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Convenient Synthesis and Antimicrobial Evaluation of Multicyclic Thienopyridines

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*Thieno[2,3-*b*]pyridines **7**, **8**, and **10** could be obtained via the S-alkylation of 3-cyano-4,6-di-2-furyl-2(1*H*)pyridinethione (**3**) with a variety of alkylating agents. These compounds were conveniently converted into novel pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines 12–15 and 17–20 and thieno[2,3-*b*;4,5-*b*′]dipyridine 11 derivatives. Structures of the products have been determined by elemental analyses and spectral data studies. All the tested compounds were found to exhibit moderate antimicrobial activity.*

Keywords Multicyclic pyridines; pyridothienopyrimidine; thienodipyridine; thienopyridine

INTRODUCTION

3-Cyano-2(1H)-pyridinethiones are of interest because of their use as intermediates for the synthesis of the biologically active deazafolic acid and for deazaaminopterin ring synthesis.[1,2] On the other hand, fused pyrimidines continue to attract considerable attention because of their great practical usefulness, primarily, due to a very wide spectrum of biological activities. Thienopyrimidine derivatives are characterized by a very broad spectrum of biological activities, which includes several activities such as antiallergic,[3] antiatherosclerotic,[4] antibacterial,[5–7] anticancer,[8] antiviral,[9,10] antihypertensive,[11,12] antidepressant,[13] antihistaminic,[14] antimicrobial,[15–19] and neurotropic[20] activities. Various thieno[2,3-*d*]pyrimidine and thieno[3,2-*d*]pyrimidine derivatives show pronounced antitumor[21,22] and radioprotective[23] activities. Thus, it was of interest to synthesize ring systems combining both the pyridine and the thienopyrimidine moieties for testing their antimicrobial activities.

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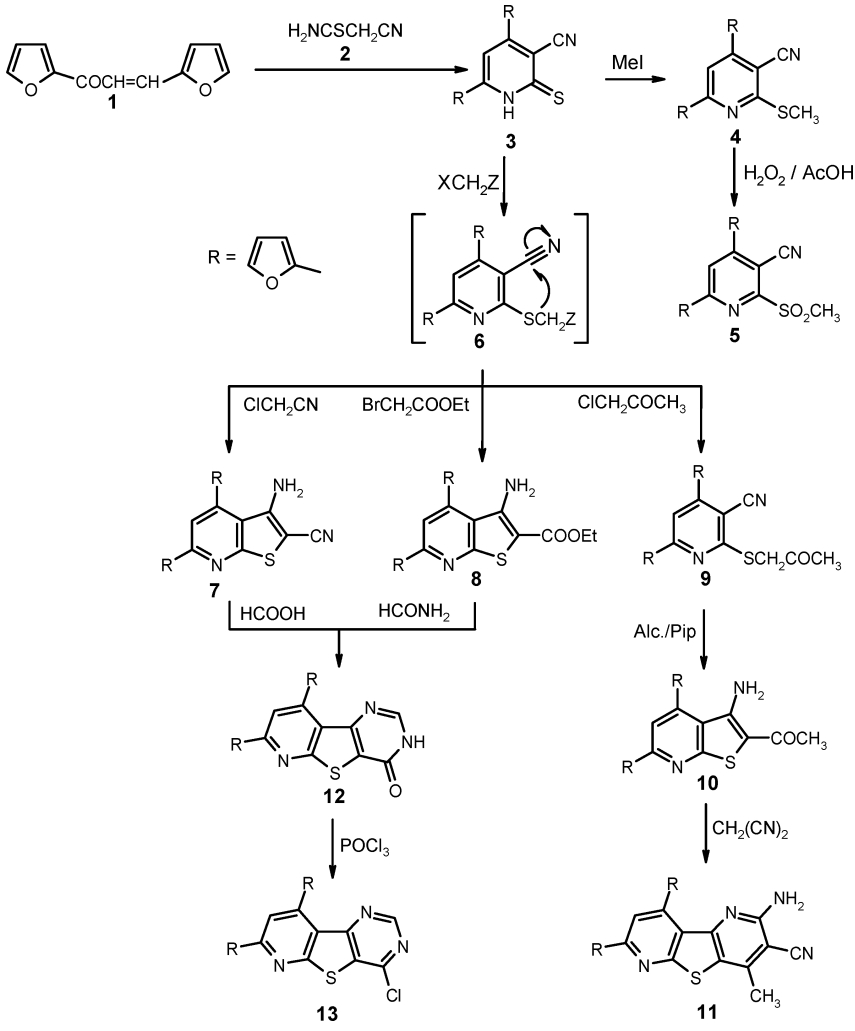
RESULTS AND DISCUSSION

Treatment of 1,3-di-2-furylpropenone (**1**) with 2-cyanothioacetamide (**2**) in methoxide solution afforded 3-cyano-4,6-di-2-furyl-2(1*H*)pyridinethione (**3**) in moderate yield after crystallization from methanol. The structure of the product was supported by its elemental analysis and spectral data. Compound **3** was alkylated with methyl iodide, chloroacetonitrile, ethyl bromoacetate, and chloroacetone in DMF-KOH to give different product in each case (Scheme 1).



