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MICROWAVE ASSISTED SYNTHESIS AND BIOLOGICAL STUDY OF SOME NOVEL S-TRIAZINE DERIVATIVES WITH SUBSTITUTED AMINES

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Abstract: We report the synthesis and result of biological evaluation of newly designed Novel series of s - triazine derivative with substituted amines by microwave assisted method. The strategy involved the reaction of Cynuaric chloride with 2 - amino pyrazene in the presence of sodium carbonate and 1, 4 - dioxane to construct intermediate product. The intermediate 4, 6 – dicchloro - N - (pyridine-2-yl) - 1, 3, 5-triazine - 2-amine **(1)** was substituted with various substituted amines moieties to furnish the final 8 target compounds i.e. **2, 3, 5, 7, 8, 9, and 10** respectively. The synthesized compounds were characterized by different characterization techniques like IR, UV, Mass spectrometry, ^{1}H NMR, ^{13}C NMR. These compounds were screened for their Antimicrobial activity against three microbial species (Escherichia coli, Pseudomonas fluorescens and staphylococcus aureus), Antifungal activity against two fungal species (Aspergillus niger and Candida albicans) and Antiviral Activity against two viruses (Dengue and Hepatitis B.). Among the tested derivatives from diethyl amine (5) and methoxyamine (9) show the highest biological activity than the rest derivatives.

Keywords: 2 - amino pyrazine, 4,6-dicchloro- N- (pyridine-2-yl)-1,3,5-triazine-2-amine, 1,4-dioxane.

1. INTRODUCTION

Heterocyclic compounds are playing a part in the formation of organic matter in the universe and have vast significance in sustaining life. These compounds have attracted attention due to their undisputed effective physicochemical and pharmacological properties.

TRIAZINE APPLICATIONS

Triazines are a six-membered conjugated carbon–nitrogen atom cyclic ring, comprised of many active pharmaceutical ingredients with an attractive therapeutic profile.1,3,5-triazine, a six-membered heterocyclic ring, is one of the oldest classes of organic compound. It is still used in many chemotherapeutic agents due to their interesting pharmacological properties. Symmetrical and asymmetrical isomers of triazine are generally distinguished by the different arrangement of nitrogen in the benzene ring. 1,2,3-triazine, 1,2,4-triazine and 1,3,5-triazine or *s*-triazine [Fig.1].

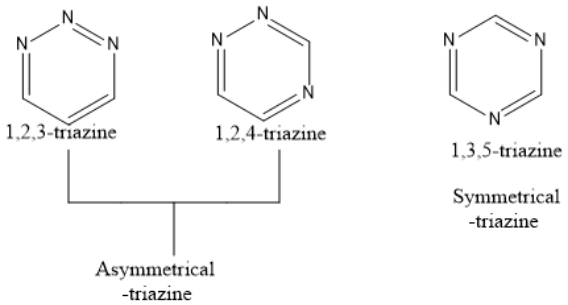
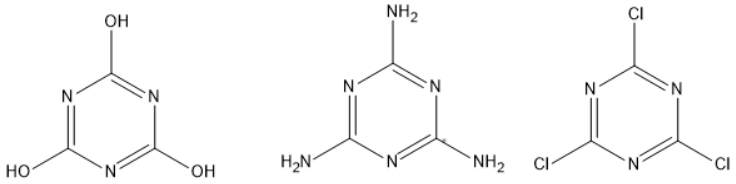


Figure 1: Triazine isomers.

1,3,5-triazine was unknowingly first synthesized by Nef in 1895 by treating hydrogen cyanide with ethanol in an ether solution saturated with hydrogen chloride. The resulting salt was then treated with base and distilled to give 1,3,5-triazine in low yields, 10%. Nef incorrectly identified the product as a dimeric species. However, in 1954, Grundmann and Kreutzberger proved the compound to be a trimmer of hydrogen cyanide; *s*-triazine. Triazine is thermally stable unless heated to above 600 °C where it decomposes to form hydrogen cyanide. The triazine ring is fairly resistant to electrophilic substitution. However, it may readily undergo ring cleavage with nucleophiles and is very sensitive to hydrolysis by water and other hydroxyl-compounds to a lesser degree. A variety of heterocycle can be prepared from 1,3,5-triazine by treatment with bifunctional amines or related compounds, and it may be used as an alternative for HCN in reactions. The most commonly used triazine derivatives are shown below in [Fig.2], cyanuric acid , melamine , and cyanuric chloride [1-3].



Cyanuric Acid **Melamine** **Cyanuric Chloride**

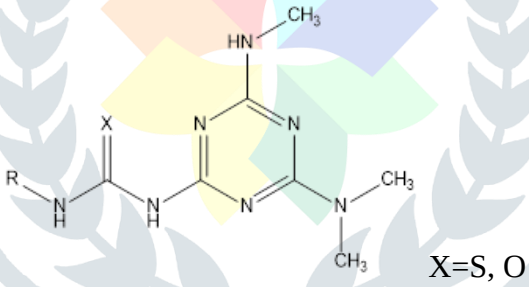
Figure 2: Common triazine derivatives

The integration of certain bioactive pharmacophores in the existing drug molecules exerts a remarkable influence on the biological profiles of these molecules. In this review, our main intention is to emphasize on the different biological activities exhibited by 1,3,5-triazine derivatives [4].

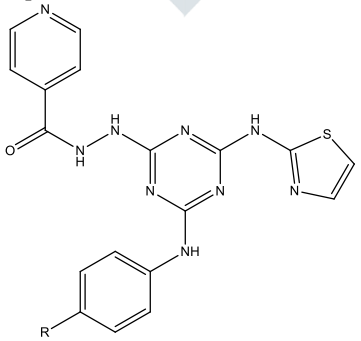
PHARMACOLOGICAL ACTIVITIES

Anti-microbial activity

The researcher has reported that 1,3,5 -triazine core molecule exhibiting excellent antimicrobial activity including anti-bacterial and anti-fungal activity. The triazine derivatives were synthesized starting from cyanuric chloride (2,4,6 trichloro 1,3,5 triazine) and different nucleophile. All the synthesized compounds were screened for their minimum inhibitory concentration against two gram - positive (*Staphylococus aureus* and *Bacillus subtilis*) and two gram negative (*E.coli* and *Pseudomonas aeruginosa*) by broth dilution method. The results showed the synthesized compounds produced good deal of activity against gram positive bacteria, while they were moderately active against *E. coli* and much less active *against P. aeruginosa* of gram-negative bacterial strains [5].



The 1,3,5 triazine based Thiazole derivatives were synthesized. All the newly synthesized compounds were evaluated against gram positive bacteria and gram-negative bacteria and fungi. Results revealed that majority of synthesized compounds showed varying degrees of inhibition against the species. The obtained anti-microbial activity of tested compounds could be correlated to structural variations and modifications of the respective compounds. The presence of nitro (NO2) group at position 2 and 4 in the structure produced highest inhibition at MIC 12.5&25 µg/mL [6].

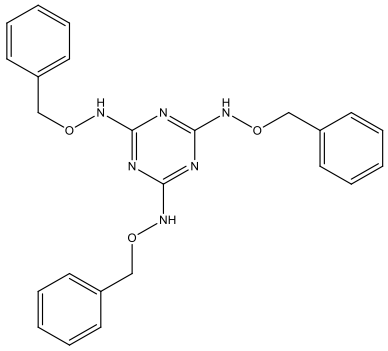


The Thiazole 1,3,5- triazine derivatives were synthesized and they were screened for Anti-fungal activity (i,e) minimum inhibitory concentration and minimum fungicidal concentration against *Candida albicans, C.glabrata, C.neoformans* & *Aspergillus niger* using broth dilution method. The results depicted that target compounds exhibit numerous degree of inhibition pattern on tested fungal strains. The compound with rigid di-phenyl fragment along with substituted phenyl thiazole fragment exerts significant to potent activity against all strains [7].

Anti- tubercular activity

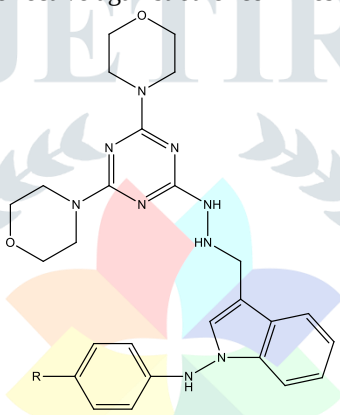
The one pot synthesis of 2,4,6 tri substituted 1,3,5 triazine were carried out by the reactions of cyanuric chloride with aromatic /aliphatic amines ,amide and water under microwave using catalyst. The compound showed highest anti-tuberculosis activity (72%

inhibition) against *Mycobacterium tuberculosis* [8]. The series of novel 6-aryl-2,4 disubstituted schiffs base 1,3,5 triazine derivatives are synthesized and evaluated for invitro anti-bacterial activity against E.coli and staphylococcus aureus strain and invitro anti-fungal activity against candida albicans and Aspergillus niger strains by using serial dilution method. The results revealed that the compound with chlorine electron with drawing group produced good anti-bacterial and anti-fungal activity when compared to other compounds against the strains. The presence of electron withdrawing group is responsible for enhanced activity against the strains [9].



Anti – cancer activity

The 6-hydrazinyl -2, 4 bismorpholino pyrimidine and 1,3,5 triazine derivatives were synthesized. These synthesized compounds were evaluated for their Anti-proliferative activity against H 460 (human lung cancer), HT-29 (human colon cancer) & MDA-MB-231(human breast cancer) cancer cell lines together by MTT assays. The 1,3,5 triazine derivatives were potent than the pyrimidine derivatives against H 460 cancer cell lines but less effective against other cell lines [10].



The tri arm shaped 1,3,5 triazine hydrazone were synthesized and evaluated for anti -cancer activity. The anti- proliferative activity of synthesized compounds was carried out against human liver carcinoma cell lines (Hep G2) and human cervix carcinoma cell lines (He La). The compounds which possess a nitro group showed 58.91 % inhibition against Hep G 2 cells whereas compounds with chloro substituents produce 28.36% inhibition against HeLa cells [11]. The series of 21 compounds of 2-(4-cyano -3-trifluoro methyl phenyl - amino)-4-(quinoline 4-yloxy)-6- (piperazinyl) or piperidinyl triazine were synthesized .The invitro anti- cancer activity was studied against human prostate cancer cell lines DU-145.Among them compound 33 was found to be active against with GI 50 of 14.1µg/ml concentration [12].

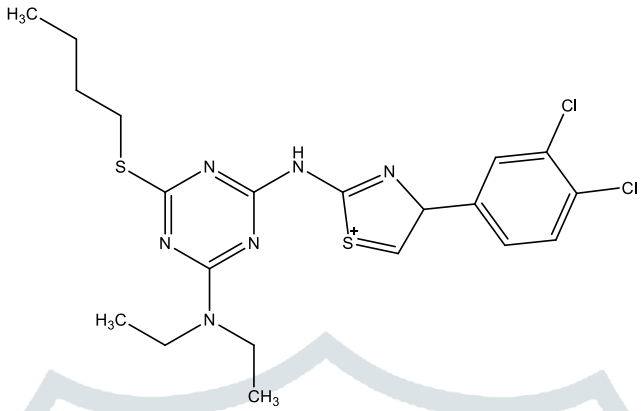
Interestingly, the di and tri substituted s-triazine were synthesized which were assessed for anti -cancer evaluation against four cancer cell lines such as PA-1 (ovarian cancer), A549 (lung cancer), MCF-7 (breast cancer) and HT-29(colon cancer). The tri substituted s-triazine was more potent than the disubstituted compounds [13]. The 2, 4 diamino 1,3,5 triazine derivatives were synthesized and subjected to evaluate their invitro anti-tumor activity against a tumor cell lines. Among the synthesized compounds the one with 5-nitro thienyl moiety showed excellent activity (log GI50<-8.00 to -5.00) to all cell lines and found potent against some cell lines of leukemia, CNS cancer (SF -539) and breast cancer T-47D [14]. The metformin (N, N Dimethyl biguanide) analogs and metformin salts that inhibit the proliferation and invasion of HS578T Triple negative breast cancer cells are compared with metformin alone. The designed metformin derivatives showed potent invitro and in vivo anti-tumor effect [15] The microwave assisted one pot synthesis of trisubstituted 1,3,5 triazine derivatives. The photo toxicity of the titled compounds was investigated first on a cell line of human tumor HL-60 (human promyelotic leukemia). This given compound produced activity and substitution for a methyl group leads to inactive derivatives [16].

Anti-inflammatory activity

The triamino triazine aniline methoxyamine derivatives bearing 4-methyl -1,4-diazepan 1-yl substituents. The synthesized derivatives showed excellent in vitro and in vivo oral activity in animal model of acute and chronic inflammatory diseases with IC 50 of 44 and 85nM against p38α and TNFα respectively [17]. The 2-alkyl/aryl -4,6 dimethoxy -s-triazine analogs were synthesized and anti-inflammatory activity was studied. The compounds bearing phenyls, (s)-2-Me) Bu and thiophene substituents were found to be active against rest of the compounds [18]. In vitro anti-inflammatory evaluation of bis (dimethyl amino)-s-triazinyl derivatives showed 16, 46 and 100% Inhibition of inflammation at dose levels of 7.5, 30 and 75mg/kg respectively [19].

Anti-malarial activity

A library of 22 derivatives of 9-anilinoacridine triazine as hybrid antimalarial agents was synthesized. The in vitro activity was determined against Chloroquine (CQ) sensitive 3D7 strain of Plasmodium falciparum and their cytotoxicity was determined on VERO cell line. In this evaluation (IC50 = 4.21 nM) and (IC50 = 4.27 nM) were two-times more potent with reference to Chloroquine (IC50 = 8.15 nM) [20]. The hybrid phenyl thiazolyl -1,3,5 triazine were synthesized and evaluated for anti-malarial chemotherapy. The given compound showed excellent anti-malarial activity with % dead (ring and schizonots) =12.0 at 50µg/ml dose [21].



Alzheimer's disease treatment

The symmetrical triazine analogs were synthesized to inhibit the multiple pathologies human AchE, BuchF and amyloid -β-aggregation in the treatment of Alzheimer's disease. The height inhibition of ameloid β-fibils with 89.9% was shown by the synthesized compounds [22, 23].

Anti – Viral Agents

The synthesis of benimidazolyl and triazolyl 1,3,5 – triazone derivatives were carried out and their invitro pharmacological profile showed that were active against HSV – 1 in VERO cells. The results displayed the best inhibition activity at 3.5ug/ml (SI =358) than acyclovir [24].

