An efficient synthesis of 2,4,7-trisubstituted pyrimido[1,2-<a>][1,3,5]triazin-6-ones

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PAPER

An efficient synthesis of 2,4,7-trisubstituted pyrimido[1,2-*a*][1,3,5]triazin-6-ones

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A method for the preparation of novel pyrimido[1,2-*a*][1,3,5]triazin-6-one derivatives functionalized in positions 2, 4, and 7 of the ring was developed. Diversity in the derivatization of the pyrimido[1,2-*a*][1,3,5]triazin-6-one scaffold was successfully achieved by the introduction of substituents into positions 2 and 7 *via* two complementary approaches for the synthesis of key intermediates *viz.* pyrimidinylguanidines. Variations in position 4 of the pyrimido[1,2-*a*][1,3,5]triazine ring were made available by the regioselective introduction of various substituents *via* the triazine ring closure with corresponding aldehydes. The scope of the method was illustrated by the preparation of library of 66 pyrimido[1,2-*a*][1,3,5]triazin-6-ones, which was demonstrated to be a source for new selective anticancer agents. Tautomeric preferences and anticancer properties were also explored for the prepared compounds.

Introduction

1,3,5-Triazine has been a very popular heterocycle in medicinal chemistry allowing construction of structurally diverse molecules with various biological activities.[1] In the last decade, fused 1,3,5-triazine derivatives have been the focus of medicinal chemists' investigations and the derivatives have been recognized as privileged scaffolds in drug design.[2] However, pyrimido[1,2-*a*]triazines have not been explored extensively due to the limited number of effective methods available for their synthesis that allow the generation of diversely substituted library of potentially bioactive compounds with this heterocyclic system.[3] Some pyrimido[1,2-*a*][1,3,5]triazines and their benzofused analogues (1,3,5-triazino[2,1-*b*]quinazolines) were reported to be useful as agricultural herbicides[4] and fungicides.[5] The compounds constructed using this scaffold were found to possess antibacterial activity against *Klebsiella pneumonia*, antifungal activity against *Microsporum canis*;[6] they were also identified as ligands for 5-HT receptors[6] and potential anticancer agents.[7]

In our previous work[8] on exploration of the synthetic utility of pyrimidinylguanidines for the synthesis of pyrimido[1,2-*a*][1,3,5]triazines, we observed an unexpected rearrangement of the products. In continuation of our work on the synthesis of pyrimido[1,2-*a*][1,3,5]triazines and their fused analogues,[7-9] we report herein an effective approach for the synthesis of a diversely substituted library of pyrimido[1,2-*a*][1,3,5]triazin-6-ones.

Recently, the synthesis of pyrimido[1,2-*a*][1,3,5]triazines with a partially hydrogenated pyrimidine ring was reported.[10] In this paper, we describe a synthesis of pyrimido[1,2-*a*][1,3,5]triazines with a partially hydrogenated triazine ring. Particularly, we focus on the preparation of compounds possessing amino-substitutions that are common in well-known anticancer 1,3,5-triazines (Figure 1).

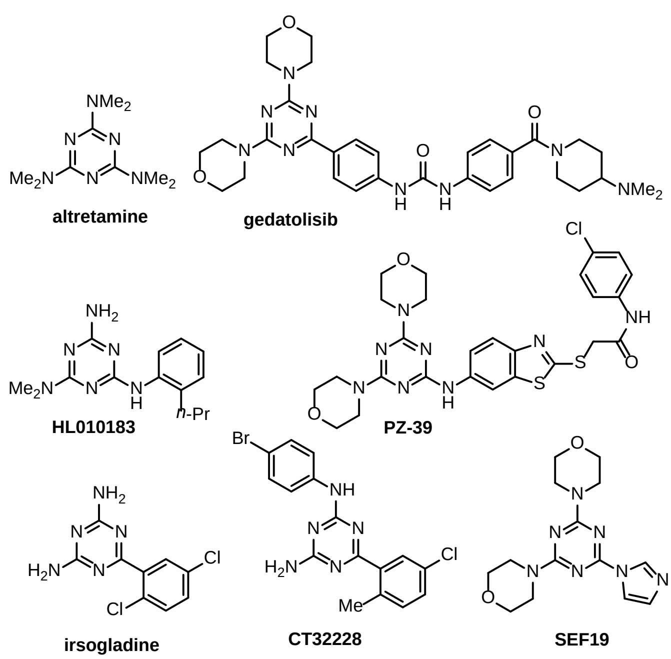
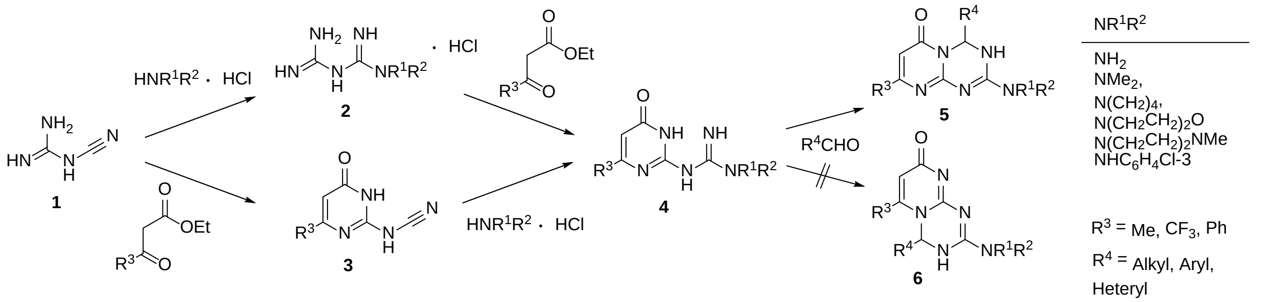


Fig. 1 Some 1,3,5-triazines possessing anticancer activity.



Scheme 1 Synthesis of (6-oxo-1,6-dihydropyrimidin-2-yl)guanidines (**4**) and 4-substituted 2-amino-1,4-dihydropyrimido[1,2-*a*][1,3,5]triazine-6-ones (**5**).

Despite very different targets, these compounds share some similarity in the substitution of amino groups. For example, primary amino group is common for anticancer agent HL010183[11], irsogladine[12] possessing antiangiogenic and anticancer properties and the lysophosphatidic acid acyltransferase inhibitor CT32228 demonstrating very good antileukemic profile.[13] The dimethylamino substitution on the triazine ring is typical for HL010183 and anticancer drug altretamine (hexamethylmelamine).[14] Morpholine can be found connected to the triazine ring of a dual phosphoinositide 3-kinase/mTOR inhibitor gedatolisib, which is currently under clinical trials by by Pfizer as an anticancer agent.[15] This structural motif is also present in the structure of a reversing anticancer multidrug inhibitor of ABCG2 transporter PZ-39,[16] and in an aromatase inhibitor SEF19, effective against experimental tumors.[17]

Results and discussion

The synthesis of pyrimidinylguanidines **4**, key intermediates for the desired pyrimido[1,2-*a*][1,3,5]triazines, was performed *via* two alternative pathways utilizing the same readily available reagents: cyanoguanidine (**1**), various amines in form of hydrochlorides and *β*-keto esters (Scheme 1). In the first approach, biguanides **2**, successfully prepared from cyanoguanidine (**1**), were subjected to the treatment with *β*-keto esters thus providing pyrimidinylguanidines **4**. However, we found that in addition to the pyrimidine ring closure, 2,4-diamino-1,3,5-triazines were also formed in this reaction as biguanide can act as both tri- and penta-atomic synthon.[18] The low selectivity of the process was the main drawback of this approach that motivated us to explore another sequence of the reactions *via* the initial formation of the pyrimidine ring upon treatment of **1** *β*-keto esters. The reaction of resulting pyrimidinylcyanamides **3** with amines under microwave irradiation (*i*-PrOH, 160°C, 15 min) was used to convert them into pyrimidinylguanidines **4**. Despite the fact that the structure of the final product **4** did not depend on the sequence of the reagent introduction, our attempts to carry out the synthesis of **4** in a one-pot three-component manner were unsuccessful.

The annulation of a 1,3,5-triazine ring to the pyrimidine ring was achieved using the reaction of pyrimidinylguanidines **4** with various aldehydes (Scheme 1). The ring closure proceeded regioselectively to N-1 of **4** thus affording pyrimido[1,2-*a*][1,3,5]triazin-6-ones **5**. The formation of the 1,3,5-triazine ring was confirmed by signals of a proton at C-4 (5.53-7.15 ppm) in ^{1}H NMR spectra and the C-4 signal in ^{13}C NMR spectra (54.9-64.8 ppm). The formation of regioisomeric products **6** was excluded on the basis of 2D NOESY experiments. The absence of cross-peaks between protons of R^4 substituents and a proton at sp^3-hybridized carbon of the 1,3,5-triazine ring with signals of R^3 substituents in the pyrimidine ring suggested selective annulation of the triazine ring to N-1 and the formation of **5**. The structure assignments were further conformed by X-ray crystallography data of compound **5v** (Figure 2).[19]

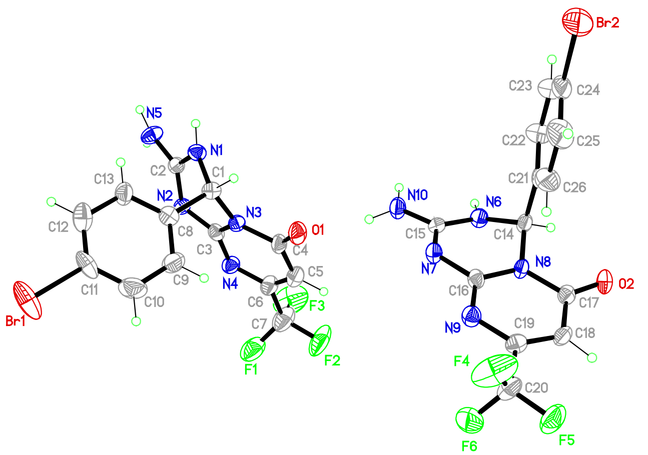


Fig. 2 Molecular structure of **5v**.[19]

