

Synthesis and characterization of new quinazolinylmethylsulfanylpuridines, quinazolinylthieno[2,3-*b*]pyridines and pyrido[3'',2'':4',5'] thieno[3',2':4,5]pyrimido[6,1-*b*]quinazolines

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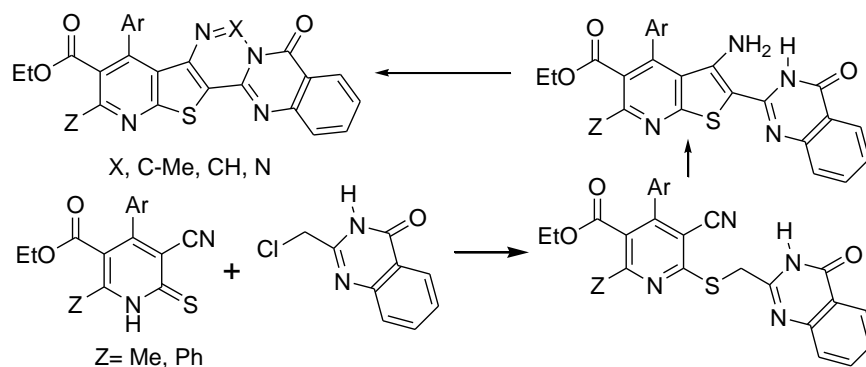
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Abstract

Reaction of 2-chloromethylquinazoline-4(3*H*)-one with some 3-cyanopyridine-2(1*H*)-thiones gave the corresponding thioethers which upon treatment with appropriate base, underwent intramolecular *Thorpe-Ziegler* reaction affording the isomeric 3-amino-2-(3,4-dihydro-4-oxo-2-quinazolinyl)thieno[2,3-*b*]pyridines. In contrast, the reaction of 2-chloromethylquinazoline-4(3*H*)-one with 3-cyanoquinoline-(1*H*)-thione gave 3-amino-2-(3,4-dihydro-4-oxo-2-quinazolinyl)thieno[2,3-*b*]quinoline directly. Reaction of the resulting aminothienopyridines/quinoline with some reagents namely; acetic anhydride, triethyl orthoformate and/ or nitrous acid were carried out and their products were identified.



Keywords: Thienopyridines, pyridothienopyrimidines, pyridothienotriazine, quinazolines, pyridothienopyrimido[6,1-*b*]quinazolines

Introduction

Quinazoline-4(3*H*)-ones are important class of heterocyclic compounds which possess a broad spectrum of biological and pharmaceutical activities such as antifungal,¹ antitumour,² hypotensive,³ anti-cancer,^{4,5} anti-HIV,⁶ anti-inflammatory⁷ and anti-bacterial.⁸ In particular, quinazoline-4(3*H*)-ones substituted at 2 and 3-position play a pivotal role in the hypotensive activity.⁹⁻¹¹ Several bio-active natural products such as febrifugine (A) and isofebrifugine (B) contain quinazolinone moieties with potential anti-malarial activity.¹² Pyridine derivatives abundantly exist in nature and they play a vital role in the field of heterocyclic chemistry.¹³ Such compounds are widely used for many applications in medicinal science.¹⁴ Many thienopyridines have been synthesized and studied in relation to their biological and pharmacological importance.^{15,16} Some of them proved to possess antiviral,^{17,18} anti-diabetic,¹⁹ antimicrobial,^{20,21} antitumor,²² antiparasitic,²³ and neurotropic activities.²⁴

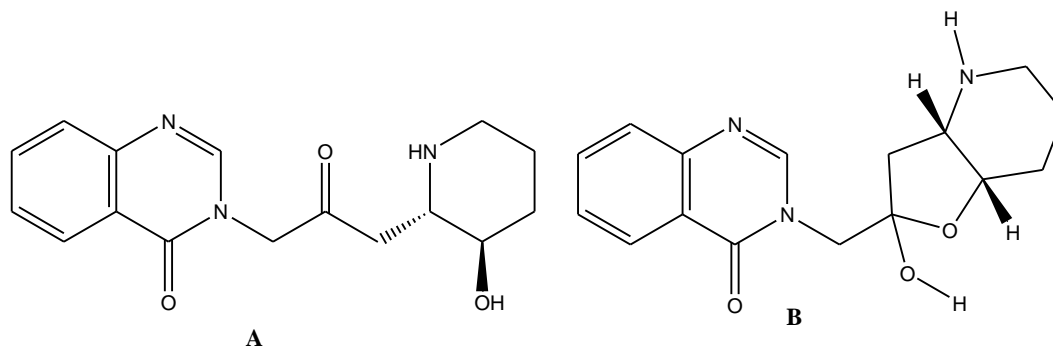


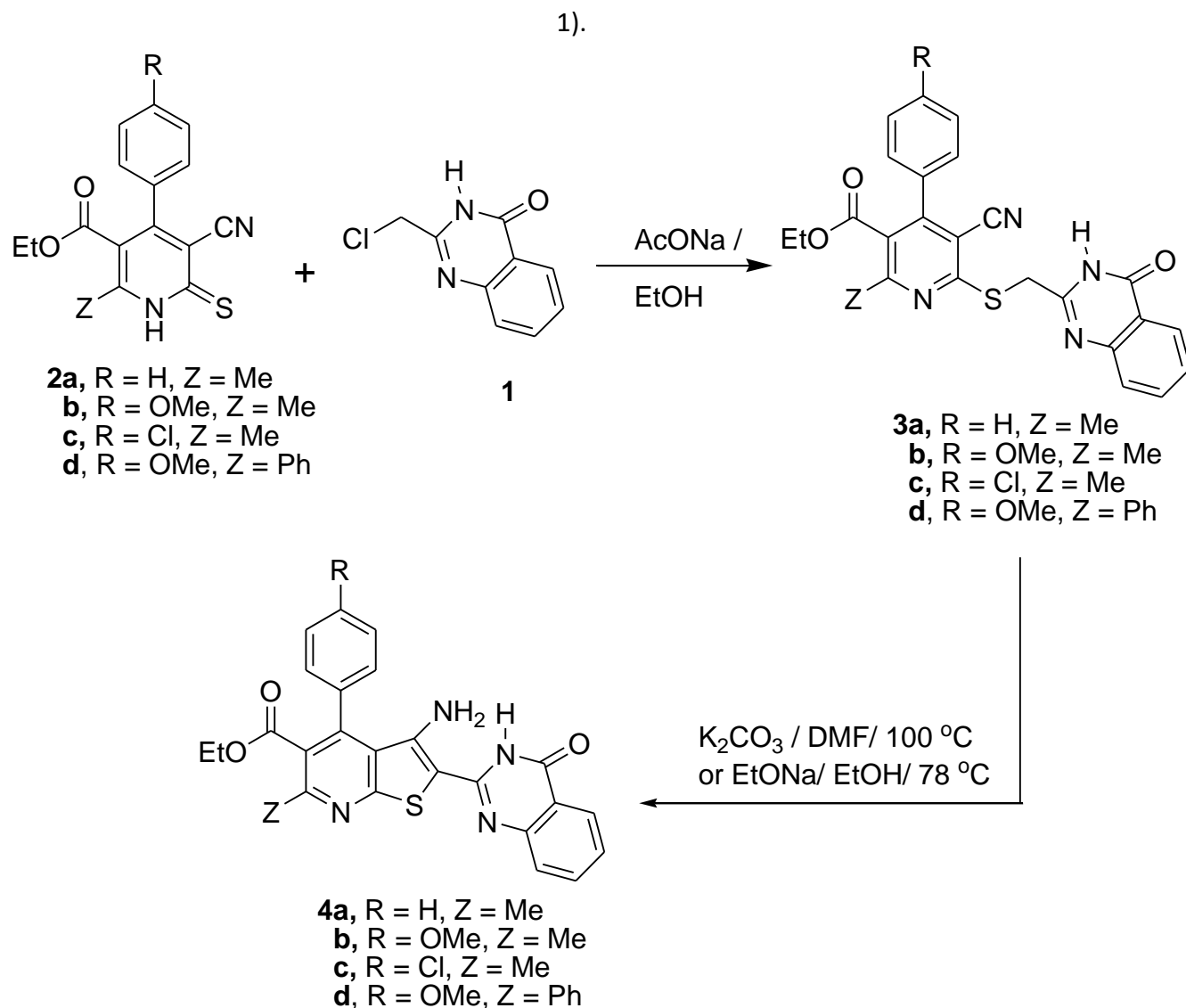
Figure 1. The chemical structure of Febrifugine (A) and isofebrifugine (B).

