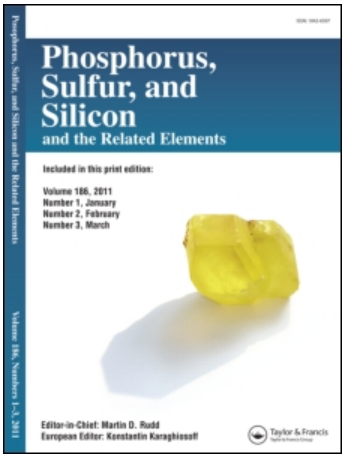

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BENZOQUINOLINES II. SYNTHESIS OF SOME NEW BENZO[h] PYRIMIDO [4′,5′:4,5]THIENO[2,3-b]QUINOLINE DERIVATIVES AND RELATED FUSED HEXACYCLIC SYSTEMS*

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Reaction of 8-amino-7-(2 furyl)-5,6-dihydrobenzo[h]thieno[2,3-b]quinoline-9-carbonitrile (**3a**) with phenyl isothiocyanate, triethyl orthoformate, ethylenediamine and/or sodium azide afforded benzo[h]thieno[2,3-b]quinolines **4, 7, 20** and **25** respectively. Cyclization of thiourea derivative **4** furnished thioxopyrimidine derivative **5**. The dithioxopyrimidine **6** was prepared by reaction of **3a** with carbon disulfide. On treatment of **7** with hydrazine hydrate, 10-amino-7-(2-furyl)-11-imino-5,6,10,11-tetrahydrobenzo[h]pyrimido[4′,5′:4,5]thieno [2,3-b]quinoline (**8**) was obtained. Compounds **8, 20** and **25** were used as key intermediates in the synthesis of the fused hexacyclic compounds **9–19, 21–24** and **26–28** respectively. 8-Amino-7-(2-furyl)-5,6-dihydrobenzo[h]thieno[2,3-b]quinoline-9-carboxamide (**3b**) was reacted with some reagents, namely triethyl orthoformate, benzaldehyde, carbon disulfide, phenyl isothiocyanate, and/or acetic anhydride to give the corresponding benzo[h]pyrimido [4′,5′: 4,5]thieno[2,3-b]quinolines **29, 30, 31, 32** and **34**. Compound **29** underwent some sequence reactions to give **37–42**. Some of the prepared compounds were tested *in vitro* for their antibacterial and antifungal activities.

Keywords: Benzo[h]thieno[2,3-b]quinoline; ; benzo[h]pyrimido[4′,5′:4,5] thieno[2,3-b]quinoline; benzo[h][1,2,4]triazolo[2″,3″:1′,6′]pyrimido[4′,5′:4,5] thieno[2,3-b]quinoline; benzo [h]imidazolo[1″,2″:1′,6′]pyrimido[4′,5′:4,5] thieno[2,3-b]quinoline; benzo[h] tetrazolo[1″,5″:1′,6′]pyrimido[4′,5′: 4,5]thieno[2,3-b]quinolin; benzo[h][1,2,4]triazolo [4″,3″: 1′,6′]pyrimido [4′,5′: 4,5]thieno[2,3-b]quinoline

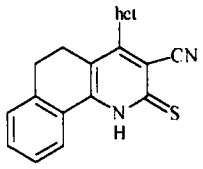
The chemistry of benzo[h]quinoline and pyridothienopyrimidine derivatives has been of increasing interest, since many of these compounds have found useful applications as antimalarial[1], anticancer[2], antibacterial[3,4], as metabolite agents[5] and for their pharmacological properties. Synthesis of

* Part I: Reference No. 19.

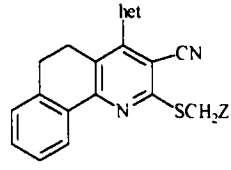
† Correspondence Author.

substituted derivatives of the pyridothienopyrimidine system, which feature a variety of pharmacological activities have been reported in a number of papers. Such derivatives have analgesic[6], antipyretic[7,8], antianaphylactic[9,10] and antiinflammatory[11–14] effects. Moreover, some of these compounds are clinically effective antialergic[15] or potential antineoplastic[16] agents and a few of them have a significant hypocholesterolenic activity[17,18]. Encouraged by all these facts and as a continuation of our earlier work on benzo[h] quinoline[19–21], we undertook the synthesis of the title compounds which might exhibit enhanced activities owing to the presence of both benzoquinoline and pyridothienopyrimidine moieties in addition to other pharmacophores in their structures. The antibacterial and antifungal testings of some synthesized compounds are hereby included.

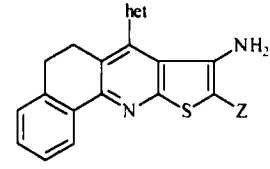
8-Amino-7-(2-furyl)-5,6-dihydrobenzo[h]thieno[2,3-b]quinoline-9-carbonitrile (**3a**) and its 9-carboxamide analogue (**3b**) seem to be suitable precursors for the target compounds. Thus, the reaction of benzoquinolinethione **1** with chloroacetonitrile or chloroacetamide in the presence of sodium acetate afforded the corresponding S-alkylated products **2a** or **2b**. The latter compounds (**2a** and **2b**) were readily cyclized into the required **3a** and **3b** upon treatment with sodium ethoxide in boiling ethanol.



1. het= 2-furyl

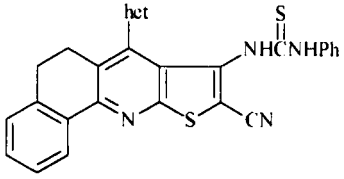


2a. Z= CN
2b. Z= $CONH_2$



3a. Z= CN
3b. Z= $CONH_2$

Reaction of compound **3a** with phenyl isothiocyanate in heated pyridine gave the thiourea derivative **4** which underwent smooth ring closure on treatment with sodium methoxide in boiling methanol to furnish 7-(2-furyl)-11-imino-10-phenyl-9-thioxo-5,6,8,9,10,11-hexahydrobenzo [h]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline(**5**). In contrast, the 9,11-dithioxo-7-(2-furyl)-5,6,8,9,10,11-hexahydrobenzo[h]pyrimido[4′,5′:4,5] thieno[2,3-b]quinoline (**6**) was prepared *via* interaction of **3a** with carbon disulfide.



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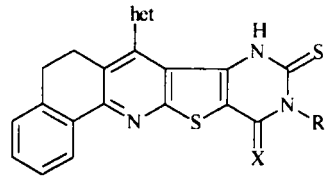
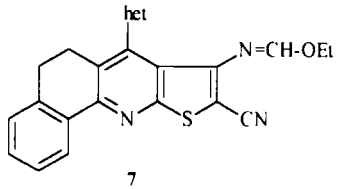


5. X= NH. R= Ph
6. X= S. R= H

Condensation of **3a** with triethyl orthoformate by refluxing in acetic anhydride led to the formation of methanimidate derivative **7** in nearly quantitative yield. On treatment of **7** with hydrazine hydrate in dioxane at room temperature, the desired compound, 10-amino-7-(2-furyl)-11-imino-5,6,10,11-tetrahydrobenzo[h]pyrimido[4′,5′:4,5]thieno[2,3-b] quinoline (**8**) was obtained.



