International Journal of Scientific Research in Chemistry (IJSRCH)
© 2019 IJSRCH | Volume 4 | Issue 1 | ISSN : 2456-8457

Synthesis and Characterizations of Some New 1,3,5-triazine-2,4,6-Triamine based Derivatives as Potent Antimicrobial and Antiinfective Agents

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ABSTRACT

1,2,4-Triazines are the six membered heterocyclic compounds containing three nitrogen in its structure with general formula $C_3H_3N_3$ .Some novel 1,3,5-triazine-2,4,6-triamine have been synthesized and characterized by elemental analyses. Introduction of -OCH_3, -F, -NO_2, -Cl and –Br groups to the heterocyclic frame work enhanced antibacterial and antifungal activities. The products have been tested for their antibacterial activity against gram (+)ve(POSITIVE) and gram (-)ve(NEGATIVE) bacteria and also on different strains of fungi.
Keywords: 1, 3, 5-triazine-2, 4, 6-triamines, Antibacterial activity, Antifungal activity.

I. INTRODUCTION

Medicinal chemistry is an area that applies the basic structural information of chemistry and biology to the advanced knowledge, leading to the introduction of new bioactive agents. Hence, the medicinal chemist must have a basic background in the biological sciences, especially biochemistry and pharmacology that apply in new formation of derivatives. Due to binding ability to various enzymes and wide variety of applications, s-triazine become the keystone of organic chemistry in pharmaceutical field.

This section describes the biological importance of various s-triazine derivatives. The recent literature also supports the immense application of following heterocyclic core in terms of anti-microbial, anti-malarial, anti-infective etc. 1,2,4-Triazines and their derivatives have been widely studied in terms of their synthetic methodologies and reactivity since some of these derivatives were reported to have promising biological activities.

s-triazine and its moiety are widely used within the pharmaceutical, plastic, rubber industries, chemical factories, dyestuffs, optical bleaches, surface active agents. Currently to fight against drug resistance problems and to alleviate opportunistic microbial infections, many researchers have reported heterocycles molecules exhibiting excellent biological activity including anti-infective, antimicrobial, anti-cancer etc.

In recent decades, problems of multi-drug resistantmicroorganisms have reached on alarming level in many countries around the world. A numbersof recent clinical reports describe the increasingccurrence of meticillin-resistant S. aureus and other antibiotic-resistant human pathogenic microorganisms in United State, European countries and other developing countries. Infections caused by those microorganisms pose a serious challenge to the medical community and the need for an effective therapy has led to a search for novel antimicrobialagentsand antifungleagents[1]. In this work, we report the synthesis and biological activity of some newly synthesized cyanuric chloride based

derivatives. Several derivatives of s-triazine show antimicrobial[2], antibacterial[3], and herbicidal activities[4]. They are also used for the treatmentof HIV infection[5-6]. Cyanuric chloride derivatives are widely used in commercial chemicals. Some trisubstituted-1,3,5-triazines are also used as liposome[7].

Several investigators found s-triazine nucleus as potential therapeutic agents for diseases due to bacteria, malaria and cancer[8]. Trichlorotriazine derivatives have found extensive use in the synthesis of "activated"dyes. 1,3,5-Triazine derivatives also possess biological activities like antitubercular,antitumor[9], anti-inflammatory[10]. 1,3,5-triazines represent a widely used lead structure with multitude of interesting applications in numerous field[11]. Cyanuric chloride is a heterocyclic organic compound commonly used for immobilization of proteins[12-14].

It has been reported that s-triazine derivatives are used as templates for molecular imprinting and for the construction of three-helix bundle protein[15]. Cyanuric chloride is an essential organic intermediate of which three chlorines can be replaced by –NH2, –OH, –SH or –NHR step by step with high yield. Cyanuric chloride derivatives have been studied for decades, especially its amino derivatives, which depends on the activity of amine nucleophiles[16]. Thiourea and Urea derivatives possess antibacterial[17] and antifungal activity. It is also lead a human immuno deficiency virus type (HIV-1)[18], and found as antagonist[19-20].

Over the last few years, the thiourea moiety has been of interest to design molecules as receptor antagonists, as natural product mimics or as synthetic intermediates to amidinesorguanidines[21]. Thiourea not only confers antibacterial, antitubercular or antileprotic activity also urea confers antibacterial and antifungle activity, antibacterial, anticancer, anticonvulsant, antithyroidal, antibacterial[22-28], diuretic[29] and insecticidal activity[30].

