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Synthesis and Study of Biological Active S-triazines

Noosrat Kortiwala, Jitesh Patel, Vikas Desai*

Department of Chemistry, B.K.M. Science College, Valsad-396001, Gujarat, India

ABSTRACT

Some novel s-triazines were synthesized in laboratory by substituting the cyanuric choloride, with 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol, aryl flouro amines, aryl ureas and aryl amines, The structure of synthesized s-triazines was determined by IR and NMR spectra. The synthesized compounds showed potential biological activity against the bacterial strains, out of which compounds 6-2b, 6-7b and 6-10b showed good activity against E. coli and 6-8b against Klebsiella pneumoniae and 6-4b against Staphylococcus auerus whereas 6-2b, 6-4b and 6-7b are most active against Aspergillus clavatus and Aspergillus niger and 6-1b, 6-8b and 6-9b are most active against Candida albicans fungal strains

Keywords: S-triazines, Cyanuric chloride, Synthesis, Biological activities, Bacterial, Fungal

INTRODUCTION

There is a worldwide research for development of antibacterial drugs to overcome the need of new drugs that can fight bacterial resistance and bring cure to varied diseases occurring in a human body. In this regard, chemists all over the world have been finding innovative ways to synthesize novel heterocyclic drugs of significant importance. The research as described in this paper is relating to the synthesis and biological evaluation of new s-triazines with varied combinations and improved activities.

Triazines are prepared from cyanuric acid by trimerization (1,3,5-triazine). Triazines are weak base. Triazines have much weaker resonance energy than benzene, so nucleophilic substitution is preferred than electrophilic substitution. 1,3,5-Triazine is stable crystalline substance which on prolonged heating can break the ring with acid or by heating with alcohol and ammonium chloride. Thiourea as a substituent in triazines is found to be of interesting pharmacological beneficial combination. Over the last few years, the thiourea moiety has been of interest to design molecules as receptor antagonists, as natural product mimics or as synthetic intermediates to amidines or guanidines [1]. Thiourea not only confers antibacterial, antitubercular or antileprotic activity, but has also been reported to possess antifungal as well as antiviral properties [2]. The s-triazine derivatives have now far shown good antibacterial [3], antitumor, anti-TB, anti-HIV [4], antimicrobial [5-7], anticonvulsant [8], antimalarial [9] and antihypertensive [10].

MATERIALS AND METHODS

All the chemicals used for synthesis were of analytical grade. Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by Thin Layer Chromatography (TLC) that was performed on E-Merck pre-coated 60 F254 plates and the spots were rendered visible by exposing to short UV light and iodine. The Infra-Red (IR) spectra were, recorded on a Fourier Transform Infrared (FTIR) spectrophotometer at Shimadzu, Model: FTIR-8400S With DRS. Proton-Nuclear Magnetic Resonance (^{1}H-NMR) spectra of the compounds were recorded with Bruker NMR spectrometer 400 MHz spectrometer using Dimethyl Sulfoxide (DMSO) as a solvent and Tetramethylsilane (TMS) as an internal reference.

General procedure for preparation of 4,6-dichloro-N-(substituted phenyl)-1,3,5-triazin-2-amine

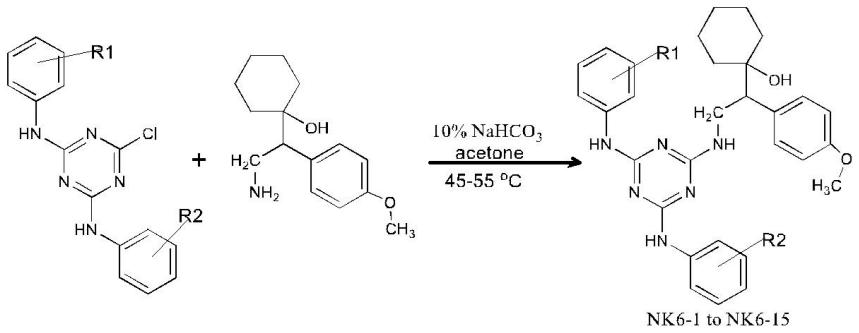
To a stirred solution of cyanuric chloride (0.1 M) in acetone at 0-5°C, the solution of substituted primary amine was added (1 M) in acetone and pH was maintained neutral by the addition of 10% sodium carbonate solution (0.1 M). The stirring was continued at 0-5°C for 2 h. After the completion of reaction the stirring was stopped and the solution was treated with crushed ice. The solid product obtained was filtered and dried. The crude product was purified by crystallization from absolute alcohol to get the title compound.

