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# Synthesis of new pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines and related heterocycles

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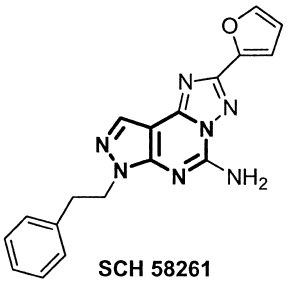
**Abstract**—The reaction between 5-amino-4-imino-1(2)-substituted-1(2)*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidines and several commercially available reactants afforded new heterocycles with a conserved pyrazolo[3,4-*d*]pyrimidine nucleus. The key intermediates employed proved to be suitable compounds by virtue of their two vicinal amino and imino groups that were used to obtain five, six and seven-membered rings.

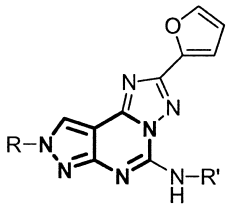

## 1. Introduction

Adenosine is present in different tissues in the mammalian organism where it has a variety of important physiological functions such as the synthesis of nucleic acids or implications in energy metabolism production.[1–3] Adenosine interacts with four cell surface receptor subtypes (ARs) classified as $A_1$, $A_{2A}$, $A_{2B}$ and $A_3$, belonging to the family of G protein-coupled receptors.[4] Efforts made in medicinal chemistry in the past 20 years have led to the discovery of a variety of selective antagonists for the $A_{2A}$ and the $A_3$ adenosine receptor subtypes. Among these, it was demonstrated that the structural requirement for reaching $A_{2A}$ and $A_3$ antagonist behavior is the tricyclic heterocyclic pyrazolo[1,5-*c*]-1,2,4-triazolo[4,3-*e*]pyrimidine structure, $N^7$-substituted for molecules designed as $A_{2A}$ antagonists and $N^8$-substituted for molecules planned as $A_3$ antagonists.[5–14] Until now, the best results in terms of $A_{2A}$ and $A_3$ antagonistic affinity and selectivity are respectively achieved by the synthesis of **SCH 58261**[5] and the 5-*N*-(substituted-phenylcarbamoyl)amino-$N^8$-substituted-pyrazolo-triazolo-pyrimidines, belonging to **MRE** analogs (Fig. 1).[10,11] Along with the tricyclic structure, another structural requirement necessary for the activity and, above all, the receptor anchorage was found to be the presence of the 2-furyl group at the 2-position of the tricyclic core.[5]

Starting from these SAR observations and in continuation to



SCH 58261



MRE series

R= alkyl, R'= (substituted)phenyl urea or amide

**Figure 1.** Potent and selective $A_{2A}$ and $A_3$ adenosine receptor antagonists.

*Keywords*: Reactivity studies; Adenosine antagonists; Pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines; 5-Amino-4-imino-1(2)-substituted-1(2)*H*-pyrazolo[3,4-*d*]pyrimidines.
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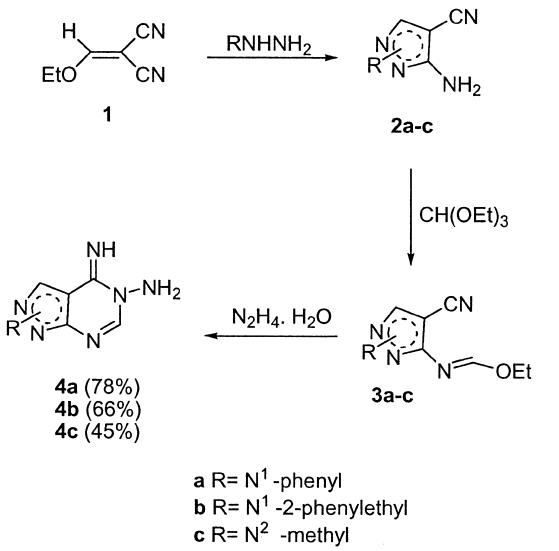



**Scheme 1.**

our interest in the synthesis of pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines[15] we decided to design and synthesize new adenosine ligands, maintaining the pyrazolo[3,4-*d*]pyrimidine nucleus and to replace the 2-(2-furyl)-triazole moiety with other five, six and seven-membered rings, fused to the pyrazolo[3,4-*d*]pyrimidine ring system and functionalized by the introduction of several functions, such as ester, acid, amide, hydrazide, and alkyl groups.

For this purpose we started from the key intermediates **4a–c** (5-amino-4-imino-1(2)-substituted-1(2)*H*-pyrazolo[3,4-*d*]pyrimidines), easily obtained from the $N^1$ or $N^2$-substituted amino-cyano-pyrazoles (Scheme 1).[16,17] These substrates proved to be versatile compounds by virtue of their vicinal amino and imino functions, evaluating the reactivity in several cyclization reactions performed with the aim of obtaining new heterocycles with a conserved pyrazolo[3,4-*d*]pyrimidine core. The substituents selected for the pyrazole nitrogen of **4a–c** were mainly 1-phenyl but 1-(2-phenylethyl) like SCH 58261, and 2-methyl like the MRE series were also chosen for comparison reasons.

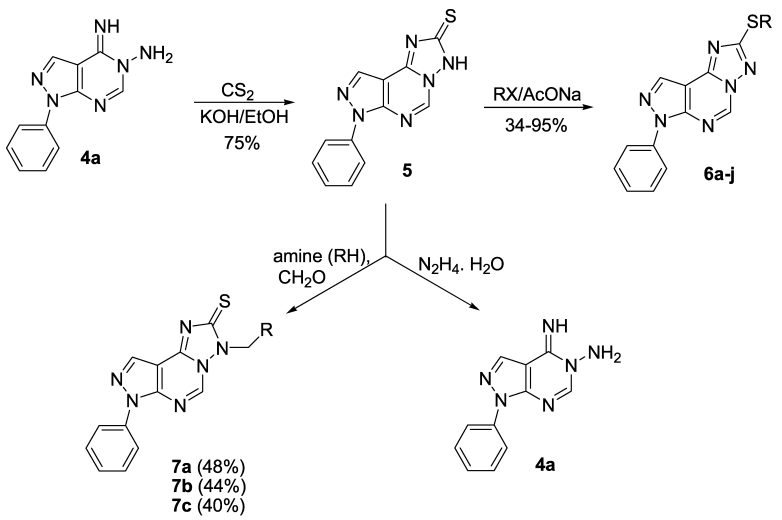
In our chemical reactivity studies described here, we principally employed the intermediate **4a** (5-amino-4-imino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine), due to its easy preparation, high reactivity and good yield of reactions. The major limitations of compounds **4b** and **4c** were their low solubility in organic solvents employed in the clusters of reactions performed and, at the same time, the restricted yield of reactions.

The new heterocycles obtained will be evaluated in pharmacological assays to determine their antagonist properties versus the $A_{2A}$ and $A_3$ adenosine receptor subtypes.

## 2. Results and discussions

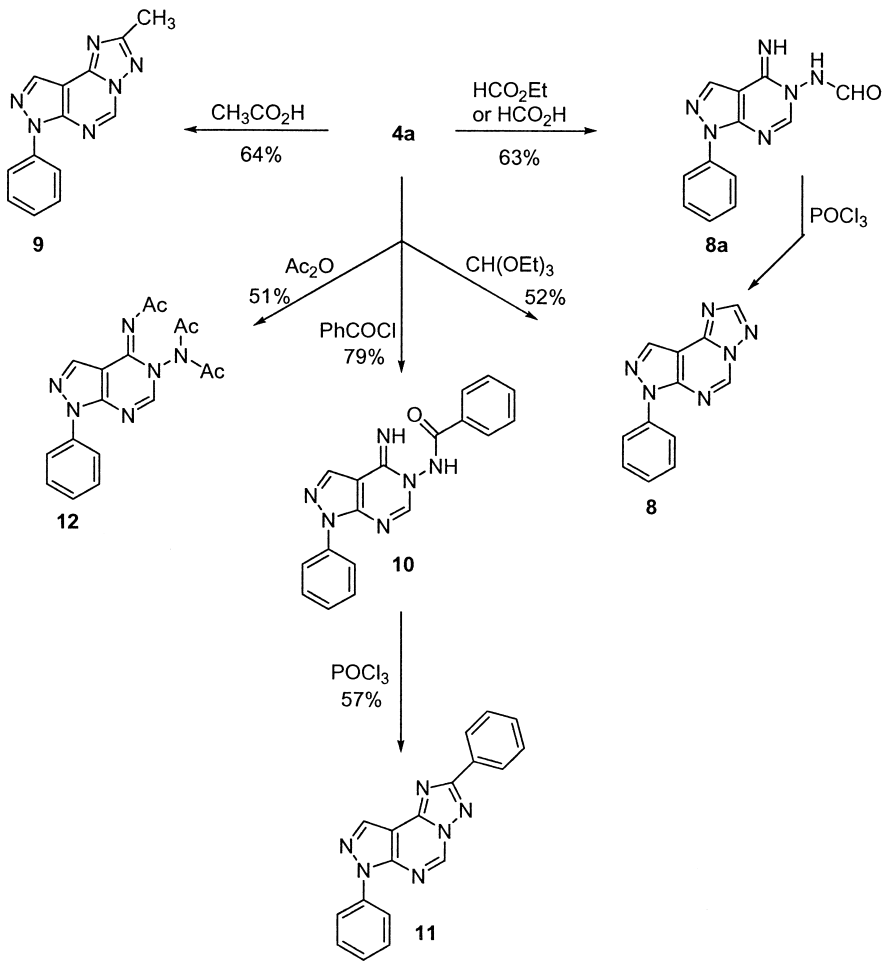
The $N^1$ or $N^2$-substituted amino-cyano-pyrazoles[16,17] were reacted with triethylorthoformate to give the corresponding ethoxymethylene amino derivatives **3a–c**. These latter compounds were used as intermediates for the preparation of the key compounds **4a–c** by cyclization with hydrazine hydrate, as depicted in Scheme 1.

