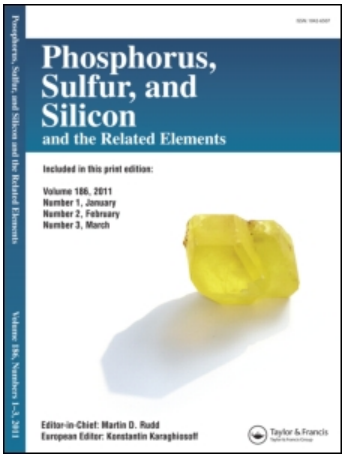

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SYNTHESIS AND REACTIONS OF SOME NEW HETEROCYCLIC COMPOUNDS CONTAINING THE THIENYLTHIENO[2,3-*B*]PYRIDINE MOIETY

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*(4-Aryl-3-cyano-6-(2-thienyl)pyridin-2-ylthio)acethydrazides (**5a–c**), 3-amino-4-aryl-6-(2-thienyl)thieno[2,3-b]pyridine-2-carbohydrazides (**6a–c**) and 3-amino-4-phenyl-6-(2-thienyl)thieno[2,3-b]pyridine-2-carboxylic acid (**30**) were prepared and employed as key intermediates in the synthesis of the title compounds.*

Keywords: Cyanopyridinethiones; imidazolothienopyridines; pyranothienopyridines; pyrazolinothienopyridines; pyridothienopyrimidines; thienopyridines

INTRODUCTION

Pyridine derivatives have occupied a unique position in medicinal chemistry. The naturally occurring B_6 vitamins pyridoxine, pyridoxal, pyridoxamine, and codecarboxylase[1] contain a pyridine nucleus. In addition, many pyridines are reported to be useful as herbicides,[2,3] bactericides,[4,5] fungicides,[6] inseticides,[7,8] and pharmaceuticals.[9–16] In particular, several thieno[2,3-b]pyridine derivatives are known to possess antibacterial,[17–19] antihypertensive,[20] and gonadotropin-releasing hormone-antagonizing[21,22] activity. Pyridothienopyrimidine derivatives have found applications as analgesics,[23] antipyretics[24] and anti-inflammatories.[25] Encouraged by these facts, and as a continuation of our previous work [26–33] on thieno[2,3-b]pyridines, we undertook the synthesis of the title compounds, which might exhibit enhanced

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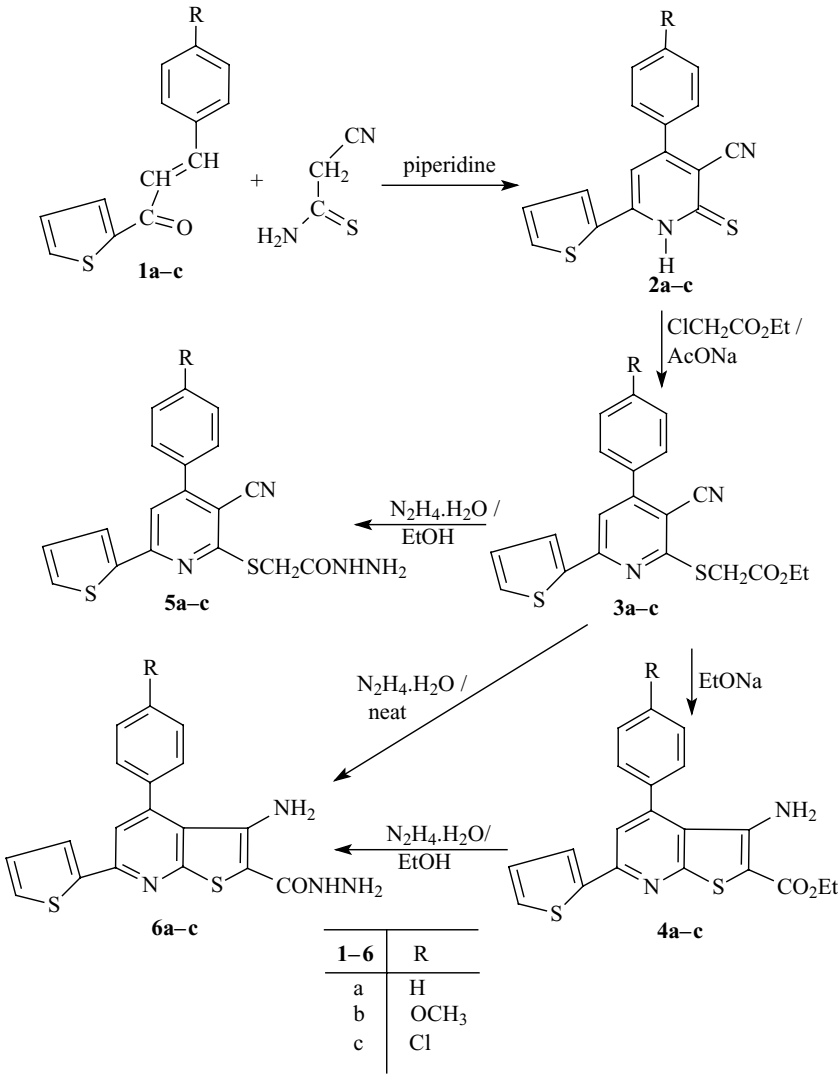
activities owing to the incorporation of different pharmacophores into their structures.

RESULTS AND DISCUSSION

4-Aryl-3-cyano-6-(2-thienyl)pyridine-2(1*H*)-thiones (**2a–c**) were used as starting materials in this investigation. They were prepared in analogy to the method described before by the reaction of 3-aryl-1-(2-thienyl)prop-2-en-1-ones (**1a–c**) with cyanothioacetamide in the presence of piperidine as a basic catalyst.[31] The reaction of **2a–c** with ethyl chloroacetate in the presence of sodium acetate gave ethyl (4-aryl-3-cyano-6-(2-thienyl)-2-pyridinylthio)acetates (**3a–c**). The latter compounds underwent intramolecular *Thorpe-Ziegler* cyclization to afford thieno[2,3-b]pyridines **4a–c** upon treatment with a catalytic amount of sodium ethoxide in refluxing ethanol. Heating the esters **3a–c** with hydrazine hydrate in refluxing ethanol produced the corresponding acethydrazide derivatives **5a–c**. When this reaction was performed under neat conditions, the products were assigned as 3-amino-4-aryl-6-(2-thienyl)thieno[2,3-b] pyridine-2-carbohydrazides (**6a–c**). Compounds **6a–c** were also obtained by the reaction of *o*-aminoesters **4a–c** with hydrazine hydrate in boiling ethanol (Scheme 1).

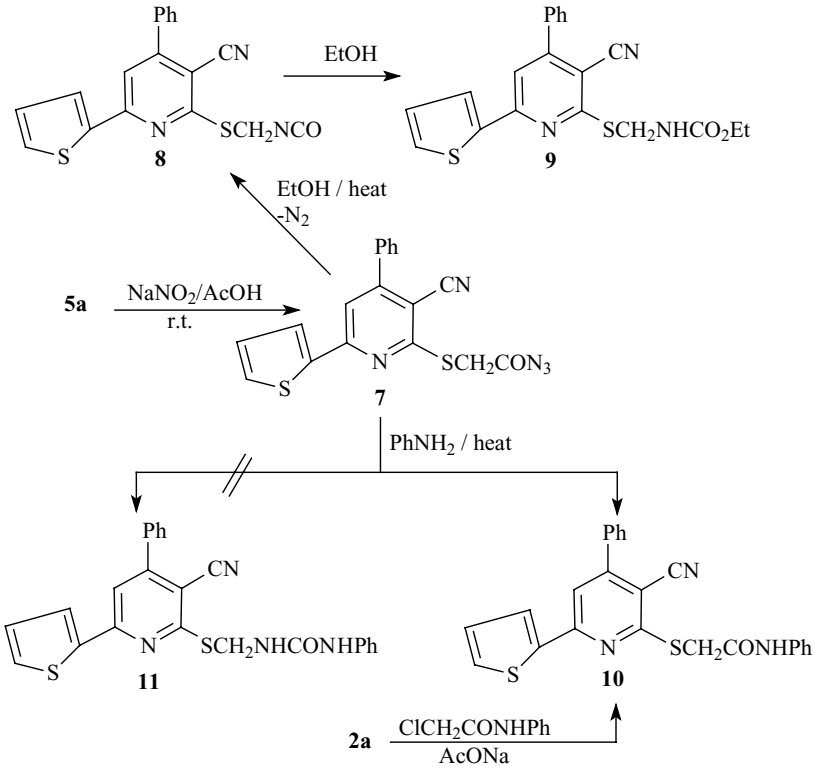
On treatment of acethydrazide **5a** in glacial acetic acid with sodium nitrite solution at room temperature, the carboazide derivative **7** was obtained. When the acid azide **7** was heated in ethanol *Curtius* rearrangement occurred, whereby the isocyanate intermediate **8** was formed. The latter intermediate reacted concomitantly with the ethanol, which was used as a solvent, to give the corresponding ethyl carbamate **9**. It is worthy of note that when the acid azide **7** was heated in an excess of aniline, *Curtius* rearrangement did not occur and the product proved to be the anilide **10** rather than the expected urea derivative **11**. The latter reaction may proceed via nucleophilic substitution mechanism. The compound **10** was also prepared by the direct reaction of **2a** with chloro-*N*-phenylacetamide in the presence of sodium acetate (Scheme 2).