2. EXPERIMENTAL SECTION

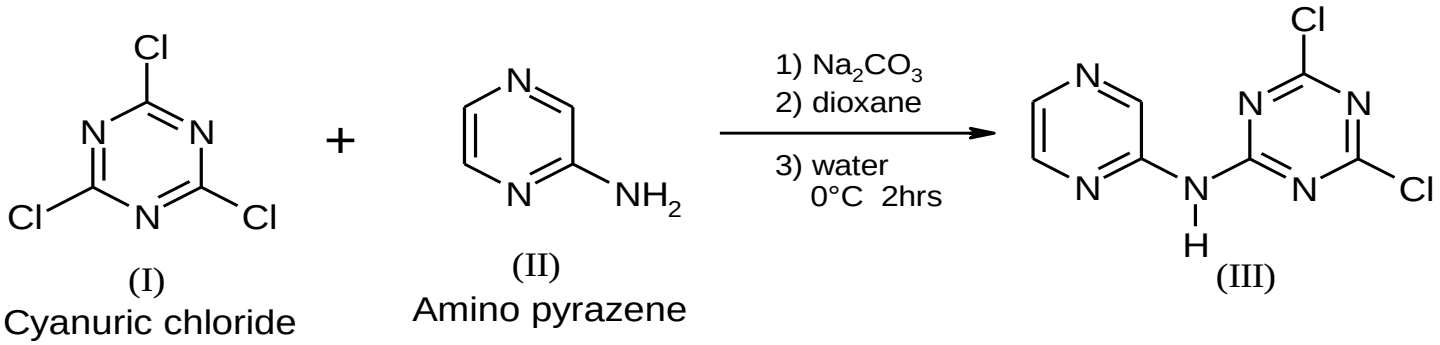
2.1. Material

The chemicals were procure from commercial sources and were used without further purification. Progress and identification of reaction checked by Silica gel chromatographic sheets were used for thin layer chromatography (TLC) using pre coated aluminium backed plates (silica gel 60 F_{254} grade, Merck DC) with spot visualized by UV light. Melting points were recorded on an electric digital melting point apparatus Bio Technic India BTI-34 apparatus in an open capillary and are uncorrected. Structures of intermediate and hybrid analogues compound confirm on the basis of FT-IR, ^{1}H-NMR, and ^{13}C- NMR. FTIR was recorded on FT-IR Shimadzu spectrometer and UV-1800 Spectrophotometer at Shri. Shivaji Science College, Amravati. ^{1}H- NMR and ^{13}C-NMR spectra were recorded on Bruker Advance Neo 500 MHz NMR Spectrometer using DMSO-d^{6} as a solvent at SAIF, Punjab. Cynuaric chloride is an excellent and most fascinating chemical having medicinal chemistry applications due to the numerous biological activities. The first substitution of chlorine in cyanuaric chloride is exothermic; therefore, the temperature of the reaction mixture maintained at 0^{0}C. The second chlorine substitution can be performed at room temperature and then the third position is substituted under reflux of solvent. A careful control of the reaction temperature during the substitution will allow the synthesis of desired derivative by the sequential and very selective addition of amine nucleophile (Fig.5) [25]. Microwave synthesis represents a major role in synthetic chemistry, as conventional heating long known to be inefficient and time consuming process. Microwave synthesis gives the chemists more time to expand their creativity, test new theories and develop new processes. Instead of spending hours or even days synthesizing a single compound, chemists can now perform the same reaction in minutes. Using microwave irradiation produced the desired products in less time, good yield and higher purity. Thus microwave synthesis acts as a potential tool for green chemistry [26].

2.2. Scheme of Work

The synthetic scheme includes following steps in Figure.1.

Scheme-I



Scheme-II

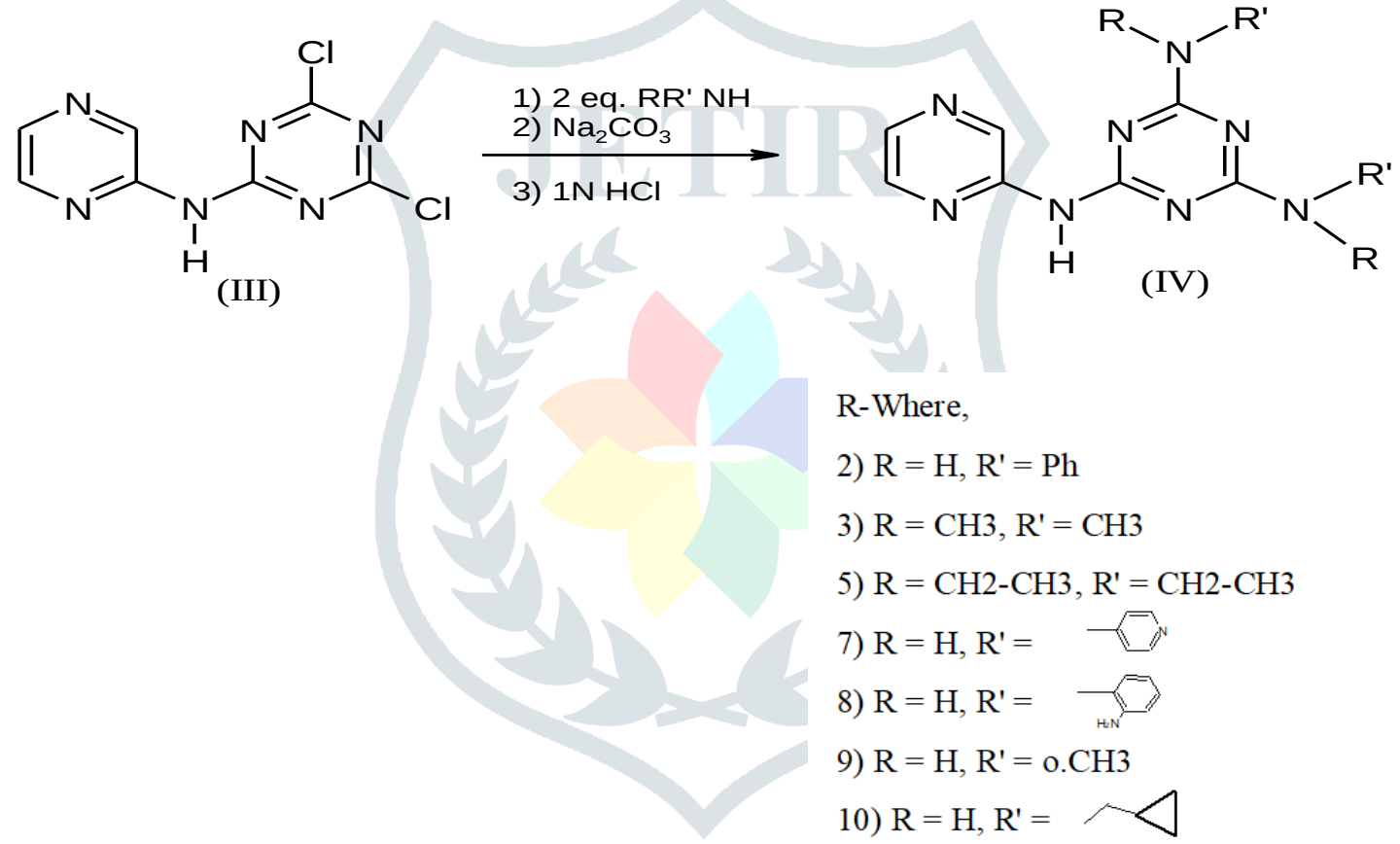


Figure 1: The reaction scheme for the synthesis of target product**.**

2.3. Methodology

Synthesis of 4, 6 - dicchloro-N - (pyridine-2-yl) -1, 3, 5-triazine - 2 - amine (1)

A monosubstituted 1, 3, 5-triazine was prepared selectively by substituting one chlorine ion of 2,4,6- trichloro-1,3,5-triazine (9.2205g, 0.05M) was dissolve in 1, 4 dioxane (70 mL) and maintained the temperature at 0-5 ^{0}C using ice. After that 2-amino pyrazine (4.755g, 0.05M) was added to the above solution in the presence of sodium carbonate (0.95g, 9.0mmol) as an acid scavenger of the liberated hydrochloric acid. When the addition of 2 - amino pyrazine was completed the reaction mixture was stirred for another 2 hrs. , maintaining the temperature at 0-5 ^{0}C. After the reaction was completed the reaction mixture was neutralized with 1N hydrochloric acid. The progress of reaction is monitored by TLC (Ethyl acetate / Hexane 1: 4). The content of the flask was poured into crushed ice and the solid that separated out was filtered, washed with water, dried and recrystallized from ethanol to give the yellow colour precipitate of 4, 6 - trichloro -N- (pyrazine - 2- yl) -1, 3, 5 - triazine -2- amine. The product was obtained as yellow solid, 10.2 g Yield: 84.40 % ; m.p: 190 - 200 ^{o}C; IR (KBr): 3474 (NH, amine) cm^{-1}, 2854 (C-H), 1421 - 1689 cm^{-1} (C=C) and (C=N), 1041-1321 (C-N), 547 - 831cm^{-1}, (C-Cl); ^{1}H -NMR: (500 MHz, DMSO - d_6): δ 7.01-8.33 (m, 3H, Ar - H), δ 3.99 (s, 1H, NH); ^{13}C-

NMR: (500 MHz, DMSO-d^6): 56.13, 66.13, 68.78, 108.26, 110.53, 129.59, 133.94, 136.63, 151.73, 155.74, 162.66, 16.32; MS: m/z = 243.05 ($M^{+)}$, 207.60, 148.98.

Microwave assisted Synthesis of Novel S-triazine derivatives with substituted amines (2, 3, 5, 7, 8, 9, and 10)

To a 250 mL of two necked round bottom flask was added (2.430 g, 0.01 M) 4, 6 –dicchloro - N - (pyridine-2-yl) - 1, 3, 5 - triazine - 2 - amine, 40 mL of distilled water, 1, 4- dioxane (1:1), sodium carbonate (0.95 g, 9.0 mmol) and to this mixed the appropriate amine drop wise. When the addition of amine was completed the flask was kept in microwave oven and irradiated for 10 min at 100 ^{0}C at 140 W. After the reaction was completed reaction mixture cooled at room temperature and neutralized with 1N hydrochloric acid. The progress of reaction is monitored by TLC (Ethyl acetate / Hexane 1:4). The content of the flask was poured into crushed ice and the solid that separated out was filtered, washed with water, dried and recrystallized from ethanol.

N^2, N^4 - dibenzyl - N^6 - (pyrazin-2-yl) - 1, 3, 5-triazine-2, 4, 6-triamine (2)

The product was obtained as yellow solid, 2.99 g Yield: 83.98 %; m.p: 110-115 ºC; IR (KBr): 3319.49 (NH, amine) cm^{-1}, 3134 cm^{-1}(C-H), 1425-1683 cm-1(C=C) and (C=N), 960-1257 cm^{-1}; ^{1}H-NMR: (500 MHz, DMSO - d_6): δ 5.89-9.77 (m, 13H, Ar-H), δ 3.37 (s, 3H, NH); ^{13}C-NMR: (500MHz, DMSO - d^6): 113.80, 119.86, 122.86, 128.70, 137.61, 140.72, 144.69, 164.52, 164.63, 167.67.

N^2, N^2, N^4, N^4 - tetramethyl - N - (pyrazine -2 -yl) - 1, 3, 5-triazine - 2, 4, 6-triamine (3)

The product was obtained as yellow solid, 1.88 g Yield: 72.53 %; m.p: 265-270 ºC; IR (KBr): 3278.99 (NH, amine) cm^{-1}; ^{1}H-NMR: (500 MHz, DMSO - d_6): δ 5.84-9.75 (m, 3H, Ar-H), δ 3.34 (1H, NH), δ 3.06 (12H, CH_3); ^{13}C-NMR: (500MHz, DMSO - d^6): 38.90, 137.20, 138.49, 146.56,158.35, 166.46, 183.96..

N^2, N^2, N^4, N^4 - tetraethyl - N6 - (pyrazine -2- yl) - 1, 3, 5-triazine-2, 4, 6-triamine (5)

The product was obtained as yellow solid, 0.96 g Yield: 30.40 %; m.p: 225-230 ºC; IR (KBr): 3257.77 (NH, amine) cm^{-1}; ^{1}H-NMR: (500 MHz, DMSO-d_6): δ 5.88-9.83 (m, 3H, Ar-H), δ 3.37 (s, 1H,NH), δ 2.88-2.89 (8H, CH_2), δ 1.16-1.19 (12H, CH_3) ; ^{13}C-NMR: (500MHz, DMSO - d^6): 10.89, 41.15, 137.49, 138.33, 146.65, 157.20, 164.59, 181.08.

N^2 - (pyrazin-2-yl) - N^4, N^6 - di (pyridine-4-yl) -1, 3, 5-triazine -2, 4, 6-triamine (7)

The product was obtained as yellow solid, 1.90 g Yield: 45.62 %; m.p: 232-240 ºC; IR (KBr): 3304.06 (NH, amine) cm^{-1}; ^{1}H-NMR: (500 MHz, DMSO-d_6): δ 5.31-8.24 (m, 11H, Ar-H), δ 3.36 (3H, NH); ^{13}C-NMR: (500MHz, DMSO - d^6): 119.90, 123.6, 135.84, 136.44, 144.85, 151.20, 156.33, 157.82, 165.22, 168.62.

N^2, N^4- bis (2-aminophenyl) - N6 - (pyrazine-2-yl) - 1, 3, 5 – pyrimidine - 2, 4, 6-triamine (8)

The product was obtained as yellow solid, 1.99 g Yield: 51.49 %; m.p: 235-240 ºC; IR (KBr): 3321.42 (NH, amine) cm^{-1}; ^{1}H-NMR: (500 MHz, DMSO - d_6): δ 6.51-8.95 (m, 11H, Ar-H), 3.41-3.63 (s, 3H, NH), δ 6.27-6.37 (m,4H,NH_2); ^{13}C-NMR: (500MHz, DMSO - d^6): 121.21, 121.67, 123.34, 124.31, 125.31, 125.85, 128.36, 128.46, 129.07, 129.53, 129.99, 130.14, 130.74, 136.27, 137.19, 139.12, 139.43, 141.78, 142.18, 145.64, 147.77, 153.45, 163.03.

N^2, N^4 - dimethoxy - N^6 - (pyrazine-2-yl) - 1, 3, 5 - triazine - 2, 4, 6 - triamine (9)

The product was obtained as yellow solid, 0.59 g Yield: 22.44 %; m.p: 187-190 ºC; IR (KBr): 3218.10 (NH, amine) cm^{-1}; ^{1}H-NMR: (500 MHz, DMSO-d_6): δ 5.85-9.76 (m, 3H, Ar-H), δ 3.39- (s, 3H, NH), δ 3.66-3.67 (6H, OCH_3); ^{13}C-NMR: (500MHz, DMSO - d^6): 78.22, 78.46, 116.61, 129.05, 143.39, 157.70, 171.04, 179.56.

N^2, N^4 - bis (cyclopropylmethyl) - N6 - (pyrazine-2-yl) - 1, 3, 5 - triazine - 2, 4, 6 - triamine (10)

To a 250 mL of two necked round bottom flask 1.7137 ml (0.02M) cyclopropanemethyl amine dissolved in 10 ml of chloroform is added to a molar solution of 2.430 g, (0.01 M) 4, 6 –dicchloro - N - (pyridine-2-yl) - 1, 3, 5 - triazine - 2 – amine in 10 ml chloroform ,which is previously cooled to -10ºC. After the addition, the mixture is allowed to room temperature. The reaction mixture is then cooled again at 0ºC and an aqueous solution containing 1M of sodium carbonate is added and reaction mixture stirs for 1-2hrs at room temperature. The organic phase is separated off and dried over sodium sulphate and solvent is evaporated under reduced pressure. Product was recrystallized by ethanol.

The product was obtained as yellow solid, 1.87 g Yield: 49.16%; m.p: 198-200 ºC; IR (KBr): 3204.27 (NH, amine) cm^{-1}; ^{1}H-NMR: (500 MHz, DMSO-d_6): δ 5.73-9.62 (m, 3H, Ar-H), δ 3.26 (3H, NH), δ 0.70-2.35 (4H,CH_2), δ 0.69 (2H,CH), δ 0.16- 0.37 (8H,CH_2); ^{13}C-NMR: (500MHz, DMSO - d^6): 3.08, 3.73, 8.47, 43.36, 116.62, 119.52, 129.04, 141.76, 149.92, 161.53, 163.10 .

3. BIOLOGICAL ASSAY

The biological activity may be measured in different ways depending on the level at which the investigation is conducted, when the critical site and mechanism of action of chemicals are known. Biological activity can be measured directly in terms of the degree of inhibition or enhancement of an enzyme system as measured in Vitro. More usually, however, biological activity is measured in an indirect manner through in vivo, observations of the end results of chain of events by the interaction of chemicals with some unknown biochemical component [27,28].

The wide spectrum of biological activity of s- triazine derivatives has been observed in the literature survey. So, the attempt was made to screen the synthesized compounds for its antibacterial, antifungal and antiviral activities. Some of the representative compounds synthesized in the present work were screened for antimicrobial activities against gram (+ve) and gram (-ve) bacteria and on some selected fungi and viruses.

