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SYNTHESIS OF SOME NEW s-TRIAZINE DERIVATIVES AND EVALUATED FOR THEIR ANTIBACTERIAL ACTIVITY

C. K. Naik[*,1] and V. A. Desai[2]
[1]B. K. M. Science Colloge, Valsad-396001
[2]Veer Narmad South Gujarat University, Surat
E-mail: chiragmaster@yahoo.co.in

ABSTRACT

A new series of s-triazine derivatives, aryl amino s-triazine and aryl ureido s-triazine has been synthesized by the condensation of aryl amine and aryl ureido with 2- [4'- methyl - 6' - chloro -2*H*- chromen -2' -one-7'-oxy]-4-(3'-acetyl aminophenyl)-6-chloro s-triazine in acetone as a solvent and Potassium carbonate using as a neutralizing agent. The structures of all these compounds were confirmed on the basis of their analytical and spectral data[1]. The title compounds were characterized by IR, ^{1}H NMR and elemental analysis and screening for their antibacterial activity.

Keywords: s-Triazine, cyanuric chloride, and antibacterial activity.

INTRODUCTION

s-Triazine derivatives play a vital role in may biological processes and synthetic drugs. They also play a vital role owing to their wide range of pharmacological activities and industrial importance as novel fiber-reactive betaines for dyes and pigments[2]. We believe that some melamine derivatives will probably have potential antineoplastic and antibiotic action. Some s-triazine derivatives used as cation exchangers, reactive azo-dyes and as carrier for the preparation of immobilized enzymes. Literature survey revealed that various s-triazine have been known to exhibit a broad spectrum of biological activity. Certain s-Triazine derivatives have been found to possess a wide variety of biological activities viz, Antimycobacterial [3], anticancer[4,5], antitumour[6], and antiinflammatory[7] activities. In addition, many s-Triazine derivatives have been found to exhibit antiviral[8], antibacterial[9], diabetes[10] and herbicidal[11] activity.

EXPERIMENTAL

Melting points were taken in open capillary tubes and were uncorrected. IR spectra (KBr in cm^{-1}) were recorded on Shimadzu 8201 PC FTIR spectrophotometer. ^{1}H NMR spectrum was recorded using 300 MH_Z NMR Spectrophotometer and chemical shifts are reported in δ ppms relative to TMS as an internal standard in $CDCl_3$ Solvent. Purity of the compound was monitored by TLC (silica gel 60 F_{254} 1.05554.0007) and was visualized by UV light of 254 nm.

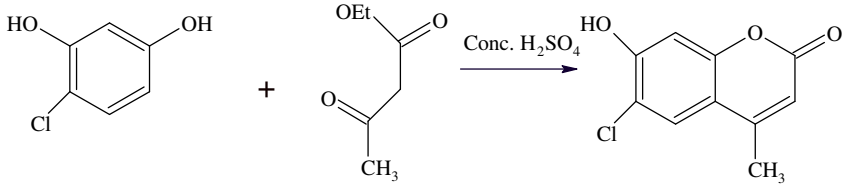
General Procedure

Synthesis of 7 - hydroxy - 6 - chloro - 4 - methyl -coumarin (III)

Take 100 ml 98% sulphuric acid and cool to 0°C. To that 10 gm of 4-chloro resorcinol dissolved in 12 ml ethyl acetoacetate was then added slowly at such a rate that the temperature of the reaction mixture did not rise above 10 °C, the mixture was stirred at room temperature over night. The homogeneous reaction mass was quenched in crushed ice and the solid obtained was filtered, washed with water till it was acid free. Material dried and crystallized in ethanol, yield equal to 76% with M.P. equal to 102 °C(Scheme-1).

