Synthesis of thieno[2,3-*b*][1,6]naphthyridines and pyrimido[4',5':4,5] thieno[2,3-*b*][1,6]naphthyridines

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3-Cyano-6-methyl-5,6,7,8-tetrahydro[1,6]naphthyridine-2(1*H*)-thione (**3a**) and 3-cyano-6-methyl-4-(2'-thienyl)-5,6,7,8-tetrahydro[1,6]naphthyridine-2(1*H*)-thione (**3b**) were reacted with α-halo compounds to give the intermediates **4a–j** which upon refluxing in ethanolic sodium ethoxide afforded the thieno[2,3-*b*][1,6]naphthyridine derivatives **5a–l**. Further annellation of pyridine and pyrimidine rings to the remaining free bond of the fused thiophene ring was achieved, providing tetrahydro-pyrido[2',3':4,5]- and -pyrimido[4',5':4,5]-thieno[2,3-b][1,6]naphthyridines. Some of the synthesised compounds were screened against different strains of bacteria.

Keywords: fused 1,6-naphthyridines, thiophenes, pyrimidines

Considerable recent attention has been focused on procedures for the modification of 1,6-naphthyridine derivatives with the aim of searching for new biologically active compounds. 1,6-Naphthyridine derivatives are used in the treatment of infectious diseases caused by various pathogenic bacteria,[1-3] in the treatment of depression,[4] as anticonvulsive agents[5,6] and benzodiazepine receptor antagonists.[7] In addition to the previous mentioned properties of annulated 1,6-naphthyridines, some of these compounds have been prepared as potential anticancer agents,[8-10] as antimalarials,[11] antidiabetics,[12] and as HIV integrase inhibitors for the treatment of HIV infection (AIDS).[13,14]

Prompted by the important medicinal applications of naphthyridines and also as a continuation of our work for the synthesis of various heterocycles incorporating the thiophene moiety in search of biologically active substances,[15-20] we here describe the synthesis and reactions of some new 1,6-naphthyridines and thieno[2,3-*b*][1,6]naphthyridines.

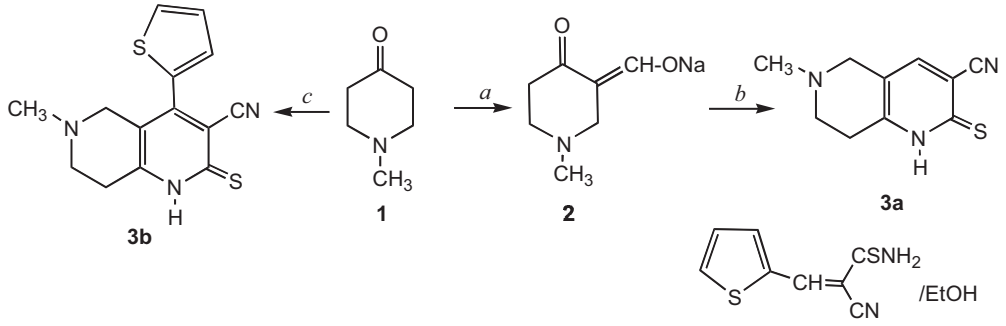
Results and discussion

The starting compounds for the synthesis of the desired heterocycles, 6-methyl-1,2,5,6,7,8-hexahydro-2-thioxo-1,6-naphthyridine-3-carbonitrile (**3a**) and its 2'-thienyl derivative (**3b**) were prepared by reacting the sodium salt of 3-formyl-1-methyl-4-piperidone with cyanothioacetamide[21] and thienylidene-cyanothioacetamide with 1-methyl-4-piperidone[22], respectively (Scheme 1).

The 1,6-naphthyridinethiones **3a,b** reacted readily with α-halo-ketones, -esters, or -amides (the halogen fragment was chlorine except in the case of phenacyl bromide) in basic medium to afford the corresponding 2-(substituted-thio) derivatives **4a**–**j** (compounds **5k**,**l** were obtained directly under the reaction conditions) which underwent intramolecular Thorpe–Ziegler cyclisation under the influence of ethanolic sodium ethoxide to form thieno[2,3-*b*][1,6]naphthyridine derivatives **5a**–**j** (Scheme 2). The structures of **5a–l** were confirmed by the IR spectra of the cyclised products which revealed, where appropriate, the disappearance of the cyano group absorption, and the appearance of bands assignable to an amino group (Table 1). Low carbonyl stretching frequencies of around 1590–1680 cm^{-1} were found in the IR spectra as a result of intramolecular hydrogen bonding with the *ortho*-amino group.[18]

Alkaline hydrolysis of the amino ester **5c** using ethanolic sodium hydroxide gave the corresponding sodium salt **6**, which formed the oxazinone derivative **7** when boiled in acetic anhydride, while hydrazinolysis of **5c** with hydrazine hydrate gave the corresponding 2-carbohydrazide derivative **8** (Scheme 3). Reaction of the *o*-aminoaldehyde **5k** with malononitrile under Friedländer reaction conditions took place via intramolecular addition of the amino group to a cyano function of the intermediate produced by initial intermolecular condensation to afford 2-amino-3-cyano-9-methyl-7,8,9,10-tetrahydropyrido[2',3':4,5]thieno[2,3-*b*][1,6]naphthyridine (**9**) in good yield.

The reaction of **5e** with triethyl orthoformate in the presence of catalytic amount of acetic acid led to the formation of the pyrimido[4',5':4,5]thieno[2,3-*b*][1,6]naphthyridine derivative **10**. Treatment of the latter compound with phosphorus oxychloride afforded the corresponding 4-chloro derivative **11**. The chlorine atom in **11** underwent displacement when reacted with hydrazine hydrate and with thiourea to produce the hydrazino and mercapto derivatives **12**, **13**, respectively. A series of *S*-alkylated derivatives **14a–e** could be obtained by reaction of **13** with a variety of α-halo compounds in ethanol in presence of sodium acetate. Another pyrimidine derivative (**15**) was obtained through the reaction of o-amino-amide derivative **5e** with acetic anhydride (Scheme 4).



Scheme 1 *Reagents: a*, $HCO_2Et/Na/Et_2O$; *b*, $NCCH_2CSNH_2/EtOH$; *c*, piperidine.

