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Microwave-assisted efficient one-pot synthesis of N^2-(tetrazol-5-yl)-6-aryl/heteroaryl-2,3-dihydro-1,3,5-triazine-2,4-diamines

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Abstract

An efficient one-pot synthesis of N^2-(tetrazol-5-yl)-6-aryl/heteroaryl-1,3,5-triazine-2,4-diamine derivatives was developed by reacting 5-amino-1,2,3,4-tetrazole with aromatic aldehydes and cyanamide in pyridine under controlled microwave heating with high yields. X-ray crystallography confirmed the structure of obtained products.

Keywords

N^2-(tetrazol-5-yl)-6-aryl/heteroaryl-1,3,5-triazine-2,4-diamines; Microwave irradiation; one-pot synthesis; X-ray crystallography.

Introduction

The family of triazines are of considerable interest in fields related to organic and medicinal chemistry. 2,4-Diaminotriazines are privileged scaffolds that exhibit a diversity of biological activities as anti-bacterial [1], anti-HSV-1 [2], anti-tumor [3], anti-HIV [4], inhibitor of Trypanosoma brucei [5], angiogenesis inhibitor [6], anti-plasmodial antifolates [7] and anti-microbial [8]. Moreover and in particular N^2,6-disubstituted-1,3,5-triazine-2,4-diamines possess a wide range of chemotherapeutic activities [9-12].

Tetrazole derivatives are a potent class of heterocyclic compounds with a wide range of biological activities owing to their unique structure. They play an important role not only as a bioisostere of carboxylic acid group but also as flexible ligands which can adopt easily to different binding modes [13,14]. Tetrazole derivatives exhibit a wide spectrum of biological activities as anti-

bacterial [15], anti-cancer [16], anti-inflammatory [17], anti-diabetic [18], antitubercular [19] and analgesic [20] agents.

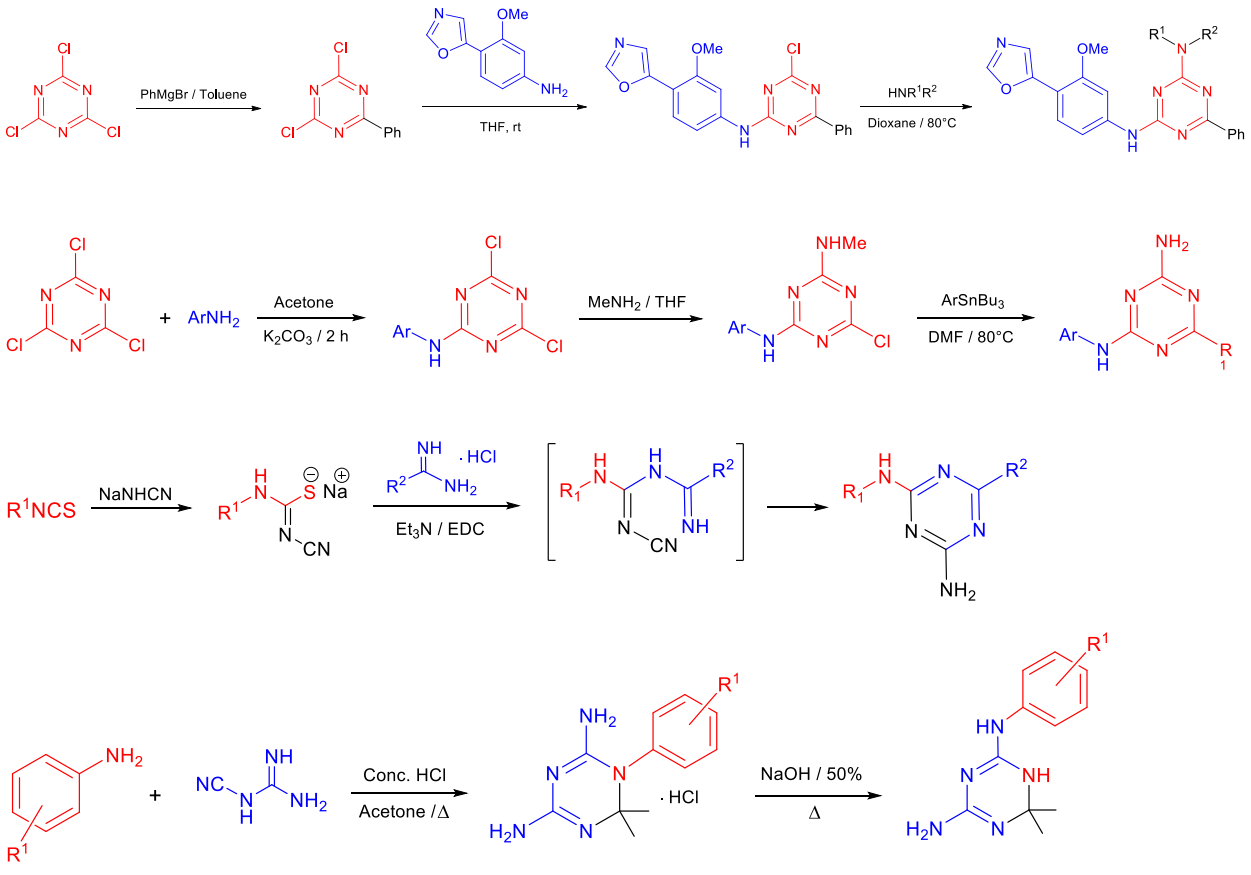
It is well established that many medical disorders can be caused as a result of defects in more than one specific biological target as receptor or enzyme. A promising strategy overcomes the classical one-target, one-molecule approach is the design of stable chemical hybrid molecules which are combination of two biologically active scaffolds acting at different targets [21-25]. Accordingly, we reasoned that heterocycles incorporating both N^2-(tetrazol-5-yl) ring system and 1,3,5-triazine-2,4-diamine scaffold could be very effective biologically relevant heterocycles.