When **4a** was allowed to react with $CS_2$, the pyrazolo-triazolo-pyrimidine-2-thione **5** was obtained. This latter compound, was alkylated using several alkylating agents (RX) in refluxing ethanol in the presence of anhydrous sodium acetate to give the corresponding derivatives **6a–j**. The Mannich bases **7a–c** were obtained via the reaction of the thione **5** with formaldehyde and the corresponding amines. In a trial to prepare the hydrazino derivative via the




**6a** R= $CH_2CO_2Et$, 34%; **6b** R= $CH_2CO_2H$, 80%; **6c** R= $CO_2Et$, 48%; **6d** R= $CH_2COCH_3$, 42%; **6e** R= $CH_2CONH_2$, 39%; **6f** R= $CH_2CN$, 91%; **6g** R= $CH_3$, 95%; **6h** R= Et, 48%; **6i** R= $CH_2CONHC_6H_4CH_3$, 56%; **6j** R= $CH(CN)_2$, 37%.
**7a** R= $NC_4H_8O$, **7b** R= $NHCH_2C_6H_5$, **7c** R= $NHC_6H_5$

**Scheme 2.**




**Scheme 3.**

reaction of **5** with hydrazine hydrate, unexpectedly the reaction product was found to be compound **4a** (Scheme 2).

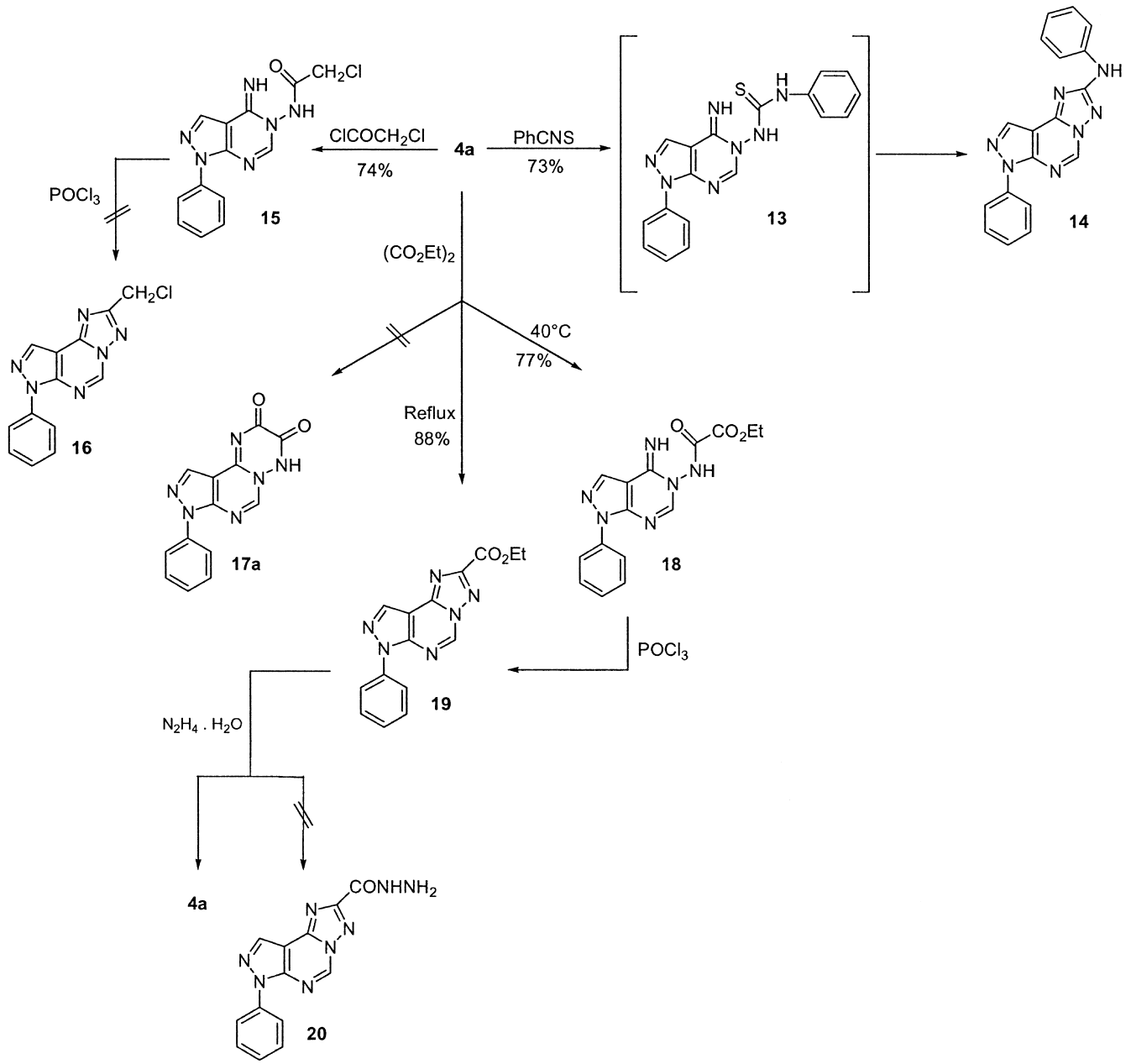
As described in Scheme 3, reaction of **4a** with triethylorthoformate afforded the corresponding 7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **8**; however, its reaction with ethyl formate did not afford **8** but gave the intermediate formylamino derivative **8a** which could be ring closed in refluxing phosphoryl chloride to give **8**. Other 2-substituted derivatives of **8** could be synthesized as shown in Scheme 3. The 2-methyl derivative **9** was obtained by boiling **4a** in glacial acetic acid. However, upon heating compound **4a** in refluxing acetic anhydride the reaction product was identified as the triacetyl derivative **12** and not the expected product **9**. Compound **11** (the 2-phenyl analog of **9**) could not be obtained directly by the reaction of **4a** with benzoylchloride which gave the benzoylamino derivative **10**. This latter compound could be cyclized into **11** in boiling $POCl_3$ (Scheme 3).

On the other hand, as depicted in Scheme 4, the 2-phenylamino derivative **14** was obtained when **4a** was treated with phenylisothiocyanate in refluxing pyridine. Obviously this reaction proceeded via the thiourea intermediate **13** with concomitant dehydrosulfurization. Also, the reaction of **4a** with chloroacetyl chloride did not afford the chloromethyl derivative **16** but resulted in the formation of chloroacetylamino derivative **15**, which could not be cyclized into **16** in boiling $POCl_3$. Interestingly, upon warming **4a** in diethyl oxalate the intermediate **18** was obtained. This upon heating in boiling $POCl_3$ gave the ester **19**. Alternatively, compound **19** could be obtained directly from **4a** by heating under reflux with diethyl oxalate and no evidence for the formation of the possible dioxotriazine derivate **17a** was observed.

Interestingly, hydrazinolysis of the ester **19** did not afford the expected carbohydrazide derivative **20** but resulted in ring opening of the triazole ring giving back the aminoimino compound **4a**.

In Scheme 5, reaction of **4a** with an excess of diethyl malonate gave directly the ester **23**. As was the case with compound **19**, hydrazinolysis of compound **23** did not afford the expected hydrazide derivative but also resulted in opening of the triazole ring with the formation of the aminoimino compound **4a**. The interaction of compounds **4a–c** with an equimolar ratio of ethyl chloroformate gave the corresponding triazino derivative **21a–c**, whereas the reaction of **4a** with an excess of same reagent gave the diethoxycarbonylamino compound **22**. When compound **4a** was subjected to the diazotization reaction conditions, the tetrazolo derivative **24** was formed.

Treatment of compounds **4a–c** with oxalyl chloride in refluxing dry benzene afforded the corresponding dioxo-

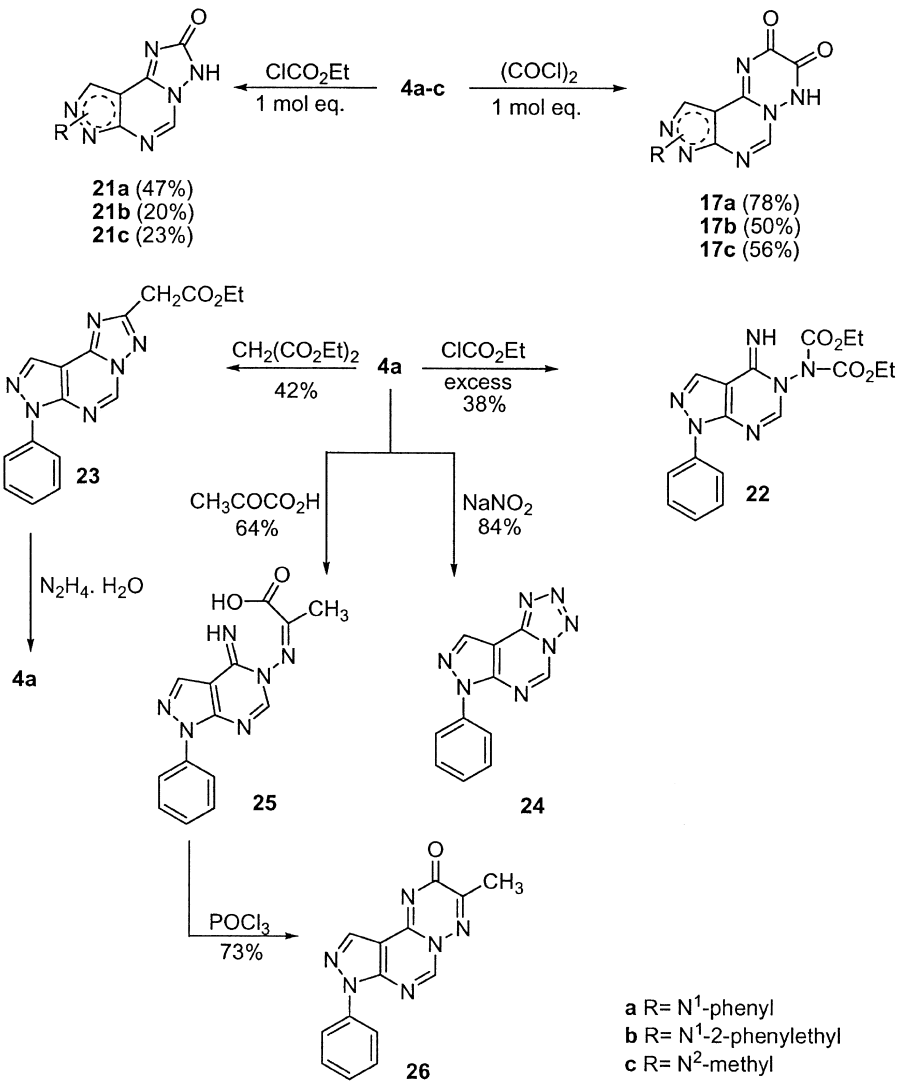



**Scheme 4.**

triazine compounds **17a–c**. However, reaction of **4a** with pyruvic acid gave the intermediate **25**, which was cyclized in boiling $POCl_3$ to give the triazinone compound **26** (Scheme 5).

