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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL s-TRIAZINE DERIVATIVES INCORPORATING QUINOLINE MOIETY

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ABSTRACT

s-Triazine derivatives based quinoline demonstrate a wide range of biological activity. In the present investigation, 4,7-dichloroquinoline was taken as starting material and treated with ethylene diamine, which afforded 4-substituted 7-chloroquinoline. It was further reacted with 1,5-disubstituted cyanuric chloride yielding 1,3,5-triazine chloroquinoline derivatives. All the synthesized compounds were characterized using IR, ^{1}H, ^{13}C NMR, mass spectral studies and elemental analysis. The final compounds were screened for their antibacterial activity using *E. coli*, *S. aureus* and *S. typhi* and antifungal activity.

Key words: Cyanuric chloride, Dichloroquinoline, Ethylene diamine, Antibacterial activity, Antifungal activities.

INTRODUCTION

Various heterocyclic compounds posses wide range of biological and pharmacological activities.[1] Among a wide variety of heterocycles that have been explored for developing pharmaceutically important molecules such as s-triazines and quinoline have played an important role in the present medicinal chemistry.[2-5] Literature survey reveals that the nitrogen containing heterocycles posses a wide range of activities. In the present work, it has been observed that cyanuric chloride is the best starting compound for the preparation of substituted triazines.[6-7] Chalcones show impressive physiological properties and some of them posses wide range of activities such as antibacterial, antitubercular, etc.[8-10] Quinoline derivatives posses various activities like antibacterial, antifungal, antitubercular, anti-inflammatory, herbicidal, anticancer, antidepressant, antioxidant etc.[11-18]

The symmetrical triazine ring system is ordinarily abbreviated as s-triazine, although the designation 1, 3, 5-triazine is also common, particularly in the British literature. In this convention, the numbers refer to positions of the ring-nitrogen atoms.

In the early German literature, the s-triazine system was known as kyanidine (cyanidine) or γ-triazine.[19] The designation s-triazine is preferred by both; chemical abstracts and the ring index. Ring

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nitrogen positions 1, 3 and 5 are equivalent, as are ring-carbon positions 2, 4 and 6. *s*–Triazine is an extremely volatile crystalline solid, which melts at 86°C and boils at 114°C at one atmosphere. It is easily soluble in ether and in ethanol at -5°C. The relatively high melting point and extreme volatility are in accord with a highly symmetrical molecular structure. Because of its volatility, *s*-triazine can be isolated from reaction mixtures by entrainment in a stream of nitrogen or dry air.[20-22] The density of the highly refracting rhombohedral crystals has been determined to be approximately 1.38 g/cm^3. The heat of combustion for *s*-triazine has been calculated to be 424.4, the heat of fusion, the heat of vaporization, 12.15 and the resonance energy, 20.0 kilo.cal/mole. *s*-Triazine exhibits a high degree of thermal stability.[23] It can be purified without appreciable loss by repeated distillation over metallic sodium. Introduction of ring-nitrogen atoms has little effect on the boiling points but causes a linear increase in the melting points.

The case of displacement of chlorine atoms in 2,4,6-trichloro-1,3,5-triazine by various nucleophiles, in the presence of a hydrochloride acceptor usually sodium carbonate, bicarbonate, hydroxide or tertiary amines, makes this reagent useful for the preparation of mono-, di- and tri-substituted 1,3,5-triazines. The substitution of chlorine can be controlled by temperature to run in a stepwise manner. Mono-substitution of chlorine occurs below or at 0°C, disubstitution at 40-45°C and trisubstitution above 120°C. The substitution pattern also depends on the structure of the nucleophile, its basic strength and steric factors, the substituent already present in the s-triazine ring and the nature of solvent used.[24-25] By controlling the temperature, time and optimization of variables, such as solvent and base, the substitution of chlorine in 2, 4, 6-trichloro-1, 3, 5-triazine with different substituent can be accomplished in one pot with the correct order of addition of nucleophiles.[26-28]

In this paper, we have reported the novel s-triazine derivatives from N2-2-(7-chloroquinoline-4-yl)amino ethyl –N4,N6-bis 4-nitro phenyl-1,3,5 –triazine,2,4,6 triazine. First 4,7-dichloroquinoline was reacted with ethylene diamine to get 4-substituted 7-chloroquinoline. It is reacted with bisubstituted cyanuric chloride. The compounds are characterized by spectral analysis. Antibacterial activities and Antifungal activities of these compounds are studied.