A little attention has been paid for the synthesis of N^2,6-disubstituted-1,3,5-triazine-2,4-diamines which utilize a multistep route. First route performs the nucleophilic substitution of chlorine atoms in cyanuric chloride with Grignard reagents, ammonia or amines [26,27] which suffers from the high reactivity of Grignard reagents that prevent further elaborated functionalization. Moreover, such protocol requires temperature control and shows dependence on amine nucleophile reactivity [28]. Another route was developed that rely on the reaction of substituted biguanidines with acetic anhydrides, chlorides or carboxylates [29-33]. Liu et al. [34] reported a one-pot synthesis of N^2,6-disubstituted-1,3,5-triazine-2,4-diamines in 44-72% yields that employed the reaction of isothiocyanates with sodium hydrogen cyanamide and amidines in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and heating at 75 °C for 3 h. Recently, Ma et al. [35] described a one-pot two steps procedure for the synthesis of 6-substituted-N^2-phenyl-1,6-dihydro-1,3,5-triazine-2,4-diamines *via* reaction of aromatic amines, cyanoguanidine and ketones which afforded the corresponding 6-substituted-1-aryl-1,6-dihydro-1,3,5-triazine-2,4-diamines in 21-56% yields followed by Dimroth rearrangement utilizing sodium hydroxide (50%) in aqueous ethanol (Scheme 1).

Although, these methods have specific merits, they sometimes suffer from drawbacks as extended reaction temperatures, lengthy procedures, low yields and atom economy which consume excess reagents. Extensive efforts have

been devoted to adopting green methodologies in synthetic heterocyclic chemistry. The utility of microwave heating technique as an energy source has several merits that include operational simplicity, high reaction yields, enhanced rates and increased energy efficiency [36-42].

In continuation of our efforts in performing green methodologies in the synthesis of biologically relevant heterocycles from simple starting materials [43-46], we developed an efficient synthesis of *N*^{2}-(tetrazol-5-yl)-6-aryl/heteroaryl-1,3,5-triazine-2,4-diamines through one-pot reaction of cyanamide **1**, aromatic aldehydes **2** and 5-aminotetrazole **3** in pyridine under controlled microwave heating (Scheme 2).



