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Original article

Microwave-assisted synthesis of pyrimido[4,5-*b*][1,6]naphthyridin-4(3*H*)-ones with potential antitumor activity

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ABSTRACT

The 6,7,8,9-tetrahydropyrimido[4,5-*b*][1,6]naphthyridin-4(3*H*,5*H*,10*H*)-ones **4**,**5a**–**g** and their oxidized forms **6**,**7a**–**g** were obtained from the catalyst-free reaction of 6-amino-2-methylthiopyrimidin-4(3*H*)-one **3** and (*E*)-3,5-*bis*(benzylidene)-1-alkyl-4-piperidones **1**,**2a**–**g** under Microwave irradiation and their subsequent oxidation process with *p*-chloranil. Eighteen of the new compounds were evaluated in the US National Cancer Institute (NCI), where compound **4g** presented a remarkable activity against 57 cancer cell lines, with the most important GI_{50} values ranging from 1.48 to 9.92 μM from in vitro assays.

1. Introduction

The microwave-assisted organic synthesis (MAOS) [1] has become an interesting field of the synthetic organic chemistry in recent years, since it allows dramatically reducing the reaction times and increases the yield percentages, compared with conventional synthetic methods. This has allowed the synthesis of different heterocyclic systems such as quinolines [2], quinazolines [3], pyrimidines [4], pyridines [5], pyrazines [6], diazepines [7], triazines [8], like others, extending the "chemical space" and the development of new molecules with potential biological activity and possible development of new drugs.

Analogous compounds to (*E*)-3,5-*bis*(benzylidene)-4-piperidones **1**,**2a**–**g** presented noteworthy cytotoxic activity against leukemia cell lines and colon cancer, among others [9–11]. The incorporation of these active pharmacophores in the structure of new heterocyclic compounds could potentiate their biological activity. An interesting target is 1,6-naphthyridines which have a wide variety of biological properties [12–18]. Compound **A**, BAY 94-8862, a potent nonsteroidal antagonist of the mineralocorticoid receptor (MR) with IC_{50} of 18 nM, is under investigation in a clinical phase II trial [19] (Fig. 1). Compound **B** is an efficient $hS1P_1$ (sphingosine-1-phosphate receptor) agonists with an EC_{50} of 18 nM [20]. Compound **C** (Torin 2) is highly potent and selective mammalian target of rapamycin (mTOR) inhibitor, with EC_{50} of 0.25 nM [21,22] (Fig. 1).

Continuing with our current studies on the synthesis of novel heterocyclic structures with potential antitumor activity [23–27], we are reporting here the synthesis and antitumor evaluation of novel pyrimido[4,5-*b*][1,6]naphthyridin-4(3*H*)-one derivatives **4**–**7**.

2. Results and discussion

2.1. Chemistry

We developed a catalyst-free methodology using microwave irradiation for the formation of naphthyridines **4** and **5**. Firstly, the treatment of equimolar amounts of (*E*)-3,5-*bis*(benzylidene)-4-piperidones **1**,**2a**–**g** with aminopyrimidone **3** in *N*,*N*-dimethylformamide under microwave irradiation resulted in the formation of pyrimidonaphthyridines **4**,**5a**–**g** (Scheme 1), with reaction times from 3 to 15 min at 200 W of power and temperatures of 150–160 °C (Table 1). The reaction products were easily obtained in acceptable to good yields (49–86%) after purification by recrystallization from ethanol. Oxidized derivatives **6**,**7a**–**g** were obtained by treatment of pyrimidonaphthyridines **4**,**5a**–**g** with *p*-chloranil (as oxidizing agent) [28] under reflux in

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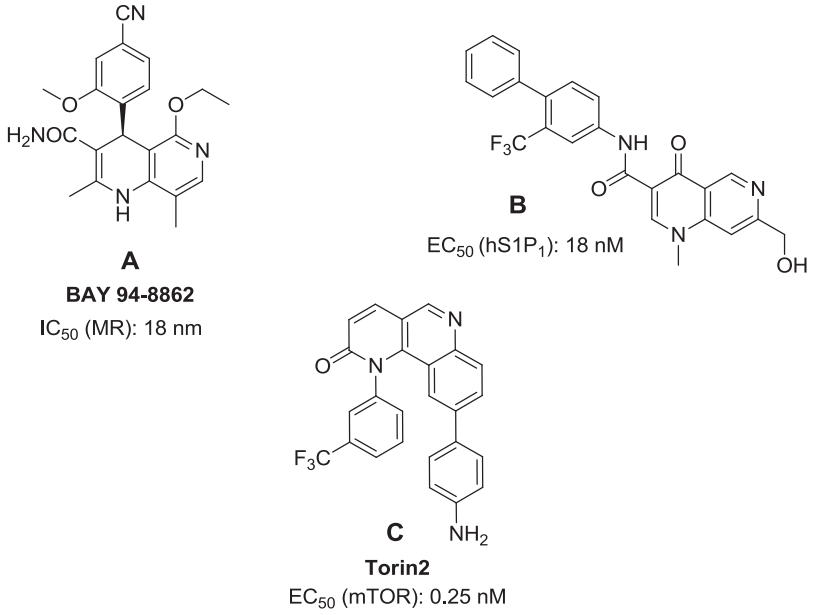


Fig. 1. Some 1,6-naphthyridines with remarkable biological activity.

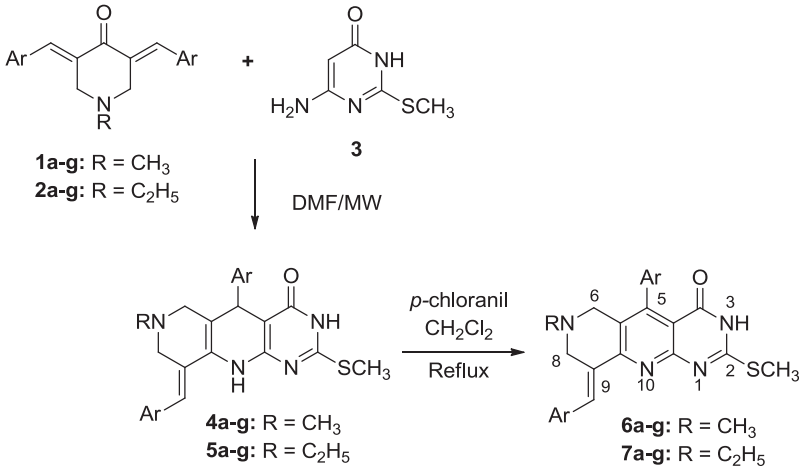
dichloromethane with reaction times of 2–3 h. Purification of these compounds was carried out both by recrystallization from ethanol or by column chromatography on silica gel using a mixture of CH_2Cl_2:CH_3OH (30:1) as eluent. The yields of these compounds ranged from 19 to 43% (Table 1).

The main difference with other previously used protocols is the absence of acid [29] or basic [30] catalysts, which has been used for the formation of analogs of the naphthyridines **4** and **5**.

The spectroscopic data are consistent with structure **5b**, which was taken as a basis for structural discussion. This compound shows the stretching band of the NH-group overlapped with the stretching vibration band of the NH-amide at 3396 cm^{-1} while the carbonyl band appears at 1634 cm^{-1}. ^1H NMR shows a singlet at 4.45 ppm corresponding to the proton H-5, a singlet at 8.49 ppm corresponding to the 10-NH proton. In the ^{13}C NMR spectrum the presence of a signal at 41.1 ppm corresponding to C-5, confirms that such structure corresponds to the dihydro derivative **5b**. The molecular ion peak (*m*/*z* 598) in the mass spectrum and the presence of the fragment *m*/*z* 443 (corresponding to the loss of the fragment C_6H_4Br) also demonstrates that this structure is the reduced form **5b**.

The IR spectrum of the oxidized compound **6b** shows the stretching band of the NH-amide at 3447 cm^{-1} and the carbonyl band at 1661 cm^{-1}. In the ^1H NMR spectrum of **6b** signals due to the H-5 and 10-NH disappear while in the ^{13}C NMR spectrum the signal of C-5 is observed at 148.3 ppm, as expected due to the oxidation process. The molecular ion peak (*m*/*z* 582) in the mass spectrum as well as the presence of the fragment *m*/*z* 427 (corresponding to the loss of the fragment C_6H_4Br) also confirm that the structure corresponds to the oxidized compound **6b**.

In Scheme 2, we postulate a plausible mechanism for the cyclocondensation reaction to form the pyrimidonaphthyridines **4** and **5**. Firstly, we assume according with the literature [30–32], that the initial step involves a Michael type addition of the C-5



a: Ar = 4-ClC_6H_4 , **b:** Ar = 4-BrC_6H_4, **c:** Ar = 4-$NO_2C_6H_4$, **d:** Ar = 4-$CH_3C_6H_4$, **e:** Ar = 4-$OCH_3C_6H_4$, **f:** Ar = 3,4-$OCH_2OC_6H_3$, **g:** Ar = 3,4,5-*tri*$OCH_3C_6H_2$

Scheme 1. Synthesis of novel pyrimido[4,5-*b*][1,6]naphthyridin-4(3*H*)-ones (**4**–**7**)**a**–**g**.

Table 1
Yields and reaction time of pyrimidonaphthyridine **4**,**5a**–**g** and **6**,**7a**–**g**.

