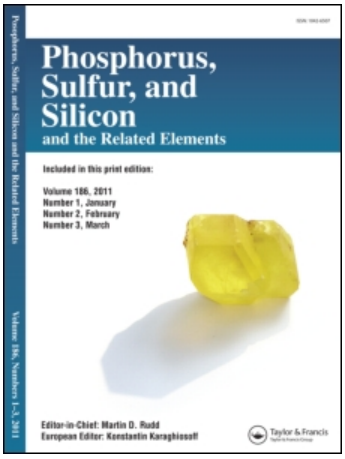

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SYNTHESIS AND REACTIONS OF 2-CHLOROMETHYL-13-(2-FURYL)-3,4,11,12-TETRAHYDRO-4-OXOPYRIMIDO[4',5':4,5]THIENO[2,3-b]-BENZO[h]QUINOLINE

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SYNTHESIS AND REACTIONS OF 2-CHLOROMETHYL-13-(2-FURYL)-3,4,11,12-TETRAHYDRO-4-OXOPYRIMIDO[4′,5′:4,5]THIENO[2,3-b]-BENZO[h]QUINOLINE

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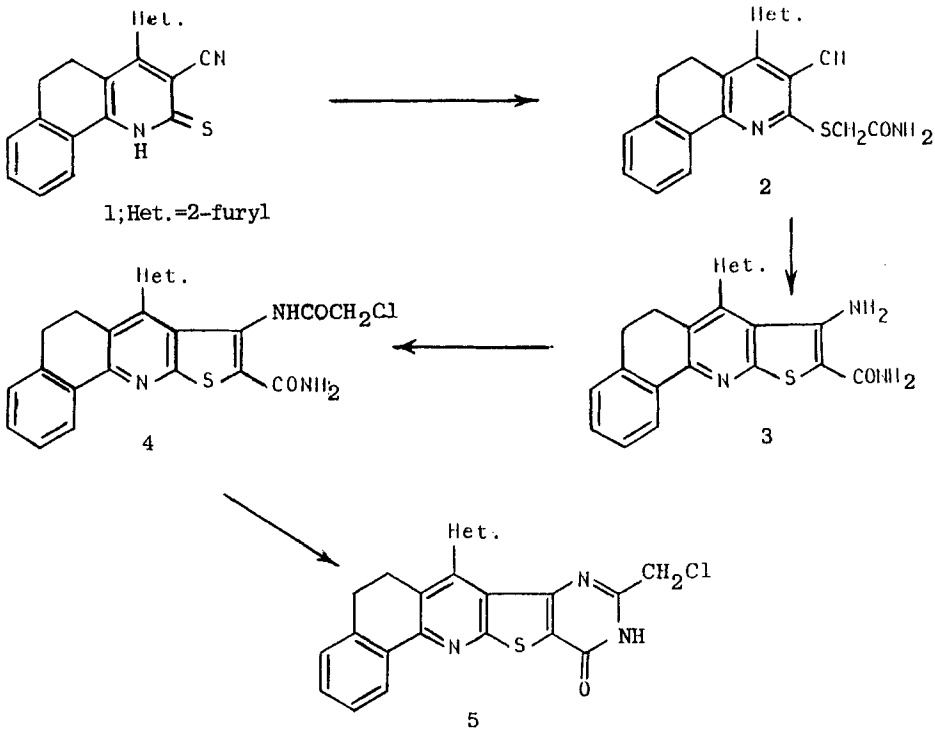
3-Amino-2-carbamoyl-5,6-dihydro-4-(2-furyl)-thieno[2,3-b]-benzo[h]quinoline (**3**) was synthesized and allowed to react with chloroacetyl chloride to give N-chloroacetyl derivative **4**. Cyclization of **4** into the title compound **5** was achieved in boiling acetic anhydride. Reactions of **5** with thiophenol, morpholine and/or thiourea afforded pyrimidinones **6**, **7** and **8** respectively. Chlorination of **5** and **6** with phosphorus oxychloride gave the promising di- and monochloro derivatives (**9** and **10**) which were subjected for further reactions to produce other new pryrimido[4′,5′:4,5]thieno[2,3-b]-benzo[h]quinolines **11–18**.

Key words: Benzo[h]quinolines, thieno[2,3-b]-benzo[h]quinolines, pyrimido[4′,5′:4,5]thieno[2,3-b]-benzo[h]quinolines.