3.1. Antimicrobial activity

The disc diffusion method is based on the fact that for a given antibiotic. The entire compounds were screened for antimicrobial activity by disc diffusion method. Antimicrobial susceptibility testing with discs diffusion method is a simple and rapid method and provides a reproducible means of testing bacterial sensitivity to various antibiotics and chemotherapeutical agents. The inoculum can be prepared by making a direct broth or saline suspension of isolated colonies of the Gram - positive organism, viz., *Staphylococcus aureus* and Gram - negative organism, *viz., E.Coli, Pseudomonas fluorescens* from 18 to 24 hr. , Mueller-Hinton agar plate. The suspension is adjusted to match the 0.5 McFarland turbidity standards, using saline and a vortex mixer. Optimally, within 15 min after adjusting the turbidity of the inoculum suspension, a sterile cotton swab is dipped into the adjusted suspension and then the dried surface of an agar plate is inoculated by streaking the swab over the entire sterile agar surface. Any surface moisture to be absorbed before applying the drug impregnated disc. The plates containing bacterial inoculums are received a disc of *Ofloxacin* and synthesized compound, whereas the control plate was inoculated with DMSO which shows no inhibition of bacterial growth. Each disc must be pressed down to ensure complete contact with the agar surface. Then plates are inverted and placed in an incubator set to 35 ºC within 15 min after the discs are applied. They were then incubated at 37 ºC for 24 hr., after which the inhibition halo was measured with a milimetric ruler. This qualitative screening was performed to verify positive antimicrobial activity of the synthesized compound. Each test was carried out in triplicate. These results are further quantified in terms of percentage of inhibition in reference to Ofloxacin as standard [29,30].

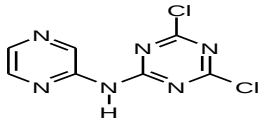
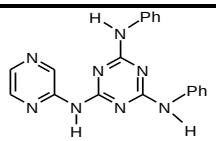
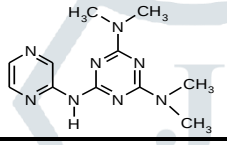
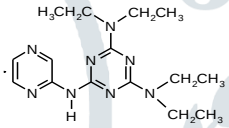
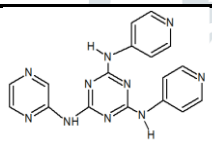
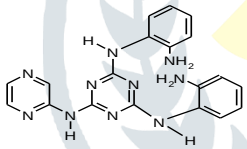
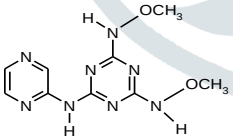
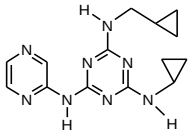
3.2. Antifungal Activity

The antifungal test methods are classified into three main group diffusion, dilution and bio-autographic methods. Out of these three methods we acquired diffusion method. The synthesized compounds, Novel 1, 3, 5-triazine derivatives of substituted amines were screened for their antifungal activity against *Candida albicans* and Aspergillus *niger* using modified diffusion method recommended by CLSI, using fungicidal *Fluconazole* as standard drug. The fungal strains were cultured on potato dextrose agar (PDA) and incubated at 35 °C for 24 hours and for 5 days on potato dextrose agar slant for the mold fungi. Using a sterile loop, pure colonies of the Candida species were transferred into a tube containing sterile normal saline. For the mold, 1 mL of sterile distilled water supplemented with 0.1 % Tween 20 was used to cover and re-suspend the colonies. The sterile 6 mm disks that were impregnated with test compound (with a concentration of 0.1 mg / 10 mL) were placed over the plate. Standard antifungal drug *Fluconazole* was used as positive control and sterile distilled water as negative control and incubated at 35 °C for 48 hours. The zone of inhibition was measured in millimeter [31,32].

4. RESULT AND DISCUSSION

Present study was undertaken to synthesized some novel 1, 3, 5-triazine derivatives. All the synthesized compounds were then theme for their biological evaluation. The target compounds 1 - 10 were synthesized by two step method represents in scheme - I and II. First step involves the formation of 4, 6-dicchloro-N-(pyridine-2-yl)-1, 3, 5-triazine-2-amine **(1)** by the interaction of molar ratio of cyanuaric chloride and 2-amino-pyrazine in the presence of sodium carbonate and 1, 4 dioxane at 0 - 5 ºC for 2hrs. The structure was elucidated by spectroscopy. IR peak at 3474 (br, NH, amine) cm^{-1} confirm the presence of amine group. Characteristic IR band at 2854 (C-H), 1421 - 1689 cm^{-1} (C=C) and (C=N), 1041-1321(C-N), 547 - 831cm^{-1}, (C-Cl) provide significant indication for the formation of compound. ^{1}H-NMR spectrum (500 MHz, DMSO - $d_{6)}$ of compound **(1)** showed multiple signals at δ 7.01 - 8.33 for 3H of aromatic ring and δ 3.99 singlet's for 1H of (NH) amine group. The targeted compound second and third chlorine atom of cyanuaric chloride was replaced by substituted amines using suitable solvent and formed final **2 - 10** compounds respectively. The synthesized compounds were stable and soluble in DMSO. All the synthesized compounds were characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR and Mass spectroscopy. Compounds **2 - 10** derivatives endowing amine substituent were confirmed by IR peak at 3200 - 3600 cm^{-1}. Further confirmation of all synthesized compounds was done using ^{1}H NMR spectroscopic data. Additional proton peak in the range from 4.0 - 5.0 ppm of (NH), in ^{1}H NMR confirmed the substitution with amines. Physical Data of Newly Synthesized compounds given in Table: 1

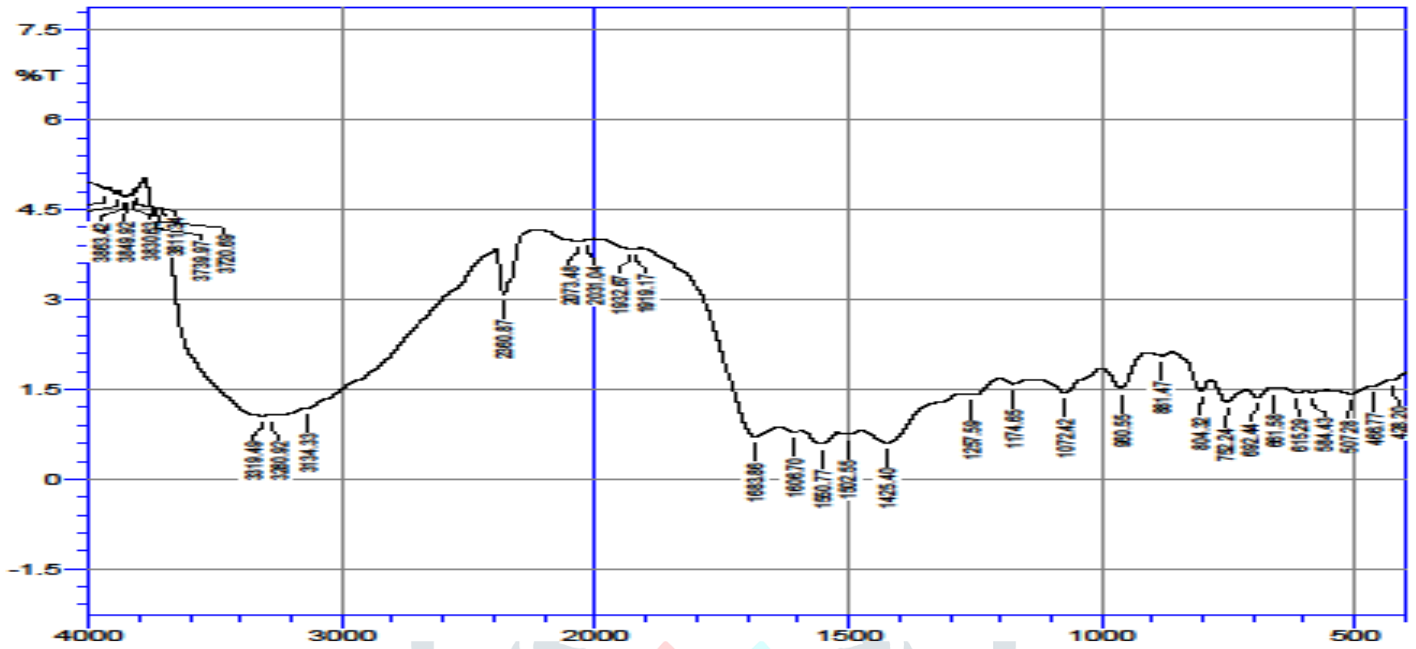
Table – 1: Physical Data of Newly Synthesized compounds

Sr. No.	Name of Compounds	Structure of Compound	Molecular Formula	Molecular Weight (g/mole)	Colour	% Yield	M.P. (ºC)
1.	1		$C_7H_4Cl_2N_6$	243.05	yellow	84.40	229
2.	2		$C_{19}H_{16}N_8$	356.38	Yellow	83.98	
3.	3		$C_{11}H_{16}N_8$	260.29	Yellow	72.53	
4.	5		$C_{15}H_{24}N_8$	316.40	Yellow	30.40	179
5.	7		$C_{17}H_{14}N_{10}$	358.35	Yellow	31.03	42-252
6.	8		$C_{19}H_{18}N_{10}$	386.41	Yellow	51.4	42-298
7.	9		$C_9H_{12}N_8O_2$	264.24	Yellow	22.44	42-269
8.	10		$C_{15}H_{20}N_8$	312.38	Yellow	57.39	

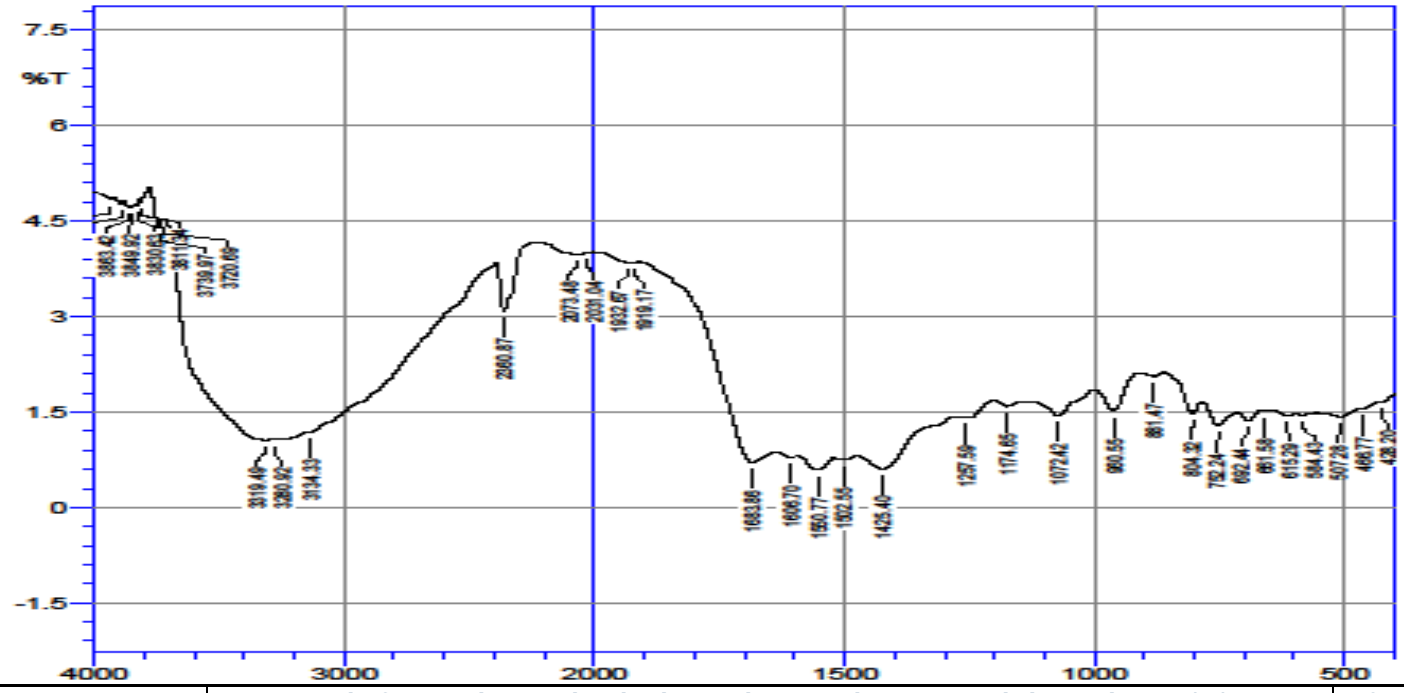
5.2. Fourier Transform infrared (FT-IR) analysis

The infrared spectra of the synthesized compounds were recorded in the range 4000 - 500 cm^{-1}. The FT-IR spectrum of compound (1) showed stretching bands at 3174 cm^{-1} (N-H), 2854 cm^{-1} (C-H), 1421 - 1689 cm^{-1} (C=C) and (C=N), 1041 - 1321cm^{-1} (C-N), 547 - 831 cm^{-1} (C-Cl). The FT-IR spectrum of compound (2) showed stretching bands at 3319 cm^{-1} (N-H), 3134 cm^{-1} (C-H), 1425 - 1683 cm^{-1} (C=C) and C=N), 960 - 1257cm^{-1} (C-N). The FT-IR spectrum of compound (3) showed stretching bands at 3278 cm^{-1} (N-H), 2987 cm^{-1} (C-H), 1411-1683 cm^{-1} (C=C) and C=N), 958 - 1246 cm^{-1} (C-N). The FT-IR spectrum of compound (5) showed stretching bands at 3278 cm^{-1} (N-H), 2933 - 3130 $cm^{-1,}$ (C-H), 1419 - 1681 cm^{-1} (C=C) and C=N), 956 - 1267 cm^{-1} (C-N). The FT-IR spectrum of compound (7) showed stretching bands at 3263 - 3304 cm^{-1} (N-H), 2920 - 3128 $cm^{-1,}$ (C-H), 1419 - 1683 cm^{-1} (C=C) and C=N), 960-1180 cm^{-1} (C-N). The FT-IR spectrum of compound (8) showed stretching bands at 3265 - 3321 cm^{-1} (N-H), 3068 cm^{-1} (C-H), 1421 - 1685 cm^{-1}(C=C) and C=N), 906 - 1305 cm^{-1} (C-N). The FT-IR spectrum of compound (9) showed stretching bands at 3218-3373 cm^{-1} (N-H), 2683-2898 $cm^{-1,}$ (C-H), 1412 - 1665 cm^{-1} (C=C) and C=N), 956-1179 cm^{-1} (C-N) and (C-O). The FT-IR spectrum of compound (10) showed stretching bands at 3115-3204 cm^{-1} (N-H), 3002 - 3032 $cm^{-1,}$ (C-H), 1395 - 1731 cm^{-1} (C=C) and C=N), 949-1253 cm^{-1} (C-N) which were assigned to the aromatic stretching frequencies respectively (Figure.2).

