

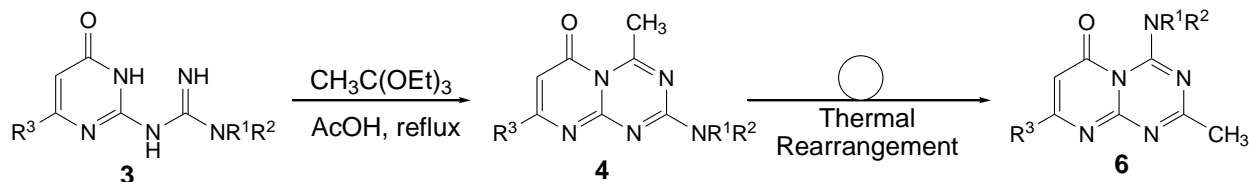
# Regioselective synthesis of pyrimido[1,2-*a*][1,3,5]triazin-6-ones via reaction of 1-(6-oxo-1,6-dihydropyrimidin-2-yl)guanidines with triethylorthoacetate: observation of an unexpected rearrangement

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## Graphical Abstract



## Abstract

A novel thermal rearrangement, involving pyrimidine ring opening and subsequent ring closure leading to recyclization of the system, was identified in the reaction of (6-oxo-1,6-dihydropyrimidin-2-yl)guanidines **3** (where NR<sup>1</sup>R<sup>2</sup> = NH<sub>2</sub>, NH alkyl, NH aralkyl, NHCH<sub>2</sub>Ph(R)) with triethyl orthoacetate, affording 4-substituted-2-methyl-6*H*-pyrimido[1,2-*a*][1,3,5]triazin-6-ones **6** and their ring opened products. However, no such rearrangement was observed with (6-oxo-1,6-dihydropyrimidin-2-yl)guanidines **3** bearing a tertiary amino or anilino substituent (i.e. where NR<sup>1</sup>R<sup>2</sup> = N(CH<sub>3</sub>)<sub>2</sub>, indoline, morpholino, NHAr). As expected, 2-substituted-4-methyl-6*H*-pyrimido[1,2-*a*][1,3,5]triazin-6-ones **4** were obtained as the final products. Experimental

structural determination and theoretical studies were carried out to get an understanding of the observed thermal rearrangement. In addition, an attempt to obtain similar pyrimido[1,2-*a*][1,3,5]triazin-6-ones using *N,N*-dimethylacetamide dimethyl acetal (DMA-DMA) as one carbon inserting synthon had furnished triazine ring annulated product **14** bearing *N,N*-dimethyl enamino substituent at position 4 as a result of further reaction with a second molecule of DMA-DMA.

**Keywords:** pyrimidines, triazines, guanidines, pyrimido[1,2-*a*][1,3,5]triazines, X-ray crystal structure, rearrangement

## Introduction

1,3,5-triazine nucleus is a prominent structural core present in numerous biologically active compounds. Hexamethylmelamine, irsogladine and 5-aza-2'-deoxycytidine, which are structurally based on the 1,3,5-triazine scaffold, have been found to exhibit anti-cancer and antiangiogenic properties<sup>1</sup>. Various 1,3,5-triazine derivatives fused to quinazoline<sup>2</sup>, benzimidazole<sup>3</sup>, pyrazole<sup>4,5</sup> and 1,2,4-triazine<sup>6</sup> have been reported to show anti-cancer properties. Moreover, numerous derivatives of pyrimidine fused systems such as pyrido[2,3-*d*]pyrimidine (PD-0332991)<sup>7</sup> and pyrimido[1,2-*a*]pyrimidine (**4**)<sup>8</sup> have also demonstrated promising anticancer properties as well. Due to the close structural similarity with the above pyrimido fused bicyclic scaffolds and reports on antiproliferative activity from 1,3,5-triazino fused heterocycles, the derivatives of pyrimido[1,2-*a*][1,3,5]triazine scaffold were anticipated to possess anticancer property (Fig. 1). To date, heterocyclic compounds possessing a pyrimido[1,2-*a*][1,3,5]triazine moiety have been reported to exhibit antimicrobial<sup>9</sup>, potent fungicidal and average serotonergic

(5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptor) activities<sup>10</sup> as well as GSK-3 $\beta$  inhibitory activity with potential for the treatment of neurodegenerative diseases<sup>11</sup>

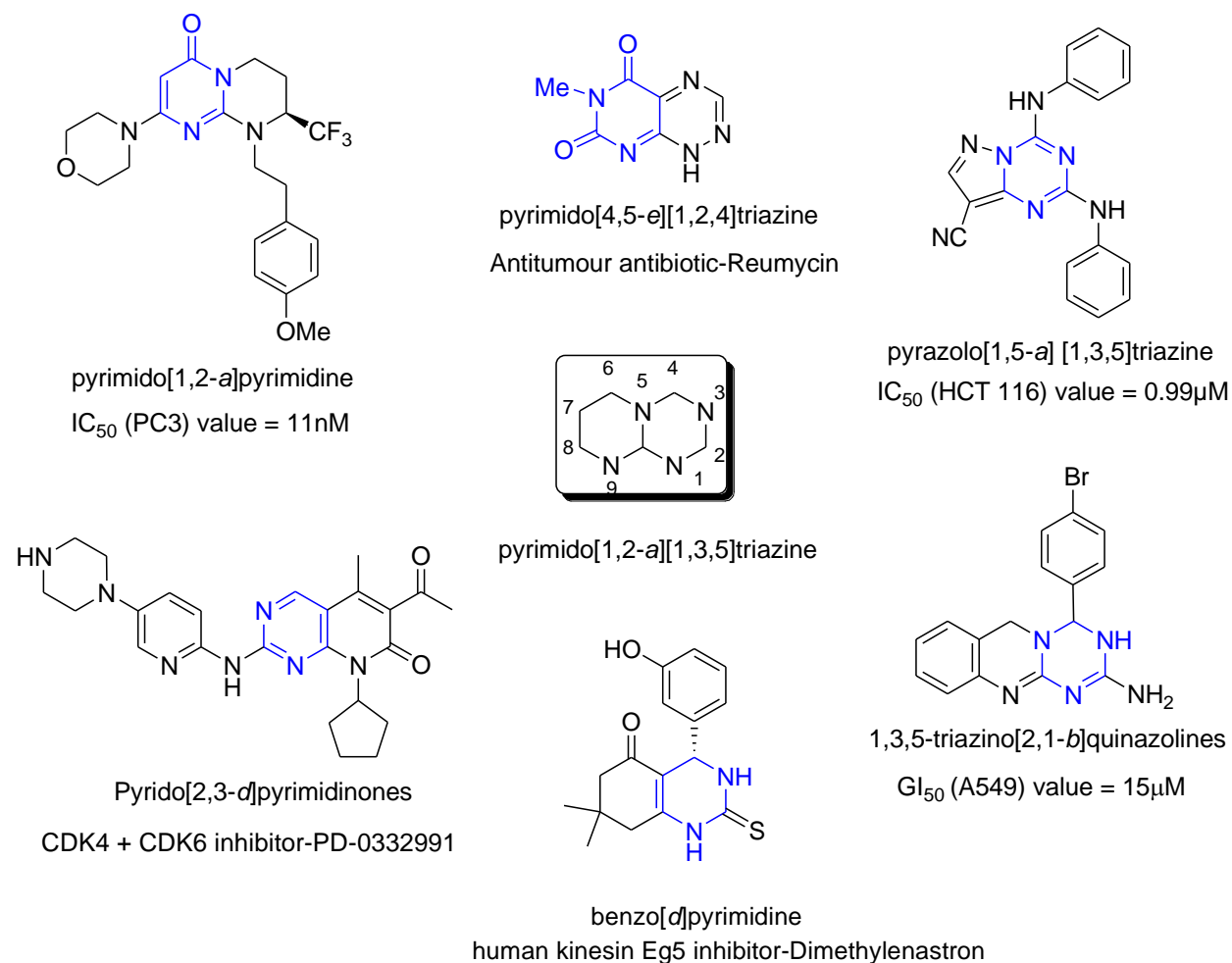


Fig. 1 Structurally similar nitrogen containing heterocyclic scaffolds

In the literature, synthetic access to pyrimido[1,2-a][1,3,5]triazine analogues (in which one of the four nitrogen atoms is located at the junction of the two cycles) is rather limited and most of the synthetic approaches described cannot provide the flexibility of different substitution at various positions around the fused rings. The synthesis of pyrimido[1,2-a][1,3,5]triazine system<sup>12</sup> can be categorized into two approaches: (1) annulation of pyrimidine onto a 1,3,5-triazine scaffold<sup>13</sup>; (2) annulation of the 1,3,5-triazine ring onto a pyrimidine scaffold<sup>14</sup>. The latter approach has been

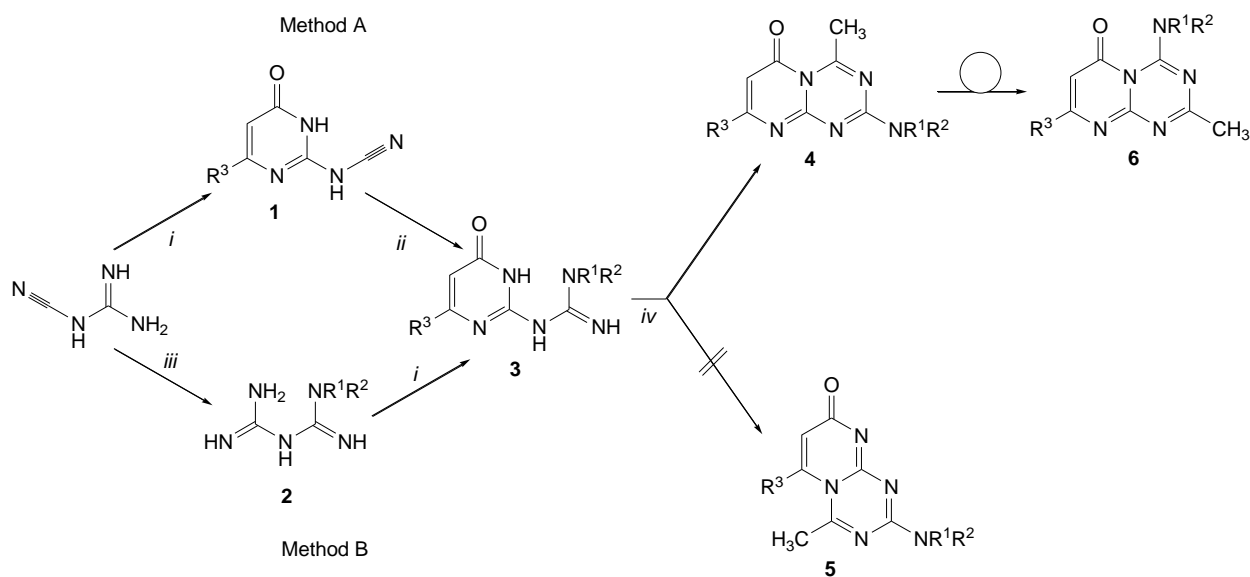
largely adopted for the preparation of pyrimido[1,2-*a*][1,3,5]triazines and most authors largely focussed on the formation of dioxo/dithio/oxothiooxo derivatives of the scaffold<sup>14g-p</sup>. Therefore, there is a need to find more practical approaches for the synthesis of these pyrimido[1,2-*a*][1,3,5]triazines.