Entry	Ar	Compound 4 R = CH_3		Compound 5 R = C_2H_5		Compound 6[a] R = CH_3		Compound 7[a] R = C_2H_5	
		(%)	MW (min)[b]	(%)	MW (min)[c]	(%)	rt (h)	(%)	rt (h)
a	4-ClC_6H_4	80	5	86	3	39	2	42	2
b	4-BrC_6H_4	78	5	85	3	43	2	40	2
c	4-$NO_2C_6H_4$	75	5	71	5	30	2	35	2
d	4-$CH_3C_6H_4$	70	7	76	10	29	2	33	2
e	4-$OCH_3C_6H_4$	55	10	61	10	21	3	25	3
f	3,4-$OCH_2OC_6H_3$	63	10	65	10	30	3	23	3
g	3,4,5-*tri* $OCH_3C_6H_2$	49	15	52	15	25	3	19	3

[a] Yields for the oxidation process from **4** and **5**.
[b] Temperature of 160 °C and 200 W of power.
[c] Temperature of 150 °C 200 W of power.

carbon atom of the pyrimidone **3** to a vinylic double bond of the *bis*(benzylidene)piperidone **1**,**2** to give the Michael adduct **8**. Then, this adduct undergoes an intramolecular nucleophilic addition (with loss of water) to afford the isolated products **4** and **5**.

2.2. In vitro anticancer activity

The two-stage screening process started with the evaluation of eighteen compounds (**4a**, **4b**, **4d**–**g**, **5a**, **5b**, **5d**–**g**, **6a**, **6d**–**g** and **7f**) selected by NCI, against the 60 cell lines at a single dose of 10.0 μM. The output from the single dose screening was reported as a mean graph available for analysis by the COMPARE program. The results of the primary assay showed that 17 of such compounds were essentially inactive, whereas compound **4g** was active (Table 2).

Then, the second screening was made in order to determine the cytostatic activity of compound **4g** against the 60 cell lines panel representing mainly, melanoma, leukemia and cancers of lung, colon, brain, breast, ovary, kidney and prostate. Compound **4g** was evaluated at five concentration levels (100, 10, 1.0, 0.1 and 0.01 μM). The test consisted of a 48 h continuous drug exposure protocol by using sulforhodamine B (SRB) protein assay to estimate cell growth. Details of this evaluation method and the complementary information related with the activity pattern over all cell lines have been published [33–35]. The compound **4g** showed a remarkable activity against 57 human tumor cell lines, being SR (Leukemia), the most sensitive strains (GI_{50} = 1.48 μM and LC_{50} > 100 M), also showing significant activity in the cell line LOX IMVI (Melanoma) (GI_{50} = 1.66 μM and LC_{50} = 9.37 μM), and HL-60(TB) (Leukemia) (GI_{50} = 2.26 μM and LC_{50} > 100 M). Its LC_{50} values between 6.08 μM and >100 μM reflect that this compound should be a lead structure for the development of a potential antitumor agent.

3. Conclusion

Cyclocondensation reaction between 6-amino-2-methylthiopyrimidin-4(3*H*)-one **3** and *bis*-(benzylidene)piperidones **1**,**2** for the formation of pyrimidonaphthyridines **4** and **5** was performed. Microwave irradiation was used as energy source, in the absence of acid or basic catalysts, as the reaction media. Treatment of dihydropyrimidonaphthyridines **4** and **5** with *p*-chloranil leads to the desired oxidized derivatives **6** and **7** in moderated yields. Anticancer screening data revealed that among the eighteen pyrimidonaphthyridines evaluated, derivative **4g** showed the highest activity against different cancer cell lines with remarkable values in leukemia and melanoma panels. This compound could be a leader structure for synthesizing new pyrimidonaphthyridine analogs with the aim to increase the antitumor activity of this family of compounds.

4. Experimental

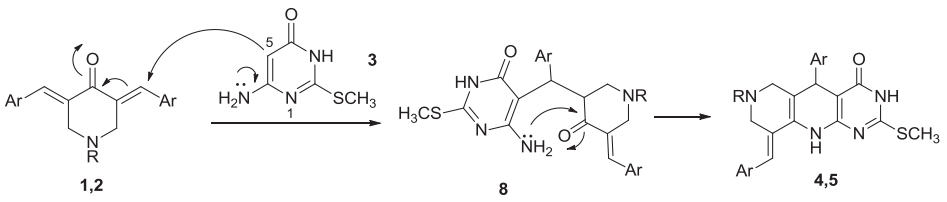
All melting points were measured using a Büchi melting point apparatus and are uncorrected. Microwave reactions were performed in glass vessels (10 mL) using a CEM Focused Microwave Synthesis System™ apparatus, Model Discover, with power output from 0 to 300 W. TLC analyses were performed on Merck TLC-plates aluminum silica gel 60 F254. IR spectra (KBr disks) were recorded on a Perkin Elmer 1650 spectrometer (USA). ^1H and ^{13}C NMR spectra were run on a Bruker DPX 400 spectrometer operating at 400 and 100 MHz, respectively, using dimethyl sulfoxide-d_6 as solvent and tetramethylsilane as internal standard. Mass spectra were obtained on a Shimadzu GCMS-QP 2010 spectrometer (equipped with a direct inlet probe) operating at 70 eV. Elemental analyses were obtained using a LECO CHNS-900 elemental analyzer.

4.1. General procedure for the synthesis of compounds *1* and *2*

A mixture of the corresponding 1-methyl(ethyl)-4-piperidone (1 mmol), the appropriate aldehyde (1 mmol), 20% aq NaOH (0.5 mL) and 95% EtOH (30 mL) was stirred at room temperature for 2–6 h. The formed solid was filtered and washed with ethanol. No further purification was needed and products were used such as were obtained.

4.2. General procedure for the synthesis of compounds *4* and *5* under microwave irradiation

A mixture of equimolar amounts of piperidone **1** or **2** (1 mmol) and aminopyrimidone **3** (1 mmol) in *N*,*N*-dimethylformamide (0.3 mL), was subjected to microwave irradiation for 3–15 min at



Scheme 2. Proposed mechanism for the formation of pyrimidonaphthyridines **4** and **5**.

Table 2
In vitro testing results expressed as growth inhibition of cancer cell lines for compound **4g**.

Compound **4g**[a]			
Most sensitive cell lines (GI_{50} < 20 μM)			
Panel	Cell line	GI_{50}(μM)[b]	LC_{50}(μM)[c]
Leukemia	HL-60(TB)	2.26	>100
	MOLT-4	2.92	>100
	SR	1.48	>100
Non-small cell lung cancer	A549/ATCC	3.26	62.5
	EKVX	8.44	>100
	HOP-62	2.46	41.3
	HOP-92	3.40	53.4
	NCI-H226	6.17	60.6
	NCI-H23	3.54	>100
	NCI-H322M	6.60	46.1
	NCI-H460	2.30	>100
	NCI-H522	2.04	15.5
Colon cancer	COLO 205	2.11	12.6
	HCC-2998	1.91	6.90
	HCT-116	1.66	6.05
	HCT-15	2.07	13.6
	HT29	2.35	16.3
	KM12	1.70	6.08
	SW-620	2.00	9.69
CNS cancer	SF-268	1.66	6.96
	SF-295	2.24	26.9
	SF-539	3.64	>100
	SNB-19	8.65	50.0
	SNB-75	7.36	57.8
	U251	1.76	9.75
Melanoma	LOX IMVI	1.66	9.37
	MALME-3M	2.82	55.5
	M14	2.98	50.9
	MDA-MB-435	2.51	39.8
	SK-MEL-2	9.92	>100
	SK-MEL-28	2.10	8.79
	SK-MEL-5	2.83	34.7
	UACC-257	2.24	29.1
	UACC-62	2.06	18.5
Ovarian cancer	IGROV1	3.10	85.8
	OVCAR-3	2.64	23.4
	OVCAR-4	4.99	81.0
	OVCAR-5	4.83	48.7
	OVCAR-8	2.89	>100
	NCI/ADR-RES	3.60	>100
	SK-OV-3	3.07	51.0
Renal cancer	786-0	4.01	87.3
	A498	9.58	46.7
	ACHN	1.93	6.53
	CAKI-1	2.15	11.9
	RXF 393	1.81	6.61
	SN12C	2.98	78.1
	TK-10	6.07	46.9
	UO-31	1.57	7.54
Prostate cancer	PC-3	3.63	>100
	DU-145	3.60	34.8
Breast cancer	MCF7	4.98	50.0
	MDA-MB-231/ATCC	3.14	50.3
	HS 578T	8.88	>100
	BT-549	2.98	29.5
	T-47D	3.69	>100
	MDA-MB-468	2.20	38.8

[a] Data obtained from NCI's in vitro disease-oriented human tumor cell lines screen [35].
[b] GI_{50} was the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. Determined at five concentration levels (100, 10, 1.0, 0.1 and 0.01 μM).
[c] LC_{50} is a parameter of cytotoxicity and reflects the molar concentration needed to kill 50% of the cells.

a power of 200 W and temperatures of 150–160 °C. The reaction mixture was cooled and cold water was added. The precipitate formed was filtered and recrystallized from ethanol to obtain compounds **4** and **5** as yellow solids.

