A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2024** (8) 202412212

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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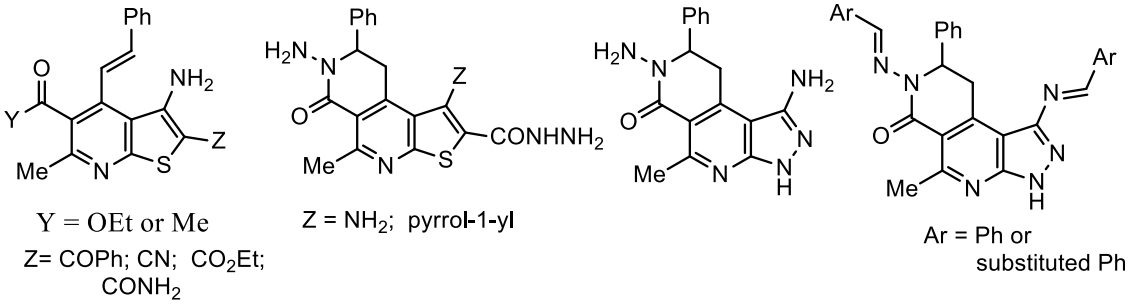
Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

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-3*H*-pyrazolo[3,4-*c*][2,7]naphthyridine-6(7*H*)-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(7*H*)-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]naphthyridines

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 have 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] Iκβ-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]

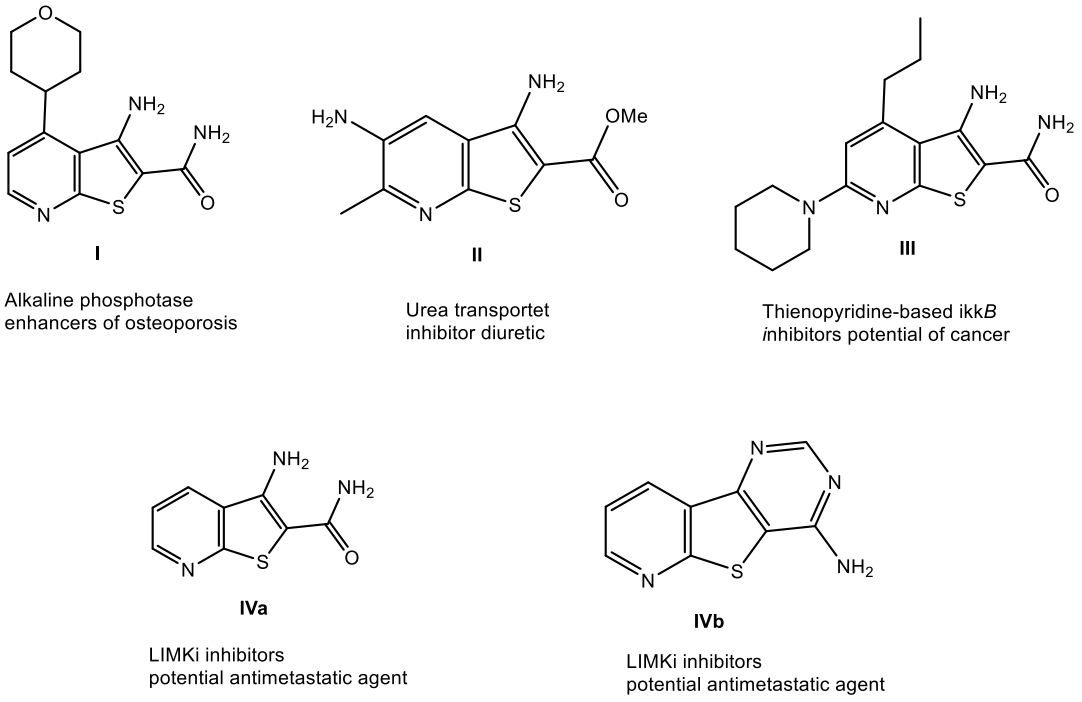


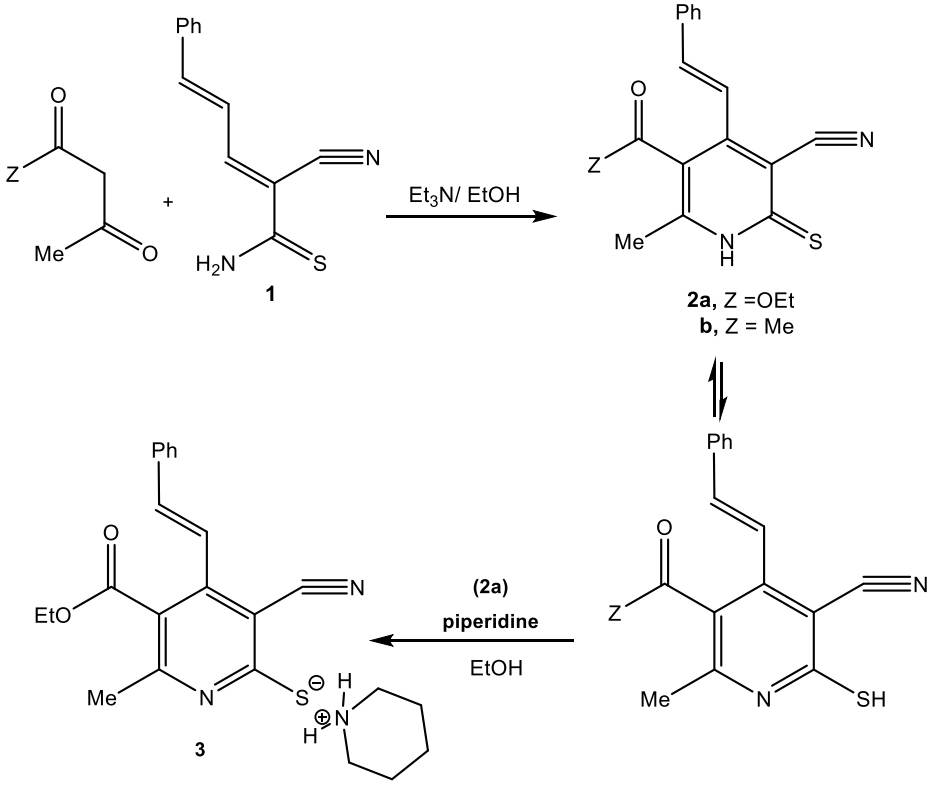
Figure 1. Selected examples of promising thieno[2,3-*b*]pyridine drug candidates targeting various biological receptors and showing a wide diversity of biological activities.