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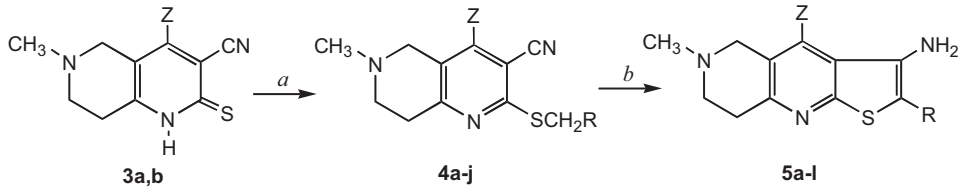


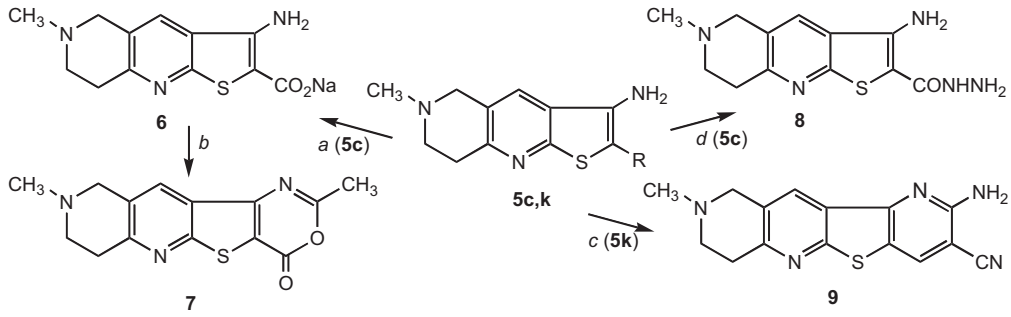
3a,b **4a-j** **5a-l**

4, 5	Z	R
a	H	$COCH_3$
b	H	COPh
c	H	CO_2Et
d	2-thienyl	CO_2Et
e	H	$CONH_2$

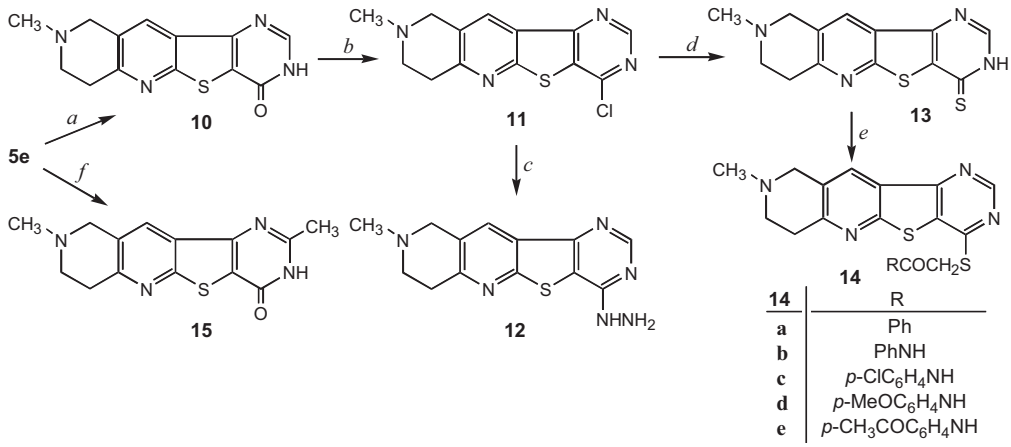
4, 5	Z	R
f	H	$CONHC_6H_4Cl$-*p*
g	2-thienyl	$CONHC_6H_4Cl$-*p*
h	H	$CONHC_6H_4COCH_3$-*p*
i	H	$CONHC_6H_4OMe$-*p*
j	H	CN

5	Z	R
k	H	CHO
l	2-thienyl	CN

Scheme 2 *Reagents: a*, XCH_2R/EtOH/AcONa; *b*, NaOEt/EtOH



Scheme 3 *Reagents: a*, NaOH/EtOH; *b*, Ac_2O; *c*, $CH_2(CN)_2$/EtOH/piperidine; *d*, $N_2H_4.H_2O$/EtOH



14	R
a	Ph
b	PhNH
c	*p*-ClC_6H_4NH
d	*p*-$MeOC_6H_4NH$
e	*p*-$CH_3COC_6H_4NH$

Scheme 4 *Reagents: a*, $CH(OEt)_3$/AcOH; *b*, $POCl_3$; *c*, $N_2H_4.H_2O$/EtOH; *d*, $SC(NH_2)_2$/EtOH; *e*, $ClCH_2COR$/EtOH/AcONa; *f*, Ac_2O

The pyrimido[[4',5':4,5]thieno[2,3-*b*][1,6]naphthyridine derivatives **16** and **17a,b** were obtained from the reaction of **5j** with formamide and by reacting **5j** and **5l** with carbon disulfide in pyridine, respectively. Compound **17a** was subjected to reaction with two moles of 2-chloro-*N*-(4-chlorophenyl)acetamide under reflux in ethanol in the presence of fused sodium acetate to afford the di-(*S*-alkylated) derivative **18**. The reactivity of the amino group in **5l** was tested by its reaction with triethyl orthoformate in acetic anhydride; ethoxymethylene derivative **19** was afforded (Scheme 5).

Biological activity

Nine of the compounds synthesised here were tested for their antibacterial activity against several strains of microorganism, and some inhibition of growth was observed. This work will be published elsewhere.

Experimental

Melting points were measured on a Gallenkamp apparatus. IR spectra were recorded on a Pye-Unicam SP3-100 spectrophotometer using KBr discs. ^1H 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 Elementar Analysen system GmbH VarioEL V2.3. Chlorine analyses were performed using a standard method through combustion followed by titration with mercury nitrate in presence of diphenylcarbazole as indicator.

6-Methyl-1,2,5,6,7,8-hexahydro-2-thioxo-1,6-naphthyridine-3-carbonitrile (**3a**)[21] and its 4-(2-thienyl) analogue (**3b**)[22] were prepared following literature procedures.

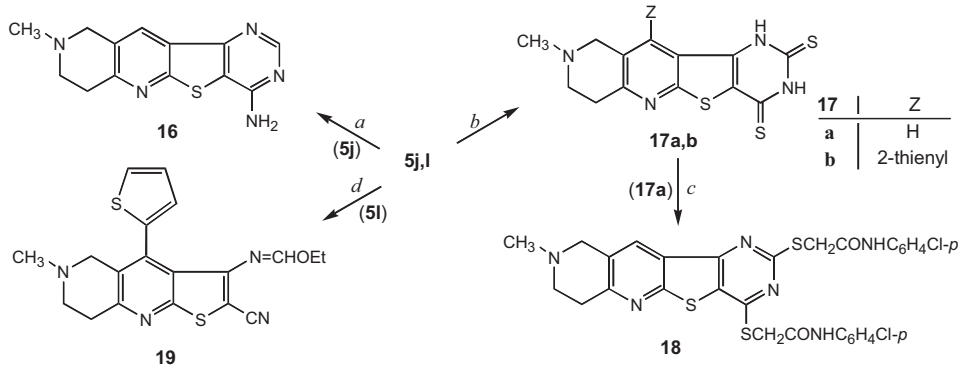
Reaction of the thiones **3a,b** *with halo compounds: general procedure. Formation of the nitriles* **4a–j** *and the amino-thienonaphthyridines* **5k, l**

The cyano-thione **3a** or **b** (0.01 mol) and the appropriate halo-compound (the chloride except for the synthesis of the phenacylthio compound **4b**, when phenacyl bromide was used) (0.01 mol) and

anhydrous sodium acetate (2 g) were taken in ethanol (30 ml) and heated to reflux for 1 hr, then cooled. The solid products which were produced were filtered off and recrystallised from the indicated solvent. The physical properties and spectral data are summarised in Tables 1 and 2.

