

# Microwave Mediated Synthesis of Novel 1,3,5-Triazine Derivative and their Biological Evaluation

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**Abstract:** 1,3,5-Triazine derivative are synthesized by replacement of chloride ions of Cyanuric chloride and 1,3,5-Triazine derivative are showing promising biological activity such as Antibacterial, Antifungal, Antimalarial, Antivirus, Anticancer that's why interest of researches on synthesis of 1,3,5-Triazine derivatives always in focused. The present study reported the synthesis of 2,4,6-Trisubstituted 1,3,5-Triazine derivatives by Microwave mediated Method which gave the desired result in less time with higher yield. The structure of 1,3,5-Triazine derivatives have been elucidated by Spectral of IR, NMR and MASS. The derivative of 1,3,5-Triazine are evaluated for their In vitro Antibacterial activity against Gram Positive and Gram Negative Bacterial species and shown good Antibacterial effect.

**Keywords:** Antibacterial activity, Microwave irradiation, 1,3,5-Triazine.

## 1. Introduction

Triazine is a class of nitrogen containing heterocyclic. They have a planar six-member benzene ring like structure with three carbons replaced with nitrogen. The three isomers of Triazine are distinguished from each other by the positions of their nitrogen atoms, and are referred to as 1,2,3-Triazine, 1,2,4-Triazine and 1,3,5-Triazine. 1,3,5-Triazine, also called the S-Triazine, attracted many researches, as its symmetrical structure facilitates to synthesize diverse set of analogue as 2,4,6-mono, di or tri-substituted, symmetrical and nonsymmetrical compounds bearing different substituent.

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Its analogues, melamine, cyanuric acid and cyanuric chloride are important starting compounds for various materials with wide range of applications in development of pharmaceuticals, textile, plastic and rubber industries. These compounds are also used as pesticides, dyestuffs, optical bleaches, explosives and surface active agents.

1,2,3-Triazine derivatives are the new member of heterocyclic compounds. In older literature, Vtriazine or  $\beta$

triazine are also found along with 1,2,3-triazine isomer<sup>1</sup>. Heterocyclic moiety fused with 1,2,3- triazine-4-ones show high chemically-reactivity and biological activity<sup>2</sup>. As a comparison with 1,2,4- and 1,3,5-triazine isomers, the 1,2,3-triazine isomer is the least studied isomer because the nucleus of 1,2,3-triazine isomer is the least stable as compare to rest isomers and synthetic routes are also limited<sup>3</sup>. Newly discovered 1,2,3-triazines are more effective drugs along with less adverse effects. Tubercidin, toyocamycin, sangivamycin, 2-azaadenosine and 2- aza-2-desamino-5,8-dideazafolic acid are the 1,2,3- triazine moiety containing drugs which show different pharmacological activities.

## 2. Methodology and Experiment

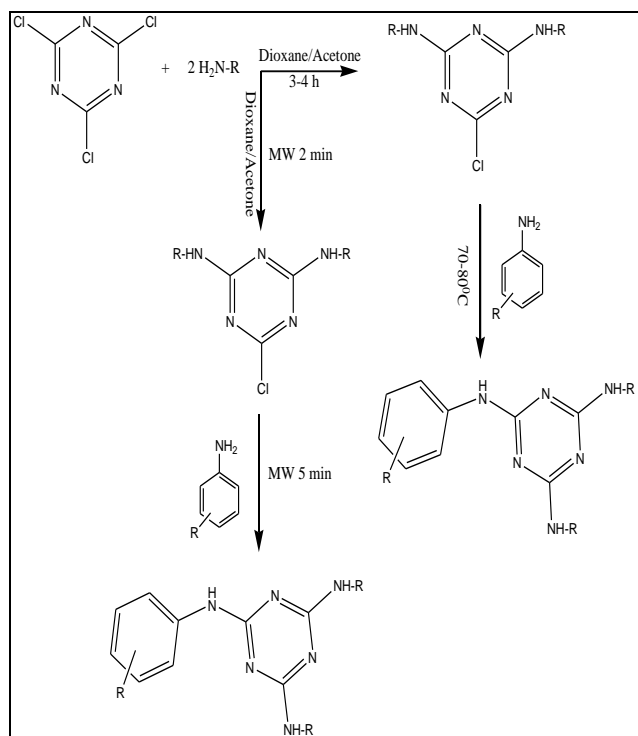
It has been known that amines react with cyanuric chloride, providing access to amine-functionalized 1,3,5-triazine compounds.