Since orthoesters are versatile one-carbon building blocks in ring annulation reactions, it was expected that unsymmetrically substituted pyrimidin-2-yl guanidine **3** (acting as a penta atomic synthon) would react with this one-carbon building block to yield, theoretically, either one of the regioisomeric pyrimido[1,2-*a*][1,3,5]triazin-6-ones **4** or **5** or both as product/s. However, the possibility of structure **5** was excluded, as no cross-peaks were found between the R<sup>3</sup> group protons of pyrimidine ring and methyl group protons of triazine ring in 2D NOESY experiment (Scheme 1). Moreover, according to DFT calculations in gas phase, the structure **5** was found to be highly unfavourable energetically (*vide infra*). In addition, a regioisomeric product similar to **4** was observed exclusively when other one-carbon inserting synthon like aldehyde was used with similar substrate<sup>15</sup>. However, to our surprise, product **4** (Table 1) was found readily rearranged *in-situ* to a thermodynamically more favourable product of type **6** and its ring-opened product **6'** (Scheme 3), depending upon the NR<sup>1</sup>R<sup>2</sup> group present in the starting material guanidine (Table 2). Herein, the details of this unexpected thermal rearrangement are presented.

## Results and Discussion

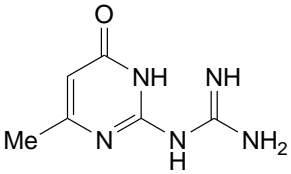
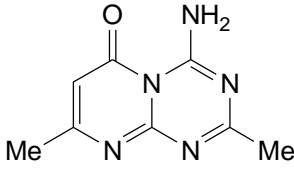
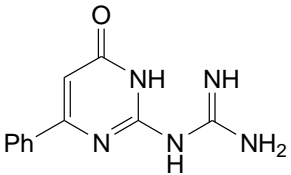
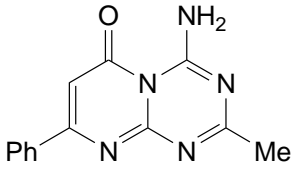
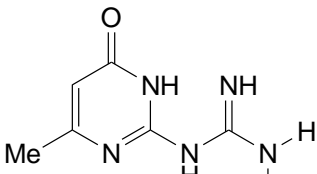
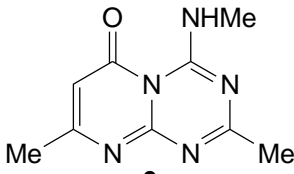
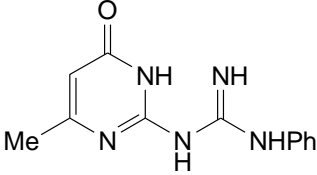
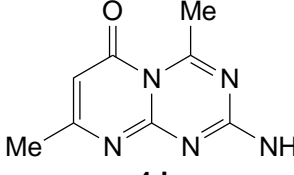
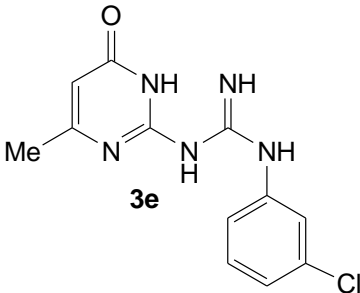
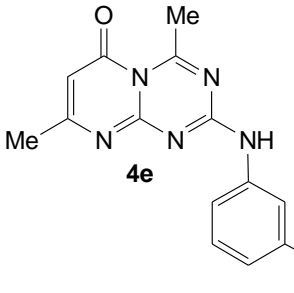
The starting material *N*-(4-substituted-6-oxo-1,6-dihydropyrimidin-2-yl)guanidines, **3**, were prepared either by method A or B (Scheme 1). In method A, **3** was synthesized *via* microwave (MW) assisted nucleophilic addition of amines onto (4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)cyanamide **1** using either concentrated hydrochloric acid or trimethyl silyl chloride (TMSCl)

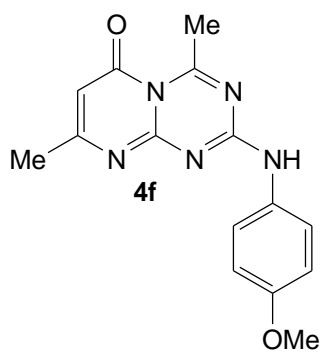
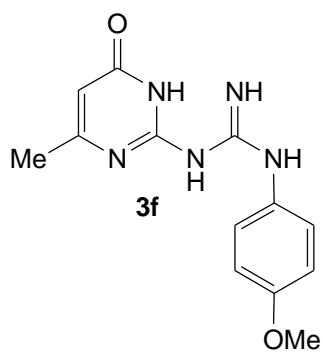
catalyzed conditions; whereas in method B, cyclocondensation of  $\beta$ -keto ester with substituted biguanides **2** yielded **3** as reported by Curd and Rose<sup>16</sup> (Scheme 1). Method A was found to be more versatile and robust for molecular library generation. In the presence of protic acid (method A procedure 1) or TMSCl (method A procedure 2) catalyzed conditions, the reaction times were shorter, workup was easy obviating the need of column chromatography and appreciable yields of **3** (56-93%) were obtained with a variety of primary and secondary amines with alkyl, aryl and aralkyl substituents. In the latter case (i.e. method A procedure 2), TMSCl not only acted as a source of anhydrous HCl, but it also activated cyanamide **1** as shown in scheme 2.



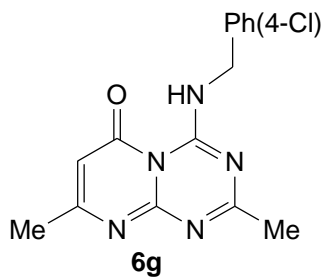
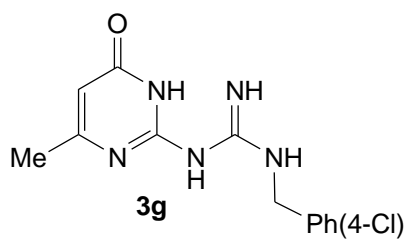
**Scheme 1.** Reagents and Conditions: (i) ethyl 3-oxobutanoate/ ethyl 4,4,4-trifluoro-3-oxobutanoate, aq. NaOH, r.t., 12h (77%); (ii) procedure 1 HNR<sup>1</sup>R<sup>2</sup>.HCl, MW, 160°C, 15 min or procedure 2 NR<sup>1</sup>R<sup>2</sup>, TMSCl, CH<sub>3</sub>CN, 12 min., 160°C followed by *i*PrOH, 125°C, 30 sec. (62%-79%); (iii) HNR<sup>1</sup>R<sup>2</sup>.HCl, C<sub>4</sub>H<sub>9</sub>OH, reflux, 6h (40%); (iv) CH<sub>3</sub>C(OEt)<sub>3</sub>, AcOH, reflux, 3-9h

**Table 1** Structures and yields of intermediates and isolated pyrimido[1,2-*a*][1,3,5]triazin-6-one products

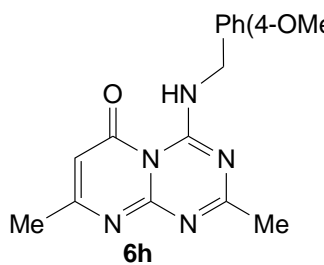
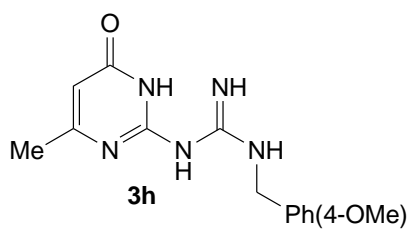
<b>3</b>	Isolated Product	Isolated Yield (%)
 <p data-bbox="459 663 492 684"><b>3a</b></p>	 <p data-bbox="894 663 927 684"><b>6a</b></p>	70
 <p data-bbox="459 905 492 926"><b>3b</b></p>	 <p data-bbox="894 905 927 926"><b>6b</b></p>	58
 <p data-bbox="459 1167 492 1188"><b>3c</b></p>	 <p data-bbox="894 1146 927 1167"><b>6c</b></p>	60
 <p data-bbox="459 1409 492 1430"><b>3d</b></p>	 <p data-bbox="894 1409 927 1430"><b>4d</b></p>	52
 <p data-bbox="459 1667 492 1688"><b>3e</b></p>	 <p data-bbox="894 1667 927 1688"><b>4e</b></p>	73



