A Facile One Pot Synthesis of 2, 4-Diamino-6-substituted s-Triazine Derivatives

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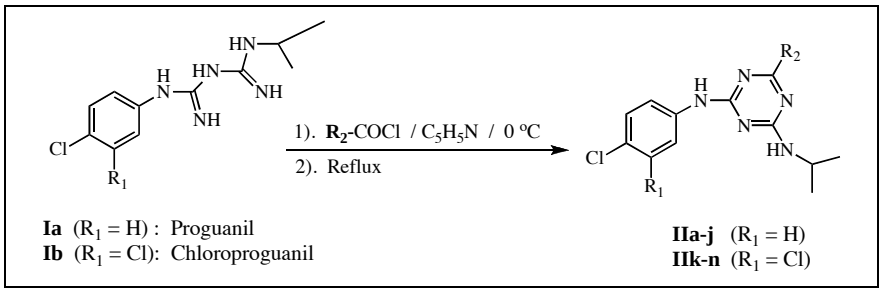

A novel and facile one-pot procedure for the preparation of 2,4-diamino-6-substituted-s-triazine derivatives (**IIa-n**) was reported. The scope of its application was demonstrated with a number of examples. The new procedure involved treatment of proguanil or chloroproguanil with acyl chloride or alky chlorooxoacetate in pyridine at ice cold temperature followed by reflux overnight to give good yields of the desired products.

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INTRODUCTION

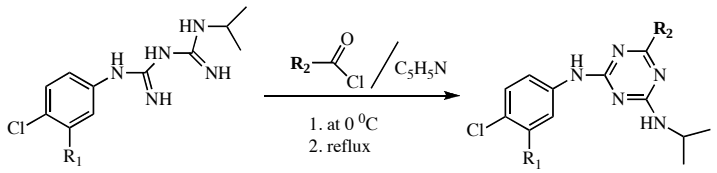
As part of our efforts in search of malaria prophylactic and/or therapeutic agents, a series of imidazolidinedione (IZ) derivatives were found to possess profound activity against liver stage malaria in rodent and non-human primate models [1-4]. Subsequently, the IZ compounds were found to metabolize to s-triazine derivatives in microsomal preparations and in animals [4]. Active in mice tests, the triazines were considered the active metabolite of the IZ compounds. This finding prompted us to develop methods to prepare a series of *N*,*N*'-disubstituted s-triazine-2,4-diamine and 6-substituted pyrimidine-2,4-diamine derivatives as potential antimalarial agents.

The 1,3,5-triazine (s-triazine) ring is well represented in synthetic compounds endowed with biological activities. Its chemistry continues to draw the attention of many researchers throughout the world. Several reviews emphasize synthetic approaches and reactivity of this heterocycle [5-8] and a well documented application of the pharmacological properties of its derivatives are widely reported [4,9,10]. 6-Substituted-1,3,5-triazine-2,4-diamines have often been found to be synthetic targets as chemotherapeutic agents [11-15]. Previous synthetic methods for such compounds mainly relied on four routes, which required two, three or four steps. One route starts with cyanuric chloride, which can sequentially be reacted with Grignard reagents [11,16], ammonia, and amines to give the desired s-triazines. The utility of this procedure is limited by the fact that Grignard reagents are highly reactive and therefore prevent versatile functionalities for further elaboration. The other route involves the reaction of substituted isothiocyanates with sodium hydrogencyanamide, followed by amidines in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) [17-18]. This procedure appears more general. In another study, Insuasty *et al.* [19] prepared another series of pyrazolo[1,5-*a*]-1,3,5-triazines by the reaction of *S*,*S*-diethyl aroyliminodithoicarbonates and aroyl isothiocyanates with 5-amino-3-methylpyrazole in dimethylformamide under reflux. Subsequently, Montalbetti *et al.* [20] prepared a series of 4,6-diamino-1,3,5-triazines by acetone-potassium carbonate catalyzed reaction of 2,4-dichloro-6-morpholin-1,3,5-triazine and chloroanilines followed by the Suzuki coupling reaction to introduce an aryl substituent at the 2-position.

RESULTS AND DISCUSSION

The one pot reaction involved the treatment of an acylchloride or alkyl chlorooxoacetate with proguanil (**Ia**) or chloroproguanil (**Ib**) in anhydrous pyridines at 0 °C, allowed to warm up to room temperature and then reflux overnight. The yields of the triazines (**IIa-n**) ranged from 52% to 77%, which are, for the most part, significantly higher than any methods previously reported. This simple method can be applied to prepare a wide variety of 6-substituted 2,4-diaminotriazine derivatives using various aliphatic or aromatic acylchlorides and substituted biguanides **Ia,b** as starting material to give the corresponding triazines **IIa-n** in one step. The starting materials, reagents, yields and products of the one pot synthesis are shown in Table 1.