The aforementioned findings prompted us to study the reaction of 2-chloromethylquinazoline-4(3*H*)-one (**1**) with tri-substituted 3-cyanopyridine-2(1*H*)-thiones **2a-d** and/ or 3-cyanoquinoline-2(1*H*)-thione (**2e**) in order to get novel heterocyclic compounds, incorporating both quinazoline and pyridine moiety together with other pharmacophores such as thiophene, pyrimidine and quinoline nucleus.

Results and Discussion

Although versatile compound, 2-chloromethylquinazoline-4(3*H*)-one (**1**) was prepared early by many chemists, its reactions with any compound of the type **2a-e**, 3-cyanopyridine-2(1*H*)-thiones has not been reported till now. Therefore, we began this investigation from the reaction 2-chloromethylquinazoline-4(3*H*)-one (**1**) with 3-cyanopyridine-2(1*H*)-thiones **2a-d** by refluxing in ethanol containing sodium acetate trihydrate as a basic catalyst. The products which isolated were identified as quinazolinylmethylsulfanylpurine derivatives **3a-d** (Scheme 1). Their IR spectra showed characteristic absorption bands around 3250 cm^{-1} for (NH), 2220 for ($\text{C}\equiv\text{N}$), 1720 for ($\text{C}=\text{O}$, ester) and 1670 for ($\text{C}=\text{O}$, quinazolinone). Their ^1H NMR spectra showed the presence of a singlet signal at δ 4.36-4.61 corresponds to SCH_2 group in addition to the other signals which are in accordance with their proposed structures.

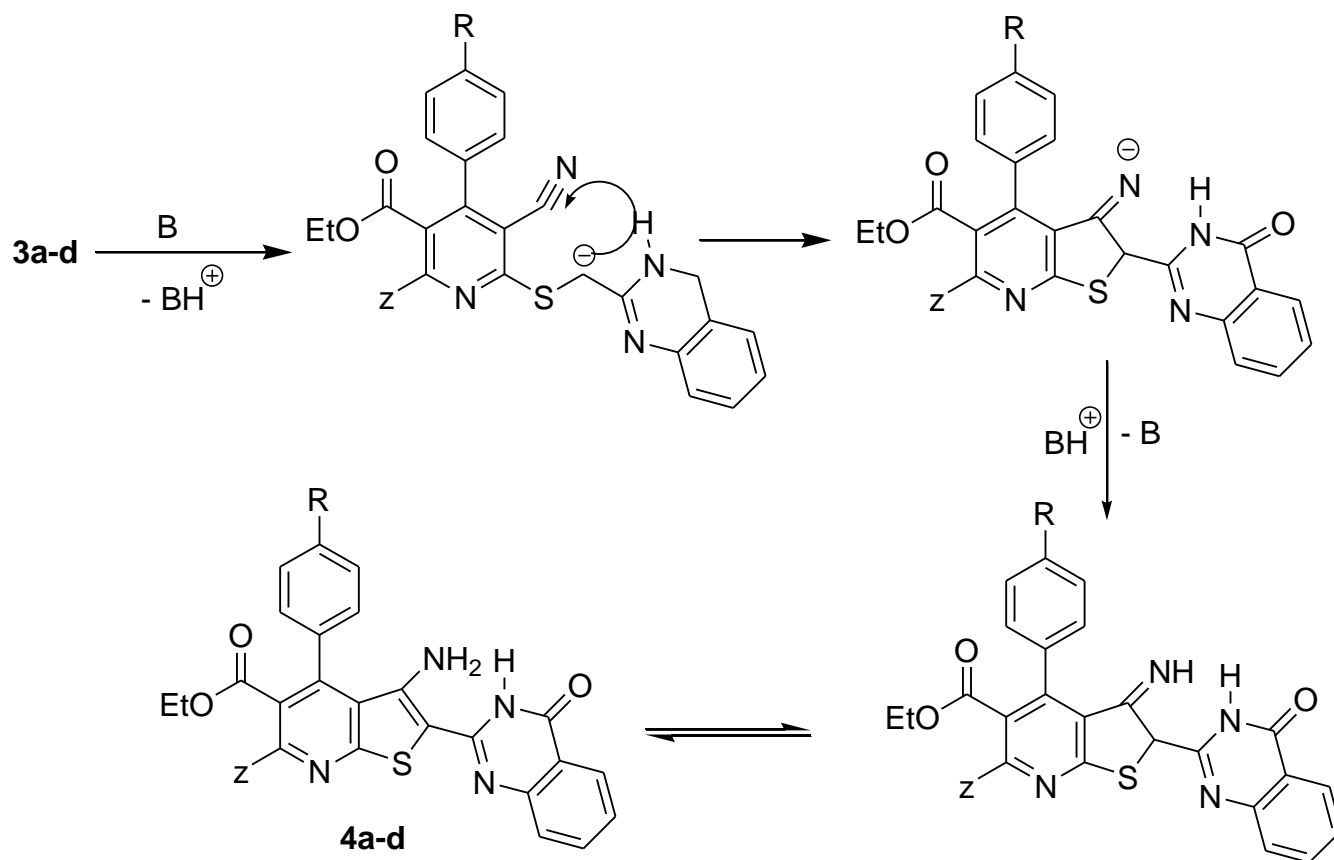
Upon heating compounds **3a-d** in ethanol containing sodium ethoxide at boiling temperature or in DMF containing anhydrous K_2CO_3 at 100 $^\circ\text{C}$, they underwent intramolecular *Thorpe-Ziegler* cyclization affording 3-amino-2-(3,4-dihydro-4-oxo-2-quinazolinyl)thieno[2,3-*b*]pyridines **4a-d** in nearly quantitative yields (Scheme



Scheme 1. Synthesis of compounds **3a-d** and **4a-d**.