2- [4'- methyl - 6' - chloro -2H- chromen -2' -one-7'-oxy] - 4 - (3' - acetyl aminophenyl) - 6 - chloro -s - triazine (VII)

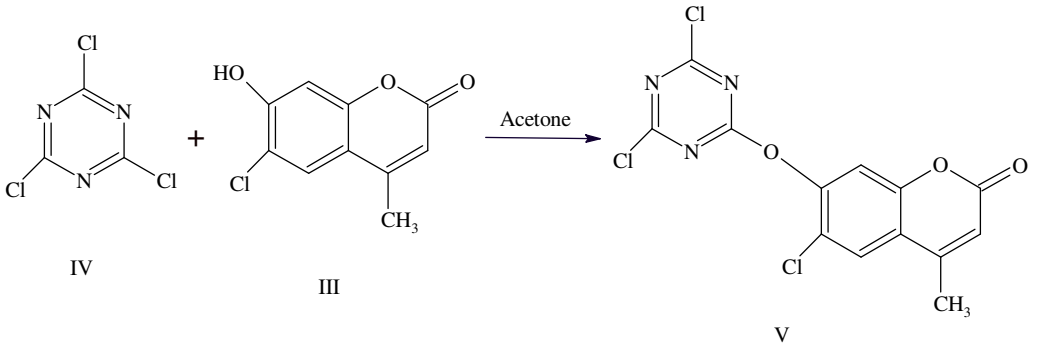
The above compound (III) was added slowly to the solution of 0.01 mol cyanuric chloride in 50 ml acetone with constant stirring with in 4 hours at 0°C, during the reaction proceed sodium carbonate solution was added to neutralize HCl evolved Reaction was monitored by TLC (ethyl alcohol 4 ml + Toluene 6ml). After completion of reaction, the reaction mass was quenched in crushed ice and the solid obtained was filtered, washed with water and crystallized in ethanol to get 2- [4'- methyl - 6' - chloro -2H- chromen -2' -one-7'-oxy] -4,6 - dichloro -s - triazine (VI) Yield 60% and MP: 130 °C.



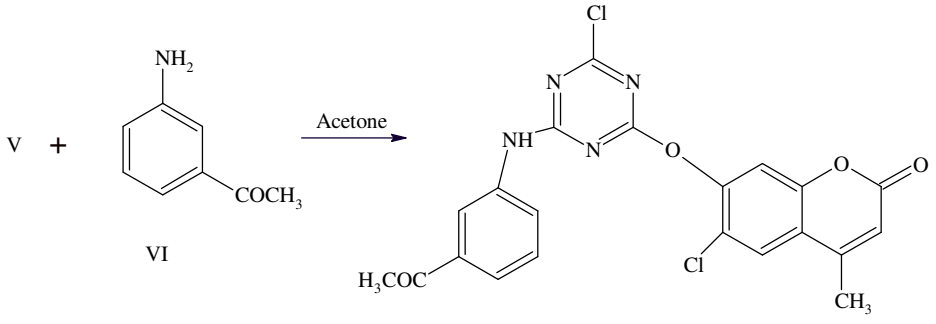
I II III

Scheme-1: Synthesis of 7 - hydroxy - 6 - chloro - 4 - methyl -coumarin (III)

0.01 mole 3-amino acetophenone was dissolved in 25 ml acetone, which was added slowly to 0.01 mole compound (VI) in 50 ml acetone at such a rate that the temperature of the reaction mixture did not rise above 28 °C and addition completed in 4 to 5 hours. During the reaction proceed sodium carbonate solution was added to neutralize HCl evolved (Scheme-2). Reaction was monitored by TLC (ethyl alcohol 4 ml + Toluene 6ml). After completion of reaction, the reaction mass was quenched in crushed ice and the solid obtained was filtered, washed with water and crystallized in ethanol to get 2- [4'- methyl - 6' - chloro -2*H*- chromen -2' -one-7'-oxy] - 4 - (3' - acetyl aminophenyl) - 6 - chloro -s - triazine (VIII) Yield 67% and MP: 141 °C.