Cyclisation of compounds **4a–j**: *general procedure. Formation of thieno[2,3-b][1,6]naphthyridine derivatives* **5a–j**

To a solution of a nitrile **4a–j** (5 mmol) in absolute ethanol (20 ml) was added a few drops of ethanolic sodium ethoxide, and the mixture was heated for 20 min. The solid product was filtered off and



Scheme 5 *Reagents: a*, $HCONH_2$; *b*, CS_2/pyridine; *c*, $ClCH_2CONHC_6H_4Cl$-*p*; *d*, $CH(OEt)_3/Ac_2O$

Table 1 Physical, analytical and spectroscopic properties of compounds **4a–j**

No.	Molecular formula (MW)	M. p./°C (solvent)	Yield/% colour	Analytical data calcd/found				IR (ν_{max}, cm^{-1})	^1H NMR (δ, ppm)
				C	H	N	S		
4a	$C_{13}H_{15}N_3OS$ (261.34)	220 (ethanol)	59 pale yellow	59.75 59.64	5.78 5.71	16.08 16.13	12.27 12.39	2200 (CN), 1690(CO)	($CDCl_3$) 2.21 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.72 (t, *J* = 5.6 Hz, 2H, CH_2), 2.85 (t, *J* = 6.0 Hz, 2H, CH_2), 3.36 (s, 2H, CH_2), 4.15 (s, 2H, CH_2), 7.55 (s, 1H, CH)
4b	$C_{18}H_{17}N_3OS$ (323.41)	145 (ethanol)	74 yellow	66.85 67.02	5.30 5.35	12.99 12.89	9.91 10.10	2200 (CN), 1680 (CO)	($CDCl_3$) 2.27 (s, 3H, CH_3), 2.44–2.68 (m, 4H, $2CH_2$), 3.32 (s, 2H, CH_2), 4.54 (s, 2H, CH_2), 7.20–7.55 (m, 6H, ArH)
4c	$C_{14}H_{17}N_3O_2S$ (291.37)	210 (ethanol)	68 pale yellow	57.71 57.82	5.88 5.91	14.42 14.32	11.00 11.13	2200 (CN), 1670 (CO)	($CDCl_3$) 1.28 (t, *J* = 8 Hz, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.75 (t, *J* = 8 Hz, 2H, CH_2), 3.1 (t, *J* = 5.6 Hz, 2H, CH_2), 3.6 (s, 2H, CH_2), 3.78 (s, 2H, CH_2), 4.23–4.3 (q, *J* = 8 Hz, 2H, CH_2), 7.45 (s, H, CH)
4d	$C_{18}H_{19}N_3O_2S_2$ (373.49)	102 (ethanol)	71 pale yellow	57.89 57.70	5.13 5.22	11.25 11.13	17.17 17.28	2220 (CN), 1735 (CO)	(DMSO–d_6) 1.35 (t, *J* = 8 Hz, 3H, CH_3), 2.54 (s, 3H, CH_3), 2.86 (t, *J* = 5.4 Hz, 2H, CH_2), 3.26 (t, *J* = 4.5 Hz, 2H CH_2), 3.52 (s, 2H, CH_2), 4.13 (s, 2H, CH_2), 4.33 (q, *J* = 8.2 Hz, 2H, CH_2), 7.2–7.31 (m, 2H, 2CH), 7.4 (d, *J* = 4.2, 1H, CH)
4e	$C_{12}H_{14}N_4OS$ (262.33)	220 (ethanol)	77 pale yellow	54.94 54.91	5.38 5.30	21.36 21.29	12.22 12.35	3350, 3150 (NH_2), 2220(CN), 1670 (CO)	(DMSO–d_6) 2.5 (s, 3H, CH_3), 2.64 (t, *J* = 4.5 Hz, 2H, CH_2), 2.85 (t, *J* = 6 Hz, 2H, CH_2), 3.4 (s, 2H, CH_2), 3.92 (s, 2H, CH_2), 7.15 (s, 2H, NH_2), 7.6 (s, 1H, CH)
4f	$C_{18}H_{17}ClN_4OS$ (372.87)	189 (dioxan)	72 yellow	57.98 58.08	4.60 4.69	15.03 15.13	8.60 8.49	3230(NH), 2200 (CN), 1660 (CO)	(DMSO–d_6) 2.4 (s, 3H, CH_3), 2.76 (t, *J* = 4 Hz, 2H, CH_2), 2.85 (t, *J* = 6.2 Hz, 2H, CH_2), 3.55 (s, 2H, CH_2), 4.3 (s, 2H, CH_2), 7.45 (d, *J* = 4 Hz, 2H, 2 CH), 7.85 (d, *J* = 3.8 Hz, 2H, 2CH), 8.05 (s, 1H, CH), 10.85 (s, 1H, NH)
				Cl calc. 9.51, found 9.62					
4g	$C_{22}H_{19}ClN_4OS_2$ (454.99)	208 (ethanol)	68 pale yellow	58.08 58.20	4.21 4.26	12.31 12.39	14.09 13.98	3250 (NH), 2200 (CN), 1665 (CO)	($CDCl_3$) 2.34 (s, 3H, CH_3), 2.66 (t, *J* = 4 Hz, 2H, CH_2), 2.95 (t, *J* = 4.6 Hz, 2H, CH_2), 3.32 (s, 2H, CH_2), 3.82 (s, 2H, CH_2), 7.03–7.5 (m, 7H, ArH), 8.09 (s, 1H, NH)
				Cl calc. 7.79, found 7.88					
4h	$C_{20}H_{20}N_4O_2S$ (380.46)	164 (ethanol)	59 yellow	63.14 63.24	5.30 5.39	14.73 14.61	8.43 8.37	3250 (NH), 2200 (CN), 1665, 1590 (2CO)	($CDCl_3$) 2.39 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.86 (t, *J* = 4.8 Hz 2H, CH_2), 3.18–3.22 (m, 4H, 2 CH_2), 4.11 (s, 2H, CH_2), 6.65–7.4 (m, 4H, ArH), 7.93 (s, 1H, CH), 9.21 (s, 1H, NH)
4i	$C_{19}H_{20}N_4O_2S$ (368.45)	181 (ethanol)	73 yellow	61.94 62.10	5.47 5.58	15.21 15.39	8.70 8.62	3250 (NH), 2200 (CN), 1650 (CO)	($CDCl_3$) 2.47 (s, 3H, CH_3), 2.74 (t, *J* = 4 Hz, 2H, CH_2), 3.04 (t, *J* = 5.2 Hz, 2H, CH_2), 3.53 (s, 2H, CH_2), 3.75 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 6.8 (d, *J* = 4 Hz, 2H, 2CH), 7.4 (d, *J* = 4.2 Hz, 2H, 2CH), 7.5 (s, 1H, CH), 8.88 (s, H, NH)
4j	$C_{12}H_{12}N_4S$ (244.31)	124 (EtOH/ H_2O)	54 pale yellow	58.99 59.10	4.95 4.98	22.93 23.09	13.12 13.00	2220 br. (2CN)	($CDCl_3$) 2.45 (s, 3H, CH_3), 2.74 (t, *J* = 3.2 Hz, 2H, CH_2), 3.05 (t, *J* = 3.2 Hz, 2H, CH_2), 3.1 (s, 2H, CH_2), 5.2 (s, 2H, CH_2), 7.9 (s, 1H, CH)

