Synthesis of some Pyrimido[4',5':4,5]thieno[2,3-*b*]quinolines and Related Heterocycles

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Several thieno[2,3-*b*]quinolines **6a-i** have been synthesized. These compounds were used as key intermediates in the synthesis of oxazino[4',5':4,5]thieno[2,3-*b*]quinoline **8**, pyrimido[4',5':4,5]-thieno[2,3-*b*]quinolines **9-12**, triazino[4',5':4,5]thieno[2,3-*b*] quinolines **14** and imidazo[4',5':4,5]-thieno[2,3-*b*]quinolines **17**.

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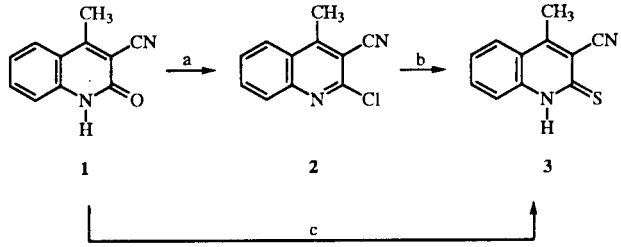
As part of a study designed to investigate tetracyclic ring systems possessing a thienopyridine nucleus, and in continuation with our work on the synthesis of new poly-fused heterocycles of anticipated anti-neoplasic activity [1-5], we report the synthesis of the title compounds .

The treatment of **1** with phosphoryl chloride gave the corresponding chloro derivative **2** which gave in turn the thiolactam **3** when treated with thiourea in boiling ethanol (Scheme 1).

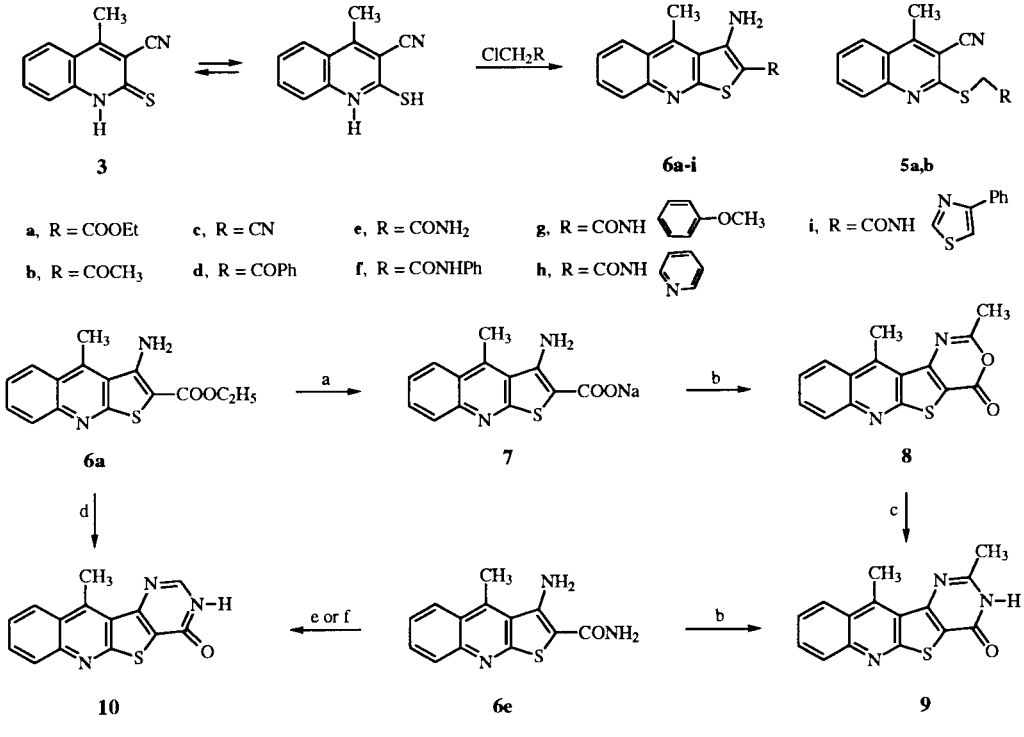
An approach to the synthesis of the thieno[2,3-*b*]quinoline derivative **6a-i** involving the interaction of the thiolactam **3** with some active methylene chloro compounds

Scheme 1



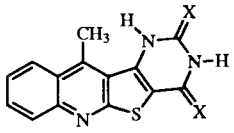
a, $POCl_3$ b, H_2NCSNH_2, NaOH, HCl c, P_2S_5/Pyridine

Scheme 2



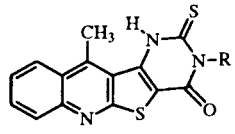
a, $NaOH/CH_3OH$ b, Ac_2O c, CH_3COONH_4 d, $HCONH_2$ e, $CH(OC_2H_5)_3/Ac_2O$ f, HCOOH

Scheme 3



11a,b

a, X = O
b, X = S

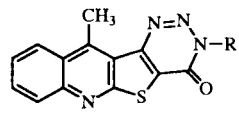


12a-d

a, R = H
b, R = phenyl
c, R = 2-pyridyl
d, R = 4-phenylthiazol-2-yl

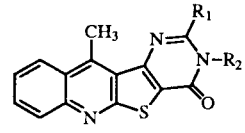
4a-i in boiling ethanol in the presence of sodium ethoxide is reported. Obviously this reaction occurred through the intermediacy of **5** which could be obtained when a less basic catalyst (sodium acetate) was used. Saponification of the amino ester **6a** using alcoholic sodium hydroxide gave the amino acid **7** which afforded the 2,11-dimethyloxazino[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **8** upon heating under reflux in glacial acetic acid (Scheme 2). Treatment of **8** with ammonium acetate in boiling acetic acid led to 2,11-dimethylpyrimido[4',5':4,5]thieno-[2,3-*b*]quinolin-4(3*H*)-one **9**. The same product **9** was obtained when **6e** was heated under reflux in acetic anhydride. On the other hand, when **6e** was treated with formamide or triethyl orthoformate in acetic anhydride the product was 11-methylpyrimido[4',5':4,5]thieno-[2,3-*b*]quinolin-4(3*H*)-one **10**. A third route for the synthesis of **10** involved the interaction of **6a** with formamide. The pyrimidothienoquinoline **11a** was obtained when **6a** was interacted with carbon disulphide in boiling pyridine. However when **6e,f,h,i** were used in this reaction, the derivatives **12a-d** were produced respectively. The fusion of the amino amide **6e** with urea gave the dione derivative **11b** (Scheme 3). *Ortho* amino amides have proved valuable for synthesizing various heterocycles. Diazotisation and self coupling of the amino amides **6a-i** led to the triazino derivatives **13a-e** respectively (Scheme 4). The pyrimidothienoquinoline **14a** also could be obtained when the amino amide **6e** was reacted with benzoyl chloride or benzaldehyde. Alternatively, compound **14a** was obtained by reacting the oxazino compound **8** with aniline. Condensation of **8** with ethyl glycinate, hydrazine hydrate or thiosemicarbazide led to the pyrimidothienoquinolines **14b-e** respectively (Scheme 4). It is worth mentioning that compound **14c** could be also obtained by reacting **9** with ethyl chloroacetate. The amino function of **14d** gave the expected Schiff's base **14f** and the acetyl derivative **14g**. Another synthesis of **14g** involved the treatment of amino hydrazide **15** with acetic

