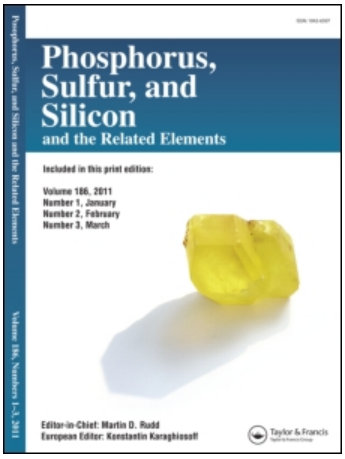

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SYNTHESIS OF 2-THIOXOPYRIDO[2,3-*d*]PY RIMIDINE-4- ONES AND 1,4-BRIDGED BIS-2-THIOXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINE CARBOXYLIC ACID ETHYL ESTER DERIVATIVES

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SYNTHESIS OF 2-THIOXOPYRIDO[2,3-*d*]PYRIMIDINE-4-ONES AND 1,4-BRIDGED BIS-2-THIOXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINE CARBOXYLIC ACID ETHYL ESTER DERIVATIVES

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The synthesis and structural characterization of 2-thioxopyrido[2,3-*d*]pyrimidinethiones **5,9,12** and 4,4′-(1,4-phenylene)-di-(2-thioxo-1,2,3,4-tetrahydropyrimidines) **16–22** are described.

Keywords: Synthesis; 6-amino-2-thiouracils; terephthalaldehyde; 2-thioxopyrido[2,3-*d*]pyrimidine-4-ones; 4,4′-(1,4-phenylene)-di-(2-thioxopyrimidine)

Pyrimidine-2-thiones as an isolated ring or a condensed nucleus, are present in several compounds of biological and medicinal interest. For example, 1,4-dihydropyrimidine-2-thiones have long been used as antitumor agents [1], anticancer [2], antimicrobial [3] and hypolipidemic or fungicidal [4] activity. Also, pyrido[2,3-d]pyrimidines and their oxo and thioxo derivatives deserve great interest by virtue of their biological and physiological properties [5,6]. Prompted by the aforesaid biological and pharmaceutical activities, and in continuation of our interest aimed at developing new approaches for the synthesis of polyfunctionally substituted heterocyclic compounds of expected biological activity [7–11], the present work is aimed at synthesizing pyrido[2,3-*d*]pyrimidine-2-thione

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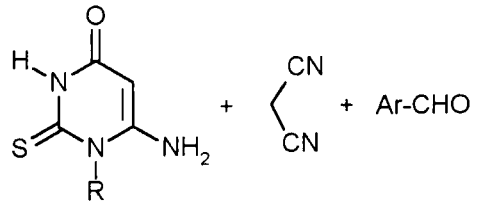
and 4,4′-(1,4-phenylene)-di-(2-thioxopyrimidine) derivatives in high yields by a one-pot method from basic laboratory reagents.

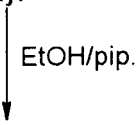
Thus, reacting a mixture of 6-amino-2-thiouracils **1a,b**, malononitrile **2** and aromatic aldehydes **3** in equimolar proportions in ethanol in the presence of piperidine afforded 2-thioxopyrido[2,3-*d*]pyrimidine-4-ones **5a-h** (Scheme 1). The products were fully characterized through spectral and elemental analysis (see experimental), the structure of **5** was indicated by broad IR bands at 3450–3200 cm^{-1} corresponding to the chelated amino groups and at 2220–2200 cm^{-1} corresponding to CN group. The structure elucidation for the system **5** shall be discussed here in detail for **5a**. The ^{1}H-NMR spectrum in DMSO-d_6 contained four sharp singlets at δ (12.80, 12.20, 9.65, 4.55) ppm for 3-H, 1-H, 8-H, and 5-H respectively. Structural proof was obtained through a two component condensation of **1a,b** and **4** in equimolar proportions under the previous conditions which also afforded **5** (see experimental and tables I,II).

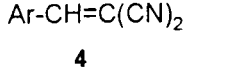
In contrast, the condensation of terephthalaldehyde **6** with **2** and **1a,b** under the previous conditions afforded the corresponding 5,5′(1,4-phenylene)-di-(2-thioxopyrido[2,3-d]pyrimidine-4-ones) **9a,b** (scheme 2). The formation of **9a,b** were rationalized in terms of the initial formation of **7** followed by the Michael addition of **1** to the ylidinic bond forming dihydropyrido[2,3-*d*]pyrimidine intermediate **8** which underwent oxidation to fully aromatized products **9a,b**. Similarly, compounds **12a-c** were synthesized by treatment of **1b** with **6** and **10a-c** (scheme 2). The structures of compounds **9a,b** and **12a-c** were established on the basis of satisfactory analytical and spectral data; for example, the ^{1}H-NMR spectrum in DMSO-d_6 of compound **9a** showed the absence of the 5-H band compared with compound **5a**. (see experimental and tables I,II).

