SYNTHESIS OF SOME 2-(SUBSTITUTED THIO)PYRIDINES AND THIENO[2,3-*b*]PYRIDINES

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Pyridine heterocycles occupy a unique position in medicinal chemistry. The naturally occurring B_6 vitamine (pyridoxol, pyridoxal, pyridoxamine), some alkaloids and coenzymes[1] contain pyridine nucleus. Many thienopyridine derivatives have been investigated because of the various biological activities such as against diabetes mellitus, as analgetics, anti-inflammatories, sedatives, and anticoagulants[2 – 10].

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr, cm^{-1}) were recorded on a Pye–Unicam SP 3-100 spectrophotometer. The ^1H NMR spectra (δ, ppm) were recorded on a Varian EM-390 90 MHz NMR spectrometer using TMS as internal standard. The mass spectra were obtained using an AET MS-9 mass spectrophotometer operating at 70 eV. The yields, melting points and analytical data of all reported compounds are given in Table I.

3-Cyano-6-(4-hydroxyphenyl)-2-mercapto-4-phenylpyridine (*IIa*)

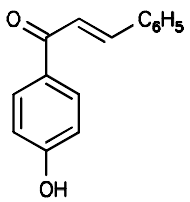
A mixture of chalcone *I* (2.91 g, 13 mmol) and cyanothioacetamide (1.3 g, 13 mmol) in sodium methoxide solution (1 g sodium dissolved in 50 ml absolute methanol) was heated to 50 °C for 48 h. The reaction mixture was acidified with dilute HCl. The crystalline compound thus formed was collected and recrystallized from ethanol as orange prisms. IR spectrum: 3 450 (OH); 2 200 (C≡N); 1 600 (C=N).

3-Cyano-6-(4-hydroxyphenyl)-2-methylthio-4-phenylpyridine (*IIb*)

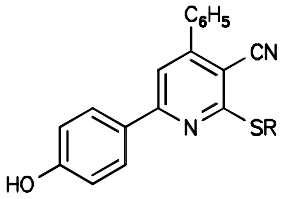
A mixture of *IIa* (3.04 g, 10 mmol), methyl iodide (0.71 g, 15 mmol) and anhydrous sodium acetate (2 g) in ethanol (50 ml) was refluxed for 3 h, then allowed to cool and diluted with water. The precipitated solid was collected and recrystallized from ethanol to form buff needles. IR spectrum: 3 440 (OH); 2 220 (C≡N).

Ethyl-4-(3-cyano-2-methylthio-4-phenyl-2-pyridyl) Phenoxyacetate (*IIIa*)

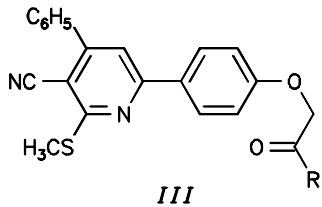
To a suspension of *IIb* (3.18 g, 10 mmol) and anhydrous potassium carbonate (1.51 g, 11 mmol) in acetone (50 ml), ethyl chloroacetate (1.07 ml, 10 mmol) was added. The mixture was refluxed for 21 h, then allowed to cool and diluted with water. The product thus precipitated was collected by



