Available online at www.pelagiaresearchlibrary.com

Pelagia Research Library

Der Chemica Sinica, 2012, 3(2):430-434

Der Chemica Sinica
Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and antimicrobial screening of some new *s*-Triazine based Piperazine and Piperidine derivatives

Kalpesh S. Parikh*and Sandip P. Vyas

Department of Chemistry, Sheth M.N. Science College, Patan(Gujarat), India

---

ABSTRACT

4,6-dimethoxypyrimidin-2-amine reacts with trichloro s-triazine. Finally various piperazine and piperidine 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:2,4,6-trichloro-1,3,5-triazine,4,6-dimethoxypyrimidin-2-amine, microbial activity.

INTRODUCTION

Due to the increasing number of multidrug resistant developed by the microbes, Currently used antimicrobial agent are ineffective and antibacterial and antifungal diseases are very common, therefore, the design and synthesis of new antimicrobial molecules has been of enormous interest in recent year.

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. In a view of its adaptable chemistry, we are promoted for sequential introduction of various piperazine and piperidine substituents into the 1,3,5-triazine ring. Piperazine and piperidine occupied a unique place in the realm of pharmacological activities[10-12].

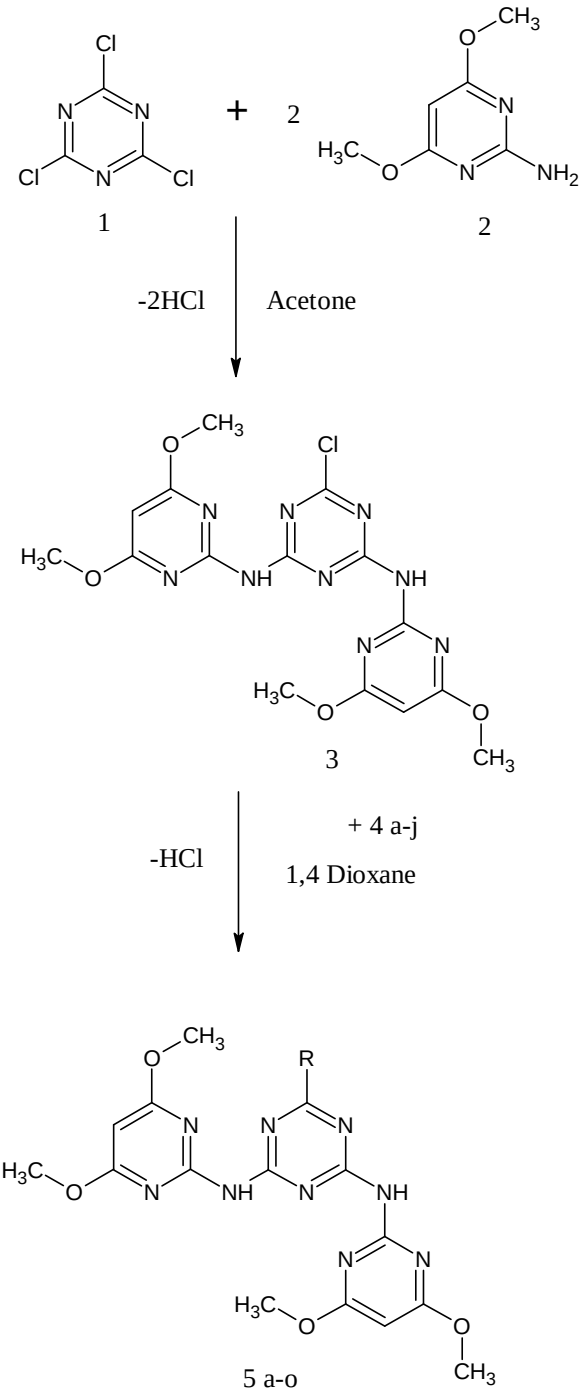
MATERIALS AND METHODS

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.



Scheme-1

Synthesis route to *s*-triazine derivatives

Preparation of 6-(3,5-dimethyl piperidin-1-yl)-*N*,*N*'-di(dimethoxy pyrimidin-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, 3,5-dimethyl piperidine(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 Piperazine and Piperidine derivative information depicted in Table-1, physical constant data are given in Table-2 and synthetic scheme in Figure-1.

