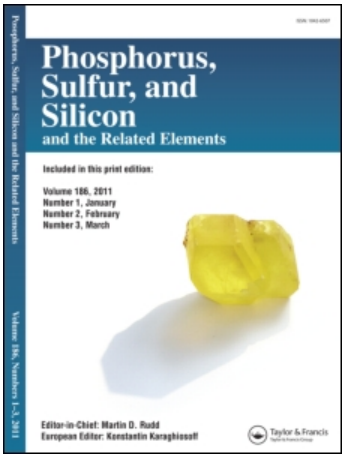

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STUDIES ON THIAZOLOPYRIDINES. PART 3: REACTIVITY OF THIAZOLO[3,2-*a*]-3-AZA[1,8]NAPHTHYRIDINE TOWARDS SOME NUCLEOPHILES

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*A variety of new thiazolo[3,2-*a*]pyridine derivatives **2a–h** having 3-indolyl group were produced by refluxing **1a** with different benzylidenemalononitrile derivatives. Reactivity of compound **4** toward some nitrogen nuclcophiles was investigated. Thus, the novel pyrazoles **6a,b** were obtained when compound **4** was allowed to react with hydrazine and phenyl hydrazine in ethanol under reflux. On the other hand, pyrazolo[3′,4′:4,5]thiazolo[3,2-*a*]-3-aza[1,8]naphthyridine **8** was formed by condensation of compound **4** with benzoyl hydrazine. Finally, condensed heterocyclic compounds containing pyran rings **9** and **10** were obtained by treatment compound **4** with active ethylene compounds.*

Keywords: Thiazolo[3,2-*a*]-3-aza[1,8]naphthyridine; thiazolo[3,2-*a*]pyridine

Derivatives of thiazolo[3,2-*a*]pyridines are important as antimicrobial[1] bactericide,[2] coronary dialators, antihypertensive, and muscle relaxants.[3] It was reported that [1,8]naphthyridine derivatives are useful as antihypertensive, diluritic, and antibacterial agents.[4–6] On the basis of the above facts, we report the synthesis of some novel thiazolo[3,2-*a*]pyridines **2a–h** to evaluate the antimicrobial properties of them. Also, we investigated the reactivity of compound **4** towards some nitrogen and carbon nucleophiles.

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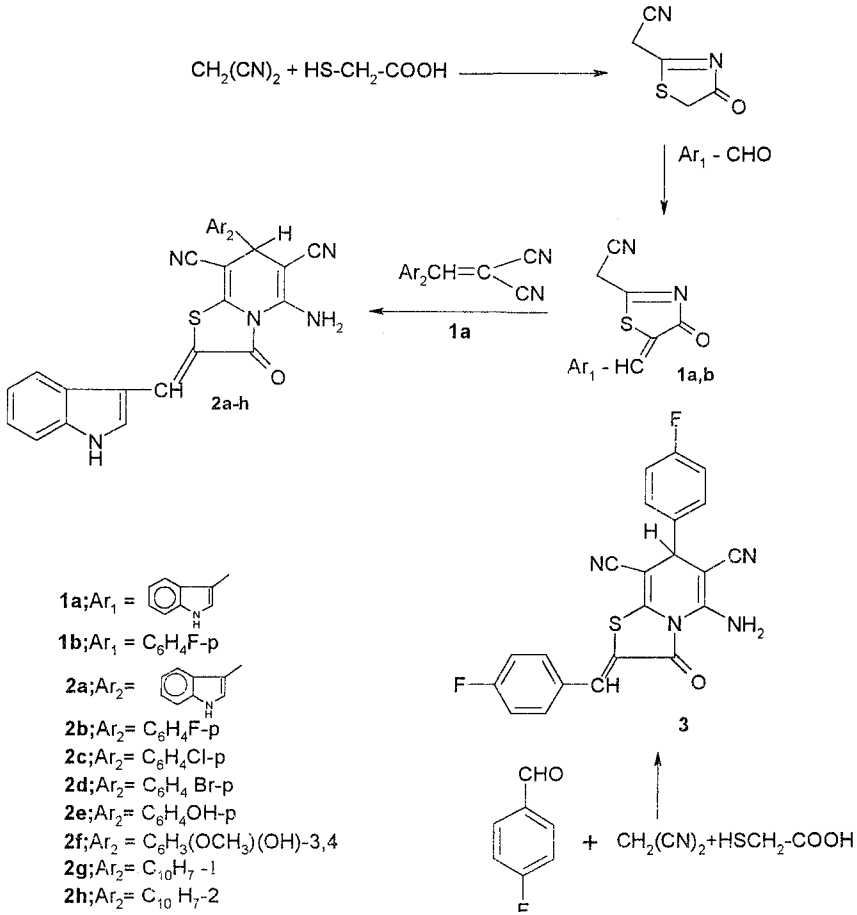
RESULTS AND DISCUSSION

