

## Synthesis of new pentaheterocyclic systems based on the triazolo[3,4-*a*]-2,7-naphthyridine core

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Dedicated to Professor Girolamo Cirrincione

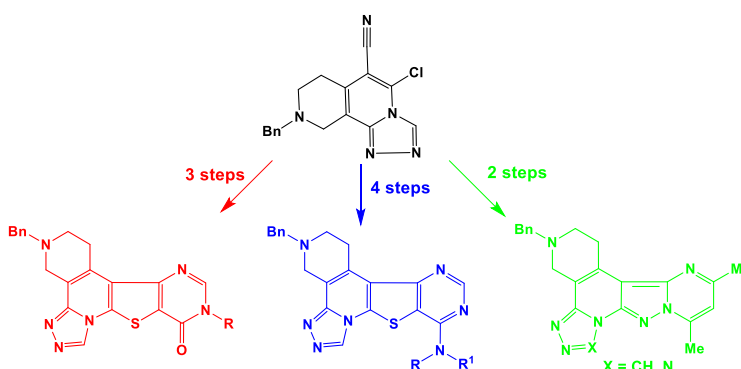
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### Abstract

An efficient synthesis of new pentaheterocyclic systems based on the triazolo[3,4-*a*]-2,7-naphthyridine core is described. Thus, by cyclocondensation of thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridine with formamide, the corresponding thieno[3,2-*d*]pyrimidine was obtained, starting from which the *N*-alkyl, 11-chloro and 11-amino(hydrazino) derivatives were synthesized. Furthermore, reaction of pyrazolo[3,4-*c*][1,2,4]triazolo(tetrazolo)-2,7-naphthyridines, formed via a condensation/cyclization process, with acetylacetone gave new pentaheterocyclic pyrazolo[3,4-*c*][1,2,4]triazolo(tetrazolo)-2,7-naphthyridine system.



**Keywords:** Triazolo[3,4-*a*]-2,7-naphthyridine, pyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridines, alkylation, cyclization, pyrazolo[3,4-*c*][1,2,4]triazolo(tetrazolo)-2,7-naphthyridines

## Introduction

The interest in the synthesis of naphthyridine derivatives is due to their practical importance. In fact, they have an exceptionally broad spectrum of biological activities and are used in medicine, industry, agriculture and other fields.<sup>1-3</sup> Among all naphthyridines, 2,7-isomer derivatives are amongst the only compounds whose synthesis and properties have not yet been thoroughly investigated.<sup>3</sup> Over the last several decades, the interest in derivatives of 2,7-naphthyridine has been growing due to their wide spectrum of biological activity. It has been reported that they possess antitumor,<sup>4</sup> antiproliferative<sup>5</sup> and antimalarial<sup>6</sup> activities. Furthermore, they are potent and selective inhibitors of various kinases, such as acetylcholinesterase (AChE) and butyrylcholinesterase (BChE),<sup>7</sup> PDK-1,<sup>8,9</sup> PDE5,<sup>10</sup> Bruton tyrosine kinase (Btk)<sup>11</sup> and c-Kit/VEGFR-2.<sup>12</sup>

Compounds containing a 2,7-naphthyridine scaffold are also found in various living organisms, e.g. plants or marine organisms, and usually the relevant alkaloids obtained from these organisms possess biological activities.<sup>13-15</sup>

2,7-Naphthyridines occupy a special place in our research in the field of the synthesis of fused heterocyclic systems - in our previous papers we have examined their reactivity with several amines and found a new unexpected rearrangement,<sup>16,17</sup> other chemical transformations leading to heterocyclizations<sup>18,19</sup> and an azide-tetrazole equilibrium.<sup>20</sup> Furthermore, in our recent paper we successfully synthesized furo[2,3-*c*]-2,7-naphthyridines<sup>21</sup> whose synthesis until recently failed. Some of these investigations revealed that bicyclic 1,3-dihydroxy-2,7-naphthyridines showed antiarrhythmic activity,<sup>22</sup> while tricyclic pyrazolo[3,4-*c*]-2,7-naphthyridines<sup>23</sup> and triazolo[3,4-*a*]-, as well as some triazolo[5,1-*a*]-2,7-naphthyridines,<sup>24</sup> displayed high neurotropic activity.

