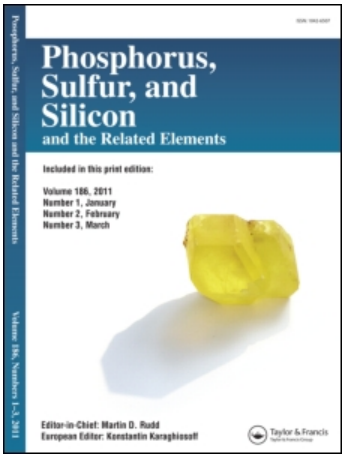

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HETEROCYCLIZATION OF AMINOTHIAZOLES

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HETEROCYCLIZATION OF AMINOTHIAZOLES

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Several new 2-arylidinoamino-4-(3-coumaryl)thiazole derivatives were synthesized via the reaction of 2-amino-4-(coumaryl)thiazole with aromatic aldehydes and other reagents. Structural elucidations were based on elementary analysis and spectral data studies.

Keywords: 2-Arylidino-amino-4-(3-coumaryl) thiazole; 4-coumaryl 2-aminothiazole; thiazoles

Thiazoles are one of the most intensively investigated classes of aromatic five-membered heterocycles. Thiazoles derivatives find now a wide varity of applications ranging from bacteriostatics, antibiotics, CNS regulants to high selling diuretics.[1–5]

All these facts were the deriving force to continue the previous studies on the 4-Coumaryl 2-aminothiazole.

RESULTS AND DISCUSSION

Aminothiozoles **1** was prepared and reacted with aromatic aldehydes in boiling n-butanol gave the corresponding 2-arylidino-amino-4-(3-coumaryl) thiazole **2a–e**. The reaction of **2a** with thioglycolic acid in dry benzene gave 3-(4-(3-coumaryl)-thiazol-2-yl)-2H-2-phenyl-thiazolidin-4-one **3**. On the other hand the reaction of **2a** with benzoyl isothiocyanate in ethanol produced the corresponding 1,3,5-oxadiazine derivative **4** Scheme 1.

Compound **1** reacted with CS_2 in ethanolic KOH at room temperature to give potassium dithiocarbazate **5** which reacted with hydrazine

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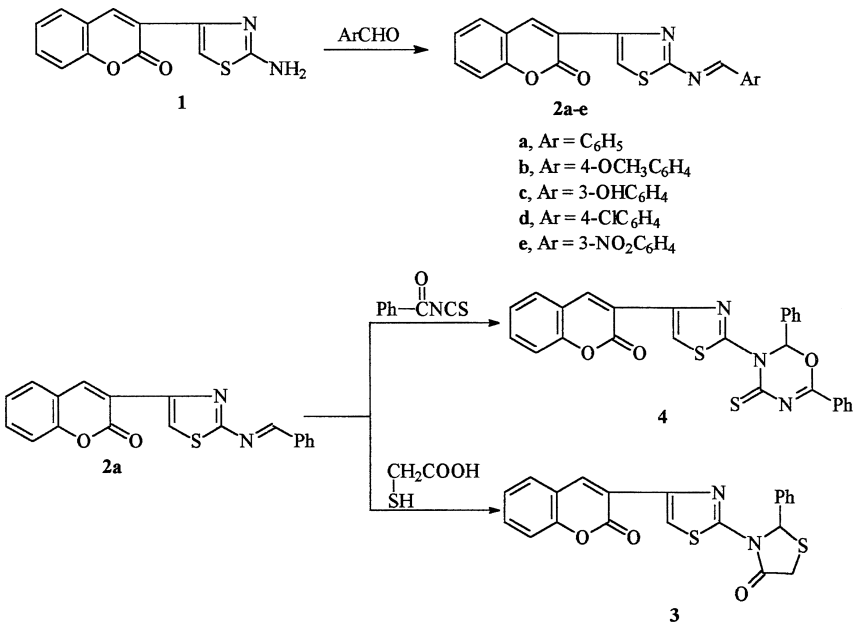
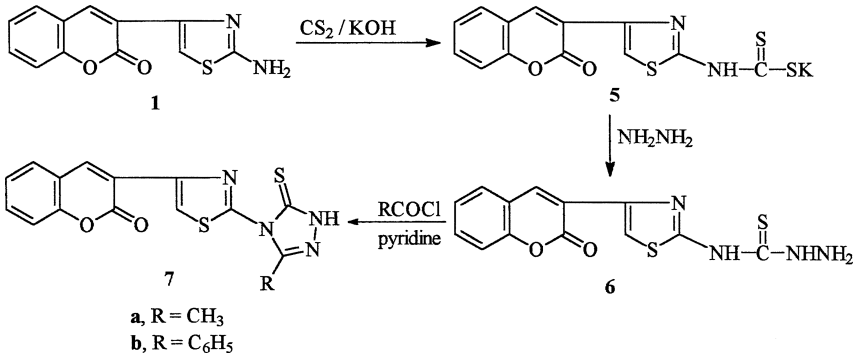


