Synthesis of Novel Pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidines, Pyrido [3'',2'':4',5']thieno[3',2':4,5]pyrimido[1,6-*a*]benzimidazoles and Related Fused Systems

E. A. Bakhite*

Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt

A. G. Al-Sehemi

Department of Chemistry, Teachers College at Abha, B.O.Box. 249, Saudi Arabia

Y. Yamada*

Department of Chemistry, Faculty of Education, Utsunomiya University, Utsunomiya 321-8505, Japan

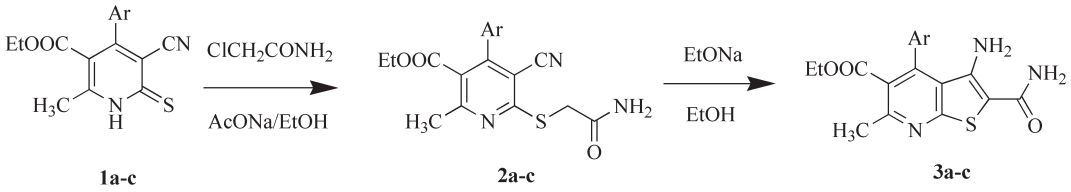
Received December 6, 2004

3-Amino-4-aryl-5-ethoxycarbonyl-6-methylthieno[2,3-*b*]pyridine-2-carboxamides **3a-c** were prepared from ethyl 4-aryl-3-cyano-6-methyl-2-thioxo-1,2-dihydropyridine-5-carbonylates **1a-c** and reacted with some carbonyl compounds to give tetrahydropyridothienopyrimidine derivatives **6a-c**, **7a-c** and **8a-c**, respectively. Treatment of compound **3c** with chloroacetyl chloride led to the formation of a next key compound, ethyl 2-chloromethyl-4-oxo-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate **9**. Also, 3-amino-2-benzimidazolylthieno[2,3-*b*]pyridine-5-carboxylate **5** and 2-(3'-aminothieno [2,3-*b*]pyridin-2'-yl)-4-oxo-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate **17** were prepared from **1c**. The compounds **5**, **9** and **17** were used as good synthons for other pyridothienopyrimidines and pyridothienopyrimidobenzimidazoles as well as for related fused polyheterocyclic systems.

J. Heterocyclic Chem., **42**, 1069 (2005).

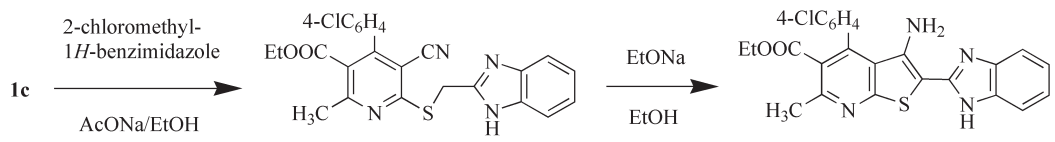
The biological activities of condensed pyrimidines as sedatives, antibacterials and antimalarials are well documented [1,2]. Numerous thieno[2,3-*b*]pyridines have been investigated in relation with their biological and pharmacological activities. Some of them proved to possess antibacterial [3,4], antiviral [5], antihypertensive [6] and immunostimulating [7] activities. Others are useful as gonadtropin-releasing hormone antagonists [8-13] and as lipoxygenase inhibitors [14]. Recently, certain thieno[2,3-*b*]pyridine derivatives were prepared as antinflammatory agents, particularly for treating arthritis and bone resorption inhibiting agents [15]. Pyridothienopyrimidine derivatives have been found in applications as analgesics [16], antipyretics [17] and anti-inflammatories [18]. Encouraged by all these facts and as a continuation of our program directed towards the synthesis of new condensed thieno[2,3-*b*]pyridines [19-21], we undertook the synthesis of the title compounds which may show good biological and medical applications.

Scheme 1



1a-c **2a-c** **3a-c**

a: Ar=phenyl
b: Ar=4-$CH_3OC_6H_4$
c: Ar=4-ClC_6H_4



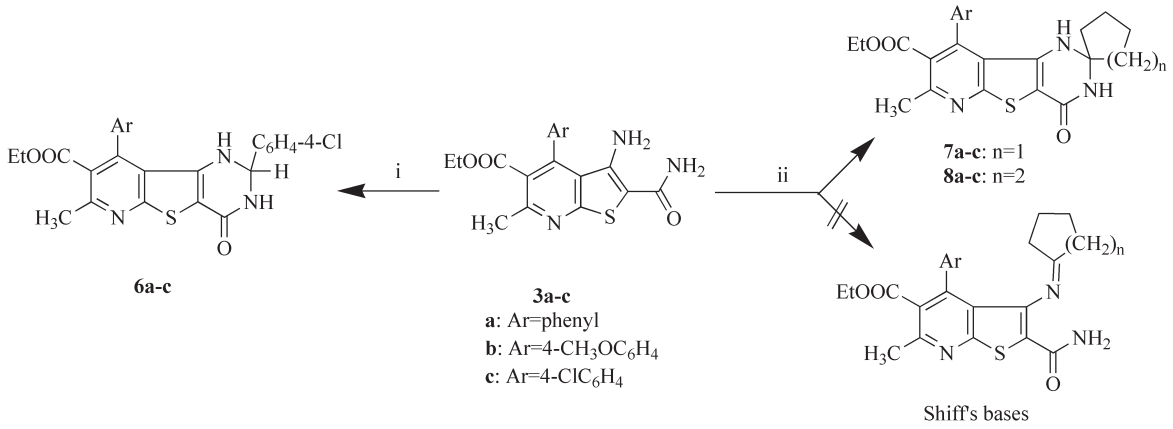
4 **5**

The reaction of ethyl 4-aryl-3-cyano-6-methyl-2-thioxo-1,2-dihydropyridine-5-carbonylates **1a-c** [22] with chloroacetamide in the presence of sodium acetate gave 4-aryl-3-cyanopyridin-2-ylthioacetamides **2a-c**. Upon treatment of these compounds with sodium ethoxide in ethanol, they underwent intramolecular *Thorpe-Ziegler* cyclization to give 3-amino-4-arylthieno[2,3-*b*]pyridine-2-carboxamides **3a-c**. Similarly, the reaction of **1c** with 2-chloromethyl-1*H*-benzimidazole led to the formation of benzimidazolyl derivative **4**. The latter compound was cyclized into ethyl 3-amino-2-(1'*H*-2'-benzimidazolyl)-4-(4'-chlorophenyl)-6-methylthieno[2,3-*b*]pyridine-5-carboxylate (**5**) upon treatment with sodium ethoxide (Scheme 1).

The compounds **3a-c** and **5** were used as starting compounds in this investigation. Thus, refluxing of *vic*-aminoamides **3a-c** with 4-chlorobenzaldehyde in acetic acid or in ethanol containing a few drops of concentrated hydrochloric acid afforded the corresponding tetrahydropyridothienopyrimidines **6a-c**. Upon treatment of **3a-c** with cyclopentanone and with cyclohexanone under the same conditions, the products were respectively identified as spiro compounds **7a-c** and **8a-c**, rather than Schiff's bases [23] (Scheme 2).

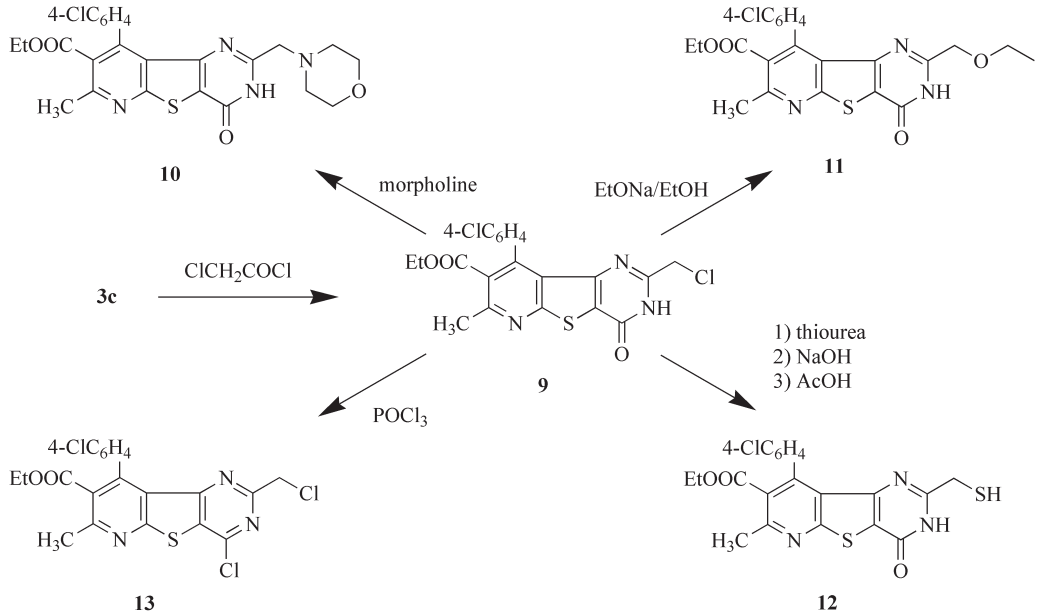
The cyclocondensation of **3c** with chloroacetyl chloride resulted in the formation of ethyl 2-chloromethyl-9-(4'-chlorophenyl)-7-methyl-4-oxo-3,4-dihydropyrido[3',2':4,5]-

