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A novel one-pot three-component synthesis of 4-aryl-6-alkylamino/piperidinyl-1,3,5-triazine-2-amines under controlled microwave irradiation

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Dedicated to the memory of Prof. Dr. M. H. Elnagdi

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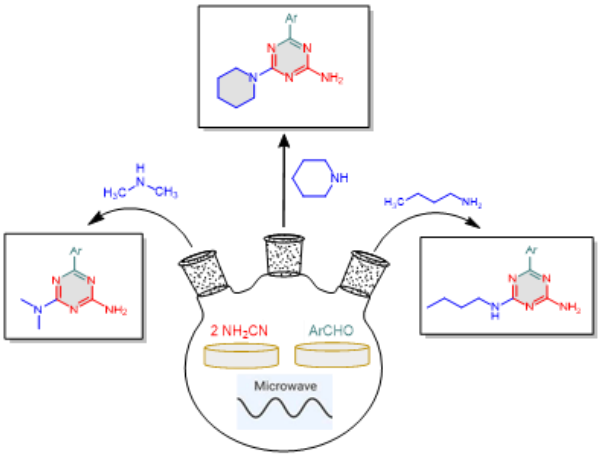
Abstract

1,3,5-Triazine derivatives are an important class of heterocyclic compounds with great interest in medicine, agriculture, electronics, and other industries. In this article, we report on the synthesis of 4-aryl-6-alkylamino/piperidinyl-1,3,5-triazine-2-amines *via* one-pot, multi-component reactions of cyanamide, aromatic aldehydes and an amine (piperidine, aqueous dimethylamine and butylamine) using microwave irradiation under neat conditions. The structure of the obtained products was confirmed by ^{1}H-NMR and ^{13}C-NMR spectra, mass spectrometry and, in two cases, X-ray diffraction.



Keywords: 1,3,5-Triazines, microwave irradiation, three-component reaction, neat conditions.

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Introduction

Triazine derivatives are considered versatile pharmacophores with diverse biological activities.[1–4] Among the three different triazine ring systems [1,2,3; 1,2,4; 1,3,5] 1,3,5-triazines (*s*-triazines) have been recognized as contributing most to the biological function of a wide range of small molecules therapeutics.[5–12] 1,3,5-Triazine derivatives have been reported to have immense and varied bioactivities such as antitubercular,[13] anticancer,[14,15] anti-HIV,[16] antimalarial,[17] antimicrobial,[18] antidiabetic[19] and herbicidal activities.[20] Additionally, several 1,3,5-triazine derivatives possess interesting industrial applications such as cation exchangers, reactive azo dyes and transporters for the preparation of immobilized enzymes.[21] Examples of biologically active 1,3,5-triazines are given in Figure 1.

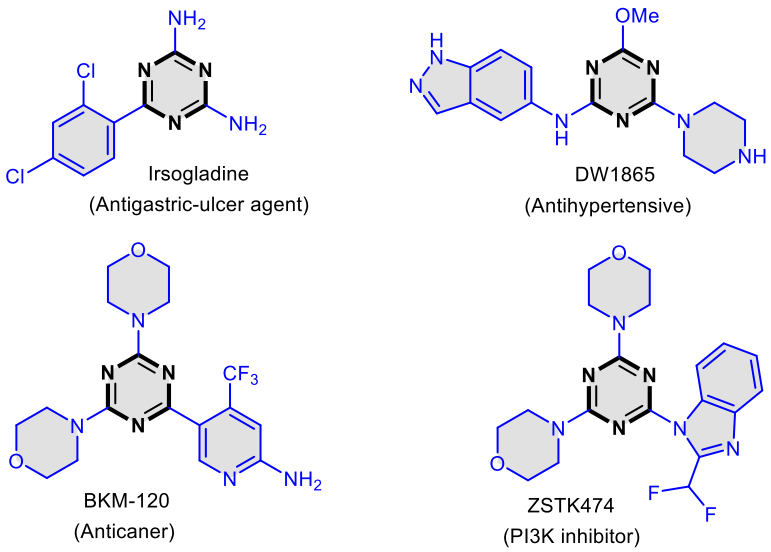


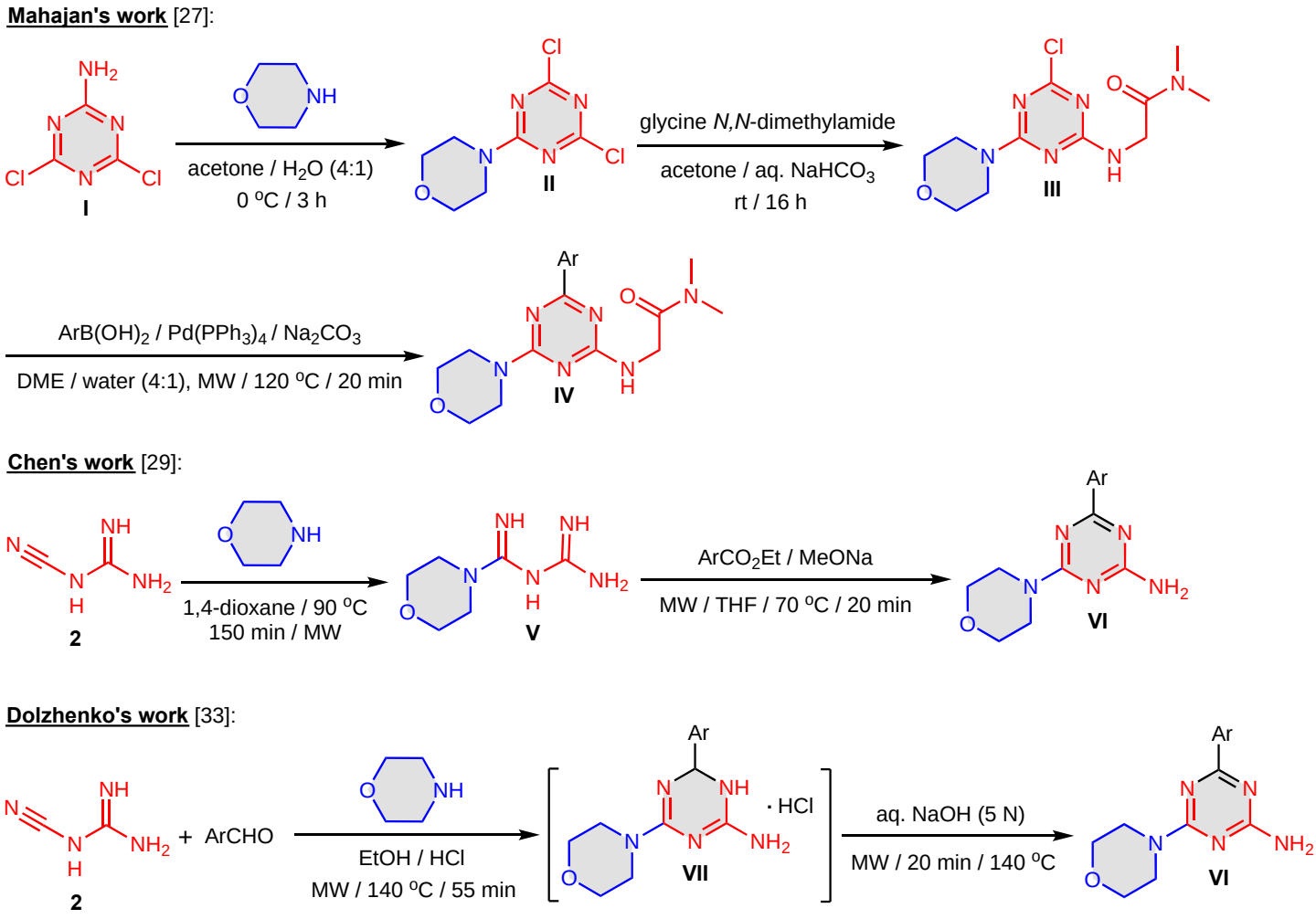
Figure 1. Examples of biologically active 1,3,5-triazine derivatives.