The condensation of acethydrazide **5a** with aromatic aldehydes yielded the corresponding hydrazones **12a–c** which underwent intramolecular *Thorpe-Ziegler* cyclization upon heating with catalytic amounts of sodium ethoxide in ethanol to furnish N^1-arylmethylene-3-amino-4-phenyl-6-(2-thienyl)thieno[2,3-b]pyridine-2-carbohydrazides (**13a–c**).[33] The compounds **13a–c** were also synthesized through direct condensation of **6a** with the respective aldehydes in boiling ethanol. Treatment of **13a–c** with triethyl orthoformate in refluxing acetic



SCHEME 1

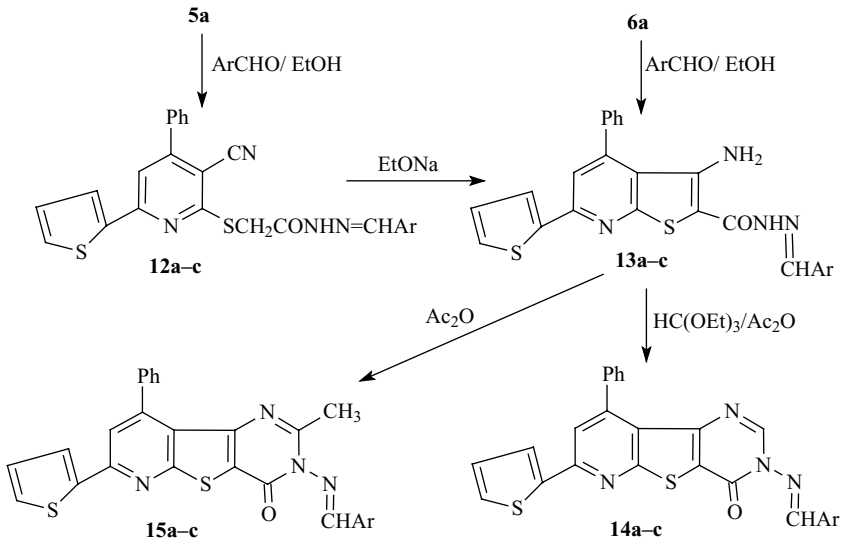
anhydride led to the fomation of the corresponding pyridothienopyrimidinones **14a–c**. Also, heating of **13a–c** with acetic anhydride at reflux temperature afforded 3-arylmethyleneamino-2-methyl-9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-ones (**15a–c**) (Scheme 3).



SCHEME 2

On heating of **6a** with urea in decalin for 4 hours, the product was identified as 3-amino-9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-2,4(1*H*,3*H*)-dione (**16**). Heating of compound **6a** with formic acid led to the formation of *N*-formylaminopyrimidinone derivative **17**. In contrast, heating of **6a–c** with acetic acid at reflux temperature for 8 h furnished the corresponding pyrazolinothienopyridines **18a–c**.[34] The latter reaction may proceed via acetylation followed by elimination of an acetamide molecule. The interaction of **6a–c** with acetic anhydride at reflux temperature afforded 9-aryl-3-diacetylamino-2-methyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-ones (**19a–c**). When compounds **6a–c** were allowed to react with acetylacetone, the dimethylpyrazolyl derivatives **20a–c** were obtained in high yields (Scheme 4).

The cyclocondensation of carbohydrazide derivatives **6a–c** with triethyl orthoformate by heating in DMF produced 3-ethoxymethyleneaminopyrimidine-4(3*H*)-ones **21a–c**. Treatment of compound **21a** with

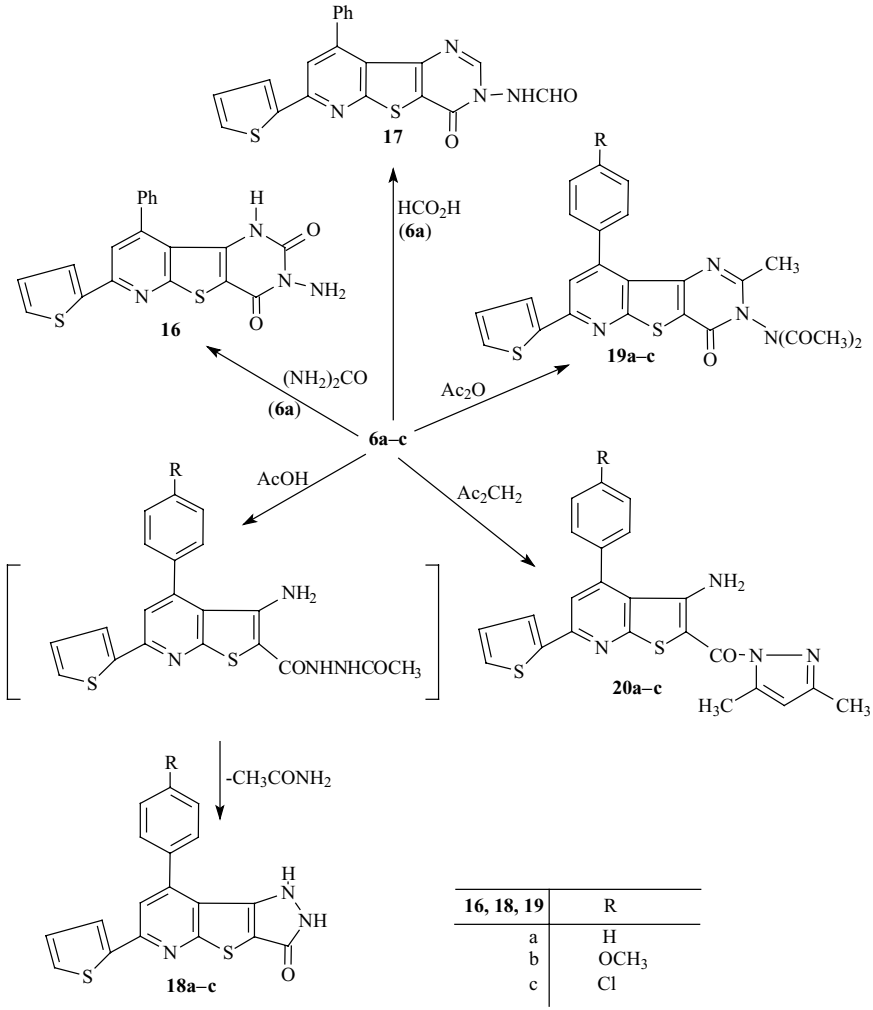


12–15	Ar
a	C_6H_5
b	C_6H_4-OCH_3(p)
c	C_6H_4-Cl(p)

SCHEME 3

hydrazine hydrate under neat conditions resulted in the formation of *N*-aminopyrimidinone derivative **22**, while the interaction of **21a** with hydrazine hydrate in dioxane at room temperature furnished 3-hydrazinomethyleneaminopyrimidinone derivative **23**. When the latter compound (**23)** was fused with hydrazine hydrate, it gave compound **22**. The reactivity of the amino group of **22** was tested via condensation with benzaldehyde to give the Schiff's base **14a** or treating with acetic anhydride to produce the diacetyl derivative **24** (Scheme 5).

The compound **6a** was also reacted with carbon disulfide in hot pyridine to produce 1,3,4-oxadiazole-5(4*H*)-thione derivative **25**.[26] Upon treatment of **25** with ethyl chloroacetate in the presence of sodium acetate, the *S*-alkylated compound **26** was isolated. Diazotization of **6a–c** in acetic acid with sodium nitrite solution at room temperature resulted in the formation of the acid azides **27a–c**. On heating of **27a–c** in isopropyl alcohol at reflux temperature, they underwent *Curtius* rearrangement, forming the isocyanate intermediates **28a–c**