Scheme 1: Efficient methods for the synthesis of 1,3,5-triazine-2,4-diamine derivatives.

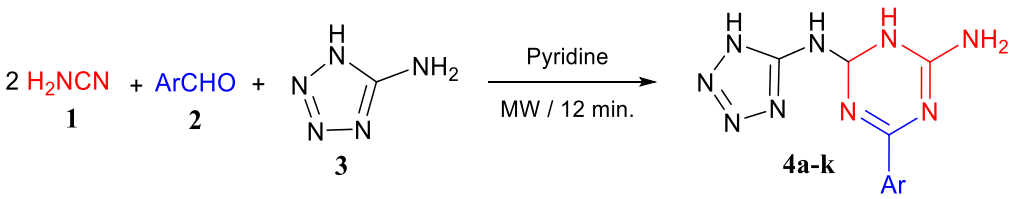
Results and discussions

With the initial aim of optimizing the reaction conditions, we began our study by reacting equimolar amount of cyanamide **1**, aromatic aldehydes **2** and 5-aminotetrazole **3** in pyridine and the reaction was promoted by microwave heating at 120°C over 12 min. After cooling at room temperature and working up the reaction mixture, a solid product was obtained in low yield (40%) and confirmed to be 6-(4-chloro-phenyl)-N^2-(1*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine **4a** *via* analytical and spectral data. The mass spectrum of the reaction product showed a molecule ion peak m/z= 290.1 (M^+). The ^{1}H NMR revealed four singlet signals at δ = 11.22, 10.81, 8.72 and 6.17 ppm each integrated for one proton which were assigned to the triazine-NH, NH at N^2-(tetrazole-5-yl) tetrazole NH triazine CH-2 protons in addition to two broad singlets at signals at δ = 8.59 and 7.32 ppm for NH_2 function as well as signals for aromatic protons. ^{13}C NMR spectrum was in support of the proposed structure. Based on the established product, we could reveal that two molecules of cyanamide **1** participate in the reaction course and the yield was increased to 92% when the molar ratio of reactants **1,2,3** was 2:1:1. We next surveyed a structurally diverse group of aromatic aldehydes **2** with cyanamide **1** and 5-aminotetrazole **3** under the same experimental conditions and the results are summarized in (Table 1) (Scheme 2). Irrespective of the aryl group either electron-donating or electron-withdrawing, the reaction proceeded smoothly and gave a variety of 1,3,5-triazine-2,4-diamines **4** in high yields.

The effect of solvent was also examined, other solvents were screened under the same experimental conditions and our results revealed that utilizing dioxane, CH_3CN, THF, catalyst-free ethanol resulted in no product formation. The same products were obtained with lower yields under much longer conventional heating. These examples demonstrated the advantages of microwave heating as an efficient energy source.

Table 1: Microwave three-component synthesis of triazines **4a-K**.

Entry	Ar	Product	Yield (%)
1	4-ClC_6H_4	**4a**	92
2	3,4-$OMeC_6H_3$	**4b**	90
3	4-$OMeC_6H_4$	**4c**	89
4	C_6H_5	**4d**	93
5	benzo[*d*]dioxal	**4e**	88
6	2-$OMeC_6H_4$	**4f**	88
7	4-MeC_6H_4	**4g**	87
8	2-ClC_6H_4	**4h**	92
9	3-$NO_2C_6H_4$	**4i**	93
10	2-furyl	**4j**	91
11	4-$NMe_2C_6H_4$	**4k**	88



Scheme 2: Synthesis of N^2-(tetrazol-5-yl)-6-aryl/heteroaryl-2,3-dihydro-1,3,5-triazine-2,4-diamines **4a-k**.

The structure proposed for the reaction products was established on the bases of analytical and spectral data (MS, ^{1}H NMR, ^{13}C NMR and elemental analyses). Moreover, the structure of **4** was unequivocally supported by single-crystal X-ray diffraction of **4j** (Fig. 1). A plausible mechanism for the formation of products **4** is postulated in (Scheme 3).