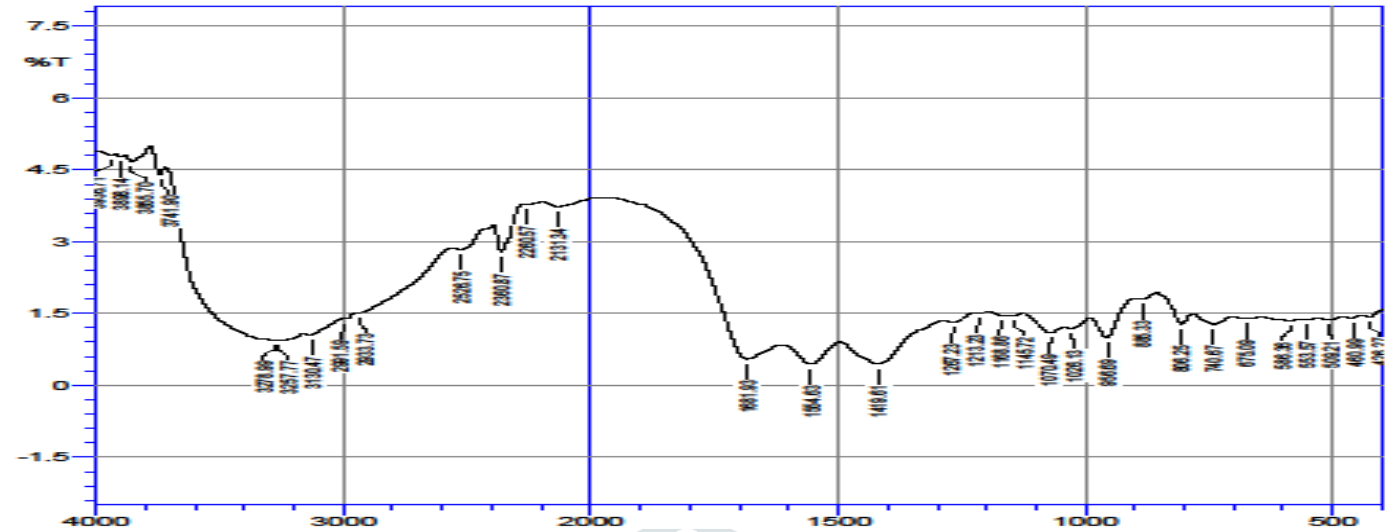
1. FT-IR of Compound (1)



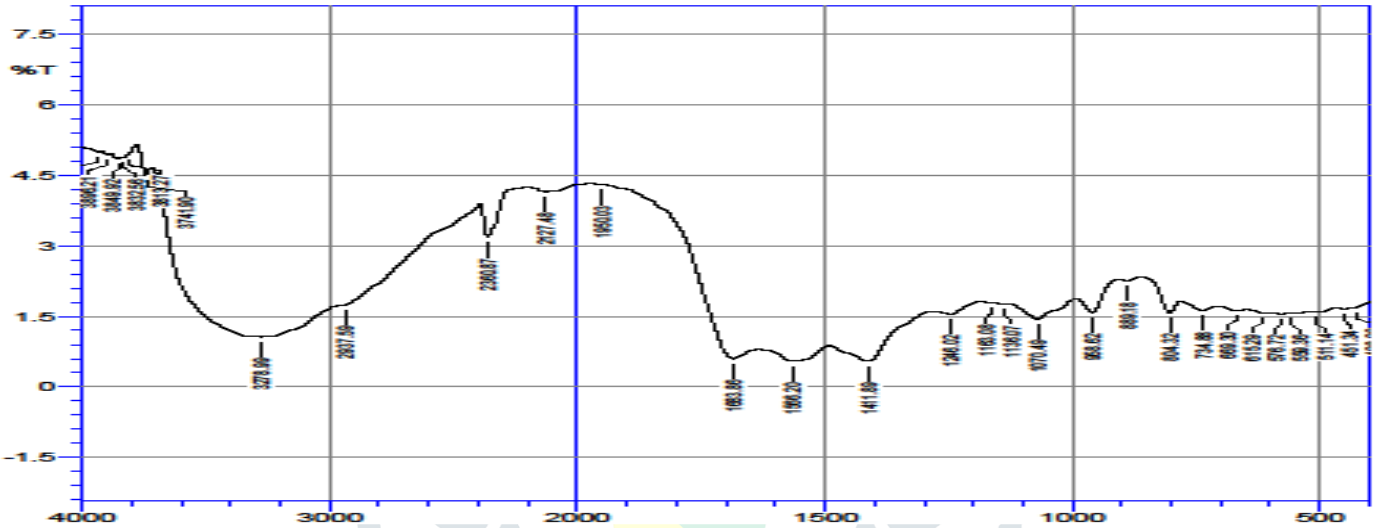
2. FT-IR of Compound (2)



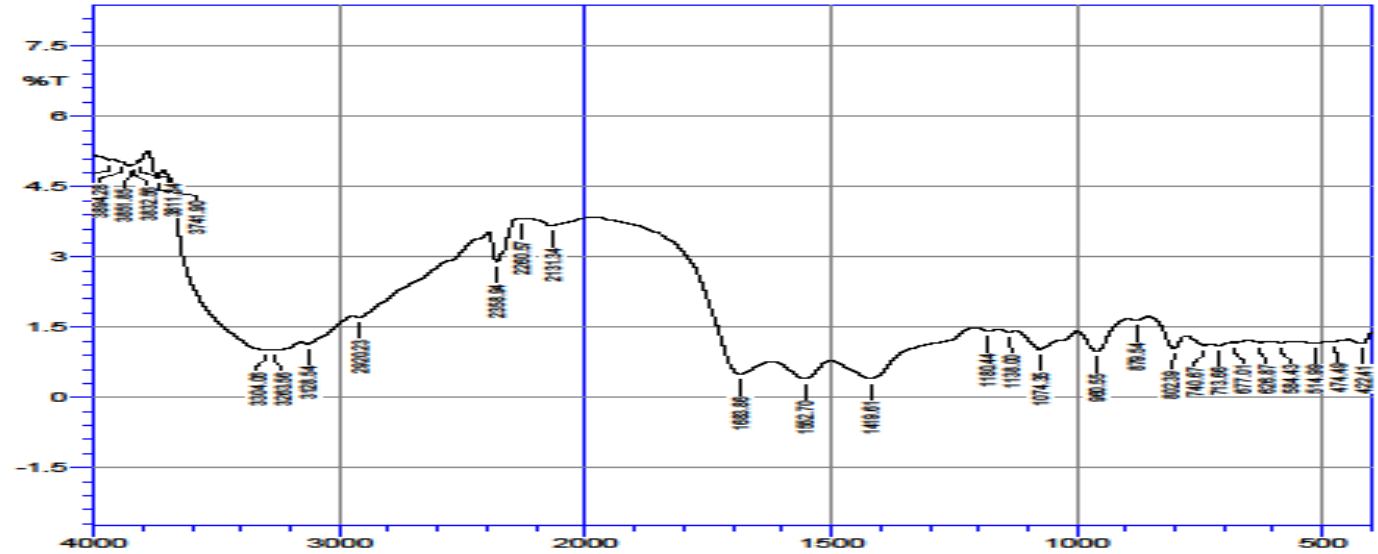
3. FT-IR of Compound (3)



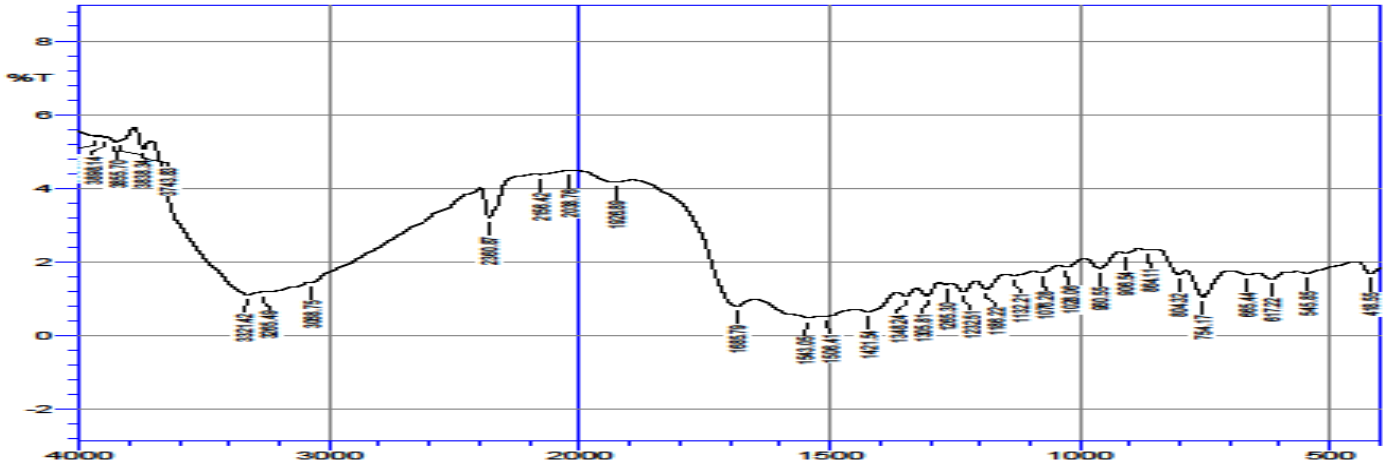
4. FT-IR of Compound (5)



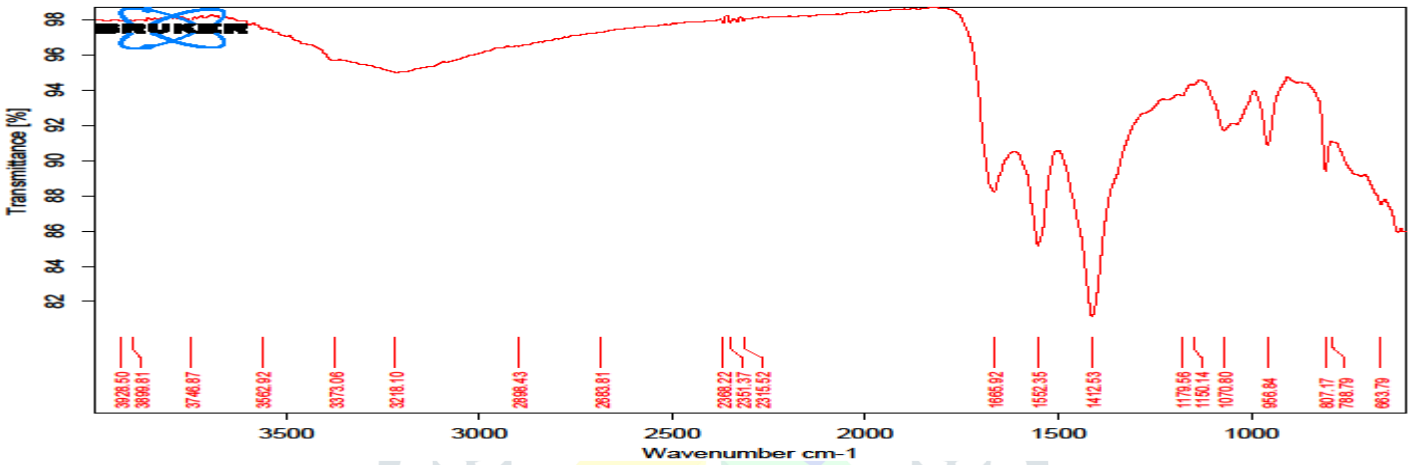
5. FT-IR of Compound (7)



6. FT-IR of Compound (8)



7. FT-IR of Compound (9)



8. FT-IR of Compound (10)

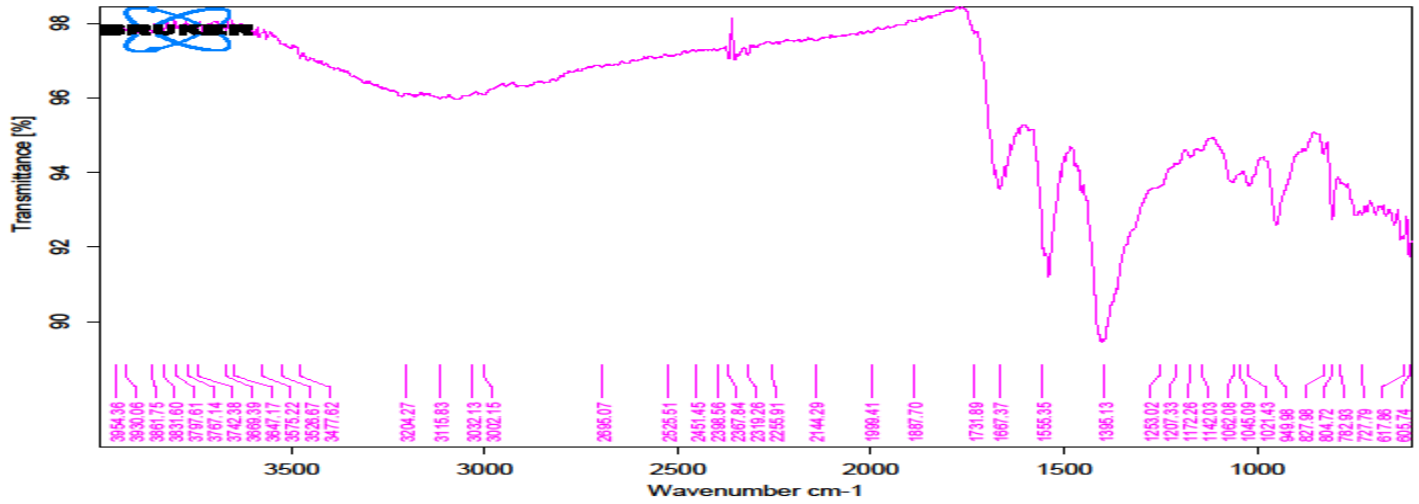


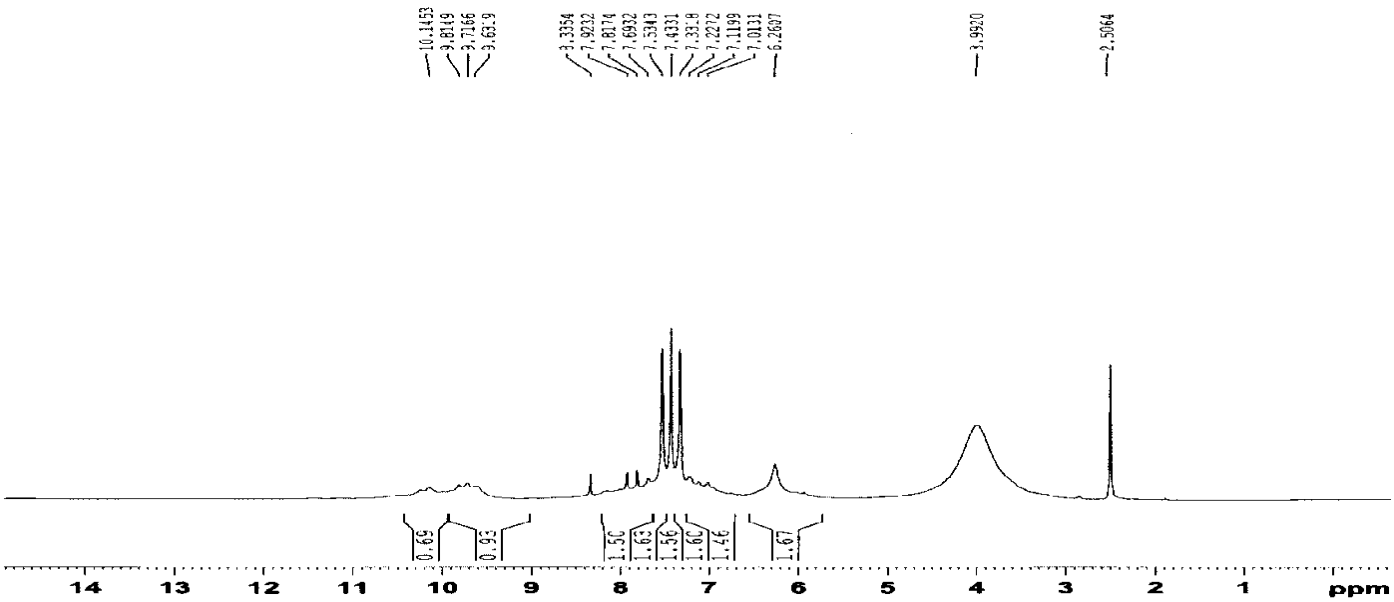
Figure 2: The FT-IR spectra of compound (1) 4, 6-dicchloro-N-(pyrazin-2-yl) - 1, 3, 5-triazine - 2-amine, N^2, N^4 - dibenzyl - N^6 - (pyrazin-2-yl) - 1, 3, 5-triazine - 2, 4, 6-triamine (2), N^2, N^2, N^4, N^4 - tetramethyl - N - (pyrazin-2-yl)-1, 3, 5-triazine-2, 4, 6-triamine (3), N^2, N^2, N^4, N^4 - tetraethyl - N^6 (pyrazin-2-yl) - 1, 3, 5-triazine-2, 4, 6-triamine (5), N^2-(pyrazin-2-yl)-N^4, N^6-di (pyridine-4-yl) - 1, 3, 5-triazine-2, 4, 6-triamine (7), N2, N4 - bis (2-aminophenyl) - N6 - (pyrazine-2-yl) - 1, 3, 5-pyrimidine - 2, 4, 6-triamine (8), N^2, N^4-dimethoxy-N^6-(pyrazine-2-yl)-1, 3, 5 – triazine - 2,4,6 - triamine (9), N^2, N^4 - bis (cyclopropylmethyl) - N6 - (pyrazine-2-yl) - 1, 3, 5 – triazine - 2, 4, 6 - triamine (10)