We are going to make some new kind of synthesis and characterization of some triazine based cyanuric derivatives carrying the above biodynamic heterocyclic systems with the hope to achieve enhanced biological activity[31-32].

II. METHODS AND MATERIAL

Biological activity:

Antibacterial activity: Antibacterial activity was carried out by broth dilution method[17]. The strains used for the activity were secured from Institute of Microbial Technology. The compounds 1a-1l were observed for their antibacterial activity against *E. coli, S. aureus, E. pyogenes and P. aeruginosa*,at concentrations of 1000, 500, 200, 100, 50, 25, 12.5 µg/mL respectively (Table 2).

Antifungal activity: Same compounds were tested for antifungal activity against *C. Albicans A. Niger and A. Clavatus* at a concentrations of 1000, 500, 200, 100 and 50 µg/ml respectively (Table 2).

The result of this test is affected by the size of the inoculums. The test mixture should contain 10^8 organisms/ml. "K. *Nystatin*" was used as the standard drug for antifungal activity which showed 100µg/ml MFC against fungi, used for the antifungal activity[32].

III. RESULTS AND DISCUSSION

Experimental section:

Melting points were taken in open capillaries using paraffin bath. IR spectra were recorded on FTIR-BRUKER ALPHA-E (10044239) spectrometer (V_{max} in cm^{-1}); Purity was checked by TLC using TLC aluminum sheets silica gel 60, supplied by E.Merck.

The spots were located by keeping the plates in iodine vapor.

NMR Spectra: 1H NMR spectra, were recorded in C. CDCl3 solution on a Bruker Avance DPX 200 MHz spectrometer Chemical shifts are reported as δ (ppm) relative to TMS as internal standard.
13C-NMR (100 MHz, DMSO-*d*6): δ ppm.

Experimental:
Preparation:

A. Preparation of 6-methyl-1,3-benzothiazol-2-amine:

A 250 ml conical flask was filled with a mixture of 5 gm 4-methyl aniline and 9 gm KSCN (potassium thiocyanate). Then add 20 ml glacial acetic acid in this mixture with constant stirring. Take 3.6 ml Br_2 in separating funnel contain 5 ml glacial acetic acid in it. Poured this solution drop by drop in conical flask with constant stirring. The solution was stirred for 6 to 8 hour. The reaction mixture was poured into crushed ice with constant stirring and neutralized with dil. NaOH. The solid was filtered and washed with water. The product was recrystallized from alcohol. Which is benzothiazol. The yield was 70 % with m.p 165-170^0 C.

B. Preparation of 6-chloro-N^2,N^4-bis(6-methyl-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4-diamine:

A 250 ml conical flask was filled with a mixture of 5 gm (1 mol) 2,4,6-trichloro-1,3,5,-triazine, 40 ml acetone and 8.91 gm (2 mole) of 6-methyl-1,3-benzothiazol-2-amine (benzothiazol). To this mixture 4 % NaOH was added drop wise to neutralize solution. The solution was stirred for 4 to 5 hour. The reaction mixture was poured into cold water with constant stirring. The solution was neutralized by dil. HCl adding slowly drop by drop. The precipitate was filtered and washed with cold distilled water. The compound was recrystallized from acetone. The yield was 69 % with m.p 210-218^0 C.

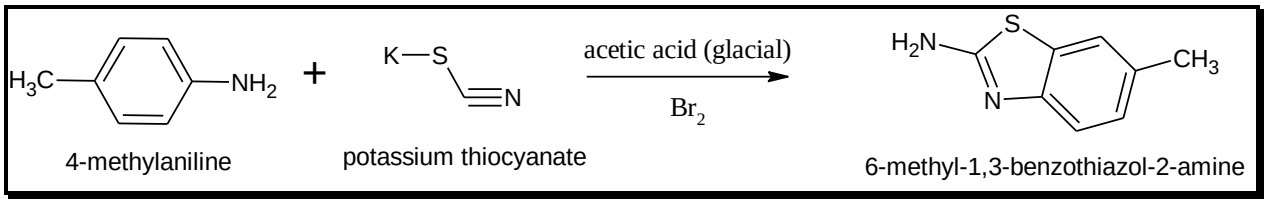
Preparation of N^6-aryl-N^2,N^4-bis(6-methyl-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4,6-triamine:

A 250 ml RBF was filled with a mixture of 0.01 mol 6-chloro-N^2,N^4-bis(6-methyl-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4-diamine (1 gm), 10 ml 1,4-dioxane and 0.01 mol substituted aniline. The solution was neutralized by dil. 8% NaOH drop by drop to adjust pH. The reaction mixture was refluxed for 2.5 to 3 hour not more than 70^0 C. The reaction mixture was poured into cold water with constant stirring and neutralized with dil. HCl. The product was filtered and washed with cold distilled water. The compound was dried and recrystallized from methanol. DMF m.p 275^0 C, Yield 65 %.