General procedure for preparation of 6-chloro-N2-(Substituted phenyl)-N4-(Substituted phenyl)-1,3,5-triazine-2,4-diamine

The solution of substituted aryl ureas (or substituted fluoro amines) (0.1 M) in acetone (50 ml) was added drop wise to well-stirred slurry of 4,6-dichloro-N-(substituted phenyl)-1,3,5-triazin-2-amine (0.1 M) in acetone (90.00 ml), maintaining the temperature 45°C. The pH was adjusted neutral by the addition of 10% $NaHCO_3$ solution (0.1 ml). The temperature was maintained to room temperature for around 6 h. After the completion of reaction, the solution was poured in ice-cold water. The solid product obtained was filtered and dried. The crude product was purified by re-crystallization from absolute alcohol to get the title compound.

General procedure for preparation of 1-(2-(4-(2-substituted phenyl)-6-(2-substituted phenyl)-1,3,5-triazin-2-ylamino)-1-(4-methoxyphenyl) ethyl)cyclohexanol

A mixture of 6-chloro-N2-(Substituted phenyl)-N4-(Substituted phenyl)-1,3,5-triazine-2,4-diamine (0.005 M) and 1-[2-amino-1-(4-ethoxyphenyl)ethyl]cyclohexanol (0.005 M) with in acetone (50.00 ml.) was refluxed on a heating mantle with continuous stirring at 50-60°C for 4-6 h. The pH was adjusted neutral by the addition of 10% $NaHCO_3$ solution (0.005 M). After the completion of reaction, the content was added to cold-water. The pH of solution was maintained neutral. The product obtained (NK6-1 to NK6-10) was purified by re-crystallization from chloroform (Table 1).