*4.2.1. (E)-9-(4-Chlorobenzylidene)-5-(4-chlorophenyl)-7-methyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**4a**)*

It was obtained from **1a** in 80% yield; mp 257–259 °C; FTIR (KBr) υ = 3409 (NH), 2939, 1634 (C=O), 1509, 1238, 1090 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.14 (s, 3H, NCH_3), 2.54 (s, 3H, SCH_3), 2.67 (d, J = 16.3 Hz, 1H, CH_2), 2.99 (d, J = 16.3 Hz, 1H, CH_2), 3.18 (d, J = 13.8 Hz, 1H, CH_2), 3.40 (d, J = 13.8 Hz, 1H, CH_2), 4.46 (s, 1H, 5-CH), 7.06 (s, 1H, =CH), 7.25 (d, J = 8.4 Hz, 2H, Ar–H), 7.30 (d, J = 8.4 Hz, 2H, Ar–H), 7.33 (d, J = 8.3 Hz, 2H, Ar–H), 7.45 (d, J = 8.3 Hz, 2H, Ar–H), 8.51 (s, 1H, NH), 12.03 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 13.1 (SCH_3), 41.0 (C-5), 45.2 (NCH_3), 54.5 (CH_2), 56.4 (CH_2), 93.4 (C), 114.3 (C), 121.0 (CH), 127.8 (C), 128.6 (2CH), 128.8 (2CH), 129.7 (C), 129.8 (2CH), 131.2 (2CH), 131.3 (C), 131.9 (C), 136.0 (C), 145.1 (C), 154.1 (C), 160.2 (C), 162.0 (C); MS (EI): m/z 500/498/496 (8/39/58) $[M]^+$, 499/497/495 (21/79/98, $[M - H]^+$), 387/385 (38/100, $[-ClC_6H_4]$), 371 (28), 342 (22), 294 (11), 261 (14), 247 (14). Anal. Calcd. For $C_{25}H_{22}Cl_2N_4OS$ (496.1): C, 60.36; H, 4.46; N, 11.26; S, 6.45. Found: C, 60.45; H, 4.52; N, 11.32; S, 6.51.

*4.2.2. (E)-9-(4-Bromobenzylidene)-5-(4-bromophenyl)-7-methyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**4b**)*

It was obtained from **1b** in 78% yield; mp 254–255 °C; FTIR (KBr) υ = 3395 (NH), 2937, 1633 (C=O), 1507, 1237, 1070 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.56 (s, 3H, NCH_3), 2.75 (s, 3H, SCH_3), 3.48 (d, J = 15.4 Hz, 1H, CH_2), 3.81 (d, J = 15.4 Hz, 1H, CH_2), 4.92–4.29 (m, 2H, CH_2), 4.52 (s, 1H, 5-CH), 7.22 (d, J = 8.2 Hz, 2H, Ar–H), 7.29 (d, J = 8.2 Hz, 2H, Ar–H), 7.41 (s, 1H, =CH), 7.51 (d, J = 8.3 Hz, 2H, Ar–H), 7.66 (d, J = 8.3 Hz, 2H, Ar–H), 8.90 (s, 1H, NH), 12.20 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.5 (SCH_3), 40.5 (C-5), 44.6 (NCH_3), 54.0 (CH_2), 55.9 (CH_2), 92.8 (C), 113.7 (C), 119.3 (C), 119.9 (C), 120.6 (=CH), 127.3 (C), 129.2 (C), 129.7 (2CH), 131.0 (2CH), 131.1 (2CH), 131.2 (2CH), 135.8 (C), 144.9 (C), 153.5 (C), 159.7 (C), 161.4 (C); MS (EI): m/z 588/586/584 (8/62/100, $[M]^+$), 431/429 (60/77, $[-BrC_6H_4]$), 415 (36), 386 (17), 261 (22), 247 (16), 28 (78). Anal. Calcd. For $C_{25}H_{22}Br_2N_4OS$ (584.0): C, 51.21; H, 3.78; N, 9.56; S, 5.47. Found: C, 51.28; H, 3.86; N, 9.63; S, 5.54.

*4.2.3. (E)-7-Methyl-2-(methylthio)-9-(4-nitrobenzylidene)-5-(4-nitrophenyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**4c**)*

It was obtained from **1c** in 75% yield; mp 305–307 °C; FTIR (KBr) υ = 3466 (NH), 2936, 1638 (C=O), 1515, 1345, 1228, 1082 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.58 (s, 3H, NCH_3), 2.79 (s, 3H, SCH_3), 3.53 (d, J = 16.3 Hz, 1H, CH_2), 3.91 (d, J = 16.3 Hz, 1H, CH_2), 4.07–4.23 (m, 1H, CH_2), 4.28 (d, J = 13.6 Hz, 1H, CH_2), 4.76 (s, 1H, 5-CH), 7.56 (d, J = 8.8 Hz, 2H, Ar–H), 7.61 (s, 1H, =CH), 7.62 (d, J = 8.8 Hz, 2H, Ar–H), 8.22 (d, J = 8.5 Hz, 2H, Ar–H), 8.31 (d, J = 8.5 Hz, 2H, Ar–H), 9.07 (s, 1H, NH), 12.30 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 13.2 (SCH_3), 41.0 (C-5), 42.4 (NCH_3), 51.4 (CH_2), 53.3 (CH_2), 93.0 (C), 108.9 (C), 124.2 (4CH), 128.4 (C), 129.5 (=CH), 130.9 (4CH), 142.3 (2C), 147.0 (2C), 152.0 (2C), 153.9 (C), 161.7 (C); MS (EI): m/z 518 (23, $[M]^+$), 517 (45, $[M - H]^+$), 396 (24, $[-NO_2C_6H_4]$), 394 (16), 380 (18), 261 (4), 247 (5), 94 (33), 79 (23), 47 (100), 28 (71). Anal. Calcd. For $C_{25}H_{22}N_6O_5S$ (518.1): C, 57.91; H, 4.28; N, 16.21; S, 6.18. Found: C, 57.97; H, 4.35; N, 16.30; S, 6.23.

*4.2.4. (E)-7-Methyl-9-(4-methylbenzylidene)-2-(methylthio)-5-(p-tolyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**4d**)*

It was obtained from **1d** in 70% yield; mp 233–235 °C; FTIR (KBr) υ = 3416 (NH), 2923, 1638 (C=O), 1510, 1239, 1041 cm^{-1}; ^1H NMR

(400 MHz, DMSO-d_6) δ (ppm): 2.13 (s, 3H, NCH_3), 2.23 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.53 (s, 3H, SCH_3), 2.71 (d, J = 16.2 Hz, 1H, CH_2), 2.96 (d, J = 16.2 Hz, 1H, CH_2), 3.18 (d, J = 13.4 Hz, 1H, CH_2), 3.42 (d, J = 13.4 Hz, 1H, CH_2), 4.38 (s, 1H, 5-CH), 7.03 (s, 1H, =CH), 7.05 (d, J = 7.9 Hz, 2H, Ar–H), 7.12 (d, J = 7.9 Hz, 2H, Ar–H), 7.16 (d, J = 8.3 Hz, 2H, Ar–H), 7.20 (d, J = 8.3 Hz, 2H, Ar–H), 8.43 (s, 1H, NH), 11.91 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 13.1 (SCH_3), 21.1 (CH_3), 21.3 (CH_3), 41.0 (C-5), 45.2 (NCH_3), 54.7 (CH_2), 56.6 (CH_2), 93.9 (C), 114.2 (C), 121.8 (=CH), 127.5 (C), 127.9 (2CH), 128.5 (C), 129.2 (2CH), 129.4 (2CH), 129.5 (2CH), 134.2 (C), 135.7 (C), 136.5 (C), 143.4 (C), 154.1 (C), 159.8 (C), 162.1 (C); MS (EI): m/z 394 (16), 380 (18), 365 (0.4, [$-CH_3C_6H_4$]), 261 (4), 247 (5), 94 (33), 79 (23), 47 (100), 28 (71). Anal. Calcd. For $C_{27}H_{28}N_4OS$ (456.2): C, 71.02; H, 6.18; N, 12.27; S, 7.02. Found: C, 71.10; H, 6.22; N, 12.35; S, 7.09.

4.2.5. (E)-9-(4-Methoxybenzylidene)-5-(4-methoxyphenyl)-7-methyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6] naphthyridin-4(3H,5H,10H)-one (**4e**)

It was obtained from **1e** in 55% yield; mp 203–205 °C; FTIR (KBr) υ = 3410 (NH), 2936, 1633 (C=O), 1507, 1255, 1033 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.58 (s, 3H, NCH_3), 2.75 (s, 3H, SCH_3), 3.15 (d, J = 16.2 Hz, 1H, CH_2), 3.44 (d, J = 16.2 Hz, 1H, CH_2), 3.70 (d, J = 12.7 Hz, 1H, CH_2), 3.83 (s, 6H, $2OCH_3$), 3.93 (d, J = 12.7 Hz, 1H, CH_2), 4.41 (s, 1H, 5-CH), 7.01 (d, J = 8.5 Hz, 2H, Ar–H), 7.07 (d, J = 8.8 Hz, 2H, Ar–H), 7.10–7.14 (m, 3H, Ar–H and =CH), 7.48 (d, J = 8.5 Hz, 2H, Ar–H), 8.27 (s, 1H, NH), 12.48 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.8 (SCH_3), 42.2 (C-5), 45.5 (NCH_3), 52.5 (CH_2), 54.2 (CH_2), 55.0 (OCH_3), 55.3 (OCH_3), 99.4 (C), 113.6 (2CH), 114.3 (2CH), 116.8 (C), 120.7 (=CH), 125.6 (C), 128.8 (2CH), 129.8 (C), 130.6 (C), 131.8 (2CH), 138.4 (C), 151.2 (C), 151.8 (C), 158.8 (C), 160.0 (C), 162.0 (C); MS (EI): m/z 381 (1, [$-OCH_3C_6H_4$]), 358 (100), 339 (8), 251 (17), 170 (40), 74 (33), 43 (15). Anal. Calcd. For $C_{27}H_{28}N_4O_3S$ (488.2): C, 66.37; H, 5.78; N, 11.47; S, 6.56. Found: C, 66.45; H, 5.83; N, 11.52; S, 6.61.