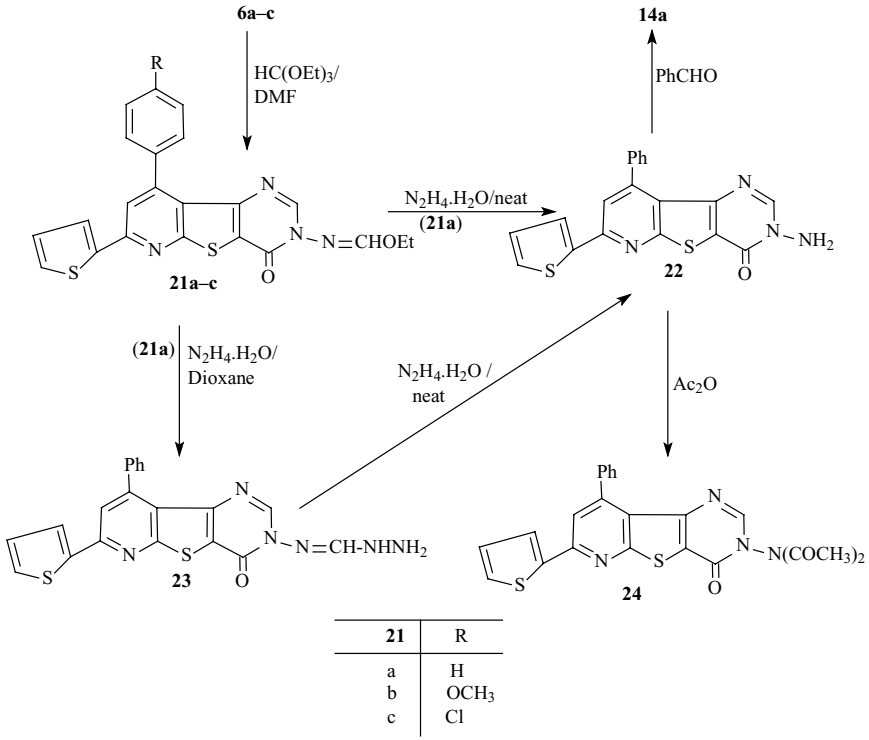


16, 18, 19	R
a	H
b	OCH_3
c	Cl

SCHEME 4

followed by intramolecular cycloaddition reaction to afford the imidazolone derivatives **29a–c**[26] (Scheme 6).

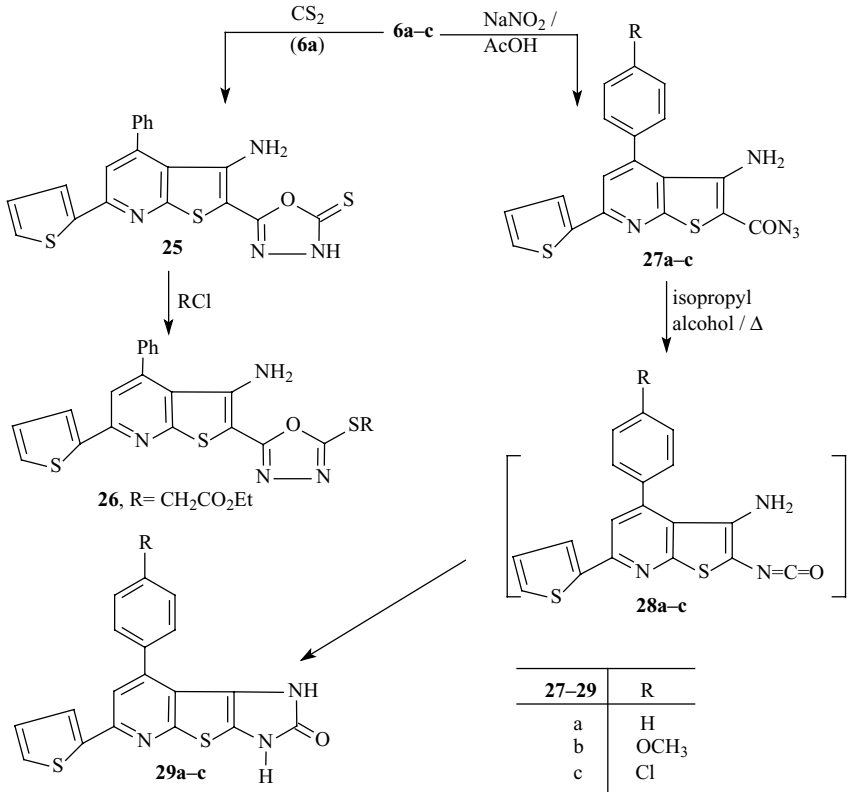
Saponification of **4a** with an ethanolic sodium hydroxide solution followed by acidification with acetic acid gave 3-amino-4-phenyl-6-(2-thienyl)thieno[2,3-b] pyridine-2-carboxylic acid (**30**), which underwent ring closure reaction upon treatment with acetic anhydride to furnish 2-methyl-9-phenyl-7-(2-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-d]oxazin-4-one (**31**). The oxazinone derivative **31** was recyclized



SCHEME 5

into some pyrimidinone derivatives upon treatment with certain reagents. Thus, the reaction of **31** with aniline or with ethyl glycinate hydrochloride gave the pyrimidinone derivatives **32** and **33**, respectively. Also, the reaction of **31** with hydrazine hydrate gave 3-amino-2-methyl-9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno[3,2-d]-pyrimidine-4(3*H*)-one (**34**). The latter compound (**34**) was reacted, in turn, with aromatic aldehydes or acetic anhydride to give the corresponding pyrimidinone derivatives **15a–c** and **19a**, which were prepared from the hydrazones **13a–c** or *o*-aminocarbohydrazide **6a**, respectively (Scheme 7).

In contrast, heating of *o*-aminocarboxylic acid **30** with orthophosphoric acid at 100°C resulted in decarboxylation followed by hydrolysis of the imino group to give 4-phenyl-6-(2-thienyl)thieno[2,3-b]pyridine-3(2*H*)-one (**35**).[33] On treatment of the ketone **35** with arylmethylenemalononitriles in ethanol containing catalytic amounts of piperidine, a cycloaddition reaction occurred and 2-amino-4,9-diaryl-7-(2-thienyl)-4*H*-pyrano[2′,3′:4,5]thieno[2,3-b]pyridine-3-carbonitriles



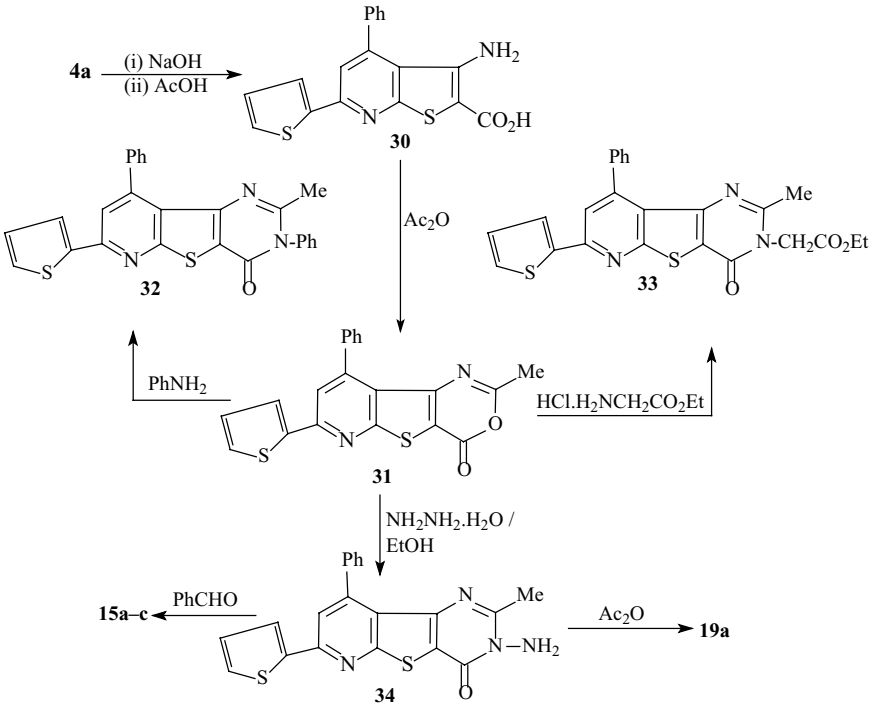
SCHEME 6

(**37a**,**b**) were obtained in high yield (Scheme 8). The structures of compounds **37a**,**b** were further confirmed by another route of preparation via condensation of compound **35** with aromatic aldehydes followed by the treating of the formed chalcones **36a**,**b** with malononitrile (Scheme 8).[33]

The structural formulas of all newly synthesized compounds were established and confirmed on the basis of their elemental analyses and spectral data (see Table I and the Experimental sectin below).

