Synthesis and characterization of some new thieno[2,3-b]pyridines, thieno[2,3-c][2,7]naphthyridinones and pyrazolo[3,4-c][2,7]naphthyridinones with expected biological activity

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Abstract

Ethyl 5-cyano-1,6-dihydro-2-methyl-4-styryl-6-thioxonicotinate, its piperidinium pyridine-6-thiolate and 3-acetyl-5-cyano-1,6-dihydro-2-methyl-4-styryl-6-thioxopyridine were used as starting materials for synthesizing novel series of S-substituted methylthiopyridine-5-carbonitriles and thieno[2,3-b]pyridines with expected biological activity. Also, some novel thieno[2,3-c][2,7]naphthyridinones were synthesized. Moreover, 1,7-diamino-8,9-dihydro-5-methyl-8-phenyl-3H-pyrazolo[3,4-c][2,7]naphthyridine-6(7H)-one was synthesized by heating ethyl 5-cyano-1,6-dihydro-2-methyl-4-styryl-6-thioxonicotinate with hydrazine hydrate 99% under neat conditions. The obtained promising aminopyrazolo[3,4-c][2,7]naphthyridine-6(7H)-one was used as a precursor to get other novel derivatives with expected biological and medicinal importance. Structures of all new compounds were elucidated by elemental and spectral analysis.

Keywords: Pyridines; thieno[2,3-b]pyridines; thienonaphthyridinones; pyrazolo[3,4-c][2,7]naphthyridinones

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Introduction

Thienopyridines have gained substantial consideration from researchers due to their high therapeutic values.1-5 Thieno[2,3-c]pyridine nucleus shared in some approved drugs e.g. ticlopidine, clopidogrel and prasugrel (P2Y12) Receptor blocker platelet aggregation inhibitors in the peripheral vascular, coronary artery and cerebrovascular diseases.1 The research on the isomeric thieno[2,3-b]pyridines has been showing similar progress as well. A large number of biologically active compounds have been synthesized with the fused thieno[2,3-b]pyridine structural moiety as given in Figure 1. For instance, the plain thieno[2,3-b]pyridine scaffold that is mainly substituted at C2,3 and/or C4,6 has shown stimulatory activity against alkaline phosphatase (see compound I which is a potential drug candidate in the treatment of osteoporosis) (Figure 1).2

On the other hand, closely related 2,3-disubstituted thieno[2,3-b]pyridines II, III and 1Va (Figure 1) displayed potent inhibition of rat urea transporter (UT-B),3 IκB-kinase,4 and LIM domain kinase 1 (LIMK1)5 suggesting that these derivatives may act as a diuretic, potential antiproliferative or immunoprotective and antimetastatic agents, respectively. Furthermore, it is noticeable that the LIMK1 inhibitory activity has been amenable to a 4-fold increase as a result of extra-fusion of the plain thieno[2,3-b]pyridine scaffold with pyrimidine ring without any other structural modifications (see compounds IVa,b, Figure 1).5

![Diagram](image-url)

**Figure 1.** Selected examples of promising thieno[2,3-b]pyridine drug candidates targeting various biological receptors and showing a wide diversity of biological activities.

Naphthyridine derivatives are reported to possess anticancer,6,7 antimalarial,8 anti-inflammatory,9,10 antiallergic,11 and antiprotozoal12 activity as well as inhibitory activity against bacterial topoisomerase,13 human acetylcholinesterase at as picomolar level,14 fibroblast activation protein,15 and HIV-1 integrase.16 2,7-Naphthyridine moiety is found in a number of biologically important alkaloids17,18 such as meridine19 and PKD-1 inhibitor.20
Encouraged by the above findings and as a continuation of our ongoing work on exploration the synthetic utility of ethyl 5-cyano-2-methyl-4-styryl-6-thioxo-1,6-dihydropyridine-3-carboxylate (2a),\textsuperscript{21-22} we reported herein some reactions of this compound and its 5-ethanone analogue 2b with various reagents hoping to get new sulfanylpyridines, thieno[2,3-\textit{b}]pyridines, thieno[2,3-\textit{c}][2,7]naphthyridinones and pyrazolo[3,4-\textit{c}][2,7]naphthyridinones with expected biological activity.

**Results and Discussion**

The key compounds, ethyl 5-cyano-1,6-dihydro-2-methyl-4-styryl-6-thioxonicotinate (2a)\textsuperscript{21,22} and 3-acetyl-5-cyano-1,6-dihydro-2-methyl-4-styryl-6-thioxopyridine (2b)\textsuperscript{23} were synthesized according to the methods described before. The acidity of pyridinethiol 2a was checked by its reaction with piperidine, wherein the piperidinium pyridine-6-thiolate 3 was obtained (Scheme 1).

![Scheme 1. Synthesis of starting materials 2a, b and 3.](image)

Reaction of piperidinium thiolate 3 with some alkylating agents namely; iodoethane, \(\omega\)-bromoacetophenone, chloroacetonitrile, ethyl bromoacetate or 2-chloroacetamide by stirring in ethanol for one hour gave sulfanylpyridines 4, 5, 6, 7 and 8 in nearly quantitative yields (Scheme 2).
Scheme 2. Synthesis of compounds 4-8.