SCHEME 1

Thus, the reaction of **3** with methyl iodide gave the methyl sulfide **4**, as evident from its elemental analysis and spectral data, in good yield. Attempts to affect direct displacement of the methyl sulfide group of **4** with hydrazine were unsatisfactory, giving only intractable mixtures. Moreover, the corresponding sulfone (**5**), prepared by oxidation of **4** with hydrogen peroxide in acetic acid also failed to give any recognizable product upon reaction with hydrazine hydrate.

On the other hand, **3** was cyclized with the appropriate alkylating agents such as chloroacetonitrile and ethyl bromoacetate in DMF in the presence of potassium hydroxide at room temperature to form the non-isolable *S*-alkylated intermediate **6**, which via nucleophilic substitution and intramolecular cyclocondensation gave the corresponding polyfunctionally substituted 3-amino-4,6-di-(2-furyl)-2-substituted-thieno[2,3-*b*]pyridines **7**, **8** in good yields (Scheme 1). The IR spectra of compounds **7**, **8** revealed the absence of NH and C=S bands, and the amino group appears at 3496–3249 cm^{-1} in the form of two bands due to intramolecular association between the 3-NH_2 and 2-C≡N or 2-$COOC_2H_5$ group of compounds **7**, **8**, as observed in other cyclicenamino ester[24]. ^1H NMR spectra (DMSO-d_6) of compounds **7**, **8** showed a broad singlet at δ 6.21–6.57 (b, 2H) assigned for the NH_2 group and a singlet at δ 7.84–8.31 (s, 1H) assigned for the 5-H of the thieno[2,3-*b*]pyridine ring. Furthermore, the IR spectrum of compound **8** revealed the absence of cyano group and the characteristic absorption band of the carbonyl group at 1684 cm^{-1}. The ^1H NMR spectrum (DMSO-d_6) of compound **8** showed a triplet at δ 1.30 (t, 3H, $J = 3.7$ Hz) and a quartet at δ 4.31 (q, 2H, $J = 2.5$ Hz) assigned for the ethyl group (-CH_2CH_3). Moreover, compounds **7**, **8** showed signals at δ 6.76 (dd, 1H, $J = 4.0, 4.0$ Hz), 7.52 (d, 1H, $J = 3.8$ Hz), and 7.99 (d, 1H, $J = 3.8$ Hz), which were assigned to the protons 4-H, 3-H, and 5-H of the two furyl moieties of the thieno[2,3-*b*]pyridine ring. Assignment of structures **7**, **8** was also confirmed by their mass spectra, which showed peaks corresponding to their molecular ions at *m/z* 307 (M^+) and 354 (M^+), respectively.

Whereas, compound **3** was found to react smoothly with chloroacetone in DMF in the presence of potassium hydroxide at room temperature to give the corresponding 2-oxopropylthionicotinonitrile derivative **9** (Scheme 1) in good yield. Elemental analyses and the spectral characteristics of compound **9** are in agreement with the proposed structure. Thus, in IR spectrum, the strong absorption band of the cyano group was observed at 2218 cm^{-1}. The ^1H NMR spectrum (DMSO-d_6) showed, beside the signals due to the furyl and thienopyridine moieties, two singlets at δ 2.32 (3H, CH_3CO) and 4.22 (2H, SCH_2). Mass spectrum showed a peak at *m/z* 324 (M^+). Upon refluxing in ethanol containing catalytic amount of piperidine, compound **9** underwent self

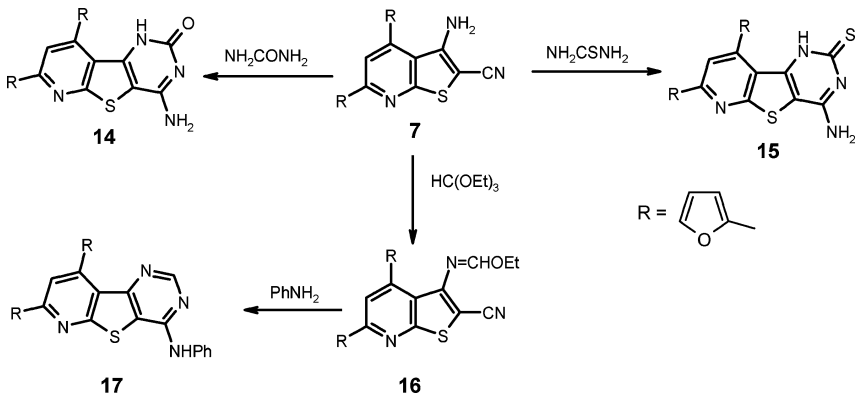
condensation with the formation of 1-(3-amino-4,6-di-2-furylthieno[2,3-*b*]pyridin-2-yl)ethanone (**10**) in good yield. Structure **10** was evident from the spectral data. Thus, IR spectrum of compound **10** revealed absorption bands at 3480 cm^{-1} and 3289 cm^{-1} corresponding to NH_2 and the characteristic absorption band of the carbonyl group at 1596 cm^{-1}, and the absence of cyano group absorption. Its ^1H NMR spectrum (DMSO-d_6) showed, beside the signals due to the furyl and thienopyridine moieties, signals at δ 2.38 (s, 3H, CH_3) and at δ 7.25 (br, 2H, NH_2) along with the disappearance of the signal at 4.22 because of the methylene group.

