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Microwave-assisted selective and efficient synthesis of 1,3,5-triazinyl mono and bisureas

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ABSTRACT

An efficient and sustainable microwave-assisted approach for the one-step preparation of a wide range of 1,3,5-triazinyl mono- and bisureas has been developed, combining solvent-free conditions and microwave irradiation. In these conditions the very unreactive amino groups of 1,3,5-triazine-2,4-diamines successfully react with phenylisocyanate to yield selectively mono and bisureas.

This protocol resulted in the shortest reaction times reported so far and is generally applicable for the preparation of these valuable heterocyclic systems.

1. Introduction

Most biologically active natural products and synthetic compounds contain heterocyclic moieties in their structures.[1] They are known for their numerous pharmaceutical and medicinal applications and therefore, novel methods to synthesize such compounds are of major importance in the field of synthetic organic chemistry. Substituted 1,3,5-triazines are one of the most important and well known heterocycles with applications in several scientific fields, e.g., they are one of the classical heterocyclic compounds used in chemotherapy,[2] they are widely used in supramolecular chemistry because this remarkable heterocycle can be involved in all supramolecular interactions, coordination bonds, hydrogen bonding, electrostatic and charge-transfer attractions, and aromatic-stacking interactions.[3] Moreover, substituted triazines are well known for their excellent optoelectronic properties,[4] and they are used in supramolecular electronics.

The combination of urea moieties with hydrogen bonding donors[5] and a conjugated triazine core results in interesting building blocks with intriguing properties in crystal engineering and supramolecular polymers.[6] In addition, *N*,*N*′-disubstituted ureas have been used to synthesize crystalline solids with different architectures, ranging from one-dimensional chains and nanotubes, to two-dimensional sheets and three-dimensional frameworks.[7] Lastly, difunctional triazinyl mono- and bisureas possess very interesting self-assembly properties, which allows them to hierarchically arrange into supramolecular nanostructures as a result of non-covalent interactions in aqueous[8] or hydrophobic environments.[9] These unique properties have resulted in applications such as ambipolar thin film devices[10] and polyurea networks with 2D porous structures.[11]

Despite the importance and numerous applications of triazinylureas, synthetic methods for their preparation are limited. Previous synthetic strategies usually involve the alcoholysis of cyanoamino-*s*-triazines in the presence of hydrogen chloride.[12]

Since isocyanates are known to react with amides, the reaction between isocyanates and triazinylamines has been proposed as one of the main approaches for the synthesis of 1,3,5-triazinyl ureas. However, triazine amino groups are very unreactive since chemically act as amidines rather than amines and phenylisocyanate is also a low reactive isocyanate.

Described procedures are based on processes, which use hazardous solvents and harsh reaction conditions[13] and include the use or large excesses of more reactive alkyl isocyanates (up to 10-folds), reflux in solvents like pyridine and DMSO for large periods of time[14,15] and purification by column chromatography.[13,15,16] In

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many examples these reactions were applied to more reactive aminopyrimidines.

Other alternatives include the use of sodium hydride in THF,[17] or preparation in two steps by reaction of aminotriazines with phosgene or ethylchloroformiate and subsequent reaction with amines.[18]

Our research group has studied the reaction between amino *s*-triazines and different substrates like haloacetic acids, hydrazines, and aldehydes, resulting in unsuccessful reactions;[19] showing, in this sense, the poor nucleophilic character of the amino group coupled to the triazine ring.

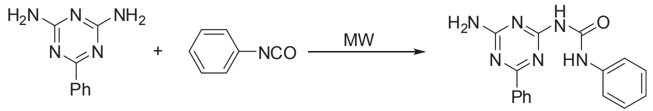
Currently, new research avenues are focused on the development of sustainable synthetic routes[20] with short reaction times,[21] easy and fast purification, and atom economy. To this end, the application of non-conventional heating methods,[22] such as microwave irradiation,[23,24] or solvent-free processes,[25] can lead to a plethora of promising heterocyclic compounds and solve the problems of very unreactive compounds.[26]

As part of our on-going research toward the design of new heterocycles we describe a new way of synthesis, which makes possible to obtain *s*-triazinyl mono and bisureas, highlighting the environmentally benign and sustainable nature of the solvent-free (in most of the cases), microwave-assisted heterogeneous method and emphasizing the formation of self-complementary quadruple hydrogen-bonded arrays of the molecules obtained.

2. Results and discussion

Optimization of the synthetic protocol for the preparation of *s*-triazinyl mono and bisureas was performed by reacting 6-phenyl-1,3,5-triazine-2,4-diamine (**1a**) and phenylisocyanate (**2**) in solvent-free conditions under microwave irradiation and using different irradiation powers and temperatures (Table 1). The optimal **1a**/**2** ratio was found to be 1:2.1, reducing the excess of the isocyanate from 9, as previously described,[13] to 1.1 equiv. Interestingly, these conditions did not promote the formation of the bisurea **4a**, even using an excess of phenylisocyanate. Reducing the amount of **2** produced an incomplete reaction and traces of triazine **1a** were detected in the reaction crude (Table 1, entry 4). Only 30 min of reaction in solvent-free conditions were needed to obtain **3a** in 44% yield (Table 1, entry 1) but the yield did not improve upon further irradiation (Table 1, entry 3).

Table 1
Synthesis of [1,3,5]-triazinylmonourea (**3a**)



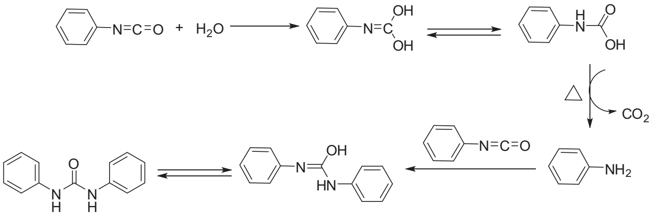
1a **2** **3a**

Entry[a]	Solvent[b]	P (W)	t (min)	T (°C)	Yield[c] (%)
1	—	25	30	105	44
2	—	CH	30	105	**3a**/**1a** 63:37[d]
3	—	25	60	105	45
4[e]	—	25	30	105	Traces of **1a**
5	DMSO	25	30	105	Complex mixture
6	Toluene	25	15	100	68
7	Toluene	CH	15	100	**3a**/**1a** 68:32[d]

[a] Phenylisocyanate (2.1 equiv).
[b] Solvent, 1 mL/mmol of **2**.
[c] Isolated yields.
[d] Not isolated. Ratio **1**/**3**, determined by ^{1}H NMR.
[e] Phenylisocyanate (1 equiv).