5.3. Proton nuclear magnetic resonance (^{1}H NMR) analysis.

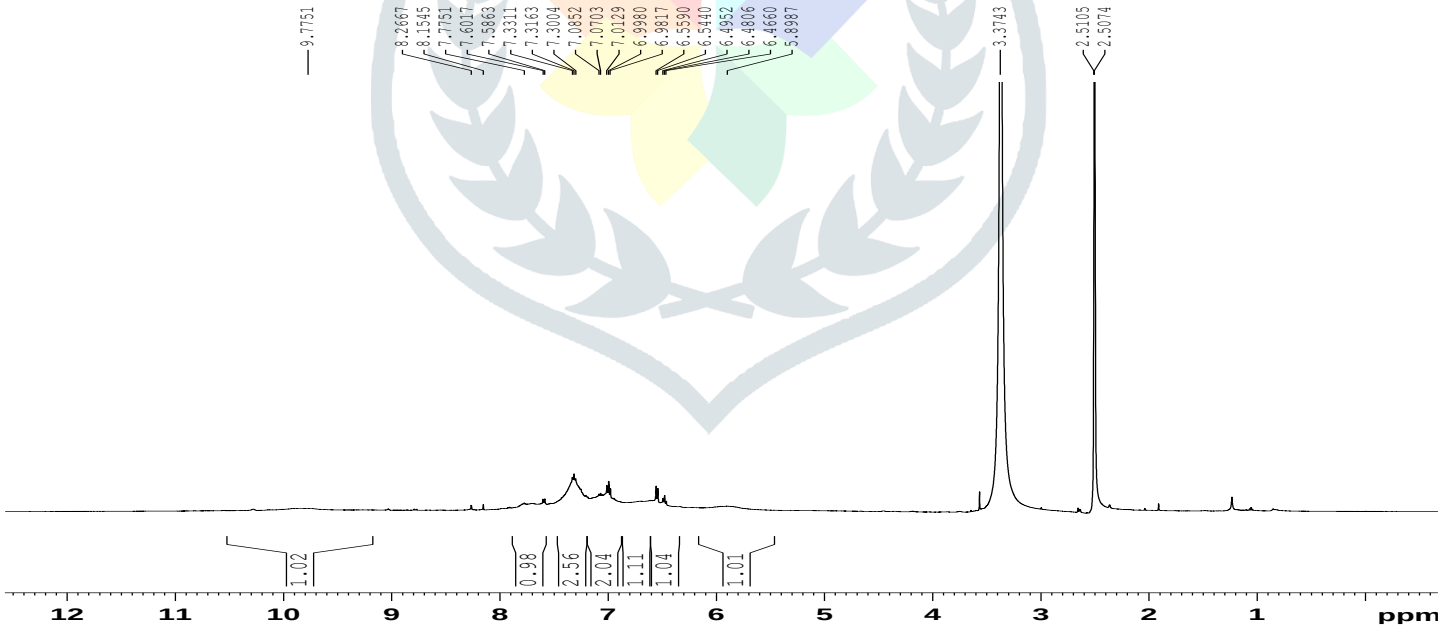
The ^{1}H NMR spectra for the synthesized compounds were recorded in d^6 DMSO. The proton NMR spectrum of compound (1) shows aromatic proton multiple signals at δ (6.26 - 8.33) and the (N-H) singlet absorption occurs at δ (3.99). The proton NMR of compound (2) also shows aromatic proton multiple signals at δ (5.89 - 9.77) and the singlet absorption occurs for three (NH) at δ (3.37) due to same chemical environment. Compound (3) shows aromatic proton multiple signals at δ (5.84 - 9.75) and the (N-H) singlet occurs at δ (3.34) and methyl proton shows signal at δ (3.06). Compound (5) shows aromatic proton multiple signals at δ (5.88-9.83) and the (N-

H) singlet occurs at δ (3.37), methyl proton shows two signals, at δ (2.88 - 2.89) for CH_2 proton and δ (1.16 - 1.19) for CH_3 proton due to different environment. The proton NMR spectrum of compound (7) shows aromatic proton multiple signals at δ (6.00 - 8.24) and the (N-H) singlet absorption occurs at δ (3.99 - 531). The proton NMR of compound (8) also shows aromatic proton multiple signals at δ (6.51 - 9.64) and the br. singlet absorption occurs for three (N-H) groups at δ (3.41 - 3.63) and four proton of (NH_2) group show shows absorption at δ (6.27 - 6.37). The proton NMR spectrum of compound (9) shows aromatic proton multiple signals at δ (5.85 - 9.76) and the (N-H) absorption occurs at δ (3.39) and the methyl proton of methoxy group shows signal at δ (3.67 - 3.72). The proton NMR spectrum of compound (10) shows aromatic proton multiple signals at δ (5.73 - 9.62), the (N-H) absorption occurs at δ (3.26) and four proton of (CH_2) group show signal between δ (0.70 - 2.35), for two proton of CH group show absorption at δ (0.69) and eight proton of (CH2) group of cyclopropanemethylamine shows signal between δ (0.16 - 0.37) (Figure. 3).

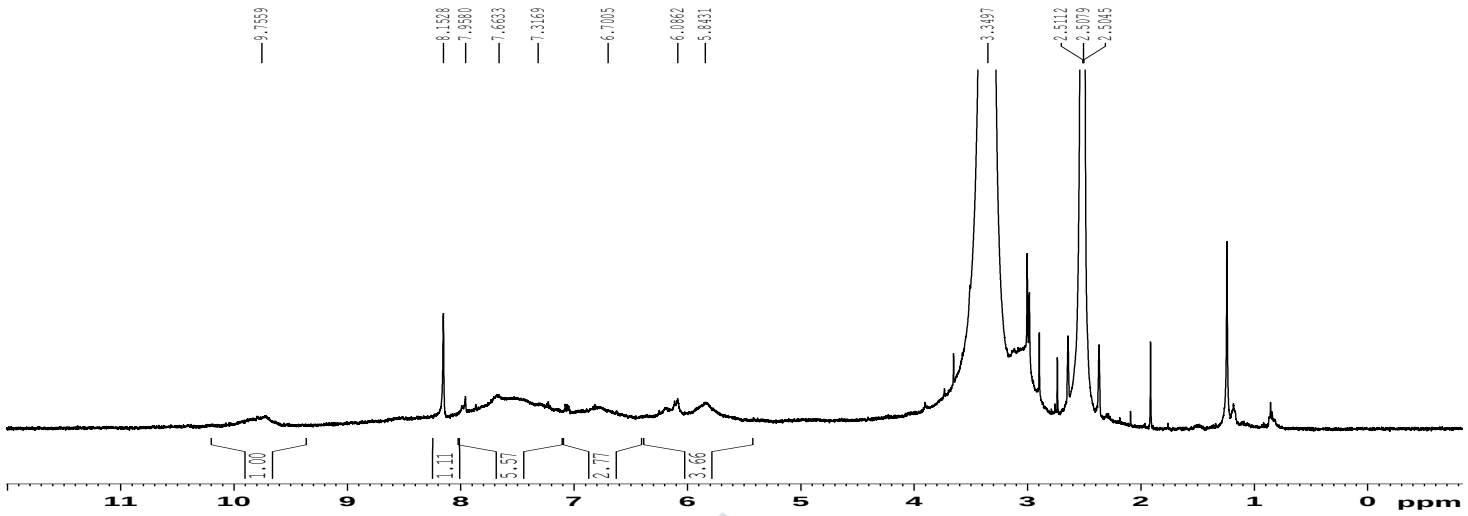
1. Proton NMR Spectra of Compound (1)



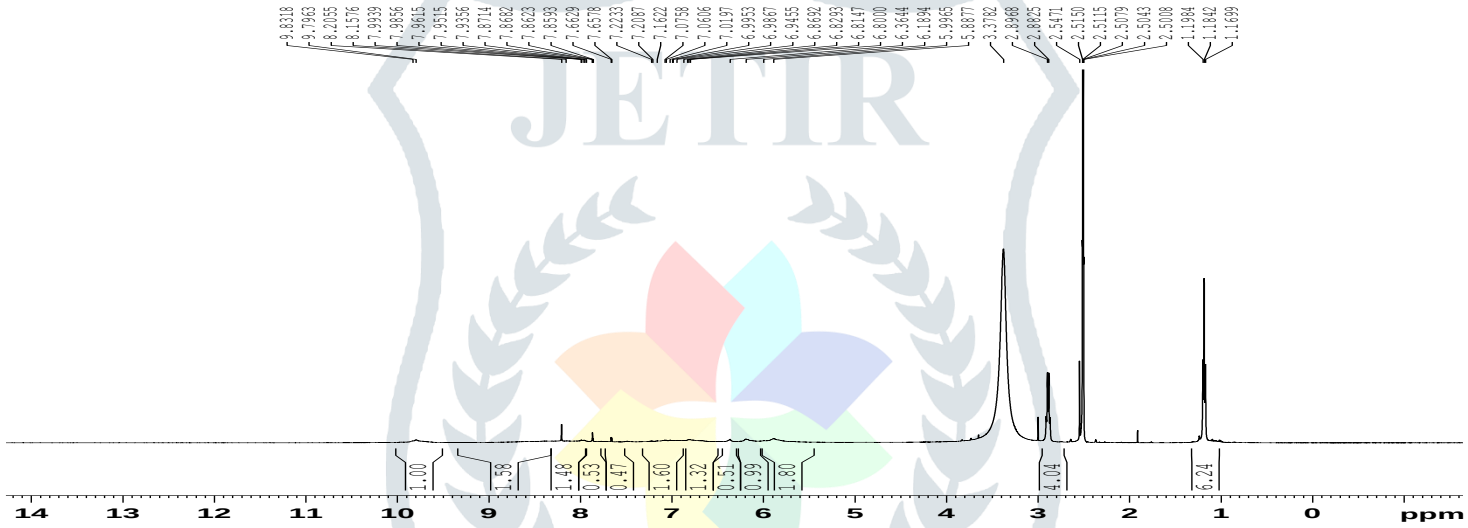
2. Proton NMR Spectra of Compound (2)



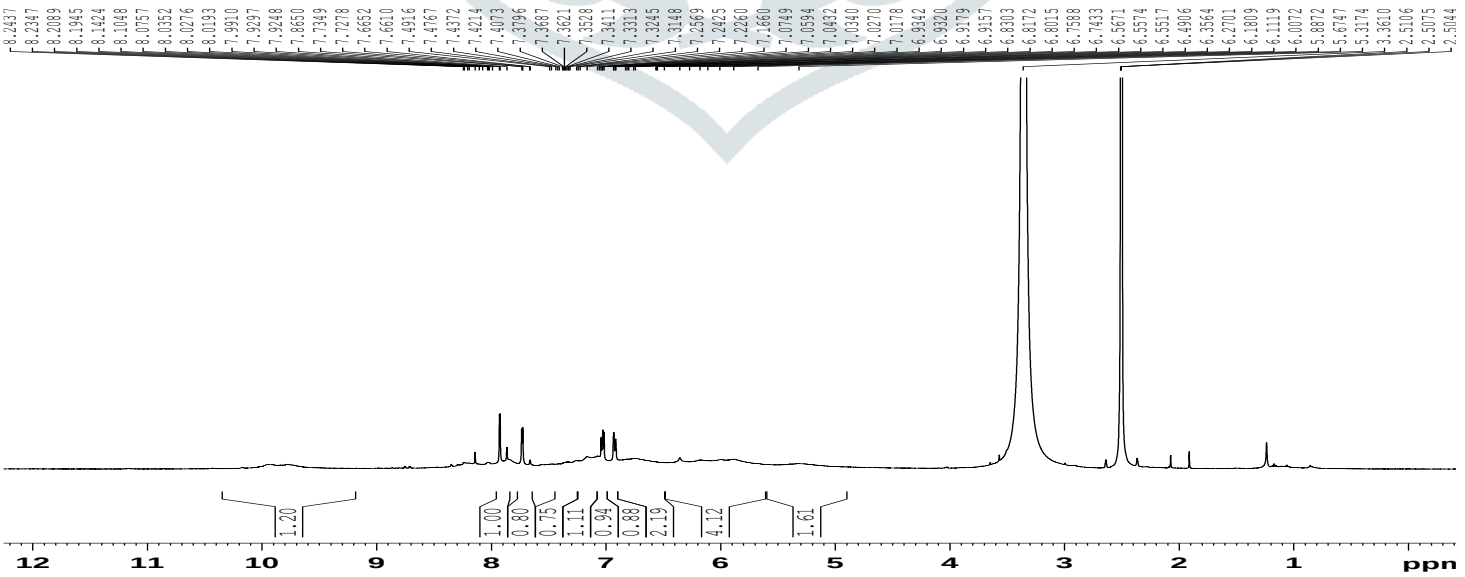
3. Proton NMR Spectra of Compound (3)



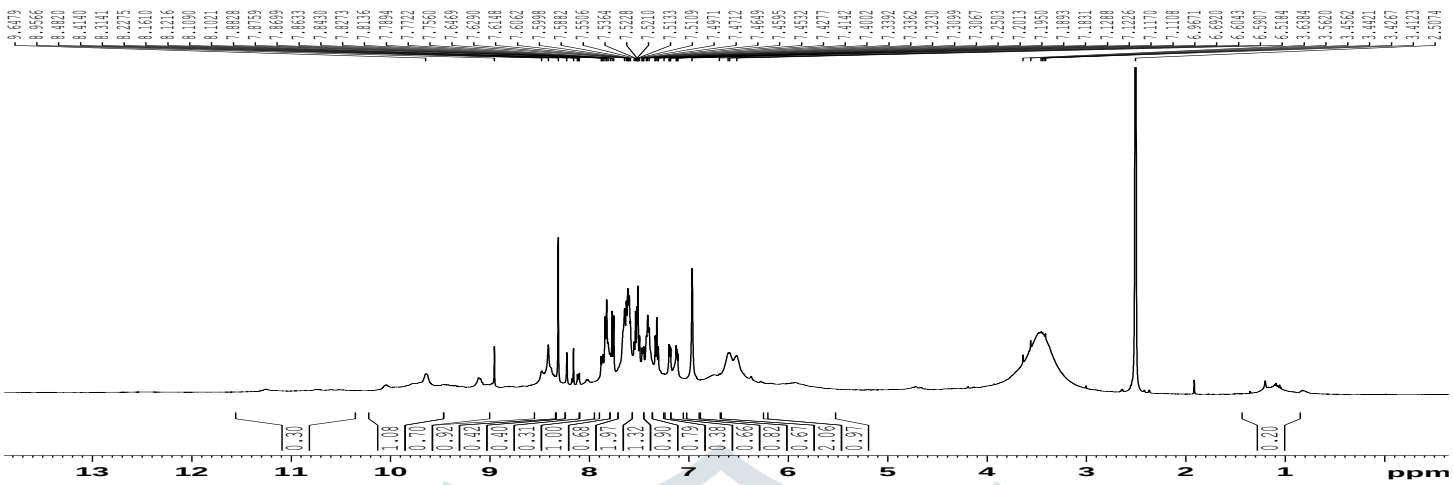
4. Proton NMR Spectra of Compound (5)



