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Synthesis of Novel Substituted 4,6-Dimethoxy-N-phenyl-1,3,5-triazin-2-amine Derivatives and Their Antibacterial and Antifungal Activities

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An efficient and convenient method of synthesis of 2-chloro-4,6-dimethoxy-1,3,5-triazine from cyanuric chloride in a short reaction time followed by synthesis of biological active novel substituted 4,6-dimethoxy-N-phenyl-1,3,5-triazin-2-amine (**4a-x**) using substituted anilines and heterocyclic amines, anhydrous K_2CO_3 in dry THF as solvent has been developed. Advantages of this methodology are short reaction time, excellent yield of products, easy work-up procedure. The synthesized compounds were confirmed by FT-IR, ^{1}H NMR, mass spectral data. All the synthesized derivatives **(4a-x)** were screened for their antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa* species and antifungal activities against *Candida albicans* MTCC 227, *Candida glabrata* NCIM 3236, *Candida tropicalis* NCIM 3110 and *Aspergillus niger* NCIM 545 species.

Keywords: Antimicrobial Activity, Cyanuric chloride, Substituted 1,3,5-triazin-2-amine.

INTRODUCTION

1,3,5-Triazines (*s*-triazine) is an important class of heterocyclic compounds found in various natural products with a broad range of biological activities, such as antimycobacterial agents[1], focal adhesion kinase (FAK) inhibitors with anti-angiogenic activity on HUVEC cells[2], HIV-1 non-nucleoside reverse transcriptase inhibitors adenosine receptor[3], antiamoebic[4], cathepsin B inhibitor[5], adenosine receptor antagonist[6], antiviral[7], anticancer[8], antimicrobial[9], antileishmanial[10], carbonic anhydrase inhibitor[11] and antimalarial[12].

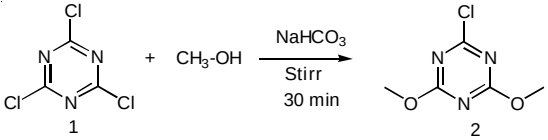
Recently, *s*-triazine attracted many researchers as its symmetrical structure facilitates to synthesize diverse set of analogue and provides the basis for designing biological relevant molecules with wide spread applications such as the therapeutics[13-19]. Some derivative of cyanuric chloride (CC), especially dimethoxy analogue is important starting compound used for synthesis of substituted 4,6-dimethoxy-N-phenyl-1,3,5-triazin-2-amine derivatives.

In this article, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) was prepared by using cyanuric chloride, methanol and catalytic amount of sodium bicarbonate followed by synthesis of novel substituted 4,6-dimethoxy-N-phenyl-1,3,5-triazin-2-amines (**4a-x**) by using CDMT, substituted anilines/heterocyclic amines and anhydrous K_2CO_3 in dry THF. All the synthesized compounds were screened against antimicrobial activity.

EXPERIMENTAL

The reagent grade chemicals were obtained from commercial sources and purified by either distillation or recrystallization before use. The purity of synthesized compounds has been checked by thin layer chromatography. Melting points were determined by open capillary method and are uncorrected. IR spectra are recorded on FT-IR Bruker with KBr disc. ^{1}H NMR spectra are recorded in DMSO-d_6 on a Bruker DRX-400 MHz using TMS as internal standard. The chemical shift is reported as parts per million (ppm) and mass spectra were determined on Jeol-SX-102 (FAB) spectrometer.

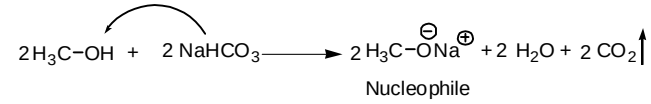
Synthesis of 2-chloro-4,6-dimethoxy-1,3,5-triazine (2): To 57 mL of methanol and 5 mL of water 16.8 g (0.2 mol) of sodium bicarbonate and 18.5 g (0.1 mol) of cyanuric chloride (**1**) were added. The temperature of reaction mixture increased to 35 °C. The reaction mixture was further refluxed for 0.5 h until CO_2 was completely removed. Then the contents were poured onto ice cold water and filtered. The white solid product (**2**) obtained was dried in desiccators (**Scheme-I**). m.p. 74-76 °C, ^{1}H NMR (400 MHz, DSMO-d_6) δ ppm: 4.05 (s, 6H).



