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Synthesis and Reactions of New Hydrazinyl-2,7-naphthyridines and Pyrimidothieno[2,3-*c*][2,7]naphthyridine Morpholine Derivatives

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Abstract—The reaction of 7-methyl-1-(morpholin-4-yl)-3-sulfanylidene-2,3,5,6,7,8-hexahydro-2,7-naphthyridine-4-carbonitrile with hydrazine hydrate gave 1-hydrazinyl-7-methyl-3-sulfanylidene-2,3,5,6,7,8-hexahydro-2,7-naphthyridine-4-carbonitrile which was used as a key intermediate for the synthesis of new fused naphthyridine-based heterocyclic systems. The condensation of 1-amino-7-methyl-5-(morpholin-4-yl)-6,7,8,9-tetrahydrothieno[2,3-*c*][2,7]naphthyridine-2-carbonitrile with different reagents afforded fused tetra- and pentacyclic systems. The structure of the newly synthesized compounds was confirmed by elemental analysis and spectral techniques.

Keywords: 2,7-naphthyridines, hydrazinyl, pyrimidothienonaphthyridine, morpholine

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INTRODUCTION

In our previous paper [1], we described a novel methodology for the synthesis of morpholino-2,7-naphthyridine and morpholino-thieno[2,7]naphthyridine derivatives (Fig. 1). The high level of interest in these compounds stems from their broad range of biological activity such as antimicrobial and anticancer activities [1–7]. In this paper, we report the synthesis of a new series of 2,7-naphthyridine derivatives from 7-methyl-1-(morpholin-4-yl)-3-sulfanylidene-2,3,5,6,7,8-hexahydro-2,7-naphthyridine-4-carbonitrile (**1**) and 1-amino-7-methyl-5-(morpholin-4-yl)-6,7,8,9-tetrahydrothieno[2,3-*c*][2,7]naphthyridine-2-carbonitrile (**11**).

2,7-Naphthyridine (2,7-diazanaphthalene) derivatives are a minor class of aromatic alkaloids [8–10] found in plants, sponges, tunicates, and bryozoans [11]. Examples are neozeylanicine isolated from *Neonauclea zeylanica* (*Rubiaceae*) [12] and 3-acetyl-2,7-naphthyridine from *Valeriana officinalis* (*Valerianaceae*) [13] that are long known bicyclic 2,7-naphthyridine alkaloids. Perlolidine is a tricyclic alkaloid isolated from a variety of plants, including *Lolium perenne* (*Poaceae*) [14]. Furthermore, the 2,7-naphthyridine ring system is present in a number of *Annonaceae* alkaloids, including sampangine (antimicrobial agent), eupolauridine from *Cleistopholis patens* [15] and *Cananga odorata* [16], as well as a number of pyridoacridone alkaloids from marine organisms [17], such as the cytotoxic pentacyclic alkaloid ascididemin from the tunicate *Didemnum* sp. (Fig. 2). Gross et al. [18] recently reported the isolation of two new bicyclic naphthyridine alkaloids, lophocladine A and lophocladine B from the red alga *Lophocladia* sp. (Fig. 2). Jasminine and jasmidine from *Jasminum* species are also examples of natural products with a naphthyridine skeleton [19–21]. Furthermore, naphthyridine and its

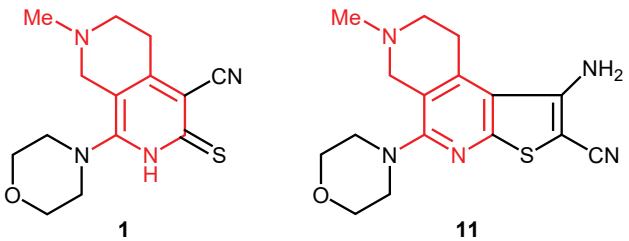


Fig. 1. Structures of morpholino- and morpholino-thieno-2,7-naphthyridines.

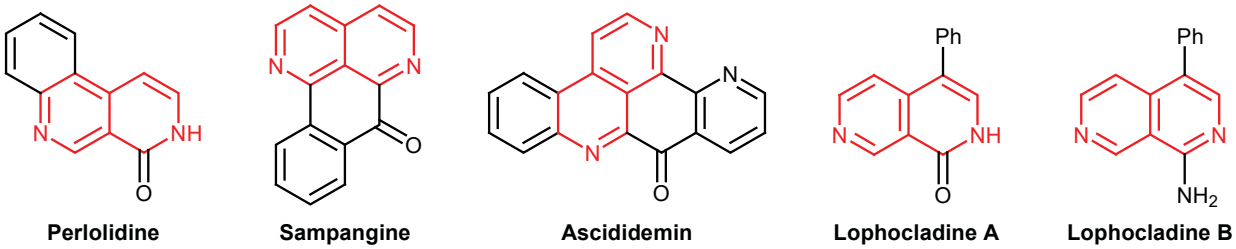


Fig. 2. Structures of some 2,7-naphthyridine alkaloids.

derivatives exhibit a wide range of biological activities, including anticancer [22, 23], antimalarial [24], anti-inflammatory [25, 26], antiallergic [27], and antiprotozoal [28], as well as inhibitory activity against bacterial topoisomerase [29], human acetylcholinesterase at a picomolar level [30], fibroblast activation protein [31], and HIV-1 integrase [32]. In the agricultural field, a naphthyridine analog has been reported as a fungicide, insecticide, and herbicide [33–35] in barley, wheat, maize, and rice crops [36]. The significant pharmaceutical and agricultural activities of naphthyridine derivatives encouraged us to take up the synthesis of these new heterocycles via a greener method. Several methods [37–41] for the synthesis of naphthyridine derivatives have been reported in the literature, but all these have both some advantages and disadvantages. The aim of this work was to synthesize a series of novel 2,7-naphthyridine derivatives and study their spectral properties.

