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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF A NEW SERIES OF *s*-TRIAZINES DERIVED WITH PYRIMIDINES

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ABSTRACT

4, 6-Dimethoxypyrimidin-2-amine condensed with trichloro s-triazine. Finally various aromatic amines derivatives were allowed to react and the product were characterized by conventional and instrumental methods. Their structures were determined and important biochemical properties were studied.

Keywords: *s*-Triazine derivatives, 4, 6-dimethoxypyrimidin-2-amine, Antimicrobial Study.

INTRODUCTION:

Nitrogen containing heterocyclic play vital role in any industries. Among them 1, 3, 5-triazine represent a widely used lead structure with multitude of interesting application in numerous fields[1]. Several derivatives of *s*-triazine show antibacterial[2] and antimicrobial[3] activities. The replacement of a chlorine atom in cynuric chloride by basic group is greatly facilitated by the ring nitrogen atom of the symmetrically built *s*-triazine nucleus. 2,4,6 -trichloro -*s*-triazine derivatives prepared[4] by replacement of one chlorine atom at 0-5°C, second one at 35-45°C and third one at 80-100°C. Pyrimidines and their derivatives posseses several interesting biological activities such as antimicrobial[5], antitumor and antifungal[6] activities. Many pyrimidine derivatives are used for thyroid drugs and leukemia.

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MATERIALS AND METHODS:

The reagent grade chemicals were obtained from commercial sources and purified by either distillation or recrystallization before use. Purity of synthesized compounds has been checked by thin layer chromatography. Melting points were determined by open capillary method and are uncorrected. IR spectra are recorded on FT-IR Bruker with KBr disc. ^{1}H NMR spectra are recorded in DMSO-d6 on a Bruker DRX-400 MHz using TMS as internal standard. The chemical shift is reported as parts per million (ppm) and mass spectra were determined on Jeol-SX-102(FAB) spectrometer.

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

In a conical flask, cyanuric chloride (0.01 mol) was taken acetone (25 mL) and 4,6-dimethoxypyrimidin-2-amine (0.02 mol) was added to it. To this mixture 10% $NaHCO_3$ was added drop wise at room temperature. The solution was stirred for 4 hours. The reaction mixture was poured onto crushed ice with constant stirring. The solid was filtered and washed with water. The product was recrystallized from acetone.

Preparation of 6-phenyl-N, N'-bis (4, 6-dimethoxypyrimidin-2-yl)-1, 3, 5-triazine-2, 4-diamine

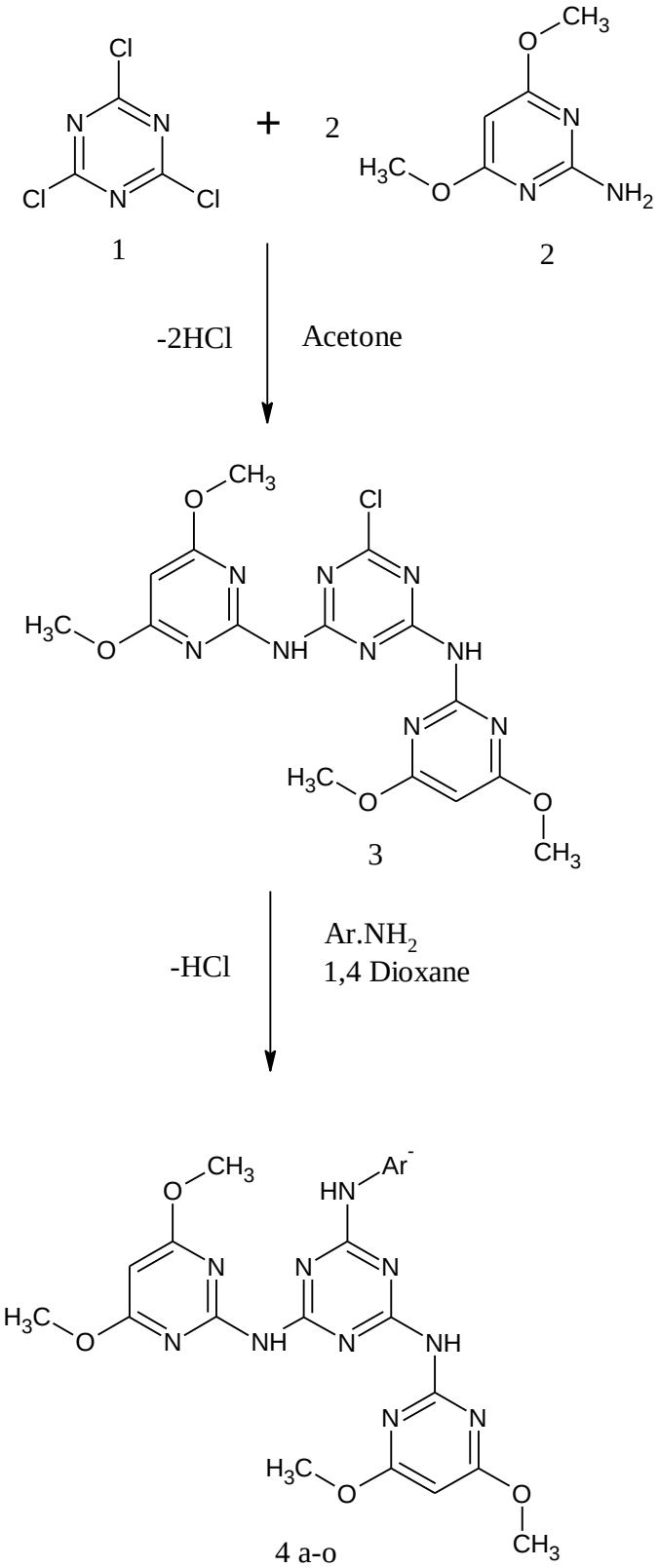
In a conical flask 6-chloro-N,N'-bis(4,6-dimethoxypyrimidin-2-yl)-1,3,5-triazine-2,4-diamine(0.01 mol) and 1,4 -dioxane (20 mL) was taken. To this mixture, p-toludine (0.01 mol) was added. The P^{H} was adjusted neutral by adding 10% NaHCO3. Then the reaction mixture was refluxed for 6 hrs. The reaction mixture was poured onto crushed ice with constant stirring. The solid was filtered and washed with water. The product was recrystallized from methanol.Their physical constant data are given in Table 1 and Synthetic scheme in Figure-1.