In a comparative study,[18] it was reported that the reaction of the 3-amino-4-imino-3,4-dihydrothieno[2,3-*d*]pyrimidine with acetylacetone gave 2-methythieno[3,2-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine and its reaction with ethoxymethylenemalononitrile or ethyl ethoxymethylenecyanoacetate led to the formation of the parent thieno[3,2-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidine.

In contrast, in our hands when the aminoimino compound **4a** was allowed to react with acetylacetone under the same reaction conditions reported for the reaction described above we got a product with a different mp and spectral data to those obtained for **9**. The NMR spectrum of the products formed from the reaction between **4a–c** and acetylacetone (compounds **27a–c**) showed two additional methyl signals. This is in agreement with the structure of 5,7-dimethyl-1(2)-substituted-1(2)*H*-azolo[3′,4′:4,5]pyrimido[1,6-*b*]triazepines **27a–c**. It is noteworthy that when the reaction was carried out with **4a** in benzoylacetone, the product was identified as the intermediate azomethine compound **28** which could be cyclized to the corresponding triazepine **29** by heating in refluxing phosphoryl chloride (Scheme 6). The reaction between **4a** and ethyl benzoylacetate led to the formation of the triazepine **31**. On the other hand the reaction of **4a** with ethoxymethylenemalononitrile or ethyl ethoxymethylenecyano-acetate did not afford the triazolo derivative **8**, as would be expected from the same reaction reported for the amino-imino derivative of the thieno-pyrimidine,[18] however the reaction products were identified




**Scheme 5.**

as the triazepine–aminonitrile and aminoester derivatives **30a**,**b**, respectively. Compound **32** was finally obtained from the reaction between **4a** and benzoylacetonitrile.

In conclusion, the amino ester **30b** could be hydrolyzed to the corresponding amino acid **30c**, however, the hydrazinolysis of the ester function of **30b** did not lead to the corresponding amino hydrazide derivative but gave back the amino imino derivative **4a**.

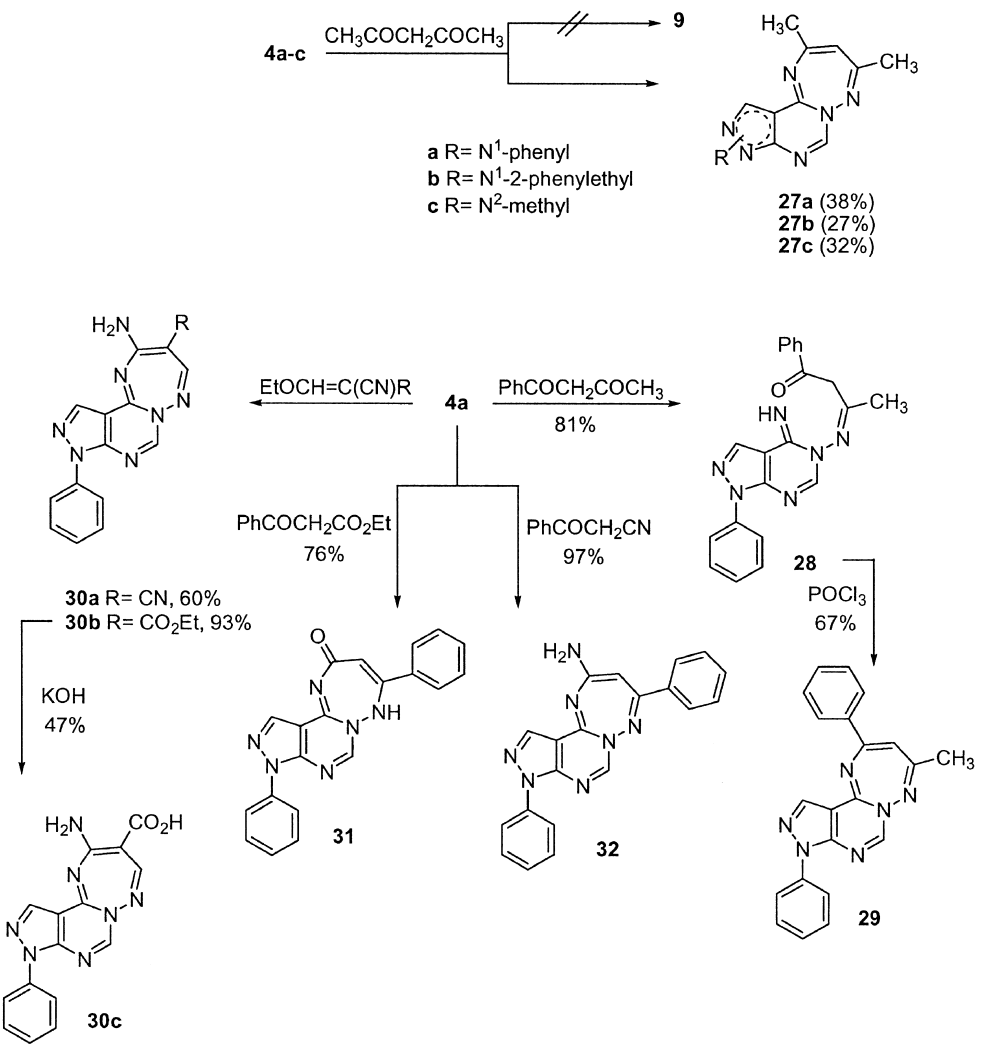
## 3. Conclusion

New heterocycles were obtained from the reaction between 5-amino-4-imino-1(2)-substituted-1(2)*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidines **4a**–**c** and several commercially available reactants. All the compounds obtained and described in this work retain the pyrazolopyrimidine core while third fused heterocyclic nucleus (five, six or seven-membered) was constructed via easily accessible intermediates. A SAR study of the newly synthesized compounds to evaluate their affinity and selectivity toward $A_{2A}$ and $A_3$ adenosine receptor subtypes will be the subject of another publication.

## 4. Experimental

### 4.1. General

Reactions were routinely monitored by thin-layer chromatography (TLC) on silica gel (precoated $F_{245}$ Merck plates) and products visualized with iodine or potassium permanganate solution. $^1$H NMR spectra were determined in $CDCl_3$, $CF_3COOD$ or DMSO-$d_6$ solutions with a Bruker AC 200 spectrometer. Peak positions are given in parts per million ($\delta$) downfield from tetramethylsilane as internal standard, and $J$ values are given in Hz. IR spectra were recorded on Pye Unicam SP 300 spectrometer using KBr Wafer technique. Mass spectra were obtained with a Shimadzu QP5050 DI 50 spectrometer. Light petroleum ether refers to the fractions boiling at 40–60 °C. Melting points were determined on a Buchi–Tottoli instrument and are uncorrected. Chromatographies were performed using Merck 60–200 mesh silica gel. All products reported




**Scheme 6.**

showed $^1$H NMR spectra in agreement with the assigned structures. Analyses were performed by the micro-analytical laboratory of Dipartimento di Chimica, University of Ferrara. Compounds **3a–c** were prepared according to known procedures.[16,17]

**4.1.1. General procedures for the preparation of 5-amino-4-imino-1(2)-substituted-1(2)*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidines 4a–c.** A mixture of compounds **3a–c** (5.24 g, 22 mmol) and hydrazine hydrate (8 mL, 80%) in ethanol (20 mL) was heated under reflux for 2 h. The white precipitate formed after cooling was filtered off and dried. Recrystallization from ethanol afforded the required products **4a–c** as white crystals.

*5-Amino-4-imino-1-phenyl-1H-4,5-dihydropyrazolo[3,4-d]pyrimidine* **4a**. Yield 78% (3.84 g), white crystals, mp 235 °C. [Found: C, 58.56; H, 4.35; N, 37.10. $C_{11}H_{10}N_6$ requires: C, 58.39; H, 4.46; N, 37.15]. IR cm$^{-1}$: 3330, 3200 (NH and $NH_2$), 1630 (C=N); $^1$H NMR (DMSO-$d_6$): $\delta$ 4.90 (s, 2H, $NH_2$), 7.63–7.17 (m, 5H, phenyl), 8.23 (s, 1H, CH-pyrazole), 8.30 (s, 1H, CH-pyrimidine), 9.43 (s, 1H, NH). MS: *m*/*z* 226.24 ($M^+$).

