Synthesis and Spectral Characteristics of Novel Fluorescent Dyes Based on Pyrimido[4,5-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine

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Different derivatives of a novel heterocyclic system, *i.e.*, pyrimido[4,5-*d*][1,2,4]triazolo[4,3-*a*]-pyrimidine, are synthesized in moderate-to-good yields. These compounds exhibit excellent photochromism upon photoirradiation. The photophysical characterizations of these new compounds were evaluated by UV/VIS absorption and fluorescence emission studies. The emission spectra in various solvents are also presented and discussed. The changes are due to the intramolecular H-bonding of pyrimido-triazolo-pyrimidine with H_2O, and photoinduced electron and general solvent effect. These compounds display high fluorescence quantum yields and are reported as new fluorophores.

Introduction. – Fluorescence-spectroscopic techniques have attracted considerable attention due to their high sensitivity in systems containing intrinsic fluorophores and systems in which they might be introduced. During the last few decades, the application of fluorescence spectroscopy has experienced a remarkable increase in biological sciences. The fluorescence spectroscopy is considered to be one of the primary research tools in biochemistry and biophysics [1–7].

Many organic molecules, especially heterocyclic compounds, have fluorescence properties, which are also of interest in many disciplines such as emitters for electroluminescence devices [8], molecular probes for biochemical research [9], photoconducting materials [10], fluorescent whitening agents [11], and in traditional textile and polymer fields [12]. Among these compounds, those containing the pyrimidine moiety have been used successfully as fluorescent compounds [13–15].

Further, pyrimido[4,5-*d*]pyrimidines are an important class of annulated uracils, which show biologically important activities [16] because of their structural resemblance to purine-pteridine systems [17–19]. There are several reports for the preparation of this fused heterocycle, derivatives of which are useful as anticancer [20], nucleoside transport inhibiting [21], and dihydrofolate reductase inhibiting agents [22]. Most of these preparations rely on cyclocondensation reactions of pyrimidine intermediates [23–29]. A literature search revealed that no fluorophore system has been reported with a triazole moiety fused to the pyrimido[4,5-*d*]pyrimidine ring system.

In continuation of our previous works on fused pyrimidines [30–33] and heterocyclic fluorescent compounds [34–35], we synthesized a new pyrimido[4,5-*d*]-

pyrimidine system with a fused triazole moiety heterocyclic system. The photoluminescence activities of these compounds are also evaluated.

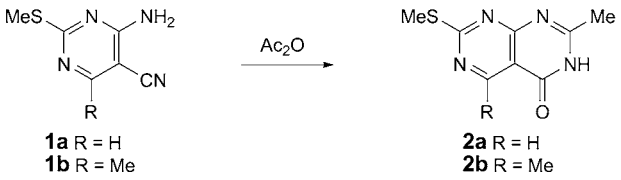
Results and Discussion. – *Synthesis.* The aminopyrimidine-carbonitrile derivatives **1a** and **1b**, used as starting materials, were prepared as described [36]. Reaction of **1a** and **1b** with Ac_2O afforded **2a** as a known compound and **2b** as a new one, respectively, as described in [37] with a slight modification, respectively (*Scheme 1*).

The reaction can be rationalized by a *Dimroth* rearrangement, which is an isomerization involving an O/N-translocation through a ring-opening ring-closure sequence [38][39] (*Scheme 2*).

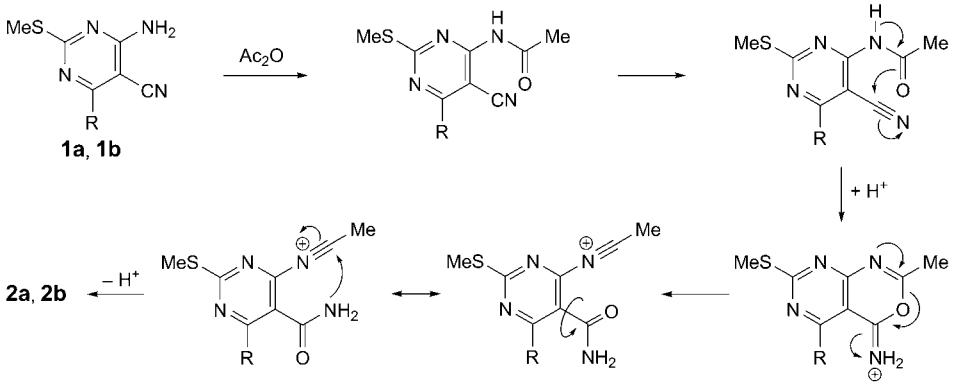
The ^{1}H-NMR spectrum of **2a**, as an example, showed a *singlet* at 2.14 ppm indicating the presence of Me group, a *singlet* corresponding to one H-atom of the NH group in the new fused pyrimidine ring which disappeared by adding D_2O. In the IR spectrum of **2a**, the disappearance of the stretching vibration peak of the CN group at 2221 cm^{-1} also confirmed the desired cyclization.