Formation of slurry in solvent-free conditions was thought to limit conversion. Therefore, we added small aliquots of solvent to homogenize the reaction. Addition of 1 mL of DMSO led to the formation of a complex mixture of products, and monourea **3a** was obtained in low yield (Table 1, entry 5). The rapid heating inherent to this highly polar solvent justifies this result. In contrast, the use of toluene (1 mL/mmol of **2**) enables a better control over the reaction temperature and resulted in a 68% yield of **3a** in only 15 min (Table 1, entry 7). In a non-polar solvent, microwaves are directly absorbed by the substrates and the solvent homogenize the temperature. In consequence, in these conditions the advantages of microwave irradiation are more pronounced.[27]

Anhydrous solvents were required to prevent the formation of 1,2-diphenylurea that cannot be separated from the reaction product. Formation of this side product can be explained by the sequence of reactions shown in Scheme 1. Addition of water to phenylisocyanate produces phenylcarbamic acid, which releases carbon dioxide to produce aniline. Addition to phenylisocyanate yields 1,2-diphenylurea. It should remarked that under conventional heating in comparable conditions did not produce the complete conversion of the starting material and gave low yields of the desired monoureas (Table 1, entries 2 and 7).



Scheme 1. Reactions leading to the formation of phenylurea in the presence of water.

Triazinyl urea **3a** was characterized by NMR techniques. The NH moieties of the urea group were differentiated by 1D-NOESY experiments, finding that Ph–NH-3 is deshielded with regard to triazine-NH-1. This deshielding must be a consequence of the formation of an intramolecular hydrogen bond with a nitrogen atom of the triazine ring (Fig. 1a). The NH_2 group shows two signals at δ=7.74 and 7.85. This effect has been shown in related triazinediamines and is due to a restricted rotation of the aminotriazine bond.[28] Variable temperature experiments did not produce the coalescence of the NH groups. In consequence thermodynamic parameters of the rotation process were determined by 2D-EXSY experiments at 298 K, temperature of a slow process, in DMSO.

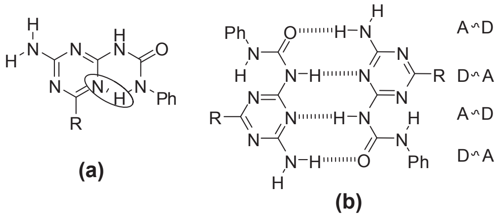


Fig. 1. (a) Intramolecular hydrogen bond of the triazine ring. (b) Dimers stabilized by quadruple hydrogen bonds.

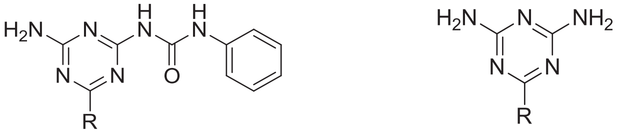
Rate constants can be deduced from the spectra according to the following equation:

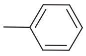
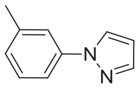
$$R = -\ln A/\tau_m = -X(\ln \Lambda)X^{-1}/\tau_m$$

where $A_{ij}=I_{ij}/M_j$, τ_m is the mixing time. $I_{ij}(\tau_m)/M_j$ and X are the square matrix of eigenvectors of A_i such that $X^{-1}AX=\Lambda=\text{diag}\ (\lambda_i)$, with λ_i the ith eigenvalue of A. I_{ij} can be deduced by measuring the volume of each peak intensity directly from the spectrum. M_j is the volume of the diagonal peak of the spectrum registered with a mixing time close to 0 and without any chemical exchange.

Free energies of activation were calculated from the rate constants according to Sandström[29] showing a value of 76.67 kJ mol^{-1} for monourea **3a** (Table 2 and Fig. 2). This value is much higher than the observed for previously described triazinediamines[28] and is in agreement with the proposed aggregation of triazinylureas **3** into dimers strongly stabilized by quadruple hydrogen bonds (Fig. 1b).[30]

Table 2
Coalescence temperatures and calculated activation free energies ($\Delta G^{\ddagger}$) for compounds **3a** and **3i** and comparison with literature results



R	Temp. EXSY (K)	$\Delta G^{\ddagger}$ (kJ mol^{-1})	Coalescence temp (K)	$\Delta G^{\ddagger}$ (kJ mol^{-1})[28]
 **a**	298	76.67	284	60.71
 **i**	298	76.46	287	60.26

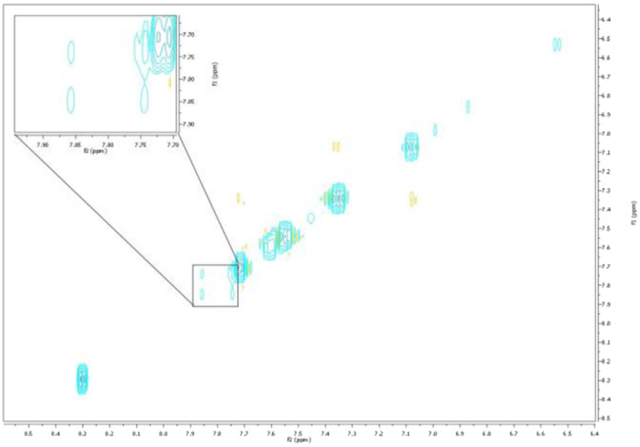
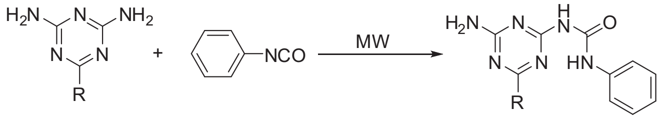


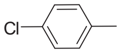
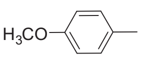
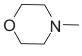
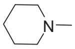
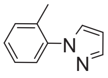
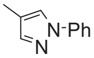
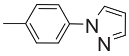
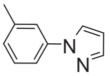
Fig. 2. 2D-EXSY spectrum of compound **3a** at 298 K in DMSO.