Scheme 1: One Pot Reaction



Ia (R_1 = H) : Proguanil
Ib (R_1 = Cl): Chloroproguanil

IIa-j (R_1 = H)
IIk-n (R_1 = Cl)

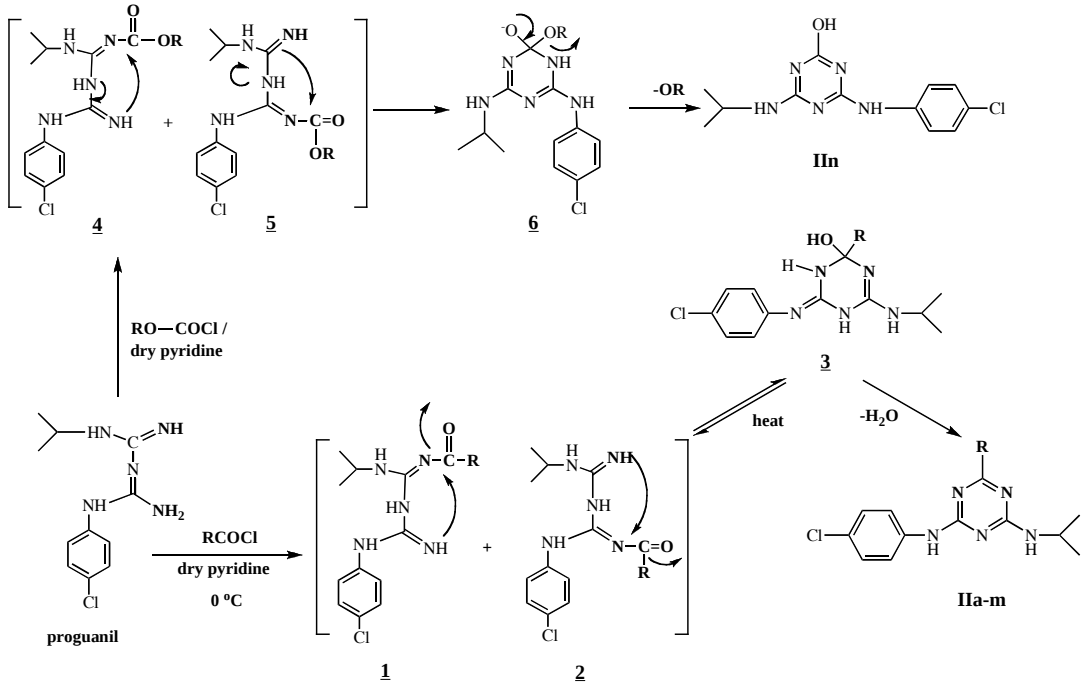
Table 1

Yields of s-Triazines from Coupling of Biguanides with Acylchlorides or Alkyl-chlorooxoacetates.

Compound	Biguanide	Acyl Chloride	R_2	Yields (%)
IIa	**Ia**	CH_3COCl	CH_3	52.2
IIb	**Ia**	$(CH_3)_2CHCOCl$	$CH(CH_3)_2$	64.4
IIc	**Ia**	$(CH_3)_2CHCH_2COCl$	$(CH_3)_2CHCH_2$-	72.8
IId	**Ia**	$(CH_3CH_2)_2CHCOCl$	$(CH_3CH_2)_2CH$-	56.3
IIe	**Ia**	PhCOCl	Ph-	51.2
IIf	**Ia**	*p-Cl*-PhCOCl	*p-Cl*-Ph	77.4
IIg	**Ia**	*p-Me*-PhCOCl	*p-Me*-Ph	49.1
IIh	**Ib**	PhCOCl	-Ph	71.1
IIi	**Ia**	$CH_3CH_2CH_2COCl$	$-CH_2CH_2CH_3$	47.3
IIj	**Ib**	$(CH_3CH_2)_2CHCOCl$	$-CH(CH_2CH_3)_2$	60.6
IIk	**Ib**	$CH_3OCOCOCl$	$-COOCH_3$	28.7
IIl	**Ib**	$CH_3CH_2OCOCOCl$	$-COOCH_2CH_3$	32.9
IIm	**Ib**	$PhCH_2OCOCOCl$	$-COOCH_2Ph$	76.6
IIn	**Ia**	CH_3CH_2OCOCl	-OH	72.5

The possible mechanism of the one pot reaction is proposed as shown in Scheme 2. Treating proguanil with an equal molar amount of acyl chloride at low temperature, the primary amino group of the proguanil reacts with acylchlorides to give a mixture of mono-amide intermediates **1** and **2** which cyclized to form 2-aryl-amino-4-isopropylamino-6–alkyl/aryl-1,2,5,6-tetrahydro-[1,3,5]-triazin-6-ol (**3**), from which a water molecule was eliminated to give the desired s-triazines (**IIa-m**). When ethyl chloroformate was used as an acylating agent,