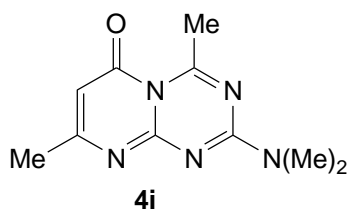
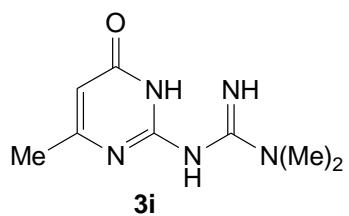
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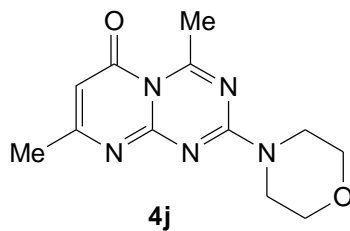
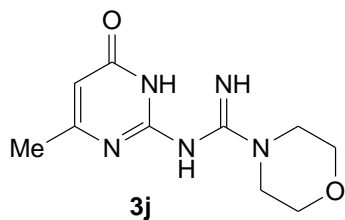
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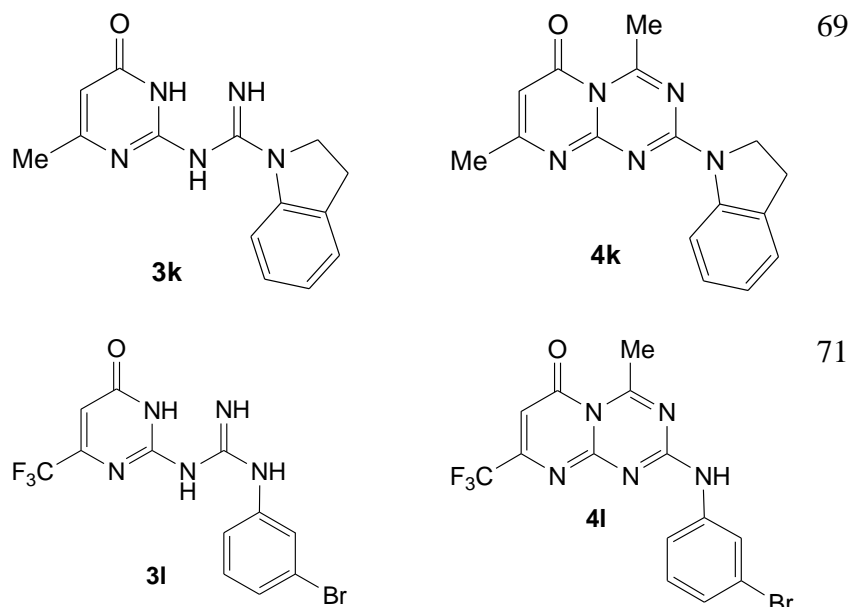
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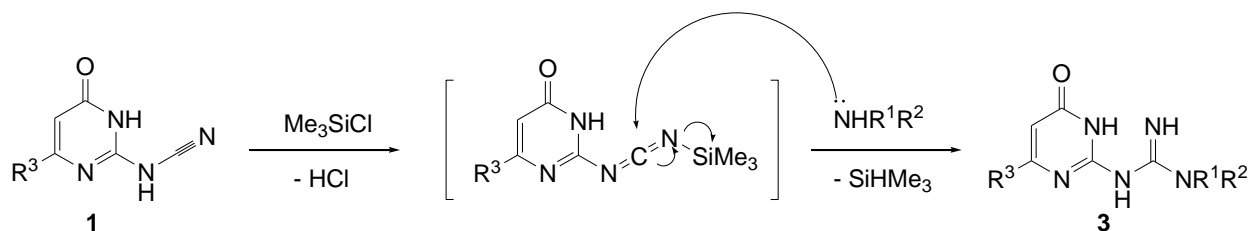
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Solvents used for crystallisation: <sup>a</sup> EA, <sup>b</sup> 80EA:20Hex, <sup>c</sup> 90EA:10MeOH; <sup>d</sup> EtOH

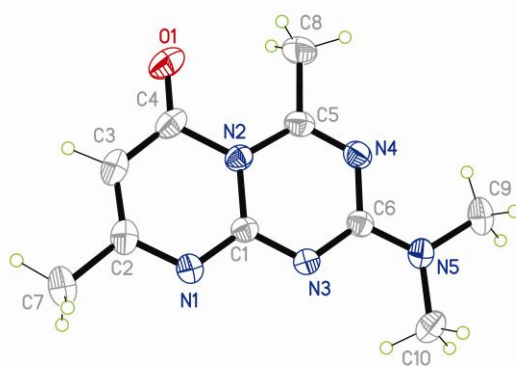


**Scheme 2.** Synthesis of 1,6 dihydropyrimidinyl guanidines **3** under TMSCl catalyzed conditions

The structures of the products were deduced from their mass spectra, NMR data and elemental analyses. The reactions were carefully monitored using TLC and the reactions were stopped immediately when no trace of the starting material was observed. The reaction proceeded only on heating at 100°C. The reaction between these guanidines (**3**) and triethyl orthoacetate (in presence of glacial acetic acid) yielded product **4** predominantly when the guanidine **3** contained a tertiary amino group (**3i-k**) ( $\text{NR}^1\text{R}^2 = \text{N}(\text{CH}_3)_2, -\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$ , indolino). Similarly when an aryl secondary amino group was included as in **3d**, **3e**, **3f** and **3l** ( $\text{NR}^1\text{R}^2 = \text{NHPH}$ ,  $\text{NHPH}(3\text{-Br})$ ,  $\text{NHPH}(3\text{-Cl})$ ,  $\text{NHPH}(4\text{-OMe})$ ), the predominant compound was **4**. Product **4** was characterized by



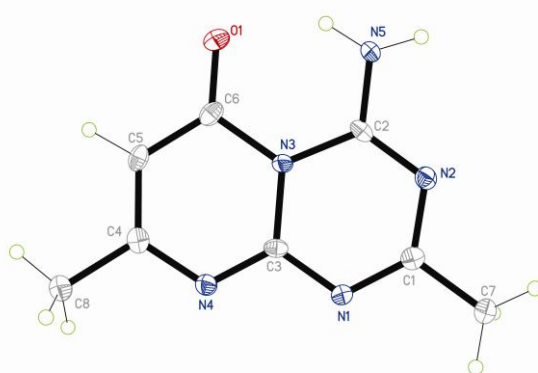
the diagnostic methyl peak of the triazine ring at  $\delta$ 2.85-2.91 in  $^1\text{H}$  NMR and 26.2-27.8 in  $^{13}\text{C}$  NMR as well as X-ray crystallography of **4i** (Fig. 2; please refer to supporting information for structural details). However, upfield shift to  $\delta$ 2.18-2.29 in  $^1\text{H}$  NMR and 25.2-25.6 in  $^{13}\text{C}$  NMR were observed, surprisingly, in isolated products when unsubstituted (**3a**), alkylsubstituted (**3b**) or aralkyl guanidines (**3g**, **3h**) were used as a substrate under similar conditions. Therefore, the product obtained from reactants **3a**, **3b**, **3c**, **3g** and **3h** was expected to have a structure different from **4** even though the mass spectra showed expected values corresponding to structure **4**. Hence, to confirm this aspect, X-ray crystallographic study of the product obtained from **3a** was performed.



**Figure 2.** X-ray crystal structure of 2-(dimethylamino)-4,8-dimethyl-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one **4i** (displacement ellipsoids are drawn at 50% probability level) CCDC 791289

The fact that there were clearly differentiated chemical shifts at  $\delta$  10.18 and 9.26 for the product obtained by the reaction of triethyl orthoacetate with **3a** in the  $^1\text{H}$  NMR spectrum supported the existence of hydrogen bonding between the peri-carbonyl and the proximate exocyclic N-H which is not possible in structure **4**. Moreover, similar lowfield shifts of NH proton in  $^1\text{H}$  NMR from 10.18-13.20 ppm were observed in **6b-c** and **6g-h**. X-ray crystallographic study<sup>17</sup> of this

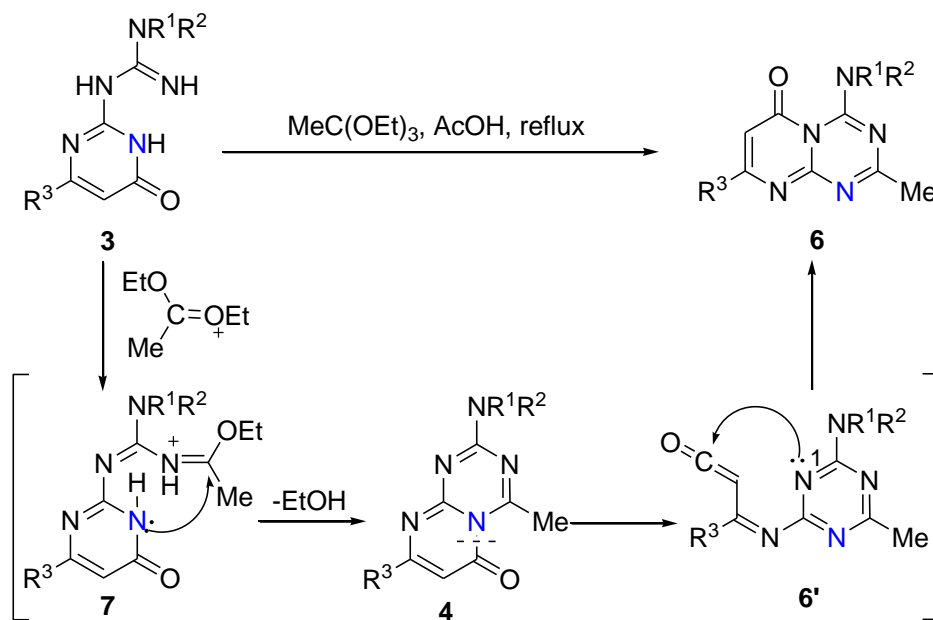
product (Figure 3) revealed that the product **4a** (not isolated) underwent a smooth rearrangement to an isomeric product **6a** *in-situ* as suspected from NMR studies. So, structure **6** was assigned to the rearranged product with upfield shift, in the cases of **3a**, **3b**, **3c**, **3g** and **3h**. Moreover, NMR studies were found to be consistent with the X-ray crystallographic data of **6a** (Figure 3) where hydrogens attached to N5 have unequal bond lengths and the amino group was found to be locked in the plane of pyrimido[1,2-*a*][1,3,5]triazine nucleus due to the  $\pi$ -electron delocalization with the heterocycle.