The optimized reaction conditions were used to synthesize various triazinylmonoureas starting from a wide variety of 6-substituted-1,3,5-triazine-2,4-diamines. Compound **3b**, containing a chlorine atom in *para* position, was also obtained under solvent-free conditions in 76% yield (Table 3, entry 1). Similar results were observed for compound **3f**, which was obtained in 65% yield (Table 1, entry 6). However, in the case of **3c**, formation of triazinylbisurea **4c** was observed (Table 1, entry 2). This result can be rationalized by the strong electron donating effect of the *p*-OCH_3 group, which could favor the formation of **4c**. Again, the use of a small amount of toluene allows controlling the reaction temperature, allowing the isolation of **3c** in 80% yield (Table 1, entry 3). Similarly with compounds **3g**, **3h**, and **3i** addition of a small amount of solvent (1,4-dioxane) gave the best results (Table 1, entries 7–9).

Table 3
Synthesis of [1,3,5]-triazinylmonoureas (**3**)



1a-i **2** **3a-i**

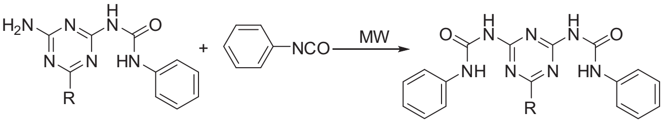
Entry[a]	Compd	Solvent[b]	P (W)	t (min)	T (°C)	Yield (%)[c]
1	 **3b**	—	25	30	110	76
2	 **3c**	—	25	45	115	88:12[f]
3		Toluene	25	45	100	80
4	 **3d**	—	25	50	115	85
5	 **3e**	—	25	35	116	98
6	 **3f**	—	25	45	111	65
7	 **3g**	1,4-Dioxane	25	60	110	54
8	 **3h**	1,4-Dioxane	25	35	100	70
9	 **3i**	1,4-Dioxane	25	30	113	98

[a] Phenylisocyanate (2.1 equiv).
[b] Solvent, 1 mL/mmol of **2**.
[c] Isolated yields.
[f] Ratio **3c**/**4c**, determined by ^1H NMR.

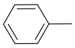
It was experimentally observed that when the R group is an aliphatic heterocycle (Table 3, entries 4 and 5), the respective monoureas **3d** and **3e** were obtained under solvent-free conditions in very good yields.

Synthesis of bisureas was performed by reaction of monoureas **3a**–**i** and phenylisocyanate **2**. Table 4 contains the reaction conditions used for the synthesis of the new triazinylbisureas.

Table 4
Synthesis of [1,3,5]-triazinylbisureas (**4**)

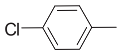
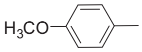
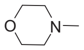
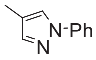
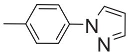
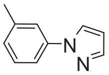


3a-i **2** **4a-i**

Entry[a]	Compd	Solvent[b]	P (W)	t (min)	T (°C)	Yield[c] (%)
1	 **4a**	—	50	45	152	47:53[d]
2		—	80	60	172	68
3		Ph_2O	80	60	202	62:38[d]

(*continued on next page*)

Table 4 (*continued*)

Entry[a]	Compd	Solvent[b]	*P* (W)	*t* (min)	*T* (°C)	Yield[c] (%)
4	 **4b**	—	80	60	152	42
5		Ph$_2$O	120	60	203	24
6	 **4c**	—	80	60	162	83
7		Bu$_2$O	80	60	140	93:3[d]
8	 **4d**	—	80	60	161	98
9		Bu$_2$O	60	60	142	75:25[d]
10	 **4g**	Ph$_2$O	80	60	162	58
11	 **4h**	—	80	60	152	55:45[d]
12		Ph$_2$O	150	60	210	27:73[d]
13	 **4i**	—	80	60	160	89:11[d]
14		[d]	150	60	204	79:21[d]

[a] Phenylisocyanate (4 equiv).

[b] Solvent 1 mL/mmol of **2**.

[c] Isolated yields.

[d] Ratio of **3**/**4** determined by ^{1}H NMR.

The DADA array (D=donor and A=acceptor) leads to very strong dimers in the solid state and in solution,[30] to the extent of inhibiting the reaction of the free amine with phenylisocyanate. Higher temperatures aid in breaking these interactions and favor the formation of bisurea **4**. In this way, it was necessary to increase the reaction temperature to obtain these new compounds (Table 4, entry 1 vs 2).

It is well known that heating heterogeneous reaction mixtures with microwave irradiation may provoke the preferential absorption of electromagnetic energy by one of the components, resulting in considerable local temperature differences, improving the outcome of reactions.[31,32] In these reports, the locally increased temperatures enhance solubility of the solid reagents, resulting in higher reaction rates. Our results are in agreement with these findings since we actually observed in many derivatives our best results when no solvent was used (Table 4, 2–9).

It is known that the high stability of bisurea dimers is caused by intermolecular hydrogen bonds between urea moieties. The geometrical arrangement of the hydrogen-bonding donors and acceptors is crucial to the stability of this dimer.[33,34] In agreement with this, it was found that the strong intermolecular hydrogen bonds in (pyrazol-1-yl)phenyl derivatives **3h**,**i** made the solvent-free reaction even more difficult, and mixtures of mono and bisurea derivatives were found. Considering this fact and in order to homogenize the mixture of reagents prompted us to the use of a high boiling point solvent. In this way higher yield and conversions were obtained using diphenylether (Table 4, entries 11 vs 12 and 14 vs 11 and 13) due to higher reaction temperatures. When the pyrazole ring is directly bonded to the triazine ring it was possible to obtain derivative **4g** pure in 58% yield using diphenylether (Table 4, entry 10).

This new protocol is one of the fastest and greenest described so far since yields of similar 2,4-substituted-*s*-triazines synthesized using classical heating have been reported to be only 16% after 16 h of reflux in toxic solvents like pyridine and using 10 fold excess of a more reactive alkyl isocyanate to give exclusively monoureas.[13] Following this method, derivatives **4a**–**i** could be obtained (Table 4) with considerably reduced both reaction time and excess of isocyanate.