4.2.6. (E)-5-(Benzo[d][1,3]dioxol-5-yl)-9-(benzo[d][1,3]dioxol-5-ylmethylene)-7-methyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido [4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**4f**)

It was obtained from **1f** in 63% yield; mp 187–190 °C; FTIR (KBr) υ = 3423 (NH), 2884, 1635 (C=O), 1503, 1234, 1037 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.16 (s, 3H, NCH_3), 2.40 (s, 3H, SCH_3), 2.75 (d, J = 15.9 Hz, 1H, CH_2), 2.93 (d, J = 15.9 Hz, 1H, CH_2), 3.19 (d, J = 13.6 Hz, 1H, CH_2), 3.37–3.44 (m, 1H, CH_2), 4.32 (s, 1H, 5-CH), 5.92 (m, 2H, OCH_2O), 6.03 (s, 2H, OCH_2O), 6.68–6.72 (m, 1H, Ar–H), 6.73–6.78 (m, 3H, Ar–H), 6.83 (s, 1H, Ar–H), 6.90 (s, 1H, =CH), 6.93 (d, J = 8.0 Hz, 1H, Ar–H), 7.83 (s, 1H, NH), not observed (1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 13.3 (S–CH_3), 41.6 (C-5), 45.5 (N–CH_3), 54.9 (CH_2), 56.8 (CH_2), 94.1 (C), 101.0 (OCH_2O), 101.5 (OCH_2O), 108.1 (CH), 108.6 (CH), 108.7 (CH), 109.6 (CH), 113.5 (C), 120.8 (CH), 121.0 (=CH), 123.5 (CH), 128.0 (C), 128.5 (C), 131.4 (C), 141.5 (C), 145.7 (C), 146.4 (C), 147.3 (C), 147.7 (C), 154.4 (C), 162.4 (C), 167.0 (C); MS (EI): m/z 395 (2, [$-OCH_2OC_6H_3$]), 386 (100), 353 (12), 170 (33), 74 (40), 43 (18). Anal. Calcd. For $C_{27}H_{24}N_4O_5S$ (516.2): C, 62.78; H, 4.68; N, 10.85; S, 6.21. Found: C, 62.86; H, 4.74; N, 10.92; S, 6.28.

4.2.7. (E)-7-Methyl-2-(methylthio)-9-(3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6] naphthyridin-4(3H,5H,10H)-one (**4g**)

It was obtained from **1g** in 49% yield; mp 183–185 °C; FTIR (KBr) υ = 3378 (NH), 2938, 1639 (C=O), 1504, 1237, 1125 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.20 (s, 3H, NCH_3), 2.54 (s, 3H, SCH_3), 2.80 (d, J = 16.2 Hz, 1H, CH_2), 3.00 (d, J = 16.2 Hz, 1H, CH_2), 3.30 (d, J = 13.8 Hz, 1H, CH_2), 3.51 (d, J = 13.8 Hz, 1H, CH_2), 3.63 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.71 (s, 6H, $2OCH_3$), 3.79 (s, 6H, $2OCH_3$), 4.41 (s, 1H, 5-CH), 6.54–6.57 (m, 4H, Ar–H), 7.01 (s, 1H, =CH), 8.41 (s, 1H, NH), 11.96 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 13.3 (SCH_3), 41.9 (C-5), 45.6 (NCH_3), 54.4 ($2CH_2$), 56.5 ($2OCH_3$), 56.6 ($2OCH_3$), 60.3 (OCH_3), 60.4 (OCH_3), 107.6 (2CH), 109.0 (C), 115.4 (2CH), 123.8 (C), 125.2 (=CH), 127.1 (C), 128.6 (C), 130.5 (C), 134.7 (C), 138.7 (C), 141.0 (C), 152.8 (2C), 155.0 (2C), 156.1 (C), 157.2 (C), 162.2 (C); MS (EI): m/z 478 (100), 441 (2, [$-tri$$OCH_3C_6H_2$]), 399 (11), 311 (45), 170 (21), 74 (35). Anal. Calcd. For $C_{31}H_{36}N_4O_7S$ (608.2): C, 61.17; H, 5.96; N, 9.20; S, 5.27. Found: C, 61.23; H, 6.05; N, 9.27; S, 5.31.

4.2.8. (E)-9-(4-Chlorobenzylidene)-5-(4-chlorophenyl)-7-ethyl-2-(methylthio)-5,6,7,8,9,10-hexahydropyrimido[4,5-b][1,6] naphthyridin-4(3H)-one (**5a**)

It was obtained from **2a** in 86% yield; mp 247–249 °C; FTIR (KBr) υ = 3410 (NH), 2933, 1635 (C=O), 1509, 1238, 1091 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.84 (t, J = 7.0 Hz, 3H, $NCH_2\underline{CH_3}$), 2.21–2.37 (m, 2H, $NC\underline{H_2}CH_3$), 2.53 (s, 3H, SCH_3), 2.70 (d, J = 16.4 Hz, 1H, CH_2), 3.08 (d, J = 16.4 Hz, 1H, CH_2), 3.19 (d, J = 13.6 Hz, 1H, CH_2), 3.48 (d, J = 13.6 Hz, 1H, CH_2), 4.46 (s, 1H, 5-CH), 7.05 (s, 1H, =CH), 7.23–7.27 (m, 2H, Ar–H), 7.27–7.35 (m, 4H, Ar–H), 7.44 (d, J = 7.8 Hz, 2H, Ar–H), 8.50 (s, 1H, NH), 12.03 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.5 ($NCH_2\underline{CH_3}$), 13.1 (SCH_3), 41.0 (C-5), 50.8 ($N\underline{CH_2}CH_3$), 52.2 (CH_2), 54.1 (CH_2), 93.4 (C), 114.2 (C), 121.0 (=CH), 128.0 (C), 128.6 (2CH), 128.8 (2CH), 129.7 (C), 129.8 (2CH), 131.3 (2CH), 131.3 (C), 131.8 (C), 136.0 (C), 145.1 (C), 154.0 (C=O), 160.1 (C), 162.0 (C); MS (EI): m/z 514/512/510 (16/32/53, [M]$^+$), 513/511/509 (18/74/100, [M – H]$^+$), 401/399 (12/32, [$-ClC_6H_4$]), 385 (19), 369 (13), 124 (15), 111 (14), 57 (27), 44 (59), 43 (52). Anal. Calcd. For $C_{26}H_{24}Cl_2N_4OS$ (510.1): C, 61.06; H, 4.73; N, 10.95; S, 6.27. Found: C, 61.12; H, 4.85; N, 11.05; S, 6.30.

4.2.9. (E)-9-(4-Bromobenzylidene)-5-(4-bromophenyl)-7-ethyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**5b**)

It was obtained from **2b** in 85% yield; mp 251–253 °C; FTIR (KBr) υ = 3396 (NH), 2931, 1634 (C=O), 1507, 1237, 1096 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.85 (t, J = 7.0 Hz, 3H, $NCH_2\underline{CH_3}$), 2.22–2.37 (m, 2H, $NC\underline{H_2}CH_3$), 2.53 (s, 3H, SCH_3), 2.70 (d, J = 16.4 Hz, 1H, CH_2), 3.08 (d, J = 16.4 Hz, 1H, CH_2), 3.19 (d, J = 13.8 Hz, 1H, CH_2), 3.49 (d, J = 13.8 Hz, 1H, CH_2), 4.45 (s, 1H, 5-CH), 7.03 (s, 1H, =CH), 7.20 (d, J = 8.5 Hz, 2H, Ar–H), 7.24 (d, J = 8.5 Hz, 2H, Ar–H), 7.46 (d, J = 8.5 Hz, 2H, Ar–H), 7.58 (d, J = 8.5 Hz, 2H, Ar–H), 8.49 (s, 1H, NH), 11.99 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.5 ($NCH_2\underline{CH_3}$), 13.1 (SCH_3), 41.1 (C-5), 50.8 ($N\underline{CH_2}CH_3$), 52.2 (CH_2), 54.1 (CH_2), 93.3 (C), 114.1 (C), 119.8 (C), 120.4 (C), 121.1 (=CH), 128.1 (C), 129.7 (C), 130.2 (2CH), 131.5 (2CH), 131.6 (2CH), 131.7 (2CH), 136.4 (C), 145.6 (C), 154.0 (C), 160.2 (C), 162.3 (C); MS (EI): m/z 603/601/599 (3/20/41, [M + H]$^+$), 602/600/598 (8/19/15, [M]$^+$), 445/443 (6/11, [$-BrC_6H_4$]), 429 (11), 262 (8), 168 (17), 152 (24), 57 (42), 44 (100), 43 (86). Anal. Calcd. For $C_{26}H_{24}Br_2N_4OS$ (598.0): C, 52.01; H, 4.03; N, 9.33; S, 5.34. Found: C, 52.09; H, 4.11; N, 9.42; S, 5.40.