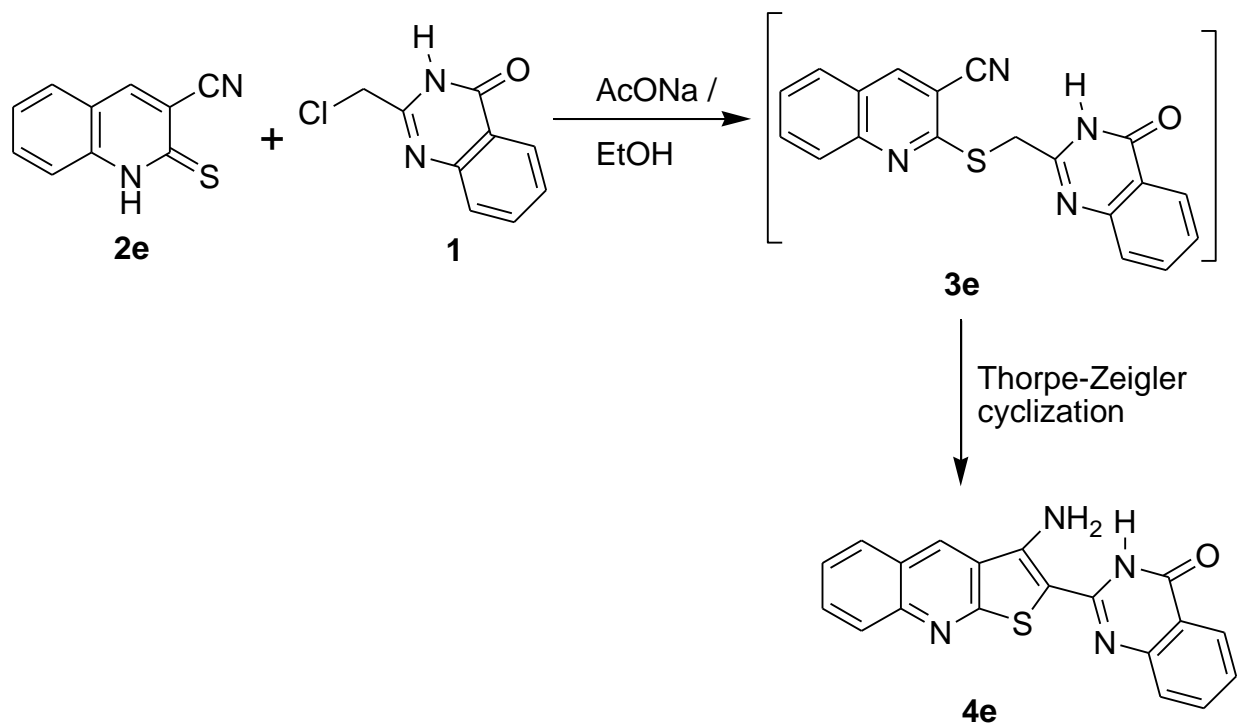
The IR spectra of **4a-d** revealed the disappearance of $\text{C}\equiv\text{N}$ band and the presence of two absorption bands around 3460, 3200 cm^{-1} characteristic for (NH_2) beside the other bands. The ^1H NMR spectra of **4a-d** showed the presence of a singlet signal (exchangeable with D_2O) around δ 6.50 instead of the signal of SCH_2 group which exists in the spectra of compounds **3a-d**.

The mechanism of the latter cyclization is depicted in Scheme 2.



Scheme 2. Mechanism of conversion of compounds **3a-d** to **4a-d**.

In contrast, reaction of **1** with 3-cyanoquinoline-2(1*H*)-thione (**2e**) by refluxing in ethanol containing sodium acetate trihydrate, 3-aminothieno[2,3-*b*]quinoline **4e** was separated directly without isolation of the intermediate **3e**. The ease of spontaneous cyclization of this intermediate may be due to the absence of any steric effects since there is no any substituent at 4-position of **3e**. The pathway of this reaction is given in Scheme 3.

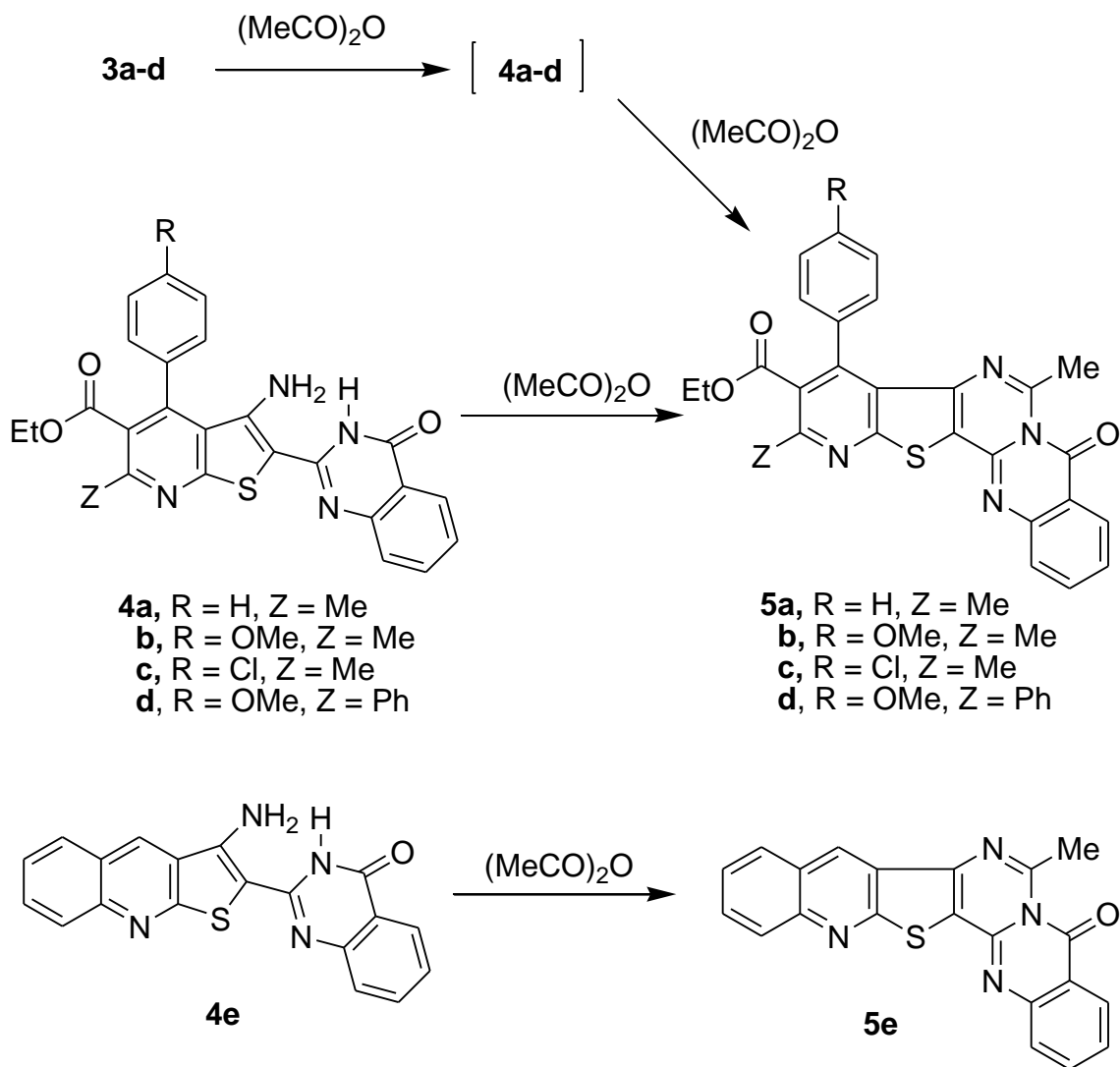


Scheme 3. Synthesis of compound **4e**.

