ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

# Synthesis and Biological Evaluation of Novel 6-Aryl-2,4-Disubstituted Schiff's Base 1,3,5-Triazine Derivatives as Antimicrobial Agents

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## ABSTRACT

Novel Schiff's bases of 1,3,5-triazine derivatives were designed and synthesized from cyanuric chloride. The structures of all compounds have been confirmed by FT-IR, $^{1}$H NMR and Mass spectral analysis. Biological activities of synthesized compounds were evaluated by using serial dilution method in dimethyl sulphoxide media against bacterial and fungal strain cultures by comparing with standard Streptomycin and Fluconazole drug. Results reveals that the synthesized novel triazine based Schiff's bases are more potent than its DIPOD (Dialdehyde). The present work suggests that triazine based Schiff's base derivatives may become a lead compound for anti-microbial drugs.

**Keywords:** Schiff's base, Triazine, Cyanuric Chloride, Antimicrobial activity.

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ISSN: 0975-8585

## INTRODUCTION

s- Triazine derivatives represent an important class of compounds due to their potent biological activities. They are known to be anti-protozoals [1], anticancer agents [2], estrogen receptor modulators [3], antimalarials [4, 5], cyclin-dependent kinase modulators [6], and antimicrobials [7]. It has been reported that s-triazine derivatives are used as templates for molecular imprinting [8] and for the construction of three-helix bundle protein [9].

6-Aryl-2, 4-disubstituted 1,3,5-triazines, along with their derivatives are a class of attractive compounds in modern chemical industry [10]. They are widely employed as flame-retardant additives in common resins [11] or pivotal structural unit in fire-resistant polymers [12]. Chemically modified 6-aryl-2,4-diamino-triazines have also been reported as new ligands with potential multicoordination modes [13], crosslinkers in coatings [14], capsule of vermin-repellent microcapsules with slow-release potentiality [15], corrosion resistant agent on metal surfaces [16] and candidates of antiulcerous drugs [17] and allergy inhibitors [18]. In last decade the investigations concerning 6-substituted-2, 4-diamino-1,3,5-triazines were focused in their properties in molecular recognition [19-21].

Although various triazine derivatives are reported in literature for biological application, antimicrobial activities of these classes of compounds have received little attention. Synthesis of compounds containing triazine with nitrogen heteroatom is known in the literature as described above, however there are no reports available describing synthesis and antimicrobial activities of 6-aryl-2,4-disubstituted Schiff's base 1,3,5-triazine derivatives. To find out the effect of Schiff's base on biological system, an attempt is made here to synthesize novel Schiff's base derivatives derived from 4, 4'-((6-(4-(diethylamino) phenyl)-1,3,5-triazine-2,4 diyl)bis(oxy)) dibenzaldehyde (DIPOD). The DIPOD was prepared by reacting cyanuric chloride with N, N-diethyl aniline, followed by the reaction of 4-(4,6-dichloro-1,3,5-triazin-2-yl)-N,N-diethylaniline with 2 equivalents of 4-hydroxybenzaldehyde. The compounds are characterized by modern spectral analysis. Antimicrobial activities of these compounds are evaluated against bacterial strain (E. coli and S. aureus) and fungal strain (C. albicans and A. niger).

## EXPERIMENTAL

### Materials and methods

All commercial reagents and solvents were procured from s. d. fine chemicals (India) and were used without purification. The reaction was monitored by TLC using on 0.25 mm E-Merck silica gel 60 $F_{254}$ precoated plates, which were visualized with UV light. The FT-IR spectra were recorded on Perkins-Elmer 257 spectrometer using KBr discs. $^{1}$H-NMR spectra were recorded on VXR 400-MHz instrument using TMS as an internal standard. Mass spectra were recorded on Finnigan mass spectrometer.

**Biological activity**

All compounds were evaluated for in vitro antibacterial activities against E. coli and S. aureus strains and in vitro antifungal activity against C. albicans and A. niger strains by using serial dilution method.

**General**

Incubator at 35 and 37 °C; pipettes of various sizes (Gilson); sterile tips 5, 10, 50, 100, 200; sterile normal saline; sterile isosensitest agar (Southern Group Laboratory, SGL); antibiotic solutions (Sigma–Aldrich); sterile solution of 10% (v/v) DMSO in water (Sigma–Aldrich) were used for microbial studies.