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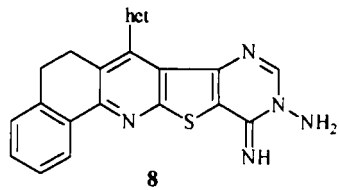
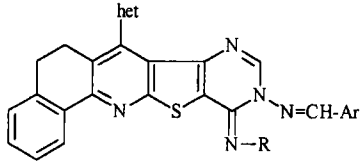


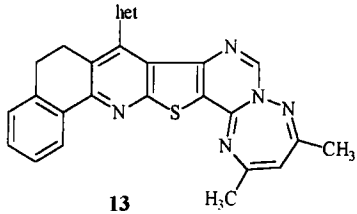
8

The compound **8** proved to be a versatile synthon for other new compounds. Thus, the reaction of **8** with benzaldehyde or 4-chlorobenzaldehyde by refluxing in ethanol gave the Schiff's bases **9a** and **9b**. When the above reaction was performed in glacial acetic acid instead of ethanol, the products were identified as acetylimino-derivatives **10a** and **10b**. Condensation of **8** with triethyl orthoformate furnished 7-(2-furyl)-8,9-dihydrobenzo[h][1,2,4]triazolo[2″,3″:1,′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b] quinoline (**11**). On fusion of **8**with acetylacetone at reflux temperature, the product was identified as 2-methyl-1,2,4-triazole derivative **12**, not the expected triazepine compound **13**[22]. The structure of **12** was confirmed by another route of preparation through the interaction of **8**with acetic anhydride. Compound **8** was reacted also with diethyl malonate to give ethyl [7-(2-furyl)-8,9-dihydrobenzo[h][1,2,4]triazolo[2″,3″:1′,6′]pyrimido [4′,5′:4,5]thieno[2,3-b]quinolin-2-yl]acetate(**14**). The compound **15** was prepared by reaction of the ester **14** with hydrazine hydrate in boiling ethanol. Other new fused 1,2,4-triazolo derivatives **16** and **19** were obtained upon treatment of **8** with carbon disulfide and/or phenyl isothiocyanate

respectively. Reaction of **16** with phenacyl bromide or with ethyl chloroacetate in the presence of sodium acetate afforded the corresponding S-alkylated products **17** and **18**.



	R	Ar
9a	H	C_6H_5
9b	H	4-Cl-C_6H_4
10a	$COCH_3$	C_6H_5
10b	$COCH_3$	4-Cl-C_6H_4



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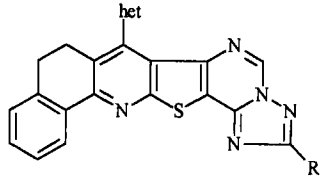
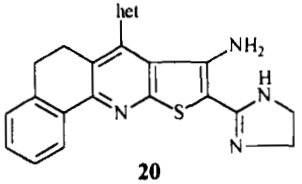


11, R= H
12, R= CH_3
14, R= CH_2CO_2Et
15, R= $CH_2CONHNH_2$
16, R= SH
17, R= SCH_2COPh
18, R= SCH_2CO_2Et
19, R= NHPh

Incorporating the imidazolyl moiety into benzopyrimidothienoquinoline structure was achieved by converting the nitrile group of **3a** into dihydroimidazolyl residue followed by some subsequent reactions. Thus, treatment of **3a** with ethylenediamine in the presence of carbon disulfide led to the formation of 8-amino-9-(4,5-dihydroimidazolyl-2-yl)-7-(2-furyl)-5,6-dihydrobenzo[h]thieno[2,3-b]quinoline (**20**). The reaction of **20** with triethyl orthoformate, benzaldehyde, 4-chlorobenzaldehyde or carbon disulfide afforded benzo[h]imidazolo[1″,2″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline derivatives **21, 22a, 22b** and **23** respectively. On treatment of **20** with nitrous acid, it underwent diazotization followed by self coupling to furnish 7-(2-furyl)-2,3,8,9-tetrahydrobenzo[h]imidazolo[1″,2″:1′,6′][1,2,3]triazino[4′,5′:4,5]thieno[2,3-b]quinoline (**24**) in excellent yield.

The present investigation was also extended to the synthesis of other new heterocycles containing benzopyrimidothienoquinoline nucleus fused with another pharmacophore, a tetrazole ring. The synthesis started from 8-amino-7-(2-furyl)-9-(1H-tetrazol-5-yl)-5,6-dihydrobenzo[h]thieno [2,3-b]quinoline (**25**) which was prepared by heating of **3a** with sodium



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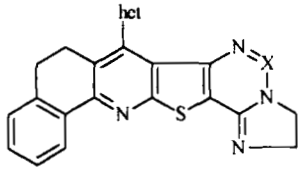
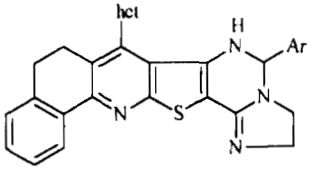
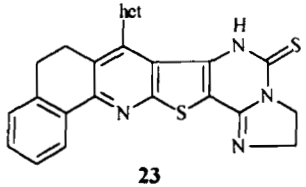


21. X= CH
24. X= N

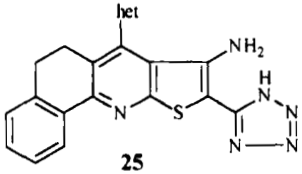


22a. Ar= C_6H_5
22b. Ar= 4-Cl-C_6H_4



23

azide and ammonium chloride in DMF followed by acidification with acetic acid. The reaction of **25**with triethyl orthoformate, 4-chlorobenzaldehyde and/or carbon disulfide afforded benzo[h]tetrazolo[1″,5″:1′,6′] pyrimido[4′,5′:4,5] thieno[2,3-b]quinolines **26, 27** and **28** respectively.



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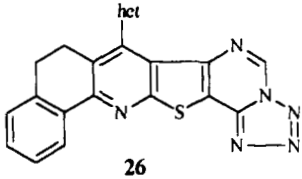

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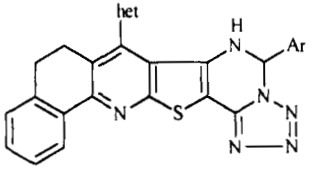
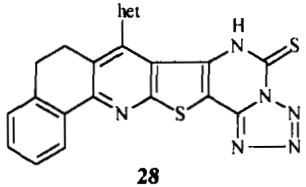


27, Ar= 4-Cl-C_6H_4

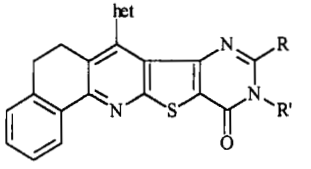


28

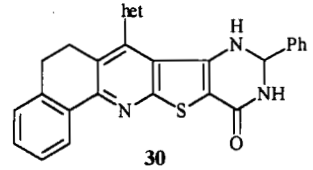
The other precursor, **3b** was reacted with triethyl orthoformate in boiling acetic anhydride to give 7-(2-furyl)-11-oxo-5,6,10,11-tetrahydrobenzo[h] pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (**29**). The reaction of **3b** with benzaldehyde by heating in acetic acid or in methanol containing catalytic amounts of HCl afforded the tetrahydropyrimidinone derivative **30**. When

compound **3b** was allowed to react with carbon disulfide or with phenyl isothiocyanate, the corresponding thioxopyrimidinone derivatives **31** and **32** were produced. 9-Ethylthiopyrimidinone **33** was obtained upon treatment of **32** with ethyl iodide in an ethanolic sodium hydroxide solution. On refluxing of **3b** with acetic anhydride for long time, the product was identified as a mixture of pyrimidinone derivative **34** and 8-diacetylamino-7-(2-furyl)-5,6-dihydrobenzo[h]thieno[2,3-b]quinoline-9-carbonitrile (**35**). Compound **34** underwent N-alkylation upon treatment with ethyl chloroacetate in DMF containing potassium carbonate to give the useful ester **36**.

Also, some structural isomers of triazolo compounds **11, 12, 16** and **18** were synthesized by using 7-(2-furyl)-11-hydrazino-5,6-dihydrobenzo[h]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline(**38**)as a key intermediate. The latter compound was obtained by chlorination of **29** followed by treatment of the resulting chloropyrimidine **37** with hydrazine hydrate. Compound **38** was reacted with formic acid, acetic acid and/or carbon disulfide to give the benzo[h][1,2,4]triazolo[4″,3″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b]quinolines **39, 40** and **41** respectively. Reaction of **41** with ethyl chloroacetate afforded the ester **42**.



