One-pot Synthesis of 1,6-Naphthyridines, Pyranopyridines and Thiopyranopyridines

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A one-step synthesis of [1,6]naphthyridine-2(1*H*)-thione (**3a**), pyrano[3,4-*b*]pyridine-2(1*H*)-thione (**3b**), thiopyrano[3,4-*b*]pyridine-2(1*H*)-thione (**3c**) and 6-oxoquinoline-2(1*H*)-thione (**3d**) through the reaction of benzylidene-cyanothioacetamide (**1**) with cyclic ketones **2a – d** is described. The reaction of **3a – d** with organyl chlorides yielded the 2-alkylthio-3-cyanopyridines **4a – p** which upon refluxing in ethanolic sodium ethoxide afforded the thieno[2,3-*b*]pyridine derivatives **5a – n**. Some of the synthesized compounds were screened for the activity against bacteria and fungi.

Key words: 1,6-Naphthyridine, Thienonaphthyridine, Pyranopyridine, Thiopyranopyridine

Introduction

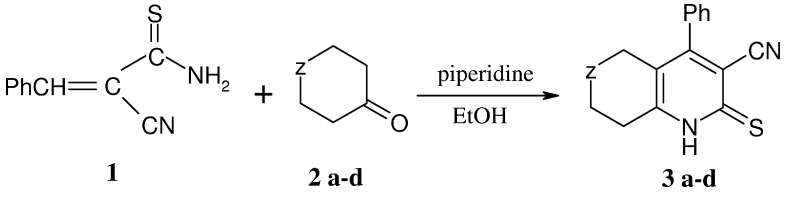
The synthesis of various derivatives of heterocyclic compounds including the 1,6-naphthyridine moiety has been reported in relation with their pharmaceutical activity [1 – 7]. Several 1,6-naphthyridines have general antibacterial activity [8] and curative power in cardiac insufficiencies and infarction [9]. Many 1,6-naphthyridine compounds display excellent anticonvulsant activity [10], and a novel class of macrocyclic 1,6-naphthyridines are anti-human cytomegalovirus (HCMV) inhibitors [11]. Derivatives bearing other substituents can exhibit potent antitumor activity, *viz.* topoisomerase I-targeting anticancer activity [12], and act as potent inhibitors of spleen tyrosine kinase (SYK) [13]. Also, they have been used as antiviral agents inhibiting both the strand transfer process of HIV-1 integrase and the viral replication in cells [14, 15].

The bronchodilator drug benafentrine has been developed based on 1,6-naphthyridine derivatives, which are phosphodiesterase III/V inhibitors [16]. Prompted by the important medicinal applications of naphthyridines and also as continuation of our work for the use of cyanothioacetamide for the synthesis of various heterocycles with interesting biological activities, herein we describe the synthesis and reactions of new 1,6-naphthyridines and thieno[2,3-*b*][1,6]naphthyridines [17 – 20].

Results and Discussion

Synthesis

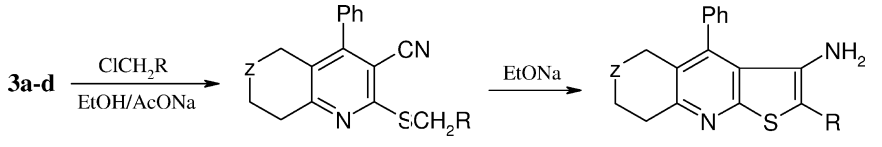
The reaction of benzylidene cyanothioacetamide (**1**) with cyclic ketones **2a – d** in ethanol containing a few drops of piperidine afforded the condensed 3-cyanopyridine-2(1*H*)-thiones **3a – d** in 38 – 55 % yield (Scheme 1). The structure assigned for **3a – d** was established on the basis of elemental analysis and spectral data. Thus, the IR spectrum of compound **3a** revealed bands at 3480 cm^{-1} (N–H vibration), 2220 cm^{-1} (C≡N) and 1260 cm^{-1} (C=S). The ^1H NMR spectrum showed a singlet at δ = 2.37 ppm for N–CH_3, two triplet signals at 2.68 and 2.87 ppm for two CH_2, a singlet at 3.1 ppm for N–CH_2 and a singlet at 12.9 ppm for NH groups (the latter exchangeable with D_2O) in addition to the signals for aromatic protons.



1 **2 a-d** **3 a-d**

2, 3	Z
a	N-CH_3
b	O
c	S
d	C=O

Scheme 1.

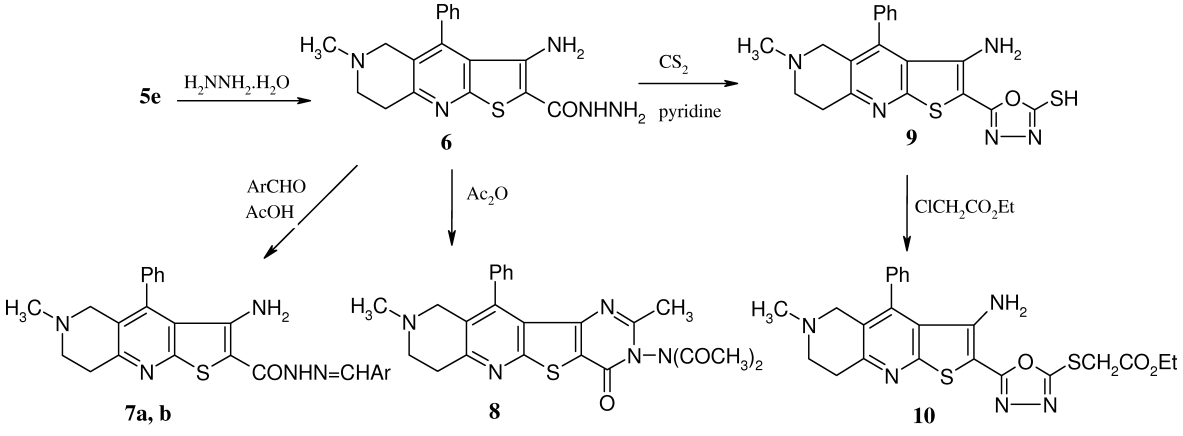


4a–p **5 a–n**

4, 5	Z	R
a	N-CH_3	$COCH_3$
b	CO	$COCH_3$
c	N-CH_3	COC_6H_5
d	N-CH_3	COC_6H_4-4-CH_3
e	N-CH_3	$CO_2C_2H_5$
f	CO	$CO_2C_2H_5$
g	S	$CO_2C_2H_5$
h	N-CH_3	$CONH_2$
i	CO	$CONH_2$
j	N-CH_3	$CONHC_6H_5$
k	N-CH_3	$CONHC_6H_4$-4-Cl
l	N-CH_3	$CONHC_6H_4$-4-OCH_3
m	S	$CONHC_6H_4$-4-OCH_3
n	N-CH_3	CN

4	Z	R
o	N-CH_3	H
p	N-CH_3	C_6H_5

Scheme 2.