3. Conclusions

We have demonstrated that microwave irradiation results in fast, efficient, and green synthesis of triazine derivatives, which offers numerous advantages for the versatile synthesis of many interesting supramolecular building blocks. Reaction time and excess of isocyanate were significantly reduced, solvents were eliminated or reduced to a minimum, and products were obtained with simple purification procedures, just washing with a solvent (diethyl ether or ethanol). The most remarkable achievement is that non-reactive amino groups joined to the triazine ring are able to react with phenylisocyanate. This is in agreement with the Loupy's postulate that remarks that ‘the beneficial effect of microwave irradiation is especially evident with the most unreactive compounds’.[35] Similarly we have determined computationally that reactions with activation energies of 20–30 kcal mol^{-1} are expected to be improved under microwave irradiation by thermal effects.[36] The new synthesized molecules possess interesting structures with potential applications in supramolecular chemistry. We are currently studying the properties of the synthesized products in metal complexation, crystal engineering, and molecular recognition relying on sustainable methods.

4. Experimental section

4.1. General

All reagents and anhydrous solvents were purchased from commercial sources and used without further purification. To maintain the anhydrous conditions during the reaction time a desiccant was coupled between the argon line and the reaction flask. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

NMR spectra were recorded on a Varian Unity 500 spectrometer with TMF as the internal standard. The 2D exchange spectra (EXSY) were acquired in the phase-sensitive mode using the States–Haberkorn method.[37] Typically, a 3.1 kHz spectral width, 16 transients of 2048 data points were collected for each 400 *t*1 increments. A 1-s relaxation delay, an 11-s (908) pulse width, and a 0.165-s acquisition time were used. The free induction decays were processed with square cosine-bell filters in both dimensions and zero filling was applied prior to double Fourier transition. Determination of the kinetic parameters required two experiments with mixing times of 1 s (optimized) for the exchange experiment and 0.02 s for the non-exchange spectra, respectively. The cross peak/diagonal ratio was determined by integrating the volume under the peaks.

IR spectra were obtained with Nicolet-550 FTIR and Thermo Nicolet-IR-100 spectrophotometers. The mass spectra were recorded on a VG AutoSpec (Waters) apparatus using electron impact (EI) or fast atom bombardment (FAB). Reactions under microwave irradiation were performed in a CEM Discover monomode reactor. Temperature was measured with the IR pyrometer included in the microwave reactor.

4.2. Synthesis of [1,3,5]-triazinylmonoureas

The corresponding [1,3,5]-triazinylmonourea (**1a**–**i**) and phenylisocyanate (**2**) were mixed in 1:2.1 ratio and irradiated under microwave under argon in solvent-free conditions or with the appropriate solvent at the time, temperature, and power indicated in Table 1.

*4.2.1. 1-(4-Amino-6-phenyl-[1,3,5]-triazin-2-yl)-3-phenylurea (**3a**).* 6-Phenyl-[1,3,5]-triazine-2,4-diamine (**1a**) (1 mmol, 0.187 g) and phenylisocyanate (**2**) (2.1 mmol, 0.298 g) were dissolved in toluene (1 mL) and irradiated at 25 W for 15 min at 100 °C. The crude was washed with anhydrous diethyl ether (2×1 mL) and dried under vacuum. Compound **3a** was obtained as a white solid (0.198 g, 68%). Mp 302–304.7 °C. ν_{max} (neat) 3153, 1651, 1525 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 7.08 (t, ^3J=7.32 Hz, 1H, H-4 Ph), 7.35 (t, ^3J=8.05 Hz, 2H, H-3,5 Ph), 7.55 (t, ^3J=7.56 Hz, 2H, H-3′,5′ Ph), 7.60 (t, ^3J=7.07 Hz, 1H, H-4′ Ph), 7.71 (d, ^3J=7.32 Hz, 2H, H-2,6 Ph), 7,74 (br s, 1H, NH$_2$), 7.85 (br s, 1H, NH$_2$), 8.29 (d, ^3J=8.29 Hz, 2H, H-2′,6′ Ph), 10 (s, 1H, N$_1$–H), 11.56 (s, 1H, N$_3$–H). δ_C (125 MHz, DMSO, 25 °C) 119.57 (C-2,6 Ph), 123.14 (C-4 Ph), 127.96 (C-2′,6′ Ph), 128.50 (C-3′,5′ Ph), 128.80 (C-3,5 Ph), 132.1 (C-4′ Ph), 135.76 (C-1′ Ph), 138.45 (C-1 Ph), 151.44 (CO), 163.51 (C-4 Triazine), 166.04 (C-2 Triazine), 170.71 (C-6 Triazine). HRMS (EI): found 306.1221. $C_{16}H_{14}N_6O$ requires 306.1229.

*4.2.2. 1-[4-Amino-6-(4-chlorophenyl)-[1,3,5]-triazin-2-yl]-3-phenylurea (**3b**).* 6-(4-Chlorophenyl)-[1,3,5]-triazine-2,4-diamine (**1b**) (0.5 mmol, 0.11 g) and phenylisocyanate (**2**) (1.05 mmol, 0.11 mL) were mixed and irradiated at 15 W for 30 min at 110 °C. The crude was washed with anhydrous diethyl ether (2×1 mL) and dried under vacuum. Compound **3b** was obtained as a white solid (0.136 g, 76%). Mp >300 °C (decomp.). ν_{max} (neat) 3408, 3304, 3194, 1525 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 7.08 (t, ^3J=7.32 Hz, 1H, H-4 Ph), 7.35 (t, ^3J=8.05 Hz, 2H, H-3,5 Ph), 7.62 (d, ^3J=8.29 Hz, 2H, H-3′,5′ Ar), 7.72 (d, ^3J=7.81 Hz, 2H, H-2,6 Ph), 7.78 (br s, 1H, NH$_2$), 7.92 (br s, 1H, NH$_2$), 8.28 (d, ^3J=8.29 Hz, 2H, H-2′,6′ Ar), 10.05 (s, 1H, N$_1$–H), 11.48 (s, 1H, N$_2$–H). δ_C (125 MHz, DMSO, 25 °C) 119.62 (C,2,6 Ph), 123.16 (C-4 Ph), 128.68 (C-2′,6′ Ph), 128.78 (C-3,5 Ph), 129.70 (C-3′,5′ Ph), 134.66 (C-1′ Ph), 136.91 (C-4′ Ph), 138.42 (C-1 Ph), 151.37 (CO), 163.50 (C-2 Triazine), 165.94 (C-4 Triazine), 169.80 (C-6 Triazine). MS (EI): *m*/*z* found: 340.0847. $C_{16}H_{13}ClN_6O$ requires 340.0839.

