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DESIGN AND CHARACTERIZATION OF SOME NEW NON-SYMMETRIC SUBSTITUTED TRIAZINES AND TRIAZINE DERIVATIVES

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Keywords:

2,4,6-trichloro-1,3,5-triazine, 1-Naphthol, 4-Phenyl phenol, 2-Mercapto benzothiazole, Thiophenol, Antimicrobial activity

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ABSTRACT: Attempts were made to carry out the laboratory synthesis of non-symmetric mono-, di- and tri- substituted 1, 3, 5-triazines by the action of the electron-donating substituent on 2, 4, 6-trichloro-1, 3, 5-triazines by aromatic nucleophilic substitution reaction mechanism (S_NAr reaction) by temperature controlled. The introduction of the amino group (-NH-), ether (-O-) and thiol (-S-) Linker Bridge show more promising antibacterial activity. The yield of newly synthesized compounds was quite well, and their structures were confirmed by using IR, ^{1}H NMR, and Mass spectral data.

INTRODUCTION: The chemical compound 1,3,5-triazine, also called s-triazine, it is an organic chemical compound whose chemical structure has a six-membered heterocyclic aromatic ring consisting of three carbon atoms and three nitrogen atoms. It is soluble in most organic solvents and very soluble in water. By using 2, 4, 6-trichloro-1, 3, 5-triazine (Cyanuric chloride), three chlorides can be replaced by amine, alcohol, Sulphur and Grignard reagents [1]. All of the s-triazine derivatives that have wide practical applications. 1, 3, 5-Triazine is having - mono, di- or tri-substituted, symmetrical and non-symmetrical compounds bearing different substituents. In 2, 4, 6-Trichloro-1, 3, 5-triazine the ease of displacement of chlorine atoms by various nucleophiles, in the presence of a hydrochloride acceptor (usually sodium carbonate, bicarbonate), makes this reagent useful for the preparation of mono-, di- and tri-substituted 1, 3, 5-triazines.

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The substitution pattern depends on the structure of the nucleophile, its basic strength, and steric factors, the substituent already present in the s-triazine ring and the nature of the solvent used [2]. By controlling the temperature, time and optimization of variables, such as solvent and base, the substitution of chlorine in cyanuric chloride with different substituents can be accomplished in one pot, if the correct order of addition of nucleophiles is followed (*e.g.,* O-nucleophiles followed by N-nucleophiles). This was then reacted with separately prepared mono-substituted dichloro-s-triazine [3]. The tri-substituted derivatives were obtained by nucleophilic reaction with an amine or by a Suzuki coupling reaction with phenylboronic acid. s-Triazine derivatives have received considerable attention due to their potent biological activity such as anticancer [4, 5], estrogen receptor modulators, antimitotic, antivirals, and antimalarial. It has been reported that triazine derivatives possess potent antimicrobial activity [6, 7, 8].

In the context of identification of new chemical entities for cancer therapy, s-triazine as core scaffold as many reports indicate its significance and structural modifications were made at three

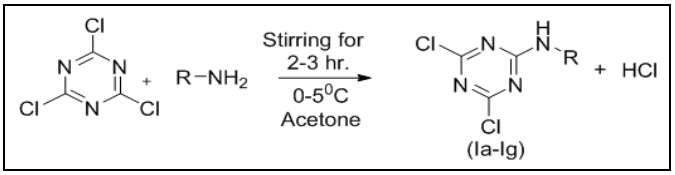
positions (1st, 3rd and 5th positions) with various pharmacophores [9]. s-triazine compounds containing both -C=N- moiety and thiol group are of interest in agriculture and biological processes [10]. 1,3,5-triazine derivatives are an important class of small molecules with anti-cancer [11, 12, 13] and anti-viral activity, among others. These compounds are known to be VLA-4 integrin antagonists, anti-inflammatory agents [14], sorbitol dehydrogenase inhibitors [15], estrogen receptor modulators potential anti-trypanosome drugs [16], anti-malarial agents [17], hypolipidemic agents [18, 19, 20] and antimicrobial agents [21, 22, 23, 24, 25].