Further treatment of compounds **2a** and **2b** with $NH_2NH_2 \cdot H_2O$ in boiling EtOH gave quantitatively the corresponding hydrazine substituted derivatives **3a** and **3b**, respectively (*Scheme 3*). As an example, the ^{1}H-NMR spectrum of **3a** showed two broad *singlet*s at 4.57 and 6.63 ppm corresponding to NH_2 and NH moieties, respectively, which disappeared on deuteration. The mass spectrum exhibited the molecular-ion peak at 192. The elemental-analysis data along with further spectroscopic data confirmed the structure of **3a**. Then, we prepared various derivatives of

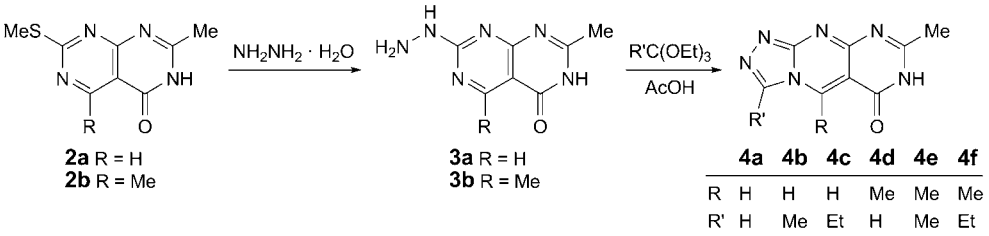
Scheme 1



Scheme 2. *Mechanism of Preparation of Compounds* **2a** *and* **2b** via Dimroth *Rearrangement*



Scheme 3



pyrimido-triazolo-pyrimidine by the reaction of **3a** and **3b** with some triethyl-orthoesters in boiling AcOH. When the starting materials were completely consumed, (monitored by TLC), the products **4a**–**4f** precipitated upon cooling and addition of H_2O to the reaction mixture (*Scheme 3*).

The structures of compounds **4a**–**4f** were confirmed from their elemental analyses, IR, and ^{1}H- and ^{13}C-NMR spectra. For instance, the mass spectrum of **4f** displayed the molecular-ion peak at *m*/*z* 244, which was in agreement with the proposed structure. The IR spectrum of **4f** showed an absorption band due to the NH group at 3125 cm^{-1}, and disappearance of the NH_2 and NH bands corresponding to the hydrazine moiety in the starting material. The ^{1}H-NMR spectrum of **4f** exhibited a *triplet* for the Me group at 1.37 ppm, a *quadruplet* for CH_2 at 3.41 ppm, and two *singlet*s for the other two Me groups at 2.41 and 2.82 ppm. The NH signal appeared at 13.5 ppm. The ^{13}C-NMR spectrum of **4f** displayed eleven distinct resonances in agreement with the suggested structure.

Photophysical Study. The absorption spectrum of **4a** was scanned in MeOH (1×10^{-5} M soln.) and is shown in *Fig. 1*. The wavelength of maximum absorption (λ_{max}) in 272 nm shows the highest intensity in the range of 200–800 nm. All the absorption and emission spectra of compounds **4a**–**4f** were recorded in MeOH, and their λ_{max} and

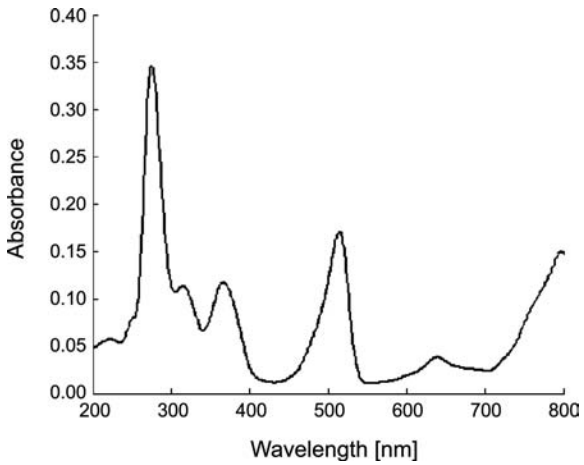


Fig. 1. *UV/VIS Absorption spectrum of compound* **4a** *in dilute MeOH solution* (1×10^{-5} M)

