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Synthesis, structural elucidation and anti-microbial screening of quinoline based s-triazinyl substituted aryl amine derivatives

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ABSTRACT

A series of ten 2,4,6-trisubstituted s-triazines was synthesized with 4-Hydoxy benzonitrile, benzimidazole and different substituted arylamine derivatives and all the products were characterized by conventional and instrumental methods. The title compound was then examined for their in vitro microbial activity against gram negative bacteria and gram positive bacteria and two fungal species. Structure of final compound was affirmed by IR,[1]H NMR, Mass Spectra and followed by elemental analysis.

Keywords:2,4,6-trichloro-1,3,5-triazine,8-hydroxyquinoline,4-hydroxy benzonitrile, substituted aryl amine,anti microbial activity.

INTRODUCTION

During the last few years, the potential of s-triazinederivatives in agrochemical and medicinal properties have been subjected to investigation. Literature survey reveals that substituted s-triazinederivatives are associated with a number of pronounced biological activities [1-4].

s-Triazineis a six-membered heterocyclic ring, with three nitrogenssituated at 1st, 3rd and 5th positions. Its analoguesmelamine, cyanuricacid and cyanuricchloride are important starting compounds for various materials with wide range of applications in textile, plastic, pharmaceuticaland rubber industries. These compounds are also used as pesticides, dyestuffs, optical bleaches, explosives and surface active agents [5-7].

s-Triazinering is an important pharmacophoreand its coupling with other rings could furnish new biologically active compounds. These derivatives exhibit various types of biological propertiessuch as anti HIV, anti tuberculosis, anticancer, antimycobacterial, antifungal, and antibacterial [8-11] .

MATERIALS AND METHODS

All melting points were determined using open capillary tubes on electronic apparatus and were uncorrected. The IR spectra (4000-400 cm^{-1}) of synthesized compounds were recorded on Shimadzu 8400-s FTIR spectrometer with KBrpellets.To monitor the reactions, establish the identity, purity of reactants and products, thin layer chromatography was performed on TLC coated with silica gel using appropriate mobile phase system and spots were visualized under UV radiation.

Nuclear magnetic resonance spectra was recorded using Bruker400 MHz model spectrometer using DMSO as a solvent and TMS as internal standard (Chemical shifts in δ ppm). All new compounds were subjected to elemental analysis and the results obtained were in acceptable range.

General Experiment

Step -1

To a stirred solution of cyanuricchloride (0.1mole) in acetone (100ml) at 0-5°C, the solution of 4-hydroxy Benzonitrile(0.1mole) in acetone (90ml) was added drop wise in two hours. During the reaction 10%$NaHCO_3$was added to maintain the reaction mixture neutral. The progress of reaction was monitored by TLC using actone:toluene (2:8) as eluent. After the completion of the reaction, the stirring was stopped and the solution was treated with crushed ice. The product obtained was filtered and dried. The crudeproduct was purified and recrystalizedfrom alcohol. The yield was 85% having melting point 255 $^{\circ}$C and FTIR (KBr) 2223 cm^{-1}.

Step -2

To a stirred solution of 4-[(4,6-dichloro-1,3,5-triazin-2-yl)oxy]benzonitrile(1) in acetone at room temperature, the solution of 8-hydroxy quinolone in acetone was slowly added in two hours and the temperature was raised to 45^{0}C during two hours with addition of10% solution of $NaHCO_3$to maintain the reaction mixture neutral and further maintained for two hours. The progress of reaction was monitored by TLC using Acetone :Toulene (2 : 8)aseluent. After completion of reaction the solution was poured into ice cold water and the solid product which was obtained after filtration was dried and recrystallized from absolute alcohol to give the title compound which having 75% of yield, melting point 266°C and FTIR (KBr) 2223 Cm^{-},1255Cm^{-}(C-O-C).

Step 3

To a solution of 4-{[4-chloro-6-(quinoline-4-yl)-1,3,5-triazin-2-yl]oxy}benzonitrile(0.01 mol in 1,4-Dioxane 20 ml)appropriate different substituted aryl amines derivatives were added and the reaction mixture was refluxed for 6-10 hours. 10% $NaHCO_3$was used for neutralization of the reaction mixture. After the completion of reaction the solution was treated with crushed ice and neutralized by dil. HCl, the precipitate thus obtained were dried and recrystallized form absolute alcohol and yield was 75% the product had m.p.185-189°C.

