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Design, Synthesis, Characterization and Biological Evaluation of Various N-substituted Piperazine Annulated s-Triazine Derivatives

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Abstract

In an effort to discover new candidate, ten compounds were synthesized in a series of 2,4,6-trichloro-1,3,5-s-triazine analogues which in substitution with anisole, 4-hydroxy coumarin and different N-substituted piperazine derivatives on the C-6 position of s-triazine ring. The title compounds were screened for their in vitro antimicrobial activity against two gram-negative bacteria (E. coli, K. pneumoniae), two gram-positive bacteria (S. aureus, B. subtilis) and two fungal species (C. albicans and S. cerevisiae) using the disc diffusion method. Most of the synthesized compounds appeared with promising antimicrobial activity. The structure of the novel compounds were elucidated on the basis of IR, ^{1}H NMR and elemental analysis.

Keywords: s-triazine, N-substituted piperazines, antimicrobial activity.

Introduction

Significant progress has been achieved by combinational therapy to combat microbial infections still antimicrobial resistance appears to be a major concerns to the public health and scientific communities worldwide. Further, infection spread by various pathogens fail to response the treatment resulting in prolonged illness and greater risk of death and need for an effective therapy which tends to screen the newly synthesized derivatives against the representative strains of bacteria and fungi.

s-Triazine nucleus has been found to be privileged scaffold with extensive array of biological activities such as antimicrobial[1-3], antiprotozoal[4], anticancer[5], antimalarial[6], antiviral[7,8], NNRTI's[9] and anti-angiogenic[10]. Several reports appeared that s-triazine nucleus is a potential scaffold for therapeutic agent against diseases caused by bacteria, malaria and cancer. Cyanuric chloride (2,4,6 trichloro- 1,3,5 s-triazine) the starting material is a very inexpensive, commercially available reagent and the different reactivities of the substituent chlorine atoms, which are controlled by the temperature makes its use even more attractive. On the other hand, it is known that substituted piperazine motif is an important heterocyclic scaffold as constituent of several biologically active molecules[11,12]. Piperazine heterocycles are also noteworthy structural units in drug research[13, 14]. The piperazine nucleus is capable of binding to multiple receptors with high affinity and therefore piperazine has been classified as a privileged structure[15]. For instance, linezolid, eperezolid, AZD2563 and itraconazole, which are currently important antibiotics used for the treatment of microbial infections, contain a piperazine ring in their structures. The polar nitrogen atoms in the piperazine ring confer bioactivity to molecules and enhance favorable interaction with macromolecules[16]. Piperazinyl linked Ciprofloxacin dimers are potent antibacterial, antimalarial and potential antipsychotic agents[17,18]. Further, diphenyl piperazine derivatives possess broad pharmacological action on central nervous system (CNS), especially on dopaminergic neurotransmission[19]. So, we prompted to introduce biologically active various N-substituted piperazine derivatives to the s-triazine core and indentified the new compounds with good antibacterial and antifungal activity. Herein, we have combined three potential units, which are s-triazine nucleus, anisole moiety, 4-hydroxy coumarin in one core and studied biological behavior of the resultant systems having various N-substituted piperazine derivatives.

Material and Methods

All chemicals and solvents procured were of analytical grade and used directly without further purification. All melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using silica gel-G coated Al-plates (0.5 mm thickness, Merck, Germany) using appropriate mobile phase system and spots were visualized under UV and Iodine chamber. ^{1}H NMR spectra were recorded on a Bruker Avance-II 400 MHz spectrophotometer (Bruker Bioscience, USA) using DMSO as a solvent and TMS as internal standard (chemical shifts in δ ppm). Infra Red spectra were recorded on FT Shimadzu spectrophotometer (Shimadzu, Tokyo, Japan) using KBr pallets. Elemental analyses were carried out on Heraeus Rapid Analyser (Heraeus, Germany) and functions were within 0.4% of the theoretical value.

2,4-Dichloro-6-(4-methoxyphenyl)-1,3,5-triazine[20] **(1):** A mixture of cyanuric chloride (0.1 mol, 18.4 g) and anisole (0.1

mol, 12 ml) in toluene (30 ml) was added at 0-5^{0}C drop wise within 2 h. The mixture was then stirred for 15 h at R.T. The progress of reaction was monitored by TLC using hexane: ethyl acetate (8:2) as eluent. After the completion of reaction, resultant mass was neutralized with 50% HCl. The solid product obtained was filtered, washed with water and dried. The crude product was purified by recrystallization from acetone to get the title compound. mp 110-112 ^{o}C