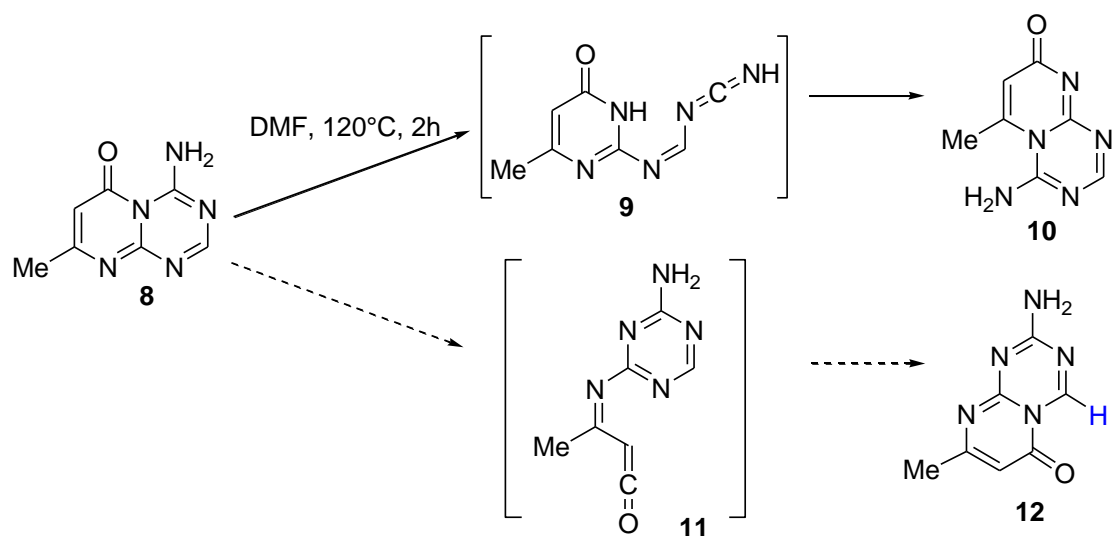
**Figure 3.** X-ray crystal structure of 4-amino-2,8-dimethyl-6*H*-pyrimido[1,2-*a*][1,3,5]triazin-6-one **6a** CCDC 788427

The proposed mechanism for the formation of rearranged product **6** is depicted in Scheme 3. The reaction starts with the exchange of alkoxy groups of the orthoester (in excess) under acid catalysis, which then reacted with the guanidine **3** (nucleophile) to give iminium ion intermediate **7**. Subsequent loss of EtOH gave **4**. Thermal rearrangement is then assumed to proceed at around 100°C for substrates **3a**, **3b**, **3c**, **3f** and **3g** (i.e. when either  $R^1$  or  $R^2 = H$ ) according to scheme 3. The mechanism may have involved: a) acid catalyzed ethanolytic ring opening of pyrimidine at amide linkage with the formation of ring open triazine carbenone **6'** (acrylic acids were isolated); b) intramolecular nucleophilic attack by N-1 nitrogen of 1,3,5-triazine on the carbonyl group and subsequent ring closure that gave final product **6**. It is worth mentioning that the thermally

assisted rearrangement of 4-amino-8-methylpyrimido[1,2-*a*][1,3,5]triazin-6-one **8** to 4-amino-6-methylpyrimido[1,2-*a*][1,3,5]triazin-6-one **10** was reported<sup>14b</sup> to have resulted from 1,3,5-triazine ring opening *via* carbodiimide intermediate **9** (Scheme 4). However, the rearrangement involving pyrimidine ring opening similar to the one proposed in scheme 3 (depicted using hashed arrows in scheme 4) leading to product **12** *via* ketene intermediate **11** could not be avoided. Moreover, careful analysis of the provided <sup>1</sup>H NMR spectral data seems to corroborate structure **12** (2-amino-8-methylpyrimido[1,2-*a*][1,3,5]triazin-6-one) as ~1.2 ppm downfield shift of the methine proton (in blue) signal on the triazine ring after the rearrangement can only be accounted to the deshielding effect of the neighboring carbonyl group in **12**.



**Scheme 3.** Proposed mechanism for the formation of compound **6**



**Scheme 4.** Alternate plausible mechanism for the rearrangement in pyrimido[1,2-*a*][1,3,5]triazin-6-ones *via* pyrimidine ring opening leading to regioisomeric product **12** instead of proposed **10**.

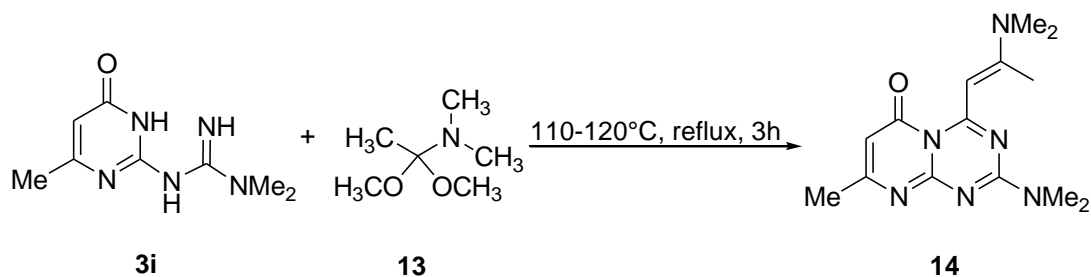
Intramolecular hydrogen bonding between the 4-amino hydrogen and carbonyl oxygen (Figure 3) as well as involvement of amino group (directly attached to the ring) in  $\pi$ -electron delocalization with the pyrimido[1,2-*a*][1,3,5]triazin-6-one nucleus provides additional stability to the rearranged product **6** which might provide the driving force for such a rearrangement. Therefore, an attempt was made to assess the relative stability of the two possible cyclocondensation products- **4** and **6** in gas phase for substitutions **a** ( $R^1=R^2=H$ ) and **i** ( $R^1=R^2=Me$ ) using Gaussian 03 software package<sup>18</sup>. Regioisomer **5** was also included in the study as the similar cyclization of benzimidazol-2-yl guanidines (unsymmetrically substituted in the phenylene fragment) with one carbon inserting reagents did not proceed regioselectively in one of our previous works<sup>3</sup>. The results of these calculations are presented in Table 2. Rearranged product **6a** was found to be energetically more favourable than **4a** whereas **4i** was found to be more favourable over **6i** (Table 2). This was found to be in agreement with the

experimental observation. Theoretical calculations at B3LYP/6-311G 2d,2p// B3LYP/6-311G d,p explained the formation of exclusively one regioisomeric product as both **5a** and **5i** were highly energetically unfavourable (might be due to steric factors).

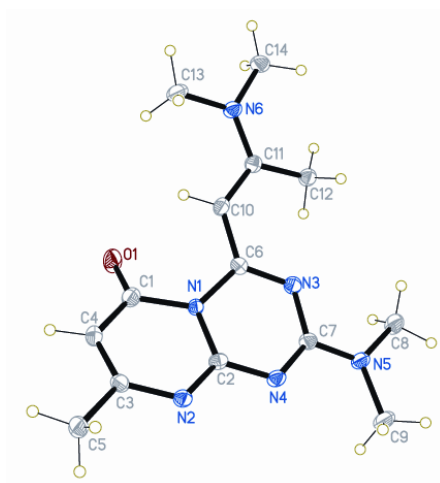
**Table 2** Relative energies according to *ab-initio* calculations

	Relative energies, kcal/mol		
	<b>4</b>	<b>5</b>	<b>6</b>
<b>a</b> R <sup>1</sup> =R <sup>2</sup> =H	4.14	21.81	0.00
<b>i</b> R <sup>1</sup> =R <sup>2</sup> =CH <sub>3</sub>	0.00	17.65	8.72

In an attempt to obtain similar pyrimido[1,2-*a*][1,3,5]triazin-6-ones, the reaction of **3i** with another one carbon electrophilic synthon-DMA-DMA **13** (*N,N*-dimethylacetamide dimethyl acetal) yielded a product having *m/z* 288.3 (Scheme 5). The product formation started after 1 hour and completed in 2.5-3h. The <sup>1</sup>H NMR and <sup>13</sup>C spectra of the compound had two sets of NMe<sub>2</sub> signals at 3.10 and 3.15 as well as 37.1 and 37.3 ppm respectively. Based on the above observations, results of DEPT experiment, as well as the 2D NOESY crosspeaks, it was suggested that a second molecule of DMA-DMA could have contributed to the =C(CH<sub>3</sub>)-NMe<sub>2</sub> fragment, although the stereochemistry around the double bond in the enamine substituent at position 4 could be *E* or *Z*. The structure **14**, a new heterocyclic pyrimido[1,2-*a*][1,3,5]triazin-6-one, was assigned based on the crystal structure (Figure 4). Analogous product was obtained with **3j** also.

