SYNTHESIS CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF 1, 2, 4- TRIAZINE DERIVATIVES

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ABSTRACT

Triazines have a high significance in the field of medicinal chemistry with broad-spectrum of pharmacological activities. Thus triazine can be useful for design and formation of novel drugs. In this research, some new type of antimicrobial agents were synthesized so we choose 1,2,4 Triazine derivatives linked with Schiff bases. 1,2,4-Triazine derivatives were synthesized by refluxing (2,4-dinitrophenyl)hydrazine with formaldehyde four 4 hour then intermediate formohydrazide was further catalyze to cyclize into Benzo[e][1,2,4]-triazin-6-amine. In presence of NaOH Schiff bases were formed using different substituted ketones. Characterization of newly synthesized triazine compounds were formed as Molecular formula, Physical state, Color, Melting point, Yield, Solubility and R_f - value. Structure of synthesized Triazine derivatives were elucidated using spectrogram data as well as physical method e.g Elemental analysis, FT-IR, ^1H NMR and mass. Biological evaluation of synthesized trazine derivatives was performed against (*S.aureus)* and (*P.aeruginosa)* Antimicrobial activities were estimated by disk diffusion method. Firstly, minimum inhibitory concentration (MIC) values obtained. Antimicrobial activities of synthesized trazine derivatives were evaluated in the term of zone of inhibition. Over all

observation about all synthesized trazine derivatives was better effect in comparison to standard drug possessed Tri- 2 against *S. aureus;* Tri- 5 against *P. Aeruginosa;* and Good (moderate) effect show by Tri- 3 and Tri- 5 against *A. Niger.* All five synthesized compounds were effective against both fungal strains except Tri-1 has no effect against *S. aureus*.

KEYWORDS: Triazines, Synthesis, Antimicrobial, Multidrug Resistant, Schiff Bases

INTRODUCTION

The biological potential of 1,2,4-triazine derivatives is cleared from the literature and clinically used drugs[1]. The literature revealed that 1,2,4-triazine derivatives possess diverse biological potential, easy synthetic routes for the synthesis and attracted researchers for development of new chemotherapeutic agents and it also revealed the importance of the nucleus[2,3]. Triazines have a high significance in the field of medicinal chemistry with broad-spectrum of pharmacological activities[4]. Thus triazine can be useful for design and formation of novel drugs[5]. Some triazine derivatives are currently being evaluated in clinical trials[6]. Triazine may lead to potent type drugs with no or fewer side effects as compared to presently available pharmacological agents[7]. Since the 1980s, a re-emergence of tuberculosis has occurred that is often multidrug resistant (MDR) and enhanced by human immunodeficiency virus infection[8]. The severity and difficulty in treating MDR strains necessitates the use of several, sometimes six to seven different drugs[9].

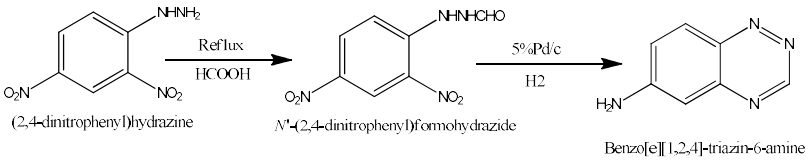
In this research we want to synthesize some new type of antimicrobial agent so we choose 1,2,4 Triazine derivatives. The selection 1,2,4 Triazine derivatives as antimicrobial agent due to 1,2,4 Triazine derivatives already reported for antibacterial antifungal activity and Schiff bases are well known for antimicrobial activity. These are basic points which provide us a strong rational for the research i.e. synthesis and antimicrobial screening of 1,2,4 Triazine and their derivatives.

MATERIALS AND METHOD

2,4 dinitrophenyl Hydrazine, Acetophenone, 1-(p-tolyl)ethanone, 1-(4-methoxyphenyl)ethanone, 1-(4-hydroxyphenyl)ethanone and 1-(3-nitrophenyl)ethanone were purchased from Sigma Aldrich Co. and other reagents used belongs to lab reagent great.