IR spectra of 4-8 exhibited two absorption bands at 2223- 2218 cm\(^{-1}\) characteristic for (CN) and 1725-1702 cm\(^{-1}\) for (CO, ester) besides other bands corresponding to the other functional groups of each. \(^1\)H NMR of 4 showed two signals due to SCH\(_2\)CH\(_3\) group. \(^1\)H NMR of 5-8 displayed a singlet at \(\delta\) 4.02-5.11 for SCH\(_2\) group.

Intramolecular Thorpe-Zeigler cyclization of the latter compounds (5, 6, 7 and 8) into the corresponding thienopyridines 9, 10, 11 and 12 needs different basic conditions. Thus, heating ketone 5 in ethanol for 30 mins, in the absence of any catalyst, furnished thienopyridine 9. On refluxing of acetonitrile derivative 6 in ethanol containing a catalytic amount of AcONa for 30 mins, the expected thienopyridine 10 was isolated. Cyclization of ester 7 into its isomer 11 needs heating in ethanol in the presence of a catalytic amount of AcONa for 2 hours. In contrast, cyclization of acetamide 8 into thienopyridine 12 was achieved when anhydrous sodium carbonate was used as a catalyst in boiling ethanol (Scheme 3).

Thienopyridines 9, 10, 11 and 12 were also synthesized by independent methods. Thus, heating compound 2a with \(\omega\)-cyanoacetophenone, in ethanol in the presence of an equimolar quantity of sodium acetate for 30 mins. gave thienopyridine 9. Refluxing of compound 2a with chloroacetonitrile in ethanol containing a slightly excess quantity of AcONa for 30 mins. led to the formation of thienopyridine 10. Heating 2a with ethyl bromoacetate in ethanol containing a slightly excess amount of AcONa for 2 hours furnished \(\omega\)-aminoester 11. Compound 12 was obtained by reacting 2a with 2-chloroacetamide in boiling ethanol in the presence of a slightly excess molar quantity of anhydrous Na\(_2\)CO\(_3\) (Scheme 3).
Scheme 3. Synthesis of compounds 9-12.

By taking the above reactions in our consideration, we can conclude that the order of activity of methylene groups in compounds 5, 6, 7 and 8 towards intramolecular Thorpe-Zeigler cyclization is: -CH₂COOPh > -CH₂CN > -CH₂CO₂Et > -CH₂CONH₂. The above fact based on the following findings: (i) cyclization of 5 into 9 takes place in boiling ethanol without catalyst, (ii) cyclization of 6 or 7 into 10 or 11 requires boiling in ethanol in the presence of AcONa, as a mild basic catalyst, for 30 mins. or 2 hours respectively and (iii) cyclization of 8 into 12 was achieved by boiling in ethanol containing a catalytic quantity of Na₂CO₃ as a moderate basic catalyst.
In a similar manner, reaction of ethanone analogue 2b with ω-bromoacetophenone, chloroacetonitrile, ethyl bromoacetate or 2-chloroacetamide by heating in ethanol containing anhydrous Na$_2$CO$_3$, gave poly functionally substituted thieno[2,3-b]pyridines 13, 14, 15 and 16 (Scheme 4).


Heating of 7 or 11 with an excess molar amount of hydrazine hydrate 99% furnished diaminothienonaphthyridinecarbohydrazide (17) (Scheme 5).

Scheme 5. Synthesis of compound 17.
Reaction of cyclic ester 11 with 2,5-dimethoxytetrahydrofuran is reported to give the pyrrolyl derivative 18. Fusion of 18 with an excess molar amount of hydrazine hydrate 99% afforded aminopyrrolylthienonaphthyridinecarbohydrazide 19. The latter compound 19 was condensed with two molar ratios of 4-methoxybenzaldehyde to give bis(4-methoxybenzylidene) derivative 20 (Scheme 6).


The above formation of 2,7-naphthyridines promoted us to check the action of hydrazine hydrate on the starting compound 2a under the same (above) conditions. Thus, heating of 2a with an extra amount of hydrazine hydrate at 100 °C led to the formation of a colorless crystalline solid with melting point 238 °C in excellent yield. This structure of this product was assigned as dianinopyrazolophanthyridinone 24 among four proposed structures 21-24 with the same molecular formula, C16H16N6O (Scheme 7).

The diaminopyrazolonaphthyridinone 24 was utilized as a key intermediate for building other novel pyrazolonaphthyridinones. Thus, condensation of 24 with two molar ratios of benzaldehyde or its derivatives by heating in ethanol gave the promising dibenzylidenes 25a-f in excellent yields. Reaction of 20 with two molar ratios of acetylacetone by refluxing in ethanol furnished dihydropyrimidopyrazolonaphthyridinone 26 which exists predominantly in the enol form (Scheme 8).
IR and \(^1\)HNMR spectra of 25a-f and 26 proved the disappearance of the two amino groups and appearance of two azomethine groups.


All new compounds were characterized by elemental and spectral analyses (cf. Experimental Section and Figures S1-S51).