Table. *Photophysical Data for Maximum Absorption* (abs) *and Fluorescence* (flu) *of Products* **4a**–**4f** *in MeOH*

Compound	λ_{abs} [nm]	$\varepsilon \times 10^{-4}$ [M^{-1} cm^{-1}][a])	λ_{flu} [nm]	Φ_F^b)	*Stokes* shift
4a	272	3.50	420	0.75	148
4b	271	2.15	423	0.87	152
4c	272	3.80	425	0.80	153
4d	272	2.80	420	0.72	148
4e	271	2.35	420	0.70	149
4f	273	3.05	418	0.67	145

[a]) Extinction coefficient. [b]) Quantum yield.

λ_{flu} values are compiled in the *Table*. Values of the extinction coefficient (ε) are calculated as the slope of the plot of absorbance *vs.* concentration, and have a precision of the order of 5%.

While the bicyclic compounds **2a** and **2b**, and **3a** and **3b** exhibit low fluorescence, they become strongly fluorescent after a triazole ring is fused to compounds **3**. The fluorescence maxima of **4a**–**4f** were in the range of 418–425 nm. The relative fluorescence quantum yields were determined by using a 10^{-6} M solution of fluorescein in MeOH as a standard ($\Phi_F = 0.95$) [40]. As shown in *Fig. 2*, **4a**–**4f** exhibited good-to-excellent fluorescence quantum yields. The highest value was obtained for compound **4b**.

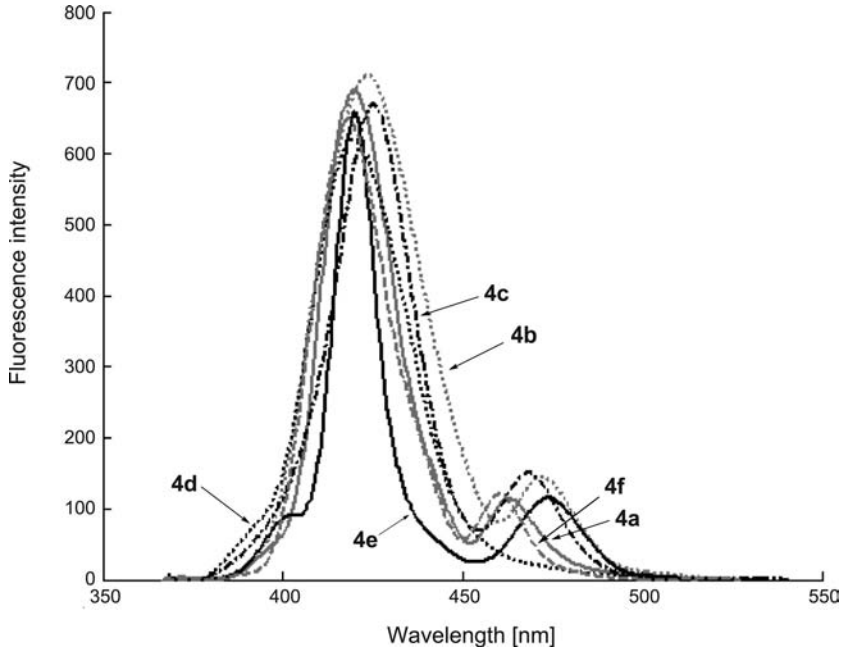


Fig. 2. *Emission spectrum of compounds* **4a**–**4f** *at* $\lambda_{ex.}$ *272 nm in dilute MeOH solution* (1×10^{-6} M)

The emission spectra of chemical compounds can be influenced by the surrounding medium, and solvents can bring about a change in the position, intensity, and shape of absorption bands [41]. Photophysical properties of **4a** have been studied in a number of organic solvents and H_2O. *Fig. 3* shows the emission spectra of **4a** in $CHCl_3$, DMF, THF, H_2O, MeOH, EtOH, and MeCN, demonstrating no significant shifts in these solvents. The fluorescence intensity maxima were found to vary with the nature of the solvent, which can be attributed to solvatochromic properties [42]. As it can be seen, H_2O showed the highest emission value which can be of advantage of using these compounds in biological media.

