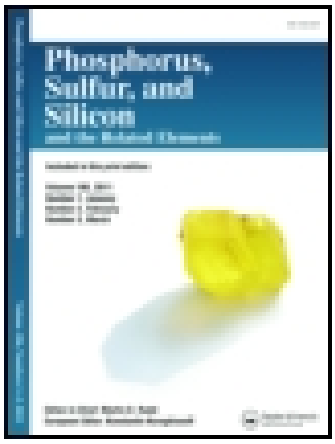

Phosphorus, Sulfur, and Silicon and the Related Elements

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Studies on Thiazolopyridines. Part 1: Antimicrobial Activity of Some Novel Fluorinated Thiazolo[3,2-a]Pyridines and Thiazolo[2′,3′:1,6]Pyrido[2,3-d]Pyrimidines

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STUDIES ON THIAZOLOPYRIDINES. PART 1: ANTIMICROBIAL ACTIVITY OF SOME NOVEL FLUORINATED THIAZOLO[3,2-a]PYRIDINES AND THIAZOLO[2′,3′:1,6]PYRIDO[2,3-d]PYRIMIDINES

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Ternary condensation of aromatic aldehydes, malononitrile and thioglycolic acid (2:2:1 molar ratio) in ethanol/piperidine afforded the corresponding thiazolo[3,2-a]pyridines ***1a–d****. Thiazolo[2′,3′:1,6]-pyrido[2,3-d]pyrimidine* ***4*** *was obtained by refluxing of compound* ***1a*** *with acetic anhydride. Also, thiazolopyrido pyrimidine* ***6*** *was produced by refluxing of* ***1a*** *with triethylorthoformate followed by treatment with hydrazine hydrate. Refluxing* ***1a*** *with formic acid yielded the thiazolopyridopyrimidine* ***8*** *which on chlorination with thionyl chloride furnished the chloro derivative* ***9****. Finally, amino thiazolo[2′,3′:1,6]pyrido[2,3-d]pyrimidine* ***10*** *was obtained by treatment of* ***1a*** *with formamide. The structures of these compounds were established on the basis of elemental analyses, IR,* ^{1}*H NMR, and mass spectral data. Also, the antimicrobial activity of some synthesized compounds is reported.*

Keywords: Antimicrobial activity; thiazolo[3,2-a]pyridines; thiazolo-[2′,3′:1,6]pyrido[2,3-d]pyrimidines

INTRODUCTION

A wide range of biological activities has been attributed to fused thiazoles. For an example, thiazolopyridines are important as anti-inflammatory and antibacterial agents.[1–4] On the other hand, fused pyrimidines were found to possess wide biological activities such as

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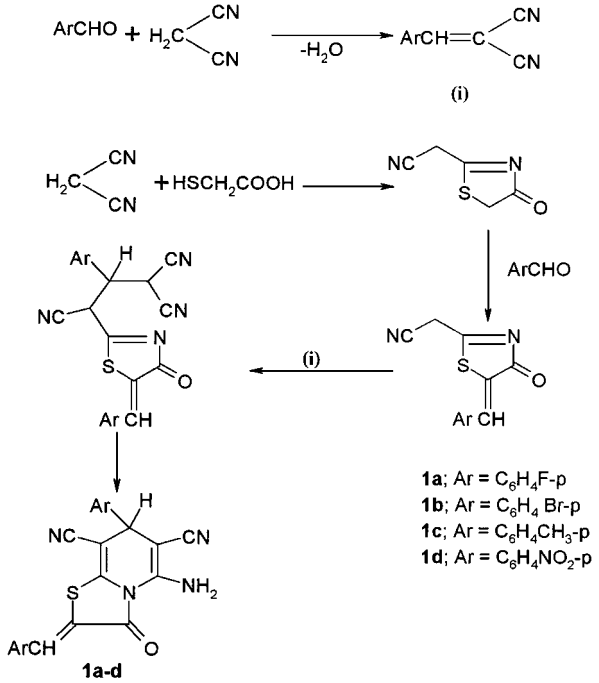
antimicrobial,[5,6] antiparkinsonian,[7] leishmanicidal, and herbicidal.[8] In continuing our efforts[9–11] to evaluate heterocyclic compounds for antimicrobial activity, we synthesized the thiazolo[3,2-a]pyridines and thiazolo[2′,3′:1,6]pyrido[2,3-d]pyrimidines.