EXPERIMENTAL

All melting points are uncorrected and measured on a Gallenkamp apparatus. IR spectra were recorded on a Shimadzu 470 IR

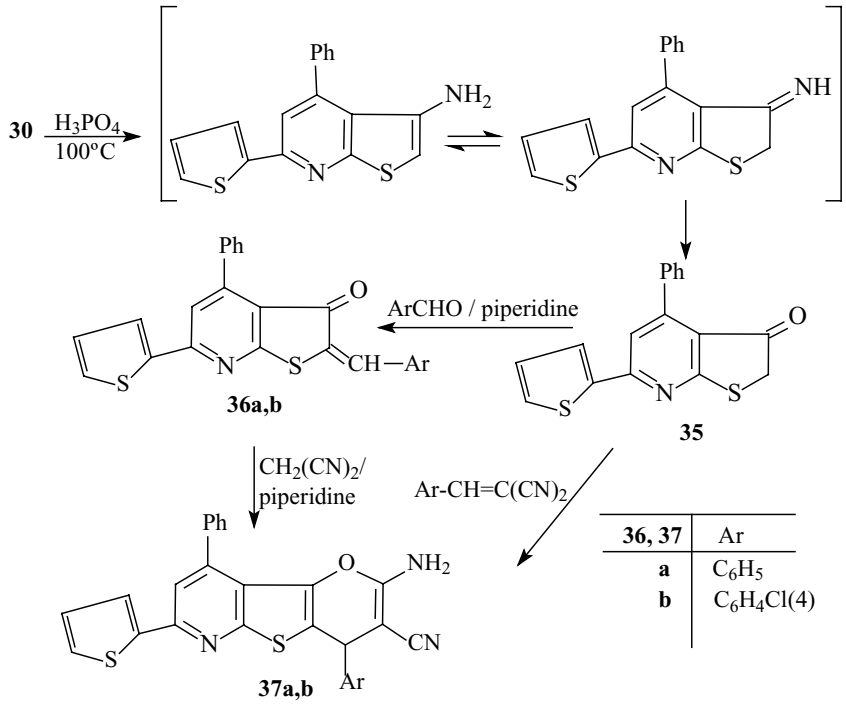


SCHEME 7

spectrophotometer (KBr; ν max in cm^{-1}); ^1H NMR spectra on a Varian EM-390, 90 MHz spectrometer with TMS as internal standard (δ in ppm); MS on a Jeol JMS-600 mass spectrometer and elemental analyses on an Elementar Analysensystem GmbH VARIOEL V2.3 July 1998 CHNS Mode. Melting points, yields, and analytical data of all newly synthesized compounds are listed in Table I.

4-Aryl-3-cyano-6-(2-thienyl)pyridine-2(1*H*)-thiones (2a–c)

To a solution of chalcone **1a–c** (20 mmol) and cyanothioacetamide (2.0 g, 20 mmol) in ethanol (50 ml), a few drops of piperidine were added. The reaction mixture was refluxed for 4 h. The solid that formed while hot was collected and recrystallized from acetic acid as orange needles of **2a–c**. IR: ν = 3190–3180 (NH), 2210 (C≡N) cm^{-1}. ^1H NMR of **2a** (DMSO-d_6): δ = 8.3 (m, 1H, CH thienyl), 7.6–8.2 (m, 6H: 5ArH's and CH pyridine), 7.3 (m, 1H, CH thienyl), 7.1 (m, 1H, CH thienyl) ppm. ^1H NMR of **2b** (TFA): δ = 7.8–8.2 (m, 5H: 2ArH's, 2CH thienyl and CH



SCHEME 8

pyridine), 7.2–7.5 (m, 3H: 2ArH's and CH thienyl), 4.0 (s, 3H, OCH_3) ppm. ^{1}H NMR of **2c** (DMSO-d_6): $\delta = 8.2$ (d, 1H, CH thienyl), 7.5–7.8 (m, 6H: 4ArH's, CH thienyl and CH pyridine), 7.2 (m, 1H, CH thienyl) ppm. MS of **2a**: 295 ($M^+ + 1$, 100%); 294 (M^+, 100%); 261 (M^+-SH, 30%); 250 (M^+-CS, 37%); 190 (14%);147 (21%); 77 ($C_6H_5^+$, 7%); 44 (CS^+, 3%).

Ethyl (4-Aryl-3-cyano-6-(2-thienyl)pyridin-2-ylthio)-acetates (3a–c)

A mixture of **2a–c** (20 mmol), ethyl chloroacetate (2.2 ml, 20 mmol) and sodium acetate trihydrate (3.0 g, 22 mmol) in ethanol (60 ml) was heated under reflux for 2 h. The precipitate that formed on cooling was collected and recrystallized from ethanol to give pale yellow crystals of **3a–c**. IR: $\nu = 2210$ (C≡N), 1730 (C=O) cm^{-1}. ^{1}H NMR of **3a** ($CDCl_3$): $\delta = 7.6$–8.2 (m, 8H: 5ArH's, 2CH thienyl and CH pyridine), 7.3 (m, 1H, CH thienyl), 4.1–4.4 (m, 4H, SCH_2 and OCH_2), 1.2–1.4 (t, 3H, CH_3 of ester) ppm. ^{1}H NMR of **3b** ($CDCl_3$): $\delta = 7.0$–7.8 (m, 8H: 4ArH's, 3CH thienyl and CH pyridine), 4.2–4.5 (m, 4H, SCH_2 and OCH_2), 3.9 (s, 3H,

TABLE I Melting Points, Yields, and Analytical Data of all Newly Synthesized Compounds

Compound	m.p. (°C)/ yield (%)	Formula (M.W.)	Calculated/found				
			% C	% H	% N	% S	% Cl
2a	245/43	$C_{16}H_{10}N_2S_2$	65.28	3.42	9.52	21.78	
		(294.40)	65.02	3.26	9.25	21.82	
2b	250/62	$C_{17}H_{12}N_2OS_2$	62.94	3.73	8.63	19.77	
		(324.42)	62.65	3.95	8.54	19.85	
2c	242/47	$C_{16}H_9ClN_2S_2$	58.44	2.76	8.52	19.50	10.78
		(329.86)	58.19	2.98	8.36	19.81	10.90
3a	162/95	$C_{20}H_{16}N_2O_2S_2$	63.13	4.24	7.36	16.86	
		(380.49)	63.02	4.14	7.76	16.94	
3b	180/97	$C_{21}H_{18}N_2O_3S_2$	61.44	4.42	6.82	15.62	
		(410.51)	61.73	4.12	6.55	15.86	
3c	145–150/95	$C_{20}H_{15}ClN_2O_2S_2$	57.89	3.64	6.75	15.46	8.54
		(414.94)	57.58	3.50	6.85	15.22	8.39
4a	182/90	$C_{20}H_{16}N_2O_2S_2$	63.13	4.24	7.36	16.86	
		(380.49)	63.34	4.11	7.77	16.89	
4b	185/90	$C_{21}H_{18}N_2O_3S_2$	61.44	4.42	6.82	15.62	
		(410.51)	61.71	4.67	6.80	15.30	
4c	205/89	$C_{20}H_{15}ClN_2O_2S_2$	57.89	3.64	6.75	15.46	8.54
		(414.94)	57.99	3.36	6.54	15.70	8.90
5a	215/86	$C_{18}H_{14}N_4OS_2$	58.10	3.85	15.29	17.50	
		(366.47)	58.30	3.99	15.62	17.42	
5b	190/82	$C_{19}H_{16}N_4O_2S_2$	57.56	4.07	14.13	16.18	
		(396.49)	57.96	4.21	14.46	16.58	
5c	193/80	$C_{18}H_{13}ClN_4OS_2$	53.93	3.27	13.98	15.99	8.84
		(400.91)	53.40	3.24	13.70	16.12	9.00
6a	260/84	$C_{18}H_{14}N_4OS_2$	58.99	3.85	15.29	17.50	
		(366.47)	59.13	3.66	15.11	17.77	
6b	220/85	$C_{19}H_{16}N_4O_2S_2$	57.56	4.07	14.13	16.18	
		(396.49)	57.85	4.00	14.45	16.19	
6c	160/80	$C_{18}H_{13}ClN_4OS_2$	53.93	3.27	13.98	15.99	8.84
		(400.91)	53.96	3.12	13.60	16.08	8.98
7	115/80	$C_{18}H_{11}N_5OS_2$	57.28	2.94	18.55	16.99	
		(377.45)	57.51	2.75	18.70	16.81	
9	180/82	$C_{21}H_{17}N_3O_3S_2$	59.56	4.05	9.92	15.14	
		(423.52)	59.70	4.19	9.99	15.35	
10	200/90	$C_{24}H_{17}N_3OS_2$	67.42	4.01	9.83	14.10	
		(427.55)	67.70	4.22	9.90	14.00	
12a	235/95	$C_{25}H_{18}N_4OS_2$	66.06	3.99	12.33	14.11	
		(454.58)	65.81	4.18	12.65	14.25	
12b	238/98	$C_{26}H_{20}N_4O_2S_2$	64.44	4.15	11.56	13.23	
		(484.60)	64.66	4.37	11.91	13.00	
12c	237/90	$C_{25}H_{17}ClN_4OS_2$	61.40	3.50	11.46	13.11	7.25
		(489.03)	61.58	3.28	11.70	13.22	7.17

(Continued on next page)

TABLE I Melting Points, Yields, and Analytical Data of all Newly Synthesized Compounds (Continued)