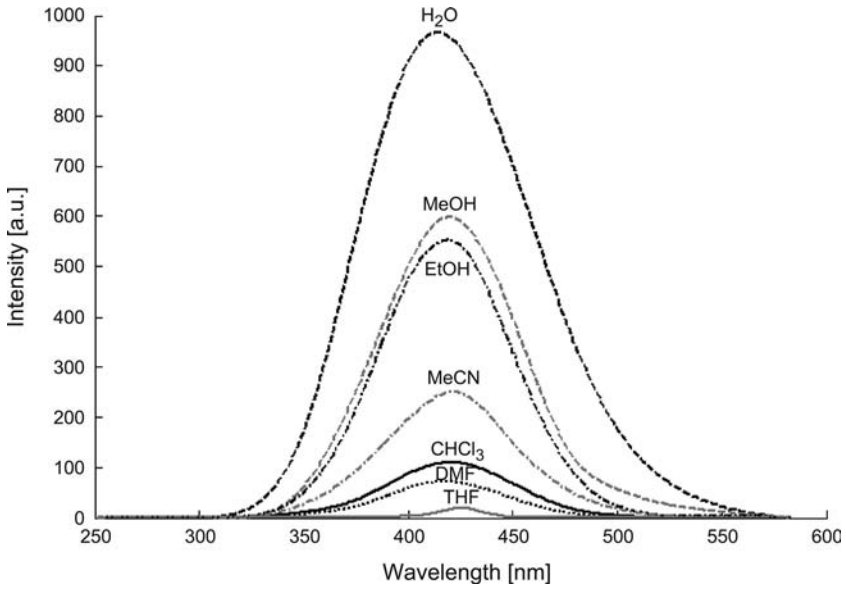


Fig. 3. *Fluorescence intensity of a solution of compound* **4a** (5×10^{-5} M) *in solvents such as $CHCl_3$, DMF, THF, H_2O, MeOH, EtOH, and MeCN at $\lambda_{ex.}$ 272 nm*

Conclusions. – We have accomplished the synthesis of a novel fluorescent heterocyclic system **4a** – **4f** containing a triazole moiety fused to a pyrimido-pyrimidine ring system by simple procedures in moderate-to-good yields. Their photophysical properties were also evaluated. Due to their interesting fluorescence properties, *i.e.*, their strongly emissive character in H_2O, these new heterocyclic pyrimido-triazolo-pyrimidine derivatives can be used as fluorescent markers and probes for studies in biochemistry and pharmacology.

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Experimental Part

General. M.p.: *Electrothermal* type *9100* melting-point apparatus. UV/VIS Spectra: *Varian 50 Bio* UV/VIS spectrophotometer. Fluorescence spectra: *Varian Cary Eclipse* spectrofluorophotometer. IR Spectra: *Avatar 370* FT-IR *Thermo Nicolet*; only relevant absorptions are given. ^{1}H- and ^{13}C-NMR spectra: *Bruker AVANCE DRX-400 Fourier* transformer spectrometer; at 400 and 100 MHz, resp; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Varian MAT CH-7* at 70 eV. Elemental analyses: *Thermo Finnigan Flash EA* microanalyzer; in %.

General Procedure for the Synthesis of Compounds **2a** *and* **2b**. Compound **1a** (10 mmol, 1.66 g) or **1b** (10 mmol, 1.8 g), which were prepared as described in procedure [36], was heated under reflux in Ac_2O (20 ml). The reaction was monitored by TLC ($CHCl_3$/MeOH 10 : 1). After the reaction was complete (*ca.* 3 h), the mixture was cooled and poured into ice-cold H_2O. The resulting precipitate was filtered off, dried, and recrystallized from dioxane.

2-Methyl-7-(methylsulfanyl)pyrimido[4,5-d*]pyrimidin-4(3*H*)-one* (**2a**). Yield: 1.98 g (95%). Orange powder. M.p. 284–286° (dec.) ([37]: 288–290°).