The method developed for the synthesis of pyrimido[1,2-*a*][1,3,5]triazin-6-ones **5** was found to be general and after minor modifications can be applied for various substrates. This was demonstrated by the preparation of a series of pyrimido[1,2-*a*][1,3,5]triazin-6-ones **5** bearing different substituents in positions 2, 4 and 7 of the heterocyclic system (Table 1). The range of alkyl, aryl and hetaryl substituents was successfully introduced to a newly formed triazine ring by corresponding aldehydes. The synthesis can tolerate use of various pyrimidinylguanidines **4**, which involve only minor adjustment of solvents required to achieve an adequate solubility of the starting guanidines, allowing incorporation of diverse amino-substituents in position 2 of the triazine ring. It was demonstrated that only unsubstituted guanidine nitrogen participated in the reaction if another available nitrogen atom was substituted with an aryl group (**5bm-5bn**). That was confirmed by two distinct signals for NH protons at 8.38-8.52 and 9.70-9.82 ppm in ^{1}H NMR spectra of **5bm-5bn**. In order to further improve efficiency of our method, we explored effect of microwave irradiation on the outcome of the reaction. Moderate to good yields of **5** were obtained using conventional heating whereas yields were improved considerably with shortening reaction times by using focused microwave irradiation in the same solvents.

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Table 1. Synthesis of 2,4,7-trisubstituted pyrimido[1,2-*a*][1,3,5]triazin-6-ones (**5**)

Compound	NR^1R^2	R^3	R^4	Yield,[a] %	Compound	NR^1R^2	R^3	R^4	Yield, %
5a	NH_2	Me	Ph	61[b], 79[c]	**5ah**	NMe_2	Me	4-$MeOC_6H_4$	55[f], 73[g]
5b	NH_2	Me	4-MeC_6H_4	55[b], 77[c]	**5ai**	NMe_2	Me	4-FC_6H_4	63[f], 76[g]
5c	NH_2	Me	4-$MeOC_6H_4$	60[b], 72[c]	**5aj**	NMe_2	Me	4-$CF_3C_6H_4$	76[f]
5d	NH_2	Me	4-FC_6H_4	67[b], 87[c]	**5ak**	NMe_2	Me	4-CNC_6H_4	54[f]
5e	NH_2	Me	4-$CF_3C_6H_4$	65[b]	**5al**	NMe_2	Me	2-furyl	69[f], 76[g]
5f	NH_2	Me	Me	61[b]	**5am**	NMe_2	Me	2-pyridyl	77[f], 92[g]
5g	NH_2	Me	isopropyl	70[b]	**5an**	NMe_2	Me	4-ClC_6H_4	66[f], 85[g]
5h	NH_2	Me	cyclohexyl	77[b]	**5ao**	NMe_2	Me	4-BrC_6H_4	79[f]
5i	NH_2	Me	$PhCH_2CH_2$	79[b]	**5ap**	NMe_2	Me	4-OHC_6H_4	75[f]
5j	NH_2	Me	2-furyl	54[b], 78[c]	**5aq**	morpholino	Me	Ph	64[f], 75 [g]
5k	NH_2	Me	2-thienyl	52[b]	**5ar**	morpholino	Me	4-MeC_6H_4	76[f], 79[g]
5l	NH_2	Me	2-pyridyl	63[b], 81[c]	**5as**	morpholino	Me	4-$MeOC_6H_4$	94[f], 96[g]
5m	NH_2	CF_3	Ph	62[d], 89[e]	**5at**	morpholino	Me	4-FC_6H_4	53[f], 88[g]
5n	NH_2	CF_3	4-MeC_6H_4	65[d], 86[e]	**5au**	morpholino	Me	4-$CF_3C_6H_4$	79[f]
5o	NH_2	CF_3	4-$MeOC_6H_4$	52[d], 79[e]	**5av**	morpholino	Me	4-CNC_6H_4	50[f]
5p	NH_2	CF_3	4-FC_6H_4	63[d], 81[e]	**5aw**	morpholino	Me	2-furyl	59[f], 71[g]
5q	NH_2	CF_3	4-$CF_3C_6H_4$	69[d]	**5ax**	morpholino	Me	2-thienyl	57[f]
5r	NH_2	CF_3	2-furyl	57[d], 70[e]	**5ay**	morpholino	Me	2-pyridyl	55[f], 90[g]
5s	NH_2	CF_3	2-thienyl	55[d]	**5az**	morpholino	Me	4-BrC_6H_4	51[f]
5t	NH_2	CF_3	2-pyridyl	75[d], 82[e]	**5ba**	morpholino	CF_3	Ph	69[f], 86[g]
5u	NH_2	CF_3	4-ClC_6H_4	80[d]	**5bb**	morpholino	CF_3	4-MeC_6H_4	83[f], 93[g]
5v	NH_2	CF_3	4-BrC_6H_4	78[d]	**5bc**	morpholino	CF_3	4-$MeOC_6H_4$	86[f], 95[g]
5w	NH_2	Ph	Ph	65[d], 80[e]	**5bd**	morpholino	CF_3	4-FC_6H_4	63[f], 90[g]
5x	NH_2	Ph	4-MeC_6H_4	65[d], 86[e]	**5be**	morpholino	CF_3	4-$CF_3C_6H_4$	69[f]
5y	NH_2	Ph	4-$MeOC_6H_4$	69[d], 85[e]	**5bf**	morpholino	CF_3	2-furyl	57[f], 78[g]
5z	NH_2	Ph	4-FC_6H_4	57[d], 80[e]	**5bg**	morpholino	CF_3	4-$NO_2C_6H_4$	58[f]
5aa	NH_2	Ph	4-$CF_3C_6H_4$	69[d]	**5bh**	morpholino	CF_3	2-pyridyl	60[f], 76[g]
5ab	NH_2	Ph	2-furyl	65[d], 86[e]	**5bi**	morpholino	CF_3	4-BrC_6H_4	72[f]
5ac	NH_2	Ph	2-pyridyl	71[d], 86[e]	**5bj**	morpholino	CF_3	4-CNC_6H_4	88[f]
5ad	NH_2	Ph	4-BrC_6H_4	67[d]	**5bk**	pyrrolidino	Me	4-MeC_6H_4	69[f]
5ae	NH_2	Ph	4-ClC_6H_4	69[d]	**5bl**	*N*-methylpiperazino	Me	4-MeC_6H_4	53[f]
5af	NMe_2	Me	Ph	69[f], 83[g]	**5bm**	3-ClC_6H_4NH	Me	4-MeC_6H_4	65[f], 86[g]
5ag	NMe_2	Me	4-MeC_6H_4	72[f], 87[g]	**5bn**	3-ClC_6H_4NH	Me	5-($HOCH_2$) fur-2-yl	38[f]

[a] Isolated yields after recrystallization;
[b] AcOH, reflux, 5-9 h;
[c] AcOH, microwave irradiation, 150°C, 25 min;
[d] DMF, reflux, 3-8 h;
[e] DMF, microwave irradiation, 165-170°C, 20 min;
[f] EtOH, piperidine, reflux, 4-12 h;
[g] EtOH, piperidine, microwave irradiation, 140°C, 20 min

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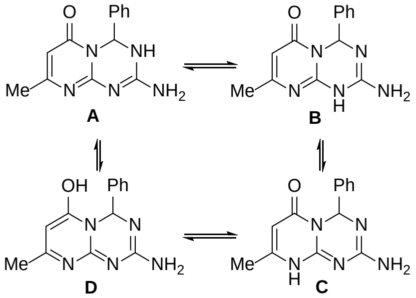

Fig. 3 Prototropic tautomerism in **5a**.

Compounds **5** might be involved in several tautomeric interconversions (Figure 3). To assess tautomeric preferences for compounds **5**, *ab intio* calculations were performed at three different levels of theory using 2-amino-7-methyl-4-phenyl-1(3)(8),4-dihydropyrimido[1,2-*a*][1,3,5]triazine-6-one (**A-C**) and its 6-hydroxy tautomer **D** as a model compound and compared their relative stability in gaseous state (Table 2). Tautomer **B** was found to be the most preferred species. However, the difference in energy between molecules **A-C**, involved in annular tautomerism in **5a**, is relatively small while while the hydroxy tautomer **D** was considerably less stable.

It should be noted that the experimental observations contradict the results of the theoretical *ab initio* calculations of the tautomeric preferences. On the basis of NMR data, the 3*H*-form **A** was suggested to be predominant in the DMSO solution. The coupling of a proton at the sp^3-hybridized carbon (C-4) and a proton at the endocyclic nitrogen was observed in ^{1}H NMR spectra (^3J = 0-4.9 Hz) for several compounds **5**. Despite the *J* value being small and not always detectable, the 2D NOESY experiments clearly indicated the location of the NH proton in the vicinity of the sp^3-hybridized carbon as the signal of the migrating proton gave cross peaks with the proton signal at C-4 and proton signals of the R^4 substituent.

