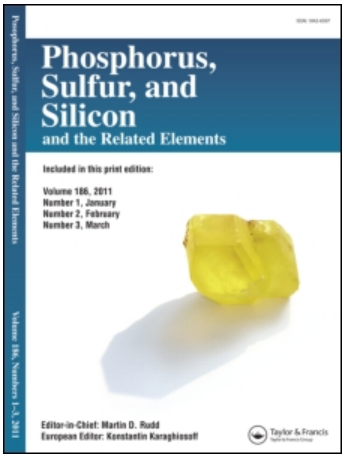

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A NOVEL SYNTHESIS OF THIENOPYRIDINE, PYRROLOQUINOLINOTHIOPHENE, PYRAZOLOPYRIDIN-3-YL-PHENYLTHIOUREA AND THIAZOLYLPYRAZOLOPYRIDINE DERIVATIVES

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Dibenzalacetones **1a-c** reacted with cyanothioacetamide (**2**) to give the new styrylpyridinethione derivatives **3a-c** which were used as the starting materials for the synthesis of other several heterocyclic compounds. Reactions with chloroacetone (**4**), N-arylmaleimides **7a,b**, and ethyl iodide gave 2-S-acetonyl pyridines **5a-c**, pyrrolo[3,4-f]quinolines **9a-f**, and 2-S-ethylpyridines **11a-c**, respectively. Several cycloaddition reactions were carried out on **3a-c, 5a-c**, and **6a-c** with dienophiles **7a,b**, to afford the corresponding cycloadducts **9a-f, 10a-f**, and **8a-f**, respectively. Structures were established based on elemental analyses and spectral data. The antimicrobial activity of the newly synthesized compounds was tested.

Keywords: Thienopyridine; Pyrroloquinoline; Pyrroloquinolinothiophene; Pyrazolopyridine; Phenylthiourea

INTRODUCTION

The reported biological activities of pyridines [1–3], as well as thienopyridines [4,5] and pyrazolopyridines [6,7], stimulated our interest in the synthesis of several new derivatives of that ring system which was required for our medicinal chemistry program. Cyanothioacetamide (**2**) and pyridinethiones **3a-c** are versatile reagents, and their utility in heterocyclic synthesis has gained a considerable recent attention [8–14] and seemed highly suitable for the synthesis of the desired heterocycles.

* To Receive Any Correspondence

RESULTS AND DISCUSSION

It has been found that equimolecular amounts of dibenzalacetone (**1a**) and cyanothioacetamide (**2**) reacted in ethanolic sodium ethoxide to afford a product of molecular formula $C_{20}H_{14}N_2S$ corresponding to the addition of one mole of **1a** to one mole of (**2**) with the loss of a water molecule. Based on IR, ^{1}H-NMR and elemental analysis such a reaction product could be formulated as the styrylpyridinethione **3a** (cf. Tables I and II).

In a similar manner, each of **1b,c** reacted with **2** to yield the corresponding styrylpyridinethiones **3b,c**, respectively. The structures of **3b,c** were also established based on IR, ^{1}H-NMR, and elemental analyses (cf. Tables I and II). Moreover, the mass spectra of **3a-c** gave m/z = 314, 374, and 383, respectively, which represented molecular weights of the molecular formulae $C_{20}H_{14}N_2S$, $C_{22}H_{18}N_2SO_2$, and $C_{20}H_{12}N_2SCl_2$ of the assigned structures (cf. Chart 1).

The synthetic potential of **3a-c** was demonstrated via their reactions with chloroacetone (**4**) to give products formed by dehydrochlorination. The structures of that reaction products were established based on IR, ^{1}H-NMR, and elemental analyses (cf. Tables I and II). By considering the above-mentioned data, these products could be formulated as the 2-S-acetonylpyridine derivatives **5a-c**, respectively. Further confirmation of the structures **5a-c** was given via their cyclization using 10% ethanolic KOH solution to afford thieno[2,3-b]pyridine derivatives **6a-c**, respectively. The IR spectra of **6a-c** showed no bands of CN group and instead the bands of the newly born NH_2 group were detected. The ^{1}H-NMR spectra of **6a-c** also revealed no signals of -SCH_2- protons but revealed signals for NH_2 protons. Considering the previous results, we can conclude that both -SCH_2- and CN groups in **5a-c** are involved in the cyclization step to afford **6a-c**, respectively (cf. Tables I and II). Moreover, the mass spectra of both **5a** and **6a** as selective examples gave the same m/z= 370 which represented the molecular weights of the molecular formula $C_{23}H_{18}N_2SO$ of the assigned structures (cf. Chart 1). It is remarkable to report here that the two protons at positions 3 and 4 of the pyridine ring in both **5a-c** and **6a-c** were not revealed in the ^{1}H-NMR spectra, and this proved that compounds **5a-c** and **6a-c** suffered dehydrogenation under the applied reaction condition. Structure of **6a-c** was established based on IR, ^{1}H-NMR and elemental analyses (cf. Tables I and II). The dienic nature of both **6a-c** and **3a-c** was investigated through their reactions with N-arylmaleimides **7a,b**