IV III V



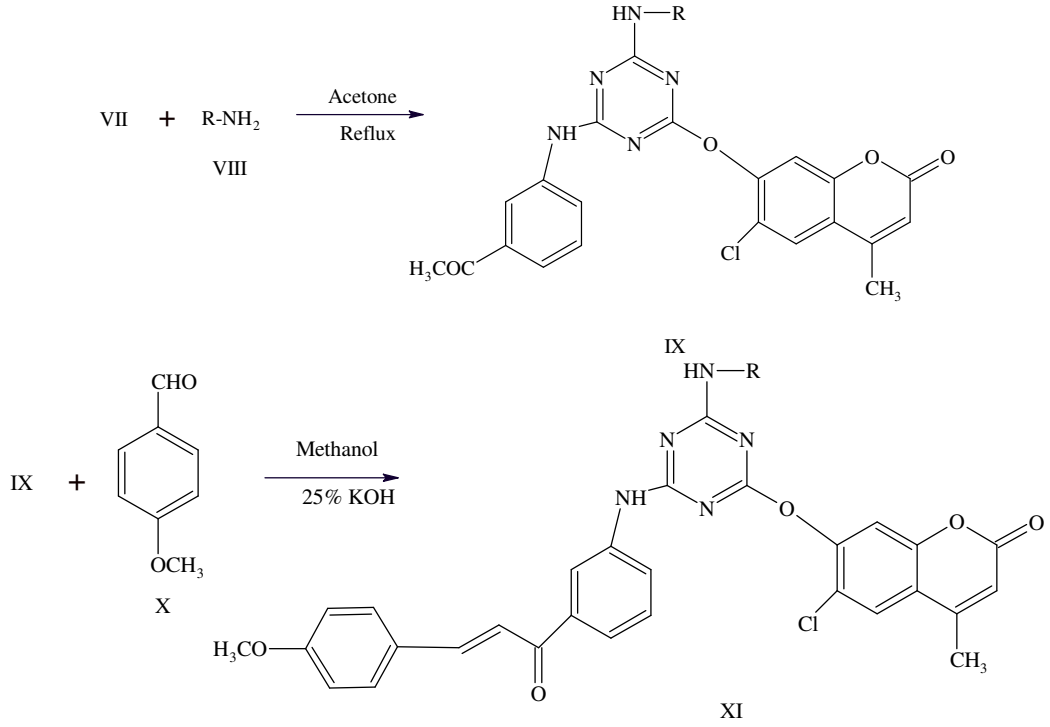
VI VII

Scheme-2: 2- [4'- methyl - 6' - chloro -2*H*- chromen -2' -one-7'-oxy] - 4 - (3' - acetyl aminophenyl) - 6 - chloro - s - triazine (VII)

2- [4'- methyl - 6' - chloro -2H- chromen -2' -one-7'-oxy]-4-[3'- {3'' (-4''' - methoxy phenyl) - 2'' - propane - 1''-one}] phenyl amino-6-arylamino-S-triazine (XI)

A mixture of 0.01 mole substituted amine and 0.01 mole compound (VIII) was reflux in 50 ml acetone. During the reaction proceed sodium carbonate solution was added to neutralize HCl evolved. Reaction was monitored by TLC (ethyl alcohol 4 ml + Toluene 6ml). After completion of reaction, the reaction mass was cool to room temperature and quenched in crushed ice and the solid obtained was filtered, washed with water and crystallized in alcohol to get 2- [4'- methyl - 6' - chloro -2*H*- chromen -2' -one-7-oxy]-4-(3'-acetyl aminophenyl)-6-arylamino-s-triazine (IX).