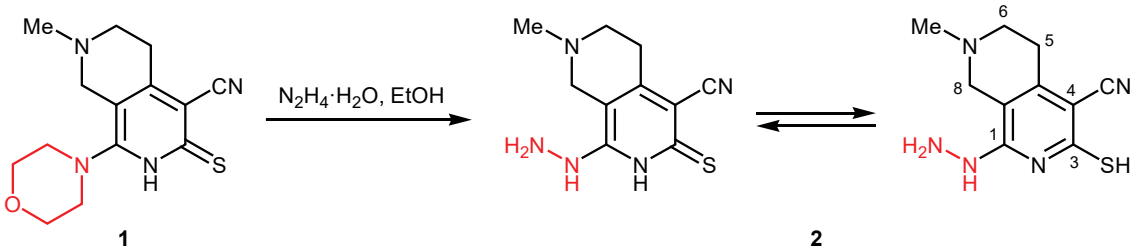
RESULTS AND DISCUSSION

7-Methyl-1-(morpholin-4-yl)-3-sulfanylidene-2,3,5,6,7,8-hexahydro-2,7-naphthyridine-4-carbonitrile (**1**) [1] was gently refluxed with hydrazine hydrate in ethanol to give 1-hydrazinyl-7-methyl-3-sulfanylidene-2,3,5,6,7,8-hexahydro-2,7-naphthyridine-4-carbonitrile (**2**) in a high yield (Scheme 1). The IR spectrum of **2** showed absorption bands at 3204, 3290, and 3326 cm^{-1}, which are characteristic of NH_2 and NH groups. The ^1H NMR spectrum of **2** in DMSO-d_6 displayed broadened singlets at δ 5.79 and 13.84 ppm for the NH_2 and NH protons, whereas signals characteristic for the morpholine ring disappeared. The mass spectrum of **2** contained the molecular ion peak at *m*/*z* 235.27.

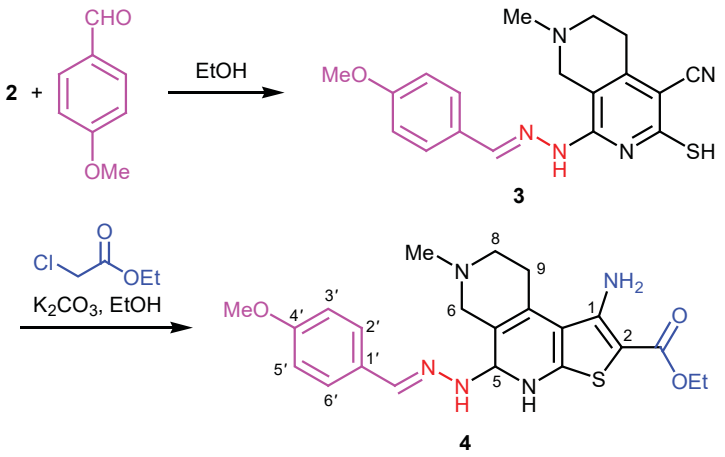
Hydrazinyl-substituted naphthyridine **2** was used as a key intermediate for the synthesis of new fused heterocyclic systems. The condensation of **2** with 4-methoxybenzaldehyde in ethanol produced a new fused polyheterocyclic system, (*E*)-1-[2-(4-methoxybenzylidene)hydrazinyl]-7-methyl-3-sulfanyl-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitrile (**3**) which was alkylated with ethyl chloroacetate in the presence of potassium carbonate in ethanol to give ethyl 1-amino-5-[2-(4-methoxybenzylidene)hydrazinyl]-7-methyl-4,5,6,7,8,9-hexahydrothieno[2,3-*c*][2,7]naphthyridine-2-carboxylate (**4**) (Scheme 2). The ^1H NMR spectra of **3** and **4** showed signals characteristic for the phenyl group and a singlet at δ 8 ppm due to the CH=N group. The ^1H NMR spectrum of **3** displayed no NH_2 signal which appeared again in the spectrum of **4** at δ 6.2 ppm.

Compound **2** underwent ring closure upon heating with triethyl orthoformate in glacial acetic acid to give 9-methyl-5-sulfanyl[1,2,4]triazolo[3,4-*a*][2,7]naphthyridine-6-carbonitrile (**5**). The reaction of **2** with carbon disulfide in pyridine produced dithioxo[1,2,4]triazolo[3,4-*a*][2,7]naphthyridine-6-carbonitrile **7**. The Thorpe–Ziegler cyclization of **5** and **7** on heating in ethanol in the presence of potassium carbonate afforded 1-aminotetrahydrothieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-[2,7]naphthyridine-6-carboxylates **6** and **8**, respectively (Scheme 3). The IR spectra of **5** and **7** lacked absorption bands assignable to N–H stretchings of the hydra-

Scheme 1.



Scheme 2.