Pyrimidine derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity.[1–6] In particular, it has been reported that 2-substituted pyrimidines are more potent than the corresponding 4-analogues.[7] These facts prompted us to take up this project for synthesizing novel 2-substituted pyrimidothienobenzoquinoline derivatives (**5–18**) which might exhibit enhanced potency owing to their incorporation of various pharmacophores.

2-Chloromethyl-13-(2-furyl)-3,4,11,12-tetrahydro-4-oxopyrimido[4′,5′:4,5]thieno-[2,3-b]-benzo[h]quinoline (**5**) was thought to be a suitable precursor for the desired compounds. This compound **5** was prepared as effected in Scheme I. Thus, interaction of thioxo-derivative **1** with chloroacetamide in the presence of sodium acetate afforded (3-cyano-5,6-dihydro-4-(2-furyl)-benzo[h]quinolin-2-ylthio)acetamide **2** which was readly cyclized into thieno[2,3-b]-benzo[h]quinoline **3** upon treatment with sodium ethoxide. Chloroacetylation of **3** followed by ring closure in boiling acetic anhydride furnished 2-chloromethylpyrimidinone **5**.

Reaction of compound **4** with thiophenol in an ethanolic sodium hydroxide solution gave 13-(2-furyl)-2-phenylthiomethyl-3,4,11,12-tetrahydro-4-oxopyrimido[4′,5′:4,5]thieno[2,3,b]-benzo[h]quinoline (**6**) in excellent yield. Also, refluxing of **4** with slightly excess amount of morpholine resulted in the formation of pyrimidinone **7**. The latter compounds (**6** and **7**) were also obtained upon reaction of



SCHEME I

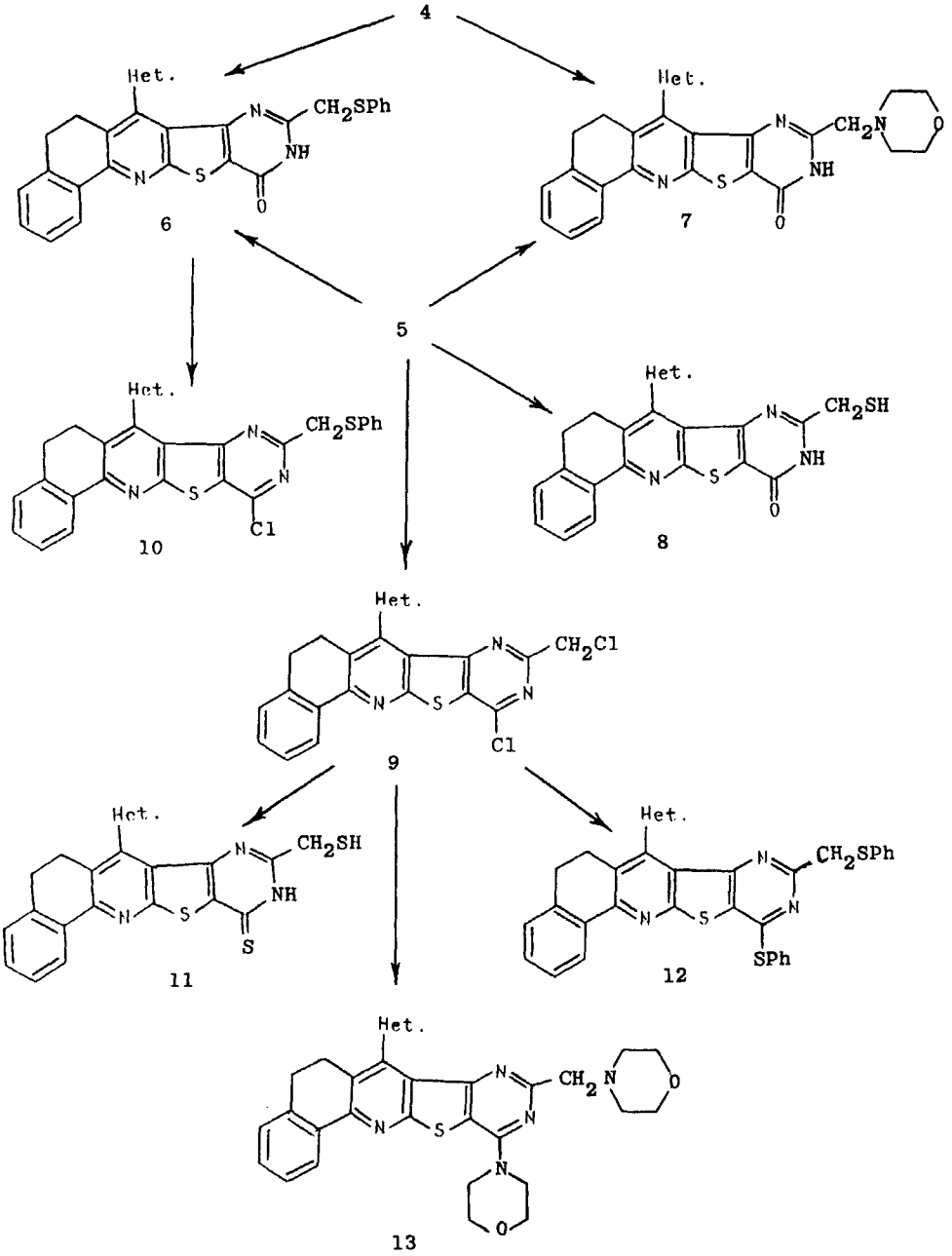
5 with sodium thiophenolate or morpholine respectively. Moreover, treatment of **5** with thiourea afforded 13-(2-furyl)-2-mercaptomethyl-3,4,11,12-tetrahydro-4-oxopyrimido[4′,5′:4,5]thieno[2,3-b]-benzo[h]quinoline (**8**) in good yield (Scheme II).