	R	R'
29	H	H
33	SEt	Ph
34	Me	H
36	Me	CH_2CO_2Et



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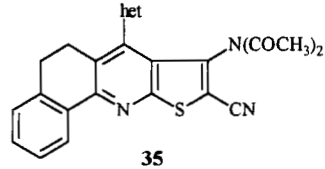

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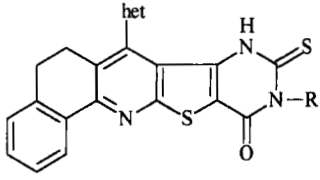
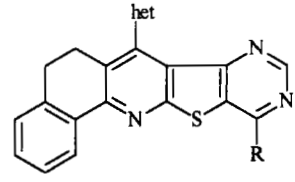
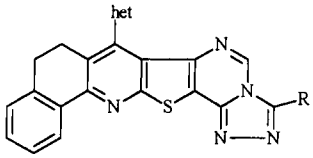


31, R= H
32, R= Ph

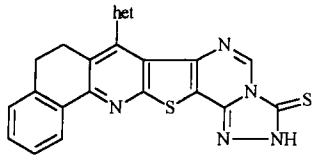


37, R= Cl
38, R= $NHNH_2$

The structures of all newly synthesized compounds were in agreement with their elemental analyses (Table I) and spectroscopic data (Experimental part). Its important to note that the ^{1}HNMR spectra of compounds **8, 20** and **25** showed no signal for NH proton and this can be explained by the rapid proton exchange as reported before[23–25].



39, R= H
40, R= Me
42, R= SCH_2CO_2Et



41

TABLE I Melting points, yields and analytical data of all newly synthesized compounds

Compd.	*M.p., °C Yield, %*	*Formula (M.W.)*	*Calculated / Found*			
			% C	*% H*	*% N*	*% S*
2a	190–191	$C_{20}H_{13}N_3OS$	69.95	3.82	12.24	9.34
	92	(343.4)	70.21	3.79	12.12	9.41
3a	235–236	$C_{20}H_{13}N_3OS$	69.95	3.82	12.24	9.34
	95	(343.4)	70.16	3.67	12.39	9.52
4	146–147	$C_{27}H_{18}N_4OS_2$	67.76	3.79	11.71	13.40
	80	(478.6)	67.41	3.70	11.57	13.49
5	>300	$C_{27}H_{18}N_4OS_2$	67.76	3.79	11.71	13.40
	96	(478.6)	67.66	3.71	11.50	13.75
6	>300	$C_{21}H_{13}N_3OS_3$	60.12	3.12	10.02	22.93
	82	(419.5)	60.45	3.19	9.81	23.20
7	163–164	$C_{23}H_{17}N_3O_2S$	69.16	4.29	10.52	8.03
	98	(399.5)	69.48	4.22	10.67	8.21
8	262–263	$C_{21}H_{15}N_5OS$	65.44	3.92	18.17	8.32
	89	(385.4)	65.78	3.99	18.11	8.60
9a	>300	$C_{28}H_{19}N_5OS$	71.02	4.04	14.79	6.77
	79	(473.5)	71.31	4.27	14.93	7.08
9b	297–299	$C_{28}H_{18}ClN_5OS$	66.20	3.57	13.79	6.31[a]
	76	(508.0)	66.00	3.45	13.90	6.59

Compd.	M.p., °C Yield, %	Formula (M.W.)	Calculated / Found			
			% C	% H	% N	% S
10a	262–263	$C_{30}H_{21}N_5O_2S$	69.89	4.11	13.58	6.22
	73	(515.6)	70.07	4.39	13.32	6.36
10b	289–290	$C_{30}H_{20}ClN_5O_2S$	65.51	3.66	12.73	5.83[b]
	71	(550.0)	65.42	3.79	12.94	5.77
11	>300	$C_{22}H_{13}N_5OS$	66.82	3.31	17.71	8.11
	93	(395.4)	66.73	3.30	17.82	8.00
12	291–292	$C_{23}H_{15}N_5OS$	67.47	3.69	17.10	7.83
	78[c] 90[d]	(409.5)	67.58	3.45	17.22	7.77
14	193–194	$C_{26}H_{19}N_5O_3S$	64.85	3.98	14.54	6.66
	72	(481.5)	64.84	3.99	14.43	6.35
15	266–267	$C_{24}H_{17}N_7O_2S$	61.66	3.67	20.97	6.86
	96	(467.5)	61.53	3.62	21.12	6.66
16	280–281	$C_{22}H_{13}N_5OS_2$	61.81	3.07	16.38	15.00
	85	(427.5)	62.16	3.01	16.11	15.17
17	220–221	$C_{30}H_{19}N_5O_2S_2$	66.04	3.51	12.84	11.75
	86	(545.6)	66.00	3.47	12.62	11.57
18	178–179	$C_{26}H_{19}N_5O_3S_2$	60.81	3.73	13.64	12.49
	82	(513.6)	60.71	3.78	13.86	12.40
19	>300	$C_{28}H_{18}N_6OS$	69.12	3.73	17.27	6.59
	77	(486.5)	69.35	3.72	17.00	6.55
20	235–236	$C_{22}H_{18}N_4OS$	68.37	4.69	14.50	8.30
	95	(386.5)	68.57	4.63	14.71	8.42
21	229–230	$C_{23}H_{16}N_4OS$	69.68	4.07	14.13	8.09
	87	(396.5)	69.42	4.06	14.41	8.17
22a	256–258	$C_{29}H_{22}N_4OS$	73.40	4.67	11.81	6.76
	90	(474.6)	73.71	4.65	11.78	6.90
22b	280–281	$C_{29}H_{21}ClN_4OS$	68.43	4.16	11.01	6.30[e]
	93	(509.0)	68.40	4.13	11.12	6.37
23	>300	$C_{23}H_{16}N_4OS_2$	64.47	3.76	13.07	14.96
	87	(428.5)	64.40	3.58	13.21	14.81
24	261 (dec.)	$C_{22}H_{15}N_5OS$	66.48	3.80	17.62	8.07
	87	(397.4)	66.19	3.81	17.46	8.11

Compd.	M.p., °C Yield, %	Formula (M.W.)	Calculated / Found			
			% C	% H	% N	% S
25	192–193	$C_{20}H_{14}N_6OS$	62.16	3.65	21.75	8.30
	75	(386.4)	62.37	3.39	21.88	8.53
26	223–224	$C_{21}H_{12}N_6OS$	63.63	3.05	21.20	8.09
	80	(396.4)	63.86	3.11	21.41	8.32
27	242–243	$C_{27}H_{17}ClN_6OS$	63.72	3.37	16.51	6.30[f]
	78	(509.0)	63.89	3.51	16.47	6.38
28	>300	$C_{21}H_{12}N_6OS_2$	58.87	2.82	19.61	14.96
	70	(428.5)	58.79	2.70	19.50	14.86
29	>300	$C_{21}H_{13}N_3O_2S$	67.91	3.53	11.31	8.63
	86	(371.4)	67.81	3.48	11.56	8.47
30	>300	$C_{27}H_{19}N_3O_2S$	72.14	4.26	9.35	7.13
	85	(449.5)	72.18	4.26	9.45	7.31
31	>300	$C_{21}H_{13}N_3O_2S_2$	62.52	3.25	10.41	15.89
	71	(403.5)	62.45	3.17	10.28	15.96
32	>300	$C_{27}H_{17}N_3O_2S_2$	67.62	3.57	8.76	13.37
	55	(479.6)	67.38	3.41	8.56	13.42
33	294–295	$C_{29}H_{21}N_3O_2S_2$	68.62	4.17	8.28	12.63
	82	(507.6)	68.91	4.16	8.14	12.77
34	>300	$C_{22}H_{15}N_3O_2S$	68.56	3.92	10.90	8.32
	32	(385.4)	68.47	3.78	11.20	8.14
35	190	$C_{24}H_{17}N_3O_3S$	67.44	4.01	9.83	7.50
	50	(427.5)	67.32	4.11	9.81	7.81
36	241–242	$C_{26}H_{21}N_3O_4S$	66.23	4.49	8.91	6.80
	87	(471.5)	66.12	4.47	8.77	6.54
37	248	$C_{21}H_{12}ClN_3OS$	64.70	3.10	10.78	8.22[g]
	78	(389.9)	64.77	3.14	10.42	8.36
38	>300	$C_{21}H_{15}N_5OS$	65.44	3.92	18.17	8.32
	90	(385.4)	65.50	3.73	18.39	8.24
39	>300	$C_{22}H_{13}N_5OS$	66.82	3.31	17.71	8.11
	85	(395.4)	66.48	3.27	17.80	8.19
40	>300	$C_{23}H_{15}N_5OS$	67.47	3.69	17.10	7.83
	86	(409.5)	67.82	3.56	17.09	7.70