Compound	m.p. (°C)/ yield (%)	Formula (M.W.)	Calculated/found				
			% C	% H	% N	% S	% Cl
13a	295/99	$C_{25}H_{18}N_4OS_2$	66.06	3.99	12.33	14.11	
		(454.58)	66.25	4.18	12.59	14.36	
13b	297/98	$C_{26}H_{20}N_4O_2S_2$	64.44	4.16	11.56	13.23	
		(484.60)	64.42	4.35	11.80	13.02	
13c	290/95	$C_{25}H_{17}ClN_4OS_2$	61.40	3.50	11.46	13.11	7.25
		(489.03)	61.68	3.71	11.31	13.27	7.06
14a	275/92	$C_{26}H_{16}N_4OS_2$	67.22	3.47	12.06	13.80	
		(464.57)	67.41	3.12	12.22	13.60	
14b	310/90	$C_{27}H_{18}N_4O_2S_2$	65.57	3.67	11.33	12.97	
		(494.59)	65.23	3.80	11.03	13.01	
14c	305/90	$C_{26}H_{15}ClN_4OS_2$	62.58	3.03	11.25	12.85	7.11
		(499.02)	62.25	3.01	11.07	12.76	7.30
15a	260/90	$C_{27}H_{18}N_4OS_2$	67.76	3.79	11.71	13.40	
		(478.59)	67.82	3.39	11.40	13.11	
15b	300/91	$C_{27}H_{17}ClN_4OS_2$	63.21	3.34	10.92	12.50	6.91
		(513.05)	63.12	3.48	10.95	12.21	6.54
16	>300/65	$C_{19}H_{12}N_4O_2S_2$	58.15	3.08	14.28	16.34	
		(392.46)	58.11	3.25	14.38	16.42	
17	320/89	$C_{20}H_{12}N_4O_2S_2$	59.39	2.99	15.85	13.85	
		(404.47)	59.65	3.11	16.07	13.66	
18a	>320/60	$C_{18}H_{11}N_3OS_2$	61.87	3.17	12.03	18.35	
		(349.44)	61.85	3.22	12.25	18.19	
18b	300/80	$C_{19}H_{13}N_3O_2S_2$	60.14	3.45	11.07	16.90	
		(379.46)	60.50	3.71	11.08	17.21	
18c	290/90	$C_{18}H_{10}ClN_3OS_2$	56.32	2.63	10.95	16.71	9.24
		(383.88)	56.18	2.86	11.04	16.91	9.06
19a	250/71	$C_{24}H_{18}N_4O_3S_2$	60.74	3.82	11.81	13.51	
		(474.56)	60.62	3.90	11.99	13.41	
19b	250/80	$C_{25}H_{20}N_4O_4S_2$	59.51	3.99	11.10	12.71	
		(504.58)	59.62	3.75	11.11	12.65	
19c	265/70	$C_{24}H_{17}ClN_4O_3S_2$	56.63	3.37	11.07	12.60	6.97
		(509.00)	56.43	3.40	11.00	12.37	7.10
20a	195–198/82	$C_{23}H_{18}N_4OS_2$	64.16	4.21	13.01	14.90	
		(430.55)	64.34	4.11	13.29	15.20	
20b	180/78	$C_{24}H_{20}N_4O_2S_2$	62.59	4.38	12.16	13.92	
		(460.57)	62.22	4.43	12.02	13.80	
20c	198/80	$C_{23}H_{17}ClN_4OS_2$	59.41	3.69	12.05	13.79	7.62
		(464.99)	59.62	3.85	11.98	13.65	7.85
21a	300/88	$C_{22}H_{16}N_4O_2S_2$	65.97	4.03	13.99	8.02	
		(400.53)	65.95	4.06	14.15	8.06	
21b	220/75	$C_{23}H_{18}N_4O_3S_2$	59.72	3.92	12.11	13.86	
		(462.55)	59.87	3.92	12.03	13.60	
21c	215/80	$C_{22}H_{15}ClN_4O_2S_2$	56.59	3.24	11.99	13.73	7.59
		(466.96)	56.23	3.54	12.25	13.80	7.70

TABLE I Melting Points, Yields, and Analytical Data of all Newly Synthesized Compounds (Continued)

Compound	m.p. (°C) yield (%)	Formula (M.W.)	Calculated/found % C	% H	% N	% S	% Cl
22	320/80	$C_{19}H_{12}N_4OS_2$	60.62	3.21	14.88	17.03	
		(376.46)	60.28	3.41	14.84	17.16	
23	195/90	$C_{20}H_{14}N_6OS_2$	57.40	3.37	20.08	15.32	
		(402.50)	57.11	3.62	20.08	15.14	
24	243/71	$C_{23}H_{16}N_4O_3S_2$	59.99	3.50	12.17	13.92	
		(460.56)	60.21	3.38	11.89	13.66	
25	248/71	$C_{19}H_{12}N_4OS_3$	55.86	2.96	23.55	31.71	
		(408.53)	55.93	2.88	23.75	31.12	
26	186/87	$C_{23}H_{18}N_4O_3S_3$	55.85	3.67	11.33	19.45	
		(494.62)	55.43	3.80	11.40	19.43	
27a	150/95	$C_{18}H_{11}N_5OS_2$	57.28	2.99	18.55	16.99	
		(377.45)	57.21	2.59	18.35	17.11	
27b	190/90	$C_{19}H_{13}N_5O_2S_2$	56.00	3.22	17.19	15.74	
		(407.47)	56.12	3.11	17.09	15.84	
27c	110/90	$C_{18}H_{10}ClN_5OS_2$	52.49	2.45	17.00	15.57	8.61
		(411.90)	52.55	2.66	17.11	15.35	8.43
29a	220/50	$C_{18}H_{11}N_3OS_2$	61.87	8.17	12.03	18.35	
		(349.43)	61.83	3.12	12.09	18.40	
29b	230/60	$C_{19}H_{13}N_3O_2S_2$	60.14	3.45	11.07	16.90	
		(377.46)	60.14	3.25	11.14	17.10	
29c	260/65	$C_{18}H_{10}ClN_3OS_2$	56.32	2.63	10.95	16.70	9.24
		(383.89)	56.12	2.25	11.16	16.90	9.12
30	214/86	$C_{18}H_{12}N_2O_2S_2$	61.34	3.43	7.95	18.20	
		(352.44)	61.12	3.65	8.01	18.38	
31	279/84	$C_{20}H_{12}N_2O_2S_2$	63.81	3.21	7.44	17.04	
		(376.45)	63.66	3.11	7.23	17.00	
32	312/93	$C_{26}H_{17}N_3OS_2$	69.15	3.79	9.31	14.20	
		(451.56)	69.00	3.97	9.14	13.93	
33	179/76	$C_{24}H_{19}N_3O_3S_2$	62.45	4.15	9.10	13.89	
		(461.57)	62.73	4.56	9.23	13.78	
34	288/86	$C_{20}H_{14}N_4OS_2$	61.52	3.61	14.35	16.42	
		(390.48)	61.31	3.39	14.56	16.60	
35	211/80	$C_{17}H_{11}NOS_2$	65.97	3.59	4.53	20.74	
		(309.21)	65.93	3.57	4.52	20.77	
36a	215/78	$C_{24}H_{15}NOS_2$	72.50	3.81	3.52	16.14	
		(397.25)	72.45	3.88	3.91	16.31	
36b	212/83	$C_{24}H_{14}ClNOS_2$	66.61	3.27	3.24	14.85	8.22
		(431.74)	66.74	3.33	3.40	14.91	8.35
37a	301/80	$C_{27}H_{17}N_3OS_2$	69.95	3.96	9.06	13.83	
		(463.58)	70.22	3.87	9.01	13.93	
37b	327/85	$C_{27}H_{16}ClN_3OS_2$	65.11	3.24	8.44	12.88	7.13
		(498.08)	65.30	2.99	8.60	12.85	7.09

OCH_3), 1.2–1.4 (t, 3H, CH_3 of ester) ppm. ^{1}H NMR of **3c** ($CDCl_3$): δ = 7.0–7.5 (m, 8H: 4ArH's, 3CH thienyl and CH pyridine), 3.9–4.2 (m, 4H, SCH_2 and OCH_2), 1.0–1.2 (t, 3H, CH_3 of ester) ppm.

Ethyl 3-Amino-4-aryl-6-(2-thienyl)thieno[2,3-b]pyridine-2-carboxylates (4a–c)

Compounds **3a–c** (20 mmol) were suspended in sodium ethoxide solution (0.05 g sodium in 30 ml abs. ethanol) and heated under reflux for 5 min. The solid that formed after cooling was collected and recrystallized from ethanol-chloroform mixture to give yellow crystals of **4a–c**. IR: ν = 3490, 3390 (NH_2), 1660 (C=O) cm^{-1}. ^{1}H NMR of **4a** ($CDCl_3$): δ = 7.67–6.68 (d, 1H, CH thienyl), 7.45–7.56 (m, 6H, 5ArH's and CH thienyl), 7.41 (s, 1H, CH pyridine), 7.11–7.13 (d, 1H, CH thienyl), 5.63 (br, 2H, NH_2), 4.29–4.35 (q, 2H, OCH_2), 1.35–13.39 (t, 3H, CH_3 of ester) ppm. ^{1}H NMR of **4b** ($CDCl_3$): δ = 7.1–7.8 (m, 8H: 4ArH's, 3CH thienyl and CH pryidine), 5.8 (s, 2H, NH_2), 4.2–4.5 (q, 2H, OCH_2), 4.0 (s, 3H, OCH_3), 1.3–1.5 (t, 3H, CH_3 of ester) ppm.