Treatment of 1-(3-amino-4,6-di-2-furylthieno[2,3-*b*]pyridin-2-yl)ethanone (**10**) with the malononitrile in refluxing ethanolic sodium ethoxide, afforded 2-amino-7,9-di-2-furyl-4-methylpyrido[2′,3′:4,5]-thieno[2,3-*b*]pyridine-3-carbonitrile (**11**).

The structure of compound **11** was established on the basis of its elemental analyses and spectral data. The IR spectrum of compound **11** showed absorption bands 3374 cm^{-1} and 3198 cm^{-1} corresponding to NH_2, and the characteristic absorption band of the cyano group at 2213 cm^{-1}, and the absence of carbonyl group absorption at 1596 cm^{-1}. Its ^1H NMR spectrum revealed signals at δ 2.01 (s, 3H, CH_3) and δ 6.43 (br, 2H, NH_2) and its mass spectrum showed a peak at m/z 372 (M^+).

Compound **7**, as a typical enaminonitrile derivative,[25] reacted with formic acid upon heating for several hours to yield 7,9-di-2-furylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (**12**) (Scheme 1). IR spectrum of compound **12** revealed NH and carbonyl absorption bands at 3423 and 1662 cm^{-1}, respectively, as well as the absence of the cyano absorption at 2197 cm^{-1}. Its ^1H NMR spectrum (DMSO-d_6) revealed, beside the signals due to the furyl and thienopyridine moieties, signals at δ 8.57 (s, 1H, proton on C-2 of pyrimidine ring) and δ 12.56 (s, 1H, NH, of pyrimidine ring). Compound **12** was also obtained by heating **8** in formamide at 180°C for 2 h. 4-chloro-7,9-di-2-furylpyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**13**) was obtained by the reaction of **12** with $POCl_3$ under reflux for 1 h.

Next, Compound **7** was fused with each of urea and thiourea to afford the corresponding pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine derivatives **14** and **15**, respectively (Scheme 2). The spectral characteristics of compounds **14** and **15** are in agreement with the proposed structure. In the IR spectra of compounds **14** and **15**, the absence of the cyano absorption indicates that cyclization was completed. Their ^1H NMR showed signals at δ 7.32–7.41 corresponding to the NH_2 peaks and at δ 12.89–12.97 corresponding to the NH pyrimidine ring and all other signals are exactly matching their structures. Compound **7** reacted with triethylorthoformate in presence of acetic acid at 140°C to give ethyl