Compd.	M.p., °C Yield, %	Formula (M.W.)	Calculated / Found			
			% C	% H	% N	% S
41	269–270	$C_{22}H_{13}N_5OS_2$	61.81	3.07	16.38	15.00
	90	(427.5)	61.90	3.18	16.71	15.33
42	196–197	$C_{26}H_{19}N_5O_3S_2$	60.81	3.73	13.64	12.49
	78	(513.6)	60.77	3.82	13.44	12.27

a. Calculated: 6.98% Cl, found: 7.19% Cl;
b. Calculated: 6.45% Cl, found: 6.70% Cl;
c. Method A;
d. Method B;
e. Calculated: 6.96% Cl, found: 6.90% Cl;
f. Calculated: 6.96% Cl, found: 7.31% Cl;
g. Calculated: 9.09% Cl, found: 9.28% Cl

Some of the synthesized compounds were evaluated *in vitro* for their antimicrobial activities against three strains of bacteria and two fungal species (Table II) using filter paper disc diffusion method[26,27]. The results indicated that most of the tested compounds exhibit moderate to strong activities against *Staphylococcus aureus* and *Sarcina spp.* Only compound **25** showed a very strong activity against *Staphylococcus aureus*. All tested compounds showed no activity against *Escherichia coli* except for compounds **25** and **33** which exhibited strong potency against it. Among all tested compounds only **4, 8, 20, 21, 25, 33** and **36** showed a moderate activity against *Aspergillus fumigatus*. The compounds **8, 21, 25** and **33** exhibited a moderate activity against *Aspergillus niger*. Rest of the tested compounds showed no activity against the two fungal species used. Compound **25** exhibits growth inhibition activities against all microorganisms under investigation. In contrast, compounds **7, 22a** and **30** showed no activity against any bacterial or fungal species used.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were measured on a Shimiadzu 470 IR-spectrophotometer using KBr disc technique (wavenumbers in cm^{-1}). ^{1}HNMR spectra were recorded on a Varian EM-390 90 MHz ^{1}HNMR spectrometer using tetramethylsilane as internal standard; chemical shifts are given in ppm (δ-scale). Mass spectra were measured on a Jeol

JMS-600 apparatus. Elemental analyses were carried out on a Perkin Elmer 240C elemental analyzer. Melting points, yields and analytical data of all newly synthesized compounds are listed in Table I.

TABLE II Biological screening of some synthesized compounds (inhibition zones in mm)

Compd. No.	*Staphylococcus aureus*	*Sarcina spp.*	*Escherichia coli*	*Aspergillus fumigatus*	*Aspergillus niger*
4	++	++	–	+	–
6	+	+	–	–	–
7	–	–	–	–	–
8	++	++	–	+	+
11	+	+	–	–	–
12	++	++	–	–	–
20	++	++	–	+	–
21	++	+	–	+	+
22a	–	–	–	–	–
25	+++	++	++	+	+
27	+	+	–	–	–
30	–	–	–	–	–
33	+	+	++	+	+
36	++	++	–	+	–
Tyrosyd	+	+++	++	+++	++

-: No activity; +: moderate activity (inhibition zone: 5–10 mm); ++: strong activity (inhibition zone: 11–15 mm); +++: very strong activity (inhibition zone: 16–20 mm).

[(3-Cyano-4-(2-furyl)-5,6-dihydrobenzo[h]quinolin-2-yl)thio] acetonitrile (2a)

A mixture of 1 (ref.[19]; 15.2 g, 50 mmol), chloroacetonitrile (3.2 mL; 50 mmol) and anhydrous sodium acetate (4.10 g, 50 mmol) in ethanol (200 mL) was refluxed for 3 h and left to cool. The precipitated solid was collected and recrystallized from ethanol. ^{1}HNMR ($CDCl_3$): 8.40 m, 1H (furyl-H); 7.30–7.80 m, 4H (aromatic); 7.00 m, 1H (furyl-H); 6.60 m, 1H (furyl-H); 4.15 s, 2H (SCH_2); 3.00 m, 4H ($2XCH_2$). IR spectrum: 2220, 2200 (2 C≡N).

[(3-Cyano-4-(2-furyl)-5,6-dihydrobenzo[h]quinolin-2-yl)thio] acetamide (2b)

It was prepared by the reported method[21].

8-Amino-7-(2-furyl)-5,6-dihydrobenzo[h]thieno[2,3-b]quinoline-9-carbonitrile (3a)

A suspension of compound 2a (10.30 g, 30 mmol) in ethanol (100 mL) containing dissolved sodium (0.46 g, 20 mmol) was heated under reflux for 20 min. The precipitate separated on cooling was filtered off and recrystallized from ethanol. ^{1}HNMR spectrum ($CDCl_3$): 8.45 m, 1H (furyl- -H); 7.30–7.80 m, 4H (aromatic); 6.70 m, 2H (furyl-H); 4.60 s, 2H (NH_2); 90 s, 4H ($2XCH_2$). IR spectrum: 3450, 3350 (NH_2); 2200 (C≡N).

8-Amino-7-(2-furyl)-5,6-dihydrobenzo[h]thieno[2,3-b]quinoline-9-carboxamide (3b)

It was prepared by the reported method[21].

N-[9-Cyano-7-(2-furyl)-5,6-dihydrobenzo[h]thieno[2,3-b]quinolin-8-yl]-N′-phenylthiourea (4)

A mixture of 3a (3.43 g, 10 mmol) and phenyl isothiocyanate (1.20 mL, 10 mmol) in pyridine (20 mL) was heated on a water bath for 4 h. The reaction mixture was cooled, poured into ice-water (50 mL) and acidified with acetic acid. The precipitate was filtered off and recrystallized from ethanol. IR spectrum: 3200–3100 (2NH); 2200 (C≡N).

7-(2-Furyl)-11-imino-10-phenyl-9-thioxo-5,6,8,9,10,11-hexahydrobenzo [h]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (5)

Compound 4 (2.39 g, 5 mmol) in methanol (30 mL) containing dissolved sodium (0.23 g, 10 mmol) was heated under reflux for 30 min. The solid thus separated after cooling and acidification with acetic acid was collected and recrystallized from dioxane. ^{1}HNMR spectrum (CF_3CO_2D): 8.25 m, 1H (furyl-H); 7.30–8.00 m, 9H (aromatic); 7.00 m, 2H (furyl-H); 2.90–3.25 m, 4H ($2XCH_2$). IR spectrum: 3450, 3380 (2NH); 1620 (C=N); 1180 (C=S).MS: 478(M^+, 61%); 479(M^+ +1,29%); 477(M^+ −1, 100%).