I

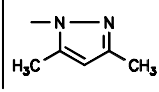


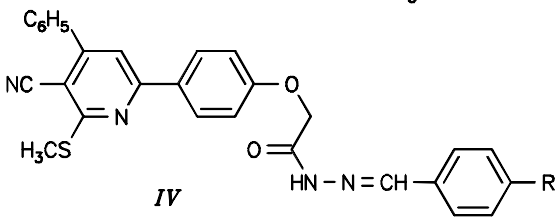
II



III

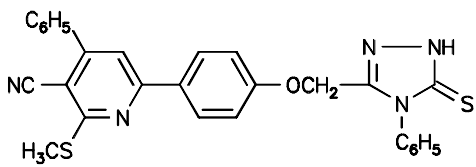
	R
a	H
b	CH_3

	R
a	OC_2H_5
b	$NHNH_2$
c	NHNHCNHPh (=S)
d	

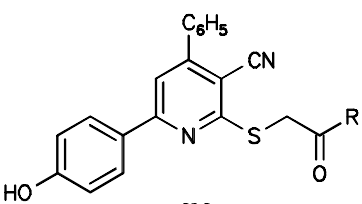


IV

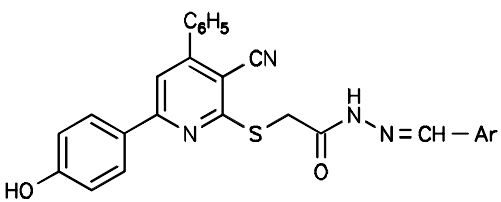
	R
a	H
b	OCH_3
c	$N(CH_3)_2$
d	Cl



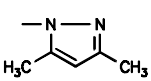
V



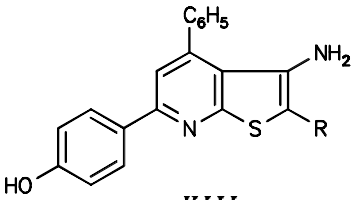
VI



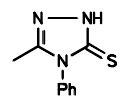
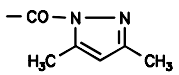
VII

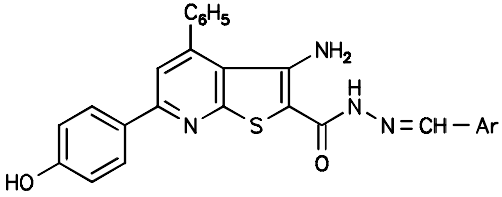
	R
a	OC_2H_5
b	$HNNH_2$
c	HNNHCSNHPh
d	

	Ar
a	C_6H_5
b	$4\text{-}CH_3OC_6H_4$
c	$4\text{-}ClC_6H_4$



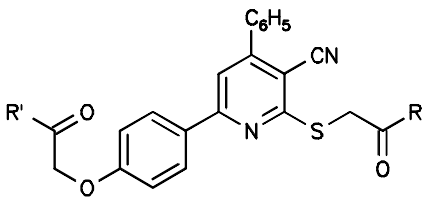
VIII

	R
a	$COOC_2H_5$
b	
c	



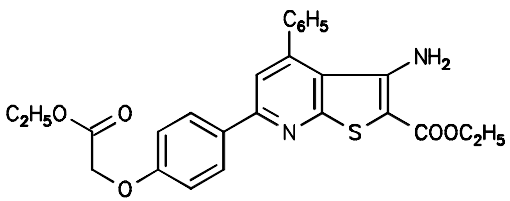
IX

	Ar
a	C_6H_5
b	$4\text{-}CH_3OC_6H_4$
c	$4\text{-}ClC_6H_4$

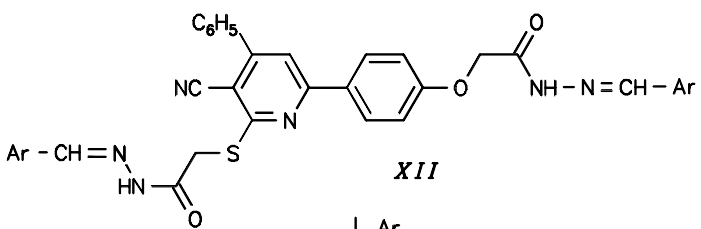


X

	R	R'
a	OC_2H_5	OC_2H_5
b	$NHNH_2$	$NHNH_2$



XI



XII

	Ar
a	C_6H_5
b	$4\text{-}CH_3OC_6H_4$
c	$4\text{-}ClC_6H_4$

filtration and crystallized from ethanol as pale yellow needles. ^{1}H NMR spectrum (CD_3SOCD_3): 1.4 t, 3 H (C–CH_3); 2.6 s, 3 H (SCH_3); 4.3 q, 2 H (CH_2); 4.7 s, 2 H (OCH_2); 7.0 – 8.0 m, 10 H (arom.). IR spectrum: 2 955 (–CH aliph.); 2 200 (C≡N); 1 740 (C=O).

4-(3-Cyano-2-methylthio-4-phenyl-6-pyridyl)phenoxyacethydrazide (*IIIb*)

A mixture of ester *IIIa* (4.04 g, 10 mmol) and 99% hydrazine hydrate (0.5 ml, 10 mmol) in absolute ethanol (50 ml) was refluxed for 8 h. The solid product was collected and recrystallized from dioxane as white needles. ^{1}H NMR spectrum ($CDCl_3$): 2.5 s, 3 H (CH_3); 4.7 s, 2 H (OCH_2); 5.1 s, 2 H (NH_2); 9.3 s, 1 H (NH); 7.3 – 8.7 m, 10 H (arom.). IR spectrum: 3 100, 3 265 ($NHNH_2$); 2 200 (C≡N); 1 710 (C=O).