**Medium**

Isosensitest medium was used throughout the assay, as it is pH buffered. Although NCCLS recommends the use of Mueller Hinton medium for susceptibility testing, the isosensitest medium had comparable results for most of the tested bacterial strains [22].

**Preparation of the plates**

Plates were prepared under aseptic conditions. A sterile 96 well plate was labeled. A volume of 100 µL of test material in 10% (v/v) DMSO (usually a stock concentration of 4 mg/ml) was pipetted into the first row of the plate. To all other wells 50 µL of nutrient broth was added. Serial dilutions were performed using a multichannel pipette. Tips were discarded after use such that each well had 50 µL of the test material in serially descending concentrations. To each well, 10 µL of resazurin indicator solution was added. Using a pipette 30 µL strength isosensitised both added to each well to ensure that the final volume was single strength of the nutrient broth. Finally, 10 µL of bacterial suspension ($5 \times 10^6$ cfu / mL) was added to each well to achieve a concentration of $5 \times 10^5$ cfu/ mL. Each plate was wrapped loosely with cling film to ensure that bacteria did not become dehydrated. Each plate had a set of control column with a broad-spectrum antibiotic as positive control, a column with all solutions with the exception of the test compound, and a column with all solutions with the exception of the bacterial solution, adding 10 µL of nutrient broth instead. The plates were prepared in triplicate, and placed in an incubator set at 37°C for 18–24 h. The color change was then assessed visually. Any color changes from purple to pink or colorless were recorded as positive. The lowest concentration at which color change occurred was taken as the MIC value. The average of three values was calculated and that was the MIC for the test material and bacterial or fungal strain [23].

ISSN: 0975-8585

**Synthesis of Compounds**

**Synthesis of 4-(4, 6-dichloro-1,3,5-triazin-2-yl)-N,N-diethylaniline (3)**

A mixture of N,N-diethylaniline (27 g, 0.2 mol) and cyanuric chloride (18.4 g, 0.1 mol) was heated at 70 $^{o}$C for 8 h under a slow stream of dry nitrogen gas, Reaction monitored by TLC and after completion the mixture was extracted with hot chloroform (200 mL) and the white crystalline hydrochloride salt of N,N-diethylaniline removed by filtration. Slow cooling and evaporation of the chloroform extract to a volume of 50 mL yielded good crystals of the Synthesis of 4-(4,6-dichloro-1,3,5-triazin-2-yl)-N,N-diethylaniline. Obtained product was recrystallized two times from acetone. (Yield: 11.68 g, 40%)
(Yield: 11.68 g, 40%); m.p.: 156 $^{o}$C (Recrystallized from Acetone)

**FT- IR (KBr) υ max. cm$^{-1}$**: 567, 715, 824, 839, 1164, 1232, 1515, 1610, 2967.

**$^{1}$H NMR (400 MHz, $CDCl_3$, 25 $^{o}$C) (δ: ppm):** 1.25 (t, 6H, - $CH_3$), 3.46 (q, 4H, - $CH_2$), 6.65-6.69 (dd, 2H, J = 9.2, 2.8 Hz, Ar-H), 8.29-8.33 (dd, 2H, J = 9.2, 2.8 Hz, Ar-H).

**$^{13}$C NMR (75 MHz, DMSO – $d_6$, 25 $^{o}$C) (δ: ppm):** 15.6 (s, - $CH_3$), 49 (s, - $CH_2$), 114.6 (s, Ar-C), 125.6 (Ar-C), 130.7 (s, Ar-C), 154.2 (Substituted Ar-C), 172.3 (s, N = C), 179.5 (N =C).

**HRMS**: 299.032(M+1; 45%), 298.123(40%), 161.221(100%), 105.201(80%).

4, 4'-((6-(4-(Diethylamino) phenyl)-1,3,5-triazine-2,4 diyl)bis(oxy)) dibenzaldehyde (**5**)

p- Hydroxybenzaldehyde (**4**) (2.426 g, 0.022 mol) and 4-(4, 6-dichloro-1,3,5-triazin-2-yl)-N,N-diethylaniline (**3**) (3 g, 0.011 mol) were added to a suspension of $K_2CO_3$ (3.04 g, 0.022 mol) in 50 mL of benzene. The mixture was refluxed for 22 h. The reaction mixture was then cooled and the solid was removed by filtration and washed with hot ethyl acetate twice. The filtrate was extracted with 10% $Na_2CO_3$ twice and with $H_2O$ once. The organic layer was dried over anhydrous $Na_2SO_4$ and then concentrated. The white powder was recrystallized from 20 mL of ethanol to afford 3.31 g of 4,4'-((6-(4-(diethylamino)phenyl)-1,3,5-triazine-2,4 diyl)bis(oxy)) dibenzaldehyde (**5**) as a white fluffy precipitate (80%).
(Yield: 3.31 g, 80%); m. p.: 150 $^{o}$C (recrystallized from ethanol)