*5-Amino-4-imino-1-(2-phenylethyl)-1H-4,5-dihydropyrazolo[3,4-d]pyrimidine* **4b**. Yield 66% (3.27 g), white crystals, mp 264 °C. [Found: C, 61.33; H, 5.24; N, 32.88. $C_{13}H_{14}N_6$ requires: C, 61.40; H, 5.55; N, 33.05]. IR cm$^{-1}$: 3260, 3180 (NH and $NH_2$), 1590 (C=N); $^1$H NMR DMSO-$d_6$): $\delta$ 3.14 (t, 2H, $CH_2$, $J$=7.2 Hz), 4.49 (t, 2H, $CH_2$, $J$=7.2 Hz), 4.82 (bs, 2H, $NH_2$), 7.12–7.23 (m, 5H, phenyl), 8.03 (s, 1H, CH-pyrazole), 8.28 (s, 1H, CH-pyrimidine), 9.07 (s, 1H, NH). MS: *m*/*z* 255.2 ($M^+$).

*5-Amino-4-imino-2-methyl-2H-4,5-dihydropyrazolo[3,4-d]pyrimidine* **4c**. Yield 45% (1.95 g), white crystals, mp >300 °C. [Found: C, 43.79; H, 4.80; N, 50.98. $C_6H_8N_6$ requires: C, 43.90; H, 4.91; N, 51.19]. IR cm$^{-1}$: 3320, 3210 (NH and $NH_2$), 1615 (C=N); $^1$H NMR (DMSO-$d_6$): $\delta$ 3.74)s, 3H, $CH_3$), 6.56 (bs, 2H, $NH_2$), 7.98 (s, 1H, CH-pyrazole), 8.20 (s, 1H, CH-pyrimidine), 11.78 (s, 1H, NH). MS: *m*/*z* 165.2 ($M^+$).

**4.1.2. 7-Phenyl-7*H*-2,3-dihydro-2-thioxopyrazolo[4,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine 5.** To a stirred suspension of compound **4a** (5.24 g, 22 mmol) in ethanol (20 mL), ethanolic potassium hydroxide (30 mL, 0.01 mol) and $CS_2$ (2 mL) were added dropwise. The reaction mixture was then heated under reflux for 6 h. After cooling and evaporation of the solvent, the potassium salt obtained was dissolved in

water and acidified with 2 N aqueous HCl. The solid product formed was collected and recrystallized from ethanol into yellow crystals. Yield 0.30 g (75%), mp 275–277 °C. [Found: C, 53.50; H, 3.36; N, 31.19. $C_{12}H_8N_6S$ requires: C, 53.72; H, 3.01; N, 31.33]. IR; $cm^{-1}$ 3350 (NH), 1630 (C═N), 1190 (C═S). $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.55 (m, 3H, phenyl), 7.93–8.13 (m, 2H, phenyl), 8.60 (s, 1H, CH-pyrazole), 9.03 (s, 1H, CH-pyrimidine), 9.47 (s, 1H, NH). MS: *m/z* 268.27 ($M^+$).

**4.1.3. General procedures for the preparation of 7-phenyl-7*H*-2-substituted-mercaptopyrazolo[4,3-*e*]-[1,2,4]triazolo[1,5-*c*] pyrimidines 6a–j.** To a mixture of compound **5** (0.228 g, 0.001 mol) and sodium acetate (1.64 g, 0.02 mol) in ethanol (15 mL) was added the respective halo compound (RX, 0.001 mol), then the reaction mixture was heated under reflux for 4 h. After cooling the solid products formed were filtered, washed with water and recrystallized from the proper solvent.

*2-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thioethyl acetate* **6a**. Using ethyl chloroacetate, compound **6a** was obtained as white crystals from ethanol. Yield 34% (0.10 g), mp 133–135 °C. [Found: C, 54.42; H, 4.20; N, 23.50. $C_{16}H_{14}N_6SO_2$ requires: C, 54.22; H, 3.98; N, 23.72]. IR $cm^{-1}$: 3050 (CH arom.), 2950 (CH aliph.), 1750 (C═O); $^1H$ NMR ($CDCl_3$): $\delta$ 1.30 (t, 3H, $CH_2CH_3$, $J$=7.3 Hz), 4.07 (s, 2H, $CH_2$), 4.20 (q, 2H, $CH_2CH_3$, $J$=7.3 Hz), 7.43 (m, 3H, phenyl), 8.03 (m, 2H, phenyl), 8.37 (s, 1H, CH-pyrazole), 8.93 (s, 1H, CH-pyrimidine). MS: *m/z* 355.19 ($M^+$).

*2-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thioacetic acid* **6b**. Using chloroacetic acid **6b** was obtained as yellow crystals from ethanol–dioxane (1:1). Yield 0.26 g, (80%), mp 295–297 °C. [Found: C, 51.44; H, 2.98; N, 25.56. $C_{14}H_{10}N_6SO_2$ requires: C, 51.52; H, 3.08; N, 25.76]. IR $cm^{-1}$ 3050 (CH arom.), 2900–2820 (CH aliph.), 3100–2400 (OH), 1700 (C═O), 1640 (C═N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 4.13 (s, 2H, $CH_2$), 5.07 (m, 1H, OH), 7.57 (m, 3H, phenyl), 8.10 (m, 2H, phenyl), 8.70 (s, 1H, CH-pyrazole), 9.57 (s, 1H, CH-pyrimidine).

*Ethyl-2-(7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thio formate* **6c**. Using ethylchloroformate **6c** was obtained as yellow crystals from benzene. Yield 0.163 g, (48%), mp 295–297 °C. [Found: C, 52.75; H, 3.70; N, 24.46. $C_{15}H_{12}N_6SO_2$ requires: C, 52.93; H, 3.55; N, 24.69]. IR $cm^{-1}$ 3080 (CH arom.), 1730 (C═O), 1640 (C═N). $^1H$ NMR ($CDCl_3$): $\delta$ 1.37 (t, 3H, $CH_2CH_3$, $J$=7.2 Hz), 4.37 (q, 2H, $CH_2CH_3$, $J$=7.2 Hz), 7.47 (m, 3H, phenyl), 8.13 (m, 2H, phenyl), 8.53 (s, 1H, CH-pyrazole), 9.20 (s, 1H, CH-pyrimidine).

*1-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thiopropanone* **6d**. Using chloroacetone **6d** was obtained as buff crystals from ethanol. Yield 0.131 g, (42%), mp 188–189 °C. [Found: C, 53.70; H, 3.61; N, 26.80. $C_{14}H_{12}N_6SO$ requires: C, 53.83; H, 3.87; N, 26.91]. IR $cm^{-1}$ 3050 (CH arom.), 1700 (C═O), 1640 (C═N). $^1H$ NMR ($CDCl_3$): $\delta$ 2.37 (s, 3H, $CH_3$), 4.13 (s, 2H, $CH_2$), 7.43 (m, 3H, phenyl), 8.13 (m, 2H, phenyl), 8.43 (s, 1H, CH-pyrazole), 9.00 (s, 1H, CH-pyrimidine).

*2-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)thio acetamide* **6e**. Using chloroacetamide **6e** was obtained as fluffy yellow crystals from dioxane. Yield 0.126 g, (39%), mp 255–57 °C. [Found: C, 51.53; H, 3.38; N, 29.97. $C_{14}H_{11}N_7SO$ requires: C, 51.68; H, 3.41; N, 30.14]. IR $cm^{-1}$ 3350, 3180 ($NH_2$), 3050 (CH arom.), 2900 (CH aliph.), 2220 (C≡N), 1640 (C═N). $^1H$ NMR ($CF_3$-COOD): $\delta$ 4.40 (s, 2H, $CH_2$), 5.15 (bs, 2H, $NH_2$), 7.77 (m, 5H, phenyl), 9.07 (s, 1H, CH-pyrazole), 9.53 (s, 1H, CH-pyrimidine).

*2-(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thioacetonitrile* **6f**. Using chloroacetonitrile **6f** was obtained as pale yellow crystals from ethanol. Yield 0.28 g, (91%), mp 180–182 °C. [Found: C, 54.53; H, 2.88; N, 31.67. $C_{14}H_9N_7S$ requires: C, 54.71; H, 2.95; N, 31.90]. IR $cm^{-1}$ 3080 (CH arom.), 2950, 2900 (CH aliph.) and 2220 (C≡N). $^1H$ NMR ($CDCl_3$): $\delta$ 4.05 (s, 2H, $CH_2$), 7.48 (m, 3H, phenyl), 8.03 (m, 2H, phenyl), 8.07 (s, 1H, CH-pyrazole), 9.07 (s, 1H, CH-pyrimidine).

*2-Methylthio-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine* **6g**. Using methyl iodide **6g** was obtained as white platelets from ethanol. Yield 0.27 g, (95%), mp 208–210 °C. [Found: C, 55.16; H, 3.46; N, 29.59. $C_{13}H_{10}N_6S$ requires: C, 55.30; H, 3.57; N, 29.70]. IR $cm^{-1}$ 3050 (CH arom.), 2980 (CH aliph.), 1640 (C═N). $^1H$ NMR ($CDCl_3$): $\delta$ 2.73 (s, 3H, $CH_3$), 7.47 (m, 3H, phenyl), 8.17 (m, 2H, phenyl), 8.43 (s, 1H, CH-pyrazole), 8.83 (s, 1H, CH-pyrimidine).

*2-Ethylthio-7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine* **6h**. Using ethyl iodide **6h** was obtained as white crystals from ethanol. Yield 0.14 g, (48%), mp 168–170 °C. [Found: C, 56.60; H, 4.18; N, 28.14. $C_{14}H_{12}N_6S$ requires: C, 56.74; H, 4.08; N, 28.36]. IR $cm^{-1}$ 3050 (CH arom.), 2950 (CH aliph.), 1640 (C═N). $^1H$ NMR ($CDCl_3$): $\delta$ 1.5 (t, 3H, $CH_3$, $J$=7.2 Hz), 3.30 (q, 2H, $CH_2$, $J$=7.2 Hz), 7.43 (m, 3H, phenyl), 8.03 (m, 2H, phenyl), 8.40 (s, 1H, CH-pyrazole), 8.98 (s, 1H, CH-pyrimidine).