as dienophiles. Thus, **3a-c** and **6a-c** reacted with N-phenylmaleimide (**7a**) and N-(p-chlorophenyl)maleimide (**7b**) in anisole to afford the cycloadducts **9a-f** and **8a-f**, respectively, which could be formulated as the pyrrolo[3,4-f]quinoline and pyrrolo[3,4-f]quinolino[2,3:6′,7′]thiophene, respectively. The IR (cm^{-1}) spectra showed the two widely separated bands of -CO-N-Ar-CO- grouping at 1780 and 1690 cm^{-1} characteristic of the cycloadducts (cf. Tables I and II). Compounds **9a-f** reacted chloroacetone (**4**) in pyridine to afford the corresponding 2-S-acetonylpyrrolo[3,4-f]-quinoline **10a-f**, respectively. The structures **10a-f** were established based on elemental analyses, IR, and ^{1}H-NMR spectral data. A further confirmation of the structure of **10a-f** was given either through their synthesis via another route by reaction of **5a-c** with N-arylmaleimides **7a,b** in anisole or by their cyclization in ethanol containing the catalytic amounts of triethylamine to afford the previously obtained **8a-f**, respectively. It remarkable to report here that compounds **8a-f** obtained either by cyclization of **10a-f** or by cycloaddition of **6a-f** to **7a,b** were identical in all aspects (m.p., IR, ^{1}H-NMR and elemental analyses) (cf. Tables I, II and Chart 1).

The synthetic potential of **3a-c** was further demonstrated via reactions with different reagents. Thus, each of **3a-c** reacted with ethyl iodide to afford the corresponding 2-S-ethylpyridine derivatives **11a-c**, respectively. Elemental analyses, IR, and ^{1}H-NMR data were the basis for establishment of the structure of **11a-c**. On the other hand, compounds **11a-c** reacted with hydrazine hydrate to afford a sulfur-free product in each case. The IR spectra of these reaction products were found entirely free from the absorption band of the CN group, and instead the newly born NH_2 group was detected in each case. Based on the above facts, these reaction products could be formulated as pyrazolo[3,4-b]pyridine derivatives **12a-c** respectively. Conclusive evidence for the structure of **12a-c** was obtained via their synthesis through another route. Thus, **3a-c** reacted with hydrazine hydrate to afford products which were found completely identical in all aspects with **12a-c** previously obtained via the reaction of **11a-c** with hydrazine hydrate (cf. Chart 2).

The work was extended to shed more light on the activity and synthetic potential of the NH_2 group in each of **12a-c**. Thus, it has been found that **12a** reacted with phenyl isothiocyanate (**13**) to give the corresponding pyrazolo[3,4-b]pyridin-3-ylphenylthiourea derivative **14a**. The IR and ^{1}H-NMR spectral data of **14a** were found to be in a good agreement with