Scheme 2



(i) 4-chlorobenzaldehyde/AcOH or EtOH-HCl
(ii) cyclopentanone or cyclohexanone/AcOH or EtOH-HCl

Scheme 3



thieno[3,2-*d*] pyrimidine-8-carboxylate (**9**) which proved to be a good synthon for other pyridothienopyrimidine derivatives as well as for related polycyclic systems. Thus, the reaction of **9** with morpholine and with sodium ethoxide gave the corresponding pyrimidinone derivatives **10** and **11**, respectively. The interaction of **9** with thiourea produced an adduct which upon treatment with sodium hydroxide followed by acidification with acetic acid furnished the mercaptomethylpyrimidinone derivative **12**. Heating of compound **9** with an excess amount of phosphorous oxychloride afforded the dichloro derivative **13** (Scheme 3).

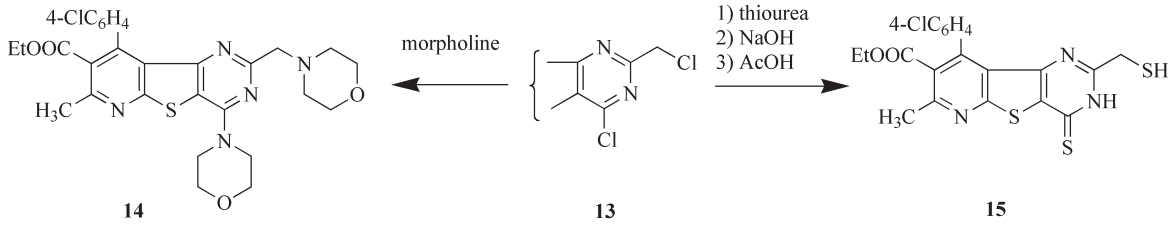
Preferential replacement of a chlorine atom in **13** was not possible due to the equally mobile nature of both the chlorine atoms [24]. All such reactions led to the formation of disubstituted products. Thus, it gave ethyl 9-(4'-chlorophenyl)-7-methyl-4-morpholino-2-morpholinomethylpyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**14**) with morpholine and ethyl 9-(4'-chlorophenyl)-7-methyl-2-mercaptomethyl-4-thioxo-3*H*-pyrido[3',2':4,5]-thieno[3,2-*d*]pyrimidine-8-carboxylate (**15**) upon treatment with thiourea followed by heating the resulting product with sodium hydroxide and then acidified with acetic acid (Scheme 4).

compound underwent intramolecular *Thorpe-Zeigler* cyclization upon heating with sodium ethoxide in ethanol to furnished 2-(thieno[2,3-*b*]pyridin-2'-yl)-pyrido-[3',2':4,5]thieno[3',2'-*d*]pyrimidine-4(3*H*)-one derivative **17** (Scheme 5).

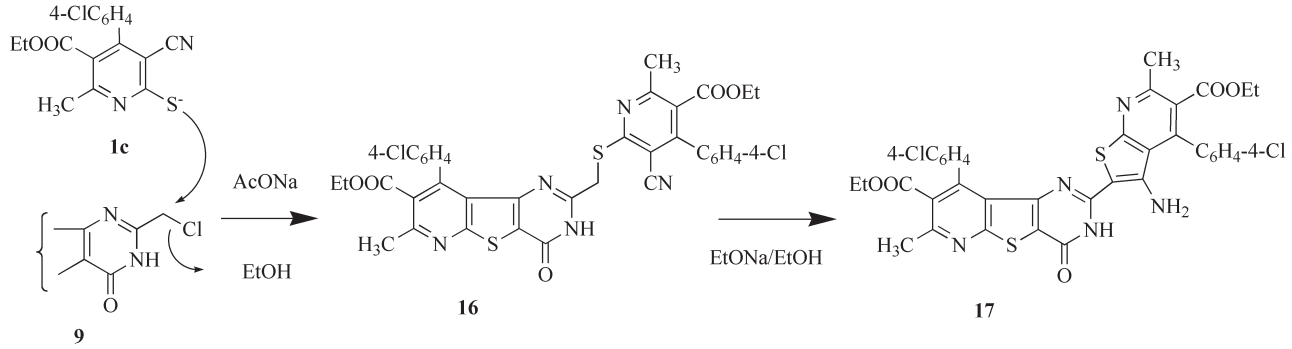
Furthermore, compound **5**, also having the γ-aminoimine structure, was used as the key intermediate for synthesizing some heterocyclic compounds containing both theino[2,3-*b*]pyridine and benzimidazole moieties. Thus, the reaction of **5** with triethyl orthoformate, acetic anhydride, 4-chlorobenzaldehyde and carbon disulfide led to the formation of pyrido[3",2":4',5']thieno[3',2':4,5]pyrimido[1,6-*a*]benzimidazoles **22**, **23**, **24** and **25**, respectively. Treatment of **5** with nitrous acid resulted in diazotisation followed by the self coupling to give the corresponding pyrido[3'',2'':4',5']thieno[3',2':4,5][1,2,3]triazino[1,6-*a*]benzimidazole derivative **26** (Scheme 7).

In conclusion, 1,3-diamino compound **3** and 3-aminoimine compound **5**, investigated are good starting materials to construct fused polyheterocyclic system. And the reactive chloromethyl compound **9**, thus obtained, has the advantage of a building block for complex heterocyclic compounds. Moreover, 3-aminoimine compound **17**, pre-