Replacement of one, two or all the three chlorine atoms of the 2,4,6-trichloro-s-triazine by amino group depends upon the reaction temperature. Mono amination takes place at 0-15°C, Diamination at 20-50°C and Triamination at 80-100°C, depending upon the nucleophilic character of the solvent and the amine.

Microwave synthesis represents a major breakthrough in synthetic chemistry methodology; a dramatic change in the way chemical synthesis is performed. Conventional heating, long known to be inefficient and time consuming, has been recognized to be creatively limiting too. Microwave synthesis gives the chemists more time to expand their creativity, test new theories and develop new processes. Instead of spending hours or even days synthesizing a single compound, chemists can now perform the same reaction in minutes. The problem associated with waste disposal of solvents has been overcome by performing reactions without a solvent under microwave irradiation. Coupling of microwave irradiation with the use of mineral-supported catalysed reactions, under solvent-free conditions, provides clean chemical processes with the advantage of enhanced reaction rates, higher yields, greater selectivity, and greater ease of manipulation. Thus microwave synthesis acts as a potential tool for green chemistry.

### A. Scheme of Work

The synthetic scheme includes following steps.



### B. Chemical and Equipment

Cyanuric chloride was procured from Avra Chemicals, aniline, acetone, 1,4-dioxane, sodium carbonate, diethylamine, diphenylamine, morpholine, 2-nitroaniline, 3-nitroaniline, 4-nitroaniline, hydrochloric acid, ethanol, sodium hydroxide, chloroform and all other chemicals used were of analytical or synthetic grade and purchased from Oxford Fine Chemicals. All the chemicals were used as received without any further purification.

Digital balance (Wesar), Heating mantle (Biotechnic), domestic microwave (Bajaj) were used during the study.

Purity of compound is determined by TLC and Rf value of compound has determine by using solvent system Hexane, Acetic acid, Acetone. Solubility of synthesized compound has determined using different solvent system Water, Ethanol, Chloroform, DMSO.

The spectral characteristics were used to elucidate the structures of the synthesized compounds. The purity and homogeneity of the synthesized compounds was confirmed by single spots on the TLC plate. Spectral analyses (IR, NMR & Mass) of the compounds satisfactorily supported the structures of the synthesized compounds.

### C. Experimental Procedure

#### 1) Experimental Procedures (Conventional Synthesis)

The experimental scheme was adapted from the reports of Solanki and Tailor and optimized to the conditions of the laboratory. The scheme involved nucleophilic substitution of

cyanuric chloride in successive steps to yield the desired compounds. The steps involved in the reaction protocol are presented in figure 1.

#### a) Synthesis of 4,6-dichloro-N,N-diethyl-1,3,5-triazin-2-amine:

Diethylamine (0.01 mol, 0.73g (1.02mL) in 10mL acetone) was added slowly to cyanuric chloride (0.01 mol, 1.845g in 30mL acetone) with constant stirring for 5 hours at 0 to 5°C. Intermittently, sodium carbonate solution (0.005 mol, 0.53g in 10 mL water) was added drop wise to neutralize the HCl evolved over the course of the reaction. The progress of the reaction was monitored by TLC. The content of the flask was poured into crushed ice and the solid that separated out was filtered, washed with water, dried and recrystallised from alcohol to give the 4,6-dichloro-N,N-diethyl-1,3,5-triazin-2-amine.