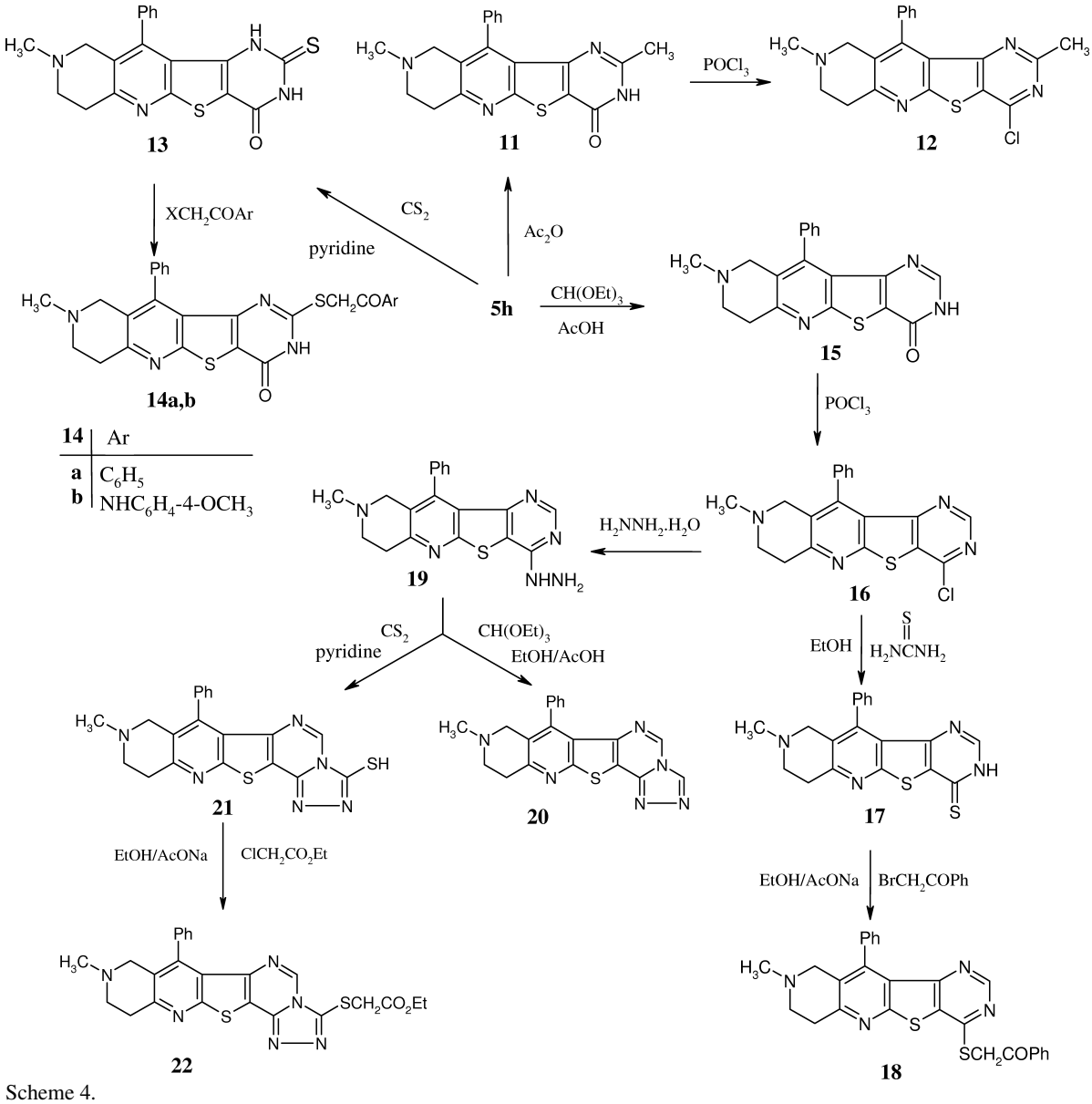


7a, R= C_6H_4-4-$N(CH_3)_2$
7b, R= C_6H_4-4-Cl

Scheme 3.

A series of *S*-alkylated derivatives **4a – p**, containing an active methylene group attached to the S atom, could be obtained *via* the interaction of **3a – d** with a variety of organyl chlorides in ethanol in presence of anhydrous sodium acetate (Scheme 2). Compounds **4a – p** undergo Thorpe-Ziegler cyclization when exposed to ethanolic sodium ethoxide, leading to the corresponding thieno-annulated heterocycles **5a – n**. The conversion of **4** to **5** was confirmed by the IR spectra of the cyclized products which revealed the disappearance of the cyano group absorption and the appearance of bands attributed to an NH_2 group.

Hydrazinolysis of amino ester **5e** with hydrazine hydrate in absolute ethanol afforded the corresponding carbohydrazide derivative **6**, which in turn was used as a precursor intermediate to produce other fused heterocyclic compounds (Scheme 3). Condensation of carbohydrazide **6** with aromatic aldehydes in refluxing ethanol yielded the corresponding carbohydrazone derivatives **7a,b** while its reaction with acetic anhydride afforded the diacetylaminopyrimidothienonaphthyridine derivative **8**. Refluxing of **6** with carbon disulfide in pyridine yielded the oxadiazolyl derivative **9**, which in turn was easily alkylated with ethyl chloroac-



Scheme 4.

etate in ethanol in the presence of sodium acetate to give the *S*-alkylated derivative **10**.

According to known examples of cyclization with *ortho*-amino-arenecarboxylic acid derivatives, *o*-aminothiophenecarboxamide **5h** was used to build up several pyrimidothienonaphthyridines (Scheme 4). Thus, reaction of **5h** with acetic anhydride afforded the pyrimidine compound **11** which upon refluxing with phosphorus oxychloride gave the corresponding 4-chloro derivative **12**. Another pyrimidine derivative **13** was obtained through the reaction of **5h** with carbon disulfide in pyridine. Compound **13** was reacted with phenacyl bromide or *p*-methoxy-chloroacetanilide to give compounds **14a** and **14b**, respectively.

Also, the reaction of **5h** with triethyl orthoformate in the presence of a catalytic amount of acetic acid led to the formation of the pyrimidothieno[2,3-*b*][1,6]naphthyridine derivative **15** which was easily transformed to the corresponding chloro compound **16** by refluxing in phosphorus oxychloride. The mercap-

topyrimidine derivative **17** was obtained through the reaction of the chloro compound **16** with thiourea in ethanol, which in turn was reacted with phenacyl bromide in ethanol catalyzed by anhydrous potassium carbonate to afford the benzoylmethylthio derivative **18**.

Furthermore, the chlorine atom in **16** underwent a nucleophilic displacement reaction when reacted with hydrazine hydrate to afford the hydrazino derivative **19**. The hydrazino compound **19** was used as a key intermediate to synthesize a new ring system, namely 7,8,9,10-tetrahydro[1,2,4]triazolo[4″,3″:1′,6′] pyrimido[4′,5′:4,5]-thieno[2,3-*b*][1,6]naphthyridine **20** or the thioxo derivative **21** through the reaction with triethyl orthoformate or carbon disulfide, respectively. Finally, the triazolethione **21** was reacted with ethyl chloroacetate in ethanol in the presence of anhydrous sodium acetate to give the thioester derivative **22**.

Biological activity

Some of the synthesized compounds were screened for their *in vitro* antimicrobial activity against four strains of bacteria (*Bacillus cereus*, *Escherichia coli*, *Serratia marcescens* and *Staphylococcus aureus*, reference is chloramphenicol) and six fungal species (*Aspergillus flavus*, *Aspergillus niger*, *Candida albicans*, *Geotrichum candidum*, *Scopulariopsis brevicaulis* and *Trichophyton rubrum*, reference is clotrimazole) using the filter paper disc method. As fungicide there is no activity of the tested compounds except compound **3a** which showed activity against *Candida albicans* and *Geotrichum candidum*, (8 mm inhibition zone for both), and compound **5k** against *Candida albicans* with 10 mm as inhibition zone. The antibacterial activity, as expressed by the growth of the inhibition zones of the tested microorganism, are summarized in Table 1. It is obvious that, as bactericides all the tested compounds showed activity against *Serratia marcescens*, and most of them showed activity against the rest of bacteria.

Table 1. The antimicrobial activity of selected compounds[a].

Compd. no.	*B. cereus*	*E. coli*	*S. marcescens*	*S. aureus*
3a	10	18	10	18
3b	12	6	8	–
3c	8	–	11	6
4e	–	6	7	6
4m	–	8	8	–
4o	–	–	7	–
4q	–	9	9	–
5d	7	–	9	–
5e	8	–	9	6
5f	–	6	9	6
5g	–	6	8	–
5h	9	7	8	6
5k	6	8	8	8
5n	–	–	8	–
12	7	7	6	6
16	8	–	8	–
18	6	–	8	6
19	9	–	8	–
20	–	–	9	–
Control	36	30	30	22

[a] The numbers express the growth of the inhibition zones of the tested microorganisms (diameter in mm).

Experimental Section

Melting points are uncorrected and were measured on a Gallenkamp apparatus. IR spectra were recorded on a Pye-Unicam SP3-100 spectrophotometer using KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 250 spectrometer. MS spectra were measured on a Jeol JMS-600 mass spectrometer. Elemental analyses were determined using a Perkin-Elmer 240C microanalyzer.

*2-Benzylidene-cyanothioacetamide (**1**)*

This compound was synthesized according to a literature procedure [21].