As an extension of our synthetic methodology, it was found that the ternary condensation of **6, 13** and thiourea **14a** or urea **15**, in a molar ratio 1:2:2, in ethanol containing catalytic amount of hydrochloric acid yielded the corresponding 4,4′-(1,4-phenylene)-di-(1,2,3,4-tetrahydropyrimidine) **16a** and **17**, respectively (Scheme 3) and their structures were deduced on the basis of analytical and spectral data. Further confirmation of structure **17** was made by comparison with an authentic sample, prepared from the oxidation of **16a** by hydrogen peroxide, which showed agreement in M.P., IR and ^{1}H-NMR data (see Experimental). Also, the N(1)-methyl derivative **16b** was prepared by refluxing **6, 13** and methyl thiourea **14b** under the same reaction conditions mentioned above for **16a** (Scheme 2). The



1a, R=H **2** **3a-h**
b, R= 2-chlorophenyl





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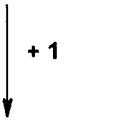
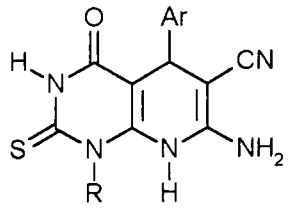
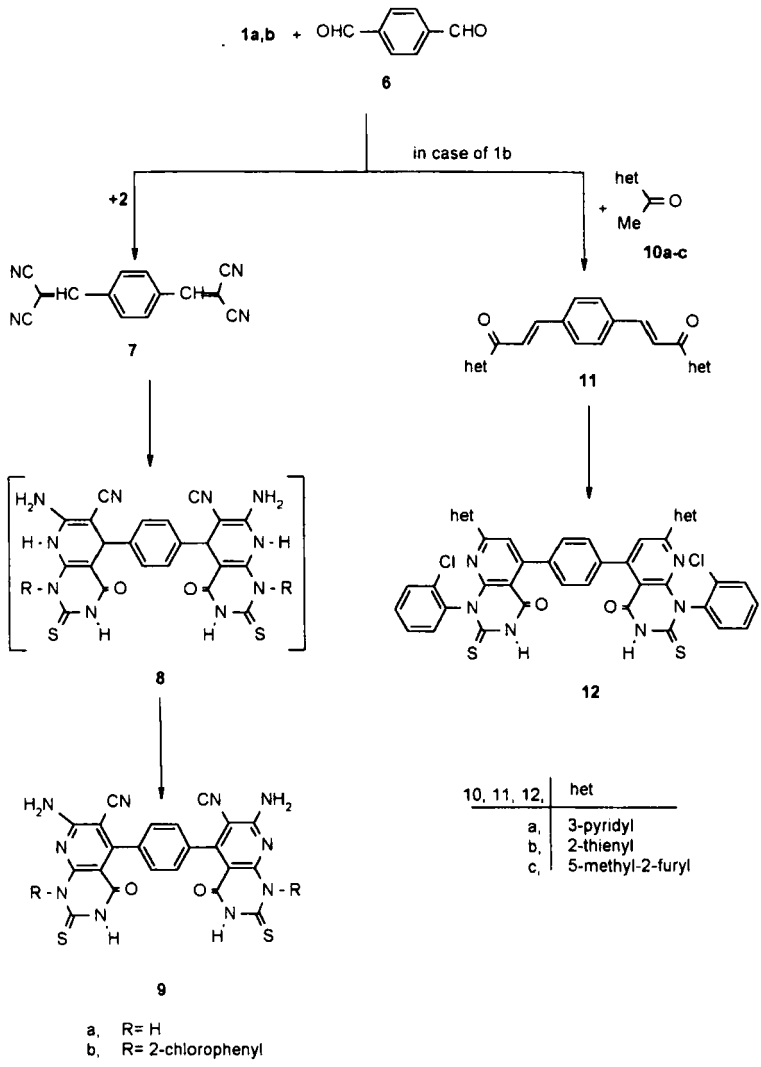