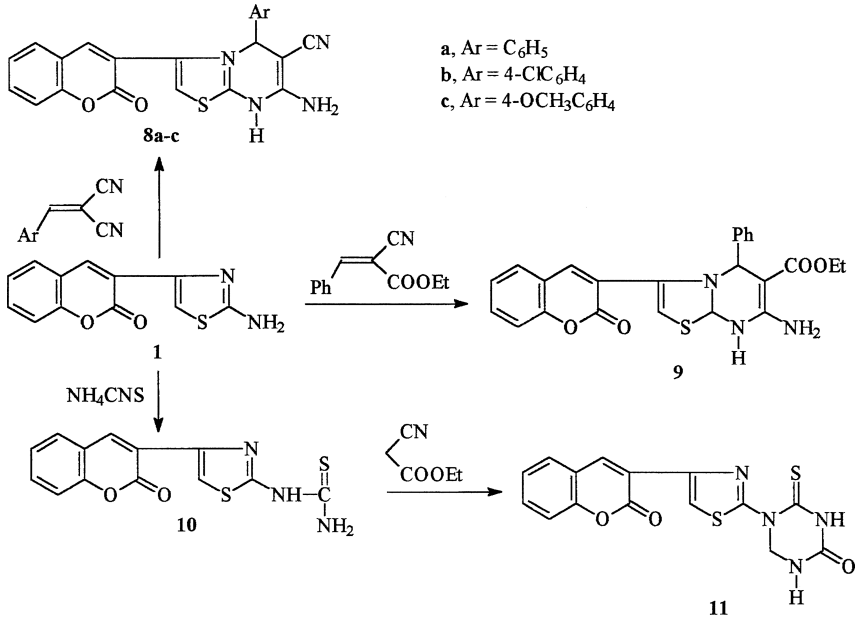
SCHEME 1

to give thiosemicarbazide derivative **6**. Reaction of thiosemicarbazide **6** with acid chloride in pyridine afforded thioxo thiazole derivative **7a**,**b** (Scheme 2). Heating mixture of 2-amino-4(3-coumaryl)-thiazole **1** and arylidinemolononitrite **6** in n-butanol gave the thiazolo [3,2-a] pyrimidine derivatives **8a–c**.



SCHEME 2

In the same way compound **1** reacted with ethyl benzylidine cyanoacetate in ethanol to give thiazolo [3,2-a] pyrimidine-6-carboxylate derivative **9**. The reaction of ammonium thiocyanate with **1** in DMF gave 1-[4(3-coumaryl)-thiazol-2-yl] thiourea **10**. Formation of **10** may proceed via the addition of the amino group to the electrophilic carbon of isothiocyonate to give thiourea derivative **10**. The reaction of compound **10** with ethylcyanoacetate[6] in n-butanol gave thioxo-pyrimidin-4-one derivative **11** (Scheme 3).