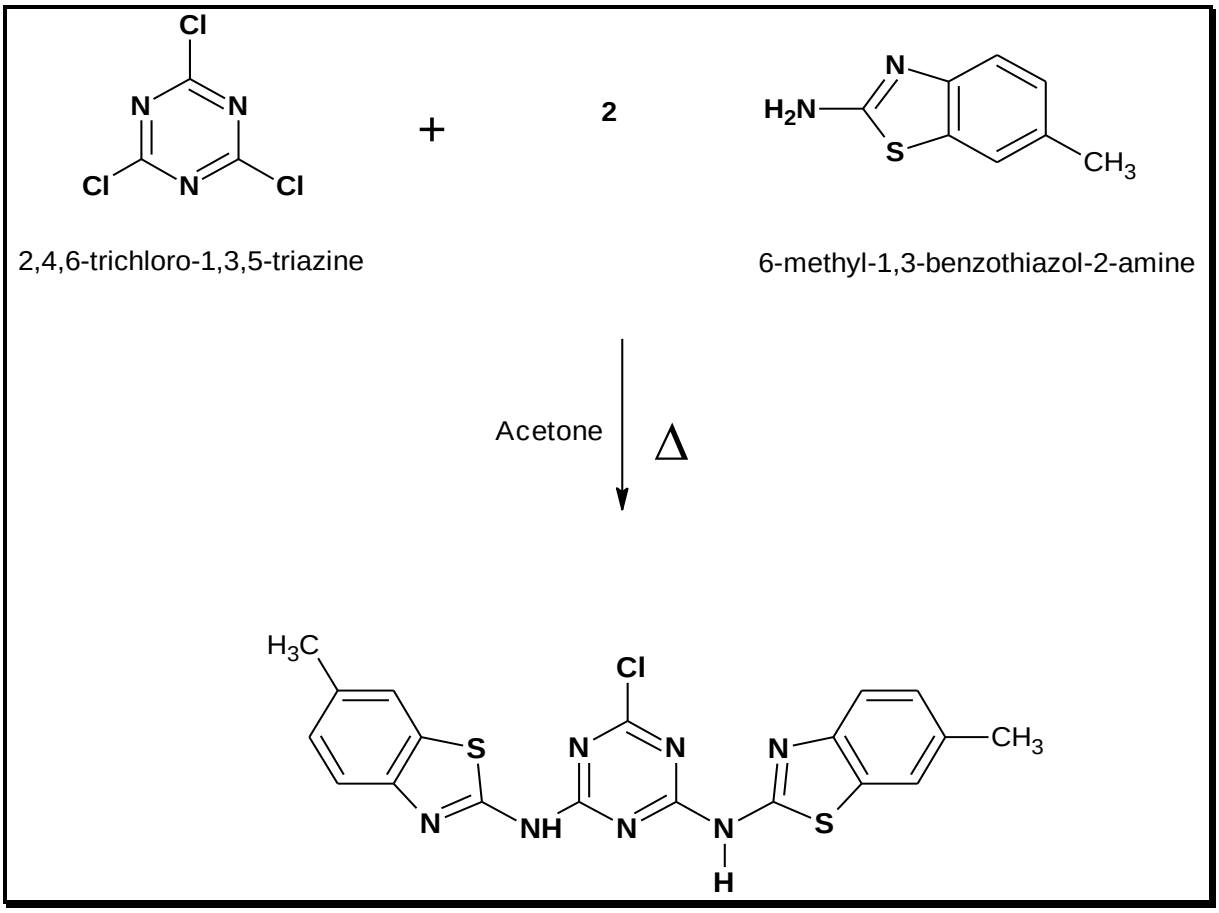
The purity of compounds was routinely checked on TLC aluminum sheet silica gel 60 F_{245} (E. Merck) using benzene-methanol (4.5:0.5 v/v) or benzene-ccl_4–methanol (2.5:2.0:0.5 v/v) as irrigate and was developed in an iodine chamber.