The elemental and spectral analyses of compound **4e** are in accordance with its proposed structure (see Experimental part).

The compounds **4a-d** and **4e** having the γ -aminoimine structure, were utilized as new precursors for synthesizing novel fused heterocyclic compounds containing pyridothienopyrimidoquinazolinone, quinolinothienopyrimidoquinazolinone and pyridothienotriazinoquinazolinone moiety.

Thus, heating compounds **4a-e** with acetic anhydride, under neat conditions, at reflux temperature furnished the corresponding 6-methylpyridothienopyrimido[6,1-*b*]quinazolinones **5a-e** in good yields (Scheme 4).

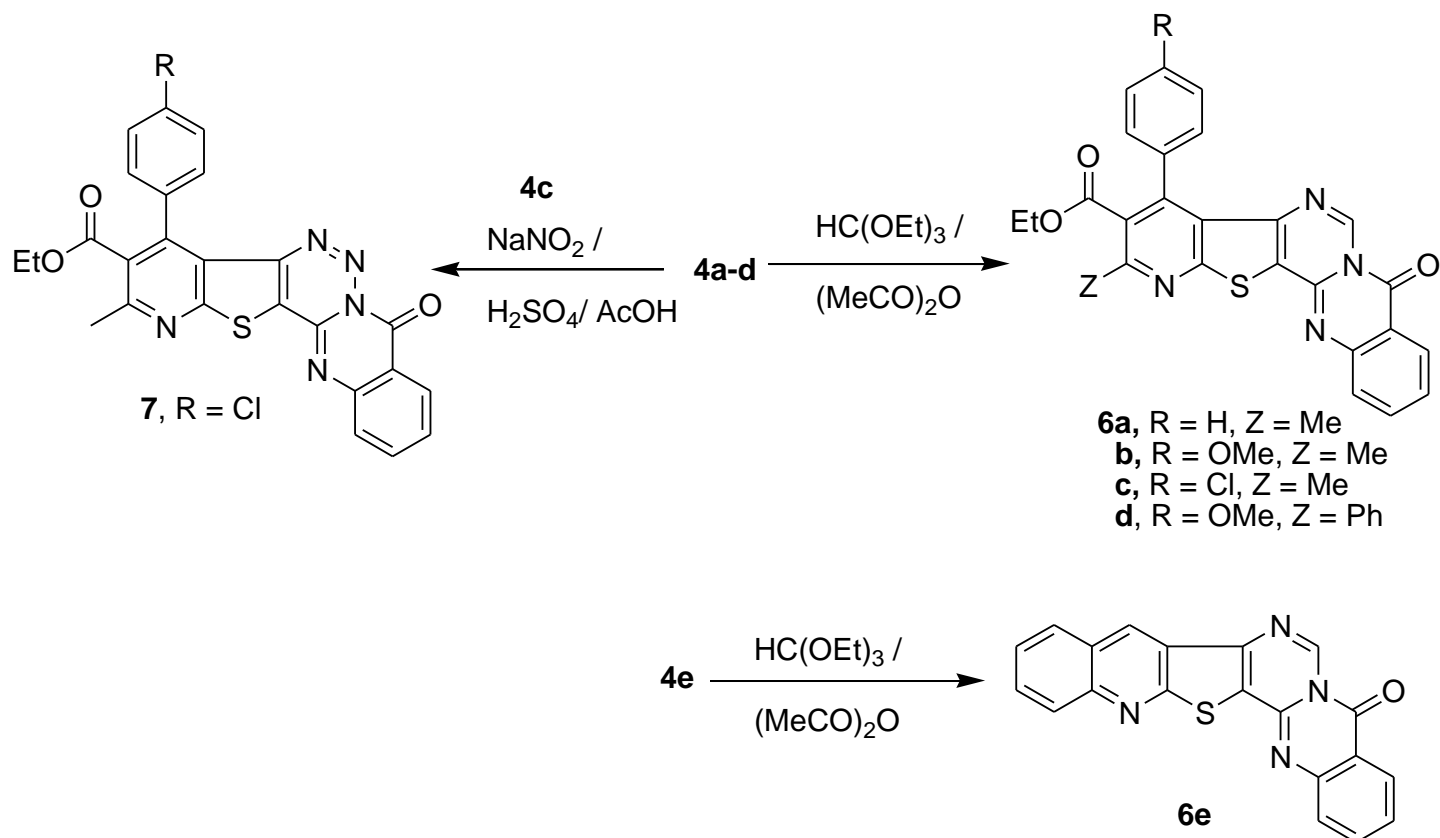


Scheme 4. Synthesis of compounds **5a-e**.

In a creative experiment, an attempt to react compounds **3a-d** with acetic anhydride under neat conditions at reflux temperature has been succeeded and the products were identified as 6-methylpyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-*b*]quinazolinones **5a-d** (Scheme 4). The pathway of the latter reaction may be involve: (i) initial cyclization of **3a-d** into thienopyridines **4a-d** by action of the last traces of acetic acid which often associated with acetic anhydride and (ii) usual acetylation of compounds **4a-d** followed by cyclodehydration affording **5a-d**. To prove the former step (i), an attempt to cyclize **3a-d** into **4a-d** by heating in acetic acid was succeeded.

The elemental and spectral analyses of compounds **5a-e** are in accordance with their proposed structures (Exp. part). Their IR spectra showed the disappearance of characteristic absorption bands which corresponds to the amino and imino groups. Their ^1H NMR spectra exhibited an additional singlet signal at 2.80-3.10 ppm equivalent to a new methyl group attached to the pyrimidine moiety.

Treatment of compounds **4a-e** with triethyl orthoformate in the presence of acetic anhydride, furnished the fused pentacyclic compounds, pyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-*b*]quinazolinones **6a-e**. The triazinone analogue **7** was obtained *via* diazotisation of **4c** using H_2SO_4 -AcOH mixture and sodium nitrite solution at low temperature (Scheme 5).



Scheme 5. Synthesis of compounds **6a-e** and **7**.

The structures of compounds **6a-e** and **7** were proved by elemental and spectral analyses. Their IR spectra showed the disappearance of characteristic absorption bands which corresponds to the amino and imino groups. The ¹H NMR spectra of **6a-e** exhibited a new singlet signal around δ 9.25 ppm equivalent to CH of pyrimidine moiety.