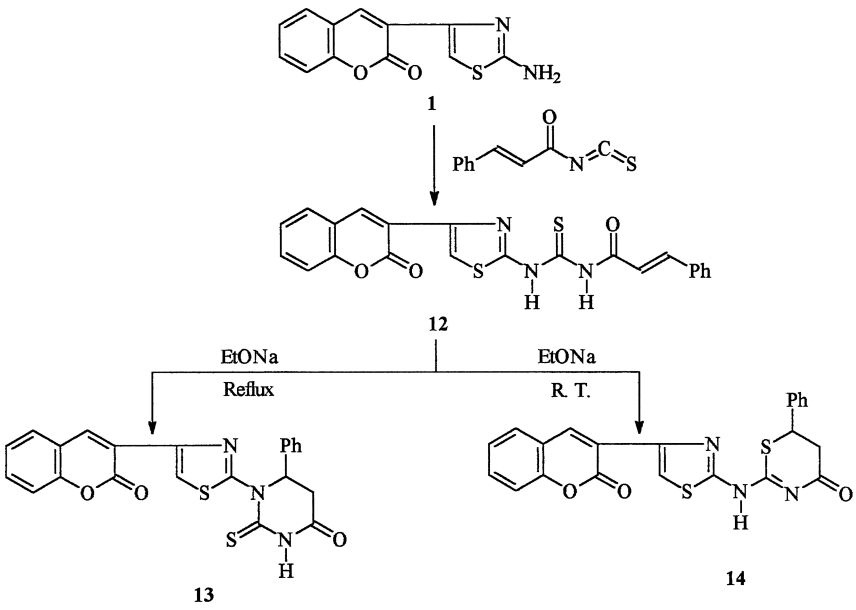
SCHEME 3

Addition of aminothiazole **1** to cinnamoyl isothiocyanate[7] afforded 1[4(3-coumaryl)-thiazol-2-yl]-3-cinnamoylthiourea **12**.

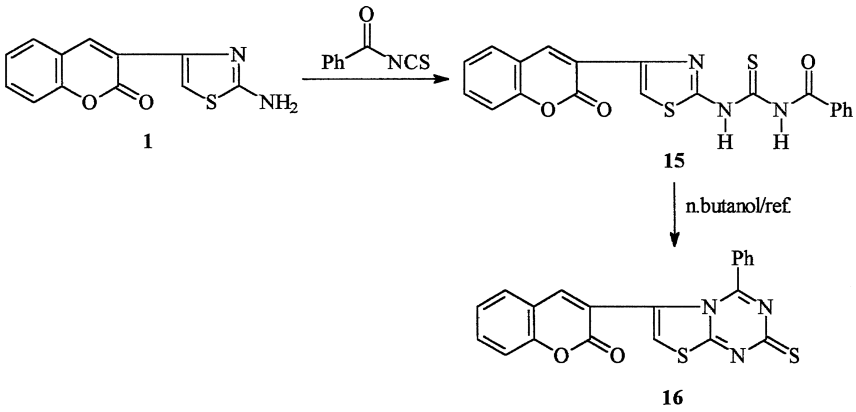
Depending on the reaction condition,[8] **12** cyclized to give either pyrimidine or thiazine moiety. Thus, refluxing of **12** and sodium ethoxide produced 1[4(3-coumaryl)-thiazol-2-yl]-6-phenylthiouracil **13**. While keeping of **12** in ethanolic sodium ethoxide solution afforded 1,3-thiazine derivative **14** (Scheme 4).

Also, thiourea derivative **15** was obtained by addition of aminothiazole **1** to benzoyl isothiocyanate[9] **4**. Cyclization of **15** in n-butanol provided S-triazine derivative **16** (Scheme 5).

Diazotized **1** coupled with β-naphthol[10] to yield 4(3-coumaryl)2-(2-hydroxy-1-naphthoylazo)-triazole **17** (Scheme 6).