4.2.10. (E)-7-Ethyl-2-(methylthio)-9-(4-nitrobenzylidene)-5-(4-nitrophenyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**5c**)

It was obtained from **2c** in 71% yield; mp 225–227 °C; FTIR (KBr) υ = 3321 (NH), 2923, 1630 (C=O), 1514, 1343, 1241, 1090 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.85 (t, J = 7.2 Hz, 3H, $NCH_2\underline{CH_3}$), 2.25–2.41 (m, 2H, $NC\underline{H_2}CH_3$), 2.54 (s, 3H, SCH_3), 2.69 (d, J = 16.7 Hz, 1H, CH_2), 3.17 (d, J = 16.7 Hz, 1H, CH_2), 3.26 (d, J = 13.8 Hz, 1H, CH_2), 3.56 (d, J = 13.8 Hz, 1H, CH_2), 4.68 (s, 1H, 5-CH), 7.23 (s, 1H, =CH), 7.53 (d, J = 8.8 Hz, 2H, Ar–H), 7.56 (d, J = 8.8 Hz, 2H, Ar–H), 8.17 (d, J = 8.8 Hz, 2H, Ar–H), 8.25 (d, J = 8.8 Hz, 2H, Ar–H), 8.62 (s, 1H, NH), 12.10 (br s,

1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.5 ($NCH_2\underline{C}H_3$), 13.1 (SCH_3), 41.8 (C-5), 50.7 ($N\underline{C}H_2CH_3$), 52.2 (CH_2), 54.1 (CH_2), 92.8 (C), 115.0 (C), 120.9 (=CH), 124.0 (4CH), 128.6 (C), 129.2 (2CH), 130.6 (2CH), 132.2 (C), 144.2 (C), 146.2 (C), 146.6 (C), 153.6 (C), 154.2 (C), 161.0 (C), 162.5 (C). MS (EI): *m/z* 367 (4), 236 (14), 135 (15), 123 (15), 57 (100), 43 (94). Anal. Calcd. For $C_{26}H_{24}N_6O_5S$ (532.2): C, 58.64; H, 4.54; N, 15.78; S, 6.02. Found: C, 58.72; H, 4.59; N, 15.85; S, 6.11.

*4.2.11. (E)-7-Ethyl-9-(4-methylbenzylidene)-2-(methylthio)-5-(p-tolyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**5d**)*

It was obtained from **2d** in 76% yield; mp 233–235 °C; FTIR (KBr) υ = 3421 (NH), 2925, 1637 (C=O), 1509, 1235, 1084 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.78–0.91 (m, 3H, $NCH_2C\underline{H}_3$), 2.23 (s, 3H, CH_3), 2.27–2.37 (m, 5H, CH_3 and $NC\underline{H}_2CH_3$), 2.54 (s, 3H, SCH_3), 2.74 (d, J = 16.1 Hz, 1H, CH_2), 3.05 (d, J = 16.1 Hz, 1H, CH_2), 3.21 (d, J = 13.3 Hz, 1H, CH_2), 3.51 (d, J = 13.3 Hz, 1H, CH_2), 4.37 (s, 1H, 5-CH), 6.98–7.27 (m, 9H, Ar–H and =CH), 8.43 (s, 1H, NH), 11.97 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.1 ($NCH_2\underline{C}H_3$), 12.6 (SCH_3), 20.7 (CH_3), 20.8 (CH_3), 40.6 (C-5), 50.5 ($N\underline{C}H_2CH_3$), 51.8 (CH_2), 53.9 (CH_2), 93.4 (C), 119.7 (C), 121.4 (=CH), 123.6 (C), 127.4 (2CH), 128.7 (2CH), 129.0 (2CH), 129.0 (2CH), 129.6 (C), 131.6 (C), 134.4 (C), 136.0 (C), 141.1 (C), 142.5 (C), 155.2 (C), 160.0 (C); MS (EI): 379 (0.1, [$-CH_3C_6H_4$]) 333 (7), 231 (19), 205 (92), 163 (67), 145 (100), 104 (66). Anal. Calcd. For $C_{28}H_{30}N_4OS$ (470.2): C, 71.46; H, 6.43; N, 11.90; S, 6.81. Found: C, 71.52; H, 6.52; N, 11.98; S, 6.87.

*4.2.12. (E)-7-Ethyl-9-(4-methoxybenzylidene)-5-(4-methoxyphenyl)-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**5e**)*

It was obtained from **2e** in 61% yield; mp 185–188 °C; FTIR (KBr) υ = 3388 (NH), 2932, 1640 (C=O), 1509, 1250, 1031 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.85 (t, J = 7.2 Hz, 3H, $NCH_2C\underline{H}_3$), 2.26–2.35 (m, 2H, $NC\underline{H}_2CH_3$), 2.50 (3H, SCH_3, overlapping with DMSO), 2.75 (d, J = 16.3 Hz, 1H, CH_2), 3.03 (d, J = 16.3 Hz, 1H, CH_2), 3.21 (d, J = 13.4 Hz, 1H, CH_2), 3.51 (d, J = 13.4 Hz, 1H, CH_2), 3.70 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.35 (s, 1H, 5-CH), 6.81 (d, J = 8.8 Hz, 2H, Ar–H), 6.94–6.98 (m, 3H, Ar–H and =CH), 7.15 (d, J = 8.5 Hz, 2H, Ar–H), 7.22 (d, J = 8.8 Hz, 2H, Ar–H), 8.26 (s, 1H, NH), not observed (1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.6 ($NCH_2\underline{C}H_3$), 13.1 (SCH_3), 40.7 (C-5), 51.0 ($N\underline{C}H_2CH_3$), 52.4 (CH_2), 54.4 (CH_2), 55.4 (OCH_3), 55.5 (OCH_3), 94.1 (C), 113.6 (C), 113.9 (2CH), 114.3 (2CH), 121.3 (=CH), 127.7 (C), 127.8 (C), 128.9 (2CH), 129.6 (C), 130.9 (2CH), 138.8 (C), 154.1 (C), 158.1 (C), 158.5 (C), 160.3 (C), 162.1 (C); MS (EI): 395 (2, [$-OCH_3C_6H_4$]), 349 (15), 231 (17), 221 (73), 163 (61), 145 (88), 120 (100), 55 (70), 29 (62). Anal. Calcd. For $C_{28}H_{30}N_4O_3S$ (502.2): C, 66.91; H, 6.02; N, 11.15; S, 6.38. Found: C, 66.99; H, 6.11; N, 11.20; S, 6.47.

*4.2.13. (E)-5-(Benzo[d][1,3]dioxol-5-yl)-9-(benzo[d][1,3]dioxol-5-ylmethylene)-7-ethyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**5f**)*

It was obtained from **2f** in 65% yield; mp 201–203 °C; FTIR (KBr) υ = 3309 (NH), 2925, 1636 (C=O), 1496, 1241, 1036 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.87 (t, J = 7.0 Hz, 3H, $NCH_2C\underline{H}_3$), 2.27–2.39 (m, 2H, $NC\underline{H}_2CH_3$), 2.54 (s, 3H, SCH_3), 2.77 (d, J = 16.3 Hz, 1H, CH_2) 3.06 (d, J = 16.3 Hz, 1H, CH_2), 3.23 (d, J = 13.6 Hz, 1H, CH_2), 3.51 (d, J = 13.6 Hz, 1H, CH_2), 4.36 (s, 1H, 5-CH), 5.95 (d, J = 4.0 Hz, 2H, OCH_2O), 6.04 (s, 2H, OCH_2O), 6.70 (dd, J = 7.9, 1.6 Hz, 1H, Ar–H), 6.74–6.81 (m, 3H, Ar–H), 6.84–6.86 (m, 1H, Ar–H), 6.92–6.97 (m, 2H, Ar–H and =CH), 8.41 (s, 1H, NH), 11.98 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.6 ($NCH_2\underline{C}H_3$), 13.1 (SCH_3), 41.0 (C-5), 50.9 ($N\underline{C}H_2CH_3$), 52.3 (CH_2), 54.2 (CH_2), 93.9 (C), 101.2 (OCH_2O), 101.5 (OCH_2O), 108.3 (CH), 108.4 (CH), 108.7 (CH), 109.5 (CH), 113.8 (C), 120.8 (CH), 121.9 (=CH), 123.5 (CH), 127.8 (C), 128.0 (C), 131.1 (C), 140.5 (C), 146.1 (C), 146.6 (C), 147.5 (C), 147.7 (C), 153.9 (C), 159.8 (C), 162.0 (C); MS (EI): *m/z* 409 (1, [$-OCH_2OC_6H_3$]), 363 (10), 235 (85), 231 (21), 163 (55), 145 (100), 134 (70), 74 (40), 55 (32). Anal. Calcd. For $C_{28}H_{26}N_4O_5S$ (530.2): C, 63.38; H, 4.94; N, 10.56; S, 6.04. Found: C, 63.46; H, 5.01; N, 10.63; S, 6.08.