RESULTS AND DISCUSSION

Ternary condensation of aromatic aldehydes, malononitrile and thioglycolic acid (2:2:1 molar ratio) in absolute ethanol in the presence of a catalytic amount of piperidine yielded 5-amino-2-arylmethylidene-7-aryl-6,8-dicyano-3-oxo-2,3-dihydro-7H-thiazolo[3,2-a]pyridines **1a–d** in good yields. The structures of **1a–d** were determined on the basis of elemental analyses, IR, ^{1}H-NMR, and mass spectra. The IR spectrum of thiazolopyridine **1a** showed primary amino bands at 3400 cm^{-1} and 3300 cm^{-1} and a cyano stretch at 2200 cm^{-1}. ^{1}H-NMR spectrum of **1a** in DMSO-d$_6$ showed a signal in the region δ 4.67, attributed to the pyridine[10] H. Also, the mass spectra of **1a**,**b** are fully consistent with assigned structures. Thus, compound **1a** revealed a molecular ion peak at



SCHEME 1

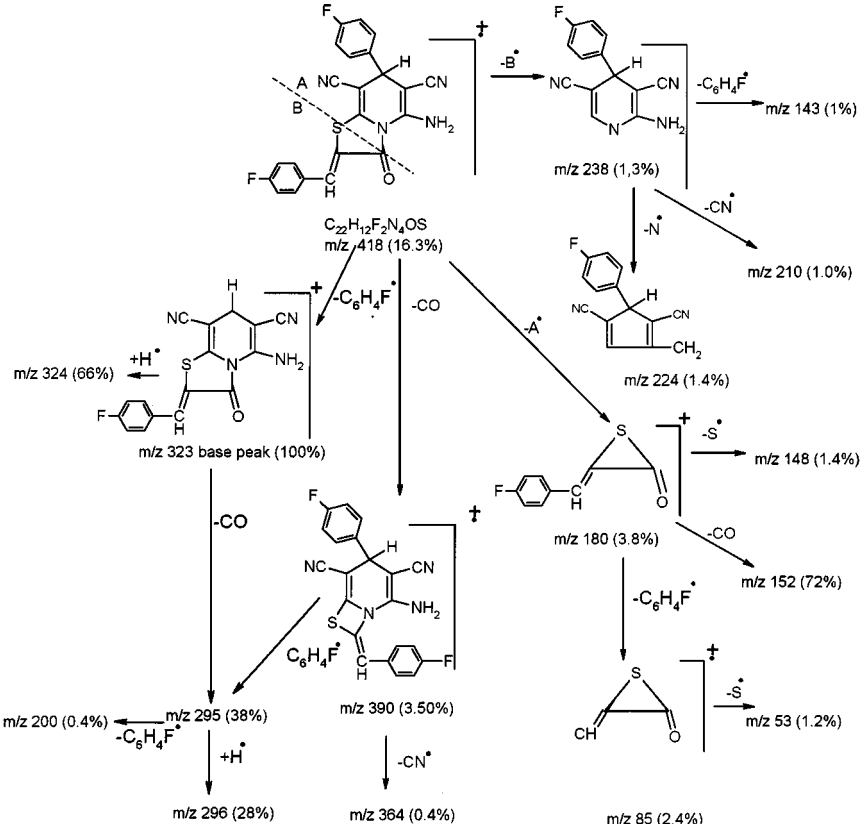
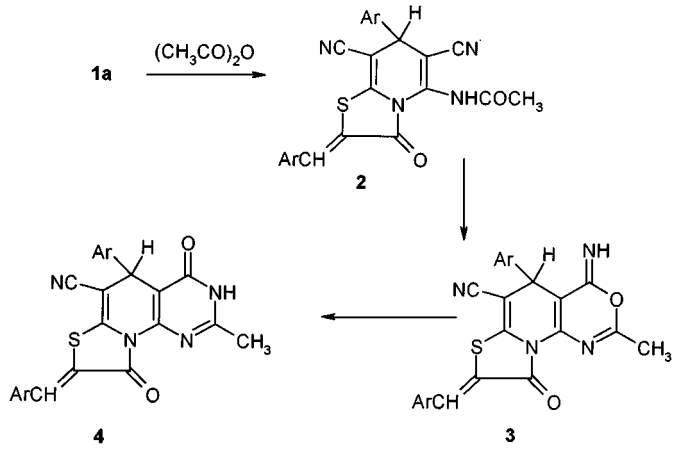


FIGURE 1 Fragmentation pattern of compound **1a**.