The present investigation was extended to the synthesis of 1,4-disubstituted pyrimido[4′,5′:4,5]thieno[2,3-b]-benzo[h]quinolines started from chloropyrimidines **9** and **10** which were prepared by heating of **5** and/or **6** in excess amounts of phosphorus oxychloride at reflux temperature (Scheme II).

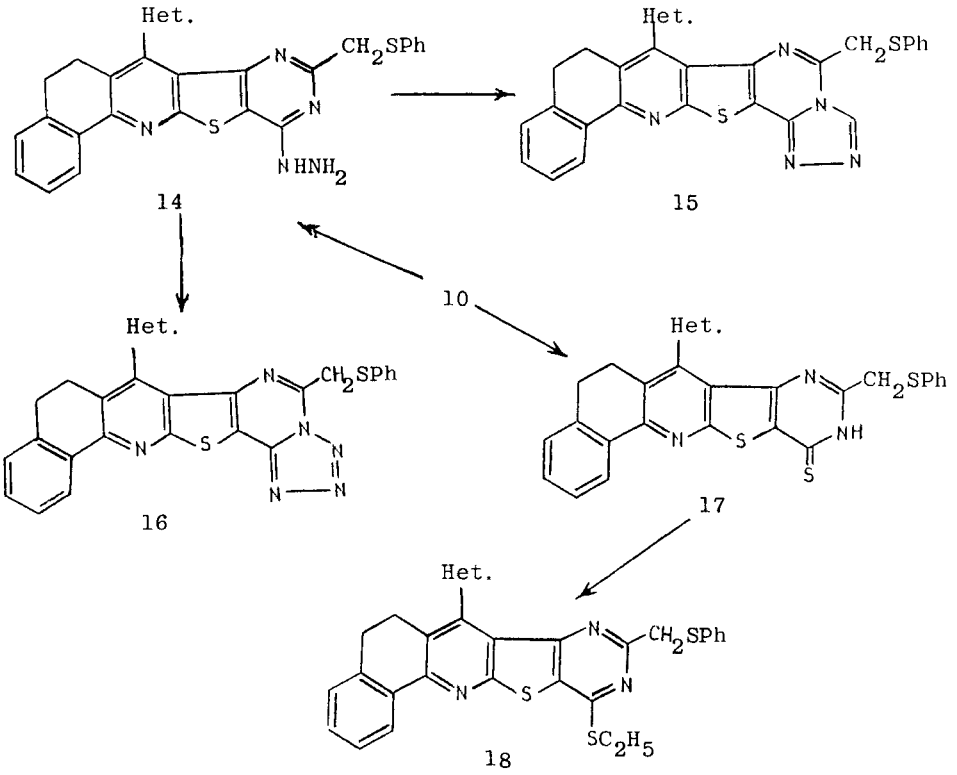
Preferential replacement of a chlorine in **9** was not possible due to the equally mobile nature of both the chlorine atoms.[8] All such reactions led to the formation of disubstituted products. Thus, it gave 13-(2-furyl)-2-mercaptomethyl-3,4,11,12-tetrahydro-4-thioxopyrimido[4′,5′:4,5]thieno[2,3-b]-benzo[h]quinoline (**11**) with thiourea, dithioether **12** with thiophenol and dimorpholino compound **13** with morpholine (Scheme II).