N^1-[4-(3-Cyano-2-methylthio-4-phenyl-6-pyridyl)phenoxyacetyl]-N^4-phenyl-3-thiosemicarbazide (*IIIc*)

A mixture of *IIIb* (3.90 g, 10 mmol) and phenylisothiocyanate (1.27 ml, 10 mmol) in absolute ethanol (40 ml) was refluxed for 3 h. The crystalline product was collected and recrystallized from dioxane as white crystals. IR spectrum: 3 360, 3 200 (NH); 2 215 (C≡N); 1 720 (C=O).

3-Cyano-6-[4-3′,5′-dimethylpyrazol-1′-yl)carbonylmethoxyphenyl]-2-methylthio-4-phenylpyridine (*IIId*)

To a mixture of *IIIb* (1.95 g, 5 mmol) and acetylacetone (0.5 ml, 5 mmol) in ethanol (30 ml), few drops of glacial acetic acid was added. The resulting mixture was refluxed for 3 h, concentrated and allowed to cool. The separated product was collected and recrystallized from ethanol as white needles. ^{1}H NMR spectrum (CD_3SOCD_3): 2.4 s, 3 h (CH_3); 2.6 s, 3 H (CH_3); 2.9 s, 3 H (SCH_3); 4.6 s, 2 H (OCH_2); 5.7 s, 1 H (CH-pyrazole); 7.1 – 7.7 m, 10 H (arom.). IR spectrum: 2 910 (CH aliph.); 2 220 (C≡N); 1 710 (C=O).

N^1-Arylidene-4-(3-cyano-2-methylthio-4-phenyl-6-pyridyl)phenoxyacethydrazides (*IVa – IVd*)

To a solution of *IIIb* (3.90 g, 10 mmol) in ethanol (30 ml), an ethanolic solution of appropriate aldehyde (10 mmol) was added. The resulting mixture was refluxed for 4 h. On cooling, the product was collected and recrystallized from dioxane, dioxane–ethanol or ethanol as needle crystals. IR spectra of compounds *IVa – IVd:* 3 200 – 3 230 (NH); 2 215 – 2 220 (C≡N); 1 670 – 1680 (C=O).

3-Cyano-2-methylthio-6-[4-(4′-phenyl-5-thioxo-3,4-dihydro-1,2,4-triazol-3-ylmethoxy)phenyl]-4-phenylpyridine (*V*)

Compound *IIIc* (5.25 g, 10 mmol) was dissolved in alcoholic sodium hydroxide solution (8%, 20 ml) and heated on a water bath for 3 h. The solution was filtered and the clear filtrate was acidified with dilute HCl. The separated product was collected, dried and crystallized from dioxane as white needles. ^{1}H NMR spectrum (CD_3SOCD_3): 2.3 s, 3 H (SCH_3); 5.2 s, 2 H (OCH_2); 10.5, 1 H (NH); 8.0 – 7.3 m, 15 H (arom.). IR spectrum: 3 450 (NH); 2 210 (C≡N); 1 600 (C=N).

Ethyl[3-Cyano-6-(4-hydroxyphenyl)-4-phenyl-2-pyridylthio]acetate (*VIa*)

To a suspension of *IIa* (3.04 g, 10 mmol) and anhydrous sodium acetate (2 g) in ethanol (50 ml), ethyl chloroacetate (1.07 ml, 10 mmol) was added. The mixture was refluxed for 3 h and allowed to cool. The precipitated product was filtered, washed with water and recrystallized from ethanol as buff

crystals. ^{1}H NMR spectrum (CD_3SOCD_3): 1.5 t, 3 H (CH_3); 3.5 s, 2 H (SCH_2); 4.3 q, 2 H ($C-CH_2$); 7.7 – 7.4 m, 10 H (arom.); 10.5 s, 1 H (OH). IR spectrum: 3 400 (OH); 2 220 (C≡N); 1 730 (C=O).