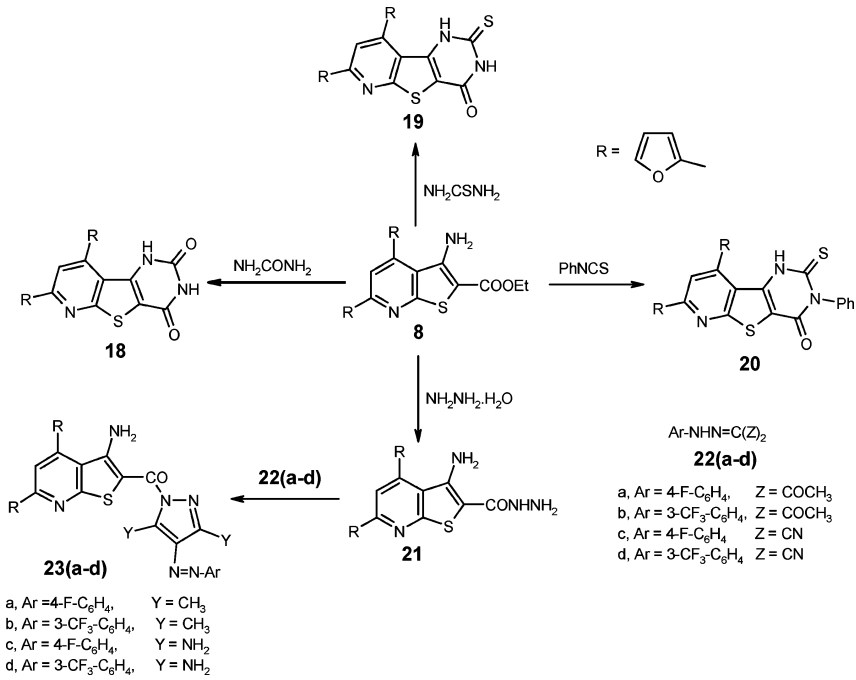


SCHEME 2

(2-cyano-4,6-di-2-furylthieno[2,3-*b*]-pyridin-3-yl)imidoformate (**16**) in a moderate yield. The structure of compound **16** was established on the basis of its elemental analyses and spectral data. The IR spectrum of compound **16** revealed cyano absorption band at 2248 cm^{-1}, and the absence of amino absorption bands at 3400–3100 cm^{-1}. Its ^1H NMR spectrum (DMSO-d_6) revealed signals at δ 1.22 (t, 3H, $J = 8.2$ Hz, CH_3), 4.33 (q, 2H, $J = 9.6$ Hz, CH_2), and δ 8.66 (s, 1H, CH═O) and its mass spectrum showed a peak at m/z 363 (M^+). Compound **16** was further reacted with aniline to afford 4-phenylaminopyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine derivative, **17**. The IR spectrum of compound **17** revealed absorption band at 3452 cm^{-1} (NH) and the absence of cyano absorption band at 2248 cm^{-1}. Its ^1H NMR spectrum (DMSO-d_6) revealed signals at δ 6.21 (1H, br, s, NH), 8.82 (s, 1H, proton on C-2 of pyrimidine ring) along with the furyl and phenyl signals and its mass spectrum showed a peak at m/z 410 (M^+).

Compound **8** also reacted with each of urea, thiourea, and phenyl isothiocyanate to afford the corresponding pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine derivatives **18–20**, respectively. Structures **18–20** were established on the basis of their elemental analyses and spectral data. IR and Mass spectra of compounds **18–20** are in agreement with the proposed structures. Their ^1H NMR spectra (DMSO-d_6) revealed the absence of ethyl ester protons signals, indicating complete cyclization.

Finally, compound **8** reacted with 85% excess of hydrazine hydrate in refluxing ethanol to give 3-amino-4,6-di-2-furylthieno[2,3-*b*]pyridine-2-carbohydrazide (**21**) (Scheme 3). The structure of compound **21** was confirmed by spectral data and elemental analyses. Its ^1H NMR spectrum (DMSO-d_6) revealed the absence of ethyl ester protons signals, and its IR data are in agreement with



SCHEME 3

the proposed structure. Compound **21**, reacted with the azobenzeneacetylacetone derivatives **22a**, **b** in glacial acetic acid to yield the (3-amino-4,6-di-2-furylthieno[2,3-b]pyridin-2-yl)-[4-arylazo-3,5-dimethyl-1-pyrazolylmethanone **23a**, **b** (Scheme 3). The reaction proceeds in two stages, *viz*., the initially formed hydroxypyrazoline subsequently loses water by an acid-catalysed reaction.[26–28] Compound **21** when reacted with azobenzenemalononitrile derivatives **22c,d** in a similar manner gave (3-amino-4,6-di-2-furylthieno[2,3-b]pyridin-2-yl)-4-arylazo-3,5-diamino-1-pyrazolylmethanone **23c**, **d**. Characterization and spectral data of compounds **23a–d** are shown in Tables II and III.

Antimicrobial Activity

The antibacterial and antifungal activities were carried out in the Microbiology Division of the Microanalytical Center at Cairo University, using the diffusion plate method.[29–31] A bottomless cylinder containing a measured quantity (1 mL, 20 mg/mL) of the sample is placed on a plate (7 cm diameter) containing a solid bacterial medium (nutrient agar broth) or a fungal medium (Dox's medium), which has been

heavily seeded with the spore suspension of the test organism. After incubation (24 h for bacteria and 5 days for fungi), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (% inhibition = sample inhibition zone (cm)/plate diameter $\times$ 100). All measurements were done in DMSO as a solvent, which has zero inhibition activity. The obtained results were compared with some reference antibiotics that were purchased from Egyptian markets. As shown in Table I, all the tested compounds were found to exhibit moderate activity against both *Escherichia coli* and *Staphylococcus aureus* microorganisms with respect to the used reference tetracyclin. The antifungal activity of all the tested compounds was found to be similar or higher than the used reference Amfoterisin B.

EXPERIMENTAL

Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on Shimadzu FT-IR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were

TABLE I Antibacterial and Antifungal Activities of Some of the Synthesized Compounds

Sample[a]	Escherichia coli Inhibition (%)[b]	Staphylococcus aureus Inhibition (%)[b]	Candida albicans Inhibition (%)[b]
Control: DMSO	0.0	0.0	0.0
3	17.2	18.6	15.8
4	17.2	20.0	18.6
7	15.8	15.8	15.8
8	17.2	17.2	17.2
10	17.2	15.7	15.7
14	18.6	17.2	18.6
15	18.6	20.0	17.2
18	17.2	18.6	17.2
19	17.2	15.8	15.8
20	17.2	17.2	17.2
21	17.2	15.8	17.2
23a	17.2	15.8	17.2
23b	15.8	15.8	15.8
23d	15.8	17.2	15.8
Tetracyclin	34.0	32.0	—
Amfoterisin B	—	—	16.0

[a]Compound **15** is the only one that exhibited inhibition (15.8%) against *Aspergillus flavus* among the tested compounds;
[b]100% inhibition means no growth of either bacteria or fungi allover the plate.

determined in DMSO-d_6 at 300 MHz on a Varian mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

4,6-di-(2-Fury)l-2-sulfanylpyridine-3-carbonitrile (3)

A mixture of **1** (20.7 g, 110 mmoles) and cyanothioacetamide **2** (10 g, 100 mmoles) was heated under reflux in methoxide solution (2.3 g of Na in 100 mL methanol) for 7 h. The reaction mixture was cooled and stirred at room temperature over night. The precipitate was filtered, washed with water, and recrystallized from methanol (Tables II and III).