(4-Aryl-3-cyano-6-(2-thienyl)pyridin-2-ylthio)-acethydrazides (5a–c)

A mixture of ester **3a–c** (20 mmol) and hydrazine hydrate 99% (1.0 ml, 20 mmol) in ethanol (50 ml) was heated under reflux for 4 h. The precipitate thus formed while hot was collected and recrystallized from chloroform-ethanol mixture as pale yellow crystals of **5a–c**. IR: ν = 3420–3300, 3200–3100 ($NHNH_2$), 2200 (C≡N), 1650 (C=O) cm^{-1}. ^{1}H NMR of **5a** (DMSO-d_6): δ = 9.4 (s, 1H, NH), 8.2 (d, 1H, CH thienyl), 7.4–8.0 (m, 7H: 5ArH's, CH thienyl and CH pyridine), 7.2–7.3 (t, 1H, CH thienyl), 4.3 (s, 2H, NH_2), 4.0 (s, 2H, SCH_2) ppm.

3-Amino-4-aryl-6-(2-thienyl)thieno[2,3-b]pyridine-2-carbohydrazides (6a–c)

Method A

Compound **3a–c** (20 mmol) and hydrazine hydrate 99% (5.0 ml, 100 mmol) were heated under reflux for 2 h. The reaction mixture was triturated with ethanol (10 ml) and allowed to cool. The solid product was collected and recrystallized from dioxane as canary yellow needles of **6a–c**. IR: ν = 3420, 3300 (NH_2), 3250, 3150 ($NHNH_2$), 1620 (C=O) cm^{-1}. ^{1}H NMR of **6a** (DMSO-d_6): δ = 9.2 (br, 1H, NH), 8.0 (d, 1H, CH thienyl), 7.1–7.8 (m, 7 H, 4ArHs, 2 CH thienyl and CH pyridine), 6.0 (s, 2H, NH_2 at C-3), 4.6 (br, 2H, NH_2 of hydrazide), 3.9 (s, 3H, OCH_3)

ppm. MS of **6a**: 366 (M^+, 90%); 351 (M^+-NH, 100%); 355 (M^+-$NHNH_2$, 100%); 333 (M^+-$NHNH_2$-H_2, 100%); 306 (86%); 261(21%); 153 (16%); 44 (CS^+, 16%).

Method B

To a solution of ester **4a–c** (20 mmol) in absolute ethanol (50 ml), hydrazine hydrate 99% (2 ml, 40 mmol) was added. The mixture was refluxed for 2 h and then left to cool. The compounds which obtained upon recrystallization were identical to those described in method A.

(3-Cyano-4-phenyl-6-(2-thienyl)pyridin-2-ylthio)acetic Acid Azide (7)

To a cold solution of **5a** (3.66 g, 10 mmol) in glacial acetic acid (25 ml), sodium nitrite solution 10% (7.7 ml, 11 mmol) was added dropwise with stirring during 5 mins at room temperature. The precipitate that formed was collected, dried in air, and utilized in the next reaction without purification. IR: $\nu = 2210$ (C≡N), 2160 (N_3), 1660 (C=O) cm^{-1}.

Ethyl *N*-(3-cyano-4-pheny-6-(2-thienyl)pyridin-2-ylthio)methylcarbamate (9)

Compound **7** (1.1 g, 3 mmol) was heated under reflux in abs. ethanol (20 ml) for 2 h. The reaction mixture was then concentrated and left to cool. The solid crystals were collected and recrystallized from ethanol as pale yellow needles of **9**. IR: $\nu = 3400$ (NH), 2200 (C≡N), 1710 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 7.2$–8.3 (m, 9H: 5ArHs, 3 CH thienyl and CH pyridine), 6.0 (br, 1H, NH), 5.2 (s, 2H, SCH_2), 4.0–4.3 (q, 2H, OCH_2), 1.1–1.4 (t, 3H, CH_3) ppm.

Reaction of the Acid Azide 7 with Aniline

Compound **7** (0.75 g, 2 mmol) in aniline (5 ml) was gently refluxed for 3 h. The reaction mixture was triturated with ethanol (10 ml) and left to cool. The white precipitate which obtained upon recrystallization from ethanol was identified as 3-cyano-4-phenyl-2-(*N*-phenyl)carbamoylmethylthio-6-(2-thienyl)pyridine (**10**). IR: $\nu = 3300$ (NH), 2210 (C≡N), 1660 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 10.7$ (s, 1H, NH), 8.2 (d, 1H, CH thienyl), 7.0–7.8 (m, 13H, 10ArHs, 2CH thienyl and CH pyridine), 4.3 (s, 2H, SCH_2) ppm.

This compound was also prepared by refluxing a mixture of **2a** (0.59 g, 2 mmol) and chloro-*N*-phenylacetamide (0.34 g, 2 mmol) in ethanol

(10 ml) containing sodium acetate trihydrate (0.41 g, 3 mmol) for 2 h; yield: 0.74 g (86%).

N^1-Arylmethylene-(3-cyano-4-phenyl-(2-thienyl)pyridin-2-ylthio)acethydrazides (12a–c)

To a solution of acethydrazide **5a** (3.66 g, 10 mmol) in ethanol (50 ml), an ethanolic solution of aromatic aldehyde (10 mmol) was added. The resulting mixture was heated under reflux for 4 h. The solid that formed while hot was collected and recrystallized from dioxane to give yellow crystals of **12a–c**. IR: ν = 3390–3300 (NH), 2210 (C≡N), 1670 (C=O) cm^{-1}. ^{1}H NMR of **12b** (DMSO-d_6): δ = 9.2 (s, 1H, NH), 8.2–8.3 (m, 2H, CH thienyl and N=CH), 7.0–8.0 (m, 12H: 9ArHs, 2 CH thienyl and CH pyridine), 4.8 (s, 2H, SCH_2), 3.8 (s, 3H, OCH_3) ppm.

3-Amino-*N*^{1}-arylmethylene-4-aryl-6-(2-thienyl)thieno-[2,3-b]pyridine-2-carbo-hydrazides (13a–c)

Method A

Compound **12a–c** (10 mmol) in ethanol (30 ml) containing dissolved sodium (0.05 g) was heated under reflux for 15 min. The solid that formed was collected by filtration and recrystallized from ethanol-chloroform mixture to give yellow needles of **13a–c**. IR: ν = 3490, 3300 (NH_2), 3150 (NH), 1620 (C=O) cm^{-1}. MS of compound **13b**: 485 (M^+, 50%); 454 (M^+-OCH_3, 4%); 380 (M^+-$C_6H_4OCH_3$, 10%); 351 (M^+-N=$CHC_6H_4OCH_3$, 15%); 336 (M^+-NHN=$CHC_6H_4OCH_3$, 15%); 335 (M^+-1-NHN=$CHC_6H_4OCH_3$, 100%); 308 (M^+-CONHN=$CHC_6H_4OCH_3$, 42%); 77 ($C_6H_5^+$, 5%); 44 (CS^+, 15%).

Method B

A mixture of **6a** (3.66 g, 10 mmol) and the respective aldehyde (10 mmol) in ethanol (30 ml) was refluxed for 3 h and then left to cool. The solid obtained upon recrystallization was identical in all aspects with those described in method A (Yield, 78–83%).

3-Arylmethyleneamino-9-phenyl-7-(2-thienyl)pyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-ones (14a–c)

Method A

A mixture of **13a–c** (2 mmol) and triethyl orthoformate (5 ml) in acetic anhydride (10 ml) was heated under reflux for 5 h. and then allowed to cool. The solid product was collected and recrystallized from ethanol as pale yellow crystals of **14a–c**. IR: ν = 1670 (C=O) cm^{-1}. ^{1}H NMR of **14a**

(TFA) $\delta = 9.0$ (s, 1H, CH=N), 8.9 (s, 1H, CH pyrimidine), 7.4–8.4 (m, 14H, 10 ArHs: 3CH thienyl and CH pyridine) ppm. MS of compound **14a**: 464 (M^+, 36%); 360 ((M^+-N=CHC_6H_5, 100%); 305 (M^+-CO-HCN, 33%); 106 (46%); 103 ($C_6H_5CN^+$, 35%); 77 ($C_6H_5^+$, 42%).

Method B

To a suspension of **22** (1.8 g, 5 mmol) and benzaldehyde (0.5 ml, 5 mmol) in ethanol (20 ml), few drops of piperidine were added. The resulting mixture was refluxed for 6 h. The solid that formed while hot was collected and recrystallized from ethanol to give **14a** (Yield, 87%). The products obtained by the two synthetic routes are identical in all aspects.

