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Synthesis, characterization and antimicrobial activity of some novel s-triazine derivatives incorporating quinoline moiety

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ABSTRACT

This paper discuss a series of s-Triazine derivatives based quinoline demonstrate a wide range of biological activity.In the present investigation 4,7 –dichloroquinoline as taken as starting material and treated with ethylene diamine afforded 4-substituted 7-chloroquinoline,Whichfurther reacted with 1,5-disubstituted cyanuric chloride yielded 1,3,5-triazine chloroquinoline derivatives.All the synthesized compounds were characterized using IR ,H^{1},C^{13}NMR, mass spectral studies and elemental analysis. The final compounds were screened for their anti bacterial activity using E.coli,S-aureus and S.typhi and antifungal activity.

Keywords: cyanuric chloride dichloroquinoline ethylene diamine antibacterial activity antifungal activities.

INTRODUCTION

Cyanuric chloride is an essential organic intermediate of which three chlorine can be replaced by $–NH_2$ -OH, -SH (or) , -NHR step by step with high yield. cyanuric chloride derivatives have been studied for decads, especially its amino derivatives. It is generally accepted that the first chlorine of cyanuric chloride can be easily substituted by –NH2 group at 0-5°C the second one at 30-50°C and third one typically above 80°C which depends on the activity of amino nucleophiles.

s-Triazine derivatives represent an important class of compounds due to their potential to be biologically active.They are known to be anti –protozoals(Baliniet al.,2005)anti-cancer agents(Menicagli et al.,2004) estrogen receptor (Modulators Henkee et al.,2001; Agarwal et al.,2005)cyclin -dependent Kinase Modulators (Kuo et al.,2005) and antimicrobials Koc et al.,2010.

It has been reported that s-triazine derivativesare are used as templates for molecule inprinting (Tahmassebi and Sasaki,1994) and for the construction of three- helix bundle protein(Tahmassebiand Sasaki 1998).In this paper we have reported the novel s-triazine derivatives from N^2-2-(7-chloro quinoline -4-yl)amino ethyl –N^4,N^6-bis 4-nitro phenyl-1,3,5 –triazine,2,4,6 -triazine. This will be prepared by first 4,7 -dichloroquinoline reacted with ethylenediamine, get 4- substituted 7-chloroquinoline.It is reacted with bisubstituted cyanuric chloride. The compounds are characterized by spectral analysis. Anti-bacterial activites and anti-fungal activites of these compounds are studied.

MATERIALS AND METHODS

Chemicals:- Cyanuric chloride , 4,7- dichloroquinoline, ethylenediamine were used as received from Aldrich Chem. Sodiumbicorbonate,HCl, P.nitroaniline, Aniline were used as received from Merck

Methods:- The reaction was monitored by TLC using on 0.25 mm E-Merckslica gel 60 F_{254} Pre coated Plates, Which were visualized with UV light.The FT-IR spectra was recorded on a Perkin –Elmer257 spectrometer using KBr disks. ^{1}HNMR and ^{13}C was recorded on a VXR 400MHZ instrument using TMS as an internal Standard. Mass Spectra was recorded on a Finni-gan mass spectrometer.

Biological Activity:- All compounds were evaluated for in vitroantibacterial activities against *Escherichia coli* and staphylococcus aureus strains and in vitro anti fungal actiivity against *Candida canalbis* and *Aspergillus niger* strains by using serial dilution method.

Scheme:-

STEP 1

Synthesis of N^{1}-(7-Chloro quinoline -4-yl)ethane-1,2- diamine

A mixture of 4,7 -dichloroquinoline (1.8g 0.01mol) and ethylene diamine (0.06g 0.01mol) was heated and the reaction was monitored by TLC, after completion reaction mixture was extracted and the crystals of 4- substituted 7-chloroquinoline were removed by filteration. The product was recrystalized two times from acetone.

STEP 2

Synthesis of 4,6 –dichloro –N^{1}(4-nitro-phenyl)-1,3,5-triazine-2 amine

P .Nitro aniline 2.76g(0.01mol) was added slowly to cyanuric chloride 1.845g (0.01mol) in acetone (35ml) with constant stirring for 4Hr at 0°c. Sodiumcorbonate sol 10% was added to neutralize HClevoled during the reaction. Finally the content were poured in to crushed ice the solid separated was filter washed with water dried, and recrystalized from ethanol to give compound,.