Scheme 4



13a-e

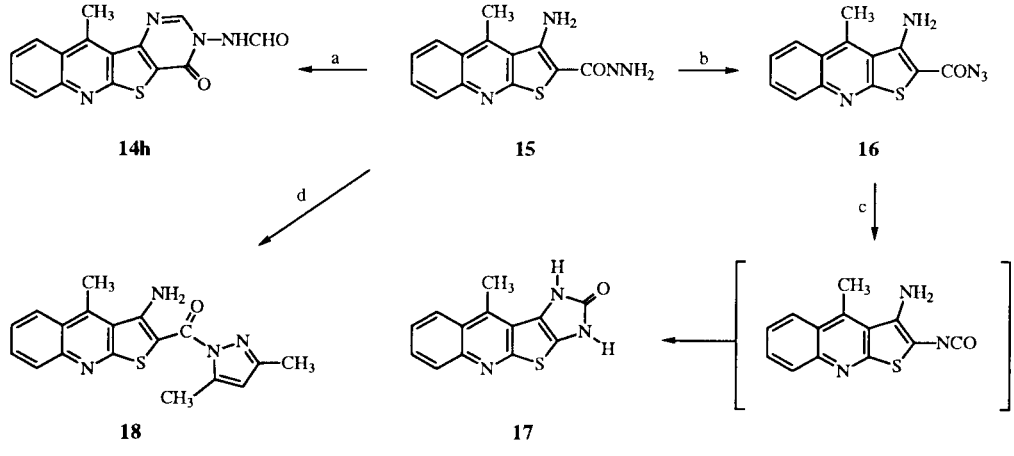
a, R = H
b, R = Phenyl
c, R = 4-$CH_3OC_6H_5$
d, R = 2-pyridyl
e, R = 4-phenylthiazol-2-yl



14a-h

a, R_1 = Ph, R_2 = H
b, R_1 = CH_3, R_2 = Ph
c, R_1 = CH_3, R_2 = $CH_2COOC_2H_5$
d, R_1 = CH_3, R_2 = NH_2
e, R_1 = CH_3, R_2 = $NHCSNH_2$
f, R_1 = CH_3, R_2 = N=CHPh
g, R_1 = CH_3, R_2 = $NHCOCH_3$
h, R_1 = H, R_2 = NHCHO

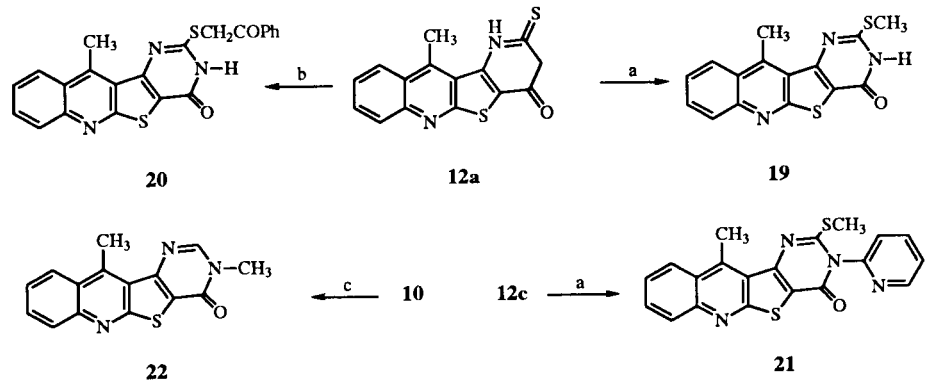
Scheme 5



14h **15** **16** **18** **17**

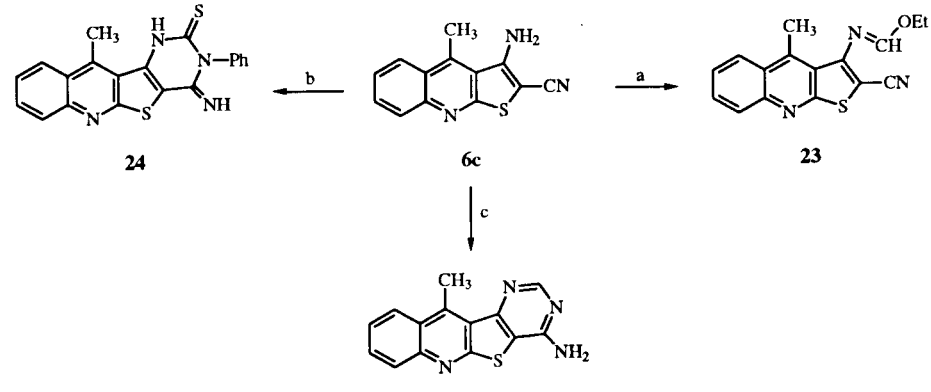
a, HCOOH, b, $NaNO_2$/AcOH, c, xylene (reflux), d, $CH_3COCH_2COCH_3$

Scheme 6



a, MeI/AcONa b, $PhCOCH_2Br$ c, MeI, Na_2CO_3/DMF

Scheme 7



a, $CH(OC_2H_5)_3$ b, PhNCO c, $HCONH_2$

anhydride. The formyl amino derivative **14h** was obtained upon treating the amino hydrazide **15** with formic acid (Scheme 5). The amino hydrazide **15** was obtained upon treatment of the amino ester **6a**, or its precursor **5a**, with hydrazine hydrate. The interaction of **15** with nitrous acid gave the corresponding amino azide **16** which was subjected to Curtius rearrangement in refluxing xylene to give the imidazothienoquinoline **17**. The interaction of **15** with acetyl acetone furnished the pyrazolyl derivative **18**.