*N-(p-Tolyl)-2-(7-phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-thioacetamide* **6i**. Using 2-chloro-*N*-(*p*-tolyl)-acetamide **6i** was obtained as yellow crystals from ethanol. Yield 0.13 g, (56%), mp 183–185 °C. [Found: C, 60.62; H, 3.98; N, 23.42. $C_{21}H_{17}N_7SO$ requires: C, 60.70; H, 4.12; N, 23.60]. IR $cm^{-1}$ 3300 (NH), 3030 (CH arom.), 2900 (CH aliph.), 1650 (C═O). $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.33 (s, 3H, $CH_3$), 4.37 (s, 2H, $CH_2$), 7.03 (m, 2H, phenyl), 7.47 (m, 5H, phenyl), 8.10 (m, 2H, phenyl), 8.60 (s, 1H, CH-pyrazole), 8.77 (s, 1H, CH-pyrimidine), 10.57 (s, 1H, NH).

*(7-Phenyl-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-2-ylthio) malononitrile* **6j**. Using bromomalononitrile **6j** was obtained as buff crystals from ethanol–dioxane (1:1). Yield 0.122 g, (36.7%), mp 205–207 °C. [Found: C, 53.99; H, 2.60; N, 33.84. $C_{15}H_8N_8S$ requires: C, 54.21; H, 2.43; N, 33.72]. IR $cm^{-1}$ 3080 (CH arom.), 2900 (CH aliph.), 2200 (C≡N), 1640 (C═N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.51 (m, 4H, phenyl and $CH(CN)_2$), 8.01 (m, 2H, phenyl), 8.60 (s, 1H, CH-pyrazole), 9.03 (s, 1H, CH-pyrimidine).

**4.1.4. General procedure for the preparation of 3-substituted-7-phenyl-7*H*-2,3-dihydro-2-thioxo-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines 7a–c.** A mixture of **5** (0.268 g, 0.001 mol), 36% aqueous formaldehyde (1 mL), methanol (20 mL) and selected amines (0.001 mol) was stirred at room temperature for about 3 h. The solid products formed were filtered off and recrystallized from the proper solvent.

*3-(Morpholin-4-yl-methyl)-7-phenyl-7H-2,3-dihydro-2-thioxopyrazolo[4,3-e][1,2,4] triazolo[1,5-c]pyrimidine* **7a**. Using morpholine **7a** was obtained as white crystals (methanol). Yield 0.174 g, (48%), mp 152–154 °C. [Found: C, 55.40; H, 4.42; N, 26.71. $C_{17}H_{17}N_7SO$ requires: C, 55.57; H, 4.66; N, 26.68]. IR $cm^{-1}$ 2900, 2800 (CH aliph.), 1640 (C═N), 1150 (C═S). $^1H$ NMR ($CDCl_3$): $\delta$ 2.67 (t, 4H, NC$H_2$, $J$=3.2 Hz), 3.67 (t, 4H, OC$H_2$, $J$=3.2 Hz), 5.03 (s, 2H, $CH_2$), 7.40 (m, 3H, Phenyl), 7.98 (m, 2H, Phenyl), 8.40 (s, 1H, CH-pyrazole), 8.93 (s, 1H, CH-pyrimidine).

*3-(Benzylaminomethyl)-7-phenyl-7H-2,3-dihydro-2-thioxo-pyrazolo[4,3-e][1,2,4] triazolo[1,5-c]pyrimidine* **7b**. Using benzylamine **7b** was obtained as white crystals (ethanol–dioxane 2:1). Yield 0.17 g, (44%), mp 218–220 °C. [Found: C, 61.70; H, 4.25; N, 25.54. $C_{20}H_{17}N_7S$ requires: C, 61.99; H, 4.42; N, 25.31]. IR $cm^{-1}$ 3100 (NH), 3050 (CH arom.), 2980 (CH aliph.), 1640 (C═N), 1210 (C═S). $^1H$ NMR ($CF_3COOD$): $\delta$ 5.00 (s, 2H, $CH_2$), 6.30 (s, 2H, $CH_2$), 7.66 (m, 10H, phenyl), 8.93 (s, 1H, CH-pyrazole), 9.43 (s, 1H, CH-pyrimidine).

*3-(Phenylaminomethyl)-7-phenyl-7H-2,3-dihydro-2-thioxo-pyrazolo[4,3-e][1,2,4] triazolo[1,5-c]pyrimidine* **7c**. Using aniline **7c** was obtained as white crystals (ethanol–dioxane; 1:1). Yield 0.15 g, (40%), mp 170–173 °C. [Found: C, 61.31; H, 4.20; N, 26.39. $C_{19}H_{15}N_7S$ requires: C, 61.11; H, 4.05; N, 26.26]. IR $cm^{-1}$ 3100 (NH), 3030 (CH arom.), 2900 (CH aliph.), 1640 (C═N), 1230 (C═S). $^1H$ NMR ($CF_3COOD$): $\delta$ 4.03 (s, 2H, $CH_2$), 7.70 (m, 10H, Phenyl), 8.93 (s, 1H, CH-pyrazole), 9.46 (s, 1H, CH-pyrimidine).

**4.1.5. 7-Phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidine 8.** A mixture of **4a** (0.226 g, 0.001 mol) and triethylorthoformate (5 mL) in dimethylformamide (5 mL) was refluxed for 1 h. After cooling and dilution with ice/water (30 mL), the solid product formed was filtered off and recrystallized from ethanol to furnish **8** as gray crystals. Yield 0.123 g, (52%), mp 178–180 °C. [Found: C, 61.25; H, 3.56; N, 35.31. $C_{12}H_8N_6$ requires: C, 61.01; H, 3.41; N, 35.58]. IR $cm^{-1}$ 3050 (CH-arom.), 1630 (C═N).$^1H$ NMR ($CDCl_3$): $\delta$ 7.46 (m, 3H, phenyl), 8.65 (m, 2H, phenyl), 8.36 (s, 1H, CH-pyrazole), 8.50 (s, 1H, CH-pyrimidine), 9.17 (s, 1H, CH-triazole). MS: $m/z$ 236.2 ($M^+$).

**4.1.6. 5-Formylamino-4-imino-1-pheny-1*H*-4,5-dihydro-pyrazolo[3,4-*d*]pyrimidine 8a.** A mixture of **4a** (0.226 g, 0.001 mol) and ethyl formate (5 mL) in dimethylformamide (5 mL) was heated under reflux for about 5 h. After cooling, the solid product formed was collected, washed with water (30 mL) and recrystallized from ethanol to afford **8a** as white crystals. Yield 0.16 g, (63%), mp 271–273 °C. [Found: C, 56.83; H, 3.92 N, 32.98. $C_{12}H_{10}N_6O$ requires: C, 56.68; H, 3.96; N, 33.06]. IR $cm^{-1}$ 3200 (NH), 3020 (CH-arom.), 1630 (C═N), 1660 (C═O). $^1H$ NMR ($CDCl_3$): $\delta$ 7.55 (m, 3H, phenyl), 8.11 (m, 2H, phenyl), 8.33 (s, 1H, CHO), 8.36 (s, H, CH-pyrazole), 8.40 (s, 1H, CH-pyrimidine), 10.24 (m, 2H, 2NH). MS: $m/z$ 254.25 ($M^+$).

**4.1.7. 2-Methyl-7-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine 9.** A mixture of **4a** (0.226 g, 0.001 mol) and acetic acid (15 mL) was refluxed for 5 h. After cooling and dilution with ice/water (20 mL), the white precipitate formed was filtered off and recrystallized from ethanol to give white crystals. Yield 0.16 g, (64%), mp 185–187 °C. [Found: C, 62.53; H, 4.29 N, 33.35. $C_{13}H_{10}N_6$ requires: C, 62.39; H, 4.03; N, 33.58]. IR $cm^{-1}$ 3050 (CH-arom.), 1640 (C═N).$^1H$ NMR ($CDCl_3$): $\delta$ 2.65 (s, 3H, $CH_3$), 7.46 (m, 3H, phenyl), 8.13 (m, 2H, phenyl), 8.48 (s, 1H, CH-pyrazole), 9.06 (s, 1H, CH-pyrimidine). MS: $m/z$ 250 ($M^+$).

**4.1.8. *N*-(4-Imino-1-phenyl-1*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-5-yl)benzamide 10.** To a stirred solution of **4a** (0.452 g, 0.002 mol) in pyridine (5 mL), benzoyl chloride (0.28 g, 0.002 mol) was added dropwise and stirring was continued for 6 h. After dilution with ice/water mixture (35 mL) the solid product formed was collected by filtration and recrystallized from ethanol to furnish white crystals. Yield 0.52 g, (79%), mp 265–267 °C. [Found: C, 65.27; H, 4.42 N, 25.32. $C_{18}H_{14}N_6O$ requires: C, 65.44; H, 4.27; N, 25.44]. IR $cm^{-1}$ 3230 (NH), 3050 (CH-arom.), 1700 (C═O), 1630 (C═N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.51 (m, 6H, phenyl), 8.06 (m, 4H, phenyl), 8.26 (s, 1H, CH-pyrazole), 8.50 (s, 1H, CH-pyrimidine), 10.33 (s, 1H, NH), 10.83 (bs, 1H, N*H*CO). MS: $m/z$ 330.95 ($M^+$).

**4.1.9. 2,7-Diphenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine 11.** A solution of **10** (0.20 g, 0.64 mmol) in $POCl_3$ was heated under reflux for 8 h. After cooling, the reaction mixture was poured into ice/water mixture (35 mL) and neutralized with ammonium hydroxide solution. The solid product formed was filtered off and recrystallized from ethanol to give buff crystals. Yield 0.18 g, (57%), mp 178–180 °C. [Found: C, 69.50; H, 3.77: N, 26.74. $C_{18}H_{12}N_6$ requires: C, 69.22; H, 3.87; N, 26.91]. IR $cm^{-1}$ 3230 (NH), 3050 (CH-arom.), 1700 (C═O), 1630 (C═N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.50 (m, 6H, phenyl), 8.04 (m, 4H, phenyl), 8.36 (s, 1H, CH-pyrazole), 8.47 (s, 1H, CH-pyrimidine). MS: $m/z$ 312.32 ($M^+$).