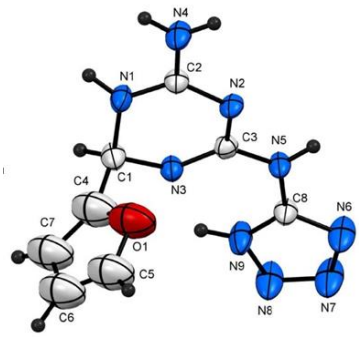
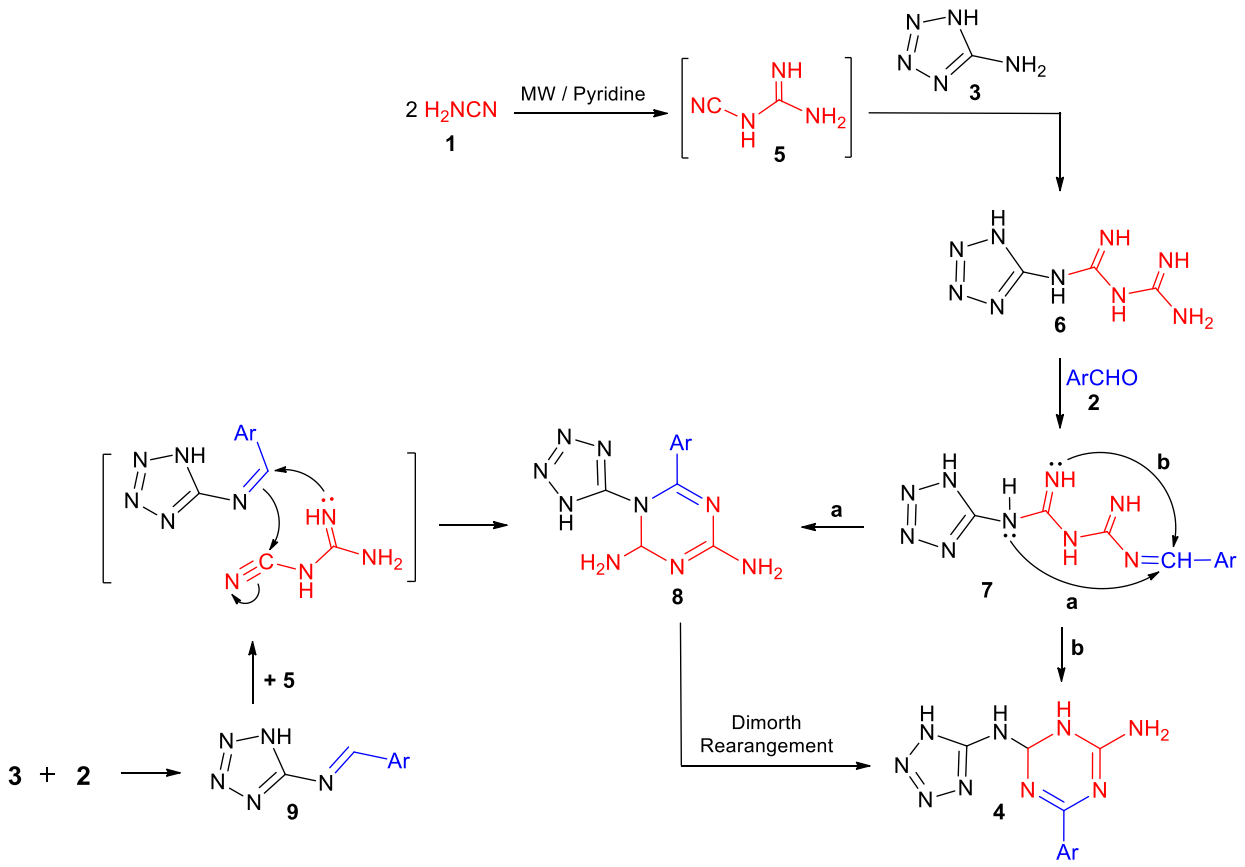


Figure 1: ORTEP diagram of compound **4j**.