Conclusions

We have successfully used the easily available ethyl 5-cyano-2-methyl-4-styryl-6-thioxo-1,6-dihydropyridine-3-carboxylate and 3-acetyl-5-cyano-2-methyl-4-styryl-6-thioxo-1,6-dihydropyridine as starting materials in the synthesis of novel series of functionally substituted methylsulfanylpyridines, thieno[2,3-b]pyridines, thieno[2,3-c][2,7]naphthyridinones and pyrazolo[3,4-c][2,7]naphthyridinones with expected biological activity owing to incorporation of several pharmacophores into their structures. These promising compounds were obtained in a very pure state with excellent yields.
Experimental Section

General. Melting points were determined on a Gallen-kamp apparatus. IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; \( \nu_{\text{max}} \) in cm\(^{-1} \)). \(^1\)H NMR spectra were recorded on a Bruker 400 MHz spectrometer using CDCl\(_3\) or DMSO-\(d_6\) as a solvent and tetramethylsilane (TMS) as internal reference. \(^13\)C NMR and Dept 135 spectra were recorded on a Bruker 100 MHz spectrometer using CDCl\(_3\) or DMSO-\(d_6\) as a solvent and tetramethylsilane (TMS) as internal reference. Coupling constants (\(J\) values) are given in Hertz (Hz). Elemental analyses were performed on Perkin Elmer 2400 LS Series CHN/O analyzer. MS analyses were performed on a Thermo Scientific single quadrupole mass spectrometer Model: ISQ 7000.

Reaction of piperidinium thiolate 3 with iodoethane, \(\omega\)-cyanoacetophenone, chloroacetonitrile; ethyl bromoacetate or 2-chloroacetamide; Formation of sulfanylpyridines 4, 5, 6, 7 and 8; general procedure

Compound 3 (2.04 g, 0.005 mol) and iodoethane, \(\omega\)-cyanoacetophenone, chloroacetonitrile; ethyl bromoacetate or 2-chloroacetamide (0.005 mol) in EtOH (35 mL) was stirred at 25 °C for one hour. The product that obtained was assigned as compound 4, 5, 6, 7 or 8, respectively.

**Compound 4.** Yield: 1.58 g (90%); mp 147-148 °C. IR: 2221 (CN); 1730 (CO). \(^1\)H NMR: 7.05-7.55 (m, 7H: CH=CH & aryl-H's), 4.25-4.30 (q, 2H, OCH\(_2\)), 2.41 (s, 3H, CH\(_3\)), 1.24-1.27 (t, 3H, CH\(_3\)) ppm. Anal. Calcd. For C\(_{20}\)H\(_{20}\)O\(_2\)S (352.12): C, 68.16; H, 5.72; N, 7.95; S, 9.10%. Found: C, 68.35; H, 5.62; N, 8.13; S, 8.92%.

**Compound 5.** Yield: 2.10 g (95%); mp 122-123 °C. IR: 3057 (CH, arom.); 2974, 2910 (CH, aliph.). 2223 (CN); 1725 (CO, ester); 1682 (CO, nonconjugated ketone). \(^1\)H NMR: 7.22-7.78 (m, 11H, CH=C & aryl-H's), 6.87-6.89 (d, 1H, C=CH), 5.11 (s, 2H, SCH\(_2\)), 4.31-4.35 (q, 2H, OCH\(_2\)), 2.66 (s, 3H, CH\(_3\)), 1.24-1.27 (t, 3H, CH\(_3\)) ppm. Anal. Calcd. For C\(_{26}\)H\(_{22}\)N\(_2\)O\(_3\)S (442.13): C, 70.57; H, 5.01; N, 6.33; S, 7.24%. Found: C, 70.28; H, 5.17; N, 6.41; S, 6.98%.

**Compound 6.** Yield: 1.70 g (94%); mp 184-186 °C. IR: 2980, 2932, 2902 (CH, aliph.). 2247 (CN, nonconjugated); 2220 (CN, conjugated); 1718 (CO, ester). \(^1\)H NMR: 6.66-7.70 (m, 7H: CH=CH & aryl-H's), 5.02 (s, 2H, SCH\(_2\)), 4.09-4.13 (q, 2H, OCH\(_2\)), 2.58 (s, 3H, CH\(_3\)), 1.25-1.27 (t, 3H, CH\(_3\)) ppm. Anal. Calcd. For C\(_{20}\)H\(_{17}\)N\(_2\)O\(_2\)S (363.10): C, 66.10; H, 4.71; N, 11.56; S, 8.82%. Found: C, 65.93; H, 5.06; N, 11.42; S, 9.06%.

**Compound 7.** Yield: 1.98 g (97%); mp 70-71°C. IR: 2982 (CH, aliph.). 2219 (CN); 1748 (CO, nonconjugated ester); 1724 (CO, conjugated ester). \(^1\)H NMR: 6.60-7.63 (m, 7H: CH=CH & aryl-H's), 4.16-4.37 (m, 6H: OCH\(_2\) & SCH\(_2\)), 2.52 (s, 3H, CH\(_3\)), 1.21-1.27 (t, 6H: two CH\(_3\)) ppm. Anal. Calcd. For C\(_{22}\)H\(_{22}\)N\(_2\)O\(_4\)S (410.13): C, 64.37; H, 5.40; N, 6.82; S, 7.81%. Found: C, 64.12; H, 5.34; N, 6.91; S, 8.07%.