**4.1.10. 4-(Acetyl-imino)-5-diacetylamino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 12.** A suspension of **4a** (0.45 g, 0.002 mol) in acetic anhydride (10 mL) was heated under reflux for 1 h. After cooling, the solvent was concentrated under reduced pressure, then the reaction mixture was poured into ice-water (40 mL) to give a solid precipitate which was filtered off and recrystallized from petroleum ether 60/80 to furnish **12** as buff crystals. Yield 0.36 g, (51%), mp 112–115 °C. [Found: C, 57.76; H, 4.62; N, 23.76. $C_{17}H_{16}N_6O_3$ requires C, 57.95; H, 4.58; N, 23.85]. IR $cm^{-1}$ 3100 (CH arom.), 2910 (CH aliph.), 1718 (C═O). $^1H$ NMR ($CDCl_3$): $\delta$ 2.43 (s, 6H, 2$CH_3$), 2.50 (s, 3H, $CH_3$), 7.52 (m, 3H, phenyl), 8.06 (m, 2H, phenyl), 8.23 (s, 1H, CH-pyrazole), 8.72 (s, 1H, CH-pyrimidine). MS: $m/z$ 352 ($M^+$).

**4.1.11. 2-Phenylamino-7-phenyl-7*H*-pyrazolo[4,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine 14.** A suspension of **4a** (0.226 g, 0.001 mol) and phenylisothiocyanate (0.135 g, 0.001 mol) in pyridine (10 mL) was heated under reflux for 5 h. After cooling the reaction mixture was poured into ice/water (30 mL) and neutralized with diluted 10% HCl to give a buff solid precipitate. This product was collected and crystallized from ethanol–DMF (3:1) to furnish **14** as a buff powder. Yield 0.24 g, (73.4%), mp 274–276 °C. [Found: C, 65.94; H, 3.86; N, 29.76. $C_{18}H_{13}N_7$ requires C, 66.04; H, 4.00; N, 29.95]. IR $cm^{-1}$ 3100 (NH), 3050 (CH arom.), 1650 (C═N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.50 (m, 8H, phenyl), 8.04 (m, 2H, phenyl), 8.22 (s, 1H, NH), 8.63 (s, 1H, CH-pyrazole), 9.03 (s, 1H, CH-pyrimidine). MS: *m/z* 371.94 ($M^+$).

**4.1.12. *N*-(4-Imino-1-phenyl-1*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-3-yl)-2-chloro acetamide 15.** A mixture of **4a** (0.226 g, 0.002 mol) and chloroacetyl chloride (0.112 g, 0.001 mol) in dioxane (10 mL) was refluxed for 6 h. The white precipitate formed was collected and recrystallized from ethanol to give fluffy white crystals. Yield 0.22 g, (74%), mp 205–208 °C. [Found: C, 55.52; H, 3.77; N, 27.55. $C_{13}H_{11}ClN_6O$ requires C, 55.86; H, 3.66; N, 27.76]. IR $cm^{-1}$ 3150 (NH), 2980, 2780 (CH-aliph.), 1710 (C═O), 1630 (C═N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 4.50 (s, 2H, $CH_2$), 7.58 (m, 3H, phenyl), 8.12 (m, 2H, phenyl), 8.45 (s, 1H, CH-pyrazole), 8.80 (s, 1H, CH-pyrimidine), 8.91–9.1 (bs, 2H, 2NH). MS: *m/z* 302.76 ($M^+$).

**4.1.13. General procedure for the synthesis of 1(2)-substituted-1(2)*H*,7*H*-5,6-dioxo-5,6-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-*b*] [1,2,4]triazine 17a–c.** To a solution of **4a–c** (0.001 mol) in dry benzene (10 mL), oxalyl chloride (0.126 g, 0.001 mol) was added. The reaction mixture was heated under reflux for 8 h. The solids formed were collected by filtration and recrystallized from a mixture of ethanol/benzene (1:1) to afford **17a–c** as yellow crystals

*1-Phenyl-1H,7H-5,6-dioxo-5,6-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-b] [1,2,4]triazine* **17a**. Yield 0.23 g, (78%), yellow crystals, mp >300 °C. [Found: C, 55.60; H, 2.68; N, 29.79. $C_{13}H_8N_6O_2$ requires: C, 55.71; H, 2.88; N, 29.99]. IR $cm^{-1}$ 3200 (NH), 3080 (CH arom.), 2900 (CH aliph.), 1730 (C═O), 1710 (C═O). $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.48 (m, 5H, arom.); 7.98 (s, 1H, CH-pyrazole), 8.23 (s, 1H, CH-pyrimidine), 10.82 (bs, 1H, NH). MS: *m/z* 280 ($M^+$).

*1-(2-Phenylethyl)-1H,7H-5,6-dioxo-5,6-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-b] [1,2,4]triazine* **17b**. Yield 0.135 g (50.52%), yellow crystals, mp >300 °C. [Found C, 58.22; H, 3.81; N, 27.02. $C_{15}H_{12}N_6O_2$ requires: C, 58.44; H, 3.92; N, 27.26]. IR $cm^{-1}$ 3400 (NH), 2920 (CH arom.), 2650 (CH aliph.), 1740 (C═O), 1700 (C═O). $^1H$ NMR (DMSO-$d_6$): $\delta$ 3.23 (t, 2H, $CH_2$, $J$=7.2 Hz), 4.67 (t, 2H, $CH_2$, $J$=7.2 Hz), 7.24 (m, 5H, arom.), 8.09 (s, 1H, CH-pyrazole), 8.35 (s, 1H, CH-pyrimidine), 9.32 (bs, 1H, NH). MS: *m/z* 309.2 ($M^+$).

*2-Methyl-2H,7H-5,6-dioxo-5,6-dihydropyrazolo[3′,4′:4,5]pyrimido[1,6-b] [1,2,4]triazine* **17c**. Yield 0.166 g (56%), yellow crystals, mp >300 °C. [Found: C, 43.92; H, 2.51; N, 38.65. $C_8H_6N_6O_2$ requires: C, 44.04; H, 2.77; N, 38.52]. IR $cm^{-1}$ 3340 (NH), 1700 (C═O), 1660 (C═O). $^1H$ NMR (DMSO-$d_6$): $\delta$ 3.40 (s, 3H, $CH_3$), 8.20 (s, 1H, CH-pyrazole), 8.45 (s, 1H, CH-pyrimidine), 9.30 (bs, 1H, NH). MS: *m/z* 219.3 ($M^+$).

**4.1.14. Ethyl *N*-(4-imino-1-phenyl-1*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-5-yl)-carbamoyl formate 18.** A mixture of **4a** (0.226 g, 0.001 mol) and diethyl oxalate (5 mL) was warmed with stirring at 40 °C for 30 min. The solid precipitate formed was collected and recrystallized from dioxane to furnish **18** as buff crystals. Yield 0.25 g, (77%), mp 298–300 °C. [Found: C, 55.41; H, 4.56 N, 25.46. $C_{15}H_{14}N_6O_3$ requires C, 55.21; H, 4.32; N, 25.76]. IR $cm^{-1}$ 3200 (NH), 3050 (CH arom.), 1710 (C═O), 1670 (C═O) and 1630 (C═N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.33 (t, 3H, $CH_2CH_3$, $J$=7.3 Hz), 4.30 (q, 2H, $CH_2H_3$, $J$=7.3 Hz), 7.40 (m, 3H, phenyl), 8.08 (m, 2H, phenyl), 8.23 (s, 1H, CH-pyrazole), 8.37 (s, 1H, CH-pyrimidine), 8.88 (s, 2H, 2NH). MS: *m/z* 326 ($M^+$).

**4.1.15. Ethyl (1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-yl) carboxylate 19.** A mixture of **4a** (0.226 g, 0.001 mol) and diethyl oxalate (5 mL) was refluxed for 8 h. The reaction mixture was then concentrated at reduced pressure and left to cool. The solid product formed was filtered off and recrystallized from ethanol to furnish **19** as buff crystals. Yield 0.27 g, (88%), mp 212–214 °C. [Found: C, 58.34; H, 3.96 N, 26.99. $C_{15}H_{12}N_6O_2$ requires: C, 58.43; H, 3.92; N, 27.26]. IR $cm^{-1}$ 3050 (CH-arom.), 1730 (C═O). 1650 (C═N).$^1H$ NMR ($CDCl_3$): $\delta$ 1.52 (t, 3H, $CH_2CH_3$, $J$=7.4 Hz), 4.55 (q, 2H, $CH_2H_3$, $J$=7.4 Hz), 7.46 (m, 3H, phenyl), 8.06 (m, 2H, phenyl), 8.53 (s, 1H, CH-pyrazole), 9.23 (s, 1H, CH-pyrimidine).

**4.1.16. General procedure for the preparation of 7(8)-substituted-7(8)*H*-2-oxo-2,3-dihydropyrazolo[4,3-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidines 21a–c.** A mixture of **4a–c** (0.001 mol) and ethyl chloroformate (0.001 mol) in dry benzene (10 mL) was heated under reflux for 8 h. After cooling and triturating with ethanol the solid formed was filtered off and recrystallized from dioxane/ethanol (1:2) to furnish compounds **21a–c** as crystals.