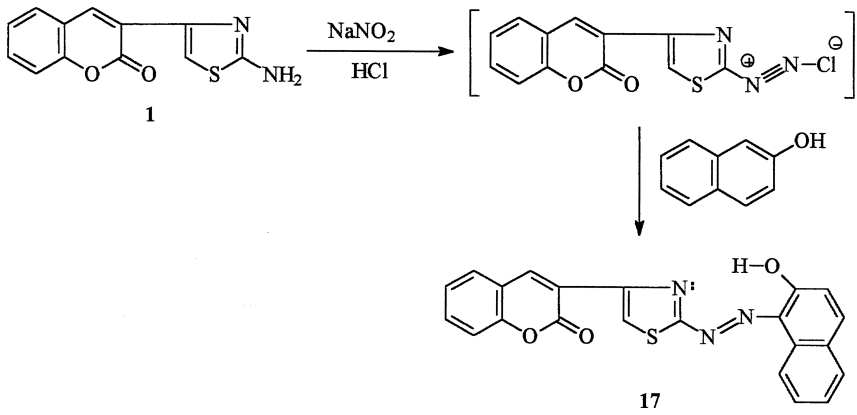
SCHEME 4



SCHEME 5

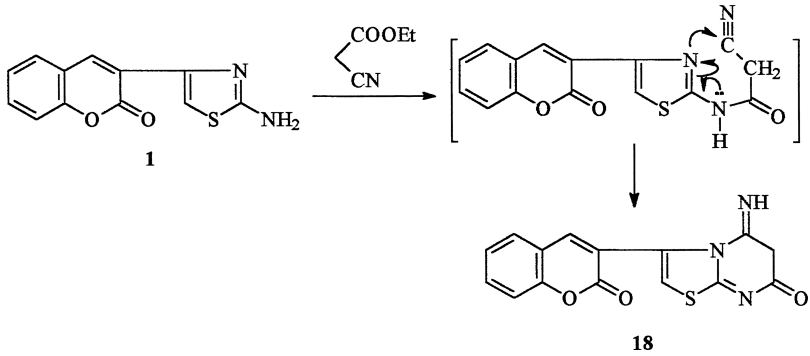
The reaction of 2-aminothiazole derivative **1** with ethyl cyanoacetate in dry methanol produced 3[4(3-coumaryl)]-5-imino-6H-7oxothiaxolo[3,2-a] pyrimidine **18** (Scheme 7).

The structure of newly synthesized heterocyclic derivatives were established on the basis of elementary analysis, IR and ^{1}H-NMR spectral data studies (cf. Tables I and II).



1 17

SCHEME 6



1 18

SCHEME 7

EXPERIMENTAL

Melting points are uncorrected; the infrared spectra were recorded for KBr discs using a Perkin-Elmer model 1430 ratio recording spectrometer. ^{1}H-NMR spectra (δ ppm) were obtained in (^{2}H) chloroform on a Varian Gemini 200 MHz Spectrometer Elemental analyses were carried out by the Microanalytical Center at Cairo University.

2-Arylidine amino-4(3-coumaryl) thiazole 2a–e

To a solution of 2-amino-4(3-coumaryl) thiazole **1** (0.01 mol) in n-butanol (30 ml), the appropriate aldehydes namely benzaldehyde, p-methoxy benzaldehyde, m-hydroxy benzaldehyde, p-chlorobenzaldehyde and/or m-nitro benzaldehyde (0.01 mol) was added and heated under reflux for