*4.2.14. (E)-7-Ethyl-2-(methylthio)-9-(3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H,5H,10H)-one (**5g**)*

It was obtained from **2g** in 52% yield; mp 169–170 °C; FTIR (KBr) υ = 3316 (NH), 2936, 1642 (C=O), 1588, 1505, 1235, 1125 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.88 (t, J = 7.3 Hz, 3H, NCH_2CH_3), 2.36–2.45 (m, 2H, NCH_2CH_3), 2.45 (s, 3H, SCH_3), 2.85 (d, J = 16.4 Hz, 1H, CH_2), 3.08 (d, J = 16.4 Hz, 1H, CH_2), 3.16 (d, J = 14.8 Hz, 1H, CH_2), 3.31–3.36 (m, 1H, CH_2, overlapping with water), 3.69 (s, 3H, OCH_3), 3.70 (s, 6H, $2OCH_3$), 3.77 (s, 3H, OCH_3), 3.79 (s, 6H, $2OCH_3$), 4.42 (s, 1H, 5-CH), 6.57 (s, 4H, Ar–H), 6.98 (s, 1H, =CH), 8.30 (s, 1H, NH), not observed (1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.2 (NCH_2CH_3), 12.4 (SCH_3), 41.1 (C-5), 50.2 (NCH_2CH_3), 51.9 (CH_2), 54.8 (CH_2), 55.9 ($2OCH_3$), 55.9 ($2OCH_3$), 59.9 (OCH_3), 60.0 (OCH_3), 93.0 (C), 105.1 (2CH), 106.6 (2CH), 113.0 (C), 121.0 (C), 121.3 (=CH), 127.7 (C), 128.1 (C), 132.3 (C), 136.2 (C), 136.5 (C), 152.6 (2C), 152.7 (2C), 153.7 (C), 161.1 (C), 162.3 (C); MS (EI): *m/z* 622 (34, [M]$^+$), 523 (36), 424 (39), 353 (16), 257 (52), 181 (100), 167 (22), 58 (72), 45 (45), 43 (34). Anal. Calcd. For $C_{32}H_{38}N_4O_7S$ (622.3): C, 61.72; H, 6.15; N, 9.00; S, 5.15. Found: C, 61.80; H, 6.19; N, 9.09; S, 5.22.

*4.3. General procedure for the synthesis of compounds **6** and **7***

Hydronaphthyridines **4** and **5** (1 mmol) were treated with *p*-chloranil (1 mmol) in refluxing dichloromethane, with reaction times of 2–3 h and TLC control. The reaction mixtures were cooled to ambient temperature and the precipitates formed were filtrated and purified by column chromatography on silica gel using a mixture of CH_2Cl_2:CH_3OH (30:1) as eluent to afford compounds **6** and **7** as yellow solids.

*4.3.1. (E)-9-(4-Chlorobenzylidene)-5-(4-chlorophenyl)-7-methyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**6a**)*

It was obtained from **1a** in 39% yield; mp 234–236 °C; FTIR (KBr) υ = 3456 (NH), 2849, 1664 (C=O), 1547, 1373, 1090 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.45 (s, 3H, NCH_3), 2.50 (s, 3H, SCH_3, overlapping with DMSO), 4.16 (s, 2H, CH_2), 4.48 (s, 2H, CH_2), 7.30 (d, J = 8.4 Hz, 2H, Ar–H), 7.33 (d, J = 8.4 Hz, 2H, Ar–H), 7.46 (d, J = 8.3 Hz, 2H, Ar–H), 7.51 (d, J = 8.3 Hz, 2H, Ar–H), 8.39 (s, 1H, =CH), not observed (1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 13.1 (SCH_3), 46.6 (NCH_3), 54.5 (CH_2), 54.8 (CH_2), 106.3 (C), 120.1 (C), 127.5 (2CH), 127.9 (=CH), 130.2 (2CH), 130.5 (2CH), 132.5 (C), 133.9 (C), 134.4 (C), 137.4 (2CH), 137.7 (C), 143.0 (C), 146.7 (C), 152.5 (C), 155.7 (C), 157.4 (C), 160.5 (C); MS (EI): *m/z* 498/496/494 (5/32/40, [M]$^+$), 405/403/401 (3/27/39), 385/383 (37/100, [$-ClC_6H_4$]), 369 (16), 275 (47), 124 (35). Anal. Calcd. For $C_{25}H_{20}Cl_2N_4OS$ (494.1): C, 60.61; H, 4.07; N, 11.31; S, 6.47. Found: C, 60.69; H, 4.12; N, 11.38; S, 6.53.

*4.3.2. (E)-9-(4-Bromobenzylidene)-5-(4-bromophenyl)-7-methyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**6b**)*

It was obtained from **1b** in 43% yield; mp 240–242 °C; FTIR (KBr) υ = 3447 (NH), 2935, 1661 (C=O), 1545, 1372, 1071 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.24 (s, 3H, NCH_3), 2.62 (s, 3H, NCH_3), 3.16 (s, 2H, CH_2), 3.61 (s, 2H, CH_2), 7.16 (d, J = 8.0 Hz, 2H, Ar–H), 7.42 (d, J = 8.3 Hz, 2H, Ar–H), 7.64 (d, J = 8.3 Hz, 2H, Ar–H), 7.61 (d, J = 8.0 Hz, 2H, Ar–H), 8.07 (s, 1 H, =CH), not observed (1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 13.2 (SCH_3), 43.8 (NCH_3),

52.0 ($2CH_2$), 109.8 (C), 120.6 (2C), 124.4 (C), 128.6 (=CH), 129.4 (2CH), 130.8 (2CH), 130.9 (C), 131.3 (4CH), 131.5 (2C), 148.3 (C), 152.7 (C), 154.6 (C), 158.6 (C), 160.5 (C); MS (EI): *m/z* 587/585/583 (32/74/37, $[M + H]^+$), 586/584/582 (28/65/35, $[M]^+$), 493/491/489 (30/53/28), 429/427 (89/100, $[-BrC_6H_4]$), 417 (25), 319 (55), 168 (42). Anal. Calcd. For $C_{25}H_{20}Br_2N_4OS$ (582.0): C, 51.39; H, 3.45; N, 9.59; S, 5.49. Found: C, 51.44; H, 3.52; N, 9.65; S, 5.52.

4.3.3. (E)-7-Methyl-2-(methylthio)-9-(4-nitrobenzylidene)-5-(4-nitrophenyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**6c**)

It was obtained from **1c** in 30% yield; mp 212–213 °C; FTIR (KBr) υ = 3463 (NH), 2931, 1642 (C=O), 1515, 1344, 1107 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.23 (s, 3H, NCH_3), 2.63 (s, 3H, SCH_3), 3.42 (s, 2H, CH_2, overlapping with water), 3.90 (s, 2H, CH_2), 7.49 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.67 (d, *J* = 9.0 Hz, 2H, Ar–H), 7.76 (d, *J* = 8.0 Hz, 2H, Ar–H), 8.31 (d, *J* = 9.0 Hz, 2H, Ar–H), 8.47 (s, 1H,]CH), not observed (1H, NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 12.9 (SCH_3), 43.8 (NCH_3), 54.5 (CH_2), 55.1 (CH_2), 108.0 (C), 121.2 (2CH), 121.4 (2CH), 125.8 (2CH), 127.3 (C), 127.9 (]CH), 128.0 (2CH), 135.6 (C), 141.5 (C), 143.5 (C), 144.3 (C), 144.9 (C), 147.6 (C), 152.8 (C), 155.7 (C), 158.5 (C), 160.2 (C); MS (EI): *m/z* 516 (31) $[M]^+$, 423 (42), 394 (100) $[-NO_2C_6H_4]$, 380 (25), 286 (43), 135 (21). Anal. Calcd. For $C_{25}H_{20}N_6O_5S$ (516.1): C, 58.13; H, 3.90; N, 16.27; S, 6.21. Found: C, 58.20; H, 3.99; N, 16.34; S, 6.27.

4.3.4. (E)-7-Methyl-9-(4-methylbenzylidene)-2-(methylthio)-5-(p-tolyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**6d**)

It was obtained from **1d** in 29% yield; mp 237–239 °C; FTIR (KBr) υ = 3379 (NH), 2923, 1687 (C=O), 1544, 1373, 1178 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.21 (s, 3H, NCH_3); 2.26–2.41 (m, 6H, $2CH_3$); 2.64 (s, 3H, SCH_3); 3.35 (s, 2H, CH_2), 3.79 (s, 2H, CH_2), 7.06 (d, *J* = 7.4 Hz, 2H, Ar–H); 7.24 (d, *J* = 7.4 Hz, 2H, Ar–H); 7.28 (d, *J* = 7.5 Hz, 2H, Ar–H); 7.38 (d, *J* = 7.5 Hz, 2H, Ar–H); 8.11 (s, 1H,]CH); 12.39 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.9 (SCH_3); 20.8 (CH_3) 20.8 (CH_3) 44.0 (NCH_3) 52.1 ($2CH_2$) 111.5 (C) 120.9 (C) 127.3 (2CH) 128.5 (]CH) 129.2 (2CH) 129.4 (C) 129.6 (4CH) 133.1 (C) 134.2 (C) 136.5 (C) 137.8 (C) 144.2 (C) 150.5 (C) 154.7 (C) 160.3 (C) 160.5 (C); MS (EI): *m/z* 454 (10, $[M]^+$), 363 (100, $[-CH_3C_6H_4]$), 361 (45), 349 (22), 255 (61), 104 (51). Anal. Calcd. For $C_{27}H_{26}N_4OS$ (454.2): C, 71.34; H, 5.76; N, 12.32; S, 7.05. Found: C, 71.41; H, 5.85; N, 12.39; S, 7.12.