3-Arylmethyleneamino-2-methyl-9-phenyl-7-(2-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-ones (15a–c)

Compound **13a–c** (2 mmol) in acetic anhydride (15 ml) were heated under reflux for 4 h and left to cool. The precipitated solid was collected and recrystallized from dioxane as pale yellow crystals of **15a–c**. IR: $\nu =$ 1670 (C=O) cm^{-1}. ^1H NMR of **15c** (TFA): $\delta = 9.0$ (s, 1H, N=CH), 7.5–8.4 (m, 13H, 9ArHs, 3CH thienyl and CH pyridine), 2.9 (s, 3H, CH_3) ppm. MS of compound **15a**: 478 (M^+, 15%); 374 (M^+-N=CHC_6H_5, 100%); 103 (M^+- C_6H_5CN, 12%).

3-Amino-9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine-2,4(1*H*,3*H*)dione (16)

A mixture of **6a** (0.72 g, 2 mmol) and urea (0.18 g, 3 mmol) in decalin (15 ml) was heated under reflux for 4 h. The precipitate that formed while hot was collected and recrystallized from ethanol-chloroform mixture as buff crystals of **16**. IR: $\nu =$ 3480, 3300 (NH_2), 3200–2900 (NH), 1720–1660 (2C=O) cm^{-1}. MS: 392 (M^+, 6%), 376 (M^+-NH_2, 23%), 361 (M^+-NH_2-NH, 9%), 333 (M^+-NH_2-NH-CO, 11%), 305 (M^+-NH_2-NH-2CO, 11%), 129 (100%), 44 (CS^+, 85%).

3-Formylamino-9-phenyl-7-(2-theinyl)pyrido[3′,2′:4,5]-thieno[3,2-d]pyrimidin-4(3*H*)-one (17)

Compound **6a** (0.72 g, 2 mmol) in formic acid 85% (20 ml) was refluxed for 4 h. The cooled reaction mixture was diluted with water whereupon a white solid precipitated. It was collected and crystallized from ethanol to give **17**. IR: $\nu =$ 3250 (NH), 1720 (C=O), 1680 (C=O) cm^{-1}. ^1H NMR

(DMSO-d_6): $\delta = 8.6$ (s, 1H, CH pyrimidine), 8.4 (s, 1H, NH), 8.1–8.2 (d, 1H, CH thienyl), 8.0 (s, 1H, CH pyridine), 7.8–7.9 (d, 1H, CH thienyl), 7.6–8.0 (m, 6H: ArHs and CHO), 7.3–7.5 (t, 1H, CH thienyl) ppm.

8-Aryl-6-(2-thienyl)-Δ^3-pyrazolino[3′,4′:4,5]thieno-[2,3-b]pyridine-3-ones (18a–c)

Compound **6a–c** (2 mmol) in glacial acetic acid (15 ml) was heated under reflux for 8 h. The solid product thus formed while hot was collected and recrystallized from ethanol to give pale yellow crystals of **18a–c**. IR: $\nu =$ 3300, 3200 (2NH), 1620 (C=O) cm^{-1}. MS of compound **18a**: 350 ($M^+ + 1$, 26%); 349 (M^+, 42%), 44 (CS^+, 15%).

9-Aryl-3-diacetylamino-2-methyl-7-(2-thienyl)pyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-ones (19a–c)

A suspension of compound **6a–c** (3 mmol) in acetic anhydride (20 ml) was refluxed for 3 h. The reaction mixture was diluted with water (20 ml) and allowed to stand at room temperature for 2 h. The precipitated solid was collected and recrystallized from ethanol as white fine crystals of **19a–c**. IR: $\nu = 1730$ (2C=O), 1700–1680 (C=O) cm^{-1}. ^{1}H NMR of **19a** ($CDCl_3$): $\delta = 7.4$–7.9 (m, 8H: 5ArHs and 2CH thienyl and CH pyridine), 7.2 (t, 1H, CH thienyl), 2.4 (s, 6H, 2X$COCH_3$), 2.1 (s, 3H, CH_3) ppm. MS of **335a**:475 ($M^+ + 1$, 7%), 474 (M^+, 88%), 389 ($M^+ -$ 1-2$COCH_3$, 100%), 432 ($M^+ +$ 1-$COCH_3$, 83%).

1-(3-Amino-4-aryl-6-(2-thienyl)thieno[2,3-b]pyridin-2-yl)-carbonyl-3,5-dimethyl-1*H*-pyrazoles (20a–c)

A mixture of **6a–c** (2 mmol) in acetylacetone (5 ml) was heated under reflux for 6 h. The reaction mixture was triturated with ethanol (5 ml) and then left to cool. The precipitated solid was collected by filtration and recrystallized from ethanol to give yellow crystals of **16a–c**. IR: $\nu =$ 3490, 3330 (NH_2), 1630 (C=O) cm^{-1}. ^{1}H NMR of **20a** ($CDCl_3$): $\delta =$ 7.5–7.8 (m, 8H, 5ArHs, 2CH thienyl and CH pyridine), 7.1–7.3 (t, 1H, CH thienyl), 6.7 (br, 2H, NH_2), 6.0 (s, 1H, CH pyrazole), 2.7 (s, 3H, CH_3 pyrazole), 2.4 (s, 3H, CH_3 pyrazole) ppm. MS of compound **20a**: 430 (M^+, 70%), 431 ($M^+ + 1$, 20%), 415 (M^+-CH_3, 1%), 333 (M^+-dimethypyrazolyl radical, 100%); 305 (M^+-dimethylpyrazolylcarbonyl radical, 21%).

9-Aryl-3-ethoxymethyleneamino-7-(2-thienyl)pyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-ones (21a–c)

A mixture of **6a–c** (2 mmol) and triethyl orthoformate (3 ml) in DMF (10 ml) was refluxed for 6 h. The solid that formed on cooling was

collected and recrystallized from DMF as orange crystals of **21a–c**. IR: ν = 1660 (C=O) cm^{-1}. ^1H NMR of **21a** (TFA): δ = 9.1 (s, 1H, N=CH), 8.7 (s, 1H, CH pyrimidine), 7.3–8.2 (m, 9H: 5ArHs, 3CH thienyl and CH pyridine), 7.4–7.5 (d, 1H, CH thienyl), 4.3–4.5 (q, 2H, OCH_2), 1.2–1.5 (t, 3H, CH_3) ppm. ^1H NMR of **21c** (TFA): δ = 9.0 (s, 1H, N=CH), 8.7 (s, 1H, CH pyrimidine and CH pyridine), 8.1–8.5 (m, 3H, 2CH thienyl and CH pyridine), 7.5–7.9 (m, 5H: 4ArHs and CH thienyl), 4.4–4.7 (m, 2H, OCH_2), 1.4–1.7 (t, 3H, CH_3) ppm.

3-Amino-9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno-[3,2-d]pyrimidine-4(3*H*)-one (22)

A mixture of **21a** or **23** (3 mmol) and hydrazine hydrate (10 ml) was heated under reflux for 4 h. The reaction mixture was triturated with ethanol (5 ml) and then left to cool. The precipitated solid was collected by filtration and recrystallized from ethanol-chloroform mixture as yellow crystals of **22**. IR: ν = 3450, 3290 (NH_2), 1660 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ = 8.3 (s, 1H, CH pyrimidine), 7.1–8.2 (m, 9H: 5ArHs, 3CH thienyl and CH pyridine), 6.0 (s, 2H, NH_2) ppm.

3-Hydrazinomethyleneamino-9-phenyl-7-(2-thienyl) pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-one (23)

To a suspension of compound **21a** (0.4 g, 1 mmol) in dioxane (5 ml), hydrazine hydrate (1 ml) was added. The reaction mixture was stirred at room temperature for 1 h. The formed precipitated was filtered, washed with water, dried in air and recrysallized from dioxane as white needles of **23**. IR: ν = 3320, 3250 ($NHNH_2$), 1650 (C=O) cm^{-1}.

3-Diacetylamino-9-phenyl-7-(2-thienyl)-pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-one (24)

A suspension of compound **22** (1.1 g, 3 mmol) in acetic anhydride (20 ml) was refluxed for 3 h. The reaction mixture was diluted with water (20 ml) and allowed to stand at room temperature for 2 h. The precipitated solid was collected and recrystallized from ethanol as white fine crystals of 24. IR: ν = 1730 (2C=O), 1700–1680 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.2 (s, 1H, CH pyrimidine), 7.8 (d, 1H, CH thienyl), 7.7 (s, 1H, CH pyridine), 7.2–7.6 (m, 7H: 5ArHs and 2CH thienyl), 2.4 (s, 6H, $2XCOCH_3$) ppm.