Table 2. Tautomeric preference for **5a** according to *ab initio* calculations[20]

Level of theory	Relative energies of tautomers, kcal/mol			
	A	**B**	**C**	**D**
	gaseous phase (ε = 1)			
HF/6-311**	2.9	0	3.5	28.3
B3LYP/6-311++**	3.3	0	2.9	24.1
MP2/6-311++G**	5.0	0	4.2	23.4
	DMSO (ε = 46.7)			
HF/6-311**	0	2.3	3.7	27.2
B3LYP/6-311++**	0	1.8	3.6	24.3
MP2/6-311++G**	0	3.5	4.2	30.1

In crystal structure, we also found the 3*H*-form, where the proton at N-3 was involved in intermolecular hydrogen bonding to N-1 of another molecule thus facilitating potential interconversion of forms **A** and **B**. The discrepancy between the experimental and theoretical data of gaseous state can be attributed to the effect of the solvent. The solvent influence was confirmed by the single point energy calculations performed considering the presence of DMSO as a solvent using the polarizable continuum model.[21]

Anticancer properties of compounds **5** were evaluated using a standard MTT assay.[22] Some of the tested compounds demonstrated antiproliferative activity against the A549 lung cancer cell line. In particular, **5j** was found to inhibit growth of this type of cells with an IC_{50} value of 6.0±0.4 µM. Moreover, the effect of this compound against cancerous cells was found to be highly selective. Thus no significant inhibition in the growth of normal human lung fibroblast cells (MRC-5) were observed when **5j** was applied at the concentrations up to 100 µM.

Conclusions

In summary, we have successfully developed an efficient method for the synthesis of bioactive pyrimido[1,2-*a*][1,3,5]triazin-6-ones. This method allows the preparation of libraries of variously substituted compounds with this heterocyclic system from easily available reagents. Shortening reaction time and higher yields were demonstrated to be advantages of carrying out this reaction under microwave irradiation. Moreover, the method is currently applied to obtain 2-thioxo derivatives of 1,3,5-triazine fused heterocyclic systems.

Experimental

General

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. NMR spectra were recorded on a Bruker DPX-300 or a Bruker Avance DRX-400 at 298 K using Me_2SO-d_6 as a solvent and TMS as an internal reference. ^{1}H 2DNOESY spectra were acquired using a 150 ms mixing time. The raw data were processed using Topspin 2.1 (Bruker Scientific Inc.). IR spectra were performed on a Perkin Elmer Spectrum 100 FT-IR spectrophotometer in potassium bromide pellets. Mass spectra were obtained using either a QTRAP 2000 LC-MS mass spectrometer using atmospheric pressure chemical ionization (APCI) mode or 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_{254} plates (Merck, Germany). HPLC analysis was performed on an Agilent Eclipse XDB-C18 (4.6x250 mm, 5 µm) column at 30ºC, with a flow rate of 1 mL/min. 5-90% Gradients of MeOH/MeCN (solvent A) and H_2O (solvent B) were used as mobile phases. Microwave-assisted reactions were conducted using a Biotage Initiator microwave synthesizer at maximal power of 400 W. Elemental analyses were performed on a Perkin Elmer 2400 Elemental Analyzer Series II.

Typical procedure for the synthesis of intermediates 4

Method A: Into a 5 mL microwave vessel was added N-(4-substituted-6-oxo-1,6-dihydropyrimidin-2-yl)cyanamide **3** (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. The data of the products corresponds to that reported in the literature.[8]

Method B: Pyrimidine ring annulation of biguanides **2** with β-keto esters to obtain **4** was done using method described by Curd et al.[23]

General procedure for the synthesis of 2-amino-8-methyl-4-(het)aryl-3,4-dihydropyrimido[1,2-*a*][1,3,5]triazin-6-ones (5a-5l).

Procedure 1: A mixture of guanidine **4** (0.5 g, 2.5 mmol) and an appropriate aldehyde (5.0 mmol) in acetic acid (3 mL) was heated under reflux for 5-9 h. The excess solvent was removed under reduced pressure and the solid obtained was neutralized using sodium carbonate solution (50%). The precipitate formed was filtered and purified by either recrystallization (EtOH) or column chromatography (dichloromethane/methanol - 8.5/1.5).
Procedure 2: A mixture of guanidine **4** (1.5 mmol) and an appropriate aldehyde (1.8 mmol) in 0.2-0.3 mL of acetic acid was irradiated in a 10 mL vial using a Biotage microwave synthesizer at 150°C for 25 min. After cooling, the precipitated crude product was filtered, washed with cold ethyl acetate followed by aqueous sodium carbonate, dried under vacuum and recrystallized.

2-Amino-8-methyl-4-(4-methylphenyl)-3,4-dihydropyrimido [1,2-a][1,3,5]triazin-6-one (**5b**): mp 267-268°C; MS (APCI) *m/z* 270.1 (MH^+); Anal. Calcd. C, 62.44; H, 5.61; N, 26.01; found C, 61.98; H, 5.36; N, 26.02. ^1H NMR (300 MHz, Me_2SO-d_6): δ 2.04 (3H, s, 8-Me), 2.26 (3H, s, 4'-Me), 5.69 (1H, s, H-7), 6.82 (1H, d, J = 2.6 Hz, H-4), 7.00 (2H, br s, NH_2), 7.11 (2H, d, J = 8.3 Hz, H-3' and H-5'), 7.16 (2H, d, J = 8.3 Hz, H-2' and H-6'), 8.23 (1H, d, J = 3.0 Hz, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 20.5 (4'-Me), 23.8 (8-Me), 59.6 (C-4), 102.1 (C-7), 125.2 (C-2' and C-6'), 128.9 (C-3'and C-5'), 137.2 (C-1'), 137.7 (C-4'), 154.2 (C-9a), 157.4 (C-2), 160.5 (C-6), 165.6 (C-8); IR (KBr); ν 3331 NH, 3080 CH, 2922, 1688 C=O, 1663, 1592, 1487, 1366. HPLC: purity 98.5%, t_R 11.4 min (MeOH:H_2O); purity 100%, t_R 7.7 min (CH_3CN:H_2O).

2-Amino-4-(4-methoxyphenyl)-8-methyl-3,4-dihydropyrimido [1,2-a][1,3,5]triazin-6-one (**5c**): mp 252-253°C; MS (APCI) *m/z* 289.1 (MH^+); Anal. Calcd. C, 58.94; H, 5.30; N, 24.55; found C, 58.73; H, 5.09; N, 24.43.^1H NMR (300 MHz, Me_2SO-d_6): δ 2.04 (3H, s, Me), 3.72 (3H, s, OMe), 5.69 (1H, s, H-7), 6.80 (1H, s, H-4), 6.91 (2H, d, J = 8.7 Hz, H-3' and H-5'), 7.00 (2H, br s, NH_2), 7.16 (2H, d, J = 8.7 Hz, H-2' and H-6'), 8.20 (1H, s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 23.7 (8-Me), 55.1 (OMe), 59.6 (C-4), 102.2 (C-7), 113.8 (C-3' and C-5'), 126.6 (C-2'and C-6'), 132.2 (C-1'), 154.1 (C-9a), 157.4 (C-2), 159.2 (C-4'), 160.4 (C-6), 165.5 (C-8); IR (KBr); ν 3319 NH, 3083 CH, 2929 CH, 2837, 1687 C=O, 1661, 1612, 1585, 1487, 1395. HPLC: purity 100%, t_R 12.6 min (MeOH:H_2O); purity 100%, t_R 7.1 min (CH_3CN:H_2O).

2-Amino-4-(furan-2-yl)-8-methyl-3,4-dihydropyrimido[1,2-a] [1,3,5]triazin-6-one (**5j**): mp >300°C; MS (APCI) *m/z* 246.2 (MH^+); Anal. Calcd. C, 53.87; H, 4.52; N, 28.56; found C, 53.70; H, 5.03; N, 28.61. ^1H NMR (300 MHz, Me_2SO-d_6): δ 2.02 (3H, s, Me), 5.64 (1H, s, H-7), 6.19 (1H, d, J = 3.0 Hz, H-3'), 6.38 (1H, dd, J = 3.5, 1.6 Hz, H-4'), 6.87 (1H, s, H-4), 7.10 (2H, br s, NH_2), 7.58 (1H, d, J = 1.0 Hz, H-5'), 8.25 (1H, s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 23.8 (8-Me), 55.4 (C-4), 101.8 (C-7), 106.9 (C-3'), 110.3 (C-4'), 142.8 (C-5'), 152.0 (C-2'), 153.9 (C-9a), 157.7 (C-2), 160.0 (C-6), 165.5 (C-8); IR (KBr); ν 3344 NH, 3066 CH, 2804, 2697, 1669 br C=O, 1490. HPLC: purity 97.5%, t_R 15.9 min (MeOH:H_2O); purity 100%, t_R 7.9 min (CH_3CN:H_2O).

General methods for the synthesis of 2-amino-4-(het)aryl-8-trifluoromethyl-3,4-dihydro-pyrimido[1,2-*a*][1,3,5]triazin-6-one ***(5m-5v)***
Procedure 1: A mixture of **4** (0.5 g, 2.5 mmol) and an appropriate aldehyde (3.0 mmol) in DMF (5 mL) was heated under reflux for 3-8 h. After 2 hours, more amount (up to 0.5 equivalent) of the aldehyde was added to facilitate the completion of reaction. The reaction mixture was concentrated under vacuum, filtered, washed with diethyl ether and recrystallized from DMF.
Procedure 2: A mixture of guanidine **4** (1.5 mmol) and an appropriate aldehyde (2.0 mmol) in DMF (1.0 mL) was irradiated in a 10mL vial using a Biotage initiator microwave synthesizer at 165 °C for 20 min. After cooling, the precipitated product was filtered, washed with diethyl ether and recrystallized.