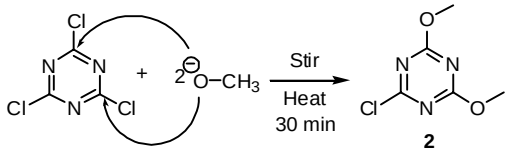
Scheme-I: Synthesis of 2-chloro-4,6-dimethoxy-1,3,5-triazine

Possible mechanism of 2-chloro-4,6-dimethoxy-1,3,5-triazine: Methanol (2 mol) reacts with sodium bicarbonate (2 mol) to form methoxy anion as nucleophile (step-I). Then two chlorine atoms of cyanuric chloride (**1**) are substituted by methoxy anion with the formation of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**2**) (step-II).

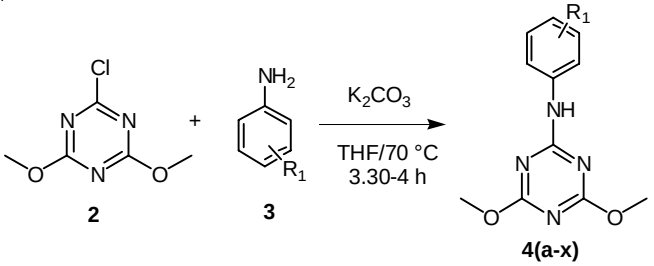
Step-I: Formation of nucleophile



Step-II: Syntheis of 2-chloro-4,6-dimethoxy-1,3,5-triazine



General procedure for the synthesis of substituted 4,6-dimethoxy-N-phenyl-1,3,5-triazin-2-amines (4a-x): 2-Chloro-4,6-dimethoxy-1,3,5-triazine (1 mmol) (**2**), substituted aniline (1 mmol)/heterocyclic amines (**3**) (1 mmol), anhydrous K_2CO_3 (2 mmol) were added in dry THF (5 mL) taken in a round-bottom flask. The reaction mixture was refluxed at 70 °C for 4 h. After completion of the reaction the product is confirmed on thin-layer chromatography (TLC) using eluent (2:8 mL, ethyl acetate-hexane). The reaction mixture was quenched with water and the crude product was extracted with ethyl acetate (3 times) and organic layer was separated and dried over anhydrous Na_2SO_4. The solvent evaporated on rotavapour. The Crude material was purified by column chromatography (ethyl acetate-*n*-hexane) and product **4(a-x)** with good yield (70-75 %) were obtained **(Scheme-II)**. Yield and melting points of synthesized 4,6-dimethoxy-N-phenyl-1,3,5-triazin-2-amine derivatives are given in Table-1.



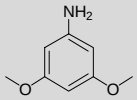
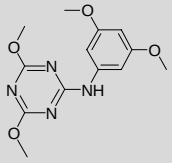
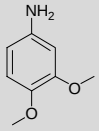
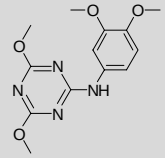
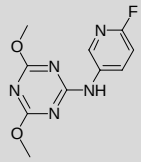
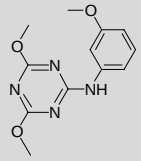
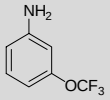
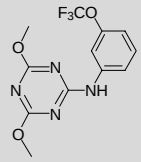
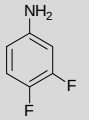
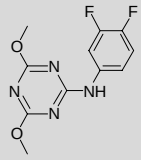
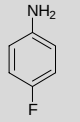
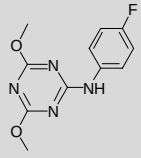
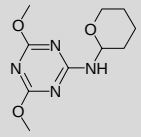
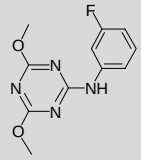
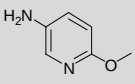
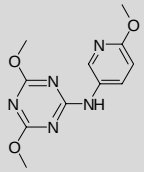
Scheme-II: Synthesis of substituted 4,6-dimethoxy-N-phenyl-1,3,5-triazin-2-amines from substituted anilines and 2-chloro-4,6-dimethoxy-1,3,5-triazine