**FT- IR (KBr) υ max. cm$^{-1}$**: 505, 726, 831, 1565, 1705, 2729, 2929, 2972, 3069.

**$^{1}$H NMR (400 MHz, $CDCl_3$, 25 $^{o}$C) (δ: ppm):** 1.19 (t, 6H, -$CH_3$), 3.43 (q, 4H, -$CH_2$), 6.58 (dd, 2H, J = 9.1, 2.7, Ar-H), 6.61 (dd, 2H, J = 9.1, 2.7, Ar-H), 7.41-7.44 (dd, 4H, J = 8.4, 1.8 Hz, Ar- H), 7.95-8.08 (dd, 4H, J = 8.8, 1.8 Hz, Ar-H), 10.04 (s, 2H, Aldehyde H).
**$^{13}$C NMR (75 MHz, DMSO – $d_6$, 25 $^{o}$C) (δ: ppm):** 12.3 ($CH_3$), 43.9 ($CH_2$), 110.7 (Ar-C), 119.2 (Ar-C), 122.5 (Ar-C), 130.9 (Ar-C), 131.1 (Ar-C), 133.7 (Ar-C), 151.5 (Substituted Ar-C), 156.2 (Substituted Ar-C), 171.53 (N = C), 174.4 (N = C), 192.9 (Aldehyde C).

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**HRMS:** 469.201 (M+ 1; 76%), 440.109 (35%), 347.398 (15%), 322.234 (17%), 279.365 (100%), 175.423 (22%).

**Synthesis of DIPOD Schiff's bases 7a.**

A Suspension of 4,4'-((6-(4-(diethylamino) phenyl)-1,3,5-triazine-2,4diyl)bis(oxy)) dibenzaldehyde **5** (1 g, 0.0023 mol) in 50 mL of methanol was added to a solution of aniline **6a** (0.44g, 0.0047 mol) in 20 mL of methanol, 3-4 drops conc. HCl. The mixture was stirred at reflux temperature for 4 h, after completion of Schiff's base formation (monitored by TLC), the suspension becomes thicker as a white to buff white fluffy precipitate formed. The reaction mixture was filtered and solid residue washed with 20 mL methanol to obtained pure DIPOD Schiff's bases **7a**
(Yield: 1.07 g, 73%); m. p.: 195 $^{o}$C. (Recrystallized from ethanol)

**FT - IR (KBr) υ max. cm$^{-1}$**: 691, 803, 1142, 1195, 1368, 1497, 1547, 2975.

**$^{1}$H NMR (400 MHz, CDCl$_3$, 25 $^{o}$C) (δ: ppm):** 1.11 (t, 6H, -$CH_3$), 3.42 (q, 4H, -$CH_2$), 6.74 (d, 2H, J = 8.8 Hz, Ar-H), 7.29 (d, 2H, J = 8.4 Hz, Ar- H), 7.32 (d, 2H, J = 8.4 Hz, Ar-H), 7.46-7.50 (d, 8H, J = 8.4 Hz, Ar-H), 7.96-8.00 (dd, 4H, J = 8.2, 2.0 Hz, Ar-H), 8.10-8.17 (d, 4H, J = 8.2 Hz, Ar-H), 8.69 (s, 2H, CH=N).

**$^{13}$C NMR (75 MHz, DMSO – d$_6$, 25 $^{o}$C) (δ: ppm):** 12.5 ($CH_3$), 44.5 ($CH_2$), 113.2 (Ar-C), 119.8 (Ar-C), 124.4 (Ar-C), 128.0 (Ar-C), 131.5 (Ar-C), 132.7 (Ar-C), 134.6 (Ar-C), 149.6 (Ar-C), 150.7(Ar-C), 152.3 (Substituted Ar-C), 157.2 (Substituted Ar-C), 159.8 ( Substituted Ar-C), 173.1 (N = C), 175.6 (N = C), 179.5(N=C).