TABLE I Melting Points and Analytical Data of Products

No.	m.p. (°C)	Solvent	Yield %	Mol. formula (mol. Wt)	Analysis calcd/found C%	H%	N%	S%	Cl
2a	216	EtOH	50	$C_{19}H_{12}N_2O_2S$	68.65	3.63	8.43	9.65	
				(332.29)	68.61	3.52	8.39	9.60	
2b	132	EtOH	60	$C_{20}H_{14}N_2O_3S$	66.27	3.89	7.72	8.83	
				(362.43)	66.35	3.95	7.61	8.80	
2c	98	EtOH	60	$C_{19}H_{12}N_2O_3S$	65.47	3.46	8.04	9.18	
				(348.41)	65.53	3.51	8.20	9.00	
2d	141	EtOH	60	$C_{19}H_{11}N_2O_2SCl$	62.21	3.02	7.63	8.73	9.68
				(366.73)	62.41	3.22	7.54	8.70	9.60
2e	195	EtOH	60	$C_{19}H_{11}N_3O_4S$	60.46	2.39	11.13	8.48	
				(377.29)	60.61	3.16	11.09	8.40	
3	291	MeOH	55	$C_{21}H_{14}N_2O_3S_2$	62.05	3.46	6.89	15.74	
				(406.48)	61.91	3.61	6.98	15.70	
4	288	Xylene	40	$C_{27}H_{16}N_3O_3S_2$	65.57	3.25	8.49	7.73	
				(494.56)	65.64	3.10	8.60	7.70	
6	173	EtOH/H_2O	40	$C_{13}H_{10}N_4O_2S_2$	49.04	3.16	17.59	4.97	
				(318.37)	49.42	3.31	17.41	4.80	
7a	210	EtOH	40	$C_{15}H_{10}N_4O_2S_2$	52.60	2.94	16.36	18.69	
				(342.39)	52.77	3.10	16.08	18.60	
7b	187	EtOH	40	$C_{20}H_{12}N_4O_2S_2$	59.39	2.98	13.85	15.82	
				(404.46)	59.51	3.19	13.69	15.80	
8a	193	EtOH	50	$C_{21}H_{14}N_4O_2S$	65.27	3.64	14.49	8.28	
				(386.42)	65.03	3.82	14.61	8.20	
8b	238	EtOH	50	$C_{21}H_{13}N_4O_2SCl$	59.93	3.11	13.31	7.60	8.43
				(420.87)	60.08	3.28	13.42	7.53	8.40
8c	249	EtOH	50	$C_{22}H_{15}N_4O_3S$	63.60	3.63	13.48	7.70	
				(415.44)	63.95	3.41	13.72	7.70	
9	264	EtOH	40	$C_{23}H_{19}N_3O_4S$	63.72	4.41	9.69	7.38	
				(433.479)	63.98	4.55	9.44	7.20	
10	214	EtOH	50	$C_{13}H_9N_3O_2S_2$	51.47	2.98	13.85	21.10	
				(303.36)	51.63	3.21	13.60	21.00	
11	242	n-butanol	50	$C_{16}H_{10}N_4O_3S_2$	51.88	2.71	15.12	17.28	
				(370.408)	51.62	2.88	15.25	17.20	
12	331	EtOH	60	$C_{22}H_{15}N_3O_3S_2$	60.95	3.48	9.69	14.76	
				(433.50)	61.21	3.21	9.84	14.60	
13	331	EtOH	55	$C_{22}H_{15}N_3O_3S_2$	60.95	3.48	9.69	14.76	
				(433.50)	60.88	3.45	9.64	14.60	
14	328	EtOH	60	$C_{22}H_{15}N_3O_3S_2$	60.95	3.48	9.69	14.76	
				(433.50)	60.81	3.44	9.82	14.60	
15	318	EtOH	60	$C_{20}H_{13}N_3O_3S_2$	58.95	3.20	10.31	15.71	
				(407.469)	58.72	3.08	10.39	15.70	
16	290	n-butanol	60	$C_{20}H_{11}N_3O_2S_2$	61.68	2.84	10.78	22.11	
				(289.44)	61.81	2.89	10.86	22.00	
17	336	EtOH	60	$C_{22}H_{13}N_3O_3S$	66.15	3.27	10.52	8.01	
				(399.42)	66.29	3.39	10.31	8.00	
18	249	AcOH	60	$C_{15}H_9N_3O_3S$	57.87	2.91	13.49	10.28	
				(311.31)	57.97	2.68	13.60	10.20	

