Synthesis and Characterizations of N^2 -(Aryl)- N^4 , N^6 -bis (6, 7-dichloro-1, 3-benzothiazol-2-yl)-1, 3, 5-triazine-2, 4, 6-triamines as Biological Potent Agents

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Abstract: Some novel N^2 -(Aryl)- N^4 , N^6 -bis (6, 7-dichloro-1, 3-benzothiazol-2-yl)-1, 3, 5-triazine-2, 4, 6-triamines (**4a-u**) have been synthesized and characterized by elemental analyses, IR, NMR, and mass spectra. The products have been tested for their antibacterial activity against gram (+)ve and gram (-)ve bacteria and also on different strains of fungi. Introduction of -OH, -OCH₃, -NO₂, -Cl and -Br groups to the heterocyclic frame work enhanced antibacterial and antifungal activities.

Keywords: 1, 3, 5-Triazine-2, 4, 6-Triamines, Antibacterial activity, Antifungal activity.

Introduction

Antibacterial and antifungal diseases are very common all over the world. Currently used antimicrobial agents are not effective due to the resistance developed by the microbes. And therefore, it is an ongoing effort to synthesize new antimicrobial agents. The *s*-triazine¹⁻⁶ have been associated with a wide range of therapeutic activities⁷⁻¹² such as antibacterial, fungicidal, antimalarial, anticancer, antiviral, antiulcer, antiarthritic, local anesthetic, anticonvulsant, algacide and disinfectant, hypoglycemic, analgesic, sedative and anti inflammatory, anathematic and antitubercular.

Desai and co-workers¹³ synthesized 2-(4-methoxy/2-methyl phenyl)-4-phenyl acetyl hydrazino-6-isonicotinyl hydrazino-*s*-triazines and tested them for their anti-HIV activity against susceptible human host cell (CEM cell line) over a wide range of concentrations. Recently new *s*-triazine derivatives were reported for their antitubercular, anti-AIDS and anti cancer activities¹⁴⁻¹⁶. The medicinal utilities of compounds described in this section inspired us to synthesize some new *s*-triazine. It is our ongoing project to synthesize new bioactive molecules.

In view of these observations we have synthesized *s*-triazine, **4a-u** (Scheme 1, Table 1) by the condensation of cyanuric chloride with different aromatic amines at different temperature in acetone. 6-chloro-*N,N'*-bis(6,7-dichloro-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4-diamine(**3**) afforded the title compounds with various aromatic amines (**4a-u**) respectively (Scheme 1). The series of compounds were characterization by IR, NMR, MS and elemental analysis.

Scheme 1

Table 1. Physical constant of the compounds (**4a-u**).

Compd.	-Ar	Mol. Formula	m.p °C.	Yield %	C, %		N, %	
					Calc.	Found	Calc.	Found
4a	-C ₆ H ₅	C ₂₃ H ₁₂ Cl ₄ N ₈ S ₂	215	80	45.50	45.56	18.40	18.48
4b	-4-NO ₂ -C ₆ H ₄	C ₂₃ H ₁₁ Cl ₄ N ₉ O ₂ S ₂	160	78	42.40	42.41	19.30	19.35
4c	-3,4-(Cl) ₂ -C ₆ H ₃	C ₂₃ H ₁₀ Cl ₆ N ₈ S ₂	220	76	40.90	40.91	16.50	16.59
4d	-3-NO ₂ -C ₆ H ₄	C ₂₃ H ₁₁ Cl ₄ N ₉ O ₂ S ₂	205	77	42.40	42.41	19.30	19.35
4e	-4-CH ₃ -C ₆ H ₄	C ₂₄ H ₁₄ Cl ₄ N ₈ S ₂	180	75	46.40	46.47	18.00	18.06
4f	-4-OCH ₃ -C ₆ H ₄	C ₂₄ H ₁₄ Cl ₄ N ₈ OS ₂	175	76	45.30	45.30	17.58	17.61
4g	-2-OH-4-NO ₂	C ₂₃ H ₁₁ Cl ₄ N ₉ O ₃ S ₂	180	78	41.38	41.40	18.80	18.89
4h	-2-OH-C ₆ H ₄	C ₂₃ H ₁₂ Cl ₄ N ₈ OS ₂	168	73	44.30	44.39	18.00	18.01
4i	-2-C ₄ H ₃ N ₂	C ₂₁ H ₁₀ Cl ₄ N ₁₀ S ₂	235	70	41.40	41.46	23.00	23.03
4j	-2-Cl-C ₆ H ₄	C ₂₃ H ₁₁ Cl ₅ N ₈ S ₂	225	70	43.10	43.11	17.40	17.49
4k	-3-Cl-C ₆ H ₄	C ₂₃ H ₁₁ Cl ₅ N ₈ S ₂	170	76	43.10	43.11	17.40	17.49
4l	-2,4,5-(Cl) ₃ -C ₆ H ₂	C ₂₃ H ₉ Cl ₇ N ₈ S ₂	140	70	38.90	38.93	15.70	15.79
4m	-2-OCH ₃ -C ₆ H ₄	C ₂₄ H ₁₄ Cl ₄ N ₈ OS ₂	169	75	45.30	45.30	17.58	17.61
4n	-2,4-(NO ₂) ₂ -C ₆ H ₃	C ₂₃ H ₁₀ Cl ₄ N ₁₀ O ₄ S ₂	160	77	39.60	39.67	20.10	20.11
4o	-3,4-(Cl) ₂ -2-NO ₂ -C ₆ H ₂	C ₂₃ H ₉ Cl ₆ N ₉ O ₂ S ₂	140	79	38.30	38.36	17.50	17.50

Experimental

Melting points were taken in open capillaries using paraffin bath and are uncorrected. IR spectra were recorded on FTIR-Perkin-Elmer spectrometer ($V_{\max}$ in cm^{-1}); ^1H NMR spectra were recorded on BRUKER AVANCE 300 FT-NMR spectrometer using CDCl_3 as a solvent and mass spectra carried out on JEOL SX 102/DA-600 mass spectrometer respectively. All the compounds were analyzed for carbon, hydrogen and nitrogen and the result were within $\pm 0.4\%$ of theoretical values. 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. 6,7-Dichloro-1,3-benzothiazol-2-amine was prepared by methods as described in literature¹⁸⁻¹⁹.