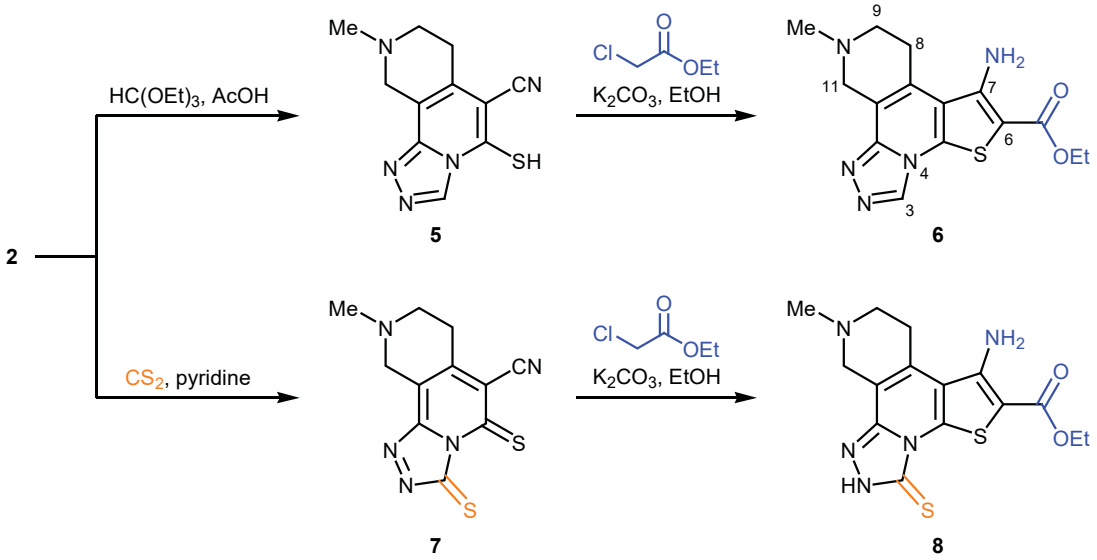


zinyl group, whereas band typical of NH_2 group appeared in the spectra of **6** and **8** with simultaneous disappearance of C≡N stretching band. Likewise, the ^{1}H NMR spectra of **5** and **7** revealed disappearance of signals corresponding to the H_2NNH group in the starting material and appearance of signals due to the NH_2 and ethyl groups in the spectra of **6**, **8**. For example, the C≡N stretching band of **5** was observed in the IR spectrum at 2212 cm^{-1}; it vanished in the spectrum of the cyclization product, while NH_2 bands appeared at 3335 and 3424 cm^{-1}. The NH_2 protons of **6** resonated at δ 6.75 ppm in the ^{1}H NMR spectrum.

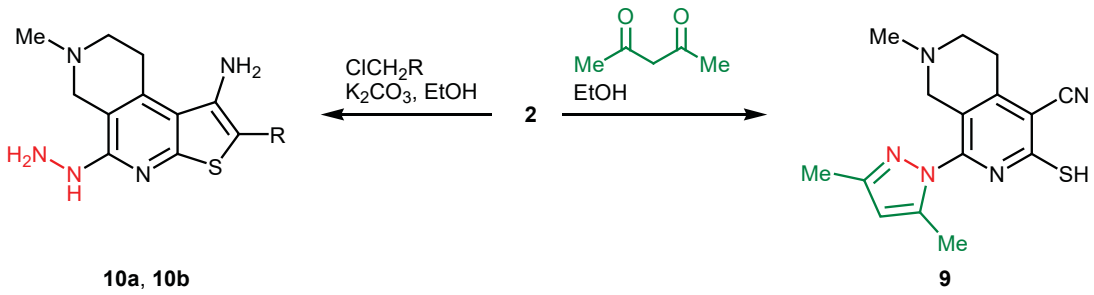
1-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-7-methyl-3-sulfanyl-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitrile (**9**) was synthesized by reacting hydrazinyl derivative **2** with acetylacetone in ethanol. The ^{1}H NMR spectrum of **9** showed a singlet at δ 8.1 ppm due to CH proton of the pyrazole ring, whereas no $NHNH_2$ signals were present. The mass spectrum of **9** displayed a peak at *m*/*z* 298 matching the molecular ion. The alkylation of **2** with α-halo carbonyl compounds such as ethyl chloroacetate and chloroacetonitrile in the presence of potassium carbonate in ethanol produced tetrahydrothieno[2,3-*c*][2,7]naphthyridine derivatives **10a** and **10b** (Scheme 4). The IR spectra of **10a** and **10b** showed disappearance of the C≡N band upon cyclization and appearance of the NH_2 band. The ^{1}H NMR spectra of **10a** and **10b** showed signals corresponding to two primary amino groups. The molecular ion peaks were observed in the mass spectra of **10a** and **10b** at *m*/*z* 321 and 274, respectively.

1-Amino-7-methyl-5-(morpholin-4-yl)-6,7,8,9-tetrahydrothieno[2,3-*c*][2,7]naphthyridine-2-carbonitrile (**11**) [1] reacted with a slight excess of triethyl

Scheme 3.



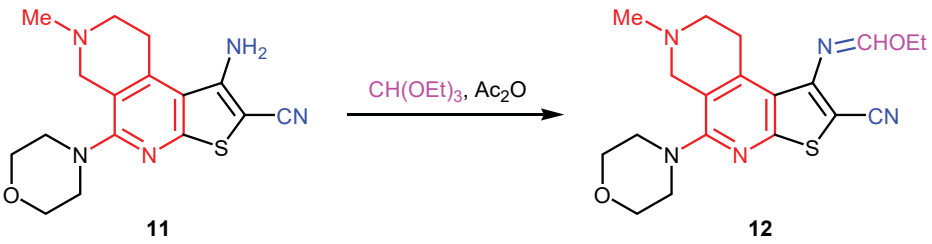
Scheme 4.



10a, **10b** **9**

10, R = COOEt (**a**), CN (**b**).

Scheme 5.