Alkylation of **12a** with methyl iodide or ω-bromoacetophenone in ethanol in the presence of sodium acetate led to **19** and **20** respectively. The alkylation of **12c** with methyl iodide gave the desired compound **21**. On the other hand, the alkylation of **10** with methyl iodide gave the *N*-methylpyrimidinone derivative **22** (Scheme 6). 3-Amino-4-methylthieno[2,3-*b*]quinoline-2-carbonitrile **6c** was allowed to react with triethyl orthoformate, phenyl isocyanate and formamide to give **23**, **24** and **25** respectively (Scheme 7).

EXPERIMENTAL

All melting points are uncorrected and they were measured on a Kofler melting point apparatus. Elemental analysis was carried out on an elemental analyzer 240°C. The ir spectra were recorded on a pye Unicam SP3-100 and a Schimadzu 470 spectrophotometers in potassium bromide discs (ν cm^{-1}). The nmr spectra were recorded on a varian EM-390 (90 MHz) spectrophotometer using TMS as an internal standard. The chemical shifts are expressed as δ ppm.

3-Cyano-4-methylquinolin-2(1*H*)-one (**1**).

A mixture of 2-aminoacetophenone (25 g, 0.2 mole), ethyl cyanoacetate (45.2 g, 0.4 mole) and ammonium acetate (74 g, 1 mole) was heated under reflux for 1 hour. After cooling, the precipitate was filtered off, washed with ethanol and recrystallized from ethanol-dioxane (2:1) as colorless platelets, mp >300°, in quantitative yield; ir: ν cm^{-1} 3150 (NH); 2220 (C≡N), 1670 (C=O); ^1H nmr: δ 12.16 (s, 1H, NH), 7.05-8.10 (m, 4H, Ar), 2.73 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_8N_2O$: C, 71.72; H, 4.39; N, 15.21. Found: C, 71.42; H, 4.18; N, 15.35.

2-Chloro-4-methylquinoline-3-carbonitrile **2**.

A mixture of compound **1** (5 g, 0.027 mole) and phosphoryl chloride (15 ml) was heated under reflux for 3 hours. The excess phosphoryl chloride was then eliminated *in vacuo* and the residual solid was worked up in an ammonium hydroxide-ice mixture, filtered, washed with water and crystallized from ethanol as white crystals, mp 145-147°, yield 90%; ir: ν cm^{-1} 2220 (C≡N); 760 (C-Cl); ^1H nmr (deuteriochloroform): δ 7.70-8.20 (m, 4H, Ar-H), 3.10 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_7N_2Cl$: C, 65.18; H, 3.48; N, 13.82; Cl, 17.50. Found: C, 64.89; H, 3.47; N, 13.87; Cl, 17.64.

3-Cyano-4-methylquinoline-2(1*H*)-thione **3**.

Method [A].

A mixture of chloro derivative **2** (2 g, 0.01 mole) and thiourea (2.3 g, 0.01 mole) in ethanol (30 ml) was heated under reflux for 1 hour, then sodium hydroxide (20 ml, 10%) was added. The reaction mixture was cooled, acidified with HCl (15 ml, 50%) and the solid product was collected and crystallized from DMF-water (3:1) as yellow crystals, mp >300°, yield quantitative; ir: ν cm^{-1} 3380 (NH), 2240 (C≡N), 1220 (C=S).

Anal. Calcd. for $C_{11}H_8N_2S$ (200.24): C, 65.98; H, 4.03; N, 13.99; S, 16.01. Found: C, 66.27; H, 4.23; N, 14.18; S, 15.88.

Method [B].

A mixture of **2** (2 g, 0.01 mole) and phosphorus pentasulphide (4.44 g, 0.01 mole) in dry pyridine (25 ml) was heated under reflux for 4 hours. After cooling, the reaction mixture was diluted with cold water and acidified with hydrochloric acid. The precipitate was filtered, washed with water and crystallized from DMF-water, yield 89%.

Alkylation of 3-Cyano-4-methylquinoline-2(1*H*)-thione.

General Procedure.

Compound **3** (1 g, 0.005 mole) was dissolved in ethanolic solution of NaOH (20 ml, 10%), then the alkylating agent (0.05 mole) was added and the mixture was heated under reflux for 15 minutes. After cooling, the reaction mixture was poured onto a cold water and the solid product formed was collected and recrystallized from the proper solvent.

Ethyl (3-Cyano-4-methylquinolinylthio)acetate **5a**.

This compound was obtained from **3** and ethyl chloroacetate as yellow crystals (ethanol), mp 145-147°, yield 53%; ir: ν cm^{-1} 2225 (C≡N) and 1725 (C=O); ^1H nmr (DMSO-d_6): δ 7.50-8.40 (m, 4H, Ar), 6.60 (s, 2H, CH_2), 4.30-4.70 (q, 2H, CH_2, ester), 3.40 (s, 3H,CH_3), 1.40-1.70 (t, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.91; H, 4.92; N, 9.78; S, 11.20. Found: C, 62.61; H, 4.66; N, 9.50; S, 10.92.

2-Acetylmethylthio-4-methyl-3-quinolinecarbonitrile **5b**.

This compound was obtained from **3** and chloroacetone as yellow crystals (ethanol), mp 118-120°, yield 60%; ir: ν cm^{-1}, 2220 (C≡N) and 1725 (C=O).

Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93; S, 12.51. Found: C, 65.36; H, 4.86; N, 11.20; S, 12.61.

Cyclization of 2-Alkylthio-4-methylquinoline-3-carbonitrile: Formation of 3-Amino-2-substituted-4-methylthio[2,3-*b*]quinolines **6a-i**.

Method (A) for Compounds **6a,b**.

The mercapto derivative **5a** or **5b** (0.005 mole) was heated under reflux in ethanolic sodium ethoxide solution (0.5 g, 0.02 g-atom of sodium in 25 ml of absolute ethanol) for 30 minutes. After cooling, the solid product was filtered and recrystallized from ethanol.

Method (B) for Compounds **6c-i**.

To a solution of compound **3** (0.005 mole) in ethanolic sodium ethoxide solution (0.5 g, 0.02 g-atom of sodium in 25 ml of absolute ethanol), alkylating agent (0.005 mole) was added and the mixture was heated under reflux for 1 hour. After cooling, the solid product was collected and recrystallized from the proper solvent.