*4.2.3. 1-[4-Amino-6-(4-methoxyphenyl)-[1,3,5]-triazin-2-yl]-3-phenylurea (**3c**).* 6-(4-Methoxyphenyl)-[1,3,5]-triazine-2,4-diamine (**1c**) (0.5 mmol, 0.11 g) and phenylisocyanate (**2**) (1.05 mmol, 0.11 mL) were dissolved in toluene (1 mL) and irradiated at 25 W for 45 min at 110 °C. The crude was washed with anhydrous diethyl ether (2×1 mL) and dried under vacuum. Compound **3c** was obtained as a white solid (0.134, 80%). Mp 275–278.8 °C. ν_{max} (neat) 3194, 1651, 1558 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 3.84 (s, 3H, OCH$_3$), 7.06–7.09 (m, 3H, H-4 Ph, H-3′,5′ Ar), 7.34 (t, ^3J=8.05 Hz, 2H, H-3,5 Ph), 7.64 (br s, 1H, NH$_2$), 7.71 (d, ^3J=7.32 Hz, 2H, H-2,5 Ph), 7.76 (br s, 1H, NH$_2$), 8.26 (d, ^3J=8.78 Hz, 2H, H-2′,6′ Ar), 9.91 (s, 1H, N$_1$–H), 11.58 (s, 1H, N$_3$–H). δ_C (125 MHz, DMSO, 25 °C) 55.42 (OCH$_3$), 113.86 (C-3′,5′ Ar), 119.56 (C-2,6 Ph), 123.10 (C-4 Ph), 128.00 (C-1′ Ar), 128.81 (C-2′,6′ Ar), 129.85 (C-3,5 Ph), 138.49 (C-1 Ph), 151.51 (CO), 162.54 (C-4′ Ar), 163.38 (C-2 Triazine), 165.91 (C-4 Triazine), 170.28 (C-6 Triazine). MS (EI): *m*/*z* found: 336.1333. $C_{17}H_{16}N_6O_2$ requires 336.1335.

*4.2.4. 1-(4-Amino-6-morpholino-[1,3,5]-triazin-2-yl)-3-phenylurea (**3d**).* 6-Morpholino-[1,3,5]-triazine-2,4-diamine (**1d**) (1 mmol, 0.186 g) and phenylisocyanate (**2**) (2.1 mmol, 0.23 mL) were mixed and irradiated at 25 W for 50 min at 110 °C. The crude was washed with anhydrous diethyl ether (2×1 mL) and dried under vacuum. Compound **3d** is obtained as a white solid (0.269 g, 85%). Mp 280 °C (decomp.). ν_{max} (neat) 3186, 1685, 1514 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 3.61–3.63 (m, 4H, H-2,6 Morpholine), 3.67–3.69 (m, 4H, H-3,5 Morpholine), 7.03 (t, ^3J=7.32 Hz, 2H, H-4 Ph, NH$_2$), 7.30 (t, ^3J=7.81 Hz, 3H, H-3,5 Ph, NH$_2$), 7.67 (d, ^3J=7.32 Hz, 2H, H-2,6 Ph), 9.39 (s, 1H, N$_1$–H), 11.67 (s, 1H, N$_3$–H). δ_C (125 MHz, DMSO, 25 °C) 43.33 (CH$_2$–N), 66.02 (CH$_2$–O), 119.54 (C-2,6 Ph), 123.06 (C-4 Ph), 128.89 (C-3,5 Ph), 138.72 (C-1 Ph), 151.93 (CO), 163.16 (C-2 Triazine), 164.44 (C-4 Triazine), 165.64 (C-6 Triazine). MS (EI): *m*/*z* found: 315.1438. $C_{14}H_{17}N_7O_2$ requires 315.1444.

*4.2.5. 1-(4-Amino-6-piperidino-[1,3,5]-triazin-2-yl)-3-phenylurea (**3e**).* 6-Piperidino-[1,3,5]-triazine-2,4-diamine (**1e**) (1 mmol, 0.194 g) and phenylisocyanate (**2**) (2.1 mmol, 0.23 mL) were mixed and irradiated at 25 W for 35 min at 110 °C. The crude was dried under vacuum and compound **3e** was obtained as a white solid (0.307 g, 98%). Mp 284–286.8 °C. ν_{max} (neat) 3186, 1667, 1498 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 1.49 (br s, 4H, H-3,5 Piperidine), 1.62 (br s, 2H, H-4 Piperidine), 3.69 (t, ^3J=5.62 Hz, 4H, H-2,6 Piperidine), 6.94 (br s, 1H, NH$_2$), 7.03 (t, ^3J=7.81 Hz, 1H, H-4 Ph), 7.13 (br s, 1H, NH$_2$), 7.30 (t, ^3J=7.56 Hz, 2H, H-3,5 Ph), 7.65 (d, ^3J=7.32 Hz, 2H, H-2,6 Ph), 9.29 (s, 1H, N$_1$–H), 11.74 (s, 1H, N$_3$–H). δ_C (125 MHz, DMSO, 25 °C) 24.29 (C-3,5 Piperidine), 25.34 (C-4 Piperidine), 30.68 (C-2,6 Piperidine), 119.24 (C-2,6 Ph), 122.76 (C-4 Ph), 128.73 (C-3,5 Ph), 138.72 (C-1 Ph), 151.81 (CO), 163.05 (C-2 Triazine), 163.79 (C-4 Triazine), 165.59 (C-6 Triazine). MS (EI): *m*/*z* found: 313.1653. $C_{15}H_{19}N_7O$ requires 313.1651.

