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Aymn E. Rashad <sup>a</sup>, Mohamed I. Hegab <sup>a</sup>, Randa E. Abdel-Megeid <sup>a</sup>, Mamdouh M. Ali <sup>b</sup> & Farouk M. E. Abdel-Megeid <sup>a</sup>

<sup>a</sup> Photochemistry Department, National Research Centre, Dokki, Cairo, Egypt

<sup>b</sup> Biochemistry Department, National Research Centre, Dokki, Cairo, Egypt

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## SYNTHESIS AND ANTITUMOR EVALUATION OF SOME NEWLY SYNTHESIZED PYRAZOLOPYRIMIDINE AND PYRAZOLOTRIAZOLOPYRIMIDINE DERIVATIVES

Aymn E. Rashad,<sup>1</sup> Mohamed I. Hegab,<sup>1</sup>  
Randa E. Abdel-Megeid,<sup>1</sup> Mamdouh M. Ali,<sup>2</sup>  
and Farouk M. E. Abdel-Megeid<sup>1</sup>

<sup>1</sup>Photochemistry Department, National Research Centre, Dokki, Cairo, Egypt

<sup>2</sup>Biochemistry Department, National Research Centre, Dokki, Cairo, Egypt

*A series of novel pyrazolo[3,4-d]pyrimidine 2b, 3, 5b, pyrazolotetraazopyrimidine 4, and pyrazolotriazolopyrimidine derivatives 6a,b–10a,b have been synthesized and characterized by elemental analysis and spectroscopic data. Furthermore, the cytotoxicity and in vivo antitumor evaluation of some prepared compounds have been assessed, and derivatives 1a and 6b revealed promising activity in comparison to that of Cisplatin.*

*Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements to view the free supplemental file.*

**Keywords** Antitumor activity; pyrazolo[3,4-*d*]pyrimidine; pyrazolotetraazopyrimidine; pyrazolotriazolopyrimidine

### INTRODUCTION

In the last few decades, the chemistry of pyrazolopyrimidines has received considerable attention due to their synthetic and effective biological importance.<sup>1–3</sup> Also, due to the presence of pyrazolo[3,4-*d*]pyrimidine moiety in some important drugs, and because of their structural resemblance to purines, interest in the construction of such molecules has been aroused.<sup>4,5</sup> Several substituted pyrazolo[3,4-*d*]pyrimidine derivatives demonstrated significant antimicrobial,<sup>6</sup> antimycobacterial,<sup>7</sup> antitumor,<sup>8</sup> and antiviral activity.<sup>9,10</sup>

As a continuation of our work on azoloazines,<sup>6,10–13</sup> we aimed to incorporate a fused pyrimidine moiety into the 1-position of the pyrazolo[3,4-*d*]pyrimidine ring system to obtain a new heterocyclic system, which was used as a building block for many fused heterocyclic pyrazolotriazolopyrimidines expected to possess notable chemical and pharmacological activities.<sup>12–15</sup> In addition, triazolopyrimidines often display increased toxicity and improved antitumor properties when compared to those of purines.<sup>16,17</sup>

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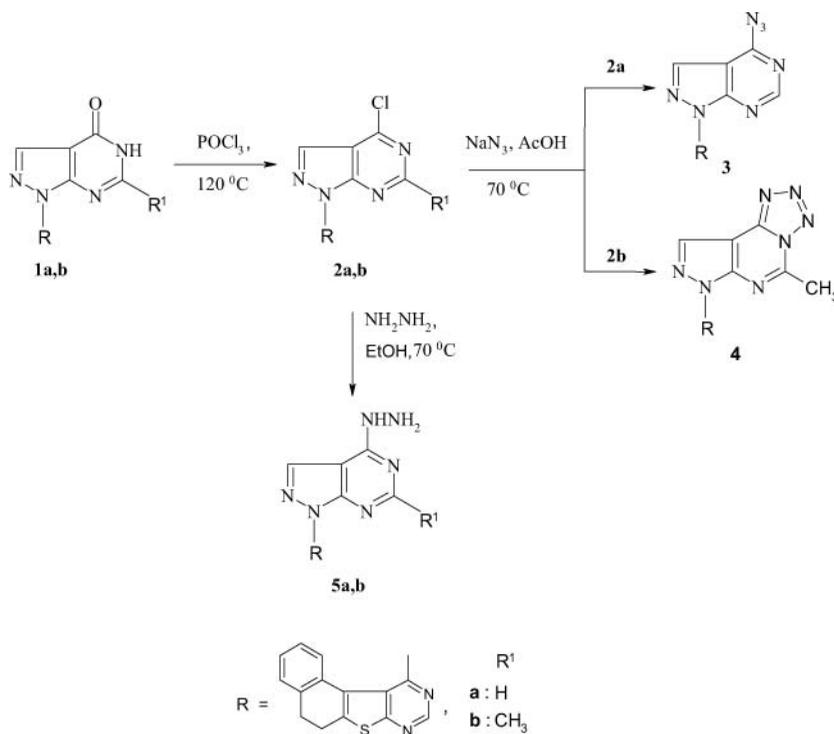
Address correspondence to Aymn E. Rashad, Photochemistry Department, National Research Centre, Dokki, Cairo 12622, Egypt. E-mail: aymnelzeny@yahoo.com

