Synthesis and characterization of new quinazolinylmethylsulfanylpyridines, quinazolinylnthieno[2,3-b]pyridines and pyrido[3″,2″′:4′,5′]thieno[3′,2′′:4,5]pyrimido[6,1-b]quinazolines

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Abstract

Reaction of 2-chloromethylquinazoline-4(3H)-one with some 3-cyanopyridine-2(1H)-thiones gave the corresponding thioethers which upon treatment with appropriate base, underwent intramolecular Thorpe-Zeigler 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(3H)-one with 3-cyanoquinoline-(1H)-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

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Introduction

Quinazoline-4(3H)-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(3H)-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(3H)-one (1) with tri-substituted 3-cyanopyridine-2(1H)-thiones 2a-d and/ or 3-cyanoquinoline-2(1H)-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(3H)-one (1) was prepared early by many chemists, its reactions with any compound of the type 2a-e, 3-cyanopyridine-2(1H)-thiones has not been reported till now. Therefore, we began this investigation from the reaction 2-chloromethylquinazoline-4(3H)-one (1) with 3-cyanopyridine-2(1H)-thiones 2a-d by refluxing in ethanol containing sodium acetate trihydrate as a basic catalyst. The products which were isolated were identified as quinazolinylmethylsulfanylpyridine derivatives 3a-d (Scheme 1). Their IR spectra showed characteristic absorption bands around 3250 cm⁻¹ for (NH), 2220 for (C≡N), 1720 for (C=O, ester) and 1670 for (C=O, quinazolinone). Their 1H NMR spectra showed the presence of a singlet signal at δ 4.36-4.61 corresponds to SCH₂ 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 K₂CO₃ at 100 °C, they underwent intramolecular Thorpe-Zeigler 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 C≡N band and the presence of two absorption bands around 3460, 3200 cm⁻¹ characteristic for (NH₂) beside the other bands. The ³¹H NMR spectra of 4a-d showed the presence of a singlet signal (exchangeable with D₂O) around δ 6.50 instead of the signal of SCH₂ 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(1H)-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.
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 pyridothenopyrimidoquinazolinone, quinolinothienopyrimidoquinazolinone and pyridothenotriazinoquinazolinone moiety.

Thus, heating compounds 4a-e with acetic anhydride, under neat conditions, at reflux temperature furnished the corresponding 6-methylpyridothenopyrimido[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]quinazolineones 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 $^1$H 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]quinazolineones 6a-e. The triazinone analogue 7 was obtained via diazotisation of 4c using H$_2$SO$_4$-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 $^1$H NMR spectra of 6a-e exhibited a new singlet signal around $\delta$ 9.25 ppm equivalent to CH of pyrimidine moiety.