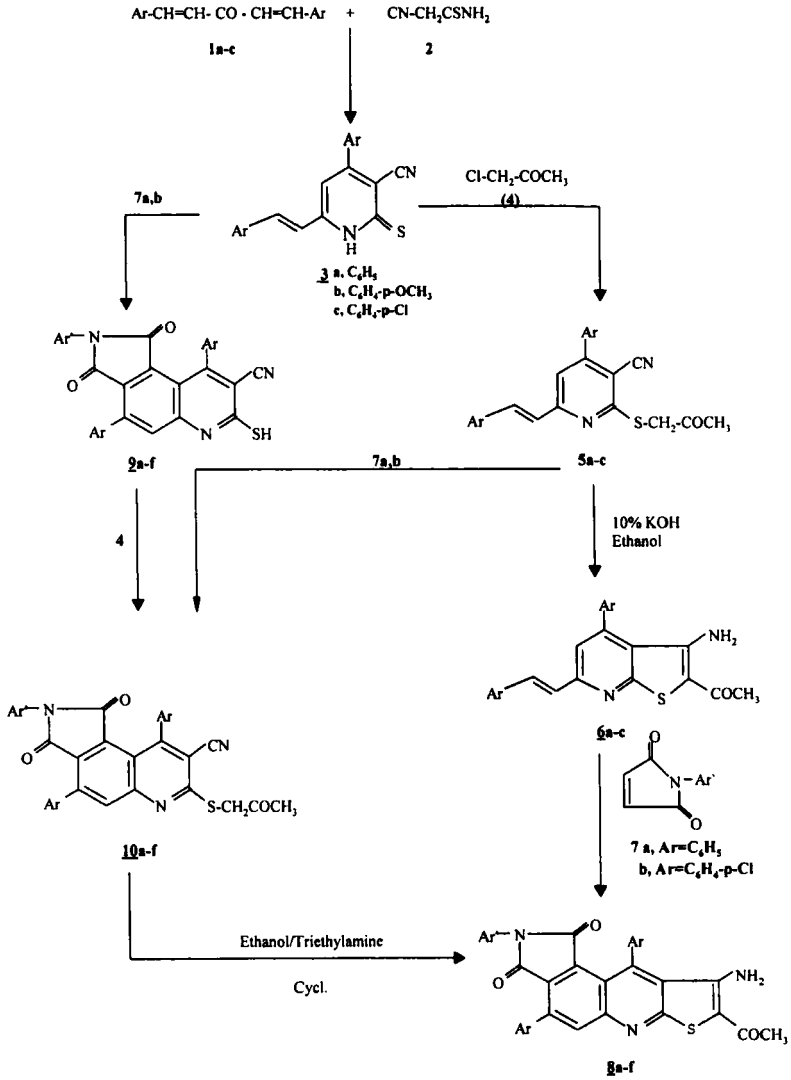


CHART 1

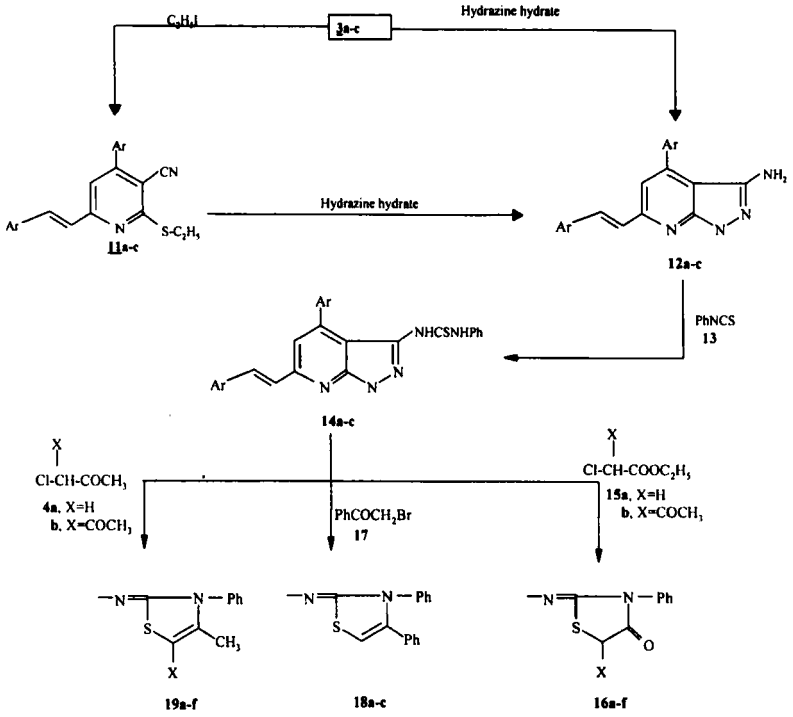
the assigned structure (cf. Table II and Chart 2). Similarly, **12b,c** reacted with **13** to afford the corresponding thiourea derivatives **14b,c** whose structure establishment was based on the data given from IR, ^{1}H-NMR

and elemental analyses (cf. Tables I and II). Compounds **14a-c** were used as good starting materials for preparation of several polyfunctional thiazolyl pyrazolopyridines with expected biological activities. Compounds **14a-c** reacted with both ethyl chloroacetate and ethyl α-chloroacetoacetate **15a,b** in boiling ethanol in the presence of sodium acetate to give reaction products formed via dehydrochlorination followed by cyclization through ethanol elimination. The IR spectra of these reaction products showed the presence of NH, acetyl CO, C=N, and ring CO groups. Their ^{1}H-NMR spectra revealed only one D_2O-exchangeable (NH) protons. By considering the above data in addition to elemental analyses, these reaction products were formulated as 3-(3′-phenylthiazolidin-4′-on-2′-yl) aminopyrazolo[3,4-b]pyridine derivatives **16a-c** and 3-(3′-phenylthiazolidin-4′-on-5′-acetyl-2′-yl)aminopyrazolo-[3,4-b]pyridine derivatives **16d-f**, respectively (cf. Chart 2). Under similar experimental conditions **14a-c** reacted with ω-bromoacetophenone **(17)** to give products formed through dehydrobromination followed by cyclization via dehydration. By considering spectral data (Table II) and elemental analyses (Table I), these reaction products could be formulated as 3-(3′,4′-diphenylthiazolidin-2′-yl) aminopyrazolo[3,4-b]pyridine derivatives **18a-c**, respectively. Furthermore, compounds **14a-c** reacted with chloroacetone **(4a)** and α-chloroacetylacetone **(4b)** under the same previous experimental conditions to afford the corresponding 3-(3′-phenyl-4′-methylthiazolidin-2′-yl)aminopyrazolo[3,4-b]pyridine derivatives **19a-c** and 3-(3′-phenyl-4′-methyl-5′-acetylthiazolidin-2′-yl)aminopyrazolo[3,4-b]-pyridine derivatives **19d-f** respectively (cf. Chart 2).

The synthesis of **16a-f**, **18a-c**, and **19a-f** involved first formation of corresponding thioenol through migration of the hydrogen atom of the NH group adjacent to the phenyl group in the phenyl thiourea residue.

ANTIMICROBIAL ACTIVITY

The antimicrobial activity of some of the newly synthesized heterocyclic compounds was tested against four types of microorganisms as shown in table III. Compounds **5b, 6b, 8b, 12a, 16b,e, 11a,b** and **19b,e** exhibited slight activity against the tested organisms *Bacillus Subtilis, Esherchia Coli, Aspergillus Terreus, and Candida Spp.* On the other hand, com-



16, 19	Ar	X
a,	C_6H_5,	H
b,	C_6H_4-p-OCH_3	H
c,	C_6H_4-p-Cl	H
d,	C_6H_5	H
e,	C_6H_4-p-OCH_3	H
f,	C_6H_4-p-Cl	H

CHART 2

pounds **5c, 6c, 8c, 14a,b, 16a,d**, and **19a,d** showed a moderate activity against the tested organisms while compounds **8f, 10f, 14c, 16c,f, 18c**, and **19c,f** were found to be the most active. In all cases, the compounds were dissolved in DMF/EtOH in a unique concentration of 0.03 mg%.