Table -1. Various substituted piperazine and piperidine derivatives used as coupling agents

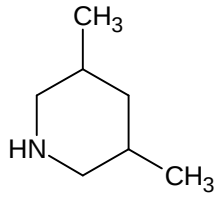
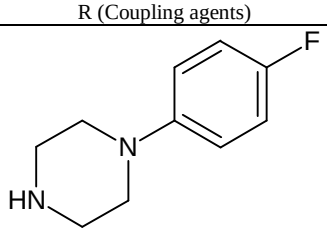
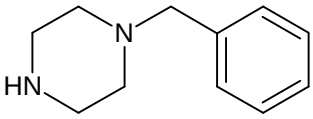
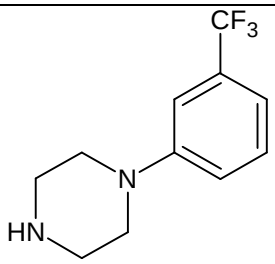
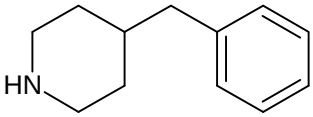
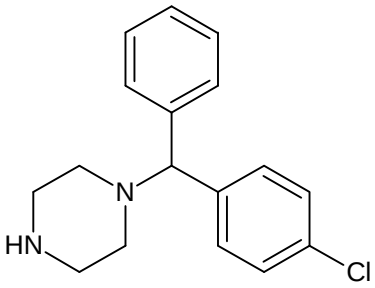
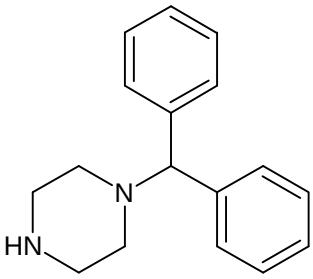
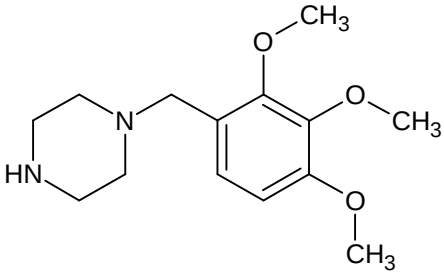
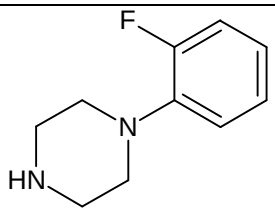
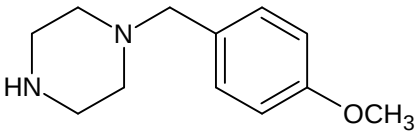
4	R (Coupling agents)	4	R (Coupling agents)
4a	 3,5-dimethylpiperidine	4f	 1-(4-fluorophenyl)piperazine
4b	 1-benzylpiperazine	4g	 1-[3-(trifluoromethyl)phenyl]piperazine
4c	 4-benzylpiperidine	4h	 1-[(4-chlorophenyl)(phenyl)methyl]piperazine
4d	 1-(diphenylmethyl)piperazine	4i	 1-(2,3,4-trimethoxybenzyl)piperazine
4e	 1-(2-fluorophenyl)piperazine	4j	 1-(4-methoxybenzyl)piperazine