Similarly, reaction of compound **10** with hydrazine hydrate afforded 4-hydrazinopyrimidine **14** which, in turn, was fused with triethyl orthoformate to give *s*-triazolo compound **15** and diazotised to produce the tetrazolo derivative **16**. On treatment of **10** with thiourea, 4-thioxopyrimidine **17** was obtained. Ethylation of **17** with ethyl iodide yielded 11,12-dihydro-4-ethylthio-13-(2-furyl)-2-phenyl-thiomethylpyrimido[4′5′:4,5]thieno[2,3-b]-benzo[h]quinoline (**18**) in high yield (Scheme III).

The structures of all compounds prepared were elucidated and confirmed on the basis of their elemental analyses (Table I) and spectroscopic data (Table II).



SCHEME II



SCHEME III

EXPERIMENTAL

All melting points were determined on a Fisher John melting point apparatus and are uncorrected. IR Spectra were measured on a Pye-Unicam SP 3-100 spectrophotometer using KBr disc technique (wave numbers in cm^{-1}). ^{1}H-NMR Spectra were recorded on a Varian EM 360L 60 MHz spectrometer using TMS as internal standard; chemical shifts were given in ppm (δ-Scale) and mass spectrum of compound **3** on a MAT-312 spectrometer. The elemental analyses were carried out on a Perkin Elmer 240C elemental analyzer.

3-Cyano-5,6-dihydro-4-(2-furyl)-benzo[h]quinoline-2(1H)-thione (**1**): It was prepared according to the reported method.[9]

(3-Cyano-5,6-dihydro-4-(2-furyl)-benzo[h]quinoline-2-ylthio) acetamide (**2**): A mixture of 1 (15.2 g, 0.05 mol), chloroacetamide (4.7 g, 0.05 mol) and anhydrous sodium acetate (4.1 g, 0.05 mol) in ethanol (200 ml) was refluxed for 3 hr and left to cool. The precipitated solid was collected and recrystallized from ethanol as white needles of **2**.

3-Amino-2-carbamoyl-5,6-dihydro-4-(2-furyl)-thieno[2,3-b]-benzo[h]quinoline (**3**): A suspension of compound **2** (14.4 g, 0.04 mol) in ethanol (200 ml) containing dissolved sodium (250 mg) was refluxed for 20 mins. The precipitate separated on cooling was filtered off and recrystallized from dioxane as yellow crystals of **3**.

2-Carbamoyl-3-chloroacetylamino-5,6-dihydro-4-(2-furyl)thieno[2,3-b]-benzo[h]quinoline (**4**): Compound **3** (7.22 g, 0.02 mol) in chloroacetyl chloride (35 ml) was heated under reflux for 15 mins. The reaction mixture was cooled and poured into ice-water (150 ml). The precipitate was filtered off and crystallized from ethanol to give **4** in white needles.