Above compound (IX) 0.01 mole dissolved in 50 ml methanol and 25 % KOH solution added to it. Then 4-methoxy benzaldehyde added under constant stirring at room temperature. After 24 hours the reaction mixture was poured into crushed ice and neutralize with HCl. The resulting product 2- [4'- methyl - 6' - chloro -2*H*- chromen -2' -one-7'-oxy]-4-[3'- {3'' (-4''' - methoxy phenyl) - 2'' - propane - 1''-one}] phenyl amino-6-arylamino-S-triazines (XI) separated out was filtered, washed with water and crystallized from alcohol.



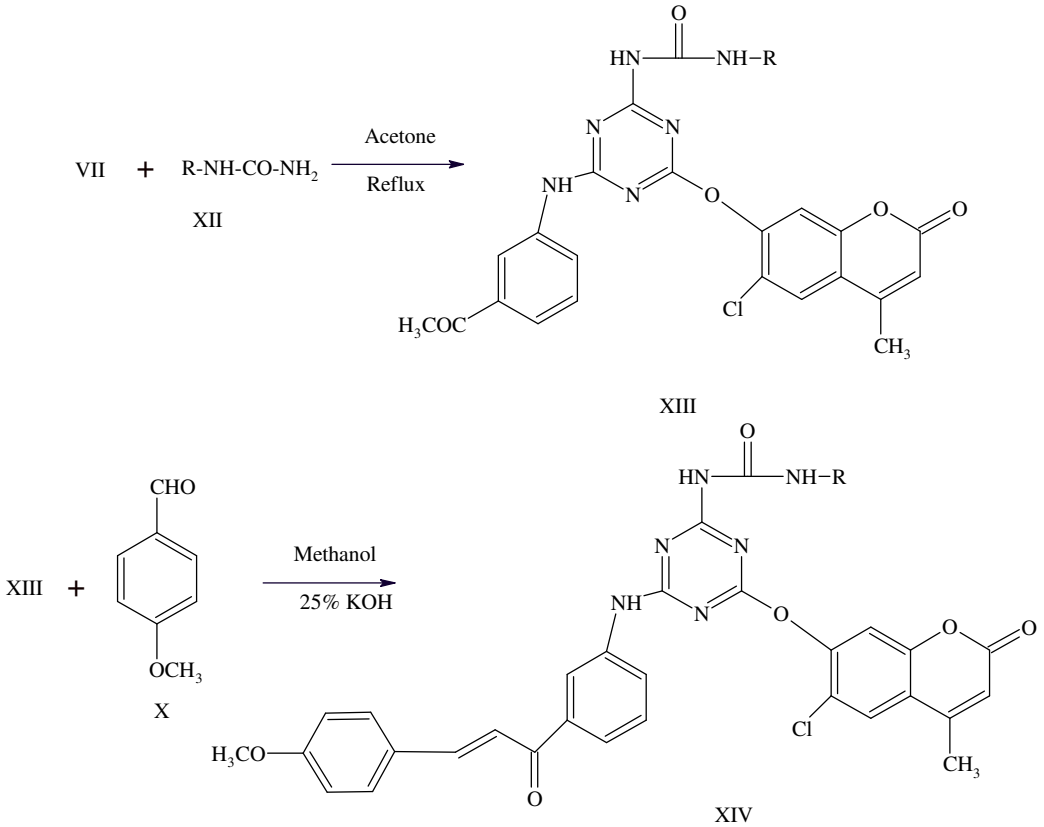
Scheme-3: 2- [4'- methyl - 6' - chloro -2*H*- chromen -2' -one-7'-oxy]-4-[3'- {3'' (-4''' - methoxy phenyl) - 2'' - propane - 1''-one}] phenyl amino-6-arylamino-S-triazine (XI)

2- [4'- methyl - 6' - chloro -2H- chromen -2' -one-7'-oxy]-4-[3'- {3'' (-4''' - methoxy phenyl) - 2'' - propane - 1''-one}] phenyl amino-6-arylamino-S-triazine (XIV)

A mixture of 0.01 mole substituted urea and 0.01 mole compound (VIII) was reflux in 50 ml acetone. During the reaction proceed sodium carbonate solution was added to neutralize HCl evolved. Reaction was monitored by TLC (ethyl alcohol 4 ml + Toluene 6ml). After completion of reaction, the reaction mass was cool to room temperature and quenched in crushed ice and the solid obtained was filtered, washed with water and crystallized in alcohol to get 2- [4'- methyl - 6' - chloro -2*H*- chromen -2' -one-7-oxy]-4-(3'-acetyl aminophenyl)-6-arylureido-s-triazine (XIII).