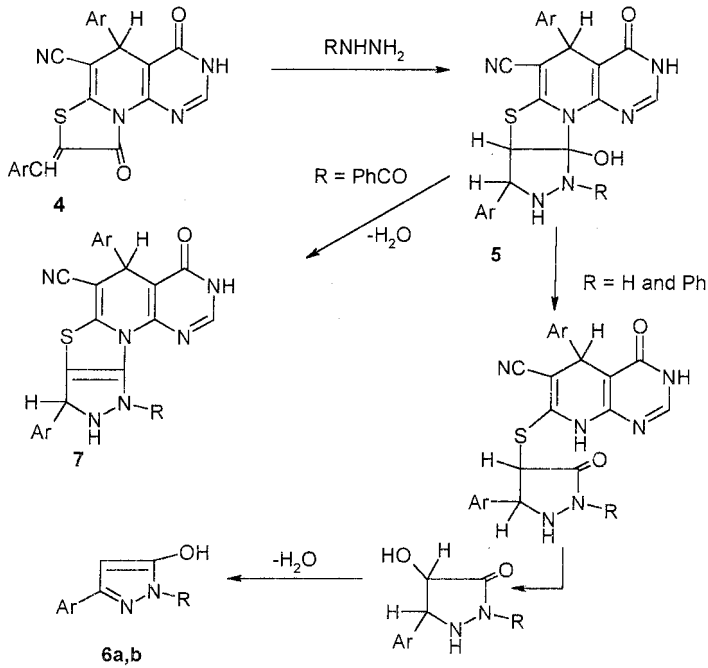
5-Amino-6,8-dicyano-7-(3-indolyl)-2-(3-indolylmethylidene)-3-oxothiazolo [3,2-*a*]pyridine **2a** was produced by refluxing thiazolinone derivative **1a** with benzylidenemalononitrile of indol-3-carboxaldehyde in ethanol and a catalytic amount of piperidine. The structure of compound **2a** was determined on the basis of elemental analyses and spectral data. Its IR spectrum revealed the presence of bands at 3350, 3300, 3224 cm^{-1} (NH_2, NH), 2206 cm^{-1} (C≡N), and 1689 cm^{-1} (C=O, thiazolidinone), and ^{1}HNMR spectrum in ($CDCl_3$) displayed signal in the region δ 4.40 assigned to pyridine-H and at δ 7.20 ppm (indole-H). In the same manner a series of thiazolo[3,2-*a*]pyridines **2b–h** were formed



SCHEME 1

as result of interaction of **1a** with different arylidenemalononitries. In addition, ternary condensation[7] of 4-fluorobenzaldehyde malononitrile and thioglycolic acid (2:2:1 molar ratio) in absolute ethanol catalyzed by piperidine afforded the novel thiazolo[3,2-*a*]pyridine derivatives **3** in high yields (Scheme 1).

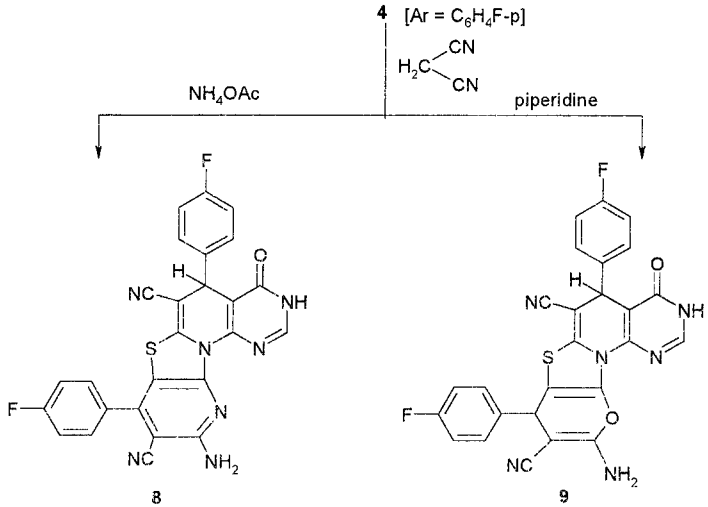
Thiazolo[3,2-*a*]-3-aza[1,8]naphthyridine **4**[7] proved to be a key intermediate in the synthesis of novel heterocyclic derivatives and was produced by heating compound **3** with formic acid. The reactivity of compound **4** toward hydrazines as nitrogen nucleophiles was investigated. Thus, when compound **4** was allowed to react with hydrazine hydrate and phenyl hydrazine in absolute ethanol under reflux, the novel pyrazoles **6a**,**b** were obtained on the bases of analytical and spectral data. Infrared spectra of compound **6a**,**b** revealed the absence of amino, cyano, and carbonyl functions. The ^{13}C-NMR spectrum of compounds **6a** in $CDCl_3$ exhibited the following signals: 165.82, 163.22, 160.82, 130.52, 130.43, 130.26, 116.08, 115.87, and 115.45 ppm. The formation of **6a**,**b** is assumed to proceed via the initial formation of **5** followed by ring fission[8] to form **6** (Scheme 2). On the other hand,