TABLE I Characterization data of the newly synthesized compounds:

Comp.	*Solvent of Cyrst.*	*M. P. (C)*	*Yield (%)*	*Molecular Formula*	*% Of Analysis Calcd./Found*				
					C	*H*	*N*	*S*	*Cl*
3a	Ethanol	190	78	$C_{20}H_{14}N_2S$	76.43	4.46	8.92	10.19	----
					76.2	4.6	9.1	10.3	----
3b	Acetic acid	265	67	$C_{22}H_{18}N_2SO_2$	70.59	4.81	7.49	8.56	----
					70.3	4.6	7.6	8.4	----
3c	Ethanol	200	65	$C_{20}H_{12}N_2SCl_2$	62.66	3.13	7.31	8.36	18.54
					62.8	3.3	7.5	8.1	18.3
5a	Ethanol	147	61	$C_{23}H_{18}N_2SO$	74.59	4.86	7.57	8.65	----
					74.7	4.6	7.7	8.7	----
5b	Acetic acid	78	83	$C_{25}H_{22}N_2SO_3$	69.77	5.12	6.51	7.44	----
					69.5	5.0	6.7	7.4	----
5c	Ethanol	150	65	$C_{23}H_{16}N_2SOCl_2$	62.87	3.64	6.38	7.29	16.17
					63.0	3.7	6.5	7.4	16.3
6a	Ethanol	212	56	$C_{23}H_{18}N_2SO$	74.59	4.86	7.57	8.65	----
					74.3	5.0	7.3	8.5	----
6b	Ethanol	195	76	$C_{25}H_{22}N_2SO_3$	69.77	5.12	6.51	7.44	----
					69.9	5.3	6.3	7.3	----
6c	Ethanol	170	87	$C_{23}H_{16}N_2SOCl_2$	62.87	3.64	6.38	7.29	16.17
					62.6	3.5	6.1	7.0	16.1
8a	Acetic acid	230	60	$C_{33}H_{21}N_3SO_3$	73.47	3.90	7.79	5.94	----
					73.6	4.1	7.5	6.2	----

Comp.	Solvent of Cyrst.	M. P. (C)	Yield (%)	Molecular Formula	% Of Analysis Calcd./Found				
					C	H	N	S	Cl
8b	DMF	214	67	$C_{33}H_{20}N_3SO_3Cl$	69.05	3.49	7.32	5.58	6.19
					69.2	3.1	7.5	5.7	5.9
8c	Acetic acid	>300	73	$C_{35}H_{25}N_3SO_5$	70.12	4.17	7.01	5.34	----
					70.3	4.0	7.2	5.1	----
8d	Ethanol	198	70	$C_{35}H_{24}N_3SO_5Cl$	66.30	3.79	6.63	5.05	5.60
					66.1	3.9	6.5	4.9	5.6
8e	Ethanol	225	80	$C_{33}H_{19}N_3SO_3Cl_2$	60.69	3.13	6.91	5.26	11.68
					60.8	2.9	7.1	5.4	11.5
8f	DMF	315	66	$C_{33}H_{18}N_3SO_3Cl_3$	61.63	2.80	6.54	4.98	16.58
					61.7	3.0	6.7	5.2	16.7
9a	Acetic acid	245	68	$C_{30}H_{17}N_3SO_2$	74.54	3.52	8.70	6.63	----
					74.3	3.7	8.5	6.6	----
9b	Ethanol	235	64	$C_{30}H_{16}N_3SO_2Cl$	69.57	3.09	8.12	6.18	6.86
					69.7	3.2	8.2	6.3	7.0
9c	Ethanol	180	60	$C_{32}H_{21}N_3SO_4$	70.72	3.87	7.73	5.89	----
					70.9	3.6	7.6	6.0	----
9d	Ethanol	140	71	$C_{32}H_{209}N_3SO_4Cl$	66.49	3.46	7.27	5.54	6.15
					66.6	3.5	7.5	5.7	6.3
9e	Acetic acid	190	59	$C_{30}H_{15}N_3SO_2Cl_2$	65.22	2.72	7.61	5.80	12.86
					65.4	2.9	7.8	6.0	13.0
9f	Ethanol	165	82	$C_{30}H_{14}N_3SO_2Cl_3$	61.38	2.39	7.16	5.46	18.16
					61.5	2.5	7.0	5.6	18.3

Comp.	*Solvent of Cyrst.*	*M. P. (C)*	*Yield (%)*	*Molecular Formula*	*% Of Analysis Calcd./Found*				
					C	*H*	*N*	*S*	*Cl*
10a	Acetic acid	217	66	$C_{33}H_{21}N_3SO_3$	73.47	3.90	7.79	5.94	----
					73.5	4.1	8.0	6.2	----
10b	Ethanol	197	77	$C_{33}H_{20}N_3SO_3Cl$	69.05	3.49	7.32	5.58	6.19
					69.2	3.6	7.5	5.3	6.3
10c	DMF	229	59	$C_{35}H_{25}N_3SO_5$	70.12	4.17	7.01	5.34	----
					70.0	4.3	7.2	5.5	----
10d	Ethanol	210	81	$C_{35}H_{24}N_3SO_5Cl$	66.30	3.79	6.6	5.05	5.6
					66.5	4.0	6.4	5.2	5.8
10e	DMF	>300	69	$C_{33}H_{19}N_3SO_3Cl_2$	65.13	3.13	6.91	5.26	5.61
					64.9	3.3	7.1	5.3	5.8
10f	Acetic acid	256	73	$C_{33}H_{18}N_3SO_3Cl_3$	61.63	2.80	6.54	4.98	16.58
					61.8	3.0	6.7	5.2	16.7
11a	Ethanol	170	76	$C_{22}H_{18}N_2S$	77.19	5.26	8.19	9.36	----
					77.0	5.1	8.3	9.5	----
11b	Ethanol	138	58	$C_{24}H_{22}N_2SO_2$	71.64	5.47	6.97	7.96	----
					71.8	5.6	7.2	8.1	----
11c	Acetic acid	165	65	$C_{22}H_{16}N_2SCl_2$	64.23	3.89	6.81	7.79	17.27
					64.3	4.1	6.6	8.0	17.4
12a	Ethanol	201–3	73	$C_{20}H_{16}N_4$	76.92	5.13	17.95	----	----
					77.1	5.3	18.2	----	----
12b	Ethanol	238	81	$C_{22}H_{20}N_4O_2$	70.97	5.38	15.05	----	----
					71.1	5.5	15.2	----	----