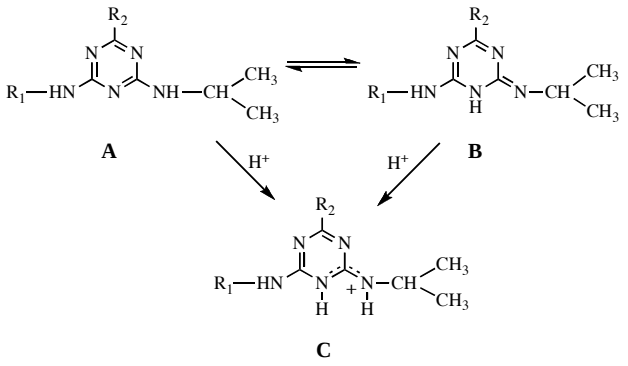
Scheme 2: Mechanism of One Pot Reaction



2-hydroxy-s-triazine (**IIn**) was formed, instead of the 2-ethoxy-s-triazine analog, involving elimination of ethoxy rather than the hydroxy group from the intermediate **6**.

The ^{1}H NMR spectra of **IIa-d, IIh-i, III** and **IIm** in $CDCl_3$ or DMSO-d_6 showed a pure single compound but the spectra of **IIe-g, IIj-l,** and **IIn** in the same solvent indicated the formation of two tautomers, **A** and **B**, as shown in Scheme 3. The NMR data in $CDCl_3$ indicated the ratio between the **B** and **A** tautomers of the new triazines is about 6:4 by integration. The ratio is solvent dependent. The most striking difference in chemical shifts of the two tautomers is the N-C*H* proton of the isopropyl group. The **B** tautomer N-C*H* proton (~ 4.2 ppm) is about 0.2 ppm up field to the same proton of the **A** tautomer (~ 4.4 ppm). Without N*H* in the **B** for coupling, the N-C*H*$(CH_3)_2$ proton appeared as sharp multiplets, in contrast to a broad multiplets for the same proton in the **A**, a sign of further -N*H*-C*H*-coupling. A single tautomer **C** formed when a drop of trifluoroacetic acid or deuterated acetic acid was added to the $CDCl_3$ or DMSO-d_6 solution.

Scheme 3: Formation of Tautomers A and B



The NMR spectra of the tautomers were provided separately in the experimental section. The final products were characterized by ^{1} H NMR, ^{13} C NMR, MS, and elemental analysis. The NH protons of the s-triazine **IIa-n** at the 2- and the 4-positions were confirmed by deuterium oxide exchange studies.

In conclusion, we have described an efficient, one pot, and versatile method for the preparation of 2,4-diamino-s-triazine derivatives by treatment of biguanides with acyl chlorides or alkyl chlorooxoacetates.

EXPERIMENTAL

Melting points were determined on a Mettler FP62 melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed using HPTLC-HLF normal phase 150 micron silica gel plates (Analtech, Newark, DE). Visualization of the developed chromatogram was performed by UV absorbance or by staining with iodine vapor. Liquid chromatography was performed using a Horizon HPFC System (Biotage, Charlottesville, VA) with Flash 25M or 40M cartridges (KP-Sil Silica, 32-63 μm, 60 A°). Preparative TLC was performed using silica gel GF tapered uniplates (Analtech, Newark, DE). ^{1}H NMR and ^{13}C NMR spectra were recorded in deuteriochloroform, unless otherwise noted, on a Bruker Avance 300 spectrometer (Bruker Instruments, Inc, Wilmington, DE). Chemical shifts are reported in parts per million on the δ scale from an internal standard of tetramethylsilane. When the compounds formed two tautomers, the chemical shifts with * indicated the peaks were shared by both tautomers in NMR spectra. Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Where analyses are indicated by symbols of the elements, the analytical results obtained were within ± 0.4% of the theoretical values. Mass analysis based on electron impact (EI) was done on a Hewlett Packard (Agilent; Santa Clara, CA) 5973 Mass Selector adapted with a HPP7 Direct Insertion Probe (Scientific Instrument Services; Ringoes, NJ) using a steep temperature gradient at either low voltage (5eV) to identify masses present or high voltage (70eV) to obtain fragmentation data. An LC/UV-VIS/Trap MS was also