Spectral Analysis of 4-({4-[(4-methylphenyl)amino]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl}oxy)benzonitrile. **IR**3414(KBr,cm^{-1}): (-NH),2918(C-H),2220-2225(CN),1259(C-O-C),1475(-CH_2),814(S-triazine C-N str.); **^{1}H NMR** (400 MHz,DMSO-d_6)- δ 8.91-7.90(1H,d,quinoline), 2.50 (3H,s,-CH_3), 6.71-6.87 (4H,m,Ar-H),7.48-7.23(4H,m,Ar-H),7.62-7.50(4H,m,Ar-H),7.70-7.64(2H,m,Ar-H),9.55(1H,s,-NH),**Mass Spectra**-(m/z) ;415.59 (M+2).

Spectral Analysis of 4-({4-[(4-fluorophenyl)amino]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl}oxy)benzonitrile. **IR**3420(KBr,cm^{-1}): (-NH),2818(C-H),2220-2245(CN),1241(C-O-C),1435(-CH_2),816(S-triazine C-N str.), 1015-1400(C-F); **^{1}H NMR** (400 MHz,DMSO-d_6)- δ 8.81-7.70(1H,d,quinoline),6.81-6.87 (4H,m,Ar-H),7.48-7.23(4H,m,Ar-H),7.66-7.50(4H,m,Ar-H),7.77-7.63(2H,m,Ar-H),9.55(1H,s,-NH),**MassSpectra**-(m/z) ;432.04(M+2).

Spectral Analysis of 4-({4-[(4-chlorophenyl)amino]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl}oxy)benzonitrile**IR** 3316 (KBr,cm^{-1}): (-NH),2866(C-H),2220-2225(CN),1239(C-O-C),1470(-CH_2),806(S-triazine C-N str.),611-800(C-Cl); **^{1}H NMR** (400 MHz,DMSO-d_6)- δ 8.90-7.90(1H,d,quinoline), 6.69-6.88 (4H,m,Ar-H),7.44-7.26(4H,m,Ar-H),7.65-7.51(4H,m,Ar-H),7.71-7.66(2H,m,Ar-H),9.85(1H,s,-NH),**Mass Spectra**-(m/z) ;446.98 (M+2).

Spectral Analysis of of 4-({4-[(4-nitrophenyl)amino]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl}oxy)benzonitrile **IR** 3488 (KBr,cm^{-1}): (-NH),1545-1620(-NO_2),2980(C-H),2218-22(CN),1247(C-O-C),1473(-CH_2),823(S-triazine C-N str.); **^{1}H NMR** (400 MHz,DMSO-d_6)- δ 8.91-7.90(1H,d,quinoline), 2.50 (3H,s,-CH_3), 6.71-6.87 (4H,m,Ar-H),7.48-7.23(4H,m,Ar-H),7.62-7.50(4H,m,Ar-H),7.70-7.64(2H,m,Ar-H),9.55(1H,s,-NH),**Mass Spectra**-(m/z) ;457.77 (M+2).

Spectral Analysis of of 4-({4-[(4-methoxyphenyl)amino]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl}oxy)benzonitrile **IR** 3436 (KBr,cm^{-1}): (-NH),2814 (C-H),2220-2228(CN),1239(C-O-C),1468(-CH_2),808(S-triazine C-N str.), 1082-1150(C-O); **^{1}H NMR** (400 MHz,DMSO-d_6)- δ 8.91-7.90(1H,d,quinoline), 3.55 (3H,s,-CH_3), 6.68-6.86 (4H,m,Ar-H),7.38-7.33(4H,m,Ar-H),7.64-7.55(4H,m,Ar-H),7.71-7.65(2H,m,Ar-H),9.57(1H,s,-NH),**Mass Spectra**-(m/z) ;443.81 (M+2).

Spectral Analysis of 4-({4-[(3-chloro-4-fluorophenyl)amino]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl}oxy)benzonitrile**IR** 3452 (KBr,cm^{-1}): (-NH),2912(C-H),2220-2230(CN),1250(C-O-C),1471(-CH_2),812(S-triazine C-N str.), 1026-1400(C-F),623-800(C-Cl); **^{1}H NMR** (400 MHz,DMSO-d_6)- δ 8.91-7.90(1H,d,quinoline), 2.50

(3H,s,-CH_3), 6.71-6.87 (4H,m,Ar-H),7.48-7.23(4H,m,Ar-H),7.62-7.50(4H,m,Ar-H),7.70-7.64(2H,m,Ar-H),9.55(1H,s,-NH),**Mass Spectra**-(m/z) ;465.87 (M+2).