Naphthyridine derivatives are reported to possess anticancer,[6,7] antimalarial,[8] anti-inflammatory,[9,10] antiallergic,[11] and antiprotozoal[12] 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 alkaloids [17,18] such as meridine[19] 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**),[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-*b*]pyridines, thieno[2,3-*c*][2,7]naphthyridinones and pyrazolo[3,4-*c*][2,7]naphthyridinones with expected biological activity.

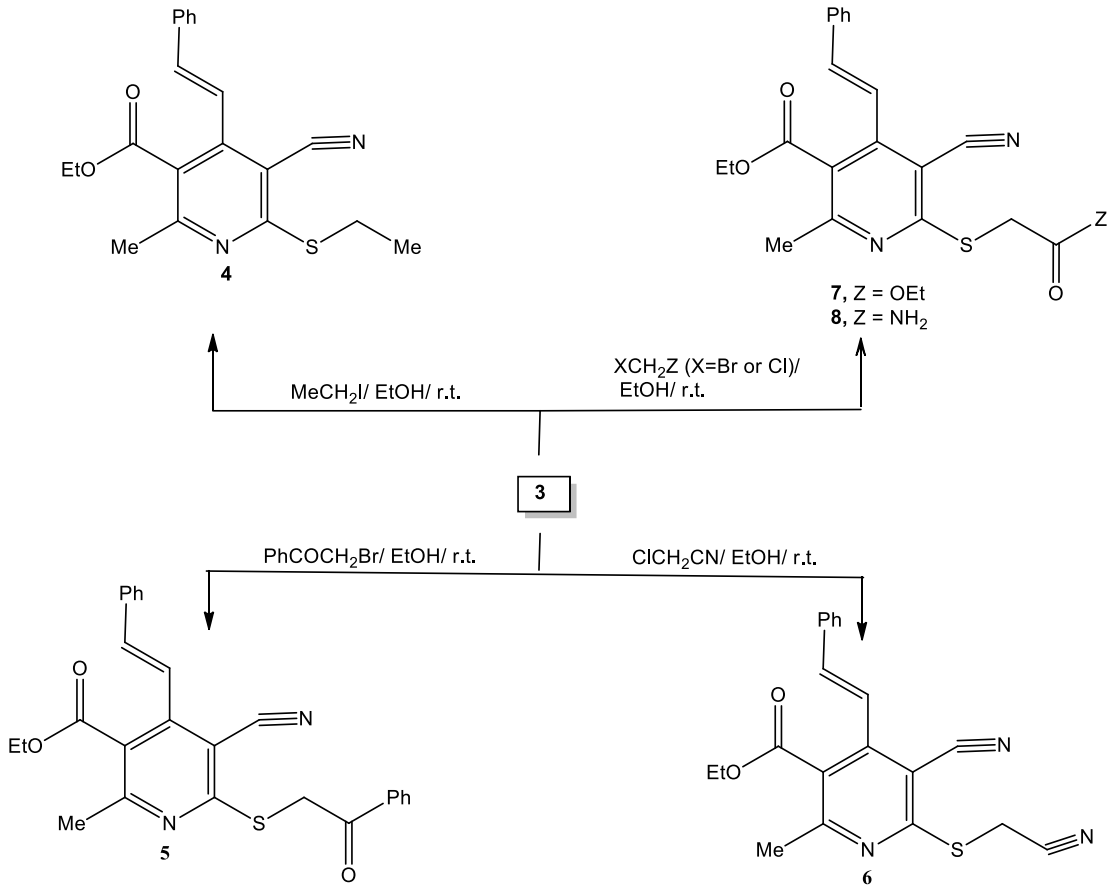
Results and Discussion

The key compounds, ethyl 5-cyano-1,6-dihydro-2-methyl-4-styryl-6-thioxonicotinate (**2a**)[21,22] and 3-acetyl-5-cyano-1,6-dihydro-2-methyl-4-styryl-6-thioxopyridine **(2b)**[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).[24]



Scheme 1. Synthesis of starting materials **2a,b** and **3**

Reaction of piperidinium thiolate **3** with some alkylating agents namely; iodoethane, ω-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).