MATERIALS AND METHODS: Solvents and reagents were purchased from Sigma-Aldrich and Merck. Unless otherwise stated, the normal workup from organic solvent involved drying over Na_2SO_4 and rotary evaporation. Progress of the reactions was monitored by thin-layer chromatography (TLC) using aluminum sheets coated with silica gel F_{254} (Merck) and suitable solvent systems. Spots were visualized by a Spectroline UV Lamp (254 or 365 nm) or I_2 vapour. The IR spectra were recorded (KBr discs) on a Perkin Elmer 1650 FT-IR instrument.

NMR spectra were recorded on a Bruker Avance II 400 MHZ NMR spectrometer (SAIF Punjab University Chandigarh) using DMSO as a solvent and TMS as an internal standard with the 1H resonant frequency of 400 MHZ. Chemical shifts are reported in parts per million (ppm) and are referenced relative to residual solvent (e.g., CHCl3 at δH 7.26 ppm for $CDCl_3$, DMSO at δH 2.50 ppm for DMSO-d6). Melting points were obtained in open capillary tubes using a MEL-Temp II melting point apparatus and uncorrected. Mass spectra (MS) were recorded on a Perkin-Elmer Q-Mass 910 instrument by using electron impact (EI) at 70 eV. The antimicrobial activity and *in-vitro* cytotoxicity were carried at the lab of biotechnology at Shri Shivaji Science College, Amravati, Faculty of Biotechnology, SGBAU.

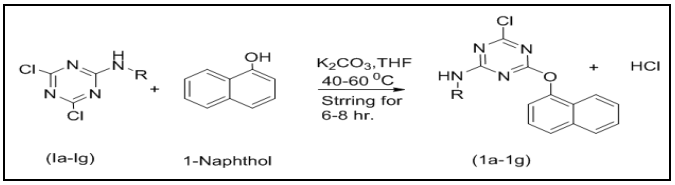
General Synthesis of Procedure:

General Procedure for Synthesis of mono-substituted triazine derivative *i.e.* 4, 6-dichloro-N-(2, 5-dimethyl phenyl)-1, 3, 5-triazin-2-amine (Step-I): To a stirred solution of cyanuric chloride (0.01mol) in acetone (10 ml) at 0-5 °C. The solution of 2,5-dimethyl aniline in acetone (4.5 ml) was added and pH being maintained neutral by the addition of 10% sodium bi-carbonate solution from time to time as per the requirement of reaction condition. The stirring was continued at 0-5 °C for 2-3 h. After the completion of the reaction the stirring was stopped, and the solution was treated with crushed ice. The solid product obtained was filtered and dried over sodium sulphate. The crude product was purified by crystallization from ether to get the title compound. The same material used for the next step.



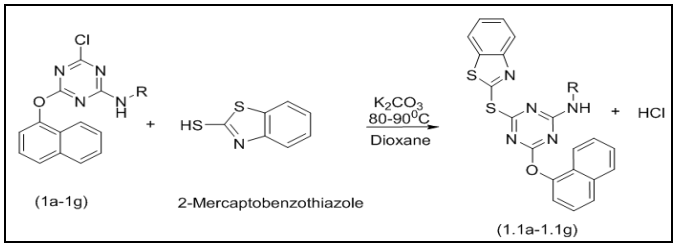
SCHEME 1

General Procedure for Preparation of di-substituted triazine derivative *i.e.* 4-chloro-N-(2,5-dimethylphenyl)-6-(naphthalen-1-yloxy)-1,3,5-triazin-2-amine (Step-II): To stirred the mixture of 4, 6-dichloro-N-(2, 5-dimethylphenyl)-1, 3, 5-triazin-2-amine (0.01mol) 1-naphthol (0.01mol) and K_2CO_3 (0.03mol) in 20 ml THF or acetone solvent. A solution of 10% $NaHCO_3$ was added and stirred for 6-8 h at 40- 60 °C. The progress reaction was observed by TLC using ether: ethyl acetate (8:2) solvent system as an eluent. After the completion of the reaction the resultant mixture was poured into crushed ice. The solid product obtained was filtered. Wash with distilled water and dried it.