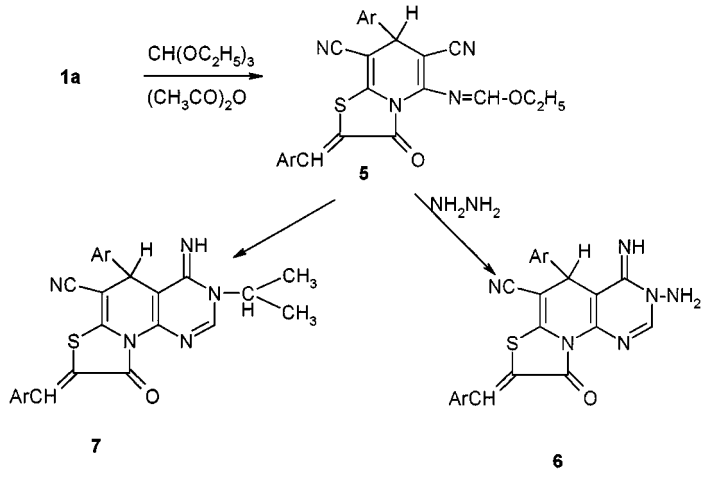
m/z 418 (18.3%) corresponding to the molecular formula $C_{22}H_{12}F_2N_4OS$ (Figure 1). A reaction mechanism[12] is proposed for the formation of the thiazolopyridines **1a–d** and is illustrated in Scheme 1.

Compound **1a** was refluxed with acetic anhydride to yield a 1:1 adduct, for which three possible structures **2**, **3**, and **4** were considered. The structure of **4** was established on the basis of its spectral data. Thus, the IR spectrum showed the presence of a secondary amino function (3400 cm^{-1}), a cyano function (2200 cm^{-1}), and carbonyl functions at 1710 cm^{-1} (thiazolidinone) and 1665 cm^{-1} (pyrimidinone). The ^{1}H-NMR spectrum exhibited a singlet at δ 2.34 and was assigned to the methyl protons. A one proton singlet in the region δ 4.67 was assigned to pyridine −H and a multiplet at δ 7.16–7.89 was assigned to aromatic protons. The formation of **4** from **1a** and acetic anhydride is assumed to proceed through Dimroth rearrangement[13] of the initial cyclization product **3** under the applied reaction conditions, Scheme 2.



SCHEME 2

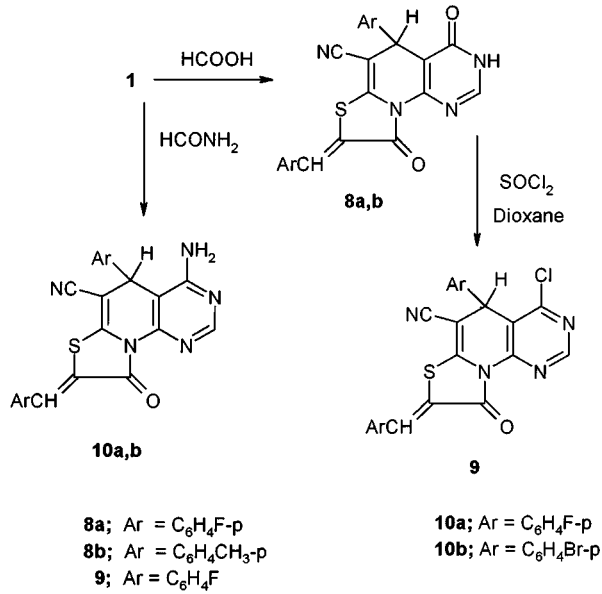
Ethoxymethylene derivative **5** was obtained by refluxing **1a** with triethyl orthoformate in the presence of acetic anhydride. The structure of compound **5** was determined on the basis of its elemental analyses and spectral data. The IR spectrum revealed the absence of amino function. The ^{1}H-NMR spectrum in DMSO-d_6 exhibited methyl (t) and methylene



SCHEME 3

(q) functions, attributed to the OCH_2CH_3 fragment, in addition to a singlet at δ 4.65 ppm which was assigned to pyridine-H. Treatment of **5** with hydrazine hydrate in ethanol at room temperature furnished the novel thiazolopyridopyrimidine derivative **6** in good yield. The ^{1}H-NMR spectrum of compound **6** in DMSO-d_6 showed the absence of a OCH_2CH_3 fragment. Also, compound **5** underwent aminolysis and cyclization by refluxing with isopropylamine in absolute ethanol to give **7** (Scheme 3).