**HRMS**: 619.721 (M+1; 23), 576.402 (20%), 422.437 (100%), 397.598 (80%), 354.409 (40%), 223.004 (10%).

**Synthesis of DIPOD Schiff's bases 7b.**

A Suspension of 4,4'-((6-(4-(diethylamino)phenyl)-1,3,5-triazine-2,4diyl)bis(oxy)) dibenzaldehyde **5** (1 g, 0.0023 mol) in 50 mL of methanol was added to a solution of p-chloro aniline **6b** (0.61g, 0.0047 mol) in 20 mL of methanol, 3-4 drops conc. HCl. The mixture was stirred at reflux temperature for 4 h, after completion of Schiff's base formation (monitored by TLC), the suspension becomes thicker as a white to buff white fluffy precipitate formed. The reaction mixture was filtered and solid residue washed with 20 mL methanol to obtained pure DIPOD Schiff's bases **7b.**
(Yield: 1.38 g, 83%); m. p.: 230 $^{o}$C (Recrystallized from ethanol)

**FT-IR (KBr) υ max. cm$^{-1}$**: 804, 840, 1042, 1142, 1203, 1342, 1364, 1550, 2975.

**$^1$H NMR (400 MHz, $CDCl_3$, 25 $^oC$) (δ: ppm):** 1.14 (t, 6H, $-CH_3$), 3.43 (q, 4H, $-CH_2$), 6.74 (d, 2H, J = 9.0 Hz, Ar-H), 7.31(d, 2H, J = 8.6 Hz, Ar- H), 7.34 (d, 2H, J = 8.6 Hz, Ar-H), 7.48-7.51 (d, 6H, J = 8.6 Hz, Ar-H), 7.99-8.05 (d, 4H, J = 8.0, 2.0 Hz, Ar-H), 8.13-8.19 (d, 4H, J = 8.0 Hz, Ar-H), 8.72 (s, 2H, CH=N).

**$^{13}$C NMR (75 MHz, DMSO – $d_6$, 25 $^oC$) (δ: ppm):** 12.5 ($CH_3$), 44.7 ($CH_2$), 113.6 (Ar-C), 120.0 (Ar-C), 124.7 (Ar-C), 131.7 (Ar-C), 132.7 (Ar-C), 134.9 (Ar-C), 150.0 (Ar-C), 151.3 (Ar-C), 152.7 (Substituted Ar-C), 157.9 (Substituted Ar-C), 160.1 (Substituted Ar-C), 174.0 (N = C), 175.8 (N = C), 179.7 (N=C).

**HRMS**: 690.613 (M+1; 20%), 644.087 (76%), 456. 376 (100%), 431.475 (58%), 388.987 (96%), 257.098 (30%).

**Synthesis of DIPOD Schiff's bases 7c.**

A Suspension of 4,4'-((6-(4-(diethylamino)phenyl)-1,3,5-triazine-2,4diyl)bis(oxy)) dibenzaldehyde **5** (1 g, 0.0023 mol) in 50 mL of methanol was added to a solution of p-methoxy aniline **6c** (0.59g, 0.0047 mol) in 20 mL of methanol, 3-4 drops conc. HCl. The mixture was stirred at reflux temperature for 4 h, after completion of Schiff's base formation (monitored by TLC), the suspension becomes thicker as a white to buff white fluffy precipitate formed. The reaction mixture was filtered and solid residue washed with 20 mL methanol to obtained pure DIPOD Schiff's bases **7c.**
(Yield: 1.27 g, 79%); m. p.: 235 $^oC$. (Recrystallized from ethanol)

**FT-IR (KBr) υ max. $cm^{-1}$**: 805, 836, 1144, 1201, 1243, 1345, 1366, 1547, 2978.

**$^1$H NMR (400 MHz, $CDCl_3$, 25 $^oC$) (δ: ppm):** 1.09 (t, 6H, $-CH_3$), 3.41 (q, 4H, $-CH_2$), 3.53 (s, 6H, $-OCH_3$), 6.73 (d, 2H, J = 8.8 Hz, Ar-H), 7.28 (d, 2H, J = 8.5 Hz, Ar- H), 7.31 (d, 2H, J = 8.5 Hz, Ar-H), 7.45-7.48 (d, 8H, J = 8.5 Hz, Ar-H), 7.94-7.97 (d, 2H, J = 7.9 Hz, Ar-H), 8.01-8.04 (d, 4H, J = 8.2 Hz, Ar-H), 8.67 (s, 2H, CH=N).