Scheme 4

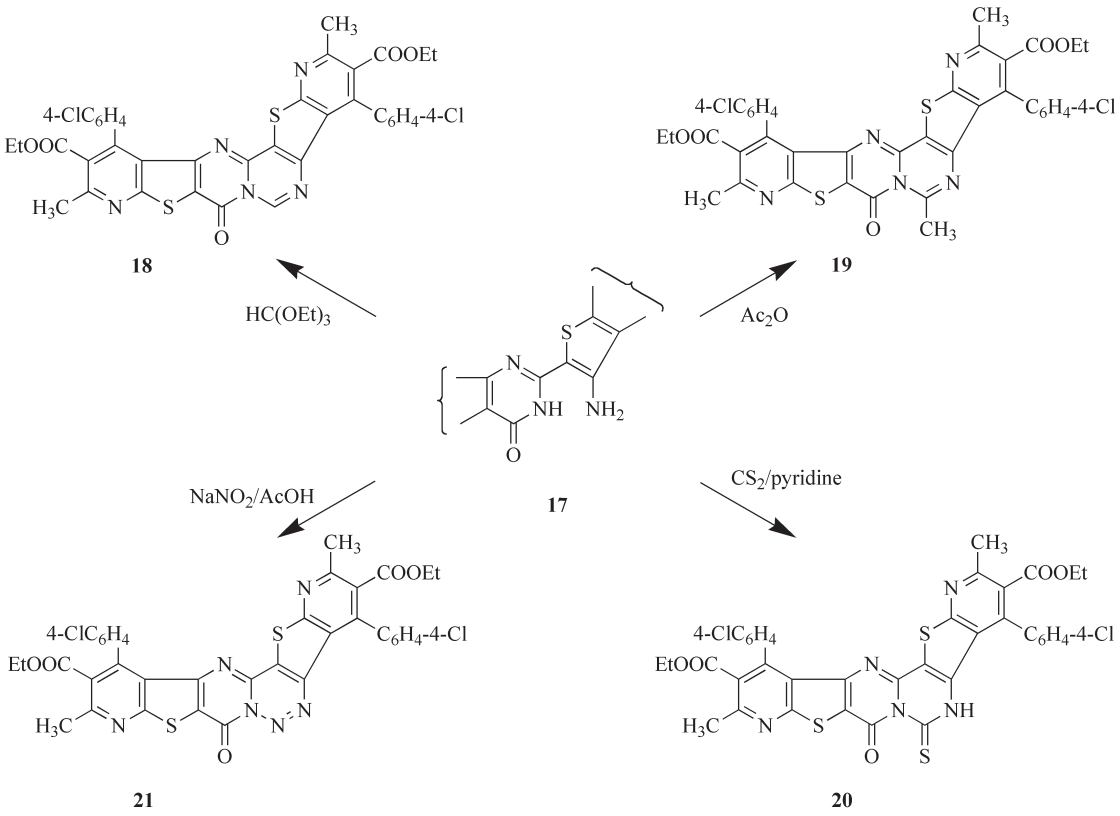


Scheme 5

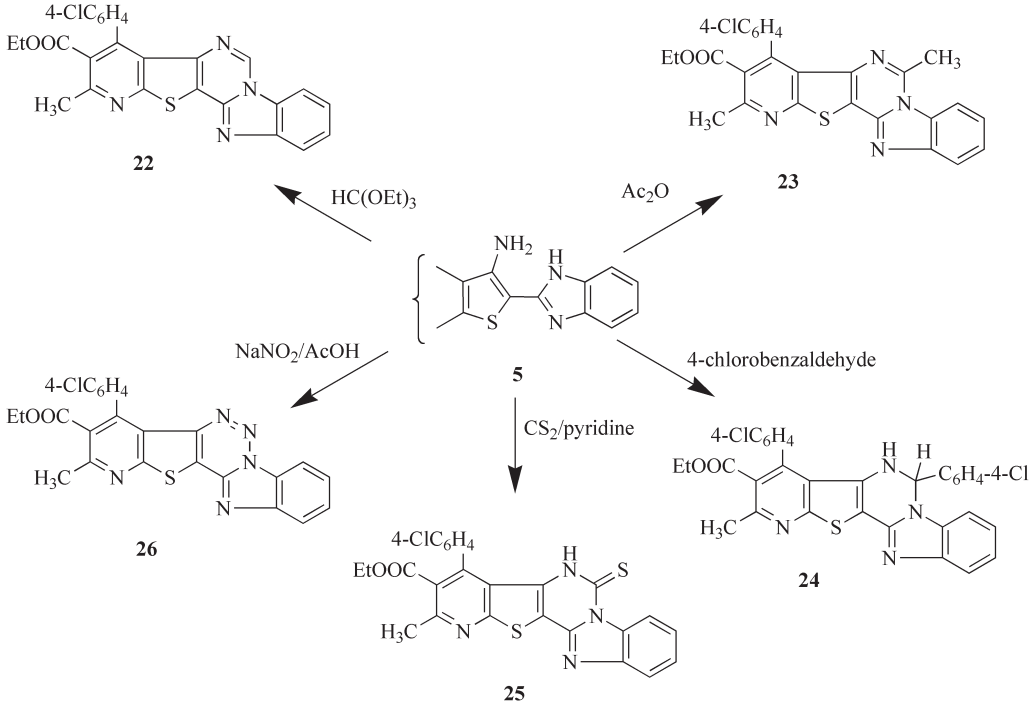


Moreover, treatment of 2-chloromethylpyrimidinone **9** with the pyridine-2(1*H*)-thione **1c** in refluxing ethanol containing sodium acetate, resulted in nucleophilic displacement reaction and formation of compound **16**. This pared by coupling reaction between **9** and **1**, is a good synthon for more complex fused polyheterocyclic systems. The structural formulae of all compounds prepared were confirmed by elemental and spectral analyses.

Scheme 6



Scheme 7



EXPERIMENTAL

All melting points were determined on a Gallan-Kamp apparatus and are uncorrected. The ir spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr). The ^{1}H nmr spectra were taken on a Varian EM-390, 90 MHz spectrometer with TMS as internal standard. Mass spectra were recorded on either a JEOL JMS-600 spectrometer (Assiut University) or a JEOL AX-500 spectrometer (Utsunomiya University). Elemental analyses were performed on an Elementar Analyses system GmbH VARIOEL $V_{2.3}$ 1998 CHNS Mode.

Ethyl 4-Aryl-3-cyano-6-methyl-2-thioxo-1,2-dihydropyridine-5-carbonylates **1a-c**.

These compounds were prepared according to a reported procedure [22].

General Procedure for the Preparation of (4-Aryl-3-cyano-5-ethoxycarbonyl-6-methyl)pyridin-2-ylthioacetamides **2a-c**.

To a suspension of compound **1a-c** (0.02 mol) and sodium acetate trihydrate (3.0 g, 0.022 mol) in ethanol (50 mL), chloroacetamide (1.9 g, 0.02 mol) was added. The resulting mixture was heated at reflux for 3 hours. The precipitate that formed on cooling was collected and recrystallized from ethanol.

(3-Cyano-5-ethoxycarbonyl-6-methyl-4-phenyl)pyridin-2-ylthioacetamide (**2a**).

This compound was obtained as colorless needles, mp 160-163 °C, yield 96%, ir: 3400, 3300 (NH_2), 2210(CN); 1720,1670 (2C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 7.2-7.5 (m, 5H, ArH's); 6.6 (br, 2H, NH_2); 3.8-4.1(m, 4H, OCH_2 and SCH_2); 2.6 (s, 3H, CH_3 at C-6); 0.7-0.9 (t, 3H, CH_3 of ester); ms: m/z 355 (M^+, 46%).

Anal. Calcd. for $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.83; S, 9.00. Found: C, 60.75; H, 4.90; N, 12.03; S, 9.19.

(3-Cyano-5-ethoxycarbonyl-4-(4'-methoxyphenyl)-6-methyl)pyridin-2-ylthioacetamide (2b).

This compound was obtained as colorless needles, mp 142-145 °C, yield 95%, ir: 3400, 3300 (NH_2), 2210(CN); 1720,1670 (2C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 6.9-7.3 (dd, 4H, ArH's); 6.7 (br, 2H, NH_2); 3.8-4.2 (m, 7H: OCH_2, SCH_2 and OCH_3); 2.7 (s, 3H, CH_3 at C-6); 0.8-1.0 (t, 3H, CH_3 of ester); ms: m/z 385 (M^+, 100%).

Anal. Calcd. for $C_{19}H_{19}N_3O_4S$: C, 59.20; H, 4.97; N, 10.91; S, 8.30. Found:C, 59.32; H, 4.91; N, 11.11; S, 8.46.

(4-(4'-Chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-methyl)-pyridin-2-ylthioacetamide (**2c**).

This compound was obtained as colorless needles, mp 161-162 °C, yield 96%, ir: 3400, 3300 (NH_2), 2210(CN); 1720,1670 (2C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 7.3-7.6 (dd, 4H, ArH's); 6.8 (br, 2H, NH_2); 4.0-4.3 (m, 4H, OCH_2 and SCH_2); 2.8 (s, 3H, CH_3 at C-6); 0.9-1.2 (t, 3H, CH_3 of ester); ms: m/z 389 (M^+, 100%).

Anal. Calcd. for $C_{18}H_{16}ClN_3O_3S$: C, 55.52; H, 4.14; N, 10.80; S, 8.22; Cl, 8.99. Found:C, 55.29; H, 4.26; N, 10.73; S, 8.35; Cl, 9.18.

General Procedures for the Preparation of 3-Amino-4-aryl-5-ethoxycarbonyl-6-methylthieno[2,3-*b*]pyridine-2-carboxamides **3a-c**.

Method A.

Compound **2a-c** (0.01 mol) was suspended in sodium ethoxide solution (0.12 g of sodium in 30 mL of absolute ethanol) and then heated at reflux for 5 minutes. The solid that formed on cooling was collected and recrystallized from ethanol.

Method B.

To a suspension of compound **1a-c** (0.01 mol) in sodium ethoxide solution (0.35 g sodium in 40 mL absolute ethanol), chloroacetamide (0.94 g, 0.01 mol) was added. The resulting mixture was refluxed for 20 minutes. The formed yellow precipitate was collected and recrystallized from ethanol to give yellow crystals of **3a-c**. These products were identical to those described in method A in all aspects.

3-Amino-5-ethoxycarbonyl-6-methyl-4-phenylthieno[2,3-*b*]pyridine-2-carboxamide (**3a**).

This compound was obtained as yellow crystals, mp 219-220 °C, yield 93% (Method A), 81% (Method B), ir: 3490, 3450, 3300, 3200 ($2NH_2$); 1720, 1650 (2 C=O) cm^{-1}; ^{1}H nmr (DMSO): δ 7.2-7.7 (m, 7H, $CONH_2$ and ArH's); 5.7 (s, 2H, NH_2 at C-3); 3.9-4.2 (q, 2H, OCH_2); 2.6 (s, 3H, CH_3 at C-6); 0.7-1.0 (t, 3H, CH_3 of ester); ms: m/z 355 (M^+, 100%).