recrystallised from the solvent indicated in the Table. The physical properties and spectral data are summarised in Table 2.

2,9-Dimethyl-7,8,9,10-tetrahydro-4H[1,3]oxazino[4',5':4,5]thieno [2,3-b][1,6]naphthyridine-4-one (**7**)

The ester **5c** (0.01 mol) was heated for 3 h in ethanolic sodium hydroxide (30 ml, 25%) under reflux. The sodium salt (**6**) which precipitated was collected by filtration, dried, and introduced to the next step without further purification. A mixture of the sodium salt (0.57 g, 2 mmol) and acetic anhydride (20 ml) was refluxed for 2 h, then cooled. The solid product was collected and recrystallised from acetic acid to give yellow crystals (0.38 g, 66%) of the fused oxazinone **7,** m.p. 174–175°C. IR: ν_{max} 1760 cm^{-1} (CO). NMR (DMSO-d_6): δ_H 2.35 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.65 (t, J = 5.2 Hz, 2H, CH_2), 3.15 (t, J = 4.8 Hz, 2H, CH_2), 3.6 (s, 2H, CH_2), 7.6 (s, 1H, CH). Anal. Calcd. for $C_{14}H_{13}N_3O_2S$ (287.33): C, 58.52; H, 4.56; N, 14.62; S, 11.16. Found: C, 58.64; H, 4.59; N, 14.69; S, 11.07%.

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

A mixture of ester **5c** 2.9 g (0.01 mol) and hydrazine hydrate 0.5 ml (0.1 mol) in ethanol (30 ml) was heated under reflux for 5 h.