Spectral Analysis of 4-({4-[(3-chlorophenyl)amino]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl}oxy)benzonitrile**IR** 3396 (KBr,cm^{-1}): (-NH),2822(C-H),2226-2238(CN),1254(C-O-C),1485(-CH_2),810(S-triazine C-N str.), 619-800(C-Cl); **^{1}H NMR** (400 MHz,DMSO-d_6)- δ 8.91-7.90(1H,d,quinoline), 2.50 (3H,s,-CH_3), 6.71-6.87 (4H,m,Ar-H),7.48-7.23(4H,m,Ar-H),7.62-7.50(4H,m,Ar-H),7.70-7.64(2H,m,Ar-H),9.85(1H,s,-NH),**Mass Spectra**-(m/z) ;446.83 (M+2).

Spectral Analysis of 4-({4-[(3-methylphenyl)amino]-6-(quinolin-4-yloxy)-1,3,5-triazin-2-yl}oxy)benzonitrile **IR**3448 (KBr,cm^{-1}): (-NH),2978(C-H),2219-2235(CN),1259(C-O-C),1489(-CH_2),818(S-triazine C-N str.); **^{1}H NMR** (400 MHz,DMSO-d_6)- δ 8.88-7.90(1H,d,quinoline), 2.40 (3H,s,-CH_3), 6.61-6.88 (4H,m,Ar-H),7.45-7.23(4H,m,Ar-H),7.62-7.50(4H,m,Ar-H),7.70-7.64(2H,m,Ar-H),9.55(1H,s,-NH),**Mass Spectra**-(m/z) ;428.06 (M+2).

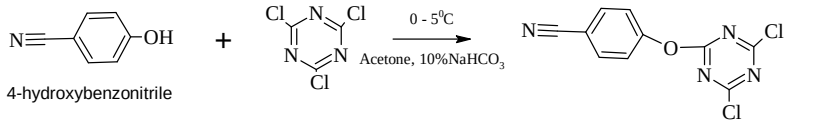
Spectral Analysis of 4-({4-[(3-bromophenyl)amino]-6-(quinolin-4-yloxy)-1,3,5-triazin-2-yl}oxy)benzonitrile **IR** 3380 (KBr,cm^{-1}): (-NH),2944(C-H),2241-2225(CN),1255(C-O-C),1477(-CH_2),809(S-triazine C-N str.), 512-600(C-Br); **^{1}H NMR** (400 MHz,DMSO-d_6)- δ 8.87-7.91(1H,d,quinoline), 6.69-6.89 (4H,m,Ar-H),7.47-7.25(4H,m,Ar-H),7.64-7.52(4H,m,Ar-H),7.35-7.45(2H,m,Ar-H),9.75(1H,s,-NH),**Mass Spectra**-(m/z) ;492.01 (M+2).

Spectral Analysis of of 4-({4-[(4-dimethylaminophenyl)amino]-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl}oxy)benzonitrile **IR** 3424 (KBr,cm^{-1}): (-NH),2908(C-H),2220-2233(CN),1255(C-O-C),1470(-CH_2),806(S-triazine C-N str.); **^{1}H NMR**(400 MHz,DMSO-d_6)- δ 8.91-7.90(1H,d,quinoline), 2.50 (3H,s,-CH_3), 6.71-6.87 (4H,m,Ar-H),7.48-7.23(4H,m,Ar-H),7.62-7.50(4H,m,Ar-H),7.70-7.64(2H,m,Ar-H),9.75(1H,s,-NH),**Mass Spectra**-(m/z) ;465.18 (M+2)

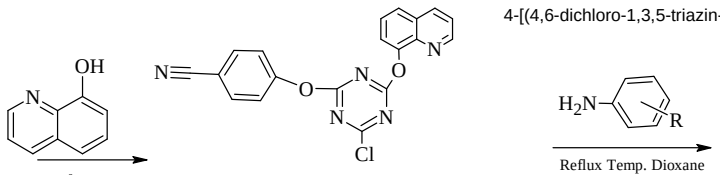
Spectral Analysis of 4-{[4-(phenylamino)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]oxy}benzonitrile **IR** 3455 (KBr,cm^{-1}): (-NH),29225(C-H),2218-2230(CN),1244(C-O-C),1469(-CH_2),814(S-triazine C-N str.); **^{1}H NMR**(400 MHz,DMSO-d_6)- δ 8.81-7.88(1H,d,quinoline), 6.70-6.85 (4H,m,Ar-H),7.48-7.23(4H,m,Ar-H),7.62-7.50(4H,m,Ar-H),7.70-7.64(2H,m,Ar-H),9.55(1H,s,-NH),**Mass Spectra**-(m/z) ;411.64 (M+2).