Anal. Calcd. for $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.83; S, 9.00. Found:C, 60.55; H, 4.93; N, 11.61; S, 9.26.

3-Amino-5-ethoxycarbonyl-4-(4'-methoxyphenyl)-6-methylthieno[2,3-*b*] pyridine-2-carboxamide (**3b**).

This compound was obtained as yellow crystals, mp 214-215 °C, yield 94% (Method A), 78% (Method B), ir: 3490, 3450, 3300, 3200 ($2NH_2$); 1720, 1650 (2 C=O) cm^{-1}; ^{1}H nmr (DMSO): δ 7.0-7.3 (m, 6H, $CONH_2$ and ArH's); 5.6 (s, 2H, NH_2 at C-3); 3.9-4.2 (m, 5H, OCH_2 and OCH_3); 2.6 (s, 3H, CH_3 at C-6); 0.9-1.1 (t, 3H, CH_3 of ester); ms: m/z 385 (M^+, 100%).

Anal. Calcd. for $C_{19}H_{19}N_3O_4S$: C, 59.20; H, 4.97; N, 10.91; S, 8.30. Found: C, 59.18; H, 4.98; N, 10.85; S, 8.25.

3-Amino-4-(4'-chlorophenyl)-5-ethoxycarbonyl-6-methylthieno[2,3-*b*]pyridine-2-carboxamide (**3c**).

This compound was obtained as yellow crystals, mp 219-220 °C, yield 93%, (Method A), 83% (Method B), ir: 3490, 3450, 3300, 3200 ($2NH_2$); 1720, 1650 (2 C=O) cm^{-1}; ^{1}H nmr (DMSO): δ 7.5-7.8 (dd, 4H, ArH's); 7.3 (s, 2H, $CONH_2$); 5.8 (s, 2H, NH_2 at C-3); 4.0-4.3 (q, 2H, OCH_2); 2.7 (s, 3H, CH_3 at C-6); 1.0-1.3 (t, 3H, CH_3 of ester); ms: m/z 389 (M^+, 100%).

Anal. Calcd. for $C_{18}H_{16}ClN_3O_3S$: C, 55.52; H, 4.14; N, 10.80; S, 8.22; Cl, 8.99. Found: C, 55.51; H, 4.20; N, 10.89; S, 8.55; Cl, 9.32.

Ethyl 2-(1'*H*-2'-Benzimidazolylmethylthio)-4-(4'-chlorophenyl)-3-cyano-6-methyl-2-thioxopyridine-5-carbonylate (**4**).

To a suspension of ethyl 4-(4'-chlorophenyl)-3-cyano-6-methyl-1,2-dihydropyridine-5-carboxylate (**1c**) (6.66 g, 0.02 mol) and sodium acetate trihydrate (3.0 g, 0.022 mol) in ethanol (50 mL), 2-chloromethyl-1*H*-benzimidazole (3.3 g, 0.02 mol) was added. The resulting mixture was heated at reflux for 3 hours. The precipitate that formed was collected and recrystallized from ethanol as colorless needles of **4**, mp 159-160 °C, yield 88%; ir: 3300 (NH); 2200 (CN), 1720 (C=O) cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 7.1-7.6 (m, 8H, ArH's); 4.4 (s, 2H, SCH_2); 3.8-4.1 (q, 2H, OCH_2); 2.7 (s, 3H, CH_3 at C-6), 0.8-1.1 (t, 3H, CH_3 of ester); ms: m/z 462 (M^+, 96%).

Anal. Calcd. for $C_{24}H_{19}ClN_4O_2S$: C, 62.33; H, 4.14; N, 12.12; S, 6.92; Cl, 7.57. Found: C, 62.20; H, 4.27; N, 12.21; S, 6.88; Cl, 7.78

Ethyl 3-Amino-2-(1'*H*-2'-benzimidazolyl)-4-(4'-chlorophenyl)-6-methylthieno [2,3-*b*]pyridine-5-carboxylate (**5**).

Compound **4** (4.63 g, 0.01 mol) was suspended in sodium ethoxide solution (0.24 g of sodium in 30 mL of absolute ethanol) and then heated at reflux for 5 minutes. The solid that formed on cooling and acidification with acetic acid was collected and recrystallized from ethanol to give yellow crystals of **5**, mp 159-160°C, yield 88%; ir: 3480, 3300, 3200 (NH, NH_2); 1720 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): 7.2-7.7 (m, 8H, ArH's); 6.8 (br, 2H, NH_2); 3.9-4.2 (q, 2H, OCH_2); 2.7 (s, 3H, CH_3 at C-6), 0.8-1.1 (t, 3H, CH_3 of ester); ms: m/z 462 (M^+, 100%).

Anal. Calcd. for $C_{24}H_{19}ClN_4O_2S$: C, 62.33; H, 4.14; N, 12.12; S, 6.92; Cl, 7.57. Found: C, 62.39; H, 4.20; N, 12.41; S, 7.14; Cl, 7.70.

General Procedure for the Preparation of Ethyl 9-Aryl-2-(4'-chlorophenyl)-7-methyl-4-oxo-1,2,3,4-tetrahydropyrido-[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylates **6a-c**.

A mixture of **3a-c** (0.002 mol) and the respective aldehyde (0.002 mol) in glacial acetic acid (15 mL) or in ethanol (20 mL) containing few drops of concentrated hydrochloric acid was heated at reflux for 3 hours. The product was collected and recrystallized from acetic acid.

Ethyl 2-(4'-Chlorophenyl)-7-methyl-9-phenyl-4-oxo-1,2,3,4-tetrahydropyrido [3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**6a**).

This compound was obtained as yellow needles, mp 248-250 °C, yield 87%, ir: 3400, 3200 (2NH); 1720, 1650 (2 C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 7.2-7.6 (m, 9H, ArH's); 6.0 (s, 1H, CH at C-2); 4.1-4.4 (q, 2H, OCH_2); 2.9 (s, 3H, CH_3 at C-7); 9.0-1.2 (t, 3H, CH_3 of ester); ms: m/z 477 (M^+, 67%).

Anal. Calcd. for $C_{25}H_{20}ClN_3O_3S$: C, 62.88; H, 4.22; N, 8.81; S, 6.70; Cl, 7.33. Found: C, 62.69; H, 4.30; N, 8.74; S, 6.65; Cl, 7.55.

Ethyl 2-(4'-Chlorophenyl)-9-(4'-methoxyphenyl)-7-methyl-4-oxo-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**6b**).

This compound was obtained as yellow needles, mp 242-243 °C, yield 90%, ir: 3400, 3200 (2NH); 1720, 1650 (2 C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 7.0-7.5 (m, 8H, ArH's); 6.0 (s, 1H, CH at C-2); 4.1-4.4 (q, 2H, OCH_2); 3.9 (s, 3H, OCH_3); 3.1 (s, 3H, CH_3 at C-7); 1.0-1.3 (t, 3H, CH_3 of ester); ms: m/z 507 (M^+, 70%).

Anal. Calcd. for $C_{26}H_{22}ClN_3O_4S$: C, 61.53; H, 4.37; N, 8.28; S, 6.30; Cl, 6.90. Found: C, 61.81; H, 4.44; N, 8.26; S, 6.19; Cl, 7.20.

Ethyl 2,9-Di(4'-chlorophenyl)-7-methyl-4-oxo-1,2,3,4-tetrahydropyrido[3',2':4,5] thieno[3,2-*d*]pyrimidine-8-carboxylate (**6c**).

This compound was obtained as yellow needles, mp 260-262 °C, yield 88%, ir: 3400, 3200 (2NH); 1720, 1650 (2 C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 7.3-7.7 (m, 8H, ArH's); 6.1 (s, 1H, CH at C-2); 4.2-4.5 (q, 2H, OCH_2); 3.0 (s, 3H, CH_3 at C-7); 1.0-1.3 (t, 3H, CH_3 of ester); ms: m/z 511 (M^+, 100%).

Anal. Calcd. for $C_{25}H_{19}Cl_2N_3O_3S$: C, 58.70; H, 3.75; N, 8.22; S, 6.26: Cl, 13.69. Found: C, 58.66; H, 3.70; N, 8.25; S, 6.17: Cl, 3.90.

General Procedure for the Preparation of Spiro Compounds **7a-c** and **8a-c**.

A mixture of **3a-c** (0.002 mol) and cyclopentanone or cyclohexanone (0.002 mol) in glacial acetic acid (15 mL) or in ethanol (20 mL) containing a few drops of concentrated hydrochloric acid was heated at reflux for 3 hours. The product was collected and recrystallized from ethanol.