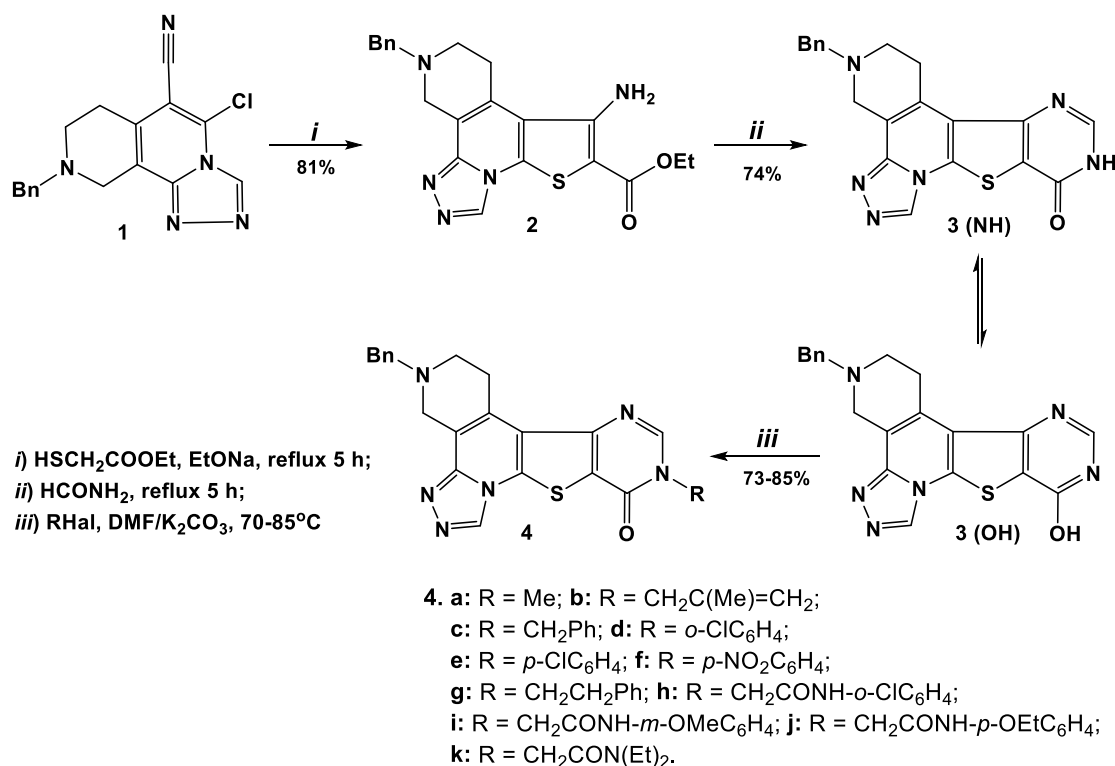
Continuing our investigation in the 2,7-naphthyridine field, herein we are describing the synthesis of new pentaheterocyclic systems, which could be interesting from both a chemical and biological point of view.

## Results and Discussion

9-Benzyl-5-chloro-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-6-carbonitrile (**1**)<sup>24</sup> was used as starting compound for the synthesis. Its reaction with ethyl mercaptoacetate led to the cyclization of a thiophene ring with formation of ethyl 7-amino-10-benzyl-8,9,10,11-tetrahydrothieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-6-carboxylate (**2**). Finally, compound **2** was converted into the 5-benzyl-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-11(10*H*)-one (**3**) by cyclocondensation with formamide (Scheme 1). In solution, compound **3** can show the lactam-lactim tautomerism, because of the proton-transfer of a hydrogen atom between the two basic centers (**3NH/3OH**). However, the spectroscopic data strongly provided evidence that under neutral conditions the equilibrium was effectively shifted towards the lactam form **3 (NH)**, both in the solid state and in solution. In fact, in the IR spectra of compound **3** the absorption bands characteristic for the C=O (1688 cm<sup>-1</sup>) and NH (3083 cm<sup>-1</sup>) groups were observed; moreover, in the <sup>1</sup>H NMR spectra (DMSO/CCl<sub>4</sub>, 1/3) the slightly broadened NH singlet proton signal at 12.96 ppm was present.

Nevertheless, under basic conditions, thieno[3,2-*d*]pyrimidine **3** could act as an ambident heterocyclic nucleophile, and therefore its alkylation could give only one product (i.e. either the *N*- or *O*-alkylated compounds) or a mixture of the two.<sup>25</sup> As a matter of fact, the alkylation of thieno[3,2-*d*]pyrimidine **3** with different alkyl halides led specifically to the formation of *N*-alkyl derivatives of pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine **4a-k** in high yields (Scheme 1). The reactions were carried out in DMF by heating the mixture at

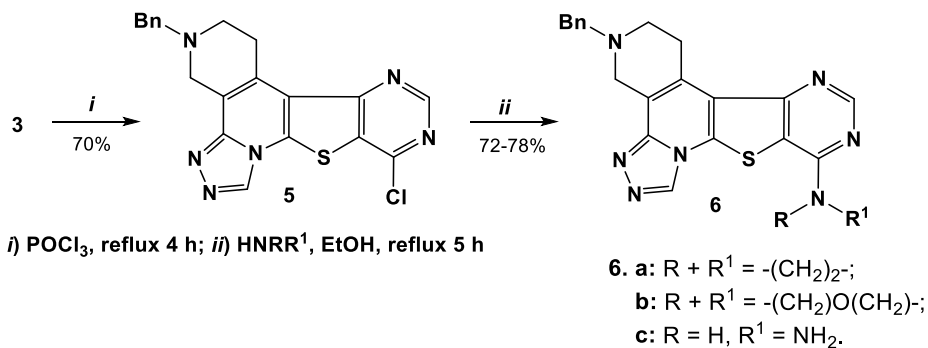
70–85 °C for 5 h, under stirring and in the presence of  $K_2CO_3$ . An examination of the crude reaction mixtures by  $^1H$  NMR spectroscopy demonstrated that the product only contained traces of the *O*-alkylated isomers, while the *N*-alkylated compounds **4** were the main reaction products. Of note was that the traces of the *O*-alkylated compounds completely disappeared after the recrystallization from DMF.



**Scheme 1.** Synthesis of, and subsequent alkylation of pyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridine **3**.