**Compound 8.** Yield: 1.69 g (89%); mp 171-172°C. IR: 3304, 3268, 3199 (NH\(_2\)); 2980, 2927 (CH, aliph.); 2219 (CN); 1702 (CO, ester); 1670 (CO, amide). \(^1\)H NMR: 7.23-7.68 (m, 9H: NH\(_2\), CH=CH & aryl-H's), 4.33-4.37 (q, 2H, OCH\(_2\)), 4.02 (s, 2H, SCH\(_2\)), 2.55 (s, 3H, CH\(_3\)), 1.22-1.25 (t, 3H, CH\(_3\)) ppm. \(^13\)C NMR & Dept 135: 169.10, 169.03, 166.68, 163.29, 158.85, 148.23, 139.69 (CH=C), 135.48, 135.39, 130.17 (CH), 127.83 (CH), 123.68 (CH), 121.47 (C=CH), 115.39, 102.30, 62.42 (OCH\(_2\)), 34.44 (SCH\(_2\)), 23.94 (CH\(_3\)), 14.35 (CH\(_3\)) ppm. Anal. Calcd. For C\(_{20}\)H\(_{19}\)N\(_3\)O\(_3\)S (381.11): C, 62.98; H, 5.02; N, 11.02; S, 8.40%. Found: C, 62.77; H, 5.09; N, 11.13; S, 8.11%.

3-Amino-2-benzoyl-5-ethoxy carbonyl-6-methyl-4-styrylthieno[2,3-b] pyridine (9)

(A) Compound 5 (0.88 g, 0.002 mol) in EtOH (30 mL) was refluxed for 30 mins. The product was recrystallized from EtOH to give orange needles of compound 9. Yield: 2.01 g (91%); mp 284-285 °C. IR: 3476, 3270 (NH\(_2\)), 1709 (CO). \(^1\)H NMR: 6.66-7.85 (m, 13H: NH\(_2\), CH=CH & aryl-H's), 6.89-6.92 (d, 1H, C=CH), 4.30-4.34 (q, 2H, OCH\(_2\)), 2.67 (s, 3H, CH\(_3\)), 1.25-1.28 (t, 3H, CH\(_3\)) ppm. \(^13\)C NMR & Dept 135: 190.58, 168.02, 162.76, 157.29, 150.96, 142.58, 140.77, 138.51 (C=CH), 135.05, 131.28 (CH), 129.52 (CH), 129.14 (CH), 129.03 (CH), 128.37 (CH), 128.03 (CH), 127.87(CH), 126.98(CH), 125.89, 120.82 (CH=CH), 119.62, 105.78, 61.83 (OCH\(_2\)), 23.48 (CH\(_3\)), 14.24 (CH\(_3\))
ppm. Anal. Calcd. For C_{26}H_{22}N_{2}O_{3}S (442.13): C, 70.57; H, 5.01; N, 6.33; S, 7.24%. Found: C, 70.67; H, 5.24; N, 6.13; S, 7.15%.

(B) A suspension of 2a (0.64 g, 0.002 mol), phenacyl bromide (0.40 g, 0.002 mol) and AcONa.3H_{2}O (0.28 g, 0.002 mol) in EtOH (30 mL) was refluxed for 30 mins. The product upon recrystallization gave orange needles of 9; yield: 0.76 g (86%).

**Ethyl 3-amo-2-cyano-6-methyl-4-styrylthieno[2,3-b]pyridine-2-carboxylate (10)**

(A) Compound 6 (0.36 g, 0.001 mol) and AcONa.3H_{2}O (0.05 g) in EtOH (25 mL) were refluxed for 30 mins. The product was recrystallized from EtOH to afford canary needles of 10. Yield: 0.33 g (91%); mp 257-258 °C. IR: 3470, 3335, 3226 (NH); 2975, 2934 (CH, aliph.); 2201 (CN); 1731 (CO, ester). ^{1}H NMR: 7.38-7.51 (m, 6H: CH=C & ary-l-H's), 6.84-6.87 (d, 1H, C=CH), 6.39 (s, 2H, NH_{2}), 4.31-4.35 (q, 2H, OCH_{2}), 2.66 (s, 3H, CH_{3}), 1.26-1.28 (t, 3H, CH_{3}) ppm. ^{13}C NMR: 167.75, 161.41, 156.77, 149.70, 141.43, 138.93, 134.90, 129.62, 129.16, 129.02, 126.98, 126.30, 120.33, 118.51, 114.77, 61.97, 23.30, 14.23 ppm. Anal. Calcd. For C_{20}H_{17}N_{2}O_{2}S (363.10): C, 66.11; H, 4.72; N, 11.57; S, 8.83%. Found: 66.30; H, 4.80; N, 11.88; S, 8.65%.

(B) A ternary mixture of 2a (0.64 g, 0.002 mol), chloroacetonitrile (0.002 mol) and AcONa.3H_{2}O (0.38 g) in EtOH (35 mL) was refluxed for 30 mins. The product upon recrystallization from EtOH gave canary needles of 10; yield: 0.60 g (83%).

**3-Amino-2,5-diethoxycarbonyl-6-methyl-4-styrylthieno[2,3-b]pyridine (11)**

(A) A suspension of 7 (2.05 g, 0.005 mol) and AcONa.3H_{2}O (0.25 g) in EtOH (30 mL) was refluxed for 2.5 h. The precipitated solid upon recrystallized from EtOH gave canary needles of compound 11. Yield: 1.90 g (93%); mp 116-117°C. IR: 3491, 3349 (NH_{2}); 2982 (CH, aliph.); 1714 (CO); 1671 (CO). ^{1}H NMR: 7.75-7.78 (d, 1H, CH=C), 7.65-7.66 (d, 2H, ary-l-H's), 7.36-7.45 (m, 3H, ary-l- H's), 6.79-8.3 (d, 1H, C=CH), 6.61 (s, 2H, NH_{2}), 4.23-4.30 (m, 4H, 2 OCH_{2}), 2.57 (s, 3H, CH_{3}), 1.28-1.31 (t, 3H, CH_{3}), 1.15-1.18 (t, 3H, CH_{3}) ppm. ^{13}C NMR & Dept 135: 168.03, 164.87, 160.66, 156.26, 149.29, 142.94, 138.30 (CH), 135.88, 129.51(CH), 129.27 (CH), 127.73 (CH), 126.03, 121.87(CH), 120.57, 95.82, 61.97 (OCH_{2}), 60.77 (OCH_{2}), 23.27 (CH_{3} at C-6), 14.38 (CH_{3}), 14.41 (CH_{3}) ppm. Anal. Calcd. For C_{22}H_{22}N_{2}O_{4}S (410.13): C, 64.37; H, 5.40; N, 6.82; S, 7.81%. Found: C, 64.12; H, 5.34; N, 6.91; S, 7.96%.