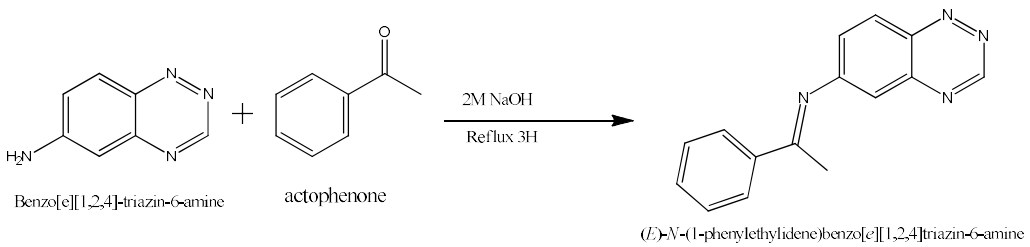
Methods of Synthesis of 1,2,4 Triazine Derivatives

Synthesis of Benzo[e][1,2,4]-triazin-6-amine by modified Bischler triazine synthesis method: (2,4-dinitrophenyl)hydrazine (0.001 mol) was taken in a round bottom flask and added formic acid (0.001 mol) then reflux for 4 hour. A intermediate N'-(2,4-dinitrophenyl) formohydrazide was formed. Then 5% palladium with charcoal was added as reduction catalyst which reduces the NO_2 group into NH_2 then cyclization occurs and Benzo[e][1,2,4]-triazin-6-amine was prepared. Reflux the mixture until the reaction completed (6-8 hours), reaction completion was determined by TLC. Prepared compound was recrystallized and stored in locking bag.



Synthesis of Schiff Bases from Benzo[e][1,2,4]-triazin-6-amine using different substituted ketones

(a) Synthesis of (E)-N-(1-phenylethylidene)benzo[e][1,2,4]triazin-6-amine (TRI-1): Acetophenone (0.001 mol) was mixed with 2M NaOH (10mL) in a beaker and a solution in methanol of Benzo[e][1,2,4]-triazin-6-amine (0.001mol) was added (50mL) then reflux for 3Hour. Reaction completion was determined by TLC; the mixture was cooled, filtered and evaporated under reduced pressure. The product obtained was re-crystallized.



(b) Synthesis of (E)-N-(1-(p-tolyl)ethylidene)benzo[e][1,2,4]triazin-6-amine (TRI-2): 1-(p-tolyl)ethanone (0.001 mol) was mixed with 2M NaOH (10mL) in a beaker and a solution in methanol of Benzo[e][1,2,4]-triazin-6-amine (0.001mol) was added (50mL) then reflux for

3Hour. Reaction completion was determined by TLC; the mixture was cooled, filtered and evaporated under reduced pressure. The product obtained was re-crystallized.

(c) Synthesis of (E)-N-(1-(4-methoxyphenyl)ethylidene)benzo[e][1,2,4]triazin-6-amine (TRI-3): 1-(4-methoxyphenyl)ethanone (0.001 mol) was mixed with 2M NaOH (10mL) in a beaker and a solution in methanol of Benzo[e][1,2,4]-triazin-6-amine (0.001mol) was added (50mL) then reflux for 3Hour. Reaction completion was determined by TLC; the mixture was cooled, filtered and evaporated under reduced pressure. The product obtained was re-crystallized.

(d) Synthesis of (E)-4-(1-(benzo[e][1,2,4]triazin-6-ylimino)ethyl)phenol (TRI-4): 1-(4-hydroxyphenyl)ethanone (0.001 mol) was mixed with 2M NaOH (10mL) in a beaker and a solution in methanol of Benzo[e][1,2,4]-triazin-6-amine (0.001mol) was added (50mL) then reflux for 3Hour. Reaction completion was determined by TLC; the mixture was cooled, filtered and evaporated under reduced pressure. The product obtained was re-crystallized.

(e) Synthesis of (E)-N-(1-(3-nitrophenyl)ethylidene)benzo[e][1,2,4]triazin-6-amine (TRI-5): 1-(3-nitrophenyl)ethanone (0.001 mol) was mixed with 2M NaOH (10mL) in a beaker and a solution in methanol of Benzo[e][1,2,4]-triazin-6-amine (0.001mol) was added (50mL) then reflux for 3Hour. Reaction completion was determined by TLC; the mixture was cooled, filtered and evaporated under reduced pressure. The product obtained was re-crystallized.

Methods of Characterization of Newly Synthesized Compound

Physical Evaluation of Newly Synthesized Compound: Color, consistency, physical stat and smell were observed by visual inspection and recorded.