Scheme 1: s-triazines derivatives

Table 1: Characterization data of compounds Nk6-1 to NK6-10

S. No.	R1=	R2=	Molecular formula Molecular weight (g/mol)	Yield %	Melting point (°C)	Elemental analysis		
						%C Calculation (Found)	%H Calculation (Found)	%N Calculation (Found)
NK6-1	2,3-F	4-NO2	$C_{30}H_{31}F_2N_7O_4$	90	118-122	60.99	5.28	16.57
			591.61			(60.95)	(5.20)	(16.52)
NK6-2	2,4,6-F-5-Br	4-Cl	$C_{30}H_{29}BrClF_3N_6O_2$	88	166-169	53.14	4.31	12.39
			677.94			(53.10)	(4.29)	(12.36)
NK6-3	2-F	2,4-NO2	$C_{30}H_{31}FN_8O_6$	81	113-115	58.24	5.05	18.11
			618.61			(58.20)	(5.00)	(18.05)
NK6-4	3,4-F	4-Cl	$C_{30}H_{31}ClF_2N_6O_2$	75	132-134	62.00	5.37	14.46
			581.05			(61.96)	(5.35)	(14.40)
NK6-5	3,4-F	4-CH3	$C_{31}H_{34}F_2N_6O_2$	95	105-108	66.41	6.11	14.99
			560.63			(66.39)	(6.08)	(14.97)
NK6-6	2,5-F	3,4-Cl	$C_{30}H_{30}Cl_2F_2N_6O_2$	86	128-130	58.53	4.91	13.65
			615.50			(58.50)	(4.89)	(13.60)
NK6-7	2,5-F	3,4-Cl	$C_{30}H_{30}Cl_2F_2N_6O_2$	73	141-143	58.53	4.91	13.65
			615.50			(58.51)	(4.88)	(13.62)
NK6-8	3,4-F	2-CH3	$C_{31}H_{34}F_2N_6O_2$	80	111-115	66.41	6.11	14.99
			560.63			(66.40)	(6.09)	(14.95)
NK6-9	1(4-methyl phenyl) urea	2-Cl	$C_{32}H_{36}ClN_7O_3$	85	136-138	63.82	6.02	16.28
			602.12			(63.80)	(6.00)	(16.24)
NK6-10	1(4-methoxy phenyl) urea	2,3-Cl	$C_{32}H_{35}Cl_2N_7O_4$	89	102-104	58.89	5.40	15.02
			652.57			(58.87)	(5.38)	(15.00)
NK6-11	2-F	2,3-Cl	$C_{30}H_{31}Cl_2FN_6O_2$	84	144-146	60.30	5.22	14.06
			597.50			(60.28)	(5.20)	(14.01)
NK6-12	1(4-methylphenyl) urea	4-CH3	$C_{33}H_{39}N_7O_3$	77	152-154	68.13	6.75	16.85
			581.70			(68.10)	(6.72)	(16.83)
NK6-13	1(4-methyl phenyl)urea	2-CH3	$C_{33}H_{39}N_7O_4$	90	163-165	66.30	6.57	16.40
			597.70			(66.28)	(6.55)	(16.37)
NK6-14	1(4-methyl phenyl) urea	3,4-Cl	$C_{32}H_{35}Cl_2N_7O_3$	91	109-112	60.37	5.54	15.40
			636.57			(60.34)	(5.50)	(15.38)
NK6-15	2-F	2-Cl	$C_{30}H_{30}Cl_2F_2N_6O_2$	83	151-153	63.98	6.82	14.92
			563.06			(63.96)	(6.80)	(14.90)

Antimicrobial activity

All synthesized compounds were evaluated for antibacterial test procedure. All necessary controls like drug control, vehicle control, agar control, organism control and known antibacterial drugs control were used. All Microbial Type Culture Collection (MTCC) and gene bank cultures were tested against synthesized compounds and reference drugs. Mueller Hinton Broth was used as nutrient medium to grow and dilute the drug suspension for the test bacteria and Sabouraud dextrose broth was used for fungal nutrition. Inoculums size for test strain was adjusted to 108 Colony Forming Unit (CFU) per milliliter for bacteria and 106 for fungus, by comparing the turbidity. DMSO was used as diluent vehicle to get desired concentration of compounds and reference drugs to test against standard bacterial strains.

Antibacterial activities were screened against gram positive and Gram-negative bacterias. Antifungal activities were screened against *Candida albicans, Aspergillus niger* and *Aspergillus clavatus* (Table 2).

Table 2: Antimicrobial data of compounds NK6-1 to NK6-10

Compound No.	Antibacterial activity (Minimal inhibition concentration)				Antifungal activity (Minimal fungicidal concentration)		
	Gram-negative		Gram-positive				
	Escheriea coli **MTCC 443**	***Klebsiella pneumoniae*** **MTCC 109**	***Staphylococcus aureus*** **MTCC 96**	***Streptococcus pyogenes*** **MTCC 442**	***Candida albicans*** **MTCC 227**	***Aspergillus niger*** **MTCC 282**	***Aspergillus clavatus*** **MTCC 1323**
NK6-1	100	100	125	100	250	500	500
NK6-2	62.5	100	125	200	500	250	250
NK6-3	200	125	100	125	1000	500	500
NK6-4	100	200	62.5	125	500	250	250
NK6-5	125	100	100	200	500	500	1000
NK6-6	200	100	125	200	500	500	500
NK6-7	62.5	200	200	250	1000	250	250
NK6-8	125	62.5	125	100	250	250	500
NK6-9	200	100	100	125	250	500	500
NK6-10	62.5	100	100	200	1000	500	1000
Standard drugs (µg/ml)							
Ampicillin	100	--	250	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	23	25	50	50	-	-	-
Nystatin	-	-	-	-	100	100	100
Griseofulvin	-	-	-	-	500	100	100