TABLE I

Melting points, yields, and analytical data of the prepared compounds

Compound	M.P.(°C) Yield (%)	Formula (M.W)	Calculated/Found %C	%H	%N	%S	%Cl
2	224	$C_{20}H_{15}N_3O_2S$	66.47	4.18	11.63	8.87	-
	89	(361.4)	66.49	4.35	11.71	8.60	-
3	233	$C_{20}H_{15}N_3O_2S$	66.47	4.18	11.63	8.87	-
	85	(361.4)	66.67	4.12	11.96	8.97	-
4	246	$C_{22}H_{16}ClN_3O_3S$	60.34	3.68	9.60	7.32	8.10
	93	(437.9)	60.54	3.67	9.79	7.13	8.00
5	> 300	$C_{22}H_{14}ClN_3O_2S$	62.93	3.36	10.01	7.64	8.44
	65	(419.9)	63.17	3.35	10.17	7.82	8.75
6	286 (87)*	$C_{28}H_{19}N_3O_2S_2$	68.13	3.88	8.51	12.99	-
		(493.6)	68.06	3.74	8.19	12.87	-
7	300	$C_{26}H_{22}N_4O_3S$	66.37	4.71	11.91	6.81	-
	(81)*	(470.5)	66.42	4.81	12.01	6.50	-
8	> 300	$C_{22}H_{15}N_3O_2S_2$	63.29	3.62	10.06	15.36	-
	90	(417.5)	63.08	3.77	10.19	15.42	-
9	181	$C_{22}H_{13}Cl_2N_3OS$	60.28	2.99	9.59	7.31	16.18
	66	(438.3)	60.21	2.99	9.17	7.48	16.32
10	158	$C_{28}H_{18}ClN_3OS_2$	65.68	3.54	8.21	12.52	6.92
	71	(512.0)	65.73	3.54	8.00	12.71	6.66
11	273(dec.)	$C_{22}H_{15}N_3OS_3$	60.95	3.49	9.69	22.18	-
	75	(433.6)	61.11	3.43	9.50	22.37	-
12	145	$C_{34}H_{23}N_3OS_3$	69.72	3.96	7.17	16.42	-
	88	(585.8)	69.67	3.95	7.43	16.26	-
13	196	$C_{30}H_{29}N_5O_3S$	66.77	5.42	12.98	5.94	-
	83	(539.6)	66.90	5.35	12.72	6.14	-
14	226	$C_{28}H_{21}N_5OS_2$	66.25	4.17	13.80	12.63	-
	90	(507.6)	66.11	4.18	13.95	12.79	-
15	241	$C_{29}H_{19}N_5OS_2$	67.29	3.70	13.53	12.39	-
	87	(517.6)	67.37	3.90	13.50	12.42	-
16	191	$C_{28}H_{18}N_6OS_2$	64.84	3.50	16.20	12.36	-
	75	(518.6)	64.79	3.62	16.42	12.68	-
17	249	$C_{28}H_{19}N_3OS_3$	65.99	3.76	8.24	18.87	-
	78	(509.7)	65.88	3.70	8.15	18.72	-
18	144	$C_{30}H_{23}N_3OS_3$	67.01	4.31	7.81	17.89	-
	89	(537.7)	67.32	4.17	7.93	17.95	-

* Yield of method A.

TABLE II

IR and ^{1}H-NMR spectral data of the prepared compounds

Compound No.	Spectral data*
2	IR: 3380, 3180(NH_2); 2210(C≡N); 1630(C=O). ^{1}H-NMR: 8.40, 7.20, 6.90(3m,3H,3CH furyl); 7.40-8.10(m,4H, arom.); 4.3 (s,2H,NH_2); 3.9(s,2H,SCH_2); 3.05(s,4H,CH_2-CH_2).
3	IR: 3480, 3310(NH_2); 3410, 3160(NH_2); 1650(C=O). MS: 362 (100%, M^+); 344(42%, M-H_2O); 343(40%, M-H_2O-H).
4	IR: 3380, 3180(NH_2); 3290(NH); 1650(C=O).
5	IR: 3200-2400(NH); 1650(C=O). ^{1}H-NMR:8.4(m,1H,CH furyl); 7.3-7.9(m,4H, arom.); 6.8(s,2H,2CH furyl); 4.4(s,2H,CH_2); 3.0(s,4H,CH_2-CH_2).
6	IR: 3180-2480(NH); 1660(C=O).
7	IR: 3240-2600(NH); 1650(C=O). ^{1}H-NMR: 8.4(m,1H,CH furyl); 7.2-7.7(m,4H, arom.); 6.6(s,2H,2CH furyl); 3.5-3.8(m,6H, CH_2N + CH_2-O-CH_2), 3.0(s,4H, CH_2-CH_2); 2.6(t,4H, CH_2-N-CH_2).
8	IR: 3600-2400(NH, SH); 1650(C=O).
9	IR: 1600(C=N). ^{1}H-NMR: 8.4(m,1H,CH furyl); 7.3-7.9(m,4H, arom.); 6.8(s,2H,2CH furyl); 4.4(s,2H,CH_2); 3.0(s,4H, CH_2-CH_2).
10	IR: 1590(C=N). ^{1}H-NMR: 8.5(m,1H,CH furyl); 7.0-7.7(m,9H, arom.); 6.6(s,2H,2CH furyl); 4.2(s,2H,CH_2S); 2.9(s,4H, CH_2-CH_2).
11	IR: 3600-2400(NH,SH).
12	IR: 1600(C=N).
13	IR: 1600(C=N). ^{1}H-NMR: 8.5(m,1H,CH furyl); 7.2-7.8(m,4H, arom.); 6.6(s,2H,2CH furyl); 3.6-4.1(m,14H: 6CH_2 morpholinyl and CH_2N); 3.0(s,4H,CH_2-CH_2); 2.5-2.8(t,4H,CH_2-N-CH_2).