The structure of the obtained *N*-alkylated compounds **4a–k** was supported by IR,  $^1H$  and  $^{13}C$  NMR spectroscopic data and by elemental analysis. In the IR spectra of compounds **4a–k** an absorption band at 1674–1691  $cm^{-1}$  was observed, thus suggesting the presence of a carbonyl group of amidic type. In the  $^1H$  NMR spectra of **4b–k** the presence of two proton singlets at 4.66–5.44 ppm, deemed characteristic of the  $NCH_2$  group was observed, while the broad signal of the  $NH$  group at 12.96 ppm, typical of starting compound **3**, was absent. The  $^{13}C$  NMR spectra were also in agreement with the *N*-alkylated structures **4** depicted in Scheme 1.

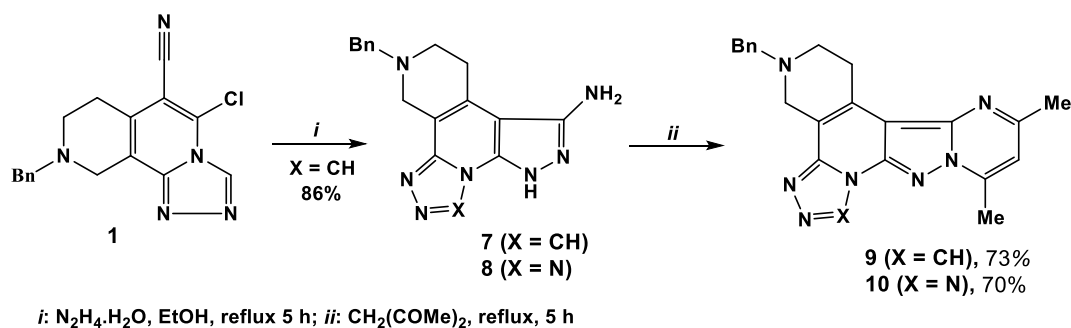
Furthermore, we also synthesized compounds **6**, thereby adding an amino group on the scaffold's pyrimidine ring. To this end, thieno[3,2-*d*]pyrimidine **3** was reacted with phosphorus oxychloride giving the desired 5-benzyl-11-chloro-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridine (**5**), which, in turn by reaction with cyclic amines and hydrazine hydrate led to the amino and hydrazine pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine derivatives **6a–c** (Scheme 2).



**Scheme 2.** Synthesis of 11-chloro- **5** and 11-amino(hydrazino) **6** derivatives of pyrimido[4',5':4,5]thieno[2,3-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridine.

From the synthetic and biological points of view, it was also of interest to obtain pyrazolo[3,4-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridine **7**. In our previous work,<sup>20</sup> we synthesized pyrazolo[3,4-c]tetrazolo[5,1-a]-2,7-naphthyridine **8**, and it was found that in the solid state and in solution, it existed exclusively in the tetrazole form. As expected, heating compound **1** with hydrazine hydrate in ethanol at reflux afforded the corresponding 10-benzyl-8,9,10,11-tetrahydro-5*H*-pyrazolo[3,4-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridin-7-amine (**7**). Compounds **7** and **8** were then heated at reflux (5 h) with acetylacetone to obtain the 5-benzyl-9,11-dimethyl-4,5,6,7-tetrahydropyrimido[1',2':1,5]pyrazolo[3,4-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridine (**9**) and 5-benzyl-9,11-dimethyl-4,5,6,7-tetrahydropyrimido[1',2':1,5]pyrazolo[3,4-c]tetrazolo[5,1-a]-2,7-naphthyridine (**10**), respectively, *via* the well known Knorr synthesis of pyrazoles (Scheme 3).<sup>26</sup>

It should be noted, that as expected,<sup>19</sup> in compound **10** the azido-tetrazole tautomerism did not occur. In fact, in the <sup>1</sup>H NMR spectrum of compound **10** the double set of signals is absent, confirming the presence of only one isomer. Moreover, in the IR spectrum no characteristic azide group signal was observed. Thus, the spectral data showed that compound **10**, like its parent **8**, exists exclusively in the tetrazolo form.



**Scheme 3.** Synthesis of new pentacyclic heterocyclic systems: pyrazolo[3,4-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridine **9** and pyrimido[1',2':1,5]pyrazolo[3,4-c]tetrazolo[5,1-a]-2,7-naphthyridine **10**.

## Conclusions

In summary, in this paper we report an efficient synthesis of some new original heterocyclic systems, namely: tricyclic thieno[2,3-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridine **2**, tetracyclic pyrimido[4',5':4,5]thieno[2,3-

c)[1,2,4]triazolo[3,4-*a*]-2,7-naphthyridine **3** obtained by cyclocondensation of compound **2** with formamide and pyrazolo[3,4-*c*]tetrazolo[5,1-*a*]-2,7-naphthyridine **8**, as well as pentacyclic pyrimido[1',2':1,5]pyrazolo[3,4-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridine **9** and pyrimido[1',2':1,5]pyrazolo[3,4-*c*]tetrazolo[5,1-*a*]-2,7-naphthyridine **10** respectively, *via* the well known Knorr synthesis of pyrazoles. It was found that alkylation of compound **3** led to the formation of *N*-alkyl derivatives of pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine **4**. Moreover, it was observed that compound **10** exists only in the tetrazolo form, indicating that the azido-tetrazole tautomerism does not occur.