4,6-Di-2-Furyl-2-(methylthio)nicotinenitrile (4), 3-Amino-4,6-di-2- furylthieno[2,3-b]pyridine-2-carbonitrile (7), Ethyl 3-Amino-4,6-di-2-furylthieno[2,3-b]pyridine-2-carboxylate (8) and 4,6-Di-2-furyl-2-[(2-oxopropyl)thio] nicotinenitrile (9). General Procedure

A mixture of **3** (2.68 g, 10 mmol) and potassium hydroxide (0.62 g, 11 mmol) in *N*,*N*-dimethylformamide (20 mL) was stirred for 2 h at room temperature. Each of methyl iodide, chloroacetonitrile, ethyl bromoacetate, and chloroacetone (10 mmol each) was added and stirring was continued for 2 h. The resulting solid was collected and recrystallized from the proper solvent (Tables II and III).

4,6-Di-2-Furyl-2-(methylsulfonyl)nicotinenitrile (5)

To a stirred mixture of **4** (0.85 g, 3 mmol) in glacial acetic acid (10 mL) was added 30% H_2O_2 solution (10 mL), and the mixture was heated under reflux for 30 min. After cooling, H_2O was added; the resulting solid was collected and recrystallized from ethanol (Tables II and III).

1-(3-Amino-4,6-di-2-furylthieno[2,3-b]pyridin-2-yl)-ethanone (10)

A solution of **9** (3.24 g, 10 mmol) in ethanol (30 mL) containing 0.5 mL piperidine was heated under reflux for 2 h. After cooling, the resulting solid was collected by filtration and recrystallized from ethanol/dioxin (Tables II and III).

2-Amino-7,9-di-2-furyl-4-methylpyrido[2′,3′:4,5]thieno[2,3-b]pyridine-3-carbonitrile (11)

A mixture of **10** (3.24 g, 10 mmol) and malononitrile (0.73 g, 11 mmol) was heated under reflux in ethoxide solution (0.23 g of Na in 30 mL ethanol) for 7 h. The reaction mixture was cooled and stirred at room

TABLE II Physical and Analytical Data of the Newly Synthesized Compounds

Compound	Color	m.p. (°C) Solvent	Yield (%)	Mol. Formula (Mol. Wt)	Elemental Analysis (%) Calcd/Found C	H	N	S
3	Red	233-4	48	$C_{14}H_8N_2O_2S$	62.68	3.01	10.44	11.95
		MeOH		(268.30)	62.57	3.11	10.53	11.77
4	Beige	168-9	70	$C_{15}H_{10}N_2O_2S$	63.82	3.57	9.92	11.36
		EtOH/Dioxane		(282.32)	63.67	3.68	10.0	11.19
5	Yellow	192-3	53	$C_{15}H_{10}N_2O_4S$	57.32	3.21	8.91	10.20
		EtOH		(314.32)	57.55	3.22	8.89	10.36
7	Beige	259-60	85	$C_{16}H_9N_3O_2S$	62.53	2.95	13.67	10.43
		EtOH/DMF		(307.33)	62.28	3.11	13.82	10.51
8	Yellow	127-8	85	$C_{18}H_{14}N_2O_4S$	61.01	3.98	7.90	9.05
		EtOH		(354.39)	60.89	4.08	8.05	8.88
9	Brown	158-9	73	$C_{17}H_{12}N_2O_3S$	62.95	3.73	8.64	9.89
		EtOH/Dioxane		(324.36)	63.11	3.66	8.77	9.78
10	Deep Red	193-5	77	$C_{17}H_{12}N_2O_3S$	62.95	3.73	8.64	9.89
		EtOH/Dioxane		(324.36)	62.88	3.88	8.61	10.02
11	Purple	251-2	44	$C_{20}H_{12}N_4O_2S$	64.51	3.25	15.04	8.61
		Dioxane		(372.41)	64.67	3.17	14.89	8.73
12	Gray	>300	70	$C_{17}H_9N_3O_3S$	60.89	2.71	12.53	9.56
		DMF		(335.34)	61.02	2.63	12.59	9.33
13	Brown	131-2	38	$C_{17}H_8ClN_3O_2S$	57.72	2.28	11.88	9.06
		DMF		(353.79)	57.86	2.19	11.69	9.21
14	Dark brown	274-5	42	$C_{17}H_{10}N_4O_3S$	58.28	2.88	15.99	9.15
		DMF/H_2O		350.36	58.11	3.01	16.12	9.01
15	Brown	154-5	33	$C_{17}H_{10}N_4O_2S_2$	55.73	2.75	15.29	17.50
		DMF/H_2O		(366.42)	55.89	2.82	15.41	17.39
16	Dark brown	195-6	45	$C_{19}H_{13}N_3O_3S$	62.80	3.61	11.56	8.82
		Benzene		(363.40)	63.01	3.47	11.71	8.68
17	Dark brown	233-4	64	$C_{23}H_{14}N_4O_2S$	67.30	3.44	13.65	7.81
		Benzene		(410.46)	67.44	3.57	13.49	7.99
18	Brown	183-4	37	$C_{17}H_9N_3O_4S$	58.12	2.58	11.96	9.13
		DMF/H_2O		(351.34)	57.97	2.71	11.77	9.29
19	Dark brown	212-3	34	$C_{17}H_9N_3O_3S_2$	55.58	2.47	11.44	17.45
		DMF/H_2O		(367.41)	55.41	2.61	11.31	17.61
20	Yellow	225-6	64	$C_{23}H_{13}N_3O_3S_2$	62.29	2.95	9.47	14.46
		EtOH		(443.51)	62.11	2.78	9.33	14.30
21	Yellow	246-7	53	$C_{16}H_{12}N_4O_3S$	56.46	3.55	16.46	9.42
		EtOH/Dioxane		(340.36)	56.66	3.67	16.31	9.55
23a	Beige	>300	46	$C_{27}H_{19}FN_6O_3S$	61.59	3.64	15.96	6.09
		DMF/H_2O		(526.55)	61.78	3.51	15.77	6.21
23b	Beige	288-9	33	$C_{28}H_{19}F_3N_6O_3S$	58.33	3.32	14.58	5.56
		DMF/H_2O		(576.56)	58.19	3.22	14.71	5.39
23c	Brown	>300	39	$C_{25}H_{17}FN_8O_3S$	56.81	3.24	21.20	6.07
		DMF/H_2O		(528.53)	56.66	3.36	21.04	5.91
23d	Beige	290-1	41	$C_{26}H_{17}F_3N_8O_3S$	53.98	2.96	19.37	5.54
		DMF/H_2O		(578.54)	54.15	3.05	19.21	5.61