Table 2

Elemental analysis of alkyltriazines

Compd	Formula	Molecul. Weight	Calcd				Found			
			C	H	Cl	N	C	H	Cl	N
IIa	$C_{13}H_{16}ClN_5$	278.21	56.22	5.81	12.76	25.21	56.01	5.78	12.98	24.95
IIb	$C_{15}H_{20}ClN_5$	306.19	58.91	6.59	11.59	22.90	58.77	6.55	11.81	22.69
IIc	$C_{16}H_{22}ClN_5$	320.47	60.08	6.93	11.08	21.90	60.17	7.07	11.35	21.84
IId	$C_{17}H_{24}ClN_5$	334.68	61.16	7.25	10.62	20.98	61.56	7.22	10.75	20.43
IIe	$C_{18}H_{18}ClN_5$	340.57	63.62	5.34	10.43	20.61	63.77	5.40	10.34	20.53
IIf	$C_{18}H_{17}Cl_2N_5$	374.66	57.76	4.58	18.95	18.71	58.04	4.58	18.82	18.69
IIg	$C_{19}H_{20}ClN_5$	354.20	64.49	5.70	10.02	19.79	64.71	5.80	9.84	19.53
IIh	$C_{18}H_{17}Cl_2N_5$	374.24	57.76	4.58	18.95	18.71	57.70	4.52	18.87	18.68
IIi	$C_{15}H_{20}ClN_5$	306.24	58.91	6.59	11.59	22.90	59.10	6.63	11.52	22.85
IIj	$C_{17}H_{24}Cl_3N_5$	404.76	50.44	5.98	26.28	17.30	50.49	5.98	26.16	17.21
IIk	$C_{14}H_{15}Cl_2N_5O_2$	356.03	47.21	4.24	19.91	19.66	47.20	4.30	20.23	19.17
III	$C_{15}H_{17}Cl_2N_5O_2$	370.23	48.66	4.63	19.15	18.92	48.73	4.70	19.27	18.69
IIm	$C_{20}H_{19}Cl_2N_5O_2$	432.07	55.57	4.43	16.40	16.20	55.62	4.42	16.55	16.16
IIn	$C_{12}H_{14}ClN_5O$	280.57	51.52	5.04	12.67	25.04	51.78	5.06	12.49	24.95

employed for purity analysis and chromophore properties. The system consisted of an Agilent 1100 Series LC-UV/VIS system online with a ThermoFinnigan (now ThermoFisher; Waltham, MA) LCQ MS equipped with electrospray ionization (ESI) source. Samples were analyzed using shallow acetonitrile:buffer gradients at low flow rate.

General procedure for the synthesis of *N,N'*-(disubstituted)-6-alkyl or 6-aryl-[1,3,5]-triazine-2,4-diamines (IIa-n). The solution of **Ia** or **Ib** (2.0 g, 7.90 mmol) in dry pyridine (20 mL) was cooled to 0 °C. Acyl chloride (8.69 mmol) was added drop wise to the solution with stirring. After the addition of acyl chloride was completed, the mixture was allowed to stir at room temperature for 2 hours and then heated to reflux overnight with an oil bath. The pyridine was removed under reduced pressure and the excess acyl chloride was decomposed with crushed ice. The resulting crude product was extracted with ethyl acetate twice (2 x 50 mL). The ethyl acetate extracts were combined, washed with water, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with a flash silica gel column to give the s-triazines. All the s-triazines **IIa-n** were prepared by the same procedure. The reagents, acyl chlorides, biguanides, products and the yields of the one pot reaction are listed in Table 1. The physical properties of the new s-triazines are described as follows. When the compounds formed two tautomers, the chemical shifts with * indicated the peaks were shared by both tautomers in NMR spectra.

***N*-(4-Chlorophenyl)-*N'*-isopropyl-6-methyl-[1,3,5]-triazine-2,4-diamine (IIa).** White solid, mp 172 °C {lit. [21] mp 173.5-174° C}; ^{1}H NMR ($CDCl_3$): δ 7.57 (d, *J* = 9.00 Hz, 2H, aromatic), 7.27 (d, *J* = 9.00 Hz, 2H, aromatic), 7.00 (br, 1H, NH), 5.09 (br, 1H, NH), 4.16 (m, 1H, CH), 2.30 (s, 3H, CH_3), 1.24 (d, *J* = 6.00 Hz, 6H, CH_3 x 2). ^{13}C NMR (DMSO-d_6): δ 174.68, 165.08, 164.37, 139.57, 128.65, 125.82, 121.42, 42.14, 25.19, and 22.64. MS: (m/z) 278.21(M^+). *Anal*. Calcd. for $C_{13}H_{16}ClN_5$: C, 56.22; H, 5.81; Cl, 12.76; N, 25.21. Found: C, 56.01; H, 5.78; Cl, 12.98; N, 24.95.

***N*-(4-Chlorophenyl)-*N'*-isopropyl-6-isopropyl-[1,3,5]-triazine-2,4-diamine (IIb).** White solid, mp 142 °C; ^{1}H NMR ($CDCl_3$): δ 7.59 (d, *J* = 9.00 Hz, 2H, aromatic), 7.27 (d, *J* = 9.00 Hz, 2H, aromatic), 7.05 (br, 1H, NH), 5.12 (br, 1H, NH), 4.15 (m, 1H, CH), 2.77 (m, 1H, CH), 1.25 (d, *J* = 6.00 Hz, 12H, CH_3 x 4). ^{13}C NMR ($CDCl_3$): δ 177.56, 165.32, 164.34, 137.79, 128.72, 127.68, 121.00, 42.64, 36.96, 22.68, and 20.85. MS: (m/z) 306.19 (M^+). *Anal*. Calcd. for $C_{15}H_{20}ClN_5$: C, 58.91; H, 6.59; Cl, 11.59; N, 22.90. Found: C, 58.77; H, 6.55; Cl, 11.81; N, 22.69.