*7-Phenyl-7H-2-oxo-2,3-dihydropyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine* **21a**. Yield 0.13 g (47%), buff crystals, mp 258–260 °C. [Found: C, 57.30; H, 2.98; N, 33.18. $C_{12}H_8N_6O$ requires: C, 57.14; H, 3.19; N, 33.32]. IR $cm^{-1}$ 3300 (NH), 1680 (C═O), 1640 (C═N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.44 (m, 3H, phenyl), 7.98 (m, 2H, phenyl), 8.40 (s, 1H, CH-pyrazole), 8.63 (s, 1H, CH-pyrimidine), 10.52 (bs, 1H, NH). MS: *m/z* 252.23 ($M^+$).

*7-(2-phenylethyl)-7H-2-oxo-2,3-dihydropyrazolo[4,3-e]-[1,2,4]triazolo[1,5-c]pyrimidine* **21b**. Yield 0.10 g (20%), buff crystals, mp 290 °C. [Found: C, 59.71; H, 4.26; N, 29.95. $C_{14}H_{12}N_6O$ requires: C, 59.99; H, 4.32; N, 29.98]. IR $cm^{-1}$ 3440 (NH), 3090 (CH arom.), 1685 (C═O). $^1H$ NMR (DMSO-$d_6$): $\delta$ 3.21 (t, 2H, $CH_2$, $J$=7.2 Hz), 4.60 (t, 2H, $CH_2$, $J$=7.2 Hz), 7.23 (m, 5H, arom.), 7.88 (s, 1H, CH-pyrazole), 8.11 (s, 1H, CH-pyrimidine), 11.41 (bs, 1H, NH). MS: *m/z* 281.32 ($M^+$).

*8-Methyl-8H-2-oxo-2,3-dihydropyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidine* **21c**. Yield 60 mg (23%), buff crystals, mp >300 °C. [Found: C, 44.35; H, 3.02; N, 44.08. $C_7H_6N_6O$ requires: C, 44.21; H, 3.18; N, 44.19]. IR $cm^{-1}$ 3450 (NH), 3180 (CH aliph.), 1690 (C=O). $^1H$ NMR (DMSO-$d_6$): $\delta$ 3.73 (s, 3H, $CH_3$), 7.43 (s, 1H, CH-pyrazole), 8.01 (s, 1H, CH-pyrimidine), 11.79 (bs, 1H, NH). MS: *m/z* 191.16 ($M^+$).

**4.1.17. 5-(*N*,*N*-Diethoxycarbonylamino)-4-imino-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 22.** A mixture of **4a** (0.226 g, 0.001 mol) and ethyl chloroformate (0.162 g, 0.0015 mol) in dry benzene (10 mL) was heated under reflux for 8 h. The reaction mixture was concentrated to one-third its volume and triturated with ethanol to give buff solid product which was filtered off and recrystallized from petroleum ether 60/80 to furnish **22** as buff crystals. Yield 0.14 g (38%), mp 118–120 °C. [Found: C, 55.30; H, 4.79: N, 22.45. $C_{17}H_{18}N_6O_4$ requires: C, 55.13; H, 4.90; N, 22.69]. IR $cm^{-1}$ 3290 (NH), 3050 (CH-arom.), 3980, 3910 (CH-aliph.), 1740 (C=O), 1630 (C=N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.30 (m, 6H, $2CH_2CH_3$), 4.26 (m, 4H, $2CH_2CH_3$), 7.36 (m, 3H, phenyl), 8.06 (m, 2H, phenyl), 8.37 (s, 1H, CH-pyrazole), 8.73 (s, 1H, CH-pyrimidine), 8.92 (bs, 1H, NH). MS: *m/z* 370.1 ($M^+$).

**4.1.18. Ethyl (1-phenyl-1*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-yl)acetate 23.** A suspension of **4a** (0.226 g, 0.001 mol) and diethyl malonate (5 mL) was heated under reflux over its boiling point for 10 h. The yellow solid product formed was filtered off and crystallized from dioxane into yellow crystals. Yield 0.14 g, (42%), mp >300 °C. [Found: C, 59.48; H, 4.50: N, 25.99. $C_{16}H_{14}N_6O_2$ requires: C, 59.62; H, 4.38; N, 26.08]. IR $cm^{-1}$ 3050 (CH arom.), 2950, 2800 (CH aliph.), 1730 (C=O), 1630 (C=N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.23 (t, 3H, $CH_2CH_3$), 4.11 (q, 2H, $CH_2CH_3$), 5.15 (s, 2H, $CH_2$), 7.46 (m, 3H, phenyl), 8.13 (m, 2H, phenyl), 8.40 (s, 1H, CH-pyrazole), 8.70 (s, 1H, CH-pyrimidine). MS: *m/z* 322.32 ($M^+$).

**4.1.19. 7-Phenyl-7*H*-pyrazolo[4,3-*e*]-1,2,3,4-tetrazolo[1,5-*c*]pyrimidine 24.** To a cold solution of **4a** (0.226 g, 0.001 mol) in acetic acid (10 mL) was added an ice-cold solution of sodium nitrite (0.21 g/5 mL $H_2O$, 0.003 mol) with stirring during five minutes. Stirring was then continued for 2 h. The reaction mixture was poured into water (60 mL) and the solid formed was filtered off and recrystallized from ethanol to afford **24** as buff crystals. Yield 0.20 g, (84%), mp 200–202 °C. [Found: C, 55.47; H, 2.89; N, 41.29. $C_{11}H_7N_7$ requires: C, 55.69; H, 2.97; N, 41.34]. IR $cm^{-1}$ 3060 (CH arom.), 2910 (CH aliph.), 1640 (C=N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 7.56 (m, 3H, phenyl), 8.01 (m, 2H, phenyl), 8.90 (s, 1H, CH-pyrazole), 10.16 (s, 1H, CH-pyrimidine). MS: *m/z* 237.22 ($M^+$).

**4.1.20. 2-(4-Imino-1-phenyl-1*H*-4,5-dihydropyrazolo[3,4-*d*]pyrimidin-5-ylimino) propionic acid 25.** A solution of **4a** (0.45 g, 0.002 mol) and pyruvic acid (0.208 g, 0.002 mol) in ethanol (15 mL) was heated under reflux for 5 h. After cooling, the reaction mixture was poured into water (60 mL). The solid precipitate formed was filtered off and recrystallized from ethanol–dioxane (1:1) to give buff crystals. Yield 0.38 g, (64.4%), mp 258–260 °C. [Found: C, 56.78; H, 3.96; N, 28.30. $C_{14}H_{12}N_6O_2$ requires: C, 56.75; H, 4.08; N, 28.37]. IR $cm^{-1}$ 3150 (NH), 2600–2400 (OH), 1695 (C=O), 1600 (C=N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.21 (s, 3H, $CH_3$), 7.47 (m, 3H, phenyl), 8.20 (m, 2H, phenyl), 8.57 (s, 1H, CH-pyrazole), 8.80 (s, 1H, CH-pyrimidine), 9.12 (bs, 1H, NH), 11.20 (bs, 1H, OH). MS: *m/z* 296.87 ($M^+$).

**4.1.21. 6-Methyl-1-phenyl-1*H*-5-oxo-pyrazolo[3′,4′:4,5]-pyrimido[1,6-*b*]-1,2,4-]triazine 26.** A solution of **25** (0.18 g, 0.0006 mol) and $POCl_3$ (10 mL) was heated under reflux for 1 h. After cooling, the reaction mixture was poured into ice-water (50 mL) and neutralized with ammonia solution to give dark buff precipitate. The solid was filtered off and recrystallized from ethanol to afford **26** as buff crystals. Yield 0.124 g (73.4%), mp 294–296 °C. [Found: C, 60.88; H, 3.98; N, 28.30. $C_{14}H_{10}N_6O$ requires: C, 60.42; H, 4.08; N, 28.37]. IR $cm^{-1}$ 3050 (CH arom.), 2900 (CH aliph.), 1640 (C=O). $^1H$ NMR ($CF_3COOD$): $\delta$ 2.73 (s, 3H, $CH_3$), 7.70 (m, 3H, phenyl), 7.90 (m, 2H, phenyl), 9.13 (s, 1H, CH-pyrazole), 9.23 (s, 1H, CH-pyrimidine). MS: *m/z* 278.20 ($M^+$).

**4.1.22. General procedure for the preparation of 5,7-dimethyl-1(2)-substituted-1(2)*H*-pyrazolo[4′,3′:4,5]-pyrimido[1,6-*b*][1,2,4]triazepines 27a–c.** A mixture of **4a–c** (0.001 mol) and acetylacetone (0.01 mol) in ethanol (15 mL) was heated under reflux for 1 h. After cooling, the solid formed was collected and crystallized from ethanol to afford **27a–c** as crystals.

*5,7-Dimethyl-1-phenyl-1H-pyrazolo[4′,3′:4,5]pyrimido-[1,6-b][1,2,4]triazepine* **27a**. Yield 0.112 g, (38%), white crystals, mp 152–153 °C. [Found: C, 65.95; H, 4.70; N, 28.68. $C_{16}H_{14}N_6$ requires: C, 66.19; H, 4.86; N, 28.95]. IR $cm^{-1}$ 3050 (CH arom.), 2900 (CH aliph.), 1565 (C=N). $^1H$ NMR ($CDCl_3$): $\delta$ 2.37 (s, 3H, $CH_3$), 2.80 (s, 3H, $CH_3$), 6.03 (s, 1H, CH-triazepine), 7.34 (m, 3H, phenyl), 8.15 (m, 2H, phenyl), 8.73 (s, 1H, CH-pyrazole), 8.82 (s, 1H, CH-pyrimidine). MS: *m/z* 290 ($M^+$).