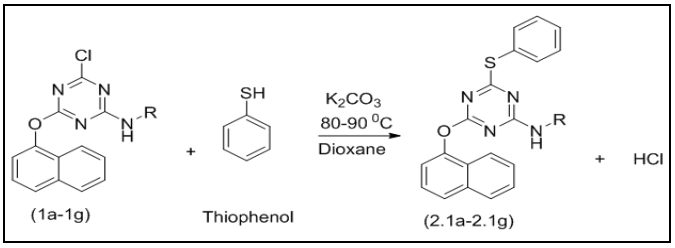


SCHEME 2

General Procedure for Preparation of tri-substituted triazine derivative *i.e.* 4-(benzo[d] thiazol-2- ylthio)-N-(2, 5-dimethyl phenyl)-6-(naphthalen-1-yloxy)-1, 3, 5-triazin-2-amine (Step-III): In round bottom flask the mixture of 4-chloro-N-(2, 5-dimethylphenyl)-6 -(naphthalen-1-yloxy)-1, 3, 5-triazin-2-amine (0.01mol) and 2-mercaptobenzothiazole or thiophenol (0.01mol) was taken in dioxane (20 ml). Anhydrous K_2CO_3 (0.03 mol) was added to it.



SCHEME 3(I)



SCHEME 3(II)

Where, R= a = C_8H_{10}, b = $C_6H_4NO_2$, c = C_2H_5, d = C_7H_7O, e = C_7H_7, f = C_6H_5, g = C_3HSN

Refluxed the reaction mixture at 80-90 °C for 18-20 h. The progress of the reaction was observed by TLC using ether: ethyl acetate (8:2) solvent system as an eluent. After the reaction, the reaction mass was poured into ice. The product was extracted with 25 ml of ethyl acetate, and then the organic layer was washed with water. The organic layer was separated and dried over Na_2SO_4 and kept for dryness. The product was recrystallized from n-hexane to give a clean product. Suck dried the solid under vacuum to afforded light yellow colored solid yield.

RESULTS AND DISCUSSION: The target compounds and respective intermediates were synthesized as outline in the scheme. Cyanuric chloride is an excellent starting compound for the straight forward preparation of highly structured multi-topic molecules. The first step consist of the nucleophilic substitution of first chlorine atom of cyanuric chloride by 2,5-dimethyl aniline give of 4,6-dichloro-N-(2, 5-dimethylphenyl)-1,3,5-triazin-2-amine with an efficient yield. It is exothermic; therefore, the temperature of the reaction mixture has to be maintained at 0 °C. Appearance of IR absorption peak at 3270 cm^{-1} show the attachment of 2° amine group. The intermediate 4-chloro-N-(2, 5-dimethylphenyl)-6-(naphthalen-1-yloxy)-1, 3, 5-triazin-2-amine obtained by reaction of 4, 6-dichloro-N-(2, 5-dimethylphenyl)-1, 3, 5-triazin-2-amine with 1-naphtol at room temperature.

It displayed an absorption band at 1112 cm^{-1} which showed the presence of CO linkage. The target compounds are obtained by third chlorine atom of cyanuric chloride was replaced by 2-mercapto benzothiazole to formed 4-(benzo[d] thiazol-2-ylthio)-N-(2, 5-dimethylphenyl)-6 -(naphthalen-1-yloxy)-1, 3, 5-triazin-2-amine. The appearance of IR absorption peak at 667 cm^{-1} show the attachment of C-S linkage). The appearance of mass at m/z 508(M+1) show the formation of the target molecule. Melting points were determined in an open capillary tube and are uncorrected. ^{1}H NMR signal at δ 3.5 (1H, s, Ar-NH-) and δ 6.8-7.9 (m, aromatic protons) MS: m/z 508(M+1).

TABLE 1: LIST OF COMPOUND

Comp no.	Molecular formulae	R-	Yield	M. P.
1.1a	$C_{28}H_{21}N_5OS_2$	C_8H_{10}	91%	101 °C
1.1b	$C_{26}H_{16}N_6O_3S_2$	$C_6H_4N_1O_2$	89%	130 °C
1.1c	$C_{22}H_{17}N_5OS_2$	C_2H_5	84%	140 °C
1.1d	$C_{27}H_{19}N_5OS_2$	C_7H_7	69%	110 °C
1.1e	$C_{27}H_{19}N_5O_2S_2$	C_7H_7O	79%	145 °C
1.1f	$C_{25}H_{19}N_4OS$	C_3H_2NS	63%	95 °C
1.1g	$C_{26}H_{17}N_5OS_2$	C_6H_5	78%	110 °C
1.1h	$C_{25}H_{16}N_6OS_2$	C_5H_4N	68%	190 °C
1.1i	$C_{24}H_{21}N_5OS_2$	C_4H_9	65%	120 °C