EXPERIMENTAL

Materials and instruments used

Cyanuric chloride, 4,7-dichloroquinoline, and ethylenediamine were used as received from Aldrich Chem. Sodiumb carbonate, p-nitroaniline, and aniline were used as received from Merck.

Visualization of spot on TLC plates was effected by UV- illumination exposure of iodine vapour and heating the plates dipped in $KMnO_4$ stain. Silica gel for column chromatography was purchased from Sigma Aldrich. All synthesized compounds were recrystallised in absolute alcohol.

The reaction was monitored by TLC using on 0.25 mm E. Merck silica gel precoated plates, which were visualized with UV light. Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D and are uncorrected.

The FT-IR spectra were recorded on Perkin-Elmer 257 spectrometer using KBr disks. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MH_Z model spectrometer (Varian India Pvt. Ltd., Mumbai, India) using DMSO as a solvent and TMS as an internal standard with ^{1}H resonant frequency of 400 MH_Z and ^{13}C resonant frequency of 100 MH_Z. Mass spectra were recorded on a Perkin-Elmer Q-Mass 910 instrument.

General procedure for the synthesis of N^1-(7-chloro quinoline-4-yl)ethane-1,2-diamine 1(a-c)

A mixture of 4,7-dichloroquinoline (1.8 g 0.01 mol) and ethylene diamine (0.06 g 0.01 mol) was heated and the reaction was monitored by TLC. After completion, reaction mixture was extracted and the crystals of 4-substituted 7-chloroquinoline were removed by filtration. The product was recrystallized two times from acetone.

Synthesis of 4-4 ((6–((-7-chloro quinoline- 4-yl) amino) ethyl)amino) 1,3,5–triazine-2,4–diyl)bis (oxyl)bis (3-methoxybenzaldehyde) (2a-c)

Vanilline (1.5 g; 0.01 mol) was added slowly to cyanuric chloride (1.845 g; 0.01 mol) in acetone (35 mL) with constant stirring for 4 hr at 0°C. Sodium bicarbonate solution (10%) was added to neutralize HCl evolved during the reaction. The reaction was monitored by TLC, finally the content were poured into crushed ice. The solid was filtered, washed with water, dried, and recrystalized from ethanol.

Vanilline (1.5 g; 0.01 mol) was added slowly to 4,6-dichloro-N(4-nitro-phenyl)-1,3,5-triazine-2-amine 2.85 g (0.01 mol) in acetone (35 mL) with constant stirring for 4 hr at room temperature. Sodium bicarbonate solution (10%) was added to neutralize HCl evoled during the reaction. Finally, the contents were poured into crushed ice. The solid was separated, filtered, washed with dried and recrystallized from ethanol.

Bi substituted cyanuric chloride 4.1 g (0.01 mol) was added slowly to N^1–(7-chloro quinoline-4-yl) ethane-1,2-diamine. 2.21 g (0.01 mol) in acetone (35 mL) with constant stirring for 6 hr above 60°C. Sodium bicarbonate solution (10%) was added to neutralize HCl evoled during the reaction. Reaction was monitored by TLC. After the completion of reaction, the content were poured in ice. The solid was filtered, washed with water dried and recrystallized from ethanol.