(B) A mixture of 2a (1.62 g, 0.005 mol), ethyl bromoacetate (0.55 ml, 0.005 mol) and AcONa.3H_{2}O (0.95 g) in EtOH (50 mL) was refluxed for 3 h. The product was identical to that given above; yield: 1.70 g (83%).

**3-Amino-5-ethoxycarbonyl-6-methyl-4-styrylthieno[2,3-b]pyridine-2-carboxamide (12)**

(A) A mixture of 8 (0.76 g, 0.002 mol) and anhyd. Na_{2}CO_{3} (0.25 g) in EtOH (30 mL) was refluxed for two hours. The solid that separated was recrystallized from methanol to give compound 12 as yellow needles. Yield: 0.71 g (94%); mp 276-277°C. IR: 3476, 3270 (NH_{2}), 1709 (CO). ^{1}H NMR: 7.39-7.70 (m, 13H: NH_{2}, CH=C & ary-l-H's), 6.77-6.80 (d, 1H, C=CH), 2.52 (s, 3H, CH_{3}), 2.43 (s, 3H, CH_{3}) ppm. ^{13}C NMR and Dept 135: 205.31 (C=O), 189.58(C=O), 161.31, 156.49, 151.97, 142.18, 141.14, 140.21(CH), 135.86, 133.84, 131.74(CH), 129.74(CH), 129.28(CH), 129.01(CH), 128.02(CH), 127.81(CH), 121.68(CH), 120.08, 103.94, 32.82(CH_{3}), 23.45 (CH_{3}) ppm. Anal. Calcd. For C_{20}H_{19}N_{3}O_{5}S (381.11): C, 62.98; H, 5.02; N, 11.02; S, 8.40%. Found: C, 62.68; H, 4.79; N, 11.22; S, 8.34%.

(B) A mixture of 2a (0.64 g, 0.002 mol), 2-chloroacetamide (0.002 mol) and anhyd. Na_{2}CO_{3} (0.25 g) in EtOH (30 mL) was refluxed for 2 hours. The solid that obtained was recrystallized from methanol to give 12; yield: 0.69 g (91%).

**Reaction of 2b with ω-bromoacetoephone, chloroacetonitrile, ethyl bromoacetate and 2-chloroacetamide; Construction of thienopyridines 13, 14, 15 or 16; general procedure**

A mixture of 2b (0.60 g, 0.002 mol), ω-bromoacetoephone, chloroacetonitrile, ethyl bromoacetate or 2-chloroacetamide (0.002 mol) in EtOH (30 mL) and anhyd. Na_{2}CO_{3} (0.25 g) was refluxed for 3 hours. The separated solid was recrystallized from methanol to furnish canary crystals of 13, 14, 15 or 16, respectively.
Compound 13. Yield: 0.80 g (97%); mp 289-290 °C. IR: 3476, 3270 (NH2), 1709 (CO). ¹H NMR: 7.39-7.70 (m, 13H: NH2, CH=CH-alkyl-h's), 6.77-6.80 (d, 1H, C=CH), 2.52 (s, 3H, CH3), 2.43 (s, 3H, CH3) ppm. ¹³C NMR and Dept 135: 205.31 (C=O), 189.58 (C=O), 161.31, 156.49, 151.97, 142.18, 141.14, 140.21 (CH), 135.86, 133.84, 131.74 (CH), 129.74 (CH), 129.28 (CH), 129.01 (CH), 128.02 (CH), 127.81 (CH), 121.68 (CH), 120.08, 103.94, 32.82 (CH3), 23.45 (CH3) ppm. Anal. Calcd. For C25H29N2O2S (412.12): C, 72.79; H, 4.89; N, 6.79; S, 7.24%. Found: C, 72.54; H, 4.70; N, 6.79; S, 6.98%.

Compound 14. Yield: 0.56 g (93%); mp 261-262°C. IR: 3472, 3345, 3230 (NH2), 2978, 2932 (CH, aliph.); 2200 (CN); 1710 (CO). ¹H NMR: 7.82-7.85 (d, 1H, C=CH), 7.42-7.67 (m, 2H, aryI-h's), 7.38-7.40 (m, 3H, alkyI-h's), 6.69-6.73 (d, 1H, C=CH), 6.47 (s, 2H, NH2), 2.52 (s, 3H, CH3), 2.42 (s, 3H, CH3) ppm. ¹³C NMR & Dept 135: 205.16 (C=O), 160.07 (C=N), 155.60, 151.67, 141.20, 140.20 (CH), 135.85, 134.04, 129.69 (CH), 129.28 (CH), 121.60 (CH), 119.37, 115.80, 32.80 (CH3), 23.23 (CH3) ppm. Anal. Calcd. For C19H15N3OS (303.09): C, 68.45; H, 4.53; N, 12.60; S, 9.62%. Found: C, 68.73; H, 4.39; N, 12.42; S, 9.85%.