In conclusion, we succeeded in our aim of synthesizing new pentaheterocyclic systems based on triazolo[3,4-*a*]-2,7-naphthyridine core. Our future goal is the prediction of their biological activities by PASS, and then the evaluation of their neurotropic and antiarrhythmic activities, as well as other eventually predicted activities. Furthermore, molecular docking studies will be performed.

## Experimental Section

**General.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in DMSO- $d_6$ , DMSO/ $\text{CCl}_4$  (1/3) and  $\text{CDCl}_3$  solutions (300 MHz for  $^1\text{H}$  and 75 MHz for  $^{13}\text{C}$ , respectively) on a Varian Mercury 300VX spectrometer. Chemical shifts were reported as  $\delta$  (parts per million) relative to TMS as internal standard. IR spectra were recorded on Nicolet Avatar 330-FT-IR spectrophotometer and the reported wave numbers were given in  $\text{cm}^{-1}$ . Melting points were determined on a MP450 melting point apparatus. Elemental analyses were performed on an Elemental Analyzer Euro EA 3000. Compounds **1**<sup>24</sup> and **8**<sup>20</sup> were already described. Please note that for all new compounds the recording of  $^{13}\text{C}$ -NMR spectra was attempted. Unfortunately, in many cases, obtaining the  $^{13}\text{C}$  NMR spectra proved to be problematic and the spectra obtained were of very poor quality, probably due to a combination of the following reasons: a) low solubility of these compounds; b) suppression of aromatic carbon signals due to the large number of nitrogen atoms in the molecules; c) and in some cases the compounds decomposed during the longer acquisition time of the  $^{13}\text{C}$  NMR spectra.

**Procedure for the synthesis of ethyl 7-amino-10-benzyl-8,9,10,11-tetrahydrothieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-6-carboxylate (**2**).** Compound **1** (10.0 mmol, 3.20 g) and ethyl mercaptoacetate (11.0 mmol, 1.20 mL) are added to a solution of sodium ethoxide prepared from sodium (11.0 mmol, 0.25 g) and absolute ethanol (50 mL). The reaction mixture was heated at reflux for 5 h, cooled, and poured onto ice. The resulting crystals were filtered off, washed with water, dried and recrystallized from ethanol. Brown solid; yield 81%; mp 208–210 °C; IR  $\nu/\text{cm}^{-1}$ : 3293, 3201 ( $\text{NH}_2$ ), 1670 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  1.38 (t, *J* 7.1 Hz, 3H,  $\text{CH}_2\text{CH}_3$ ), 2.82 (t, *J* 5.7 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.26 (t, *J* 5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.78 (br s, 2H,  $\text{NCH}_2$ ), 3.88 (s, 2H,  $\text{CH}_2\text{Ph}$ ), 4.30 (q, *J* 7.1 Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 6.67 (br s, 2H,  $\text{NH}_2$ ), 7.20–7.40 (m, 5H, Ph), 9.17 (s, 1H, 3-CH). Anal. calcd. for  $\text{C}_{21}\text{H}_{21}\text{N}_5\text{O}_2\text{S}$ : 407.4899, C 61.90; H 5.19; N 17.19%. Found: C 62.29; H 5.40; N 17.46%.

**Procedure for the synthesis of 5-benzyl-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-11(10*H*)-one (**3**).** A mixture of compound **2** (10.0 mmol, 4.10 g) and formamide (50 mL) was heated at reflux for 5 h with stirring. The mixture was cooled, and resulting crystals were filtered off, washed with water, dried and recrystallized from DMF. Brown solid; yield 74%; mp > 360 °C; IR  $\nu/\text{cm}^{-1}$ : 3083 (NH), 1688 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ , 1/3)  $\delta$  2.90 (t, *J* 5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.47 (t, *J* 5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.80 (s, 2H,  $\text{NCH}_2$ ), 3.82 (br s, 2H,  $\text{CH}_2\text{Ph}$ ), 7.22–7.46 (m, 5H, Ph), 8.31 (s, 1H, 9-CH), 9.76 (s, 1H, 1-CH), 12.96 (br s, 1H, NH).  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ )  $\delta$  26.87, 49.01, 50.06, 61.49, 118.31, 120.47, 127.06,

128.24, 128.73, 131.68, 135.51, 135.89, 137.92, 146.98, 147.70, 153.21, 156.96, 165.63. Anal. calcd. for C<sub>20</sub>H<sub>16</sub>N<sub>6</sub>OS: 388.4469 C 61.84; H 4.15; N 21.63%. Found: C 62.17; H 4.31; N 21.87%.

**General procedure for the synthesis of *N*-alkyl derivatives of pyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridine 4a–k.** To a stirred suspension of compound **3** (1.0 mmol, 0.39 g) and K<sub>2</sub>CO<sub>3</sub> (2.0 mmol, 0.28 g) in absolute DMF (20 mL), the corresponding alkyl halides (1.10 mmol) were added. The reaction mixture was maintained at 70–85 °C for 5 h. Then it was cooled at room temperature and water was added (50 mL). The resulting crystals were filtered off, washed with water, dried and recrystallized from DMF.