Comp.	Solvent of Cyrst.	M. P. (C)	Yield (%)	Molecular Formula	% Of Analysis Calcd./Found				
					C	H	N	S	Cl
12c	Ethanol	218-20	77	$C_{20}H_{14}N_4Cl_2$	62.99	3.67	14.70	----	18.64
					63.1	3.8	14.80	----	18.4
14a	Ethanol	223–5	58	$C_{27}H_{21}N_5S$	72.48	4.70	15.66	7.16	----
					72.6	4.5	15.8	7.3	----
14b	Ethanol	187–9	75	$C_{29}H_{252}N_5SO_2$	68.64	4.93	13.81	6.31	----
					68.8	5.1	14.0	6.3	----
14c	Ethanol	256–8	59	$C_{27}H_{19}N_5SCl_2$	62.79	3.68	13.57	6.20	13.76
					63.0	3.4	13.7	6.0	13.9
16a	Acetic acid	304–6	81	$C_{29}H_{21}N_5SO$	71.46	4.31	14.37	6.57	----
					71.2	4.5	14.3	6.7	----
16b	Ethanol	287	73	$C_{31}H_{25}N_5SO_3$	68.01	4.57	12.80	5.85	----
					68.1	4.6	12.6	6.0	----
16c	Acetic acid	>300	65	$C_{29}H_{19}N_5SOCl_2$	62.59	3.42	12.59	5.76	12.77
					62.7	3.4	12.7	5.9	12.6
16d	Acetic acid	240	69	$C_{31}H_{23}N_5SO_2$	70.32	4.35	13.23	6.05	----
					70.5	4.1	13.5	6.2	----
16e	Ethanol	286	66	$C_{33}H_{27}N_5SO_4$	67.23	4.58	11.88	5.43	----
					67.4	4.7	12.0	5.4	----
16f	Acetic acid	197	73	$C_{31}H_{21}N_5SO_2Cl_2$	62.21	3.51	11.71	5.35	11.87
					62.4	3.6	11.5	5.1	12.0
18a	Ethanol	220–2		$C_{35}H_{25}N_5S$	76.78	4.57	12.80	5.85	----
					77.0	4.5	12.8	5.7	----

Comp.	Solvent of Cyrst.	M. P. (C)	Yield (%)	Molecular Formula	% Of Analysis Calcd./Found				
					C	H	N	S	Cl
18b	Touene-Pet. Ether	158-60	65	$C_{37}H_{29}N_5SO$	73.15	4.78	11.53	5.85	----
					73.3	4.5	11.4	5.7	----
18c	Acetic acid	258-60	69	$C_{35}H_{23}N_5SCl_2$	68.18	3.73	11.36	5.19	11.53
					68.3	3.5	11.4	5.2	11.7
19a	Acetic acid	301–3	78	$C_{30}H_{23}N_5S$	74.23	4.74	14.43	6.60	----
					74.4	4.8	14.2	6.4	----
19b	Ethanol	>300	82	$C_{32}H_{27}N_5SO_2$	70.46	4.96	12.84	5.87	----
					70.6	5.1	12.6	6.0	----
19c	Ethanol	187–9	67	$C_{30}H_{21}N_5SCl_2$	64.98	3.79	12.64	5.78	12.82
					65.1	3.9	12.4	5.9	12.6
19d	Acetic acid	237–9	56	$C_{32}H_{25}N_5SO$	72.87	4.74	13.28	6.07	----
					73.0	4.5	13.4	6.1	----
19e	Acetic acid	275–7	69	$C_{34}H_{29}N_5SO_3$	69.51	4.94	11.93	5.45	----
					69.6	5.1	12.1	5.6	----
19f	Acetic acid	256–8	77	$C_{32}H_{23}N_5SOCl_2$	64.43	3.86	11.74	5.37	11.91
					64.6	4.0	11.9	5.5	12.2

TABLE II IR and ^{1}H-NMR spectral data of the new compounds:

Comp.	*IR (cm^{-1})*	*^{1}H-NMR (δppm)*
3a	3200(NH); 3090(aromatic and styryl CH); 2980(sat. CH); 2220(CN); 1614(C=C) and 1560(C=S).	5.4(s, 1H, pyridine H-5); 7.2- 8.0(m, 10H, ArH's); 8.2(dd, 2H, CH styryl) and 13.5(s, 1H, NH).
3b	3250(NH); 3080(aromatic and styryl CH); 2970(sat. CH); 2217(CN); 1618(C=C) and 567(C=S).	3.8(s, 6H, two OCH_3); 5.5(s, 1H, pyridine H-5); 6.9–8.0(m, 8H, ArH's); 8.5(dd, 2H, CH styryl) and 13.8(s, 1H, NH).
3c	3223(NH); 3069(aromatic and styryl CH); 2969(sat. CH); 2221(CN); 1621(C=C) and 573(C=S).	5.7(s, 1H, pyridine H-5); 6.9- 8.0(m, 8H, ArH's); 8.3(dd, 2H, CH styryl) and 3.1(s, 1H, NH).
5a	3087(aromatic and styryl CH); 2978(sat. CH); 2217(CN); 1713(CO acetonyl) and 1614(C=C).	2.1(s, 3H, $COCH_3$); 3.2(s, 2H, – SCH_2CO-); 5.2(s, H, pyridine H- 5); 7.0–7.9(m, 10H, ArH's) and 8.2(dd, 2H, CH styryl).
5b	3079(aromatic and styryl CH); 2969(sat. CH); 2213(CN); 1715(CO acetonyl) and 1608(C=C).	2.0(s, 3H, $COCH_3$); 2.9(s, 2H, – SCH_2CO-); 3.6(s, 6H, two OCH_3); 5.4(s, 1H, pyridine H-5); 7.1- 8.0(m, 8H, ArH's) and 8.5(dd, 2H, CH styryl).
5c	3089(aromatic and styryl CH); 2879(sat. CH); 2217(CN); 1713(CO acetonyl) and 1606(C=C).	2.2 (s, 3H, $COCH_3$); 3.1(s, 2H, – SCH_2CO-); 5.2(s, 1H, pyridine H- 5); 6.9–7.8(m, 8H, ArH's) and 8.4(dd, 2H, CH styryl).
6a	3398, 3253(NH_2); 3078(aromatic and styryl CH); 2985(sat. CH); 1663(CO H-bonded); 1618(C=N) and 1604(C=C).	2.1(s, 3H, $COCH_3$); 4.5(s, or., 2H, NH_2); 5.4(s, 1H, pyridine H-5); 6.9–8.0(m, 10H, ArH's) and 8.4(dd, 2H, CH styryl).
6b	3400, 3260(NH_2); 3083(aromatic and styryl CH); 2978(sat. CH); 669(CO H-bonded); 1615(C=N) and 1600(C=C).	2.3 (s, 3H, $COCH_3$); 3.4(s, 6H, two OCH_3); 4.6(s, br., 2H, NH_2); 5.1(s, 1H, pyridine H-5); 7.0–7.9(m, 8H, ArH's) and 8.5(dd, 2H, CH styryl).
6c	3389, 3265(NH_2); 3092(aromatic and styryl CH); 2987(sat. CH); 1668(CO H-bonded); 1621(C=N) and 1604(C=C).	2.3(s, 3H, $COCH_3$); 4.1(s, br., 2H, NH_2); 5.3(s, 1H, pyridine H-5); 6.9–8.1(m, 10H, ArH's) and 8.6(dd, 2H, CH styryl).
8a	3400, 3229(NH_2); 3079(aromatic and styryl CH); 2979(sat. CH); 1780, 1690(-CO-NPh-CO-); 1652(CO H- bonded); 1612(C=N) and 1604 (C=C).	2.3(s, 3H, $COCH_3$); 4.5(s, br., 2H, NH_2) and 6.9–8.2(m, 16H, ArH's).
8c	3421, 3253(NH_2); 3091(aromatic and styryl CH); 2975(sat. CH); 1776, 1695(-CO-NPh-CO-); 1658(CO H- bonded); 610(C=N) and 1603 (C=C).	2.2(s, 3H, $COCH_3$); 3.1(s, 6H, two OCH_3); 4.7(s, br., 2H, NH_2) and 7.1–8.2(m, 14H, ArH's).