*3-Cyano-6-methyl-4-phenyl-5,6,7,8-tetrahydro[1,6]naphthyridine-2(1H)-thione, 3-cyano-4-phenyl-5,6,7,8-tetrahydropyrano[4,3-b]pyridine-2(1H)-thione, 3-cyano-4-phenyl-5,6,7,8-tetrahydrothiopyrano[4,3-b]pyridine-2(1H)-thione, and 3-cyano-6-oxo-4-phenyl-5,6,7,8-tetrahydroquinoline-2(1H)-thione (**3a**–**d**); general procedure*

A mixture of benzylidene-cyanothioacetamide **1** (1.87 g, 0.01 mol) and cyclic ketones **2a**–**d** (0.01 mol) in ethanol (30 mL) in the presence of a few drops of piperidine was refluxed for 1 h. The solid product separated from the hot mixture was filtered off and recrystallized from the appropriate solvent.

3a: Yellow crystals (dioxane). – M. p. 218 °C. – Yield 1.07 g (38 %). – IR (KBr): ν = 3480 (NH), 2220 (C≡N), 1130 (C=S) cm^{-1}. – ^{1}H NMR (250.13 MHz, [D$_6$]-DMSO, 25 °C, TMS): δ = 2.37 (s, 3 H, N–CH$_3$), 2.68 (t, J = 6 Hz, 2 H, CH$_2$), 2.87 (t, J = 5.6 Hz, 2 H, CH$_2$), 3.10 (s, 2 H, N–CH$_2$), 7.38 – 7.60 (m, 5 H, Ar-H), 12.90 (s, 1 H, NH). – MS (EI, 70 eV): *m/z* (%) = 281.67 (100) [M]$^+$. – C$_{16}$H$_{15}$N$_3$S (281.37): calcd. C 68.30, H 5.37, N 14.93, S 11.39; found C 68.22, H 5.48, N 14.85, S 11.50.

3b: Yellow crystals (dioxane). – M. p. 238 °C. – Yield 1.18 g (44 %). – IR (KBr): ν = 3170 (NH), 2220 (C≡N), 1135 (C=S) cm^{-1}. – ^{1}H NMR (250.13 MHz, [D$_6$]-DMSO, 25 °C, TMS): δ = 3.17 (t, J = 6 Hz, 2 H, CH$_2$), 3.90 (t, J =

6 Hz, 2 H, CH_2), 4.17 (s, 2 H, CH_2), 7.21 – 7.53 (m, 5 H, H-Ar), 13.70 (s, 1 H, NH). – MS (EI, 70 eV): *m/z* (%) = 268.51(100) $[M]^+$. – $C_{15}H_{12}N_2OS$ (268.33): calcd. C 67.14, H 4.51, N 10.44, S 11.95; found C 67.22, H 4.55, N 10.39, S 12.04.

3c: Yellow crystals (acetic acid). – M. p. 285 °C. – Yield 1.56 g (55 %). – IR (KBr): ν = 3170 (NH), 2220 (C≡N), 1140 (C=S) cm^{-1}. – ^1H NMR (250.13 MHz, $[D_6]$-DMSO, 25 °C, TMS): δ = 2.87 (t, *J* = 6.2 Hz, 2 H, CH_2), 3.08 (t, *J* = 6 Hz, 2 H, CH_2), 3.32 (s, 2 H, CH_2), 7.39 – 7.56 (m, 5 H, Ar-H), 14.45 (s, 1 H, NH). – ^{13}C NMR (63 MHz, $[D_6]$-DMSO): δ = 22.32, 25.60, 28.27 (all CH_2), 112.90 (C-3), 116.52 (C-4a), 118.64 (C≡N), 126.81, 128.44, 128.89, (all CH-Ar), 133.52 (C–C pyrid.), 151.32 (C–C-Ar), 155.29 (C-8a), 183.57 (C=S). – MS (EI, 70 eV): *m/z* (%) = 284.0 (100), 284.98 (11.1) $[M]^+$. – $C_{15}H_{12}N_2S_2$ (284.39): calcd. C 63.35, H 4.25, N 9.85, S 22.55; found C 63.27, H 4.19, N 9.94, S 22.67.

3d: Red crystals (dioxane). – M. p. > 300 °C. – Yield 1.42 g (51 %). – IR (KBr): ν = 3180 (NH), 2220 (C≡N), 1670 (C=O), 1140 (C=S) cm^{-1}. – ^1H NMR (250.13 MHz, $[D_6]$-DMSO, 25 °C, TMS): δ = 2.52 (t, *J* = 8 Hz, 2 H, CH_2), 2.80 (t, *J* = 8.2, 2 H, CH_2), 3.44 (s, 2 H, CH_2), 7.42 – 7.62 (m, 5 H, Ar-H), 12.87 (s, 1 H, NH). – MS (EI, 70 eV): *m/z* (%) = 280.45 (3.9) $[M]^+$. – $C_{16}H_{12}N_2OS$ (280.34): calcd. C 68.55, H 4.31, N 9.99, S 11.44; found C 68.67, H 4.38, N 10.07, S 11.36.

*Reaction of **3a – d** with different organyl chlorides. Formation of **4a – p**; general procedure*

A mixture of **3a – d** (0.01 mol) and the organic chloride (0.01 mol) in ethanol (30 mL) in the presence of anhydrous sodium acetate (2 g) was refluxed for 1 h, then cooled. The solid product was filtered off, washed with water and air dried. The physical properties and spectroscopic data are summarized in Table 2.

*Cyclization of compounds **4a – p**. Formation of thieno[2,3-b] pyridine derivatives **5a – n**; general procedure*

To a solution of **4a – p** (0.01 mol) in absolute ethanol (20 mL) were added a few drops of ethanolic sodium ethoxide, and the mixture was heated for 30 min. The solid product was filtered off and recrystallized from the appropriate solvent. The physical properties and spectral data are summarized in Table 2.

*3-Amino-6-methyl-4-phenyl-5,6,7,8-tetrahydrothieno[2,3-b] [1,6]naphthyridine-2-carbohydrazide (**6**)*

A mixture of the ester derivative **5e** (3.67 g, 0.01 mol) and hydrazine hydrate (2 mL, 0.04 mol) in ethanol (30 mL) was heated under reflux for 5 h, then cooled. The solid product was filtered off and recrystallized from ethanol to give yellow crystals of **6**. – M. p. 260 °C. – Yield 2.43 g (69 %). – IR (KBr): ν = 3480, 3350, 3300 (2 NH_2), 3250 (NH), 1680 (C=O) cm^{-1}. – ^1H NMR (250.13 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.30 (s, 3 H, N–CH_3), 2.54 (t, *J* = 6 Hz, 2 H, CH_2), 2.86 (t, *J* = 5.6, 2 H, CH_2), 3.12 (s, 2 H, CH_2), 4.40 (s, 2 H, NH_2), 5.6 (s, 2 H, NH_2), 7.45 – 7.68 (m, 5 H, Ar-H), 9.10 (s, 1 H, NH). – MS (EI, 70 eV): *m/z* (%) = 353.13 (100) $[M]^+$. – $C_{18}H_{19}N_5OS$ (353.44): calcd. C 61.17, H 5.42, N 19.81, S 9.07; found C 61.28, H 5.46, N 19.75, S 9.20.

*Arylidene 3-amino-6-methyl-4-phenyl-5,6,7,8-tetrahydrothieno[2,3-b][1,6]naphthyridine-2-carbohydrazones (**7a, b**); general procedure*

A mixture of the carbohydrazide **6** (350 mg, 1 mmol) and the appropriate aromatic aldehyde (1.2 mmol) in ethanol (30 mL) was heated under reflux for 4 h, then cooled. The solid product was collected by filtration and recrystallized from ethanol.

7a: Orange crystals. – M. p. 264 °C. – Yield 353 mg (73 %). – IR (KBr): ν = 3480, 3330 (NH_2), 3220 (NH), 1650 (C=O) cm^{-1}. – ^1H NMR (250.13 MHz, $[D_6]$-DMSO, 25 °C, TMS): δ = 2.17 (s, 3 H, N–CH_3), 2.53 (t, *J* = 6.2 Hz, 2 H, CH_2), 2.80 (s, 6 H, 2 N–CH_3), 2.90 (t, *J* = 5.6 Hz, 2 H, CH_2), 3.17 (s, 2 H, CH_2), 6.00 (s, 2 H, NH_2), 6.80 (d, *J* = 7.5, 2 H, 2CH), 7.30 (d, *J* = 7.2 Hz, 2 H, 2 CH), 7.50 (s, 5 H, Ar-H), 7.90 (s, 1 H, N=CH), 9.15 (s, 1 H, NH). – $C_{27}H_{28}N_6OS$ (484.62): calcd. C 66.92, H 5.82, N 17.34, S 6.62; found C 66.83, H 5.91, N 17.22, S 6.58.