2,5-Dimethyl-7-(methylsulfanyl)pyrimido[4,5-d*]pyrimidin-4(3*H*)-one* (**2b**). Yield: 1.99 g (90%). Orange powder. Yield: 90%. M.p. 215° (dec.). IR (KBr): 3166 (NH), 1676 (C=O), 1613 (C=N). ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.12 (*s*, Me); 2.30 (*s*, Me); 3.34 (*s*, MeS); 13.40 (*s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 14.5; 20.4; 24.7; 109.3; 156.2; 163.5; 167.8; 168.0; 176.4. EI-MS: 222 (M^+). Anal. calc. for $C_9H_{10}N_4OS$ (222.27): C 48.63, H 4.53, N 25.21, S 14.43; found: C 48.60, H 4.48, N 25.14, S 14.39.

General Procedure for the Synthesis of Compounds **3a** *and* **3b**. A mixture of compound **2a** (10 mmol, 2.08 g,) or **2b** (10 mmol, 2.23 g), and an excess amount of $NH_2NH_2 \cdot H_2O$ (1 ml) in EtOH (30 ml) were heated at reflux for 5 h. After cooling the mixture, the resulting crude solid was collected by filtration, washed with cold H_2O, and recrystallized from EtOH, resp.

7-Hydrazinyl-2-methylpyrimido[4,5-d*]pyrimidin-4(3*H*)-one* (**3a**). Yield: 1.73 g (90%). Brown powder. M.p. 179–180°. IR (KBr): 3411 (NH), 3300, 3182 (NH_2), 3125 (NH), 3035 (CH), 1659 (C=O), 1610 (C=N). ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.14 (*s*, Me); 4.57 (*s*, NH_2); 6.63 (*s*, NH); 8.15 (*s*, CH); 13.37 (*s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 25.4; 109.5; 156.3; 158.9; 166.5; 167.8; 170.1. EI-MS: 192 (M^+). Anal. calc. for $C_7H_8N_6O$ (192.08): C 43.75, H 4.20, N 43.73; found: C 43.71, H 4.15, N 43.69.

7-Hydrazinyl-2,5-dimethylpyrimido[4,5-d*]pyrimidin-4(3*H*)-one* (**3b**). Yield: 1.64 g (80%). Brown powder. M.p. 232° (dec.). IR (KBr): 3317 (NH), 3257, 3166 (NH_2), 3109 (NH), 1678 (C=O), 1584 (C=N). ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.14 (*s*, Me); 2.37 (*s*, Me); 4.54 (*s*, NH_2); 6.60 (*s*, NH); 13.35 (*s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 21.4; 25.2; 108.9; 156.1; 161.9; 165.3; 167.4; 170.3. EI-MS: 206 (M^+). Anal. calc. for $C_8H_{10}N_6O$ (206.09): C 46.60, H 4.89, N 40.76; found: C 46.53, H 4.81, N 40.73.

General Procedure for the Synthesis of Compounds **4a**–**4f**. *Representative Procedure for the Synthesis of Compound* **4a**. Compound **3a** (5 mmol, 0.96 g) and $HC(OEt)_3$ (5 mmol, 0.74 g) were heated under reflux in AcOH (15 ml) for 6 h (monitored by TLC). After the completion of the reaction, the solvent was removed under reduced pressure, the residue was washed with cold H_2O and recrystallized from AcOEt/hexane 1 : 1.

8-Methylpyrimido[4,5-d*]-1,2,4-triazolo[4,3*-a*]pyrimidin-6(7*H*)-one* (**4a**). Yield: 0.85 g (90%). Yellow powder. M.p. 272°. IR (KBr): 3116 (NH), 3060 (CH), 1712 (C=O), 1603 (C=N). ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.51 (*s*, Me); 9.1 (*s*, H–C(3)); 9.58 (*s*, H–C(5)); 13.1 (*s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 22.3; 117.8; 134.2; 147.8; 148.1; 157.5; 158.9; 164.4. EI-MS: 202 (M^+), 188 ([M – Me]$^+$). Anal. calc. for $C_8H_6N_6O$ (202.06): C 47.53, H 2.99, N 41.57; found: C 47.48, H 2.92, N 41.50.