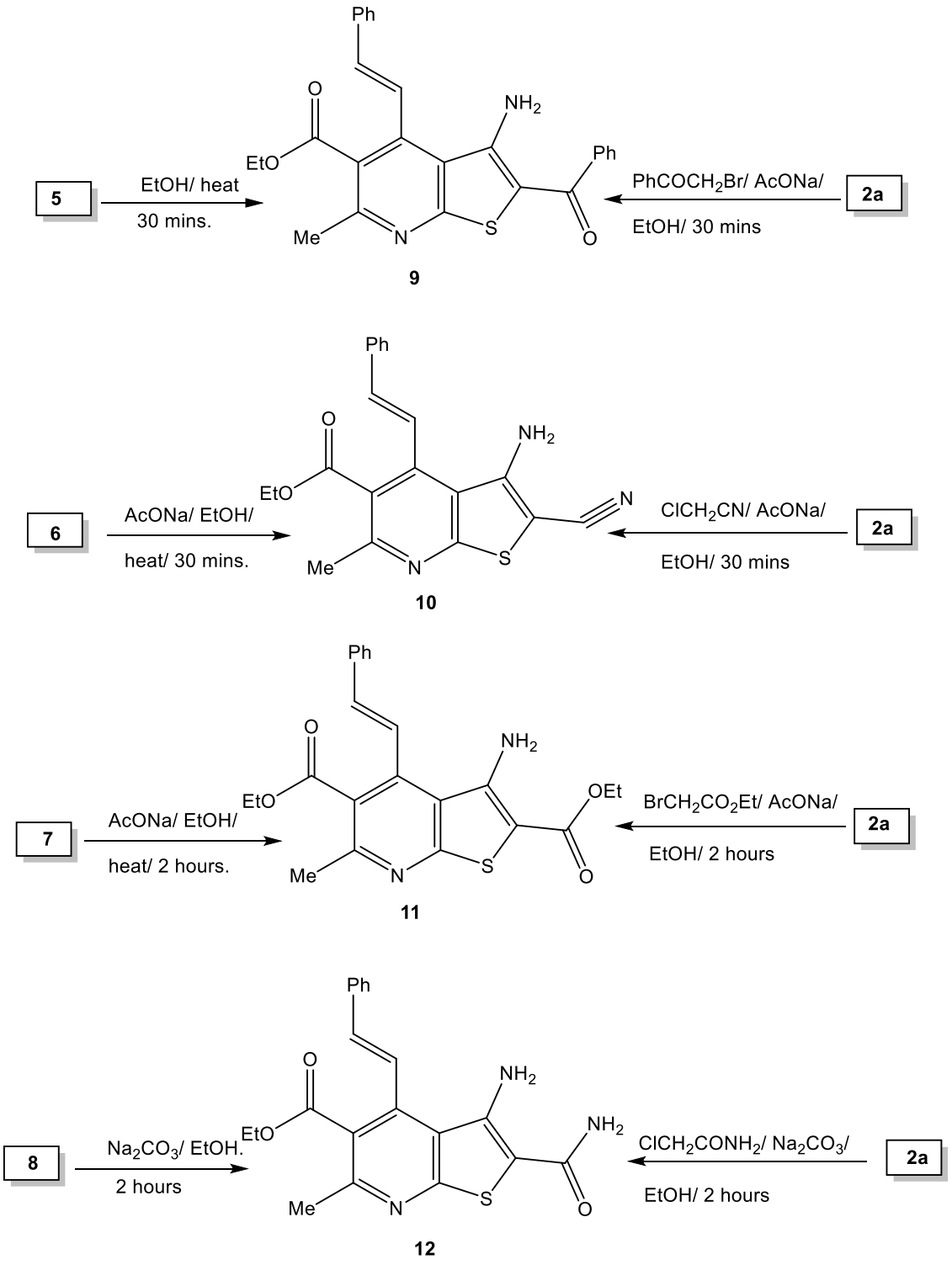


Scheme 2. Synthesis of compounds **4-8**

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. ^1H NMR of **4** showed two signals due to SCH_2CH_3 group. ^1H NMR of **5-8** displayed a singlet at δ 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 thienpyridine **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).