Ethyl 3-Amino-4-methylthieno[2,3-*b*]quinoline-2-carboxylate **6a**.

This compound was obtained from **5a** as yellow crystals (ethanol), mp 220-202°, yield quantitative; ir: ν cm^{-1} 3410, 3300 (NH_2), 1660 (C=O); ^1H nmr (DMSO-d_6): δ 7.40-8.30 (m, 4H, Ar), 7.00 (s, 2H, NH_2), 4.10-4.40 (q, 2H, CH_2, ester), 3.28 (s, 3H, CH_3), 1.15-1.40 (t, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.91; H, 4.92; N, 9.78; S, 11.20. Found: C, 62.81; H, 4.86; N, 9.60; S, 11.12.

2-Acetyl-3-amino-4-methylthieno[2,3-*b*]quinoline **6b**.

This compound was obtained from **5b** as yellow crystals (ethanol), mp 220-202°, yield quantitative, ir: ν cm^{-1} 3440, 3260 (NH_2), 1630 (C=O).

Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93; S, 12.51. Found: C, 65.83; H, 4.82; N, 11.00; S, 12.38.

3-Amino-4-methylthieno[2,3-*b*]quinoline-2-carbonitrile **6c**.

This compound was obtained from **3** and chloroacetonitrile as yellow crystals (dioxane), mp 290-292°, yield 84%; ir: ν cm^{-1} 3380, 3500 (NH_2), 2220 (C≡N); ^1H nmr (deuteriotrifluoreacetic acid): δ 7.80-8.80 (m, 4H, Ar), 3.75 (s, 3H, CH_3).

Anal. Calcd. for $C_{13}H_9N_3S$: C, 65.25; H, 3.97; N, 17.56; S, 13.40. Found: C, 65.47; H, 3.79; N, 17.55; S, 13.20.

3-Amino-2-benzoyl-4-methylthieno[2,3-*b*]quinoline **6d**.

This compound was obtained from **3** and ω-bromoacetophenone as scarlet red crystals (ethanol), mp 204-206°, yield 40%; ir: ν cm^{-1} 3380, 3500 (NH_2), 1650 (C=O); ^1H nmr (deuteriotrifluoreacetic acid): δ 7.50-8.70 (m, 4H, Ar), 3.60 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{14}N_2OS$: C, 71.67; H, 4.43; N, 8.80; S, 10.07. Found: C, 71.68; H, 4.37; N, 8.73; S, 10.44.

3-Amino-4-methylthieno[2,3-*b*]quinoline-2-carboxamide **6e**.

This compound was obtained from **3** and chloroacetamide as yellow crystals from dioxane, mp 278-280°, yield 78%; ir: ν cm^{-1} 3380, 3320 and 3180 (NH_2), 1660 (C=O); ^1H nmr (DMSO-d_6): δ 7.10-8.00 (m, 4H, Ar), 3.35 (s, 3H, CH_3), 7.20 (s, 2H, NH_2), 4.10 (s, 2H, $CONH_2$).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.42; H, 4.51; N, 16.08; S, 12.64.

3-Amino-4-methylthieno[2,3-*b*]quinoline-2-*N*-phenylcarboxamide **6f**.

This compound was obtained from **3** and chloroacetamide as yellow crystals (ethanol), mp 250-253°, yield 87%; ir: cm^{-1} 3420, 3300 (NH_2, NH) 1650 (C=O); ^1H nmr (DMSO-d_6):

δ 7.15-8.50 (m, 9H, Ar), 3.50 (s, 3H, CH_3), 4.15 (s, 2H, NH_2), 9.50 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60; S, 9.62. Found: C, 68.75; H, 4.50; N, 12.65; S, 9.33.

3-Amino-4-methylthieno[2,3-*b*]quinoline-2-*N*-(4-methoxyphenyl) carboxamide **6g**.

This compound was obtained from **3** and *N*-(chloroacetyl)-*p*-anisidine as yellow crystals (ethanol), mp 226-228°, yield 53%; ir: ν cm^{-1} 3480, 3420 (NH_2), 3340 (NH), 1660 (C=O); ^1H nmr (deuteriotrifluoreacetic acid): δ 7.90-8.65 (m, 4H, Ar-H), 7.00 (d, 2H, Ar-H), 7.42 (d, 2H, Ar-H), 4.00 (s, 3H, CH_3), 3.50 (s, 3H, OCH_3).

Anal. Calcd. for $C_{20}H_{17}N_3O_2S$: C, 66.10; H, 4.71; N, 11.56; S, 8.82. Found: C, 66.07; H, 4.72; N, 11.38; S, 8.75.

3-Amino-4-methylthieno[2,3-*b*]quinoline-2-*N*-(2-pyridyl)carboxamide **6h**.

This compound was obtained from **3** and 2-(chloroacetylamino)pyridine as orange crystals (acetone/ethanol; 1:1), mp 227-230°, yield 47%; ir: ν cm^{-1} 3380, 3330 (NH_2), 3240 (NH), 1680 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 7.20-8.75 (m, 8H, Ar), 3.45 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75; S, 9.59. Found: C, 64.39; H, 3.93; N, 16.74; S, 9.35.

3-Amino-4-methylthieno[2,3-*b*]quinoline-2-*N*-(4-phenylthiazol-2-yl)carboxamide **6i**.

This compound was obtained from **3** and 2-(chloroacetylamino)-4-phenylthiazole as orange crystals (dioxane), mp 265-267°, yield 33%; ir: ν cm^{-1} 3500, 3420 (NH_2), 3300 (NH), 1680 (C=O); ^1H nmr (DMSO-d_6): δ 7.30-8.40 (m, 11H, Ar + NH), 4.00 (NH_2), 3.50 (s, 3H, CH_3).

Anal. Calcd. for $C_{22}H_{16}N_4OS_2$: C, 63.44; H, 3.78; N, 13.45; S, 15.40. Found: C, 63.52; H, 3.96; N, 13.15; S, 15.76.

Sodium 3-Amino-4-methylthieno[2,3-*b*]quinoline-2-carboxylate **7**.

The amino ester **6a** was heated under reflux in ethanolic NaOH (30 ml, 10%) for 2 hours. The solid product obtained after cooling was filtered off, washed thoroughly with ethanol and dried. This compound was used as such in the next procedure.

2,11-Dimethyloxazino[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **8**.