TABLE III Spectral data of the newly synthesized compounds

Compound	Spectral data
3	IR: 2220 (CN), 3195 (NH) ^{1}H NMR: 6.67 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 7.76 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 8.02 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings), 8.21(s, 1H, 5-H of the pyridinethione ring), 14.10 (b, 1H, NH)
4	IR: 2209 (CN) ^{1}H NMR: 2.69 (s, 3H, CH_3), 6.75 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 7.66 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 7.93 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings), 8.08(s, 1H, 5-H of the pyridinethione ring)
5	IR: 2218 (CN) ^{1}H NMR: 3.41 (s, 3H, SCH_3), 6.65 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 7.73 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 7.88 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings), 8.01(s, 1H, 5-H of the pyridinethione ring)
7	IR: 3496, 3249 (NH2), 2197 (CN) ^{1}H NMR: 6.57 (br, 2H, NH_2), 6.75 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 7.72 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 7.92 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings), 8.31(s, 1H, 5-H of the thienopyridine ring)
8	IR: 3486, 3352 (NH2), 1744 (CO) ^{1}H NMR: 1.30 (t, 3H, J = 3.7 Hz, CH_3), 4.31 (q, 2H, J = 2.5 Hz, CH_2), 6.21 (br, 2H, NH_2), 6.76 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 7.52 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 7.48 (s, 1H, 5-H of the thienopyridine ring), 7.99 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings)
9	IR: 2218 (CN), 1723 (CO) ^{1}H NMR: 2.32 (s, 3H, CH_3CO), 4.22 (s, 2H, SCH_2), 6.69 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 7.73 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 8.01 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings), 8.17 (s, 1H, 5-H of the pyridinethione ring)
10	IR: 3480, 3289 (NH_2), 1596 (CO) ^{1}H NMR: 2.38 (s, 3H, CH_3CO), 6.85 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 7.25 (br, 2H, NH_2), 7.50 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 7.73 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings), 7.82 (s, 1H, 5-H of the thienopyridine ring)
11	IR: 3374, 3198 (NH_2), 2213 (CN) ^{1}H NMR: 2.01 (s, 3H, CH_3), 6.43 (br, 2H, NH_2), 6.65 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 7.69 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 7.95 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings), 8.13 (s, 1H, 5-H of the thienopyridine ring)
12	IR: 3423 (NH), 1662 (CO) ^{1}H NMR: 6.71 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 7.72 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 8.02 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings), 8.25 (s, 1H, 5-H of the thienopyridine ring), 8.57 (s, 1H, Proton on C-2 of pyrimidine ring), 12.56 (s, 1H, NH of pyrimidine ring)

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TABLE III Spectral data of the newly synthesized compounds *(Continued)*