5

3, 5	R	Ar
a,	H,	4-pyridyl
b,	H,	2-thienyl
c,	H,	4-methoxyphenyl
d,	H,	3,4-dimethoxyphenyl
e,	H,	2-bromophenyl
f,	2-chlorophenyl	4-pyridyl
g,	2-chlorophenyl	2-thienyl
h,	2-chlorophenyl	3,4,5-trimethoxyphenyl

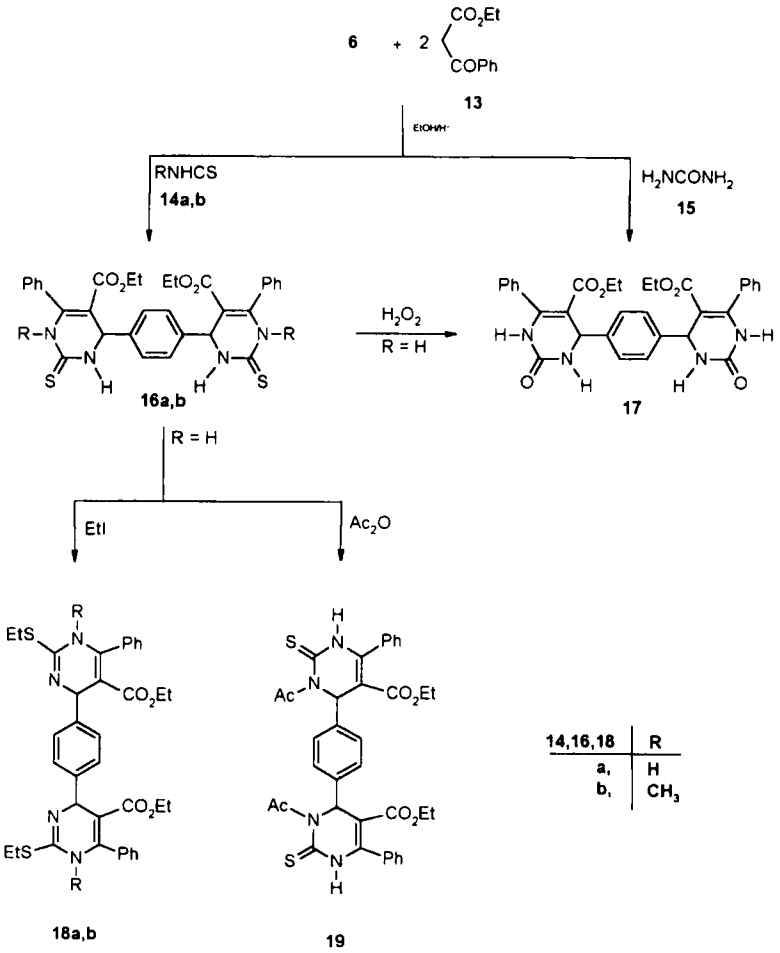
SCHEME 1



SCHEME 2

position of the N-methyl group on the pyrimidine ring follows from ^{1}H-NMR spectroscopic data. Thus the signals for the protons at C-4 and N-3 appears as doublets (δ 5.30 and δ 10.10 ppm, J = 4.6 Hz). Therefore, the product was identified as N(1)-methyl and not as N(3)-methyl deriva-

tive. The reaction of **16a,b** with ethyl iodide in DMF and in the presence of sodium ethoxide afforded the S-ethylated compounds **18a,b** in excellent yield (Scheme 3). The action of acetic anhydride on **16a** led to the 3-acetyl derivative **19**. The site of acetylation in **19** was determined from ^{1}H-NMR spectrum. The signal for the C-4 proton collapsed from a doublet in **16a** (δ 5.25 ppm, J = 4.6 Hz) to a singlet in **19** (δ 6.50 ppm). This downfield shift is attributed to the anisotropic effect of the carbonyl group at N(3).