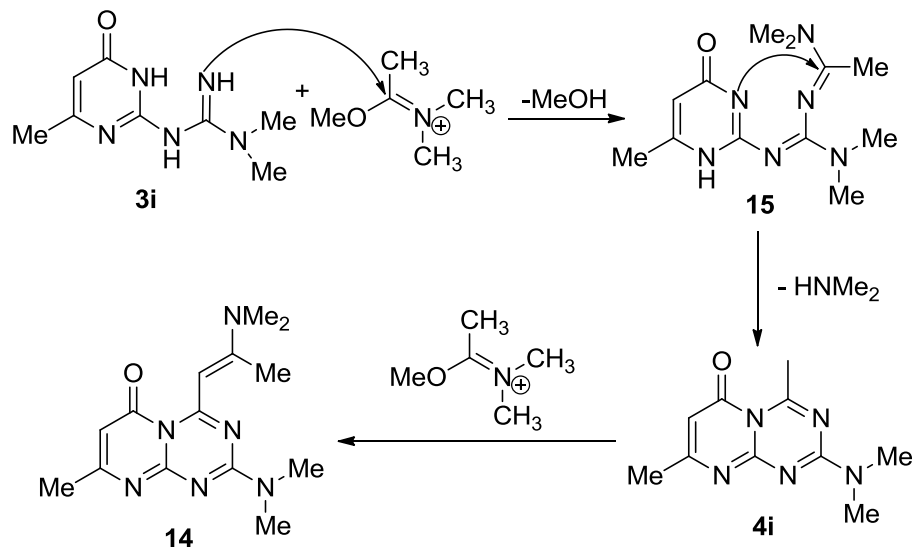


**Scheme 5**



**Figure 4** X-ray crystal structure of (*E*)-2-(dimethylamino)-4-(2-(dimethylamino)prop-1-enyl)-8-methyl-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one **14** (displacement ellipsoids are drawn at 50% probability level), CCDC 838638

A reaction mechanism for the formation of the product is proposed in scheme 6. The mechanism of formation of 1,3,5-triazine **14** can be rationalized through the reaction with an iminium ion  $\text{MeC(OMe)}=\text{NMe}_2$  derived from **13** to form the required enamine **15**; this is followed by cyclisation and tautomerization with the loss of  $\text{HNMe}_2$  to give **4i** and subsequent reaction with the electrophile from the second molecule of DMA-DMA) leading to the isolated product **14**.



**Scheme 6.** Mechanistic rationale for the formation of **14**

The comparison of bond lengths obtained from X-ray crystal structures of three pyrimido[1,2-*a*][1,3,5]triazin-6-ones **6a**, **4i** and **14** revealed interesting findings (Table III, supporting information). The C4 $\equiv$ N3 bond length (C5 $\equiv$ N4 according to crystallographic numbering) in triazine ring of **4i** was found to be unusually short (1.289Å) suggesting higher order of double bond character whereas C4 $\equiv$ N5 bond length (C6 $\equiv$ N1 according to crystallographic numbering) of **14** was unusually large suggesting more sp<sup>3</sup> character of bridge head nitrogen. The pyrimidine and 1,3,5-triazine rings were found to be coplanar for both **6a** and **4i** in the crystal structures as well as in their optimized geometries obtained from DFT calculations (*vide infra*). However, C=O of pyrimidine ring bent downwards while position 4 enamine side chain of triazine ring is twisted upwards (torsional angle C1-N1-C6-N3 = 20.6°) increasing O $\cdots$ C10 bond distance in **14** to 2.762 Å compared to O $\cdots$ C8 bond distance which is 2.64 Å. Stereochemistry of the enamine fragment at position 4 was found to be *E*.

Next, the antiproliferative activity of the synthesized compounds was assessed using MTT assay<sup>19</sup>. In particular, lung A549 and MDA-MB-231 breast cancer cell lines were used. No

appreciable antiproliferative activity was obtained for all the synthesized compounds except for 2-(3-chlorophenylamino)-4,8-dimethyl-6*H*-pyrimido[1,2-*a*][1,3,5]triazin-6-one (**4e**) which demonstrated IC<sub>50</sub> value of 37.5±2.8 μM and 51.2±3.5 μM for A549 and MDA-MB231 cell line respectively.

## Conclusion

In summary, the reactions of *N*-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidines with triethyl orthoacetate were investigated. 2-amino-4-methylpyrimido[1,2-*a*][1,3,5]triazin-6-ones **4** and the products of unexpected rearrangement, namely 4-amino-2-methylpyrimido[1,2-*a*][1,3,5]triazin-6-ones **6**, were obtained depending upon the starting guanidine. The rearrangement involved opening of the pyrimidine ring as was shown by isolation of acrylic acid intermediates. The requirements for the rearrangement were discussed on the basis of results obtained from experimental and theoretical studies. This approach opened the opportunities to insert different substituents at position 2 and position 4 of triazine ring, depending upon the starting guanidine. The attempt to obtain similar pyrimido[1,2-*a*][1,3,5]triazin-6-ones using DMA-DMA was unsuccessful, as unexpected cyclocondensation product **14** formed as a result of overreaction. Further work is in progress to explore the propensity of the reagent to form C-C bond formation.

## Experimental

### General

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. NMR spectra were recorded on a Bruker DPX-300 spectrometer using Me<sub>2</sub>SO-*d*<sub>6</sub> as a solvent and TMS as an internal reference. IR spectra were performed on a Perkin Elmer Spectrum 100 FT-IR spectrophotometer in potassium bromide pellets. Mass spectra were obtained on a Shimadzu



LCMS-IT-TOF system using electron spray ionization (ESI) mode. The course of the reactions was monitored by TLC on Silica gel 60 F<sub>254</sub> plates (Merck, Germany). HPLC analysis was performed on an Agilent Eclipse XDB-C18 (4.6x250 mm, 5 μm) column at 30°C, with a flow rate of 1mL/min. 5-90% Gradients of MeOH/MeCN (solvent A) and H<sub>2</sub>O (solvent B) were used as mobile phases. Microwave reactions were conducted using a commercially available monomode microwave unit (CEM Discover). Elemental analyses were performed on the Perkin Elmer 2400 Elemental Analyzer Series II.

Crystal structure determinations: The single-crystal X-ray diffraction study was carried out on a Bruker APEX diffractometer attached to a CCD detector and graphite-monochromated MoK<sub>α</sub> radiation (λ, 0.71073 Å) using a sealed tube. Absorption corrections were made with the program SADABS<sup>20</sup> and the crystallographic package SHELXTL<sup>21</sup> was used for all calculations.

General method for the preparation of **3a-j**

Method A Procedure 1: Into a 5 mL microwave vessel was added N-(4-substituted-6-oxo-1,6-dihydropyrimidin-2-yl)cyanamide (2 mmol) followed by amine hydrochloride (2.12 mmol) and isopropanol/ACN (1.0 ml). The vial was sealed and the mixture was irradiated at 160-170°C for 15 min and allowed to cool. The white solid obtained was filtered, washed with solution of sodium hydrogen carbonate and cold water and dried.

Procedure 2: Into a 5 mL microwave vessel was added N-(4-substituted-6-oxo-1,6-dihydropyrimidin-2-yl)cyanamide (2 mmol), amine (2.1 mmol) followed by the slow addition of a 2 N solution of TMSCl (1.04 mL, 2.1 mmol, 1.1 equiv) in CH<sub>3</sub>CN under cold conditions. After the vial was capped, reaction mixture was irradiated for 12 min at 160 °C. After the mixture was cooled to approximately 60°C, *i*PrOH (0.55mL, 6 mmol, 3.0 equiv) was added. The mixture was stirred for 10 s and then irradiated a second time at 125°C for 30 s. Upon cooling, the

hydrochloride salts of guanidines **3** precipitated, and it was collected, washed with cold CH<sub>3</sub>CN and then with solution of sodium hydrogen carbonate and cold water and finally dried to obtain slightly better yields of pyrimidinyl guanidines.

Method B: Biguanides were synthesized according to Uohama et al<sup>22</sup> and subsequent pyrimidine ring annulation was done using method described by Curd and Rose<sup>16</sup>.

Experimental data for some representative compounds:

**N-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (3a)**. Yield: 93%; Method B; mp >300°C; lit<sup>23</sup> mp 304-305°C; <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.08 (3H, s, Me), 5.58 (1H, s, H-5), 8.03 (4H, br. s, guanidino NHs), 11.52 (1H, br. s, NH); <sup>13</sup>C NMR (75 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 23.2 (Me), 103.0 (CH), 158.5, 159.8, 163.0 (br. s), 166.9 (br. s).

**1-(6-oxo-4-phenyl-1,6-dihydropyrimidin-2-yl)guanidine (3b)**. Yield: 37%; Method B (using NaOMe instead of aq NaOH in second step); mp 273°C (decomposed); lit<sup>24</sup> mp 273°C; LC-MS (APCI) m/z = 229.1 (MH<sup>+</sup>); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.24 (1H, s, CH), 7.87 (2H, d, *J* = 7.9 Hz, H-2' and H-6'), 7.38–7.49 (3H, m, H-3', H-4' and H-5'), 8.27 (4H, br. s, NHC(=NH)NH<sub>2</sub>), 11.53 (1H, s, NH).

**N-methyl-N'-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (3c)**. Yield 62%; Method A (procedure 1/2); mp 272-273°C; TLC (silica gel, MeOH:CH<sub>2</sub>Cl<sub>2</sub>, 1:6): *R*<sub>f</sub> 0.38. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 2.03 (3H, s, CH<sub>3</sub>), 2.75 (3H, d, <sup>3</sup>*J* = 4.5 Hz, NCH<sub>3</sub>), 5.49 (1H, s, H-5), 7.96-9.20 (3H, br. s, NH-C(=NH)NH), 10.86 (1H, br. s, NH).

**1-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-3-phenylguanidine (3d)**. Yield 90%; Method A (procedure 1/2) or Method B; mp 248-249°C; lit<sup>25</sup> mp 244-246°C; <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.09 (3H, s, Me), 5.60 (1H, s, CH), 7.00 (1H, t, *J* = 7.2 Hz, H-4'), 7.26 (2H, t, *J* = 7.5 Hz,

H-3' and H-5'), 7.66 (2H, d,  $J = 7.5$  Hz, H-2' and H-6'), 8.12 (2H, br. s., NH-C(=NH)N), 9.04 (1H, s, NH), 11.18 (1H, s, NH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{Me}_2\text{SO}-d_6$ ): 23.5 (Me), 103.7 (C-6), 120.3, 122.3, 128.6, 138.9, 155.9, 158.3, 163.0, 163.7.