## DISCUSSION

## Chemistry

Compounds **1a**<sup>18</sup> and **1b**<sup>18</sup> were converted into their corresponding 4-chloro derivatives **2a**<sup>10</sup> and **2b**, respectively, when heated with phosphorus oxychloride at reflux temperature. The mass spectra of compounds **2a**<sup>10</sup> and **2b** gave fragments showing the isotopic pattern due to the presence of a chlorine atom (see the Experimental section and ref.<sup>10</sup>).

When derivatives **2a**<sup>10</sup> and **2b** were treated with sodium azide in glacial acetic acid at 70°C, they afforded compounds **3** and **4**, respectively. Analytical and spectral data of the latter compounds are in agreement with the proposed structures. In particular, the IR spectrum of compound **3** showed an absorption frequency at 2188 cm<sup>-1</sup> indicative for the azido group, while IR spectrum of compound **4** did not. This data indicates that compound **3** has the azido structure, without excluding the tetrazolo structure in tautomeric equilibrium; while compound **4** has only the tetrazolo structure (Scheme 1).



Scheme 1

The absence of the azido group and the formation of the tetrazolo structure in compound **4** may be due to the electron-donating effect of the CH<sub>3</sub> group, which stabilizes the tetrazolo structure.

Meanwhile, when compounds **2a**<sup>10</sup> and **2b** were treated with hydrazine hydrate at reflux temperature, they afforded the corresponding hydrazino derivatives **5a**<sup>18</sup> and **5b**, respectively. The IR and <sup>1</sup>H NMR spectra of the latter compounds revealed signals characteristic for NH<sub>2</sub> and NH, and their MS gave the molecular ion peaks as base peaks (see the Experimental section).

On the other hand, the synthesis of [1,2,4]triazolo[4,3-*c*]pyrimidines and [1,2,4]triazolo[1,5-*c*]pyrimidines fused to nitrogen-rich heterocyclic moieties have attracted the attention of many investigators,<sup>19–21</sup> and many derivatives have been described and proved to have pronounced biological activities.<sup>16,17,22–25</sup> Actually, previous observations revealed that [1,2,4]triazolo[4,3-*c*]pyrimidines can isomerize by a Dimroth rearrangement under different reaction conditions (acid, base, or heat) to the more thermodynamically stable [1,2,4]triazolo[1,5-*c*]pyrimidine.<sup>13,23,24</sup>

Thus, heating compounds **5a**<sup>18</sup> or **5b** with formic acid or triethyl orthoformate at reflux temperature gave compounds **6a** and **6b** or **7a** and **7b**, respectively (Scheme 2). Likewise, heating of compounds **5a**<sup>18</sup> or **5b** with acetic acid/acetic anhydride at reflux temperature or triethyl orthoacetate at room temperature gave compounds **8a** and **8b** or **9a** and **9b**, respectively (Scheme 2). The <sup>1</sup>H NMR spectra of triazolo[4,3-*c*]pyrimidine derivatives **7a,b** or **9a,b** revealed that the substituents at C-3 and C-5 showed signals more downfield than those in their isomeric triazolo[1,5-*c*]pyrimidine derivatives **6a,b** or **8a,b** at C-2 and C-5. This confirmed that the products obtained from the reaction of the hydrazino derivatives **5a**<sup>18</sup> and **5b** with orthoesters differ than those obtained from the reaction with acids. The spectral data revealed not only this observation, but also the physical data, where the melting points (mp) and rates of flow (*R<sub>f</sub>* values) of triazolo[4,3-*c*]pyrimidine derivatives were higher than those of triazolo[1,5-*c*]pyrimidine derivatives.