7b: Yellow crystals. – M. p. 295 °C. – Yield 372 mg (71 %). – IR (KBr): ν = 3480, 3320 (NH_2), 3220 (NH), 1650 (C=O) cm^{-1}. – ^1H NMR (250.13 MHz, $[D_6]$-DMSO, 25 °C, TMS): δ = 2.53 (s, 3 H, N–CH_3), 2.97 (t, *J* = 6 Hz, 2 H, CH_2), 3.32 (t, *J* = 5.6 Hz, 4 H, 2 CH_2), 6.25 (s, 2 H, NH_2), 7.42 – 7.91 (m, 9 H, Ar-H), 8.14 (s,1 H, N=CH), 10.42 (s, 1 H, NH). – $C_{25}H_{22}ClN_5OS$ (475.99): calcd. C 63.08, H 4.66, Cl 7.45, N 14.71, S 6.74; found C 63.15, H 4.59, Cl 7.38, N 14.80, S 6.79.

*3-Diacetylamino-2,9-dimethyl-11-phenyl-7,8,9,10-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-b][1,6]-naphthyridin-4-one (**8**)*

A sample of compound **6** (1.06 g, 3 mmol) in acetic anhydride (10 mL) was heated under reflux for 3 h. The solvent was removed under reduced pressure, and the residue was triturated with cold ethanol. The solid product was collected and recrystallized from ethanol to give buff crystals of **8**. – M. p. 284 °C. – Yield 740 mg (54 %). – IR (KBr): ν = 1675 (C=O) cm^{-1}. – ^1H NMR (250.13 MHz, $[D_6]$-DMSO, 25 °C, TMS): δ = 2.05 (s, 6 H, 2 $COCH_3$), 2.30 (s, 3 H, N–CH_3), 2.48 (s, 3 H, CH_3), 2.73 (t, *J* = 5.6 Hz, 2 H, CH_2), 3.13

(t, J = 5.6 Hz, 2 H, CH_2), 3.28 (s, 2 H, CH_2), 7.30 – 7.50 (m, 5 H, Ar-H). – $C_{24}H_{23}N_5O_3S$ (461.54): calcd. C 62.46, H 5.02, N 15.17, S 6.95; found C 62.58, H 5.11, N 15.25, S 6.87.

*3-Amino-6-methyl-4-phenyl-2-(5-mercapto-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydrothieno[2,3-b][1,6]naphthyridine (**9**)*

A mixture of the carbohydrazide **6** (760 mg, 2 mmol) and carbon disulfide (4 mL) in pyridine (10 mL) was heated for 24 h on a steam bath. The solid product was collected, washed with ethanol and recrystallized from dioxane to give orange crystals of **9**. – M. p. 288 °C. – Yield 380 mg (48 %). – IR (KBr): ν = 3480, 3320 (NH_2) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.35 (s, 3 H, N–CH_3), 2.60 (t, J = 6 Hz, 2 H, CH_2), 2.84 (t, J = 5.6, 2 H, CH_2), 3.10 (s, 2 H, CH_2), 3.46 (s, 1 H, SH), 5.8 (s, 2 H, NH_2), 7.55 – 7.56 (m, 5 H, Ar-H). – $C_{19}H_{17}N_5OS_2$ (395.50): calcd. C 57.70, H 4.33, N 17.71, S 16.21; found C 57.82, H 4.41, N 17.63, S 16.08.

*3-Amino-6-methyl-4-phenyl-2-(5-ethoxycarbonylmethylthio-1,3,4-oxadiazol-2-yl)-5,6,7,8-tetrahydrothieno[2,3-b][1,6] naphthyridine (**10**)*

A mixture of the mercapto derivative **9** (390 mg, 1 mmol), ethyl chloroacetate (0.12 mL, 1 mmol) and fused sodium acetate (2 g) in ethanol (30 mL) was heated under reflux for 3 h then cooled. The solid product was filtered off, washed with water and recrystallized from ethanol to give yellow crystals of **10**. – M. p. 170 °C. – Yield 260 mg (55 %). – IR (KBr): ν = 3480, 3320 (NH_2), 1710 (C=O) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 1.20 (t, J = 8 Hz, 3 H, CH_3), 2.35 (s, 3 H, N–CH_3), 2.57 (t, J = 6 Hz, 2 H, CH_2), 2.95 (t, J = 6 Hz, 2 H, CH_2), 3.17 (s, 2 H, CH_2), 4.05 (s, 2 H, CH_2), 4.15 (q, J = 8 Hz, 2 H, CH_2), 5.60 (s, 2 H, NH_2), 7.43 – 7.66 (m, 5 H, Ar-Ar). – $C_{23}H_{23}N_5O_3S_2$ (481.59): calcd. C 57.36, H 4.81, N 14.54, S 13.31; found C 57.25, H 4.73, N 14.65, S 13.19.

*2,9-Dimethyl-11-phenyl-7,8,9,10-tetrahydropyrimido [4′,5′:4,5]thieno[2,3-b][1,6]naphthyridine-4(3H)-one (**11**)*

A mixture of **5h** (680 mg, 2 mmol) in acetic anhydride (20 mL) was refluxed for 5 h, the solvent was removed under reduced pressure, and the brown residue was triturated with ethanol. The solid product was collected and recrystallized from dioxane to give yellow crystals of **11**. – M. p. > 300 °C. – Yield 320 mg (45 %). – IR (KBr): ν = 3400 (NH), 1650 (C=O) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.10 (s, 3 H, N–CH_3), 2.60 (t, J = 5.6 Hz, 2 H, CH_2), 2.85 (s, 3 H, CH_3), 3.44 (t, J = 6 Hz, 2 H, CH_2), 4.04 (s, 2 H, CH_2), 7.30 – 7.54 (m, 5 H, Ar-H), 8.06 (s, 1 H, NH). – $C_{20}H_{18}N_4OS$ (362.45): calcd. C 66.28, H 5.01, N 15.46, S 8.85; found C 66.40, H 5.11, N 15.52, S 8.73.

*4-Chloro-2,9-dimethyl-11-phenyl-7,8,9,10-tetrahydro-pyrimido[4′,5′:4,5]thieno[2,3-b][1,6]naphthyridine (**12**)*

A mixture of the pyrimidinone derivative **11** (720 mg, 2 mmol) in phosphorus oxychloride (15 mL) was refluxed for 4 h, then cooled. The reaction mixture was poured into an ice/water mixture and neutralized with Na_2CO_3. The solid product was collected by filtration and recrystallized from ethanol to afford compound **12** as pale yellow crystals. – M. p. 285 °C. – Yield 500 mg (66 %). – IR (KBr): revealed no absorption for C=O. – ^{1}HNMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.21 (s, 3 H, N–CH_3), 2.64 (t, J = 5.6 Hz, 2 H, CH_2), 2.90 (s, 3 H, CH_3), 3.48 (t, J = 6 Hz, 2 H, CH_2), 4.10 (s, 2 H, CH_2), 7.28 – 7.62 (m, 5 H, Ar-H). – MS (EI, 70 eV): *m/z* (%) = 380.01 (100) $[M]^+$. – $C_{20}H_{17}ClN_4S$ (380.89): calcd. C 63.07, H 4.50, Cl 9.31, N 14.71, S 8.42; found C 62.98, H 4.58, Cl 9.22, N 14.66, S 8.55.