#### b) Synthesis of 6-chloro-N<sup>2</sup>,N<sup>2</sup>,N<sup>4</sup>,N<sup>4</sup>-tetraethyl-1,3,5-triazine-2,4-diamine:

Diethylamine (0.01 mol, 0.73g (1.02mL) in 10mL acetone) was added slowly to the 4,6-dichloro-N,N-diethyl-1,3,5-triazin-2-amine (0.01 mol, 2.21g in 35mL acetone) with constant stirring for 7.5 hours at room temperature. Intermittently, sodium carbonate solution (0.005 mol, 0.53g in 10 mL water) was added drop wise to neutralize the HCl evolved over the course of the reaction. The progress of the reaction was monitored by TLC. The content of the flask was poured into crushed ice and the solid that separated out was filtered, washed with water, dried and recrystallised from alcohol to give the 6-chloro-N<sup>2</sup>,N<sup>2</sup>,N<sup>4</sup>,N<sup>4</sup>-tetraethyl-1,3,5-triazine-2,4-diamine.

#### c) General procedure for synthesis of target compounds:

Aromatic amine (0.01 mol) and 6-chloro-N<sup>2</sup>,N<sup>2</sup>,N<sup>4</sup>,N<sup>4</sup>-tetraethyl-1,3,5-triazine-2,4-diamine. (0.01 mol) were dissolved in acetone (40mL). The reaction mixture was refluxed for 8 hours. Intermittently, sodium carbonate solution (0.005 mol, 0.53g in 10 mL water) was added drop wise to neutralize the HCl evolved over the course of the reaction. The progress of the reaction was monitored by TLC. The content of the flask was poured into crushed ice and the solid that separated out was filtered, washed with water, dried and recrystallised from alcohol to give the target compound.

#### 2) Experimental Procedures (Microwave assisted synthesis)

##### a) Synthesis of 4,6-dichloro-N,N-diethyl-1,3,5-triazin-2-amine:

To a 50 mL round bottom flask was added 1.8 g (0.01 mol) cyanuric chloride, 15 mL of 1,4-dioxane, 4.5 mL DMF, 2.5 g sodium hydrogen carbonate, and 0.01 mol diethylamine. The flask was kept in microwave oven and irradiated for 6 min at low power. The content of the flask was poured into crushed ice and the solid that separated out was filtered, washed with water, dried and recrystallised from alcohol to give 4,6-dichloro-N,N-diethyl-1,3,5-triazin-2-amine.

##### b) Synthesis of 6-chloro-N<sup>2</sup>, N<sup>2</sup>, N<sup>4</sup>, N<sup>4</sup>-tetraethyl-1,3,5-triazine-2,4-diamine:

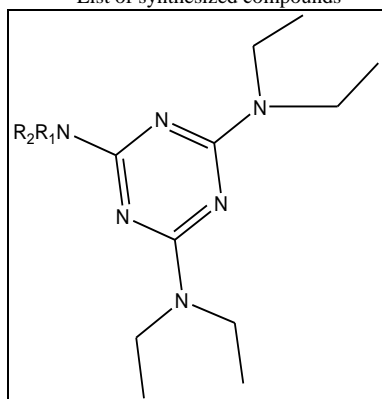
To a 50 mL round bottom flask was added 2.21g (0.01 mol)

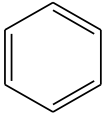
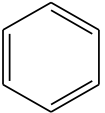
4,6-dichloro-N,N-diethyl-1,3,5-triazin-2-amine, 15 mL of 1,4-dioxane, 4.5 mL DMF, 2.5 g sodium hydrogen carbonate, and 0.01 mol diethylamine. The flask was kept in microwave oven and irradiated for 2.5 min at low power. The content of the flask was poured into crushed ice and the solid that separated out was filtered, washed with water, dried and recrystallised from alcohol to give 6-chloro-N<sup>2</sup>,N<sup>2</sup>,N<sup>4</sup>,N<sup>4</sup>-tetraethyl-1,3,5-triazine-2,4-diamine.