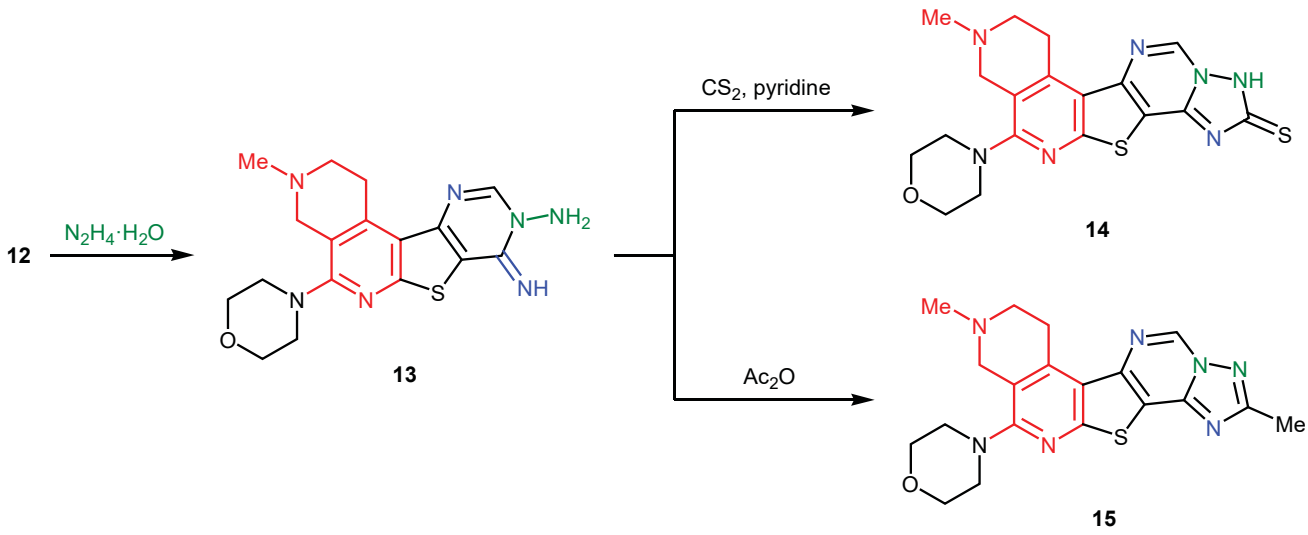


11 **12**

orthoformate in acetic anhydride to give ethyl (*E*)-*N*-[2-cyano-7-methyl-5-(morpholin-4-yl)-6,7,8,9-tetrahydrothieno[2,3-*c*][2,7]naphthyridin-1-yl]formimidate (**12**) (Scheme 5). The IR spectrum of **12** retained the C≡N stretching band at 2200 cm^{-1}, but the NH_2 absorption typical of **11** disappeared. The ^1H NMR spectrum of **12** in $CDCl_3$ showed a singlet at δ 8 ppm characteristic for the CH=N proton and triplet and quartet characteristic for ethyl group, while no amino group signal was present.

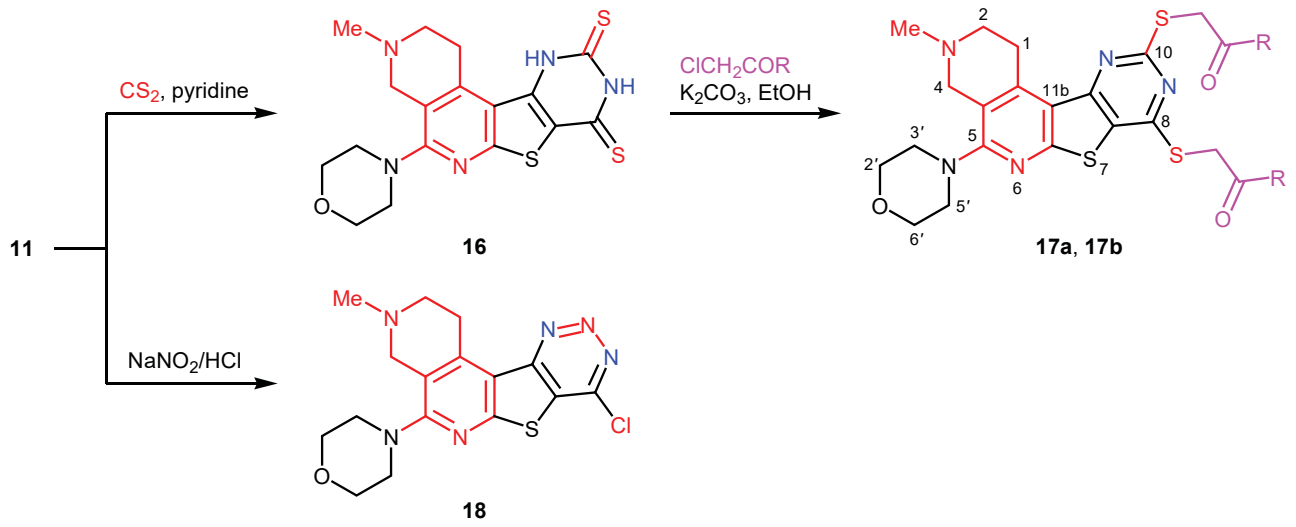
Formimidate **12** was stirred with an equivalent amount of hydrazine hydrate in dioxane at room temperature to give 8-imino-3-methyl-5-(morpholin-4-yl)-1,3,4,8-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-*c*][2,7]naphthyridin-9(2*H*)-amine (**13**). The IR spectrum of **13** revealed appearance of absorption bands characteristic for NH and NH_2 groups and disappearance of band characteristic for C≡N group. The ^1H NMR spectrum of **13** showed a signal at δ 5.8 ppm for the NH_2 group and a signal at δ 10.4 ppm for the =NH group. The mass spectrum contained a peak at *m*/*z* 371 matching the molecular ion. Amino imino derivative **13** was used as a versatile precursor for other triazolo heterocyclic compounds, tetrahydro[1,2,4]triazolo-

Scheme 6.



13 **14** **15**

Scheme 7.



17, R = OEt (**a**), Ph (**b**).

[1″,5″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-*c*][2,7]naphthyridine-2(3*H*)-thione **14** and dimethyltetrahydro[1,2,4]triazolo[1″,5″:1′,6′]pyrimido[4′,5′:4,5]-thieno[2,3-*c*][2,7]naphthyridine **15**, via the reactions with carbon disulfide in pyridine and with acetic anhydride, respectively (Scheme 6). The IR and ^{1}H NMR spectra of **14** and **15** two compounds revealed disappearance of absorption bands and signals characteristic for NH_2 group. The ^{1}H NMR of **15** in DMSO-d_6 showed a sharp signal at δ 2.4 ppm. The mass spectra of **14** and **15** displayed the molecular ion peak at *m*/z 413 and 395, respectively.

The reaction of compound **11** with carbon disulfide in pyridine produced a new fused heterocyclic system, 3-methyl-5-(morpholin-4-yl)-1,2,3,4-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-*c*][2,7]naphthyridine-8,10(9*H*,11*H*)-dithione (**16**), whose ^{1}H NMR spectrum showed disappearance of signals characteristic for NH_2 group and appearance of new signals at δ 12.7 and 13.8 ppm typical of two NH groups. The alkylation of dithione **16** with α-halo carbonyl compounds (ethyl chloroacetate and phenacyl chloride) in the presence of potassium carbonate in ethanol afforded the corresponding *S*-alkyl derivatives **17a** and **17b**. The ^{1}H NMR spectra of **17a** and **17b** showed no NH proton signals but signals due to substituents on the sulfur atoms appeared at the expected positions; in particular, protons of the phenyl rings of **17b** resonated in the region δ 7.43–8.02 ppm. The molecular ion peak of **17a** was observed at *m*/*z* 577 in the mass spectrum. Chlorotriazine derivative **18** was obtained by treatment of **11** in concentrated aqueous HCl with a solution of sodium nitrite at room temperature. The IR and ^{1}H NMR spectra of **18** revealed disappearance of absorption bands and signals characteristic for NH_2 and CN groups (Scheme 7).