4- Chloro-N -(2, 5-dimethyl phenyl)-6-(naphthalene-1-yloxy)-1, 3, 5-triazine-2-amine (1a): Colourless solid was obtained, m.p.135 °C. ^{1}H NMR δ ppm (400 MHz,$CDCl_3$) : δ 8.18 (s,1H,NH), δ 7.99 (dd, 1Hz, J=8.5, J=2.3Hz, Ar-H), δ 7.72 (d, 1H, J=8.5Hz, Ar-H), δ 7.29 (d, 1H, J=2.5Hz, Ar-H), δ 6.65-7.80 (m, Ar-H), δ 2.30 (s, 3H, Ar-CH_3), IR (cm^{-1}): 3350.40 (NH, amine), 3310.27, 3123.1, 1652.35, 1342.3, 1263, 1060 (C-O), 1020, 905, 850.1 MS (m/z) at 377.30 (M+1).

4- Chloro-6 -(naphthalene-3-yloxy) -N-(4-nitrophenyl)-1,3,5-triazine-2-amine (1b): Yellow colour solid was obtained, m.p. 155-158 °C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 8.03 (s, 1H, Ar-NH), δ 8.01 (dd, 2H, J=8.5Hz), δ 7.5 (m, 2H,

J=8.2Hz, J=2.5Hz), δ 7.4 (dd, 2H, J=8.3Hz, J=2.5Hz), δ 7.32-7.81 (m, 4H, Ar-H), IR (cm^{-1}) : 3409.40, 3060.27 (NH, amine), 1553.1, 652.35, 1225.3, 1363, 1160, 874, 805, 758.1 MS (m/z) at 392.09 (M+1).

4-Chloro-N-ethyl-6-(naphthalene-1-yloxy)-1,3,5-triazine-2-amine (1c): Dark brown colour solid was obtained, m.p.160^{0}C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 7.4 (dd, 1H, J=8.1, Ar-H) δ 7.76 (dd, 1H, J=8.3Hz, Ar-H), δ 7.9 (t, NH), δ 7.26-7.91 (m, Ar-H), δ 3.47 (t, NH), δ 1.19 (t,3H,CH_3), δ 3.47 (q, 2H, CH_2), IR (cm^{-1}): 3346.00, 3230.87, 3223.01, 1553.35, 1440.6, 1356, 1248, 1120, 859, 850.3 MS (m/z) at 301.20 (M+1).

4-Chloro-6-(naphthalene-1-yloxy)-N-p-tolyl-1, 3, 5-triazine-2-amine (1d): Brown colour solid was obtained, m.p.155 °C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 7.95 (dd, 2H, J=8.2,J=2.6, Ar-H), δ 6.88-7.12 (dd, 2H, J=8.5, J=2.2, Ar-H), δ 6.75-7.91 (m, 7H, Ar-H), δ 2.27 (s, 3H, Ar-CH_3), IR (cm^{-1}): 3452.50, 3341.75, 3255.02, 1655.85, 1523.82, 1460, 1342.08, 1223, 869, 854.3 MS (m/z) at 363.3 (M+1).

N-tert-butyl-4-chloro-6-(naphthalene-1-yloxy)-1, 3, 5,-triazine-2-amine (1e): White colour solid was obtained, m.p.135 °C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 7.08-8.27 (m, Ar-H),δ 3.34 (s, 1H, NH), δ 1.33-1.67 (s, 9H, CH_3), IR (cm^{-1}): 3460.00, 3335.42, 3263.12, 1452.28, 1420.83, 1345, 1152, 1108, 975, 825.3 MS (m/z) at 333.01 (M+1).

4-Chloro-6-(naphthalene-1-yloxy)-N-o-tolyl-1, 3, 5-triazin-2-amine (1f): Light purple colour solid was obtained, m.p.148 °C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 6.85-8.26 (m, Ar-H), δ 7.43 (dd, 1H, J=7.8, J=2.2) δ 2.55 (s, CH_3), IR (cm^{-1}): 3486.16, 3365.70, 3298.52, 1826.52, 1562.29, 1458, 1356, 1193, 894, 883 MS (m/z) at 362.81 (M+1).