***N*-(4-Chlorophenyl)-*N'*-isopropyl-6-isobutyl-[1,3,5]-triazine-2,4-diamine (IIc).** White solid, mp 153 °C; ^{1}H NMR ($CDCl_3$): δ 7.59 (d, *J* = 9.00 Hz, 2H, aromatic), 7.29 (d, *J* = 9.00 Hz, 2H, aromatic), 6.99 (br, 1H, NH), 5.10 (br, 1H, NH), 4.17 (m, 1H, CH), 2.39 (d, *J* = 6.00 Hz, 2H, CH_2), 2. 21 (m, 1H, CH), 1.26 (d, *J* = 6.00 Hz, 6H, CH_3 x 2), 1.00 (d, *J* = 6.00 Hz, 6H, CH_3 x 2). ^{13}C NMR ($CDCl_3$): δ 178.04, 165.05, 164.08, 137.61, 128.73, 127.77, 121.00, 47.85, 42.63, 27.50, 22.65, and 22.54. MS: (m/z) 320.47 (M^+). *Anal.* Calcd. for $C_{16}H_{22}ClN_5$: C, 60.08; H, 6.93; Cl, 11.08; N, 21.90. Found: C, 60.17; H, 7.07; Cl, 11.35; N, 21.84.

***N*-(4-Chlorophenyl)-*N'*-isopropyl-6-(1-ethylpropyl)-[1,3,5]-triazine-2,4-diamine (IId).** White solid, mp 87.5 °C; ^{1}H NMR ($CDCl_3$): δ 7.61 (d, *J* = 9.00 Hz, 2H, aromatic), 7.29 (d, *J* = 9.00 Hz, 2H, aromatic), 7.04 (br, 1H, NH), 5.14 (br, 1H, NH), 4.17 (m, 1H, CH), 2.23 (m, 1H, CH), 1.64 (m, 4H, CH_2 x 2), 1.27 (d, *J* = 6.00 Hz, 6H, CH_3 x 2), 0.88 (t, *J* = 9.00 Hz, 6H, CH_3 x 2). ^{13}C NMR ($CDCl_3$): δ 181.59, 165.08, 164.20, 137.86, 128.63, 127.53, 120.86, 51.70, 42.60, 31.56, 26.65, 22.62, 22.58, 14.07, 12.08. MS: (m/z) 334.68 (M^+). *Anal*. Calcd. for $C_{17}H_{24}ClN_5$: C, 61.16; H, 7.25; Cl, 10.62; N, 20.98. Found: C, 61.56; H, 7.22; Cl, 10.75; N, 20.43.

***N*-(4-Chlorophenyl)-*N'*-isopropyl-6-phenyl-[1,3,5]-triazine-2,4-diamine (IIe).** White solid, mp 206.6 °C; *Major tautomer* (60%): ^{1}H NMR ($CDCl_3$): δ 8.31 (m, 2H, aromatic)*, 7.63 (m, 2H, aromatic)*, 7.51 (m, 1H, aromatic)*, 7.47 (d, *J* = 9.00 Hz, 2H, aromatic)*, 7.30 (d, *J* = 9.00 Hz, 2H, aromatic)*, 7.20 (br, 1H, NH)*, 5.31 (br, 1H, NH)*, 4.21 (m, 1H, CH)*, 1.28 (d, *J* = 6.00 Hz, 6H, CH_3 x 2). ^{13}C NMR (DMSO-d_6): δ 170.27*, 165.43*, 164.81*, 139.53*, 137.23*, 131.83*, 128.75*, 128.25*, 126.05*, 121.74, 42.42*, 22.70*. MS: (m/z) 340.57 (M^+). *Anal*. Calcd. for $C_{18}H_{18}ClN_5$: C, 63.62; H, 5.34; Cl, 10.43; N, 20.61. Found: C, 63.77; H, 5.40; Cl, 10.34; N, 20.53. *Minor tautomer* (40%): ^{1}H NMR ($CDCl_3$): δ 8.35 (m, 1H, aromatic), 7.55 (d, *J* = 9.00 Hz, 1H, aromatic), 7.12 (br, 1H, NH), 5.12 (br, 1H, NH), 4.43 (m, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 170.40, 165.33, 164.53, 139.58, 137.31, 131.92, 128.34, 125.93, 22.88.