6-Chloro-*N, N'*-bis (6,7-dichloro-1,3-benzothiazol-2-yl)-1,3,5-triazine-2,4-diamine (**3**)

In a conical flask, 2,4,6-trichloro-1,3,5-triazine (**1**) (0.01 mol) was taken in acetone (20 mL) and 6,7-dichloro-1,3-benzothiazol-2-amine (**2**) (0.02 mol) was added to it. To this mixture, 4% NaOH was added drop wise at room temperature. The solution was stirred for 4 h. The reaction mixture was poured onto crushed ice with constant stirring. The solution was neutralized with dil. HCl. The solid was filtered and washed with water. The product was recrystallized from acetone. m.p. 250 °C; yield 79.00%. Anal. Found; C, 37.15; N, 17.80; cal. for $\text{C}_{17}\text{H}_6\text{Cl}_5\text{N}_7\text{S}_2$: C, 37.01; N, 17.84%.

*N*²,*N*⁴-Bis(6,7-dichloro-1,3-benzothiazol-2-yl)-*N*⁶-phenyl-1,3,5- triazine-2,4,6-triamine (**4a**)

In a round bottom flask, 6-chloro-*N, N'*-bis (6, 7-dichloro-1, 3-benzothiazol-2-yl)-1, 3, 5-triazine-2, 4-diamine. (**3**) (0.01 mol) and 1,4-dioxane (20 mL) was taken. To this mixture, aniline (0.01 mol) was added. The pH was adjusted to neutral by adding 8% NaOH. This the reaction mixture was refluxed for 2.5 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. 215 °C; Yield 68% Anal. Found; C, 45.56; N, 18.40; cal. for $\text{C}_{23}\text{H}_{12}\text{Cl}_4\text{N}_8\text{S}_2$: C, 45.50; N, 18.40%.

IR (KBr): 3454 (-N-H str., sec. amine), 3083 (-C-H str., aromatic), 1527 (>C=N- str., ter. amine), 1350 (C-NO₂ str., aromatic), 1122 (C-S-C str., thiazol), 952 (C-Cl str., aromatic), 808 (disubstituted aromatic), 1431 (C=N str., sec. amine), ^1H NMR(CDCl_3): 10.08 δ (s, -NH-, 2H), 9.44 δ (s, -NH-, 1H), 6.54 – 7.6 δ (m, Ar-H, 8H), MS: m/z 604.01 with 68% relative intensity [M^+]. The compounds (**4b-u**) similarly prepared, their m.p.s and yields are given in Table 1.

Biological activity

Antibacterial activity

Antibacterial activity was carried out by broth dilution method¹⁷. Concentrations of 1000, 500, 200, 100, 50, 25, 12.5 $\mu\text{g/mL}$ 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, and 100 $\mu\text{g/mL}$ respectively (Table 2). The result of this test is affected by the size of the inoculum. The test mixture should contain 10^8 organisms/mL. The standard drug used in the present study was “Gentamycin” for evaluating

antibacterial activity which showed (0.25, 0.05, 0.5 & 1 µg/mL MBC against *S. aureus*, *E. pyogenes* and *P. aeruginosa* respectively. “K. Nystatin” was used as the standard drug for antifungal activity which showed 100 µg/mL MFC against fungi, used for the antifungal activity.

Table 2. Antibacterial and antifungal activities.

S. No.	Minimal bactericidal concentration (MBC) in µg/mL				Minimal fungicidal concentration(MBC) in µg/mL		
	<i>E.coli</i>	<i>P.aeru ginosa</i>	<i>S.aureus</i>	<i>S.pyogenus</i>	<i>C.albicans</i>	<i>A.nigar</i>	<i>A.clavatus</i>
	MTCC - 443	MTCC -1688	MTCC -96	MTCC - 442	MTCC -227	MTCC -282	MTCC -1323
4a	100	200	100	500	500	500	500
4b	50	500	100	500	500	500	500
4c	25	500	100	250	100	100	100
4d	50	50	500	500	50	50	50
4e	100	250	500	500	500	500	500
4f	250	500	100	250	100	100	100
4g	250	500	500	250	500	1000	1000
4h	500	50	50	500	500	500	500
4i	500	50	500	1000	1000	1000	1000
4j	1000	1000	500	500	500	500	500
4k	100	100	100	500	200	200	200
4l	100	250	250	500	50	50	50
4m	50	200	500	500	50	200	200
4n	250	250	250	500	50	50	50
4o	100	250	500	250	200	500	500
4p	100	500	250	500	200	200	200
4q	500	500	250	500	1000	500	500
4r	200	100	250	250	100	100	100
4s	100	250	250	500	500	500	500
4t	500	500	250	500	250	250	250
4u	200	100	250	250	500	500	500

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