Compound 15. Yield: 0.70 g (92%); mp 128-129°C. IR: 3496, 3350 (NH2), 2980 (CH, aliph.); 1705 (CO); 1672 (CO). ¹H NMR: 7.80-7.84 (d, 1H, C=CH), 7.65-7.67 (d, 2H, aryI-h's), 7.37-7.46 (m, 3H, alkyI-h's), 6.71-6.75 (d, 1H, C=CH), 6.61 (s, 2H, NH2), 4.26-4.30 (q, 2H, OCH2), 2.50 (s, 3H, CH3), 2.41 (s, 3H, CH3), 1.28-1.31 (t, 3H, CH3) ppm. ¹³C NMR and Dept 135: 205.43 (C=O), 164.94, 160.00, 155.33, 149.45 141.31, 139.86 (CH), 135.92, 133.63, 129.65 (CH), 129.28 (CH), 127.88 (CH), 121.88 (CH), 120.59, 60.74 (OCH2), 32.84 (CH3), 23.27 (CH3), 14.84 (CH3) ppm. Anal. Calcd. For C21H20N2O2S (380.12): C, 66.29; H, 5.30; N, 7.36; S, 8.43%. Found: C, 66.11; H, 5.21; N, 7.19; S, 8.33%.

17-Diamino-5-methyl-6-oxo-8-phenyl-6,7,8,9-tetrahydrothieno[2,3-c][2,7]naphthyridine-2-carbohydrazide (17). A suspension of compound 7 or 11 (2.05 g, 0.005 mol) in hydrazine hydrate 99% (4 mL, 0.08 mol) was heated at 100 °C for 4 h. The product was recrystallized from dioxane to give 17 as yellowish white needles. Yield: 1.72 g (90%); mp 280-281°C. IR: 3464, 3403, 3327, 3296, 3204 (3 NH2, NH); 3023 (CH, alom.); 2929 (CH, aliph.); 1640 (CO). ¹H NMR: δ 9.12 (s, 1H, NH), 7.25-7.28 (m, 2H, aryI-h's), 7.13-7.20 (m, 3H, alkyI-h's), 6.75 (s, 2H, NH2), 5.25 (s, 2H, NH2), 5.10-5.11 (d, 1H, CβH, of cyclohexene ring), 4.43 (s, 2H, NH2 of carbohydrazide), 3.94-4.08 (m, 2H, CβH of cyclohexene ring), 2.90 (s, 3H, CH3) ppm. Anal. Calcd. For C19H18N2O2S (351.10): C, 64.94; H, 4.88; N, 11.96; S, 9.12%. Found: C, 65.12; H, 4.71; N, 11.82; S, 9.00%.

7-Amino-5-methyl-6-oxo-8-phenyl-1-(1H-pyrro1-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c][2,7]naphthyridine-2-carbohydrazide (19). It was synthesized by reaction of 18 ²² with hydrazine hydrate 99% in a similar procedure given for compound 17. Yield: 2.05 g (95%); mp 256-257°C. IR: 3400, 3298, 3208, 3117 (NH2, NNH2), 3031 (CH, alom.), 1648 (2 CO). ¹H NMR: 8.37 (s, 1H, NH), 6.40-7.23 (m, 11H, aryI-h's & pyrrole-h's), 5.22 (s, 2H, NH2), 4.85 (s, 1H, CβH of cyclohexene ring), 4.49 (s, 2H, NH2 of carbohydrazide), 3.29 (m, 2H, CβH of cyclohexene ring), 2.96 (s, 3H, CH3) ppm. Anal. Calcd. For C22H20N2O2S (432.14): C, 61.10; H, 4.66; N, 19.43; S, 7.41%. Found: C, 60.87; H, 5.02; N, 19.21; S, 7.19%.

N'-4-(Methoxybenzylidene)-7-(4-methoxybenzylidene)amino-5-methyl-6-oxo-8-phenyl-1-(1H-pyrro1-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c][2,7]naphthyridine-2-carbohydrazide (20). A mixture of 19 (0.86 g, 0.002 mol) and 4-methoxybenzaldehyde (0.56 g, 0.004 mol) in EtOH (20 mL) was heated under reflux for 3 h. The solid that separated while hot was crystallized from dioxane to yield pale yellow crystals of compound 20. Yield: 2.48 g (93%); mp 298-300 °C. IR: 3427, 3281, 3108, (NH2, NH), 1651 (2 CO). ¹H NMR: 9.09 (s, 1H, CH, azomethine), 8.94 (s, 1H, NH), 8.55 (s, 1H, CH, azomethine), 6.40-8.20 (m, 17H: aryI-h's
Compound 25e (1.62 g, 0.005 mol) in hydrazine hydrate 99% (5 mL, 0.1 mol) was heated under reflux for 2 h. The precipitate that separated on cooling was recrystallized from EtOH to give compound 24. Yield: 1.41 g (92%); mp 238-240 °C. IR: 3310, 3200, 3147 (N-H, NH), 3031 (CH, arom.), 2925, 2819 (CH, aliph.), 1650 (CO), 1605 (CN). 1H NMR: 12.08 (s, 1H, NH), 7.25-7.26 (m, 2H, aryl-H's), 7.16-7.20 (m, 3H, aryl-H's), 5.31 (s, 2H, NH2), 5.05-5.11 (m, 3H: NH and C3H of cyclohexene ring), 3.71-3.83 (m, 2H, C6H of cyclohexene ring), 2.85 (s, 3H, CH3). MS: m/z 308.26 (M+, 30%). Anal. Calcd. For C16H18N6O3 (308.14): C, 62.32; H, 5.23; N, 27.26%. Found: C, 62.32; H, 5.23; N, 27.29%.