Table 2 Selected bond lengths and bond angles for compound **4j**.

Bond lengths		Bond angles	
Atom numbers	Geometric parameter (A°)	Atom numbers	Geometric parameter (°)
O1-C5	1.360 (9)	C1-N1-C2	121.6 (4)
C4-C7	1.326 (11)	C2-N2-C3	115.0 (4)
C1-C4	1.465 (9)	N1-C2-N4	118.2 (4)
N6-N7	1.336 (7)	C1-C4-C7	136.2 (8)
N5-N3	1.339 (6)	C4-O1-C5	109.8 (6)
N1-C1	1.453 (6)	N6-N7-N8	109.9 (5)
C1-C4	1.465 (12)	N8-N9-C8	104.4 (4)
N3-C1	1.459 (6)	N2-C3-N5	116.1 (4)
		O1-C4-C1	116.6 (6)
		O1-C5-C6	106.2 (7)



Scheme 3: A plausible mechanism to account for the formation of products **4**.

Dimerization of cynamide **1** in basic medium to cyanoguanidine **5** and subsequent reaction with 5-aminotetrazole **3** yielded tetrazolylbiguanidine **6** which undergoes a condensation reaction with aromatic aldehydes **2** to afford **7**. Nucleophilic attack of the secondary amine in **7** to the arylidine carbon will give rise to the formation of 6-aryl-1-(1*H*-tetrazol-5-yl)-1,2-dihydro-1,3,5-triazine-2,4-diamine intermediate **8** (route a)- alternatively, intermediate **8** could be obtained by condensation of 5-aminotetrazole **3** with aldehydes **2** followed by addition of cyanoguanidine **5** to the formed Schiff's base **9** while the nucleophilic attack of primary amine in **7** to the same imine carbon will produce the corresponding N^2-(tetrazole-5-yl)-6-aryl-1,3,5-triazine-2,4-diamines **4** (route b). Product **4** was the sole isolable product as under the reaction conditions compound **8** will undergo Dimroth rearrangement forming **4**.

Conclusion

The synthesis of biologically relevant 6-aryl/heteroaryl-N^2-(5*H*-tetrazole-5yl)-2,3-dihydro-1,3,5-triazine-2,4-diamines has been achived under controlled microwave heating via a simple one-pot, three-comonent reaction of cyanamide 1, aldehydes 2 and 5-amino-1,2,3,4-tetrazole 3 in excellent yields. The process proved to be an efficient synthetic route with high atom economy, short reaction times and simple work-up procedure. This protocol appears to be general with diversity of amines and aldehydes.

Experimental

All chemicals were purchased from Aldrich or Merck Companies. The ^{1}H NMR (600 MH_Z) and ^{13}C NMR (150 MH_Z) were run in a Bruker DPX instrument (δ ppm). Mass spectra were measured by using VG Autospec Q MS 30 and MS 9 (AEI) spectrometer, with EI (70 eV) mode. Melting points were recorded in a Gallaenkamp melting point apparatus and are uncorrected. X-ray crystallographic structure determinations were performed by using Rigaku Rapid II and Bruker X8 Prospector single crystal X-ray Diffractometers. All X-ray crystal structure data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk CCDC1961565 for compound **(4j).** All reactions were monitored by using TLC with 1:1 ethyl acetate-petroleum ether as eluent and were carried out until starting materials were completely consumed.

General procedure for the synthesis of N^2-,6-di-substituted-1,3,5-triazoine-2,4-diamine derivatives:

A solution of **1** (2 mmol), **2** (1 mmol) and **3** (1 mmol) in pyridine (10 mL) was heated under reflux in a Milestone Microwave Labstation at 120°C for 12 min. The solvent was removed under reduced pressure and the solid product was isolated by filtration and recyclization from DMF.