***N*-(4-Chlorophenyl)-*N'*-isopropyl-6-*p*-chlorophenyl-[1,3,5]-triazine-2,4-diamine (IIf).** White solid, mp 194.5 °C; *Major tautomer* (65%): ^{1}H NMR ($CDCl_3$), δ 8.27 (d, *J* = 9.00 Hz, 2H, aromatic)*, 7.62 (d, *J* = 9.00 Hz, 2H, aromatic)*, 7.42 (d, *J* = 9.00 Hz, 2H, aromatic), 7.31 (d, *J* = 9.00 Hz, 2H, aromatic), 7.12 (br, 1H, NH)*, 5.28 (br, 1H, NH)*, 4.21 (m, 1H, CH)*, 1.29 (d, *J* = 6.00 Hz, 6H, CH_3 x 2)*. ^{13}C NMR: (DMSO-d_6): δ 169.27*, 165.34*, 164.74*, 139.39*, 136.65*, 136.09*, 129.96*, 128.91*, 128.77*, 126.14*, 121.78*, 42.43*, 22.66*. MS: (m/z) 374.66 (M^+). *Anal.* Calcd. for $C_{18}H_{17}Cl_2N_5$: C, 57.76; H, 4.58; Cl, 18.95; N, 18.71. Found: C, 58.04; H, 4.58; Cl, 18.82; N, 18.69. *Minor tautomer* (35%): ^{1}H NMR ($CDCl_3$): δ 8.34 (d, *J* = 9.00 Hz, 1H, aromatic), 7.55 (d, *J* = 9.00 Hz, 1H, aromatic), 7.04 (br, 1H, NH), 5.12 (br, 1H, NH), 4.40 (m, 1H, CH), 1.25 (d, *J* = 6.00 Hz, CH_3 x 2). ^{13}C NMR (DMSO-d_6): δ 169.41, 165.26, 164.43, 139.46, 136.77, 136.16, 130.05, 128.69, 126.02, 22.87.

***N*-(4-Chlorophenyl)-*N'*-isopropyl-6-*p*-tolyl-[1,3,5]-triazine-2,4-diamine (IIg).** White solid; mp 224.1 °C; *Major tautomer* (60%): ^{1}H NMR (DMSO-d_6): δ 9.72 (br, 1H, NH)*, 7.91 (d, *J* = 9.00 Hz, 2H, aromatic)*, 7.86 (d, *J* = 9.00 Hz, 2H, aromatic)*, 7.61 (br, 1H, NH)*, 7.36 (d, *J* = 9.00, 2H, aromatic), 7.33 (d, *J* = 9.00, 2H, aromatic), 4.15 (m, 1H, CH)*, 2.38 (s, 3H, CH_3), 1.21 (d, *J* = 6.00 Hz, 6H, CH_3 x 2)*. ^{13}C NMR (DMSO-d_6): δ 170.21*, 165.39*, 164.76*, 141.74*, 139.58, 134.50*, 129.38, 128.76*, 128.26*, 125.94*, 121.65, 42.36, 22.72*, 21.53. MS (m/z): 354.20 (M^+). *Anal.* Calcd. for $C_{19}H_{20}ClN_5$: C, 64.49; H, 5.70; Cl, 10.02; N, 19.79. Found: C, 64.71; H, 5.80; Cl, 9.84; N, 19.53. *Minor tautomer* (40%), ^{1}H NMR (DMSO-d_6): δ 9.60 (br, 1H, NH), 8.24 (d, *J* = 9.00 Hz, 1H, aromatic), 7.20 (d, *J* = 9.00 Hz, 1H, aromatic), 7.31 (d, *J* = 9.00 Hz, 1H, aromatic), 7.45 (br, 1H, NH), 4.31 (m, 1H, CH), 1.22 (d, *J* = 6.00 Hz, 6H, CH_3 x 2). ^{13}C NMR (DMSO-d_6): δ170.35, 165.28, 164.49, 141.86, 134.59, 128.68, 128.36, 125.82, 22.90.

***N*-(3,4-Dichlorophenyl)-*N'*-isopropyl-6-phenyl-[1,3,5]-triazine-2,4-diamine (IIh).** White solid, mp 187.7 °C; *Major tautomer* (75%): ^{1}H NMR ($CDCl_3$): δ 8.15 (br, 1H, aromatic), 7.91 (d, *J* = 7.8 Hz, 2H, aromatic), 7.80 (d, *J* = 7.42 Hz, 1H, aromatic) *, 7.66 (d, *J* = 7.8 Hz, 2H, aromatic) *, 7.56 (d, *J* = 8.64 Hz, 1H, aromatic), 7.39 (m, 1H, aromatic), 7.19 (br, 1H, NH) *, 5.35 (br.d, *J* = 6.0 Hz, NH_2)*, 4.19 (m, 1H, CH) *, 1.31 (d, *J* = 6.5 Hz, 6H, CH_3 x 2). ^{13}C NMR (DMSO-d_6): δ 170.36*,