When compounds **1a**,**c** were refluxed with formic acid, the reaction afforded the thiazolopyridopyrimidine **8a**,**b**. Chlorination of **8a** with thionyl chloride in dioxane under reflux produced the chloro derivative **9**. Also, cyclization of **1a**,**b** with formamide[13] under reflux yielded the thiazolopyridopyrimidine **10a**,**b**, Scheme 4.



SCHEME 4

ANTIMICROBIAL ACTIVITY

Antimicrobial activity of the compounds **1a**, **5**, **6**, **8a**, **9**, and **10a** was tested in vitro against *Sataphylococcus aureus* (NCTC-7447), *Bacillus cereus* (ATCC-14759), *Serratia marcesents* (IMRU-70), *Proteus merabitis* (NCTC-289), *Aspergillus ochraceus Wilhelm* (AUCC-230), and *Penicillium chrysogenum Thom* (AUCC-530). The tested

TABLE I Antimicrobial Activity of Some Synthesized Compounds

Compd. no	*Sataphylococcus aureus* (NCTC-7447)	*Bacillus cereus* (ATCC-14759)	*Serratia marcesents* (IMRU-70)	*Proteus merabitis* (NCTC-289)	*Aspergillus ochraceus Wilhelm* (AUCC-230)	*Penicillium chrysogenum Thom* (AUCC-530)
1a	*c*	*b*	*b*	*c*	*a*	*a*
5	*c*	*b*	*b*	*b*	*b*	*a*
6	*b*	*c*	*b*	*c*	*b*	*b*
8a	*c*	*b*	*b*	*b*	*b*	*a*
9	*c*	*b*	*b*	*c*	*b*	*c*
10a	*b*	*c*	*c*	*b*	*b*	*c*
Reference	*d*	*d*	*d*	*d*	*d*	*d*

[a]Less active (0.2–0.5 mm).
[b]Moderately active (0.6–1.4 mm).
[c]Highly active (1.5–2.0 mm).
[d]Very highly active.

compounds were dissolved in DMF at a concentration of 250 mg/mL by the agar diffusion technique.[14] Streptomycin (25 ug) and Mycostatin (30 ug) were used as reference for the antibacterial and antifungal activities respectively. The inhibition zones were measured after 24 h incubation (in mm), and the results were represented in Table I. The majority of the synthesized compounds exhibited various antimicrobial activity toward all the microorganisms used with their minimal inhibitory concentration (MIC).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Shimadzu 440 IR spectrophotometer using the KBr technique (Shimadzu, Japan) ^{1}H-NMR spectra were record in DMSO-d_6 at 200 MHz on a Varian Gemeini NMR spectrometer using TMS as an internal reference. Mass spectra were performed by a Shimadzu-GC-MS-QP 100 EX (Shimadzu, Japan). Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University.

5-Amino-2-arylmethylidene-7-aryl-6,8-dicyano-3-oxo-2,3-dihydro-7H-thiazolo[3,2-a]pyridines (1a–d)

A mixture of aromatic aldehyde (0.02 mol), malononitrile (0.02 mol) and thioglycolic acid (0.01 mol) in absolute ethanol (20 mL) was refluxed for 2 h in the presence of piperidine (0.5 mL). The reaction mixture was poured into ice/HCl and the obtained product was recrystallized to give **la–d** (Table II).