Comp.	*IR (cm^{-1})*	*^{1}H-NMR (δppm)*
8f	3408, 3262(NH_2); 3090(aromatic and styryl CH); 2970(sat. CH); 1782, 1693(-CO-NPh-CO-); 1655(CO H- bonded); 1614(C=N) and 1600 (C=C).	2.4(s, 3H, $COCH_3$); 4.6(s, br., 2H, NH_2) and 7.0–8.1(m, 13H, ArH's).
9a	3092(aromatic and styryl CH); 2513(SH); 2219(CN); 1780, 1695(- CO-NPh-CO-); 1618(C=N) and 600(C=C).	2.7(s, 1H, SH) and 7.1–8.0(m, 6H, ArH's).
9d	3089(aromatic and styryl CH); 2510(SH); 2222(CN); 1785, 1691(- CO-NAr-CO-); 1621(C=N) and 1602(C=C).	2.5 (s, 1H, SH); 3.2(s, 6H, two OCH_3) and 7.0–8.2(m, 13H, ArH's).
9f	3097(aromatic and styryl CH); 2508(SH); 2220(CN); 1782, 1694(- CO-NAr-CO-); 1611(C=N) and 1600(C=C).	2.6(s, 1H, SH); 3.5(s, 2H,- SCH_2CO-) and 6.9–7.8(m, 16H, ArH's).
10a	3089(aromatic and styryl CH); 2965(CN); 2222(CN); 1780, 1689 (- CO-NPh-CO-); 1710(CO acetonyl); 1618(C=N) and 1600(C=C).	2.1(s, 3H, $COCH_3$); 3.5(s, 2H, SCH_2CO-) and 6.9–8.1(m, 16H, ArH's).
10d	3095(aromatic CH); 2970(sat CH); 2217(CN); 1782, 1685(-CO-NAr- CO-); 1715(CO acetonyl); 1617(C=N) and 1602(C=C).	2.0(s, H, $COCH_3$); 3.1(s, 6H, two OCH_3); 3.7(s, 2H, – SCH_2CO-) and 6.9–8.1(m, 13H, ArH's).
10f	3089(aromatic CH); 2978(sat. CH); 2217(CN); 1784, 1689 (- CO-NPh-CO-); 1717(acetonyl CO); 1612(C=N) and 1603(C=C).	2.3(s, 3H, $COCH_3$); 3.5(s, 2H, – SCH_2CO-) and 7.0–8.1(m, 13H, ArH's).
11a	3080(aromatic and styryl-CH); 2990(sat. CH); 2220(CN); 1615(C=N) and 1600(C=C).	1.1(t, 3H, $\underline{CH_3}CH_2$-); 3.4(q, 2H, $CH_3\underline{CH_2}$-); 5.2(s, 1H, pyridine H-5); 6.9–7.8(m, 10H, ArH's) and 8.6(dd, 2H, styryl CH).
11b	3092(aromatic and styryl-CH); 2983(sat. CH); 2222(CN); 1619(C=N) and 1600(C=C).	1.0(t, 3H, $\underline{CH_3}CH_2$-); 3.1(q, 2H, $CH_3\underline{CH_2}$-); 5.2(s, 1H, pyridine H-5); 7.0–7.9(m, 8H, ArH's) and 8.2(dd, 2H, styryl CH).
11c	3078(aromatic and styryl-CH); 2989(sat. CH); 2218(CN); 1621(C=N) and 1605(C=C).	1.2(t, 3H, $\underline{CH_3}CH_2$-); 3.6(q, 2H, $CH_3\underline{CH_2}$-); 5.4(s, 1H, pyridine H-5); 7.1–7.8(m, 8H, ArH's) and 8.4(dd, 2H, styryl CH).
12a	3428, 3268, 3187(NH_2 and NH); 3085(aromatic and styryl-CH); 1619(C=N) and 1601(C=C).	4.8(s, br., 2H, NH_2); 5.5(s, 1H, pyridine H-5); 6.1–6.4(s, 1H, NH); 7.1–7.9(m, 8H, ArH's) and 8.4(dd, 2H, styryl CH).
12b	3468, 3326, 3200(NH_2 and NH); 3078(aromatic and styryl-CH); 1621(C=N) and 1600(C=C).	3.4(s, 6H, two OCH_3); 4.5(s, br., 2H, NH_2); 5.3(s, 1H, pyridine H-5); 6.1–6.4(s, 1H, NH); 7.0–7.9(m, 8H, ArH's) and 8.5(dd, 2H, styryl CH).

Comp.	*IR (cm^{-1})*	*^{1}H-NMR (δppm)*
12c	3466, 3236, 3196(NH_2 and NH); 3082(aromatic and styryl-CH); 1615(C=N) and 1603(C=C).	4.9(s, br., 2H, NH_2); 5.0(s, 1H, pyridine H-5); 6.0–6.3(s, 1H, NH); 7.0–8.1(m, 8H, ArH's) and 8.6(dd, 2H, styryl CH).
14a	3380, 3235(NH); 3078(aromatic and styryl-CH); 1620(C=N); 1601(C=C) and 1536(C=S).	5.1(s, 1H, pyridine H-5); 6.0–6.4(s, 3H, three NH); 7.0–7.9(m, 15H, ArH's) and 8.7(dd, 2H, styryl CH).
14b	3379, 3238(NH); 3078(aromatic and styryl-CH); 2879(sat. CH); 1623(C=N); 1605(C=C) and 1556(C=S).	3.1(s, 6H, two OCH_3); 5.3(s, 1H, pyridine H-5); 6.1–6.4(s, 3H, three NH); 6.9–7.7(m, 13H, ArH's) and 8.3(dd, 2H, styryl CH).
14c	3368, 3247(NH); 3078(aromatic and styryl-CH); 1618-(C=N); 1601(C=C) and 1550(C=S).	5.5(s, 1H, pyridine H-5); 6.0–6.4(s, 3H, three NH); 7.0–7.7(m, 13H, ArH's) and 8.1(dd, 2H, styryl CH).
16a	3159(NH); 3078(aromatic and styryl-CH); 2975(sat. CH); 1725(thiazolone CO); 1622(C=N) and 1600(C=C).	4.3(s, 2H, thiazolone-CH_2); 5.1(s, 1H, pyridine H-5); 6,4(s, br., 1H, NH lost after D_2O exchange); 7.0- 7.9(m, 5H, ArH's) and 8.5(dd, 2H, styryl CH).
16e	3183(NH); 3088(aromatic and styryl-CH); 2979(sat. CH); 1731(thiazolone CO); 1695(acetyl CO); 1619(C=N) and 1603(C=C).	1.2(s, 3H, $COCH_3$); 3.1(s, 6H, two OCH_3); 4.5(s, 2H, thiazolone-CH_2); 5.3(s, H, pyridine H-5); 6.2(s, br., 1H, NH lost after D_2O exchange); 6.9–7.8(m, 3H, ArH's) and 8.4(dd, 2H, styryl CH).
18b	3165(NH); 3083(aromatic and styryl-CH); 2977(sat. CH); 1620(C=N) and 1600(C=C).	3.1(s, 6H, two OCH_3); 5.3(s, 1H, pyridine H-5); 6.2(s, br., 1H, NH lost after D_2O exchange); 7.0–7.8(m, 19H, ArH's and thiazole H-5) and 8.4(dd, 2H, styryl CH).
19a	3152(NH); 3073(aromatic and styryl-CH); 2973(sat. CH); 1620(C=N) and 1606(C=C).	1.3(s, 3H, CH_3); 5.4(s, 1H, pyridine H-5); 6.4(s, br., lh, NH lost after D_2O exchange); 7.0–7.9(m, 16H, ArH's) and 8.6(dd, 2H, styryl CH).
19f	3147(NH); 3079(aromatic and styryl-CH); 2984(sat. CH); 1697(acetyl CO); 1617(C=N) and 1602(C=C).	1.0(s, 3H, CH_3);.7(s, 3H, $COCH_3$); 5.1(s, H, pyridine H-5); 6.2(s, br., 1H, NH lost after D_2O exchange); 7.0–7.8(m, 13H, ArH's) and 8.3(dd, 2H, styryl CH).