Calculation of % yield: Percentage of Yield was calculated by following formula:

$$\% \textbf{ Yield } = \frac{\textbf{Practical yield}}{\textbf{Theoretical yield}} \textbf{ X 100}$$

Determination of melting point: Melting points of newly synthesized compounds were determined by open capillary method using the digital melting point apparatus and were uncorrected. Compounds were placed in one end sealed capillary and placed in the caves made for the capillary. Thermometer was already placed in their caves because it is digital apparatus.

The temperature at which compound start melting and the temperature at which it completely melts were recorded as the melting point range.

Solubility of compounds in different solvents: The various solvents such as water, ethanol, chloroform, ether, benzene, methanol, dimethyl formamide (DMF) and dimethyl sulphoxide (DMSO) were taken for dissolving intermediates and final products. 10 mg of each compound was weighed and added to 10 ml of each solvent individually taken in 50 ml beaker. Observation was recorded observed for different compounds.

Thin Layer Chromatography: Thin layer chromatographic analysis of compounds was done on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.3 mm on previously cleaned TLC plates of 20 x 10 cm. using conventional spreader. The plates were placed in hot air oven at 105 °C for 30 min. The solution of compounds was applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of the products. $CHCl_3$:CH_3OH (9:1) is used as mobile phase. The spots were visualized by exposure to iodine vapor.

Methods of Structural Elucidation by Spectral Analysis of Synthesized Compound:

Elemental analysis: Elemental analysis of compounds was done on Vario micro elemental analyser (Elementar Germany).

FT-IR spectral analysis: IR spectra of the compound were obtained from FT-IR spectrophotometer using KBr pellets, recorded on Bruker FT-IR. 100 mg of dehydrated KBr was accurately weighed. To this added 1 mg of compound and mixed well. The mixture was placed in an evacuable die and subjected to a pressure of 5-6 tons for 5 min. A transparent disc was produced which was then placed in a pellet holder and IR spectra were taken.

^{1}H-NMR spectral analysis: ^{1}H NMR spectra of compounds was recorded on Bruker NMR spectrophotometer in deuterium- substituted chloroform as solvent of compounds and TMS (tetra methyl silane) was used as internal standard. Chemical shift was measured as delta-value (δ-value) in ppm (parts per million).

Method of *in-vitro* Evaluation of Anti-microbial Activity of synthesized compounds:

Bacterial strains: *Staphylococcus aureus*, and *Pseudomonas aeruginosa,* pure isolates were obtained from Hi-Media Laboratories. All samples were cultured and subcultured again for purity. Colony morphology and Gram staining were done to confirm the identity of working strains.

Antibacterial susceptibility assays

a) Disk Diffusion Assay: The antibacterial susceptibility was initially assayed by the agar disk diffusion method. Concentrations synthesized compounds were prepared in DMSO. Bacteria cell suspensions were adjusted to 0.5 McFarland turbidity standards to prepare 1 × 108 bacterial/ml inoculum. Each bacterial suspension was inoculated on Mueller-Hinton agar plates and the plates were then allowed to dry for 5 minutes. The sterile filter paper disks (Whatman No. 1, diameter = 6 mm) were soaked in 10µl of synthesized compounds. Synthesized compounds - soaked filter paper disks were then placed on the inoculated Mueller-Hinton agar plates. Cefotaxime (30µg) disk was used as the positive control, and 10% DMSO-soaked filter paper disk was used as the negative control. Plates were incubated for 18 hr at 35 ± 2°C. After incubation, the zones of inhibition were recorded as the diameter of the growth-free zones measured in mm using a Vernier caliper.

Antifungal Susceptibility Testing

Fungal Strains: The assays were performed with strain of *Candida albicans* and *Aspergilus Niger* pure isolates were obtained from Hi-Media Laboratories. These strains were maintained in SDA at 35°C and 4°C until used in tests.