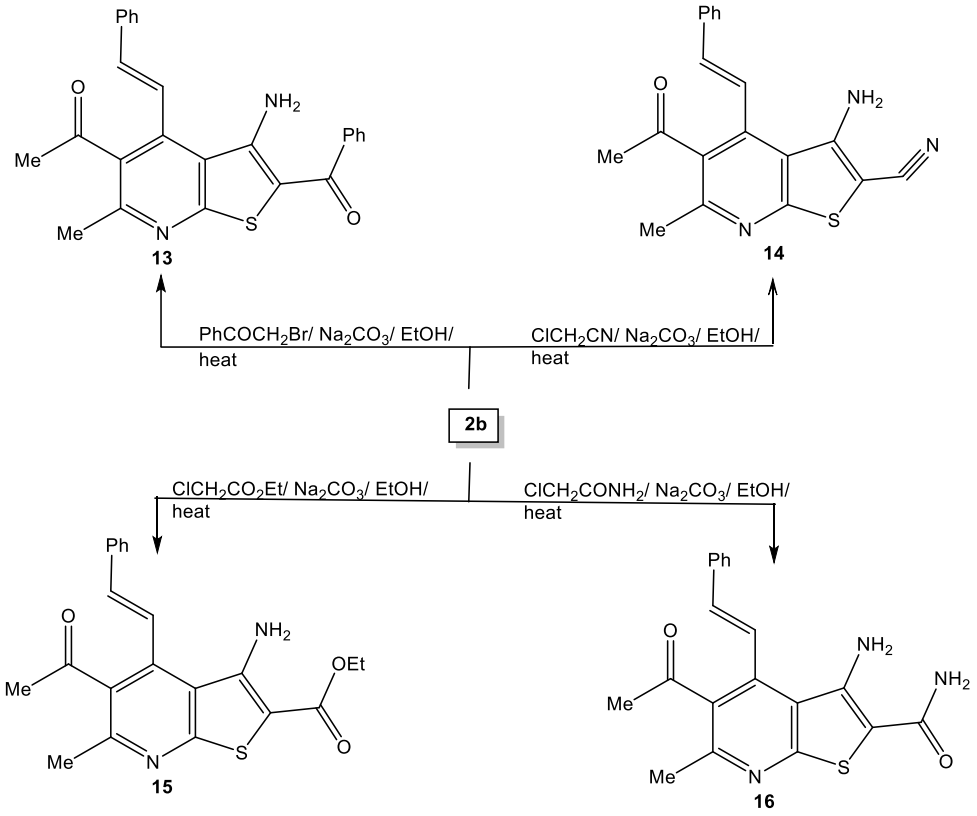
Thienopyridines **9**, **10**, **11** and **12** were also synthesized by independent methods. Thus, heating compound **2a** with ω-cyanoacetophenone, in ethanol in the presence of an equimolar quantity of sodium acetate for 30 mins. gave thienopyridine **9**. Refluxing of compound **2a** with chloroacetonitrile 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 *o*-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_2CO_3 (Scheme 3).



Scheme 3. Synthesis of compounds **9-12**

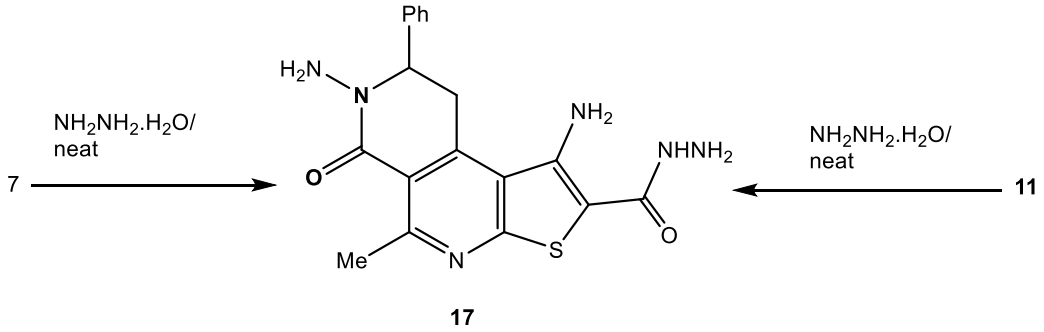
By taking the above reactions in our consideration, we can conclude that the order of activity of methylene groups in compounds **5, 6**, **7** and **8** towards intramolecular Thorpe-Zeigler cyclization is: $-CH_2COPh > -CH_2CN > -CH_2CO_2Et > -CH_2CONH_2$. The above fact based on the following findings: (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 Na_2CO_3 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_2CO_3, gave poly functionally substituted thieno[2,3-*b*]pyridines **13**, **14**, **15** and **16** (Scheme 4).



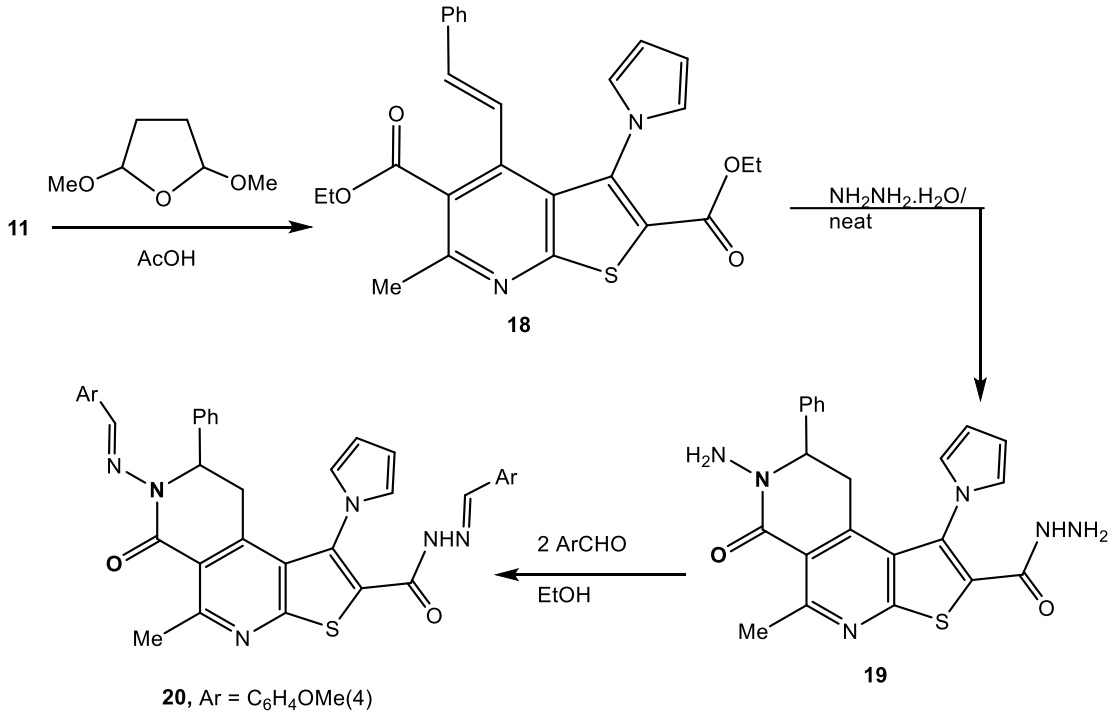
Scheme 4. Synthesis of thieno[2,3-b]pyridines **13-16**.