9,11-Dithioxo-7-(2-furyl)-5,6,8,9,10,11-hexahydrobenzo[h]pyrimido [4′,5′:4,5]thieno[2,3-b]quinoline (6)

To a solution of 3a (1.71 g, 5 mmol) in pyridine (15 mL), carbon disulfide (2 mL) was added. The resulting mixture was heated under reflux on a water bath for 10 h and allowed to cool. The solid that formed was collected by filtration and recrystallized from pyridine. IR spectrum: 3340, 3120 (2NH).

Ethyl N-[9-cyano-7-(2-furyl)-5,6-dihydrobenzo[h]thieno[2,3-b] quinolin-8-yl]methanimidate (7)

A mixture of 3a (17.17 g, 50 mmol) and triethyl orthoformate (20 mL) in redistilled acetic anhydride (100 mL) was refluxed for 3 h. The crystalline product that separated on cooling was collected and recrystallized from ethanol. ^{1}HNMR spectrum ($CDCl_3$): 8.40 m, 1H (furyl-H); 7.65 s, 1H (N=CH); 7.10–7.50 m, 4H (aromatic); 6.40 s, 1H (furyl-H); 6.60 s, 1H (furyl-H); 3.90 q, 2H (OCH_2); 2.80 s, 4H ($2XCH_2$); 1.35 t, 3H (CH3). IR spectrum: 2200 (C≡N); 1620 (C=N).

10-Amino-7-(2-furyl)-11-imino-5,6,10,11-tetrahydrobenzo[h] pyrimido [4′,5′:4,5]thieno[2,3-b]quinoline (8)

To a stirred suspension of **7** (12.00 g, 30 mmol) in dioxane (150 mL), hydrazine hydrate 80% (5 mL, 80 mmol) was added. The reaction mixture was stirred at room temperature for 4 h whereby a heavy precipitate formed. It was collected by filtration, washed with water and recrystallized from dioxane. ^{1}HNMR spectrum (CD_3SOCD_3): 8.70 s, 1H (pyrimidine-H); 8.40 m, 1H (furyl-H); 7.10–7.60 m, 4H (aromatic); 6.50 s, 1H (furyl-H); 6.70 s, 1H (furyl-H); 5.30 s, 2H (NH_2); 2.90 s, 4H ($2XCH_2$). IR spectrum: 3400, 3300, 3150 (NH_2, NH); 1620 (C=N).

10-Benzylideneamino-7-(2-furyl)-11-imino-5,6,10,11-tetrahydrobenzo [h] pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (9a)

To a mixture of 8 (0.77 g, 2 mmol) and benzaldehyde (0.21 mL, 2 mmol) in ethanol (20 mL), five drops of piperidine was added. The resulting mixture was heated under reflux for 3 h. The solid that separated while hot

was collected and recrystallized from dioxane. IR spectrum: 3200 (NH); 1600 (C=N).

10-(4-Chlorobenzylideneamino)-7-(2-furyl)-11-imino-5,6,10,11-tetrahydrobenzo[h]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline(9b)

This compound was synthesized in analogy to the method described above by reaction of **8** with 4-chlorobenzaldehyde. The product was recrystallized from dioxane. ^{1}HNMR spectrum (CF_3CO_2D): 9.40 s, 1H (N=CH); 8.80 s, 1H (pyrimidine-H); 8.30 m, 1H (furyl-H); 7.35–8.20 m, 8H (aromatic); 7.10 s, 1H (furyl-H); 6.85 s, 1H (furyl-H); 2.90–3.40 m, 4H ($2XCH_2$). IR spectrum: 3200 (NH); 1600 (C=N).

11-Acetylimino-10-benzylideneamino-7-(2-furyl)-5,6,10,11-tetrahydrobenzo[h]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (10a)

A mixture of 8 (0.77 g, 2 mmol) and benzyaldehyde (0.21 mL, 2 mmol) in glacial acetic acid (10 mL) was refluxed for 3 h. The precipitate that formed after cooling was collected and recrystallized from acetic acid. IR spectrum: 1680 (C=O); 1590 (C=N).

11-Acetylimino-10-(4-chlorobenzylideneamino)-7-(2-furyl)-5,6,10,11-tetrahydrobenzo[h]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (10b)

This compound was synthesized in analogy to the method described above by reaction of **8** with 4-chlorobenzaldehyde. The product was recrystallized from acetic acid. ^{1}HNMR specturm ($CDCl_3$): 9.60 s, 1H (N=CH); 8.95 s, 1H (pyrimidine-H); 8.50 m, 1H (furyl-H); 7.30–8.25 m, 8H (aromatic); 7.20 s, 1H (furyl-H); 7.00 s, 1H (furyl-H); 3.00–3.40 m, 4H ($2XCH_2$); 2.25 s, 3H (CH_3). IR spectrum: 1680 (C=O); 1590 (C=N).

7-(2-Furyl)-8,9-dihydrobenzo[h][1,2,4]triazolo[2″,3″:1′,6′]pyrimido [4′,5′:4,5]thieno[2,3-b]quinoline (11)

Compound 8 (0.77 g, 2 mmol) in triethyl orthoformate (15 mL) was heated under reflux for 2 h. The solid which formed was collected and recrystallized from acetic acid. ^{1}HNMR (CF_3CO_2D): 9.80 s, 1H (triazole-H); 9.35

s, 1H (pyrimidine-H); 8.30 d, 1H (furyl-H); 7.60–8.10 m, 4H (aromatic); 7.35 d, 1H (furyl-H); 7.00 s, 1H (furyl-H); 3.25 t, 2H (CH_2); 3.50 t, 2H (CH2). IR spectrum: 1600 (C=N).

7-(2-Furyl)-2-methyl-8,9-dihydrobenzo[h] [1,2,4]triazolo [2″,3″:1′,6′] pyrimido [4′,5′:4,5]thieno[2,3-b]quinoline (12)

A) Compound **8** (0.77 g, 2 mmol) in acetylacetone (10 mL) was gently heated under reflux for 3 h. The solid that separated after cooling was collected and recrystallized from dioxane to give **12**. ^{1}HNMR spectrum (CF_3CO_2D): 9.65 s, 1H (pyrimidine-H); 8.25 d, 1H (furyl-H); 7.50–8.00 m, 4H (aromatic); 7.30 d, 1H (furyl-H); 6.90 m, 1H (furyl-H); 3.50 t, 2H (CH_2); 3.20 t, 2H (CH_2); 3.00 s, 3H (CH_3). IR spectrum: 1610 (C=N). MS: 409 (M^+, 53%); 410 (M^+ +1,11%); 408 (M^+ −1,100%).

B) A solution of **8** (0.77 g, 2 mmol) in acetic anhydride (15 mL) was refluxed for 2 h. The reaction mixture was cooled to give a solid which upon recrystallization was identical with that described above.

Ethyl [7-(2-furyl)-8,9-dihydrobenzo[h][1,2,4]triazolo[2″,3″:1′,6′] pyrimido[4′,5′:4,5]thieno[2,3-b]quinolin-2-yl]acetate (14)

A suspension of 8 (1.92 g, 5 mmol) in diethyl malonate (20 mL) was gently refluxed for 4 h, then cooled and triturated with ethanol (15 mL). The separated crystalline solid was collected and recrystallized from ethanol. ^{1}HNMR spectrum ($CDCl_3$): 9.15 s, 1H (pyrimidine-H); 8.50 m, 1H (furyl-H); 7.20–7.70 m, 4H (aromatic); 6.80 s, 2H (furyl-H); 4.40 q, 2H (OCH_2); 4.10 s, 2H (CH_2CO); 3.00 s, 4H ($2XCH_2$); 1.40 t, 3H (CH_3). IR spectrum: 1730 (C=O); 1610 (C=N).