Above compound (XIII) 0.01 mole dissolved in 50 ml methanol and 25 % KOH solution added to it. Then 4-methoxy benzaldehyde added under constant stirring at room temperature. After 24 hours the reaction mixture was poured into crushed ice and neutralize with HCl. The resulting product 2- [4'- methyl - 6' - chloro -2*H*- chromen -2' -one-7'-oxy]-4-[3'- {3'' (-4''' - methoxy phenyl) - 2'' - propane - 1''-

one}] phenyl amino-6-arylureido-s-triazines (XIV) separated out was filtered, washed with water and crystallized from alcohol.



Scheme-4: 2- [4'- methyl - 6' - chloro -2*H*- chromen -2' -one-7'-oxy]-4-[3'- {3" (-4'" - methoxy phenyl) - 2" - propane - 1"-one}] phenyl amino-6-arylureido-s-triazine (XIV)

RESULTS AND DISCUSSION

Scheme-1 involves condensation of 4-chlororesorcinole (I) and ethyl acetoacetate (II) in presence of concentrate sulfuric acid to afforded 7 - hydroxy - 6 - chloro - 4 - methyl -coumarin (III).

Scheme-2 involves condensation of coumarin (III) and cyanuric chloride (IV) in acetone to afforded desired s-triazine derivative (V), which was on further condensation with 3-amino acetophenone (VI) to get 2- [4'- methyl - 6' - chloro -2*H*- chromen -2' -one-7'-oxy] - 4 - (3' - acetyl aminophenyl) - 6 - chloro -s - triazine (VII) .

Scheme-3 involves condensation of s-triazine derivative (VII) and substituted arylamine (VIII) to afforded desired s-triazine derivative (IX), which was further condense with 4-methoxy benzaldehyde (X) in presence of methanol as a solvent and 25% KOH to afford 2- [4'- methyl - 6' - chloro -2*H*- chromen -2'-one-7'-oxy]-4-[3'- {3" (-4'" - methoxy phenyl) - 2" - propane - 1"-one}] phenyl amino-6-arylamino-s-triazine (XI).

Scheme-4 involves condensation of s-triazine derivative (VII) and substituted arylureido (XII) to afford desired s-triazine derivative (XIII), which was further condense with 4-methoxy benzaldehyde (X) in presence of methanol as a solvent and 25% KOH to afford 2- [4'- methyl - 6' - chloro -2*H*- chromen -2'-one-7'-oxy]-4-[3'- {3" (-4'" - methoxy phenyl) - 2" - propane - 1"-one}] phenyl amino-6-arylureido-s-triazine (XIV).

Antibacterial activity

The target molecules were tested for antibacterial activity against the variety of test organisms *E.coli, B.substillis* (Gram-negative bacteria) and *S. aureus, S.paratyphi-A* (Gram-positive bacteria) bacteria. Screening was carried out in acetone solution at concentration of 40 µg/ml. agar cup-plate Method [12] was employed using nutrient agar culture medium. Under the similar condition, control experiment was carried out using Penicillin-G as a standard drug for comparison. The antibacterial screening results are given in Table-2. All compounds were active against both gram-positive and gram-negative bacteria at concentration of 40 µg/ml. The degree of inhibition varied with the test compound as well as with bacterium.