Other derivative compounds of the series were prepared by using similar method. The purity of these derivatives were analyzed through melting point measurements. In view of tremendous application of these compounds, we have prepared a library of molecules. We have undertaken to investigate the role of functional groups on molecular geometry, conformation and generation of supramolecular assemblies in the solid state. Furthermore the synthesized derivatives have also been evaluated for their antibacterial, antiinfective activity by Broth Dilution method.

Reaction work:
Reaction – A: Preparation of 6-methyl-1,3-benzothiazol-2-amine:

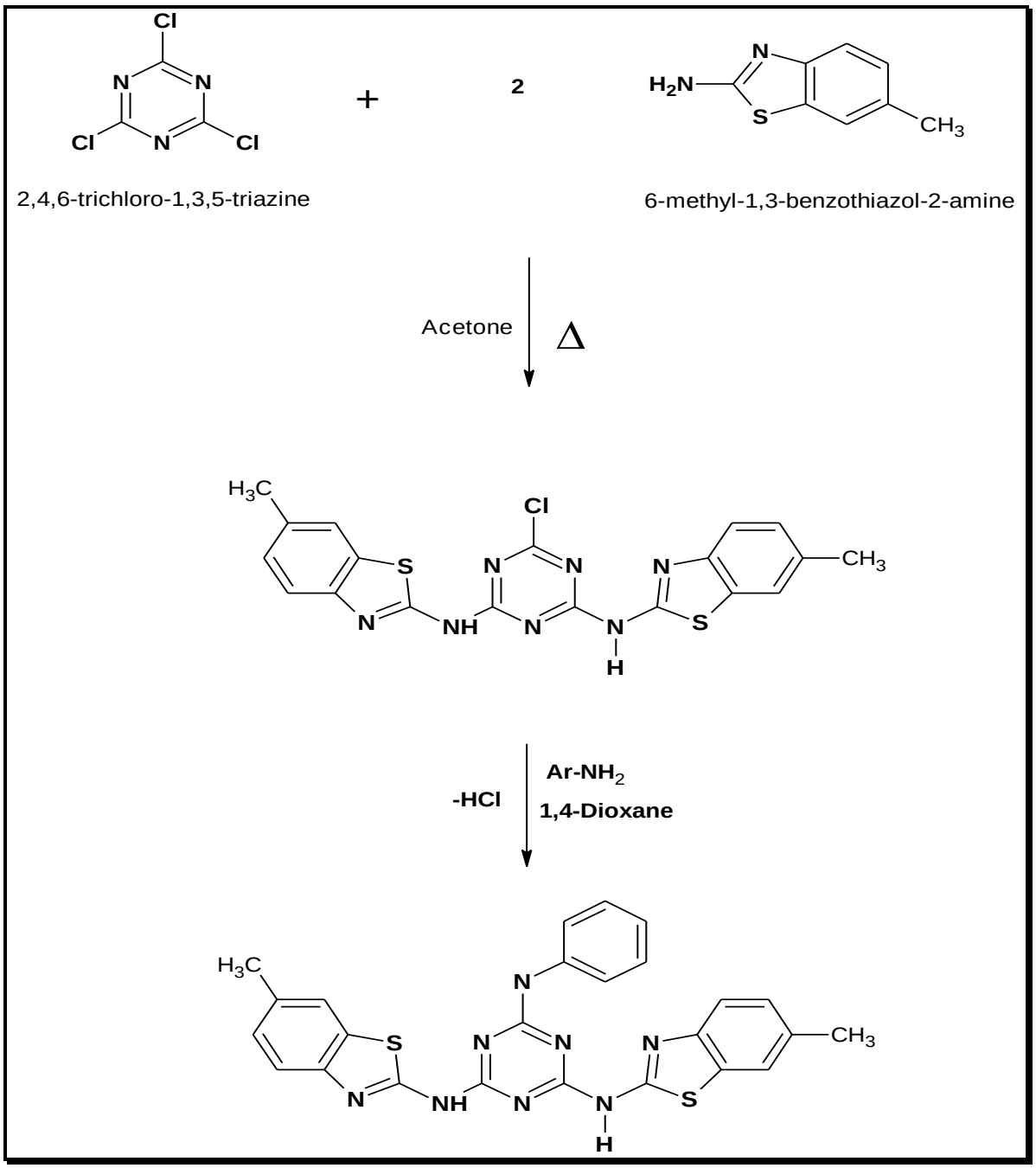


Reaction – B: Preparation of 6-chloro-N²,N⁴-bis(6-methyl-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4-diamine:



6-chloro-N²,N⁴-bis(6-methyl-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4-diamine

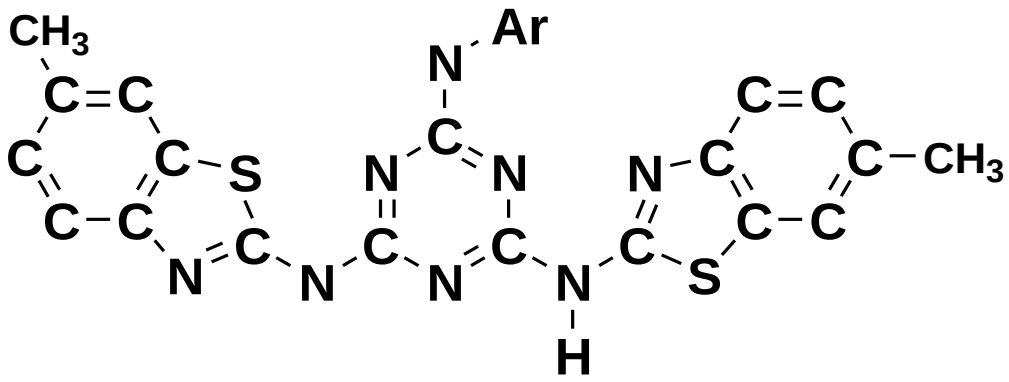
Reaction – C: Preparation of N⁶-aryl-N²,N⁴-bis(6-methyl-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4,6-triamine:



N⁶-phenyl-N²,N⁴-bis(6-methyl-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4,6-triamine

Physical Experimental data:

Table 1: Physical constants of N⁶-aryl-N²,N⁴-bis(6-methyl-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4,6-triamine:



Where Ar = Different aryl group

Sr No.	Code No	-Ar	MOLECULAR FORMULA	M. P. °C	YIELD (%)	% OF CARBON		% OF NITROGEN		MOLECULAR WEIGHT
						FOUND	REQD.	FOUND	REQD.	
1	4CH1	-C_6H_5	$C_{25}H_{20}N_8S_2$	275°C	56	60.42	60.46	22.51	22.56	496.60
2	4CH2	-3-Cl-C_6H_4	$C_{25}H_{19}ClN_8S_2$	286-290°C	58	56.52	56.54	21.08	21.10	531.05
3	4CH3	-4-Cl-C_6H_4	$C_{25}H_{19}ClN_8S_2$	200-202°C	54	56.51	56.54	21.05	21.10	531.05
4	4CH4	-3-NO_2-C_6H_4	$C_{25}H_{19}N_9O_2S_2$	288-290°C	57	55.40	55.44	23.25	23.28	541.60
5	4CH5	-4-NO_2-C_6H_4	$C_{25}H_{19}N_9O_2S_2$	292-293°C	59	55.39	55.44	23.24	23.28	541.60
6	4CH6	-4-Br-C_6H_4	$C_{25}H_{19}BrN_8S_2$	285°C	51	52.15	52.17	19.45	19.47	575.50
7	4CH7	-4-F-C_6H_4	$C_{25}H_{19}FN_8S_2$	248-250°C	62	58.30	58.35	21.74	21.77	514.60
8	4CH8	-2-C_5H_4N	$C_{22}H_{19}N_9S_2$	236-240°C	54	57.90	57.93	25.30	25.33	497.59
9	4CH9	-4-C_5H_4N	$C_{22}H_{19}N_9S_2$	274-276°C	62	57.89	57.93	25.29	25.33	497.59
10	4CH10	-N-CH_3-C_6H_4	$C_{26}H_{22}N_8S_2$	251-256°C	61	61.12	61.15	21.90	21.94	510.63
11	4CH11	-4-CH_3-C_6H_4	$C_{26}H_{22}N_8S_2$	259-262°C	54	61.10	61.15	21.89	21.94	510.63
12	4CH12	-2-NO_2-C_6H_4	$C_{25}H_{19}N_9O_2S_2$	269-272°C	59	55.40	55.44	23.21	23.28	541.60
13	4CH13	-3-OH-C_6H_4	$C_{25}H_{20}N_8OS_2$	278-280°C	58	58.55	58.58	21.85	21.86	512.60
14	4CH14	-4-OCH_3-C_6H_4	$C_{26}H_{22}N_8OS_2$	281-283°C	57	59.26	59.30	21.22	21.28	526.63