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



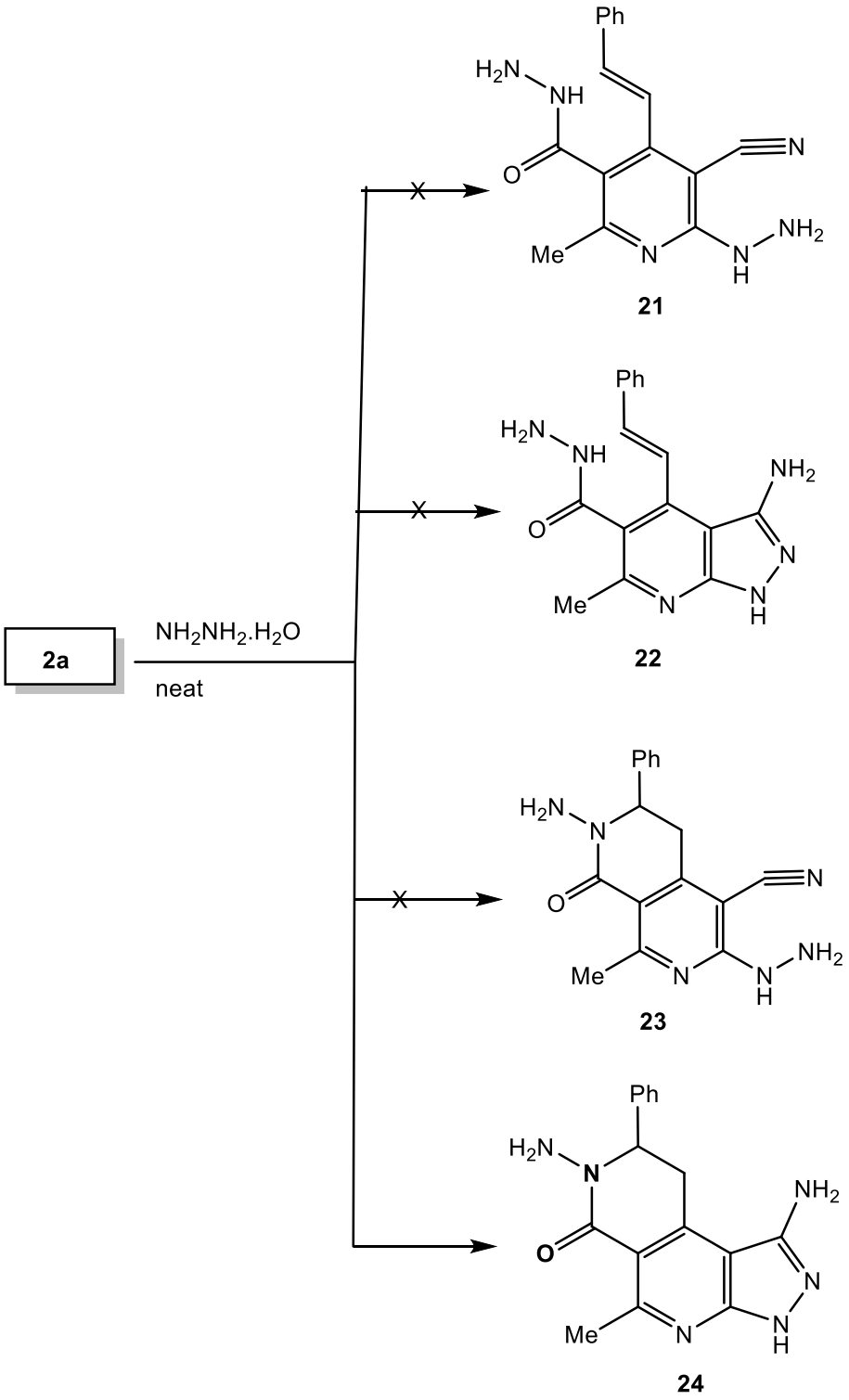
Scheme 5. Synthesis of compound **17**

Reaction of cyclic ester **11** with 2,5-dimethoxytetrahydrofuran is reported to give the pyrrolyl derivative **18**.[22] Fusion of **18** with an excess molar amount of hydrazine hydrate 99% afforded aminopyrrolyl-thienonaphthyridinecarbohydrazide **19**. The latter compound **19** was condensed with two molar ratios of 4-methoxybenzaldehyde to give bis(4-methoxybenzylidene) derivative **20** (Scheme 6).