Compound	Spectral data
13	^{1}H NMR: 6.70 (dd, 2H, $J = 4.0$, 4.0 Hz 4-H of two furyl rings), 7.75 (d, 2H, $J = 3.8$ Hz, 3-H of two furyl rings), 7.99 (d, 2H, $J = 3.8$ Hz, 5-H of two furyl rings), 8.17 (s, 1H, 5-H of the thienopyridine ring), 9.66 (s, 1H, Proton on C-2 of pyrimidine ring)
14	IR: 3349, 3111 (NH_2), 1662 (CO) ^{1}H NMR: 6.76 (dd, 2H, $J = 4.0$, 4.0 Hz 4-H of two furyl rings), 7.41 (br, 2H, NH_2), 7.78 (d, 2H, $J = 3.8$ Hz, 3-H of two furyl rings), 7.93 (d, 2H, $J = 3.8$ Hz, 5-H of two furyl rings), 8.19 (s, 1H, 5-H of the thienopyridine ring), 12.97 (s, 1H, NH of pyrimidine ring)
15	IR: 3308, 3137 (NH_2) ^{1}H NMR: 6.75 (dd, 2H, $J = 4.0$, 4.0 Hz 4-H of two furyl rings), 7.32 (br, 2H, NH_2), 7.75 (d, 2H, $J = 3.8$ Hz, 3-H of two furyl rings), 8.01 (d, 2H, $J = 3.8$ Hz, 5-H of two furyl rings), 8.24 (s, 1H, 5-H of the thienopyridine ring), 12.89 (s, 1H, NH of pyrimidine ring)
16	IR: 2248 (CN) ^{1}H NMR: 1.22 (t, 3H, $J = 8.2$ Hz, CH_3), 4.33 (q, 2H, $J = 9.6$ Hz, CH_2), 6.73 (dd, 2H, $J = 4.0$, 4.0 Hz 4-H of two furyl rings), 7.77 (d, 2H, $J = 3.8$ Hz, 3-H of two furyl rings), 7.98 (d, 2H, $J = 3.8$ Hz, 5-H of two furyl rings), 8.11 (s, 1H, 5-H of the thienopyridine ring), 8.66 (s, 1H, CH-O)
17	IR: 3542 (NH) ^{1}H NMR: 6.21 (br, 1H, NH), 6.78 (dd, 2H, $J = 4.0$, 4.0 Hz 4-H of two furyl rings), 7.01–7.53 (m, 5H, phenyl protons), 7.69 (d, 2H, $J = 3.8$ Hz, 3-H of two furyl rings), 7.99 (d, 2H, $J = 3.8$ Hz, 5-H of two furyl rings), 8.15 (s, 1H, 5-H of the thienopyridine ring), 8.82 (s, 1H, proton on C-2 of pyrimidine ring)
18	IR: 3430, 3352 (2NH), 1732, 1656 (2CO) ^{1}H NMR: 6.63 (dd, 2H, $J = 41.0$, 4.0 Hz 4-H of two furyl rings), 7.82 (d, 2H, $J = 3.8$ Hz, 3-H of two furyl rings), 7.87 (d, 2H, $J = 3.8$ Hz, 5-H of two furyl rings), 8.25 (s, 1H, 5-H of the thienopyridine ring), 12.76, 12.83 (2s, 2H, NH protons of pyrimidine ring)
19	IR: 3378, 3238 (2NH), 1656 (CO) ^{1}H NMR: 6.69 (dd, 2H, $J = 4.0$, 4.0 Hz 4-H of two furyl rings), 7.79 (d, 2H, $J = 3.8$ Hz, 3-H of two furyl rings), 8.22 (d, 2H, $J = 3.8$ Hz, 5-H of two furyl rings), 8.31 (s, 1H, 5-H of the thienopyridine ring), 12.25, 12.89 (2s, 2H, NH protons of pyrimidine ring)
20	IR: 3413 (NH), 1705 (CO) ^{1}H NMR: 6.71 (dd, 2H, $J = 4.0$, 4.0 Hz 4-H of two furyl rings), 7.08-7.62 (m, 5H, phenyl protons), 7.74 (d, 2H, $J = 3.8$ Hz, 3-H of two furyl rings), 8.19 (d, 2H, $J = 3.8$ Hz, 5-H of two furyl rings), 8.15 (s, 1H, 5-H of the thienopyridine ring), 12.19 (s, 1H, NH of pyrimidine ring)
21	IR: 3414-3199 (NH_2, NH), 1650 (CO) ^{1}H NMR: 4.38 (br, 2H, N-NH_2), 6.70 (br, 2H, NH_2), 6.75 (dd, 2H, $J = 4.0$, 4.0 Hz 4-H of two furyl rings), 7.55 (d, 2H, $J = 3.8$ Hz, 3-H of two furyl rings), 7.38 (s, 1H, 5-H of the thienopyridine ring), 7.89 (d, 2H, $J = 3.8$ Hz, 5-H of two furyl rings), 9.39 (br, 1H, NH)

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TABLE III Spectral data of the newly synthesized compounds *(Continued)*