RESULTS AND DISCUSSION

Chemistry

The new s-triazines derivatives have been synthesized from cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) and different substituents. Cyanuric chloride is very weak base because of low basicity as well as the ring nitrogen atom. The replacement of a chlorine atom by substituted amino compounds in the cyanuric chloride by basic group is greatly facilitated by the ring nitrogen atom of the symmetrically built s-triazine nucleus. At 0°C cyanuric chloride is therefore already susceptible to alcoholysis and aminolysis as well as hydrolysis. All three chlorine are substituted by the nucleophiles selectively at different reaction temperatures. Generally, it is accepted that the first chlorine of cyanuric chloride is easily substituted by NH_2-group at 0-5°C, the second one at 40-50°C and the third one typically above 80°C, which depends on the activity of amine nucleophiles [11,12]. Considering a key factor here for s-triazine synthesis with different combinations, the nature of the reactive group and the order of entry of the group shall be considered. So, a less reactive amino was introduced before a more reactive one [13].

The s-triazines derivatives were synthesized as shown in Scheme 1 above. In first step of synthesis, 1st chlorine atom is replaced by substituted primary amine at 0-5°C, the second chlorine atom is replaced by substituted aryl ureas (or substituted fluoro amines) at temperature around 45°C and the 3rd chlorine atom is replaced by the complex 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol at 50-60°C. The compounds were tested for purity by TLC and elemental analysis. Spectral datas i.e., IR and NMR, of newly synthesized compounds were in accordance to the proposed molecules.

The s-triazines were confirmed by spectral datas corresponding to it. For the general IR spectra the range for an absorption band observed for Aromatic =CH str. was 3000-3003 cm^{-1}, C=C str. at 1576-1578 cm^{-1} and C-N str. at 1390-1395 cm^{-1}. For alkane C-H str. (asym.) the range observed was 2975-2979 cm^{-1}. For secondary amine, the range for N-H str. was found at 3340-3348 cm^{-1} and for N-H bending 1554-1555 cm^{-1}. The s-triazine nucleus with C-N str. and C=N str. had range in between 808-814 cm^{-1} and 1603-1610 cm^{-1} respectively.

The ^{1}H-NMR signals were found at range δ=3.73-3.77 (s, 3H, -OCH_3), δ=3.39-3.45 (s, 1H, -CH_2), δ=2.88-2.95 (s, 1H, -CH=), δ=6.77 (t, 1H, -F-CH), δ=6.75-8.29 (m, 13H, Ar-H & NH-), δ=9.41-9.54 (s, 2H, NH-, s-triazine), δ=9.06-9.08 (t, 1H, NH-CH_2, s-triazine), δ=1.10-1.67 (d, 2H, Ar-H).

Antimicrobial screening

All the synthesized novel compounds (NK6-1 to NK6-10) were screened for their antibacterial and antifungal activities against the corresponding bacterial strains i.e., *S. aureus, S. pyogenes, E. coli, K. pneumoniae* and fungal strains i.e., *A. niger, C. albicans* and *A. clavatus* (Table 2).

CONCLUSION

By support of the above achieved spectral data the synthesis of compounds NK6-1 to NK6-10 is confirmed. All the compounds are active against Gram-positive as well as Gram-negative bacterias especially more active against Gram-negative bacteria: *Escherichia coli* and fungi: *A. niger*. Among the synthesized compounds showing high activity are 6-2b, 6-7b and 6-10b against *E. coli* and 6-8b against *K. pneumoniae* and 6-4b against *S. auerus* here as compounds 6-1b and 6-5b showed good activity against gram negative organisms and compounds 6-3b and 6-9b showed good activity against gram positive organisms. Rest of compounds showed good to moderate activity. All the synthesized compounds have been screened against fungal strains *C. albicans*, *A. clavatus* and *A. niger*. Compounds 6-2b, 6-4b and 6-7b are most active against *A. clavatus* and *A. niger* and 6-1b, 6-8b and 6-9b are most active against *C. albicans* strains. Remaining compounds showed good to moderate activity.

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