*5,7-Dimethyl-1-(2-phenylethyl)-1H-pyrazolo[4′,3′:4,5]-pyrimido[1,6-b][1,2,4]triazepine* **27b**. Yield 85 mg (27%), white crystals, mp 210 °C. [Found: C, 67.72; H, 5.36; N, 26.66. $C_{18}H_{18}N_6$ requires: C, 67.90; H, 5.70; N, 26.40]. IR $cm^{-1}$ 3250 (CH arom.), 2940 (CH aliph.), 1580 (C=N). $^1H$ NMR ($CDCl_3$): $\delta$ 2.36 (s, 3H, $CH_3$), 2.79 (s, 3H, $CH_3$), 3.26 (t, 2H, $CH_2$, $J$=7.3 Hz), 4.73 (t, 2H, $CH_2$, $J$=7.3 Hz), 6.07 (s, 1H, CH-triazepine), 7.23 (m, 5H, arom.), 8.66 (s, 1H, CH-pyrazole), 8.68 (s, 1H, CH-pyrimidine). MS: *m/z* 319.2 ($M^+$).

*2,5,7-Trimethyl-2H-pyrazolo[4′,3′:4,5]pyrimido[1,6-b]-[1,2,4]triazepine* **27c**. Yield 90 mg (32%), white crystals, mp 255 °C. [Found: C, 57.97; H, 5.11; N, 36.97. $C_{11}H_{12}N_6$ requires: C, 57.88; H, 5.30; N, 36.82]. IR $cm^{-1}$ 3000 (CH aliph.), 1610 (C=N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.41 (s, 3H, $CH_3$), 2.82 (s, 3H, $CH_3$), 3.32 (s, 3H, N–$CH_3$), 6.21 (s, 1H, CH-triazepine), 8.38 (s, 1H, CH-pyrazole), 8.51 (s, 1H, CH-pyrimidine). MS: *m/z* 228.3 ($M^+$).

**4.1.23. 3-(4-Imino-1-phenyl-1*H*-1,4-dihydropyrazolo[3,4-*d*]pyrimidin-5-yl-imino)-1-phenylbutan-1-one 28.** A mixture of **4a** (0.226 g, 0.001 mol) and benzoylacetone (0.162 g, 0.001 mol) in ethanol (20 mL) was

refluxed for 10 h. The solvent was evaporated under reduced pressure and the solid formed was collected and recrystallized from ethanol to give white crystals. Yield 0.3 g, (81%), mp 150–152 °C. [Found: C, 67.95; H, 4.70; N, 22.58. $C_{21}H_{18}N_6O$ requires: C, 68.09; H, 4.90; N, 22.69]. IR $cm^{-1}$ 3400 (NH), 3030 (CH arom.), 2900 (CH aliph.), 1605 (C═O), 1585 (C═N). $^1H$ NMR ($CDCl_3$): $\delta$ 2.33 (s, 3H, $CH_3$), 3.27 (s, 2H, $CH_2$), 6.43 (s, 1H, NH), 7.43 (m, 8H, Phenyl), 8.23 (m, 2H, Phenyl), 8.28 (s, 1H, CH-pyrazole), 8.63 (s, 1H, CH-pyrimidine). MS: *m/z* 370.2 ($M^+$).

**4.1.24. 1,5-Diphenyl-7-methyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepine 29.** A mixture of **28** (0.19 g, 0.512 mmol) and $POCl_3$ (15 mL) was heated under reflux for 2 h. After cooling, the reaction mixture was poured into a mixture of ice-cold water and neutralized with ammonium hydroxide solution. The solid formed was collected and recrystallized from petroleum ether (60/80) to afford **29** as white crystals. Yield 0.12 g, (67%), mp 113–115 °C. [Found: C, 71.38; H, 4.60; N, 23.58. $C_{21}H_{16}N_6$ requires C, 71.57; H, 4.58; N, 23.85]. IR $cm^{-1}$ 3030 (CH arom), 1590 (C═N). $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.42 (s, 3H, $CH_3$), 6.50 (s, 1H, CH-triazepine), 7.42 (m, 6H, Phenyl), 7.53 (m, 2H, Phenyl), 8.20 (m, 2H, Phenyl), 8.57 (s, 1H, CH-pyrazole), 8.77 (s, 1H, CH-pyrimidine). MS: *m/z* 352.38 ($M^+$).

**4.1.25. 5-Amino-1-phenyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepine-6-carbonitrile 30a.** A mixture of **4a** (0.226 g, 0.001 mol) and ethoxymethylene malononitrile (0.122 g, 0.001 mol) in ethanol (10 mL) was refluxed for 4 h. The precipitate formed after cooling was filtered off and recrystallized from methanol to furnish **30a** as white crystals. Yield 0.18 g, (60%), mp 288–290 °C. [Found: C, 59.31; H, 3.48; N, 36.88. $C_{15}H_{10}N_8$ requires C, 59.59; H, 3.33; N, 37.07]. IR $cm^{-1}$ 3400, 3300 ($NH_2$), 1620 ($NH_2$), 2220 (C≡N). $^1H$ NMR ($CF_3CO_2D$): $\delta$ 5.80 (bs, 2H, $NH_2$), 7.70 (s, 5H, phenyl), 8.10 (s, 1H, CH-triazepine), 9.23 (s, 1H, CH-pyrazole), 9.30 (s, 1H, CH-pyrimidine). MS: *m/z* 302.29 ($M^+$).

**4.1.26. Ethyl (5-amino-1-phenyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepin-6-yl)carboxylate 30b.** A mixture of compound **4a** (0.226 g, 0.001 mol) and ethyl ethoxymethylene cyanoacetate (0.16 g, 0.001 mol) in ethanol (10 mL) was refluxed for 4 h. After cooling, the solid precipitate was filtered off and recrystallized from ethanol to furnish **30b** as white crystals. Yield 0.28 g, (93%), mp 215–217 °C. [Found: C, 58.67; H, 4.54; N, 28.40. $C_{12}H_{15}N_7O_2$ requires C, 58.44; H, 4.33; N, 28.07]. IR $cm^{-1}$ 3300, 3400 ($NH_2$), 1680 (C═O). $^1H$ NMR ($CF_3CO_2D$): $\delta$ 1.50 (t, 3H, $CH_2CH_3$, $J$=7.2 Hz), 4.46 (q, 2H, $CH_2CH_3$, $J$=7.2 Hz), 7.67 (s, 5H, phenyl), 8.27 (s, 1H, CH-triazepine), 9.20 (s, 1H, CH-pyrazole), 9.30 (s, 1H, CH-pyrimidine). MS: *m/z* 349.35 ($M^+$).

**4.1.27. 5-Amino-1-phenyl-1*H*-pyrazolo[3′,4′:4,5]pyrimido[1,6-*b*][1,2,4]triazepin-6-carboxylic acid 30c.** A mixture of **30b** (0.349 g, 0.001 mol) and potassium hydroxide (0.56 g, 0.01 mol) in ethanol (15 mL) was heated under reflux for 1 h. The solvent was evaporated and the solid precipitate formed was dissolved in water and the aqueous phase was acidified with acetic acid. The precipitate was filtered off and crystallized from ethanol to afford **30c** as white crystals. Yield 0.15 g (47%), mp 295–297 °C. [Found: C, 56.14; H, 3.74; N, 29.98. $C_{15}H_{11}N_7O_2$ requires: C, 56.07; H, 3.45; N, 30.52]. IR $cm^{-1}$ 3050 (CH arom.), 1720 (C═O). $^1H$ NMR (DMSO-$d_6$): $\delta$ 5.31 (bs, 2H, $NH_2$), 7.52 (m, 3H, phenyl), 8.09 (m, 2H, phenyl), 8.23 (s, 1H, CH-pyrazole), 8.37 (s, 1H, CH-pyrimidine), 8.50 (s, 1H, CH-triazepine), 12.47 (bs, 1H, OH).

**4.1.28. 1,7-Diphenyl-1*H*,8*H*-5-oxopyrazolo[3′,4′:4,5]-pyrimido[1,6-*b*][1,2,4]triazepine 31.** A suspension of **4a** (0.226 g, 0.001 mol) and ethylbenzoyl acetate (1.66 g, 0.009 mol) in ethanol (7 mL) was heated under reflux for 10 h. After concentration, the solid product formed was filtered off and recrystallized from methanol to give **31** as yellow crystals. Yield 0.27 g, (76%,), mp 192–94 °C. [Found: C, 67.58; H, 4.11; N, 23.56. $C_{20}H_{14}N_6O$ requires: C, 67.78; H, 3.98; N, 23.72]. IR $cm^{-1}$ 3080 (CH arom.), 1730 (C═O), 1640 (C═N). $^1H$ NMR ($CDCl_3$): $\delta$ 5.97 (s, 1H, CH-triazepine), 7.43 (m, 6H, Phenyl), 7.83 (m, 2H, Phenyl), 8.20 (m, 2H, Phenyl), 8.67 (s, 1H, CH-pyrazole), 8.93 (s, 1H, CH-pyrimidine), 11.06 (bs, 1H, NH). MS: *m/z* 354.10 ($M^+$).

**4.1.29. 5-Amino-1,7-diphenyl-1*H*-pyrazolo[3′,4′:4,5]-pyrimido[1,6-*b*][1,2,4]triazepine 32.** A suspension of **4a** (0.45 g, 0.002 mol) and benzoylacetonitrile (0.290 g, 0.002 mol) in ethanol (20 mL) was heated under reflux for 10 h. After concentration and cooling, the solid formed was filtered off and recrystallized from ethanol to give **32** as scarlet red crystals. Yield 0.68 g, (97%), mp 141–143 °C. [Found: C, 67.61; H, 4.58; N, 27.51. $C_{20}H_{15}N_7$ requires C, 67.97; H, 4.28; N, 27.75]. IR $cm^{-1}$ 3400, 3280 ($NH_2$), 3040 (CH arom.), 1600 (C═N). $^1H$ NMR ($CDCl_3$): $\delta$ 4.00 (s, 2H, $NH_2$), 5.77 (s, 1H, CH-triazepine), 7.43 (m, 5H, Phenyl), 7.83 (m, 3H, Phenyl), 8.23 (m, 2H, Phenyl), 8.70 (s, 1H, CH-pyrazole), 9.00 (s, 1H, CH-pyrimidine). MS: *m/z* 353.10 ($M^+$).

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