Being a potent and biologically active scaffold in drug discovery, the development of 1,3,5-triazine derivatives as anticancer reagents is a particularly important and inspiring goal to construct libraries of compounds with improved potency.[9,22]

It has been reported that 1,3,5-triazines with two amino substituents at positions 2,4- and 6-aryl/heteroaryl moieties, exhibited potent anticancer activity.[23,24] Closely related structures with 4-aryl/heteroaryl-6-arylamino-1,3,5-triazines and 4-aryl-6-cyclohexyl-1,3,5-triazine-2-amines demonstrated tryptophan hydroxylase potent inhibition[25] and were selectively bound to 5-HT6, serotonin.[26] Consequently, the development of new methods for the synthesis 4-aryl-6-cyclohexyl/alkylamino-1,3,5-triazine-2-amines with diverse substituents will enable the generation of desirable structural properties thus offering a wide range of biological activities, however, little attention has been paid to the synthesis of these scaffolds.

One general approach for the synthesis of the targeted molecules relies on the sequential nucleophilic substitution reaction of cyanuric chloride (**I**) with morpholine to give **II**. Treatment of **II** with glycine amide and subsequent Suzuki cross coupling of the formed 2-substituted-4-chloro-6-morpholino-1,3,5-triazine **III** furnishes the corresponding 4-aryl-1,3,5-triazine derivative **IV**.[27] A drawback associated with this protocol is the requirement for temperature control and dependence on the amine nucleophilicity.[28] Another general and commonly utilized protocol involves the reaction of cyanoguanidine **2** with cyclic amines (e.g. morpholine) followed by reaction of the formed biguanide derivative **V** with diverse acid derivatives, for example esters, in

basic medium as well as amides and alcohols.[29–32] Very recently, Dolzhenko and his co-workers[33] have developed a two-step one-pot methodology for the synthesis of 2-amino-4-aryl-6-morpholino-1,3,5-triazines **VI**. The reaction was carried out by heating a mixture of cyanoguanidine, aromatic aldehydes and morpholine in EtOH/HCl under microwave irradiation at 140 °C for 55 minutes to give the intermediate **VII** which underwent dehydrogenation upon treatment with aq. NaOH (5 N) under microwave heating at 140 °C for 20 minutes (Scheme 1).



Scheme 1. Various synthetic approaches for the synthesis of 2-amino-(or substituted amino)-4-aryl-6-morpholino-1,3,5-triazine derivatives.

Although these methods have their specific advantages, they suffer from drawbacks such as long reaction times, low yields and atom economy which consumes excess reagents, multistep procedures and sometimes harsh reaction conditions.

In continuation of our interest in performing simple, efficient and green synthesis of biologically relevant heterocycles,[34–38] we herein developed an efficient protocol for the synthesis of 2-amino-4-aryl-6-alkylamino/piperidinyl-1,3,5-triazine derivatives *via* a one-step, multi-component reaction (MCR) of cyanamide (**1**) [or 2-cyanoguanidine (**2**)], an aromatic aldehyde **3** with piperidine (**4**), dimethylamine (**5**) or butylamine (**6**) under controlled microwave heating (Scheme 2).

Results and Discussion

For optimizing the reaction conditions, we initially examined the reaction of cyanamide (**1**) (1 mmol), 4-chlorobenzaldehyde (**3a**) (1 mmol) and piperidine (**4**) (1.5 mmol) under neat conditions and the reaction was promoted by MW irradiation at 100 °C for 5 minutes which afforded the desired product 4-(4-chlorophenyl)-6-(piperidin-1-yl)-1,3,5-triazin-2-amine (**7a**) in 44% yield. The structure of **7a** was established based on analytical and spectral data. Its mass spectrum disclosed a molecular ion peak at *m/z* = 289.25 (M^+) corresponding to the molecular formula $C_{14}H_{16}ClN_5$. The ^{1}H-NMR spectrum revealed four signals at δ = 1.51, 1.61-1.64, 3.74 and 3.84 ppm which were assigned for piperidinyl protons in addition to singlet signal at δ = 6.88 ppm for NH_2 as well as signals for aromatic protons. The ^{13}C-NMR spectrum was in agreement with the proposed structure. Based on the established structure we concluded that the reaction incorporated two molecules of cyanamide (**1**). Thus, we were delighted to observe that using two molar ratios of cyanamide (**1**) increased the yield to 93%. We examined the reaction in solvents such as EtOH, pyridine, DMF and AcOH but only solventless conditions gave the target product **7a**. These results demonstrated the efficiency of neat conditions as a green method in the synthesis of such compounds.

We next examined a range of aromatic aldehydes under the same experimental conditions and found that the reaction proceeds smoothly affording a variety of 1,3,5-triazine derivatives, irrespective of the aryl group substituent, either electron-donating or electron-attracting, with excellent yields. Increasing or decreasing the reaction temperature had no significant effect on the reaction course. The structure of the reaction products was established based on their spectral and analytical data. Moreover, single crystal X-ray diffraction analysis of compounds **7a** and **7b** unambiguously confirmed the structure of these products (Figure 2) and Tables 1 and 2.