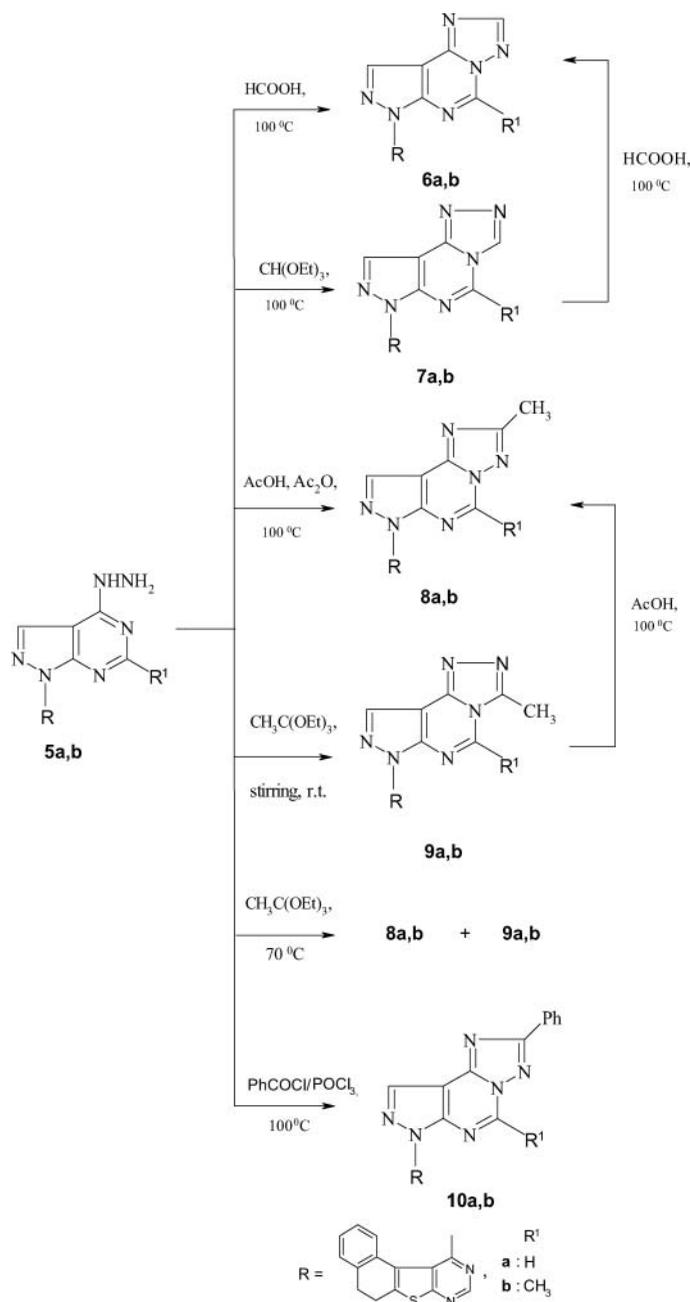
It was noticed that when triazolo[4,3-*c*]pyrimidine derivatives **7a,b** and **9a,b** were heated in acid medium, they isomerized to the thermodynamically more stable triazolo[1,5-*c*]pyrimidine derivatives **6a,b** and **8a,b**, respectively. These results and isomerizations were in agreement with those reported in some recent reports.<sup>12,13,23–25</sup>

In contrast, when compounds **5a**<sup>18</sup> and **5b** were heated at reflux temperature with triethyl orthoacetate, two products were isolated and were separated on a silica gel column; one of them was the expected triazolo[4,3-*c*]pyrimidine derivative **9a,b** and the other was the triazolo[1,5-*c*]pyrimidine derivatives **8a,b** (Scheme 2). The formation of compound **8a,b** in this reaction can be accounted by the partial isomerization via a Dimroth reaction of product **9a,b** under the effect of heat.

In addition, benzoylation of compounds **5a**<sup>18</sup> and **5b** with benzoyl chloride, in phosphorus oxychloride, yielded substituted triazolo[1,5-*c*]pyrimidine derivatives **10a** and **10b**, respectively (Scheme 2). The spectral data and elemental analyses of compounds **6a,b–10a,b** confirmed their structures.

### Antitumor Activity

As shown in the Supplementary Materials (available online; Table I, Figures 1 and 2), in the ascites tumor model, the administration of prepared compounds significantly increased ( $P < 0.05$ ) the life span of the animals as compared with the control group (animals in the EAC injected alone) except compound **5a**, which revealed an insignificant change. There is a gradual increase in life span using the prepared compounds from compound **5a**, **8a**, **6a**, and **6b** to compound **1a**. The increase in life span was 9%, 32%, 45%, 64%, and 73%, respectively. The standard reference drug (Cisplatin 2 mg/kg body weight [b. w.]) exhibited an 86% ( $P < 0.05$ ) increase in life span of the animals. All the animals in the EAC-injected alone group were dead after 22 days.