TABLE II Physical and Analytical Data of the Synthesized Compounds

Compd. no	Yield (%)	Solvent cryst.	m.p. (°C)	Mol. formula (M.Wt)	Calculated/found (%) C	H	N
1a	85	DMF/EtOH	258–260	$C_{22}H_{12}F_2N_4OS$ (418)	63.15 63.20	2.87 2.80	13.39 13.40
1b	82	DMF/EtOH	278–280	$C_{22}H_{12}Br_2N_4OS$ (540)	48.88 48.80	2.22 2.20	10.37 10.30
1c	77	DMF/EtOH	240–242	$C_{24}H_{18}N_4OS$ (410)	70.24 70.30	4.39 4.30	13.65 13.60
1d	75	DMF/EtOH	243–245	$C_{22}H_{12}N_6O_5S$ (472)	55.93 55.90	2.54 2.60	17.79 17.70
4	62	EtOH	200–202	$C_{24}H_{14}F_2N_4O_2S$ (460)	62.60 62.70	3.04 3.00	12.17 12.20
5	78	EtOH	246–248	$C_{25}H_{16}F_2N_4O_2S$ (474)	63.29 63.10	3.37 3.40	11.81 11.70
6	70	EtOH	182–183	$C_{23}H_{14}F_2N_6OS$ (460)	60.00 60.10	3.04 3.00	18.27 18.30
7	65	EtOH	170–172	$C_{26}H_{19}F_2N_5OS$ (487)	64.06 64.10	3.90 3.90	14.37 14.40
8a	90	DMF	272–274	$C_{23}H_{12}F_2N_4O_2S$ (446)	61.88 61.80	2.69 2.60	12.55 12.50
8b	76	DMF	215–217	$C_{25}H_{18}N_4O_2S$ (438)	68.49 68.50	4.10 4.20	12.79 12.60
9	65	benzene	120–122	$C_{23}H_{11}ClF_2N_4OS$ (464.5)	59.40 59.40	2.79 2.70	12.05 12.00
10a	80	DMF	>300	$C_{23}H_{13}F_2N_5OS$ (445)	62.02 62.10	2.92 2.80	15.73 15.70
10b	81	DMF	>300	$C_{23}H_{13}Br_2N_5OS$ (567)	48.67 48.70	2.29 2.30	12.34 12.40

The mass spectrum of compound **1a** exhibited a molecular ion peak at m/z 418 (16.3%) with a base peak at m/z 323 (M^+—C_6H_4F, 100%). Other significant peaks were observed: 419 (10.2%), 420 (3.5%), 390 (3.5%), 295 (32%), 238 (1.3%), 296 (28%), 210 (1.0%), 200 (0.4%), and 76 (1.7%). Also the mass spectrum of compound **1b** showed a molecular ion peak at m/z 540 (11.2%) with a base peak at m/z 385.

2-(4-Fluorophenyl)methylidene-9-(4-fluorophenyl)-3,8-dioxo-6-methyl-2,3,7,8-tetrahydro-9H-thiazolo[2′,3′:1,6]-pyrido[2,3-d]pyrimidin-10-carbonitrile (4)

A solution of **1a** (0.01 mol) in acetic anhydride (5 mL) was refluxed for 4 h. The solid product, thus formed, after cooling was filtered off and recrystallized to give **4** (Table II).

2-(4-Fluorophenyl)methylidene-7-(4-fluorophenyl)-2,3-dihydro-5-ethoxymethyleneamino-7H-3-oxo-thiazolo[3,2-a]-pyri mi din-6,8-dicarbonitrile (5)

A mixture of **1a** (0.01 mol) and triethyl orthoformate (2 mL) in acetic anhydride (10 mL) was refluxed for 10 h. The reaction mixture was cooled, diluted with cold water and solid product was collected and recrystallized to give **5** (Table II).