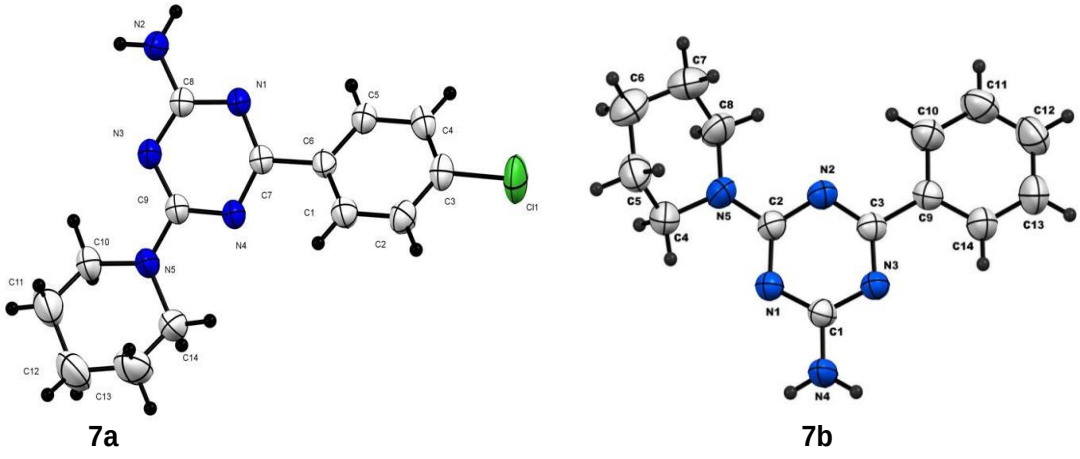


Figure 2. Single crystal X-ray structures of compounds **7a** (CCDC 2300761 contains the crystallographic data for compound **7a**) and **7b** (CCDC 2241375 contains the crystallographic data for compound **7b)**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk).

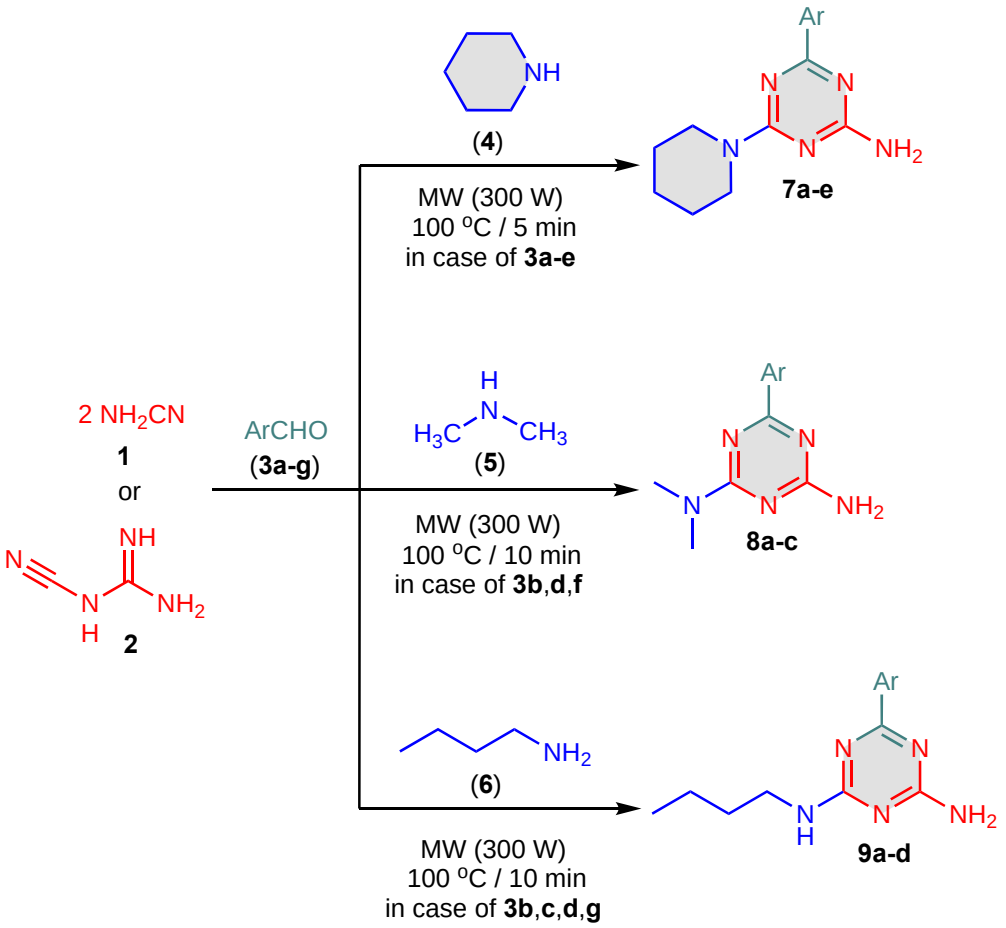
Table 1. Selected bond lengths and bond angles for compound **7a**

Atom numbers	Geometric parameter (Å)	Atom numbers	Geometric parameter (°)
N1-C7	1.333 (4)	C7-N1-C8	113.9 (3)
N1-C8	1.345 (4)	C8-N3-C9	115.0 (3)
N3-C8	1.340 (4)	H2A-N2-H2B	120 (3)
N3-C9	1.341 (4)	C7-N4-C9	114.4 (3)
N4-C7	1.327 (4)	N1-C7-N4	126.8 (3)
N5-C9	1.344 (4)	N1-C8-N3	125.5 (3)
N5-C10	1.464 (4)	N1-C8-N2	117.1 (3)
		C7-C6-C5	120.5 (3)
		N5-C10-C11	111.6 (4)

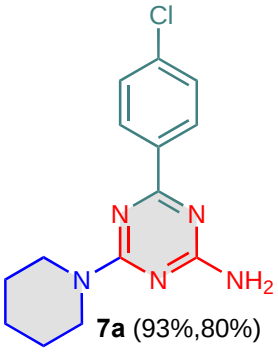
Table 2. Selected bond lengths and bond angles for compound **7b**

Atom numbers	Geometric parameter (Å)	Atom numbers	Geometric parameter (°)
N1-C1	1.339 (2)	C1-N1-C2	114.5 (1)
N1-C2	1.343 (2)	N1-C1-N3	125.6 (1)
C2-N5	1.346 (2)	N1-C1-N4	117.7 (1)
N3-C3	1.335 (2)	C2-N2-C3	115.1 (1)
C1-N4	1.338 (2)	N2-C2-C5	117.2 (1)
N5-C8	1.459 (3)	C4-N5-C8	114.3 (2)
C6-C5	1.513 (4)	C3-C9-C10	120.4 (1)
C7-H7A	0.97	N1-C2-N2	128.5 (1)
		C2-N5-C4	122.9 (2)

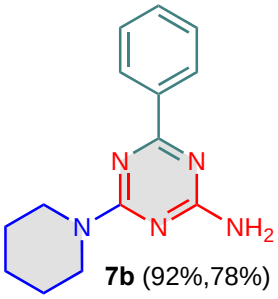
In order to shed further light on the generality of our protocol, piperidine (**4**) was replaced by aqueous dimethylamine (40%) (**5**) or butylamine (**6**). The reaction with each amine proceeded smoothly affording the corresponding 4-aryl-6-dimethylamino-1,3,5-triazine-2-amines **8a-c** and 4-aryl-6-butylamino-1,3,5-triazine-2-amines **9a-d**, respectively, in high yields (Scheme 2). Compounds **7a-e, 8a-c** and **9a-d** could be alternatively synthesized via reaction of 2-cyanoguanidine (**2**) (1 mmol), aromatic aldehydes **2a-e** (1 mmol), and amines **4-6** (1.5 mmol) under the same experimental reaction conditions.