SCHEME 3

TABLE I Physical and analytical data for the prepared compounds

Mp (T/°C) (solvent)	*Yield (%)*	*M.F (M_r)*	*Found (required) (%)*			
			C	*H*	*N*	
252–254 (EtOH)	75	$C_{13}H_{10}N_6OS$ (298.32)	52.50	3.50	28.20	1(
			(52.34)	(3.38)	(28.17)	(1(
378–380 (dioxane)	68	$C_{12}H_9N_5OS_2$ (303.35)	47.60	3.00	23.20	2
			(47.51)	(2.99)	(23.10)	(2
> 400 (DMF)	70	$C_{15}H_{13}N_5O_2S$ (327.35)	55.10	3.90	21.30	9
			(55.03)	(4.00)	(21.40)	(9
350–352 (EtOH)	75	$C_{16}H_{15}N_5O_3S$ (357.37)	53.80	4.30	19.50	8
			(53.77)	(4.23)	(19.60)	(8
380–382 (DMF)	68	$C_{14}H_{10}N_5OSBr$ (376.23)	44.80	2.50	18.70	8
			(44.69)	(2.68)	(18.62)	(8
330–332 (DMF)	75	$C_{19}H_{13}N_6OSCl$ (408.86)	55.70	3.30	20.40	7
			(55.81)	(3.20)	(20.56)	(7
342–344 (MeOH)	80	$C_{18}H_{12}N_5OS_2Cl$ (413.89)	52.30	2.80	16.80	1!
			(52.23)	(2.92)	(16.92)	(1!
324–326 (ETOH)	75	$C_{23}H_{20}N_5O_4SCl$ (497.95)	55.50	4.20	14.20	6

Mp (T/°C) (solvent)	Yield (%)	M.F (M_r)	Found (required) (%)			
			C	H	N	
			(55.47)	(4.05)	(14.07)	(6.
> 400 (DMF)	80	$C_{22}H_{12}N_{10}O_2S_2$(512.52)	51.40	2.30	27.50	12
			(51.55)	(2.36)	(27.33)	(12
360–362 (DMF)	78	$C_{34}H_{18}N_{10}O_2S_2Cl_2$ (733.59)	55.50	2.30	19.20	8.
			(55.66)	(2.47)	(19.09)	(8.
304–306 (DMF)	84	$C_{42}H_{24}N_8O_2S_2Cl_2$ (807.70)	62.50	2.90	13.60	7.
			(62.45)	(3.00)	(13.87)	(7.
300–302 (EtOH)	84	$C_{40}H_{22}N_6O_2S_4Cl_2$ (817.80)	58.60	2.80	10.30	15
			(58.74)	(2.71)	(10.28)	(15
290–292 (EtOH)	81	$C_{42}H_{26}N_6O_4S_2Cl_2$ (813.71)	62.10	3.30	10.40	7
			(61.99)	(3.22)	(10.33)	(7
288–290 (DMF)	82	$C_{32}H_{30}N_4O_4S_2$ (598.71)	64.37	5.10	9.50	10
			(64.19)	(5.05)	(9.36)	(10
284.286 (AcOH)	71	$C_{34}H_{34}N_4O_4S_2$ (626.76)	65.30	5.60	9.10	10
			(65.15)	(5.47)	(8.94)	(10
289–300 (EtOH)	69	$C_{32}H_{30}N_4O_6$ (566.59)	67.70	5.50	9.80	

Mp (T/°C) (solvent)	Yield (%)	M.F (M_r)	Found (required) (%)			
			C	H	N	
			(67.83)	(5.34)	(9.89)	
135–137 (EtOH)	76	$C_{36}H_{38}N_4O_4S_2$ (654.81)	66.20	5.60	8.70	9
			(66.03)	(5.85)	(8.56)	(9
258–260 (DMF)	73	$C_{38}H_{42}N_4O_4S_2$ (682.87)	66.90	6.40	8.30	9
			(66.83)	(6.20)	(8.20)	(9
276–278 (AcOH)	68	$C_{36}H_{34}N_4O_4S_2$ (650.78)	66.60	5.40	8.50	9
			(66.44)	(5.27)	(8.61)	(9
135–137 (EtOH)	64	$C_{38}H_{38}N_4O_4S_2$ (678.83)	67.40	5.70	8.10	9
			(67.23)	(5.64)	(8.25)	(9

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TABLE II Spectral data for the prepared compounds