Table-2. Physical constants and elemental analysis of *s*-triazines

Com. no.	Molecular Formula	F.W.	M.P °C	Yield %	% of C Found, (calcd.)	% of H Found, (calcd.)	% of N Found, (calcd.)
5a	$C_{22}H_{30}N_{10}O_4$	498.53	292	77	53.01 (53.00)	6.08 (6.07)	28.11 (28.10)
5b	$C_{26}H_{31}N_{11}O_4$	561.59	277	75	55.62 (55.61)	5.58 (5.56)	27.45 (27.43)
5c	$C_{27}H_{32}N_{10}O_4$	560.60	267	81	57.86 (57.85)	5.76 (5.75)	24.99 (24.98)
5d	$C_{32}H_{35}N_{11}O_4$	637.69	272	78	60.28 (60.27)	5.54 (5.53)	24.18 (24.16)
5e	$C_{25}H_{28}FN_{11}O_4$	565.55	250	89	53.07 (53.09)	4.98 (4.99)	27.25 (27.24)
5f	$C_{25}H_{28}FN_{11}O_4$	565.55	279	72	53.08 (53.09)	4.97 (4.99)	27.26 (27.24)
5g	$C_{26}H_{28}F_3N_{11}O_4$	615.56	288	85	50.74 (50.73)	4.59 (4.58)	25.05 (25.03)
5h	$C_{32}H_{34}ClN_{11}O_4$	672.13	300	80	57.19 (57.18)	5.11 (5.10)	22.93 (22.92)
5i	$C_{29}H_{37}N_{11}O_7$	651.67	279	81	53.44 (53.45)	5.73 (5.72)	23.66 (23.64)
5j	$C_{26}H_{31}N_{11}O_5$	577.59	289	79	54.08 (54.07)	5.42 (5.41)	26.69 (26.68)

RESULTS AND DISCUSSION

Antimicrobial Activity

All the newly synthesized compounds were tested for their in vitro antibacterial and antifungal activity (MIC-minimum inhibitory concentration) by broth dilution method[13]with two gram positive bacteria *S. aureus* and *B. subtilis*, 2 gram negative bacteria *E.coli, P. aeruginosa* and fungai species like *C. albicans, A. niger* organisms taking ciprofloxacin, ampicillin, chloramphenicol, norfloxacin, flucanazole, griseofulvin and Nystatin as standard control drug. Muller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for test. DMSO was used as a diluents which is ineffective to the growth of microbes.

The antibacterial results revealed that the compound 5g bearing 1-(3-Triflouoromethyl-phenyl)-piperazine derivative to the basic S-Triazine nucleus containing 4,6-dimethoxypyrimidin-2-amine proved more beneficial compound compared to other analogues against *E.coli*. The compounds 5b, 5c, 5g and 5h containing 3,5-Dimethyl-piperidine , 1-(2-Fluoro-phenyl)-piperazine, 1-(4-Fluoro-phenyl)- piperazine, 1-(3-Trifluro methyl-phenyl)-piperazine, 1-[(4-Chloro-phenyl)-phenyl-methyl]- piperazine and 1-(2,3,4-Trimethoxy-benzyl)- piperazinesubstituents respectively shown the best activity against S. aureus, whereas 5c and 5j having 4-benzyl-piperidine and 1-(4-Methoxy-phenyl)-piperazine respectively proved as beneficial coupling agent to the final moiety for the best activity against *B. subtilis*. The biological screening results for fungal species revealed that compound 5j bearig 1-(4- Methoxy-phenyl)-piperazine constituent exhibited higher activity against both fungal species C. albicans and A.niger, in addition, the compound 5g and 5h having 1-(3-Trifluro methyl-phenyl)-piperazine and 1-[(4-Chloro-phenyl)-phenyl-methyl]- piperazine respectively exhibited similar inhibitory concentration to that of compound 5j bearing 1-(4-Methoxy-phenyl)-piperazine against A.niger. In short, we made an attempt to increase the biological activity by increasing the volume of the substituents attached to the piperazine ring system led to different biological potency, depending on the nature, position and number of the atoms or groups introduced, whereas, high potency has been observed in the final scaffolds due to the presence of piperazine systems with halogen, fluro atom(s), methoxy group(s) and piperidine entity. Their antimicrobial activity data given in Table-3.

Spectra study of 6-(3,5-dimethylpiperidin-1-yl)-*N*,*N*'-di(dimethoxy pyrimidin-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), 808(s-Triazine C-N Str.); ^{1}H NMR: 5.65δ (s, C-NH-, 2H), 9.4δ (s, C-NH-,1H), 6.6-8.738 (m, Ar-H, 10H), 3.82δ(m, piperazine, 8H) 2.40δ(s, -CH_2, 2H); MS: m/z. 498 with 75% relative intensity[M^+].

Table 3. Antimicrobial study (MIC µg/mL) of synthesized compound 5 a-j.