6-(4-Chlorophenyl)-N^2-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine (4a). Colorless crystals; mp: 320-322°C, yield 0.268 g, 92%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 6.17 (S, 1H), 7.32 (S, 1H), 7.46 (d, 2H, *J* = 8.4 Hz), 7.53 (d, 2H, *J* = 9.2 Hz), 8.58 (s, 1H), 8.73 (brs, 1H), 10.82 (s, 1H), 11.22 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 61.52, 127.84, 128.94, 133.70, 139.75, 154.45, 157.61, 158.0; anal. calcd. for

$C_{10}H_{10}ClN_9$: C, 41.17; H, 3.46; Cl, 12.15; N, 43.12. Found: C, 41.22; H, 3.42; Cl, 12.11; N, 43.24. EIMS m/z: 290.1 (M^+).

6-(4-Methoxyphenyl)-*N*^{2}-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine (4c). Colorless crystals; mp: 306-308°C, yield 0.255 g, 89%. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 3.74 (s, 3H), 6.07 (s, 1H), 7.0, 7.01 (dd, 2H, *J* = 8.4, 1.8 Hz), 7.38 (s, 1H), 7.39 (d, 2H, *J* = 8.4 Hz), 8.29 (s, 1H), 8.60 (s, 1H), 10.69 (s, 1H), 11.15 (s, 1H). ^{13}C NMR (150 MHz, DMSO-*d*$_6$): δ 55.26, 62.01, 114.29, 127.51, 132.45, 154.57, 157.79, 158.14, 159.92, 162.33; anal. calcd. for $C_{11}H_{13}N_9O$: C, 45.99; H, 4.56; N, 43.88. Found: C, 45.89; H, 4.52; N, 43.90.

6-Phenyl-*N*^{2}-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine (4d). Colorless crystals; mp: 317-319°C, yield 0.277 g, 93%. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 6.15 (s, 1H), 7.22 (s, 1H), 7.40-7.46 (m, 5H), 8.50 (br, s, 1H); 8.71 (s, 1H); 10.77 (s, 1H), 11.20 (s, 1H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$), δ 62.2, 125.9, 128.9, 129.1, 154.5, 157.7, 158.0, anal. calcd. for $C_{10}H_{11}N_9$: C, 46.69; H, 4.30; N, 49.0. Found: C, 46.76; H, 4.41; N, 48.85. EIMS m/z: 257.3 (M^+).

6-(Benzo[*d*][1,3]dioxol-5-yl)-*N*^{2}-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine (4e). Colorless crystals; mp: 304-306°C, yield 0.265 g, 88%. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 6.04 (t, 3H, *J* = 8.4 Hz), 6.90-7.12 (m, 4H), 8.02 (brs, 1H), 8.55 (s, 1H), 10.68 (s, 1H), 11.10 (s, 1H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$), δ 56.0, 62.0, 101.4, 106.3, 108.29, 119.63, 134.38, 147.76, 147.93, 154.49, 157.72, 158.15; anal. calcd. for $C_{11}H_{11}N_9O_2$: C, 43.85; H, 3.68; N, 41.94. Found: C, 43.76; H, 3.59, N, 41.79.

6-(2-Methoxyphenyl)-*N*^{2}-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine (4f). Colorless crystals; mp: 310-312°C, yield 0.247 g, 88%. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 3.89 (s, 3H), 6.27 (s, 1H), 7.02 (t, 1H, *J* = 8.4 Hz), 7.12 (d, 1H, J = 8.4), 7.20, 7.21 (dd, 1H, *J* = 8.4, 1.8 Hz), 7.38-7.41 (m, 1H), 8.04 (br, s, 1H), 8.36 (s, 1H), 10.87 (s, 1H), 11.07 (s, 1H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$), δ 55.85, 58.74, 111.65, 120.42, 125.28, 127.77, 130.50, 154.61, 156.3, 157.97, 158.2; anal. calcd. for $C_{11}H_{13}N_9O$: C, 45.99; H, 4.56; N, 43.88. Found: C, 46.10; H, 4.69; N, 43.81.