2-Amino-4-(4-methylphenyl)-8-(trifluoromethyl)-3,4-dihydro pyrimido[1,2-a][1,3,5]triazin-6-one (**5n**): mp 251-252°C (DMF); TLC (silica gel, 8.5:1.5 DCM:MeOH): R_f 0.5; MS (ESI) *m/z*: 324.060 $[MH]^+$; Anal. Calcd. for $C_{14}H_{12}F_3N_5O$: C, 52.01; H, 3.74; N, 21.66; found: C, 51.87; H, 3.50; N, 21.63. ^1H NMR (300 MHz, Me_2SO-d_6): δ 2.27 (3H, s, Me), 6.22 (1H, s, H-7), 6.88 (1H, d, J = 2.3 Hz, H-4), 7.14 (2H, d, J = 7.9 Hz, H-3' and H-5'), 7.19 (2H, d, J =7.9 Hz, H-2' and H-6'), 7.40 (2H, br s, NH_2), 8.49 (1H, d, J = 2.3 Hz, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 20.6 (4'-Me), 60.2 (C-4), 100.8 (q, $^3J_{C\text{-}F}$ = 3.1 Hz, C-7), 120.8 (q, $^1J_{C\text{-}F}$ = 275.0 Hz, CF_3), 125.2 (C-2' and C-6'), 129.2 (C-3' and C-5'), 136.4 (C-4'), 138.3 (C-1'), 153.3 (q, $^2J_{C\text{-}F}$ = 33.5 Hz, C-8), 155.9, 157.6, 160.3; IR (KBr); ν 3419 NH, 3345, 3154, 2954CH, 2821, 1684, 1658 C=O, 1552, 1491, 1424, 1298, 1276. HPLC: purity 100%, t_R 4.90 min (MeOH:H_2O).

2-Amino-4-(4-methoxyphenyl)-8-(trifluoromethyl)-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5o**): mp 225-226°C (DMF); TLC (silica gel, 8.5:1.5 DCM:MeOH): R_f 0.40; Anal. Calcd. for $C_{14}H_{12}F_3N_5O_2$: C, 49.56; H, 3.57; N, 20.64; found: C, 49.31; H, 4.09; N, 19.83. ^1H NMR (300 MHz, Me_2SO-d_6): δ 3.73 (3H, s, OMe), 6.22 (1H, s, H-7), 6.86 (1H, s, H-4), 6.95 (2H, d, J = 8.7 Hz, H-3' and H-5'), 7.20 (2H, d, J = 8.7 Hz, H-2' and H-6'), 7.36 (2H, br s, NH_2), 8.49 (1H, s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 55.1 (OMe), 60.1 (C-4), 100.9 (q, $^3J_{C\text{-}F}$ = 3.5 Hz, C-7), 114.0 (C-3'and C-5'), 120.8 (q, $^1J_{C\text{-}F}$ = 275.6 Hz, CF_3), 126.6 (C-2' and C-6'), 131.4 (C-1'), 153.3 (q, $^2J_{C\text{-}F}$ = 33.0 Hz, C-8), 155.7, 157.5, 159.5 (C-4'), 160.3. HPLC: purity 96.5%, t_R 4.95 min (MeOH:H_2O).

2-Amino-4-(4-fluorophenyl)-8-(trifluoromethyl)-3,4-dihydro pyrimido[1,2-a][1,3,5]triazin-6-one (**5p**): mp 260-261°C

(MeOH); TLC (silica gel, 8.5:1.5 DCM:MeOH): R_f 0.7; MS (ESI) *m/z*: 328.034 $[MH]^+$; Anal. Calcd. for $C_{13}H_9F_4N_5O$: C, 47.71; H, 2.77; N, 21.40; found: C, 47.38; H, 2.81; N, 21.24. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 6.23 (1H, s, H-7), 6.91 (1H, d, J = 3.8 Hz, H-4), 7.21-7.34 (4H, m, H2', H6', H3' and H5'), 7.46 (2H, br s, NH_2), 8.50 (1H, d, J = 3.8 Hz, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 59.9 (C-4), 100.9 (q, $^3J_{C-F}$ = 2.7 Hz, C-7), 115.7 (d, $^2J_{C-F}$ = 21.8 Hz, C-3' and C-5'), 120.8 (q,$^1J_{C-F}$ = 275.6 Hz, CF_3), 127.5 (d, $^3J_{C-F}$ = 8.8 Hz, C-2' and C-6'), 135.6 (d, $^4J_{C-F}$ = 2.8 Hz, C-1'), 153.4 (q, $^2J_{C-F}$ = 33.3 Hz, C-8), 155.8, 157.5, 160.3, 162.1 (d, $^1J_{C-F}$ = 245.2 Hz, C-4').

2-Amino-8-(trifluoromethyl)-4-[4-(trifluoromethyl)phenyl]-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5q**): mp 150-151°C (DMF); TLC (silica gel, 8.5:1.5 DCM:MeOH): R_f 0.7; MS (ESI) *m/z*: 378.021 $[MH]^+$; Anal. Calcd. for $C_{14}H_9F_6N_5O$: C, 44.57; H, 2.40; N, 18.56; found: C, 44.30; H, 2.37; N, 18.48. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 6.27 (1H, s, H-7), 7.00 (1H, d, J = 2.2 Hz, H-4), , 7.48 (2H, d, J = 8.3 Hz, H-2' and H-6'), 7.38 (2H, br s, NH_2), 7.81 (2H, d J = 8.3 Hz, H-3' and H-5'), 8.62 (1H, J = 2.2 Hz, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 60.2 (C-4), 100.9 (q, $^3J_{C-F}$ = 3.4 Hz, C-7), 120.8 (q, $^1J_{C-F}$ = 275.4 Hz, 8-CF_3), 123.9 (q, $^1J_{C-F}$ = 275.4 Hz, 4'-CF_3), 125.9 (q, $^3J_{C-F}$ = 3.5 Hz, C-3'and C-5'), 126.2 (C-2'and 6'), 129.3 (q, $^2J_{C-F}$ = 31.8 Hz, C-4'), 143.7 (d, $^4J_{C-F}$ = 1.2 Hz, C-1'), 153.5 (q, $^2J_{C-F}$ = 33.7 Hz, C-8), 155.8, 157.5, 160.4; IR (KBr); ν 3336 br NH, 3166 br, 2949, 1684, 1550, 1496, 1419, 1329, 1278, 1219. HPLC: purity 99.4%, t_R 6.03 min (MeOH:H_2O).

2-Amino-4-(furan-2-yl)-8-(trifluoromethyl)-3,4-dihydro pyrimido[1,2-a][1,3,5]triazin-6-one (**5r**): mp 226-227°C (DMF); TLC (silica gel, 8.5:1.5 DCM:MeOH): R_f 0.5; MS (ESI) *m/z*: 300.025 $[MH]^+$; Anal. Calcd. for $C_{11}H_8F_3N_5O_2$: C, 44.16; H, 2.69; N, 23.41; found: C, 43.21; H, 3.04; N, 22.81. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 6.21 (1H, s, H-7), 6.33 (1H, d, J = 3.0 Hz, H-3'), 6.44 (1H, dd, J = 3.0 Hz, J = 1.9 Hz, H-4'), 6.95 (1H, s, H-4), 7.19 (2H, br s, NH_2), 7.65 (1H, d, J = 0.8 Hz, H-5'), 8.45 (1H, s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 55.3 (C-4), 100.8 (q, $^3J_{C-F}$ = 3.2 Hz, C-7), 107.8 (C-3'), 110.5 (C-4'), 120.8 (q, $^1J_{C-F}$ = 275.2 Hz, CF_3), 143.5 (C-5'), 150.7 (C-2'), 153.4 (q, $^2J_{C-F}$ = 33.5 Hz, C-8), 155.6, 157.8, 159.9; IR (KBr); ν 3294 NH, 3153, 2941, 2817, 1697, 1664 C=O, 1496, 1410, 1299, 1277, 1229. HPLC: purity 100%, t_R 4.03 min (MeOH:H_2O).

General methods for the synthesis of 4-substituted 2-amino-8-phenyl-3,4-dihydropyrimido[1,2-*a*][1,3,5]triazin-6-one (5w-5af)

Procedure 1: A mixture of **4** (0.5 g, 2.5 mmol) and an appropriate aldehyde (3.0 mmol) in DMF (5 mL) was heated under reflux for 3-8 h. After 2 hours, more amount (up to 0.5 equivalent) of the aldehyde was added to facilitate the completion of reaction. The reaction mixture was concentrated under vacuum, filtered, washed with diethyl ether and recrystallized from suitable solvent.

Procedure 2: A mixture of guanidine **4** (1.5 mmol) and an appropriate aldehyde (2.0 mmol) in DMF (1.0 mL) was irradiated in a 10mL vial using a Biotage initiator microwave synthesizer at 170°C for 20 min. After cooling, the precipitated product was filtered, washed with diethyl ether and recrystallized.

2-Amino-4,8-diphenyl-3,4-dihydropyrimido[1,2-a][1,3,5] triazin-6-one (**5w**): mp 260-261°C (MeOH-AcOEt); TLC (silica gel, MeOH:CH_2Cl_2, 1:6): R_f 0.43; MS (ESI) m/z = 318.1 (MH^+). ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 6.44 (1H, s, H-7), 6.93 (1H, s, H-4), 7.11 (2H, br s, NH_2), 7.24-7.55 (8H, m, H_{Ar}), 8.00 (2H, dd, J = 7.0 Hz, 3.2 Hz, H-2''and H-6''), 8.36 (1H, br s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 60.0 (C-4), 99.1 (C-7), 125.3, 126.6 (C-7), 128.3 (C-2' and C-6'), 128.5, 128.6, 130.0, 137.1 (C-4'), 140.0 (C-1'), 151.2, 154.5 (br, C-2), 157.5 (C-9a), 161.2 (C-6), 161.8 (C-8). HPLC: purity 100%, t_R 11.0 min (MeOH:H_2O).