*4.2.6. 1-[4-Amino-6-(2-1H-pyrazol-1-ylphenyl)-[1,3,5]-triazin-2-yl]-3-phenylurea (**3f**).* 6-(2-Pyrazol-1-ylphenyl)-[1,3,5]-triazine-2,4-diamine (**1f**) (0.125 mmol, 0.031 g) and phenylisocyanate (**2**) (0.26 mmol, 0.03 mL) were mixed and irradiated at 25 W for 45 min at 110 °C. The crude was dried under vacuum. Compound **3f** was obtained as a white powder (0.03 g, 65%). Mp 268–272 °C. ν_{max} (neat) 3188, 1693, 1519 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 6.36 (d, ^3J=1.47 Hz, 1H, H-4 Pyrazole), 7.04 (t, ^3J=7.32 Hz, 1H, H-4 Ph), 7.31 (t, ^3J=7.32 Hz, 2H, H-3,5 Ph), 7.51–7.58 (m, 5H, H-3 Pyrazole, H-2,6 Ph, H-5′ Ar, NH$_2$), 7.66 (d, ^3J=3.9 Hz, 2H, H-3′,4′ Ar), 7.7 (d, ^3J=7.81 Hz, 2H, H-6′ Ar, NH$_2$), 7.94 (d, ^3J=2.44 Hz, H-5 Pyrazole), 9.83 (s, 1H, N$_1$–H), 11.2 (s, 1H, N$_3$–H). δ_C (125 MHz, DMSO, 25 °C) 107.05 (C-4 Pyrazole), 119.66 (C-2,6 Ph), 123.11 (C-4 Ph), 124.54 (C-3′ Ar), 127.32 (C-5′ Ar), 128.70 (C-3,5 Ph), 130.34 (C-6′ Ar), 130.52 (C-5 Pyrazole), 130.62 (C-3,5 Ph), 132.24 (C-5 Ph), 138.17 (C-1′ Ar), 138.25 (C-1 Ph), 140.39 (C-3 Pyrazole), 151.25 (CO), 162.83 (C-2 Triazine), 165.81 (C-4 Triazine), 173.10 (C-6 Triazine). MS (EI): *m*/*z* found: 372.1461. $C_{19}H_{17}N_9O$ requires 372.1447.

*4.2.7. 1-[4-Amino-6-(1-phenyl-1H-pyrazol-4-yl)-[1,3,5]-triazin-2-yl]-3-phenylurea (**3g**).* 6-(1-Phenyl-1*H*-pyrazol-4-yl)-[1,3,5]-triazine-2,4-diamine (**1g**) (0.5 mmol, 0.125 g) and phenylisocyanate (**2**) (1.05 mmol, 0.12 mL) were dissolved in anhydrous 1,4-dioxane (1 mL) and irradiated at 25 W for 60 min at 110 °C. The crude was washed with ethanol (2×1 mL) and dried under vacuum. Compound **3g** was obtained as a white solid (0.098, 54%). Mp 298 °C (decomp.). ν_{max} (neat) 3172, 1697, 1595 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 7.07 (t, ^3J=7.32 Hz, 1H, H-4 Ph), 7.35 (t, ^3J=7.81 Hz, 2H, H-3,5 Ph), 7.39 (t, ^3J=7.32 Hz, 1H, H-4′ Ar), 7.55 (t, ^3J=7.92 Hz, 2H, H-3′,5′ Ar), 7.60 (br s, 1H, NH$_2$), 7.72 (d, ^3J=7.32, 2H, H-2,6 Ph), 7.79 (br s, 1H, NH$_2$), 7.91 (d, ^3J=7.81, 2H, H-2′,6′ Ar), 8.25 (s, 1H, H-3 Pyrazole), 8.9 (s, 1H, H-5 Pyrazole), 9.86 (s, 1H, N$_1$–H), 11.52 (s, 1H, N$_3$–H). δ_C (125 MHz, DMSO, 25 °C) 103.41 (C-4 Pyrazole), 118.99 (C-2,6 Ph), 119.65 (C-2′,6′ Ar), 123.03 (C-4 Ph), 123.16 (C-4′ Ar), 128.82 (C-3,5 Ph), 129.05 (C-5 Pyrazole), 129.72 (C-3′,5′ Ar), 138.46 (C-1′ Ar), 139.28 (C-1 Ph), 140.97 (C-3 Pyrazole), 151.37 (CO), 163.25 (C-2 Triazine), 165.77 (C-4 Triazine), 168.82 (C-6 Triazine). MS (EI): *m*/*z* found: 372.1447. $C_{19}H_{17}N_9O$ requires 372.1447.

*4.2.8. 1-[4-Amino-6-(4-1H-pyrazol-1-ylphenyl)-[1,3,5]-triazin-2-yl]-3-phenylurea (**3h**).* 6-(4-Pyrazol-1-ylphenyl)-[1,3,5]-triazine-2,4-diamine (**1h**) (0.5 mmol, 0.125 g) and phenylisocyanate (**2**) (1.05 mmol, 0.12 mL) were dissolved in anhydrous 1,4-dioxane

(1 mL) and irradiated at 25 W for 35 min at 110 °C. The crude was washed with ethanol (2×1 mL) and dried under vacuum. Compound **3h** was obtained as a white solid (0.13 g, 70%). Mp >283 °C (decomp.). ν_{max} (neat) 3155, 1683, 1523 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 6.61 (t, ^3J=1.46 Hz, 1H, H-4 Pyrazole), 7.08 (t, ^3J=7.32 Hz, 1H, H-4 Ph), 7.35 (t, ^3J=8.05 Hz, 2H, H-3,5 Ph), 7.73 (d, ^3J=7.32 Hz, 2H, H-2,6 Ph), 7.76 (br s, 1H, NH$_2$), 7.82 (d, ^3J=1.46 Hz, 1H, H-3 Pyrazole), 7.88 (br s, 1H, NH$_2$), 8.04 (d, ^3J=9.21 Hz, 2H, H-3′,5′ Ar), 8.40 (d, ^3J=9.21 Hz, 2H, H-2′,6′ Ar), 8.63 (d, ^3J=2.44 Hz, 1H, H-5 Pyrazole), 10.03 (s, 1H, N$_1$—H), 11.54 (s, 1H, N$_3$—H). δ_C (125 MHz, DMSO, 25 °C) 108.52 (C-4 Pyrazole), 117.94 (C-3′,5′ Ar), 119.61 (C-2,6 Ph), 123.16 (C-4 Ph), 128.09 (C-5 Pyrazole), 128.82 (C-3,5 Ph), 129.41 (C-2′,6′ Ar), 133.20 (C-1′ Ar), 138.47 (C-1 Ph), 141.72 (C-3 Pyrazole), 142.27 (C-4′ Ar), 151.45 (CO), 163.47 (C-2 Triazine), 165.96 (C-4 Triazine), 169.92 (C-6 Triazine). MS (EI): *m*/*z* found: 372.1447. $C_{19}H_{17}N_9O$ requires 372.1451.