Scheme 2

## EXPERIMENTAL

### Chemistry

All melting points are uncorrected and were measured using an Electro-thermal IA 9100 apparatus (Shimadzu, Japan). IR spectra were recorded as potassium bromide pellets

on a Perkin-Elmer 1650 Spectrophotometer, National Research Centre, Cairo, Egypt.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were determined on a Jeol-Ex-300 NMR spectrometer, and chemical shifts were expressed as part per million; ppm ( $\delta$  values) against TMS as internal reference (Faculty of Science, Cairo University, Cairo, Egypt). Mass spectra were recorded on EI + Q1 MSLMR UPLR, National Research Centre, Cairo, Egypt. Microanalyses were operated using Mario Elmentar apparatus, Organic Microanalysis Unit, National Research Centre, Cairo, Egypt, and the results were within the accepted range of the calculated values. Column chromatography was performed on (Merck) Silica gel 60 (particle size 0.06–0.20 mm).

Compounds **1a**,<sup>18</sup> **1b**,<sup>18</sup> **2a**,<sup>10</sup> and **5a**<sup>18</sup> were prepared as reported in the literature.

#### 4-Chloro-6-methyl-1-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-1H-pyrazolo[3,4-d]pyrimidine (**2b**)

Compound **1b**,<sup>18</sup> (0.01 mol) was refluxed in phosphorus oxychloride (20 mL) for 2 h. The solution was cooled and poured with stirring onto ice, and the solid that formed was filtered off, washed several times with water, dried, and purified on silica gel column using petroleum ether: ethyl acetate (3:1) as an eluent to give compound **2b**. Yield 80%, mp 190–192°C; IR  $\nu_{\text{max}}$  1534  $\text{cm}^{-1}$  of the C=N, and absence of the C=O and NH groups;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.56 (s, 3H, C<sub>6</sub>-CH<sub>3</sub>), 2.90–3.00 (m, 4H, C<sub>5'</sub>-CH<sub>2</sub>+C<sub>6'</sub>-CH<sub>2</sub>), 7.20–7.30 (m, 4H, 3Ar-H+C<sub>3</sub>-H), 8.00 (s, 1H, C<sub>9</sub>-H), 8.35 (d, 1H, Ar-H,  $J = 7.5$  Hz); EIMS,  $m/z$  (%): 406 (M<sup>+</sup>,  $^{37}\text{Cl}$ , 39.98), 404 (M<sup>+</sup>,  $^{35}\text{Cl}$ , 100); Anal. calcd. for C<sub>20</sub>H<sub>13</sub>ClN<sub>6</sub>S (404.06): C, 59.33; H, 3.24; N, 20.76; S, 7.92. Found: C, 59.45; H, 3.56; N, 20.87; S, 7.61.

#### Synthesis of 3 and 4

A mixture of compound **2a**<sup>10</sup> or **2b** (0.01 mol) was added to glacial acetic acid (20 mL) containing sodium azide (0.01 mol) with stirring at 70°C for 1 h. Then the reaction mixture was cooled, filtered, washed with a small amount of water then cold ethanol, dried, and recrystallized from ethanol to give compound **3** or **4**, respectively.

**4-Azido-1-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-1H-pyrazolo[3,4-d]pyrimidine (3)**. Yield 60%, mp 216–218°C; IR  $\nu_{\text{max}}$  2188  $\text{cm}^{-1}$  of the azide group;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.80–3.00 ppm (m, 4H, C<sub>5'</sub>-CH<sub>2</sub>+C<sub>6'</sub>-CH<sub>2</sub>), 7.20–7.30 (m, 4H, 3Ar-H+C<sub>3</sub>-H), 8.10 (s, 1H, C<sub>9</sub>-H), 8.35 (d, 1H, Ar-H,  $J = 7.50$  Hz), 8.90 (s, 1H, C<sub>6</sub>-H); Anal. calcd. for C<sub>19</sub>H<sub>11</sub>N<sub>9</sub>S (397.42): C, 57.42; H, 2.79; N, 31.72; S, 8.07. Found: C, 57.52; H, 2.54; N, 31.91; S, 8.23.