Ethyl 7-Methyl-9-phenyl-2,2-tetramethylene-4-oxo-1,2,3,4-tetrahydropyrido [3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**7a**).

This compound was obtained as yellow needles, mp 272-273 °C, yield 91%, ir: 3400, 3200 (2NH); 1720, 1650 (2 C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.3-7.7 (m, 5H, ArH's); 6.6 (s, 1H, CONH); 4.0-4.3(q, 2H, OCH_2); 3.7 (s, 1H, NH); 2.7 (s, 3H, CH_3 at C-7); 1.7-2.0 (br, 6H, $(CH_2)_3$ of cyclopentylidene ring); 1.4 (br, 2H, CH_2 of cyclopentylidene ring); 1.1-1.3 (t, 3H, CH_3 of ester); ms: m/z 421 (M^+, 70%).

Anal. Calcd. for $C_{23}H_{23}N_3O_3S$: C, 65.54; H, 5.50; N, 9.97; S, 7.59. Found: C, 65.48; H, 5.69; N, 10.15; S, 7.76.

Ethyl 9-(4'-Methoxyphenyl)-7-methyl-2,2-tetramethylene-4-oxo-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**7b**).

This compound was obtained as yellow needles, mp 278-279 °C, yield 88%, ir: 3400, 3200 (2NH); 1720, 1650 (2 C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.3-7.6 (m, 5H, ArH's); 6.8 (s, 1H, CONH); 4.0-4.3 (q, 2H, OCH_2); 3.5 (s, 1H, NH); 2.7 (s, 3H, CH_3 at C-7); 1.9-2.2 (m, 4H, $(CH_2)_2$ of cyclohexylidene ring); 1.3-1.6 (m, 4H, $(CH_2)_2$ of cyclohexylidene ring); 1.1-1.3 (t, 3H, CH_3 of ester); 0.6-0.9 (m, 2H, CH_2 of cyclohexylidene ring); ms: m/z 435 (M^+, 31%).

Anal. Calcd. for $C_{24}H_{25}N_3O_3S$: C, 66.18; H, 5.79; N, 9.65; S, 7.35. Found: C, 66.25; H, 5.98; N, 9.51; S, 7.53.

Ethyl 9-(4'-Chlorophenyl)-7-methyl-2,2-tetramethylene-4-oxo-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**7c**).

This compound was obtained as yellow needles, mp 250-252 °C, yield 92%, ir: 3400, 3200 (2NH); 1720, 1650 (2 C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.1-7.4 (dd, 4H, ArH's); 6.7 (s, 1H, CONH); 4.0-4.2 (q, 2H, OCH_2); 3.9 (s, 3H, OCH_3); 3.6 (s, 1H, NH); 2.7 (s, 3H, CH_3 at C-7); 1.8-2.0 (br, 6H, $(CH_2)_3$ of cyclopentylidene ring); 1.4 (br, 2H, CH_2 of cyclopentylidene ring); 1.1-1.3 (t, 3H, CH_3 of ester); ms: m/z 451 (M^+, 42%).

Anal. Calcd. for $C_{24}H_{25}N_3O_4S$: C, 63.84; H, 5.58; N, 9.31; S, 7.09. Found: C, 63.67; H, 5.64; N, 9.18; S, 7.38.

Ethyl 7-Methyl-9-phenyl-2,2-pentamethylene-4-oxo-1,2,3,4-tetrahydropyrido [3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**8a**).

This compound was obtained as yellow needles, mp 247-248 °C, yield 80%, ir: 3400, 3200 (2NH); 1720, 1650 (2 C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.0-7.4 (dd, 4H, ArH's); 6.8 (s, 1H, CONH); 4.0-4.3 (q, 2H, OCH_2); 3.9 (s, 3H, OCH_3); 3.6(s, 1H, NH); 2.8 (s, 3H, CH_3 at C-7); 1.9-2.2 (m, 4H, $(CH_2)_2$ of cyclohexylidene ring); 1.3-1.8 (m, 4H, $(CH_2)_2$ of cyclohexylidene ring) 0.9-1.2 (t, 3H, CH_3 of ester); 0.6-0.9(m, 2H, CH_2 of cyclohexylidene ring); ms: m/z 465 (M^+, 40%).

Anal. Calcd. for $C_{25}H_{27}N_3O_4S$: C, 64.49; H, 5.85; N, 9.03; S, 6.87. Found: C, 64.28; H, 5.88; N, 9.11; S, 6.84.

Ethyl 9-(4-Chlorophenyl)-7-methyl-2,2-pentamethylene-4-oxo-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**8b**).

This compound was obtained as yellow needles, mp 258-259 C, yield 85%, ir: 3400, 3200 (2NH); 1720, 1650 (2 C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.4-7.7 (dd, 4H, ArH's); 6.7 (s, 1H, CONH); 4.1-4.4 (q, 2H, OCH_2); 3.8 (s, 1H, NH); 2.9 (s, 3H, CH_3 at C-7); 1.8-2.1 (br, 6H, $(CH_2)_3$ of cyclopentylidene ring); 1.5 (br, 2H, CH_2 of cyclopentylidene ring); 1.1-1.3 (t, 3H, CH_3 of ester); ms: m/z 455 (M^+, 32%).

Anal. Calcd. for $C_{23}H_{22}ClN_3O_3S$: C, 60.64; H, 4.87; N, 9.23; S, 7.03; Cl, 7.68. Found: C, 60.53; H, 4.81; N, 9.31;S, 7.00; Cl, 7.50.

Ethyl 9-(4-Chlorophenyl)-7-methyl-4-oxo-2,2-pentamethylene-1,2,3,4-tetrahydropyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**8c**).

This compound was obtained as yellow needles, mp 271-272 °C, yield 90%, ir: 3400, 3200 (2NH); 1720, 1650 (2 C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.3-7.7 (dd, 4H, ArH's); 6.9 (s, 1H, CONH); 4.0-4.3 (q, 2H, OCH_2); 3.8 (s, 1H, NH); 2.8 (s, 3H, CH_3 at C-7); 1.8-2.1 (m, 4H, $(CH_2)_2$ of cyclohexylidene ring); 1.3-1.7 (m, 4H, $(CH_2)_2$ of cyclohexylidene ring); 1.0-1.2 (t, 3H, CH_3 of ester); 0.6-0.9 (m, 2H, CH_2 of cyclohexylidene ring); ms: m/z 469 (M^+, 30%).

Anal. Calcd. for $C_{24}H_{24}ClN_3O_3S$: C, 61.39; H, 5.16; N, 8.95; S, 6.82; Cl, 7.45. Found: C, 61.25; H, 5.31; N, 8.98; S, 6.70; Cl, 7.76.

Ethyl 2-Chloromethyl-9-(4'-chlorophenyl)-7-methyl-4-oxo-3,4-dihydropyrido [3',2':4,5]thieno[3,2-*d*] pyrimidine-8-carboxylate (**9**).

Compound **3c** (1.95 g, 0.005 mol) in chloroacetyl chloride (15 mL) was heated on a water bath for 3 hours. The product that formed on cooling was collected and recrystallized from ethanol to give **9** in the form of colorless crystals, mp 279-280 °C, yield 87%, ir: 3320-3000 (NH); 1710, 1650 (2 C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 7.4-7.8 (dd, 4H, ArH's); 4.2-4.5 (m, 4H, CH_2Cl and OCH_2); 3.1 (s, 3H, CH_3 at C-7); 1.1-1.4 (t, 3H, CH_3 of ester); ms: m/z 447 (M^+, 100%).

Anal. Calcd. for $C_{20}H_{15}Cl_2N_3O_3S$: C, 53.69; H, 3.38; N, 9.40; S, 7.15; Cl, 15.65. Found: C, 53.42; H, 3.33; N, 9.68; S, 7.18; Cl, 16.11.

Ethyl 9-(4'-Chlorophenyl)-7-methyl-2-morpholinomethyl-4-oxo-3,4-dihydropyrido[3',2':4,5]thieno[3,2-*d*] pyrimidine-8-carboxylate (**10**).

Compound **9** (2.24 g, 0.005 mol) in morpholine (5 mL) was heated on a water bath for 3 hours. The reaction mixture was then triturated with ethanol (15 mL) and left to cool. The precipitate was collected and recrystallized from ethanol to give colorless crystals of **10**, mp 275-276 °C, yield 90%, ir: 3200-3000 (NH); 1720, 1660 (2 C=O) cm^{-1}; ^1H nmr (DMSO): δ 7.3-7.6 (dd, 4H, ArH's); 4.0-4.3 (q, 2H, OCH_2); 3.6-3.8 (t, 4H, CH_2OCH_2); 3.3 (s, 2H, CH_2N); 2.7 (s, 3H, CH_3 at C-7); 2.3-2.5 (t, 4H, CH_2NCH_2); 0.9-1.2 (t, 3H, CH_3 of ester); ms: m/z 498 (M^+, 15%).