Scheme 6. Synthesis of compounds **19** and **20**

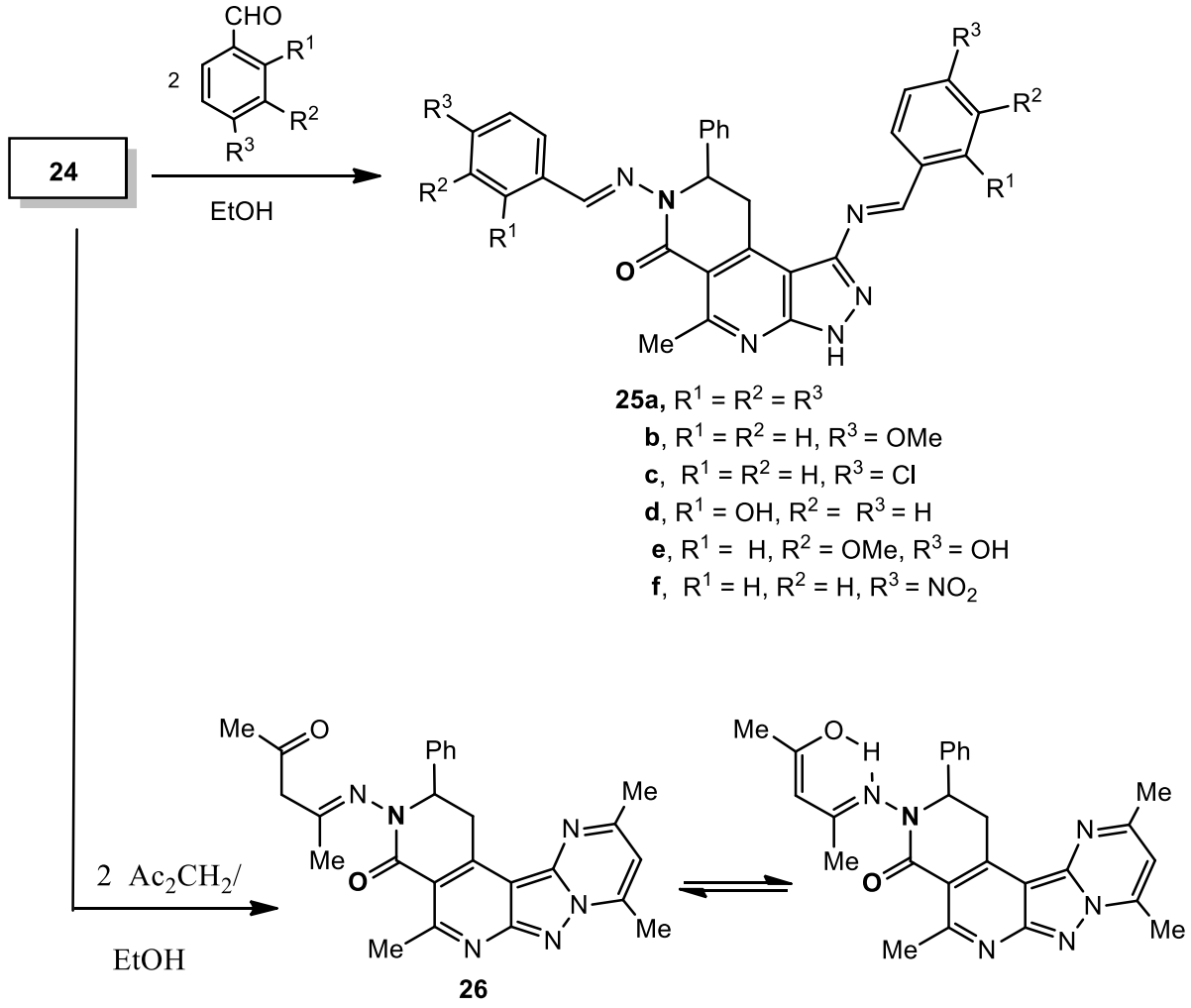
The above formation of 2,7-naphthyridines promoted us to check the action of hydrazine hydrate on the starting compound **2a**.under the same (above) conditions. Thus, heating of **2a** with an extra amount of hydrazine hydrate at 100 ºC led to the formation of a colorless crystalline solid with melting point 238 ˚C in excellent yield. This structure of this product was assigned as diaminopyrazolonaphthyridinone **24** among four proposed structures **21**-**24** with the same molecular formula, $C_{16}H_{16}N_6O$ (Scheme 7).



Scheme 7. Synthesis of diaminopyrazolonaphthyridinone **24**

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.