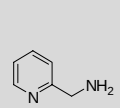
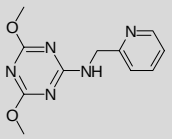
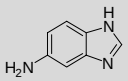
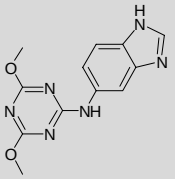
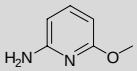
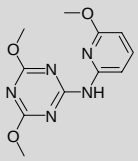
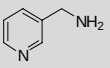
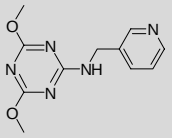
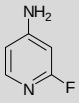
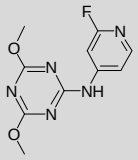
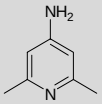
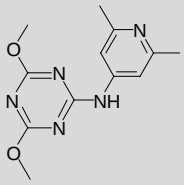
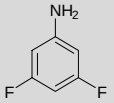
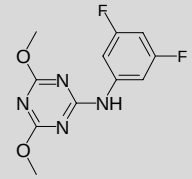
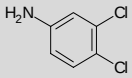
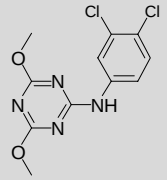
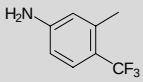
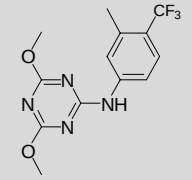
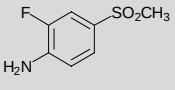
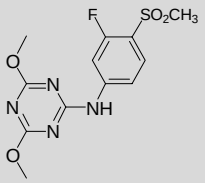
Spectral data

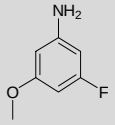
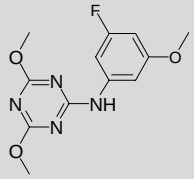
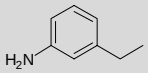
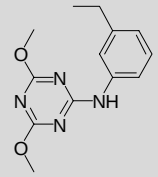
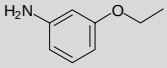
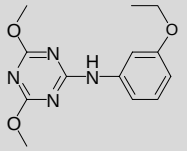
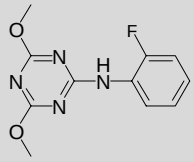
4,6-Dimethoxy-N-(3,5-dimethoxyphenyl)-1,3,5-triazin-2-amine (4a): m.f.: $C_{13}H_{16}N_4O_4$, Off-white solid; FTIR (KBr, ν_{max}, cm^{-1}): 3338 (N-H str. of *sec*-amine), 2836 (C-H), 1629 (Ar-C=C), 1207 (C-O); 809 (C-N, *s*-triazine). ^{1}H NMR (400 MHz, DSMO-d_6): δ ppm: 3.72 (s, 6H), 3.77 (s, 6H), 6.21 (s, 1H), 7.05 (s, 2H), 10.06 (s, 1H), MS(ESI): *m/z* 292.40 (M+1).

4,6-Dimethoxy-N-(3,4-dimethoxyphenyl)-1,3,5-triazin-2-amine (4b): m.f.: $C_{13}H_{16}N_4O_4$, Off-white solid; FTIR (KBr,

TABLE-1
YIELD AND MELTING POINTS OF SUBSTITUTED 4,6-DIMETHOXY-N-PHENYL-1,3,5-TRIAZIN-2-AMINE DERIVATIVES

Compd.	Reactants (**3**)	Products (**4**)	Yield (%)	m.p. (°C)
4a			75	126-128
4b			73	120-122
4c			72	182-184
4d			73	108-110
4e			70	125-126
4f			70	168-170
4g			72	142-144
4h			73	110-111
4i			72	163-194
4j			72	210-212