EXPERIMENTAL

The melting points were measured using a Gallenkamp melting point apparatus. The IR spectra were recorded in KBr on a Shimadzu 470 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded in chloroform-*d* ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6) on Bruker and JEOL spectrometers at 400 MHz for ^{1}H using tetramethylsilane as internal standard. The mass spectra were run on a Jeol JMS-600 mass spectrometer. Elemental analysis was performed at the Assiut University Central Laboratory using a Vario El V2 CHNS analyzer.

1-Hydrazinyl-7-methyl-3-sulfanylidene-2,3,5,6,7,8-hexahydro-2,7-naphthyridine-4-carbonitrile (2). A mixture of 7-methyl-1-(morpholin-4-yl)-3-sulfanylidene-2,3,5,6,7,8-hexahydro-2,7-naphthyridine-4-carbonitrile [1] (**1**, 5 g, 0.01 mol) and hydrazine hydrate (99.9%, 1.5 g, 0.03 mol) in ethanol (10 mL) was gently refluxed for 3 h. After cooling, the precipitate was washed and recrystallized from methanol. Yield 86%, brown crystals, mp 280–282°C. IR spectrum, ν, cm^{-1}: 3204, 3271 (NH_2), 3326 (NH), 2965, 3011 (C–H_{aliph}), 2190 (C≡N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.31 s (3H, CH_3), 2.51–2.56 m (4H, 5-H, 6-H), 3.02 s (2H, 8-H), 5.79 s (2H, NH_2), and 13.84 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm:

28.88 (CH_3), 45.69 (C^5), 50.52 (C^8), 53.61 (C^6), 98.70 (C^{8a}), 104.32 (C^4), 117.39 (CN), 139.85 (C^1), 153.25 (C^{4a}), 175.76 (C^3). Mass spectrum: *m*/*z* 235.27 (I_{rel} 100%) $[M]^+$. Found, %: C 51.01; H 5.55; N 29.74; S 13.60. $C_{10}H_{13}N_5S$. Calculated, %: C 51.04; H 5.57; N 29.76; S 13.62. *M* 235.31.

1-[(*E*)-2-(4-Methoxybenzylidene)hydrazinyl]-7-methyl-3-sulfanyl-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitrile (3). A mixture of compound **2** (1 g, 0.004 mol) and 4-methoxybenzaldehyde (0.5 g, 0.004 mol) in ethanol was refluxed for 1 h. After cooling, the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 66%, brown crystals, mp 305°C. IR spectrum, ν, cm^{-1}: 3341 (NH), 2932, 2990 (C–H_{aliph}), 2200 (C≡N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.06 s (3H, NCH_3), 3.16 s (3H, OCH_3), 2.88 s (2H, CH_2), 3.41–3.46 m (2H, CH_2), 4.65 s (2H, CH_2), 6.87 d (2H, H_{arom}), 7.32 d (2H, H_{arom}), 8.04 s (1H, N=CH), 10.89 s (1H, NH). Mass spectrum: *m*/*z* 353.24 $[M]^+$. Found, %: C 61.16; H 5.40; N 19.81; O 4.50; S 9.06. $C_{18}H_{19}N_5OS$. Calculated, %: C 61.17; H 5.42; N 19.82; O 4.53; S 9.07. *M* 353.44.

Ethyl 1-amino-5-[(*E*)-2-(4-methoxybenzylidene)-hydrazinyl]-7-methyl-4,5,6,7,8,9-hexahydrothieno-[2,3-*c*][2,7]naphthyridine-2-carboxylate (4). A mixture of compound **3** (0.5 g, 0.001 mol), ethyl chloroacetate (0.17 g, 0.001 mol), and anhydrous potassium carbonate (0.5 g, 0.003 mol) in ethanol was refluxed for 1 h. After cooling, the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 75%, dark brown crystals, mp 225°C. IR spectrum, ν, cm^{-1}: 3296, 3331 (NH_2), 3401, 3494 (NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.04 t (3H, C**H**$_3$CH$_2$), 2.06 s (3H, CH_3), 2.37 s (2H, 8-H), 2.62 t (2H, 9-H), 3.79 s (3H, OCH_3), 3.43 q (2H, OCH_2), 4.76 s (2H, 6-H), 6.21 s (2H, NH_2), 6.92 d (2H, H_{arom}), 7.62 d (2H, H_{arom}), 8.15 s (1H, 5-H), 8.24 s (1H, CH=N), 10.06 s and 10.42 s (1H each, NH). ^{13}C NMR spectrum, δ_C, ppm: 18.53 (**C**H_3CH_2), 30.98 (C^9), 25.44 (7-CH_3), 45.51 (C^6, C^8), 56.68 (OCH_3), 60.77 (OCH_2), 62.89 (C^5), 114.52 ($C^{3'}$, $C^{5'}$), 128.70 ($C^{2'}$, $C^{6'}$), 115.29 (C^2), 123.68 ($C^{1'}$), 127.13 and 127.80 (C^{9a}, C^{9b}), 141.71 (C^1), 149.65 (C^{5a}), 149.88 (CH=N), 158.29 (C^{3a}), 165.3 (C=O). Mass spectrum: *m*/*z* 441.57 $[M]^+$. Found, %: C 59.82; H 6.15; N 15.85; O 10.85; S 7.24. $C_{22}H_{27}N_5O_3S$. Calculated, %: C 59.84; H 6.16; N 15.86; O 10.87; S 7.26. *M* 441.55.

9-Methyl-5-sulfanyl-7,8,9,10-tetrahydro[1,2,4]-triazolo[3,4-*a*][2,7]naphthyridine-6-carbonitrile (5). A mixture of compound **2** (1 g, 0.004 mol) and triethyl orthoformate (0.6 g, 0.004 mol) in 1 mL of acetic acid was refluxed until the reaction was complete. After cooling, the solid product was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 90%, orange crystals, mp 365–366°C. IR spectrum, ν, cm^{-1}: 2212 (C≡N), 3117 (C–H_{aliph}). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.90 s (3H, CH_3), 2.09 s (2H, CH_2), 2.95 s (2H, CH_2), 4.35 s (2H, CH_2), 9.20 s (1H, CH). Mass spectrum: *m*/*z* 245.28 $[M]^+$. Found, %: C 53.85; H 4.51; N 28.53; S 13.05. $C_{11}H_{11}N_5S$. Calculated, %: C 53.86; H 4.52; N 28.55; S 13.07. *M* 245.30.