The sodium salt **7** (10 g) was heated under reflux in acetic anhydride (30 ml) for 3 hours. The solid precipitate obtained on cooling was filtered and recrystallized from dioxane as yellow crystals, mp 295-297°, yield 67%; ir: ν cm^{-1} 1740 (C=O); ^1H nmr (deuteriochloroform): δ 7.90-8.70 (m, 4H, Ar-H), 2.70 (s, 3H, CH_3 oxazine), 3.70 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{10}N_2O_2S$: C, 63.82; H, 3.58; N, 9.93; S, 11.36. Found: C, 63.84; H, 3.34; N, 9.64; S, 11.22.

2,11-Dimethylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **9**.

Method (A):

A mixture of **3** (0.01 mole), ammonium acetate (0.02 mole) was heated under reflux in acetic acid for 3 hours. The solid product obtained after cooling was filtered off and recrystallized from dioxane/DMF (3/1), yellow crystals, mp >360°, yield 60%; ir: ν cm^{-1} 3150 (NH), 1680 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.00-8.90 (m, 4H, Ar-H), 3.70 (s, 3H, CH_3), 2.70 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.90; N, 14.94; S, 11.40. Found: C, 63.75; H, 3.87; N, 14.76; S, 11.61.

Method (B):

A solution of **6e** (1.28 g, 0.05 mole) in acetic anhydride (10 ml) was heated under reflux for 10 hours. After cooling the solid compound was collected and recrystallized from dioxane/DMF (3/1) as yellow crystals, yield 30%.

Method (C):

A solution of **3c** (1 g, 0.004 mole) in acetic anhydride (20 ml) was heated under reflux for 10 hours. The solid product obtained after cooling was collected and recrystallized, yield 26%. The melting point and the spectral data obtained following both the two methods B and C are the same as those obtained according to method A.

11-Dimethylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **10**.

Method (A):

A mixture of **6e** (0.5 g, 0.002 mole), triethyl orthoformate (3 ml) and acetic anhydride (20) was heated under reflux for 3 hours. The solid precipitate was collected and recrystallized from DMF as buff needles, mp >360°, yield 77%; ir ν cm^{-1} 3150 (NH), 1670 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.00-9.00 (m, 5H, Ar-H), 4.00 (s, 3H, CH_3).

Anal. Calcd. for $C_{14}H_9N_3OS$: C, 62.90; H, 3.39; N, 15.72; S, 12.00. Found: C, 63.14; H, 3.59; N, 15.49; S, 12.24.

Method (B):

A mixture of **6e** (0.5 g, 0.002 mole) and formic acid (20 ml) was heated under reflux for 5 hours. The solid product thus formed on cooling was collected and recrystallized from (DMF) as buff needles, yield 64%.

11-Methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinoline-(1H,3H)2,4-dithione **11a**.

A mixture of **6c** (1.19 g, 0.005 mole), carbon disulphide (2 ml) and dry pyridine (20 ml) was heated under reflux for 8 hours. The precipitate was collected after cooling and recrystallized from pyridine as red crystals, mp >300° ir: ν cm^{-1} 3150 (NH), 1220 (C=S)

Anal. Calcd. for $C_{14}H_9N_3S_3$: C, 53.30; H, 2.87; N, 13.32; S, 30.49. Found: C, 53.03; H, 3.16; N, 13.33; S, 30.35.

11-Methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinoline-(1*H*,3*H*)-2,4-dione **11b**.

A mixture of **6e** (0.5 g, 0.002 mole) and urea (1.3 g, 0.022 mole) was fused over a small flame for 30 minutes. The solid product obtained after cooling was stirred with water (15 ml) for 5 minutes and then it was filtered and recrystallized from DMF as yellow crystals, mp >300°, yield 80%, ir: ν cm^{-1} 3150 (NH), 1650 (C=O), 1580 (C=O).

Anal. Calcd. for $C_{14}H_9N_3O_2S$: C, 59.35; H, 3.20; N, 14.83; S, 11.31. Found: C, 59.20; H, 3.45; N, 14.71; S, 11.20.

11-Methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-3,4-dihydro-4-oxo-2(1*H*)-thione **12a**.

This compound was obtained using **6e** following the same procedure as that of **11a**, yellow crystals from DMF, mp >300°,

yield 91%; ir: ν cm^{-1} 3430 (NH), 1650 (C=O), 1200 (C=S); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.20-8.85 (m, 4H, Ar-H), 3.87 (s, 3H, CH_3).

Anal. Calcd. for $C_{14}H_9N_3OS_2$: C, 56.17; H, 3.03; N, 14.04; S, 21.42. Found: C, 56.51; H, 2.89; N, 14.25; S, 21.24.

11-Methyl-3-phenylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-3,4-dihydro-4-oxo-2(1*H*)-thione **12b**.

This compound was obtained using **6f** following the same procedure as that of **11a**, yellow crystals from ethanol, mp >300° yield 67%; ir: ν cm^{-1} 3420 (NH), 1690 (C=O), 1200 (C=S); ^1H nmr (deuteriotrifluoroacetic acid): δ 7.60-8.80 (m, 9H, Ar-H), 3.80 (s, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{13}N_3OS_2$: C, 63.98; H, 3.49; N, 11.19; S, 17.08. Found: C, 64.14; H, 3.39; N, 11.32; S, 17.00.

11-Methyl-3-(2-pyridyl)pyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-3,4-dihydro-4-oxo-2(1*H*)thione **12c**.

This compound was obtained using **6h** following the same procedure as that of **11a**, yellow crystals from ethanol, mp 287-289°, yield 60%; ir: ν cm^{-1} 3360 (NH), 1680 (C=O), 1200 (C=S); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.20-9.20 (m, 8H, Ar-H), 3.35 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{12}N_4OS_2$: C, 60.60; H, 3.22; N, 14.88; S, 17.03. Found: C, 60.74; H, 2.94; N, 14.73; S, 16.81.

11-Methyl-3-(4-phenylthiazol-2-yl)pyrimido[4',5':4,5]thieno-[2,3-*b*]quinolin-3,4-dihydro-4-oxo-2(1*H*)-thione **12d**.

This compound was obtained using **6i** following the same procedure as that of **11a**, yellow crystals from ethanol, mp 268-270°, yield 26%; ir: ν cm^{-1} 3320 (NH), 1680 (C=O), 1210 (C=S).

Anal. Calcd. for $C_{23}H_{14}N_4OS_3$: C, 60.24; H, 3.08; N, 12.22; S, 20.97. Found: C, 60.42; H, 3.04; N, 12.19; S, 20.93.