165.33*, 164.72*, 140.80*, 137.06*, 131.97*, 131.18*, 130.75*, 128.81, 128.22*, 123.58*, 121.25*, 120.01, 42.50, 22.64*. MS: (m/z) 374.24 (M^+). *Anal.* Calcd. for $C_{18}H_{17}Cl_2N_5$: C, 57.76; H, 4.58;, Cl, 18.95; N, 18.71. Found: C, 57.70; H, 4.52; Cl, 18.87; N, 18.68. *Minor tautomer* (25%): ^{1}H NMR ($CDCl_3$): δ 7.83 (br, 1H, aromatic), 7.62 (br, 1H, aromatic), 7.09 (br, 1H, NH), 5.15 (br, 1H, NH), 4.44 (m, 1H, CH). ^{13}C NMR (DMSO-d_6): δ 170.48, 165.22, 164.46, 140.85, 137.13, 132.08, 131.24, 130.63, 128.34, 123.53, 121.07, 22.86.

***N*-(4-Chlorophenyl)-*N'*-isopropyl-6-propyl-[1,3,5]-triazine-2,4-diamine (IIi).** White solid, mp 122.1 °C; ^{1}H NMR ($CDCl_3$): δ 7.59 (d, *J* = 9.00 Hz, 2H, aromatic), 7.28 (d, *J* = 9.00 Hz, 2H, aromatic), 7.06 (br, 1H, NH), 5.12 (br, 1H, NH), 4.16 (m, 1H, CH), 2.48 (t, *J* = 9.00 Hz, CH_2), 1.78 (q, *J* = 9.00 Hz, CH_2), 1.25 (d, *J* = 6.00 Hz, 6H, CH_3 x 2), 1.00 (t, *J* = 6.00 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 178.54, 165.06, 164.18, 137.64, 128.70, 127.78, 121.12, 42.62, 40.75, 22.60, 20.91, 13.93. MS: (m/z) 306.24 (M^+). *Anal.* Calcd. for $C_{15}H_{20}ClN_5$: C, 58.91; H, 6.59; Cl, 11.59; N, 22.90. Found: C, 59.10; H, 6.63; Cl, 11.52; N, 22.85.

***N*-(3,4-Dichlorophenyl)-*N'*-isopropyl-6-(1-ethylpropyl)-[1,3,5]-triazine-2,4-diamine(IIj).** white solid, mp 142.0 °C. *Major tautomer* (85%): ^{1}H NMR ($CDCl_3$): 8.16 (br, 1H, aromatic), 7.35 (d, *J* = 8.0Hz, 1H aromatic)*, 7.28 (d, *J* = 10.0Hz, 1H, aromatic)*, 7.01 (br, 1H, NH)*, 5.18 (br, 1H, NH)*, 4.15 (m, 1H, CH), 2.26 (m, 1H, CH), 1.61 (m, 4H, CH_2 x 2)*, 1.28 (d, *J* = 6.35Hz, 6H, CH_3 x 2), 0.87 (t, *J* = 7.42 Hz, 6H, CH_3 x 2)*. ^{13}C NMR ($CDCl_3$): δ 181.77, 164.99*, 164.00, 138.73*, 132.46, 130.14, 125.50, 121.25, 118.53, 51.81, 42.82, 26.69*, 25.75, 22.62, 12.11. MS (m/z): 404.76 (M^+). *Anal.* Calcd. for $C_{17}H_{24}Cl_3N_5$: C, 50.44; H, 5.98; Cl, 26.28; N, 17.30. Found: C, 50.49; H, 5.98; Cl, 26.16; N, 17.21.

Minor tautomer (15%): ^{1}H NMR ($CDCl_3$): δ 7.95 (br, 1H, aromatic), 7.82 (br, 1H, aromatic), 6.91 (br, 1H, NH), 5.01 (br, 1H, NH), 1.72 (m, 4H, CH_2 x 2), 0.95 (t, *J* = 7.45Hz, 6H, CH_3 x 2). ^{13}C NMR ($CDCl_3$): δ 119.31, 53.42, 43.18, 22.80.

2-(3,4-Dichlorophenylamino-4-isopropylamino-[1,3,5]-triazine-6-carboxylic acid methyl ester (IIk). White solid, mp 142.5 °C. *Major tautomer* (70%): ^{1}H NMR ($CDCl_3$): δ 8.11 (br, 1H, aromatic), 7.53 (br, 1H, NH)*, 7.38 (d, *J* = 8.70 Hz, 1H, aromatic)*, 7.28 (br, 1H, aromatic)*, 5.66 (d, *J* = 7.00 Hz, 1H, NH), 4.21 (m, 1H, CH), 4.00 (s, 3H, COOMe)*, 1.31 (d, *J* = 6.51 Hz, 6H, CH_3 x 2). ^{13}C NMR ($CDCl_3$): δ 165.28*, 164.40*, 163.68*, 163.36*, 137.66*, 132.71*, 130.35*, 126.77*, 121.78*, 119.03, 53.64, .43.49, 22.29. MS: (m/z) 356.03 (M^+). *Anal.* Calcd. for $C_{14}H_{15}Cl_2N_5O_2$: C, 47.21; H, 4.24; Cl, 19.91; N, 19.66. Found: C, 47.20; H, 4.30; Cl, 20.23; N, 19.17. *Minor tautomer* (30%): ^{1}H NMR ($CDCl_3$): δ 7.90 (br, 1H, aromatic), 5.41 (d, *J* = 7.00 Hz, 1H, NH), 4.41 (m, 1H, CH), 1.27 (d, *J* = 6.51 Hz, 6H, CH_3 x 2). ^{13}C NMR ($CDCl_3$): δ 119.31, 53.42, 43.18, 22.80.