4-((4-Chloro-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one (3): A mixture of 4-hydroxy coumarin (0.01 mol, 1.62 g) and slurry of **(1)** (0.01 mol, 2.56 g) were dissolved in DMF (30 ml) and stirred at 35-40^{o}C for 6 hrs. The pH was maintained neutral by drop wise addition of 10% $NaHCO_3$ solution. The progress of reaction was monitored by TLC using toluene: acetone (8:2) as eluent. After the completion of reaction, the solution was poured into crushed ice. The solid product obtained was filtered and dried. The crude product was purified by recrystallization from acetone to get the title compound. mp 195-197 ^{o}C. IR (cm^{-1}): 3120 (C=C), 1754 (C=O), 1472 (C-H), 1164 (C-O-C), 833 (C=N), 710 (C-Cl); ^{1}H NMR: δ 3.18 (s, 3H), 5.95 (s, 1H) 6.85 (d, 2H), 6.98 (d, 2H), 7.13 (dd, 1H), 7.21 (d, 1H), 7.33 (dd, 1H), 7.41 (ddd, 1H); Anal. calcd for $C_{19}H_{12}ClN_3O_4$: C, 59.78; H, 3.17; N, 11.01 Found: C, 59.85; H, 3.22; N, 10.95.

General procedure for 4-((4-(4-Methoxyphenyl)-6-(4-substituted piperazin-1-yl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one (5a-j): A mixture of **3** (0.005 mol, 1.90 g) and the concerned N-substituted piperazine derivatives **(4a-j)** (0.005 mol) were refluxed in DMF (15 ml) for 5-6 h. The pH was adjusted to neutral by 10% $NaHCO_3$ solution. The progress of reaction was monitored by TLC using toluene: acetone (9.5:0.5) as eluent. After the completion of reaction, the solution was poured into crushed ice. The solid product thus obtained was filtered and dried. The crude product was purified by recrystallization from acetone to get the title compounds.

4-((4-(4-Methoxyphenyl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one (5a): This compound was obtained in 70% yield as a white solid; mp 56-58 ^{0}C; IR (cm^{-1}): 3059 (C=C), 1706 (C=O), 1488 (C-H), 1146 (C-O-C), 851 (C=N). ^{1}H NMR: δ 2.45 (s, 3H), 3.25 (s, 3H), 3.65-3.85 (m, 8H), 6.00 (s, 1H), 6.85-7.32 (m, 8H). Anal. calcd for $C_{24}H_{23}N_5O_4$: C, 64.71; H, 5.20; N, 15.72. Found: C, 64.68; H, 5.24; N, 15.70.

4-((4-(4-Ethylpiperazin-1-yl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one (5b): This compound was obtained in 80% yield as a white solid; mp 105-107 ^{0}C; IR (cm^{-1}): 3062 (C=C), 1714 (C=O), 1476 (C-H), 1158 (C-O-C), 849 (C=N). ^{1}H NMR: δ 2.88 (q, 2H), 2.30 (t, 3H), 3.28 (s, 3H), 3.65-3.85 (m, 8H), 5.98 (s, 1H), 6.89-7.4 (m, 8H). Anal. calcd for $C_{25}H_{25}N_5O_4$: C, 65.35; H, 5.48; N, 15.24. Found: C, 65.38; H, 5.50; N, 15.20.

Ethyl-4-(4-(4-methoxyphenyl)-6-((2-oxo-2*H*-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)piperazin-1-carboxylate (5c): This compound was obtained in 62% yield as a white solid; mp 164-166 ^{0}C; IR (cm^{-1}): 3069 (C=C), 1705 (C=O), 1432 (C-H), 1167 (C-O-C), 844 (C=N). ^{1}H NMR: δ 2.34 (q, 2H), 2.42-2.88 (m, 8H), 3.10 (t, 3H), 3.38 (s, 3H), 5.97 (s, 1H), 6.70-7.68 (m, 8H). Anal. calcd for $C_{26}H_{25}N_5O_6$: C, 62.02; H, 5.00; N, 13.91. Found: C, 62.06; H, 5.04; N, 13.94.

4-((4-(4-Acetylpiperaazin-1-yl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one (5d): This compound was obtained in 60% yield as a white solid; mp 94-96 ^{0}C; IR (cm^{-1}): 3070 (C=C), 1706 (C=O), 1446 (C-H), 1176 (C-O-C), 841 (C=N). ^{1}H NMR: δ 2.35-2.86 (m, 8H), 3.12 (s, 3H), 3.38 (s, 3H), 5.99 (s, 1H), 7.05-7.97 (m, 8H). Anal. calcd for $C_{25}H_{23}N_5O_5$: C, 63.42; H, 4.90; N, 14.79. Found: C, 63.47; H, 4.94; N, 14.76.