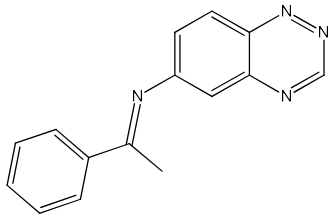
Culture Media: To test the biological activity of synthesized compounds, Sabouraud dextrose broth (SDB) and Sabouraud dextrose agar (SDA) were purchased from Hi-Media Laboratories and agar-cornmeal from HiMédia Laboratories (Mumbai, India), and RPMI-1640-L-glutamine (without sodium bicarbonate) (Sigma-Aldrich, São Paulo, SP, Brazil) culture media were used. They were prepared and used according to the manufacturers' instructions.

Statistical Analysis: Studies were performed in triplicate. Data were expressed as mean ± SEM. Multiple Comparisons Test by employing statistical software. Differences between groups were considered significant at $P < 0.05$ levels.

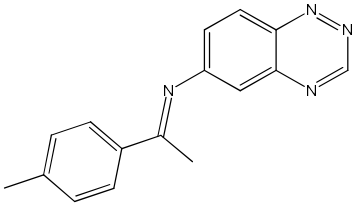
RESULT AND DISCUSSION

Characterization and Structural Elucidation of Novel Synthesized Triazine Derivatives

(A) TRI- 1: IUPAC Name: (E)-N-(1-phenylethylidene)benzo[e][1,2,4]triazin-6-amine; **Molecular weight**: 248.28; Yellowish Crystalline solid; **Melting point**: 168-170^{O}C; **Yield**: 67.27%; **Solubility**: ethanol, DMSO and Methanol; **R_f :**0.49; **Elemental analysis calculated (Found) % for $C_{15}H_{15}N_5$:** C, 72.56(71.05); H, 4.87(4.77); N, 22.57(22.01); **FT-IR (KBr): cm^{-1}** 2930 **C-H** str. (alkane); 1696 **C=N** str.(Ar), 1556 **C=C** str. (Ar); 1405 **C-H** str. **(**Ar**); ^{1}H NMR (MeOD, 500 MHz):** δ 9.88(s, 1H, CH triazine ring), 7.94(d, 2H, *J*= 9.4, CH-Ar), 7.62(d, 1H, *J*= 13.15, CH-Ar), 7.52(t, 3H, *J*= 5.45, 3.65, CH-Ar), 7.33(d, *J*= 10.55, 1H, CH-Ar), 7.16(s, 1H, CH-Ar), 1.81(s, 3H, CH_3),ppm.

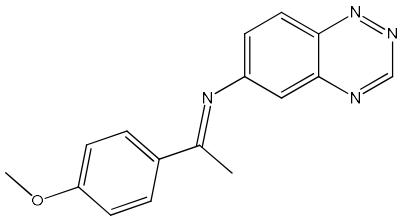


(B) TRI- 2: IUPAC Name: (E)-N-(1-(p-tolyl)ethylidene)benzo[e][1,2,4]triazin-6-amine; **Molecular weight**: 262.31; Yellow Amorphous solid; **Melting point**: 191-193 ^{O}C; **Yield**: 58.68%; **Solubility**: Ethanol, DMSO and Methanol; **R_f**: 0.57; **Elemental analysis calculated (Found) % for $C_{15}H_{15}N_5$:** C, 73.26(72.86); H, 5.38(5.27); N, 21.36(21.21); **FT-IR (KBr): cm^{-1}** 2840 **C-H** str. (alkane); 1647 **C=N** str.(Ar), 1578 **C=C** str. (Ar); 1410 **C-H** str.(Ar). **^{1}H NMR (MeOD, 500 MHz):** δ 9.88(s, 1H, CH triazine ring), 7.71(d, 2H, *J*= 9.05, CH-Ar), 7.61(d, 1H, *J*= 9.4, CH-Ar), 7.33(dd, 3H, CH-Ar), 7.16(s, 1H, CH-Ar), 2.34(s, 3H, CH_3), 1.81(s, 3H, CH_3),ppm.