Compound	Spectral data
23a	IR: 3445, 3257 (NH_2), 1640 (CO) ^{1}H NMR: 2.80 (s, 6H, 3-,5-CH_3 of pyrazol), 6.78 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 6.81 (br, 2H, NH_2), 7.12-7.44 (m, 4H, phenyl protons), 7.54 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 7.59 (s, 1H, 5-H of the thienopyridine ring), 7.93 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings)
23b	IR: 3472, 3238 (NH_2) 1665 (CO) ^{1}H NMR: 2.82 (s, 6H, 3-,5-CH_3 of pyrazol), 6.79 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 6.83 (br, 2H, NH_2), 7.18-7.51 (m, 4H, phenyl protons), 7.61 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 7.69 (s, 1H, 5-H of the thienopyridine ring), 7.99 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings)
23c	IR: 3475–3188 (NH_2), 1659 (CO) ^{1}H NMR: 6.75 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 6.81 (br, 2H, NH_2), 6.93 (br, 2H, 2 NH_2), 7.05–7.47 (m, 4H, phenyl protons), 7.62 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 7.79 (s, 1H, 5-H of the thienopyridine ring), 8.01 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings)
23d	IR: 3458-3216 (NH_2), 1651 (CO) ^{1}H NMR: 6.69 (dd, 2H, J = 4.0, 4.0 Hz 4-H of two furyl rings), 6.79 (br, 2H, NH_2), 6.98 (br, 2H, 2 NH_2), 7.14–7.53 (m, 4H, phenyl protons), 7.71 (d, 2H, J = 3.8 Hz, 3-H of two furyl rings), 7.85 (s, 1H, 5-H of the thienopyridine ring), 8.11 (d, 2H, J = 3.8 Hz, 5-H of two furyl rings)

temperature over night. The precipitate was filtered, washed with water, and recrystallized from dioxin (Tables II and III).

7,9-Di-2-Furylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (12)

Method A. A mixture of **7** (3.07 g, 10 mmol) and formic acid (20 mL) was heated under reflux for 7 h. After cooling, the reaction mixture was poured over ice and the formed solid was collected and recrystallized form *N*,*N*-dimethylformamide (Tables II and III).

Method B. Compound **8** (3.54 g, 10 mmol) was heated with formamide (20 mL) at 180°C for 2 h. After cooling, the reaction mixture was poured over ice and the formed solid was collected by filtration and recrystallized form *N*,*N*-dimethylformamide (Tables II and III).

4-Chloro-7,9-di-2-furylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine (13)

Compound **12** reacted with $POCl_3$ (20 mL) under reflux for 1 h. The reaction mixture was poured over ice, and the resulting

solid was collected by filtration and recrystallized form dilute *N*,*N*-dimethylformamide (Tables II and III).

Pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine derivatives 14, 15, 18 and 19 General Procedure

Two grams of each of compounds **7** and **8** were heated with 5 g each of urea and thiourea at 160–170°C for 30 min. The clear solution went mushy, and heating was continued for another 10 min at 180°C. The resulting solid (in each case) was dissolved in dilute sodium hydroxide and then carefully acidified with acetic acid to obtain the corresponding crude products which were recrystallized from dilute *N*,*N*-dimethylformamide (Tables II and III).

Ethyl (2-Cyano-4,6-di-2-furylthieno[2,3-b]-pyridin-3-yl)imidoformate (16)

A mixture of **7** (3.07 g, 10 mmol) and triethylorthoformate (20 mL) with catalytic amount of acetic acid were heated under reflux at 140°C for 6 hrs. The resulting dark brown solution was allowed to cool to room temperature and evaporated under vacuum. n-Hexane was added to the residue and the separated solid was filtered, washed with n-hexane and recrystallized from benzene (Tables II and III).

7,9-di-2-Furyl-N-phenylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4-amine (17)

Compound **16** (1.82 g, 5 mmol) was dissolved in ethanol (10 mL) containing aniline (1.5 mL) was heated under reflux at 110°C for 6 h. Ethanol and aniline was removed under vacuum. The crude product residue was triturated with n-hexane and crystallized from benzene (Tables II and III).

7,9-Di-2-Furyl-3-phenyl-2-thioxo-2,3-dihydropyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(1H)-one (20)

A mixture of compound **8** (3.54 g, 10 mmol) and the phenyl isothiocyanate (1.35 g, 10 mmol) in acetonitrile (30 mL) was heated under reflux for 15 h in the presence of anhydrous potassium carbonate (1.4 g). The reaction mixture was then cooled, filtered, diluted with water (10 mL), and neutralized with hydrochloric acid (2M). The resulting solid was filtered, washed with water, dried, and recrystallized from ethanol (Tables II and III).

3-Amino-4,6-di-2-furylthieno[2,3-b]pyridine-2-carbohydrazide (21)

A mixture of compound **8** (3.54 g, 10 mmol) and hydrazine hydrate (4 ml, 85% solution, 4 mmoles) in absolute ethanol (20 mL) for 24 h was heated under reflux. The reaction mixture was cooled, and the resulting solid was collected and washed with ethanol/water and recrystallized from ethanol/dioxin (Tables II and III).

3-Amino-4,6-di-2-furylthieno[2,3-b]-2-pyridyl-4-arylazo-3,5-disubstituted-1-pyrazolyl-methanone (23a-d)

A mixture of compound **21** (1.7 g, 5 mmol) and the appropriate of arylazoacetylacetone **22a**, **b** and arylazomalononitrile **22c**, **d** (5 mmol) was heated under reflux in glacial acetic acid (10 mL) with stirring for 6 h. The reaction mixture was cooled to room temperature and the separated solid was filtered, washed with water, dried, recrystallized from dilute *N*,*N*-dimethylformamide (Tables II and III).

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