**5-Methyl-7-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-7H-pyrazolo[4,3-e][1,2,4]tetrazolo[1,5-c]pyrimidine (4)**. Yield 54%, mp 235–237°C; IR  $\nu_{\text{max}}$  absence of the azide group;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.60 ppm (s, 3H, C<sub>5</sub>-CH<sub>3</sub>), 2.90–3.00 (m, 4H, C<sub>5'</sub>-CH<sub>2</sub>+C<sub>6'</sub>-CH<sub>2</sub>), 7.20–7.30 (m, 4H, 3Ar-H+C<sub>3</sub>-H), 8.00 (s, 1H, C<sub>9</sub>-H), 8.35 (d, 1H, Ar-H,  $J = 7.50$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  22.10 (C<sub>5</sub>-CH<sub>3</sub>), 24.40 (C-5'), 29.68 (C-6'), 111.25, 115.20, 118.10, 124.64, 125.80, 126.5, 126.9, 127.6, 128.0, 131.4, 135.5, 136.9, 148.4, 154.60 (15 sp<sup>2</sup> carbon atoms), 156.40 (C-5), 167.80 (C-9'); Anal. calcd. for C<sub>20</sub>H<sub>13</sub>N<sub>9</sub>S (397.42): C, 58.38; H, 3.18; N, 30.64; S, 7.79. Found: C, 58.23; H, 3.33; N, 30.25; S, 7.55.

### Synthesis of 5a and 5b

A mixture of compound **2a**<sup>10</sup> or **2b** (0.01 mol) and hydrazine hydrate (2 mL, 99%) was refluxed in dry ethanol (20 mL) for 3 or 5 h. The reaction mixture was evaporated under reduced pressure, and the residue was recrystallized from ethanol to give compounds **5a** and **5b**, respectively.

**1-(5,6-Dihydronaphtho[1',2':4,5]thieno[2,3-*d*]pyrimidin-11-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazine (5a).** Compound **5a** obtained here is identical in all respects to that reported previously.<sup>18</sup> Yield 78% (literature 86%), mp 205–207°C (literature mp 205–207°C).

**6-Methyl-1-[1-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-*d*]pyrimidin-11-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]hydrazine (5b).** Yield 84%, mp 214–216°C; IR  $\nu_{\max}$  3318, 3290, and 3150  $\text{cm}^{-1}$  of the  $\text{NH}_2/\text{NH}$  groups;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.54 ppm (s, 3H,  $\text{C}_6\text{-CH}_3$ ), 2.80–3.00 (m, 4H,  $\text{C}_5\text{-CH}_2+\text{C}_6\text{-CH}_2$ ), 4.10–4.30 (br.s, 2H,  $\text{NH}_2$ ,  $\text{D}_2\text{O}$  exchangeable), 6.50 (s, 1H,  $\text{NH}$ ,  $\text{D}_2\text{O}$  exchangeable), 7.20–7.40 (m, 4H, 3Ar-H+ $\text{C}_3\text{-H}$ ), 7.50 (d, 1H, Ar-H,  $J = 7.50$  Hz), 8.60 (s, 1H,  $\text{C}_9\text{-H}$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  21.00 ( $\text{C}_6\text{-CH}_3$ ), 24.00 (C-5'), 29.40 (C-6'), 111.2–149.3 (15  $\text{sp}^2$  carbon atoms), 152.7 (C-6), 157.90 (C-9'); EIMS,  $m/z$  (%): 400 ( $\text{M}^+$ , 42), 364 (100); Anal. calcd. for  $\text{C}_{20}\text{H}_{16}\text{N}_8\text{S}$  (400.46): C, 59.98; H, 4.03; N, 27.98; S, 8.01. Found: C, 59.62; H, 4.41; N, 27.64; S, 8.21.

### Synthesis of 6a and 6b

Compound **5a** or **5b** (0.01 mol) was refluxed in formic acid (20 mL, 85%) for 6 or 8 h. The reaction mixture was cooled and poured into water. The solid that formed was filtered off, dried, and recrystallized from dioxane to afford compound **6a** or **6b**, respectively.

**7-(5,6-Dihydronaphtho[1',2':4,5]thieno[2,3-*d*]pyrimidin-11-yl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (6a).** Yield 65%, mp 170–172°C; IR  $\nu_{\max}$  absence of the  $\text{NH}_2$ ,  $\text{NH}$  groups;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.9–3.1 ppm (m, 4H,  $\text{C}_5\text{-CH}_2+\text{C}_6\text{-CH}_2$ ), 7.1–7.4 (m, 5H, 4Ar-H+ $\text{C}_9\text{-H}$ ), 8.1 (s, 1H,  $\text{C}_9\text{-H}$ ), 8.7 (s, 1H,  $\text{C}_2\text{-H}$ ), 9.7 (s, 1H,  $\text{C}_5\text{-H}$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  24.40 (C-5'), 29.68 (C-6'), 111.25–146.32 (15  $\text{sp}^2$  carbon atoms), 151.10 (C-2), 156.40 (C-5), 167.00 (C-9'); Anal. calcd. for  $\text{C}_{20}\text{H}_{12}\text{N}_8\text{S}$  (396.43): C, 60.59; H, 3.05; N, 28.27; S, 8.09. Found: C, 60.77; H, 3.31; N, 28.01; S, 8.32.