*4.2.9. 1-[4-Amino-6-(3-1H-pyrazole-1-ylphenyl)-[1,3,5]-triazin-2-yl]-3-phenylurea (**3i**).* 6-(3-Pyrazol-1-ylphenyl)-[1,3,5]-triazine-2,4-diamine (**1i**) (0.5 mmol, 0.125 g) and phenylisocyanate (**2**) (1.05 mmol, 0.12 mL) were dissolved in anhydrous 1,4-dioxane (1 mL) and irradiated at 25 W for 30 min at 110 °C. The crude was dried under vacuum. Compound **3i** was obtained as a white solid (0.184 g, 98%). Mp 274–278 °C. ν_{max} (neat) 3184, 1691, 1529 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 6.60 (d, ^3J=1.95 Hz, 1H, H-4 Pyrazole), 7.08 (t, ^3J=7.32 Hz, 1H, H-4 Ph), 7.34 (t, ^3J=7.81 Hz, 2H, H-3,5 Ph), 7.67 (t, ^3J=7.81 Hz, 1H, H-5′ Ar), 7.75 (d, ^3J=7.81 Hz, 2H, H-2,6 Ph), 7.82 (d, ^3J=1.46 Hz, 1H, H-3 Pyrazole), 7.86 (br s, 1H, NH$_2$), 7.91 (br s, 1H, NH$_2$), 8.04 (d, ^3J=8.29 Hz, 1H, H-4′ Ar), 8.22 (d, ^3J=6.82 Hz, 1H, H-6′ Ar), 8.55 (d, ^3J=2.44 Hz, 1H, H-5 Pyrazole), 8.82 (s, 1H, H-2′ Ar), 10.08 (s, 1H, N$_1$—H), 11.54 (s, 1H, N$_3$—H). δ_C (125 MHz, DMSO, 25 °C) 108.14 (C-4 Pyrazole), 118.15 (C-2′ Ar), 119.62 (C-2,6 Ph), 121.56 (C-4′ Ar), 123.17 (C-6′ Ar), 125.62 (C-5 Pyrazole), 127.89 (C-4 Ph), 128.75 (C-3,5 Ph), 129.76 (C-5′ Ar), 137.28 (C-1′ Ar), 138.42 (C-1 Ph), 139.99 (C-3′ Ar), 141.25 (C-3 Pyrazole), 151.37 (CO), 163.56 (C-2 Triazine), 166.12 (C-4 Triazine), 170.06 (C-6 Triazine). MS (EI): *m*/*z* found: 372.1449. $C_{19}H_{17}N_9O$ requires 372.1447.

4.3. Synthesis of [1,3,5]-triazinylbisureas

The appropriate amino-[1,3,5]-triazinylmonourea (**3a**–**i**) and phenylisocyanate (**2**) were mixed in 1:4 ratio and irradiated under microwave under argon, in solvent-free conditions or with the appropriate solvent at the time, temperature, and power indicated in Table 2.

*4.3.1. 3,3′-Diphenyl-1,1′-(6-phenyl-[1,3,5-triazin-2,4-diyl)bisurea (**4a**).* 1-(4-Amino-6-phenyl-[1,3,5]-triazin-2-yl)-3-phenylurea (**3a**) (0.16 mmol, 0.05 g) and phenylisocyanate (**2**) (0.64 mmol, 0.07 mL) were mixed and irradiated at 80 W for 60 min at 170 °C. The crude was dried under vacuum and the product was purified by washing with ethanol (2×1 mL). Compound **4a** is obtained as a white solid (0.046 g, 68%). Mp >300 °C (decomp.). ν_{max} (neat) 3232, 3101, 1720, 1529 cm^{-1}. δ_H (500 MHz, DMSO, 80 °C) 7.11 (t, ^3J=7.32 Hz, 2H, H-4 Ph), 7.37 (t, ^3J=7.81 Hz, 4H, H-3,5 Ph), 7.61 (t, ^3J=7.32 Hz, 2H, H-3′,5′ Ar), 7.67 (t, ^3J=7.32 Hz, 1H, H-4′ Ar), 7.72 (d, ^3J=7.32 Hz, 4H, H-2,6 Ph), 8.37 (d, ^3J=6.83 Hz, 2H, H-2′,6′ Ar), 10.30 (s, 2H, N$_1$—H), 10.68 (s, 2H, N$_3$—H). δ_C (125 MHz, DMSO, 80 °C): δ=119.66 (C-2,6 Ph), 123.02 (C-4 Ph), 127.85 (C-2′,6′ Ar), 128.28 (C-3,5 Ph), 128.35 (C-3′,5′ Ar), 132.40 (C-4′ Ar), 134.68 (C-1′ Ar), 138.03 (C-1 Ph), 150.37 (CO), 162.76 (C-2,4 Triazine), 171.19 (C-6 Triazine). MS (EI): *m*/*z* found: 425.1593. $C_{23}H_{20}N_8O_2$ requires 425.1600.

*4.3.2. 3,3′-Diphenyl-1,1′-[6-(4-chlorophenyl)-[1,3,5]-triazin-2,4-diyl] bisurea (**4b**).* 1-[4-Amino-6-(4-chlorophenyl-[1,3,5]-triazin-2-yl)]-3-phenylurea (**3b**) (0.08 mmol, 0.03 g) and phenylisocyanate (**2**) (0.32 mmol 0.033 mL) were mixed and irradiated at 80 W for 60 min at 150 °C. The crude was dried under vacuum and the product was purified by washing with ethanol (2×1 mL). Compound **4b** was obtained as a yellowish solid (0.015 g, 42%). Mp >300 °C. ν_{max} (neat) 3240, 3116, 1699, 1525 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 7.11 (t, ^3J=7.32, 2H, H-4 Ph), 7.38 (t, ^3J=8.04 Hz, 4H, H-3,5 Ph), 7.73 (d, ^3J=6.83 Hz, 6H, H-2,6 Ph, H-3′,5′ Ar), 8.34 (d, ^3J=8.79 Hz, 2H, H-2′,6′ Ar), 10.62 (br s, 2H, N$_1$—H), 10.71 (br s, 2H, N$_3$—H). δ_C (125 MHz, DMSO, 25 °C) 119.88 (C-2,6 Ph), 123.43 (C-4 Ph), 128.81 (C-3,5 Ph), 129.08 (C-2′,6′ Ar), 129.90 (C-3′,5′ Ar), 133.79 (C-1′ Ar), 137.77 (C-4′ Ar), 138.32 (C-1 Ph), 150.77 (CO), 162.96 (C-2,4 Triazine), 170.37 (C-6 Triazine). MS (EI): *m*/*z* found: 459.1201. $C_{23}H_{19}ClN_8O_2$ requires 459.1211.