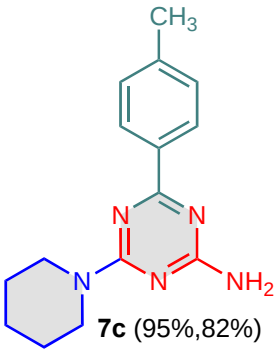
3a, Ar = 4-Cl-C_6H_4; **3b**, Ar = C_6H_5; **3c**, Ar = 4-$CH_3C_6H_4$; **3d**, Ar = 4-$OCH_3C_6H_4$; **3e**, Ar = thien-2-yl; **3f**, Ar = 3-Cl-C_6H_4; **3g**, Ar = 3-$NO_2C_6H_4$.



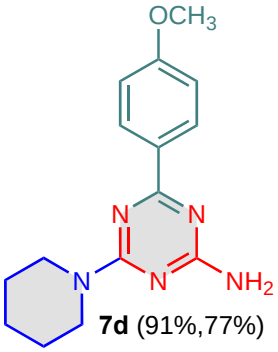
7a (93%,80%)



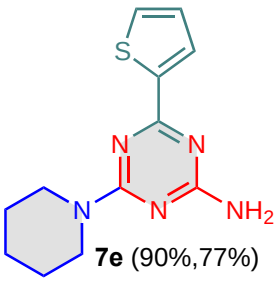
7b (92%,78%)



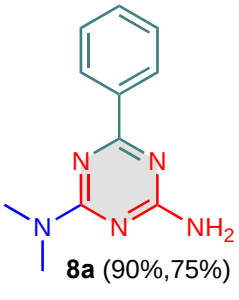
7c (95%,82%)



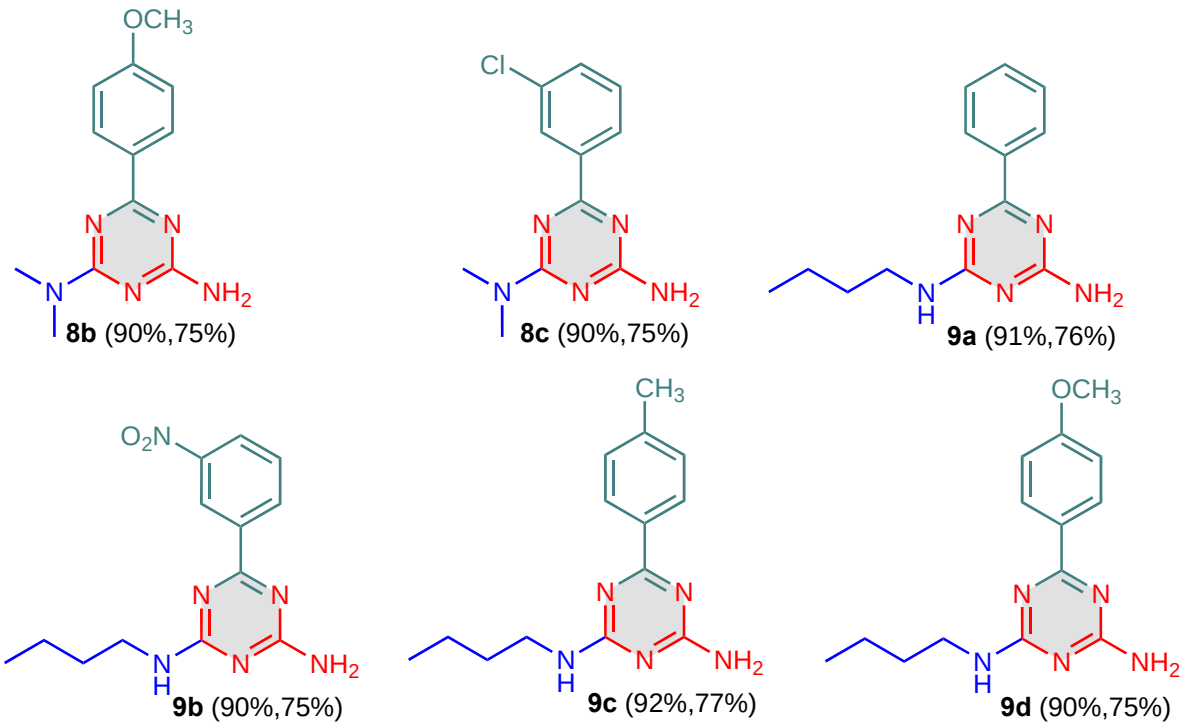
7d (91%,77%)



7e (90%,77%)

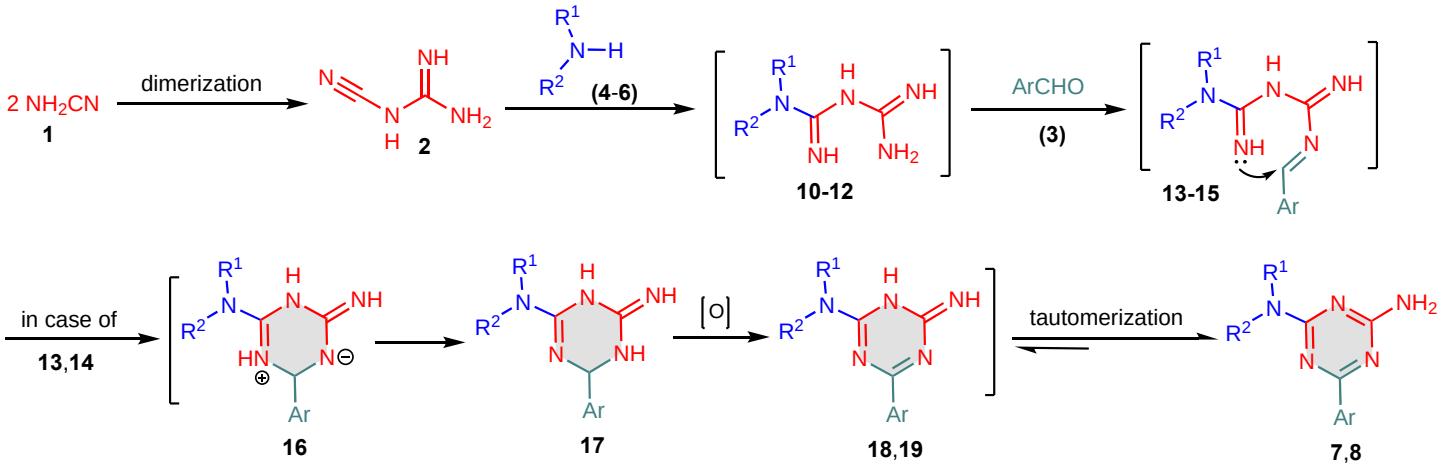


8a (90%,75%)