4k			73	88-90
4l			72	150-152
4m			72	206-208
4n			73	116-118
4o			72	180-182
4p			73	148-150
4q			70	194-196
4r			70	120-122
4s			70	122-124
4t			70	108-110

4u			70	116-118
4v			72	131-132
4w			70	94-96
4x			70	138-140

ν_{max}, cm^{-1}): 3335 (N-H str. of *sec*-amine), 2939 (C-H), 1614 (Ar-C=C), 1226 (C-O); 813 (C-N, *s*-triazine). ^{1}H NMR (400 MHz, DSMO-d_6) δ ppm: 3.71 (s, 3H), 3.74 (s, 3H), 3.91 (s, 6H), 6.90 (dd, *J* = 12 Hz, 1H), 7.14 (dd, *J* = 12 Hz, 1H), 7.52 (s, 1H), 9.95 (s, 1H), MS(ESI): *m/z*292 (M+1).

N-(6-Fluoropyridin-3-yl)-4,6-dimethoxy-1,3,5-triazin-2-amine (4c): m.f.: $C_{10}H_{10}N_5O_2F$, Off-white solid; FTIR (KBr, ν_{max}, cm^{-1}): 3337 (N-H str. of *sec*-amine), 2953 (C-H), 1628 (Ar-C=C), 1202 (C-O); 809 (C-N, *s*-triazine). ^{1}H NMR (400 MHz, DSMO-d_6) δ ppm: 3.91 (s, 6H), 7.19 (dd, *J* = 8 Hz, 1H), 8.27 (dd, *J* = 8 Hz, 1H), 8.50 (s, 1H), 10.34 (s, 1H), MS (ESI): *m/z* 251 (M+1).

4,6-Dimethoxy-N-(3-methoxyphenyl)-1,3,5-triazin-2-amine (4d): m.f.: $C_{12}H_{14}N_4O_3$, Off-white solid; FTIR (KBr, ν_{max}, cm^{-1}): 3280 (N-H str. of *sec*-amine), 2983 (C-H), 1618 (Ar-C=C), 1199 (C-O); 813 (C-N, *s*-triazine). ^{1}H NMR (400 MHz, DSMO-d_6) δ ppm: 3.74 (s, 3H), 3.91 (s, 6H), 6.62 (d, 1H), 7.24 (d,H), 7.50-7.51 (s, 1H), 10.36 (s, 1H), MS (ESI): *m/z* 262 (M+1).

4,6-Dimethoxy-N-(3-(trifluoromethoxyphenyl)-1,3,5-triazin amine (4e): m.f.: $C_{12}H_{11}N_4O_3F_3$, Off-white solid; FTIR (KBr, ν_{max}, cm^{-1}): 3297 (N-H str. of *sec*-amine), 2950 (C-H), 1618 (Ar-C=C), 1225 (C-O); 804 (C-N, *s*-triazine). ^{1}H NMR (400 MHz, DSMO-d_6) δ ppm: 3.93 (s, 6H), 6.97 (d, *J* = 8 Hz, 1H), 7.41 (t, *J* = 8 Hz, 1H), 7.63 (d, *J* = 8 Hz, 1H), 7.96 (s, 1H), 10.36 (s, 1H), MS (ESI): *m/z* 316 (M+1).

N-(3,4-Difluorophenyl)-4,6-dimethoxy-1,3,5-triazin-2-amine (4f): m.f.: $C_{11}H_{10}N_4O_2F_2$, Off-white solid; FTIR (KBr, ν_{max}, cm^{-1}): 3145 (N-H str. of *sec*-amine), 2945 (C-H), 1637 (Ar-C=C), 1214 (C-O); 810 (C-N, *s*-triazine). ^{1}H NMR (400 MHz, DSMO-d_6) δ ppm: 3.93 (s, 6H), 7.27-7.34 (m, 1H), 7.43-7.47 (m, 1H), 7.89 (s, 1H), 10.25 (s, 1H), MS (ESI): *m/z* 268 (M+1).