Ethyl 7-amino-10-methyl-8,9,10,11-tetrahydro-thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*][2,7]naphthyridine-6-carboxylate (6). A mixture of **5** (0.5 g, 0.002 mol), ethyl chloroacetate (0.24 g, 0.002 mol), and anhydrous potassium carbonate (1 g) in ethanol was refluxed. The product was washed with ethanol and recrystallized from ethanol. Yield 90%, dark green crystals, mp 220°C. IR spectrum, ν, cm^{-1}: 3335, 3424 (NH_2), 1664 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.03 t (3H, C**H**$_3$CH$_2$), 2.06 s (3H, NCH_3), 2.42 s (2H, 9-H), 2.95 s (2H, 8-H), 4.78 s (2H, 11-H), 3.44 q (2H, OCH_2), 6.75 s (2H, NH_2), 9.48 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 18.48 (**C**H_3CH_2), 25.39 (C^8), 56.68 (10-CH_3), 29.59 (C^9), 30.93 (C^{11}), 48.99 (OCH_2), 62.89 (C^3), 121.86 (C^6), 128.91 (C^{7a}), 130.88 (C^7), 132.68 (C^{11a}), 141.71 (C^{11b}), 149.65 (C^{7b}), 158.58 (C^{4a}), and 208.76 (CO). Mass spectrum: *m*/*z* 331.30 (I_{rel} 100%) $[M]^+$. Found, %: C 54.36; H 5.15; N 21.10; O 9.64; S 9.66. $C_{15}H_{17}N_5O_2S$. Calculated, %: C 54.37; H 5.17; N 21.13; O 9.66; S 9.67. *M* 331.39.

9-Methyl-3,5-di(sulfanylidene)-3,5,7,8,9,10-hexahydro[1,2,4]triazolo[3,4-*a*][2,7]naphthyridine-6-carbonitrile (7). A solution of compound **2** (1 g, 0.004 mol) in 1 mL of carbon disulfide (0.01 mol) and 5 mL of pyridine was refluxed on a steam bath for 4 h. The product was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 75%, red crystals, mp 330–332°C. IR spectrum, ν, cm^{-1}: 2205 (C≡N), 3057 (C–H_{aliph}). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.90 s (3H, CH_3), 2.09 s (2H, CH_2), 2.95 t (2H, CH_2), 4.35 s (2H, CH_2). Mass spectrum: *m*/*z* 275.13 $[M]^+$. Found, %: C 47.96; H 3.27; N 25.43; S 23.26. $C_{11}H_9N_5S_2$. Calculated, %: C 47.98; H 3.29; N 25.44; S 23.29. *M* 275.35.

Ethyl 7-amino-10-methyl-3-sulfanylidene-2,3,8,9,10,11-hexahydrothieno[2,3-*c*][1,2,4]triazolo-[3,4-*a*][2,7]naphthyridine-6-carboxylate (8). A mixture of **7** (0.5 g, 0.001 mol), ethyl chloroacetate

(0.22 g, 0.001 mol), and anhydrous potassium carbonate (1 g) in ethanol was refluxed until the reaction was complete. After cooling, the solid product was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 85%, brown crystals, mp 310–312°C. IR spectrum, ν, cm^{-1}: 3292, 3409 (NH_2), 2202 (C≡N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.32 t (3H, C**H**$_3$CH$_2$), 2.06 s (3H, CH_3), 3.01 s (2H, CH_2), 4.00 s (2H, CH_2), 4.55 s (2H, CH_2), 4.32 q (2H, OCH_2), 6.85 s (2H, NH_2), 10.22 s (1H, NH). Found, %: C 49.56; H 4.70; N 19.26; O 8.78; S 17.63. $C_{15}H_{17}N_5O_2S_2$. Calculated, %: C 49.57; H 4.71; N 19.27; O 8.80; S 17.64. *M* 363.45.

1-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-7-methyl-3-sulfanylidene-5,6,7,8-tetrahydro-2,7-naphthyridine-4-carbonitrile (9). Acetylacetone (0.2 g, 0.002 mol) was added to a solution of compound **2** (0.5 g, 0.002 mol) in anhydrous ethanol, and the mixture was refluxed for 2 h. The solid product was filtered off and recrystallized from ethanol. Yield 80%, yellow crystals, mp 313–315°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.90 s (3H, CH_3), 2.06 s (3H, CH_3), 2.15 s (3H, CH_3), 2.20–2.51 m (2H, CH_2), 2.67 s (2H, CH_2), 2.94 s (2H, CH_2), 8.14 s (1H, CH). Mass spectrum: *m*/*z* 299.02 $[M]^+$. Found, %: C 60.17; H 5.70; N 23.37; S 10.70. $C_{15}H_{17}N_5S$. Calculated, %: C 60.18; H 5.72; N 23.39; S 10.71. *M* 299.40.

Ethyl 1-amino-5-hydrazinyl-7-methyl-6,7,8,9-tetrahydrothieno[2,3-*c*][2,7]naphthyridine-2-carboxylate (10a). A mixture of compound **2** (0.5 g, 0.001 mol), ethyl chloroacetate (0.25 g, 0.002 mol), and anhydrous potassium carbonate (0.5 g, 0.003 mol) in ethanol was refluxed for 1 h. After cooling, the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 80%, pale yellow crystals, mp 305°C. IR spectrum, ν, cm^{-1}: 3493 (NH), 3296, 3402 (NH_2), 1732 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.25 t (3H, C**H**$_3$CH$_2$), 2.36 s (1H, CH_3), 3.18 s (2H, CH_2), 2.58 t (4H, CH_2), 4.23 q (2H, OCH_2), 6.63 s and 7.80 s (2H each, NH_2), 10.41 s (1H, NH). Mass spectrum: *m*/*z* 321.22 $[M]^+$. Found, %: C 52.30; H 5.95; N 21.77; O 9.94; S 9.97. $C_{14}H_{19}N_5O_2S$. Calculated, %: C 52.32; H 5.96; N 21.79; O 9.96; S 9.98. *M* 321.40.

