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Synthesis of some new *s*-Triazine based derivatives as Potent Antimicrobial Agents

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ABSTRACT

4,6-dimethoxypyrimidin-2-amine condensed with trichloro s-triazine. Finally various urea 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, 4,6-dimethoxypyrimidin-2-amine, Antimicrobial Study.

INTRODUCTION

Nitrogen containing heterocycles play main 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] ,antimicrobial[3] and herbicidal activities[4]. 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[5,6] 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[7], antitumor[8] and antifungal activities[9] . Many pyrimidine derivatives are used for thyroid drugs and leukemia. Among other urea derivatives, phenyl urea derivatives are widely used particularly in pharmaceutical chemistry. Urea derivatives possess wide therapeutic activities such as antithyroidal, hypnotic and anesthetic[10], anthelmintics antimalerial[11] anti HIV[12] and analgesic activity, antibacterial and diuretic, antibacterial and anti-inflammatory [13].

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.

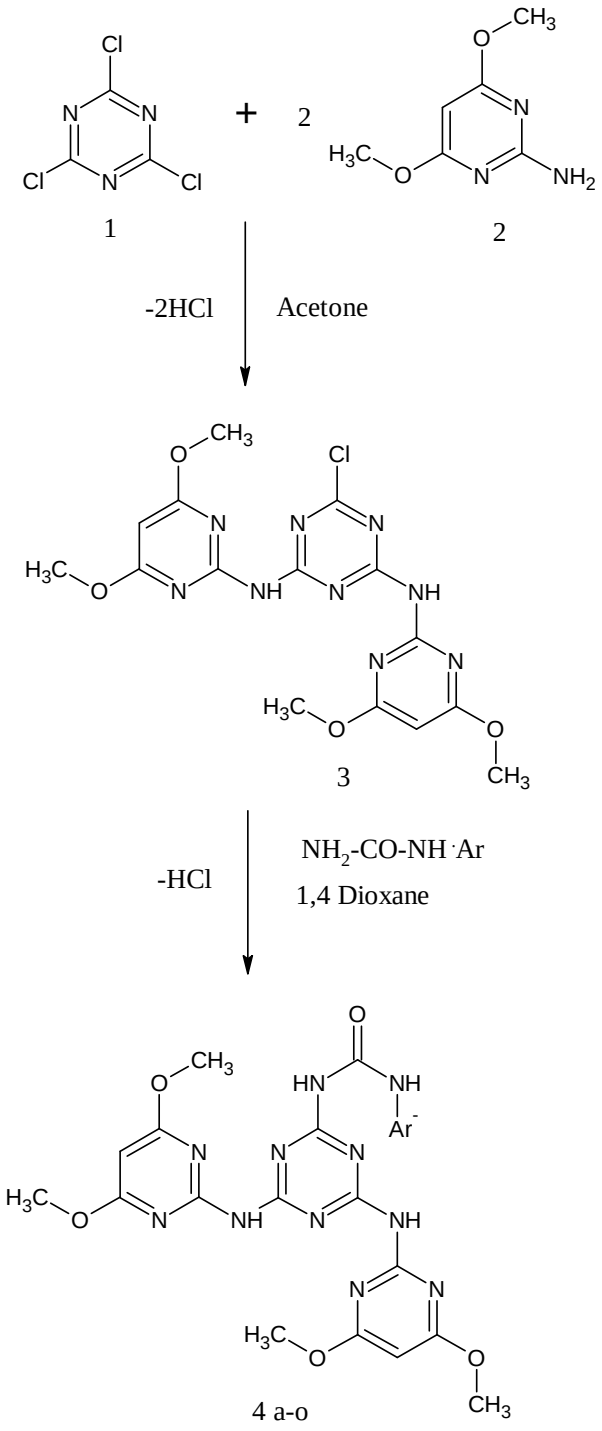
Synthetic Procedures

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 1-[4,6-bis(dimethoxypyrimidin-2-ylamino)-1,3,5-triazin-2-yl]-3-phenylurea

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, phenyl urea(0.01 mol) was added. The P^H was adjusted neutral by adding 10% $NaHCO_3$. 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.



