International Journal of Scientific Research in Chemistry (IJSRCH) | ISSN : 2456-8457
© 2016 IJSRCH | Volume 1 | Issue 1

Synthesis and Characterizations of Some New S-Triazine 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 N^2,N^4-bis(6-nitro-1,3-benzothiazol-2-yl)-N^6-aryl-1,3,5-triazine-2,4,6-triamine 1a-m 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

Organic chemistry is the chemistry of compounds that contains the element carbon. Medicinal chemistry has its womb in several armlets of chemistry and biology. However, incumbent it concerns with the rubric of mechanisms of function and action of drugs. It link biodynamic behavior with chemical reactivityand mechanisms. Rightly, therefore, medicinal chemistry is also called therapeutic chemistry in present.

The Chemistry of Heterocyclic Compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications. A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt.

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].

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. 6-nitro-1,3-benzothiazol-2-amine was prepared by methods as described in our paper and literature.

For 1a compound: IR (kbr): 3083(-C-H str., aromatic), 1527 (> C = N- str., ter. Amine), 1350 (C-NO_2 STR.), 1122 (C-S-C str., thiazol), 952 (C-Cl str., aromatic),808 (disubstituted aromatic),1431 (C = N str., sec.amine).

NMR Spectra: 1H NMR spectra, were recorded in CDCl3 solution on a Bruker Avance DPX 200 MHz spectrometer Chemical shifts are reported as δ (ppm) relative to TMS as internal standard.10.08δ (s, -NH, 2H), 9.29 δ 8048 (s, C-NO_2), (s, -NH, 1H), 8.48 6.54 δ (s, Ar-H, 8H).

13C-NMR (100 MHz, DMSO-*d*6): δ ppm, 20.67 (CH3), 22.47 (CH3), 60.14 (CH).

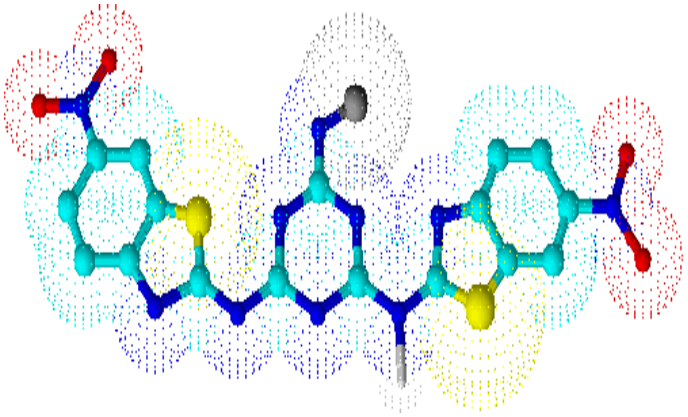
Preparation of 6-chloro-N, N'-bis (6-nitro-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4-diamine

2,4,6-trichloro-1,3,5-triazine (1) (0.01 mol) was taken in a flask add acetone (30-40 ml) in it. Mix that solution and add 6-nitro-1,3-benzothiazol-2-amine (2) (0.02 mol). 4% NaOH was added drop by drop wise at room temperature in this solution. The solution was stirred for 4 to 5 hour. The reaction mixture was poured onto crushed ice with constant stirring. The solution was neutralized byadding drop by drop dil. HCl. The precipitate was filtered and washed with cold water or cold distilled water. The compound was recrystallized from acetone or alcohol. M.p.200ºc; yield 79.00%. Anal. Found: C,43.05; N, 21.50; cal. For $C_7H_5N_3O_2S$: C, 43.07; N, 21.53%.

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

6-chloro-N, N'-bis (6-nitro-1, 3-benzothiazol-2-yl)-1, 3, 5-triazine-2, 4-diamine. (3) (0.01 mol) and 1,4-dioxane (10 ml) was taken in RBF(Round Bottom Flask). To this

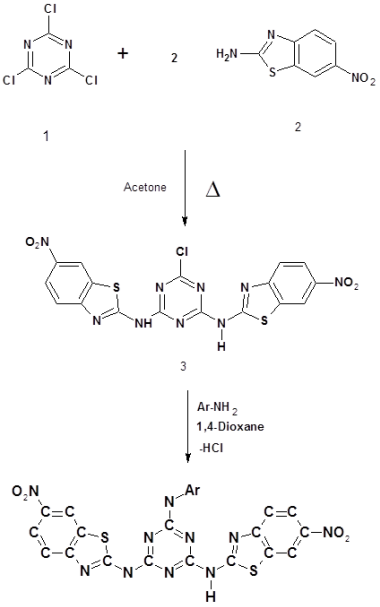
mixture, aniline (0.01 mol) was added. The pH was adjusted to neutral by adding 8% NaOH drop by drop. The reaction mixture was refluxed for 2.5 to 3 h. And was poured onto crushed ice with constant stirring. The mixture was then neutralized with dil. HCl. The product was filtered and washed with cold water. The product was dried and recrystallized from methanol. M.p. 287ºc; Yield 68% .Anal. Found: C,49.41; N, 25.06; cal. For: $C_{23}H_{14}N_{10}O_4S_2$; C, 49.46; N, 25.08% (1a).