6-(4-Methylphenyl)-*N*^{2}-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine (4g). Colorless crystals; mp: 314-316°C, yield 0.235 g, 87%. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 2.30 (s, 3H); 6.09 (s, 1H); 7.19 (s, 1H); 7.26 (d, 2H, *J* =8.4 Hz), 7.34 (d, 2H, *J* = 8.4 Hz), 8.47 (brs, 1H), 8.66 (s, 1H); 10.7 (s, 1H); 11.18 (s, 1H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$): δ 20.73, 62.08, 125.90, 129.41, 137.64, 138.69, 154.53, 157.76, 158.07, anal. calcd. for $C_{11}H_{13}N_9$: C, 48.70; H, 4.83; N, 46.47. Found: C, 48.75; H, 4.70; N, 46.56.

6-(2-Chlorophenyl)-*N*^{2}-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine (4h). Colorless crystals; mp: 324-326°C, yield 0.267 g, 92%. ^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ

6.44 (s, 1H), 7.22 (s, 1H), 7.42-7.44 (m, 1H), 7.45-7.48 (m, 2H), 7.56-7.59 (m, 1H), 8.55 (brs, 1H) 8.65 (s, 1H), 10.94 (s, 1H), 11.29 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 60.55, 127.39, 127.98, 130.30, 131.05, 131.42, 137.07, 154.52, 157.71, 158.04, 162.31, anal. calcd. for $C_{10}H_{10}ClN_9$: C, 41.17; H, 3.46; Cl, 12.15; N, 43.22. Found: C, 41.30; H, 3.34; Cl, 12.30; N, 43.38.

6-(3-Nitrophenyl)-*N*^{2}-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine (4i). Colorless crystals; mp: 298-300°C, yield 0.281 g, 93%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 6.35 (s, 1H); 7.52 (s, 1H); 7.76 (t, 1H, *J* = 7.2 Hz), 7.88 (s, 1H); 8.26 (d, 1H, *J* = 7.8 Hz), 8.34 (s, 1H), 8.88 (brs, 2H); 10.95 (s, 1H), 11.26 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 61.28, 120.92, 123.91, 130.73, 132.27, 143.13, 147.95, 154.42, 157.62, 157.94; anal.caled. for $C_{10}H_{10}N_{10}O_2$: C, 39.74; H, 3.33; N, 46.34. Found: C, 39.68; H, 3.47; N, 46.52.

6-(Furan-2-yl)-*N*^{2}-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine (4j). Colorless crystals; mp: 208-210°C, yield 0.224 g, 91%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 6.24 (s, 1H), 6.46 (d, 2H, *J* = 16.8 Hz), 7.29 (brs, 1H), 7.70 (s, 1H), 8.52 (brs, 1H), 8.69 (s, 1H), 10.76 (s, 1H), 11.21 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6); δ 56.48, 107.88, 110.61, 143.88, 152.35, 154.52, 157.68, 157.97; anal.caled. for $C_8H_9N_9O$: C, 38.87; H, 3.67; N, 50.99. Found: C, 38.68; H, 3.76; N, 51.06.

6-(4-*N,N*-Dimethylaminophenyl)-*N*^{2}-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,3,5-triazine-2,4-diamine (4k). Colorless crystals; mp: 278-280°C, yield 0.264 g, 88%. ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.91 (s, 6H), 5.96 (s, 1H), 6.59 (d, 2H, *J* = 8.4 Hz), 7.01 s, 1H); 7.20 (d, 2H, *J* = 8.4 Hz), 7.78 (brs, 1H), 8.46 (s, 1H), 10.59 (s, 1H), 11.03 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6); δ 62.36, 111.42, 112.15, 127.01, 127.17, 128.32, 151.04, 154.64, 157.90, 158.24; anal.caled. for $C_{12}H_{16}N_{10}$: C, 47.99; H, 5.37; N, 46.64. Found: C, 48.10; H, 5.43; N, 46.52.

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47. CCDC 196/565 contains the supplementary crystallographic data for compound **4j**. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via https://www.ccdc.cam.ac.uk