**$^{13}$C NMR (75 MHz, DMSO – $d_6$, 25 $^oC$) (δ: ppm):** 12.2 ($CH_3$), 44.3 ($CH_2$), 59.4 ($-OCH_3$), 113.2 (Ar-C), 119.8 (Ar-C), 124.2 (Ar-C), 131.4 (Ar-C), 132.3 (Ar-C), 134.7 (Ar-C), 149.8 (Ar-C), 151.3 (Ar-C), 152.6 (Substituted Ar-C), 157.8 (Substituted Ar-C), 159.9 (Substituted Ar-C), 173.8 (N = C), 175.4 (N = C), 179.4 (N=C).

**HRMS** = 679.202 (20%), 636.298 (40%), 452.313 (100%), 427. 031 (32%), 384.492 (38%).

**Synthesis of DIPOD Schiff's bases 7d.**

A Suspension of 4,4'-((6-(4-(diethylamino)phenyl)-1,3,5-triazine-2,4diyl)bis(oxy)) dibenzaldehyde **5** (1 g, 0.0023 mol) in 50 mL of methanol was added to a solution of 1-naphthyl amine **6d** (0.68g, 0.0047 mol) in 20 mL of methanol, 3-4 drops conc. HCl. The mixture

was stirred at reflux temperature for 4 h, after completion of Schiff's base formation (monitored by TLC), the suspension becomes thicker as a white to buff white fluffy precipitate formed. The reaction mixture was filtered and solid residue washed with 20 mL methanol to obtained pure DIPOD Schiff's bases **7d**.
(Yield: 1.11 g, 65 %); m. p.: > 300 $^{o}$C. (Recrystallized from ethanol)

**FT-IR (KBr) υ max. cm$^{-1}$**: 804, 834, 1140, 1205, 1239, 1340, 1361, 1550, 2984.

**$^{1}$H NMR (400 MHz, $CDCl_3$, 25 $^{o}$C) (δ: ppm):** 1.10 (t, 6H, -$CH_3$), 3.45 (q, 4H, -$CH_2$), 6.68 (d, 2H, J = 8.4 Hz, Ar-H), 7.30 - 7.32 (d, 4H, J = 8.6 Hz, Ar- H), 7.34-7.37 (d, 4H, J = 8.6 Hz, Ar-H), 7.43-7.49 (d, 8H, J = 8.6 Hz, Ar-H), 7.96-7.99 (d, 4H, J = 8.0 Hz, Ar-H), 8.04-8.08 (d, 4H, J = 7.8 Hz, Ar-H), 8.67 (s, 2H, CH=N).

**$^{13}$C NMR (75 MHz, DMSO – $d_6$, 25 $^{o}$C) (δ: ppm):** 12.7 ($CH_3$), 44.0 ($CH_2$), 113.2 (Ar-C), 119.8 (Ar-C), 124.2 (Ar-C), 128.7 (Ar-C), 131.4 (Ar-C), 132.3 (Ar-C), 134.7 (Ar-C), 142.6 (Ar-C), 149.3 (Ar-C), 151.0 (Ar-C), 152.4 (Substituted Ar-C), 157.6 (Substituted Ar-C), 159.4 (Substituted Ar-C), 172.9 (N = C), 175.0 (N = C), 178.3 (N=C).