3,8-Dimethylpyrimido[4,5-d*]-1,2,4-triazolo[4,3*-a*]pyrimidin-6(7*H*)-one* (**4b**). Yield: 0.92 g (85%). Red powder. M.p. 289°. IR (KBr): 3109 (NH), 3050 (CH), 2930 (Me), 1710 (C=O), 1605 (C=N). ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.52 (*s*, Me–C(3)); 2.89 (*s*, Me); 9.50 (*s*, CH); 13.1 (*s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 12.5; 22.3; 117.7; 147.2; 149.9; 152.9; 158.9; 164.4; 167.4. EI-MS: 216 (M^+). Anal. calc. for $C_9H_8N_6O$ (216.08): C 50.00, H 3.73, N 38.87; found: C 49.95, H 3.69, N 38.81.

3-Ethyl-8-methylpyrimido[4,5-d*]-1,2,4-triazolo[4,3*-a*]pyrimidin-6(7*H*)-one* (**4c**). Yield: 0.69 g (60%). Orange powder. M.p. 270°. IR (KBr): 3130 (NH), 3050 (CH), 1706 (C=O), 1610 (C=N). ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.4 (*t*, J = 7.6, *Me*CH_2); 2.32 (*s*, Me–C(8)); 2.93 (*q*, J = 8.0 Me*C*H_2);

9.83 (*s*, CH); 13.45 (*s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 10.00; 15.2; 22.3; 115.9; 146.4; 147.7; 157.3; 157.5; 158.8; 164.4. EI-MS: 230 (M^+), 202, 188, 120. Anal. calc. for $C_{10}H_{10}N_6O$ (230.09): C 52.17, H 4.38, N 36.50; found: C 52.05, H 4.32, N 36.43.

5,8-Dimethylpyrimido[4,5-d*]-1,2,4-triazolo[4,3*-a*]pyrimidin-6(7*H*)-one* (**4d**). Yield: 0.54 g (50%). Green powder. M.p. 250° (dec.). IR (KBr): 3126 (N–H), 3060 (C–H), 1703 (C=O), 1610 (C=N). ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.50 (*s*, Me–C(8)); 2.91 (*s*, Me–C(5)); 9.1 (*s*, CH); 13.5 (*s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 16.49; 22.3; 106.5; 134.0; 147.9; 153.8; 157.3; 158.8; 167.5. EI-MS: 215 (M^+), 120. Anal. calc. for $C_9H_8N_6O$ (216.08): C 50.00, H 3.73, N 38.87; found: C 49.94, H 3.68, N 38.81.

3,5,8-Trimethylpyrimido[4,5-d*]-1,2,4-triazolo[4,3*-a*]pyrimidin-6(7*H*)-one* (**4e**). Yield: 0.52 g (45%). Orange powder. M.p. 245° (dec.). IR (KBr): 3120 (NH), 1705 (C=O), 1605 (C=N). ^{1}H-NMR (400 MHz, (D_6)DMSO): 2.46 (*s*, Me–C(8)); 2.81 (*s*, Me–C(5)); 2.92 (*s*, Me–C(3)); 13.3 (*s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 12.4; 17.4; 22.3; 106.4; 147.8; 153.0; 157.3; 158.8; 167.5; 167.7. EI-MS: 231 (M^+), 174 (11). Anal. calc. for $C_{10}H_{10}N_6O$ (230.09): C 52.17, H 4.38, N 36.50; found: C 52.10, H 4.32, N 36.41.

3-Ethyl-5,8-dimethylpyrimido[4,5-d*]-1,2,4-triazolo[4,3*-a*]pyrimidin-6(7*H*)-one* (**4f**). Yield: 0.45 g (40%). Green powder. M.p. 260° (dec.). IR (KBr): 3125 (NH), 2941 (Me), 1703 (C=O), 1595 (C=N). ^{1}H-NMR (400 MHz, (D_6)DMSO): 1.37 (*t*, $J = 7.2$, *Me*CH_2); 2.47 (*s*, Me–C(8)); 2.82 (*s*, Me–C(5)); 3.41 (*q*, $J = 7.6$, MeC*H*$_2$); 13.5(*s*, NH). ^{13}C-NMR (100 MHz, (D_6)DMSO): 12.5; 22.2; 22.8; 26.0; 101.9; 149.6; 152.1; 154.2; 161.4; 164.5; 165.3. EI-MS: 244 (M^+), 229 ([M – Me]$^+$). Anal. calc. for $C_{11}H_{12}N_6O$ (244.11): C 54.09, H 4.95, N 34.41, found: C 54.01, H 4.89, N 34.37.

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