[3-Cyano-6-(4-hydroxyphenyl)-4-phenyl-2-pyridylthio]acethydrazide (*VIb*)

A mixture of *VIa* (4.78 g, 10 mmol) and 99% hydrazine hydrate (0.5 ml, 10 mmol) in absolute ethanol (50 ml) was refluxed for 4 h. The precipitated product was collected and recrystallized from ethanol as white needles. IR spectrum: 3 340 – 3 200 ($NHNH_2$, OH); 2 210 (C≡N); 1 660 (C=O).

N^1-[3-Cyano-6-(4-hydroxyphenyl)-4-phenyl-2-pyridylthio]acetyl-N^4-phenyl-3-thiosemicarbazide (*VIc*)

A mixture of *VIb* (3.76 g, 5 mmol) and phenyl isothiocyanate (0.64 ml, 5 mmol) in absolute ethanol (50 ml) was refluxed for 4 h. The product was collected and recrystallized from dioxane as white needles. IR spectrum: 3 400 – 3 240 (NH, OH); 2 215 (C≡N); 1 680 (C=O).

2-(3,5-Dimethylpyrazol-4-yl)carbonylmethylthio-3-cyano-6-(4-hydroxyphenyl)-4-phenylpyridine (*VId*)

A mixture of *VIb* (1.88 g, 5 mmol) and acetylacetone (0.5 ml, 5 mmol) in absolute ethanol (50 ml) was refluxed for 5 h. The reaction mixture was concentrated and the precipitated product was filtered, dried and recrystallized from ethanol as white needles. ^{1}H NMR spectrum (CD_3SOCD_3): 2.4 s, 3 H (CH_3); 2.7 s, 3 H (CH_3); 5.2 s, 2 H (SCH_2); 6.7 s, 1 H (CH-pyrazole); 7.5 – 7.0 m, 10 H (arom.); 9.7 s, 1 H (OH). IR spectrum: 3 410 (OH); 2 220 (C≡N); 1 675 (C=O).

N^1-Arylidene-[3-cyano-6-(4-hydroxyphenyl)-4-phenyl-2-pyridylthio]acethydrazides (*VIIa – VIIc*)

To a solution of *VIb* (1.88 g, 10 mmol) in ethanol (40 ml), an ethanolic solution of the appropriate aldehyde (10 mmol) was added. The resulting mixture was refluxed for 2 – 4 h. The solid product was collected and recrystallized from the dioxane–water mixture or dioxane to give compounds *VIIa – VIIc*. IR spectra: 3 440 – 3 450 (OH); 3 200 – 3 240 (NH); 2 210 – 2 220 (C≡N); 1 660 – 1 665 (C=O).

Cyclization of Compounds *VIa*, *VId* and *VIIa – VIIc*. General Procedure

Compound *VIa*, *VId*, *VIIa*, *VIIb* or *VIIc* (10 mmol) was suspended in sodium ethoxide solution (150 mg sodium dissolved in 50 ml ethanol). The reaction mixture was refluxed for 15 min and cooled. After acidification of the mixture with diluted HCl, the solid was collected and identified.

Ethyl 3-amino-6-(4-hydroxyphenyl)-4-phenylthieno[2,3-b]pyridine-2-carboxylate (VIIIa). The compound *VIIIa* was obtained from *VIa* and recrystallized from dioxane to form yellow needles. ^{1}H NMR spectrum ($CDCl_3$): 1.4 t, 3 H (CH_3); 4.1 q, 2 H (CH_2); 5.7 s, 2 H (NH_2); 7.2 – 7.9 m, 10 H (arom.); 9.7 s, 1 H (OH). IR spectrum: 3 480 – 3 400 (NH_2, OH); 1 680 (C=O).

3-Amino-2-(3,5-dimethylpyrazol-1-yl)carbonyl-6-(4-hydroxyphenyl)-4-phenylthieno[2,3-b]pyridine (VIIIc). The compound *VIIIc* was obtained from *VId* and recrystallized from ethanol as orange needles. IR spectrum: 3 480 – 3 410 (NH_2, OH); 1 650 (C=O).

N^1-Arylidene-2-amino-6-(4-hydroxyphenyl)-4-phenylthieno-[2,3-b]pyridine-2-carbohydrazides (IXa – IXc). The title compounds were obtained from VIIa – VIIc and recrystallized from ethanol as yellow needles. IR spectra: 3 410 – 3 140 (NH_2, NH, OH); 1 645 – 1 650 (C=O).