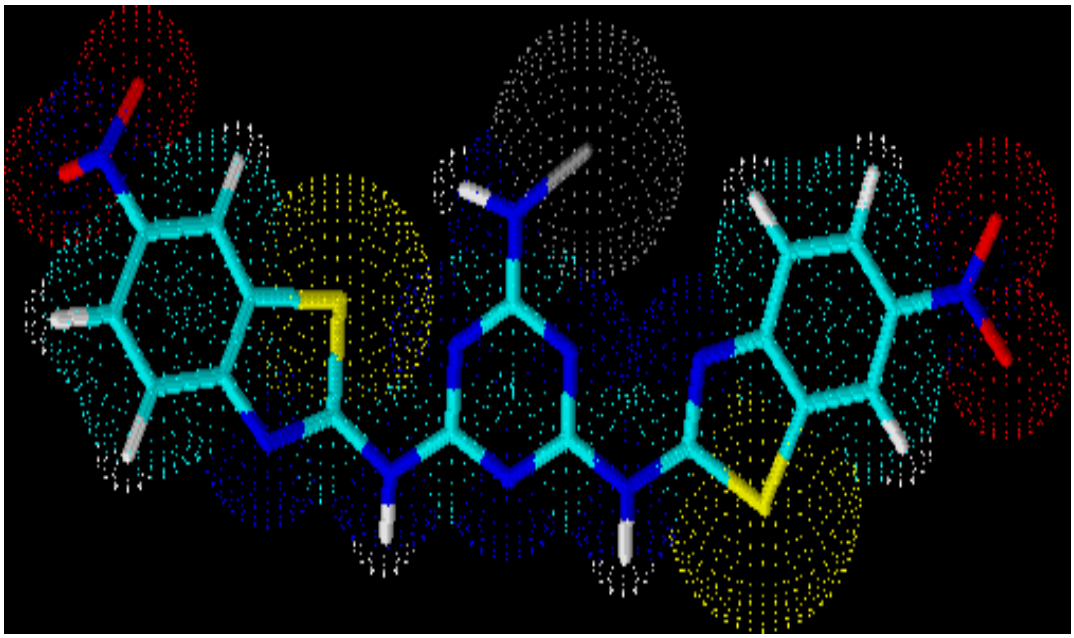


Table 2: Antibacterial activity of N^6-aryl-N^2,N^4-bis(6-methyl-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4,6-triamine:

MINIMAL BACTERIAL CONCENTRATIONS (MBC) in µg/ml						
			Gram negative bacteria		Gram positive bacteria	
			E.coli	*P.aeruginosa*	*S.aureus*	*S.pyogenus*
Sr No.	Code No	-Ar	MTCC 443	MTCC 1688	MTCC 96	MTCC 442
1	4CH1	-C_6H_5	125	250	250	250
2	4CH2	-3-Cl-C_6H_4	200	200	200	200
3	4CH3	-4-Cl-C_6H_4	100	62.5	100	125
4	4CH4	-3-NO_2-C_6H_4	250	100	62.5	125
5	4CH5	-4-NO_2-C_6H_4	100	100	125	100
6	4CH6	-4-Br-C_6H_4	100	100	100	100
7	4CH7	-4-F-C_6H_4	100	125	125	250
8	4CH8	-2-C_5H_4N	100	62.5	125	100
9	4CH9	-4-C_5H_4N	250	125	62.5	250
10	4CH10	-N-CH_3-C_6H_4	200	62.5	125	100
11	4CH11	-4-CH_3-C_6H_4	62.5	125	100	100
12	4CH12	-2-NO_2-C_6H_4	200	125	62.5	200
13	4CH13	-3-OH-C_6H_4	200	200	100	250
14	4CH14	-4-OCH_3-C_6H_4	100	100	200	250
15	Gentamycin		0.05	1	0.25	0.5
16	Ampicillin		100	--	250	100