4.3.5. (E)-9-(4-Methoxybenzylidene)-5-(4-methoxyphenyl)-7-methyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**6e**)

It was obtained from **1e** in 21% yield; mp 225–227 °C; FTIR (KBr) υ = 3385 (NH), 2935, 1681 (C=O), 1511, 1377, 1251, 1177 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.41 (s, 3H, NCH_3), 2.46 (s, 3H, SCH_3), 3.27 (s, 2H, CH_2), 3.73 (s, 2H, CH_2), 3.83 (s, 6H, $2OCH_3$), 7.03 (d, *J* = 8.8 Hz, 4H, Ar–H), 7.43 (d, *J* = 8.8 Hz, 4H, Ar–H), 7.55 (s, 1H,]CH), 11.55 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.0 (SCH_3), 44.6 (NCH_3), 54.9 ($2OCH_3$), 56.0 ($2CH_2$), 91.9 (C), 114.0 (4CH), 127.1 (3C), 131.6 (4CH and C), 133.7 (]CH), 157.6 (3C), 159.8 (2C), 160.7 (C), 163.5 (C); MS (EI): *m/z* 486 (37, $[M]^+$), 393 (44), 379 (100, $[-OCH_3C_6H_4]$), 365 (25), 271 (40), 121 (37). Anal. Calcd. For $C_{27}H_{26}N_4O_3S$ (486.2): C, 66.65; H, 5.39; N, 11.51; S, 6.59. Found: C, 66.73; H, 5.42; N, 11.58; S, 6.64.

4.3.6. (E)-5-(Benzo[d][1,3]dioxol-5-yl)-9-(benzo[d][1,3]dioxol-5-ylmethylene)-7-methyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**6f**)

It was obtained from **1f** in 30% yield; mp 250–252 °C; FTIR (KBr) υ = 3326 (NH), 2889, 1666 (C=O), 1543, 1373, 1238, 1041 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.31 (s, 3H, NCH_3), 2.62 (s, 3H, SCH_3), 3.29 (s, 2H, CH_2), 3.66–3.73 (m, 2H, CH_2), 6.03–6.12 (m, 4H, $2OCH_2O$), 6.60 (d, *J* = 7.8 Hz, 1H, Ar–H), 6.77 (s, 1H, Ar–H), 6.90–7.08 (m, 4H, Ar–H), 8.04 (s, 1H,]CH), 12.37 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.8 (SCH_3), 44.9 (NCH_3), 54.7 (CH_2), 55.1 (CH_2), 100.9 (OCH_2O), 101.3 (OCH_2O), 107.9 (CH), 108.4 (CH), 108.4 (CH), 109.5 (CH), 111.4 (C), 120.7 (CH), 124.4 (CH), 126.6 (C), 129.5 (]CH),129.9 (C), 130.7 (C), 144.0 (C), 146.4 (C), 146.9 (C), 147.1 (C), 147.5 (C), 149.4 (C), 154.5 (C), 157.1 (C), 160.4 (C), 161.4 (C); MS (EI): *m/z* 514 (21, $[M]^+$), 421 (57), 393 (100, $[-OCH_2OC_6H_3]$), 379 (17), 285 (37), 134 (29). Anal. Calcd. For $C_{27}H_{22}N_4O_5S$ (514.1): C, 63.02; H, 4.31; N, 10.89; S, 6.23. Found: C, 63.11; H, 4.38; N, 10.92; S, 6.28.

4.3.7. (E)-7-Methyl-2-(methylthio)-9-(3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**6g**)

It was obtained from **1g** in 25% yield; mp 193–195 °C; FTIR (KBr) υ = 3422 (NH), 2940, 1686 (C=O), 1590, 1330, 1124 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.34 (s, 3H, NCH_3), 2.89 (s, 3H, SCH_3), 3.62–3.64 (m, 2H, CH_2), 3.75–3.82 (m, 11H, $3OCH_3$ and CH_2) 3.86–3.87 (m, 9H, $3OCH_3$), 6.82 (s, 2H, Ar–H), 7.25 (s, 2H Ar–H), 8.31 (s, 1H,]CH), not observed (1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 13.3 (SCH_3), 41.9 (NCH_3), 54.8 ($2CH_2$), 56.0 ($2OCH_3$), 56.1 ($2OCH_3$), 60.1 (OCH_3), 60.2 (OCH_3), 105.0 (C), 106.8 (4CH), 114.4 (]CH), 120.7 (2C), 131.6 (C), 144.0 (3C), 152.9 (2C), 153.3 (C), 155.3 (2C), 156.7 (C), 157.9 (C), 161.1 (C), 162.9 (C); MS (EI): *m/z* 606 (5, $[M]^+$), 513 (42), 439 (100, $[-triOCH_3C_6H_2]$), 425 (15), 331 (57), 180 (73). Anal. Calcd. For $C_{31}H_{34}N_4O_7S$ (606.2): C, 61.37; H, 5.65; N, 9.23; S, 5.29. Found: C, 61.42; H, 5.69; N, 9.28; S, 5.34.

4.3.8. (E)-9-(4-Chlorobenzylidene)-5-(4-chlorophenyl)-7-ethyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**7a**)

It was obtained from **2a** in 42% yield; mp 224–225 °C; FTIR (KBr) υ = 3380 (NH), 2975, 1664 (C=O), 1550, 1227, 1090 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.91 (t, *J* = 7.0 Hz, 3H, $NCH_2\underline{CH_3}$), 2.59–2.72 (m, 5H, $N\underline{CH_2}CH_3$ and SCH_3), 3.36 (2H, CH_2, overlapping with water), 3.95 (br s, 2H, CH_2), 7.23 (d, *J* = 8.3 Hz, 2H, Ar–H), 7.50 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.53 (s, 4H, Ar–H), 8.17 (s, 1H,]CH), 12.52 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.9 ($2CH_3$, $NCH_2\underline{CH_3}$ and SCH_3), 50.2 ($N\underline{CH_2}CH_3$), 50.4 (CH_2), 50.5 (CH_2), 110.8 (C), 120.7 (2C), 123.9 (C), 124.0 (C), 128.1 (2CH), 128.7 (2CH), 129.3 (2CH), 131.6 (3CH, 2Ar and]CH), 132.3 (C), 141.6 (C), 144.1 (2C), 157.1 (C), 160.5 (C), 162.0 (C); MS (EI): *m/z* 512/510/508 (7/23/37, $[M]^+$), 439/437/435 (1/9/16), 385/383 (22/80, $[-ClC_7H_6]$), 324 (61), 269 (56), 219 (46), 192 (100). Anal. Calcd. For $C_{26}H_{22}Cl_2N_4OS$ (508.1): C, 61.30; H, 4.35; N, 11.00; S, 6.29. Found: C, 61.39; H, 4.42; N, 11.08; S, 6.36.

4.3.9. (E)-9-(4-Bromobenzylidene)-5-(4-bromophenyl)-7-ethyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**7b**)

It was obtained from **2b** in 40% yield; mp 263–265 °C; FTIR (KBr) υ = 3450 (NH), 3006, 1661 (C=O), 1547, 1251, 1070 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.84 (t, *J* = 7.0 Hz, 3H, $NCH_2\underline{CH_3}$), 2.38–2.44 (m, 2H, $N\underline{CH_2}CH_3$), 2.62 (s, 3H, SCH_3), 3.22 (s, 2H, CH_2), 3.67 (s, 2H, CH_2), 7.16 (d, *J* = 8.3 Hz, 2H, Ar–H), 7.43 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.61 (d, *J* = 8.3 Hz, 2H, Ar–H), 7.64 (d, *J* = 8.5 Hz, 2H, Ar–H), 8.06 (s, 1H,]CH), 12.45 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 11.4 ($NCH_2\underline{CH_3}$), 12.4 (SCH_3), 49.7 ($N\underline{CH_2}CH_3$), 51.8 (CH_2), 52.1 (CH_2), 110.9 (C), 120.2 (C), 120.7 (C), 126.5 (C), 127.9 (2CH), 129.2 (2CH), 130.4 (2CH), 130.8 (]CH), 131.1 (2CH), 133.1 (C), 135.0 (C), 136.2 (C), 148.3 (C), 155.2 (C), 157.6 (C), 161.0 (C), 161.9 (C); MS (EI): *m/z* 601/599/597

(15/41/43, $[M + H]^+$), 600/598/596 (42/68/40, $[M]^+$), 553/551/549 (5/53/29), 525/523/521 (3/21/13), 429/427 (65/71, $[-BrC_7H_6]$), 368 (55), 313 (69), 264 (54), 236 (100). Anal. Calcd. For $C_{26}H_{22}Br_2N_4OS$ (596.0): C, 52.19; H, 3.71; N, 9.36; S, 5.36. Found: C, 52.25; H, 3.79; N, 9.42; S, 5.40.