**5-Benzyl-10-methyl-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-11(10*H*)-one (4a).** Light yellow solid; yield 81%; mp 317–319 °C; IR v/cm<sup>-1</sup>: 1679 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 2.90 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.52 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.64 (s, 3H, NCH<sub>3</sub>), 3.80 (s, 2H, NCH<sub>2</sub>), 3.95 (br s, 2H, CH<sub>2</sub>Ph), 7.22–7.42 (m, 5H, Ph), 8.45 (s, 1H, 9-CH), 9.55 (s, 1H, 1-CH). Anal. calcd. for C<sub>21</sub>H<sub>18</sub>N<sub>6</sub>OS: 402.4735 C 62.67; H 4.51; N 20.88%. Found: C 63.02; H 4.69; N 21.14%.

**5-Benzyl-10-(2-methylprop-2-en-1-yl)-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-11(10*H*)-one (4b).** Yellow solid; yield 85%; mp 238–240 °C; IR v/cm<sup>-1</sup>: 1674 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 1.82 (s, 3H, CH<sub>3</sub>); 2.91 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.52 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.80 (s, 2H, NCH<sub>2</sub>), 3.82 (br s, 2H, CH<sub>2</sub>Ph), 4.66 (s, 2H, NCH<sub>2</sub>CMe), 4.95 (s, 1H, C=CH<sub>2</sub>), 4.95 (s, 1H, C=CH<sub>2</sub>), 7.22–7.45 (m, 5H, Ph), 8.39 (s, 1H, 9-CH), 9.56 (s, 1H, 1-CH). Anal. calcd. for C<sub>24</sub>H<sub>22</sub>N<sub>6</sub>OS: 442.5373 C 65.14; H 5.01; N 18.99%. Found: C 65.52; H 5.22; N 19.27%.

**5,10-Dibenzyl-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-11(10*H*)-one (4c).** Cream solid; yield 76%; mp 245–247 °C; IR v/cm<sup>-1</sup>: 1681 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 2.87 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.54 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.80 (s, 2H, NCH<sub>2</sub>), 3.82 (br s, 2H, 5-CH<sub>2</sub>Ph), 5.31 (s, 2H, 10-CH<sub>2</sub>Ph), 7.20–7.51 (m, 10H, Ph), 8.68 (s, 1H, 9-CH), 9.56 (s, 1H, 1-CH). Anal. calcd. for C<sub>27</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub>S: 478.5694 C 67.76; H 4.63; N 17.56%. Found: C 68.16; H 4.85; N 17.86%.

**5-Benzyl-10-(2-chlorobenzyl)-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-11(10*H*)-one (4d).** Cream solid; yield 79%; mp 256–258 °C; IR v/cm<sup>-1</sup>: 1683 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 2.90 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.52 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.84 (br s, 2H, NCH<sub>2</sub>), 3.92 (s, 2H, 5-CH<sub>2</sub>Ph), 5.38 (s, 2H, 10-CH<sub>2</sub>Ph), 7.17–7.52 (m, 9H, Ph), 8.60 (s, 1H, 9-CH), 9.65 (s, 1H, 1-CH). Anal. calcd. for C<sub>27</sub>H<sub>21</sub>ClN<sub>6</sub>OS: 513.0142 C 63.21; H 4.13; N 16.38%. Found: C 63.53; H 4.30; N 16.62%.

**5-Benzyl-10-(4-chlorobenzyl)-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-11(10*H*)-one (4e).** Yellow solid; yield 82%; mp 253–255 °C; IR v/cm<sup>-1</sup>: 1682 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 2.89 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.47 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.75–3.89 (m, 4H, NCH<sub>2</sub>, 5-CH<sub>2</sub>Ph), 5.35 (s, 2H, 10-CH<sub>2</sub>Ph), 7.09–7.56 (m, 9H, Ph), 8.73 (s, 1H, 9-CH), 9.78 (s, 1H, 1-CH). Anal. calcd. for C<sub>27</sub>H<sub>21</sub>ClN<sub>6</sub>OS: 513.0142 C 63.21; H 4.13; N 16.38%. Found: C 63.59; H 4.34; N 16.67%.

**5-Benzyl-10-(4-nitrobenzyl)-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-11(10*H*)-one (4f).** Yellow solid; yield 73%; mp 262–264 °C; IR v/cm<sup>-1</sup>: 1684 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 2.88 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.52 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.82 (s, 2H, NCH<sub>2</sub>), 3.94 (br s, 2H, 5-CH<sub>2</sub>Ph), 5.44 (s, 2H, 10-CH<sub>2</sub>Ph), 7.20–7.46 (m, 5H, Ph), 7.69–7.76 (m, 2H, C<sub>6</sub>H<sub>4</sub>), 8.16–8.23 (m, 2H, C<sub>6</sub>H<sub>4</sub>), 8.79 (s, 1H, 9-CH), 9.56 (s, 1H, 1-CH). Anal. calcd. for C<sub>27</sub>H<sub>21</sub>N<sub>7</sub>O<sub>3</sub>S: 523.567 C 61.94; H 4.04; N 18.73%. Found: C 62.30; H 4.22; N 19.00%.