N-(4-Fluorophenyl)-4,6-dimethoxy-1,3,5-triazin-2-amine (4g): m.f.: $C_{11}H_{11}N_4O_2F$, Off-white solid; FTIR (KBr,

ν_{max}, cm^{-1}): 3185 (N-H str. of *sec*-amine), 2955 (C-H), 1640 (Ar-C=C), 1210 (C-O); 812 (C-N, *s*-triazine). ^{1}H NMR (400 MHz, DSMO-d_6) δ ppm: 3.91 (s, 6H), 7.09 (dd, *J* = 4 Hz, 2H), 7.71 (dd, *J* = 4 Hz, 2H), 10.07 (s, 1H), MS (ESI): *m/z* 250 (M+1).

N-(Tetrahydro-2H-pyran-2-yl)-4,6-dimethoxy-1,3,5-triazin-2-amine (4h): m.f.: $C_{10}H_{16}N_4O_3$, Off-white solid; FTIR (KBr, ν_{max}, cm^{-1}): 3255 (N-H str. of *sec*-amine), 2945 (C-H), 1610 (Ar-C=C), 1205 (C-O); 807 (C-N, *s*-triazine).^{1}H NMR (400 MHz, DSMO-d_6) δ ppm: 1.51-1.58 (m, 2H), 1.77-1.81 (m, 2H), 3.37 (q, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 3,96 (t, 2H), 4.01 (t, 1H), 7.85 (s, 1H), MS (ESI): *m/z* 240 (M+1).

Biological evaluation

Antibacterial and antifungal activity: The compounds were diluted in dimethyl sulfoxide (DMSO) with 1 mg/mL concentrations for bioassay. The antimicrobial activity was evaluated by antimicrobial assay of the compounds by standard method *i.e.* agar cup plate method against a panel of human pathogenic micro organisms: Gram-positive, *Staphylococcus aureus* NCIM 2178, *B. subtilis* NCIM 2250, Gram-negative, *Escherichia coli* NCIM 2137 and *Pseudomonas aeruginosa* NCIM 2036, while for the antifungal assay studies, *Candida albicans* MTCC 227, *Candida glabrata* NCIM 3236, *Candida tropicalis* NCIM 3110 and *Aspergillus niger* NCIM 545 fungi were used. Nutrient agar was used as the culture media for antibacterial activity and potato dextrose agar and yeast peptone dextrose agar were used as the culture media for antifungal activity. The commercial available chloramphenicol and griseofulvin in DMSO served as reference drugs for antibacterial and antifungal activity respectively to compare inhibition of growth. Both the plate containing bacterial organism and fungal organism were incubated at 37 °C for 48 h. Averages of three independent determinations were recorded. Agars were melted and poured in Petri dishes according to Clinical and Laboratory Standards Institute (CLSI, M2-A5 January 2007). Approximately 10^7 cells cultures were spread and cups were prepared by sterile borer. 100 µL compounds were inoculated in each cup. The plates were incubated at 37 °C, examined after 24 h and incubated further for 48 h, where necessary. The zone of inhibition produced by each compound was measured in mm.

RESULTS AND DISCUSSION

2-Chloro-4,6-dimethoxy-1,3,5-triazine is characterized by ^{1}H NMR spectra which is confirmed by chemical shift value at δ 4.04 (6H, s) and mass spectra with *m/z* 175.5. The structure of 4,6-dimethoxy N-phenyl-1,3,5-tirazine amines/heterocyclic amines were confirmed by IR, ^{1}H NMR, Mass spectra. The IR spectra of compound **4(a-x)** shows the characteristic absorption band at ν 3225-3330 cm^{-1} (-NH- *sec*-amine), 3000-2950 cm^{-1} (-CH stretching in aliphatic), 1450-1650 cm^{-1}, (-C=C, -C-H aromatic stretching), 1199-1225 cm^{-1} (C-O stretching in