11-Methyl-3-substituted-3,4-dihydro-4-oxo-1,2,3-triazino-[4',5':4,5]thieno[2,3-*b*]quinolins **13a-e.**

General Procedure.

To a cold (0 solution of **6e-i** (0.002 mole) in diluted HCl (10 ml, 50%), was added dropwise with stirring a cold solution of sodium nitrite (0.69 g in 10 ml of water). Stirring was continued at this temperature for 20 minutes, then it was left to stand at room temperatute for 3 hours. The solid product thus formed was collected and recrystallized from ethanol/dioxane mixture (1:1).

11-Methyl-1,2,3-triazino[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **13a**.

This was obtained from **6e** as brown crystals, mp 258-260°, yield 42%; ir: ν cm^{-1} 3725 (NH), 1685 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.00-8.90 (m, 4H, Ar-H), 4.00 (s, 3H, CH_3).

Anal. Calcd. for $C_{13}H_8N_4OS$: C, 58.20; H, 3.01; N, 20.88; S, 11.95. Found: C, 58.47; H, 3.14; N, 20.97; S, 11.68.

11-Methyl-3-phenyl-1,2,3-triazino[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **13b**.

This was obtained from **6f** as white crystals, mp 270-272°, yield 70%; ir: ν cm^{-1} 1680 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.00-8.90 (m, 4H, Ar-H), 7.70 (s, 5H, Ph), 4.00 (s, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{12}N_4OS$: C, 66.26; H, 3.51; N, 16.27; S, 9.31. Found: C, 66.55; H, 3.38; N, 16.32; S, 9.42.

3-Anisyl-11-methyl-1,2,3-triazino[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **13c**.

This was obtained from **6g** as yellow crystals, mp 278-289°, yield quantitative; ir: ν cm^{-1} 1680 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.20-8.90 (m, 4H, Ar-H), 7.20 (d, 2H, Ar-H.), 7.70 (d, 2H, Ar H), 4.00 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{14}N_4O_2S$: C, 64.15; H, 3.77; N, 14.96; S, 8.69. Found: C, 64.24; H, 3.56; N, 14.79; S, 8.63.

11-Methyl-3-(2-pyridyl)-1,2,3-triazino[4',5':4,5]thieno[2,3-*b*]-quinolin-4(3*H*)-one **13d**.

This was obtained from **6h** as brown crystals, mp 238-241°, yield 45%; ir: ν cm^{-1}, 1698 (C=O); ^1H nmr (DMSO-d_6): δ 7.30-8.80 (m, 8H, Ar-H), 3.30 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{11}N_5OS$: C, 62.60; H, 3.21; N, 20.28; S, 9.28. Found: C, 62.79; H, 3.44; N, 20.60; S, 9.37.

11-Methyl-3-(4-phenylthiazol-2-yl)-1,2,3-triazino[4',5':4,5]-thieno[2,3-*b*]quinolin-4(3*H*)-one **13e**.

This was obtained from **6i** as yellow crystals, mp 260-263°, yield 52%; ir: cm^{-1} 1680 (C=O).

Anal. Calcd. for $C_{22}H_{13}N_5OS_2$: C, 61.81; H, 3.02; N, 16.38; S, 15.00. Found: C, 61.62; H, 3.08; N, 16.52; S, 14.74.

11-Methyl-3-phenylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **14a**.

Method (A):

A mixture of **6e** (0.5 g, 0.002 mole) and benzoyl chloride (10 ml) was heated under reflux for 2 hours. The excess of benzoyl chloride was extracted with benzene and the residue was crystallized from dioxane as brown crystals, mp >300°, yield 30%; ir: ν cm^{-1} 3100 (NH), 1700 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 7.70-8.90 (m, 9H, Ar), 4.00 (s, 3H, CH_3).

Anal. Calcd. for $C_{20}H_{13}N_3OS$: C, 69.95; H, 3.81; N, 12.23; S, 9.33. Found: C, 69.72; H, 4.14; N, 12.50; S, 9.35.

Method (B):

A mixture of **6e** (0.5 g, 0.002 mole) and benzaldehyde (0.002 mole) in ethanol (10) ml) was heated under reflux for 20 hours. The reaction mixture was then concentrated and the solid product formed was collected and recrystallized from dioxane as brown crystals, mp >360°, yield 40%.

2,11-Dimethyl-3-phenylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **14b**.

A mixture of **8** (0.56 g, 0.002 mole) and aniline (0.004 mole) in acetic acid (20 ml) was heated at reflux for 3 hours. After cooling, the product was collected and recrystallized from dioxane as yellow crystals, mp >300°, yield 62%; ir: ν cm^{-1} 1680 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 7.35-8.90 (m, 9H, Ar-H), 4.00 (s, 3H, CH_3), 2.70 (s, 3H, CH_3).

Anal. Calcd. for $C_{21}H_{15}N_3OS$: C, 70.56; H, 4.23; N, 11.75; S, 8.97. Found: C ,70.65; H, 4.60; N, 11.93; S, 8.91.

Ethyl [2,11-Dimethylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-on-3-yl]acetate **14c**.

Method(A):

To a solution of **9** (0.3 g, 0.001 mole) in DMF (15 ml) potassium carbonate (0.5 g, 0.006 mole) was added and the mixture was stirred at room temperature for 15 minutes, followed by the addition of ethyl chloroacetate (1.34 g, 0.001 mole) in DMF

(5 ml). Stirring was continued for 2 hours further and then the reaction mixture was diluted with water. The solid product thus formed was collected and recrystallized from ethanol as yellow needles, mp 298-300°, yield 66%; ir: ν cm^{-1} 1750 (C=O), 1660 (C=O); ^1H nmr (dueteriochloroform): δ 7.90-8.60 (m, 4H, Ar-H), 5.00 (s, 2H, CH_2), 4.10 (q, 2H, CH_2), 3.75 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 1.33 (t, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{17}N_3O_3S$: C, 62.10; H, 4.66; N, 11.43; S, 8.72. Found C, 62.35; H, 4.60; N, 11.53; S, 8.88.

Method(B):

A mixture of **8** (0.56 g, 0.002 mole) and ethyl glycinate hydrochloride (0.004) in pyridine (20 ml) was heated under reflux for 4 hours. The product formed after cooling was collected and recrystallized from ethanol as yellow needles, mp 298-300°, yield 66%.

3-Amino-2,11-dimethylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **14d**.