Scheme 8. Synthesis of pyrazolonaphthyridinones **25a-f** and **26**

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; ν_{max} in cm^{-1}). ^1H 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 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, ω-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, ω-cyanoacetophenone, chloroacetonitrile; ethyl bromoacetate or 2-chloroacetamide (0.005 mol) in EtOH (35 mL) was stirred at 25 ºC 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). ^1H 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 $C_{20}H_{20}N_2O_2S$ (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, nonoconjugated ketone). ^1H 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 $C_{26}H_{22}N_2O_3S$ (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). ^1H 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 $C_{20}H_{17}N_3O_2S$ (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). ^1H 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 (2 t, 6H: two CH_3) ppm. Anal. Calcd. For $C_{22}H_{22}N_2O_4S$ (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). ^1H 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 $C_{20}H_{19}N_3O_3S$ (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-ethoxycarbonyl-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). ^1H NMR: 6.66-7.85 (m, 13H: NH_2, CH=C & 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=C), 119.62, 105.78, 61.83 (OCH_2), 23.48 (CH_3), 14.24 (CH_3) ppm. Anal. Calcd. For $C_{26}H_{22}N_2O_3S$ (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.$3H_2O$ (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-amino-2-cyano-6-methyl-4-styrylthieno[2,3-*b*]pyridine-2-caboxylate (10)

(A) Compound **6** (0.36 g, 0.001 mol) and AcONa.$3H_2O$ (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_2); 2975, 2934 (CH, aliph.); 2201 (CN); 1731 (CO, ester). ^{1}H NMR: 7.38-7.51 (m, 6H: CH=C & aryl-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 $C_{20}H_{17}N_3O_2S$ (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.$3H_2O$ (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.$3H_2O$ (0.25 g) in EtOH (30 mL) was refluxed for 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, aryl-H's), 7.36-7.45 (m, 3H, aryl- H's), 6.79-.83 (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), 14.83 (CH_3), 14.41 (CH_3) ppm. Anal. Calcd. For $C_{22}H_{22}N_2O_4S$ (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.$3H_2O$ (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_2CO_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 & aryl-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 $C_{20}H_{19}N_3O_3S$ (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_2CO_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-bromoacetophenone, 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-bromoacetophenone, chloroacetonitrile, ethyl bromoacetate or 2-chloroacetamide (0.002 mol) in EtOH (30 mL) and anhyd. Na2CO3 (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 (NH_2), 1709 (CO). ^{1}H NMR: 7.39-7.70 (m, 13H: NH_2, CH=C & aryl-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 $C_{25}H_{20}N_2O_2S$ (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 (NH_2); 2978, 2932 (CH, aliph.); 2200 (CN); 1710 (CO). ^{1}H NMR: 7.82-7.85 (d, 1H, C=CH), 7.42-7.67 (m, 2H, aryl-H's), 7.38-7.40 (m, 3H, aryl-H's), 6.69-6.73 (d, 1H, CH=C), 6.47 (s, 2H, NH_2), 2.52 (s, 3H, CH_3), 2.42(s, 3H, CH_3) ppm.^{13}C 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), 127.89(CH), 121.60(CH), 119.37, 115.80, 32.80 (CH_3), 23.23 (CH_3) ppm. Anal. Calcd. For $C_{19}H_{15}N_3OS$ (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 (NH_2); 2980 (CH, aliph.); 1705 (CO); 1672 (CO). ^{1}H NMR: 7.80-7.84 (d, 1H, CH=C), 7.65-7.67 (d, 2H, aryl-H's), 7.37-7.46 (m, 3H, aryl-H's), 6.71-6.75 (d, 1H, C=CH), 6.61 (s, 2H, NH_2), 4.26-4.30 (q, 2H, OCH_2), 2.50 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 1.28-1.31 (t, 3H, CH_3) ppm. ^{13}C 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 (OCH_2), 32.84(CH_3), 23.27 (CH_3), 14.84 (CH_3) ppm. Anal. Calcd. For $C_{21}H_{20}N_2O_3S$ (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 %.

Compound 16. Yield: 0.66 g (94 %); mp 287-289 °C. IR: 3438, 3331, 3272, 3160 (2 NH_2); 2981 (CH, aliph.); 1703 (CO); 1660 (CO). ^{1}H NMR: 7.64-7.67 (d, 1H, CH=C), 7.29-7.45 (m, 7H: $CONH_2$ & aryl-H's), 6.77-6.81 (d, 1H, C=CH), 6.65 (s, 2H, NH_2), 2.52 (s, 3H, CH_3), 2.43 (s, 3H, CH_3) ppm. Anal. Calcd. For $C_{19}H_{17}N_3O_2S$ (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 %.

1,7-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 ºC 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 NH_2, NH); 3023 (CH, arom.); 2929 (CH, aliph.); 1640 (CO**)**. ^{1}H NMR: δ 9.12 (s, 1H, NH), 7.25-7.28 (m, 2H, aryl-H's), 7.13-7.20 (m, 3H, aryl-H's), 6.75 (s, 2H, NH_2), 5.25 (s, 2H, NH_2), 5.10-5.11 (d, 1H, C^8H, of cyclohexene ring), 4.43 (s, 2H, NH_2 of carbohydrazide), 3.94-4.08 (m, 2H, C^9H_2 of cyclohexene ring), 2.90 (s, 3H, CH_3) ppm. Anal. Calcd. For $C_{18}H_{18}N_6O_2S$ (382.12): C, 56.52; H, 4.74; N, 8.37; S, 7.24 %. Found: C, 56.22; H, 4.79; N, 8.20; S, 6.98 %.