Conclusions

In this paper, we have successfully synthesized novel series of quinazolinylmethylsulfanylpuridines, quinazolinylthieno[2,3-*b*]pyridines, pyridothienopyrimido[6,1-*b*]quinazolines and pyridothieno[1,2,3]triazino [6,1-*b*]quinazoline starting from easily available 2-chloromethylquinazoline-4(3*H*)-one (**1**) and 3-cyanopyridine-2(1*H*)-thiones **2a-e**.

Experimental Section

General. Melting points were determined on a Gallan-Kamp apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; ν max in cm⁻¹). The ¹H NMR spectra were taken on a JEOL JNM-ECS 400 (400 MHz) or a Varian EM-390, 90 MHz spectrometer. The ¹³C NMR spectra were recorded on a JEOL JNM-ECS 400 (100 MHz) spectrometer. Chemical shifts are given in δ, ppm and coupling constants (J) is given in Hz. Electron impact (EI) MS spectra were carried out on a JEOL JMS-600 spectrometer. Elemental

analyses (C, H, N and S) were performed on an Elemental Analyses system GmbH VARIOEL V2.3 1998 CHNS Mode. The purity of the obtained compounds were checked by TLC.

2-Chloromethylquinazoline-4(3H)-one (1), 4-aryl-3-cyano-5-ethoxycarbonyl-6-methylpyridine-2(1H)thione 2a-d and 3-cyanoquinoline-2(1H)-thione (2e). Compounds **1**,²⁵ **2a-d**²⁶ and **2e**²⁷ were prepared according to the reported methods.

Reaction of 2-chloromethylquinazoline-4(3H)-one (1) with compounds 2a-d; synthesis of quinazolinyl-methylsulfanylpiperidines 3a-d. To a suspension of compound **2a-d** (20 mmol) and sodium acetate trihydrate (3.0 g, 22 mmol) in ethanol (50 mL), 2-chloromethylquinazoline-4(3H)-one (**1**) (20 mmol) was added. The resulting mixture was then heated at reflux for one hour. The white precipitate that formed on cooling was collected and recrystallized from ethanol to give white plates of compounds **3a-d**.

3-Cyano-5-ethoxycarbonyl-6-methyl-4-phenyl-2-(4-oxo-3,4-dihydroquinazolin-2-yl)methylsulfanylpiperidine (3a). Obtained by reaction of 2-chloromethylquinazoline-4(3H)-one (**1**) with compound **2a**; yield: 86 %; mp 180-181 °C. IR: 2978, 2920 (C-H, aliphatic), 3252 (NH), 2219 (C≡N), 1720 (C=O, ester), 1670 (C=O, quinazolinone). ¹H NMR (DMSO-*d*₆): 12.43 (s, 1H, NH), 7.38-8.14 (m, 9H, Ar-H), 4.61 (s, 2H, SCH₂), 3.98 (q, *J* 7.0, 2H, OCH₂), 2.57 (s, 3H, CH₃), 0.85 (t, *J* 7.0, 3H, CH₃ of ester). Anal. Calcd. For C₂₅H₂₀N₄O₃S (456.12): C, 65.77; H, 4.42; N, 12.27; S, 7.02 %. Found: C, 65.62; H, 4.35; N, 12.47; S, 7.21 %

3-Cyano-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-2-(4-oxo-3,4-dihydroquinazolin-2-yl)methylsulfanylpiperidine (3b). Obtained by reaction of 2-chloromethylquinazoline-4(3H)-one (**1**) with compound **2b**; yield: 84 %; mp 200-201 °C. IR: 2977, 2918 (C-H, aliphatic), 3250 (NH), 2219 (C≡N), 1723 (C=O, ester), 1670 cm⁻¹ for (C=O, quinazolinone). ¹H NMR (400 MHz, CDCl₃): 11.37 (s, 1H, NH), 7.25-8.27 (m, 6H, Ar-H), 6.98-7.00 (d, 2H, Ar-H), 4.41 (s, 2H, SCH₂), 4.07-4.12 (q, *J* 7.2 Hz, 2H, OCH₂), 3.86 (s, 3H, OCH₃), 2.82 (s, 3H, CH₃), 0.99-1.03 (t, *J* 7.0 Hz, 3H, CH₃ of ester). ¹³C NMR and Dept 145 (100 MHz, CDCl₃): 166.26, 162.38, 161.81, 161.21, 159.38, 153.25, 153.01, 148.73, 134.71 (CH), 129.74 (2 CH), 127.47, 127.23 (CH), 127.20 (CH), 126.53 (CH), 126.09, 121.66, 114.38 (2 CH), 105.68, 103.45, 62.09 (OCH₂), 55.41 (OCH₃), 34.68 (SCH₂), 23.29 (CH₃ attached to piperidine ring), 13.70 CH₃ of ester group). MS: *m/z* 486 (M⁺, 100 %), 457 (14%, M⁺-Et), 453 (12%), 191 (12%). Anal. Calcd. for C₂₆H₂₂N₄O₄S (486.13): C, 64.18; H, 4.56; N, 11.52; S, 6.59 %. Found: C, 64.34; H, 4.58; N, 11.31; S, 6.27 %

4-(4-Chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-methyl-2-(4-oxo-3,4-dihydroquinazolin-2-yl)methylthiopyridine (3c). Obtained by reaction of 2-chloromethylquinazoline-4(3H)-one (**1**) with compound **2c**; yield: 85 %; mp 210-211°C. IR: 3074 (C-H, aromatic), 2945 (C-H, aliphatic), 3250 (NH), 2220 (C≡N), 1720 (C=O, ester), 1672 (C=O, quinazolinone). ¹H NMR (400 MHz, CDCl₃): 11.20 (s, 1H, NH), 7.25-8.27 (m, 8H, Ar-H), 4.42 (s, 2H, SCH₂), 4.08-4.11 (q, *J* =7.0 Hz, 2H, OCH₂), 2.83 (s, 3H, CH₃), 0.99-1.02 (t, *J* =7.0 Hz, 3H, CH₃ of ester). ¹³C NMR and Dept 145 NMR (100 MHz, CDCl₃): 167.52, 161.37, 160.60, 156.35, 149.33, 143.82, 130.01, 127.63, 125.40, 118.57, 114.79, 114.34, 114.17, 109.20, 61.63 (OCH₂), 34.68 (SCH₂), 23.29 (CH₃ attached to piperidine ring), 13.70 CH₃ of ester group). MS: *m/z* 490 (M⁺, 100 %), 492 (M⁺+2, 40 %); 461 (M⁺-Et, 16 %). Anal. Calcd. for C₂₅H₁₉ClN₄O₃S (490.08): C, 61.16; H, 3.90; N, 11.41; S, 6.53 %. Found: C, 61.19; H, 3.98; N, 11.30; S, 6.42 %.