**5-Benzyl-10-(2-phenylethyl)-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-*c*][1,2,4]triazolo[3,4-*a*]-2,7-naphthyridin-11(10*H*)-one (4g).** Colorless solid; yield 77%; mp 176–178 °C; IR v/cm<sup>-1</sup>: 1668 (C=O). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 2.83 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.09 (t, *J* 7.3 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Ph), 3.44 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.80 (s, 2H, NCH<sub>2</sub>), 3.91 (br s, 2H, 5-CH<sub>2</sub>Ph), 4.30 (t, *J* 7.3 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>Ph), 7.14–7.42 (m, 10H,

Ph), 8.73 (s, 1H, 9-CH), 9.53 (s, 1H, 1-CH).  $^{13}\text{C}$  NMR (75 MHz, 300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  26.69, 34.45, 47.42, 48.54, 50.48, 61.73, 117.29, 118.60, 120.21, 126.12, 126.55, 127.69, 127.98, 128.33, 128.42, 131.32, 134.72, 134.75, 137.03, 137.49, 146.72, 149.11, 152.34, 155.74. Anal. calcd. for  $\text{C}_{28}\text{H}_{24}\text{N}_6\text{OS}$ : 492.596 C 68.27; H 4.91; N 17.06%. Found: C 68.60; H 5.07; N 17.31%.

**2-(5-Benzyl-11-oxo-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridin-10(11H)-yl)-N-(2-chlorophenyl)acetamide (4h).** Cream solid; yield 75%; mp 245–247 °C; IR  $\nu/\text{cm}^{-1}$ : 1691 (C=O), 3253 (NH).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  2.88 (t,  $J$  5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.55 (t,  $J$  5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.82 (s, 2H,  $\text{NCH}_2$ ), 3.95 (br s, 2H, 5- $\text{CH}_2\text{Ph}$ ), 5.09 (br s, 2H, 10- $\text{CH}_2\text{Ph}$ ), 7.06–7.17 (m, 1H,  $\text{C}_6\text{H}_4$ ), 7.21–7.46 (m, 7H, Ph), 7.92–8.01 (m, 1H,  $\text{C}_6\text{H}_4$ ), 8.46 (s, 1H, 9-CH), 9.53 (s, 1H, 1-CH), 9.84 (s, 1H, NH).  $^{13}\text{C}$  NMR (75 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  26.69, 48.14, 48.53, 50.42, 61.68, 116.95, 118.53, 120.29, 124.55, 124.58, 125.05, 126.56, 126.64, 127.72, 128.37, 128.84, 131.45, 134.36, 134.83, 135.38, 137.51, 146.72, 150.15, 152.52, 155.82, 164.96. Anal. calcd. for  $\text{C}_{28}\text{H}_{22}\text{ClN}_7\text{O}_2\text{S}$ : 556.039 C 60.48; H 3.99; N 17.63%. Found: C 60.87; H 4.19; N 17.91%.

**2-(5-Benzyl-11-oxo-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridin-10(11H)-yl)-N-(3-methoxyphenyl)acetamide (4i).** Yellow solid; yield 80%; mp 260–262 °C; IR  $\nu/\text{cm}^{-1}$ : 1674, 1678 (C=O), 3099 (NH).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  2.88 (t,  $J$  5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.56 (t,  $J$  5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.75 (s, 3H,  $\text{OCH}_3$ ), 3.82 (s, 2H,  $\text{NCH}_2$ ), 3.94 (br s, 2H, 5- $\text{CH}_2\text{Ph}$ ), 4.95 (br s, 2H, 10- $\text{CH}_2\text{Ph}$ ), 6.52–6.60 (m, 1H,  $\text{C}_6\text{H}_4$ ), 7.05–7.19 (m, 1H,  $\text{C}_6\text{H}_4$ ), 7.20–7.48 (m, 7H, Ph), 8.47 (s, 1H, 9-CH), 9.52 (s, 1H, 1-CH), 10.32 (s, 1H, NH). Anal. calcd. for  $\text{C}_{29}\text{H}_{25}\text{N}_7\text{O}_3\text{S}$ : 551.6202 C 63.14; H 4.57; N 17.77%. Found: C 63.45; H 4.74; N 18.01%.

**2-(5-Benzyl-11-oxo-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridin-10(11H)-yl)-N-(4-ethoxyphenyl)acetamide (4j).** Yellow solid; yield 85%; mp 245–247 °C; IR  $\nu/\text{cm}^{-1}$ : 1671, 1690 (C=O), 3264 (NH).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  1.38 (t,  $J$  6.9 Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 2.87 (t,  $J$  5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.59 (t,  $J$  5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.79–4.05 (m, 6H,  $\text{NCH}_2$ , 5- $\text{CH}_2\text{Ph}$ ,  $\text{OCH}_2\text{CH}_3$ ), 4.92 (s, 2H, 10- $\text{CH}_2\text{Ph}$ ), 6.72–6.81 (m, 2H,  $\text{C}_6\text{H}_4$ ), 7.21–7.55 (m, 7H, Ph), 8.47 (s, 1H, 9-CH), 9.54 (s, 1H, 1-CH), 10.17 (s, 1H, NH). Anal. calcd. for  $\text{C}_{30}\text{H}_{27}\text{N}_7\text{O}_3\text{S}$ : 565.6468 C 63.70; H 4.81; N 17.33%. Found: C 64.05; H 5.00; N 17.59%.