Synthesis of N-2-((7-chloro quinoline-4-yl)amino)ethyl)-6-(naphthalene-1-yl) oxyl-N^4-(4-nitro phenyl)-1,3,5 triazine-2,4,6 diamine (3a-c)

p-Nitroaniline (2.76 g; 0.01 mol) was added slowly to cyanuric chloride (1.845 g; 0.01 mol) in acetone (35 mL) with constant stirring for 4 hr at 0°C. Sodium bicarbonate solution (10%) was added to neutralize HCl evoled during the reaction. The reaction was monitored by TLC, finally the content were poured into crushed ice. The solid was filtered, washed with water, dried, and recrystalized from ethanol to give compound **(3)**.

1-Naphthol (1.4 g; 0.01 mol) was added slowly to 4,6–dichloro–N(4- nitro–phenyl)-1,3,5-triazine- 2-amine (2.85 g; 0.01 mol) in acetone (35 mL) with constant stirring for 4 hr at room temp. Sodium bicarbonate solution (10%) was added to neutralize HCl evolved during the reaction. Finally the content were poured into crushed ice. The solid was filtered washed, dried and recrystallized from ethanol to give compound **(4)**.

Bisubstituted cyanuric chloride (3.93 g; 0.01 mol) was added slowly to N^1–(7-chloro quinoline-4-yl) ethane-1,2-diamine (2.21 g; 0.01 mol) in acetone (35 mL) with constant stirring for 6 hr above 60°C. sodium bicarbonate solution (10%) was added to neutralize HCl evolved during the reaction. Reaction was monitored by TLC. After the completion of reaction, the content were poured in ice. The solid was filtered, washed with water, dried and recrystallised from ethanol. The pure product was isolated by using column

chromatography. The column was started at 10% ethyl acetate in petroleum ether and slowly increased to 70% ethyl acetate. The solid dried was recrystallised by absolute ethanol.

Compound (2a): Yield 60.50% m.p 165°C (dec); IR (Kbr, cm^{-1}): 713.92 (C-Cl), 707.09 ($-CH_2$) 812.32 (C-N S–triazine), 1186.90 (-O-linkage), 1548.14 (-NH bending), 3394.11 (-NH stretching), 1697.84 (Aldyhyde carbonyl), 2841.72 (-CH methyl) ^{1}H-NMR δppm: 3.65 (t, 4H, $-CH_2$), 7.20-7.49 (m, 5H, Ar-H), 8.262-8.265 (m, 5H, Ar-H), 10.940 (s, 1H, -NH) ^{13}C-NMR δppm: 119.02-144.735 (Ar–C), 163.421, 167.049, 169.841 (C = N of s-triazine).

Compound (2b): Yield 64.45% m.p. 165°C (dec); IR (Kbr, cm^{-1}): 731.92 (-C-Cl), 707.09 ($-CH_2$), 813.21 (C-N S-triazine), 1186.93 (-O-linkage), 1548.14 (-NH bending), 1697.84 (aldehyde carbonyl) 2841.72 (C-H methyl, 3394.11 (C-NH stretching), ^{1}H-NMR δppm: 3.587 (t, 4H, $-CH_2$), 7.227-7.224 (m, 5H, -Ar-H), 8.262-8.269 (m, 5h, Ar-H), 10.948 (s, 1H, -NH) ^{13}C NMR δppm: 111.7-147.7 (Ar-C), 164.735, 168. 123, 168.841 (C=N of s-triazine).

Compound (2c): Yield 62.23% m.p. 135°C (dec); IR (Kbr, cm^{-1}): 731.92 (-C-Cl), 707.09 ($-CH_2$), 813.21 (C-N S-triazine), 1186.93 (-O-linkage), 1548.14 (-NH bending), 1697.84 (aldehyde carbonyl) 2841.72 (C-H methyl, 3394.11 (C-NH stretching), ^{1}H –NMR δppm: 3.587 (t, 4H,$-CH_2$), 7.840-7.862 (m,5H, Ar-H), 8.262-8.269 (m, 5H, Ar-H), 10.945 (s, 1H, -NH) ^{13}C NMR δppm: 119.029-144.735 (Ar-C), 163.096, 163.421, 167.049, 169.841 (C=N of s-triazine).