*9-Methyl-4-oxo-11-phenyl-1,2,3,4,7,8,9,10-octahydropyr-imido[4′,5′:4,5]thieno[2,3-b][1,6]-naphthyridine-2-thione (**13**)*

A sample of **5h** (680 mg, 2 mmol) and carbon disulfide (5 mL) in pyridine (15 mL) was heated on a water bath until the evolution of hydrogen sulfide ceased, then cooled. The solid product was filtered off, washed several times with ethanol and recrystallized from dioxane to afford orange crystals of **13**. – M. p. 275 °C. – Yield 350 mg (46 %). – IR (KBr): ν = 3380 (2br, 2NH), 1675 (C=O) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.35 (s, 3 H, N–CH_3), 2.80 (t, J = 6 Hz, 2 H, CH_2), 3.20 (t, J = 6 Hz, 2 H, CH_2), 3.90 (s, 2 H, CH_2), 7.30 – 7.72 (m, 5 H, Ar-H), 8.48, 8.60 (2 s, 2 H, 2 NH). – $C_{19}H_{16}N_4OS_2$ (380.48): calcd. C 59.98, H 4.24, N 14.73, S 16.85; found C 60.10, H 4.31, N 14.67, S 17.11.

*2-Benzoylmethylthio-9-methyl-11-phenyl-7,8,9,10-tetra-hydropyrimido[4′,5′:4,5]thieno[2,3-b][1,6]-naphthyridine-4(3H)-one (**14a**) and 9-methyl-2-(4′-methoxyphenylamino-carbonylmethylthio)-11-phenyl-7,8,9,10-tetrahydropyrimido [4′,5′:4,5]-thieno[2,3-b][1,6]naphthyridine-4(3H)-one (**14b**)*

A mixture of the pyrimidinethione derivative **13** (380 mg, 1 mmol), phenacyl bromide or 4-methoxy-chloroacetanilide (1 mmol) and fused sodium acetate (2 g) in ethanol (50 mL) was refluxed for 2 h. On cooling, the precipitated solid was collected, washed with water and recrystallized from ethanol to give **14a** and **14b**, respectively.

14a: Pale yellow crystals. – M. p. 225 °C. – Yield 340 mg (68 %). – IR (KBr): ν = 3400 (NH), 1675, 1650 (2

C=O) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.30 (s, 3 H, N–CH_3), 2.70 (t, J = 6 Hz, 2 H, CH_2), 3.10 (t, J = 6 Hz, 2 H, CH_2), 3.85 (s, 2 H, CH_2), 4.20 (s, 2 H, CH_2), 7.20 – 7.70 (m, 10 H, Ar-H), 8.60 (s, 1 H, NH). – $C_{27}H_{22}N_4O_2S_2$ (498.62): calcd. C 65.04, H 4.45, N 11.24, S 12.86; found C 65.17, H 4.53, N 11.13, S 12.97.

14b: Yellow crystals. – M. p. 216 °C. – Yield 330 mg (61 %). – IR (KBr): ν = 3380, 3300 (2 NH), 1650 (C=O) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.25 (s, 3 H, N–CH_3), 2.66 (t, J = 6 Hz, 2 H, CH_2), 3.17 (t, J = 6 Hz, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 4.10 (s, 2 H, CH_2), 4.26 (s, 2 H, CH_2), 6.80 – 7.72 (m, 9 H, Ar-H), 8.40, 9.67 (2 s, 2 H, 2 NH). – $C_{28}H_{25}N_5O_3S_2$ (543.66): calcd. C 61.86, H 4.63, N 12.88, S 11.79; found C 61.75, H 4.59, N 12.86, S 11.60.

*9-Methyl-11-phenyl-7,8,9,10-tetrahydropyrimido[4′,5′:4,5] thieno[2,3-b][1,6]naphthyridine-4(3H)-one (**15**)*

To a mixture of **5h** (1.7 g, 5 mmol) and triethyl orthoformate (10 mL), a few drops of acetic acid were added. The reaction mixture was heated under reflux for 2 h. The solid product separated from the hot mixture was collected and recrystallized from dioxane to afford **15** as pale yellow crystals. – M. p. 268 °C. – Yield 1.37 g (79 %). – IR (KBr): ν = 3430 (NH), 1655 (C=O) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.10 (s, 3 H, N–CH_3), 2.70 (t, J = 5.6 Hz, 2 H, CH_2), 3.20 (t, J = 6 Hz, 2 H, CH_2), 3.35 (s, 2 H, CH_2), 7.30 – 7.60 (m, 5 H, Ar-H), 7.88 (s, 1 H, NH), 8.00 (s, 1 H, CH). – MS (EI, 70 eV): *m/z* (%) = 347.81 (0.3) $[M]^+$. – $C_{19}H_{16}N_4OS$ (348.42): calcd. C 65.51, H 4.63, N 16.08, S 9.20; found C 65.76, H 4.69, N 16.16, S 8.99.

*4-Chloro-9-methyl-11-phenyl-7,8,9,10-tetrahydropyrimido [4′,5′:4,5]thieno[2,3-b][1,6]naphthyridine (**16**)*

A mixture of the pyrimidinone derivative **15** (1 g, 3 mmol) in phosphorus oxychloride (15 mL) was refluxed for 4 h, then cooled. The reaction mixture was poured into an ice/water mixture and neutralized with Na_2CO_3. The solid product was collected by filtration and recrystallized from dioxane to afford **16** as pale yellow crystals. – M. p. 186 °C. – Yield 600 mg (55 %). – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.16 (s, 3 H, N–CH_3), 2.54 (t, J = 5.6 Hz, 2 H, CH_2), 3.33 (t, J = 6 Hz, 2 H, CH_2), 3.50 (s, 2 H, CH_2), 7.38 – 7.50 (m, 5 H, Ar-H), 8.20 (s, 1 H, CH). – MS (EI, 70 eV): *m/z* (%) = 366.18 (100) $[M]^+$. – $C_{19}H_{15}ClN_4S$ (366.87): calcd. C 62.20, H 4.12, Cl 9.66, N 15.27, S 8.74; found C 62.31, H 4.15, Cl, 9.53, N 15.15, S 8.88.

*9-Methyl-11-phenyl-7,8,9,10-tetrahydropyrimido[4′,5′:4,5] thieno[2,3-b][1,6]naphthyridine-4(3H)-thione (**17**)*

A mixture of the chloro compound **16** (370 mg, 1 mmol) and thiourea (100 mg, 1.3 mmol) in dry ethanol (50 mL) was heated under reflux for 12 h. The solid product was filtered off, washed with water and recrystallized from dioxane to afford yellow crystals of **17**. – M. p. 230 °C. – Yield 230 mg (62 %). – IR (KBr): ν = 3250 (NH) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.77 (s, 3 H, N–CH_3), 3.30 (m, 4 H, 2 CH_2), 4.17 (s, 2 H, CH_2), 7.13 – 7.53 (m, 6 H, Ar-H + NH), 8.20 (s, 1 H, CH). – MS (EI, 70 eV): *m/z* (%) = 364.99 (31.6) $[M]^+$. – $C_{19}H_{16}N_4S_2$ (364.48): calcd. C 62.61, H 4.42, N 15.37, S 17.59; found C 62.72, H 4.39, N 15.26, S 17.52.

*4-Benzoylmethylthio-9-methyl-11-phenyl-7,8,9,10-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-b][1,6] naphthyridine (**18**)*

A mixture of compound **17** (360 mg,1 mmol), phenacyl bromide (200 mg, 1 mmol) and anhydrous potassium carbonate (2 g) in ethanol (50 mL) was refluxed for 1 h, then filtered while hot. The solid product was collected, washed with cold water and recrystallized from ethanol to form yellow crystals of **18**. – M. p. 244 °C. – Yield 280 mg (58 %). – IR (KBr): ν = 1680 (C=O) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.56 (s, 3 H, N–CH_3), 3.26 (m, 4 H, 2 CH_2), 3.85 (s, 2 H, CH_2), 4.10 (s, 2 H, CH_2), 7.2 – 7.64 (m, 10 H, Ar-H), 8.20 (s, 1 H, CH). – $C_{27}H_{22}N_4OS_2$ (482.62): calcd. C 67.20, H 4.59, N 11.62, S 13.29; found C 67.05, H 4.70, N 11.54, S 13.25.