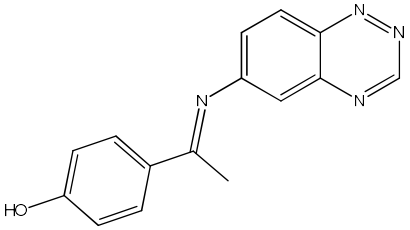


(C) TRI- 3: IUPAC Name: (E)-N-(1-(4-methoxyphenyl)ethylidene)benzo[e][1,2,4]triazin-6-amine; **Molecular weight**: 278.31; Light Yellow Crystalline solid; **Melting point** : 204-206 ^{O}C ;

Yield:63.08%; **Solubility**: Ethanol, DMSO and Methanol; **R_f**: 0.64; **Elemental analysis calculated (Found) % for $C_{15}H_{15}N_5$:** C, 69.05(67.99); H, 5.07(5.01); N, 20.13(20.15); O, 5.75(5.79); **FT-IR (KBr): cm^{-1}** 2898 **C-H** str. (alkane); 1648 **C=N** str.(Ar), 1581 **C=C** str. (Ar); 1396 **C-H** str. **(**Ar**).; ^{1}H NMR (MeOD, 500 MHz):** δ 9.88(s, 1H, CH triazine ring), 7.91(d, 2H, *J*= 3.4, CH-Ar), 7.60(d, 1H, *J*= 9.55, CH-Ar), 7.33(d, 1H, *J*= 10.1, CH-Ar), 7.16(s, 1H, CH-Ar), 7.06(d, 2H, *J*= 8.6, CH-Ar), 3.83(s, 3H, O-CH_3), 1.81(s, 3H, CH_3),ppm.

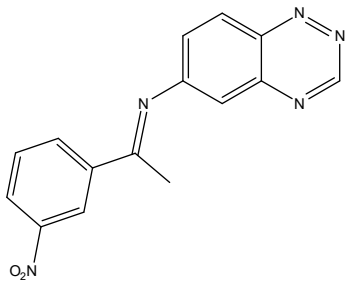


(D) TRI- 4: IUPAC Name: (E)-4-(1-(benzo[e][1,2,4]triazin-6-ylimino)ethyl)phenol; **Molecular weight**: 264.28; Brown Crystalline solid; **Melting point**: 185-188 ^{O}C ; **Yield**: 71.86%,; **Solubility** : Ethanol, DMSO and Methanol; **R_f** : 0.42; **Elemental analysis calculated (Found) % for $C_{15}H_{15}N_5$:** C, 68.17(67.85); H, 4.58(4.68); N, 21.20(21.26); O, 6.05(6.01); **FT-IR (KBr): cm^{-1}** 3360 **O-H** str.; 1644 **C=N** str.(Ar), 1597 **C=C** str. (Ar); 1376 **C-H** str (Ar).; **^{1}H NMR (MeOD, 500 MHz):** δ 9.88(s, 1H, CH triazine ring), 7.85(d, 2H, *J*= 7.3 CH-Ar), 7.63(d, 1H, *J*= 13.35, CH-Ar), 7.33(d, 1H, *J*= 10.55, CH-Ar), 7.16(s, 1H, CH-Ar), 6.85(d, 2H, *J*= 9.45, CH-Ar), 5.35(s,1H, OH), 1.81(s, 3H, CH_3),ppm.



(E) TRI- 5: IUPAC Name: (E)-N-(1-(3-nitrophenyl)ethylidene)benzo[e][1,2,4]triazin-6-amine; **Molecular weight**: 293.28; brilliant Yellow Crystalline solid; **Melting point**: 215-218 ^{O}C; **Yield**: 58.08 %; **Solubility**: Ethanol, DMSO and Methanol; **R_f:** 0.57; **Elemental analysis calculated (Found) % for $C_{15}H_{15}N_5$:** C, 67.90(67.62); H, 5.70(5.11); N, 26.40(25.96). **Elemental Analysis:** C, 61.43; H, 3.78; N, 23.88; O, 10.91; **FT-IR (KBr): cm^{-1}** 2836 **C-H** str. (alkane); 1678 **C=N** str.(Ar), 1597 **C=C** str. (Ar); 1488 **C-H** str (Ar); **^{1}H NMR (MeOD, 500**

MHz): δ 9.88(s, 1H, CH triazine ring), 8.52(s, 1H, CH-Ar), 8.33(d, 1H, *J*= 10.15, CH-Ar), 8.15 (d, 1H, *J*= 9.7, CH-Ar), 7.78(t, 1H, *J*= 5.4, 7.75, CH-Ar), 7.62(d, 1H, *J*= 11.6, CH-Ar), 7.31(d, 1H, *J*= 9.95, CH-Ar), 7.16(s, 1H, CH-Ar), 1.81(s, 3H, CH_3),ppm.