SCHEME 2

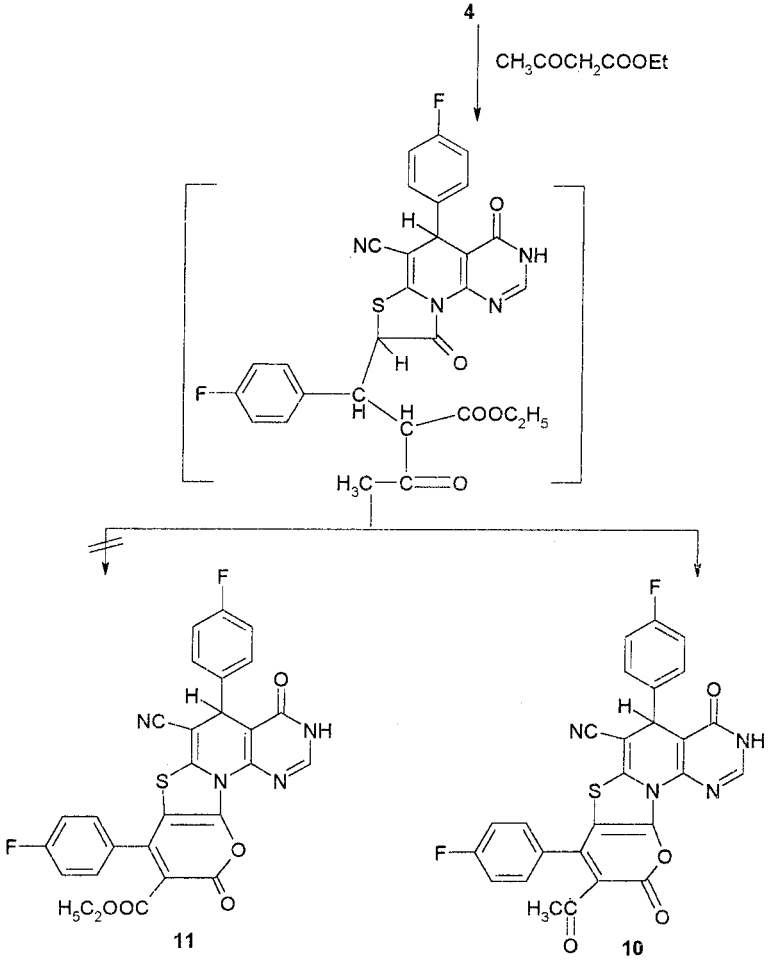
pyrazolo[3′,4′:4,5]thiazolo[3,2-*a*]-3-aza[1,8]naphthyridine **7** was obtained when compound **4** was allowed to react with benzoyl hydrazine, via the formation of **5** followed by elimination of water (Scheme 2). The IR spectrum revealed the presence of amino, cyano, and carbonyl functions.

This investigation was extended to include the reactivity of compound **4** with some active methylene compounds as nucleophiles. Thus, when compound **4** was refluxed with malononitrile (Scheme 3) in the presence of an ethanol/ammonium acetate[9] mixture pyrido[2′, 3′: 4,5]thiazolo[3,2-*a*]-3-aza[1,8] naphthyridine **8** was formed. The structure of **8** was confirmed by analytical and spectral data. The IR spectrum exhibited bands at 3400, 3350, 3180 cm^{-1}, which were assigned to NH_2 and NH 2206 cm^{-1}, (C≡N) and carbonyl function at 1666 cm^{-1}(pyrimidinone). Its ^{1}HNMR spectrum in DMSO-d_6 displayed a singlet at δ 4.91 (pyridine-H) and singlet at δ 10.82 (pyrimidine-H). The reaction of **4** with malononitrile in ethanol/piperidine[9] solution under reflux conditions gave pyrano[2′,3′: 4,5]thiazolo[3,2-*a*]-3-aza [1,8]naphthyridine] **9**. The elemental analyses and spectral data were in agreement with structure **9**.