[7-(2-Furyl)-8,9-dihydrobenzo[h][1,2,4]triazolo[2″,3″:1′,6′]pyrimido [4′,5′:4,5]thieno[2,3-b]quinolin-2-yl]acethydrazide (15)

A mixture of 14 (0.48 g, 1 mmol) and hydrazine hydrate 80% (0.5 mL, 8 mmol) in ethanol (15 mL) was refluxed for 3 h. The solid that obtained after cooling was collected and recrystallized from ethanol. ^{1}HNMR ($CDCl_3$): 9.40 br, 1H (NH); 9.10 s, 1H (pyrimidine-H); 8.40 m, 1H

(furyl-H); 7.15–7.60 m, 4H (aromatic); 6.70 m, 2H (furyl-H); 4.20 br, 2H (NH_2); 4.00 s, 2H (CH_2CO); 2.90 s, 4H ($2XCH_2$). IR spectrum: 3470–3220 (NH_2, NH); 1660 (C=O).

7-(2-Furyl)-2-mercapto-8,9-dihydrobenzo[h][1,2,4]triazolo [2″,3″:1′,6′] pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (16)

To a solution of 8 (1.54 g, 4 mmol) in pyridine (20 mL), carbon disulfide (2 mL) was added. The reaction mixture was heated under reflux on a water bath for 6 h. The cooled reaction mixture was concentrated, poured into ice-water (25 mL) and acidified with acetic acid. The solid thus precipitated was collected and crystallized from ethanol-chloroform mixture. IR spectrum: 2700–2550 (SH); 1600 (C=N).

Alkylation of 16; formation of compounds 17 and 18

A mixture of 16 (0.43 g, 1 mmol), anhydrous sodium acetate (0.17 g, 2 mmol) and the respective alkylating agent (1 mmol) in ethanol (15 mL) was refluxed for 2 h. The solid that separated on cooling was collected and recrystallized from ethanol. In this way the following compounds were prepared:

A) 7-(2-Furyl)-2-phenacylthio-8,9-dihydrobenzo[h][1,2,4]triazolo [2″,3″: 1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (17)

Obtained from 16 and phenacyl bromide. IR spectrum: 1680 (C=O); 1620 (C=N).

B) Ethyl [7-(2-furyl)-8,9-dihydrobenzo[h][1,2,4]triazolo[2″,3″:1′,6′] pyrimido[4′,5′:4,5]thieno[2,3-b]quinolin-2-ylthio]acetate (18)

Obtained from **16** and ethyl chloroacetate. ^{1}HNMR ($CDCl_3$): 9.00 s, 1H (pyrimidine-H); 8.50 m, 1H (furyl-H); 7.20–7.70 m, 4H (aromatic); 6.60 m, 2H (furyl-H); 4.20–4.35 m, 4H (SCH_2 and OCH_2); 2.90 s, 4H ($2XCH_2$); 1.25–1.50 t, 3H (CH_3). IR spectrum: 1730 (C=O, ester); 1620 (C=N).

7-(2-Furyl)-2-phenylamino-8,9-dihydrobenzo[h][1,2,4]triazolo [2″,3: 1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (19)

A mixutre of 8 (0.77 g, 2 mmol) and phenyl isothiocyanate (0.24 mL, 2 mmol) in pyridine was gently refluxed for 3 h. The solid that precipitated

after cooling was collected and recrystallized from pyridine. ^{1}HNMR (CF_3CO_2D): 9.30 s, 1H (pyrimidine-H); 8.30 m, 1H (furyl); 7.20–8.00 m, 9H (aromatic); 6.90 m, 2H (furyl-H); 3.00–3.35 m, 4H ($2XCH_2$). IR spectrum: 3290 (NH); 1610 (C=N).

8-Amino-9-(4,5-dihydroimidazol-2-yl)-7-(2-furyl)-5,6-dihydrobenzo [h] thieno[2,3-b]quinoline (20)

To a suspension of 3a (6.86 g, 20 mmol) in ethylenediamine (10 mL), carbon disulfide (4 mL) was added portionwise during 3 min. The reaction mixture was heated under reflux on a water bath for 2 h and then triturated with ethanol (40 mL). The orange crystals that precipitated was collected and recrystallized from dioxane. ^{1}HNMR (CD_3SOCD_3): 8.45 m, 1H (furyl-H); 7.00–7.50 m, 4H (aromatic); 6.60 m, 2H (furyl-H); 5.60 br, 2H (NH_2); 3.50–4.00 br, 4H ($2XCH_2$, imidazolyl); 2.90 s, 4H ($2XCH_2$, quinoline). IR spectrum: 3420, 3370 (NH_2); 3200 (NH, imidazole); 1590 (C=N). MS: 386 (M^+, 97%); 387 (M^+ +1,20%); 385 (M^+ – 1,100%).

7-(2-Furyl)-2,3,8,9-tetrahydrobenzo[h]imidazolo[1″,2″:1′,6′] pyrimido [4′,5′:4,5]thieno[2,3-b]quinoline (21)

Compound 20 (0.77 g, 2 mmol) in triethyl orthoformate (10 mL) was heated under reflux for 2 h. The solid that precipitated while hot was collected and recrystallized from acetic acid. ^{1}HNMR spectrum (CD_3SOCD_3): 8.40 s, 1H (furyl-H); 7.90 d, 1H (pyrimidine-H); 7.00–7.50 m, 4H (aromatic); 6.60 m, 2H (furyl-H); 4.00 m, 4H ($2XCH_2$, imidazole); 2.90 s, 4H ($2XCH_2$, quinoline). IR spectrum: 1630 (C=N).

7-(2-Furyl)-5-phenyl-2,3,5,6,8,9-hexahydrobenzo[h]imidazolo [1″,2″: 1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (22a)

To a mixture of 20 (0.77 g, 2 mmol) and benzaldehyde (0.21 mL, 2 mmol) in ethanol (15 mL), five drops of piperidine were added. The resulting mixture was refluxed for 4 h and left to cool. The solid that precipitated was collected and recrystallized from ethanol-chloroform mixture. ^{1}HNMR spectrum ($CDCl_3$) 8.50 m, 1H (furyl-H); 7.20–7.70 m, 9H (aromatic); 6.60 s, 1H (furyl-H); 6.40 s, 1H (furyl-H); 5.10 s, 1H (NH,

exchangeable with D_2O); 5.35 s, 1H (pyrimidine-H); 3.60–4.10 m, 4H ($2XCH_2$, imidazole); 2.90 s, 4H ($2XCH_2$, quinoline). IR spectrum: 3400 (NH); 1620 (C=N).

5-(4-Chlorophenyl)-7-(2-furyl)-2,3,5,6,8,9-hexahydrobenzo[h] imidazolo [1″,2″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (22b)

This compound was synthesized by reaction of **20** with 4-chlorobenzaldehyde in analogy to the method described above. It was recrystallized from ethanol-chloroform mixture. ^{1}HNMR spectrum ($CDCl_3$): 8.35 m, 1H (furyl-H); 7.20–7.70 m, 8H (aromatic); 6.60 m, 2H (furyl-H); 5.80 s, 1H (pyrimidine-H); 5.25 s, 1H (NH, exchangeable with D_2O); 3.90 s, 2H (CH_2, imidazole); 3.50 s, 2H (CH_2, imidazole); 2.90 s, 4H ($2XCH_2$, quinoline). IR spectrum: 3400 (NH); 1620 (C=N). MS: 509(M^+, 31%); 507(M^+ –2H,68%); 396(M^+ -2H-C_6H_4Cl,100%).

7-(2-Furyl)-5-thioxo-2,3,5,6,8,9-hexahydrobenzo[h]imidazolo [1″,2″: 1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (23)

A mixture of 20 (0.77 g, 2 mmol) and carbon disulfide (2 mL) in pyridine (15 mL) was heated under reflux on a water bath for 12 h. The solid that formed while hot was collected and recrystallized from dimethylformamide. IR spectrum: 3400 (NH); 1620 (C=N).