4-(benzo [d] thiazol-2-ylthio)-N-(2, 5-dimethyl phenyl)-6-(naphthalen-1-yloxy)-1, 3, 5-triazin-2-amine (1.1a): The product was obtained as whitesolid, m.p. 155-158 °C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 8.18 (s, 1H, NH), δ 7.99 (dd, 1Hz, J=8.4, J=2.2Hz, Ar-H), δ 7.29 (d, 1H, J=2.5Hz, Ar-H), δ 6.65-7.80 (m, Ar-H), δ 2.30 (s, 3H, Ar-CH_3), IR (cm^{-1}): 3409.40, 3060.27,1553, 652.35, 1225.3, 1363, 1160, 874, 805, 758.MS (m/z) at 508 (M+1).

4- (benzo[d] thiazole-2ylthio)-6 -naphthalen-2-yloxy)-N-(4-nitrophenyl)-1, 3, 5-triazin-2-amine (1.1b): The product was obtained as dark yellow solid, m.p. 163-166 °C.^{1}H NMR δ (400 MHz, $CDCl_3$): 6.98-8.12 (m, Ar-H), 7.55-8.23 (dd, 4H),δ 8.01 (dd, 2H, J=8.5Hz), 4.10 (exchangeable, 1H), 6.98-7.63 (m, Ar-H), IR (cm^{-1}): 3484, 3119, 3013, 1924, 1542, 1327, 1225, 1111.18, 852, 802, 750 MS (m/z), 525.29 (M+1).

4-(benzo[d] -thiazole-2-ylthio)-6 -(naphthalen-2-yloxy)-N-p-tolyl-1, 3, 5-triazin-2-amine (1.1e): The product was obtained as light yellow solid, m.p. 168-171 °C.1H NMR δ ppm (400 MHz, $CDCl_3$): δ 8.97 (s,1H) 8.62-8.58 (dd,1H), 8.14-8.12 (d,1H) 7.02-6.98 (d, 1H, Ar-H), 6.62-6.58 (m,1H), 6.44-6.42 (d, 1H), 4.10 (exchangeable, 1H), IR (cm^{-1}): 3422, 3200, 3060,3038, 1532, 1346, 1310, 1220, 1042, 824,782, MS (m/z), 492 (M+1).

4-(benzo[d] -thiazole-2-ylthio)-6 -(naphthalen-2-yloxy)-N-o-tolyl-1,3,5-triazin-2-amine (1.1j): The product was obtained as brown solid, m.p. 155-160 °C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ1.6- 2.2 (s, 3H) 7.62-7.58 (m, 5H, Ar-H), 6.7-6.9 (dd, 4H, Ar-H) 8.2-7.6 (m, 6H, Ar-H), 6.62-6.58 (d, 1H), IR (cm^{-1}): 3422, 3200, 3060,3038, 1532, 1346, 1310, 1220, 1042, 824,782. MS (m/z), 491 (M+1).

N-(2, 5-dimethylphenyl)-4-(naphthalen-1-yloxy)-6-(phenylthio)-1,3,5-triazin-2-amine (2.1a): The product was obtained as white solid, m.p. 185-190^{0}C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 6.65-7.87 (m, Ar-H), δ 7.5 (m, 2H, J=8.1Hz,J=2.3Hz), δ 2.01 (s, -CH_3), δ 2.15 (s, -CH_3). IR (cm^{-1}): 3412.31, 3243.32, 3058.16, 3010.15, 2104.74, 1692.23, 1561, 1459.10, 1371, 950.33, 920.44, 804.3. MS (m/z) at 451.25 (M+1).

4-(naphthalen-2-yloxy)-6 -(phenylsulfanyl)-N-p-tolyl-1, 3, 5-triazin-2-amine (2.1e): The product was obtained as white solid, m.p. 110-118^{0}C.^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ 2.3 (s, 3H) 7.62-7.58 (m, 5H, Ar-H), 6.7-6.9 (dd, 4H, Ar-H) 8.2-7.6 (m, 6H, Ar-H), 6.62-6.58 (d, 1H), IR (cm^{-1}): 3422, 3200, 3060,3038, 1532, 1346, 1310, 1220, 1042, 824,782. MS (m/z), 437 (M+1).

N-tert-butyl-4 -(naphthalen-1-yloxy)-6 -(phenyl sulfanyl)-1, 3, 5-triazin-2-amine (2.1i): The product was obtained as white solid, m.p. 102-106 °C. ^{1}H NMR δ ppm (400 MHz, $CDCl_3$): δ1.6-2.2

(s, 9H) 7.62-7.58 (m, 5H, Ar-H), 6.5-6.4 (dd, 4H, Ar-H) δ 7.4 (dd, 1H, J=8.1, Ar-H) δ 7.76 (dd, 1H, J=8.3Hz, Ar-H), IR (cm^{-1}): 3322, 3210, 3020,3018, 1432, 1326, 1300, 1260, 1041, 827,782. MS (m/z), 402 (M+1).