2-Amino-4-(4-methoxyphenyl)-8-phenyl-3,4-dihydropyrimido [1,2-a][1,3,5]triazin-6-one (**5y**): mp 249-250°C (MeOH-AcOEt); TLC (silica gel, MeOH:CH_2Cl_2, 1:6): R_f 0.43; MS (ESI) m/z = 348.1 (MH^+); Anal. Calcd. C, 65.69; H, 4.93; N, 20.16; found C, 65.20; H, 4.83; N, 20.09. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 3.72 (3H, s, OMe), 6.41 (1H, s, H-7), 6.87 (1H, d, J = 3.4 Hz, H-4), 6.93 (2H, d, = 8.7 Hz, H-2' and H-6'), 7.07 (2H, br s, NH_2), 7.23 (2H, d, = 8.7 Hz, H-3' and H-5'), 7.51-7.62 (3H, m, H-3'', H-4'' and H-5''), 8.00 (2H, dd, J = 7.0 Hz, 3.2 Hz, H-2''and H-6''), 8.27 (1H, d, J = 3.4 Hz, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 55.1 (OMe), 59.8 (C-4), 99.1 (C-7), 113.9, 126.6, 126.7, 128.3 (C-2' and C-6'), 129.3, 129.9, 132.2, 137.1 (C-4'), 154.5 (br, C-2), 157.5 (C-9a), 159.3 (C-1'), 161.1 (C-6), 161.7 (C-8). HPLC: purity 100%, t_R 16.5 min (MeOH:H_2O).

2-Amino-8-phenyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro pyrimido[1,2-a][1,3,5]triazin-6-one (**5aa**): mp 239-240°C (MeOH-AcOEt); TLC (silica gel, MeOH:CH_2Cl_2, 1:6): R_f 0.55. MS (ESI) m/z = 304.0 (MH^+). ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 6.49 (1H, s, H-7), 7.05 (1H, s, H-4), 7.24 (2H, br s, NH_2), 7.38-7.49 (3H, m, H-3'', H-4'' and H-5''), 7.53 (2H, d, ^3J = 7.9 Hz, H-2' and H-6'), 7.80 (2H, d, ^3J = 7.9 Hz, H-3' and H-5'), 8.04 (2H, dd, J = 7.0 Hz, 3.2 Hz, H-2''and H-6''), 8.46 (1H, s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 59.8 (C-4), 99.2 (C-7), 123.9 (q, ^1J = 271.5 Hz, CF_3), 125.8 (q, ^3J = 3.9 Hz, C-3''and C-5''), 126.3, 126.7, 128.4, 128.9, 129.1 (d, ^2J = 32 Hz, C-4''), 137.0 (C-4'), 144.4 (C-1'), 154.4 (br, C-2), 157.4 (C-9a), 161.2 (C-6), 162.0 (C-8). HPLC: purity 99.4%, t_R 24.0 min (MeOH:H_2O).

General methods for the synthesis of 2,8-disubstituted-4-aryl-3,4-dihydropyrimido[1,2-*a*][1,3,5]triazin-6-ones (5af-5az)

Procedure 1: To a stirred suspension of **4** (1.05-1.20 mmol) in ethanol (5 ml), an appropriate amount of aldehyde (1.26-1.44 mmol) and piperidine (0.48-0.60 mmol) was added. The reaction mixture was heated under reflux. After 2 hours, more amount (up to 0.5 equivalent) of the aldehyde was added to facilitate the completion of reaction. The reaction mixture was refluxed until the TLC showed no spot for the starting material (4-12 h). The reaction mixture was concentrated under vacuum, filtered, and washed with diethyl ether. The product was then recrystallized from appropriate solvent.

Procedure 2: A mixture of guanidine **4** (1.2 mmol), piperidine (0.25 mmol) and appropriate aldehyde (1.5 mmol) in 1.5 mL of absolute ethanol was irradiated in a 10mL vial using a Biotage microwave synthesizer for 20 min at 140°C. After removing solvent under vacuum the crude product was washed with diethyl ether and filtered.

2-(N,N-Dimethylamino)-8-methyl-4-phenyl-3,4-dihydro pyrimido[1,2-a][1,3,5]triazin-6-one (**5af**): mp 290-291°C (MeOH); TLC (silica gel, MeOH:CH_2Cl_2, 1:6): R_f 0.45; MS

(ESI) *m/z* 284.1 (MH^+); Anal. Calcd. C, 63.59; H, 6.05; N, 24.72; found C, 63.48; H, 5.78; N, 24.66. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.07 (3H, s, Me) 3.02 (6H, s, $N(Me)_2$), 5.74 (1H, s, H-7), 6.84 (1H, d, ^3J = 3.4 Hz, H-4), 7.17 (2H, d, ^3J = 6.8 Hz, H-2' and H-6'), 7.43 (3H, m, H-3', H-4' and H-5'), 8.74 (1H, d, ^3J = 3.4 Hz, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 23.7 (Me), 36.6 ($N(Me)_2$), 59.6 (C-4), 102.1 (C-7), 125.1 (C-2' and C-6'), 128.5 (C-4'), 128.6 (C-3'and C-5'), 139.5 (C-1'), 153.5 (C-2), 155.6 (C-9a), 160.4 (C-6), 165.7 (C-8). HPLC: purity 100%, t_R 14.8 min ($MeOH:H_2O$).

2-(N,N-Dimethylamino)-8-methyl-4-(4-methylphenyl)-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5ag**): mp 288-289°C (AcOEt); TLC (silica gel, $MeOH:CH_2Cl_2$, 1:6): R_f 0.49; MS (ESI) *m/z* 298.1 (MH^+); Anal. Calcd. C, 64.63; H, 6.44; N, 23.55; found C, 64.44; H, 6.81; N, 21.35. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.06 (3H, s, 8-Me), 2.26 (3H,s, *p*-Me) 3.01(6H, s, $N(Me)_2$), 5.73 (1H, s, H-7), 6.80 (1H, s, H-4), 7.06 (2H, d, ^3J = 7.9 Hz, H-2' and H-6'), 7.16 (2H, d, ^3J = 7.9 Hz, H-3' and H-5'), 8.68 (1H, s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 20.5 (Me), 23.8 (8-Me), 36.6 ($N(Me)_2$), 59.5 (C-4), 102.1 (C-7), 125.1 (C-2' and C-6'), 129.0 (C-3' and C-5'), 136.6 (C-1'), 137.8 (C-4'), 153.5 (C-2), 155.7 (C-9a), 160.4 (C-6), 165.8 (C-8). HPLC: purity 100%, t_R 16.6 min ($MeOH:H_2O$).

2-(N,N-Dimethylamino)-4-(4-methoxyphenyl)-8-methyl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5ah**): mp 280-281°C (AcOEt-EtOH); TLC (silica gel, $MeOH:CH_2Cl_2$, 1:6): R_f 0.48; MS (ESI) *m/z* 314.0 (MH^+); Anal. Calcd. C, 61.33; H, 6.11; N, 22.35; found C, 61.32; H, 5.65; N, 22.44. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.06 (3H, s, Me), 3.02 (6H, s, $N(Me)_2$), 3.71 (3H, s, OMe), 5.72 (1H, s, H-7), 6.79 (1H, d, ^3J = 3.4 Hz, H-4), 6.90 (2H, d, ^3J = 8.7 Hz, H-3'and H-5'), 7.10 (2H, d, ^3J = 8.7 Hz, H-2'and H-6'), 8.67 (1H, d, ^3J = 3.4 Hz, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 23.7 (Me), 36.6 ($N(Me)_2$), 55.1 (OMe), 59.4 (C-4), 102.1 (C-7), 113.9 (C-3' and C5'), 126.5 (C-2'and C-6'), 131.6 (C-1'), 153.5 (C-2), 155.7 (C-9a), 159.2 (C-4'), 160.4 (C-6), 165.7 (C-8). HPLC: purity 100% t_R 15.0 min ($MeOH:H_2O$); purity 100%, t_R 8.0 min ($CH_3CN:H_2O$).

2-(N,N-Dimethylamino)-4-(4-fluorophenyl)-8-methyl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5ai**): mp 287-288°C (AcOEt:EtOH), TLC (silica gel, $MeOH:CH_2Cl_2$, 1:9): R_f 0.70; MS (ESI) *m/z* 302.1 (MH^+); Anal. Calcd. C, 59.79; H, 5.35; N, 23.24; found C, 59.67; H, 5.29; N, 23.12. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.07 (3H, s, Me), 3.03 (6H s, $N(Me)_2$), 5.74 (1H, s, H-7), 6.83 (1H, s, H-4), 7.11-7.33 (4H, m, H-2', H-3', H-5' and H-6'), 8.72 (1H, br s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 23.1 (Me), 36.0 ($N(Me)_2$), 58.6 (C-4), 101.5 (C-7), 114.8 (d, $^2J_{C-F}$ = 21.8 Hz, C-3' and C-5'), 126.8 (d, $^3J_{C-F}$ = 8.2 Hz, C-2' and C-6'), 135.6 (d, $^4J_{C-F}$ = 3.5 Hz, C-1'), 152.7 (C-2), 154.9 (C-9a), 159.8 (C-6), 162.1 (d, $^1J_{C-F}$ = 245.1 Hz, C-4'), 165.3 (C-8). HPLC: purity 100%, t_R 16.1 min ($MeOH:H_2O$).