3-Cyano-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-phenyl-2-(4-oxo-3,4-dihydroquinazolin-2-yl)methylthiopyridine (3d). Obtained by reaction of 2-chloromethylquinazoline-4(3H)-one (**1**) with compound **2d**; yield; 86 %; mp 190-191 °C. IR: 2923 (C-H, aliphatic), 3243 (NH), 2219 (C≡N), 1721 (C=O, ester), 1685 (C=O, quinazolinone). ¹H NMR (400 MHz, CDCl₃): δ = 10.60 (s, 1H, NH, exchangeable with D₂O), 6.93-8.12 (m, 13H, Ar-H), 4.36 (s, 2H, SCH₂), 3.77-3.81 (m, 5H, OCH₂ and OCH₃), 0.76 (t, 3H, CH₃ of ester). MS: *m/z* 548 (M⁺, 100 %). Anal. Calcd. for C₃₁H₂₄N₄O₄S (548.15): C, 67.87; H, 4.41; N, 10.21; S, 5.84 %. Found: C, 67.86; H, 4.49; N, 10.01; S, 5.50 %.

Cyclization of compounds 3a-d; synthesis of quinazolinylthieno[2,3-b]pyridine derivatives 4a-d**Method A)**

To a hot solution of compound **3a-d** (10 mmol) in absolute ethanol (30 mL), a few drops of sodium ethoxide solution (0.12 g of sodium in 30 mL absolute ethanol) was added. The reaction mixture was heated under reflux for 5 minutes. The product that formed after cooling was filtered off and recrystallized from ethanol to give canary yellow needles of compounds **4a-d**.

3-Amino-5-ethoxycarbonyl-6-methyl-4-phenyl-2-(4-oxo-3,4-dihydroquinazolin-2-yl)thieno[2,3-b]pyridine (4a). It was synthesized by cyclization of compound **3a**; yield: 95 %; mp 280-282 °C. IR: 3469, 3206 (NH₂, NH), 2977 (C-H, aliphatic), 1729 (C=O, ester), 1660 (C=O, quinazolinone). ¹H NMR (400 MHz, DMSO-*d*₆): 8.80 (s, 1H, NH, exchangeable with D₂O), 7.38-8.10 (m, 9H, Ar-H), 6.53 (s, 2H, NH₂, exchangeable with D₂O), 3.98-3.99 (q, 2H, OCH₂), 2.62 (s, 3H, CH₃), 0.89 (t, 3H, CH₃ of ester). Anal. Calcd. For C₂₅H₂₀N₄O₃S (456.12): C, 65.77; H, 4.42; N, 12.27; S, 7.02 %. Found: C, 65.88; H, 4.22; N, 12.00; S, 7.19 %.

3-Amino-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-2-(4-oxo-3,4-dihydroquinazolin-2-yl)thieno[2,3-b]pyridine (4b). It was synthesized by cyclization of compound **3b**; yield: 94 %; mp 305-306 °C. IR: 2951 (C-H, aliphatic), 3464, 3200 (NH₂, NH), 1728 (C=O, ester), 1667 (C=O, quinazolinone). ¹H NMR (400 MHz, CDCl₃): 8.72 (s, 1H, NH, exchangeable with D₂O), 8.20-8.22 (d, 2H, Ar-H), 7.06-7.36 (m, 6H, Ar-H), 6.56 (broad s, 2H, NH₂, exchangeable with D₂O), 4.04-4.09 (q, *J* = 7.4, 2H, OCH₂), 3.90 (s, 3H, OCH₃), 2.70 (s, 3H, CH₃), 1.01-1.04 (t, *J* = 7.4, 3H, CH₃ of ester). ¹³C NMR and Dept 145 NMR (100 MHz, CDCl₃): 167.76, 161.64, 160.49, 155.45, 149.84, 148.83, 145.87, 134.84 (CH), 130.11, 130.06 (2 CH), 126.72 (CH), 126.23 (CH), 125.84, 125.74 (CH), 114.14 (2 CH), 113.84, 106.47, 96.65, 93.49, 61.79 (OCH₂), 55.46 (OCH₃), 23.51 (CH₃ attached to pyridine ring), 13.84 CH₃ of ester group). MS: *m/z* 486 (M⁺, 100 %), 457 (M⁺ - Et, 15%). Anal. Calcd. for C₂₆H₂₂N₄O₄S (486.13): C, 64.18; H, 4.56; N, 11.52; S, 6.59 %. Found: C, 64.11; H, 4.50; N, 11.72; S, 6.43 %.

3-Amino-4-(4-chlorophenyl)-5-ethoxycarbonyl-6-methyl-2-(4-oxo-3,4-dihydroquinazolin-2-yl)thieno[2,3-b]pyridine (4c). It was synthesized by cyclization of compound **3c**; yield 98 %; mp 317-318 °C. IR (cm⁻¹): 2951 (C-H, aliphatic), 3462, 3200 (NH₂, NH), 1729 (C=O, ester), 1667 (C=O, quinazolinone). ¹H NMR (400 MHz, CDCl₃): 8.90 (s, 1H, NH, exchangeable with D₂O), 8.18-8.20 (d, 2H, Ar-H), 7.25-7.52 (m, 6H, Ar-H), 6.47 (s, 2H, NH₂, exchangeable with D₂O), 4.04-4.10 (q, *J* 7.0, 2H, OCH₂), 2.70 (s, 3H, CH₃), 1.01-1.05 (t, *J* = 7.0, 3H, CH₃ of ester). ¹³C NMR and Dept 135 NMR (100 MHz, CDCl₃): 167.38, 161.64, 159.39, 155.58, 149.73, 148.68, 145.29, 142.74, 134.88 (CH), 130.22 (2 CH), 128.98 (2 CH), 126.70 (CH), 126.23 (CH), 125.86 (CH), 120.58, 119.85, 97.44, 61.98 (OCH₂), 23.59 (CH₃ attached to pyridine ring), 13.76 CH₃ of ester group). MS: *m/z* 490 (M⁺, 100 %), 492 (M⁺+2, 43 %); 461 (M⁺-Et, 17 %). Anal. Calcd. for C₂₅H₁₉ClN₄O₃S (490.08): C, 61.16; H, 3.90; N, 11.41; S, 6.53 %. Found: C, 61.34; H, 3.77; N, 11.15; S, 6.82 %.

3-Amino-5-ethoxycarbonyl-4-(4-methoxyphenyl)-6-phenyl-2-(4-oxo-3,4-dihydroquinazolin-2-yl)thieno[2,3-b]pyridine (4d). It was synthesized by cyclization of compound **3d**; mp 289-291 °C; yield: 95 %. IR: 3462, 3204 (NH₂, NH), 1723 (C=O, ester), 1659 (C=O, quinazolinone). ¹H NMR (400 MHz, CDCl₃): 8.89 (s, 1H, NH), 8.21-8.23 (d, 1H, Ar-H), 7.10-7.51 (m, 12H, Ar-H), 6.62 (broad s, 2H, NH₂), 4.06-4.10 (q, 2H, OCH₂), 3.93 (s, 3H, OCH₃), 1.03-1.07 (t, 3H, CH₃ of ester). MS: *m/z* 548 (M⁺, 100 %). Anal. Calcd. for C₃₁H₂₄N₄O₄S (548.15): C, 67.87; H, 4.41; N, 10.21; S, 5.84 %. Found: C, 67.96; H, 4.47; N, 10.03; S, 5.68 %.