RESULTS AND DISCUSSION:

Antimicrobial Activity

Antibacterial activity

Antibacterial activity was carried out by browth dilution method[7]. The strains used for the activity were procures from Microcare Lab., Surat. The compounds 4a-o were screened for their antibacterial activity against *Escherichia coli, Staphylocous aureus, Pseudomonas aeruginosa* and *Staphyloccous pyogenes* of concentrations of 1000, 500, 200, 100, 50, 25, 12.5 µg/mL respectively. Their Antimicrobial activity data are given in Table 2.



Scheme-1

Figure 1 Synthetic scheme for *s*-triazine derivatives

Table-1. Physical constants and elemental analysis of *s*-triazines.

Com no.	Ar-	Molecular Formula	M.P °C	Yield %	% of C Found,	% of C (calcd.)	% of H Found,	% of H (calcd.)	% of N Found,	% of N (calcd.)
4a	4-CH_3-C_6H_4	$C_{22}H_{24}N_{10}O_4$	220	72	53.64	(53.65)	4.92	(4.91)	28.43	(28.44)
4b	4-NO_2-C_6H_4	$C_{21}H_{21}N_{11}O_6$	240	76	48.17	(48.18)	4.05	(4.04)	29.45	(29.43)
4c	3,4-$(Cl)_2$-C_6H_3	$C_{21}H_{20}Cl_2N_{10}O_4$	260	74	46.04	(46.08)	3.65	(3.68)	25.57	(25.59)
4d	3-NO_2-C_6H_4	$C_{21}H_{21}N_{11}O_6$	255	76	48.15	(48.18)	4.03	(4.04)	29.45	(29.43)
4e	2-OH-4-$NO_2C_6H_3$	$C_{21}H_{21}N_{11}O_7$	260	70	46.73	(46.75)	3.92	(3.92)	28.58	(28.56)
4f	2-OH-C_6H_4	$C_{21}H_{22}N_{10}O_5$	250	74	51.02	(51.01)	4.49	(4.48)	28.32	(28.33)
4g	2-$C_4H_3N_2$	$C_{19}H_{20}N_{12}O_4$	262	70	47.52	(47.50)	4.23	(4.20)	34.99	(34.98)
4h	2-Cl-C_6H_4	$C_{21}H_{21}ClN_{10}O_4$	240	75	49.17	(49.18)	4.15	(4.13)	27.34	(27.31)
4i	3-Cl-C_6H_4	$C_{21}H_{21}ClN_{10}O_4$	245	70	49.19	(49.18)	4.14	(4.13)	27.32	(27.31)
4j	2,4,5-$(Cl)_3$-C_6H_2	$C_{21}H_{19}C_{l3}N_{10}O_4$	265	77	43.34	(43.35)	3.30	(3.29)	24.08	(24.07)
4k	2-OCH_3-C_6H_4	$C_{22}H_{24}N_{10}O_5$	248	75	51.95	(51.96)	4.75	(4.76)	27.56	(27.55)
4l	2,4-$(NO_2)_2C_6H_3$	$C_{21}H_{20}N_{12}O_8$	250	79	44.35	(44.37)	3.54	(3.55)	29.56	(29.57)
4m	2,4-$(Cl)_2$-2 NO_2-C_6H_2	$C_{21}H_{19}C_{l2}N_{11}O_6$	245	77	42.57	(42.58)	3.24	(3.23)	26.02	(26.01)
4n	3-Cl-6-OH-C_6H_3	$C_{21}H_{21}ClN_{10}O_5$	260	79	47.68	47.69	4.01	4.00	26.49	26.48
4o	3-Cl-4-F-C_6H_3	$C_{21}H_{20}ClFN_{10}O_4$	240	77	47.52	47.51	3.82	3.80	26.37	26.38