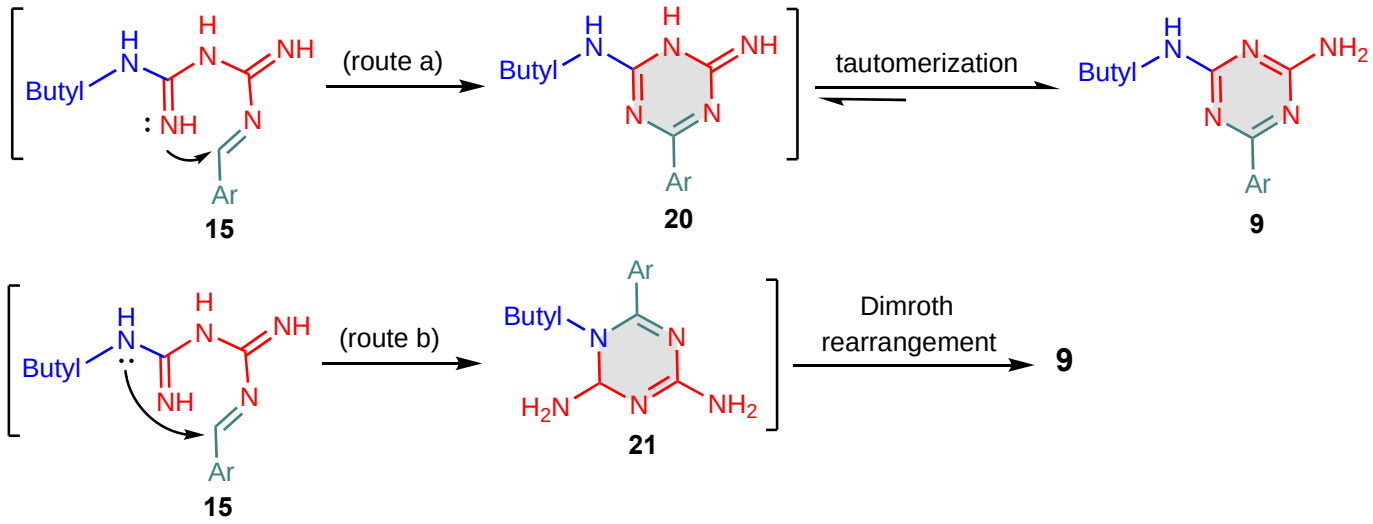
Scheme 2. Synthesis of 4-aryl-6-piperidinyl/alkylamino-1,3,5-triazine-2-amines **7a-e**, **8a-c** and **9a-d**. Yields % are for cyanamide (**1**) and 2-cyanoguanidine (**2**) reactions, respectively.

A plausible mechanism for the formation of reaction products **7, 8** and **9** is depicted in Schemes 3 and 4. For the formation of compounds **7** and **8**, it is supposed that, in a first step, dimerization of cyanamide (**1**) takes place to afford 2-cyanoguanidine (**2**). Then, addition of the amine **4-6** to the activated nitrile group of **2** forms biguanide intermediates **10-12**. Condensation of **10-12** with aromatic aldehydes **3** affords the corresponding Schiff base **13-15**. The intermediates **13**,**14** undergo cyclization *via* intramolecular addition of the imine nitrogen atom, as a nucleophile, to the arylidene carbon to give the intermediates **17** followed by air oxidation to afford 1,3,5-triazines **18**,**19** (the reactions were carried out in open systems). Tautomerization of the imino (=NH) function to amino (NH_2) group affords the final products **7** and **8** (Scheme 3). For the formation of product **9**, the nucleophilic attack may take place through addition of the imine nitrogen atom to the arylidene carbon to give the intermediate **20**, followed by tautomerization to afford **9** (route a), or *via* addition of butyl-NH_2 to the arylidene carbon in **15** to give the intermediate **21** which undergoes a Dimroth rearrangement[33] under these reaction conditions to furnish the product **9** (Scheme 4).



10-12; **13-15: 10**,**13**; NR^1R^2= piperidinyl; **11**,**14**; NR^1R^2= dimethyl amine; **12**,**15**; NR^1R^2= n-butyl amine.
18,**19: 18**, NR^1R^2= piperidinyl; **19**, NR^1R^2= dimethyl amine.

Scheme 3. Proposed mechanism for the formation of products **7** and **8**.



Scheme 4. A plausible mechanism for the formation of product **9**.

Conclusions

In conclusion, a range of 4-aryl-6-piperidin-1-yl/alkylamino-1,3,5-triazine-2-amines was achieved, for the first time, via a one-pot and efficient reaction of cyanamide, an aromatic aldehyde and a primary amine (piperidine, dimethylamine and butylamine) in excellent yields promoted by controlled microwave heating under neat conditions. The method was found to be general with a variety of secondary and primary amines. The process proved to be of high atom economy and yields, had short reaction times as well as simple work-up and isolation of the reaction products.

Experimental Section

General. Melting points were uncorrected and recorded on a Gallenkamp melting point apparatus. The progress of reaction was followed by thin layer chromatography on pre-coated Merck Silica gel ($60F_{254}$). The ^{1}H-NMR and ^{13}C-NMR spectra were measured in Bruker DPX instrument. Mass spectra were determined in VG Autospec Q MS 30 and MS 9 (AEI) spectrometer, with EI (70 eV) mode. X-ray crystallography was performed by using Rigaku Rapid II and Bruker X8 Prospector single crystal X-ray diffractometers. All the reactions were carried out in a Milestone START Microwave Labstation (temperature control by IR sensor).

General procedure for the synthesis of 4-aryl-6-alkylamino/piperidinyl-1,3,5-triazine-2-amines 7a-e, 8a-c and 9a-d

Method A. A suspension of cyanamide (**1**) (2 mmol), aromatic aldehyde **3** (1 mmol) and appropriate amine **4-6** (1.5 mmol) (in the case for dimethylamine as an aqueous solution) was heated under reflux in a milestone microwave labstation at 100 °C (with an efficient condenser) for 5 min. in the case of **4**. However, in cases of **5** and **6** the reaction time was 10 min. After cooling to rt, the resulting solid products was collected by filtration and recrystallized from EtOH or DMF in 90-95% yields.

Method B. A suspension of 2-cyanoguanidine (**2**) (1 mmol), aromatic aldehyde **3** (1 mmol) and the appropriate amine **4-6** (1.5 mmol) was subjected to the aforementioned reaction conditions (method A) to afford products **7a-e, 8a-c** and **9a-d** in moderate yields 75-82%.

