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Design, Characterization and Biological Activity of a new series of *s*-Triazines Derived with Morpholine

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ABSTRACT

4,6-dimethoxypyrimidin-2-amine condensed with trichloro s-triazine. The product of the above reaction was allowed to react with Morpholine. 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 biological properties were studied.

Keywords: *s*-Triazine derivatives, Morpholine and Antimicrobial Study.

INTRODUCTION

Nitrogen containing heterocycles 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 (Rosowsky *et al*., 2004). Several derivatives of *s*-triazine show herbicidal (Gajare *et al*., 1998), antimicrobial (Vora *et al*.,2008). 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 (Kaiser *et al*., 1951) 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 (Karale *et al*., 1957), antitumor and antifungal (Parikh *et al*., 2012) activities. Many pyrimidine derivatives are used for thyroid drugs and leukemia.

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 are reported as parts per million (ppm) and mass spectra were determined on Jeol-SX-102(FAB) spectrometer.

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Preperation of 4,6-dichloro-N-(4,6-dimethoxypyrimidin-2-yl)-1,3,5-triazin-2-amine

To a stirred solution of cyanuric chloride (0.01 mol) in acetone at low temperature, the solution of 4,6-dimethoxypyrimidin-2-amine (0.01 mol) in acetone was added and neutral P^H was maintained by adding 10% $NaHCO_3$ solution. The stirring was continued at the same temperature for 1 hours. Then stirring was stopped and solution was mixed with crushed ice. The product obtained was filtered and dried. The crude product was purified by recrystallization from Acetone.

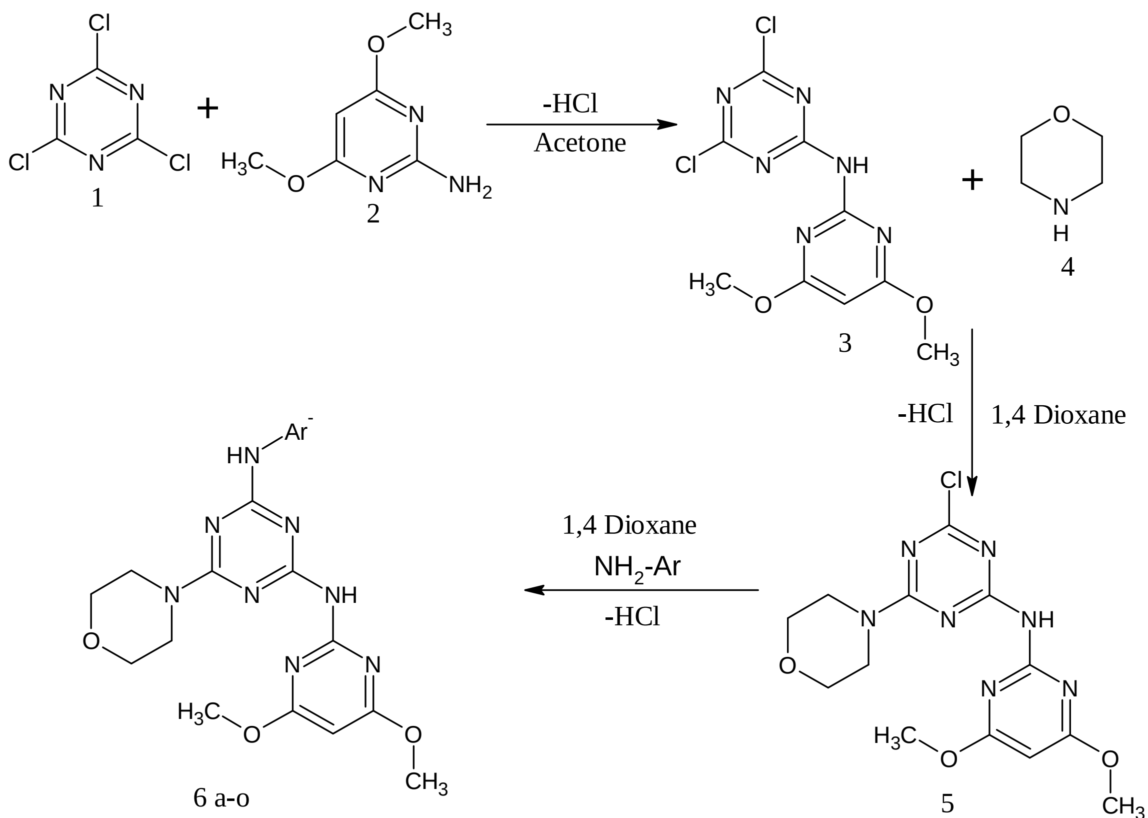
Preperation of 4-chloro-N-(4,6-dimethoxypyrimidin-2-yl)-6-(morpholin-4-yl)-1,3,5-triazin-2-amine

To a stirred solution of 4,6-dichloro-N-(4,6-dimethoxypyrimidin-2-yl)-1,3,5-triazin-2-amine (0.01 mol) in THF at 35 °C the solution of Morpholine (0.01 mol) in THF was added drop wise and neutral P^H was maintained by 10% $NaHCO_3$ solution. The stirring was continued at the same temperature for three hours. Then stirring was stopped and solution was mixed with crushed ice. The product obtained was filtered and dried. The crude product was purified by recrystallization from THF.