4-(4-Chlorophenyl)-2-(N,N-dimethylamino)-8-methyl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5an**): mp 289-290°C (AcOEt:EtOH); TLC (silica gel, $MeOH:CH_2Cl_2$, 1:6): R_f 0.52; MS (ESI) *m/z* 317.9 (MH^+); Anal. Calcd. C, 56.69; H, 5.08; N, 22.04; found C, 56.46; H, 5.19; N, 21.86. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.07 (3H, s, Me), 3.02 (6H, s, $N(Me)_2$), 5.75 (1H, s, H-7), 6.82 (1H, s, H-4), 7.18 (2H, d, ^3J = 8.7 Hz, H-2' and H-6'), 7.44 (2H, d, ^3J = 8.7 Hz, H-3'and H-5'), 8.74 (1H, s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): δ 23.6 (Me), 36.6 ($N(Me)_2$), 59.3 (C-4), 102.1 (C-7), 127.1 (C-2' and C-6'), 128.7 (C-3'and C-5'), 133.1 (C-4'), 138.5 (C-1'), 153.3 (C-2), 155.5 (C-9a), 160.3 (C-6), 165.7 (C-8). HPLC: purity 100%, t_R 19.0 min ($MeOH:H_2O$); purity 100%, t_R 12.8 min ($CH_3CN:H_2O$).

8-Methyl-2-morpholino-4-phenyl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5aq**): mp 272-273°C (EtOH); TLC (silica gel, $MeOH:CH_2Cl_2$, 1:9): R_f 0.48; MS (ESI) *m/z* 326.1 (MH^+); Anal. Calcd. C, 62.75; H, 5.89; N, 21.52; found C, 62.51; H, 5.80; N, 21.35. ^{1}H NMR (300 MHz, Me_2SO-d_6): 2.08 (3H, s, Me), 3.36-3.71 (8H, m, morpholino), 5.79 (1H, s, H-7), 6.87 (1H, br s, H-4), 7.18 (2H, d, *J* = 7.5 Hz, H-2' and H-6'), 7.30-7.40 (3H, m, H-3', H-4' and H-5'), 8.91 (1H, br s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 23.8 (8-Me), 44.5 (C-2'' and C-6''), 59.6 (C-4), 65.6 (C-3'' and C-5''), 102.6 (C-7), 125.1 (C-2' and C-6'), 128.5 (C-4'), 128.6 (C-3' and C-5'), 139.3 (C-1'), 153.5 (C-2), 155.1 (C-9a), 160.4 (C-6), 165.8 (C-8); IR (KBr); ν 3390 br NH, 2980 (CH), 1670 C=O, 1616, 1481, 1388, 1296, 1203, 966. HPLC: purity 98.4%, t_R 15.2 min ($MeOH:H_2O$).

2-Morpholino-4-(methylphenyl)-8-methyl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5ar**): mp 211-212°C (AcOEt:EtOH); TLC (silica gel, MeOH:DCM, 1:9): R_f 0.49; MS (ESI) *m/z* 340.1 (MH^+); Anal. Calcd. C, 63.70; H, 6.24; N, 20.64; found C, 61.88; H, 6.05; N, 19.87. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.07 (3H, s, 8-Me), 2.26 (3H,s, 4'-Me) 3.48-3.69 (8H, m, morpholino), 5.78 (1H, s, H-7), 6.83 (1H, s, H-4), 7.06 (2H, d, ^3J = 7.9 Hz, H-2' and H-6'), 7.16 (2H, d, ^3J = 7.9 Hz, H-3' and H-5'), 8.94 (1H, br s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 20.5 (4'-Me), 23.7 (8-Me), 44.5 (C-3'' and C-5''), 59.7 (C-4), 65.6 (C-2'' and C-6''), 102.6 (C-7), 125.1 (C-2' and C-6'), 129.1 (C-3' and C-5'), 136.5 (C-1'), 137.8 (C-4'), 153.5 (C-2), 155.0 (C-9a), 160.4 (C-6), 165.4 (C-8); IR (KBr); ν 3398 br NH, 2988 (CH), 1672 C=O, 1620, 1418, 1308, 1211, 967. HPLC: purity 99.6%, t_R 17.6 min ($MeOH:H_2O$).

4-(4-Methoxyphenyl)-8-methyl-2-morpholino-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5as**): mp 203-204°C (Ether); TLC (silica gel, MeOH:DCM, 1:9): R_f 0.53; MS (ESI) *m/z* 356.1 (MH^+); Anal. Calcd. C, 60.83; H, 5.96; N, 19.71; found C, 60.26; H, 5.86; N, 19.39. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.07 (3H, s, Me), 3.46-3.67 (8H, m, morpholino), 3.72 (3H, s, OMe), 5.78 (1H, s, H-7), 6.83 (1H, s, H-4), 6.91 (2H, d, ^3J = 8.7 Hz, H-3' and H-5'), 7.12 (2H, d, ^3J = 8.7 Hz, H-2' and H-6'), 8.89 (1H, s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 23.7 (Me) 44.7 (C-3'' and C-5''), 55.1 (OMe), 59.4 (C-4), 65.7 (C-2'' and C-6''), 102.7 (C-7), 113.9 (C-3' and 5'), 126.5 (C-2' and C-6'), 131.4 (C-1'), 153.5 (C-2), 155.1 (C-9a), 159.3 (C-4'), 160.4 (C-6), 165.7 (C-8). HPLC: purity 100%, t_R 15.3 min ($MeOH:H_2O$).

4-(4-Fluorophenyl)-8-methyl-2-morpholin-4-yl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5at**): mp 269-270°C (EtOH); TLC (silica gel, MeOH:DCM, 1:9): R_f 0.51; MS (ESI) *m/z* 344.1 (MH^+); Anal. Calcd. C, 59.47; H, 5.28; N, 20.40; found C, 59.45; H, 5.26; N, 20.15. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.08 (3H, s, 8-Me), 3.49-3.70 (8H, m, morpholino), 5.79 (1H, s, H-7), 6.86 (1H, s, H-4), 7.15-7.30 (4H, m, H-2', H-3',H-5' and H-6'), 8.90 (1H, s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 23.7 (Me), 44.5 (C-3'' and C-5''), 59.2

(C-4), 65.6 (C-2'' and C-6''), 102.7 (C-7), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz, C-3' and C-5'), 127.4 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz, C-2' and C-6'), 135.6 (d, $^{4}J_{C\text{-}F}$ = 2.4 Hz, C-1'), 153.4 (C-2), 155.0 (C-9a), 160.3 (C-6), 161.9 (d, $^{1}J_{C\text{-}F}$ = 245.2, C-4'), 165.9 (C-8). HPLC: purity 94.7%, t_R 16.1 min (MeOH:H_2O).

8-Methyl-2-morpholino-(4-trifluoromethylphenyl)-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5au**): mp 233-234°C (AcOEt); TLC (silica gel, MeOH:DCM, 1:9): R_f 0.52; MS (ESI) *m/z* 394.1 (MH^+); Anal. Calcd. C, 54.96; H, 4.61; N, 17.80; found C, 54.80; H, 4.58; N, 17.73. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.10 (1H, s, Me) 3.48-3.71 (8H, m morpholino), 5.83 (1H, s, H-7), 6.94, (1H, s, H-4), 7.41 (2H, d, ^{3}J = 7.9 Hz, H-2' and H-6'), 7.77 (2H, d, ^{3}J = 7.9 Hz, H-3' and H-5'), 9.02 (1H, br s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 44.7 (C-3'' and C-5''), 60.1 (C-4), 65.6 (C-2'' and C-6''), 102.8 (C-7), 123.9 (q, $^{1}J_{C\text{-}F}$ = 272.1 Hz, *p*-CF_3), 125.8(q, $^{3}J_{C\text{-}F}$ = 3.5 Hz, C-3'and C-5'), 126.2 (C-2' and C-6'), 129.1 (q, $^{2}J_{C\text{-}F}$ = 31.8 Hz, C-4'), 143.9 (C-1'), 153.5 (C-2), 154.8 (C-9a), 160.3 (C-6), 165.9 (C-8). HPLC: purity 100%, t_R 20.3 min (MeOH:H_2O).

4-(8-Methyl-2-morpholino-6-oxo-4,6-dihydro-3H-pyrimido[1,2-a][1,3,5]triazin-4-yl)benzonitrile (**5av**): mp 269-270°C (MeOH); TLC (silica gel, AcOEt:Hexane, 8:2): R_f 0.18; MS (ESI) *m/z* 351.1 (MH^+); Anal. Calcd. C, 61.70; H, 5.18; N, 23.99; found C, 61.60; H, 5.13; N, 23.72. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.09 (3H, s, Me), 3.48-3.69 (8H, m, morpholino), 5.82 (1H, s, H-7), 6.92 (1H, s, H-4), 7.35 (2H, d, ^{3}J = 8.3 Hz, H-2' and H-6'), 7.86 (2H, d, ^{3}J = 8.3 Hz, H-3' and H-5'), 8.99 (1H, s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 23.7 (Me), 44.7 (C-3'' and C-5''), 59.5 (C-4), 65.6 (C-2'' and C-6''), 102.7 (C-7), 111.4 (C-4'), 118.3 (CN), 126.3 (C-2' and C-6'), 132.8 (C-3' and C-5'), 144.5 (C-1'), 153.3 (C-2), 154.9 (C-9a), 160.3 (C-6), 166.1 (C-8). HPLC: purity 100%, t_R 19.1 min (MeOH:H_2O).