1-Amino-5-hydrazinyl-7-methyl-6,7,8,9-tetrahydrothieno[2,3-*c*][2,7]naphthyridine-2-carbonitrile (10b). A mixture of compound **2** (0.5 g, 0.001 mol), chloroacetonitrile (0.16 g, 0.002 mol), and anhydrous potassium carbonate (0.5 g) in ethanol was refluxed until the reaction was complete. The product was washed with ethanol and recrystallized from ethanol. Yield 81.1%, dark green crystals, mp 270°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.06 s (3H, CH_3), 2.35 s (2H, CH_2), 2.58 t (2H, CH_2), 4.76 q (2H, CH_2), 6.10 s and 6.33 s (2H each, NH_2), 10.41 s (1H, NH). Mass spectrum: *m*/*z* 274.17 $[M]^+$. Found, %: C 52.52; H 5.12; N 30.60; S 11.68. $C_{12}H_{14}N_6S$. Calculated, %: C 52.54; H 5.14; N 30.63; S 11.69. *M* 274.35.

Ethyl (*E*)-*N*-[2-cyano-7-methyl-5-(morpholin-4-yl)-6,7,8,9-tetrahydrothieno[2,3-*c*][2,7]naphthyridin-1-yl]formimidate (12). Triethyl orthoformate (0.45 g, 0.003 mol) was added to a solution of 1-amino-7-methyl-5-(morpholin-4-yl)-6,7,8,9-tetrahydrothieno[2,3-*c*][2,7]naphthyridine-2-carbonitrile (**11**) [1] (1 g, 0.003 mol) in 5 mL of acetic anhydride, and the mixture was gently refluxed for 2 h. The product was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 87.6%, pale yellow crystals, mp 170°C. IR spectrum, ν, cm^{-1}: 2200 (C≡N), 2789, 2846 ($C–H_{aliph}$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 t (3H, C**H**$_3$CH$_2$), 2.64 s (3H, CH_3), 2.94 s (2H, CH_2), 3.23 s and 3.45 s (2H each, CH_2NCH_2), 3.85 t (4H, CH_2OCH_2), 3.71 s (2H, CH_2), 4.17 s (2H, CH_2) 4.43 q (2H, C**H**$_2$CH$_3$), 8.00 s (1H, N=CH). Mass spectrum: *m*/*z* 385.14 $[M]^+$. Found, %: C 59.19; H 5.98; N 18.16; O 8.29; S 8.31. $C_{19}H_{23}N_5O_2S$. Calculated, %: C 59.20; H 6.01; N 18.17; O 8.30; S 8.32. *M* 385.49.

8-Imino-3-methyl-5-(morpholin-4-yl)-1,3,4,8-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-*c*][2,7]-naphthyridin-9(2*H*)-amine (13). A solution of compound **12** (5 g, 0.01 mol) in cold dioxane (10 mL) was stirred at room temperature, hydrazine hydrate (99.9%) was added, and the mixture was stirred for 1 h. The product was purified by recrystallization from ethanol. Yield 91%, yellow crystals, mp 293°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.06 s (3H, CH_3), 2.35 s (2H, CH_2), 3.15 t (4H, CH_2), 3.75 t (4H, CH_2), 4.75 s (2H, CH_2), 5.88 s (2H, NH_2), 8.17 s (1H, 10-H), 10.41 s (1H, NH). Mass spectrum: *m*/*z* 371.20 $[M]^+$. Found, %: C 54.96; H 5.68; N 26.39; O 4.30; S 8.61. $C_{17}H_{21}N_7OS$. Calculated, %: C 54.97; H 5.70; N 26.40; O 4.31; S 8.63. *M* 371.46.

9-Methyl-11-(morpholin-4-yl)-7,8,9,10-tetrahydro[1,2,4]triazolo[1″,5″:1′,6′]pyrimido[4′,5′:4,5]-thieno[2,3-*c*][2,7]naphthyridine-2(3*H*)-thione (14). A mixture of compound **13** (1 g, 0.002 mol) and carbon disulfide (0.2 g, 0.002 mol) in pyridine (5 mL) was refluxed in a steam bath for 4 h. The product was purified by recrystallization from ethanol. Yield 79%,

orange crystals, mp 270°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.06 s (3H, CH_3), 2.70 t (4H, CH_2), 3.19 s (2H, CH_2), 3.54 t (6H, CH_2), 4.75 s (2H, CH_2), 9.40 s (1H, 5-H), 10.26 s (1H, NH). Mass spectrum: *m*/*z* 413.11 $[M]^+$. Found, %: C 52.26; H 4.61; N 23.70; O 3.85; S 15.50. $C_{18}H_{19}N_7OS_2$. Calculated, %: C 52.28; H 4.63; N 23.71; O 3.87; S 15.51. *M* 413.52.

4-(2,9-Dimethyl-7,8,9,10-tetrahydro[1,2,4]triazolo[1″,5″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-*c*]-[2,7]naphthyridin-11-yl)morpholine (15). A mixture of compound **13** (1 g, 0.002 mol) and acetic anhydride (3 mL) was gently refluxed until the reaction was complete. After cooling, the solid product was filtered off. Yield 75%, yellow crystals, mp 235°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.06 s (3H, CH_3), 2.40 s (2H, CH_2), 2.70 t (4H, CH_2), 3.19 s (2H, CH_2), 3.54 t (4H, CH_2), 3.75 s (2H, CH_2), 9.61 s (1H, 5-H). Mass spectrum: *m*/*z* 395.47 $[M]^+$. Found, %: C 57.69; H 5.34; N 24.77; O 4.03; S 8.09. $C_{19}H_{21}N_7OS$. Calculated, %: C 57.70; H 5.35; N 24.79; O 4.05; S 8.11. *M* 395.49.