4-[4-(4-Methylamino-phenylamino)-6-(quinolin-8-yloxy)-[1,3,5]triazin-2-yloxy]-benzonitrile**IR** 3455 (KBr,cm^{-1}): (-NH),2860(C-H),2218-2237(CN),1245(C-O-C),1465(-CH_2),815(S-triazine C-N str.); **^{1}H NMR** (400 MHz,DMSO-d_6)- δ 8.81-7.87(1H,d,quinoline), 3.55 (3H,s,-CH_3), 6.78-6.88 (4H,m,Ar-H),7.44-7.33(4H,m,Ar-H),7.66-7.72(4H,m,Ar-H),7.74-7.64(2H,m,Ar-H),9.79(1H,s,-NH),**Mass Spectra**-(m/z) ;441.96 (M+2)

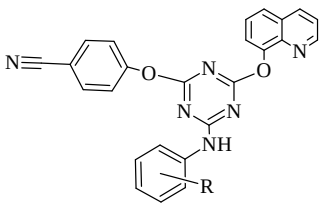
Reaction scheme



4-[(4,6-dichloro-1,3,5-triazin-2-yl)oxy]benzonitrile



4-{[4-chloro-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]oxy}benzonitrile



4-{[4-(arylamino)-6-(quinolin-8-yloxy)-1,3,5-triazin-2-yl]oxy}benzonitrile

Table-1: Various amines

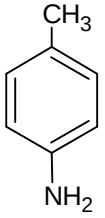
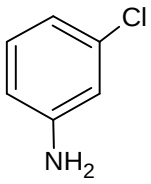
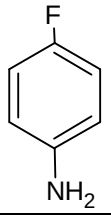
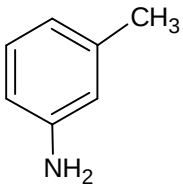
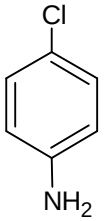
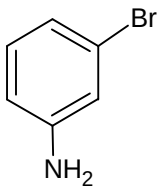
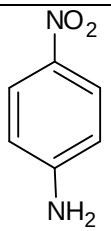
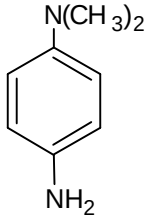
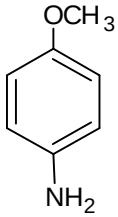
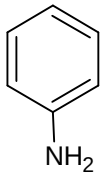
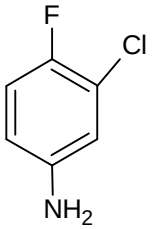
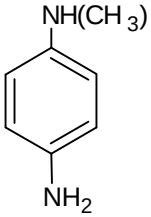
Code	Various Amines	Code	Various Amines
B1		**B7**	
B2		**B8**	
B3		**B9**	
B4		**B10**	
B5		**B11**	
B6		**B12**	

Table- 2 :Physical data of the synthesized compounds

Sr. No.	Compound	Molecular Formula	M.W.	M.P. (^{0}C)	R_f Value	% Yield	% of Carbon Calc. (Found)	% of Hydrogen Calc. (Found)	% of Nitrogen Calc. (Found)
1	JM-B1	$C_{26}H_{18}N_6O_2$	446	145-150	0.58	77	69.95 (69.77)	4.06 (4.03)	18.82 (18.06)
2	JM-B2	$C_{25}H_{15}FN_6O_2$	450	112-117	0.51	65	66.66 (66.16)	3.36 (3.29)	18.66 (18.11)
3	JM-B3	$C_{25}H_{15}ClN_6O_2$	466	91-95	0.45	80	64.31 (64.22)	3.24 (3.11)	18.00 (17.23)
4	JM-B4	$C_{25}H_{15}N_7O_4$	477	138-142	0.66	82	62.89 (62.18)	3.17 (3.08)	20.24 (20.16)
5	JM-B5	$C_{26}H_{28}N_6O_3$	462	130-133	0.55	69	67.53 (67.37)	3.92 (3.45)	18.17 (18.14)
6	JM-B6	$C_{25}H_{14}ClFN_6O_2$	484	128-130	0.38	87	61.93 (61.26)	2.91 (2.12)	17.33 (17.59)
7	JM-B7	$C_{25}H_{15}ClN_6O_2$	466	88-95	0.44	78	64.31 (64.11)	3.24 (3.02)	18.00 (17.04)
8	JM-B8	$C_{26}H_{18}N_6O_2$	446	110-115	0.54	79	69.95 (69.29)	4.06 (4.11)	18.82 (18.55)
9	JM-B9	$C_{25}H_{15}BrN_6O_2$	511	140-143	0.64	84	58.72 (58.70)	2.96 (2.72)	16.44 (16.43)
10	JM-B10	$C_{27}H_{32}N_7O_2$	475	138-140	0.53	72	68.20 (68.12)	4.45 (4.41)	20.62 (20.45)
11	JM-B11	$C_{25}H_{16}N_6O_2$	432	150-156	0.58	79	69.44 (69.11)	3.73 (3.77)	19.43 (19.37)
12	JM-B12	$C_{216}H_{19}N_7O_2$	461	148-152	0.42	65	67.67 (67.44)	4.15 (4.09)	21.25 (21.28)