c) *General procedure for synthesis of target compounds:*

To a 50 mL round bottom flask was added 2.58g (0.01 mol) 6-chloro-N<sup>2</sup>,N<sup>2</sup>,N<sup>4</sup>,N<sup>4</sup>-tetraethyl-1,3,5-triazine-2,4-diamine, 15 mL of 1,4-dioxane, 4.5 mL DMF, 2.5 g sodium hydrogen carbonate, and 0.01 mol of aromatic amine. The flask was kept in microwave oven and irradiated for 3 min at low power. The content of the flask was poured into crushed ice and the solid that separated out was filtered, washed with water, dried and recrystallised from alcohol to give the target compounds

Table 1  
List of synthesized compounds



| Code | R <sub>1</sub>  | R <sub>2</sub>  |
|------|---|---|
| TZ1  |  |  |
| TZ2  | CH <sub>3</sub>   | CH <sub>3</sub>   |
| TZ3  | H   | 2-nitrophenyl   |
| TZ4  | H   | 3-nitrophenyl   |
| TZ5  | H   | 4-nitrophenyl   |

D. Spectral Studies

1) N<sup>2</sup>, N<sup>2</sup>, N<sup>4</sup>, N<sup>4</sup>-tetraethyl-N<sup>6</sup>, N<sup>6</sup>-diphenyl-1,3,5-triazine-2,4,6-triamine, TZ1

<sup>1</sup>H NMR Spectra (δ, 300 MHz, CDCl<sub>3</sub>): 6.823-7.916 (CH-Benzene), 2.995 (CH<sub>2</sub>), 1.592 (CH<sub>3</sub>), IR (KBr): 3000-2900 cm<sup>-1</sup>

(C-C cyclic), 1600-1700 cm<sup>-1</sup> (C-C Ar), 3100-3000 cm<sup>-1</sup> (CH Ar), 1500 cm<sup>-1</sup> (C=N), 1400-1000 cm<sup>-1</sup> (C-N)

Mass – 390 (Calculated); 384.8

2) N<sup>2</sup>, N<sup>2</sup>, N<sup>4</sup>, N<sup>4</sup>-tetraethyl-N<sup>6</sup>, N<sup>6</sup>-dimethyl-1,3,5-triazine-2,4,6-triamine, TZ2

<sup>1</sup>H NMR Spectra (δ, 300 MHz, CDCl<sub>3</sub>): 3.190 (N-CH<sub>3</sub>), 2.538-2.496(CH<sub>2</sub>), 1.590 (CH<sub>3</sub>)

IR (KBr): 3000-2900 cm<sup>-1</sup> (C-C cyclic), 1600-1700 cm<sup>-1</sup> (C-C Ar), 3100-3000 cm<sup>-1</sup> (CH Ar), 1500 cm<sup>-1</sup> (C=N), 1400-1000 cm<sup>-1</sup> (C-N)

Mass – 266 (calculated); 269.2

3) N<sup>2</sup>, N<sup>2</sup>, N<sup>4</sup>, N<sup>4</sup>-tetraethyl-N<sup>6</sup>-(2-nitrophenyl)-1,3,5-triazine-2,4,6-triamine, TZ3

<sup>1</sup>H NMR Spectra (δ, 300 MHz, CDCl<sub>3</sub>): 8.025-6.833 (CH-Benzene), 3.974 (N-H), 2.991 (CH<sub>2</sub>), 1.560 (CH<sub>3</sub>)

IR (KBr): 3000-2900 cm<sup>-1</sup> (C-C cyclic), 1600-1700 cm<sup>-1</sup> (C-C Ar), 3100-3000 cm<sup>-1</sup> (CH Ar), 1500 cm<sup>-1</sup> (C=N), 1400-1000 cm<sup>-1</sup> (C-N), 1350 (N-O)

Mass – 359 (Calculated); 360.1

4) N<sup>2</sup>, N<sup>2</sup>, N<sup>4</sup>, N<sup>4</sup>-tetraethyl-N<sup>6</sup>-(3-nitrophenyl)-1,3,5-triazine-2,4,6-triamine, TZ4