Table-1: Antibacterial activity data of aryl amino s-triazine (XII) (SA-1 to SA-7)

No.	R	Antibacterial activity Diameter of zone of inhibition (in mm)			
		S. aureus	*S. paratyphi-A*	*E. coli*	*B. subtilis*
SA-1	2-Methyl phenyl	9	5	10	16
SA -2	3-Methyl phenyl	15	4	16	8
SA-3	4-Methyl phenyl	12	12	15	15
SA -4	2-Chloro phenyl	10	14	9	13
SA -5	3-Chloro phenyl	9	6	7	5
SA -6	4-Chloro phenyl	11	15	13	14
SA -7	3-Nitro phenyl	7	13	12	7
STD	Penicillin-G	27	29	30	31

Table-2: Antibacterial activity data of aryl ureido s-triazine (XIV) (SU-1 to SU-7)

No.	R	Antibacterial activity Diameter of zone of inhibition (in mm)			
		S. aureus	*S. paratyphi-A*	*E. coli*	*B. subtilis*
SU-1	2-Methyl phenyl	9	9	11	5
SU -2	3-Methyl phenyl	5	10	8	12
SU-3	4-Methyl phenyl	7	5	9	15
SU -4	2-Chloro phenyl	11	15	7	10
SU -5	3-Chloro phenyl	13	12	5	9
SU -6	4-Chloro phenyl	9	14	12	6
SU -7	3-Nitro phenyl	6	9	13	14
STD	Penicillin-G	27	29	30	31

Table-3: Physical and analytical data of compounds (SA-1 to SA-7 and SU-1 to SU-7)

No.	R	M. F.	M. P. °C	% Y	Elemental Analysis		
					% of C	% of H	% of N
					Found (Cal.)	Found (Cal.)	Found (Cal.)
SA-1	2-methyl phenyl	$C_{36}H_{28}N_5O_5Cl$	173	59	66.96 (66.92)	4.33 (4.37)	10.85 (10.84)
SA -2	3-methyl phenyl	$C_{36}H_{28}N_5O_5Cl$	180	51	66.91 (66.92)	4.36 (4.37)	10.86 (10.84)
SA-3	4-methyl phenyl	$C_{36}H_{28}N_5O_5Cl$	171	63	66.94 (66.92)	4.41 (4.37)	10.81 (10.84)

SA -4	2-chloro phenyl	$C_{35}H_{25}N_5O_5Cl_2$	179	59	63.05 (63.07)	3.76 (3.78)	10.52 (10.51)
SA -5	3-chloro phenyl	$C_{35}H_{25}N_5O_5Cl_2$	190	60	63.02 (63.07)	3.75 (3.78)	10.53 (10.51)
SA -6	4-chloro phenyl	$C_{35}H_{25}N_5O_5Cl_2$	193	62	63.04 (63.07)	3.77 (3.78)	10.48 (10.51)
SA -7	3-nitro phenyl	$C_{35}H_{25}N_6O_7Cl$	186	57	62.09 (62.08)	3.69 (3.72)	12.38 (12.41)
SU-1	2-methyl phenyl	$C_{37}H_{29}N_6O_6Cl$	191	59	64.47 (64.49)	4.24 (4.24)	12.21 (12.20)
SU-2	3-methyl phenyl	$C_{37}H_{29}N_6O_6Cl$	183	62	64.45 (64.49)	4.23 (4.24)	12.23 (12.20)
SU-3	4-methyl phenyl	$C_{37}H_{29}N_6O_6Cl$	176	67	64.53 (64.49)	4.20 (4.24)	12.24 (12.20)
SU-4	2-chloro phenyl	$C_{36}H_{26}N_6O_6Cl_2$	198	63	60.96 (60.94)	3.72 (3.69)	11.81 (11.84)
SU-5	3-chloro phenyl	$C_{36}H_{26}N_6O_6Cl_2$	194	58	60.92 (60.94)	3.68 (3.69)	11.86 (11.84)
SU-6	4-chloro phenyl	$C_{36}H_{26}N_6O_6Cl_2$	186	51	60.91 (60.94)	3.65 (3.69)	11.85 (11.84)
SU-7	3-nitro phenyl	$C_{36}H_{26}N_7O_8Cl$	184	59	60.01 (60.05)	3.62 (3.64)	13.63 (13.62)