4-(4-Chlorophenyl)-6-(piperidin-1-yl)-1,3,5-triazin-2-amines (7a). Pale yellow crystals; yield: 270 mg (93%); mp: 175-177 °C (EtOH). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.51 (s, 4H, piperidine-H); 1.61-164 (m, 2H, piperidine-H); 3.74 (brs, 2H, piperidine-H); 3.84 (brs, 2H, piperidine-H); 6.88 (s, 2H, NH_2); 7.51-7.53 (m, 2H, Ar-H); 8.26-8.28 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 24.3; 25.4; 43.5; 128.3; 129.5; 135.9; 136.0; 164.4; 167.2; 168.6. Anal. Calcd for $C_{14}H_{16}ClN_5$: C, 58.03; H, 5.57; Cl, 12.23; N, 24.17%; Found: C, 57.95; H, 5.62; Cl, 12.25; N, 24.20%. MS: (EI) *m/z* %: 289.25 (M^+).

4-Phenyl-6-(piperidin-1-yl)-1,3,5-triazine-2-amines (7b). Colorless crystals; yield: 235 mg (92%); mp: 146-148 ^{o}C[33] (EtOH). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.49 (brs, 4H, piperidine-H), 1.57-1.62 (m, 2H, piperidine-H); 3.79 (brs, 4H, piperidine-H), 6.36 (s, 2H, NH_2), 7.44-7.52 (m, 3H, Ar-H), 8.29-8.32 (dd, 2H, *J* = 6.8 Hz, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 24.9, 25.9, 43.9, 127.9, 128.2, 131.3, 137.3, 165.0, 167.8, 169.8. Anal. Calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43%; Found: C, 65.80; H, 6.77; N, 27.39%. MS: (EI); *m/z*: 255.25 (M^+).

4-(4-Tolyl)-6-(piperidin-1-yl)-1,3,5-triazine-2-amines (7c). Yellow crystals; yield: 256 mg (95%); mp: 164-166 ^{o}C (EtOH). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.51 (m, 4H, *J* = 3.2 Hz, piperidine-H), 1.61-1.66 (m, 2H, piperidine-H), 2.36 (s, 3H, CH_3), 3.79 (brs, 4H, piperidine-H), 6.80 (s, 2H, NH_2), 7.26 (d, 2H, *J* = 7.6 Hz, Ar-H); 8.18 (d, 2H, *J* = 8.0 Hz, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 21.5, 24.8, 25.9, 43.9, 128.3, 129.2, 134.9, 141.4, 165.0, 167.7, 170.1. Anal. Calcd for $C_{15}H_{19}N_5$: C, 66.89; H, 7.11; N, 26.00%; Found: C, 66.82; H, 7.18; N, 26.05%. MS: (EI) *m/z*: 269.28 (M^+).

4-(4-Methoxyphenyl)-6-(piperidin-1-yl)-1,3,5-triazine-2-amines (7d). Yellow crystals; yield: 260 mg (91%); mp: 208-210 °C (EtOH). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.50 (brs, 4H, piperidine-H); 1.61 (brs, 2H, piperidine-H); 3.69-3.85 (m, 7H, piperidine-H and OCH_3); 6.65 (s, 2H, NH_2); 6.99-7.03 (m, 2H, Ar-H); 8.22-8.30 (m, 2H, Ar-H). Anal. Calcd for $C_{15}H_{19}N_5O$: C, 63.14; H, 6.71; N, 24.54%; Found: C, 63.18; H, 6.75; N, 24.50%. MS: (EI) *m/z*: 285.23 (M^+).

4-(2-Thienyl)-6-(piperidin-1-yl)-1,3,5-triazine-2-amines (7e). Yellow crystals; yield: 235 mg (90%); mp: 290-292 ^{o}C (EtOH). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 24.8, 25.9, 43.4, 128.5, 130.9, 143.8, 165.9, 167.6, 167.8. Anal.

Calcd for $C_{12}H_{15}N_5S$: C, 55.15; H, 5.79; N, 26.80; S, 12.27%; Found: C, 55.10; H, 5.83; N, 26.77; S, 12.30%. MS: (EI) *m/z*: 261.27 (M^+).

6-Phenyl-*N*^{2},*N*^{2}-dimethyl-1,3,5-triazine-2,4-diamine (8a). Yellow solid; yield: 194 mg (90%); mp: 294-296 °C (DMF). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.10 (s, 6H, 2CH_3); 6.04 (s, 2H, NH_2), 7.14-8.36 (m, 5H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 36.3; 128.6; 128.9; 131.7; 137.2; 164.3; 166.6; 167.9. Anal. Calcd for $C_{11}H_{13}N_5$: C, 61.38; H, 6.09; N, 32.54%; Found: C, 61.33; H, 6.12; N, 32.50%.

6-(4-Methoxyphenyl)-*N*^{2},*N*^{2}-dimethyl-1,3,5-triazine-2,4-diamine (8b). Yellow crystals; yield: 220 mg (90%); mp: 230-232 °C (DMF). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.67 (s, 6H, 2CH_3), 3.85 (s, 3H, OCH_3), 6.56 (s, 2H, NH_2), 7.02-7.34 (m, 2H, Ar-H), 8.23-8.30 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 36.3; 55.4; 113.8; 127.9; 130.7; 163.1; 165.5; 165.6; 167.4. Anal. Calcd for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55; Found: C, 58.71; H, 6.21; N, 28.51%. MS: (EI) *m/z* %: 246.33 (M^+H).

6-(3-Chlorophenyl)-*N*^{2},*N*^{2}-dimethyl-1,3,5-triazine-2,4-diamine (8c). Yellow solid; yield: 225 mg (90%); mp: 320-322 °C (DMF). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.14 (s, 6H, 2 CH3); 6.15 (s, 2H, NH_2); 6.71 (s, 1H, Ar-H); 6.94-7.38 (m, 3H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 36.5; 128.8; 129.4; 131.3; 137.3; 138.0; 165.0; 169.8; 170.5. Anal. Calcd for $C_{11}H_{12}ClN_5$: C, 52.91; H, 4.84; Cl, 14.20; N, 28.05%. Found: C, 52.88; H, 4.89; Cl, 14.15; N, 28.09%. MS: (EI) *m/z*: 249.28 (M^+).

6-Phenyl-*N*^{2}-butyl-1,3,5-triazine-2,4-diamine (9a). Yellow solid; yield: 222 mg (91%); mp: 322-324 °C (DMF). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 0.89 (t, 3H, *J* = 7.2 Hz, CH_3), 1.25-1.31 (m, 2H, CH_2), 1.41-1.43 (m, 2H, CH_2), 3.13-3.19 (m, 2H, CH_2), 6.00 (t, *J* = 4.8 Hz, 1H, NH); 6.41 (s, 2H, NH_2); 6.70-6.72 (d, *J* = 6.4 Hz, 2H, Ar-H); 7.29-7.38 (m, 3H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 13.8; 19.6; 31.2; 32.8; 128.3; 129.1; 131.9; 134.9; 164.3; 166.3; 167.3. Anal. Calcd for $C_{13}H_{17}N_5$: C, 64.17; H, 7.04; N, 28.78%. Found: C, 64.13; H, 7.11; N, 28.73%.