*4-Hydrazino-9-methyl-11-phenyl-7,8,9,10-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-b][1,6]naphthyridine (**19**)*

A mixture of the chloro derivative **16** (1.1 g, 3 mmol) and hydrazine hydrate (0.3 mL, 6 mmol) in ethanol (50 mL) was refluxed for 30 min. The precipitate which separated from the hot mixture was filtered off and recrystallized from dioxane to form yellow crystals of **19**. – M. p. 262 °C. – Yield 610 mg (57 %). – IR (KBr): ν = 3300, 3200 ($NHNH_2$) cm^{-1}. – ^1H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.40 (s, 3 H, N–CH_3), 2.97 (t, J = 6 Hz, 2 H, CH_2), 3.32 (t, J = 5.6 Hz, 2 H, CH_2), 3.60 (s, 2 H, CH_2), 4.15 (s, 2 H, NH_2), 7.42 – 7.91 (m, 5 H, Ar-H), 7.82 (s, 1 H, NH), 8.22 (s, 1 H, CH). – MS (EI, 70 eV): *m/z* (%) = 362.01 (86.3) $[M]^+$. – $C_{19}H_{18}N_6S$ (362.45): calcd. C 62.96, H 5.01, N 23.19, S 8.85; found C 63.05, H 5.07, N 23.31, S 8.79.

*9-Methyl-7-phenyl-8,9,10,11-tetrahydro[1,2,4]triazolo [4″,3″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b][1,6]-naphthyridine (**20**)*

A mixture of **19** (360 mg, 1 mmol) and triethyl orthoformate (10 mL) containing a few drops of acetic acid was refluxed for 3 h. The solid product was filtered off and recrystallized from acetic acid to afford buff crystals of **20**. – M. p. 251 °C. – Yield 190 mg (52 %). – The IR (KBr) spectra re-

Table 2. Physical and spectral data for compounds **4a – p** and **5a – n**.

No.	Molecular formula (M_r)	m. p. (°C) (solvent)	Yield (%) (color)	Analytical data (calcd./found) C	H	N	S	IR (ν, cm^{-1})	^{1}H NMR (δ, ppm)	MS (*m/z*, %)
4a	$C_{19}H_{19}N_3OS$ (337.44)	160 (ethanol)	59 (pale-yellow)	67.63 67.50	5.68 5.61	12.45 12.34	9.50 9.41	2200 (CN), 1720 (CO)	$CDCl_3$: 2.26 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3) 2.68 (t, J = 5.6 Hz, 2 H, CH_2), 2.99 (t, J = 6.2 Hz, 2 H, CH_2), 3.26 (s, 2 H, CH_2), 4.20 (s, 2 H, CH_2), 7.32 – 7.55 (m, 5 H, Ar-H)	337.61 (100)
4b	$C_{19}H_{16}N_2O_2S$ (336.41)	230 (ethanol)	55 (pale-green)	67.84 67.73	4.79 4.68	8.33 8.21	9.53 9.45	2200 (CN), 1690 (CO)	($CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 2.62 (t, J = 6 Hz, 2 H, CH_2), 2.76 (t, J = 6.2, 2 H, CH_2), 3.44 (s, 2 H, CH_2), 3.95 (s, 2 H, CH_2), 7.46 – 7.58 (m, 5 H, Ar-H)	
4c	$C_{24}H_{21}N_3OS$ (399.51)	135 (ethanol)	78 (yellow)	72.15 71.98	5.30 5.19	10.52 10.62	8.02 8.14	2200 (CN), 1680 (CO)	[D_6]-DMSO: 2.28 (s, 3 H, CH_3), 2.54 – 2.70 (m, 4 H, 2 CH_2), 3.22 (s, 2 H, CH_2), 4.60 (s, 2 H, CH_2), 7.20 – 8.15 (m, 10 H, Ar-H)	399.14 (100)
4d	$C_{25}H_{23}N_3OS$ (413.54)	163 (ethanol)	60 (pale-yellow)	72.61 72.51	5.61 5.56	10.16 10.26	7.75 7.66	2210 (CN), 1680 (CO)	$CDCl_3$: 2.35 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 2.65 (t, J = 6.4 Hz, 2 H, CH_2), 3.14 – 3.25 (m, 4 H, 2CH_2), 4.40 (s, 2 H, CH_2), 7.25 – 7.8 (m, 9 H, Ar-H)	
4e	$C_{20}H_{21}N_3O_2S$ (367.46)	106 (ethanol)	78 (yellow)	65.37 65.49	5.76 5.71	11.44 11.57	8.72 8.82	2220 (CN), 1740 (CO)	[D_6]-DMSO: 1.22 (t, J = 8 Hz, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 2.67 (t, J = 6 Hz, 2 H, CH_2), 2.95 (t, 2 H, J = 6 Hz, CH_2), 3.17 (s, 2 H, CH_2), 4.10 (s, 2 H, CH_2), 4.14 (q, J = 8 Hz, 2 H, CH_2), 7.40 – 7.57 (m, 5 H, Ar-H)	367.12 (100)
4f	$C_{19}H_{18}N_2O_3S$ (354.42)	110 (ethanol/H_2O)	82 (pale-yellow)	64.39 64.5	5.12 5.20	7.90 7.95	9.05 9.17	2220 (CN), 1745 (CO)	$CDCl_3$: 1.20 (t, J = 8 Hz, 3 H, CH_3), 2.94 (t, J = 6 Hz, 2 H, CH_2), 3.96 (s, 2 H, CH_2), 3.99 (t, J = 5.6 Hz, 2 H, CH_2), 4.18 (q, 2 H, J = 8 Hz, CH_2), 4.40 (s, 2 H, CH_2), 7.18 – 7.55 (m, 5 H, Ar-H)	
4g	$C_{19}H_{18}N_2O_2S_2$ (370.48)	95 (ethanol)	80 (yellow)	61.60 61.71	4.90 4.82	7.56 7.43	17.31 17.49	2220 (CN), 1735 (CO)	$CDCl_3$: 1.20 (t, J = 7.2 Hz, 3 H, CH_3), 2.82 (t, J = 5.4 Hz, 2 H, CH_2), 3.14 (t, J = 5.6 Hz, 2 H, CH_2), 3.45 (s, 2 H, CH_2), 3.95 (s, 2 H, CH_2), 4.10 (q, J = 7.2 Hz, 2 H, CH_2), 7.15 – 7.60 (m, 5 H, Ar-H)	370.09 (87.4)
4h	$C_{18}H_{18}N_4OS$ (338.43)	210 (ethanol)	77 (pale-yellow)	63.88 64.03	5.36 5.47	16.56 16.70	9.47 9.33	3350, 3180 (NH_2), 2220 (CN), 1660 (CO)	[D_6]-DMSO: 2.40 (s, 3 H, CH_3), 2.75 (t, J = 5.6 Hz, 2 H, CH_2), 3.10 (t, J = 5.6 Hz, 2 H, CH_2), 3.44 (s, 2 H, CH_2), 4.00 (s, 2 H, CH_2), 6.90 (s, 2 H, NH_2), 7.20 – 7.60 (m, 5 H, Ar-H)	
4i	$C_{18}H_{15}N_3O_2S$ (337.39)	216 (dioxane)	63 (orange)	64.08 64.19	4.48 4.59	12.45 12.42	9.50 9.61	3450, 3350 (NH_2), 2200 (CN), 1660 (CO)	[D_6]-DMSO: 2.45 (s, 2 H, CH_2), 2.70 (t, J = 6 Hz, 2 H, CH_2), 3.44 (t, J = 5.6 Hz, 2 H, CH_2), 3.86 (s, 2 H, CH_2), 5.80 (s, 2 H, NH_2), 7.33 – 7.60 (m, 5 H, Ar-H)	
4j	$C_{24}H_{22}N_4OS$ (414.52)	156 (ethanol)	54 (yellow)	69.54 69.42	5.35 5.2	13.52 13.41	7.73 7.68	3180 (NH), 2220 (CN), 1690 (CO)	$CDCl_3$: 2.27 (s, 3 H, CH_3), 2.62 (t, J = 6 Hz, 2 H, CH_2), 3.00 (t, J = 6 Hz, 2 H, CH_2), 3.18 (s, 2 H, CH_2), 3.90 (s, 2 H, CH_2), 7.03 – 7.50 (m,10 H, Ar-H), 9.17 (s, 1 H, NH)	
4k	$C_{24}H_{21}ClN_4OS$ (448.97)	202 (ethanol)	77 (yellow)	64.21 64.32	4.71 4.65	12.48 12.36	7.14 7.19	3250 (NH), 2200 (CN), 1670 (CO)	$CDCl_3$: 2.30 (s, 3 H, CH_3), 2.71 (t, J = 4 Hz, 2 H, CH_2), 3.08 (t, J = 4 Hz, 2 H, CH_2), 3.20 (s, 2 H, CH_2), 3.98 (s, 2 H, CH_2), 7.23 – 7.50 (m, 9 H, Ar-H), 9.18 (s, 1 H, NH)	
				Cl: calcd. 7.90; found 8.02						
4l	$C_{25}H_{24}N_4O_2S$ (444.55)	193 (ethanol)	81 (yellow)	67.55 67.46	5.44 5.52	12.60 12.51	7.21 7.19	3280 (NH), 2220 (CN)	$CDCl_3$: 2.32 (s, 3 H, CH_3), 2.55 (t, J = 5.6 Hz, 2 H, CH_2), 3.10 (t, J = 6 Hz, 2 H, CH_2), 3.18 (s, 2 H, CH_2), 3.76 (s, 3 H, CH_3), 3.95 (s, 2 H, CH_2), 6.76 – 7.55 (m, 9 H, Ar-H), 9.02(s, 1 H, NH)	
4m	$C_{24}H_{21}N_3O_2S_2$ (447.57)	190 (ethanol)	76 (white)	64.41 64.33	4.73 4.62	9.39 9.27	14.33 14.25	3250 (NH), 2220 (CN), 1650 (CO)	$CDCl_3$: 2.76 (t, J = 5.6 Hz, 2 H, CH_2), 3.10 (t, J = 6 Hz, 2 H, CH_2), 3.30 (s, 2 H, CH_2), 3.60 (s, 3 H, CH_3), 3.80 (s, 2 H, CH_2), 6.63 – 7.38 (m, 9 H, H-Ar), 8.64 (s, 1 H, NH)	
4n	$C_{18}H_{16}N_4S$ (320.41)	134 (ethanol)	58 (yellow)	67.48 67.40	5.03 4.95	17.49 17.55	10.01 9.50	2220 (CN)	$CDCl_3$: 2.35 (s, 3 H, CH_3), 2.72 (t, J = 6 Hz, 2 H, CH_2), 3.11 (t, J = 6 Hz, 2 H, CH_2), 3.20 (s, 2 H, CH_2), 4.05 (s, 2 H, CH_2), 7.23 – 7.50 (m, 5 H, Ar-H).	320.38 (76.1)
4o	$C_{17}H_{17}N_3S$ (295.40)	268 (dioxane)	81 (pale-yellow)	69.12 69.23	5.80 5.91	14.22 14.03	10.85 10.94	2220 (CN)	[D_6]-DMSO: 2.50 (s, 3 H, CH_3), 3.15 (s, 3 H, CH_3), 3.32 (t, J = 6 Hz, 2 H, CH_2), 3.50 (t, J = 6.2 Hz, 2 H, CH_2), 4.28 (s, 2 H, CH_2), 7.40 – 7.60 (m, 5 H, Ar-H)	295.67 (100)
4p	$C_{23}H_{21}N_3S$ (371.50)	140 (ethanol)	65 (pale-yellow)	74.36 74.25	5.70 5.59	11.31 11.37	8.63 8.54	2220 (CN)	$CDCl_3$: 2.35 (s, 3 H, CH_3), 2.70 (t, J = 5.6 Hz, 2 H, CH_2), 3.00 (t, J = 6 Hz, 2 H, CH_2), 3.30 (s, 2 H, CH_2), 4.54 (s, 2 H, CH_2), 7.30 – 8.15 (m,10 H, Ar-H)	