17	Chloramphenicol	50	50	50	50
18	Ciprofloxacin	25	25	50	50
19	Norfloxacin	10	10	10	10

Table 3 : Antifungal activity of N^6-aryl-N^2,N^4-bis(6-methyl-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4,6-triamine

MINIMAL FUNGICIDAL CONCENTRATIONS (MFC) in µg/ml					
			Fungus		
			C.albicans	*A.nigar*	*A.clavatus*
Sr No.	Code No	-Ar	MTCC 227	MTCC 282	MTCC 1323
1	4CH1	-C_6H_5	500	500	500
2	4CH2	-3-Cl-C_6H_4	>1000	>1000	>1000
3	4CH3	-4-Cl-C_6H_4	200	250	250
4	4CH4	-3-NO_2-C_6H_4	>1000	>1000	>1000
5	4CH5	-4-NO_2-C_6H_4	500	250	200
6	4CH6	-4-Br-C_6H_4	>1000	>1000	>1000
7	4CH7	-4-F-C_6H_4	62.5	>1000	>1000
8	4CH8	-2-C_5H_4N	500	100	50
9	4CH9	-4-C_5H_4N	100	62.5	>1000
10	4CH10	-N-CH_3-C_6H_4	125	62.5	200
11	4CH11	-4-CH_3-C_6H_4	125	50	250
12	4CH12	-2-NO_2-C_6H_4	62.5	250	200
13	4CH13	-3-OH-C_6H_4	125	50	100
14	4CH14	-4-OCH_3-C_6H_4	62.5	50	125
15	Nystatin		100	100	100
16	Greseofulvin		500	100	100

IV.CONCLUSION

In this work, a series of compounds comprising of s-triazine based chalcones were successfully synthesized using this method. s-triazine provided a versatile synthetic approach for the synthesis of differently bioactive substituted triazine. The synthetic yields of the generated products ranged from 55 to 70 % and their structures were established by spectral data (IR and NMR). Finally, all of synthesized compounds have been tested by elemental and spectral analysis.

- This section is benzothiazol 6-methyl-1,3-benzothiazol-2-yl triazine derivatives compounds. Out of them -4-Cl-C_6H_4, -3-NO_2-C_6H_4, -2-C_5H_4N, -4-C_5H_4N, -N-CH_3-C_6H_4, -4-CH_3-C_6H_4, -2-NO_2-C_6H_4 were very excellent

active against *E.coli, P.aeruginosa, S.aureus* and *S.pyogenus* bacteria. -4-Cl-C_6H_4, -3-NO_2-C_6H_4, -4-NO_2-C_6H_4, -4-Br-C_6H_4, -4-F-C_6H_4, -2-C_5H_4N, -N-CH_3-C_6H_4, -4-CH_3-C_6H_4, -3-OH-C_6H_4, -4-OCH_3-C_6H_4 were good active against gram positive and negative bacteria.

- Antifungal activity results showed that compounds -4-F-C_6H_4, -2-NO_2-C_6H_4 and -4-OCH_3-C_6H_4 showed lofty activity against *C.albicans*. -4-C_5H_4N, -N-CH_3-C_6H_4, -4-CH_3-C_6H_4, -3-OH-C_6H_4 and -4-OCH_3-C_6H_4 showed lofty activity against *A.nigar*. -2-C_5H_4N showed lofty activity against *A.clavatus*. -C_6H_5, -4-NO_2-C_6H_4 and -2-C_5H_4N showed mean activity against *C.albicans, A.nigar* and *A.clavatus.*

Acknowledgement

We are thankful to our principal of M. G. Science Institute, Ahmedabad and the Ahmadabad Education Society for facilitating us a well-equipped research laboratory and library. We are also thankful to the North America Institute of Pharmaceutical Technology, Toronto for NMR data collection and Microcare laboratory & tuberculosis research centre, Surat for biological activity. For Mass data collection we are thankful to Saurastra University, Rajkot.

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Cite this article as :

S. N. Chadotra, B. B. Baldaniya, "Synthesis and Characterizations of Some New 1,3,5-triazine-2,4,6-Triamine based Derivatives as Potent Antimicrobial and Antiinfective Agents", International Journal of Scientific Research in Chemistry (IJSRCH), ISSN : 2456-8457, Volume 4 Issue 1, pp. 29-38, January-February 2019.
URL : http://ijsrch.com/IJSRCH19417