Anal. Calcd. for $C_{24}H_{23}ClN_4O_4S$: C, 57.77; H, 4.65; N,11.23; S, 6.43; Cl, 7.10. Found: C, 57.70; H, 4.72; N, 11.35; S, 6.50; Cl, 7.26.

Ethyl 9-(4'-Chlorophenyl)-2-ethoxymethyl-7-methyl-4-oxo-3,4-dihydropyrido [3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**11**).

Compound **9** (0.9 g, 0.002 mol) in sodium ethoxide solution (0.35 g of sodium in 40 mL of absolute ethanol) was heated at reflux for 1 hour. The precipitate that formed on cooling was collected and recrystallized from ethanol as colorless crystals of **11**, mp 275-276 °C, yield 90%, ir: 3200-3000 (NH); 1720, 1660 (2 C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 7.5-7.9 (dd, 4H, ArH's); 4.8 (s, 2H, CH_2O); 4.3-4.6 (q, 2H, OCH_2); 3.7-4.0 (q, 2H, OCH_2); 3.2 (s, 3H, CH_3 at C-7); 1.1-1.6 (m, 6H, two CH_3 groups); ms: m/z 457 (M^+, 19 %).

Anal. Calcd. for $C_{22}H_{20}ClN_3O_4S$: C, 57.76; H, 4.41; N, 9.19; S, 6.99; Cl,7.65. Found: C, 57.96; H, 4.21; N, 9.25; S, 7.17; Cl, 8.00.

Ethyl 9-(4'-Chlorophenyl)-2-mercaptomethyl-7-methyl-4-oxo-3,4-dihydropyrido [3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**12**).

A mixture of **9** (0.9 g, 0.002 mol) and thiourea (0.15 g, 0.002 mol) in ethanol (20 mL) was refluxed for 3 hours**.** The product that formed while hot was collected and dissolved in aqueous sodium hydroxide solution 10% (10 mL) and then heated on a water bath for 1 hour. The reaction mixture was filtered and the clear filtrate was acidified with acetic acid. The formed yellow precipitate was collected and recrystallized from ethanol-chloroform as yellow crystals of **12**, mp 270-271 °C, yield 91%, ir: 3200-3000 (NH); 2760 (SH); 1720, 1650 (2 C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 7.5-7.8 (dd, 4H, ArH's); 4.8 (s, 2H, CH_2S); 4.2-4.5 (q, 2H, OCH_2); 3.1 (s, 3H, CH_3 at C-7); 1.0-1.2 (t, 3H, CH_3 of ester); ms: m/z 445 (M^+, 100%).

Anal. Calcd. for $C_{20}H_{16}ClN_3O_3S_2$: C, 53.93; H, 3.62; N, 9.44; S, 14.37; Cl, 7.86. Found: C, 53.86; H, 3.58; N, 9.69; S, 14.45; Cl, 7.70.

Ethyl 4-Chloro-2-chloromethyl-9-(4'-chlorophenyl)-7-methylpyrido [3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**13**).

Compound **9** (1.8 g, 0.004 mol) in an excess amount of phosphorus oxychloride (20 mL) was refluxed for 4 hours. The cooled reaction mixture was poured into ice-water with vigorous stirring. The separated product was collected and recrystallized from ethanol as yellowish needles of **13**, mp 139-140 °C, yield 90%, ir: 1720 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 7.2-7.6 (dd, 4H, ArH's); 4.2 (s, 2H, CH_2 at C-2); 3.8-4.1 (q, 2H, OCH_2); 2.9 (s, 3H, CH_3 at C-7); 1.0-1.2 (t, 3H, CH_3 of ester)); ms: m/z 465 (M^+, 96%).

Anal. Calcd. for $C_{20}H_{14}Cl_3N_3O_2S$: C,51.61; H, 3.03; N, 9.03; S, 6.88; Cl, 22.56. Found: C, 51.57; H, 3.11; N, 9.17; S, 6.80; Cl, 22.55.

Ethyl 9-(4'-Chlorophenyl)-7-methyl-4-morpholino-2-morpholinomethylpyrido [3',2':4,5] thieno[3,2-*d*]pyrimidine-8-carboxylate (**14**).

Compound **13** (0.93 g, 0.002 mol) in morpholine (6 mL) was heated on a water bath for 3 hours. The reaction mixture was then triturated with ethanol (10 mL) and then left to cool. The precipitate was collected and recrystallized from ethanol to give **14** in the form of colorless crystals, mp 157-158 °C, yield 82%, ir: 1720 (C=O) cm^{-1}; ^1H nmr (DMSO): δ 7.3-7.6 (dd, 4H, ArH's); 4.1-4.3 (q, 2H, OCH_2); 3.6-3.8 (t, 8H, two CH_2OCH_2); 3.5 (s, 2H, CH_2N); 2.7 (s, 3H, CH_3 at C-7); 2.2-2.4 (t, 8H, two CH_2NCH_2); 0.9-1.2 (t, 3H, CH_3 of ester); ms: m/z 567 (M^+, 23 %).

Anal. Calcd. for $C_{28}H_{30}ClN_5O_4S$: C, 59.24; H, 5.33; N,12.34; S, 5.64; Cl, 6.17. Found: C, 58.97; H, 5.25; N, 12.40; S, 5.91; Cl, 6.10.

Ethyl 9-(4'-Chlorophenyl)-7-methyl-2-mercaptomethyl-4-thioxo-3,4-dihydropyrido[3',2': 4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**15**).

A mixture of **13** (0.93 g, 0.002 mol) and thiourea (0.3 g, 0.004 mol) in ethanol (20 mL) was refluxed for 3 hours. The product that formed while hot was collected and dissolved in aqueous sodium hydroxide solution 10% (15 mL). The reaction mixture was heated on a water bath for 1 hour and then filtered. The clear filtrate was acidified with acetic acid whereby a yellow precipitate formed. It was collected and recrystallized from ethanol-chloroform as yellow crystals of **15**, mp 254-255 °C, yield 87%, ir: 3200-3000 (NH); 2760 (SH); 1720 (C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 7.4-7.8 (dd, 4H, ArH's); 4.7 (s, 2H, CH_2S); 4.1-4.4 (q, 2H, OCH_2); 3.0 (s, 3H, CH_3 at C-7); 1.0-1.3 (t, 3H, CH_3 of ester); ms: m/z 461 (M^+, 80%).

Anal. Calcd. for $C_{20}H_{16}ClN_3O_2S_3$: C, 52.06; H, 3.50; N, 9.11; S, 20.81; Cl, 7.59. Found: C, 51.88; H, 3.56; N, 9.43; S, 20.65; Cl, 7.49.

Ethyl 9-(4'-Chlorophenyl)-7-methyl-2-(4'-(4''-chlorophenyl)-3'-cyano-5'-ethoxycarbonyl-6'-methylpyridin-2'-ylthiomethyl)-4-oxo-3,4-dihydropyrido [3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**16**).

To a suspension of compound **1c** (6.66 g, 0.02 mol) and sodium acetate trihydrate (3.0 g, 0.022 mmol) in ethanol (50 mL), compound **9** (9.0 g, 0.02 mol) was added. The resulting mixture was refluxed for 3 hours. The precipitate that formed on cooling was collected and recrystallized from ethanol as colorless needles of **16**, mp 261-262 °C, yield 82%, ir: 3200-3000 (NH); 2200(CN); 1720 (2 C=O); 1650 (C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 7.3-7.7(m, 8H, ArH's);; 4.2-4.6 (m, 6H, SCH_2 and two OCH_2); 3.2 (s, 3H, CH_3 attached to thienopyridine moiety); 2.8 (s, 3H, CH_3 attached to pyridine ring); 1.1-1.4 (m, 6H, two CH_3 of esters); ms: m/z 743 (M^+,12 %).

Anal. Calcd. for $C_{36}H_{27}Cl_2N_5O_5S_2$: C,58.14; H, 3.66; N, 9.42; S, 8.61; Cl, 9.41. Found: C, 57.78; H, 3.69; N, 9.32; S, 8.38; Cl, 9.29.

Ethyl 9-(4'-Chlorophenyl)-7-methyl-2-(3'-amino-4'-(4''-chlorophenyl)-5'-ethoxycarbonyl-6'-methylthieno[2,3-*b*]pyridin-2'-yl)-4-oxo-3,4-dihydropyrido [3',2':4,5]thieno[3,2-*d*]pyrimidine-8-carboxylate (**17**).