TABLE II Characteristic IR, and ^{1}HNMR Spectral Data of Products

No.	ν_{max}/cm^{-1}	δ_H ppm
3	1350 (C—S—S), 1550 (C═N) and 1690 (C═O)	1.25 (s, 2H, CH_2 for thiazolidine), 4.3 (s, 1H, CH for thiazolidine C2) and 7.26–8.19 (m, 11H, Arom. and thiazole)
4	1620 (C═N), 1350 (C═S) and 1300 (C—O—C)	4.3 (s, 1H, CH for oxadiazine) and 7.2–8.5 (m, 16H, 15-arom. and 1H thiazole)
7a	3200 (NH), 1690 (C═O), 1580 (C═N) and 1250 (C═S)	2.5 (s, 3H, CH_3), 7.2–8.1 (m, 6H, 5H-Arom., 1H-thiazole) and 8.9 (s, b, 1H, NH for thiazole ring)
8a	3400–3320 (NH_2) and 2240 (C≡N)	4.0 (s, b, NH_2), 4.7 (s, b, NH) and 7.3–7.9 (m, 11H, 10H-arom. and 1H thiazole)
9	3190 (NH), 2240 (C≡N) and 1710 (C═O)	4.1 (s, b, 1H, NH), 4.9 (s, b, 2H, NH_2) and 7.1–8.3 (m, 6H, 5H-arom. and 1H thiazole)
11	3280 (NH), 2250 (SH), 1690 (C═O) and 1340 (C═S)	4.1 (s, b, 1H, NH), 4.9 (s, b, 2H, NH_2) and 7.1–8.3 (m, 6H, 5H-arom. and 1H thiazole)
13	3300–3200 (NH), 2940 (CH_2), 1680 (C═O) and 1560 (C═N)	3.1 (m, 1H, pyridine H-5), 4.56 (m, 1H, CH), 7.1–7.9 (m, 11H, 10H-arom. and 1H thiazole) and 10.0 (s, b, 1H, NH cyclic)
14	3300–3200 (NH), 1690 (C═O) and 1550 (C═N)	3.12 (m, 2H, CH_2), 4.6 (m, 1H, CH), 7.1–7.9 (m, 11H, 10H-arom. and 1H thiazole) and 9.2 (s, b, 1H, NH)
15	3300–3200 (NH), 1910 (C═S), 1680 (C═O) and 1560 (C═N)	7.3–7.9 (m, 11H, 10H arom. and 1H thiazole) and 9.2–9.6 (s,b, 1H, NH)
16	1910 (C═S) and 1560 (C═N)	7.1–7.9 (m, 11H, 10H-arom. and 1H thiazole)
17	3400 (OH) and 1610 (C═N)	7.2–7.9 (m, 12H, 11H arom. and 1H thiazole)
18	3190 (NH), 1690 (C═O) and 1390 (C═N)	4.46 (s, 2H, CH_2), 7.2–7.9 (m, 6H, 5H-arom. and 1H thiazole) and 9.25 (s, b, 1H, NH)

5–7 hours . Then the solvent was removed under reduced pressure. The solid residue was digested with n-butanol and the products **2a–e** were isolated by suction. (cf. Table I).

3[4(3-Coumaryl)thiazol-2-yl]-2H-2phenyl-thiazolidin-4-one 3

Thioglycolic acid (0.01 mol) was added to a well stirred solution of (0.01 mol) of compound **2a** in 50 ml dry benzene, reflux for 5 hours, the excess solvent was evaporated under reduced pressure. On cooling a precipitate was formed, filtered and crystallized from the methanol to give **3**.

3[4(3-Coumaryl)thiazol-2-yl]-2H-2,6diphenyl-4-thioxo-1,3,5diazine 4

A mixture of **2a** (0.01 mol), benzoyl isothiocyante (0.01 mol) and triethyl amine (3 drops) in dioxane (20 ml) was refluxed for 2 hours. The

separated solid formed upon dilution with water (20 ml) was filtered, dried and recrystallized from xylene to give brown crystals of 4.

1[4(3-Coumaryl)thiazol-2-yl]thiosemicarbazide 6

Carbon disulphide (0.01 mol) was added dropwise to an ice cold solution of KOH (0.005 mol) in absolute ethanol (50 ml) containing the compound **1** (0.005 mol). The mixture was stirred at room temperature for 20 hours. The product obtained was employed in the next reaction without further purification.

To a suspension of above potassium salt, hydrazine hydrate (0.05 mol) and water (5 ml) were added and refluxed with stirring for about 1 hour until the evolution of hydrogen sulphide had ceased to evolved. Dilution with water (50 ml) and acidification with HCl allowed a precipitate to be separated, filtered, washed with cold water and recrystallized from ethanol-water, to give compound **6**.

1[4(3-Coumaryl)thiazol-2-yl]-3H-5-methyl(phenyl) 2-thioxo-triazole 7a,b

Benzoyl chloride and/or acetyl chloride (0.01 mol) was added dropwise to cold solution of thiosemicarbazide derivative **6** (0.01 mol) in dry pyridine (15 ml). The reaction mixture was heated under reflux for 5 hours, and then it poured into ice cold water. The formed precipitates were filtered off, washed with water several times and recrystallized from ethanol to give **7a** and **7b** respectively.