Table 2 Physical, analytical and spectroscopic properties of compounds **5a–l**

No.	Molecular formula (MW)	M.p./°C (solvent)	Yield/% colour	Analytical data calcd/found				IR (ν_{max}, cm^{-1})	^{1}H NMR (δ, ppm)
				C	H	N	S		
5a	$C_{13}H_{15}N_3OS$ (261.34)	246 (dioxan)	74 yellow	59.75 59.88	5.78 5.90	16.08 15.99	12.27 12.21	3360, 3250 (NH_2), 1610 (CO)	($CDCl_3$): 2.38 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.76 (t, J = 5.6 Hz, 2H, CH_2), 3.1 (t, J = 4.8 Hz, 2H, CH_2), 3.62 (s, 2H, CH_2), 6.54 (s, 2H, NH_2), 7.48 (s, 1H, CH)
5b	$C_{18}H_{17}N_3OS$ (323.41)	217 (dioxan)	74 yellow	66.85 66.88	5.30 5.41	12.99 11.31	9.91 9.79	3460, 3280 (NH_2), 1615 (CO)	($CDCl_3$) 2.43 (s, 3H, CH_3), 2.74 (t, J = 5.2 Hz, 2H, CH_2), 3.1 (t, J = 5.6 Hz, 2H, CH_2), 3.61 (s, 2H, CH_2), 6.93 (s, 2H, NH_2), 7.4–7.6 (m, 3 H, 3 CH), 7.76 (s, 1H, CH), 7.82 (d, J = 3.8 Hz, 2H, 2CH)
5c	$C_{14}H_{17}N_3O_2S$ (291.37)	220 (ethanol)	78 yellow	57.71 57.78	5.88 5.93	14.42 14.57	11.00 10.88	3410, 3270 (NH_2), 1665 (CO)	($CDCl_3$) 1.25 (t, J = 7.2 Hz, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.75 (t, J 4.6 Hz, 2H, CH_2), 3.05 (t, J = 4.6 Hz, 2H, CH_2), 3.65 (s, 2H, CH_2), 4.17 (q, J = 5.6 Hz, 2H, CH_2), 5.83 (s, 2H, NH_2), 7.55 (s, 1H, CH)
5d	$C_{18}H_{19}N_3O_2S_2$ (373.49)	170 (ethanol)	74 yellow	57.89 57.77	5.13 5.04	11.25 11.19	17.17 17.22	3460, 3350 (NH_2), 1670 (CO)	(DMSO–d_6) 1.38 (t, J = 8.0 Hz, 3H, CH_3), 2.5 (s, 3H, CH_3), 2.83 (t, J = 5.6 Hz, 2H, CH_2), 3.25 (t, J = 6.0 Hz, 2H, CH_2), 3.45 (s, 2H, CH_2), 4.3 (q, J = 8.2 Hz, 2H, CH_2), 5.69 (s, 2H, NH_2), 7.22–7.5 (m, 2H, 2CH), 7.68 (d, J = 3.2 Hz, 1H,_CH)
5e	$C_{12}H_{14}N_4OS$ (262.33)	265 (dioxan)	72 yellow	54.94 55.08	5.38 5.43	21.36 21.28	12.22 12.14	3400, 3300, 3100 (2 NH_2), 1590 (CO)	(DMSO–d_6) 2.54 (s, 3H, CH_3), 2.76 (t, J = 5.2. Hz, 2H, CH_2), 3.1 (t, J = 5.6 Hz, 2H, CH_2), 3.68 (s, 2H, CH_2), 6.38, 6.85 (2 s, 4H, 2NH_2), 7.96 (s, 1H, CH)
5f	$C_{18}H_{17}ClN_4OS$ (372.87)	200 (ethanol)	67 yellow	57.98 57.92	4.60 4.54	15.03 15.11	8.60 8.69	3410, 3300, 3195 (NH_2, NH), 1610 (CO)	(DMSO–d_6) 2.55 (s, 3H, CH_3), 2.8 (t, J = 5.2 Hz, 2H, CH_2), 3.08 (t, J = 5.0 Hz, 2H, CH_2), 3.43 (s, 2H, CH_2), 7.35 (s, 2H, NH_2), 7.42–7.82 (m, 4H, ArH), 8.23 (s, 1H, CH), 9.54 (s, 1H, NH)
				Cl calcd. 9.51, found 9.58					
5g	$C_{22}H_{19}ClN_4OS_2$ (454.99)	247 dioxan)	51 yellow	58.08 58.19	4.21 4.27	12.31 12.26	14.09 14.20	3460, 3320 (NH_2), 3100 (NH), 1580 (CO)	(DMSO–d_6) 2.1 (s, 3H, CH_3), 2.55 (t, J = 4.8 Hz, 2H, CH_2), 2.85 (t, J = 5.2 Hz, 2H, CH_2), 3.5 (s, 2H, CH_2), 5.75 (s, 2H, NH_2), 7.15–7.65 (m, 7H, ArH), 9.45 (s, 1H, NH)
				Cl calcd. 7.79, found 7.88					
5h	$C_{20}H_{20}N_4O_2S$ (380.46)	243 (ethanol)	68 yellow	63.14 63.22	5.30 5.38	14.73 14.67	8.43 8.51	3400, 3300 (NH_2), 3200 (NH), 1580 (CO)	(DMSO–d_6) 2.33 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 2,91 (t, J = 4.8 Hz 2H, CH_2), 3.15–3.24 (m, 4H, 2 CH_2), 6.65–7.40(m, 4H, ArH), 7.08 (s, 2H, NH_2), 7.93 (s, 1H, CH), 9.1(s, 1H, NH)
5i	$C_{19}H_{20}N_4O_2S$ (368.45)	245 (ethanol)	77 yellow	61.94 67.04	5.47 5.41	15.21 15.32	8.70 8.59	3385, 3320 (NH_2), 3100 (NH), 1625 (CO)	(DMSO–d_6) 2.15 (s, 3H, CH_3), 2.48 (t, J 4.4 Hz, 2H, CH_2), 2.78 (t, J 4.6 Hz, 2H, CH_2), 3.1 (s, 2H, CH_2), 3.5 (s, 3H, CH_3), 6.95 (s, 2H, NH_2), 7.28–7.32 (m, 4H, ArH), 7.9 (s, 1H, CH), 9.08 (s, 1H, NH)
5j	$C_{12}H_{12}N_4S$ (244.31)	248 (ethanol)	65 yellow	58.99 58.87	4.95 4.90	22.93 22.85	13.12 13.01	3385, 3300 (NH_2), 2200 (CN)	$CDCl_3$: 2.3 (s, 3H, CH_3), 2.56 (t, J = 4.6 Hz, 2H, CH_2), 3.15 (t, J = 4.4 Hz, 2H, CH_2), 3.4 (s, 2H, CH_2), 5.22 (s, 2H, NH_2), 7.87 (s, 1H, CH)
5k	$C_{12}H_{13}N_3OS$ (247.31)	212 (ethanol)	55 yellow	58.28 58.19	5.30 5.41	16.99 17.11	12.96 12.88	3420, 3350 (NH_2), 1630 (CO)	(DMSO–d_6) 2.5 (s, 3H, CH_3), 2.74 (t, J = 4.2 Hz, 2H, CH_2), 2.94 (t, J = 5.0 Hz, 2H, CH_2), 3.6 (s, 2H, CH_2), 7.8 (s, 2H, NH_2), 8.25 (s, 1H, CH), 10.0 (s, 1H, CHO)
5l	$C_{16}H_{14}N_4S_2$ (326.43)	155 (ethanol)	61 yellow	58.87 58.79	4.32 4.27	17.16 17.25	19.64 19.56	3440, 3320 (NH_2), 2200 (CN)	($CDCl_3$) 2.32 (s, 3H, CH_3), 2.68 (t, J = 5.2 Hz, 2H, CH_2), 3.1 (t, J = 4.6 Hz, 2H, CH_2), 3.35 (s, 2H, CH_2), 5.02 (s, 2H, NH_2), 7.07–7.65 (m, 3H, 3CH thioph)

The solid product separated from the hot mixture was filtered off and recrystallised from dioxan to give pale yellow crystals (1.9 g, 71%), m.p. 270°C. IR: ν_{max} 3460, 3350, 3300 ($2NH_2$), 3230 (NH), 1670 cm^{-1} (C=O). NMR ($CDCl_3$): δ_H 2.35 (s, 3H, CH_3), 2.46 (t, J = 6 Hz, 2H, CH_2), 2.86 (t, J = 5.6 Hz, 2H, CH_2), 3.17 (s, 2H, CH_2), 4.40 (s, 2H, NH_2), 5.8 (s, 2H, NH_2), 7.45 (s, 1H, CH), 9.10 (s, 1H, NH). MS: m/z (%) 277 (100) $[M]^+$. Anal. Calcd. for $C_{12}H_{15}N_5OS$ (277.34): C, 51.97; H, 5.45; N, 25.25; S, 11.56. Found: C, 52.1; H, 5.52; N, 25.33; S, 11.47%.

2-Amino-9-methyl-7,8,9,10-tetrahydropyrido[2',3':4,5]thieno [2,3-b][1,6]naphthyridine-3-carbonitrile (**9**)

The *o*-amino-aldehyde **5k** (1.24 g, 5 mmol) was heated to reflux for 3 h with malononitrile (0.33 g, 5 mmol) in absolute ethanol (20 ml) in presence of a few drops of piperidine. The solid product which separated from the hot mixture was filtered off and recrystallised from dioxan to give the aminonitrile **9** as yellow crystals (1.0 g, 68%), m.p. 242°C. IR: ν_{max} 3485, 3370 (NH_2), 2200 cm^{-1} (C≡N). NMR ($CDCl_3$): δ_H 2.55 (s, 3H, CH_3), 2.79 (t, J = 5.6 Hz, 2H, CH_2), 3.2 (t, J = 4.8 Hz, 2H, CH_2), 3.7 (s, 2H, CH_2), 5.25 (s, 2H, NH_2), 7.23 (s, 1H, CH), 8.1 (s, 1H, CH). MS: *m/z* (%) 295 (76) $[M]^+$. Anal. Calcd. for $C_{15}H_{13}N_5S$ (295.36): C, 61.00; H, 4.44; N, 23.71; S, 10.85. Found: C, 61.13; H, 4.53; N, 23.69; S, 10.74%.