Scheme-1

Synthesis route to *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, (calcd.)	% of H Found, (calcd.)	% of N Found, (calcd.)
4a	-H	$C_{22}H_{23}N_{11}O_5$	270	77	50.66 (50.67)	4.43 (4.45)	29.56 (29.54)
4b	*O*-NO_2	$C_{22}H_{22}N_{12}O_7$	285	80	46.65 (46.64)	3.93 (3.91)	29.69 (29.67)
4c	*m*-NO_2	$C_{22}H_{22}N_{12}O_7$	279	75	46.66 (46.64)	3.90 (3.91)	29.66 (29.67)
4d	*p*-NO_2	$C_{22}H_{22}N_{12}O_7$	272	78	46.61 (46.64)	3.89 (3.91)	29.68 (29.67)
4e	*O*-CH_3	$C_{23}H_{25}N_{11}O_5$	275	73	51.60 (51.59)	4.73 (4.71)	28.76 (28.77)
4f	*m*-CH_3	$C_{23}H_{25}N_{11}O_5$	282	75	51.58 (51.59)	4.70 (4.71)	28.75 (28.77)
4g	*p*-CH_3	$C_{23}H_{25}N_{11}O_5$	295	73	51.58 (51.59)	4.70 (4.71)	28.79 (28.77)
4h	*O* -Cl	$C_{22}H_{22}ClN_{11}O_5$	265	77	47.55 (47.53)	3.96 (3.99)	27.72 (27.71)
4i	*p*-Cl	$C_{22}H_{22}ClN_{11}O_5$	271	72	47.54 (47.53)	3.98 (3.99)	27.70 (27.71)
4j	*m* -Cl	$C_{22}H_{22}ClN_{11}O_5$	280	79	47.51 (47.53)	3.97 (3.99)	27.73 (27.71)

Table 2. Antibacterial and Antifungal activities

	Minimal bactericidal concentration (MBC) in µg/mL					Minimal fungicidal concentration (MFC) in µg/mL		
Comp. No.	*E.coli* MTCC 443	*P.aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S.pyogenus* MTCC 442		*C. albicans* MTCC	*A.nigar* MTCC	*A.clavatus* MTCC
4a	500	200	200	500		>1000	>1000	>1000
4b	50	200	500	500		>1000	>1000	>1000
4c	500	250	500	200		>1000	>1000	1000
4d	500	500	500	200		>1000	>1000	1000
4e	250	250	200	250		>1000	>1000	>1000
4f	100	200	100	500		500	500	1000
4g	500	500	500	500		>1000	>1000	>1000
4h	500	500	200	500		>1000	>1000	>1000
4i	250	250	500	500		>1000	>1000	>1000
4j	500	500	100	100		>1000	>1000	>1000
Gentamycine	0.05	1	0.25	0.5	Nystatin	100	100	100
Ampicillin	100	100	250	100	Greseofulvin	500	100	100
Chloramphenicol	50	50	50	50				

RESULTS AND DISCUSSION

Antimicrobial Activity

Antibacterial activity was carried out by browth dilution method. Each purified compound is dissolved in dimethyl sulphoxide(DMSO), Sterilized by filtration using sintered glass filter and store at 4^0C. All the synthesized compounds were screened for their antibacterial and antifungal activities against the *E. coli*, *P. aeruginosa*, *S. aureus*, *S.pyogenes*, and the fungi *C. albicans*, *A. niger* and *A. clavatus*. The compounds were tested at 500, 250, 100 and 50 µg/mL concentration using nutrient agar tubes. The highest dilution showing at least 99% inhibition is taken as MBC(minimal bacterial concentration). Control experiment was carried out under similar condition by using gentamycine, ampicillin, chloramphenicol for antibacterial activity and nystatin, greseofulvin for antifungal activity as standard drugs.

Out of ten synthesized heterocyclic compounds, compound 3b showed equal antibacterial activity as chloramphenicol (against *E.coli*) and compound 3f (against *E.coli*) and 3j (against *S. pyogenus*) showed equal antibacterial activity against *P. aeruginosa* compared to the other compounds. Against the organism *S. aureus*, compound 3f and 3j showed comparable antibacterial activity similar to standard drug.

Out of ten synthesized compounds 3f showed equal antifungal activity as greseofulvin (against *C. albicans*) and less activity against the two other organisms. Compound 3f contain methyl groups in *meta* position, compound 3f and 3i

showed marginal higher antifungal activity against *A. niger* compared to the other compounds, however less than the standard drugs. The ten compounds against *A. clavatus* seemed much less effective as antifungal. Their Antimicrobial activity data given in Table-2.

Spectra study of 1-[4,6-bis(dimethoxypyrimidin-2-ylamino)-1,3,5-triazin-2-yl]-3-phenylurea
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), 9.14(s, 2H, NH-CO-NH), 7.30-7.50(m, 5H, Ar-H); MS: m/z. 521 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 compound 4b, 4f, 4j were found to be equal active against some bacteria compared to standard antibiotic drugs. However, they could not exhibit appreciable antifungal action.

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