2-(3-Amino-4-phenyl-6-(2-thienyl)thieno[2,3-b]pyridin-2-yl)-1,3,4-oxadiazole-5(4*H*)-thione (25)

A mixture of **6a** (0.72 g, 2 mmol) and carbon disulphide (3 ml) in pyridine (10 ml) was heated on a water bath for 8 h. The precipitate that formed after cooling was collected and recrystallized from dioxane as yellow crystals of 25. IR: ν = 3490–3390 (NH_2), 3100 (NH) cm^{-1}. MS: 410 ($M^+ + 2$, 15%), 409 ($M^+ + 1$, 23%), 408 (M^+, 100%), 392 (M^+-NH_2, 16%).

2-(3-Amino-4-phenyl-6-(2-thienyl)thieno[2,3-b]pyridin-2-yl)-5-ethoxycarbonyl methylthio-1,3,4-oxadiazole (26)

A mixture of **25** (0.81 g, 2 mmol), ethyl chloroacetate (0.22 ml, 2 mmol) and sodium acetate trihydrate (0.41 g, 3 mmol) in ethanol (40 ml) was heated under reflux for 2 h. The precipitate that formed was collected, washed with water, dried in air, and recrsytallized from ethanol as pale yellow crystals of 26. IR: ν = 3490–3300 (NH_2), 1720 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.4–7.8 (m, 9H: 5ArHs, 3CH thienyl and CH pyridine), 5.5 (s, 2H, NH_2), 4.2–4.4 (q, 2H, OCH_2), 4.1 (s, 2H, SCH_2), 1.2–1.5 (t, 3H, CH_3) ppm.

3-Amino-4-aryl-6-(2-thienyl)thieno[2,3-b]pyridine-2-carbonylazides (27a–c)

To a cold solution of **6a–c** (5 mmol) in glacial acetic acid (25 ml), sodium nitrite solution 100% (7.7 ml, 11 mmol) was added dropwise with stirring during 5 min at room temperature. The formed precipitate was collected, dried in air, and utilized in the next reaction without purification. IR: ν = 3480, 3320 (NH_2), 2120 (N_3), 1680(CO) cm^{-1}.

4-Aryl-6-(2-thienyl)-1*H*-imidazolo[4′,5′:4,5]thieno[2,3-b]-pyridine-2(3*H*)-ones (29a–c)

The acid azide **27a–c** (3 mmol) was heated under reflux for 3 h in isopropyl alcohol (30 ml). The reaction mixture was cooled whereupon a precipitate formed. It was collected and recrystallized from isopropyl alcohol as brown crystals of **29a–c**. IR: ν = 3500, 2500 (NH), 1680 (C=O) cm^{-1}. MS of 27a: 349 (M^+,8%), 45 (HCS^+, 100%).

3-Amino-4-phenyl-6-(2-thienyl)-thieno[2,3-b]pyridine-2-carboxylic acid (30)

A suspension of **4a** (3.8 g, 9 mmol) in ethanolic sodium hydroxide solution 10% (50 ml) was heated under reflux for 4 h and then allowed to cool. The reaction mixture was diluted with 50 ml water, filtered, and

then the clear filtrate was acidified with dilute acetic acid. The precipitate was collected and crystallized from ethanol–chloroform mixture to give yellow crystals of 30. IR: $\nu = 3490, 3350$ (NH_2), at 3200–3000 (OH), 1640 (C=O) cm^{-1}. ^1H NMR (TFA): $\delta = 10.2$ (s, 1H, CO_2H); 7.1–8.2 (m, 9H: 5ArHs, 3CH thienyl and CH pyridine) ppm.

2-Methyl-9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]-thieno[3,2-d]oxazine-4-one (31)

Compound **30** (1.76 g, 5 mmol) in redistilled acetic anhydride (25 ml) was heated under reflux for 4 h and then left to cool. The solid product was collected by filtration and dried in air to give white needles of **31**. IR: $\nu = 1740$ (C=O) cm^{-1}. ^1H NMR (TFA): δ 7.3–8.5 (m, 9H: 5ArHs, 3CH thienyl and CH pyridine); 2.4 (s, 3H, CH_3) ppm.

3,9-Diphenyl-2-methyl-7-(2-thienyl)pyrido[3′,2′:4,5]-thieno[3,2-d]pyrimidine-4(3*H*)-one (32)

A mixture of **31** (0.37 g, 1 mmol) and aniline (0.4 ml) in glacial acetic acid (10 ml) was heated under reflux for 3 h. The reaction mixture was cooled and diluted with water, whereupon a solid precipitated. It was collected and crystallized from ethanol–chloroform mixture to give white needles of **32**. IR: $\nu = 1660$ (C=O) cm^{-1}. ^1H NMR (TFA): $\delta = 7.3$–8.3 (m, 14H: 10ArHs, 3CH thienyl and CH pyridine); 2.4 (s, 3H, CH_3) ppm.

3-Ethoxycarbonylmethyl-2-methyl-9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-one (33)

Ethyl glycinate hydrochloride (0.69 g, 4 mmol) and sodium acetate (0.5 g) were refluxed in acetic acid (20 ml) for 1 h, the precipitated sodium chloride was filtered off, compound **31** (0.75 g, 2 mmol) was added to the filtrate, and it was further refluxed for 3 h. The cooled reaction mixture was diluted with water and the precipitated solid was collected to give **33**. IR: $\nu = 1730$ (C=O, ester), 1660 (C=O, pyrimidinone) cm^{-1}. ^1H NMR spectrum (TFA): $\delta = 7.1$–8.2 (m, 9H; 5 ArHs, 3 CH thienyl and CH pyridine), 4.9 (s, 2H, NCH_2), 4.2–4.4 (q, 2H, OCH−2), 2.4 (s, 3H, CH_3 at C-2), 1.2–1.4 (t, 3H, CH_3 of ester) ppm.

3-Amino-2-methyl-9-phenyl-7-(2-thienyl)pyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-one (34)

A mixture of oxazinone **31** (0.75 g, 2 mmol) and hydrazine hydrate 99% (0.5 ml, 10 mmol) in ethanol (20 ml) was refluxed for 2 h. The product that formed was collected and recrystallized from ethanol to give white

needles of 34. IR: $\nu = 3300–3200$ (NH_2); 1660(C=O, pyrimidinone) cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 7.0–7.5$ (m, 9H: 5 ArHs, 3CH thienyl and CH pyridine), 6.0 (s, 2H, NH_2), 2.3 (s, 3H, CH_3 at C-2) ppm. MS: m/z = 390.4 (M^+, 100%), 361 (M^+-NH_2–CH_3, 100%), 77 ($C_6H_5^+$, 6%).

Reaction of Compound 30 with Orthophosphoric Acid: Formation of 4-Phenyl-6-(2-thienyl)thieno-[2,3-b]pyridine-3(2*H*)-one (35)

A solution of **30** (1.41 g, 4 mmol) in orthophosphoric acid 85% (30 ml) was heated on a water bath for 8 h. The reaction mixture was poured onto ice-water (60 ml), whereupon a solid product precipitated. It was collected by filtration, dried in air, and crystallized from benzene to give **35** as pale yellow crystals. IR: $\nu = 1680$ (C=O) cm^{-1}. ^1H NMR (TFA): $\delta = 8.1–8.2$ (d, 1H, CH thienyl), 7.9 (s, 1H, CH pyridine), 7.5–7.7 (m, 6H: 5 ArHs and CH thienyl), 6.9–7.1(t, 1H, CH thienyl), 4.4 (s, 2H, SCH_2) ppm.

Reaction of Compound 35 with Aromatic Aldehydes: Formation of Chalcones 36a,b

To a mixture of **35** (0.62 g, 2 mmol) and the respective aromatic aldehyde (2 mmol) in ethanol (15 ml) a few drops of piperidine were added. The resulting mixture was heated under reflux for 1 h. The precipitate was collected and recrystallized from chloroform to give yellow crystals of **36a,b**. IR: $\nu = 1680$ (C=O) cm^{-1}. MS of 36a: m/z = 397 (M^+, 41%); 396 (M^+-1, 24%), 28 (CO^+, 100%).

2-Amino-4-aryl-9-phenyl-7-(2-thienyl)-4*H*-pyrano-[2′,3′:4,5]thieno[2,3-b] pyridine-3-carbonitriles (37a,b)

Method A

To a mixture of **35** (1.24 g, 4 mmol) and the respective arylmethylenemalononitrile (4 mmol) in ethanol (25 ml) a few drops of piperidine were added. The reaction mixture was heated under reflux for 2 h. The precipitate that formed was collected by filtration while hot and recrystallized from dioxane as yellow crystals of **37a,b**. IR: $\nu = 3400$, 3300, 3200 (NH_2), 2200 (C≡N), 1640 (C=N) cm^{-1}. MS of **37b**: m/z = 497.08 (M^+, 4%), 431 (M^+-CN-C=CNH_2, 100%).

Method B

To a mixutre of **36a,b** (3 mmol) and malononitrile (3 mmol) in ethanol (20 ml), few drops of piperidine were added. The mixture was refluxed for 1 h. The solid that formed was collected and recrystallized to give

37a,b in 67–71% yield. These compounds were identical in all aspects to those described in method A.

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