ν_{max}/cm^{-1}	δ_H M^+
3380, 3200 (NH, NH_2), 2200 (CN), 1640 (CO)	4.55 (s, 1H, H-5), 6.00(s, 2H, NH_2), 7.20–8.80 (m, 4H, pyridyl), 9.65 (s, 1H, NH), 12.20 (s, 1H, NH), 12.80 (s, 1H, NH). With D_2O: 4.55 (s, IH, H- 5), 7.20–8.80 (m, 4H, pyridyl)
3300, 3200 (NH, NH_2), 2200 (CN), 1650 (CO)	4.65 (s, 1H, H-5), 6.35 (s, 2H, NH_2), 7.00–7.75 (m, 3H, thiophene), 7.85 (s, 1H, NH), 11.60 (s, 1H, NH), 12.20 (s, 1H, NH). With D_2O, 4.75 (s, 1H, H- 4), 7.00–7.80 (m, 3H, thiophene)
3300, 3200 (NH, NH_2), 2200 (CN), 1690 (CO)	3.60 (s, 3H, -OCH_3), 4.20 (s, 1H, H-5), 6.30 (s, 2H, NH_2), 6.70–7.20 (m, 4H, Ar-H), 7.60 (s, 1H, NH), 8.90 (s, 1H, NH), 9.60 (s, 1H, NH).
3300, 3200 (NH, NH_2), 2200 (CN), 1700 (CO)	3.65 (s, 6H, 2-OCH_3), 4.35 (s, 1H, H-5), 6.55 (s, 2H, NH_2), 7.10–7.40 (m, 3H, Ar-H), 7.60 (s, 1H, NH), 8.95 (s, 1H, NH), 9.75 (s, 1H, NH)
3300, 3200 (NH, NH_2), 2200 (CN), 1700 (CO)	4.25 (s, 1H, H-5), 6.35 (s, 2H, NH_2), 7.10–7.60 (m, 4H, Ar-H), 8.10 (s, 1H, NH), 11.20 (s, 1H, NH), 12.20 (s, 1H, NH)
3300, 3150 (NH, NH_2), 2200 (CN), 1700 (CO)	4.35 (s, 1H, H-5), 6.40 (s, 2H, NH_2), 7.20–8.30 (m, 8H, Ar-H + pyridyl protons), 9.80 (s, 1H, NH), 12.10 (s, 1H, NH)
3250, 3220 (NH, NH_2), 2215 (CN), 1690 (CO)	4.35 (s, 1H, H-5), 6.45 (s, 2H, NH_2), 7.10–8.10 (m, 7H, Ar-H + thienyl protons), 9.60 (s, 1H, NH), 12.00 (s, 1H, NH)
3320, 3200 (NH, NH_2), 2220 (CN), 1675 (CO)	3.75 (s, 9H, 3-OCH_3), 4.35 (s, 1H, H-5), 6.35 (s, 2H, NH_2), 7.20–8.10 (m, 6H, Ar-H), 9.80 (s, 1H, NH), 12.10 (s, 1H, NH)
3300, 3200 (NH, NH_2), 2200 (CN), 1680 (CO)	7.20–8.10 (m, 4H, Ar-H), 7.60 (s, 4H, $2NH_2$), 11.35 (s, 2H, 2NH), 12.20 (s, 2H, 2NH). With D_2O: 7.20–8.10 (m, 4H, Ar-H).
3300, 3200 (NH, NH_2), 2220 (CN), 1690 (CO)	7.20–8.10 (m, 12H, Ar-H), 7.50 (s, 4H, $2NH_2$), 12.35 (s, 2H, 2NH)