SCHEME 3

Finally, when ethyl acetoacetate was allowed to react with compound **4** two possible structures **10** and **11** were considered. Analytical and spectral data were consistent with the structure **10** and not structure **11**. The ^{1}H-NMR spectrum [DMSO-d_6] exhibited the presence of $COCH_3$ (s) and absence of OC_2H_5 fragment (Scheme 4).



SCHEME 4

Antimicrobial Activity

Antimicrobial activity of the compounds **2a**, **2b**, **2e**, **2g**, **2h**, **6a**, **9**, and **10**, were tested in vitro against *Staphylococcus aureus* (ATCC-6538), *Bacillus cereus* (NRRL-B-569), *Serratia marcesens* (IMRU-70), *proteus merabitis* (NTC-289), and *Aspergillus ochraceus* Wilhelm (AUCC-230). The tested compounds were dissolved in DMF at a concentration of 250 mg/ml by the agar diffusion technique.[10] Ampicillin (25 μg) and mycostatine (25 μg) were used as refrences for the antibacterial and antifungal activities. The inhibition zones (in mm) were measured after

TABLE I Antimicrobial Activity of Some Synthesized Compounds

Compd.	*Staphylococcus aureus* (ATCC-6538-P)	*Bacillus cereus* (NRRL-B-569)	*Serritia marcesens* (IMRU-70)	*Proteus merabitis* (NTC-289)	*Aspergillus ochraceus* Wilhelm (AUCC-230)
2a	++	++	+	++	R
2b	+++	+++	+++	+++	++
2e	++	+	++	+	R
2g	+++	+++	+++	+++	++
2h	++	++	++	+++	+
6a	++	+	+	+	+
9	++	++	++	+	+
10	++	++	++	++	+
Standard	++++	++++	++++	++++	++++

R = resistance.
+ = less active.
++ = moderate active.
+++ = highly active.
++++ = very highly active.
Standard for gram positive and gram negative (Ampicillin) and (mycostatin) for fungi.

24 h incubation, and the results were represented in Table I. Many of the synthesized compounds exhibited various antimicrobial activity towards all the microorganisms used with their minimal inhibitory concentration (MIC).

EXPERIMENTAL

All melting points are uncorrected (Sturart Scientific Co., UK). IR spectra were measured as KBr pellets on a Shimadzu IR 200 spectrophotometer. ^{1}H-NMR spectra were recorded in deutrated DMSO-d_6 at 200 MHz on a Varian Gemini NMR spectrometer using tetramethylsilane as an internal reference. Elemental analyses were carried out at the Microanalytical Center of Cairo University. The characteristic data for prepared compounds are given in Table II. The spectral data are collected in Table I.

5-Arylmethylidene-3-oxo-2-cyanomethyl-4,5 dihydrothiazoline (1a,b)

A mixture of aromatic aldehyde (0.01 mmol), malononitrile (0.01 mmol), and thioglycollic acid (0.01 mmol) in absolute ethanol (20 mL) was refluxed for 2 h in the presence of piperidine (0.5 mL). The reaction