TABLE III Spectral Data of the Synthesized Compounds

Compd. no	IR υ_{max} (cm^{-1})	^{1}H-NMR δ (ppm) (DMSO-d_6)
1a	3400, 3300 (NH_2), 2200 (C≡N), 1700 (C═O)	4,67 (s, 1H, pyridine −H), 7.23–7.79 (m, 9H, Ar—H + methine −H), 7.89 (s, 2H, NH_2).
1b	3400, 3250 (NH_2), 2200 (C≡N), 1700 (C≡N)	
1c	3420, 3380 (NH_2), 2200 (C≡N), 1715 (C≡N)	2.34 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 4.55 (s, 1H, pyridine −H), 7.20–7.58 (m, 9H, Ar—H + methine −H), 7.83 (s, 2H, NH_2).
1d	3450, 3400 (NH_2), 2200 (C≡N), 1690 (C≡N)	4.60 (s, 1H, pyridine −H), 6.77–7.78 (m, 9H, Ar—H + methine −H), 9.50 (broad, 2H, NH_2).
4	3400 (NH), 2200 (C≡N) 1710, 1665 (C═O)	2.34 (s, 3H, CH_3), 4.67 (s, 1H, pyridine −H), 7.16–7.89 (m, 9H, Ar—H + methine −H), 8.20 (s, 1H, CH-pyrimidine), 12.4 (s, 1H, NH).
5	2000 (C≡N), 1712 (C═O)	1.33 (t, 3H, CH_3), 4.36 (q, 2H, OCH_2), 4.65 (s, 1H, pyridine −H), 7.25–7.82 (m, 9H, Ar—H + methine −H), 8.21 (s, 1H, N═CH).
6	3350, 3300 (NH_2) 20 (C≡N), 1690 (C═O)	4.50 (s, 1H, pyridine −H), 6.40 (broad, 2H, NH_2), 7.15–7.46 (m, 9H, Ar—H + NH + methine −H), 8.40 (s, 1H, pyrimidine −H).
7	3300 (NH), 2980 (CH-aliph), 2200 (C≡N), 1700 (C═O)	1.49 (m, 6H, $2CH_3$), 3.12 (m, 1H, N—CH), 4.51 (s, 1H, pyridine −H), 6.57 (s, 1H, NH), 7.19–7.44 (m, 9H, Ar—H + methine −H), 8.25 (s, 1H, pyrimidine −H).
8a	3178 (NH), 2214 (C≡N), 1705, 1658 (C═N)	4.9 (s, 1H, pyridine −H), 7.23–7.75 (m, 9H, Ar—H + methine −H), 8.21 (s, 1H, pyrimidine −H), 12.5 (broad, 1H, NH).
9	2200 (C≡N), 1700 (C═O)	4.20 (s, 1H, pyridine −H), 7.27–7.76 (m, 9H, Ar—H + methine −H), 8.20 (s, 1H, pyrimidine −H).
10a	3400, 3300 (NH_2), 2200 (C≡N), 1700 (C═O)	
10b	3380, 3200 (NH_2), 2200 (C≡N), 1700 (C═O)	4.20 (s, 1H, pyridine −H), 6.40 (s, 2H, NH_2), 7.20 (m, 9H, Ar—H + methine −H), 8.02 (s, 1H, pyrimidine −H).

7-Amino-2-(4-Fluorophenyl)methylidene-9-(4-fluorophenyl)-8-imino-3-oxo-2,3,7,8-tetrahydro-9H-thiazolo[2′,3′:1,6]pyrido[2,3d]pyrimidin-10-carbonitrile (6)

To a solution of **5** (0.01 mol) in absolute ethanol (30 mL) was added hydrazine hydrate and the reaction was stirred at room temperature for 2 h. The solid obtained was filtered off to give **6** (Table II).

2-(4-Fluorophenyl)methylidene-9-(4-fluorophenyl)-7-isopropyl-8-imino-3-oxo-2,3,7,8-tetrahydro-9H-thiazolo[2′,3′:1,6]pyrido-[2,3d]pyrimidin-10-carbonitrile (7)

A mixture of **5** (0.01 mol) and isopropylamine (0.02 mol) in absolute ethanol (20 mL) was heated under reflux for 1 h. The reaction mixture was allowed to cool. The solid product was filtered off to give **7** (Table II).

2-(4-Fluorophenyl)methylidene-9-(4-fluorophenyl)-3,8-dioxo-2,3,7,8-tetrahydro-9H-thiazolo[2′,3′:1,6]pyrido[2,3-d]pyrimidin-10-carbonitrile (8)

A mixture of **1a** (0.01 mol) and formic acid (10 mL) was refluxed for 10 h. The solid product thus formed after cooling was filtered off to give **8** (Table II).

2-(4-Fluorophenyl)methylidene-9-(4-fluorophenyl)-8-chloro-2,3-dihydro-9H-3-oxo-thiazolo[2′,3′:1,6]-pyrido[2,3d]pyrimidin-10-carbonitrile (9)

To a suspension of **8** (0.01 mol) in anhydrous dioxane (20 mL), dimethylformamide (2 mL) and thionyl chlaride (2 mL) were added . The reaction mixture was refluxed for 2 h. The solvent was evaporated in vacuo and the solid formed was collected by filtration to give **9** (Table II).

2-(4-Fluorophenyl)methylidene-9-(4-fluorophenyl)-8-amino-2,3-dihydro-9H-3-oxo-thiazolo[2′,3′:1,6]-pyrido[2,3-d]pyrimidin-10-carbonitrile (10)

A solution of **1a** (0.01 mol) in formamide (20 mL) was refluxed for 2 h. After cooling the reaction mixture was diluted with water and solid precipitate was collected by filtration to give **10** (Table II).

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