ν_{max}/cm^{-1}	δ_H M^+
3250 (NH), 1620 (CO)	7.20–8.00 (m, 22H, Ar-H + pyridyl protons), 10.05 (s, 2H, 2NH)
3200 (NH), 1640 (CO)	7.00–8.00 (m, 20H, Ar-H + thienyl protons), 10.00 (s, 2H, 2NH)
3250 (NH), 1640 (CO)	1.65 (s, 6H, $2CH_3$), 7.0–8.0 (m, 18H, Ar-H + furyl prptons), 10.00 (s, 2H, 2NH)
3200 (NH), 1690 (CO)	0.70 (t, 6H, J=7 Hz, 2 CH_3); 3.75 (q, 4H, J=7 Hz, 2 CH_2), 5.25 (d, 2H, J = 4.6 Hz, 2 H-4), 7.30–7.50 (m, 14 Ar-H), 9.75 (d, 2H, J = 4.6 Hz, 2NH), 10.5 (s, 2H, 2NH)
3210 (NH), 1690 (CO)	0.70 (t, 6H, J = 7 Hz, 2 CH_3); 3.35 (s, 6H, 2 NCH_3), 3.70 (q, 4H, J = 7 Hz, 2 CH_2), 5.30 (d, J = 4.6 Hz, 2H, 2 H-4), 7.20–7.50 (m, 14 Ar-H), 10.1 (d, J = 4.6 Hz, 2H, 2 NH).
NH), 1690, 1650 (CO)	0.70 (t, 6H, J = 7 Hz, 2 CH_3); 3.75 (q, 4H, J = 7 Hz, 2 CH_2), 5.20 (d, 2H, J=4.6 Hz, 2 H-4), 7.30–7.60 (m, 14 Ar-H), 9.70 (d, 2H, J = 4.6 Hz, 2NH), 10.50 (s, 2H, 2NH).
NH), 1675 (CO)	0.80 (t, 6H, J=7 Hz, 2 CH_3); 1.25 (t, 6H, J=7 Hz, 2 CH_3); 2.80 (q, 4H, J=7 Hz, 2 CH_2), 3.70 (q, 4H, J=7 Hz, 2 CH_2), 5.30 (s, 2H, 2 H-4), 7.30–7.70 (m, 14-H, Ar-H), 10.50 (s, 2H, 2NH).
CO)	0.80 (t, 6H, J=7 Hz, 2 CH_3); 1.30 (t, 6H, J=7 Hz, 2 CH_3); 2.75 (q, 4H, J=7 Hz, 2 CH_2), 3.30 (s, 6H, 2 NCH_3), 3.60 (q, 4H, J = 7 Hz, 2 CH_2), 5.20 (s, 2H, 2 H-4), 7.30–7.60 (m, 14-H, Ar-H)
CO)	0.85 (t, 6H, J=7 Hz, 2 CH_3); 3.50 (t, 4H, J = 7.5 Hz, 2 NCH_2 -), 3.75 (q, 4H, J=7 Hz, 2 CH_2), 3.80 (t, 4H, J = 7.5 Hz, 2 SCH_2 -), 5.80 (s, 2H, 2 H-4), 7.20–7.60(m, 14-H, Ar-H).
CO)	0.75 (t, 6H, J = 7 Hz, 2 CH_3); 1.8 (m, 4H, thiazine protons), 3.20 (t, 4H, J=7.5 Hz, 2 SCH_2), 3.60 (t, 4H, J = 7.5 Hz, 2 NCH_2), 3.75 (q, 4H, J = 7 Hz, 2 CH_2), 5.80 (s, 2H, 2 H-4), 7.20–7.60 (m, 14-H, Ar-H).

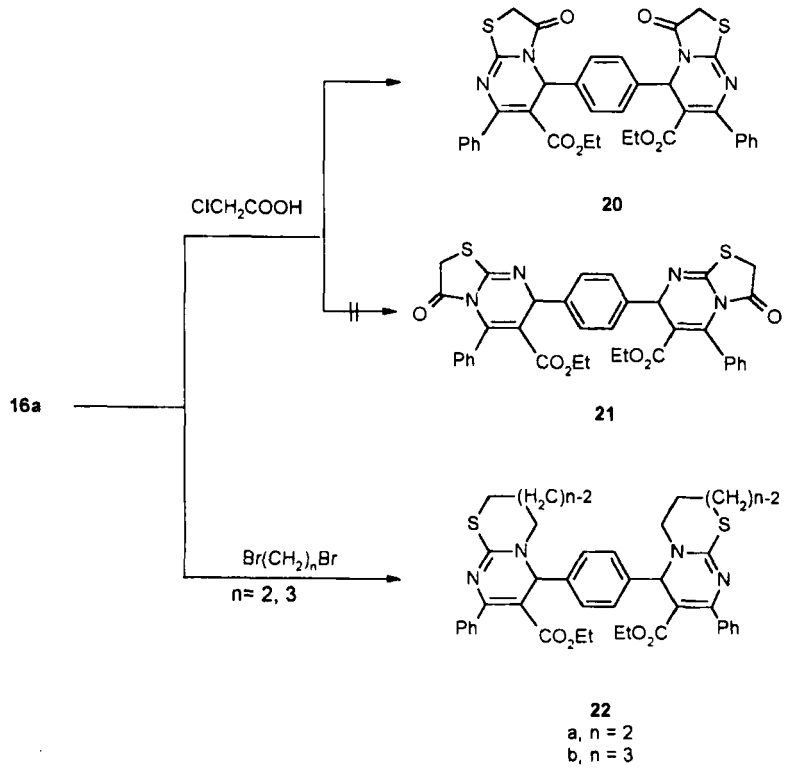
Compound **16a** can be considered as acyclic thiourea derivative, and therefore can be reacted with various dielectrophiles to yield fused pyrimidines. As reported by *Cho et al.* [12], the N-3 should bear a greater electron density than N-1 and therefore be more nucleophilic in the mesomeric anion formed by the action of base on **16a**. Thus, compound **16a** underwent cycloalkylation on heating at 60°C with chloroacetic acid to afford 5,5′-(1,4-phenylene)-di-(6-ethoxycarbonyl-7-phenyl-3-oxo-2,3- dihydro-5H-thiazolo[3,2-a]pyrimidine) **20**, rather than the isomeric structure **21** (Scheme 4). The ^{1}H-NMR spectra of **20** showed singlet for the C-4 proton, which is observed at δ 6.10 ppm. This value is in good agreement with chemical shifts observed for **19** (see Experimental). Similarly, the reaction of **16a** with 1,2-dibromoethane and/or 1,3-dibromopropane gave 5,5′-(1,4-phenylene)-di-(thiazolo[3,2-a]pyrimidine) **22a** and 6,6′-(1,4-phenylene)-di-(thiazino[3,2-a]pyrimidine) **22b** respectively. Structures **22a,b** were confirmed on the basis of their analytical and spectral data (Scheme 4 and Experimental).