STEP 3

Synthesis of 6-Chloro-$N,^{2}$ N^{4}-bis(4-nitro phenyl)- 1,3,5-trizine 2.4 -diamine

P.Nitro aniline was added slowly 2.76g(0.01mol) to 4,6 –dichloro –N^{1}(4- nitro –phenyl)-1,3,5- triazine- 2-amine2.85g(0.01mol) in acetone(35ml) with constant stirring for 4Hr at room temp.Sodium carbonate sol 10% was added to neutralize Hclevoled during the reaction. Finally the content were poured in to crushed ice the solid separated was filter washed with dried and recrystalized from ethanol to give compound.

STEP 4

Synthesis of N^{2} -2-((7-chloroquinoline-4-yl) amino ethyl –N^{4},N^{6}bis (4-nitro phenyl -1,3,5 –triazine, 2,4,6 –triazine.

Bi substituted cyanuricchloride 3.8g(0.01mol) was added slowly to N ^{1}–(7-chloro quinoline -4-yl) ethane-1,2 –diamine.2.21g(0.01mol) in acetone (35ml) with constant stirring for 6hr above 60°c. sodium carbonate solution 10% was added to neutralize HCL evoled during the reaction. Finally the content were poured in ice the solid separated was filter washed with water dried and recrystallised from ethanol to give compound.

COMPOUND (1a): Yield 60.50% m.p 165°c (dec); IR (Kbr, cm^{-1}) : 627 (C-Cl), 707.09 (-CH_2) 812(C-N S –triazine), 1306 .11 (-NO_2)) , 1511.96 (-Ar), 2447.14 (C-H methyl) ,3333.96 (Ar-NH stretch) ^{1}H –NMR δppm :3.65(t ,4H, -CH_2), 7.20-7.49 (m ,5H, Ar-H), 8.262-8.265 (m ,5H , Ar-H), 10.940 (s ,1H, -NH) ^{13}C –NMR δppm: 119.02-144.735 (Ar –C), 163.421,167.049,169.841 (C=N of S- triazine)

COMPOUND (1b): Yield 64.45% m.p 165°c (dec); IR (Kbr, cm^{-1}) :627 (-C-Cl), 707.09 (-CH_2) ,813.21 (C-N S-triazine),1309.11 (-NO_2), 1511.96 (-Ar) ,2456.15 (C-H methyl), 3328.61 (Ar –NH stretch) ^{1}H -NMRδ ppm : 3.587 (t ,4H, -CH_2), 7.227-7.224 (m ,5H, -Ar-H), 8.262-8.269 (m ,5h, Ar-H),10.948 (s ,1H,-NH) ^{13}C NMRδ ppm:111.7 -147.7 (Ar-C), 164.735 , 168. 123, 168.841 (C=N of S- triazine)

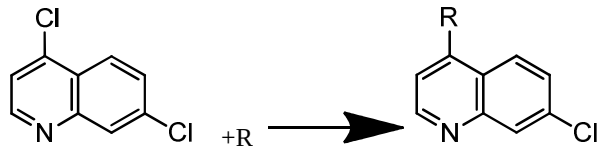
COMPOUND (1c): Yield 62.23% m.p 135°c (dec); IR (Kbr ,cm^{-1}) 627.46 (-C-Cl) ,708.26 (-CH_2), 814.07 (C-N S-triazine), 1323.28 (-NO_2), 1539.89 (-Ar) ,2554.12 (C-H methyl), 3329.56 (Ar- NH stretch) ^{1}H –NMRδ ppm:

3.587 (t, 4H,-CH_2), 7.840-7.862 (m ,5H, Ar-H),8.262-8.269 (m, 5H,Ar-H),10.945 (s,1H,,-NH) ^{13}C NMRδ ppm:119.029-144.735 (Ar-C), 163.096 ,163.421, 167.049,169.841 (C=N of S-triazine)

COMPOUND (2a): Yield 64.47% m.p 161°c (dec); IR (Kbr, cm^{-1}): 703.18 (-CH_2), 750.65 (C-Cl), 817.85(C-N S-triazine), 1329 (-NO_2) ,1574 (Ar), 1605 (C=N), 2553.11(C-H methyl), 3323.55 (Ar-NH stretch) ^{1}H –NMR δppm: 3.350 (t ,4H, -CH_2),7.388-7.406 (m, 4H, Ar-H), 8.210-8.219 (m, 4H, Ar-H),10.819 (s, 1H, -NH) ^{13}C NMRδPppm:120.294-141.831 (Ar-C), 152.407,164.407 (C=N of S-triazine)