Preperation of N-(4-nitrophenyl) -N'- (4,6-dimethoxy pyrimidin-2-yl)-6-(morpholin-4-yl)-1,3,5-triazine-2,4-diamine

To the mixture of 4-chloro-N-(4,6-dimethoxypyrimidin-2-yl)-6-(morpholin-4-yl)-1,3,5-triazin-2-amine and 4-Nitro Anilline(0.01 mol) in THF was refluxed for 5-6 hours.

The P^H was adjusted to neutral by adding 10% $NaHCO_3$ solution. After completion of reaction the content was added to cold water. The solid obtained was dried and crystallized from THF. Their physical constant data are given in Table-1 and synthetic scheme in Figure-1.



Scheme-1
Synthesis route to *s*-triazine derivatives

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

No.	Ar-	Molecular Formula	M.P °C	Yield %	% of C Found, (calcd.)	% of H Found, (calcd.)	% of N Found, (calcd.)
6a	4-CH_3-C_6H_4	$C_{20}H_{24}N_8O_3$	264	71	56.60 (56.59)	5.72 (5.70)	26.41 (26.40)
6b	4-NO_2-C_6H_4	$C_{19}H_{21}N_9O_5$	273	78	50.12 (50.11)	4.66 (4.65)	27.67 (27.68)
6c	3,4-$(Cl)_2$-C_6H_3	$C_{19}H_{20}Cl_2N_8O_3$	269	69	47.63 (47.61)	4.20 (4.21)	23.39 (23.38)
6d	3-NO_2-C_6H_4	$C_{19}H_{21}N_9O_5$	280	78	50.13 (50.11)	4.63 (4.65)	27.70 (27.68)
6e	2-OH-4-$NO_2C_6H_3$	$C_{19}H_{21}N_9O_6$	275	81	48.43 (48.41)	4.47 (4.49)	26.75 (26.74)
6f	2-OH-C_6H_4	$C_{19}H_{22}N_8O_4$	272	75	53.53 (53.51)	5.22 (5.20)	26.29 (26.28)
6g	2-$C_4H_3N_2$	$C_{19}H_{20}N_{12}O_4$	279	77	47.52 (47.50)	4.23 (4.20)	34.99 (34.98)
6h	2-Cl-C_6H_4	$C_{19}H_{21}ClN_8O_3$	268	82	51.32 (51.30)	4.77 (4.76)	25.20 (25.19)
6i	3-Cl-C_6H_4	$C_{19}H_{21}ClN_8O_3$	271	68	51.32 (51.30)	4.77 (4.76)	25.20 (25.19)
6j	2,4,5-$(Cl)_3$-C_6H_2	$C_{19}H_{19}Cl_3N_8O_3$	273	75	44.43 (44.42)	3.74 (3.73)	21.82 (21.81)
6k	2-OCH_3-C_6H_4	$C_{20}H_{24}N_8O_4$	275	80	54.55 (54.54)	5.50 (5.49)	25.45 (25.44)
6l	2,4-$(NO_2)_2C_6H_3$	$C_{19}H_{20}N_{10}O_7$	283	76	45.62 (45.60)	4.01 (4.03)	27.98 (27.99)
6m	2,4-$(Cl)_2$-2 NO_2-C_6H_2	$C_{19}H_{19}Cl_2N_9O_5$	285	72	43.50 (43.52)	3.63 (3.65)	24.06 (24.04)
6n	3-Cl-6-OH-C_6H_3	$C_{19}H_{21}ClN_8O_4$	269	84	49.53 (49.52)	4.58 (4.59)	24.33 (24.31)
6o	3-Cl-4-F-C_6H_3	$C_{19}H_{20}ClFN_8O_3$	277	65	49.32 (49.30)	4.38 (4.36)	24.22 (24.21)

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**
6a	100	200	500	500	250	250	250
6b	500	500	250	500	500	500	500
6c	250	250	500	250	500	500	500
6d	500	500	500	250	500	500	500
6e	250	250	250	500	500	500	500
6f	50	100	500	500	500	500	500
6g	250	500	250	250	500	500	500
6h	200	500	500	500	500	500	500
6i	50	200	500	500	1000	1000	1000
6j	100	250	500	250	500	500	500
6k	100	250	250	100	500	500	500
6l	50	100	1000	250	500	500	500
6m	500	500	1000	1000	500	500	500
6n	25	200	1000	1000	1000	1000	1000

RESULTS AND DISCUSSION

Antimicrobial Activity

Antibacterial activity

Antibacterial activity was carried out by browth dilution method. The strains used for the activity were procures from Institute of Microbial Technology, Chandigarh. The compounds 6a-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.

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 6a, 6j and 6k were found to be moderately active, 6f, 6i and 6l found to be active against *E.coli*, where as compound 6k found to be good active against *S. aureus*. This is due to the presence of chloro, methoxy, nitro, bromo, and hydroxyl in the *s*-triazine derivatives. Compound 6a was found to be moderately active against all the species of fungi. 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. Their Antimicrobial activity data given in Table-2.

Spectra study of N-(4-nitrophenyl) -N'- (4,6-dimethoxy pyrimidin-2-yl)-6-(morpholin-4-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), 1255(C-O-C stretching), 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), 8.07-8.09 (d, 1H, -O-C=CH-CH=CH-), 8.14-8.19(t, 1H, -O-C=CH-CH=CH), 8.77-8.78(d, 1H, -O-C=CH-CH=). MS: m/z. 514 with 78% relative intensity [M^+].

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