**2-(5-Benzyl-11-oxo-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridin-10(11H)-yl)-N,N-diethylacetamide (4k).** Light yellow solid; yield 74%; mp 211–213 °C; IR  $\nu/\text{cm}^{-1}$ : 1688, 1657 (C=O).  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  1.14 (t,  $J$  7.2 Hz, 3H,  $\text{CONCH}_2\text{CH}_3$ ), 1.34 (t,  $J$  7.2 Hz, 3H,  $\text{CONCH}_2\text{CH}_3$ ), 2.87 (t,  $J$  5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.32–3.55 (m, 6H,  $\text{NCH}_2\text{CH}_2$ ,  $\text{N}(\text{CH}_2)_2$ ), 3.91 (br s, 2H, 5- $\text{CH}_2\text{Ph}$ ), 3.80 (br s, 2H,  $\text{NCH}_2$ ), 4.91 (s, 2H, 10- $\text{CH}_2\text{Ph}$ ), 7.21–7.48 (m, 5H, Ph), 8.32 (s, 1H, 9-CH), 9.50 (s, 1H, 1-CH). Anal. calcd. for  $\text{C}_{26}\text{H}_{27}\text{N}_7\text{O}_2\text{S}$ : 501.6046 C 62.26; H 5.43; N 19.55 Found: C 62.63; H 5.63; N 19.82%.

**5-Benzyl-11-chloro-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridine (5).** A mixture of compound **3** (5.0 mmol, 1.94 g), phosphorus oxychloride (35 mL) and pyridine (1.0 mL) was heated at reflux for 4 h. Excess phosphoryl chloride was distilled off, and the residue was treated with 50 ml of ice water and neutralized with aqueous potassium hydroxide. The resulting crystals were filtered off, washed with water, dried and recrystallized from a mixture of ethanol–chloroform (1:3). Yellow solid; yield 70%; mp > 350 °C.  $^1\text{H}$  NMR (300 MHz, DMSO/ $\text{CCl}_4$ , 1/3)  $\delta$  2.92 (t,  $J$  5.7 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.62 (t,  $J$  5.6 Hz, 2H,  $\text{NCH}_2\text{CH}_2$ ), 3.84 (s, 2H,  $\text{CH}_2\text{Ph}$ ), 3.98 (br s, 2H,  $\text{NCH}_2$ ), 7.19–7.40 (m, 5H, Ph), 9.06 (s, 1H, 9-CH), 9.71 (s, 1H, 1-CH). Anal. calcd. for  $\text{C}_{20}\text{H}_{15}\text{ClN}_6\text{S}$ : 406.8922 C 59.04; H 3.72; N 20.65%. Found: C 59.38; H 3.88; N 20.90%.

**General procedure for the synthesis of compounds 6a–c.** A mixture of chloride **5** (1.0 mmol) and the relevant amines (2.20 mmol) or hydrazine hydrate (10.0 mmol) in absolute ethanol (50 mL) was heated at reflux for 5 h. The mixture was cooled and diluted with 100 mL of water, and the precipitate was filtered off, washed with water, dried, and recrystallized from a mixture of ethanol–chloroform (1:3).

**5-Benzyl-11-pyrrolidin-1-yl-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridine (6a).** Brown solid; yield 74%; mp 211–213 °C. <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 2.04–2.14 (m, 4H, N(CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>, C<sub>4</sub>H<sub>8</sub>N), 2.84 (t, *J* 5.7 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.62 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.80 (br s, 2H, NCH<sub>2</sub>), 3.77–3.87 (m, 4H, N(CH<sub>2</sub>)<sub>2</sub>, C<sub>4</sub>H<sub>8</sub>N), 3.89 (s, 2H, CH<sub>2</sub>Ph), 7.19–7.40 (m, 5H, Ph), 9.06 (s, 1H, 9-CH), 9.71 (s, 1H, 1-CH). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 25.51, 28.05, 47.89, 49.40, 51.30, 62.70, 109.24, 119.32, 120.88, 127.39, 128.50, 129.18, 133.58, 133.70, 134.19, 137.90, 148.33, 155.42, 156.28, 156.60. Anal. calcd. for C<sub>24</sub>H<sub>23</sub>N<sub>7</sub>S: 441.5526 C 65.28; H 5.25; N 22.21%. Found: C 65.61; H 5.40; N 22.44%.

**5-Benzyl-11-morpholin-4-yl-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridine (6b).** Yellow solid; yield 72%; mp 237–239 °C. <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 2.84 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.56 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.73–4.00 (m, 12H, NCH<sub>2</sub>, 5-CH<sub>2</sub>Ph, C<sub>4</sub>H<sub>8</sub>NO), 7.21–7.49 (m, 5H, Ph), 8.53 (s, 1H, 9-CH), 9.44 (s, 1H, 1-CH). <sup>13</sup>C NMR (75 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 27.09, 45.66, 48.62, 50.40, 61.81, 65.72, 108.22, 118.15, 118.86, 126.58, 127.72, 128.43, 131.65, 133.71, 134.41, 137.41, 146.89, 153.79, 156.77, 157.14. Anal. calcd. for C<sub>24</sub>H<sub>23</sub>N<sub>7</sub>OS: 457.552 C 63.00; H 5.07; N 21.43%. Found: C 63.35; H 5.18; N 21.69%.