COMPOUND (2b): Yield 66.88% m.p 165°c(dec); IR (Kbr,cm^{-1}): 702.83 (-CH_2),750.92 (C-Cl), 819.27(C-N S triazine), 1329 (-NO_2), 1574 (Ar),1605 (C=N), 2555.61 (C-H methyl), 3324.45 (Ar-NH stretch) ^{1}H-NMRδppm:3.359 (t, 4H, -CH_2), 7.386-7.450(m,4H,Ar-H),8.210-8.248 (m,4H,Ar-H),10.819(s,1H,-NH) ^{13}C-NMR δppm 120.294-141.831 (Ar-C), 152.407,164.432(C=N of S-triazine)

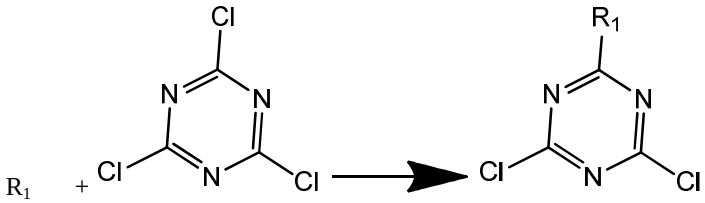
COMPOUND (2c): Yield67.23% m.p 163°c (dec);IR(Kbr, cm^{-1}) :703.88(-CH_2),750.45(C-Cl),817.86(C-N Striazine),1327 (-NO_2),1574 (Ar),1605(C=N),2543.53(C-H methyl),3331.25 (Ar-NH stretch) ^{1}H-NMR δ ppm :3.358(t,4H,-CH_2), 7.358-7.450(m,4H,Ar-H),8.215-8.250(m,4H,Ar-H),10.818(s,1H,-NH) ^{13}C-NMRδppm: 120.292, 141.826(Ar-C),152.407,166.435(C=N of S-triazine)

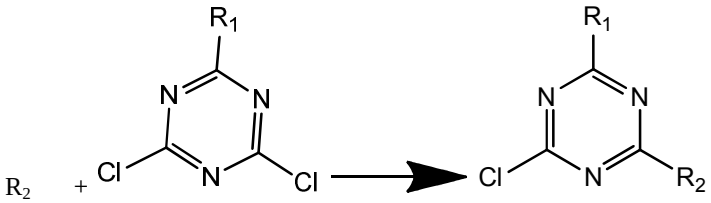


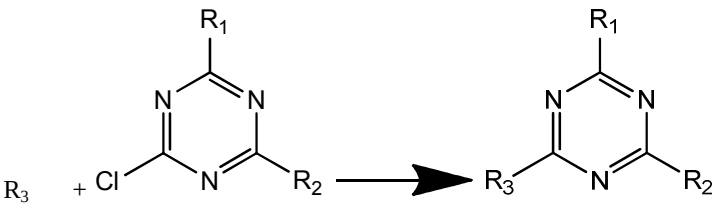
$R=NH_2-(CH_2)_n-NH_2$

--Hcl

n=2,4,6







WHERE R_1 R_2 and R_3 are given below

Table 1 Various substituted compound			
compound	**R_1**	**R_2**	**R_3**
1a	P.Nitroaniline	P.Nitroaniline	N^1-7 (Chloroquinoline-4yl)ethane 1,2Diamine
1b	P.Nitroaniline	P.Nitroaniline	N^1-7 (Chloroquinoline-4yl)butane 1,2Diamine
1c	P.Nitroaniline	P.Nitroaniline	N^1-7(Chloroquinoline-4yl)hexane 1,2Diamine
2a	P.Nitroaniline	Aniline	N^1-7(Chloroquinoline-4yl)ethane 1,2Diamine
2b	P.Nitroaniline	Aniline	N^1-7(Chloroquinoline-4yl)butane 1,2Diamine
2c	P.Nitroaniline	Aniline	N^1-7(Chloroquinoline-4yl)hexane 1,2Diamine