Method B)

To a solution of compound **3a-d** (0.01 mol) in DMF (30 ml), anhydrous K₂CO₃ (3.0 g) was added. The resulting mixture was heated on a steam bath for 4 h and then K₂CO₃ was filtered off while hot. The product that formed after dilution with water was collected and recrystallized from an ethanol-chloroform mixture to give compounds **4a-d** (yield: 87-90 %).

Method C)

Compound **3a-d** (0.01 mol) in glacial acetic acid (20 ml) was heated under reflux for one hour and then allowed to cool. The product that formed upon recrystallization gave compounds **4a-d** (yield: 78-83 %).

3-Amino-2-(4-oxo-3,4-dihydroquinazolin-2-yl)thieno[2,3-*b*]quinoline (4e). To a suspension of 2-chloromethylquinazoline-4(3*H*)-one (**1**) (20 mmol) and sodium acetate trihydrate (3.0 g, 22 mmol) in ethanol (50 mL), 3-cyanoquinoline-2(1*H*)-thione (**2e**) (20 mmol) was added. The resulting mixture was then heated at reflux for one hour. The yellow crystalline products that formed on hot was collected and recrystallized from ethanol to give compound **4e** in the form of yellow needles; yield: 97 %; mp 361-362 °C. IR: 3460, 3200 (NH₂, NH), 1660 (C=O, quinazolinone). ¹H NMR (400 MHz, DMSO-*d*₆): 8.40 (s, 1H, NH, exchangeable with D₂O), 7.40-8.51 (m, 9H, Ar-H and CH quinoline), 6.42 (s, 2H, NH₂, exchangeable with D₂O). Anal. Calcd. For C₁₉H₁₂N₄OS (344.07): C, 66.26; H, 3.51; N, 16.27; S, 9.31 %. Found: C, 66.33; H, 3.42; N, 16.00; S, 9.18 %.

Reaction of compounds 4a-e with acetic anhydride; synthesis of pyridothienopyrimidoquinazolines 5a-e. A solution of compounds **4a-e** (5 mmol) in acetic anhydride (25 mL) was heated under reflux for 3 h and then left to cool. The precipitate that formed was collected and recrystallized from ethanol in the form of pale yellow needles of **5a-e**

2,6-Dimethyl-3-ethoxycarbonyl-4-phenylpyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-*b*]quinazoline-8-one (5a). Obtained from the reaction of compound **4a** with acetic anhydride; yield: 88 %; mp 217-218 °C. IR: 1715 (C=O, ester), 1661 (C=O, quinazolinone), 1592 (C=N). ¹H NMR (400 MHz, DMSO-*d*₆): 7.37-8.11 (m, 9H, Ar-H), 4.00-4.04 (q, 2H, OCH₂), 2.89 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 0.89-0.92 (t, 3H, CH₃ of ester). Anal. Calcd. For C₂₇H₂₀N₄O₃S (480.12): C, 67.49; H, 4.20; N, 11.66; S, 6.67 %. Found: C, 67.22; H, 4.35; N, 11.24; S, 6.89 %.

2,6-Dimethyl-3-ethoxycarbonyl-4-(4-methoxyphenylpyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-*b*]quinazoline-8-one (5b). Obtained from the reaction of compound **4b** with acetic anhydride; yield: 80 %; mp 312-313 °C. IR : 2933 (C-H, aliphatic), 1721 (C=O, ester), 1666 (C=O, quinazolinone), 1596 (C=N). ¹H NMR (90 MHz, CDCl₃): 6.90-8.40 (m, 8H, Ar-H), 3.90-4.30 (q, 2H, OCH₂), 3.80 (s, 3H, OCH₃), 2.80 (s, 3H, CH₃), 2.70 (s, 3H, CH₃), 0.90 -1.20 (t, 3H, CH₃ of ester). MS: *m/z* 510 (M⁺, 100 %), 481 (M⁺-Et, 19 %), 465 (10 %). Anal. Calcd. for C₂₈H₂₂N₄O₄S (510.13): C, 65.87; H, 4.34; N, 10.97; S, 6.28 %. Found: C, 65.97; H, 4.33; N, 11.02; S, 6.49 %.

2,6-Dimethyl-4-(4-chlorophenyl)-3-ethoxycarbonylpyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-*b*]quinazoline-8-one (5c). Obtained from the reaction of compound **4c** with acetic anhydride; yield: 82 %; mp 234-235 °C. IR : 2979 (C-H, aliphatic), 1720 (C=O, ester), 1661 (C=O, quinazolinone), 1610 (C=N). ¹H NMR (90 MHz, CF₃CO₂D): 7.30-8.60 (m, 8H, Ar-H), 4.20-4.50 (q, 2H, OCH₂), 3.10 (s, 3H, CH₃), 3.00 (s, 3H, CH₃), 1.00 -1.30 (t, 3H, CH₃ of ester). MS: *m/z* 514 (M⁺, 100 %), 516 (M⁺+2, 38 %); 485 (M⁺-Et, 33 %). Anal. Calcd. for C₂₇H₁₉ClN₄O₃S (514.08): C, 62.97; H, 3.72; N, 10.88; S, 6.23 %. Found: C, 62.82; H, 3.76; N, 10.71; S, 6.18 %.

3-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-2-phenylpyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-*b*]quinazoline-8-one (5d). Obtained from the reaction of compound **4d** with acetic anhydride; yield: 83 %; mp 259-261 °C. IR: 1721 (C=O, ester), 1662 (C=O, quinazolinone), 1600 (C=N). ¹H NMR (90 MHz, CDCl₃): 6.90-7.70 (m, 13H, Ar-H), 3.90-4.30 (q, 2H, OCH₂), 3.80 (s, 3H, OCH₃), 2.80 (s, 3H, CH₃), 0.80 -1.10 (t, 3H, CH₃ of ester). Anal. Calcd. for C₃₃H₂₄N₄O₄S (572.17): C, 69.22; H, 4.22; N, 9.78; S, 5.60 %. Found: C, 69.37; H, 4.19; N, 9.92; S, 5.50 %.

7-methylquinolino[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-*b*]quinazoline-5-one (5e). Obtained from the reaction of compound **4e** with acetic anhydride; yield: 92 %; mp 295-296 °C. IR : 1660 (C=O, quinazolinone), 1600 (C=N). ¹H NMR (90 MHz, CF₃CO₂D): 7.10-8.70 (m, 9H, Ar-H and CH quinoline), 3.00 (s, 3H, CH₃). Anal. Calcd. for C₂₁H₁₂N₄OS (368.07): C, 68.46; H, 3.28; N, 15.21; S, 8.70 %. Found: C, 68.33; H, 3.40; N, 15.00; S, 8.88 %

Effect of acetic anhydride on compounds 3a-d. Compound **3a-d** (5 mmol) in acetic anhydride (30 mL) was heated under reflux for 3 h and then left to cool. The precipitate that formed was collected and recrystallized from ethanol to give pale yellow needles; these products were assigned as **5a-d**; yield (63-70 %)

Reaction of compounds 4a-e with triethyl orthoformate; synthesis of pyridothienopyrimidoquinazolines 6a-e. To a mixture of **4a-e** (5 mmol) and triethyl orthoformate (5 ml), acetic anhydride (25 mL) was added. The reaction mixture was heated under reflux for 3 h. The precipitate that formed while hot was collected and recrystallized from DMSO to give pale yellow needles of **6a-e**.