TABLE-2
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF SUBSTITUTED 4,6-DIMETHOXY-N-PHENYL-1,3,5-TRIAZIN-2-AMINE DERIVATIVES **4(a-x)**

Compound	Gram positive bacteria		Gram negative bacteria		*C. albicans*	*C. tropicalis*	*C. glabrata*	*A. niger*
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*				
4a	16	15	11	15	14	15	12	14
4b	16	13	11	13	14	14	13	13
4c	**20**	**20**	**19**	**18**	**19**	**18**	**17**	**16**
4d	16	16	15	14	14	16	11	15
4e	**25**	**24**	**21**	**21**	**24**	**23**	**21**	**22**
4f	**23**	**22**	**20**	**19**	**23**	**22**	**20**	**21**
4g	19	18	18	17	**19**	**17**	**16**	**17**
4h	16	17	15	14	14	15	17	15
4i	**20**	**21**	**19**	**18**	**18**	**17**	**16**	**17**
4j	16	15	13	14	16	15	12	13
4k	16	15	12	13	16	15	11	13
4l	**22**	**21**	**20**	**21**	**21**	**20**	**19**	**18**
4m	16	18	15	13	15	14	11	13
4n	15	14	13	11	15	12	13	15
4o	**20**	**19**	**20**	**19**	**19**	**18**	**17**	**16**
4p	16	16	18	15	15	12	11	13
4q	20	19	18	19	**19**	**18**	**17**	**16**
4r	16	18	17	16	18	20	12	18
4s	23	23	22	21	**23**	**22**	**18**	**19**
4t	**23**	**24**	**21**	**22**	**22**	**21**	**19**	**18**
4u	**20**	**22**	**19**	**21**	**19**	**18**	**16**	**17**
4v	16	15	14	13	16	15	13	15
4w	16	18	15	13	15	12	16	13
4x	**20**	**21**	**19**	**18**	**18**	**17**	**16**	**15**
Chloramphenicol (250 µg/mL)	24	25	20	22	–	–	–	–
Griseofulvin	–	–	–	–	23	24	22	21
DMSO	00	00	00	00	00	00	00	00

Zone of inhibition (mm)

aromatic compound), 802-821 cm^{-1} (C_3 N_3 in *s*-triazine ring). The chemical shift value of compounds **4(a-x)** is recorded on ^{1}H NMR instrument at frequency 400 MHz by using solvent DSMO-d_6. The compounds are characterized by peak observed for aromatic/heterocyclic *sec*-amine (-NH-) at 9.95-10.34 δ ppm (s, 1H). All the synthesized derivatives **(4a-x)** were screened for their anti-bacterial and antifungal activities. Compounds **4c, 4e, 4f, 4g, 4i, 4l, 4o, 4q, 4s, 4t, 4u, 4x** are found antibacterial against human pathogenic micro organisms (Table-2). Also compounds **4c, 4e, 4f, 4g, 4i, 4l, 4o, 4q, 4r, 4s, 4t, 4u and 4x** are found potential antifungal against *Candida albicans* MTCC 227, *Candida glabrata* NCIM 3236, *Candida tropicalis* NCIM 3110 and *Aspergillus niger* NCIM 545 (Table-2).

Conclusion

The present methodology for synthesis of 2-chloro-4,6-dimethoxy-1,3,5-triazine from cyanuric chloride has an added advantage of short reaction time of 0.5 h giving an excellent yield of 75 %. Further synthesis of substituted 4,6-dimethoxy-N-phenyl-1,3,5-triazin-2-amines (**4a-x**) using 2-chloro-4,6-dimethoxy-1,3,5-triazine and substituted anilines/heterocyclic amines (1 mmol) in dry THF offer uniqueness in synthesis in presence of anhydrous K_2CO_3 at moderate temperature (70 °C) condition, shorter reaction time, good yield (70-75 %) of product. The synthesized products (**4a-x**) showed promising antibacterial activity (zone of inhibition: 11 mm to 25 mm) and antifungal activity (zone of inhibition: 11 mm to 24 mm).

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