Table-4: IR and ^{1}H NMR data of compounds-XII and XIV (SA-1 to SA-7 and SU-1 to SU-7)

Compounds	Spectral Data
SA-1	IR (KBr cm^{-1}): 3320 (-NH), 3080 (C-H, aromatic), 1730 (C=O, Coumarin), 808 (C-N, s-triazine), 737 (C-Cl,). ^{1}H NMR [δ ppms (multiplicity, protons, assignments)]: 2.83 (s, 6H, $-CH_3$), 3.83 (s, 3H, $-OCH_3$), 6.8-8.1 (m, 17H, ArH, COCH, CH-Ar), 9.8 (s, 1H, NH).
SA-2	IR (KBr cm^{-1}): 3325 (-NH), 3090 (C-H, aromatic), 1715 (C=O, Coumarin), 8803 (C-N, s-triazine), 745 (C-Cl,). ^{1}H NMR [δ ppms (multiplicity, protons, assignments)]: 2.80 (s, 6H, $-CH_3$), 3.90 (s, 3H, $-OCH_3$), 6.6-8.3 (m, 17H, ArH, COCH, CH-Ar), 9.68 (s, 1H, NH).
SU-4	IR (KBr cm^{-1}): 2995 (C-H, aromatic), 1700 (C=O, Coumarin), 810 (C-N, s-triazine), 750 (C-Cl, chloro). ^{1}H NMR [δ ppms (multiplicity, protons, assignments)]: 2.33 (s, 3H, $-CH_3$), 3.7 (s, 3H, $-OCH_3$), 6.3-8.0 (m, 19H, ArH, COCH, CH-Ar & NH), 9.5 (s, 1H, NHCO).
SU-5	IR (KBr cm^{-1}): 2990 (C-H, aromatic), 1690 (C=O, Coumarin), 817 (C-N, s-triazine), 765 (C-Cl, chloro). ^{1}H NMR [δ ppms (multiplicity, protons, assignments)]: 2.30 (s, 3H, $-CH_3$), 3.8(s, 3H, $-OCH_3$), 6.2-7.9 (m, 19H, ArH, COCH, CH-Ar & NH), 9.57 (s, 1H, NHCO).

CONCLUSIONS

Presence of methyl group in the phenyl ring which linked with s-triazine group as SA-3, results in a significant increase in activity, particularly against, *S.aureus* and *E. coli* as compared to SA-2 and SA-4. In presence of chloro group at 4th position in the phenyl ring which linked with s-triazine group as SA-7, results in a significant increase in activity, against all bacteria as compared to SA-5 and SA-6. Replacement of the nitro group of SA-8 by a methyl group yielding compound SA-3, causes overall decrease in activity particularly against*, S. paratyphi-A.* Substitution of nitro at 3rd position to produced SA-8, which exhibits better activity against *S. paratyphi-A* in compare to SA-3 and SA-6.

Presence of nitro group in the phenyl ring which linked with s-triazine moiety as SU-8, resulting significant increase in activity, against *E. coli and B. subtilis* compare to compound SU-5, SU-6. Replacement of the nitro group of SU-8 by a methyl group yielding compound SU-3 causes overall decreasing in activity particularly against *E. coli* and *B. subtilis.* While at same place presence of chloro group yielding compound SU-6, causes increase in activity against *S. aureus* and *S. parathyphi-A* compare to compound SU-8. While replacement of methyl group at 2nd position of compound SU-9, with chloro to yielding compound SU-5, to increase activity against *S. parathyphi-A, E. coli* and *B. subtilis* .

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