4-((4-(4-Methoxyphenyl)-6-(4-phenylpiperazin-1-yl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one (5e): This compound was obtained in 68% yield as a brown solid; mp 70-72 ^{0}C; IR (cm^{-1}): 3076 (C=C), 1712 (C=O), 1424 (C-H), 1184 (C-O-C), 851 (C=N). ^{1}H NMR: δ 2.32 (t, 4H), 2.42 (t, 4H), 3.32 (s, 3H), 5.89 (s, 1H), 6.72-7.12 (m, 5H), 7.30-7.98 (m, 8H). Anal. calcd for $C_{29}H_{25}N_5O_4$: C, 68.63; H, 4.96; N, 13.80. Found: C, 68.66; H, 4.92; N, 13.84.

4-((4-(4-Benzylpiperazin-1-yl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one (5f): This compound was obtained in 70% yield as a brown solid; mp 74-76 ^{0}C; IR (cm^{-1}): 3058 (C=C), 1716 (C=O), 1446 (C-H), 1180 (C-O-C), 840 (C=N). ^{1}H NMR: δ 2.30 (t, 4H), 2.48 (t, 4H), 3.16 (s, 2H), 3.38 (s, 3H), 5.98 (s, 1H), 6.49-7.89 (m, 13H). Anal. calcd for $C_{30}H_{27}N_5O_4$: C, 69.08; H, 5.22; N, 13.43. Found: C, 69.13; H, 5.24; N, 13.45.

4-((4-(4-(2-(2-Hydroxyethoxy)ethyl)piperazin-1-yl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one (5g): This compound was obtained in 50% yield as a brown solid; mp 55-57 ^{0}C; IR (cm^{-1}): 3072 (C=C), 1707 (C=O), 1432 (C-H), 1166 (C-O-C), 843 (C=N). ^{1}H NMR: δ 2.51 (q, 2H), 3.18 (t, 4H), 3.44 (t, 4H), 3.40-3.60 (t, 6H), 3.65 (d, 1H), 3.83 (t, 3H), 5.85 (s, 1H), 7.05-7.84 (m, 8H). Anal. calcd for $C_{27}H_{29}N_5O_6$: C, 62.42; H, 5.63; N, 13.48. Found: C, 62.46; H, 5.67; N, 13.52.

4-((4-(4-Benzhydrylpiperaazin-1-yl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-one (5h)
This compound was obtained in 65% yield as a white solid; mp 58-60 ^{0}C; IR (cm^{-1}): 3059 (C=C), 1734 (C=O), 1390 (C-H), 1146 (C-O-C), 810 (C=N). ^{1}H NMR: δ 2.32 (t, 4H), 2.39 (t, 4H), 3.35 (s, 3H), 4.88 (s, 1H), 5.98 (s, 1H), 6.80-7.90 (m, 18H). Anal. calcd for $C_{36}H_{31}N_5O_4$: C, 72.35; H, 5.23; N, 11.72. Found: C, 72.38; H, 5.20; N, 11.74.

4-((4-(4-Dibenzo[b,f][1,4]thiazepin-11-yl)piperaazin-1-yl)-6-(4-methoxyphenyl)-1,3,5-triazin-2-yl)oxy)-2*H*-chromen-2-

one (5i): This compound was obtained in 82% yield as a white solid; mp 78-80 ^{0}C; IR (cm^{-1}): 3052 (C=C), 1734 (C=O), 1388 (C-H), 1165 (C-O-C), 816 (C=N). ^{1}H NMR: δ 2.30 (t, 4H), 2.92 (t, 4H), 3.37 (s, 3H), 5.85 (s, 1H), 6.82-7.98 (m, 16H). Anal. calcd for $C_{36}H_{28}N_6O_4S$: C, 67.49; H, 4.40; N, 13.12. Found: C, 67.48; H, 4.44; N, 13.14.

1-Cyclopropyl-6-fluoro-7-4-(4-(4-methoxyphenyl)-6-((2-oxo-2*H*-chromen-4-yl)oxy)-1,3,5-triazin-2-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5j): This compound was obtained in 80% yield as a white solid; mp 178-180 ^{0}C; IR (cm^{-1}): 3073 (C=C), 1728 (C=O), 1387 (C-H), 1188 (C-O-C), 811 (C=N). ^{1}H NMR: δ 1.08 (t, 2H), 1.33 (d, 2H), 2.48 (t, 4H), 2.53 (t, 4H), 3.29 (s, 3H), 4.10 (s, 1H), 5.98 (s, 1H), 7.05-8.10 (m, 11H), 11.0 (s, 1H). Anal. calcd for $C_{36}H_{29}N_6O_7F$: C, 63.90; H, 4.32; N, 12.42. Found: C, 63.92; H, 4.34; N, 12.44.