Biological Activity:

Antibacterial Activity: The synthesized compounds (2.1a-2.1e) have been evaluated for their antimicrobial activity against Gram-positive bacteria *Staphylococcus aureus*, *Streptococci*, and gram-negative bacteria *Escherichia coli* and salmonella. Microdilution susceptibility test in Muller-Hinton agar and Sabouraud Liquid Medium were used for the determination of antibacterial activity at 37 °C.

The strains used for the activity were procured from the Institute of Microbiology diagnostic laboratory, Amravati.

TABLE 2: THE TEST DONE USING THE DIFFUSION AGAR TECHNIQUE

Compound no.	Gram +ve Bacteria		Gram -ve Bacteria	
	S. aureus	*Streptococci*	*E. coli*	*S. typhi*
1.1a	-	+++	++	+++
1.2b	++	+++	+++	++
1.1c	+++	+++	++	+++
1.2d	+++	+++	-	++
1.1e	+++	+++	++	+++
1.2a	+++	+	+++	-

The test done using the diffusion agar technique, Well diameter = 0.06 cm, Inhibition values = 0.1 – 0.5 cm beyond control = + (less active), Inhibition values = 0.6 – 1.0 cm beyond control = ++ (moderate active), Inhibition values = 1.1 – 1.5 cm beyond control = +++ (highly active)

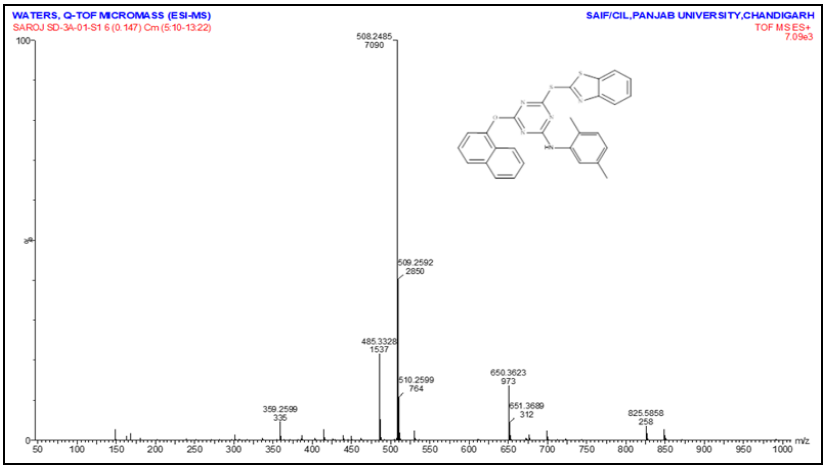


FIG. 1

CONCLUSION: In summary, we have successfully exploited to the synthesis of innovative tri-substituted triazine derivatives. The present work is focused on the development of novel s-triazine derivatives with wide therapeutic windows. The interest of organic chemists in 2, 4, 6-trichloro-1, 3, 5-triazine as a starting material is due to the temperature-dependent reactivity of three chlorine atoms that allow a sequential introduction of various substituents. In summary, we have describe a simple method for synthesis of 4-(benzo[d]thiazol-2-ylthio)-N-(2, 5-dimethyl phenyl)-6-(naphthalene-1-yloxy)-1, 3, 5-triazin-2-amine. The compound was confirmed by the spectral analysis. The sequential replacement of three chlorine atoms on cyanuric chloride with different nucleophiles provides the synthesis of a variety of substituted s-triazine molecules. In light of its operational simplicity and efficiency, this reliable method is expected to have a broad utility due to the scope of applications of the s-triazines. Antimicrobial activity of the new compounds was investigated. The majority of the compounds came out with promising activity against a wide range of pathogenic bacteria, fungi, and mycobacteria. 2, 4, 6-Trichloro-1, 3, 5-triazine (TCT) was found to be inexpensive easily available, easy to handle, and dramatic generality for various aliphatic or aromatic amines undergo smooth N-substituted triazines.

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CONFLICTS OF INTEREST: Nil

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