<sup>1</sup>H NMR Spectra (δ, 300 MHz, CDCl<sub>3</sub>): 7.913-6.828 (C-H aromatic), 4.010 (N-H), 2.996 (CH<sub>2</sub>), 1.562 (CH<sub>3</sub>)

IR (KBr): 3000-2900 cm<sup>-1</sup> (C-C cyclic), 1600-1700 cm<sup>-1</sup> (C-C Ar), 3100-3000 cm<sup>-1</sup> (CH Ar), 1500 cm<sup>-1</sup> (C=N), 1400-1000 cm<sup>-1</sup> (C-N), 1350 (N-O)

Mass – 359 (Calculated); 360.1

5) N<sup>2</sup>, N<sup>2</sup>, N<sup>4</sup>, N<sup>4</sup>-tetraethyl-N<sup>6</sup>-(4-nitrophenyl)-1,3,5-triazine-2,4,6-triamine, TZ5

<sup>1</sup>H NMR Spectra (δ, 300 MHz, CDCl<sub>3</sub>): 8.037-6.849 (CH-Benzene), 3.985 (N-H), 3.006 (CH<sub>2</sub>), 1.283 (CH<sub>3</sub>)

IR (KBr): 3000-2900 cm<sup>-1</sup> (C-C cyclic), 1600-1700 cm<sup>-1</sup> (C-C Ar), 3100-3000 cm<sup>-1</sup> (CH Ar), 1500 cm<sup>-1</sup> (C=N), 1400-1000 cm<sup>-1</sup> (C-N), 1350 (N-O)

Mass – 359 (Calculated); 360.1

E. Physical Characteristic

Table 2 shows the properties of the synthesized compound.

3. Biological Evaluations

A. Antibacterial Activity

The antibacterial action of the synthesized compounds (obtained by microwave synthesis) was evaluated against two gram positive (*Proteus mirabilis* and *Bacillus subtilis*) and two gram negative bacteria (*Pseudomonas aeruginosa* and *Staphylococcus aureus*).

Table 2  
Properties of the synthesized compound

| Compound Code | Molecular Formula   | Molecular Weight | Yield (%)           |                  | Melting Point | RF Value | Colour | Log P Value |
|---------------|---|------------------|---------------------|------------------|---------------|----------|--------|-------------|
|               |   |                  | Conventional Method | Microwave method |               |          |        |             |
| TZ1           | C <sub>23</sub> H <sub>30</sub> N <sub>6</sub>                | 390.52           | 32                  | 67               | 260           | 0.67     | Yellow | 6.01        |
| TZ2           | C <sub>13</sub> H <sub>26</sub> N <sub>6</sub>                | 266.38           | 29                  | 62               | 174           | 0.59     | Brown  | 3.56        |
| TZ3           | C <sub>17</sub> H <sub>25</sub> N <sub>7</sub> O <sub>2</sub> | 359.43           | 37                  | 79               | 180           | 0.53     | Yellow | 2.87        |
| TZ4           | C <sub>17</sub> H <sub>25</sub> N <sub>7</sub> O <sub>2</sub> | 359.43           | 34                  | 81               | 169           | 0.64     | Yellow | 2.91        |
| TZ5           | C <sub>17</sub> H <sub>25</sub> N <sub>7</sub> O <sub>2</sub> | 359.43           | 39                  | 82               | 157           | 0.66     | Yellow | 2.92        |

Table 3  
MIC of the synthesized compounds against gram positive and gram negative bacteria

| Code        | MIC ( $\mu\text{g/mL}$ ) <sup>a,b,c</sup> |                    |                      |                  |
|-------------|---|--------------------|----------------------|------------------|
|             | <i>P. mirabilis</i>                       | <i>B. subtilis</i> | <i>P. aeruginosa</i> | <i>S. aureus</i> |
| <b>TZ1</b>  | 25  | 25                 | 25                   | 25               |
| <b>TZ2</b>  | 25  | 25                 | 25                   | 25               |
| <b>TZ3</b>  | 12.5                                      | 6.25               | 12.5                 | 6.25             |
| <b>TZ4</b>  | 12.5                                      | 6.25               | 6.25                 | 6.25             |
| <b>TZ5</b>  | 12.5                                      | 6.25               | 6.25                 | 6.25             |
| Norfloracin | 2.56                                      | 1.28               | 1.28                 | 1.28             |