Table 2. Physical and spectral data for compounds **4a – p** and **5a – n** (cont.)

No.	Molecular formula	m. p. (°C)	Yield (%)	Analytical data (calcd./found)				IR	^{1}H NMR (δ, ppm)	MS
	(M_r)	(solvent)	(color)	C	H	N	S	(ν, cm^{-1})		(m/z, %)
5a	$C_{19}H_{19}N_3OS$	164	82	67.63	5.68	12.45	9.50	3480, 3300 (NH_2), 1630	$CDCl_3$: 2.05 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 2.49 (t, J = 6 Hz, 2 H, CH_2), 2.95	
	(337.44)	(ethanol)	(orange)	67.71	5.75	12.54	9.42	(CO)	(t, J = 5.6 Hz, 2 H, CH_2), 3.10 (s, 2 H, CH_2), 6.10 (s, 2 H, NH_2), 7.10 – 7.40 (m, 5 H, Ar-H)	
5b	$C_{19}H_{16}N_2O_2S$	190	75	67.84	4.79	8.33	9.53	3450, 3300 (NH_2), 1650	[D_6]-DMSO: 2.16 (s, 3H, CH_3), 2.39 (t, 2H, J = 5.5 Hz, CH_2), 3.08 (t, 2H, J =	
	(336.41)	(ethanol)	(orange)	67.90	4.83	8.27	9.41	(CO)	5.6 Hz, CH_2), 3.25 (s, 2H, CH_2), 5.80 (s, 2H, NH_2), 7.10 – 7.40 (m, 5H, Ar-H).	
5c	$C_{24}H_{21}N_3OS$	200	77	72.15	5.30	10.52	8.02	3450, 3280 (NH_2), 1640	[D_6]-DMSO: 2.10 (s, 3 H, CH_3), 2.73 (t, 2 H, J = 6 Hz, CH_2), 2.89 (t, J = 6 Hz,	399.21 (78.9)
	(399.51)	(dioxane)	(orange)	72.30	5.22	10.65	7.87	(CO)	2 H, CH_2), 2.96 (s, 2 H, CH_2), 6.50 (s, 2 H, NH_2), 7.28 – 7.55 (m, 10 H, Ar-H)	
5d	$C_{25}H_{23}N_3OS$	211	69	72.61	5.61	10.16	7.75	3450, 3270 (NH_2), 1640	$CDCl_3$: 2.33 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 2.70 (t, J = 6.4 Hz, 2 H, CH_2),	
	(413.54)	(ethanol)	(orange)	72.49	5.45	10.11	7.69	(CO)	3.15 – 3.25 (m, 4 H, 2 CH_2), 6.50 (s, 2 H, NH_2), 7.20 – 7.80 (m, 9 H, Ar-H)	
5e	$C_{20}H_{21}N_3O_2S$	188	77	65.37	5.76	11.44	8.72	3450, 3320 (NH_2), 1670	$CDCl_3$: 1.24 (t, J = 7.2 Hz, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 2.70 (t, J = 6 Hz, 2 H,	367.1 (100)
	(367.46)	(ethanol)	(yellow)	65.45	5.69	11.41	8.65	(CO)	CH_2), 3.14 (m, 4 H, 2 CH_2), 4.18 (q, J = 7.2 Hz, 2 H, CH_2), 5.28 (s, 2 H, NH_2),	
									7.19 – 7.48 (m, 5 H, Ar-H)	
5f	$C_{19}H_{18}N_2O_3S$	256	80	64.39	5.12	7.90	9.05	3490, 3350 (NH_2), 1670	$CDCl_3$: 1.23 (t, J = 7.2 Hz, 3 H, CH_3), 3.10 (t, J = 6 Hz, 2 H, CH_2), 3.90 (t, J =	353.98 (100)
	(354.42)	(acetic acid)	(yellow)	64.48	5.23	7.79	9.13	(CO)	5.6 Hz, 2 H, CH_2), 4.17 (q, J = 7.2 Hz, 2 H, CH_2), 4.40 (s, 2 H, CH_2), 5.30 (s, 2 H,	
									NH_2), 7.20 – 7.60 (m, 5 H, Ar-H)	
5g	$C_{19}H_{18}N_2O_2S_2$	212	72	61.60	4.90	7.56	17.31	3460, 3340 (NH_2), 1660	[D_6]-DMSO: 1.10 (t, J = 8 Hz, 3 H, CH_3), 2.84 (t, J = 5.6 Hz, 2 H, CH_2), 3.38 (m,	
	(370.48)	(acetic acid)	(yellow)	61.54	4.34	7.62	17.29	(CO)	4 H, 2 CH_2), 3.95 (q, J = 7.2 Hz, 2 H, CH_2), 5.28 (s, 2 H, NH_2), 7.15 – 7.8 (m, 5 H,	
									Ar-H)	
5h	$C_{18}H_{18}N_4OS$	276	77	63.88	5.36	16.56	9.47	3450, 3320, 3150	[D_6]-DMSO: 2.25 (s, 3 H, CH_3), 2.70 (t, J = 6 Hz, 2 H, CH_2), 3.10 (t, J = 6 Hz,	338.07 (100)
	(338.43)	(dioxane)	(orange)	64.01	5.42	16.48	9.55	(2NH_2), 1650 (CO)	2 H, CH_2), 3.25 (s, 2 H, CH_2), 5.55 (s, 2 H, NH_2), 6.29 (s, 2 H, NH_2), 7.30 – 7.63	
									(m, 5 H, Ar-H)	
5i	$C_{18}H_{15}N_3O_2S$	280	56	64.08	4.48	12.45	9.50	3480, 3320, 3190	[D_6]-DMSO: 2.76 (t, J = 6 Hz, 2 H, CH_2), 3.22 (t, J = 6 Hz, 2 H, CH_2), 3.31 (s,	
	(337.39)	(dioxane)	(yellow)	64.17	4.55	12.59	9.37	(2NH_2), 1630 (CO)	2 H, CH_2), 5.60 (s, 2 H, NH_2), 6.08 (s, 2 H, NH_2), 7.24 – 7.59 (m, 5 H, Ar-H).	
5j	$C_{24}H_{22}N_4OS$	210	66	69.54	5.35	13.52	7.73	3450, 3320 (NH_2), 3200	$CDCl_3$: 2.30 (s, 3 H, CH_3), 2.75 (t, J = 5.6 Hz, 2 H, CH_2), 3.15 (t, J = 6 Hz, 2 H,	
	(414.52)	(ethanol)	(yellow)	69.47	5.41	13.60	7.68	(NH), 1620 (CO)	CH_2), 3.25 (s, 2 H, CH_2), 5.70 (s, 2 H, NH_2), 7.20 – 7.70 (m, 11 H, Ar-H + NH)	