TABLE II (*Continued*)

Compound No.	Spectral data*
14	IR: 3380, 3220(NH_2); 3200-2600(NH); 1630(C=N).
15	IR: 1610(C=N). ^{1}H-NMR: 9.0(s,1H,CH triazolyl); 8.5(m,1H, CH furyl); 7.0-7.7(m,9H, arom.); 6.6(s,2H,2CH furyl); 4.2(s,2H,CH_2S); 2.9(s,4H,CH_2-CH_2).
16	IR: 1610(C=N).
17	IR: 3200-2600(NH).
18	IR: 1600(C=N). ^{1}H-NMR: 8.5(m,1H,CH furyl); 7.0-7.7(m,9H, arom.); 6.6(s,2H,2CH furyl); 4.2(s,2H,CH_2S); 3.6(q,2H, SCH_2); 3.0(s,4H,CH_2-CH_2); 1.6(t,3H,CH_3).

*All ^{1}H-NMR of the compounds were recorded in $CDCl_3$ as a solvent except for compound 15 in CF_3CO_2D.

2-Chloromethyl-13-(2-furyl)-3,4,11,12-tetrahydro-4-oxopyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]quinoline (**5**): Compound **4** (4.38 g, 0.01 mol) in redistilled acetic anhydride (100 ml) was heated under reflux for 5 hr. The solid thus separated after cooling was collected and recrystallized from chloroform-ethanol mixture as white crystals of **5**.

13-(2-Furyl)-2-phenylthiomethyl-3,4,11,12-tetrahydro-4-oxopyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]quinoline (**6**): (A) A mixture of **4** (2.19 g, 0.005 mol) and thiophenol (0.55 g, 0.005 mol) in ethanolic sodium hydroxide solution (5%, 40 ml) was heated under reflux for 30 mins. On cooling and acidification of the reaction mixture, a white precipitate was obtained. It was crystallized from chloroform-ethanol mixture as white needles of **6**.

(B) A mixture of **5** (2.1 g, 0.005 mol) and sodium thiophenolate (0.66 g, 0.005 mol) in N,N-dimethylformamide (15 mol) was refluxed for 30 mins. The reaction mixture was diluted with water (30 ml) to give a white solid of **6** (2 g, 81%) which upon crystallization was identical to that described above in all aspects.

13-(2-Furyl)-2-(N-morpholinomethyl)-3,4,11,12-tetrahydro-4-oxopyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]-quinoline (**7**): (A) A mixture of **4** (2.19 g, 0.01 mol) and morpholine (1 ml, 0.012 mol) in ethanol (100 ml) was heated under reflux for 5 hr and left to cool. The precipitated product was collected and recrystallized from dioxane to get **7** in white plates.

(B) A mixture of **5** (2.1 g, 0.01 mol) and morpholine (2 ml, 0.023 mol) was refluxed for one hour. The reaction mixture on dilution with ethanol (30 ml) and cooling gave **7** as white solid (2.15 g, 92%) which recrystallized from dioxane in white plates; identical with the sample obtained above.

13-(2-Furyl)-2-mercaptomethyl-3,4,11,12-tetrahydro-4-oxopyrimido[4'5':4,5]thieno[2,3-b]-benzo[h]quinoline (**8**): A mixture of **5** (0.84 g, 0.002 mol) and thiourea (0.23 g, 0.003 mol) in N,N-dimethylformamide (10 ml) was heated under reflux for one hour. The solid that separated was collected, dissolved in aq. alkali, reprecipitated by acidification and crystallized from N,N-dimethylformamide as pale yellow crystals of **8**.