Condensation of 24 with aryl aldehydes; Formation of dibenzylidene derivatives 25a-f. A mixture of 24 (0.92 g, 0.003 mol) and appropriate aryl aldehyde (0.006 mol) in EtOH (20 mL) was refluxed for 3 h. The product that separated while hot was crystallized from dioxane to produce yellow needles of 25a-f.

**Compound 25a.** Yield: 1.23 g (85%); mp 282-284 °C. IR: 3126 (NH); 3062, 3027 (CH, arom.); 2987, 2924, 2846 (CH, aliph.); 1663 (CO); 1605 (CN). 1H NMR: 12.08 (s, 1H, NH), 9.13 (s, 1H, CH, azomethine), 8.53 (s, 1H, CH, azomethine), 8.08-8.10 (d, 2H, aryl-H's), 7.72-7.73 (d, 2H, Ar-H's), 7.61-7.62 (d, 3H, aryl-H's), 7.43-7.44 (d, 3H, Ar-H's), 7.21-7.26 (m, 4H, aryl-H's), 7.13-7.16 (m, 1H, Ar-H), 5.92-5.94 (d, 1H, C6H of cyclohexene ring), 4.37-4.42 (d, 1H, C3H of cyclohexene ring), 4.03-4.08 (dd, 1H, C6H of cyclohexene ring), 2.95 (s, 3H, CH3) ppm. Anal. Calcd. For C30H24N6O (484.20): C, 74.36; H, 4.99; N, 17.34%. Found: C, 74.18; H, 4.72; N, 17.61%.

**Compound 25b.** Yield: 1.32 g (81%); mp 320-322 °C. IR: 3150 (NH); 3129 (CH, arom.); 2930, 2837 (CH, aliph.); 1654 (=O). 1H NMR: 13.46 (s, 1H, NH), 9.02 (s, 1H, CH, azomethine), 8.42 (s, 1H, CH, azomethine), 8.02-8.03 (d, 2H, Ar-H's), 7.66-7.67 (d, 2H, aryl-H's), 6.98-7.24 (m, 13H, aryl-H's), 5.86 (s, 1H, C6H of cyclohexene ring), 4.35-4.38 (d, 1H, C6H of cyclohexene ring), 4.00-4.03 (dd, 1H, C6H of cyclohexene ring), 3.87 (s, 3H, OCH3), 3.79 (s, 3H, CH3) ppm. 13C NMR and Dept 135: 163.05, 161.46, 161.32, 161.00 (CH), 160.28, 152.26, 152.08, 149.35 (CH), 143.34, 139.37, 131.44 (CH), 129.44 (CH), 129.14 (CH), 128.95, 127.83 (CH), 127.52, 126.33 (CH), 118.37, 115.04 (CH), 114.73 (CH), 106.68, 58.22 (CH), 55.99 (OCH3), 55.76 (OCH3), 32.37 (CH2), 26.89 (CH3) ppm. Anal. Calcd. For C32H28N6O3 (544.22): C, 70.57; H, 5.18; N, 15.43%. Found: C, C, 70.81; H, 4.89; N, 15.15%.

**Compound 25c.** Yield: 1.37 g (88%); mp 354-356 °C. IR: 3104 (NH); 3064, 3026 (CH, arom.); 2923, 2807 (CH, aliph.); 1649 (CO); 1611 (CN). 1H NMR: 13.82 (s, 1H, NH), 12.10 (s, 2H, two CH, azomethine), 8.30-8.59 m, 5H, aryl-H's), 7.96-8.01 (d, 2H, aryl-H's), 7.21-7.28 (m, 6H, aryl-H's), 5.93 (s, 1H, C6H of cyclohexene ring), 5.46 (s, 1H, C3H of cyclohexene ring), 4.02 (d, 1H, C6H of cyclohexene ring), 2.87 (s, 3H, CH3) ppm. Anal. Calcd. For C30H22Cl2N2O (552.12): C, 65.11; H, 4.01; N, 15.19%. Found: C, 65.00; H, 3.95; N, 15.31%.

**Compound 25d.** Yield: 1.36 g (88%); mp 292-294 °C. IR: 3423 (OH); 3128 (NH); 1660 (CO); 1H NMR: 12.08 (s, 1H, NH), 12.10 (s, 2H, two CH, azomethine), 8.30-8.59 m, 5H, aryl-H's), 7.87-7.89 (d, 1H, aryl-H's), 7.50-7.52 (d, 1H, aryl-H), 7.39-7.40 (d, 1H, aryl-H), 7.27-7.28 (m, 3H, aryl-H's), 7.18 (br. s, 3H, aryl-H's), 7.05-7.08 (m, 2H, aryl-H's), 6.89-6.95 (m, 2H, aryl-H's), 6.15 (s, 1H, C6H of cyclohexene ring), 4.17 (s, 2H, C3H2 of cyclohexene ring), 2.99 (s, 3H, CH3) ppm. Anal. Calcd. For C30H24N6O3 (516.19): C, 69.76; H, 4.68; N, 16.27%. Found: C, 69.85; H, 4.43; N, 16.52%.