Compound (3a): Yield 64.47% m.p 161°C (dec); IR (Kbr, cm^{-1}) 802.59 (C-N –S triazine), 682.03 (C-Cl), 1106.76 (-O-linkage), 1326.61 ($-NO_2$), 1565.38 (-Ar), 3352.94 (Ar NH sretching), 311.78 (-NH), ^{1}H -NMR δppm: 3.350 (t, 4H, $-CH_2$), 7.388-7.406 (m, 4H, Ar-H), 8.210-8.219 (m, 4H, Ar-H), 10.819 (s, 1H, -NH) ^{13}C NMR δppm: 120.294-141.831 (Ar-C), 152.407, 164.407 (C = N of s-triazine).

Compound (3b): Yield 66.88% m.p. 165°C (dec); IR (Kbr,cm^{-1})) 802.59 (C-N-S triazine), 682.03 (C-Cl), 1106.76 (-O-linkage), 1326.61 ($-NO_2$), 1565.38 (-Ar), 3352.94 (Ar NH sretching), 311.78 (-NH), ^{1}H- NMR δppm: 3.359 (t, 4H, $-CH_2$), 7.386-7.450 (m, 4H, Ar-H), 8.210-8.248 (m, 4H, Ar-H), 10.819 (s, 1H, -NH) ^{13}C-NMR δppm 120.294-141.831 (Ar-C), 152.407, 164.432 (C = N of s-triazine).

Compound (3c): Yield 67.23% m.p. 163°C (dec); IR (Kbr, cm^{-1}) 802.59 (C-N-S triazine), 682.03 (C-Cl), 1106.76 (-O-linkage), 1326.61 ($-NO_2$), 1565.38 (-Ar), 3352.94 (Ar NH sretching), 311.78 (-NH), ^{1}H-NMR δppm: 3.358 (t, 4H, $-CH_2$), 7.358-7.450 m, 4H, Ar-H), 8.215-8.250 (m, 4H, Ar-H), 10.818 (s, 1H, -NH ^{13}C-NMR δppm: 120.292, 141.826 (Ar-C), 152.407, 166.435 (C = N of s-triazine).

Table 1: Various substituted compound

Compound	R_1	R_2	R_3
1a	Vaniline	Vaniline	N^1-7 (Chloroquinoline-4yl)ethane 1,2-diamine
1b	Vaniline	Vaniline	N^1-7 (Chloroquinoline-4yl)butane 1,2-diamine
1c	Vaniline	Vaniline	N^1-7(Chloroquinoline-4yl)hexane 1,2-diamine
2a	p-Nitroaniline	1-Naphthol	N^1-7(Chloroquinoline-4yl)ethane 1,2-diamine
2b	p-Nitroaniline	1-Naphthol	N^1-7(Chloroquinoline-4yl)butane 1,2-diamine
2c	p-Nitroaniline	1-Naphthol	N^1-7(Chloroquinoline-4yl)hexane 1,2-diamine