TABLE II Spectra Data of the Synthesized Compounds

Compd.	IR υ_{max} $\nu(cm^{-1})$	^{1}H-NMR (ppm, DMSO-d_6)
1a	2200 (C≡N) , 1710 (C═O)	4.62 (s, 2H,CH_2), 6.05 (s, 1H, indole-H), 7.20–759 (m, 5H, Ar—H + methine-H), 12.16 (broad, 1H, NH)
1b	2200 (C≡N), 1719 (C═O)	4.72 (s, 2H,CH_2), 7.12–7.85 (m, 5H, Ar—H + methine-H)
2a	3350, 3300 (NH_2), 3224 (NH) 2206 (C≡N), 1689 (C═O)	4.40 (s, 1H, Pyridine-H), 7.20 (s, 1H, indole-H), 7.47–8.09 (m, 9H, Ar.H + methine-H), 8.56 (s, 2H, NH_2), 8.64, 9.26 (broad, 2H, 2NH)
2b	3400, 3325 (NH_2), 3286 (NH), 2206 (C≡N), 1712 (C═O)	4.47 (s, 1H, pyridine-H), 6.62 (s, 1H, indole-H), 7.10–7.79 (m, 9H, Ar—H + methine-H), 8.10 (broad, 2H, NH_2), 9.3 (1H, broad, NH)
2c	3425, 3379 (NH_2), 3286 (NH) 2206 (C≡N), 1712 (C═O)	4.46 (s, pyridine-H), 6.61 (s, 1H, indole-H), 7.22–7.94 (m, 9H, Ar—H + methine-H), 7.78 (broad, 2H, NH_2), 8.21 (broad, 1H, NH)
2d	3379, 3278 (NH_2), 3201 (NH), 2198 (C≡N), 1720 (C═O)	
2e		4.24 (s, 1H pyridine-H), 6.00 (s,1H, indole-H), 7.14–7.84 (m, 9H, Ar—H + methine-H), 8.22 (broad 2H, NH_2), 8.54 (broad, 1H, 1H, NH), 9.09 (broad, 1H, OH)
2f	3310, 3286 (NH_2), 3224 (NH), 2214 (C≡N), 1712 (C═O)	
2g	3379, 3287 (NH_2), 3221 (NH), 2183 (C≡N), 1705 (C═O)	4.77 (s, 1H pyridine-H), 6.05 (s, 1H, indole-H), 7.27–8.01 (m, 12H, Ar—H + methine-H), 8.17 (s, 2H, NH_2), 11.17 (broad, 1H, NH)
6a	3201 (board, NH + OH)	7.26 (s, 1H pyrazole-H), 7.26–7.84 (m, 5H, Ar—H + NH) 8.62 (s, 1H, OH)
6b	3155 (OH), 1674 (C═O)	7.06–7.65 (m, 10-H, Ar—H + CH), 12.65 (broad, 1H, OH)
7	3224 (NH), 1705 (C═O) 3409 (OH)	4.63 (s, 1H, pyridine-H), 7.14–7.74 (m, 14-H, ArH + CH), 10.82 (s, 1H, pyrimidine-H), 11.60, 12.13 (broad, 2H, 2NH)
8	3350, 3400 (NH_2), 3186 (NH), 2206 (C≡O)	4.91 (s, 1H, pyridine-H), 5.24 (broad, 2H, NH_2), 6.92–7.73 (m, 8H, Ar—H), 10.82 (s, 1H, pyrimdine-H), 11.61 (broad, 1H, NH).
9	3350, 3300 (NH_2), 3209 (NH), 2214 (C≡N), 1665 (C═O)	4.31 (s, 1H, pyridine-H), 4.93 (s, 1H, pyran-H), 5.26 (broad, 2H, NH_2), 6.88–7.72 (m, 8H, Ar—H), 7.96 (S, 1H, pyrimidine-H), 11.92 (broad, 1H, NH)
10	3201 (NH), 2214 (C≡N), 1666 (C═O)	2.4 (s, 3H, CH_3), 4.31 (s, H, pyridine-H), 7.16–7.74 (m, 8H, Ar—H), 10,82 (s, 1H, pyrimidine-H), 12.01 (broad, 1H, NH)