**HRMS:** 719.843 (40%), 590.698 (75%), 465. 521 (100%), 360.403 (56%), 259.291 (70%).

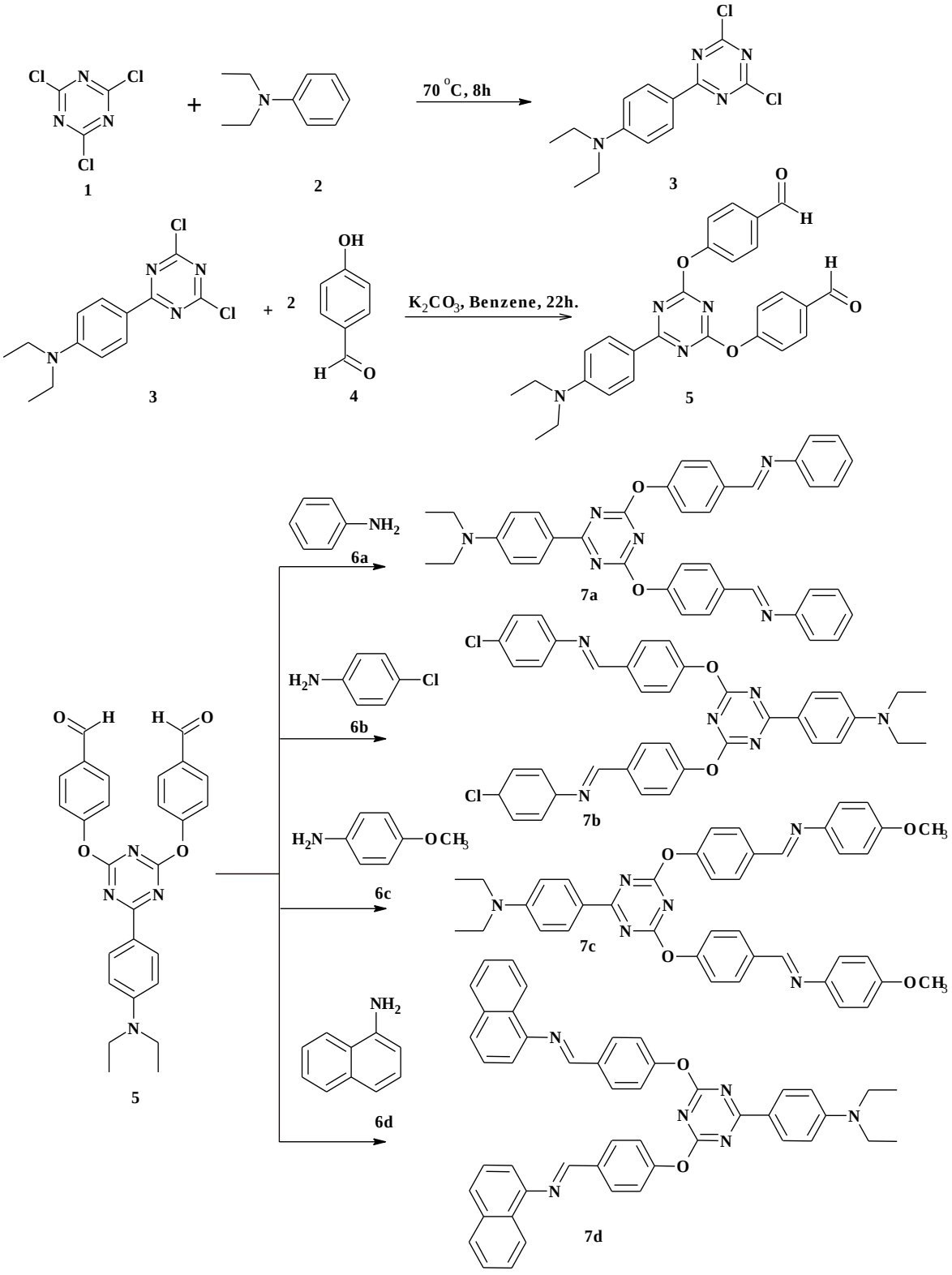
## RESULTS AND DISCUSSION

### Synthesis of Schiff's Bases

The reaction of cyanuric chloride with N, N-diethyl aniline yielded the desired dichloro 1,3,5-triazine (**3**). 4-(4, 6-Dichloro-1,3,5-triazin-2-yl)-N,N-diethylaniline (**3**) react with 2 equivalents of 4-hydroxybenzaldehyde in benzene to gave desired dialdehyde, 4,4'-((6-(4-(diethylamino)phenyl)-1,3,5-triazine-2,4 diyl)bis(oxy)) dibenzaldehyde (**5**), coded as DIPOD. Dialdehyde (**5)** was then reacted with different aromatic amines to afford the corresponding Schiff's base derivatives (**7a-7d)** as shown in **Scheme1**. In the $^{1}$H NMR spectra of DIPOD, the signal was detected at about 10.04 ppm confirms the formation of DIPOD. Further conversion of DIPOD in to dipodal Schiff's bases was confirmed by $^{1}$H NMR and Mass spectra.