**5-Methyl-7-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-*d*]pyrimidin-11-yl)-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (6b).** Yield 58%, mp 186–188°C; IR  $\nu_{\max}$  absence of the  $\text{NH}_2$ ,  $\text{NH}$  groups;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.4 ppm (s, 3H,  $\text{C}_5\text{-CH}_3$ ), 2.9–3.0 (m, 4H,  $\text{C}_5\text{-CH}_2+\text{C}_6\text{-CH}_2$ ), 7.2–7.3 (m, 4H, 3Ar-H+ $\text{C}_9\text{-H}$ ), 8.4 (s, 1H,  $\text{C}_9\text{-H}$ ), 9.1 (d, 1H, Ar-H,  $J = 7$  Hz), 9.2 (s, 1H,  $\text{C}_2\text{-H}$ );  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  22.10 ( $\text{C}_5\text{-CH}_3$ ), 24.40 (C-5'), 29.60 (C-6'), 111.25–146.32 (15  $\text{sp}^2$  carbon atoms), 151.10 (C-2), 156.80 (C-5) and 167.00 (C-9'); Anal. calcd. for  $\text{C}_{21}\text{H}_{14}\text{N}_8\text{S}$  (410.46): C, 61.45; H, 3.44; N, 27.30; S, 7.81. Found: C, 61.24; H, 3.79; N, 27.01; S, 7.54.

### General Procedure for the Synthesis of 7a and 7b

Compound **5a** or **5b** (0.01 mol) was refluxed in triethyl orthoformate (20 mL) for 6 or 8 h. The reaction mixture was evaporated under reduced pressure, and the residue was recrystallized from dioxane/methanol (1:1) to give compound **7a** or **7b**, respectively.

**7-(5,6-Dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (7a).** Yield 73%, mp 225–227°C; IR  $\nu_{\max}$  absence of the NH<sub>2</sub>, NH groups; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  3.1–3.2 ppm (m, 4H, C<sub>5</sub>–CH<sub>2</sub>+C<sub>6</sub>'–CH<sub>2</sub>), 7.2–7.5 (m, 5H, 4Ar–H+C<sub>9</sub>–H), 8.5 (s, 1H, C<sub>3</sub>–H), 9.3 (s, 1H, C<sub>9</sub>–H), 9.4 (s, 1H, C<sub>5</sub>–H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  24.40 (C-5'), 29.68 (C-6'), 111.50–146.64 (15 sp<sup>2</sup> carbon atoms), 153.00 (C-3), 160.10 (C-5), 168.90 (C-9'); Anal. calcd. for C<sub>20</sub>H<sub>12</sub>N<sub>8</sub>S (396.43): C, 60.59; H, 3.05; N, 28.27; S, 8.09. Found: C, 60.32; H, 3.22; N, 28.11; S, 8.12.

**5-Methyl-7-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (7b).** Yield 70%, mp 210–212°C; IR  $\nu_{\max}$  absence of the NH<sub>2</sub>, NH groups; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  2.80 (s, 3H, C<sub>5</sub>–CH<sub>3</sub>), 2.98–3.3 (m, 4H, C<sub>5</sub>'–CH<sub>2</sub>+C<sub>6</sub>'–CH<sub>2</sub>), 7.3–7.9 (m, 5H, 4Ar–H+C<sub>9</sub>–H), 9.1 (s, 1H, C<sub>9</sub>–H); 9.80 (s, 1H, C<sub>3</sub>–H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  22.65 (C<sub>5</sub>–CH<sub>3</sub>), 24.40 (C-5'), 29.60 (C-6'), 112.14–146.90 (15 sp<sup>2</sup> carbon atoms), 153.10 (C-3), 160.80 (C-5), 169.00 (C-9'); Anal. calcd. for C<sub>21</sub>H<sub>14</sub>N<sub>8</sub>S (410.46): C, 61.45; H, 3.44; N, 27.30; S, 7.81. Found: C, 61.34; H, 3.65; N, 27.21; S, 7.92.

### General Procedure for the Synthesis of 8a and 8b

Compound **5a** or **5b** (0.01 mol) was refluxed in a mixture of acetic acid/acetic anhydride (1:1, 20 mL) for 6 or 8 h. The formed precipitates were filtered off, dried, and recrystallized from dioxane to give compound **8a** or **8b**, respectively.