The synthesized triazine derivatives were dissolved in dimethyl sulfoxide (DMSO) and the further dilutions of the test compounds were prepared at the required quantities of 100, 50, 25, 12.5 and 6.25  $\mu\text{g/mL}$  concentrations with Mueller-Hinton broth medium.

Overnight culture of all four bacteria were prepared separately in nutrient broth, and used as a microbial source for the determination of MIC.

The sterile capped test tubes were numbered from 1 to 8 and all of the steps were carried out using aseptic technique. 10 ml of drug sample solution was added to the first tube while 2.0 ml of nutrient broth to all other tubes. Transferred 2.0 ml from the first tube to the second tube. Using a separate pipette, mixed the contents of this tube and transferred 2.0 ml to the third tube. Continue dilutions in this manner to tube number 8, being certain to change pipettes between tubes to prevent carryover of antibiotic on the external surface of the pipette. Removed 2.0 ml from tube 8 and discard it. The 9<sup>th</sup> tube, which serves as a control, receives no drug sample. Norfloracin (10 $\mu\text{g/ml}$ ) was used as standard drug. Suspended to an appropriate turbidity several colonies of the culture to be tested in 5.0 ml of nutrient broth to give a slightly turbid suspension. Added 0.2  $\mu\text{l}$  of the diluted culture suspension to each of the tubes. The final concentration of drug sample is now one-half of the original concentration in each tube. Incubated all tubes at 37°C overnight. Examined tubes for visible signs of bacterial growth.

The highest dilution without growth is the minimal inhibitory concentration (MIC). The antibacterial activity of the synthesized compounds was evaluated at various concentrations to determine the MIC of each compound.

<sup>a</sup>A set of tubes with only the inoculated broth was used as control to determine MIC

<sup>b</sup>MIC is expressed by measuring the turbidity of test and control dilution tubes. A 50% decrease in turbidity was taken as MIC.

<sup>c</sup>All values are expressed as mean of a set of three experiments

#### 4. Result and Discussion

In the present work, 2,4,6-trisubstituted 1,3,5-triazine analogs were synthesized using the nucleophilic substitution on cyanuric chloride in presence of dioxane or acetone. The microwave energy was applied for 1 minute for 2 times.

In present work we apply Green synthesis of 1,3,5- Triazines were synthesized in satisfactory using microwave assisted method. The compounds were found to be of better purity and

yield as compared to the conventional synthetic procedure. The compounds shown good antibacterial potential against both gram negative and gram positive bacterium. In the present work was able to device a green, efficient method for the synthesis of substituted 1,3,5- triazines.

Five derivative of 1,3,5-Triazine were synthesized and confirmed by physical and spectral analysis. The synthesized compounds were characterized by IR, <sup>1</sup>HNMR and Mass spectral data. All the synthesized compounds show characteristic absorption peaks in IR and NMR spectra.

The antimicrobial potential of the synthesized compounds has been evaluated by determining the minimum inhibition concentration values by broth dilution method using Mueller-Hinton broth for culturing the pathogen. The results obtained indicate that the presence of NO<sub>2</sub> functional group in the compounds was beneficial for the antibacterial potential.

The sequential replacement of three chloride atoms on cyanuric chloride with different nucleophiles provides the synthesis of a variety of substituted 1,3,5-Triazine molecules. In light of its operational simplicity and efficiency, this reliable method is expected to have a broad utility due to the scope of applications of the 1,3,5-Triazines. Antibacterial activity of the newly compounds were investigated.

The present review aims to serve as a background for the research in this area.

#### 5. Conclusion

This paper presented an overview on microwave mediated synthesis of novel 1,3,5-Triazine derivative and their biological evaluation.

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