EXPERIMENTAL

All melting points were recorded on a Gallen Kamp apparatus and are uncorrected. IR spectra were recorded (as KBr pellets) on a Shimadzu 480 spectrophotometer. The ^{1}H-NMR spectra were measured in DMSO-d_6 on 90 and 200 MHz (Varian EM-390 and Bruker WM 400) spectrometers using TMS as an internal standard, the chemical shifts are expressed as δ values (ppm). Mass spectra were determined on a Finnigan MAT 8430 mass spectrometer operating at 70 eV. Microanalysis were performed by the Micro-analytical data unit at Cairo University. Compounds **10**, **7** and **11b** were prepared by literature procedures [13–15].

Synthesis of 6-amino-1(2-chlorophenyl)-2,3-dihydro-2-thioxo-pyrimidine-4-one (1b)

To a solution of sodium ethoxide [prepared by dissolving sodium metal (10 mmol) in anhydrous ethanol (20 ml)], o-chlorophenylthiourea [16] (10 mmol) and ethylcyanoacetate (10 mmol) were added. The reaction mixture was refluxed for 4 hours, then after cooling 200 mL of hot water was added to the reaction mixture and stirring is resumed. After the com-



SCHEME 4

plete solution has taken place, the reaction mixture neutralized to litmus paper with glacial acetic acid. The product formed was filtered, washed, dried and crystallized from ethanol, yield 85%; m.p. 246–248°C (colorless crystals). IR: ν_{max} = 3450, 3320, 3150 (NH, NH_2), 1650(CO) cm^{-1}. ^{1}H-NMR: δ 5.00 (s, 1H, CH), 6.20 (s, 2H, NH_2), 7.40–7.80 (m, 4H, Ar-H), 12.10 (s, 1H, NH), With D_2O: δ 5.00 (s, 1H, CH), 7.40–7.80 (m, 4H, Ar-H). Found: C, 47.20; H, 3.30; N, 16.40; S, 12.50 %. Calcd. for $C_{10}H_8N_3SOCl$ (253.701): C, 47.34; H, 3.18; N,16.56; S, 12.64%.

General Procedure for the synthesis of compounds (5a-h)

Method A

A mixture of **1** (10 mmol), **2** (10 mmol) and **3** (10 mmol) in absolute ethanol (50 ml) containing 5 drops of piperidine was heated under reflux for

3 hours. The solid product formed was collected by filtration and recrystallized from the appropriate solvent.

Method B

A mixture of **4** (10 mmol) and **1** (10 mmol) in absolute ethanol (50 ml) containing 5 drops of piperidine was heated under reflux for 3 hours. The solid product formed was purified as in method A.

General Procedure for the synthesis of compounds (9a,b)

Method A

A mixture of **1** (20 mmol), **2** (20 mmol) and **6** (10 mmol) in absolute ethanol (50 ml) containing 5 drops of piperidine was heated under reflux for 3 hours. The solid product formed was collected by filtration and recrystallized from the appropriate solvent.

Method B

A mixture of 7 [14] (10 mmol) and **1** (20 mmol) in absolute ethanol (50 ml) containing 5 drops of piperidine was heated under reflux for 3 hours. The solid product formed was purified as in method A.

General Procedure for the synthesis of compounds (12a-c)

Method A

A mixture of **1b** (20 mmol), **10** (20 mmol) and **6** (10 mmol) in absolute ethanol (50 ml) containing 5 drops of piperidine was heated under reflux for 3 hours. The solid product formed was collected by filtration and recrystallized from the appropriate solvent.