**2-Methyl-7-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (8a).** Yield 67%, mp 194–196°C; IR  $\nu_{\max}$  absence of the NH<sub>2</sub>, NH groups; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 2.4 ppm (s, 3H, C<sub>2</sub>–CH<sub>3</sub>), 2.8–3.0 (m, 4H, C<sub>5</sub>'–CH<sub>2</sub>+C<sub>6</sub>'–CH<sub>2</sub>), 7.0–7.4 (m, 5H, 4Ar–H+C<sub>9</sub>–H), 8.1 (s, 1H, C<sub>9</sub>–H), 8.4 (s, 1H, C<sub>5</sub>–H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  22.65 (C<sub>2</sub>–CH<sub>3</sub>), 24.40 (C-5'), 29.68 (C-6'), 111.50–146.64 (15 sp<sup>2</sup> carbon atoms), 153.00 (C-2), 160.10 (C-5), 168.90 (C-9'); Anal. calcd. for C<sub>21</sub>H<sub>14</sub>N<sub>8</sub>S (410.46): C, 61.45; H, 3.44; N, 27.30; S, 7.81. Found: C, 61.56; H, 3.62; N, 27.01; S, 7.86.

**2,5-Dimethyl-7-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (8b).** Yield 64%, mp 206–208°C; IR  $\nu_{\max}$  absence of the NH<sub>2</sub>, NH groups; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  2.4 ppm (s, 3H, C<sub>2</sub>–CH<sub>3</sub>), 2.65 ppm (s, 3H, C<sub>5</sub>–CH<sub>3</sub>), 2.9 ppm (m, 4H, C<sub>5</sub>'–CH<sub>2</sub>+C<sub>6</sub>'–CH<sub>2</sub>), 7.2–7.3 (m, 5H, 4Ar–H+C<sub>9</sub>–H), 8.6 (s, 1H, C<sub>9</sub>–H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>):  $\delta$  22.10 (C<sub>2</sub>–CH<sub>3</sub>), 22.65 (C<sub>5</sub>–CH<sub>3</sub>), 24.40 (C-5'), 29.68 (C-6'), 111.50–146.64 (15 sp<sup>2</sup> carbon atoms), 153.00 (C-2), 160.10 (C-5), 168.90 (C-9'); Anal. calcd. for C<sub>22</sub>H<sub>16</sub>N<sub>8</sub>S (424.48): C, 62.25; H, 3.80; N, 26.40; S, 7.55. Found: C, 61.96; H, 3.62; N, 26.01; S, 7.86.

### General Procedure for the Synthesis of 9a and 9b

Compound **5a** or **5b** (0.01 mol) was stirred at room temperature in triethyl orthoacetate (20 mL) for 5 h, the solid product that formed was collected by filtration, dried, and recrystallized from dioxane to give compound **9a** or **9b**, respectively.

**3-Methyl-7-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (9a).** Yield 72%, mp 212–214°C; IR  $\nu_{\max}$  absence of the NH<sub>2</sub>, NH groups; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 2.8 ppm (s, 3H, C<sub>3</sub>–CH<sub>3</sub>), 2.8–3.0 (m, 4H, C<sub>5</sub>'–CH<sub>2</sub>+C<sub>6</sub>'–CH<sub>2</sub>), 7.0–7.4 (m, 5H,

4Ar-H+C<sub>9</sub>-H), 8.1 (s, 1H, C<sub>9</sub>-H), 8.9 (s, 1H, C<sub>5</sub>-H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>): δ 23.15 (C<sub>3</sub>-CH<sub>3</sub>), 24.40 (C-5'), 29.68 (C-6'), 111.50–146.64 (15 sp<sup>2</sup> carbon atoms), 152.60 (C-3), 161.18 (C-5), 168.90 (C-9'); Anal. calcd. for C<sub>21</sub>H<sub>14</sub>N<sub>8</sub>S (410.46): C, 61.45; H, 3.44; N, 27.30; S, 7.81. Found: C, 61.51; H, 3.56; N, 27.12; S, 7.64.