3[7-Amino-3(3-coumaryl)-6-cyano-5-phenyl-(4-chlorophenyl,4-methoxy-phenyl)5,8-dihydrothiazolo[3,2-a]pyrimidine 8a–c and ethyl-3[7-amino-3(3-coumaryl)-6-cyano-5-phenyl]5,8-dihydro-thiazolo[3,2-a]pyrimidin-6-carboxylate 9

To a solution of **1** (0.01 mol) in ethanol (30 ml), arylidine malononitrile namely (benzylidine, 4-chlorobenzylidine and 4-methoxy benzylidine malononitrile) and/or ethyl benzylidinecyanoacetate) (0.01 mol) and piperidine (2 ml) were added. The reaction mixture was refluxed for 8–10 hours (T.L.C. control). The mixture then cooled to room temperature, poured into crushed ice (25 gm.), and neutralized with hydrochloric acid. The precipitated compounds **8a–c** and **9** were isolated by suction.

1[4(3-Coumaryl)thiazol-2-yl]-thiourea 10

To a solution of **1** (0.01 mol) in acetic acid (20 ml), ammonium thiocyante (0.04 mol) was added and resultant solution was stirred at room temperature for 8 hours. Then poured into water (30 ml) and the precipitate solid was recrystallized from ethanol to give **10**.

1[4(3-Coumaryl)thiazol-2-yl]6-amino-3,4dihydro-2-thioxopyrimidin-4-one 11

A mixture of the thiourea derivative **10** (0.01 mol) and ethyl cyanoacetate (0.01 mol) in n-butanol (30 ml) was heated under reflux for 8 hours . After cooling the formed precipitate was filtered off, dried and recrystallized from n-butanol to give compound **11**.

1[4(3-Coumaryl)thiazol-2-yl]-3-cinnamoyl-thiourea 12 and 1[4(3-coumaryl)thiazol-2-yl]3-benzoyl-thiourea 15

A mixture of **1** (0.01 mol) and cinnamoyl isothiocyanate and/or benzoyl isothiocyanate (0.01 mol) in dioxane (30 ml) was refluxed for 4 hours the reaction mixture was poured in water and the solids formed were crystallized from ethanol to yield **12** and **15** respectively.

Cyclization of 1[4(3-coumaryl)thiazol-2-yl]-3-cinnamoyl-thiourea 12 with sodium ethoxide

a) On Hot

A mixture of **12** (0.01 mol) and sodium ethoxide (0.01 mol) were refluxed for 5 hours was crystallized from ethanol to give **13**.

b) On Cold

A mixture of **12** (0.01 mol) and sodium ethoxide (0.01 mol) were left at room temperature over night. Then acidified by ice-cold HCl (10 ml; 20%) and the resulting solid was crystallized from ethanol to give 2[2-amino-4(3-coumaryl)thiazol-2-yl] 5,6-dihydro-6-phenyl-4-oxo-1,3-thiazine **14**.

3[4(3-Coumaryl)]-5-phenyl-7-thioxo-thiazolo[3,2-a]-s-triazine 16

A solution of **15** (0.01 mol) in n-butanol (30 ml) was refluxed for 6 hours. After cooling, the precipitate formed was crystallized from n-butanol to give **16**.

4(3-Coumaryl)-2-(2-hydroxy-1-naphthylazo)thiazole 17

A solution of compound **1** (0.01 mol) in hydrochloric acid (3 ml, 50%) was cooled to 0°C and treated with sodium nitrite solution (0.3 g dissolved in the least amount of water). The solution was stirred for 30 minutes then added to a solution of 2-naphthol (0.7 g, 0.01 mol) in ethanol (20 ml) containing sodium acetate (2.5 g) the solid product **17** formed on standing was collected, washed several times with hot water, dried to give **17** crystallized from ethanol.

3[4(3-Coumaryl)]-5-imino-6,7-dihydro-7-oxo-thiazolo [3,2-a] pyrimidine 18

To a solution of sodium (0.01 mol) in dry methanol (30 ml), compound **1** (0.01 mol) and ethyl cyanoacetate (0.01 mol) were added and the resulting solution was refluxed for 5 hours. After cooling, it was diluted with water (100 ml), filtered and acidified with acetic acid. The resulting solid was washed with water, dried and crystallized from acetic acid to give **18**.

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