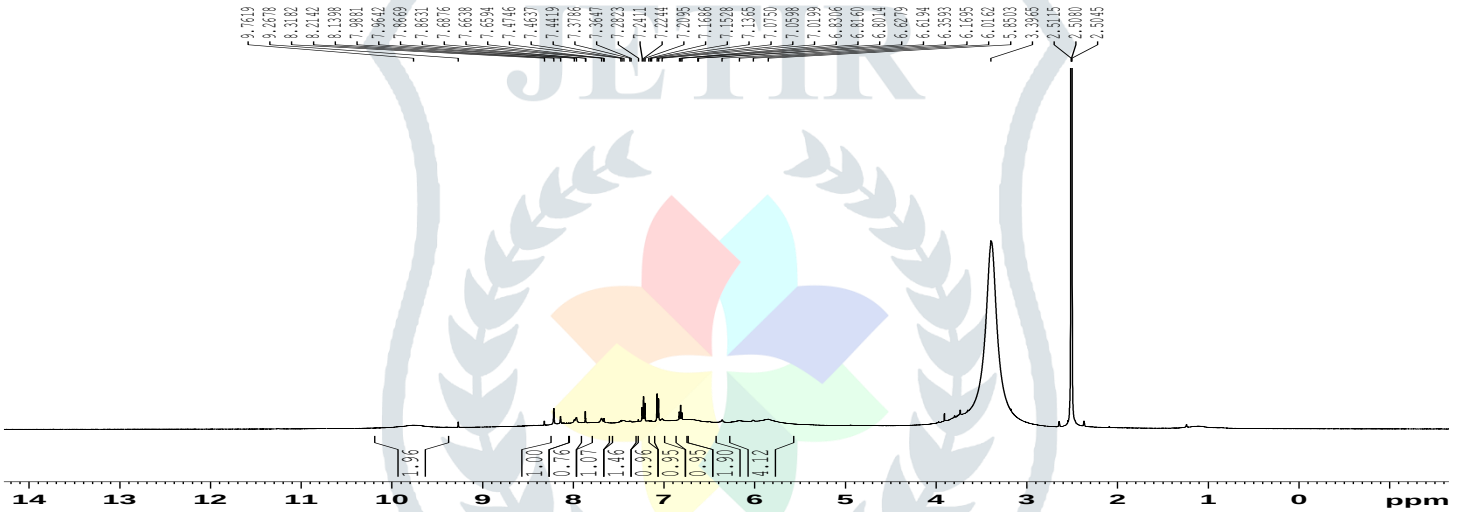
5. Proton NMR Spectra of Compound (7)



6. Proton NMR Spectra of Compound (8)



7. Proton NMR Spectra of Compound (9)



8. Proton NMR Spectra of Compound (10)

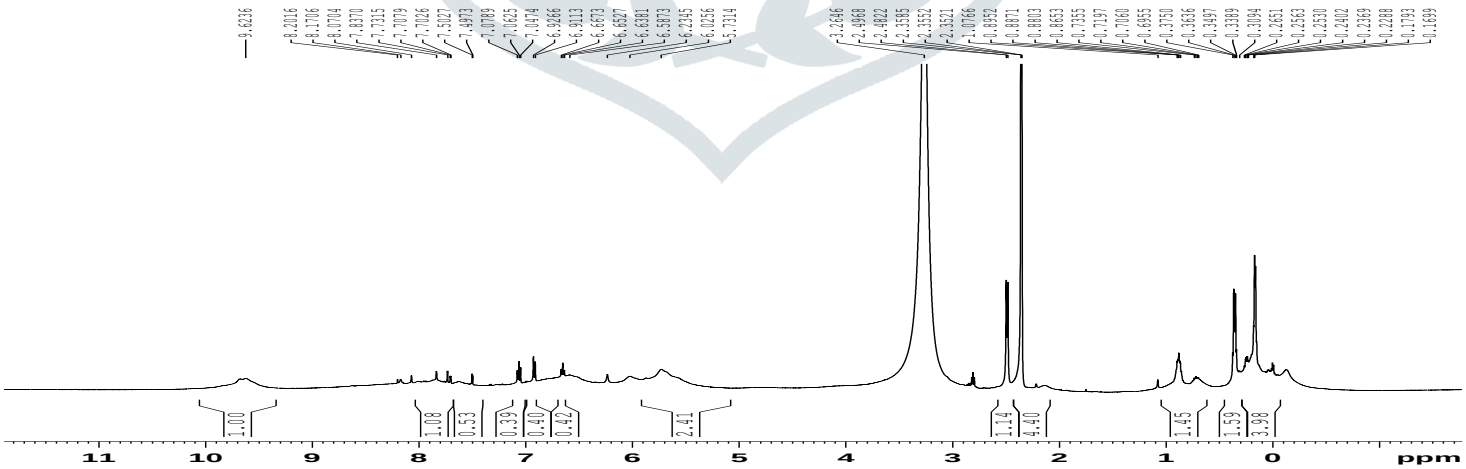
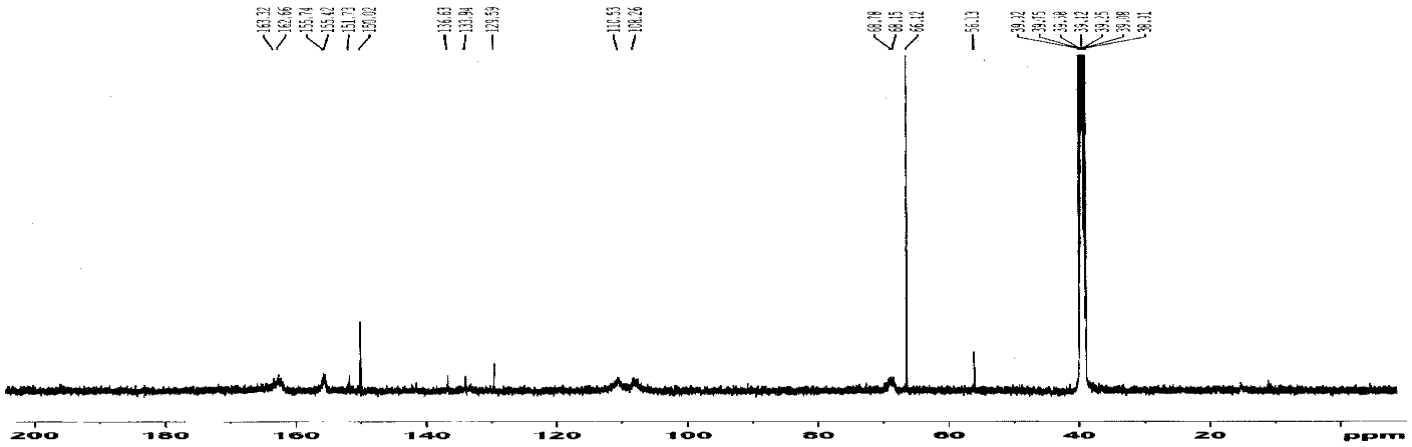


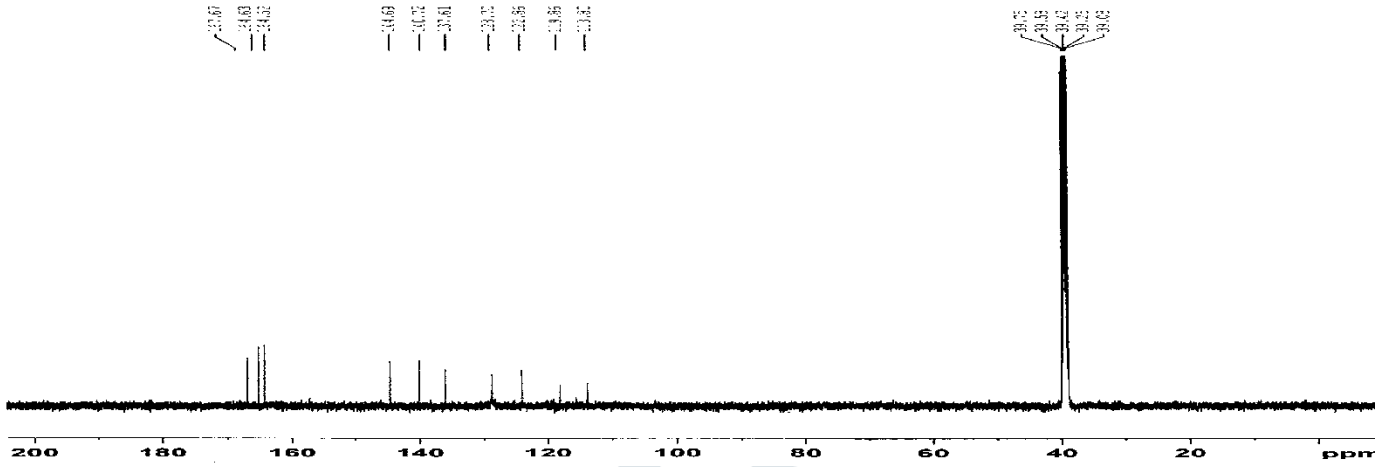
Figure 3: The ^{1}H NMR spectra of compound (1) 4, 6-dicchloro-N-(pyrazin-2-yl)-1,3,5-triazine-2-amine, N^2, N^4-dibenzyl-N^6-(pyrazin-2-yl)-1,3,5-triazine-2,4,6-triamine (2), N^2,N^2,N^4,N^4-tetramethyl-N-(pyrazin-2-yl)-1,3,5-triazine-2,4,6-triamine (3), N^2,N^2,N^4,N^4-tetraethyl-N^6 (pyrazin-2-yl)-1,3,5-triazine-2,4,6-triamine (5), N^2-(pyrazin-2-yl)-N^4,N^6-di (pyridine-4-yl)-1,3,5-triazine-2,4,6-triamine (7), N2, N4-bis (2-aminophenyl)-N6-(pyrazine-2-yl)-1,3,5-pyrimidine-2,4,6-triamine (8), N^2, N^4-dimethoxy-N^6-(pyrazine-2-yl)-1,3,5-triazine-2,4,6-triamine (9), N^2,N^4-bis (cyclopropylmethyl)-N6-(pyrazine-2-yl)-1,3,5-triazine-2,4,6-triamine (10).

5.4. Carbon nuclear magnetic resonance (^{13}C NMR) analysis.

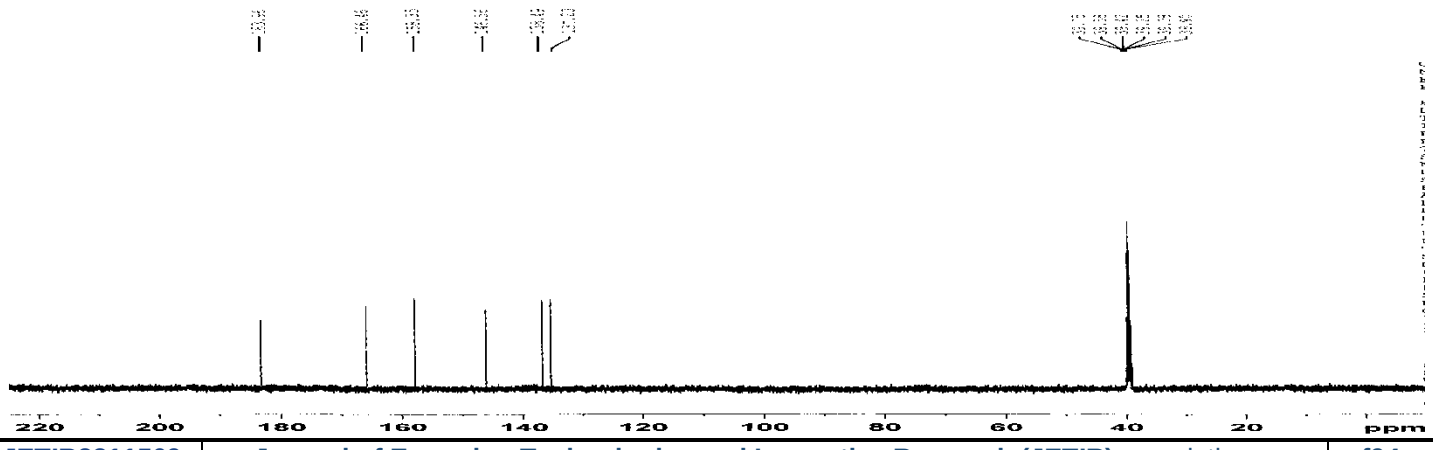
1. ^{13}C NMR Spectra of Compound (1)



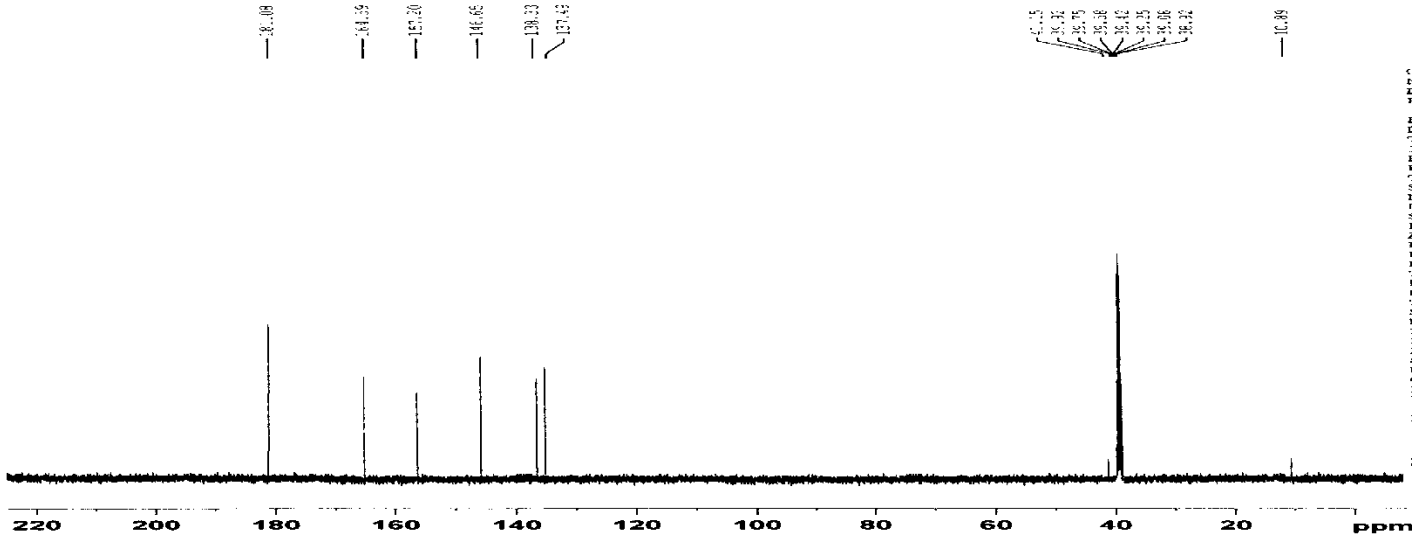
2. ^{13}C NMR Spectra of Compound (2)