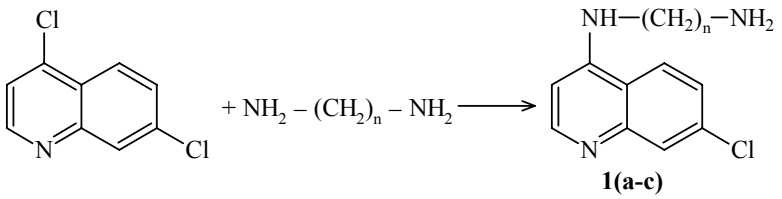
Compd.	Molecular formula (Mol. wt.)	Yield	M.P. (°C)	Elemental analysis					
				% C		%H		%N	
				Found	Cal	Found	Cal	Found	Cal
				58.58	**58.60**	**4.55**	**4.56**	**25.30**	**25.31**
1a	$C_{30}H_{25}ClN_6O_6$ 601.1	60.50	180-182	59.95	59.90	4.19	4.20	13.98	13.80
1b	$C_{32}H_{29}ClN_6O_4$ 628.18	64.45	170-175	61.40	61.39	4.65	4.61	13.36	13.35
1c	$C_{30}H_{28}ClN_9O_4$ 657.12	62.23	160-165	62.14	62.10	5.06	5.03	12.79	12.70
2a	$C_{30}H_{23}ClN_8O_3$ 599.01	64.47	222	69.23	69.20	4.00	4.05	19.35	19.30
2b	$C_{32}H_{27}ClN_8O_3$605.19	66.88	210-235	63.31	63.30	4.48	4.49	18.46	18.49
2c	$C_{34}H_{31}ClN_8O_3$ 634.22	67.23	210	64.30	64.25	4.92	4.90	17.64	17.60

RESULTS AND DISCUSSION

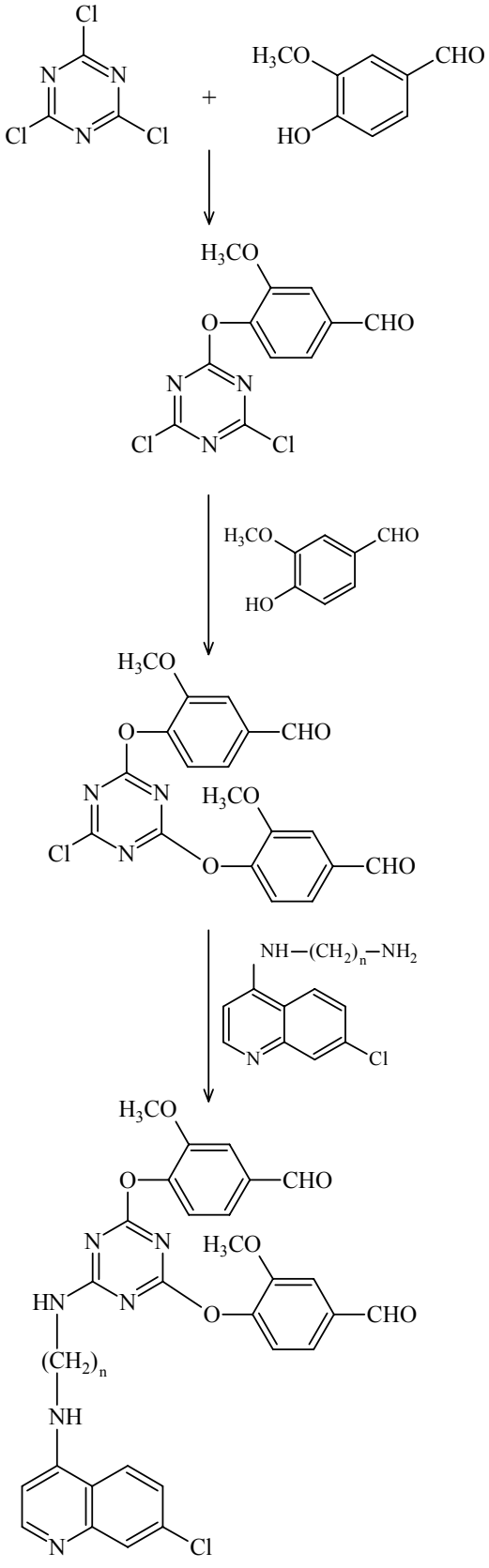
Several substituted s-triazine derivatives were effectively synthesized by a 2-3 step process. Synthesis of 4-substituted-7-chloroquinoline is the first step in the procedure. This compound is treated with s –triazine to give s-triazine derivatives. IR spectra of the entire compound showed absorption band at 3200-3500 cm^{-1} due to (Ar-NH) stretch vibration and an absorption at 918 cm^{-1} due to (-CH_2) vibration. The absorbtion at 1342 cm^{-1} showed the presence of (-NO_2) group. The absorption 813-821 cm^{-1} was attributed to the (C-N-S-triazine) vibration, which also confirmed the formation of desired s-triazine ring in all the compounds. In the NMR spectrum of the compound, CH_2 protons of the triazine ring were indicated by a pair of doublets of doublets at 3.42-3.58 ppm and 3.80-3.96 ppm. The mass spectra and elemental analysis of compound are also in agreement with their molecular formula