Compound **16** (3.72 g, 0.005 mol) was suspended in sodium ethoxide solution (0.24 g of sodium in 35 mL of absolute ethanol) and then heated at reflux for 5 minutes. The solid that formed on cooling and acidification with acetic acid was collected and recrystallized from ethanol to give yellow crystals of **17**, mp >360 °C, yield 77%, ir: 3490, 3380 (NH_2); 1720 (2C=O); 1650 (C=O) cm^{-1}; ^1H nmr (DMSO): δ 7.2-7.7 (m, 8H, ArH's); 5.6 (s, 2H, NH_2); 4.1-4.4(q, 4H, two OCH_2); 2.7 (s, 6H, two CH_3 attached to the pyridine rings); 1.0-1.2 (t, 6H, two CH_3 of esters); ms: m/z 743 (M^+, 28 %).

Anal. Calcd. for $C_{36}H_{27}Cl_2N_5O_5S_2$: C,58.14; H, 3.66; N, 9.42; S, 8.61; Cl, 9.41. Found: C, 58.12; H, 3.82; N, 9.67; S, 8.51; Cl, 9.29.

Diethyl 4,13-Di(4'-chlorophenyl)-2,11-dimethyl-8-oxo-8*H*-bis(pyrido[3',2':4,5] thieno)[2,3-*b*:3',2'-*h*]pyrimido[1,6-*a*]pyrimidine-3,12-dicarboxylate (**18**).

Compound **17** (0.75 g, 0.001 mol) in triethyl orthoformate (15 mL) was refluxed for 4 hours. The solid that formed on cooling was collected and recrystallized from ethanol-chloroform mixture as colorless crystals of **18**, mp 318-319 C, yield 73%, ir: 1720 (2C=O); 1650 (C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 9.7 (s, 1H, CH pyrimidinone); 7.4-8.0 (m, 8H, ArH's); 4.2-4.6 (q, 4H, two OCH_2); 3.1 (s, 6H, two CH_3 attached to the pyridine rings); 1.0-1.3 (t, 6H, two CH_3 of esters); ms: m/z 753 (M^+, 25 %).

Anal. Calcd. for $C_{37}H_{25}Cl_2N_5O_5S_2$: C, 58.96; H, 3.35; N, 9.30; S, 8.49; Cl, 9.29. Found: C, 59.10; H, 3.17; N, 9.03; S, 8.78; Cl, 9.67.

Diethyl 4,13-Di(4'-chlorophenyl)-2,6,11-trimethyl -8-oxo-8*H*-bis(pyrido[3',2':4,5] thieno)[2,3-*b*:3',2'-*h*]pyrimido[1,6-*a*]pyrimidine-3,12-dicarboxylate (**19**).

Compound **17** (0.75 g , 0.001 mol) in acetic anhydride (15 mL) was refluxed for 4 hours. The solid that formed on cooling was collected and recrystallized from ethanol-chloroform mixture as colorless crystals of **19**, mp 289-290° C, yield 92%, ir: 1720 (2C=O); 1650 (C=O) cm^{-1}; ^1H nmr(CF_3CO_2D): δ 7.5-8.0 (m, 8H, ArH's); 4.4-4.7(q, 4H, two OCH_2); 3.3 (s, 3H, CH_3 attached to the pyridine ring); 3.2 (s, 3H, CH_3 attached to the pyridine ring); 1.9 (s, 3H, CH_3)1.3-1.5 (t, 6H, two CH_3 of esters); ms: m/z 767 (M^+, 100 %).

Anal. Calcd. for $C_{38}H_{27}Cl_2N_5O_5S_2$: C, 59.44; H, 3.55; N, 9.13; S, 8.34; Cl, 9.12. Found: C, 59.12; H, 3.49; N, 9.24; S, 8.12; Cl, 9.13.

Diethyl 4,13-Di(4'-chlorophenyl)-2,11-dimethyl-8-oxo-6-thioxo-5,6-dihydro-8*H*-bis(pyrido[3',2':4,5]thieno)[2,3-*b*:3',2'-*h*]-pyrimido[1,6-*a*]pyrimidine-3,12-dicarboxylate (**20**).

A mixture of compound **17** (0.75 g, 0.001 mol) and carbon disulfide (5 mL) in pyridine (15 mL) was refluxed for 4 hours. The solid that formed on cooling was collected and recrystallized from dimethyl formamide as yellow crystals of **20**, mp 297-298 °C, yield 76%, ir: 3250 (NH); 1720 (2C=O); 1650 (C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 7.5-7.9 (m, 8H, ArH's); 4.4-4.7(q, 4H, two OCH_2); 3.2 (s, 6H, two CH_3 attached to the pyridine rings); 1.1-1.4 (t, 6H, two CH_3 of esters); ms: m/z 785 (M^+, 21 %).

Anal. Calcd. for $C_{37}H_{25}Cl_2N_5O_5S_3$: C, 56.56; H, 3.20; N, 8.92; S, 12.22; Cl, 8.91. Found: C, 56.77; H, 3.22; N, 9.21; S, 12.50; Cl, 9.19.

Diethyl 4,13-Di(4'-chlorophenyl)-2,11-dimethyl-8-oxo-8*H*-bis(pyrido[3',2':4,5] thieno)[3,2-*c*:3',2'-*g*]pyrimido[1,2-*c*][1,2,3]triazine-3,12-dicarboxylate (**21**).

To a solution of **17** (0.75 g , 0.001 mol) in concentrated sulfuric acid (5 mL) and glacial acetic acid (5 mL), sodium nitrite solution 10% (5 mL) was added at 0 °C over a period of 5 minutes with stirring. The reaction mixture was allowed to stand at room temperature for 30 minutes. The solid that precipitated on dilution with water was collected and recrystallized from 1,4-dioxane to give colorless needles of **21**, mp 268-269 °C, yield 79%, ir: 1720 (2C=O); 1650 (C=O) cm^{-1}; ^1H nmr (CF_3CO_2D): δ 7.5-7.9 (m, 8H, ArH's); 4.3-4.6(q, 4H, two OCH_2); 3.1 (s, 6H, two CH_3 attached to the pyridine rings); 1.1-1.3 (t, 6H, two CH_3 of esters) ms: m/z 754 (M^+, 6 %).

Anal. Calcd. for $C_{36}H_{24}Cl_2N_6O_5S_2$: C, 57.29; H, 3.21; N, 11.14; S, 8.48; Cl, 9.27. Found: C, 57.18; H, 3.25; N,11.23; S, 8.31; Cl, 9.54.

Ethyl 10-(4'-Chlorophenyl)-12-methyl-7*H*-pyrido[3'',2'':4',5']-thieno[3',2':4,5] pyrimido[1,6-*a*]benzimidazole-11-carboxylate (**22**).

To a suspension of compound **5** (0.92 g, 0.002 mol) in triethyl orthoformate (15 mL), few drops of glacial acetic acid was added. The reaction mixture was refluxed for 4 hours and then left to cool. The precipitated solid was collected and recrystallized from ethanol-chloroform mixture as colorless crystals of **22**, mp >360 °C, yield 91%, ir: 1720 (C=O) cm^{-1}; ^1H nmr (CD_3CO_2D): δ 9.0 (s, 1H, CH pyrimidine); 7.8-8.4 (m, 4H, ArH's); 7.4-7.7 (dd, 4H, ArH's); 4.1-4.4 (q, 2H, OCH_2); 3.0 (s, 3H, CH_3 at C-11); 1.1-1.3 (t, 3H, CH_3 of ester); ms: m/z 472 (M^+, 100 %).

Anal. Calcd. for $C_{25}H_{17}ClN_4O_2S$: C, 63.55; H, 3.63; N,11.87; S, 6.77; Cl, 7.41. Found: C, 63.40; H, 3.65; N, 11.81; S, 6.90; Cl, 7.66.

Ethyl 10-(4'-Chlorophenyl)-8,12-dimethyl-7*H*-pyrido[3",2":4',5']-thieno [3',2':4,5]pyrimido[1,6-*a*]benzimidazole-11-carboxylate (**23**).

Compound **5** (0.92 g, 0.002 mol) in acetic anhydride (15 mL) was refluxed for 4 hours. The solid that formed on cooling was collected and recrystallized from ethanol-chloroform mixture as colorless crystals of **23**, mp >360 °C, yield 91%, ir: 1720 (C=O) cm^{-1}; ^1H nmr (CD_3CO_2D): δ 7.8-8.4 (m, 4H, ArH's); 7.4-7.7 (dd, 4H, ArH's); 4.1-4.4 (q, 2H, OCH_2); 3.2 (s, 3H, CH_3 attached to pyrimidine ring); 3.0 (s, 3H, CH_3 attached to pyridine ring); 1.1-1.3 (t, 3H, CH_3 of ester); ms: m/z 486 (M^+, 100 %).