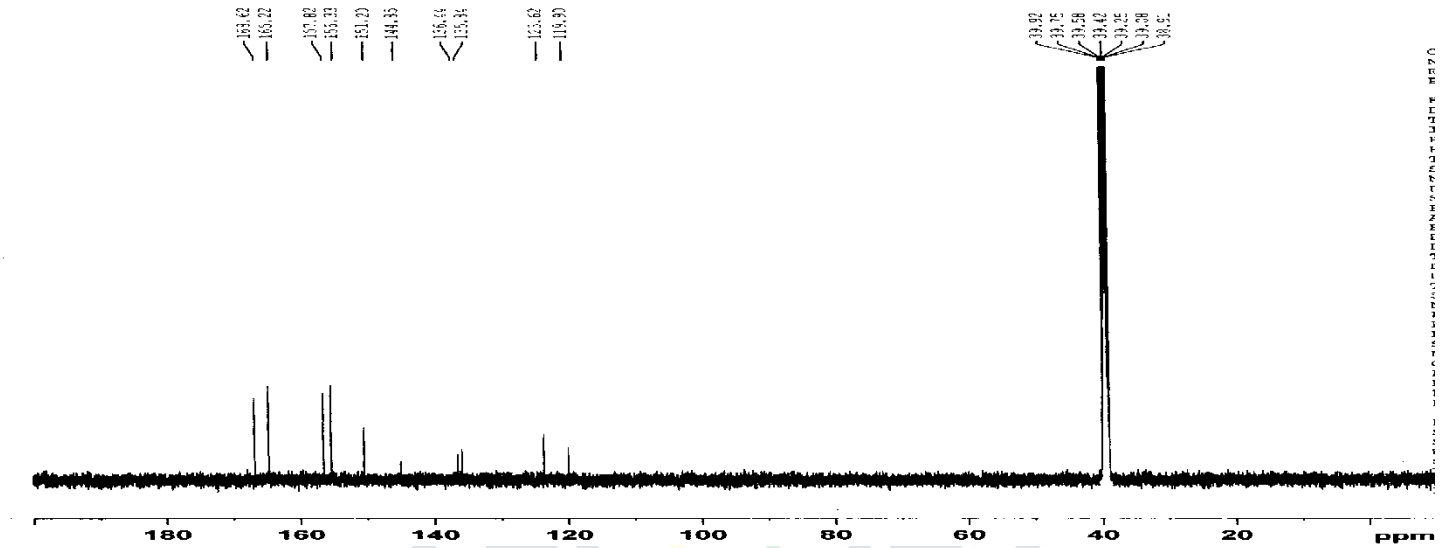
3. ^{13}C NMR Spectra of Compound (3)



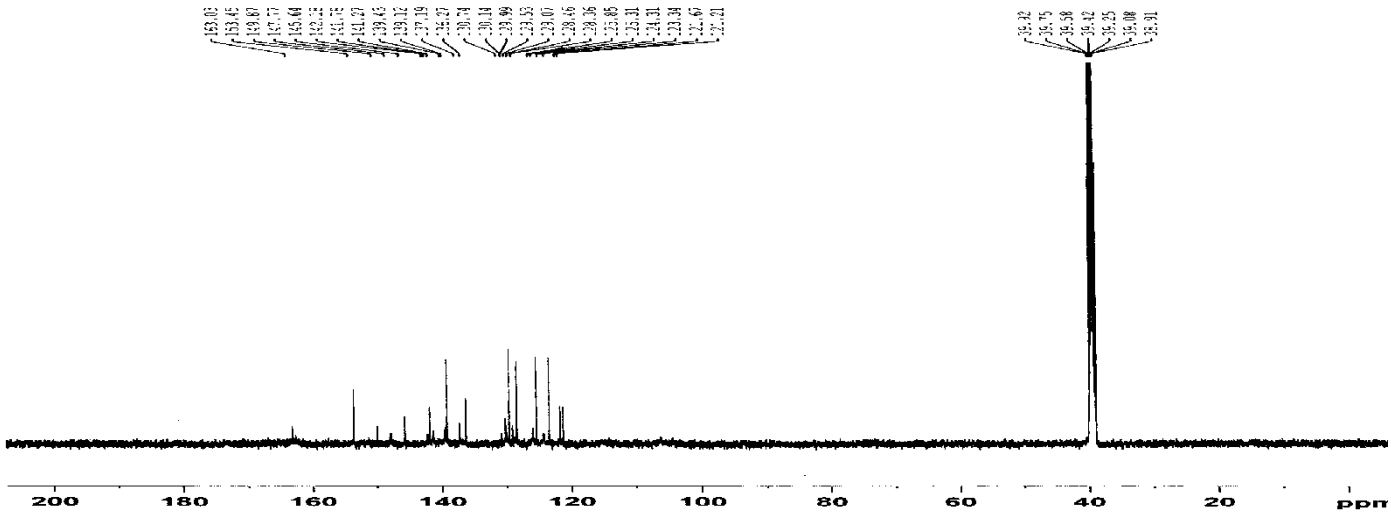
4. ^{13}C NMR Spectra of Compound (5)



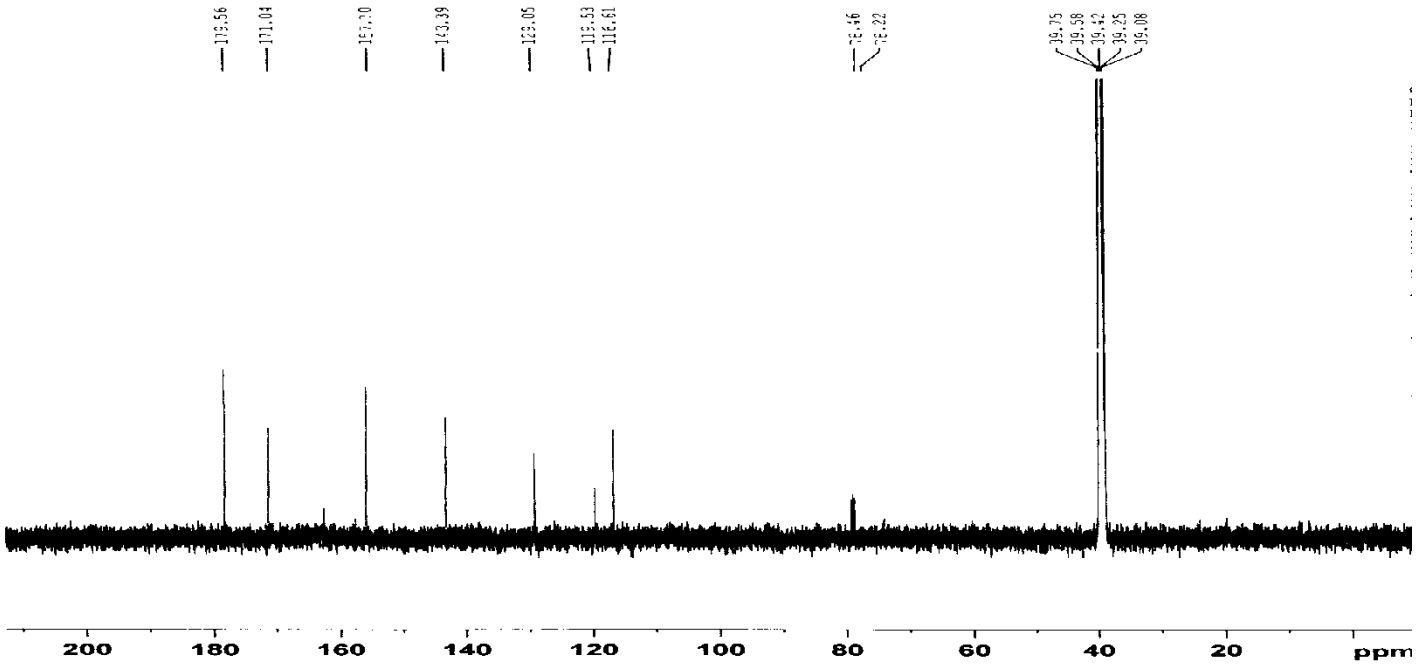
5. ^{13}C NMR Spectra of Compound (7)



6. ^{13}C NMR Spectra of Compound (8)



7. ^{13}C NMR Spectra of Compound (9)



8. ^{13}C NMR Spectra of Compound (10)

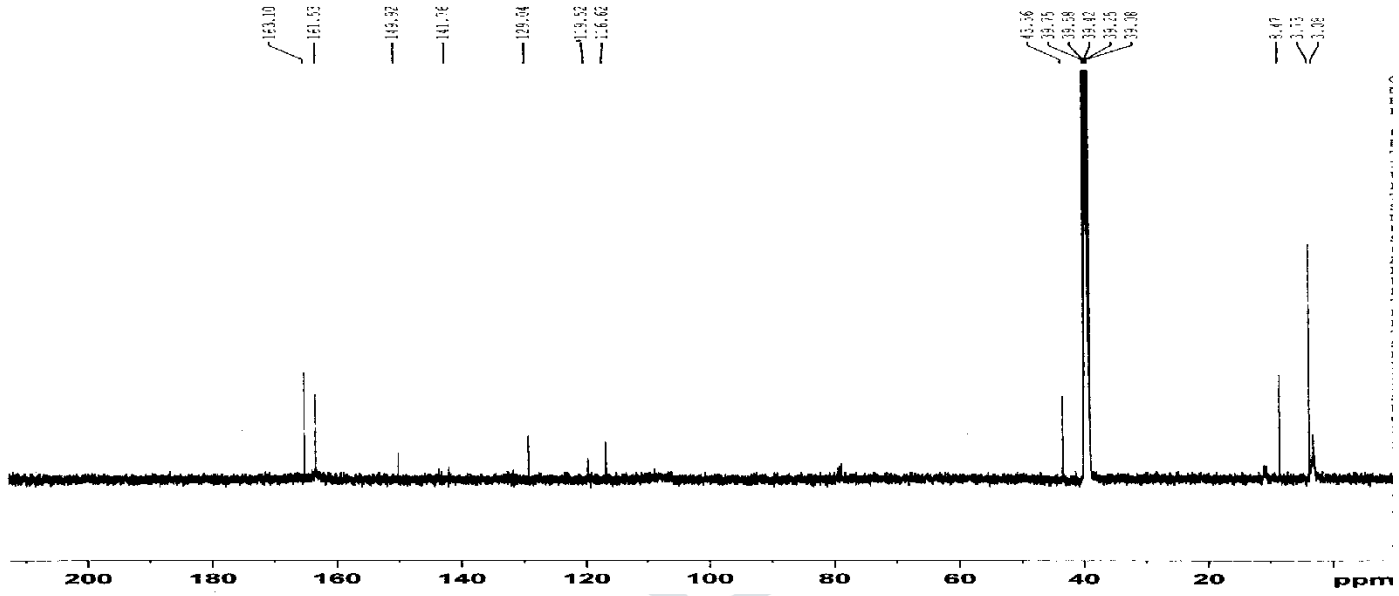


Figure 4: The [1]3C NMR spectra of compound (1) 4, 6-dicchloro-N-(pyrazin-2-yl)-1,3,5-triazine-2-amine, N^2, N^4-dibenzyl-N^6-(pyrazin-2-yl)-1,3,5-triazine-2,4,6-triamine (2), N^2,N^2,N^4,N^4-tetramethyl-N-(pyrazin-2-yl)-1,3,5-triazine-2,4,6-triamine (3), N^2,N^2,N^4,N^4-tetraethyl-N^6 (pyrazin-2-yl)-1,3,5-triazine-2,4,6-triamine (5), N^2-(pyrazin-2-yl)-N^4,N^6-di (pyridine-4-yl)-1,3,5-triazine-2,4,6-triamine (7), N2, N4-bis (2-aminophenyl)-N6-(pyrazine-2-yl)-1,3,5-pyrimidine-2,4,6-triamine (8), N^2, N^4-dimethoxy-N^6-(pyrazine-2-yl)-1,3,5-triazine-2,4,6-triamine (9), N^2,N^4-bis (cyclopropylmethyl)-N6-(pyrazine-2-yl)-1,3,5-triazine-2,4,6-triamine (10).

5. BIOLOGICAL EVALUATION

The biological evaluation of newly synthesizes derivatives summarized in Table - 2**.** All synthesized novel compounds were screened for their antibacterial and antifungal activity against three antimicrobial species (*Escherichia coli*, *Pseudomonas fluorescens* and *staphylococcus aureus*), two antifungal species (*Aspergillus niger* and *Candida albicans*) by disc diffusion method. *Ofloxacin*, *Fluconazole* were used as standard drugs for antibacterial and antifungal activity, respectively and the result shown in Table.2.

Table – 2: Biological activity of Novel s-triazine derivatives with substituted amines.

Compound No.	Antibacterial Activity (300 µg/ml)			Antifungal Activity (300 µg/ml)	
	Gram – ve		Gram + ve		
Compound No. Compound No.	*E.coli*	*Peudomonas fluorescence*	*Staphylococcus Aureus*	*Aspergillus niger*	*Candida Albicans*
1	**13**	**12**	**12**	**--**	**13**
2	**--**	**--**	**--**	**--**	**--**
3	**--**	**--**	**--**	**--**	**--**
5	**--**	**12**	**--**	**--**	**--**
7	**--**	**--**	**--**	**--**	**--**
8					
9	**12**	**12**	**8**	**10**	**12**
10	**--**	**--**	**--**	**--**	**--**
Standard Drug (µg/ml)					
Reference	**Ofloxacin**	**Ofloxacin**	**Ofloxacin**	**Fluconazole**	**Fluconazole**
Zone of inhibition	25 mm	35 mm	35 mm	17 mm	20 mm

5.1. Antibacterial Analysis

All synthesized compounds were exhibited moderate activity. Among them chloro group containing derivatives **1** was found to be highly active for bacterial strain *E.coli* and moderate activity against *Pseudomonas fluorescence* and *Staphylococcus aures*. Compound **5** show significant activities against *Peudomonas fluorescence*. Compound **9** displayed good activity against *Escherichia coli, Pseudomonas fluorescens* and moderate activity against *Staphylococcus aureus.* Among the synthesized compounds, **1** and **9** exhibit good activity against the all three bacterial species than other S- Triazine derivatives. (Figure. 5, 6, 7).

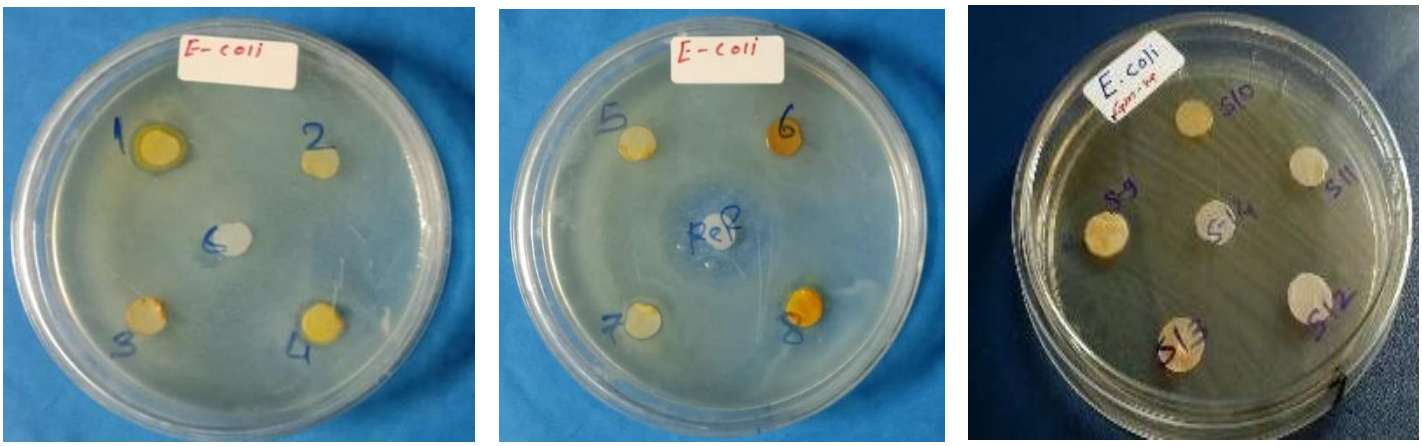


Figure 5: Antibacterial activity of Novel s-triazine derivatives with substituted amines against Gram –ve *E.Coli*

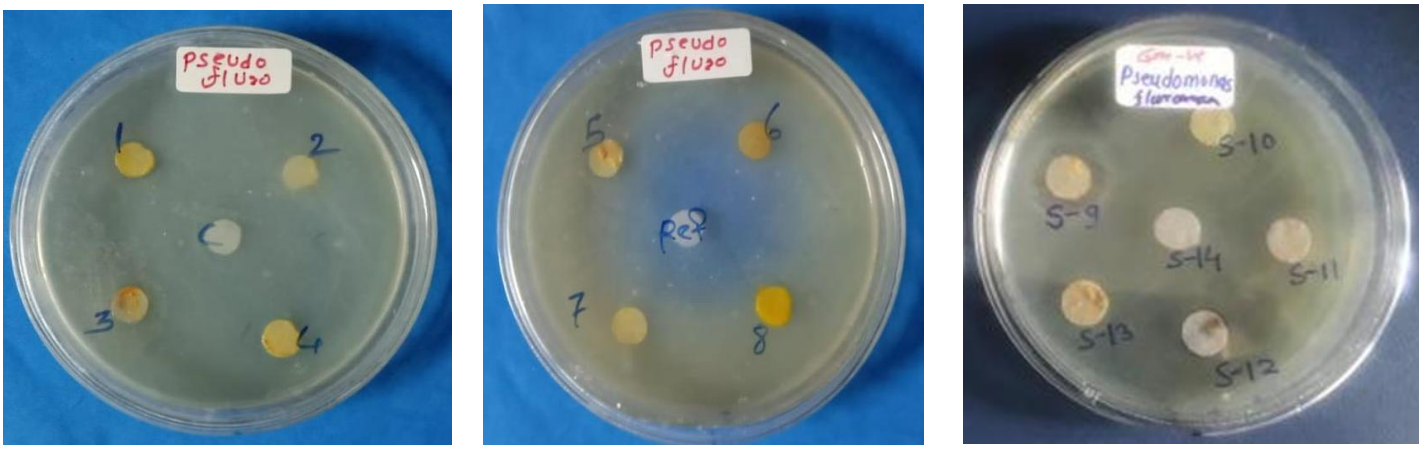


Figure 6: Antibacterial activity of Novel s-triazine derivatives with substituted amines against Gram - ve *Pseudomonas fluorescence.*

Figure 7: Antibacterial activity of Novel s-triazine derivatives with substituted amines against Gram + ve *Staphylococcus aures*.