TABLE III Antimicrobial activity of the newly synthesized compounds

Comp.	*B. Subtilis*	*E. Coli*	*A. Terreus*	*Candida Spp.*
5b	+	–	+	–
5c	++	+	++	++
6b	+	–	–	+
6c	++	+	++	++
8a	–			
8b	+	+	–	–
8c	++	+	++	+
8f	++	+	++	+++
10f	+++	++	+++	+
12a	–	–	+	+
14a	++	+	++	++
14b	++	++	–	++
14c	+++	+	++	–
16a	++	+	+	++
16b	–	–	+	+
16c	+++	+	++	+++
16d	+	+	++	++
16e	+	+	–	–
16f	+	+++	+	++
18a	–	+	+	–
18b	+	+	–	+
18c	+	++	+++	++
20a	++	+	++	++
20b	–	+	+	–
20c	++	+	++	+++
20b	+	+	+	–
20d	++	+	++	++
20e	+	+	+	–
20f	++	+	++	+++

(+++) = Strong activity; (++) = Moderate activity; (+) = Slight activity; (-) = No activity

EXPERIMENTAL

All melting points are uncorrected. The IR spectra in KBr discs were recorded on Perkin-Elmer FT-IR type 4 and Pye Unicam SP-1100 spectrophotometers. The H-NMR spectra were recorded on Varian EM 390–90 MHz, Gemini 200, Varian NMR spectrophotometer (200 MHz), and Brucker WP-80 spectrometers using $CDCl_3$, DMSO-d_6 and $(CD_3)_2CO$ as solvents and TMS as an internal standard. Chemical shifts are expressed as δ or τ ppm units. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 series A using DIP technique at 70 eV. Microanalyses were performed at Microanalytical Center of Cairo University using Perkin-Elmer 2400 CHN Elemental Analyzer.

Synthesis of 3a-c and 11a-c

A solution of **1a-c** or **3a-c** (0.01 mole) in sodium ethoxide (prepared from 0.01 atom of sodium metal in 30 ml of absolute ethanol) was treated with 0.01 mole of **2** or ethyl iodide in a respective manner. The reaction mixture was heated under reflux for 9–12 hours, then cooled, poured onto ice-cold water and acidified with conc. HCl. The solid products were filtered off, washed with water, and then crystallized from the proper solvent to afford **3a-c** and **11a-c**, respectively (cf. Tables I and II).

Synthesis of 5a-c and 10a-f

A solution of **3a-c** or **9a-f** (0.01 mole) in pyridine (15 mL) was treated with 0.01 mole of chloroacetone **(4)**. The reaction mixture was heated under reflux for 5 hours. The reaction mixture was cooled, poured onto ice-cold water and then acidified with acetic acid. The solid products were filtered off, washed with water, and crystallized from ethanol to afford **5a-c** and **10a-f**, respectively (cf. Tables I and II).

Synthesis of 6a-c and 8a-f

A solution of **5a-c** or **10a-f** (0.01 mole) in absolute ethanol (15 mL) containing the catalytic amounts of triethylamine (0.5mL) was heated under reflux for 5 hours. The reaction mixture was cooled and acidified with ace-

tic acid. The solid products were filtered off, washed with water, and crystallized from the proper solvent to afford **6a-c** and **8a-f**, respectively (cf. Tables I and II).

Synthesis of 9a-f, 10a-f and 8a-f

A solution of **3a-c, 5a-c**, or **6a-c** (0.01 mole in each case) was treated with **7a,b** in anisole (50 mL in each case). The reaction mixture was heated under reflux for 5–7 hours. The solid products obtained after cooling were filtered off and crystallized from the proper solvent to afford the corresponding cycloadducts **9a-f, 10a-f**, or **8a-f**, respectively (cf. Tables I and II).

Synthesis of 12a-c

A solution of each of **3a-c** or **11a-c** (0.01 mole) in hydrazine hydrate (15 mL) was heated under reflux for 8 hours. The reaction mixture was cooled and poured onto ice-cold water. The solid products obtained were filtered off, washed with water and crystallized from proper solvent to afford **12a-c** respectively (cf. Tables I and II).

Synthesis of 14a-c

A solution of **12a-c** (0.01 mole) in pyridine (30 mL) was treated with phenylisothiocyanate (0.01 mole). The reaction mixture was then heated under reflux for 4hrs then cooled, poured onto ice-cold water and acidified with dilute HCl. The solid products obtained were filtered off, washed with water and crystallized from ethanol to afford **14a-c** respectively (cf. Tables I and II).

Synthesis of 16a-f, 18a-c and 19a-f

A solution of each of **14a-c** (0.01 mole) in ethanol (50 mL) in the presence of sodium acetate (≅1g) was heated under reflux with each of **15a,b, 17** and **4a,b** for Shrs. The solid products obtained after cooling were filtered off, washed with water and crystallized from the proper solvent to afford **16a-f, 18a-c** and **19a-f** respectively (cf. Tables I and II).

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