7-(2-Furyl)-2,3,8,9-tetrahydrobenzo[h]imidazolo[1″,2″:1′,6′][1,2,3] triazino[4′,5′:4,5]thieno[2,3-b]quinoline (24)

To a cold stirred suspension of **20** (0.77 g, 2 mmol) in glacial acetic acid (15 mL), sodium nitrite solution 10% (4 mL) was added dropwise during 5 min. The reaction mixture was stirred at 5°C for 2 h. The precipitated solid that formed was collected and recrystallized from ethanol-chloroform mixture. ^{1}HNMR spectrum (CF_3CO_2D): 8.40 m, 1H (furyl-H); 7.20–8.00 m, 4H (aromatic); 7.10 m, 1H (furyl-H); 6.85 m, 1H (furyl-H); 4.00 s, 4H ($2XCH_2$, imidazole); 3.05 s, 4H ($2XCH_2$, quinoline). IR spectrum: 1630 (C=N). MS: 397(M^+, 13%); 396(M^+ –1,49%); 369 (M^+ -N_2,52%); 370 (M^+ -N_2 +1,100%).

8-Amino-7-(2-furyl)-9-(1H-tetrazolo-5-yl)-5,6-dihydrobenzo[h] thieno [2,3-b]quinoline (25)

A mixture of 3a (6.86 g, 20 mmol), sodium azide (1.95 g, 30 mmol) and ammonium chloride (1.60 g, 30 mmol) in DMF (30 mL) was heated on a water bath for 5 h. The reaction mixture was cooled, diluted with water (40 mL) and acidified with dilute acetic acid. The precipitated solid was collected and recrystallized from ethanol. ^{1}HNMR spectrum (CD_3SOCD_3): 8.35 m, 1H (furyl-H); 7.20–8.00 m, 4H (aromatic); 6.80 m, 2H (furyl-H); 6.50 s, 2H (NH_2); 2.80 s, 4H ($2XCH_2$). IR spectrum: 3500, 3400, 3300 (NH_2, NH); 1600 (C=N).

7-(2-Furyl)-8,9-dihydrobenzo[h]tetrazolo[1″,5″:1′,6′]pyrimido [4′,5′:4,5] thieno[2,3-b]quinoline (26)

Compound 25 (0.77 g, 2 mmol) in triethyl orthoformate (10 mL) was heated under reflux for 3 h and then allowed to cool. The solid thus formed was collected and recrystallized from ethanol. ^{1}HNMR spectrum (CD_3SOCD_3): 9.25 s, 1H (pyrimidine-H); 8.40 m, 1H (furyl-H); 7.25–8.00 m, 4H (aromatic); 7.10 m, 1H (furyl-H); 6.85 m, 1H (furyl-H); 2.80–3.30 m, 4H ($2XCH_2$). IR spectrum: 1610 (C=N).

5-(4-Chlorophenyl)-7-(2-furyl)-5,6,8,9-tetrahydrobenzo[h] tetrazolo [1″,5″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (27)

A mixture of **25** (0.77 g, 2 mmol) and 4-chlorobenzaldehyde (0.28 g, 2 mmol) in ethanol (20 mL) containing five drops of piperidine was heated under reflux for 4 h. The solid thus formed on cooling was collected and recrystallized from ethanol. ^{1}HNMR (CF_3CO_2D): 8.40 m, 1H (furyl-H); 7.30–7.80 m, 8H (aromatic); 6.60 m, 2H (furyl-H); 6.00 s, 1H (pyrimidine-H); 3.00 s, 4H ($2XCH_2$). IR spectrum: 3380 (NH); 1590 (C=N).

7-(2-Furyl)-5-thioxo-5,6,8,9-tetrahydrobenzo[h]tetrazolo[1″,5″:1′,6′] pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (28)

A mixture of 25 (0.77 g, 2 mmol) and carbon dislufide (2 mL) in pyridine (15 mL) was heated under reflux on a water bath for 12 h. The solid that separated while hot was collected and recrystallized from dimethylformamide. IR spectrum: 3380 (NH); 1630 (C=N).

7-(2-Furyl)-11-oxo-5,6,10,11-tetrahydrobenzo[h]pyrimido[4′,5′:4,5] thieno[2,3-b]quinoline (29)

A mixture of 3b (3.61 g, 10 mmol) and triethyl orthoformate (3 mL, 18 mmol) in acetic anhydride (25 mL) was refluxed for 4 h. The solid that precipitated was filtered off, washed with ethanol and recrystallized from acetic acid. ^{1}HNMR spectrum (CF_3CO_2D): 8.50 s, 1H (pyrimidine-H); 8.40 m, 1H (furyl-H); 7.15–7.80 m, 4H (aromatic); 6.60 m, 2H (furyl-H); 2.90 m, 4H ($2XCH_2$). IR spectrum: 3200–2400 (br, NH); 1650 (C=O).

7-(2-Furyl)-11-oxo-9-phenyl-5,6,8,9,10,11-hexahydrobenzo[h] pyrimido [4′,5′:4,5]thieno[2,3-b]quinoline (30)

A mixture of 3b (3.61 g, 10 mmol) and benzaldehyde (1.02 mL, 10 mmol) in acetic acid (25 mL) or in methanol (40 mL) containing few drops of HCl was refluxed for 3 h. The product that precipitated was collected and recrystallized from acetic acid. ^{1}HNMR (CD_3SOCD_3): 8.50 d, 1H (NH); 8.35 m, 1H (furyl-H); 7.30–7.50 m, 9H (aromatic); 6.90 m, 1H (furyl-H); 6.80 m, 1H (furyl-H); 5.90 t, 1H (pyrimidinone-H); 5.40 d, 1H (NH); 2.90 m, 4H ($2XCH_2$). IR spectrum: 3400, 3200 (2NH); 1650 (C=O). MS: 449 (M^+, 27%); 448 (M^+-1, 48%); 447 (M^+-2,82%); 446 (M^+-3, 100%); 419 (M^+-NO, 19%).

7-(2-Furyl)-11-oxo-10-thioxo-5,6,8,9,10,11-hexahydrobenzo[h] pyrimido [4′,5′:4,5]thieno[2,3-b]quinoline (31)

A mixture of 3b (3.61 g, 10 mmol) and carbon disulfide (3 mL) in pyridine (30 mL) was heated under reflux on a water bath for 10 h. The precipitated solid was collected and recrystallized from dimethyl-formamide. ^{1}HNMR spectrum (CF_3CO_2D): 8.40 s, 1H (furyl-H); 7.20–7.60 m, 4H (aromatic); 6.80 m, 2H (furyl-H); 2.90 m, 4H ($2XCH_2$). IR spectrum: 3360, 3100 (2NH); 1660 (C=O).

7-(2-Furyl)-11-oxo-10-phenyl-9-thioxo-5,6,8,9,10,11-hexahydrobenzo [h] pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (32)

A mixture of 3b (3.61 g, 10 mmol) and phenyl isothiocyanate (1.20 mL, 10 mmol) in acetic acid (30 mL) was refluxed for 4 h. The precipitated

product was filtered off and recrystallized from dimethylformamide. ^{1}HNMR spectrum (CF_3CO_2D): 8.35 s, 1H (furyl-H); 7.10–7.70 m, 9H (aromatic); 6.70 m, 2H (furyl-H); 2.85 m, 4H ($2XCH_2$). IR spectrum: 3360 (NH); 1660 (C=O).

9-Ethylthio-7-(2-furyl)-11-oxo-10-phenyl-5,6,10,11-tetrahydrobenzo [h] pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (33)

Compound 32 (2.40 g, 5 mmol) was dissolved in an 5% ethanol sodium hydroxide solution (20 mL) and ethyl iodide (0.85 mL, 10 mmol) was added to it. The reaction mixture was stirred at 50°C for 30 min. The crsytalline product that formed was collected and recrystallized from ethanol. ^{1}HNMR spectrum (CF_3CO_2D): 8.40 s, 1H (furyl-H); 7.10–7.60 m, 9H (aromatic); 6.60 m, 2H (furyl-H); 2.90 m, 4H ($2XCH_2$); 2.70 q, 2H (SCH_2); 1.10 t, 3H (CH_3). IR spectrum: 1660 (C=O).