6-(4-tolyl)-*N*^{2}-butyl-1,3,5-triazine-2,4-diamine (9b). Yellow solid; yield: 237 mg (92%); mp: 266-268 °C (DMF). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 0.92 (t, 3H, J = 7.6 Hz, CH_3); 1.24-1.34 (m, 2H, CH_2); 1.48-1.49 (m, 2H, CH_2); 2.39 (s, 3H, CH_3); 3.08-3.16 (m, 2H, CH_2); 6.11 (t, *J* = 4.8 Hz, 1H, NH); 6.61 (s, 2H, NH_2); 7.00-7.35 (m, 2H, Ar-H); 7.77-8.27 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 13.7; 19.5; 21.2; 31.0; 31.1; 128.7; 129.1; 155.0; 164.2; 165.5; 167.3. Anal. Calcd for $C_{14}H_{19}N_5$: C, 65.34; H, 7.44; N, 27.21%. Found: C, 65.30; H, 7.49; N, 27.23%.

6-(4-Methoxyphenyl)-*N*^{2}- butyl-1,3,5-triazine-2,4-diamine (9c). Yellow solid; yield: 246 mg (90%); mp: 328-330 °C (DMF). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 0.89 (t, 3H, *J* = 5.6 Hz, CH_3); 1.24-1.31 (m, 2H, CH_2); 1.40-1.46 (m, 2H, CH_2); 3.16-3.19 (m, 2H, CH_2); 3.86 (s, 3H, OCH_3); 6.19 (t, 1H, NH); 6.68 (s, 2H, NH_2); 7.00-7.05 (m, 2H, Ar-H); 8.21-8.27 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 13.8; 19.6; 31.2; 32.8; 55.0; 114.0; 129.1; 131.9; 162.9; 164.3; 166.3; 167.3. Anal. Calcd for $C_{14}H_{19}N_5O$: C, 61.52; H, 7.01; N, 25.62%. Found: C, 61.49; H, 7.07; N, 25.60%.

6-(3-Nitrophenyl)-*N*^{2}-butyl-1,3,5-triazine-2,4-diamine (9d). Brown solid; yield: 260 mg (90%); mp: 266-268 °C (DMF). ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.02 (t, 3H, *J* = 8.0 Hz, CH_3); 1.23-1.31 (m, 2H, CH_2); 1.43-1.47 (m, 2H, CH_2); 3.20-3.22 (m, 2H, CH_2); 6.01 (t, *J* = 4.8 Hz, 1H, NH); 6.56 (s, 2H, NH_2); 7.35 (s, 1H, Ar-H); 7.77-7.95 (m, 1H, Ar-H) 8.11-8.50 (m, 2H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 13.7; 19.6; 31.1; 32.4; 121.8; 124.9; 130.2; 130.3; 134.0; 148.0; 155.7; 165.5; 167.4. Anal. Calcd for $C_{13}H_{16}N_6O_2$: C, 54.16; H, 5.59; N, 29.15; Found: C, 54.13; H, 5.63; N, 29.12%. MS: (EI) *m/z*: 288.27 (M^+).

Supplementary Material

Supplementary data associated with this article is available in the Supplementary Material.

References

1. Carbone, D.; De Franco, M.; Pecoraro, C.; Bassani, D.; Pavan, M.; Cascioferro, S.; Parrino, B.; Cirrincione, G.; Dall'Acqua, S.; Moro, S.; Gandin, V.; Diana, P. *Int. J. Mol. Sci.* **2023**, *24*, 3679. https://doi.org/10.3390/ijms24043679
2. Carbone, D.; De Franco, M.; Pecoraro, C.; Bassani, D.; Pavan, M.; Cascioferro, S.; Parrino, B.; Cirrincione, G.; Dall'Acqua, S.; Sut, S.; Moro, S.; Gandin, V.; Diana, P. *Mar. Drugs* **2023**, *21*, 288. https://doi.org/10.3390/md21050288
3. Pecoraro, C.; De Franco, M.; Carbone, D.; Bassani, D.; Pavan, M.; Cascioferro, S.; Parrino, B.; Cirrincione, G.; Dall'Acqua, S.; Moro, S.; Gandin, V.; Diana, P. *Eur. J. Med. Chem.* **2023**, *249*, 115134. https://doi.org/10.1016/j.ejmech.2023.115134
4. Cascioferro, S.; Parrino, B.; Spanò, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Diana, P.; Cirrincione, G. *Eur. J. Med. Chem.* **2017**, *142*, 74-86. https://doi.org/10.1016/j.ejmech.2017.06.003
5. Patel, R. V; Kumari, P.; Rajani, D. P.; Chikhalia, K. H. *J. Fluor. Chem.* **2011**, *132*, 617-627. https://doi.org/10.1016/j.jfluchem.2011.06.021
6. Shah, D. R.; Modh, R. P.; Chikhalia, K. H. *Future Med. Chem.* **2014**, *6*, 463-477. https://doi.org/10.4155/fmc.13.212
7. Patel, V. R.; Keum, Y.-S.; Park, W. S. *Mini-Rev. Med. Chem.* **2014**, *14*, 768-789. https://doi.org/10.2174/1389557514666140622205904
8. Srivastava, G. K.; Alonso-Alonso, M. L.; Fernandez-Bueno, I.; Garcia-Gutierrez, M. T.; Rull, F.; Medina, J.; Coco, R. M.; Pastor, J. C. *Sci. Rep.* **2018**, *8*, 1425. https://doi.org/10.1038/s41598-018-19428-5
9. Cascioferro, S.; Parrino, B.; Spanò, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Diana, P.; Cirrincione, G. *Eur. J. Med. Chem.* **2017**, *142*, 523-549. https://doi.org/10.1016/j.ejmech.2017.09.035
10. Yu, X.; Huang, X.-P.; Kenakin, T. P.; Slocum, S. T.; Chen, X.; Martini, M. L.; Liu, J.; Jin, J. *J. Med. Chem.* **2019**, *62*, 7557-7574. https://doi.org/10.1021/acs.jmedchem.9b00869
11. Junaid, A.; Lim, F. P. L.; Tiekink, E. R. T.; Dolzhenko, A. V. *RSC Adv.* **2020**, *10*, 25517-25528. https://doi.org/10.1039/D0RA04970K
12. Singla, P.; Luxami, V.; Paul, K. *Eur. J. Med. Chem.* **2016**, *117*, 59-69. https://doi.org/10.1016/j.ejmech.2016.03.088
13. Patel, R. V; Kumari, P.; Rajani, D. P.; Pannecouque, C.; De Clercq, E.; Chikhalia, K. H. *Future Med. Chem.* **2012**, *4*, 1053-1065. https://doi.org/10.4155/fmc.12.57
14. B Dai, Q.; Sun, Q.; Ouyang, X.; Liu, J.; Jin, L.; Liu, A.; He, B.; Fan, T.; Jiang, Y. *Molecules*. **2023,** *28*, 4278. https://doi.org/10.3390/molecules28114278
15. Jagadeesh Kumar, G.; Sriramkumar Bomma, H.V.S.; Srihari, E.; Shrivastava, S.; Naidu, V.G.M.; Srinivas, K.; Jayathirtha Rao, V. *Med. Chem. Res.* **2013**, *22*, 5973–5981. https://doi.org/10.1007/s00044-013-0584-6
16. Lozano, V.; Aguado, L.; Hoorelbeke, B.; Renders, M.; Camarasa, M.-J.; Schols, D.; Balzarini, J.; San-Félix, A.; Pérez-Pérez, M.-J. *J. Med. Chem.* **2011**, *54*, 5335-5348. https://doi.org/10.1021/jm200560r