		Minimum Inhibitory Concentration					
Comp. No.	R	Gram negative		Gram positive		Fungal species	
		E. coli	*P.aeruginosa*	*S.aur eus*	*B. subtilis*	*C. albicans*	*A. niger*
5a	3,5-Dimethyl-piperidine	250	500	250	250	500	500
5b	1-Benzyl-piperazine	50	100	50	100	50	250
5c	4-Benzyl-piperidine	100	50	100	25	250	250
5d	1-Benzhydryl-piperazine	50	100	250	100	250	500
5e	1-(2-Fluoro-phenyl)-piperazine	100	50	50	50	100	250
5f	1-(4-fluoro-phenyl)-piperazine	50	50	100	50	50	250
5g	1-(3-Trifluoromethyl-phenyl)-piperazine	25	50	50	50	100	100
5h	1-[(4-Chloro-phenyl)-phenyl-methyl]-piperazine	100	50	50	50	100	100
5i	1-(2,3,4-Trimethoxy-benzyl)-piperazine	50	50	100	100	100	250
5j	1-(4-Methoxy-phenyl)-piperazine	50	250	100	25	25	100
	Ampicillin	100	100	250	100		
	Ciprofloxacin	25	25	50	50		
	Chloramphenicol	50	50	50	50		
	Norfloxacin	10	10	10	10		
	Griseofulvin					500	100
	Nystatin					100	100
	Flucanazole					10	10

CONCLUSION

A series of trisubstituted s-Triazine derivative has been successfully synthesized and tested for their anti microbial activity. S-Triazine nucleus is one of the active constituents present in many standard drugs. Herein, we have combined three potential unit, that is s-triazine nucleus. Hence, it is concluded that, trisubstituted s-Triazine are more active than mono and di-substituted s-triazine and thus, there is enough scope for further study in developing such compounds as a good lead activity. Overall conclusion placed for synthesized compounds is the most of the compounds shown very good promising activity as compared to standard drug for all representative panel of bacterial and fungal strains.

Acknowledgments
We are grateful the SAIF, Punjab University for recording the spectra and Microcare Lab.,Surat for providing Antimicrobial activities.

REFERENCES

[1] A. Rosowsky and S. F. Queener , *J. Med. Chem.*, **2004**, 47, 1475.
[2] A. S. Gajare and M. S. Shingare, *Indian J. Chem.*, **1998**, 37B, 510.
[3] P. S.Desai and K. R. Desai, *J. Indian Chem. Soc.*, **1994**,77, 155.
[4] N.Nishimura and A.Kato, *Carbohyd. Res.*, **2001**, **77**, 331.
[5] D. W. Kaiser, J. T. Thurston, J. R. Dudley, F. C. Schaefer and D. Holm-Hansen. *J. Am. Chem. Soc.*, **1951**,73, 2984.
[6] R.B. Patel and K. H. Chikhalia, *J. Indian Chem. Soc.*, **2003**,80,138.
[7] Singh, N.; Nargund, S.N.; Nargund, S.L.; Rashmi, P.; Nargund L.V.G. *Der Chemica Sinica*, **2012**, 3(1), 198.
[8] V. M. Reddy and Rama G. V.S. Sarma, *Indian J. Heterocycl Chem.*, **1993**, 3, 111.
[9] M. S Shingare, B. K. Karale, C. H. Gill, K. N. Gange, M. T. Bachute, *Indian J. Heterocycl Chem.*, **1999**, 9**,** 153.
[10] M. Stefania, R. Maddalena, V. Piero and DR. Paolo, *Farmaco*, **1999**, 54, 411-415.
[11] W. Elzbieta, W. Monika and K. Bogdan, *Eur. J. Med. Chem.*, **2006**, 41, 519-525.
[12] F. Alireza, G. Shahram, E. Saeed, N. Somayyeh, S. Nasrin, A.F. Mohammad, B. Leila, H.S. Farshad and S. Abbas, *Bioorg. & Med. Chem. Lett.* **2006**, 16, 3499-3503.
[13] P.R. Murray, E.J. Baron, M.A. Pfaller, F.C. Tenover and R.H. Yolke, *Manual of Clinical Microbiology, 4th ed., ASM: Washington,* **1999**, 1527.