RESULTS AND DISCUSSION

Results were obtained by reacting 4-hydroxy benzonitrile with cyanuricchloride in first step, in second step compound were reacted with morpholineand in third step various amine were attached with 4-{[4-chloro-6-(morpholin-4-yl)-1,3,5-triazin-2-yl]oxy}benzonitrile. The IR spectra of the compound showed absorption band at 2220-2225 cm^{-1}which proves the presence of –CN group, absorption band at 3400cm^{-1} proves the –NH stretching, 1255cm^{-1}(C-O-C stretching),1475(-CH_2stretching),806(S-triazine C-N stretching). The ^{1}H NMR of the compound 6(a-j) showed characteristic signal at δ3.34-3.70 (8H,m,morpholine), 2.50 (3H,s,-CH_3), 6.71-6.87 (2H,d,Ar-H),7.28-7.43(2H,d,Ar-H),7.92(2H,d,Ar-H),9.55(1H,s,-NH)The mass spectrum was obtained at base peak m/z 415.59.

Table-3: Antibacterial activity of synthesized compounds

Sr. No.	Code No.	Minimum Inhibitory Concentration(µg/ml)			
		Gram Positive Bacteria		Gram Negative Bacteria	
		Bacillus Pumilus MTCC-9584	*Bacillus Cereus MTCC-9762*	*Proteus Mirabilis MTCC-9242*	*Escherichia Coli MTCC-600*
1	JM-B1	500	250	500	1000
2	JM-B2	500	500	250	1000
3	JM-B3	500	1000	500	500
4	JM-B4	250	125	500	500
5	JM-B5	1000	500	500	1000>
6	JM-B6	125	500	250	1000
7	JM-B7	1000	1000	1000	1000>
8	JM-B8	1000	250	1000	500
9	JM-B9	250	1000>	500	1000>
10	JM-B10	1000>	1000	1000>	1000
11	JM-B11	1000	1000>	1000	1000>
12	JM-B12	1000>	1000	1000	1000
13	Ciprofloxacin	62.5	62.5	62.5	62.5
14	Erythromycin	125	62.5	125	125

The compound were tested using agar cup method for antimicrobial and anti fungal activity using fungal and bacterial species listed in below tables respectively. The table shows the anti microbialactivity against gram positive, gram negative bacteria and fungi. Comparison of antimicrobial activity produced by compounds with that of standard antimicrobial drug reveals that the produced compounds shows moderate to good activity against all species of bacterial and fungal strains under study.

Table-4: Antifungal activity of the synthesized compounds

		Minimum Inhibitory Concentration(µg/ml)		
		Fungus		
Sr.No.	Code No.	*Saccharomyces Cerevisiae MTCC-2928*	*Aspergilus Flavus MTCC-2206*	*Trycoderma Viride MTCC-2150*
1	JM-B1	500	1000	1000
2	JM-B2	1000>	500	1000>
3	JM-B3	1000	1000	1000
4	JM-B4	500	500	500
5	JM-B5	1000	500	500
6	JM-B6	500	1000	1000
7	JM-B7	1000	1000	1000
8	JM-B8	500	1000>	1000>
9	JM-B9	1000>	1000>	1000>
10	JM-B10	500	1000	1000
11	JM-B11	1000>	1000>	1000>
12	JM-B12	1000	1000	1000>
13	Amphotericin B	125	125	250

CONCLUSION

A series of 12 compound of s-triazinederivatives was synthesized and the structure of the compounds were well supported by the IR, ^{1}H NMR, and mass spectra. The anti bacterialand Anti fungalactivity of the compounds werestudied, which shows that the compounds had well to moderate activity against bacteria and fungi.

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