4.3.10. (E)-7-Ethyl-2-(methylthio)-9-(4-nitrobenzylidene)-5-(4-nitrophenyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**7c**)

It was obtained from **2c** in 35% yield; mp 220–222 °C; FTIR (KBr) υ = 3380 (NH), 2987, 1667 (C=O), 1545, 1256, 1085 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.85 (t, J = 7.0 Hz, 3H, NCH_2CH_3), 2.62 (s, 3H, SCH_3), 2.62–2.68 (m, 2H, NCH_2CH_3), 3.27 (s, 2H, CH_2), 3.72 (s, 2H, CH_2), 7.37 (d, J = 9.0 Hz, 2H, Ar–H), 7.65 (d, J = 9.0 Hz, 2H, Ar–H), 8.29 (d, J = 9.0 Hz, 2H, Ar–H), 8.37–8.42 (m, 3H, Ar–H and]CH), not observed (1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.6 (NCH_2CH_3), 13.7 (SCH_3), 51.2 (NCH_2CH_3), 51.6 (CH_2), 51.8 (CH_2), 107.8 (C), 120.9 (2CH), 121.2 (2CH), 125.5 (2CH), 127.0 (C), 127.6 (]CH), 127.8 (2CH), 135.3 (C), 141.3 (C), 143.2 (C), 144.0 (C), 144.6 (C), 147.3 (C), 152.6 (C), 155.5 (C), 158.3 (C), 159.9 (C); MS (EI): m/z 530 (9) $[M]^+$, 485 (29), 457 (15), 394 (100, $[-NO_2C_7H_6]$), 335 (45), 280 (41), 231 (71), 203 (92). Anal. Calcd. For $C_{26}H_{22}N_6O_5S$ (530.1): C, 58.86; H, 4.18; N, 15.84; S, 6.04. Found: C, 58.91; H, 4.25; N, 15.93; S, 6.09.

4.3.11. (E)-7-Ethyl-9-(4-methylbenzylidene)-2-(methylthio)-5-(p-tolyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**7d**)

It was obtained from **2d** in 33% yield; mp 208–210 °C; FTIR (KBr) υ = 3350 (NH), 2978, 1664 (C=O), 1545, 1229, 1088 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.82 (t, J = 6.8 Hz, 3H, NCH_2CH_3), 2.31–2.42 (m, 8H, $2CH_3$ and NCH_2CH_3), 2.62 (s, 3H, SCH_3), 3.23 (s, 2H, CH_2), 3.70 (s, 2H, CH_2), 7.04 (d, J = 7.4 Hz, 2H, Ar–H), 7.22 (d, J = 7.4 Hz, 2H, Ar–H), 7.26 (d, J = 7.5 Hz, 2H, Ar–H), 7.36 (d, J = 7.5 Hz, 2H, Ar–H), 8.09 (s, 1H,]CH), 12.37 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.4 (NCH_2CH_3 and SCH_3), 20.4 (CH_3), 20.4 (CH_3), 49.6 (NCH_2CH_3), 51.3 (CH_2), 51.7 (CH_2), 111.0 (C), 120.4 (C), 126.8 (3CH, 2Ar and]CH), 128.1 (2CH), 128.8 (2CH), 128.9 (C), 129.2 (2CH), 132.7 (C), 133.8 (C), 136.0 (C), 137.3 (C), 143.8 (C), 150.0 (C), 156.7 (C), 159.9 (C), 160.1 (C); MS (EI): m/z 468 (20) $[M]^+$, 423 (33), 395 (23), 378 (2), 363 (100, $[-CH_3C_7H_6]$), 305 (46), 249 (55), 200 (66), 172 (89). Anal. Calcd. For $C_{28}H_{28}N_4OS$ (468.2): C, 71.76; H, 6.02; N, 11.96; S, 6.84. Found: C, 71.82; H, 6.09; N, 12.07; S, 6.93.

4.3.12. (E)-7-Ethyl-9-(4-methoxybenzylidene)-5-(4-methoxyphenyl)-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**7e**)

It was obtained from **2e** in 25% yield; mp 163–164 °C; FTIR (KBr) υ = 3389 (NH), 2987, 1663 (C=O), 1544, 1233, 1085 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.85 (t, J = 7.2 Hz, 3H, NCH_2CH_3), 2.26–2.35 (m, 2H, NCH_2CH_3) 2.65 (s, 3H, SCH_3), 3.39 (2H, CH_2, overlapping with water), 3.87 (s, 3H, OCH_3) 3.95 (s, 3H, OCH_3) 4.05 (s, 2H, CH_2), 6.70 (d, J = 8.8 Hz, 2H, Ar–H), 6.96 (d, J = 8.8 Hz, 2H, Ar–H), 7.15 (d, J = 8.7 Hz, 2H, Ar–H), 7.48 (d, J = 8.7 Hz, 2H, Ar–H), 8.26 (s, 1H,]CH), not observed (1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.1 (NCH_2CH_3), 12.6 (SCH_3), 51.9 (NCH_2CH_3), 53.3 (CH_2), 53.9 (CH_2), 55.0 (OCH_3), 55.1 (OCH_3), 106.8 (C), 113.8 (2CH), 115.6 (2CH), 120.8 (]CH), 123.6 (C), 125.6 (C), 128.5 (2CH), 129.1 (C), 130.4 (2CH), 139.6 (C), 144.9 (C), 147.5 (C), 153.7 (C), 157.7 (C), 158.0 (C), 158.8 (C), 159.5 (C); MS (EI): m/z 500 (2) $[M]^+$, 455 (33), 427 (15), 379 (100, $[-OCH_3C_7H_6]$), 320 (35), 265 (55), 216 (50), 188 (95). Anal. Calcd. For $C_{28}H_{28}N_4O_3S$ (500.2): C, 67.18; H, 5.64; N, 11.19; S, 6.41. Found: C, 67.25; H, 5.69; N, 11.23; S, 6.51.

4.3.13. (E)-5-(Benzo[d][1,3]dioxol-5-yl)-9-(benzo[d][1,3]dioxol-5-ylmethylene)-7-ethyl-2-(methylthio)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**7f**)

It was obtained from **2f** in 23% yield; mp 212–214 °C; FTIR (KBr) υ = 3398 (NH), 2989, 1688 (C=O), 1541, 1239, 1036 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.02–1.11 (m, 3H, NCH_2CH_3), 1.43–1.57 (m, 2H, NCH_2CH_3), 2.63 (s, 3H, SCH_3), 3.17 (s, 2H, CH_2), 4.06 (br s, 2H, CH_2), 6.09–6.16 (m, 4H, $2OCH_2O$), 6.65 (d, J = 8.3 Hz, 1H, Ar–H), 6.79 (br s, 1H, Ar–H), 7.00 (d, J = 7.8 Hz, 1H, Ar–H), 7.05–7.09 (m, 2H, Ar–H), 7.15–7.18 (m, 1H, Ar–H), 8.26 (s, 1H,]CH), 12.58 (br s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.9 (NCH_2CH_3), 13.2 (SCH_3), 48.7 (NCH_2CH_3), 49.3 (CH_2), 56.0 (CH_2), 99.5 (C), 101.1 (CH), 101.5 (CH), 108.2 (CH), 108.3 (CH), 108.7 (CH), 109.6 (CH), 120.7 (CH), 122.2 (C), 125.0 (CH), 128.6 (C), 129.6 (C), 130.7 (C), 134.2 (]CH), 141.1 (C), 143.3 (C), 147.1 (C), 147.7 (C), 148.0 (C), 154.3 (C), 159.1 (C), 160.9 (C), 161.4 (C); MS (EI): m/z 528 (9) $[M]^+$, 483 (39), 455 (16), 393 (100, $[-OCH_2OC_7H_5]$), 334 (41), 279 (61), 230 (65), 202 (71). Anal. Calcd. For $C_{28}H_{24}N_4O_5S$ (528.2): C, 63.62; H, 4.58; N, 10.60; S, 6.07. Found: C, 63.69; H, 4.59; N, 10.68; S, 6.15.

4.3.14. (E)-7-Ethyl-2-(methylthio)-9-(3,4,5-trimethoxybenzylidene)-5-(3,4,5-trimethoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-b][1,6]naphthyridin-4(3H)-one (**7g**)

It was obtained from **2g** in 19% yield; mp 203–204 °C; FTIR (KBr) υ = 3385 (NH), 2939, 1688 (C=O), 1590, 1240, 1125 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.88–0.94 (m, 3H, NCH_2CH_3), 2.50 (2H, NCH_2CH_3, overlapping with DMSO), 2.63 (s, 3H, SCH_3), 3.62 (br s, 2H, CH_2) 3.65–3.72 (m, 12H, $4OCH_3$), 3.86 (s, 3H, OCH_3) 3.96 (s, 3H, OCH_3) 4.01 (br s, 2H, CH_2), 6.34 (s, 2H, Ar–H) 6.57 (s, 2H, Ar–H), 8.10 (s, 1H,]CH), not observed (1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 12.8 (NCH_2CH_3), 13.6 (SCH_3), 50.6 (NCH_2CH_3), 52.6 (CH_2), 55.5 (CH_2), 56.5 ($2OCH_3$), 56.5 ($2OCH_3$), 60.6 (OCH_3), 60.6 (OCH_3), 105.8 (2CH), 107.3 (2CH), 108.8 (C), 122.0 (]CH), 128.3 (C), 128.8 (C), 132.9 (C), 136.9 (C), 137.2 (C), 139.2 (C), 153.2 (2C), 154.3 (2C), 161.5 (C), 162.1 (C), 163.0 (C), 164.3 (C); MS (EI): m/z 620 (1) $[M]^+$, 575 (33), 547 (12), 439 (100, $[-triOCH_3C_7H_4]$), 380 (25), 325 (53), 276 (55), 248 (79). Anal. Calcd. For $C_{32}H_{36}N_4O_7S$ (620.2): C, 61.92; H, 5.85; N, 9.03; S, 5.17. Found: C, 62.01; H, 5.89; N, 9.12; S, 5.22.

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