5.2. Antifungal Analysis

All Synthesized scaffold were examined for their antifungal activity which is outlined in Table 2. Shows that chlorinated derivatives of s-triazine **1** display excellent inhibitory zone against Candida albicans respectively. Compound **9** also exhibited good antifungal ability against the fungal strain *Aspergillus niger and Candida albicans*. All tested compound did not potential to exhibit antifungal activity against *Aspergillus niger* (Figure. 8, 9).

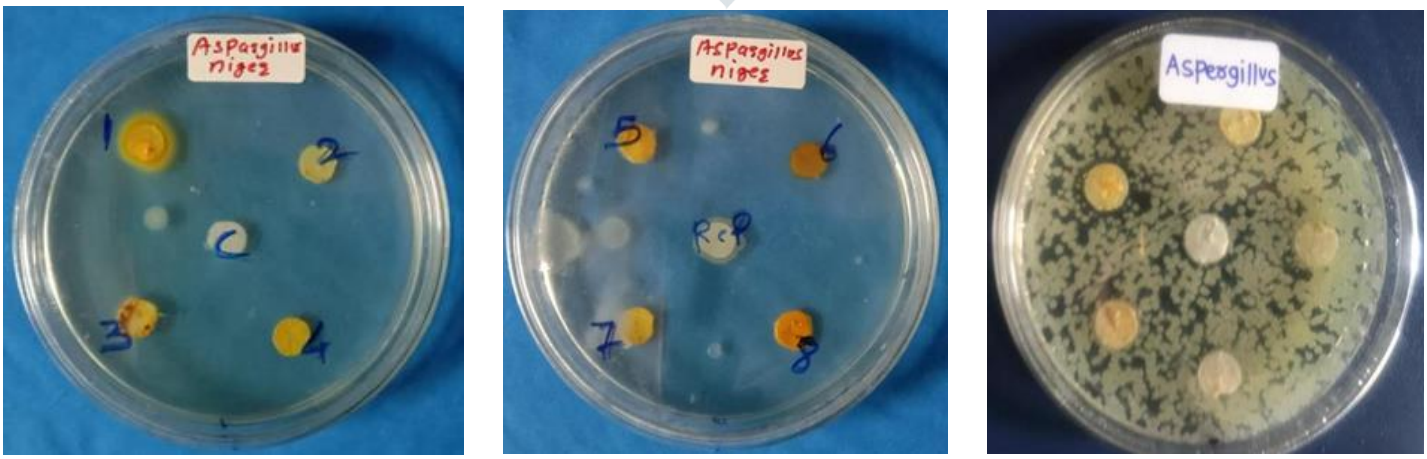


Figure 8: Antifungal activity of Novel s-triazine derivatives with substituted amines against *Aspergillus niger.*

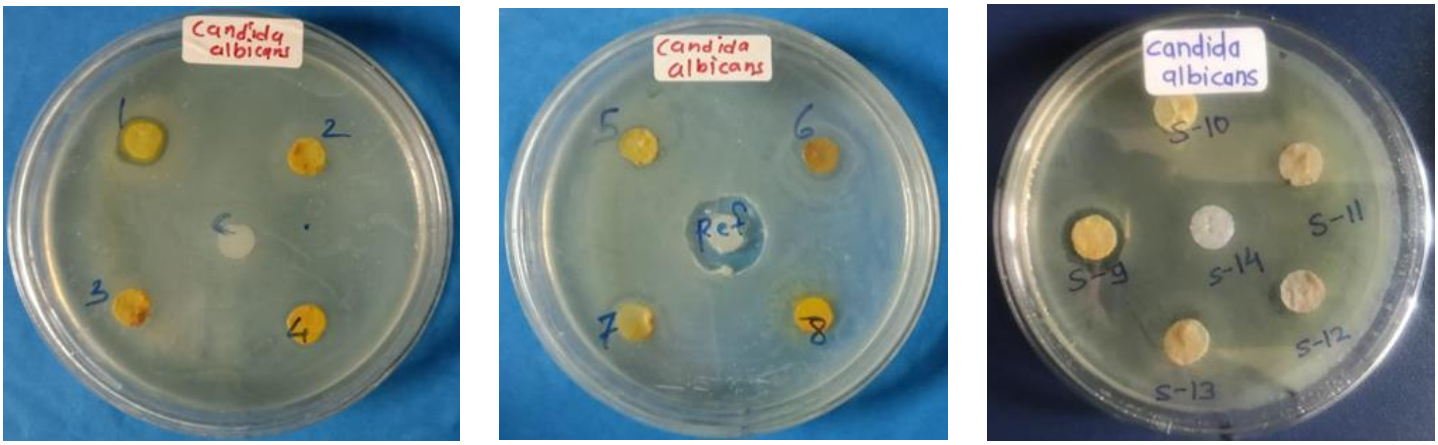


Figure 9: Antifungal activity of Novel s-triazine derivatives with substituted amines against *Candida albicans.*

6. CONCLUSIONS

A novel series of s-triazine hybrid compounds were successfully synthesized by employing aromatic nucleophilic replacement of cyanuaric chloride with various substituted amines reflux with 1, 4 - Dioxane solvent by microwave assisted method. All the target compounds 1-10 were synthesized and screened for their antibacteria, antifungal activity. These newly prepared compounds were fully characterized through the spectral and biological assays which were completely fit with the assigned structures. A number of the synthesized compounds were screened against gram-positive bacteria *(Staphylococcus aures*) gram-negative bacteria *(E.coli* and *Pseudomonas fluorescence)*, fungi (*Aspergillus niger and Candida albicans*). Out of eight compounds three came out with promising activity against pathogenic bacteria and fungi. Chloro group containing derivatives **1** was found to be highly active for bacterial strain *E.coli* and moderate activity against *Pseudomonas fluorescence* and *Staphylococcus aures*. Diethyl amine substituted N^2, N^2, N^4, N^4-tetraethyl-N6-(pyrazin-2-yl)-1, 3, 5-triazine-2,4,6-triamine (5) and Cyclopropanemethylamine substituted N^2, N^4-dimethoxy-N^6-(pyrazine-2-yl)-1 ,3, 5-triazine-2, 4, 6-triamine (9) compounds displyed better activity against *E.coli* and *Pseudomonas fluorescence* than other derivatives. Chlorinated derivatives of s-triazine **1** display excellent inhibitory zone against Candida albicans respectively. Compound **9** also exhibited good antifungal ability against the fungal strain *Aspergillus niger and Candida albicans.* These prerogative structures with enhanced bioactivities lead to provide adequate scope to develop new scaffolds for further drug discovery process.

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REFERENCES

[1] Smolin, E. M. Rapoport, L.1959. s-Triazines and Derivatives. Interscience Publishers, Inc.: New York, 13, 644.

[2] Neunhoeffer, H. Wiley, P. F. 1978. Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines. John Wiley & Sons, Inc.: New York, 33, 1335**.**

[3] Quirke, J. M. E. 1984. Comprehensive Heterocyclic Chemistry. Pergamon Press: Oxford, 3, 457.

[4] Saumya Singh, Milan K. Mandal, Anup Masih, Ashmita Saha, Surajit K. Ghosh, Hans R. Bhat, Udaya, P. Singh. 2021. 1,3,5-Triazine: A versatile pharmacophore with diverse biological activities. Arch Pharma, 6, 354.

[5] Gavade, S.N. Markad, V.L. Kodam, K.M. Shingare,M.S. Mane, D.V. 2012. Synthesis and biological evaluation of novel 2,4,6-triazine derivatives as antimicrobial agents. Bioorg. Med.Chem. Lett. 22 (15), 5075- 5077.

[6] Desai, N.C. Makwana, A.H. Rajpara, K.M. 2016. Synthesis and study of 1,3,5-triazine based thiazole derivatives as antimicrobial agents. Journal of Saudi chemical society. 20, S33S4-S341.

[7] Singh U, Bhatt H, Gahtori P. 2012. Antifungal activity, SAR and physicochemical correlation of some thiazole-1,3,5-triazine derivativesActivité antifongique, SAR et corrélations physico-chimiques de quelques dérivés du thiazole-1,3,5-triazine. Journal of Mycologie Médicale. 22(2), 134–141.

[8]. Sekar, N. Padalkar, S. Phatangare K.R. Gupta, D. Patil V.S. 2011. Prashanth, Synthesis and biological evaluation of novel 6-aryl -2,4 -disubstituted schiffs base 1,3,5- triazine derivatives as anti-microbial agents, RJPBCS, 2(3), 908-917.

[9] Kumar S, Bhat HR, Kumawat MK, Singh UP. 2013. Design and one pot synthesis of hybrid thiazolidin-4-one-1, 3, 5-triazines as potent antibacterial agents against human disease-causing pathogens, New J. Chem. 37, 2, 581–584.

[10] Machakanur SS, Patil BR, Badiger DS, Bakale RP, Gudasi KB, Annie Bligh S. 2012. Synthesis, characterization and anticancer evaluation of novel tri-arm star shaped 1, 3, 5-triazine hydrazones. J. Mol. Struct. 1011, 121–127.

[11] Patel RV, Kumari P, Rajani DP, Chikhalia KH. 2011. Synthesis and studies of novel 2-(4-cyano-3-trifluoromethyl phenyl amino) 4- (quinoline-4-yloxy)-6-(piperazinyl/ piperidinyl)-s-triazines as potential antimicrobial, antimycobacterial and anticancer agents. Eur. J. Med. Chem. 46(9), 4354–4365.

[12] Kumar GJ, Bomma HS, Srihari E et al. 2013. Synthesis and anticancer activity of some new s-triazine derivatives. Med. Chem. Res. 22(12), 5973–5981.

[13] Brzozowski Z, Sączewski F. 2002. Synthesis and antitumor activity of novel 2-amino-4-(3, 5, 5-trimethyl-2-pyrazolino)-1, 3, 5-triazine derivatives. Eur. J. Med. Chem. 37(9), 709–720.

[15] Koh M, Lee J-C, Min C, Moon A. 2013. A novel metformin derivative, HL010183, inhibits proliferation and invasion of triple-negative breast cancer cells. Bioorg. Med. Chem. 21(8), 2305–2313.

[16] Arya K, Dandia A. 2007. Synthesis and cytotoxic activity of trisubstituted-1, 3, 5-triazines. Bioorg. Med. Chem. Lett. 17(12), 3298–3304.

[17] Leftheris K, Ahmed G, Chan R et al. 2004. The discovery of orally active triaminotriazine aniline amides as inhibitors of p38 MAP kinase. J. Med. Chem. 47(25), 6283–6291.

[18] Dianzani C, Collino M, Gallicchio M et al. 2006. Evaluation of in vitro anti-inflammatory activity of some

2-alkyl-4, 6-dimethoxy-1, 3, 5- triazines. J. Pharm. Pharmacol. 58(2), 219–226.

[19] Vanderhoek R, Allen G, Settepani JA. 1973. Bis(dimethylamino)-striazinyl antiinflammatory agents, J. Med. Chem. 16(11), 1305–1306.

[20] Kumar A, Srivastava K, Raja Kumar S, Puri S, Chauhan P. 2009. Synthesis of 9-anilinoacridine triazines as new class of hybrid antimalarial agents. Bioorg. Med. Chem. Lett. 19(24), 6996–6999.

[21] Bhat HR, Singh UP, Yadav PS et al. 2011. Synthesis, characterization and antimalarial activity of hybrid 4-aminoquinoline-1, 3, 5- triazine derivatives. Arabian J. Chem., 1007.1001.

[22] Veloso AJ, Dhar D, Chow AM, 2012. Symtriazines for directed multitarget modulation of cholinesterases and amyloid-b in alzheimer's disease. ACS Chem. Neurosci. 4(2), 339–349.

[23] Veloso AJ, Chow AM, Dhar D. 2013. Biological activity of symtriazines with acetylcholine-like substitutions as multitarget modulators of alzheimer's disease. ACS Chem. Neurosci. 4, 924–929.

[24] Klenke B, Stewart M, Barrett M.P. Brun R, Gilbert I.H. 2001. Synthesis and biological evaluation of s-triazine substituted polyamines as potential new anti-trypanosomal drugs. J. Med. Chem. 44(21), 3440–3452.

[25] Nirali S. Mewada, Kishor H. Chikhalia. 2016. Synthesis and biological evaluation of novel *s*-triazine based aryl/heteroaryl entities: Design, rationale and comparative study, Journal of association of Arab Universities for Basic and Applied Sciences., 20, 8-18.

[26] Singh, B. Bhat, H.R. Kumawat, M.K. Singh, U.P. 2014. Structure-guided discovery of 1,3,5-triazine–pyrazole conjugates as antibacterial and antibiofilm agent against pathogens causing human diseases with favorable metabolic fate Bioorg Med. Chem. Lett., 3321-24(15).

[27] Dhananjay Vithalrao Mane. 2017. Synthesis of Some Biological Active Compounds, Yashwantrao Chavan Maharashtra Open University.

[28] Fatma A. el-Samahy, Mervat Elsedik, Tarek Aysha and Magda A. El-Bendary, 2016. Synthesis and antimicrobial activity of new substituted 1,3,5-triazine derivatives, International Journal of PharmaTech Research., 9(6), 436-445.

[29] CLSI: Clinical and Laboratory Standards Institute. 2012. Approved standard M100-S22. Performance standards for antimicrobial susceptibility tests, 10th ed. CLSI, Wayne, Pa.

[30] EUCAST: European Committee on Antimicrobial susceptibility Testing. EUCAST QC Tables V.2. 2010.

[31] Manju Sukumaran, Nairvasantha Sadanandan Kannadasan. 2019. Synthesis and Pharmacological Evaluation of Novel Indolo Triazine Derivatives, RGUHS Journal of Pharmaceutical Sciences, 9(2), 23-30.

[32] World Health Organization Expert Committee on Biological Standardization, Technical report series, W.H.O, Geneva, 822, 1992.