TABLE III Physical and Analytical Data of the Synthesized Compounds

Compd.	Yield (%)	Solvent cryst.	m.p (°C)	Mol. formula (m.wt)	Calculated/Found (%) C	H	N
1a	80	DMF/E	162–63	$C_{14}H_9N_3OS$	62.92	3.37	15.73
				(267)	62.81	3.30	15.82
1b	77	DMF	170–71	$C_{12}H_7FN_2OS$	58.53	2.84	11.38
				(246)	58.40	2.89	11.42
2a	74	DMF/E	106–08	$C_{26}H_{16}N_6OS$	67.82	3.47	18.26
				(460)	67.84	3.48	18.27
2b	83	DMF/E	116–17	$C_{24}H_{14}FN_5OS$	65.60	3.18	15.94
				(439)	65.61	3.19	15.92
2c	70	DMF/E	273–75	$C_{24}H_{14}ClN_5OS$	63.22	3.07	15.36
				(455.5)	63.30	2.97	15.30
2d	81	DMF/E	255–57	$C_{24}H_{14}BrN_5OS$	57.60	2.80	14.00
				(500)	57.57	2.86	14.12
2e	71	DMF/E	141–42	$C_{24}H_{15}N_5O_2S$	65.90	3.43	16.00
				(437)	65.92	3.48	15.90
2f	69	DMF/E	124–26	$C_{25}H_{17}N_5O_3S$	64.23	3.64	14.98
				(467)	64.22	3.62	14.95
2g	65	DMF/E	240–42	$C_{28}H_{17}N_5OS$	71.33	3.60	14.86
				(471)	71.34	3.63	14.82
2h	68	DMF/E	242–44	$C_{28}H_{17}N_5OS$	71.33	3.60	14.86
				(471)	71.22	3.63	15.01
6a	78	B1/E	168–70	$C_9H_7FN_2O$	60.67	3.93	15.73
				(178)	60.60	3.92	15.80
6b	69	E/B	283–85	$C_{15}H_{11}FN_2O$	70.86	4.33	11.07
				(254)	70.80	4.20	11.12
7	66	E/B	179–180	$C_{30}H_{18}F_2N_6O_2S$	63.82	3.19	14.89
				(564)	63.81	3.20	14.87
8	76	B	166–68	$C_{26}H_{13}F_2N_7OS$	61.29	2.55	19.25
				(509)	61.30	2.57	19.23
9	63	B	200–02	$C_{26}H_{14}F_2N_6O_2S$	60.93	2.73	16.40
				(512)	60.94	2.72	16.41
10	61	B	140–41	$C_{27}H_{14}F_2N_4O_4S$	61.36	2.65	10.60
				(528)	61.42	2.60	10.80

E: ethanol; b: benzene; and DMF = dimethylformamide.

mixture was poured into ice/HCl. The obtained product was recrystallized to give **1a**,**b**, Table III.

2-Arylmethylidene-5-amino-6,8-dicyano-7-aryl-7H-2,3-dihydro-3-oxo-thiazolo [3,2-*a*] pyridine (2a–h)

A mixture of (**1a**, or **1b**, 0.01 mmol), and arylidenemalononitrile (0.01 mmol) was refluxed for 2 h in absolute ethanol (20 ml) in the prescence

of piperidine (0.5 ml). The solid product was collected by filteration and recrystallized to give (**2a–h**) (Table III).

5-Hydroxy-3-(4-fluorophenyl)-pyrazoles (6a,b)

A solution of **4** (0.01 mmol) and hydrazine hydrate (0.012 mmol) or phenyl hydrazine (0.01 mmol) in absolute ethanol (30 ml) was heated under reflux conditions for 1 h. The reaction mixture was cooled and solid product was collected to give **6** (Table III).

5,8-Bis(4-fluorophenyl)-5,8,9-trihydro 3,9-dimino-10-benzoyl-6-cyano pyrazolo[3′,4′:4,5]-thiazolo[3,2-*a*]-3-aza[1,8]naphthridine (7)

To a solution of **4** (0.0 mmol) in absolute ethanol (30 ml) and benzoyl hydrazine was refluxed for 3 h and the reaction mixture was cooled the obtained solid was recrystallized to give **8** (Table III).

5,8-Bis(4-fluorophenyl)-6,9-dicyano-10-amino-3-imino-3,5-dihydro-4-oxo-pyrido[2′,3′:4,5]thiazolo-[3,2-*a*]-3-aza [1,8]naphthyridine (8)

A mixture of **4** (0.01 mmol) and malononitrile (0.01 mmol) in 20 ml ethanol was refluxed for 8 h in the presence of ammonium acetate (2 gm). The solvent was evaporated in vacuo and the solid formed was collected by filtration to give **8** (Table III).

5,8,-Bis(4-fluorophenyl)-6,9-dicyano-10-amino-3-imino-3,5-dihydro-4-oxo-pyrano[2′,3′:4,5]thiazolo[3,2-*a*] 3-aza[1,8]naphthyridine (9)

A mixture of **4** (0.0 mmol), malononitrile (0.0 mmol) and piperidine (0.5 ml) in ethanol (20 ml) was refluxed for 3 h. The obtained product was recrystallized to give **9** (Table III).

5,8 Bis-(4-fluorophenyl)-9-acetyl-4,10-dioxo-3-imino-3,5-dihydro-6 cyano-pyrano[2′,3′,4,5]thiazolo[3,2-*a*]-3-aza[1,8]naphthyridine (11)

A mixture of **4** (0.01 mmol) and ethyl acetoactate (0.01 mmol) in absolute ethanol (20 ml) was refluxed for 2 h in the presence of triethylamine (0.5 ml) The obtained solid product was recrystallized to give **10** (Table III).

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