9-Methyl-7,8,9,10-tetrahydropyrimido[4',5':4,5]thieno[2,3-b][1,6] naphthyridin-4(3H)-one (**10**)

The amino-amide **5e** (2.6 g, 0.01 mol) was heated under reflux for 2 h in triethyl orthoformate (5 ml) containing a few drops of acetic acid. The solid product was collected and recrystallised from dioxan to give pale yellow crystals (1.57 g, 58%) of **10**, m.p. 274°C. IR: ν_{max} 3450 (NH), 1650 cm^{-1} (C=O). NMR (DMSO-d_6): δ_H 2.44 (s, 3H, CH_3), 2.88 (t, J = 4.8 Hz, 2H, CH_2), 3.25 (t, J = 5.0 Hz, 2H, CH_2), 3.51(s, 2H, CH_2), 8.24 (s, 1H, CH), 8.52 (s, 1H, CH). Anal. Calcd. for $C_{13}H_{12}N_4OS$ (272.32): C, 57.34; H, 4.44; N, 20.57; S, 11.77. Found: C, 57.28; H, 4.37; N, 20.64; S, 11.83%.

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

The fused pyrimidinone derivative **10** (1.4 g, 5 mmol) was heated to reflux for 4 h in phosphorus oxychloride (15 ml), then cooled. The reaction mixture was poured into ice/water and neutralised with $NaHCO_3$. The insoluble solid product was filtered off and recrystallised from ethanol to afford white crystals (0.91 g, 63%) of **11**, m.p 223°C. NMR (DMSO-d_6): δ_H 2.56 (s, 3H, CH_3), 2.83 (t, J = 5.2 Hz, 2H, CH_2), 3.18 (t, J = 4.8 Hz, 2H, CH_2), 3.46 (s, 2H, CH_2), 8.37 (s, 1H, CH), 8.62 (s, 1H, CH). Anal. Calcd. for $C_{13}H_{11}ClN_4S$ (290.77): C, 53.70; H, 3.81; Cl, 12.19; N, 19.27; S, 11.03. Found: C, 53.62; H, 3.75; Cl, 12.26; N, 19.31; S, 10.96%.

4-Hydrazino-9-methyl-7,8,9,10-tetrahydropyrimido[4',5':4,5] thieno[2,3-b][1,6]naphthyridine (**12**)

The chloro compound **11** (1.45 g, 5 mmol) was refluxed in ethanol (50 ml) with hydrazine hydrate (0.5 ml, 10 mmol) for 30 min. The solid which separated from the hot mixture was filtered off and recrystallised from dioxan to give yellow crystals (1.0 g, 76%) of **12**, m.p. 294°C. IR: ν_{max} 3310, 3185, 3150 cm^{-1} ($NHNH_2$). NMR (DMSO-d_6): δ_H 2.8 (s, 3H, CH_3), 2.8 (t, J = 4.6 Hz, 2H, CH_2), 3.15 (t, J = 4.2 Hz, 2H, CH_2), 3.45 (s, 2H, CH_2), 4.67 (s, 2H, NH_2), 5.1(s, 1H, NH), 8.32 (s, 1H, CH), 8.57 (s, 1H, CH). Anal. calcd. for $C_{13}H_{14}N_6S$ (286.35): C, 54.53; H, 4.93; N, 29.35; S, 11.20. Found: C, 54.62, H, 5.01; N, 29.47; S, 11.31%.

9-Methyl-7,8,9,10-tetrahydropyrimido[4',5':4,5]thieno[2,3-b][1,6] naphthyridine-4(3H)-thione (**13**)

The chloro compound **11** (2.9 g, 0.01 mol) and thiourea (0.9 g, 0.012 mol) were heated under reflux in dry ethanol (50 ml) for 3 h. The solid product so obtained was recrystallised from ethanol to give yellow crystals (2.2 g, 77%) of the thione **13**, m.p. 320°C. IR: ν_{max} 3300, (NH), 1150 cm^{-1} (C=S). NMR (DMSO-d_6): δ_H 2.37 (s, 3H, CH_3), 2.87 (t, J = 4.8 Hz, 2H, CH_2), 3.15 (t, J = 5.0 Hz, 2H, CH_2), 3.44 (s, 2H, CH_2), 8.1 (s, 1H, CH), 8.44 (s, 1H, CH), 9.5 (s, 1H, NH). Anal. Calcd. for $C_{13}H_{12}N_4S_2$ (288.38): C, 54.14; H, 4.19; N, 19.43; S, 22.23. Found: C, 54.10; H, 4.22; N, 18.99; S, 22.18%.

4-(Substituted thio)-9-methyl-7,8,9,10-tetrahydropyrimido[4',5':4,5] thieno[2,3-b][1,6]naphthyridines (**14a–e**)

The thione **15** (0.29 g, 1 mmol), and anhydrous sodium acetate (2 g) were heated for 1 h in ethanol (30 ml) with phenacyl bromide (1 mmol) or the appropriate 2-chloro-N-arylacetamide (1 mmol). The solid product which formed was filtered off, washed several times with water, and recrystallised from ethanol to give the *S*-alkylated derivatives **14a–e**.

Phenacylthio compound **14a:** Yellow crystals (0.29 g, 72%), m.p. 219°C. IR: ν_{max} 1680 cm^{-1} (CO). NMR (DMSO-d_6): δ_H 2.5 (s, 3H, CH_3), 2.78 (t, 2H J = 4.8 Hz, CH_2), 3.35 (m, 4H, $2CH_2$), 5.15 (s, 2H, CH_2), 7.34-7.7 (m, 5H, ArH), 8.1(s, 1H, CH), 8.6 (s, 1H, CH). Anal. Calcd. for $C_{21}H_{18}N_4OS_2$ (406.52): C, 62.05; H, 4.46; N, 13.78; S, 15.77. Found: C, 62.20; H, 4.54; N, 13.94; S, 15.85%.

N-Phenyl acetamide **14b**: Yellow crystals (0.27 g, 65%), m.p. 235°C. IR: ν_{max} 3300 (NH), 1665 cm^{-1} (C=O). NMR (DMSO-d_6): δ_H 2.12 (s, 3H, CH_3), 2.89 (t, J = 5.2 Hz, 2H, CH_2), 3.23 (t, J = 4.8 Hz, 2H, CH_2), 3.8 (s, 2H, CH_2), 4.3 (s, 2H, CH_2), 7.17–7.55 (m, 4H, ArH), 8.29 (s, 1H, CH), 9.03 (s, 1H, CH), 10.09 (s,1H, NH). Anal. Calcd. for $C_{21}H_{19}N_5OS_2$ (421.53): C, 59.84; H, 4.54; N, 16.61; S, 15.21. Found: C, 59.68; H, 4.46; N, 16.76; S, 15.36%.