**1-(3-chlorophenyl)-3-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (3e).** Yield 90%; Method A (procedure 1/2) or Method B; mp 235-236°C; lit<sup>26</sup> mp 239°C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  2.10 (s, 3H,  $\text{CH}_3$ ), 5.62 (s, 1H, CH), 7.02 (dd, 1H,  $J = 7.9$  Hz, 1.2 Hz, H-4'), 7.26 (t, 1H,  $J = 8.1$  Hz, H-5'), 7.63 (d, 1H,  $J = 7.9$  Hz, H-6'), 7.75 (s, 1H, H-2'), 8.24 (br. s., 2H, ), 9.10 (s, 1H, NH), 11.43 (s, 1H, NH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ): 26.7 ( $\text{CH}_3$ ), 107.4 (C-5), 121.8, 122.5, 125.2, 133.4, 136.3, 144.0 (C-1'), 158.9, 161.5, 166.2, 167.0.

**1-(4-methoxyphenyl)-3-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (3f).** Yield 76%; Method A (procedure 1/2) or Method B; mp 256-258°C lit<sup>27</sup> mp 259-260°C;  $^1\text{H}$  NMR (300 MHz,  $\text{Me}_2\text{SO}-d_6$ ):  $\delta$  2.01 (3H, s, Me), 3.72 (3H, s, OMe), 4.35 (2H, d,  $J = 4.9$  Hz,  $\text{CH}_2$ ), 5.46 (1H, s, CH), 6.89 (2H, d,  $J = 8.3$  Hz, H-3' and H-5'), 7.28 (2H, d,  $J = 8.7$  Hz, H-2' and H-6'), 7.82 (2H, br. s., NH-C(=NH)N), 10.67 (1H, s, NH).

**1-(4-chlorobenzyl)-3-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (3g).** Yield 68%; Method B; mp 227-228°C;  $^1\text{H}$  NMR (300 MHz,  $\text{Me}_2\text{SO}-d_6$ ):  $\delta$  2.04 (3H, s, Me), 5.22 (2H, s,  $\text{CH}_2$ ), 5.60 (1H, s, H-5), 7.14 (2H, br. s, NH-C(=NH)N), 7.33 (2H, d,  $J = 8.7$  Hz, H-3' and H-5'), 7.47 (2H, d,  $J = 8.7$  Hz, H-2' and H-6'), 10.71 (1H, br. s, NH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{Me}_2\text{SO}-d_6$ ):  $\delta$  23.4 (Me), 42.7 ( $\text{CH}_2$ ), 101.3 (C-5), 127.8 (C3' and C-5'), 130.0 (C-2' and C-4'), 131.1 (C-1'), 137.7 (C-4'), 157.5 (C-2), 159.7 (C-4), 161.0, 162.6.

**N,N-dimethyl-N'-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)guanidine (3i).** Yield 59%; Method A (procedure 1/2) or Method B; mp 227-228°C; TLC (silica gel,  $\text{MeOH}:\text{CH}_2\text{Cl}_2$ , 1:6):  $R_f$  0.57.  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  2.03 (3H, s,  $\text{CH}_3$ ), 2.97 (6H, s,  $\text{N}(\text{CH}_3)_2$ ), 5.45 (1H, s, H-

5), 8.46 (2H, br. s, NH-C(=NH)N), 10.58 (1H, br. s, NH);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  23.6 (CH<sub>3</sub>), 36.4 (N(CH<sub>3</sub>)<sub>2</sub>), 102.2 (C-5), 157.9 (C-2), 158.3 (C-4), 162.9 (C=NH), 163.7 (C=O).

**N-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)morpholine-4-carboxamide (3j).** Yield 36%; Method A (procedure 1/2) or Method B; mp 271-272 °C (EtOH); lit<sup>28</sup> mp 272-273 °C;  $^1\text{H}$  NMR (300 MHz, Me<sub>2</sub>SO- $d_6$ ):  $\delta$  2.03 (3H, s, Me), 2.75 (3H, d,  $^3J = 4.5$  Hz, N Me), 5.49 (1H, s, H-5), 7.96-9.20 (3H, br. s, NH-C(=NH) NH), 10.86 (1H, br. s, NH).

**N-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)indoline-1-carboxamide (3k).** Yield 61%; Method A (procedure 1/2); mp 268-269 °C;  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  2.10 (3H, s, CH<sub>3</sub>), 3.15 (2H, t,  $^3J = 8.5$  Hz, CH<sub>2</sub>), 3.97 (2H, t,  $^3J = 8.5$  Hz, CH<sub>2</sub>), 6.93 (1H, t,  $^3J = 7.2$  Hz), 7.09 (1H, t,  $^3J = 7.7$  Hz), 7.17 (1H, d,  $^3J = 7.2$  Hz), 8.64 (1H, d,  $^3J = 8.3$  Hz), 11.24 (1H, s, NH).  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  23.5 (CH<sub>3</sub>), 26.4 (3'-CH<sub>2</sub>), 47.3 (2'-CH<sub>2</sub>), 103.5 (C-5), 118.1, 122.1, 124.1, 126.9, 131.6, 142.4, 157.9 (C-2), 155.3 (C-4), 162.7 (C=NH), 163.7 (C=O).

**1-(3-bromophenyl)-3-(6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-2-yl)guanidine (3l).** Yield 70%; mp 161-162 °C (EtOH);  $^1\text{H}$  NMR (300 MHz, Me<sub>2</sub>SO- $d_6$ ):  $\delta$  6.18 (1H, s, H-7), 7.12-7.28 (2H, m, H<sub>Ar</sub>), 7.74-7.89 (2H, m, H<sub>Ar</sub>), 8.32 (1H, br. s., NH), 10.19 (1H, br. s., NH), 12.05 (1H, br. s., NH);  $^{13}\text{C}$  NMR (75 MHz, Me<sub>2</sub>SO- $d_6$ ):  $\delta$  103.4 (q,  $^3J_{\text{C-F}} = 3.1$  Hz, C-7), 119.1, 120.9 (q,  $^1J_{\text{C-F}} = 274.4$  Hz, CF<sub>3</sub>), 121.4, 121.9, 122.8, 125.0, 130.4, 140.8, 150.9 (q,  $^2J_{\text{C-F}} = 33.3$  Hz, C-8), 156.2, 159.5, 163.4

**N-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)cyanamide (1).**

Yield 61%; mp >300 °C; lit<sup>29</sup> mp >300 °C; TLC (silica gel, MeOH:CH<sub>2</sub>Cl<sub>2</sub>, 1:6):  $R_f$  0.43.  $^1\text{H}$  NMR (300 MHz, Me<sub>2</sub>SO- $d_6$ ):  $\delta$  1.93 (3H, s, Me), 5.20 (1H, s, C-5), 10.22 (1H, s, NH);  $^{13}\text{C}$  NMR (75 MHz, Me<sub>2</sub>SO- $d_6$ ):  $\delta$  23.8 (Me), 98.7 (C-5), 120.9 (CN), 161.6 (C-2), 164.4 (C-4), 165.6 (C=O).

General method for the preparation of 8(2)substituted 4(8)-methylpyrimido[1,2-*a*][1,3,5] triazin-6(4)-ones **4** or **6**:

Guanidines (**3a-j**), 0.25 ml acetic acid and excess triethylorthoacetate were refluxed under nitrogen atmosphere for 0.3-9h. Solvent was evaporated to dryness on rotary evaporator, purified using column chromatography and finally recrystallised using suitable solvent.

**4,8-dimethyl-2-(phenylamino)-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (4d)**. mp 220-221°C (AcOEt); TLC (silica gel, 9:1 AcOEt:Hex):  $R_f$  0.53; LC-MS (ESI)  $m/z$  268.1141 ( $MH^+$ ); Anal. Calcd. for  $C_{14}H_{13}N_5O$ : C, 62.91; H, 4.90; N, 26.20; Found 62.61, 4.95, 26.03.  $^1H$  NMR (300 MHz,  $Me_2SO-d_6$ ):  $\delta$  2.18 (3H, s, 8-Me), 2.90 (3H, s, 4-Me), 5.92 (1H, s, H-7), 7.13 (1H, t,  $^3J = 7.4$  Hz, H-5'), 7.38 (2H, t,  $^3J = 7.7$  Hz, H-3' and H-5'), 7.86 (2H, d,  $^3J = 7.5$  Hz, H-2' and H-6'), 10.63 (1H, s, NH);  $^{13}C$  NMR (75 MHz,  $Me_2SO-d_6$ ):  $\delta$  23.7 (2-Me), 26.2 (8-Me), 103.6 (C-5), 120.4 (C-2' and C-6'), 123.9 (C-4'), 128.6 (C-3' and C-5'), 138.0 (C-1'), 152.9, 156.8 (C-2), 160.0, 163.8, 166.7; IR (KBr);  $\nu$  3109 br NH, 1685 C=O, 1627, 1535, 1244, 1036, 821, 752.

**2-(3-chlorophenylamino)-4,8-dimethyl-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (4e)**. mp 239-240°C (AcOEt); TLC (silica gel, 9:1 AcOEt:Hex):  $R_f$  0.60; LC-MS (ESI)  $m/z$  302.0708 ( $MH^+$ ); Anal. Calcd. for  $C_{14}H_{12}ClN_5O$ : C, 55.73; H, 4.01; Cl, 11.75; N, 23.21; Found: C, 55.49; H, 4.05; Cl 11.50; N, 22.98.  $^1H$  NMR (300 MHz,  $Me_2SO-d_6$ ):  $\delta$  2.19 (1H, s, 8-Me), 2.91 (1H, s, 4-Me), 5.96 (1H, s, H-7), 7.18 (1H, d,  $J = 8.3$  Hz, H-4'), 7.40 (1H, t,  $J = 8.1$  Hz, H-5'), 7.76 (1H, d,  $J = 7.9$  Hz, H-6'), 8.06 (1H, s, H-2'), 10.79 (1H, s, NH);  $^{13}C$  NMR (75 MHz,  $Me_2SO-d_6$ ): 23.8 (8-Me), 26.2 (4-Me), 104.0 (C-7), 118.7, 119.5, 123.5, 130.3, 133.0, 139.7 (C-1'), 152.7, 156.9, 160.0, 164.3, 166.7; IR (KBr);  $\nu$  3273 br NH, 3103 (CH), 3082, 1678 C=O, 1636, 1095, 866, 788,

717.

