was heated under reflux for 5 h. The solid products formed were collected by filtration and crystallized from the proper solvent to give **9a**,**b**, respectively (cf. Tables I and II).

Reactions of 3a,b with Halogen-Containing Compounds

General Procedure

A solution of **3a**,**b** (0.302 g, 1.0 mmole) and the appropriate **14a**,**b**, **19a**,**b**, **22a**,**b** and/or chloroacetonitrile (1.0 mmole) in sodium methoxide (prepared from 0.023 g, 1.0 mmole, of sodium metal in 30 mL methanol) was heated under reflux for 4 h. The mixture was cooled, poured onto ice-cold water, and acidified with hydrochloric acid. The solid products were collected by filtration, washed with water, and crystallized from the proper solvent to give **15a–d**, **21a–d**, **24a**,**b**, and **25**, respectively (cf. Tables I and II).

Cyclization of 15a-d

A solution of the appropriate **15a**,**b** (0.388 g, 1.0 mmole) in ethanol (30 mL) and potassium hydroxide (0.112 g, 2.0 mmole) was heated under

reflux for 4 h. The mixture was cooled, poured on to ice-cold water, and acidified with hydrochloric acid. The solid products were collected by filtration, washed with water, and crystallized from the proper solvent to give **16a–d**, respectively (cf. Tables I and II).

Synthesis of 7-Amino-9-(naphthyl)-4-oxo-3,4-dihydropyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-8-carbonitriles 17a,b

A solution of **16c,d** (0.359 g, 1.0 mmole) in formic acid (20 mL) was heated under reflux for 5 h. The excess solvent was evaporated by vacuum. The solids obtained were collected by filtration and crystallized from ethanol to give **17a**,**b** (cf. Tables I and II).

Synthesis of 3,6-Diamino-5-cyano-4-(naphthyl)thieno [2,3-*b*]pyridine-2-carbohydrazides 18a, b

A solution of **16a**,**b** (0.388 g, 1.0 mmole) in hydrazine hydrate (20 mL) and ethanol (20 mL) was heated under reflux for 3 h. The solid products obtained after cooling were collected by filtration and crystallized from ethanol to give **18a**,**b** (cf. Tables I and II).

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