7-Amino-5-methyl-6-oxo-8-phenyl-1-(1*H*-pyrrol-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 (NH_2, $NHNH_2$), 3031 (CH, arom.), 1648 (2 CO**)**. ^{1}H NMR: 8.37 (s, 1H, NH), 6.40-7.23 (m, 11H, aryl-H's & pyrrole-H's), 5.22 (s, 2H, NH_2), 4.85 (s, 1H, C^8H of cyclohexene ring), 4.49 (s, 2H, NH_2 of carbohydrazide), 3.29 (m, 2H, C^9H_2 of cyclohexene ring), 2.96 (s, 3H, CH_3) ppm. Anal. Calcd. For $C_{22}H_{20}N_6O_2S$ (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-(1*H*-pyrrol-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-mthoxybenzaldehyde (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, (NH_2, NH), 1651 (2 CO**)**. ^{1}H NMR: 9.09 (s, 1H, CH, azomethine), 8.94 (s, 1H, NH), 8.55 (s, 1H, CH, azomethine), 6.40-8.20 (m, 17H: aryl-H's & pyrrole-H's), 6.22 (s, 2H, NH_2), 3.97(s, 3H, OCH_3), 3.89 (s, 3H, OCH_3),), 4.86 (s,1H, C^8H of cyclohexene ring), 3.28 (m, 2H, C^9H_2 of cyclohexene ring), 2.93 (s, 3H, CH_3). Anal. Calcd. For $C_{38}H_{32}N_6O_4S$ (668.22): C, 68.25; H, 4.82; N, 12.57; S, 4.79 %. Found: C, 68.39; H, 5.08; N, 12.36; S, 4.51 %.

1,7-Diamino-5-methyl-8-phenyl-8,9-dihydro-3*H*-pyrazolo[3,4-*c*][2,7]naphthyridin-6(7*H*)-one (24). A suspension of compound **2a** (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 (NH_2, NH), 3031 (CH, arom.), 2925, 2819 (CH, aliph.), 1650 (CO**),** 1605 (CN). ^{1}H 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, NH_2), 5.05-5.11 (m, 3H: NH_2 and C^8H of cyclohexene ring), 3.71-3.83 (m, 2H, C^9H_2 of cyclohexene ring), 2.85 (s, 3H, CH_3). MS: m/z 308.26 (M^+, 30%). Anal. Calcd. For $C_{16}H_{16}N_6O$ (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). ^{1}H NMR: δ 13.53 (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, C^8H of cyclohexene ring), 4.37-4.42 (d, 1H, C^9H of cyclohexene ring), 4.03-4.08 (dd, 1H, C^9H of cyclohexene ring), 2.95 (s, 3H, CH_3) ppm. Anal. Calcd. For $C_{30}H_{24}N_6O$ (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**)**. ^{1}H 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, C^8H of cyclohexene ring), 4.35-4.38 (d, 1H, C^9H of cyclohexene ring), 4.00-4.03 (dd, 1H, C^9H of cyclohexene ring), 3.87(s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.93 (s, 3H, CH_3) ppm. ^{13}C 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 (OCH_3), 55.76 (OCH_3), 32.37 (CH_2), 26.89 (CH_3) ppm. Anal. Calcd. For $C_{32}H_{28}N_6O_3$ (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). ^{1}H 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, C^8H of cyclohexene ring), 5.46 (s, 1H, C^9H of cyclohexene ring), 4.02 (d, 1H, C^9H of cyclohexene ring), 2.87 (s, 3H, CH_3)ppm. Anal. Calcd. For $C_{30}H_{22}Cl_2N_6O$ (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**);** ^{1}H NMR: δ 13.69 (s, 1H, NH), 12.13 (s, 1H, OH), 11.93 (s, 1H, OH), 9.37-9.38 (s, 1H, CH, azomethine), 8.36 (s, 1H, CH, azomethine), 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, C^8H of cyclohexene

ring), 4.17 (s, 2H, C^9H_2 of cyclohexene ring), 2.99 (s, 3H, CH_3) ppm. Anal. Calcd. For $C_{30}H_{24}N_6O_3$ (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**);** ^{1}H 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, C^8H of cyclohexene ring), 4.34-4.38 (d, 1H, C^9H of cyclohexene ring), 4.03 (d,1H, C^9H of cyclohexene ring), 3.92 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.94 (s, 3H, CH_3) ppm. Anal. Calcd. For $C_{32}H_{28}N_6O_5$ (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**)**. ^{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^8H of cyclohexene ring), 5.47 (s, 1H, C^9H of cyclohexene ring), 4.00 (d, 1H, C^9H of cyclohexene ring), 2.84 (s, 3H, CH_3) ppm. Anal. Calcd. For $C_{30}H_{22}N_8O_5$ (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(1*H*)-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). ^{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),.4.43-4.48 (dd, 1H, CH), 4.17-4.22 (d, 1H, CH), 3.12 (s, 3H, CH_3), 2.92 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 1.96 (s, 3H, CH_3) ppm. ^{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_2 of cyclohexene ring), 29.17 (CH_3), 27.80 (CH_3), 24.68 (CH_3), 18.21 (CH_3), 17.83 (CH_3) ppm. Anal. Calcd. For $C_{26}H_{26}N_6O_2$ (454.21): C, 68.70; H, 5.77; N, 18.49 %. Found: C, 68.63; H, 6.02; N, 18.37 %.

Acknowledgements

The authors extend their appreciation to Taif University, Saudi Arabia for supporting this work through Project No. (TU-DSPP-2024-150).

Supplementary Material

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

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