**2-(4-methoxyphenylamino)-4,8-dimethyl-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (4f).** mp 177-178°C (AcOEt); TLC (silica gel, 9:1 Hex:AcOEt):  $R_f$  0.25; LC-MS (ESI)  $m/z$  298.1296 ( $MH^+$ ); Anal. Calcd. for  $C_{15}H_{15}N_5O_2$ : C, 60.60; H, 5.09; N, 23.56. Found: C, 60.47; H, 5.10; N, 23.29.  $^1H$  NMR (300 MHz,  $Me_2SO-d_6$ ):  $\delta$  2.16 (3H, s, 8-Me), 2.88 (3H, s, 4-Me), 3.75 (3H, s, OMe), 5.89 (1H, s, H-7), 6.96 (2H, d,  $J = 8.8$  Hz, H-3' and H-5'), 7.74 (2H, d,  $J = 8.8$  Hz, H-2' and H-6'), 10.52 (1H, s, NH);  $^{13}C$  NMR (75 MHz,  $Me_2SO-d_6$ ): 23.7 (4-Me), 26.2 (8-Me), 55.2 (OMe), 103.2 (C-7), 113.8 (C-2' and C-6'), 122.1 (C-3' and C-5'), 130.9 (C-1'), 153.1 (C-4'), 155.8, 156.5, 160.1, 163.5, 166.7; IR (KBr);  $\nu$  3109, 2920 (CH), 2850, 1670 C=O, 1627, 1541, 1419, 1236, 1174, 1028, 831, 788.

**2-(dimethylamino)-4,8-dimethyl-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (4i).** mp 190-191°C (AcOEt); TLC (silica gel,  $CH_2Cl_2$ ):  $R_f$  0.30; LC-MS (ESI)  $m/z$  220.1198 ( $MH^+$ ); Anal. Calcd for  $C_{10}H_{13}N_5O$ : C, 54.78; H, 5.98; N, 31.94; found: C, 54.42; H, 5.87; N, 31.69.  $^1H$  NMR (300 MHz,  $Me_2SO-d_6$ ):  $\delta$  2.12 (3H, s, 8-Me), 2.85 (3H, s, 4-Me), 3.14 (3H, s,  $N(Me)_2$ ), 3.25 (3H, s,  $N(Me)_2$ ), 5.78 (1H, s, H-7);  $^{13}C$  NMR (75 MHz,  $Me_2SO-d_6$ ):  $\delta$  23.8 (8-Me), 26.6 (4-Me), 36.3 ( $N(Me)_2$ ), 36.4 ( $N(Me)_2$ ), 101.8 (C-7), 153.1, 158.0, 160.1, 163.5, 167.2 (C=O). ; IR (KBr);  $\nu$  3420 br NH, 3034 (CH), 2978, 1714, 1670 C=O, 1620, 1516, 1317, 1238, 1192, 1078, 1033, 966, 825, 794, 717.

**4,8-dimethyl-2-morpholino-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (4j).** mp 191-192°C; TLC (silica gel, 9:1  $CH_2Cl_2$ ):  $R_f$  0.40; LC-MS (ESI)  $m/z$  262 ( $MH^+$ ); Anal. Calcd for  $C_{12}H_{15}N_5O_2$ : C, 55.16; H, 5.79; N, 26.80; found C, 55.22; H, 5.77; N, 26.86.  $^1H$  NMR (300 MHz,  $Me_2SO-d_6$ ):  $\delta$  2.13 (3H, s, 8-Me), 2.86 (3H, s, 4-Me), 3.67 (t,  $J = 4.5$  Hz, 4H,  $(CH_2)_2O$ ), 3.78 (t,  $J = 4.3$  Hz, 2H,

N(CH<sub>2</sub>), 3.89 (t,  $J = 4.3$  Hz, 2H, N(CH<sub>2</sub>), 5.81 (s, 1H, H-7); <sup>13</sup>C NMR (75 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>):  $\delta$  25.0 (8-Me), 27.8 (4-Me), 44.8 (CH<sub>2</sub>), 45.3 (CH<sub>2</sub>), 66.7 (CH<sub>2</sub>), 67.1 (CH<sub>2</sub>), 103.3 (C-7), 154.4, 158.3, 161.2, 165.5, 168.3 (C=O); IR (KBr);  $\nu$  3388 br NH, 3076 (CH), 2950, 1627 C=O, 1543, 1508, 1406, 1352, 1246, 1181, 1028, 966, 834.

**2-(indolin-1-yl)-4,8-dimethyl-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (4k).** mp 212-213°C (AcOEt); TLC (silica gel, 9:1 AcOEt:Hex):  $R_f$  0.32; Anal. Calcd for C<sub>16</sub>H<sub>15</sub>N<sub>5</sub>O: C, 65.52; H, 5.15; N, 23.88; found C, 65.27; H, 5.14; N, 23.74. <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>):  $\delta$  2.18 (3H, s, 8-Me) and 2.21 (3H, s, 8-Me), 2.94 (3H, s, 4-Me) and 3.00 (3H, s, 4-Me), 3.20 (2H, t,  $^3J = 8.5$  Hz, 3'-CH<sub>2</sub>), 4.19 (1H, t,  $^3J = 8.3$  Hz, CH<sub>2</sub>) and 4.32 (1H, t,  $^3J = 8.9$  Hz, CH<sub>2</sub>), 5.92 (2H, s, CH), 6.98-7.16 (2H, m, H-4'), 7.21-7.40 (4H, m, H-5' and H-6'), 8.29 (1H, d,  $^3J = 8.2$  Hz, H-7'), 8.49 (1H, d,  $^3J = 8.1$  Hz, H-7'); <sup>13</sup>C NMR (75 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>):  $\delta$  23.5 (Me), 26.4 (3'-CH<sub>2</sub>), 47.3 (2'-CH<sub>2</sub>), 103.5 (C-5), 118.1, 122.1, 124.1, 126.9, 131.6, 142.4, 157.9 (C-2), 155.3 (C-4), 162.7 (C=NH), 163.7 (C=O). IR (KBr);  $\nu$  3446 br NH, 2935 (CH), 2918, 2854, 1707 C=O, 1624, 1576, 1481, 1456, 1249, 1195, 785.1.

**2-(3-bromophenylamino)-4-methyl-8-(trifluoromethyl)-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (4l).** Yield: 70%; mp 216-217°C (EtOH); TLC (silica gel, 9:1 AcOEt:Hex):  $R_f$  0.90. <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>):  $\delta$  2.91 (1H, s, Me), 6.54 (1H, s, H-7), 7.32-7.42 (2H, m, H-4' and H-5'), 7.86 (1H, d,  $^3J = 6.8$  Hz, H-6'), 8.10 (1H, s, H-2'), 11.08 (1H, s, NH); 26.07 (CH<sub>3</sub>), (C-4), 103.3 (q,  $^3J_{C-F} = 2.6$  Hz, C-7), 119.5, 120.6 (q,  $^1J_{C-F} = 275.4$  Hz, CF<sub>3</sub>), 121.5, 122.8, 127.1, 130.8, 139.2, 152.6 (q,  $^2J_{C-F} = 34.0$  Hz, C-8), 155.1, 157.2, 160.2, 164.4; IR (KBr);  $\nu$  3282 NH, 3081, 2945, 1699 C=O, 1631, 1608, 1587, 1552, 1465, 1375, 1340, 1278, 1192, 1155, 1101, 1083, 925, 875, 788, 707; % purity >95%  $t_R = 7.1$  min.

**4-amino-2,8-dimethyl-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (6a).** mp 264-265°C; TLC

(silica gel, CH<sub>2</sub>Cl<sub>2</sub>): *R<sub>f</sub>* 0.55; LC–MS (ESI) *m/z* 192.0841 (MH<sup>+</sup>); Anal. Calcd for C<sub>8</sub>H<sub>9</sub>N<sub>5</sub>O: C, 50.26; H, 4.74; N, 36.63; found: C, 50.35, H, 4.95, N, 36.03. <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.18 (1H, s, 2-Me), 2.24 (1H, s, 8-Me), 6.04 (1H, s, H-7), 9.26 (1H, s, NH), 10.18 (1H, s, NH); <sup>13</sup>C NMR (75 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): 23.8 (8-Me), 25.2 (2-Me), 104.6 (C-7), 152.9, 156.8, 162.7, 167.6, 172.7; IR (KBr); ν 3294 NH, 3116 br, 1695 C=O, 1647, 1575, 1400, 1197, 1170, 1060, 821, 792, 748, 702.

**4-amino-2-methyl-8-phenyl-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (6b).** Yield: 58%; mp 258-259°C (80AcOEt:20Hex); TLC (silica gel, 9:1 AcOEt:Hex): *R<sub>f</sub>* 0.45;. <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.29 (1H, s, 2-CH<sub>3</sub>), 6.77 (1H, s, H-7), 7.44-7.61 (3H, m, H-3', H-4', H-5'), 8.12 (2H, d, *J* = 8.1 Hz, H-2' and H-6'), 9.32 (1H, s, NH), 10.22 (1H, s, NH); <sup>13</sup>C NMR (75 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): 25.2 (2-CH<sub>3</sub>), 101.2 (C-7), 127.1, 128.6, 131.1, 135.6 (C-1'), 153.4, 156.8, 162.3, 163.6, 172.9; IR (KBr); ν 3344 NH, 3213, 1674 C=O, 1624, 1570, 1544, 1448, 1382, 1220, 1174, 908, 778; % purity >95%; *t<sub>R</sub>* 8.9 min

**2,8-dimethyl-4-(methylamino)-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (6c).** mp 166-167°C (AcOEt); TLC (silica gel, 9:1 AcOEt:Hex): *R<sub>f</sub>* 0.16; LC–MS (ESI) *m/z* 206.0946 (MH<sup>+</sup>); Anal. Calcd. for C<sub>9</sub>H<sub>11</sub>N<sub>5</sub>O: C, 52.67; H, 5.40; N, 34.13; found: C, 52.49, H, 5.69, N, 32.83. <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.18 (3H, s, 2-Me), 2.28 (3H, s, 8-Me), 2.98 (3H, d, *J* = 4.9 Hz, NMe), 6.07 (1H, s, H-7), 10.90 (1H, d, *J* = 4.5 Hz, NH); <sup>13</sup>C NMR (75 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): 23.7 (8-Me), 25.6 (2-Me), 28.4 (NMe), 104.8 (C-7), 152.6, 155.5, 163.0, 167.5, 172.3; IR (KBr); ν 3324 NH, 3201, 1690 C=O, 1642, 1574, 1440, 1187, 1165, 1065, 793, 774.