Conclusions

In this paper, we have successfully synthesized novel series of quinazolinylmethylsulfanylpyridines, quinazolinylthieno[2,3-b]pyridines, pyrdothienopyrimido[6,1-b]quinazolines and pyrdothieno[1,2,3]triazino[6,1-b]quinazoline starting from easily available 2-chloromethylquinazoline-4(3H)-one (1) and 3-cyanopyridine-2(1H)-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; $v$ max in cm$^{-1}$). The $^1$H NMR spectra were taken on a JEOL JNM-ECS 400 (400 MHz) or a Varian EM-390, 90 MHz spectrometer. The $^{13}$C NMR spectra were recorded on a JEOL JNM-ECS 400 (100 MHz) spectrometer. Chemical shifts are given in $\delta$, 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 quinazolin- methylsulfanylpyridines 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)methylsulfanylpyridine (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=O, ester), 1670 (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, OCH3), 3.86 (s, 3H, OCH3), 2.82 (s, 3H, CH3), 0.99-1.03 (t, J 7.0 Hz, 3H, CH3 of ester). 13 C 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 (OCH3), 55.41 (OCH3), 34.68 (SCH2), 23.29 (CH3 attached to pyridine ring), 13.70 CH3 of ester group). MS: m/z 486 (M+, 100%), 457 (14%, M+Et), 453 (12%), 191 (12%). Anal. Calcd. for C26H22N4O2S (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)methylthio- pyridine (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, OCH3), 2.83 (s, 3H, CH3), 0.99-1.02 (t, J =7.0 Hz, 3H, CH3 of ester). 13 C NMR and Dept 145 (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 pyridine ring), 13.70 CH3 of ester group). MS: m/z 490 (M+, 100%), 492 (M+2, 40%), 461 (M+Et, 16%). Anal. Calcd. for C25H19ClN4O2S (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)methylthio pyridine (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 C31H24N4O2S (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 (NH$_2$, NH), 2977 (C-H, aliphatic), 1729 (C=O, ester), 1660 (C=O, quinazoline). $^1$H NMR (400 MHz, DMSO-d$_6$): 8.80 (s, 1H, NH, exchangeable with D$_2$O), 7.38-8.10 (m, 9H, Ar-H), 6.53 (s, 2H, NH$_2$, exchangeable with D$_2$O), 3.98-3.99 (q, 2H, OCH$_2$), 2.62 (s, 3H, CH$_3$), 0.89 (t, 3H, CH$_3$ of ester). Anal. Calcd. for C$_{25}$H$_{20}$N$_4$O$_3$S (456.12): C, 65.77; H, 4.42; N, 12.27; S, 7.02 %. Found: C, 65.88; H, 4.42; 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 (NH$_2$, NH), 1728 (C=O, ester), 1667 (C=O, quinazoline). $^1$H NMR (400 MHz, CDCl$_3$): 8.72 (s, 1H, NH, exchangeable with D$_2$O), 8.20-8.22 (d, 2H, Ar-H), 7.06-7.36 (m, 6H, Ar-H), 6.65 (broad s, 2H, NH$_2$, exchangeable with D$_2$O), 4.04-4.09 (q, J = 7.4, 2H, OCH$_2$), 3.90 (s, 3H, OCH$_3$), 2.70 (s, 3H, CH$_3$), 1.01-1.04 (t, J = 7.4, 3H, CH$_3$ of ester). $^{13}$C NMR and Dept 145 NMR (100 MHz, CDCl$_3$): 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 (OCH$_3$), 55.46 (OCH$_3$), 23.51 (CH$_3$ attached to pyridine ring), 13.84 CH$_3$ of ester group). MS: m/z 486 (M$^+$, 100 %), 457 (M$^+$ - Et, 15 %). Anal. Calcd. for C$_{26}$H$_{22}$N$_4$O$_5$S (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 (NH$_2$, NH), 1729 (C=O, ester), 1667 (C=O, quinazoline). $^1$H NMR (400 MHz, CDCl$_3$): 8.90 (s, 1H, NH, exchangeable with D$_2$O), 8.18-8.20 (d, 2H, Ar-H), 7.25-7.52 (m, 6H, Ar-H), 6.47 (s, 2H, NH$_2$, exchangeable with D$_2$O), 4.04-4.10 (q, J = 7.0, 2H, OCH$_2$), 2.70 (s, 3H, CH$_3$), 1.01-1.05 (t, J = 7.0, 3H, CH$_3$ of ester). $^{13}$C NMR and Dept 145 NMR (100 MHz, CDCl$_3$): 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 (OCH$_3$), 23.59 (CH$_3$ attached to pyridine ring), 13.76 CH$_3$ of ester group). MS: m/z 490 (M$^+$, 100 %), 492 (M$^+$ + 2, 43 %); 461 (M$^+$ - Et, 17 %). Anal. Calcd. for C$_{25}$H$_{19}$ClN$_4$O$_5$S (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 (NH$_2$, NH), 1723 (C=O, ester), 1659 (C=O, quinazoline). $^1$H NMR (400 MHz, CDCl$_3$): 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, NH$_2$), 4.06-4.10 (q, 2H, OCH$_2$), 3.93 (s, 3H, OCH$_3$), 1.03-1.07 (t, 3H, CH$_3$ of ester). MS: m/z 548 (M$^+$, 100 %). Anal. Calcd. for C$_{33}$H$_{24}$N$_4$O$_4$S (548.15): C, 67.87; H, 4.41; N, 10.21; S, 5.84 %. Found: C, 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 K$_2$CO$_3$ (3.0 g) was added. The resulting mixture was heated on a steam bath for 4 h and then K$_2$CO$_3$ was filtered off while hot. The product that formed after dilution on 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 the 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-chloro-
methylquinazoline-4(3H)-one (1) (20 mmol) and sodium acetate trihydrate (3.0 g, 22 mmol) in ethanol (50
mL), 3-cyanooquinazoline-2(1H)-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, quinazoline). 1H NMR (400 MHz, DMSO-d6): 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, quinazoline), 1592 (C=N). 1H NMR (400 MHz, DMSO-d6): 7.37-8.11 (m, 9H, Ar-
H), 4.00-4.04 (q, 2H, OCH3), 2.89 (s, 3H, CH3), 2.62 (s, 3H, CH3), 0.89-0.92 (t, 3H, CH3 of ester). Anal. Calcd. For
C27H30N4O3S (480.12): C, 76.49; H, 4.20; N, 11.66; S, 6.67 %. Found: C, 76.22; H, 4.35; N, 11.24; S, 6.89 %.

2,6-Dimethyl-3-ethoxycarbonyl-4-(4-methoxyphenyl)pyrido[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, quinazoline), 1596 (C=N). 1H NMR (90
MHz, CDCl3): 6.90-8.40 (m, 8H, Ar-H), 3.90-4.30 (q, 2H, OCH3), 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
C28H32N4O3S (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, quinazoline), 1610 (C=N). 1H NMR (90
MHz, CF3CO2D): 7.30-8.60 (m, 8H, Ar-H), 4.20-4.50 (q, 2H, OCH3), 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
C27H31ClN4O3S (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, quinazoline), 1600 (C=N). 1H NMR (90 MHz, CDCl3): 6.90-7.70
(m, 13H, Ar-H), 3.90-4.30 (q, 2H, OCH3), 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-methylquinolinol[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, quinazoline),
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, quinazoline), 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 C25H18N4O3S (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, quinazoline). 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 C27H20N4O3S (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, quinazoline), 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, quinazoline), 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 C26H22N4O4S (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, quinazoline). 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 C20H10N4O4S (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, quinazoline), 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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