8-Methyl-2-morpholino-4-(thiophen-2-yl)-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5ax**): mp 267-268°C (decomposed) (EtOH); TLC (silica gel, MeOH:DCM, 1:9): R_f 0.41; MS (ESI) *m/z* 332.1 (MH^+); Anal. Calcd. C, 54.36; H, 5.17; N, 21.13, S, 9.68; found C, 54.23; H, 5.05; N, 21.09, S, 9.60. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.05 (3H, s, Me), 3.49-3.78 (8H, m, morpholino), 5.79 (1H, s, H-7), 6.89-7.00 (2H, m, H-4, H-4'), 7.06 (1H, m, H-3'), 7.45 (1H, dd, *J* = 4.9 Hz, *J* = 1.1 Hz, H-5'), 8.97 (1H, s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 23.6 (Me), 44.6 (C-3'' and C-5''), 56.9 (C-4), 65.7 (C-2'' and C-6''), 102.8 (C-7), 125.1, 126.3, 126.7, 142.8 (C-2'), 152.7 (C-2), 154.9 (C-9a), 160.0 (C-6), 165.8 (C-8); IR (KBr); ν 3400 br NH, 3097, 2991 (CH), 1674 C=O, 1620, 1530, 1477, 881, 760. HPLC: purity 99.4%, t_R 14.1 min (MeOH:H_2O).

4-(4-Bromophenyl)-8-methyl-2-morpholino-3,4-dihydro-pyrimido[1,2-a][1,3,5]triazin-6-one (**5az**): mp 245-246°C (MeOH); TLC (silica gel, MeOH:DCM, 1:9): R_f 0.60; MS (ESI) *m/z* 404.1, 406.1 (MH^+); Anal. Calcd. C, 50.51; H, 4.49; N, 17.32; found C, 50.50; H, 4.27; N, 17.32. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.08 (3H, s, Me), 3.60 (8H, s, morpholino), 5.80 (1H,s, H-7), 6.83 (1H, s, H-4), 7.12 (2H, d, ^{3}J = 8.7 Hz, H-2' and H-6'), 7.58 (2H, d, ^{3}J = 8.3 Hz, H-3' and H-5'), 8.92 (1H, s, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 23.8 (Me), 44.5 (C-3'' and C-5''), 59.3 (C-4), 65.6 (C-2'' and C-6''), 102.6 (C-7), 121.7 (C-4'), 127.4 (C-2' and C-6'), 131.6 (C-3' and C-5'), 138.7 (C-1'), 153.4 (C-2), 154.9 (C-9a), 160.3 (C-6), 165.9 (C-8). HPLC: purity 100%, t_R 19.9 min (MeOH:H_2O).

General methods for the synthesis of 4-substituted 2-morpholino-8-trifluoromethyl-3,4-dihydro-pyrimido[1,2-*a*] [1,3,5] triazin-6-ones (5ba-5bn)

Procedure 1: The solution of *N*-(6-oxo-4-trifluoromethyl-1,6-dihydro-pyrimidin-2-yl)-morpholine-4-carboxamidine **4** (0.50 g, 1.7 mmol), aldehydes (2.0 mmol) and piperidine (0.05 ml, 0.5 mmol) in ethanol (10 ml) was heated under reflux for 12-18 h. During halfway through the reaction period, additional aldehyde (up to 0.25 mmol) was added. After completion of the reaction as observed by TLC, the precipitate obtained after cooling was filtered, washed with diethyl ether, dried and recrystallized from suitable solvents.

Procedure 2: A mixture of guanidine **4** (1.2 mmol), piperidine (0.25 mmol) and appropriate aldehyde (1.5 mmol) in 1.5 mL of absolute ethanol was irradiated in a 10 mL vial at 150°C for 20 min using a Biotage microwave synthesizer. After removing solvent under vacuum the crude product was washed with diethyl ether and filtered.

2-Morpholino-4-phenyl-8-trifluoromethyl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5ba**): mp 269-270°C (AcOEt); MS (APCI) *m/z*: 380.1 (MH^+); Anal. Calcd. for $C_{18}H_{18}F_3N_5O_2$: C, 53.83; H, 4.25; N, 18.46; found: C, 53.99; H, 3.90; N, 18.46. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 3.54-3.69 (8H, m, morpholino) 6.33 (1H, s, H-7), 6.91 (1H, br s, H-4), 7.22 (2H, d, *J* = 7.5 Hz, H-2' and H-6'), 7.35-7.43 (3H, m, H-3', H-4' and H-5'), 9.16 (1H, br s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 44.7 (C-2'' and C-6''), 60.3 (C-4), 65.6 (C-3'' and C-5''), 101.5 (q, $^{3}J_{C\text{-}F}$ = 3.5 Hz, C-7), 120.8 (q, $^{1}J_{C\text{-}F}$ = 275.4 Hz, CF_3), 125.1 (C-3' and C-5'),128.9 (C-2' and C-6'), 138.6 (C-1'), 153.4 (q, $^{2}J_{C\text{-}F}$ = 33.7 Hz, C-8), 155.0, 155.3, 160.2 (C-6); IR (KBr); ν 3385 NH, 3014, 1675 C=O, 1499, 1307. HPLC: purity 100%, t_R 11.9 min (MeOH:H_2O).

2-Morpholino-4-(4-methylphenyl)-8-trifluoromethyl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5bb**): mp 251-252°C (Diethyl ether); Anal. Calcd. for $C_{18}H_{18}F_3N_5O_2$: C, 54.96; H, 4.61; N, 17.80. Found: C, 54.86; H, 4.17; N, 17.81. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 2.27 (1H, s, Me), 3.51-3.69 (8H, m, morpholino), 6.31 (1H, s, H-7), 6.87 (1H, s, H-4), 7.09 (2H, d, *J* = 7.5 Hz, H-3' and H-5'), 7.19 (2H, d, *J* = 7.5 Hz, H-2' and H-6'), 9.12 (1H, s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 44.6 (C-2'' and C-6''), 60.2 (C-4), 65.6 (C-3'' and C-5''), 101.4 (q, $^{3}J_{C\text{-}F}$ = 2.5 Hz, C-7), 120.8 (q, $^{1}J_{C\text{-}F}$ = 275.2 Hz, CF_3), 125.0 (C-3' and C-5'),129.3 (C-2' and C-6'), 135.7 (C-1'), 138.3 (C-4'), 153.3 (q, $^{2}J_{C\text{-}F}$ = 33.0 Hz, C-8), 155.0, 155.3, 160.2 (C-6) ; IR (KBr); ν 3411 br NH, 2981 (CH), 2924, 2868, 1693 C=O, 1600, 1579, 1447, 1363, 1276, 906, 840, 790. HPLC: purity 100%, t_R 13.7 min (MeOH:H_2O).

4-(4-Fluorophenyl)-2-morpholino-8-trifluoromethyl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5bd**): mp 270-271°C (AcOEt:diethylether); Anal. Calcd. for $C_{17}H_{15}F_4N_5O_2$: C, 51.39; H, 3.81; N, 17.63; found: C, 51.34; H, 3.41; N, 17.65. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 3.54-3.74 (8H, m, morpholino), 6.33 (1H, s, H-7), 6.90 (1H, d, *J* = 4.9 Hz, H-4), 7.20-7.30 (4H, m, H2', H6', H3' and H5'), 9.15 (1H, d, *J* = 4.9 Hz, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 44.6 (C-2'' and C-6''), 59.8 (C-4), 65.5 (C-3'' and C-5''), 101.4 (q, $^{3}J_{C\text{-}F}$ = 2.4 Hz, C-7), 115.7 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz, C-3' and C-5'), 120.8 (q, $^{1}J_{C\text{-}F}$ = 278.1 Hz, CF_3), 127.4 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz, C-2' and C-6'), 134.8 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz, C-1'), 153.3 (q, $^{2}J_{C\text{-}F}$ = 33.3 Hz, C-8), 154.8, 155.1, 160.2 (C-6), 162.0 (d, $^1J_{C-F}$ = 245.2 Hz, C-4'). HPLC: purity 100%, t_R 12.6 min (MeOH:H_2O).

2-Morpholino-8-trifluoromethyl-4-(4-trifluoromethylphenyl)-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5be**): mp 288-289°C (AcOEt); Anal. Calcd. for $C_{18}H_{15}F_6N_5O_2$: C, 48.33; H, 3.38; N, 15.66. Found: C, 48.57; H, 3.14; N, 15.79. ^{1}H NMR (300 MHz, Me_2SO-d_6): 3.52-3.75 (8H, m, morpholino), 6.36 (1H, s, H-7), 6.99 (2H, d, J = 4.2 Hz, H-4), 7.45 (2H, d, J = 8.3 Hz, H-3' and H-5'), 7.80 (2H, d, J = 8.3 Hz, H-2' and H-6'), 9.23 (d, J = 4.2 Hz, NH).^{13}C NMR (75 MHz, Me_2SO-d_6): 44.7 (C-2'' and C-6''), 60.1 (C-4), 65.6 (C-3'' and C-5''), 101.6 (q, $^3J_{C-F}$ = 2.4 Hz, C-7), 120.8 (q, $^1J_{C-F}$ = 275.8 Hz, 8-CF_3), 123.8 (q,$^1J_{C-F}$ = 272.3 Hz, 4'-CF_3), 126.0 (q, $^3J_{C-F}$ = 3.3 Hz, C-3' and C-5'), 126.2 (C-2' and C-6'), 129.4 (q, $^2J_{C-F}$ = 31.8 Hz, C-4'), 143.0 (C-1'), 153.5 (q, $^2J_{C-F}$ = 33.7 Hz, C-8), 154.9, 155.2, 160.3 (C-6); IR (KBr); ν 3396 br NH, 2982 (CH), 1693 C=O, 1604, 1581, 1417, 1336, 1278. HPLC: purity 98.3%, t_R 20.4 min (MeOH:H_2O); purity 100%, t_R 7.4 min (CH_3CN:H_2O).