Table 2 Physical Data for synthesized compound

Compound	Molecular formula (Mol.Wt)	Yield	M.P°c	Elemental Analysis					
				% C		%H		%N	
				Found	Cal	Found	Cal	Found	Cal
				58.58	58.60	4.55	4.56	25.30	25.31
1a.	$C_{27}H_{25}ClN_{10}O_4$ 553	68	165 -170	55.96	55.87	4.19	4.35	23.11	22.22
1b.	$C_{28}H_{25}ClN_{10}O_4$ 601.02	69	165	58.68	56.45	4.60	4.25	20.53	21.55
1c.	$C_{30}H_{28}ClN_9O_4$ 614	55	130-137	59.96	57.67	4.20	4.99	23.88	22.55
2a.	$C_{26}H_{22}ClN_9O_2$ 529.96	70	161-162	60.48	61.55	4.71	4.25	22.67	22.00
2b.	$C_{26}H_{26}ClNO_2$ 556.02	72	163-165	61.69	61.45	5.18	5.14	21.58	21.55
2c.	$C_{30}H_{30}ClNO_2$ 584.07	65	163-165	64.30	64.25	4.92	4.80	17.64	17.60

RESULTS AND DISCUSSION

Several substituted s –triazine derivatives were effectively synthesized by 2-3 step process. synthesis of 4 substituted 7- chloroquinoline in the first step in the procedure. This compound is treated with s –triazine to give s- triazine derivatives. In the IR spectra of the entire compound showed absorption band at 3200 -3500cm^{-1} due to (Ar-NH) stretch vibration. The absorption at 918 cm^{-1} due to (- CH_2) vibration. The absorbtion at 1342 cm^{-1} show the presence of (-NO_2) group. The absorption 813-821cm^{-1}were attributed to the (C-N-S- triazine) vibration.Which also confirmed the formation of desire s- triazine ring in all the compound.

In the NMR spectrum of the compound CH_2 protons of the triazine ring resonated a pair of doublets of doublets 3.42-3.58ppm,3.80-3.96ppm.

The mass spectra and elemental analysis of compound are also in agreement with their molecular formula

Antimicrobial Activity

For the testing antimicrobial activity various microorganism were used for the study. The brothdilution on method was used for this study. The antimicrobial activity of all the compounds was studies at 1000 ppm concentration *in vitro*.Thedifferent types of microorganism used were some gram negative bacteria [*Salmonella typhimurium, Vibrio parahaemolyticus*], gram positive bacteria *Micrococcus luteusStaphylococcus aureus*],fungus -*Aspergillusniger*

Table3 Antimicrobial Activity of some trisubstituted –s-triazine

	96	106	439	3615	111	451	840	1251
1a	10	18	05	0	18	22	10	10
1b	05	10	0	10	05	08	0	10
1c	18	22	10	0	11	15	10	0
2a	12	25	10	10	18	0	0	10
2b	10	10	0	0	10	0	10	05
2c	10	20	12	0	18	22	10	22
Standard drug chloramphenicol (25μg/ml)	19	26	15	0	21	23	24	26

BACTERIA: Gram positive: *Staphylococcus aureus*(MTCC 96), *Micrococcus luteus*(MTCC 106), *Enterococcus faecalis*(MTCC 439), *Staphylococcus epidermis* (MTCC 3615), Gram negative: *Enterobacteraerogens* (MTCC 111*), Vibrio parahaemolyticus*(MTCC 451), *Yersiniaenterocolitica*(MTCC 840), *Salmonella typhimurium*(MTCC 1251)

Antifungal activity

	BC	EF	F_2	F_4	F_5	F_6
1a	11	10	10	12	12	11
1b	0	15	12	13	17	11
1c	14	14	16	11	18	12
2a	10	0	0	12	11	12
2b	0	05	10	10	0	17
2c	11	0	11	0	10	10
Standard drugNystatin(25μ/gml)	23	19	16	0	10	0

FUNGAL: BC- *Botrytis cinerea*, EF- *Epidermophytonfloccosum*, F2-*Trichophytonmentagrophytes*(66/01), F4-*Scopulariopsissp*(101/01), F5-*Aspergillusniger*(MTCC1344), F6-*Curvularialunata*(46)

CONCLUSION

In conclusion we have successfully synthesised a new series of s-triazinederivativesand moreover some of compound contains bio active heterocyclic moiety. Interestingly showed most of them good anti bacterial and antifungal activity. Among the compound 1a,1c,2c were showed good inhibition towards all 8 bacteria tested. Compounds1b,2a,2b, show moderate to low active against all the strains tested. Compounds which showed low activity where tested for higher concentration All the higher concentration synthesized compounds showed moderate activity. Naphthol, vaniline , P.Nitroaniline substituent showed good activity in all the strain tested.

The antimicrobial screening suggests that all the newly synthesised compounds showed to moderate to good activity against the tested organism.

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