17. Agarwal, A.; Srivastava, K.; Puri, S. K.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 531-533. D https://doi.org/10.1016/j.bmcl.2004.11.052
18. Solankee, A.; Kapadia, K.; Ana Ćirić; Soković, M.; Doytchinova, I.; Geronikaki, A. *Eur. J. Med. Chem.* **2010**, *45*, 510-518. https://doi.org/10.1016/j.ejmech.2009.10.037
19. Srivastava, J. K.; Dubey, P.; Singh, S.; Bhat, H. R.; Kumawat, M. K.; Singh, U. P. *RSC Adv.* **2015**, *5*, 14095-14102. https://doi.org/10.1039/C4RA16903D
20. Müller, G. Chapter 2 - History of the discovery and development of triazine herbicides. In; LeBaron, H.M.; McFarland, J.E.; Burnside, O.C. (Eds.); Elsevier: San Diego, **2008**, 13-29. https://doi.org/10.1016/B978-044451167-6.50005-2
21. Smolin, E.M.; Rapoport, L. S-Triazines and Derivatives, Volume 13; Wiley-Interscience: New York, **1959**.
22. Kumar, R.; Kumar, N.; Roy, K. R.; Singh, A. *Curr. Signal Transduct. Ther*. **2019**, *14*, 87-106. https://doi.org/10.2174/1574362413666180221113805
23. Britten, C. D.; Adjei, A. A.; Millham, R.; Houk, B. E.; Borzillo, G.; Pierce, K.; Wainberg, Z. A.; LoRusso, P. M. *Invest. New Drugs*. **2014**, *32*, 510-517. https://doi.org/10.1007/s10637-013-0062-5
24. Poirier, M.; Awale, M.; Roelli, M. A.; Giuffredi, G. T.; Ruddigkeit, L.; Evensen, L.; Stooss, A.; Calarco, S.; Lorens, J. B.; Charles, R.-P.; Reymond, J.-L. *ChemMedChem.* **2019**, *14*, 224-236. https://doi.org/10.1002/cmdc.201800554
25. Jin, H.; Cianchetta, G.; Devasagayaraj, A.; Gu, K.; Marinelli, B.; Samala, L.; Scott, S.; Stouch, T.; Tunoori, A.; Wang, Y.; Zang, Y.; Zhang, C.; David Kimball, S.; Main, A. J.; Ding, Z.-M.; Sun, W.; Yang, Q.; Yu, X.-Q.; Powell, D. R.; Wilson, A.; Liu, Q.; Shi, Z.-C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5229-5232. https://doi.org/10.1016/j.bmcl.2009.07.005
26. Łażewska, D.; Kurczab, R.; Więcek, M.; Satała, G.; Kieć-Kononowicz, K.; Handzlik, J. *Bioorg. Chem.* **2019**, *84*, 319-325. https://doi.org/10.1016/j.bioorg.2018.11.046
27. Dugar, S.; Hollinger, F. P.; Mahajan, D.; Sen, S.; Kuila, B.; Arora, R.; Pawar, Y.; Shinde, V.; Rahinj, M.; Kapoor, K. K.; Bhumkar, R.; Rai, S.; Kulkarni, R. *ACS Med. Chem. Lett.* **2015**, *6*, 1190-1194. https://doi.org/10.1021/acsmedchemlett.5b00322
28. List, M.; Puchinger, H.; Gabriel, H.; Monkowius, U.; Schwarzinger, C. *J. Org. Chem.* **2016**, *81*, 4066-4075. https://doi.org/10.1021/acs.joc.6b00355
29. Dao, P.; Garbay, C.; Chen, H. *Tetrahedron* **2013**, *69*, 3867-3871. https://doi.org/10.1016/j.tet.2013.03.039
30. Xu, Y.; Shen, B.; Liu, L.; Qiao, C. *Tetrahedron Lett.* **2020**, *61*, 151844. https://doi.org/10.1016/j.tetlet.2020.151844
31. Zeng, M.; Wang, T.; Cui, D.-M.; Zhang, C. *New J. Chem.* **2016**, *40*, 8225-8228. https://doi.org/10.1039/C6NJ01620K
32. Chaurasia, S. R.; Dange, R.; Bhanage, B. M. *Catal. Commun.* **2020**, *137*, 105933. https://doi.org/10.1016/j.catcom.2020.105933
33. Bin Shahari Ahmad; Tiekink, Edward R. T.; Dolzhenko, Anton V., M. S. J. *Synthesis* **2021**, *53*, 2457-2468. https://doi.org/10.1055/a-1401-2795
34. Moustafa, M. S.; Mekheimer, R. A.; Al-Mousawi, S. M.; Abd-Elmonem, M.; El-Zorba, H.; Hameed, A. M. A.; Mohamed, T. M.; Sadek, K. U. *Beilstein J. Org. Chem.* **2020**, *16*, 1706-1712.

https://doi.org/10.3762/BJOC.16.142
35. Mekheimer, R. A.; Abuo-Rahma, G. E. A.; Abd-Elmonem, M.; Yahia, R.; Hisham, M.; Hayallah, A. M.; Mostafa, S. M.; Abo-Elsoud, F. A.; Sadek, K. U. *J. Mol. Struct*. **2022**, *1267*, 133615. https://doi.org/10.1016/j.molstruc.2022.133615
36. Mekheimer, R. A.; Hayallah, A. M.; Moustafa, M. S.; Al-Mousawi, S. M.; Abd-Elmonem, M.; Mostafa, S. M.; Abo Elsoud, F. A.; Sadek, K. U. *Green Process. Synth.* **2021**, *10*, 201-207. https://doi.org/10.1515/gps-2021-0014
37. Dyab, A. K. F.; Sadek, K. U. *RSC Adv.* **2018**, *8*, 23241-23251. https://doi.org/10.1039/C8RA04195D
38. Abdel Hamid, A.; Abd-Elmonem, M.; Hayallah, A. M.; Abo Elsoud, F. A.; Sadek, K. U. *ChemistrySelect.* **2017**, *2*, 10689-10693. https://doi.org/10.1002/slct.201702011