Table 2. Antibacterial and Antifungal activities.

Comp. No.	Minimal bactericidal concentration (MBC) in µg/mL				Minimal fungicidal concentration (MFC) in µg/mL		
	E.coli MTCC -443	*P.aerugi nosa* MTCC -1688	*S. aureus* MTCC -96	*S.pyog enus* MTCC -442	*C. albicans* MTCC -227	*A.nigar* MTCC -282	*A.clavatus* MTCC -1323
4a	500	200	1000	1000	500	500	500
4b	500	500	1000	1000	500	500	500
4c	200	250	1000	1000	500	500	500
4d	100	100	1000	1000	500	500	500
4e	250	250	1000	1000	500	500	500
4f	250	500	1000	1000	1000	1000	1000
4g	500	250	1000	1000	1000	1000	1000
4h	500	100	1000	500	1000	1000	1000
4i	250	250	1000	1000	500	500	500
4j	100	500	1000	1000	1000	1000	1000
4k	100	500	1000	1000	1000	1000	1000
4l	250	500	1000	1000	1000	1000	1000
4m	500	500	1000	1000	500	500	500
4n	500	1000	1000	1000	1000	1000	1000
4o	500	500	1000	1000	1000	1000	1000

For antibacterial activity, in present protocol 100 µg/mL is considered as moderately active, 50 µg/mL is considered as good activity and 25 µg/mL is considered as active as compared to the standard drug gentamycin. For antifungal activity 200 µg/mL is considered as moderately active, 100 µg/mL is considered as active as compared to standard drug Nystatin.

Antifungal activity

Same compounds were tested for antifungal activity against *C. albicans A. niger* and *A. clavatus* of a concentrations of 1000, 500, 200, 100 µg/mL respectively (Table-2). The results are recorded in the form of primary and secondary screening. Each synthesized drug was diluted to obtain 1000 µg/mL concentration, as a stock solution.

The synthesized drugs found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. Secondary screening: The Drugs found active in primary screening were similarly diluted to obtain 100, 50, 25 µg/mL concentrations. 10 µL suspensions from each well was further inoculated on appropriate media and growth was noted after 24 and 48 hrs. The lowest concentration, which showed no growth after spot subculture was considered as MBC/MFC for each drug. The highest dilution showing at least 99% inhibition was taken as MBC/MFC. The result of this test is affected by the size of the inoculums. 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 & 1.0 µg/mL MBC against *S.aureus, E. Pyoganes* & *P. aeruginosa* respectively. "K. Nystation" was used as the standard drug for antifungal activity which showed 100 µg/mL MFC against fungi used for the antifungal activity. Compounds 4d, 4j were found to be moderately active, 4o found to be active against *E.coli*. This is due to the presence of chloro, methoxy, nitro, bromo, and hydroxyl in the *s*-triazine derivatives.

Spectra study of 6-phenyl-N, N'-bis(4,6-dimethoxypyrimidin-2-yl)-1,3,5-triazine-2,4-diamine

FT-IR (KBr) cm^{-1}: 3058(-N-H Str., Sec. amine), 1577(C=N Str., Sec. amine), 1498(C=N Str., ter. amine), 1363, 1400 (aromatic ring), 802(disubstituted aromatic)

^{1}H NMR: 5.65δ (s, C-NH-, 2H), 9.4δ (s, C-NH-,1H), 6.6-8.738 (m, Ar-H, 10H).

MS: m/z. 492 with 74% relative intensity $[M^{+}]$.

CONCLUSION:

The cyanuric chloride derivatives were synthesized and characterized for their structure elucidation. Various chemical and spectral data supported the structures thought of Antibacterial and Antifungal studies of these compounds indicated that compounds 4d, 4j were found to be moderately active, 4o found to be active against *E.coli*. This is due to the presence of chloro, methoxy, nitro, bromo, and hydroxyl in the *s*-triazine derivatives.

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