Reaction of compound 3b with acetic anhydride; formation of 34 and 35

Compound **3b** (3.61 g, 10 mmol) in redistilled acetic anhydride (30 mL) was heated under reflux for 8 h. The solid product that separated on cooling was filtered off and recrystallized from dimethylformamide to give a compound with m.p. >300°C. This compound was characterized as 7-(2-furyl)-9-methyl-11-oxo-5,6,10,11-tetrahydrobenzo[h]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (**34**). ^{1}HNMR spectrum (CF_3CO_2D): 8.35 s, 1H (furyl-H); 7.10–7.50 m, 4H (aromatic); 6.70 m, 2H (furyl-H); 2.90–3.15 m, 4H ($2XCH_2$); 2.20 s, 3H (CH_3). IR spectrum: 3200–2400 (br, NH); 1650 (C=O).

The mother liquor of the above crude product was diluted with water (40 mL) to give a white precipitate which on crystallization from aqueous ethanol gave a m.p. 190°C. The latter compound was identified as 8-diacetylamino-7-(2-furyl)-5,6-dihydrobenzo[h]thieno[2,3-b]quinoline-9-carbonitrile (**35**). ^{1}HNMR ($CDCl_3$): 8.35 m, 1H (furyl-H); 7.10–7.55 m, 4H (aromatic); 6.60 m, 1H (furyl-H); 6.40 m, 1H (furly-H); 2.90 s, 4H ($2XCH_2$); 2.20 s, 6H ($2XCOCH_3$). IR spectrum: 2200 (C≡N); 1720 (C=O).

Ethyl [7-(2-furyl)-9-methyl-11-oxo-5,6,10,11-tetrahydrobenzo[h] pyrimido[4′,5′:4,5[thieno[2,3-b]quinolin-10-yl]acetate (36)

To a stirred suspension of **34** (1.15 g, 3 mmol) and pot. carbonate (0.83 g, 6 mmol) in DMF (15 mL), ethyl chloroacetate (0.32 mL, 3 mmol) was added. The stirring was continued for 4 h at room temperature. The reaction mixture was then diluted with water (20 mL) whereby a solid precipitated. It was collected and crystallized from ethanol. ^{1}HNMR ($CDCl_3$): 8.50 m, 1H (furyl-H); 7.20–7.75 m, 4H (aromatic); 6.65 m, 2H (furyl-H); 4.90 s, 2H (NCH_2); 4.15–4.40 q, 2H (OCH_2); 3.00 s, 4H ($2XCH_2$); 2.40 s, 3H (CH_3); 1.20–1.40 t, 3H (CH_3). IR spectrum: 1730 (C=O, ester); 1670 (C=O, pyrimidinone).

11-Chloro-7-(2-furyl)-5,6-dihydrobenzo[h]pyrimido[4′,5′:4,5]thieno [2,3-b]quinoline (37)

Compound 29 (1.85 g, 5 mmol) in phosphorus oxychloride (40 mL) was heated under reflux for 3 h and allowed to cool. The reaction mixture was poured into ice-cold water (150 mL), whereby a solid precipitated. It was filtered off and crystallized from dioxane. ^{1}HNMR (CF_3CO_2D): 8.40 s, 1H (pyrimidine-H); 8.30 m, 1H (furyl-H); 7.10–7.75 m, 4H (aromatic); 6.65 m, 2H (furyl-H); 2.95 s, 4H ($2XCH_2$). IR spectrum: 1600 (C=N).

7-(2-Furyl)-11-hydrazino-5,6-dihydrobenzo[h]pyrimido[4′,5′:4,5] thieno [2,3-b]quinoline (38)

A mixture of 37 (1.56 g, 4 mmol) and 99% hydrazine hydrate (0.4 mL, 8 mmol) in ethanol (20 mL) was heated under reflux for 4 h. The separated product was collected and recrystallized from dioxane. IR spectrum: 3450, 3320, 3200 (NH_2, NH); 1640 (C=N).

7-(2-Furyl)-8,9-dihydrobenzo[h][1,2,4]triazolo[4″,3″:1′,6′] pyrimido [4′,5′: 4,5]thieno[2,3-b]quinoline (39)

A solution of 38 (0.39 g, 1 mmol) in formic acid (15 mL) was heated under reflux for 3 h. The solid that precipitated while hot was collected and recrystallized from DMF. ^{1}HNMR spectrum (CF_3CO_2D): 9.70 s, 1H (triazole-H); 9.20 s, 1H (pyrimidine-H); 8.30 m, 1H (furyl-H); 7.40–

8.00 m, 4H (aromatic); 7.30 m, 1H (furyl-H); 6.90 m, 1H (furyl-H); 3.45 m, 2H (CH_2); 3.25 m, 2H (CH_2). IR spectrum: 1600 (C=N).

7-(2-Furyl)-3-methyl-8,9-dihydrobenzo[h][1,2,4]triazolo[4″,3″:1′,6′] pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (40)

It was synthesized analogously from **38** and acetic acid and was recrystallized from acetic acid. ^{1}HNMR spectrum (CF_3CO_2D): 9.20 s, 1H (pyrimidine-H); 8.35 m, 1H (furyl-H); 7.40–8.00 m, 4H (aromatic); 7.20 m, 1H (furyl-H); 7.00 m, 1H (furyl-H); 3.30 m, 4H ($2XCH_2$); 2.80 s, 3H (CH_3). IR spectrum: 1600 (C=N).

7-(2-Furyl)-3-thioxo-2,3,8,9-tetrahydrobenzo[h][1,2,4]triazolo [4″,3″: 1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b]quinoline (41)

A suspension of 38 (1.54 g, 4 mmol) and carbon disulfide (2 mL) in pyridine (25 mL) was heated under reflux on a water bath for 8 h. The reaction mixture was concentrated, cooled and poured in water (25 mL). The precipitated solid was collected and crystallized from DMF. IR spectrum: 3100 (NH).

Ethyl [7-(2-furyl)-8,9-dihydrobenzo[h][1,2,4]triazolo[4″,3″:1′,6′] pyrimido[4′,5′:4,5]thieno[2,3-b]quinolin-3-ylthio]acetate (42)

A mixture of **41** (0.85 g, 2 mmol), ethyl chloroacetate (0.22 mL, 2 mmol) and sodium acetate (0.41 g, 5 mmol) in ethanol (15 mL) was refluxed for 2 h and left to cool. The precipitate that formed was collected, washed with water and recrystallized from ethanol. ^{1}HNMR spectrum ($CDCl_3$): 9.10 s, 1H (pyrimidine-H); 8.45 m, 1H (furyl-H); 7.20–7.80 m, 4H (aromatic); 6.80 m, 2H (furyl-H); 4.20–4.40 q (2H, OCH_2); 4.10 s, 2H (SCH_2); 2.95 s, 4H ($2XCH_2$); 1.25–1.50 t, 3H (CH_3). IR spectrum: 1730 (C=O).

Biological screening. The screened compounds were dissolved in DMSO to get a solution of 1% concentration. Filter paper discs (Whatman No. 1 filtere paper, 5 mm diameter) were saturated with the former solution. The discs were placed on the surface of solidified Nutrient agar dishes seeded by the tested bacteria or Czapek's Dox agar dishes seeded by

the tested fungi. The inhibition zones were measured at the end of an incubation period of 48 h (at 37°C for bacteria and at 28°C for fungi). Ticonazol (Tyrosyd) was used as a reference substance.

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