1a-1l

III. RESULTS AND DISCUSSION

Scheme 1:



1a-1l

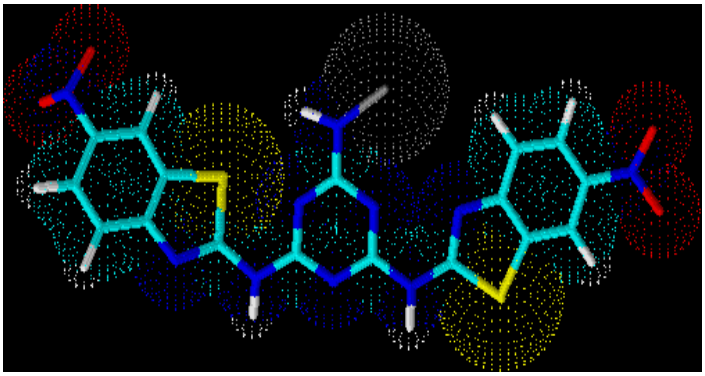


Table I. Physical constant of the compounds (1a-1l)

Sr No.	-Ar	MOLECULAR FORMULA	M. P. ^{O}C	YIELD (%)	% OF CARBON		% OF NITROGEN		Mol. Wt
					FOUND	REQD.	FOUND	REQD.	
1a	$-C_6H_5$	$C_{23}H_{14}N_{10}O_4S_2$	240	65	49.41	49.46	25.06	25.08	558.55
1b	$-3-Cl-C_6H_4$	$C_{23}H_{13}ClN_{10}O_4S_2$	186	59	46.56	46.58	23.60	23.62	592.99
1c	$-4-Cl-C_6H_4$	$C_{23}H_{13}ClN_{10}O_4S_2$	255	54	46.54	46.58	23.59	23.62	592.99
1d	$-3-NO_2-C_6H_4$	$C_{23}H_{13}N_{11}O_6S_2$	320	65	45.74	45.77	25.51	25.53	603.54
1e	$-4-NO_2-C_6H_4$	$C_{23}H_{13}N_{11}O_6S_2$	265	62	45.76	45.77	25.48	25.53	603.54
1f	$-4-Br-C_6H_4$	$C_{23}H_{13}BrN_{10}O_4S_2$	193	57	43.31	43.34	21.96	21.97	637.44
1g	$-4-F-C_6H_4$	$C_{23}H_{13}FN_{10}O_4S_2$	251	64	47.89	47.91	24.24	24.29	576.54
1h	$-2-C_5H_4N_2$	$C_{22}H_{13}N_{11}O_4S_2$	197	65	47.19	47.22	27.51	27.54	559.53
1i	$-4-C_5H_4N_2$	$C_{22}H_{13}N_{11}O_4S_2$	218	68	47.20	47.22	27.50	27.54	559.53
1j	$-N-CH_3-C_6H_4$	$C_{24}H_{16}N_{10}O_4S_2$	270	59	50.32	50.34	24.43	24.46	572.57
1k	$-4-CH_3-C_6H_4$	$C_{24}H_{16}N_{10}O_4S_2$	179	56	50.29	50.34	24.40	24.46	572.57
1l	$-2-NO_2-C_6H_4$	$C_{23}H_{13}N_{11}O_6S_2$	196	55	45.71	45.77	25.50	25.53	603.54

Table 2: Antibacterial and Antifungal Activities

SR NO.	Minimal bactericidal concentration (MBC) in µg/ml				Minimal fungicidal concentration (MFC) in µg/ml		
	E.coli	***P.aeruginosa***	***S.aureus***	***S.pyogenus***	***C.albicans***	***A.nigar***	***A.clavatus***
	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC	MTCC
	- 443	-1688	-96	- 442	-227	-282	-1323
1a	100	50	100	200	100	250	500
1b	100	100	500	500	100	100	500
1c	100	250	25	500	100	100	100
1d	50	500	500	500	50	50	50
1e	500	250	100	250	50	50	100
1f	100	250	250	500	100	100	100
1g	500	200	250	500	500	250	1000
1h	50	500	500	500	500	500	500
1i	50	500	1000	1000	50	50	50
1j	100	100	100	100	200	200	200
1k	50	50	200	50	50	50	100
1l	500	250	100	200	50	50	500

IV.CONCLUSION

As outline in Scheme-1, an important novel s-triazine derivatives, N^2, N^4-bis (6-nitro-1,3-benzothiazol-2-yl)- N^6 -aryl-1,3,5-triazine- 2,4,6-triamine has been synthesized. In this work, a series of compounds comprising of s-triazine based chalcone 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.

V. ACKNOWLEDGEMENT

We are thankful to the principal of M. G. Science Institute, Ahmadabad to providing research facilities, IR data collection and North America Institute of Pharmaceutical Technology, Toronto for NMR data collection.

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