N-(4-Chlorophenyl) acetamide **14c**: Yellow crystals (0.32 g, 72%), m.p. 200°C. IR: ν_{max} 3300 (NH), 1685 cm^{-1} (CO). NMR (DMSO-d_6): δ_H 2.47 (s, 3H, CH_3), 2.77–2.9 (t, J = 5.0 Hz, 2H, CH_2), 3.1 (t, J = 4.6 Hz, 4H, $2CH_2$), 4.3 (s, 2H, CH_2), 7.1–7.65 (m, 4H, ArH), 8.25 (s, 1H, CH), 8.9 (s, 1H, CH), 10.23 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{18}ClN_5OS_2$ (455.98): C, 55.32; H, 3.98; Cl, 7.78; N, 15.36; S, 14.06. Found: C, 56.01; H, 4.12; Cl, 7.98; N, 15.56; S, 14.25%.

N-(4-Methoxyphenyl) acetamide **14d**: Yellow crystals (0.34 g, (76%), m.p. 228°C. IR: ν_{max} 3280 (NH), 1675 cm^{-1} (CO). NMR (DMSO-d_6): δ_H 2.48 (s, 3H, CH_3), 2.9 (t, J = 5.2 Hz, 2H, CH_2), 3.25 (t, J = 4.2 Hz, 4H, $2CH_2$), 3.81 (s, 3H, CH_3), 4.63 (s, 2H, CH_2), 7.75–8.04 (m, 4H, ArH), 8.36 (s, 1H, CH), 9.1 (s, 1H, CH), 9.8 (s, 1H, NH). Anal. Calcd. for $C_{22}H_{21}N_5O_2S_2$ (451.56): C, 58.52; H, 4.69; N, 15.51; S, 14.20. Found: C, 58.65; H, 4.85; N, 15.43; S, 14.89%.

N-(4-Acetylphenyl) acetamide **14e**; orange crystals (0.27 g, 59%), m.p. 228°C. IR: ν_{max} 3250 (NH), 1670 cm^{-1} (2 C=O). NMR (DMSO-d_6): δ_H 2.63 (s, 3H, CH_3), 2.78 (s, 3H, CH_3), 2.9 (t, J = 5.0 Hz, 2H, CH_2), 3.25 (m, J = 4.6 Hz, 4H, $2CH_2$), 4.63 (s, 2H, CH_2), 7.75–8.04 (m, 4H, ArH), 8.4 (s, 1H, CH), 9.07 (s, 1H, CH), 10.4 (s, 1H, NH). Anal. Calcd. for $C_{23}H_{21}N_5O_2S_2$ (463.57): C, 59.59; H, 4.57; N, 15.11; S, 13.83. Found: C, 59.44; H, 4.55; N, 14.96; S, 13.76%.

2,9-Dimethyl-7,8,9,10-tetrahydropyrimido[4',5':4,5]thieno [2,3-b][1,6]naphthyridin-4(3H)-one **(15)**

The amino-amide **5e** (1.3 g, 5 mmol) was heated to reflux in acetic anhydride (20 ml) for 5 h, then allowed to cool. The solvent was removed under reduced pressure and the residue was triturated with water several times. The solid product was collected and recrystallised from dioxan to give pale yellow crystals (0.78 g, 55%) of **15**, m.p. 299°C. IR: ν_{max} 3400 (NH), 1670 cm^{-1} (CO). NMR (DMSO-d_6): δ_H 2.32 (s, 3H, N-CH_3), 2.60 (t, J = 5.6 Hz, 2H, CH_2), 2.85 (s, 3H, CH_3), 3.44 (t, J = 6 Hz, 2H, CH_2), 4.04 (s, 2H, CH_2), 8.16 (s, 1H, CH), 8.06 (s, 1H, NH).Anal. Calcd. for $C_{14}H_{14}N_4OS$ (286.35): C, 58.72; H, 4.93; N, 19.57; S, 11.20%. Found: C, 58.82; H, 5.03; N, 19.69; S, 10.99%.

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

The aminonitrile **5j** (0.49 g, 2 mmol) was refluxed for 3 h in formamide (10 ml), then cooled. The solid product was filtered off, washed several times with ethanol, and recrystallised from dioxan to give buff crystals (0.34 g, 62%) of **16**, m.p. 282°C. IR: ν_{max} 3310, 3150 cm^{-1} (NH_2). NMR (DMSO-d_6): δ_H 2.8 (s, 3H, CH_3), 2.8 (t, J = 4.6 Hz, 2H, CH_2), 3.15 (t, J = 5.2 Hz, 2H, CH_2), 3.45 (s, 2H, CH_2), 7.67 (s, 2H, NH_2), 8.32 (s, 1H, CH), 8.57 (s, 1H, CH). MS: *m/z* (%) 271 (44) $[M]^+$. Anal. Calcd. for $C_{13}H_{13}N_5S$ (271.34): C, 57.55; H, 4.83; N, 25.81; S, 11.82. Found: C, 57.39; H, 4.72; N, 25.71; S, 11.79%.

9-Methyl-7,8,9,10-tetrahydropyrimido[4',5':4,5]thieno[2,3-b][1,6] naphthyridine-2,4(1H,3H)-dithione (**17a**) *and its 11-(2-thienyl) analogue* (**17b**)

The aminonitrile **5j** (1.2 g, 5 mmol) or **5l** (0.65 g, 2 mmol) and carbon disulfide (5 ml) was heated in pyridine (20 ml) on a water bath for 48 h, then cooled. The solid product was filtered off, washed several times with ethanol, and recrystallised from DMF to afford orange crystals of **17a** and **17b**.

Dithione **17a** (0.93 g, 55%), m.p. 244°C. IR: ν_{max} 3410 cm^{-1} (2NH). NMR (DMSO-d_6): δ_H 2.65 (s, 3H, CH_3), 2.84–2.9 (t, J = 3.8 Hz, 2H, CH_2), 3.27-3.43 (m, 4H, $2CH_2$), 8.1 (s, 1H, CH), 8.4 (s, 2H, 2NH). Anal. Calcd. for $C_{13}H_{12}N_4S_3$ (320.44): C, 48.73; H, 3.77; N, 17.48. Found: C, 48.61; H, 3.72; N, 17.78%.

The 11-(2-thienyl) dithione **17b** (0.49 g, 61%), m.p. 286°C. IR: ν_{max} 3410 cm^{-1} br. (2NH). NMR (CF_3CO_2D): δ_H 2.52 (s, 3H, CH_3), 2.88 (m, 4H, $2CH_2$), 3.35 (s, 2H, CH_2), 7.77–8.2 (m, 3H, 3CH). Anal. Calcd. for $C_{17}H_{14}N_4S_4$ (402.56): C, 50.72; H, 3.51; N, 13.92; S, 31.86. Found: C, 50.59; H, 3.65; N, 14.22; S, 31.46%.