4-Chloro-2-chloromethyl-11,12-dihydro-13-(2-furyl)-pyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]quinoline (**9**): Compound **5** (2.1 g, 0.005 mol) in phosphorus oxychloride (60 ml) was heated under reflux for

2 hr and allowed to cool. The reaction mixture was poured into ice-cold water (200 ml), whereby a white solid was precipitated. It was filtered off and crystallized from ethanol as white crystals of **9**.

4-Chloro-11,12-dihydro-13-(2-furyl)-2-phenylthiomethyl-pyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]quinoline (**10**): This compound was synthesized in analogy to the method above by chlorination of **6** with phosphorus oxychloride. It was crystallized from chloroform-ethanol in the form of white plates.

13-(2-Furyl)-2-mercaptomethyl-3,4,11,12-tetrahydro-4-thioxopyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]quinoline (**11**): A mixture of **9** (0.44 g, 0.001 mol) and thiourea (0.15 g, 0.002 mol) in ethanol (10 ml) was heated under reflux for 2 hr and allowed to cool. The pale yellow solid that separated was collected, dissolved in aq. sodium hydroxide solution, reprecipitated by acidification and crystallized from dioxane in pale yellow needles of **11**.

11,12-Dihydro-13-(2-furyl)-4-phenylthio-2-phenylthiomethyl-pyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]quinoline (**12**): A mixture of **9** (0.44 g, 0.001 mol) and thiophenol (0.22 g, 0.002 mol) in ethanolic sodium hydroxide solution (25 ml, 5%) was refluxed for 3 hr, cooled and diluted with water. The precipitated solid was filtered off and crystallized from ethanol as pale brown needles of **12**.

11,12-Dihydro-13-(2-furyl)-4-(N-morpholino)-2-(N-morpholinomethyl)-pyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]quinoline (**13**): Compound **9** (0.44 g, 0.001 mol) in morpholine (2 ml) was heated on a water bath for 2 hr and diluted with ethanol whereby a crystalline product was precipitated. It was collected and recrystallized from ethanol in pale brown needles of **13**.

11,12-Dihydro-13-(2-furyl)-4-hydrazino-2-phenylthiomethyl-pyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]quinoline (**14**): A mixture of **10** (2.05 g, 0.004 mol) and hydrazine hydrate 99% (2 ml, 0.04 mol) in ethanol (20 ml) was heated under reflux for 4 hr. The separated product was collected and recrystallized from dioxane as white crystals of **14**.

8,9-Dihydro-7-(2-furyl)-5-methyl-s-triazolo[4",3":1',6']pyrimido[4',5':4,5]thieno[2,3,-b]-benzo[h]quinoline (**15**): A suspension of **14** (0.51 g, 0.01 mol) in triethylorthoformate (10 ml) was heated under reflux for 2 hr. The solid that precipitated while hot was collected and recrystallized from N,N-dimethylformamide as white crystals of **15**.

8,9-Dihydro-7-(2-furyl)-5-methyltetrazolo[4",3":1',6']pyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]quinoline (**16**): To a cold solution of **14** (0.51 g, 0.001 mol) in concentrated hydrochloric acid (10 ml), sodium nitrite solution (10 ml, 10%) was added dropwise with stirring. The solid thus precipitated was collected and recrystallized from chloroform-ethanol mixture.

13-(2-Furyl)-2-phenylthiomethyl-3,4,11,12-tetrahydro-4-thioxopyrimido[4',5':4,5]thieno[2,3-b]-benzo-[h]quinoline (**17**): This compound was prepared following a procedure similar to that of compound **11** by reaction of chlorocompound **10** (1.2 g, 0.002 mol) with thiourea (0.15 g, 0.002 mol). It was crystallized from dioxane as yellow needles.

11,12-Dihydro-4-ethylthio-13-(2-furyl)-2-phenylthiomethyl-pyrimido[4',5':4,5]thieno[2,3-b]-benzo[h]-quinoline (**18**): This compound was prepared following a procedure similar to that of compound **2** by reaction of thioxopyrimidine **17** with ethyl iodide in the presence of sodium acetate. It was recrystallized form dioxane in white needles.

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