**5-Benzyl-11-hydrazino-4,5,6,7-tetrahydropyrimido[4',5':4,5]thieno[2,3-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridine (6c).** Brown solid; yield 78%; mp > 360 °C; IR ν/cm<sup>-1</sup>: 3314, 3223, 3171 (NH, NH<sub>2</sub>). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 2.90 (t, *J* 5.7 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.56 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.81 (s, 2H, CH<sub>2</sub>Ph), 3.83 (br s, 2H, NCH<sub>2</sub>), 5.12 (s, 2H, NH<sub>2</sub>), 7.23–7.42 (m, 5H, Ph), 8.39 (s, 1H, 9-CH), 9.22 (s, 1H, NH), 9.74 (s, 1H, 1-CH). Anal. calcd. for C<sub>20</sub>H<sub>18</sub>N<sub>8</sub>S: 402.4768 C 59.68; H 4.51; N 27.84%. Found: C 60.08; H 4.72; N 28.13%.

**Procedure for the synthesis of 10-benzyl-8,9,10,11-tetrahydro-5H-pyrazolo[3,4-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridin-7-amine (7).** A mixture of compound **1** (2.0 mmol, 0.65 g) and of hydrazine hydrate (1.0 mL, 20.0 mmol) in absolute ethanol (20 mL) was heated at reflux for 5 h. The ethanol was distilled off to dryness and water (30 mL) was added to the residue. The separated crystals were filtered off, washed with water, dried and recrystallized from ethanol. Brown solid; yield 86%; mp 277–279 °C; IR ν/cm<sup>-1</sup>: 3174, 3292, 3399 (NH, NH<sub>2</sub>). <sup>1</sup>H NMR (300 MHz, DMSO/CCl<sub>4</sub>, 1/3) δ 2.78–2.88 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.00–3.07 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.73 (br s, 2H, NCH<sub>2</sub>), 3.78 (s, 2H, CH<sub>2</sub>Ph), 5.49 (s, 2H, NH<sub>2</sub>), 7.21–7.44 (m, 5H, Ph), 8.86 (s, 1H, CH), 11.80 (s, 1H, NH). Anal. calcd. for C<sub>17</sub>H<sub>17</sub>N<sub>7</sub>: 319.3641 C 63.93; H 5.37; N 30.70%. Found: C 63.55; H 5.55; N 30.47%.

**General procedure for the synthesis of compounds 9, 10.** A mixture of compound **7/8** (1.0 mmol) and of acetylacetone (15 mL) was heated at reflux for 5 h. The reaction mixture was cooled and the separated crystals were filtered off, washed with water, dried, and recrystallized from ethanol.

**5-Benzyl-9,11-dimethyl-4,5,6,7-tetrahydropyrimido[1',2':1,5]pyrazolo[3,4-c][1,2,4]triazolo[3,4-a]-2,7-naphthyridine (9).** Brown solid; yield 73%; mp > 300 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.67 (s, 3H, CH<sub>3</sub>), 2.86 (s, 3H, CH<sub>3</sub>), 2.94 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.45 (t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.87 (br s, 2H, NCH<sub>2</sub>), 4.07 (s, 2H, CH<sub>2</sub>Ph), 6.86 (s, 1H, 10-CH), 7.26–7.47 (m, 5H, Ph), 9.20 (s, 1H, 1-CH). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 17.52, 24.97, 26.92, 49.12, 51.27, 62.78, 96.25, 98.15, 110.80, 110.82, 114.40, 127.34, 128.48, 129.26, 130.67, 133.70, 138.12, 143.86, 143.95, 145.99, 149.41, 159.78. Anal. calcd. for C<sub>22</sub>H<sub>21</sub>N<sub>7</sub>: 383.4493 C 68.91; H 5.52; N 25.57%. Found: C 69.24; H 5.68; N 25.82%.

**5-Benzyl-9,11-dimethyl-4,5,6,7-tetrahydropyrimido[1',2':1,5]pyrazolo[3,4-c]tetrazolo[5,1-a]-2,7-naphthyridine (10).** Brown solid; yield 70%; mp 248–250 °C; IR ν/cm<sup>-1</sup>: 1635 (C=C<sub>Ar</sub>). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.61 (s, 3H, CH<sub>3</sub>), 2.88 (s, 3H, CH<sub>3</sub>), 2.89 (br t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.45 (br t, *J* 5.6 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>), 3.79 (s, 2H, NCH<sub>2</sub>), 3.97 (s, 2H, CH<sub>2</sub>Ph), 6.90 (s, 1H, 10-CH), 7.17–7.38 (m, 5H, Ph). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 17.52, 24.79, 26.98, 48.73, 51.04, 62.45, 99.77, 111.94, 112.79, 127.26, 128.33, 128.96, 135.74, 137.63, 142.97, 143.86, 146.58, 148.96, 160.45. Anal. calcd. for C<sub>21</sub>H<sub>20</sub>N<sub>8</sub>: 384.4374 C 65.61; H 5.24; N 29.15%. Found: C 65.24; H 5.43; N 28.92%.



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## Supplementary Material

The copies of  $^1\text{H}$  NMR Spectra for all new synthesized compounds have been submitted along with the manuscript, as well as some  $^{13}\text{C}$  NMR spectra.

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