Antimicrobial activity

Various microorganism were used for the study of antimicrobial activity. The broth dilution method was used for this study. The antimicrobial activity of all the compounds was studied at 1000 ppm concentration *in vitro*. The different types of microorganism used were some gram negative bacteria [*Salmonella typhimurium*, *Vibrio parahaemolyticus*], gram positive bacteria *Micrococcus luteus Staphylococcus aureus*], and fungus –*Aspergillus niger.*



Scheme 1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+
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CHO
HO
H3CO
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N
N
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Cl
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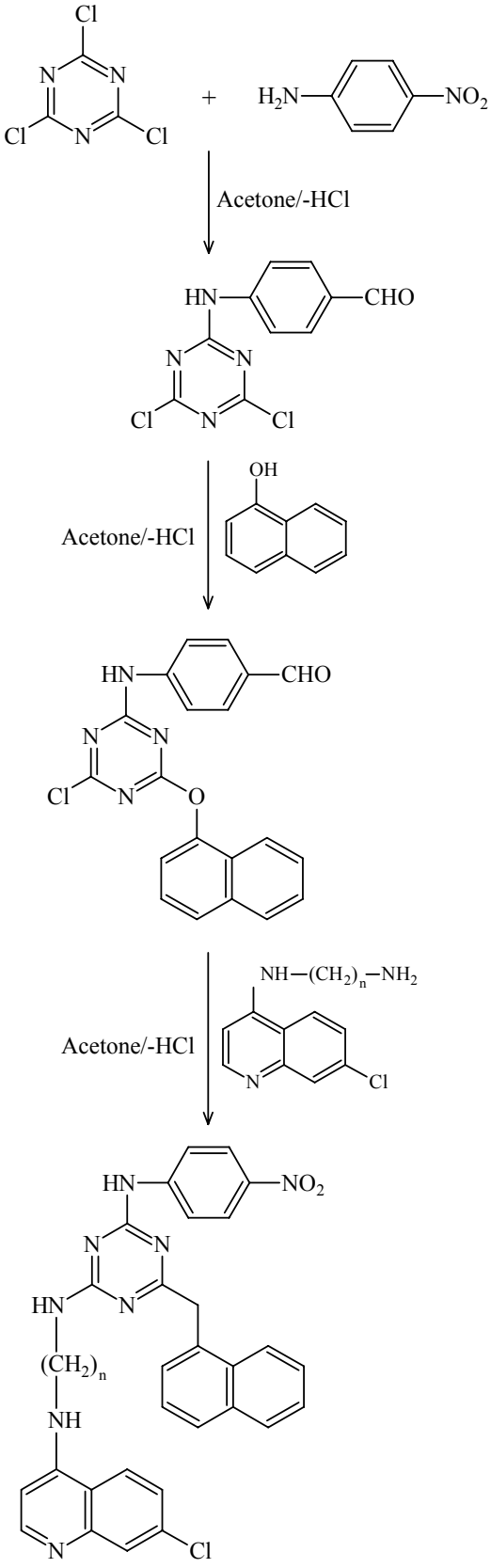
CHO
HO
H3CO
O
CHO
N
N
Cl
N
H3CO
O
CHO
NH—(CH2)n—NH2
N
Cl
H3CO
O
CHO
N
N
HN
N
H3CO
O
CHO
(CH2)n
NH
N
Cl