ISSN: 0975-8585

**Scheme 1:** Synthesis of DIPOD **(5)** and DIPOD Schiff's bases **(7a-7d)**

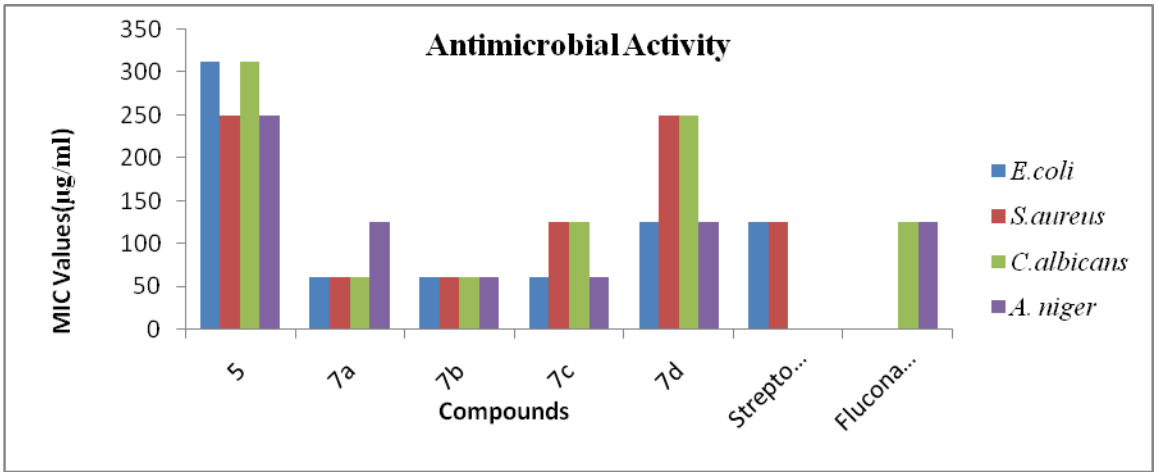


ISSN: 0975-8585

**Anti-microbial study**

To find out the interaction of Schiff's bases **7a-7d** with biological system their antimicrobial activity were evaluated for their in vitro antibacterial activity against E. coli and S. aureus strains and in vitro antifungal activity against C. albicans and A. niger strains by using serial dilution method. The minimum inhibitory concentration (MIC) measurement determined for compounds showed significant growth inhibition zones using serial dilution method. The MIC (µg/mL) values recorded in **Figure 1** indicate that most of the tested compounds displayed variable inhibitory effects on the growth of tested bacterial and fungal strains. The compounds **7b** showed good antibacterial activity against E. coli and S. aureus strain and antifungal activity against C. albicans and A. niger strain. On the other hand, compounds **7a, 7c** and **7d** exhibited moderate growth inhibitory as revealed from their MIC values. Among these compounds **7d** showed relatively poor growth inhibitory activity against both bacterial and fungal strains. Regarding the structure-activity relationship of the novel **DIPOD** Schiff's derivative **7a-7d** against the tested bacterial strain and fungal strain, the electron donating and electron withdrawing groups in target molecules **7a-7d** affect the growth inhibitory activity against tested strain. Compound **7b** containing chlorine electron withdrawing group is responsible to enhance the activity against bacterial and fungal strain. Biological study reveals that Schiff's base functionality is responsible to enhance the biological activity against tested bacterial and fungal strain, Dialdehyde (DIPOD) **5** showed very poor antimicrobial activity as compared to Schiff's base **7a-7d**. Antibacterial and antifungal activities of newly synthesized compounds indicated by MIC (µg/mL) using the modified resazurin assay.

**Figure 1. Antimicrobial activity of DIPOD (5) and its Schiff's base (7a-7d).**




MIC: Minimal inhibitory concentration values.
Bacterial strain: E. coli; S. aureus.
Fungal Strain: C. albicans; A. niger.
Solvent used: DMSO (Dimethyl sulphoxide).
Standard: Bacterial strain: Streptomycin 125µg/mL, Fungal strains: Fluconazole 125µg/mL

ISSN: 0975-8585

## CONCLUSIONS

In summary, for the first time, we have designed and synthesized 1,3,5- triazine based Schiff's base and study of their antimicrobial activity evolution. The structure of synthesized dipodal derivatives were confirmed by FT-IR, $^{1}$H NMR, Mass spectra. We believe the insights gained in this study would be useful for the development of potential drug candidates derived from cyanuric chloride in the development of novel antimicrobial drug.

## ACKNOWLEDGEMENTS

Authors are thankful to Indian Institute of Technology, Mumbai for analytical Support.

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