3-Methyl-5-(morpholin-4-yl)-1,2,3,4-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-*c*][2,7]naphthyridine-8,10(9*H*,11*H*)-dithione (16). A mixture of compound **11** (1 g, 0.003 mol) and carbon disulfide (0.23 g, 0.003 mol) in pyridine (4 mL) was refluxed in a steam bath for 4 h. The product was purified by recrystallization from ethanol. Yield 80%, orange crystals, mp 322–324°C. IR spectrum, ν, cm^{-1}: 3200, 3398 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.41 s (3H, CH_3), 2.70 t (6H, CH_2), 3.20 s (2H, CH_2), 3.47 d (4H, CH_2), 3.77 s (2H, CH_2), 12.70 s and 13.80 s (1H each, NH). Found, %: C 50.33; H 4.70; N 17.25; O 3.93; S 23.70. $C_{17}H_{19}N_5OS_3$. Calculated, %: C 50.35; H 4.72; N 17.27; O 3.94; S 23.72. *M* 405.55.

Diethyl 2,2′-{[3-methyl-5-(morpholin-4-yl)-1,2,3,4-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-*c*]-[2,7]naphthyridine-8,10-diyl]bis(sulfanediyl)}diacetate (17a). A mixture of compound **16** (0.5 g, 0.001 mol), ethyl chloroacetate (0.15 g, 0.001 mol), and anhydrous potassium carbonate (0.5 g, 0.003 mol) in ethanol was refluxed for 1 h. After cooling, the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 80%, pale yellow crystals, mp 133–134°C. IR spectrum: ν 1739 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.68 s (3H, CH_3), 1.18 t and 1.25 t (3H each, C**H**$_3$CH$_2$), 2.88 s (2H, CH_2), 4.04 q and 4.13 q (2H each, C**H**$_2$CH$_3$), 3.16–3.32 m (4H, CH_2), 3.70–3.85 m (4H, CH_2), 3.90 m and 3.96 m (4H, CH_2), 4.49 d and 4.53 d (2H each, SCH_2). ^{13}C NMR spectrum, δ_C, ppm: 14.21 (**C**H$_3$CH$_2$), 31.96 and 33.66 (SCH_2), 41.46 (3-CH_3), 49.42 (C^2), 51.23 ($C^{3'}$, $C^{5'}$), 50.46 (C^1, C^4), 61.88 and 62.20 (**C**H$_2$CH$_3$), 66.64 ($C^{2'}$, $C^{6'}$), 112.17 (C^5), 118.57 (C^{4a}), 122.56 (C^{11b}), 141.30 (C^{11c}), 154.81 (C^{6a}), 161.28 (C^{11a}), 165.78 (C^{7a}), 148.17 (C^{10}), 168.35 and 169.27 (C=O), 178.30 (C^8). Mass spectrum: *m*/*z* 577.03 $[M]^+$. Found, %: C 51.97; H 5.41; N 12.12; O 13.85; S 16.65. $C_{25}H_{31}N_5O_5S_3$. Calculated, %: C 51.97; H 5.41; N 12.12; O 13.85; S 16.65. *M* 577.73.

2,2′-{[3-Methyl-5-(morpholin-4-yl)-1,2,3,4-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-*c*][2,7]naphthyridine-8,10-diyl]bis(sulfanediyl)}bis(1-phenylethan-1-one) (17b). A mixture of compound **16** (0.5 g, 0.001 mol), phenacyl chloride (0.19 g, 0.001 mol), and anhydrous potassium carbonate (0.5 g, 0.003 mol) in ethanol was refluxed for 1 h. After cooling, the precipitate was filtered off, washed with ethanol, and recrystallized from ethanol. Yield 85%, yellow crystals, mp 230°C. IR spectrum: ν 1672 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.41 s (3H, CH_3), 3.20–3.77 m (14H, CH_2), 4.58 s and 4.80 s (2H each, SCH_2), 7.44 d and 7.54 d (2H each, H_{arom}), 7.97 d and 8.01 d (2H each, H_{arom}). Found, %: C 61.74; H 4.85; N 10.90; O 7.46; S 14.97. $C_{33}H_{31}N_5O_3S_3$. Calculated, %: C 61.76; H 4.87; N 10.91; O 7.48; S 14.99. *M* 641.82.

4-(8-Chloro-3-methyl-1,2,3,4-tetrahydro[1,2,3]-triazino[4′,5′:4,5]thieno[2,3-*c*][2,7]naphthyridin-5-yl)morpholine (18). A solution of sodium nitrite (2.3 g, 0.02 mol) in water (7.3 ml) was added dropwise over a period of 30 min to a suspension of compound **11** (2.3 g, 0.006 mol) in concentrated aqueous HCl (15 mL), cooled to 0–5°C. The mixture was stirred at 0–5°C for 2 h and then at room temperature overnight. The mixture was diluted with water (100 mL), and the solid product was filtered off, washed with water, and recrystallized from ethanol. Yield 90%, yellow crystals, mp 170°C. IR spectrum, ν, cm^{-1}: 2857, 2964 (C–H_{aliph}). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.06 s (3H, NCH_3), 2.67 t (4H, CH_2), 3.10 s (2H, CH_2), 3.36 t (4H, CH_2), 3.40 s (2H, CH_2), 3.75 s (2H, CH_2). Mass spectrum: *m*/*z* 376.31 $[M]^+$. Found, %: C 50.97; H 4.53; Cl 9.40; N 22.29; O 4.23; S 8.50. $C_{16}H_{17}ClN_6OS$. Calculated, %: C 50.99; H 4.55; Cl 9.41; N 22.30; O 4.25; S 8.51. *M* 376.86.

CONCLUSION

A series of novel fused polyheterocyclic 2,7-naphthyridine derivatives have been synthesized using 1-hydrazinyl-7-methyl-3-sulfanylidene-2,3,5,6,7,8-

hexahydro-2,7-naphthyridine-4-carbonitrile and 1-amino-7-methyl-5-(morpholin-4-yl)-6,7,8,9-tetrahydrothieno[2,3-*c*][2,7]naphthyridine-2-carbonitrile as key intermediate products, and their structure has been confirmed by IR, NMR, and mass spectra and elemental analyses. The synthesized compounds are promising as antimicrobial agents.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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