5k	$C_{24}H_{21}ClN_4OS$	160	76	64.21	4.71	12.48	7.14	3450, 3310 (NH_2), 3200	$CDCl_3$: 2.40 (s, 3 H, CH_3), 2.78 (t, J = 6 Hz, 2 H, CH_2), 3.22 (m, 4 H, 2 CH_2),	
	(448.97)	(ethanol)	(yellow)	64.33	4.76	12.57	7.24	(NH), 1680, 1625 (2CO)	5.70 (s, 2 H, NH_2), 7.20 – 7.58 (m, 9 H, Ar-H), 9.10 (s, 1 H, NH)	
				Cl: calcd. 7.90; found 7.98						
5l	$C_{25}H_{24}N_4O_2S$	250	77	67.55	5.44	12.60	7.21	3480, 3320 (NH_2), 3200	$CDCl_3$: 2.30 (s, 3 H, CH_3), 2.73 (t, J = 6 Hz, 2 H, CH_2), 3.16 (t, 2 H, J = 6 Hz,	
	(444.55)	(ethanol)	(yellow)	67.42	5.39	12.51	7.17	(NH), 1680 (CO)	CH_2), 3.35 (s, 2 H, CH_2), 3.65 (s, 3 H, CH_3), 5.50 (s, 2 H, NH_2), 6.80 – 7.78 (m,	
									9 H, Ar-H) 9.27 (s, 1 H, NH)	
5m	$C_{24}H_{21}N_3O_2S_2$	236	69	64.41	4.73	9.39	14.33	3485, 3360 (NH_2), 3050	[D_6]-DMSO: 2.48 (t, J = 5.6 Hz, 2 H, CH_2), 2.89 (t, J = 6 Hz, 2 H, CH_2), 3.36 (s,	
	(447.57)	(ethanol)	(yellow)	64.49	4.77	9.31	14.40	(NH), 1650 (CO)	2 H, CH_2), 3.73 (s, 3 H, CH_3), 6.40 (s, 2 H, NH_2), 6.67 – 7.52 (m, 9 H, Ar-H), 9.33	
									(s, 1 H, NH)	
5n	$C_{18}H_{16}N_4S$	180	68	67.48	5.03	17.49	10.01	3450, 3320 (NH_2), 2200	$CDCl_3$: 2.28 (s, 3 H, CH_3), 2.68 (t, J = 6 Hz, 2 H, CH_2), 3.11 (t, J = 6 Hz, 2 H,	
	(320.41)	(ethanol)	(yellow)	67.42	5.11	17.61	10.11	(CN)	CH_2), 3.28 (s, 2 H, CH_2), 5.88 (s, 2 H, NH_2), 7.20 – 7.50 (m, 5 H, Ar-H)	

vealed the disappearance of bands for a ($NHNH_2$) group. – ^{1}H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.30 (s, 3 H, CH_3), 2.70 (t, J = 6 Hz, 2 H, CH_2), 3.10 (t, J = 5.6 Hz, 2 H, CH_2), 3.42 (s, 2 H, CH_2), 7.20 – 7.62 (m, 5 H, Ar-H), 8.40, 8.80 (2s, 2 H, 2 CH). – MS (EI, 70 eV): *m/z* (%) = 372.00 (97) $[M]^+$. – $C_{20}H_{16}N_6S$ (372.45): calcd. C 64.50, H 4.33, N 22.56, S 8.61; found C 64.37, H 4.39, N 22.6, S 8.55.

*9-Methyl-7-phenyl-8,9,10,11-tetrahydro[1,2,4]triazolo [4″,3″:1′,6′]pyrimido[4′,5′:4,5]thieno[2,3-b]-[1,6]naphthyridine-3(2H)-thione (**21**)*

A mixture of the hydrazino derivative **19** (720 mg, 2 mmol) and carbon disulfide (5 mL) in pyridine (20 mL) was heated on a water bath for 24 h, then cooled. The solid product was filtered off and recrystallized from dioxane to form orange crystals of **21**. – M. p. 255 °C. – Yield 370 mg (46 %). – IR (KBr): ν = 3400 (NH) cm^{-1}. – ^{1}H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 2.35 (s, 3 H, N–CH_3), 2.85 (m, 4 H, 2 CH_2), 3.30 (s, 2 H, CH_2), 7.22 – 7.71 (m, 5 H, Ar-H), 8.40 (s, 1 H, CH), 9.10 (s, 1 H, NH). – $C_{20}H_{16}N_6S_2$ (404.51): calcd. C 59.39, H 3.99, N 20.78, S 15.85; found C 59.27, H 3.91, N 20.69, S 15.77.

*9-Methyl-3-ethoxycarbonylmethylthieno-7-phenyl-8,9,10,11-tetrahydro[1,2,4]triazolo[4″,3″:1′,6′]pyrimido [4′,5′:4,5]thieno[2,3-b][1,6]naphthyridine (**22**)*

A mixture of the triazolethione **21** (200 mg, 0.5 mmol) and ethyl chloroacetate (0.06 mL, 0.5 mmol) in ethanol (30 mL) containing anhydrous sodium acetate (2 g) was refluxed for 2 h, then cooled. The solid product was filtered off, washed several times with water and recrystallized from ethanol to afford yellow crystals of **22**. – M. p. 218 °C. – Yield 160 mg (66 %). – IR (KBr): ν = 1720 (C=O) cm^{-1}. – ^{1}H NMR (250.13 MHz, [D_6]-DMSO, 25 °C, TMS): δ = 1.20 (t, J = 8 Hz, 3 H, CH_3), 2.35 (s, 3 H, N–CH_3), 2.90 (m, 4 H, 2 CH_2), 3.30 (s, 2 H, CH_2), 4.05 (s, 2 H, CH_2), 4.14 (q, J = 8 Hz, 2 H, CH_2), 7.30 – 7.57 (m, 5 H, Ar-H), 8.22 (s, 1 H, CH). – $C_{24}H_{22}N_6O_2S_2$ (490.60): calcd. C 58.76, H 4.52, N 17.13, S 13.07; found C 58.87, H 4.60, N 17.25, S 12.97.

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