Anal. Calcd. for $C_{26}H_{19}ClN_4O_2S$: C, 64.19; H, 3.94; N, 11.52; S, 6.58; Cl, 7.19. Found: C, 64.20; H, 3.88; N, 11.45; S, 6.65; Cl, 7.41.

Ethyl 8,10-Di(4'-chlorophenyl)-12-methyl-8,9-dihydro-7*H*-pyrido[3",2":4',5'] thieno[3',2':4,5]pyrimido[1,6-*a*]benzimidazole-11-carboxylate (**24**).

A mixture of compound **5** (0.92 g, 0.002 mol) and 4-chlorobenzaldehyde (0.28 g, 0.002 mol) in ethanol (15 mL) containing few drops of glacial acetic acid was refluxed for 4 hours. The solid that formed on cooling was collected and recrystallized from dimethyl formamide as yellow crystals of **24**, mp 268-269 °C, yield 82%, ir: 3400 (NH); 1720 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.9-7.8 (m, 12H, ArH's); 5.4 (d, 1H, CH at C-7); 4.0-4.3 (q, 2H, OCH_2); 3.6 (d, 1H, NH); 2.9 (s, 3H, CH3 at C-11); 0.9-1.1 (t, 3H, CH_3 of ester); ms: m/z 584 (M^+, 18%).

Anal. Calcd. for $C_{31}H_{22}Cl_2N_4O_2S$: C, 63.69; H,3.80; N, 9.59; S, 5.47; Cl,11.97. Found: C, 63.91; H, 3.96; N, 9.68; S, 5.33; Cl, 12.32.

Ethyl 10-(4'-Chlorophenyl)-12-methyl-8-thioxo-8,9-dihydro-7*H*-pyrido [3",2":4',5']thieno[3',2':4,5]pyrimido[1,6-*a*]benzimidazole-11-carboxylate (**25**).

A mixture of compound **5** (0.92 g, 0.002 mol) and carbon disulfide (5 mL) in pyridine (15 mL) was heated at reflux for 4 hours. The solid that formed on cooling was collected and recrystallized from dimethyl formamide as yellow crystals of **25**, mp 350-351 °C, yield 80%, ir: 3380 (NH); 1720 (C=O) cm^{-1}; ^1H nmr (CD_3CO_2D): δ 7.7-8.3 (m, 4H, ArH's); 7.2-7.6 (dd, 4H, ArH's); 4.1-4.4 (q, 2H, OCH_2); 2.9 (s, 3H, CH_3 at C-11); 1.1-1.3 (t, 3H, CH_3 of ester); ms: m/z 504 (M^+, 100%).

Anal. Calcd. for $C_{25}H_{17}ClN_4O_2S_2$: C, 59.51; H, 3.40; N,11.11; S, 12.69; Cl, 6.94. Found: C, 59.54; H, 3.44; N, 11.21; S, 12.36; Cl, 7.16.

Ethyl 10-(4'-Chlorophenyl)-12-methyl-7*H*-pyrido[3",2":4',5']-thieno[3',2':4,5] [1,2,3]triazino[1,6-*a*]benzimidazole (**26**).

To a solution of **5** (0.92 g, 0.002 mol) in concentrated sulfuric acid (5 mL) and glacial acetic acid (5 mL), sodium nitrite solution 10% (10 mL) was added at 0 °C over a period of 5 minutes with stirring. The reaction mixture was allowed to stand at room temperature for 30 minutes. The solid that precipitated on dilution with water was collected and crystallized from 1,4-dioxane to give colorless needles of **26**, mp 307 °C, yield 85%, ir: 1720 (C=O) cm^{-1}; ^1H nmr (CD_3CO_2D): δ 7.8-8.4 (m, 4H, ArH's); 7.4-7.7 (dd, 4H, ArH's); 4.0-4.3 (q, 2H, OCH_2); 3.0 (s, 3H, CH_3 at C-11); 1.0-1.2 (t, 3H, CH_3 of ester)); ms: m/z 473 (M^+, 100%).

Anal. Calcd. for $C_{24}H_{16}ClN_5O_2S$: C, 60.89; H, 3.39; N,14.80; S, 6.76; Cl, 7.40. Found: C, 60.97; H, 3.68; N, 14.85; S, 6.93; Cl, 7.53.

REFERENCES AND NOTES

[1] K. Eichenberger, E. Schweizer and P. Schmidt, *U.S. Patent,* 2,627,76614; *Chem. Abstr.,* **74**, 88638w (1971).

[2] A. Burger, Wiley-Inter. Sciences, 3rd ed., *Medicinal Chemistry*, New York (N.Y.), **72**, 544, 719 (1970).

[3] Z. Shraideh and A.-K.Sallal, *Biomed. Lett.,* **54**, 233 (1997).

[4] J. Bompart, L. Giral, G. Malicorne and M. Puygrenier, *Eur. J. Med. Chem.,* **22**, 139 (1987).

[5] M. E. Schnute, M. M. Cudahy and A. Scott, *PCT Int. Appl. WO*, 00,53,610; *Chem. Abstr.*, **133**, 222607g (2000).

[6] I. Adachi and Y. Hiramatsu, *Jap. Pat.,* 03,52,890; *Chem. Abstr.,* **115**, 71573 (1991).

[7] T. Ooe, M. Sano, H. Kobayashi and M. Kudome *Jpn. Kokai Tokkyo Koho JP,* 07 53, 562; *Chem. Abstr.*, **123**, 256681k (1995).

[8] S. Furuya, N. Choh, K. Kato and S. Hinuma, *PCT Int. Appl. WO,* 95, 28, 405; *Chem. Abstr.*, **124**, 202226t (1996).

[9] N. Cho, M. Harada, T. Imaeda, T. Imada, H. Matsumoto, Y. Hayase, S. Sasaki, S. Furuya, N. Suzuki, S. Okubo, K. Ogi, S. Endo, H. Onda and M. Fujino, *J. Med. Chem.*, **41**, 4190(1998).

[10] S. Miki, K. Fukuoka, M. Akita, J. Kawakami, S. Furuya and Y. Ishimaru, *PCT Int, Appl. WO,* 99, 09, 033; *Chem. Abstr.*, **130**, 196644h (1999).

[11] N. Suzuki, H. Matsumoto and S. Furuya, *Eur. Pat. Appl. EP,* 781,774; *Chem. Abstr.*, **127**, 135807e (1997).

[12] S. Furuya, N. Choh, N. Suzuki and T. Imada, *PCT Int. Appl. WO,* 00,00,493 ; *Chem. Abstr.*, **132**, 64179s (2000).

[13] S. Furuya, H. Matsumoto, Y. Hayase, N. Suzuki and T. Imada, *PCT Int. Appl. WO*, 97,41,126; *Chem. Abstr.*, **128**, 13211f (1998).

[14] H. Vieweg, S. Leistner, J. Prantz, N. Bohm and G. Wagner, *Pharmazie*, **47**, 841 (1992).

[15] T. Sohda, H. Makino and A. Baba, *PCT Int. Appl. WO,* 96,14,319; *Chem. Abstr.*, **125**, 114583x (1996).

[16] C. G. Dave, P. R. Shah, K.C. Dave and V. J. Patel, *J. Indian Chem. Soc.,* **66**, 48 (1989).

[17] E. Bousquent, G. Romero F. Guerrera, A. Caruso and M. A. Roxas, *Farmaco Ed. Sci.,* **40**, 869 (1985).

[18] S. Leistner, G. Wagener, M. Guestscharo and E. Glusa, *Pharmazie,* **41**, 54 (1986).

[19] E. A. Bakhite, A. E. Abdel-Rahman, O. S. Mohamed and E. A. Thabet, *Pharmazie,* **55**, 577 (2000)..

[20] A. E. Abdel-Rahman, E. A. Bakhite, O. S. Mohamed and E. A. Thabet, *Phosphorus, Sulfur and Silicon,* **166**, 149 (2000).

[21] A. E. Abdel-Rahman, E. A. Bakhite and E. A. Al-Taifi, *J. Chin. Chem. Soc.,* **49**, 223 (2002).

[22] A. M. Abd El-Fattah; *Phosphorus, Sulfur Silicon Relat. Elem.*, **156**, 53 (2000).

[23] E. A. Bakhite, *J. Chem. Res. Synop.,* (*M*): 500 (2000); (*S*): 1201 (2000).

[24] V. F. Vaidya and Y. S. Agasimundin, *Indian J. Chem.,* **20B**, 780 (1981).