9-Methyl-2,4-bis[(4-chlorophenyl)aminomethylthio]-7,8,9,10-tetrahydropyrimido[4',5':4,5]thieno[2,3-b][1,6]naphthyridine (**18**)
The dithione **17a** 0.64 g (2 mmol), 2-chloro-*N*-(4-chlorophenyl) acetamide (0.8 g, 4 mmol) and sodium acetate (2 g) were heated to reflux in ethanol (30 ml) for 1 h, then cooled. The solid product was filtered off, washed several times with water, and recrystallised from ethanol to give **18** as yellow crystals (0.87 g, 67%), m.p. 256°C. IR: ν_{max} 3250 (2NH), 1650 cm^{-1} (2C=O). NMR (DMSO-d_6): δ_H 2.62 (s, 3H, CH_3), 2.84 (t, J = 4.2 Hz, 2H, CH_2), 3.05 (m, 4H, $2CH_2$), 4.6 (s, 4H, $2CH_2$), 7.35–7.88 (m, 8H, ArH), 8.33 (s, 1H, CH), 11.45 (s, 2H, 2NH). Anal. Calcd. for $C_{29}H_{24}Cl_2N_6O_2S_3$ (655.63): C, 53.13; H, 3.69; Cl, 10.81; N, 12.82; S, 14.67. Found: C, 52.89; H, 3.58; Cl, 11.01; N, 13.16; S, 14.99%.

3-(Ethoxymethyleneamino)-6-methyl-4-(2-thienyl)-5,6,7,8-tetrahydrothieno[2,3-b][1,6]naphthyridine-2-carbonitrile (**19**)
Compound **5l** (0.64 g, 2 mmol) was refluxed for 3 h with triethyl orthoformate (2 ml) in acetic anhydride (10 ml), then cooled. The solid product was filtered off and recrystallised from ethanol as buff crystals of **19** (59%), m.p. 178°C. IR: ν_{max} 2200 cm^{-1} (C≡N). NMR ($CDCl_3$): δ_H 1.13 (t, J = 7.8 Hz, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.72 (t, J = 5.0 Hz, 2H, CH_2), 3.18 (t, J = 4.8 Hz, 2H, CH_2), 3.35 (s, 2H, CH_2), 4.1 (q, J = 8.2 Hz, 2H, CH_2), 7.15-7.65 (m, 3H, 3CH), 7.9 (s, 1H, CH). Anal. Calcd. for $C_{19}H_{18}N_4OS_2$ (382.50): C, 59.66; H, 4.74; N, 14.65; S, 16.76. Found: C, 59.58; H, 4.69; N, 14.51; S, 16.68%.

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References

1 S. Mishio, T. Hirose, A. Minamida, J. Matsumoto and S. Minami, *Chem. Pharm. Bull*., 1985, **33**,4402.
2 A. Belicova, M. Seman, V. Milata, D.I. Ilavsky and L. Ebringer, *Folia Microbiol. (Prague)*, 1997, **42**, 193; *Chem. Abstr.*, 1997,**127**, 63 024.
3 C.G. Mohan and P.C. Mishra, *Indian J. Biochem. Biophys.*, 1997, **34**, 429; *Chem. Abstr.*, 1998, **128**, 200 547.
4 PCT Int. Apl. WO 94 12173; *Ref. Zh. Khim*., 1996, **3**, 76P.
5 PCT Int. Appl. WO 98 54184; *Chem. Abstr.*, 1999, **130**, 38 370.
6 N.E. Austin, M.S. Hadley, J.D. Harling, F.P. Harrington, G.J. Macdonald, D.E. Mitchell, G.J. Riley, T.O. Stean, G. Stemp, S.C. Stratton, M. Thompson and N. Upton, *Bioorg. Med. Chem. Lett*., 2003, **13**, 1627.
7 PCT Int. Appl. WO 99 03859; *Chem. Abstr*., 1999, **130**, 125 079.
8 L.W. Deady, T. Rodemann, L. Zhuang, B.C. Baguley and W.A. Denny, *J. Med. Chem.*, 2003, **46**, 1049.
9 A.L. Ruchelman, S.K. Singh, A.W.X.H. Ray, Y.M. Yang, T.K. Li, A. Lin, L.F. Lin and E.J. LaVoie, *Bioorg. Med. Chem.*, 2003, **11**, 2061.
10 U.S. Pat. 2003, 199 542; *Chem. Abstr*., 2003, **139**, 337 964.
11 PCT Int. Appl. WO 2003 027113; *Chem. Abstr.*, 2003, **138**, 271 665.
12 L. Zhuang, J.S. Wai, M.W. Embrey, T.E. Fisher, M.S. Egberston, L.S. Payne, J.P. Guare, J.P. Vacca, D.J. Hazuda, P.J. Felock, A.L. Wolf, K.A. Stillmock, M.V. Witmer, G.S.W.A. Moyer, L.J. Gabryelski, Y.M. Leonard, J.J. Lynch, S.R. Michelson and S.D. Young, *J. Med. Chem.,* 2003, **46**, 453
13 PCT Int. Appl. WO 2003 016309; *Chem. Abstr.*, 2003, **138**, 205 040.
14 PCT Int. Appl. WO 2003 016315; *Chem. Abstr.*, 2003, **138**, 205 068.
15 A.A. Geies, *J. Chem. Res.* (S), 1998, 290; (M) 1248
16 A.M. Kamal El-Dean, A.A. Geies, H.S. El-Kashef, S. Rault, P.D.'Allemagne and J.C. Lancelot, *J. Heterocycl. Chem.,* 2000, **37**, 1520.
17 A.A. Geies, A.M. Kamal El-Dean and M.I. Abdel-Moneam, *Z. Naturforsch.,* 1992, **47b**, 143.
18 M.Z.A. Badr, A.A. Geies, M.S. Abbady and A.A. Dahy, *Can. J. Chem.,* 1998, **76**, 469.
19 A.A. Geies, E.A. Bakhite and H.S. El-Kashef, *Pharmazie***,** 1998, **53**, 686.
20 A.A. Geies, A.A. Abd El-Hafez, J.C. Lancelot and H.S. El-Kashef, *Bull. Chem. Soc. Jpn.,* 1993, **66**, 3716.
21 V.V. Shelyakin and M.O. Lozinsky, *Chem. Heterocycl. Compds,* 2000, **36**, 496.
22 A.A. Shestopalov, A.V. Gromova, L.A. Rodinovskaya, K.G. Nikishin, V.P. Litvinov and A.M. Shestopalov, *Russian Chem. Bull., Int. Ed*., 2004, **53**, 2353.
23 F.J. Cuadrado, M.A. Perez and J.L. Soto, *J. Chem. Soc., Perkin Trans. 1,* 1984**,** 2247**.**