2-(3,4-Dichlorophenylamino-4-isopropylamino-[1,3,5]-triazine-6-carboxylic acid ethyl ester (IIl). White solid, mp 178.6 °C, ^{1}H NMR ($CDCl_3$): δ 8.00 (s, 1H, aromatic), 7.52 (d, *J* = 8.70 Hz, 1H, aromatic), 7.35 (d, *J* = 8.75Hz, 1H, aromatic), 7.25 (br, 1H, NH), 5.60 (br, 1H, NH), 4.47 (q, *J* = 6.49Hz, 2H, CH_2), 4.15 (m, 1H, CH), 1.42 (t, *J* = 7.00 Hz, 3H, CH_3), 1.29 (d, *J* = 6.42 Hz, 6H, CH_3 x 2). ^{13}C NMR ($CDCl_3$): δ 165.2, 164.4, 163.7, 163.2, 137.7, 132.6, 130.3, 126.6, 121.7, 118.9, 62.8, 43.4, 22.2, 14.1. MS: (m/z) 370.10 (M^+). *Anal.* Calcd. for $C_{15}H_{17}Cl_2N_5O_2$. C, 48.66; H, 4.63; Cl, 19.15; N, 18.92. Found: C, 48.73; H, 4.70; Cl, 19.27; N, 18.69.

2-(3,4-Dichlorophenyl)amino-4-isopropylamino-[1,3,5]-triazine-6-carboxylic acid benzyl ester (IIm). White solid, mp 216.2 °C. *Major tautomer* (75%): ^{1}H NMR ($CDCl_3$): δ 8.11 (d, *J* = 2.0 Hz, 1H, aromatic), 7.46 (m, 3H, aromatic)*, 7.37 (m, 3H, aromatic) , 7.28 (br, 1H, aromatic)*, 5.64 (d, *J* = 7.00 Hz, 1H, NH)*, 5.43 (s, 2H, CH_2)*, 4.19 (m, 1H, CH), 1.31 (d, *J* = 6.51 Hz, 6H, CH_3 x 2). ^{13}C NMR ($CDCl_3$): δ 165.1*, 164.1*, 163.4*, 163.0*, 137.5*, 134.9*, 133.0*, 132.7*, 130.3*, 128.7*, 128.6*, 126.7*, 121.7, 119.0, 68.3, 43.4, 22.2. MS: (m/z) 432.07 (M^+). *Anal.* Calcd. for $C_{20}H_{19}Cl_2N_5O_2$: C, 55.57, H, 4.43, Cl, 16.40, N, 16.20. Found: C, 55.62; H, 4.42; Cl, 16.55; N, 16.16. *Minor tautomer* (25%): ^{1}H NMR ($CDCl_3$): δ 7.90 (d, *J* = 2.0 Hz, aromatic), 4.36 (m, 1H, CH), 1.26 (d, *J* = 6.51 Hz, 6H, CH_3 x 2). ^{13}C NMR: ($CDCl_3$): δ 119.3, 67.9, 43.2, 22.8.

2-(4-Chlorophenylamino)-4-isopropylamino-[1,3,5]-triazin-6-ol (IIn). White solid, mp 357 °C; ^{1}H NMR (DMSO-d_6): δ 10.68 (br, OH), 9.51 (br, 1H, NH), 7.43 (d, *J* = 9.00 Hz, 2H, aromatic), 7.40 (d, *J* = 9.00 Hz, 2H, aromatic), 7.15 (br, 1H, NH), 4.17 (m, 1H, CH), 1.17 (d, *J* = 6.00 Hz, 6H, CH_3 x 2). ^{13}C NMR ($CDCl_3$+TFA): δ 149.07, 133.47, 132.31, 129.45, 124.38, 119.98, 116.21, 112.44, 108.67, 46.04, 20.91. MS (m/z): 280.57 (M^+). *Anal.* Calcd. for $C_{12}H_{14}ClN_5O$: C, 51.52; H, 5.04; Cl, 12.67; N, 25.04. Found: C, 51.78; H, 5.06; Cl, 12.49; N, 24.95.

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