A mixture of **8** (2.8 g, 0.01 mole) and hydrazine hydrate (0.02 mole) was heated under reflux in ethanol (50 ml) for 2 hours. The product formed after cooling was collected and recrystallized from a mixture of ethanol/chloroform (1:1) as yellow crystals, mp >300°, yield 79%; ir: ν cm^{-1} 3350, 3200 (NH_2), 1650 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 7.85-8.80 (m, 4H, Ar-H), 3.80 (s, 3H, CH_3), 2.90 (s, 3H, CH_3 pyrimidine).

Anal. Calcd. for $C_{15}H_{12}N_4OS$: C, 60.79; H, 4.08; N, 18.90; S, 10.81. Found: C, 60.96; H, 4.36; N, 18.76; S, 10.81.

N-[2,11-Dimethylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-on-3-yl]thiourea **14e**.

A mixture of **8** and thiosemicarbazide (0.56 g, 0.002 mole) was heated under reflux in acetic acid (20 ml) for 2 hours. The solid product obtained upon cooling was collected and recrystallized from dioxane as yellow crystals, mp 241-243°, yield 63%; ir: ν cm^{-1} 3450, 3300 (NH_2), 3150 (NH), 1670 (C=O), 1250 (C=S).

Anal. Calcd. for $C_{16}H_{13}N_4OS_2$: C, 54.06; H, 3.68; N, 19.70; S, 18.04. Found: C, 54.17; H, 3.92; N, 19.41; S, 18.00.

2-Benzylideneamino-2,11-dimethylpyrimido[4',5':4,5]thieno-[2,3-*b*]quinolin-4(3*H*)-one **14f**.

To a mixture of **14d** (0.58 g, 0.002 mole) and benzaldehyde (0.002 mole) in ethanol (15 ml) 3 drops of piperidine were added. The reaction mixture was then heated at reflux for 3 hours. The solid product formed while hot was collected and recrystallized as colorless crystals, mp >300°, yield 52%; ir: ν cm^{-1} 1670 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.10-8.90 (m, 9H, Ar-H), 4.50 (s, 1H, N=NH), 4.00 (s, 3H, CH_3), 3.15 (s, 3H, CH_3 pyrimidine).

Anal. Calcd. for $C_{22}H_{16}N_4OS$: C, 68.73; H, 4.19; N, 14.57; S, 8.33. Found: C, 68.55; H, 4.23; N, 14.64; S, 8.16.

3-Acetylamino-2,11-dimethylpyrimido[4',5':4,5]thieno[2,3-*b*]-quinolin-4(3*H*)-one **14g**.

A mixture of **14d** (0.01 mole) and acetic anhydride (20 ml) was heated under reflux for 3 hours and then it was allowed to cool. The solid precipitate was collected and recrystallized from acetic acid as yellow crystals mp 231-232°, yield 50%. Alternatively, the same product was obtained, in a comparable yield, when compound **15** was used instead of **14d**; ir: ν cm^{-1} 3400 (NH), 1750 (C=O, $COCH_3$), 1700 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 7.40-8.30 (m, 4H, Ar-H), 3.35 (s, 3H, CH_3, at C-11), 2.60 (s, 3H, CH_3 pyrimidine), 2.50 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56; S, 9.47. Found: C, 60.42; H, 4.32; N, 16.29; S, 9.20.

3-Formylamino-11-methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **14h**.

A mixture of **15** (0.54 g, 0.002 mole) and formic acid (10 ml) was heated at reflux for 4 hours, then it was allowed to cool. The solid precipitate was collected and recrystallized from a mixture of dioxane/DMF (2:1) as colorless crystals, mp >300°, yield 67%; ir: ν cm^{-1} 3310 (NH), 3300 (NH), 1720 (HC=O), 1680 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.70 (s, 1H, CH pyramidine), 8.10-8.80 (m, 4H, Ar-H), 8.86 (s, 1H, CHO), 3.90 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{10}N_4O_2S$: C, 58.06; H, 3.25; N, 18.06; S, 10.33. Found: C, 57.99; H, 3.22; N, 18.00; S, 10.62.

3-Amino-4-methylthieno[2,3-*b*]quinoline-2-carboxhydrazide **15**.

A mixture of **5a** (0.01 mole) and hydrazine hydrate (5 g, 0.1 mole) in ethanol was heated under reflux for 2 hours, and was then allowed to cool. The solid precipitate was filtered, washed with water and crystallized from dioxane as yellow needles, mp 252-254°, yield 98%. Alternatively, it was obtained in 95% yield using compound **6** instead of **5a**; ir: ν cm^{-1} 3510, 3420, 3350 (NH-NH_2), 1650 (C=O); ^1H nmr (DMSO-d_6): δ 9.10 (s, 1H, NH), 7.50-8.30 (m, 4H, Ar-H), 7.00 (s, 2H, NH_2), 4.40 (s, br, 2H, NH_2 carbohydrazide), 3.35 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{12}N_4OS$: C, 60.79; H, 4.08; N, 18.90; S, 10.81. Found: C, 60.96; H, 4.36; N, 18.76; S, 10.81.

3-Amino-4-methylthieno[2,3-*b*]quinoline-2-carboxyazide **16**.

A solution of sodium nitrite (0.7 g, 0.002 mole) in water (7 ml) was added with stirring to a solution of compound **15** (0.54 g, 0.002 mole) in acetic acid (10 ml) during 5 minutes at room temperature. The solid product was filtered, washed with cold water and air dried, mp 158-160° (dec), yield 80%; ir: ν cm^{-1} 3450, 3340 (NH_2), 2215 (CON_3) 1660 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.40-8.80 (m, 4H, Ar-H), 3.95 (s, 3H, CH_3).

Anal. Calcd. for $C_{13}H_9N_5OS$: C, 55.11; H, 3.21; N, 24.73; S, 11.32. Found: C ,55.30; H, 3.38; N, 24.35; S, 11.41.

10-Methylimidazo[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **17**.

The carboxyazide **16** (0.56 g, 0.002 mole) was heated at reflux in xylene (20 ml) for 30 minutes and then was allowed to cool. The solid product was filtered, washed with petroleum ether, dried and recrystallized from dioxane as colorless crystals, mp 292-294°, yield 80%; ir: ν cm^{-1} 3510, 3400 (NH), 3320 (NH), 1670 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 9.10 (s, 1H, NH), 8.20-8.80 (m, 4H, Ar-H), 3.35 (s, 3H, CH_3).