**Compound 25e.** Yield: 1.55 g (90%); mp 254-256 °C. IR: 3405 (OH); 3136 (NH); 1651 (CO); 1H NMR: 13.35 (s, 1H, NH), 9.87 (s, 1H, OH), 9.48 (s, 1H, OH), 8.95 (s, 1H, CH, azomethine), 8.40 (s, 1H, CH, azomethine), 7.66 (br. s., 1H, aryl-H), 7.47-7.49 (d, 1H, aryl-H), 7.33 (br. s., 1H, Ar-H), 7.23 (m, 4H, aryl-H's), 7.12-7.15 (m, 2H, aryl-H's), 6.95-6.98 (m, 1H, aryl-H), 6.81-6.83 (m, 1H, aryl-H), 5.83 (s, 1H, C6H of cyclohexene ring), 4.34-4.38 (d, 1H,
C\textsuperscript{9}H of cyclohexene ring), 4.03 (d, 1H, C\textsuperscript{9}H of cyclohexene ring), 3.92 (s, 3H, OCH\textsubscript{3}), 3.80 (s, 3H, OCH\textsubscript{3}), 2.94 (s, 3H, CH\textsubscript{3}) ppm. Anal. Calcd. For C\textsubscript{32}H\textsubscript{28}N\textsubscript{6}O\textsubscript{5} (576.21): C, 66.66; H, 4.89; N, 14.58%. Found: C, 66.82; H, 4.73; N, 14.29%.

**Compound 25f.** Yield: 1.56 g (91%); mp 323-325 °C. IR: 3134 (NH); 1649 (CO). \textsuperscript{1}H NMR: 13.75 (s, 1H, NH), 12.20 (s, 2H, two CH, azomethine), 8.29-8.57 m, 5H, aryl-H's), 7.98-8.00 (d, 2H, aryl-H's), 7.22-7.27 (m, 6H, aryl-H's), 5.91 (s, 1H, C\textsuperscript{8}H of cyclohexene ring), 5.47 (s, 1H, C\textsuperscript{9}H of cyclohexene ring), 4.00 (d, 1H, C\textsuperscript{9}H of cyclohexene ring), 2.84 (s, 3H, CH\textsubscript{3}) ppm. Anal. Calcd. For C\textsubscript{30}H\textsubscript{22}N\textsubscript{8}O\textsubscript{5} (574.17): C, 62.71; H, 3.86; N, 19.50%. Found: C, 62.48; H, 3.93; N, 19.37%.

**3-(4-Hydroxypent-3-en-2-ylidene)amino)-5,9,11-trimethyl-2-phenyl-2,3-dihydropyrimido[1',2':1,5]pyrazolo[3,4-c][2,7]naphthyridin-4(1H)-one (26).** A mixture of 24 (0.92 g, 0.003 mol) acetylacetone (0.30 mL, 0.003 mol) in EtOH (20 mL) was refluxed for 4 h. The obtained solid was crystallized from dioxane to give pale yellow needles of 26. Yield: 1.20 g (88%); mp 289-281°C. IR: 3269 (OH); 3030 (CH, arom.); 1668 (CO); 1626 (CN). \textsuperscript{1}H NMR: 11.73 (s, 1H, OH), 7.21-7.28 (m, 5H, aryl-H's), 7.06 (s, 1H, pyrimidine-H), 5.17 (s, 1H, C=CH), 5.12-5.14 (dd, 1H, CH), 4.43-4.48 (dd, 1H, CH), 4.17-4.22 (d, 1H, CH), 4.17-4.22 (dd, 1H, CH), 4.17-4.22 (dd, 1H, CH), 3.12 (s, 3H, CH\textsubscript{3}), 2.92 (s, 3H, CH\textsubscript{3}), 2.70 (s, 3H, CH\textsubscript{3}), 2.69 (s, 3H, CH\textsubscript{3}), 2.06 (s, 3H, CH\textsubscript{3}), 1.96 (s, 3H, CH\textsubscript{3}) ppm. \textsuperscript{13}C NMR and Dept 135: 197.01, 165.25, 164.59, 163.35, 159.80, 158.36, 146.27, 145.63, 144.40, 138.39, 129.06, 128.67 (CH), 128.33, 127.08 (CH), 126.59 (CH), 115.72, 113.32 (CH of pyrimidine ring), 101.66, 97.04 (=CH), 63.56 (CH of cyclohexene ring), 32.57 (CH\textsubscript{2} of cyclohexene ring), 29.17 (CH\textsubscript{3}), 27.80 (CH\textsubscript{3}), 24.68 (CH\textsubscript{3}), 18.21 (CH\textsubscript{3}), 17.83 (CH\textsubscript{3}) ppm. Anal. Calcd. For C\textsubscript{26}H\textsubscript{26}N\textsubscript{6}O\textsubscript{2} (454.21): C, 68.70; H, 5.77; N, 18.49%. Found: C, 68.63; H, 6.02; N, 18.37%.

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**Supplementary Material**

Copies of IR, \textsuperscript{1}H NMR and \textsuperscript{13}C NMR and MS spectra of synthesized compounds are available in the supplementary material file associated with this manuscript.

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