2-Morpholino-4-(4-nitrophenyl)-8-trifluoromethyl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5bg**): mp 294-295°C (AcOEt); TLC (silica gel, AeOEt:Hexane, 8:2): R_f 0.3. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 3.64-3.70 (8H, m, morpholino), 6.37 (1H,s, H-7), 7.02 (1H, d, ^3J = 4.5 Hz, H-4), 7.51 (2H, d, ^3J =8.7 Hz, H-2' and H-6'), 8.27 (2H, d, ^3J =8.7 Hz, H-3' and H-5'), 9.25 (1H, d, ^3J = 4.5 Hz, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 44.7 (C-3'' and C-5''), 60.0 (C-4), 65.6 (C-2'' and C-6''), 101.7 (q, $^3J_{C-F}$ = 2.9 Hz, C-7), 120.8 (q, $^1J_{C-F}$ =275.8 Hz, CF_3), 124.2 (C-2' and C-6'), 126.8 (C-3' and C-5'), 145.4 (C-1'), 147.7 (C-4'), 153.5 (q, $^2J_{C-F}$ =33.5 Hz, C-8), 154.8, 155.2, 160.3 (C-6).

2-Morpholino-4-(pyridin-2-yl)-8-(trifluoromethyl)-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5bh**): mp 260-261°C (CH_2Cl_2); MS (APCI) *m/z*: 381.5 (MH^+); Anal. Calcd. for $C_{16}H_{15}F_3N_6O_2$: C, 50.53; H, 3.98; N, 22.10; found: C, 50.29; H, 3.83; N, 21.93. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 3.50-3.71 (8H, m, morpholino), 6.27 (1H, s, H-7), 6.88 (1H, d, J = 4.5 Hz, H-4), 7.34-7.46 (2H, m, H-4' and H-5'), 7.88 (1H, dt, J = 7.9 Hz, 1.5 Hz, H-4'), 8.50 (1H, d, J = 4.5 Hz, H-3'), 9.08 (1H, d, J = 4.9 Hz, NH). ^{13}C NMR (75 MHz, Me_2SO-d_6): 44.7 (C-2'' and C-6''), 61.4 (C-4), 65.6 (C-3'' and C-5''), 101.3 (q, $^4J_{C-F}$ = 1.7 Hz, C-7), 120.8, 120.9 (q, $^1J_{C-F}$ = 275.1 Hz, CF_3), 124.1, 137.5, 149.2 (C-1'), 153.3 (q, $^2J_{C-F}$ = 33.2 Hz, C-8), 155.1 (C-2), 155.6 (C-2'), 156.1 (C-9a), 160.4 (C-6); IR (KBr); ν 3357 NH, 3068, 2970, 2845, 1656 C=O, 1208, 1070, 908. HPLC: purity 99.2%, t_R 6.2 min (CH_3CN:H_2O).

4-(2-Morpholino-6-oxo-8-trifluoromethyl-4,6-dihydro-3H-pyrimido[1,2-a][1,3,5]triazin-4-yl)benzonitrile (**5bj**): mp 269-270°C (AcOEt); Anal. Calcd. for $C_{18}H_{15}F_3N_6O_2$: C, 53.47; H, 3.74; N, 20.78. Found: C, 53.59; H, 3.91; N, 20.89. ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 3.54-3.73 (8H, m, morpholino), 6.36 (1H, s, H-7), 6.97 (1H, s, H-4), 7.41 (2H, d, J = 8.3 Hz, H-3' and H-5'), 7.89 (2H, d, J = 8.3 Hz, H-2' and H-6'), 9.23 (1H, br s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 44.7 (C-2'' and C-6''), 60.1 (C-4), 65.6 (C-3'' and C-5''), 101.6 (q, $^4J_{C-F}$ = 2.4 Hz, C-7), 111.8 (C-4'), 118.2 (CN), 120.8 (q,$^1J_{C-F}$ = 275.6 Hz, CF_3), 126.3 (C-2' and C-6'), 133.0 (C-3' and C-5'), 143.6 (C-1'), 153.5 (q, $^2J_{C-F}$ = 33.5 Hz, C-8), 154.8, 155.1, 160.3 (C-6). HPLC: purity 98.9%, t_R 12.2 min (MeOH:H_2O).

8-Methyl-2-pyrrolidino-4-(4-methylphenyl)-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5bk**): mp 202-203°C (AcOEt+EtOH); Anal. Calcd. for $C_{18}H_{21}N_5O$: C, 66.85; H, 6.55; N, 21.66. Found: C, 66.76; H, 6.71; N, 21.59. ^{1}H NMR (300 MHz, Me_2SO-d_6): 1.86 (8H, br s, pyrrolidino), 2.05 (3H,s, 8-Me), 2.26 (3H, s, 4'-Me), 5.70 (1H, s, H-7), 6.79 (1H, d, J = 3.4 Hz, H-4), 7.08 (2H, d, J = 8.3 Hz, H-3' and H-5'), 7.15 (2H, d, J = 8.3 Hz, H-2' and H-6'), 8.59 (1H, d, J = 3.7 Hz, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 20.5 (4'-Me), 23.8 (8-Me), 59.6 (C-4), 101.9 (C-7), 125.2 (C-2' and C-6'), 129.1 (C-3' and C-5'), 136.9 (C-1'), 137.7 (C-4'), 153.6 (C-9a), 160.5 (C-6), 165.7 (C-8).

8-Methyl-2-(4-methylpiperazino)-4-(4-methylphenyl)-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5bl**): mp 208-209°C (AcOEt); Anal. Calcd. for $C_{19}H_{24}N_6O$: C, 64.75; H, 6.86; N, 23.85. Found: C, 64.90; H, 6.92; N, 23.95. ^{1}H NMR (300 MHz, Me_2SO-d_6): 2.07 (3H,s, 8-Me), 2.18 (3H,s, N-Me), 2.26 (3H, s, 4'-Me), 2.27-2.39 (4H, m, $(CH_2)_2N$-CH_3), 3.46-3.67 (4H, m, $(CH_2)_2N$), 5.76 (1H, s, H-7), 6.80 (1H, s, H-4), 7.05 (2H, d, J = 8.0 Hz, H-3' and H-5'), 7.18 (2H, d, J = 7.9 Hz, H-2' and H-6'), 8.85 (1H, br s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 20.5 (4'-Me), 23.7 (8-Me), 44.0 (C-2'' and C-6''), 45.4 (NCH_3), 54.0 (C-3'' and C-5''), 59.5 (C-4), 102.5 (C-7), 125.0 (C-2' and C-6'), 129.1 (C-3' and C-5'), 136.5 (C-1'), 137.8 (C-4'), 153.5 (C-9a), 154.7 (C-2), 160.4 (C-6), 165.7 (C-8).

2-(3-Chlorophenylamino)-8-methyl-4-(4-methylphenyl)-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5bm**): mp 259-260°C Anal. Calcd. for $C_{20}H_{18}N_5OCl$: C, 63.24; H, 4.78; N, 18.44. Found: 63.31; H, 4.86; N 18.55. ^{1}H NMR (300 MHz, Me_2SO-d_6): 2.13 (3H, s, 8-Me), 2.26 (3H, s, 4'-Me), 5.87 (1H, s, H-7), 6.92 (1H, s, H-4), 7.03-7.22 (5H, m, H-3', H-5', H-2', H-6' and H-4''), 7.30-7.42 (2H, m, H-5'' and H-6''), 7.81 (1H, s, H-2''), 8.38 (1H, br s, NH), 9.70 (1H, br s, NH).

2-(3-Chlorophenylamino)-4-(5-(hydroxymethyl)furan-2-yl)-8-methyl-3,4-dihydropyrimido[1,2-a][1,3,5]triazin-6-one (**5bn**): mp 237-238°C; Anal. Calcd. for $C_{18}H_{16}N_5O_3Cl$: C, 56.04; H, 4.18; N, 18.15. Found: C, 56.44; H, 4.50; N, 18.01. ^{1}H NMR (300 MHz, Me_2SO-d_6): 2.12 (3H, s, 8-Me), 4.32 (2H, d, J = 5.6 Hz, CH_2), 5.22 (1H, t, J = 5.3 Hz, OH), 5.85 (1H, s, H-7), 6.11-6.28 (2H, m, H-3' and 4'), 6.93 (1H, s, H-4), 7.13 (1H, d, J =7.2 Hz, H-4''), 7.35 (1H, t, J =8.1 Hz, H-5''), 7.43 (1H, d, J = 7.9 Hz, H-6''), 7.79 (1H, s, H-2''), 8.53 (1H, s, NH), 9.82 (1H, s, NH); ^{13}C NMR (75 MHz, Me_2SO-d_6): 21.0, 23.2, 55.5 (CH_2), 64.8 (C-4), 104.1, 107.7, 108.1, 130.3, 133.0, 140.2, 150.3, 152.5 (C-9a), 155.8 (C-2), 159.4 (C-6), 165.7 (C-8).

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Notes and references

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