Anal. Calcd. for $C_{13}H_9N_3OS$: C, 61.16; H, 3.56; N, 16.46; S, 12.55. Found: C, 61.46; H, 3.62; N, 16.54; S, 12.33.

3-Amino-4-methyl-2-(3,5-dimethylpyrazol-1-yl)carbonylthieno [2,3-*b*]quinoline **18**.

A mixture of **15** (0.54 g, 0.002 mole) and acetyl acetone (0.002 mole) was heated under reflux in ethanol (20 ml) for 4 hours and was then allowed to cool. The solid precipitate was filtered and recrystallized from ethanol as reddish-orange crystals, mp 205-207°, yield 50%; ir: ν cm^{-1} 3540, 3340 (NH_2), 1650 (C=O); ^1H nmr (deuteriochloroform): δ 8.00-8.60 (m, 4H, Ar-H), 7.10-7.20 (b, 2H, NH_2), 6.20 (s, 1H, CH pyrazole), 3.45 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 2.38 (s, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{16}N_4OS$: C, 64.26; H, 4.79; N, 16.66; S, 9.53. Found C, 64.41; H, 5.03; N, 16.45; S, 9.44.

11-Methyl-2-methylthiopyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **19**.

To a mixture of **12a** (0.5 g, 0.0017 mole) and anhydrous sodium acetate(2 g, 0.024 mole) in ethanol (30 ml), methyl iodide (0.238 g, 0.0017 mole) was added and the reaction mixture was heated under reflux for 12 hours. The solid product obtained after cooling was collected and recrystallized from dioxane as yellow crystals, mp 267-268° yield 55%; ir: ν cm^{-1} 3480 (NH),1660 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.20-8.90 (m, 4H, Ar), 4.00 (s, 2H, CH_3), 3.00 (s, 3H, SCH_3)

Anal. Calcd. for $C_{15}H_{11}N_3OS_2$: C, 57.48; H, 3.54; N, 13.41; S, 20.46. Found: C, 57.29; H, 3.48; N, 13.50; S, 20.34.

11-Methyl-2-phenacylthiopyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **20**.

This compound was obtained following the same procedure of compound **19** using phenacyl bromide. Recrystallization from dioxane gave yellow crystals, mp >300°, yield 57%; ir: ν cm^{-1} 3550 (NH), 1690 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 7.80-8.60 (m, 9H, Ar-H), 5.35 (s, 2H, CH_2), 3.50 (s, 3H, CH_3).

Anal. Calcd. for $C_{22}H_{15}N_3O_2S_2$: C, 63.28; H, 3.63; N, 10.07; S, 15.36. Found: C, 63 33; H, 3.92; N, 10.23; S, 15.49.

11-Methyl-2-methylthio-3-(2-pyridyl)pyrimido[4',5':4,5]thieno-[2,3-*b*]quinolin-4(3*H*)-one **21**.

This compound was obtained using **12c** following the same procedure of compound **19**. Recrystallization from ethanol gave buff crystals, mp 110-112°, yield 70%; ir: ν cm^{-1} 1670 (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.20-8.90 (m, 8H, Ar-H), 4.00 (s, 2H, CH_3), 3.00 (s, 3H, SCH_3)

Anal. Calcd. for $C_{20}H_{14}N_4OS_2$: C, 61.51; H, 3.62; N, 14.35; S, 16.42. Found C, 61.36; H, 3.42; N, 14.52; S, 16.53.

3,11-Dimethylpyrimido[4',5':4,5]thieno[2,3-*b*]quinolin-4(3*H*)-one **22**.

A mixture of **10** (0.53 g, 0.002 mole), methyl iodide (0.7 g, 0.005 mole) and potassium carbonate (0.5 g) in DMF (20 ml) was stirred at room temperature for 2 hours. After dilution with water, the solid product was filtered, dried and recrystallized from EtOH/DMF (2:1) as yellow crystals, mp >300°, yield 76%; ir: ν cm^{-1} 1670 (C O); ^1H nmr (deuteriotrifluoroacetic acid): δ 9.85 (s, 1H, CH) ,7.40-8.35 (m, 4H, Ar-H), 3.40 (s, 2H, CH_3), 3.25 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94; S, 11.40. Found: C, 64.24; H, 3.97; N, 14.90; S, 11.33.

2-Cyano-3-ethoxymethyleneamino-4-methylthieno[2,3-*b*]quinoline **23**.

A mixture of **6c** (0.3, 0.0012 mole) and triethylorthoformate (3 ml) in acetic anhydride (10) ml was heated under reflux for 3 hours, then it was allowed to cool. The reaction mixture was diluted with cold water and the solid product was collected and recrystallized from ethanol as brown crystals, mp 145-147°, yield 60%; ir: ν cm^{-1} 2220 (C≡N); ^1H nmr (deuteriochloroform): δ 7.20-8.20 (m, 5H, Ar + N=CH), 4.65-4.32 (q, 2H, CH_2), 3.10 (s, 3H, CH_3), 1.38-1.60 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23; S, 10.85. Found: C, 65.00; H, 4.58; N, 14.20; S, 10.74.

4-Imino-3-phenylpyrimido[4',5':4,5]thieno[2,3-*b*]quinoline-2(1)-thione **24**.

A mixture of **5c** (0.48 g, 0.002 mole) and phenylisothiocyanate (0.27 g, 0.002 mole) in pyridine (20 ml) was heated at reflux for 20 hours. After cooling, the product formed was filtered and recrystallized from pyridine as buff crystals, mp >300°, yield 52%; ir: ν cm^{-1} 3400 (NH), 3100 (NH), 1220 (C=S).

Anal. Calcd. for $C_{20}H_{14}N_4S_2$: C, 64.14; H, 3.77; N, 14.96; S, 17.12. Found: C 64.21; H, 3.80; N, 14.80; S, 17.26.

4-Amino-11-methylpyrimido[4',5':4,5]thieno[2,3-*b*]quinoline **25**.

A mixture of **6b** (0.48 g, 0.002 mole) and formamide (10 ml) was refluxed for 2 hours. The solid product, formed after cooling, was filtered and recrystallized from acetic acid as brown crystals, mp >300°, yield 43%; ir: ν cm^{-1} 3450, 3300 (NH_2).

Anal. Calcd. for $C_{14}H_{10}N_4S$: C, 63.13; H, 3.78; N, 21.03; S, 12.03. Found: C, 63.22; H, 3.69; N, 20.96; S, 11.75.

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