3-Ethoxycarbonyl-2-methyl-4-phenylpyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-b]quinazoline-8-one

(6a). Obtained from the reaction of compound **4a** with triethyl orthoformate; yield: 85 %; mp 194-195 °C. IR: 1723 (C=O, ester), 1660 (C=O, quinazolinone), 1600 (C=N). ¹H NMR (400 MHz, CDCl₃): 9.30 (s, 1H, CH pyrimidine), 7.30-7.97 (m, 9H, Ar-H), 4.00-4.04 (q, *J* 7.0, 2H, OCH₂), 2.79 (s, 3H, CH₃), 1.06-1.09 (t, *J* 7.0, 3H, CH₃ of ester). Anal. Calcd. for C₂₆H₁₈N₄O₃S (466.10): C, 66.94; H, 3.89; N, 12.01; S, 6.87 %. Found: C, 66.65; H, 3.78; N, 12.29; S, 6.68 %

3-Ethoxycarbonyl-4-(4-methoxyphenyl)-2-methylpyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-b]quinazoline-8-one (6b).

Obtained from the reaction of compound **4b** with triethyl orthoformate; yield: 81 %; mp 218-219 °C. IR: 2963 (C-H, aliphatic), 1716 (C=O, ester), 1655 (C=O, quinazolinone). ¹H NMR (400 MHz, CDCl₃): 9.31 (s, 1H, CH pyrimidine), 8.40-8.42 (d, 1H, Ar-H), 7.00-7.88 (m, 7H, Ar-H), 4.09-4.14 (q, *J* 7.0, 2H, OCH₂), 3.92 (s, 3H, OCH₃), 2.77 (s, 3H, CH₃), 1.03-1.07 (t, *J* 7.0, 3H, CH₃ of ester). MS: *m/z* 496 (M⁺, 100 %), 467 (M⁺-Et, 12 %), 450 (19 %), 424 (12 %). Anal. Calcd. for C₂₇H₂₀N₄O₄S (496.12): C, 65.31; H, 4.06; N, 11.28; S, 6.46 %. Found: C, 65.39; H, 4.11; N, 11.20; S, 6.43 %.

3-Ethoxycarbonyl-4-(4-chlorophenyl)-2-methylpyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-b]quinazoline-8-one (6c).

Obtained from the reaction of compound **4c** with triethyl orthoformate; yield: 88 %; mp 220-221 °C. IR: 2976 (C-H, aliphatic), 1716 (C=O, ester), 1655 (C=O, quinazolinone), 1596 (C=N). ¹H NMR (400 MHz, CDCl₃): 9.28 (s, 1H, CH pyrimidine), 8.39-8.41 (d, 1H, Ar-H), 7.26-7.87 (m, 7H, Ar-H), 4.09-4.14 (q, *J* 7.0, 2H, OCH₂), 2.78 (s, 3H, CH₃), 1.03-1.07 (t, *J* 7.0, 3H, CH₃ of ester). MS: *m/z* 502 (M⁺+2, 42 %), 500 (M⁺, 100 %), 471 (M⁺-Et, 10 %), 455 (M⁺-EtO, 11 %). Anal. Calcd. for C₂₆H₁₇ClN₄O₃S (500.07): C, 62.34; H, 3.42; N, 11.18; S, 6.40 %. Found: C, 62.14; H, 3.45; N, 11.00; S, 6.19 %.

3-Ethoxycarbonyl-4-(4-methoxyphenyl)-2-phenylpyrido[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-b]quinazoline-8-one (6d).

Obtained from the reaction of compound **4d** with triethyl orthoformate; yield: 89 %; mp 239-240 °C. IR: 2980 (C-H, aliphatic), 1719 (C=O, ester), 1661 (C=O, quinazolinone), 1601 (C=N). ¹H NMR (400 MHz, CDCl₃): 9.31 (s, 1H, CH pyrimidine), 7.01-7.88 (m, 13H, Ar-H), 4.09-4.14 (q, *J* 7.0, 2H, OCH₂), 3.90 (s, 3H, OCH₃), 1.02-1.07 (t, *J* 7.0, 3H, CH₃ of ester). MS: *m/z* 558 (M⁺, 100 %), 513 (M⁺-EtO, 20 %). Anal. Calcd. for C₃₂H₂₂N₄O₄S (558.13): C, 68.80; H, 3.97; N, 10.03; S, 5.74 %. Found: C, 69.01; H, 3.87; N, 10.33; S, 5.78 %.

Quinolino[3'',2'':4',5']thieno[3',2':4,5]pyrimido[6,1-b]quinazoline-5-one (6e). Obtained from the reaction of compound **4e** with triethyl orthoformate; yield: 85 %; mp 362-363 °C. IR: 1660 (C=O, quinazolinone). ¹H NMR (90 MHz, CF₃CO₂D): 9.35 (s, 1H, CH pyrimidine), 7.10-8.70 (m, 9H, Ar-H and CH quinoline). Anal. Calcd. for C₂₀H₁₀N₄OS (354.06): C, 67.78; H, 2.84; N, 15.81; S, 9.05 %. Found: C, 67.54; H, 2.92; N, 15.57; S, 9.34 %.

3-Ethoxycarbonyl-4-(4-chlorophenyl)-2-methylpyrido[3'',2'':4',5']thieno[3',2':4,5][1,2,3]triazino[6,1-b]quinazoline-8-one (7).

To a chilled mixture of compound **4c** (0.005 mol) and conc H₂SO₄ (5 ml) in glacial acetic acid (15 ml), a sodium nitrite solution 10 % (5 ml) was added dropwise with stirring during about 10 mins. After the completion of addition, stirring was continued for 2 h. The precipitate that formed after dilution with water (10 ml) was collected and crystallized from ethanol to give compound **7** in the form of pale yellow crystals; yield: 74 %; mp 182-183 °C. IR (cm⁻¹): 2983 (C-H, aliphatic), 1710 (C=O, ester), 1665 (C=O, quinazolinone), 1606 (C=N). ¹H NMR (400 MHz, CDCl₃): 8.39-8.41 (d, 1H, Ar-H), 7.26-7.87 (m, 7H, Ar-H), 4.09-4.14 (q, *J* = 7.0, 2H,

OCH₂), 2.77 (s, 3H, CH₃), 1.03-1.07 (t, *J* 7.0, 3H, CH₃ of ester). MS: *m/z* 503 (M⁺+2, 19 %), 501 (M⁺, 44 %), 503 (M⁺+2, 19 %); 475 (M⁺+2-N₂, 100 %); 446 (23 %); 430 (22 %); 119 (20 %). Anal. Calcd. for C₂₅H₁₆ClN₅O₃S (501.07): C, 59.82; H, 3.21; N, 13.95; S, 6.39 %. Found: C, 60.11; H, 3.23; N, 13.76; S, 6.60 %.

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