**4-(4-chlorobenzylamino)-2,8-dimethyl-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (6g).** mp 133-134°C; TLC (silica gel, 9:1 AcOEt:Hex): *R<sub>f</sub>* 0.8; LC–MS (ESI) *m/z* 316.0817 (MH<sup>+</sup>); Anal. Calcd for C<sub>15</sub>H<sub>14</sub>ClN<sub>5</sub>O: C, 57.06; H, 4.47; Cl, 11.23; N, 22.18; found C, 56.99; H, 4.51; Cl 11.44; N,



22.05. <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.19 (3H, s, 8-Me), 2.25 (3H, s, 2-Me), 4.69 (2H, s, CH<sub>2</sub>), 6.08 (1H, s, H-7), 7.39 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 7.43 (2H, d, *J* = 8.7 Hz, H-2' and H-6'), 11.43 (1H, br. s., NH); <sup>13</sup>C NMR (75 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): 23.8 (2-Me), 25.6 (8-Me), 43.9 (CH<sub>2</sub>), 105.0 (C-7), 128.3 (C-3' and C-5'), 129.5 (C-2' and C-6'), 131.8 (C-4'), 136.4 (C-1'), 152.7, 155.2, 163.2, 167.6, 172.3. ; IR (KBr); ν 3170 br NH, 1689 C=O, 1618, 1411, 1377, 1344, 827, 794, 711.

**4-(4-methoxybenzylamino)-2,8-dimethyl-6H-pyrimido[1,2-*a*][1,3,5]triazin-6-one (6h).** mp 138-139°C; TLC (silica gel, 9:1 AcOEt:Hex): *R<sub>f</sub>* 0.26; LC-MS (ESI) *m/z* 312.1409 (MH<sup>+</sup>); Anal. Calcd. for C<sub>16</sub>H<sub>17</sub>N<sub>5</sub>O<sub>2</sub>: C, 61.72; H, 5.50; N, 22.49; found: C, 61.78; H, 5.42; N, 22.52. <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.19 (3H, s, 2-Me), 2.28 (3H, s, 8-Me), 3.74 (3H, s, OMe), 4.62 (2H, d, *J* = 5.7 Hz, CH<sub>2</sub>), 6.07 (1H, s, H-3), 6.91 (1H, d, *J* = 8.7 Hz, H-3' and H-5'), 7.34 (1H, d, *J* = 8.3 Hz, H-2' and H-6'), 11.36 (1H, t, *J* = 5.7 Hz, NH); <sup>13</sup>C NMR (75 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): 23.8 (8-Me), 25.6 (2-Me), 44.1 (CH<sub>2</sub>), 55.0 (OMe), 104.9 (C-7), 113.8 (C-2' and C-6'), 128.9 (C-1'), 129.2 (C-3' and C-5'), 152.6 (C-4'), 155.1, 158.6, 163.3, 167.7, 172.4; IR (KBr); ν 3109 br NH, 2950 (CH), 1683 C=O, 1629, 1516, 1458, 1379, 1342, 1172, 1114, 1026, 821, 792.

**3-(6-methyl-4-(phenylamino)-1,3,5-triazin-2(1H)-ylideneamino)but-2-enoic acid (6'd).**

LC-MS (ESI) *m/z* 285.1293 (MH<sup>+</sup>); TLC (silica gel, 9:1 AcOEt:Hex): *R<sub>f</sub>* 0.16; Anal. Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>: C, 58.94; H, 5.30; N, 24.55; found 56.18, H 4.89, N 23.58; <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.17 (3H, s, 8-Me), 2.25 (3H, s, 4-Me), 5.77 (1H, s, CH), 7.13 (1H, t, *J* = 7.3 Hz, H-4'), 7.33 (2H, t, *J* = 7.7 Hz, H-3' and H-5'), 7.84 (2H, d, *J* = 7.9 Hz, H-2' and H-6'), 10.94 (1H, s, NHPH), 12.06 (1H, br s, NH), 13.75 (1H, br s, COOH).

**3-(4-(4-methoxyphenylamino)-6-methyl-1,3,5-triazin-2(1H)-ylideneamino)but-2-enoic acid (6'f).** LC-MS (ESI) *m/z* 316.1255 (MH<sup>+</sup>); TLC (silica gel, 9:1 Hex:AcOEt): *R<sub>f</sub>* 0.11; Anal. Calcd

for C<sub>15</sub>H<sub>17</sub>N<sub>5</sub>O<sub>3</sub>: C, 57.13; H, 5.43; N, 22.21; found C, 57.44; H, 5.21; N, 22.45. <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.17 (3H, s, 8-Me), 2.24 (3H, s, 4-Me), 3.75 (3H, s, OMe), 5.74 (1H, s, CH), 6.87 (2H, d, *J* = 8.3 Hz, H-2' and H-6'), 7.74 (2H, d, *J* = 9.0 Hz, H-3' and H-5'), 10.82 (1H, s, NHPH), 11.97 (1H, s, NH), 13.72 (1H, s, COOH).

**3-(4-(4-methoxybenzylamino)-6-methyl-1,3,5-triazin-2(1*H*)-ylideneamino)but-2-enoic acid (6'h).** <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.12 (3H, s, 4-Me), 2.17 (3H, s, Me), 3.74 (3H, s, OMe), 4.57 (2H, d, *J* = 5.7 Hz, CH<sub>2</sub>), 5.66 (1H, s, H-3), 7.37 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 7.48 (1H, d, *J* = 8.3 Hz, H-2' and H-6'), 9.30 (1H, t, *J* = 5.7 Hz, NH), 11.63 (1H, br s, NH), 13.72 (1H, s, COOH).

#### Western blot analysis

Equal amounts of protein (50 μg) in each lysate sample were separated by 10% sodium dodecyl sulfate (SDS)–polyacrylamide gel. Proteins were then electroblotted on nitrocellulose membranes and the blot was probed with a primary antibody followed by a secondary antibody (rabbit anti-PARP, goat anti-β-actin) conjugated to horseradish peroxidase.

**(*E*)-2-(dimethylamino)-4-(2-(dimethylamino)prop-1-enyl)-8-methyl-6*H*-pyrimido[1,2-*a*][1,3,5]triazin-6-one (14).**

Appropriate guanidine and excess equivalent of DMA-DMA (with/without toluene) were refluxed under nitrogen atmosphere. The reaction was monitored using TLC. The solvent was evaporated to dryness on rotary evaporator, purified using column chromatography and finally recrystallized using suitable solvent.

Yield: 73%; physical appearance: orange; mp 212-213°C (MeOH:AcOEt); MS (ESI) *m/z*: 289 (MH<sup>+</sup>); Anal. calc. for C<sub>14</sub>H<sub>20</sub>N<sub>6</sub>O: C, 58.31; H, 6.99; N, 29.15; found: 58.54; H, 7.17; N, 28.89.

<sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.06 (3H, s, 9-Me), 2.64 (3H, s, 4-Me), 3.05 (6H, s, (N(Me)<sub>2</sub>), 3.05 (6H, s, (N(Me)<sub>2</sub>), 3.10 (6H, s, (NMe)<sub>2</sub>), 5.63 (1H, s, 8-CH), 6.13 (1H, s, =CH-N); <sup>13</sup>C NMR (75 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): 18.2 (4-Me), 23.6 (9-Me), 36.2 (N(Me)<sub>2</sub>), 36.4 (N(Me)<sub>2</sub>), 90.9 (=CH-N), 101.1 (C-8), 154.7, 157.5, 158.4 (C-5), 157.5, 158.4, 161.3, 164.9, 166.1.

**(E)-4-(2-(dimethylamino)prop-1-enyl)-8-methyl-2-morpholino-6H-pyrimido[1,2-*a*]**

**[1,3,5]triazin-6-one (14j).** Yield: 69%; physical appearance: yellow; mp 217-218°C (MeOH:AcOEt); MS (ESI) *m/z*: 331 (MH<sup>+</sup>); Anal. calc. for C<sub>16</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub>: C, 58.17; H, 6.71; N, 25.44; <sup>1</sup>H NMR (300 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): δ 2.06 (3H, s, 9-Me), 2.61 (3H, s, 4-Me), 3.11 (6H, s, (N(Me)<sub>2</sub>), 3.65 (4H, m, (CH<sub>2</sub>)<sub>2</sub>), 3.72 (4H, m, (CH<sub>2</sub>)<sub>2</sub>), 5.67 (1H, s, 8-CH), 6.17 (1H, s, =CH-N); <sup>13</sup>C NMR (75 MHz, Me<sub>2</sub>SO-*d*<sub>6</sub>): 18.5 (4-Me), 23.5 (9-Me), 43.8 (O(CH<sub>2</sub>)<sub>2</sub>), 65.8 (N(CH<sub>2</sub>)<sub>2</sub>), 91.2 (=CH-N), 101.5 (C-8), 154.8, 157.6, 158.0 (C-5), 161.2, 165.4, 165.9; IR (KBr); ν 3352 br., 1681 C=O, 1616, 1565, 1171, 979.

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