2(a-c)

Scheme 2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N
Cl
N
Cl
+
H2N
NO2
Acetone/-HCl
HN
CHO
N
N
Cl
N
Cl
Acetone/-HCl
OH
HN
CHO
N
N
Cl
N
O
Acetone/-HCl
NH—(CH2)n—NH2
N
Cl
HN
NO2
N
N
HN
N
(CH2)n
NH
N
Cl

3(a-c)

Scheme 3

Table 3: Antimicrobial activity of some trisubstituted –s-triazine

Compound (10 µg/mL)	*S. aureus*	*M. luteus*	*E. faecalis*	*S. epidermis*	*E. aerogens*	*V. paraha-emolyticus*	*Y. entero-colitica*	S. *typhi-murium*
1a	24 (6.25)	25 (6.25)	14 (12.5)	17 (12.5)	20 (6.25)	22 (6.25)	23 (6.25)	25.5 (6.25)
1b	23.5 (6.25)	23 (6.25)	14 (12.5)	16 (12.5)	18 (12.5)	20 (6.25)	21 (6.25)	24 (6.25)
1c	22.5 (6.25)	25 (6.25)	11 (12.5)	15 (12.5)	19 (12.5)	21 (6.25)	21 (6.25)	25 (6.25)
2a	20 (6.25)	25 (6.25)	14 (12.5)	17 (12.5)	20 (6.25)	20 (6.25)	22 (6.25)	25.5 (6.25)
2b	23 (6.25)	23 (6.25)	13 (12.5)	16 (12.5)	< 10 (50)	22 (6.25)	21 (6.25)	24 (6.25)
2c	21 (6.25)	25 (6.25)	< 10 (50)	15 (12.5)	< 10 (50)	21 (6.25)	23 (6.25)	25 (6.25)
Ciproflaxocin	24.5 (6.25)	26 (6.25)	15 (12.5)	18 (12.5)	21 (6.25	23 (6.25)	24 (6.25)	26 (6.25)

Table 4: Antifungal activity of some trisubstituted –s-triazine

Compounds No.	*B. cincera*	*E. floccosum*	*T. mentagrophytes*	*Scopulariopsissp*	*A. niger*	*C. lunata*
1a	22.5 (6.25)	35.5 (6.25)	33.5 (6.25)	24.5 (6.25)	25.5 (12.5)	22.5 (6.25)
1b	20 (6.25)	31 (6.25)	31 (6.25)	22.5.6 (6.25)	33.5 (6.25)	20 (6.25)
1c	21 (6.25)	32 (6.25)	28 (12.5)	31 (6.25)	36 (6.25)	22 (6.25)
2a	22.5 (6.25)	< 10 (50)	20.5 (6.25)	30 (6.25)	< 10 (50)	21 (6.25)
2b	20 (6.25)	< 10(50)	31 (6.25)	26.6 (6.25)	< 10 (50)	24 (6.25)
2c	21 (6.25)	21 (6.25)	28 (12.5)	28.5 (6.25)	36 (6.25)	22 (6.25)
Ketaconazole	23 (6.25)	38.5 (6.25)	34.5 (6.25)	33.5 (6.25)	38.5 (6.25)	25.5 (6.25)

CONCLUSION

A new series of s-triazinederivatives and have been successfully synthesised. Some of compounds contains bioactive heterocyclic moiety. Interestingly, most of them showed good antibacterial and antifungal activity. Among these, compounds **(1a)**, **(1c)** and **(2c)** showed good inhibition towards all 8 bacteria tested. Compounds **(1b)**, **(2a)** and **(2b)**, show moderate to low activity against all the strains tested. Compounds, which showed low activity were tested for higher concentration. At the higher concentration, all the synthesised compounds showed moderate activity. Naphthol and vaniline, substituted derivatives showed good activity in all the strains tested. The antimicrobial screening suggests that all the newly synthesised compounds showed moderate to good activity against the tested organism.

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