Evaluation of Antimicrobial Activity of Newly Synthesized Triazine Derivatives

Table No. 1: Antimicrobial activity of Triazine Derivatives

Sample Code	Diameter of zone of inhibition (mm)			
	S. aureus	***P. aeruginosa***	***C. Albicans***	***A. Niger***
TRI-1	-	10(12.5)	12(12.5)	11(12.5)
TRI-2	17(12.5)	10(6.25)	9(12.5)	12(12.5)
TRI-3	13(12.5)	12(12.5)	10(12.5)	19(12.5)
TRI-4	10(6.25)	12(6.25)	13(12.5)	13(6.25)
TRI-5	11(12.5)	18(12.5)	10(6.25)	18(6.25)
Control **(C)**	-	-	-	-
Cefotaxime **(S)**	20(6.25)	20(6.25)	20(12.5)	25(6.25)

[a] Values in brackets are MIC values (µg ml^{-1})

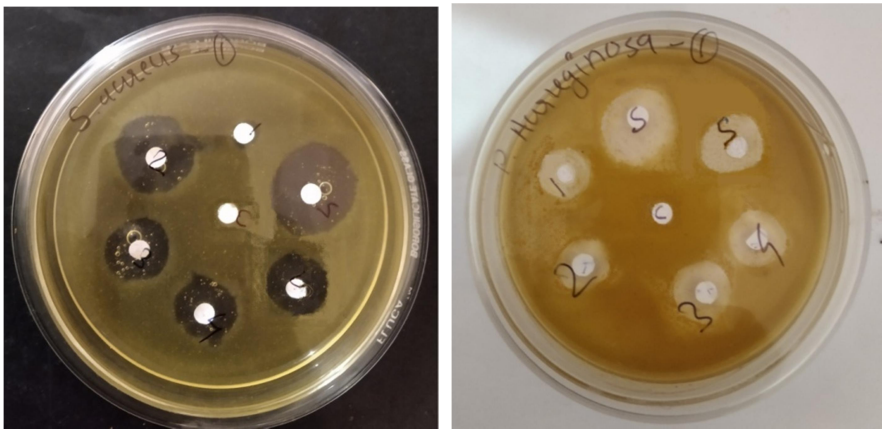


Figure No. 1: Antibacterial activity of Triazine Derivatives

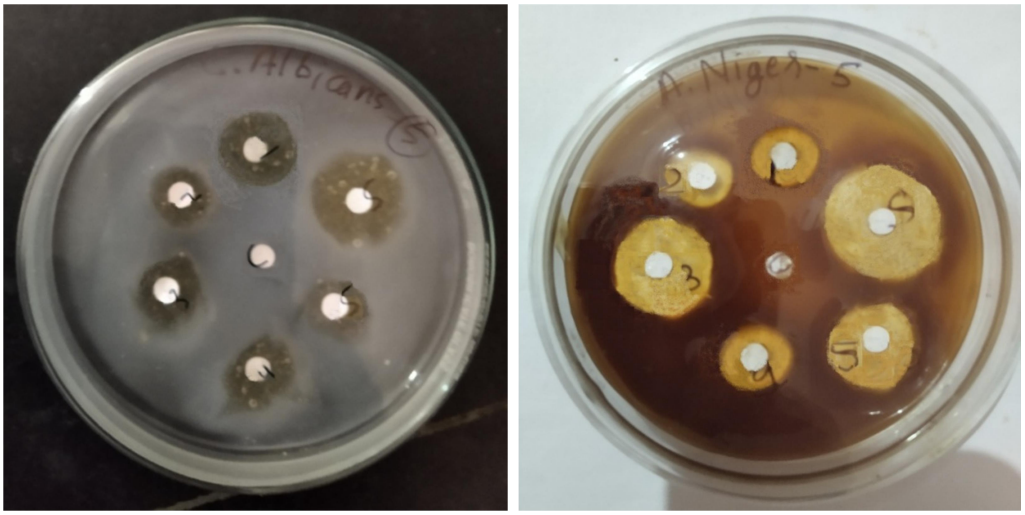


Figure No. 2: Antifungal activity of Triazine Derivatives

Statistical representation of pharmacological evaluation data

Antibacterial Activity

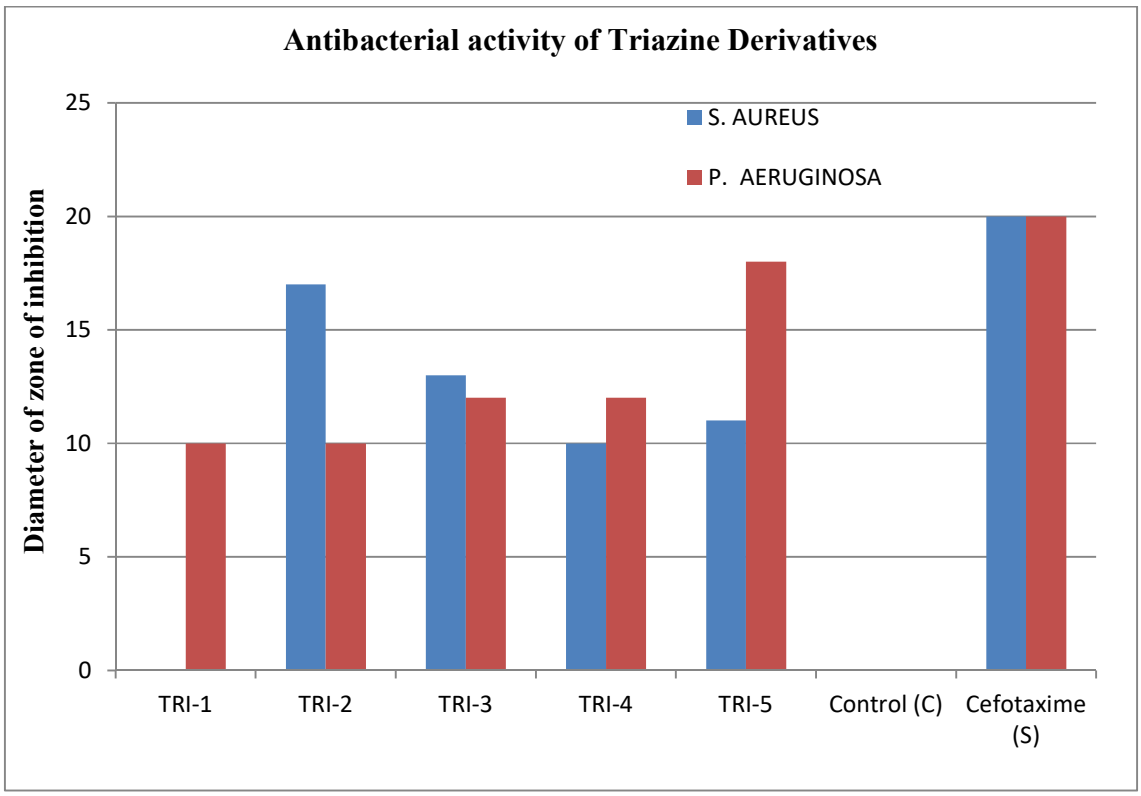


Figure 3: Antibacterial activity of Triazine Derivatives

Antifungal Activity

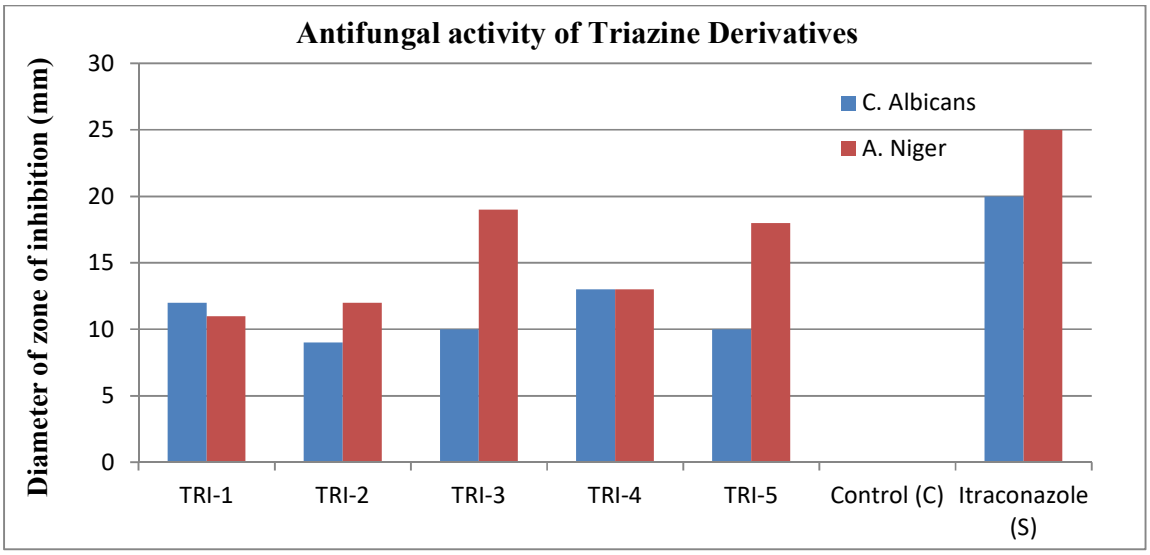


Figure 4: Antifungal activity of Triazine Derivatives

7.4 Discussion

1,2,4-Triazine derivatives were synthesized by refluxing (2,4-dinitrophenyl)hydrazine with formaldehyde four 4 hour then intermediate formohydrazide was further catalyze to cyclize into Benzo[e][1,2,4]-triazin-6-amine. In presence of NaOH Schiff bases were formed using different substituted ketones. Characterization of newly synthesized triazine compounds were formed as Molecular formula, Physical state, Color, Melting