Method B

A mixture of **11** [15] (10 mmol) and **1b** (20 mmol) in absolute ethanol (50 ml) containing 5 drops of piperidine was heated under reflux for 3 hours. The solid product formed was purified as in method A.

General Procedure for the synthesis of compounds (16a,b) and (17)

A mixture of **6** (10 mmol), **13** (20 mmol) and thiourea **14a** or methyl thiourea **14b** or urea **15** (20 mmol) in absolute ethanol (40 ml) containing 10 drops of hydrochloric acid was refluxed for 5 hours. After cooling at room temperature, the solid product so formed was collected by filtration washed with water, dried and recrystallized from the appropriate solvent.

Alternative Synthesis of compound (17) from (16a)

A mixture of **16a** (10 mmol) and potassium carbonate (20 mmol) in water (30 ml) was stirred at 80°C until a clear solution is obtained. To the stirred solution was then added 30% hydrogen peroxide (20 ml). After completion of this addition, stirring was continued for 4 hours at 60°C. After cooling to room temperature, the solution was acidified with acetic acid. the resultant precipitate was collected, washed with water and dried to give compound **17**.

General procedure for the synthesis of compounds (18a,b)

To a solution of sodium ethoxide [prepared by dissolving sodium metal (10 mmol) in anhydrous ethanol (20 ml)], the compound **16a,b** (5 mmol) was dissolved in DMF (10 ml) was added. The reaction mixture was refluxed for 15 min, cooled to room temperature and then ethyl iodide (10 mmol) was added. The solution was stirred for 1 hour at room temperature and allowed to stand overnight. The resulting product was isolated by neutralizing the reaction mixture with dil. HCl and recrystallized from the appropriate solvent.

Synthesis of 4,4′-(1,4-Phenylene)-di-(3-acetyl-5-ethoxycarbonyl-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine) (19)

A solution of **16a** (10 mmol) in acetic anhydride (15 ml) was heated under reflux for 3 hours. The solution was then poured into ice-water (150 ml) and stirred for several hours until crystallization was completed. The precipitated product was filtered, washed with water, dried and recrystallized from EtOH to give compound **19**, yield 74 %; m.p. 212–214°C (colorless crystals). IR: $\nu_{max} = 3215$ (NH), 1690, 1660 (CO) cm^{-1}. ^{1}H-NMR:

$\delta = 0.85$ (t, 6H, J = 7 Hz, 2 CH_3); 2.75 (s, 6H, 2 CH_3), 3.90 (q, 4H, J = 7 Hz, 2 CH_2), 6.50 (s, 2H, 2 H-4), 7.30–7.60 (m, 14 Ar-H), 11.70 (s, 2H, 2NH). Found: C, 63.50; H, 5.20; N, 8.10, S, 9.50 %. Calcd for $C_{36}H_{34}N_4O_6S_2$ (682.78): C, 63.32; H, 5.02; N, 8.21; S, 9.39 %.

Synthesis of 5,5′-(1,4-Phenylene)-di-(6-ethoxycarbonyl-7-phenyl-3-oxo-2,3-dihydro-5H-thiazolo-[3,2-a]-pyrimidine) (20)

To chloroacetic acid (20 mmol), melted in water bath, **16a** (10 mmol) was added portionwise. The homogeneous melt was heated at 60°C for 1 hour, and kept overnight. The solid thus obtained was washed with water until being neutral and recrystallized from ethanol to give **20** (yield 65 %), m.p. 142–144°C (straw yellow crystals). IR: $\nu_{max} = 1728$, 1692 (CO) cm^{-1}. ^{1}H-NMR: $\delta = 0.75$ (t, 6H, J = 7 Hz, 2 CH_3); 3.75 (q, 4H, J = 7 Hz, 2 CH_2), 4.20 (s, 4H, thiazole protons), 6.10 (s, 2H, 2 H-4), 7.30–7.80 (m, 14 Ar-H). Found: C, 63.80; H, 4.60; N, 8.40; S, 9.30 %. Calcd for $C_{36}H_{30}N_4O_6S_2$ (678.75): C, 63.70; H, 4.46; N, 8.25; S, 9.45 %.

General Procedure for the synthesis of compounds 22a,b

A solution of dibromoethane and/or dibromopropane (20 mmol) in DMF (10 ml) was added dropwise to **16a** (10 mmol), dissolved in a solution of 0.2 g of NaOH in H_2O (10 ml). The reaction mixture was refluxed for 3 hours. After cooling at room temperature, the solid product so formed was collected by filtration washed with water, dried and recrystallized from the appropriate solvent.

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