*4.3.3. 3,3′-Diphenyl-1,1′-[6-(4-methoxyphenyl)-[1,3,5]-triazin-2,4-diyl]bisurea (**4c**).* 1-[4-Amino-6-(4-methoxyphenyl-[1,3,5]-triazin-2-yl)]-3-phenylurea (**3c**) (0.25 mmol, 0.08 g) and phenylisocyanate (**2**) (1 mmol, 0.12 mL) were mixed and irradiated at 80 W for 60 min at 150 °C. The crude was dried under vacuum. Compound **4c** was obtained as a white solid (0.093g, 83%). Mp 255–258 °C. ν_{max} (neat) 3240, 3101, 1699, 1521 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 3.88 (s, 3H, OCH$_3$), 7.11 (t, ^3J=7.32 Hz, 2H, H-4 Ph), 7.18 (d, ^3J=8.78 Hz, 2H, H-3′,5′ Ar), 7.38 (t, ^3J=7.81 Hz, 4H, H-3,5 Ph), 7.73 (d, ^3J=7.77 Hz, 4H, H-2,6 Ph), 8.32 (d, ^3J=8.78 Hz, 2H, H-2′,6′ Ar), 10.54 (br s, 2H, N$_1$—H), 10.81 (br s, 2H, N$_3$—H). δ_C (125 MHz, DMSO, 25 °C) 55.57 (OCH$_3$), 114.28 (C-3′,5′ Ar), 119.91 (C-2,6 Ph), 123.38 (C-4 Ph), 126.98 (C-1′ Ar), 128.78 (C-3,5 Ph), 130.18 (C-2′,6′ Ar), 138.32 (C-1 Ph), 150.91 (CO), 162.79 (C-2,4 Triazine), 163.25 (C-6 Triazine). MS (FAB) found: 456.1792. $C_{24}H_{22}N_8O_3$ requires 456.1784.

*4.3.4. 3,3′-Diphenyl-1,1′-[6-morpholino-[1,3,5]-triazin-2,4-diyl]bisurea (**4d**).* 1-(4-Amino-6-morpholino-4-yl-[1,3,5]-triazin-2-yl)-3-phenylurea (**3d**) (0.25 mmol, 0.078 g) and phenylisocyanate (**2**) (1 mmol, 0.11 mL) were mixed and irradiated at 80 W for 60 min at 160 °C. The crude was dried under vacuum. Compound **4d** was obtained as a white solid (0.107 g, 98%). Mp >300 °C (decomp.). ν_{max} (neat) 3184, 3142, 1716, 1517 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 3.6–3.8 (m, 8H, NCH$_2$, OCH$_2$), 7.07 (t, ^3J=7.38 Hz, 2H, H-4 Ph), 7.34 (t, ^3J=7.85, 4H, H-3,5 Ph), 7.66 (d, ^3J=7.66 Hz, 4H, H-2,6 Ph), 10.05 (s, 2H, N$_1$—H), 10.75 (s, 2H, N$_3$—H). δ_C (125 MHz, DMSO, 25 °C) 43.54 (C-2,6 Morpholine), 65.66 (C-3,5 Morpholine), 119.89 (C-2,6 Ph), 123.24 (C-4 Ph), 128.74 (C-3,5 Ph), 138.37 (C-1 Ph), 151.19 (CO), 162.45 (C-2,4 Triazine), 163.35 (C-6 Triazine). MS (EI): *m*/*z* found: 434.1799. $C_{21}H_{22}N_8O_3$ requires 434.1815.

*4.3.5. 3,3′-Diphenyl-1,1′-[6-(1-phenyl-1H-pyrazole-4-yl)-[1,3,5]-triazin-2,4-diyl]bisurea (**4g**).* 1-[4-Amino-6-(1-phenyl-1*H*-pyrazole-4-yl)-[1,3,5]-triazin-2-yl]-3-phenylurea (**3g**) (0.13 mmol, 0.05 g), and phenylisocyanate (**2**) (0.54 mmol, 0.06 mL) were dissolved in diphenylether (1 mL) and irradiated at 150 W for 60 min at 160 °C. The crude was washed with diethyl ether (2×1 mL). Compound **4g** was obtained as a white solid (0.037 g, 58%). Mp 288–292 °C. ν_{max} (neat) 3224, 3024, 1722, 1539 cm^{-1}. δ_H (500 MHz, DMSO, 25 °C) 7.12 (t, ^3J=7.3 Hz, 2H, H-4 Ph), 7.22 (d, ^3J=2.44 Hz, 1H, H-3 Pyrazole), 7.36 (t, ^3J=7.81 Hz, 4H, H-3,5 Ph), 7.48 (t, ^3J=7.56 Hz, 1H, H-4′ Ar), 7.63 (t, ^3J=8.10 Hz, 2H, H-3′,5′ Ar), 7.77 (d, ^3J=7.32 Hz, 4H, H-2,6 Ph), 7.98 (d, ^3J=7.81 Hz, 2H, H-2′,6′ Ar), 8.71 (d, ^3J=2.44, 1H, H-5 Pyrazole), 10.83 (br s, 2H, 2×NH). δ_C (125 MHz, DMSO, 25 °C) 109.17 (C-4 Pyrazole); 119.20 (C-2′,6′ Ar), 119.76 (C-2,6 Ph), 120.82 (C-4′ Ar), 123.08 (C-4 Ph), 128.24 (C-3,5 Ph), 129.20 (C-5 Pyrazole), 129.24 (C-3′,5′ Ar), 138.01 (C-1 Ph), 139.26 (C-3 Pyrazole), 150.46 (CO), 162.74 (C-2,4 Triazine), 165.82

(C6 Triazine). MS (EI): m/z found: 491.1824. $C_{26}H_{22}N_{10}O_2$ requires 491.1818.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.01.043. These data include MOL files and InChiKeys of the most important compounds described in this article.

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