TABLE I
The yields, melting points and analytical data of the synthesized compounds

Compound	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% S
IIa	271	$C_{18}H_{12}N_2OS$	71.03	3.97	9.20	10.53
	82	(304.3)	71.41	3.73	8.98	10.19
IIb	243	$C_{19}H_{14}N_2OS$	71.67	4.42	8.79	10.07
	67	(318.4)	71.33	4.17	8.58	10.27
IIIa	130	$C_{23}H_{20}N_2O_3S$	68.30	4.98	6.92	7.92
	77	(404.4)	67.93	5.38	6.71	8.21
IIIb	215	$C_{21}H_{18}N_4O_2S$	64.60	4.64	14.35	8.21
	73	(390.4)	64.96	4.89	14.23	8.09
IIIc	173	$C_{28}H_{23}N_5O_2S_2$	63.97	4.40	13.32	12.19
	75	(525.6)	63.77	4.27	13.15	12.32
IIId	184	$C_{26}H_{22}N_4O_2S$	68.70	4.87	12.32	7.05
	63	(454.5)	68.37	4.51	12.68	7.02
IVa	235	$C_{28}H_{22}N_4O_2S$	70.27	4.62	11.71	6.70
	91	(478.5)	69.98	4.51	11.43	6.50
IVb	193	$C_{29}H_{24}N_4O_3S$	68.49	4.75	11.01	6.30
	93	(508.5)	68.11	4.32	11.33	5.98
IVc	210	$C_{30}H_{27}N_5O_2S$	69.07	5.21	13.43	6.14
	90	(521.6)	69.14	5.27	13.25	6.06
IVd	237	$C_{28}H_{21}ClN_4O_2S$	65.65	4.12	10.92	6.25
	91	(512.9)	65.44	4.32	10.75	6.07
V	231	$C_{28}H_{21}N_5OS_2$	66.21	4.16	13.84	12.62
	61	(507.8)	66.33	4.28	13.72	12.37
VIa	215	$C_{22}H_{18}N_2O_3S$	67.68	4.64	7.17	8.20
	89	(390.4)	67.25	4.53	7.47	7.94
VIb	273	$C_{20}H_{16}N_4O_2S$	63.81	4.28	14.88	8.51
	81	(376.4)	64.05	4.53	15.00	8.31
VIc	236	$C_{27}H_{21}N_5O_2S_2$	63.38	4.13	13.69	12.53
	83	(511.6)	63.51	4.33	13.61	12.76
VId	210	$C_{25}H_{20}N_4O_2S$	68.16	4.57	12.72	7.27
	76	(440.5)	67.85	4.61	12.32	7.11

TABLE I
(*Continued*)

Compound	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% S
VIIa	159	$C_{27}H_{20}N_4O_2S$	69.79	4.33	12.05	6.90
	91	(464.6)	69.62	4.53	12.23	6.74
VIIb	267	$C_{28}H_{22}N_4O_3S$	68.00	4.47	11.32	6.48
	93	(494.5)	67.83	4.75	11.04	6.22
VIIc	221	$C_{27}H_{19}ClN_4O_2S$	64.98	3.83	11.22	6.42
	89	(499.0)	64.72	4.03	11.52	6.19
VIIIa	>360	$C_{22}H_{18}N_2O_3S$	67.68	4.64	7.17	8.21
	65	(390.4)	67.23	4.30	7.23	8.33
VIIIb	>360	$C_{27}H_{19}N_5OS_2$	65.70	3.87	14.19	12.99
	67	(493.6)	65.33	3.51	14.19	12.70
VIIIc	261	$C_{25}H_{20}N_4O_2S$	68.16	4.57	12.72	7.27
	67	(440.5)	67.99	4.31	12.55	7.01
IXa	267	$C_{27}H_{20}N_4O_2S$	69.79	4.33	12.31	6.90
	70	(464.6)	69.45	4.21	12.52	6.83
IXb	231	$C_{28}H_{22}N_4O_3S$	68.00	4.47	11.32	6.48
	70	(494.5)	68.34	4.45	11.61	6.21
IXc	257	$C_{27}H_{19}ClN_4O_2S$	64.98	3.83	11.22	6.42
	73	(499.0)	64.77	3.91	11.53	6.27
Xa	131	$C_{26}H_{24}N_2O_5S$	65.54	5.07	5.87	6.72
	83	(476.4)	65.31	5.34	5.72	6.53
Xb	203	$C_{22}H_{20}N_6O_3S$	58.92	4.49	18.73	7.14
	77	(448.4)	58.71	4.32	18.51	7.32
XI	305	$C_{26}H_{24}N_2O_5S$	66.54	5.07	5.87	6.72
	65	(476.4)	65.29	5.31	5.60	6.84
XIIa	243	$C_{36}H_{28}N_6O_3S$	69.22	4.51	13.45	5.13
	87	(624.6)	69.35	4.24	13.21	5.15
XIIb	253	$C_{38}H_{32}N_6O_5S$	66.62	4.70	12.31	4.68
	91	(685.0)	66.71	4.53	12.62	4.73
XIIc	230	$C_{36}H_{26}Cl_2N_6O_3S$	62.33	3.77	12.11	4.62
	90	(693.6)	62.10	3.52	12.35	4.43