**3,5-Dimethyl-7-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[4,3-c]pyrimidine (9b).** Yield 64%, mp 236–238°C; IR ν<sub>max</sub> absence of the NH<sub>2</sub>, NH groups; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 2.9 ppm (s, 3H, C<sub>3</sub>-CH<sub>3</sub>), 2.96–3.10 (m, 7H, C<sub>5</sub>-CH<sub>3</sub>, C<sub>5'</sub>-CH<sub>2</sub>+C<sub>6'</sub>-CH<sub>2</sub>), 7.0–7.4 (m, 5H, 4Ar-H+C<sub>9</sub>-H), 8.1 (s, 1H, C<sub>9</sub>-H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>): δ 23.18 (C<sub>3</sub>-CH<sub>3</sub>), 23.60 (C<sub>5</sub>-CH<sub>3</sub>), 24.40 (C-5'), 29.68 (C-6'), 111.50–146.64 (15 sp<sup>2</sup> carbon atoms), 153.00 (C-3), 160.10 (C-5), 168.90 (C-9'); Anal. calcd. for C<sub>22</sub>H<sub>16</sub>N<sub>8</sub>S (424.48): C, 62.25; H, 3.80; N, 26.40; S, 7.55. Found: C, 61.96; H, 3.62; N, 26.01; S, 7.86.

### Reaction of 5a or 5b with Triethyl Orthoacetate at Reflux

Compound **5a** or **5b** (0.01 mol) was refluxed in triethyl orthoacetate (20 mL) for 10 h, the solid product was formed collected by filtration on heat, dried, and purified on silica gel column using petroleum ether 40–60°C:ethyl acetate (7:3) as an eluent to give products **8a** (25%) or **8b** (22%) and **9a** (64%) or **9b** (58%), respectively.

### Isomerization of 7a,b and 9a,b to 6a,b and 8a,b

Compounds **7a,b** and **9a,b** (0.01 mol) were refluxed in dry ethanol (20 mL) containing a few drops of formic acid (for **7a,b**) or acetic acid (for **9a,b**) for 6 and 9 h, respectively. The reaction mixtures were evaporated under reduced pressure, and the residues were recrystallized from dioxane to give compounds **6a** (90%), **6b** (93%), **8a** (89%), and **8b** (92%), respectively. Products obtained from these isomerizations are identical in all respects (mp, TLC, physical, and spectral data) with those prepared previously.

### General Procedure for the Synthesis of 10a and 10b

Compound **5a** or **5b** (0.01 mol) and benzoyl chloride (2 mL) were refluxed in phosphorus oxychloride (20 mL) for 5 h. The reaction mixtures were cooled and poured into ice. The solids that formed were filtered off, dried, and recrystallized from dioxane to afford compounds **10a** and **10b**, respectively.

**2-Phenyl-7-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (10a).** Yield 65%, mp 235–237°C; IR ν<sub>max</sub> absence of the NH<sub>2</sub>, NH groups; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 3.2–3.6 ppm (m, 4H, C<sub>5'</sub>-CH<sub>2</sub>+C<sub>6'</sub>-CH<sub>2</sub>), 7.2–8.5 (m, 10H, 9Ar-H+C<sub>9</sub>-H), 9.0 (s, 1H, C<sub>9</sub>-H), 9.5 (s, 1H, C<sub>5</sub>-H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>): δ 24.40 (C-5'), 29.68 (C-6'), 117.50–156.64 (21 sp<sup>2</sup> carbon atoms), 156.00 (C-2), 167.10 (C-5), 168.90 (C-9'); Anal. calcd. for C<sub>26</sub>H<sub>16</sub>N<sub>8</sub>S (472.53): C, 66.09; H, 3.41; N, 23.71; S, 6.79. Found: C, 66.36; H, 3.51; N, 23.88; S, 6.74.

**5-Methyl-2-phenyl-7-(5,6-dihydronaphtho[1',2':4,5]thieno[2,3-d]pyrimidin-11-yl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine (10b).** Yield 58%, mp 259–261°C; IR ν<sub>max</sub> absence of the NH<sub>2</sub>, NH groups; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 2.82 ppm (s, 3H, C<sub>5</sub>-CH<sub>3</sub>), 2.96–3.10 (m, 4H, C<sub>5'</sub>-CH<sub>2</sub>+C<sub>6'</sub>-CH<sub>2</sub>), 7.3–7.8 (m, 10H, 9Ar-H+C<sub>9</sub>-H), 8.6 (s, 1H, C<sub>9</sub>-H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>): δ 22.65 (C<sub>5</sub>-CH<sub>3</sub>), 24.40 (C-5'), 29.68 (C-6'), 117.50–155.40 (21 sp<sup>2</sup> carbon atoms), 156.00 (C-2), 168.00

(C-5), 169.10 (C-9'); Anal. calcd. for C<sub>27</sub>H<sub>18</sub>N<sub>8</sub>S (486.56): C, 66.65; H, 3.73; N, 23.03; S, 6.59. Found: C, 66.36; H, 3.51; N, 23.28; S, 6.74.

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