point, Yield, Solubility and R_f - value. Structure of synthesized Triazine derivatives were elucidated using spectrogram data as well as physical method e.g Elemental analysis, FT-IR, ^{1}H NMR and mass. Appearance of absorption bands in compounds at 2840 **C-H** str. (alkane) and Schiff base at 1647 **C=N** str.(Ar), which is present in all triazine derivative's in FT-IR spectrum clearly indicated. This fact was further supported by ^{1}H NMR spectrum, presence of peak 9.88 of CH of triazine ring 1.81 ppm of different derivative, corresponding to their structure. Moreover, synthesized compounds characterized by the TLC and melting point. In addition, by visual inspection synthesized compounds were also characterized.

Biological evaluation of synthesized trazine derivatives was performed against (*S.aureus)* and (*P.aeruginosa)* Antimicrobial activities were estimated by disk diffusion method. Firstly, minimum inhibitory concentration (MIC) values obtained. Antimicrobial activities of

synthesized trazine derivatives were evaluated in the term of zone of inhibition as described in tables. Tri-1 was equally and less effective on *P. aeruginosa, A. Niger,* and *C. Albicans* no effect on *S. aureus*. Tri-2 was moderately effective on *S. aureus,* less effective against both fungal strains (*A. Niger,* and *C. Albicans*) and *P. aeruginosa.* Tri-3 was moderately effective against *A. Niger,* less effective against both bacterial strains and less effective against *C. Albicans*. Tri-4 was less effective against all bacterial and fungal strain. Tri-5 was effective against *P. aeruginosa* and *A. Niger,* less effective against *S. aureus* and *C. Albicans* .

Over all observation about all synthesized trazine derivatives were better effect in comparison to standard drug possessed Tri- 2 against *S. aureus;* Tri- 5 against *P. Aeruginosa;* and Good (moderate) effect show by Tri- 3 and Tri- 5 against *A. Niger* . All five synthesized compounds were effective against both fungal strains except Tri-1 has no effect against *S. aureus*.

CONCLUSION

Schiff Base and 1,2,4-trazines are interesting groups of heterocyclic compounds exhibiting diverse pharmacological activities. They have reported wide range of applications. This study described those novel synthesized 1,2,4-trazines moderately inhibited microbial growth efficiently. These novel synthesized 1,2,4-trazine compounds can still be considered as lead candidate for the research of antimicrobial drugs while these compounds showed average to better potency against cancer microbes. These novel synthesized 1,2,4-trazine compounds also may be developed as drug for the future in the treatment of microbial infection, they can be used individualy or in combination with other antibiotic drugs to compliment the therapeutic effects. However, more *in-vitro* and *in-vivo* mechanistic studies, toxicity reduction studies are needed to expose the full possible potential and properties of these compounds.

CONFLICTS OF INTERESTS

There are Conflicts of interests

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