3-Amino-6-(4-hydroxyphenyl)-4-phenyl-2-(4-phenyl-5-thioxo-2,4-dihydro-1,2,4-triazol-3-yl)-thieno[2,3-*b*]pyridine (*VIIIb*)

Thiosemicarbazide *VIc* (5.11 g, 10 mmol) was dissolved in alcoholic sodium hydroxide solution (8%, 20 ml) and heated on a water bath for 5 h. The solution was filtered and the clear filtrate was acidified with diluted HCl. The separated product was collected and recrystallized from ethanol as orange prisms. IR spectrum: 3 490 – 3 400 (NH_2, OH); 3 310 (NH); 1 600 (C=N).

3-Cyano-2-ethoxycarbonylmethylthio-6-(4-ethoxycarbonylmethoxyphenyl)-4-phenylpyridine (*Xa*)

Method A. A mixture of *IIa* (3.04 g, 10 mmol) and ethyl chloroacetate (2.14 ml, 20 mmol) was refluxed in dry acetone (30 ml) and anhydrous K_2CO_3 (2 g) on a steam bath for 21 h. After cooling, the precipitated product was filtered, washed with water several times and recrystallized from ethanol as yellow crystals. IR spectrum: 3 000 (CH aliph.); 2 240 (C≡N); 1 730 (C=O). Mass spectrum, *m*/*z*: 476 (M^+ 32.79%).

Method B. A mixture of *VIa* (3.90 g, 10 mmol) and ethyl chloroacetate (1.07 ml, 10 mmol) was refluxed in dry acetone (30 ml) and anhydrous K_2CO_3 (2 g) for 21 h. The product obtained after recrystallization was identical to that reported in method *A* according to melting point and spectral data.

[3-Cyano-6-(4-hydrazinocarbonylmethoxyphenyl)-4-phenyl-2-pyridylthio]acethydrazide (*Xb*)

A mixture of *Xa* (4.76 g, 10 mmol) and hydrazine hydrate (1 ml, 20 mmol) in absolute ethanol (40 ml) was refluxed for 5 h. The solid product was filtered off and recrystallized from dioxane as yellow crystals. IR spectrum: 3 290 – 3 210 ($NHNH_2$); 2 210 (C≡N); 1 740 (C=O).

Ethyl 3-Amino-6-(4-ethoxycarbonylmethoxyphenyl)-4-phenylthieno-[2,3-*b*]pyridine-2-carboxylate (*XI*)

Compound *Xa* (4.76 g, 10 mmol) was suspended in sodium ethoxide solution (100 mg sodium in 50 ml ethanol). The reaction mixture was refluxed for 15 min and cooled. The solid obtained was recrystallized from ethanol–chloroform as yellow needles. IR spectrum: 3 370 – 3 290 (NH_2); 1 735 (C=O).

N^1-Arylidene[3-cyano-6-(4-N^1-arylidenephenoxyacethydrazide)-4-phenyl-2-pyridylthio]-acethydrazide (*XIIa – XIIc*)

To a solution of compound *Xb* (4.48 g, 10 mmol) in ethanol (30 ml), an ethanolic solution of the appropriate aldehyde (20 mmol) was added. The resulting mixture was refluxed for about 4 h. The solid formed on cooling was collected and recrystallized from ethanol of the dioxane–water mixture. IR spectra: 3 220 – 3 200 (NH); 2 200 – 2 210 (C≡N); 1 690 – 1 670 (C=O).

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