Results and Discussion

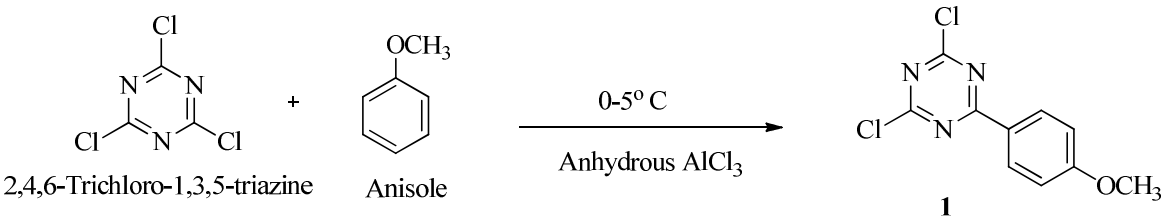
Chemistry: The triazines described were synthesized by the condensation of 2,4,6-trichloro-1,3,5-s-triazine and anisole which was furthered derivatized by substituting 4-hydroxy coumarin **2** and various N-substituted piperazines **(4a-j)** at relevant condition and sequential steps to get novel **5a-j,** as shown in **Scheme.** The nucleophiles can selectively displace the different chlorine atoms by control of the reaction temperature. In general, the first chlorine can be displaced when the temperature is maintained at 0°C, the second between 25°C-50°C, and the third substitution at above 60°C and due to reactivity the temperature can exceed 80°C. In addition, a wide range of N-substituted piperazines were introduced to the third reactive chlorine atom because the ease of reaction condition carried at reflux temperature. A series of novel compounds **5a-j** were synthesized and tested for their *in vitro* antibacterial activity against four strains of bacteria (two gram-positive and two gram-negative) and two strains of fungi. The mentioned antibacterial results revealed that the compounds **5d** and **5h** bearing N-acetyl piperazine and N-benzhydryl piperazine to the basic s-triazine nucleus containing anisole in addition to 4-hydroxy coumarin proved better compared to other analogues against *E-coli*. The compounds **5g**, **5h**, **5i** and **5j** bearing 2-(2'-hydroxy ethoxy) ethyl piperazine, N-benzhydryl piperazine, dibenzo (b, f)-thiazapine-11yl-piperazine and ciprofloxacin substituent respectively have shown the highest sensitivity against *K. pneumonia*. The compounds **5i** and **5j** having dibenzo (b, f)-thiazapine-11yl-piperazine and ciprofloxacin substituent have shown the modest activity against *S. aureus*, whereas final scaffolds **5a**, **5d**, **5i** and **5j** containing N-methyl piperazine, N-acetyl piperazine, dibenzo (b, f)-thiazapine-11yl-piperazine and ciprofloxacin substituent respectively found to be promising agents to the final moiety for the betterment of activity against *B. subtilis*. The biological screening results for fungal species showed that the compounds **5g**, **5h** and **5j** bearing 2-(2'-hydroxy ethoxy)ethyl piperazine, N-benzhydryl piperazine and ciprofloxacin constituents respectively exhibited good activity against *C. albicans* and the compound **5i** having dibenzo (b, f)-thiazapine piperazine showed promising activity against *S. cerevisiae*.

The antimicrobial screening results of the synthesized compounds are shown in table 1.

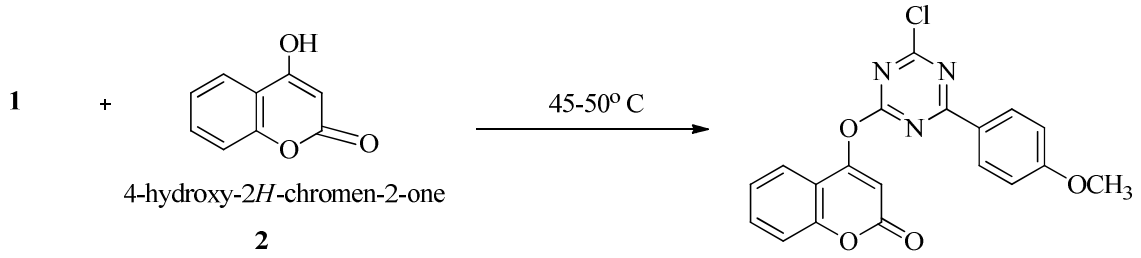
Table-1
***In vitro* antibacterial and antifungal activity of the synthesized compounds 5a-j**

Compound No.	Gram -ve		Gram +ve		Fungus	
	E. Coli	*K. pneumoniae*	*S. aureus*	*B. subtilis*	*C. albicans*	*S. cerevisiae*
5a	18	18	19	19	R	R
5b	R	18	R	R	R	R
5c	R	R	20	R	R	R
5d	23	16	R	18	R	R
5e	20	R	R	R	R	R
5f	22	R	R	R	R	R
5g	18	20	R	R	20	R
5h	24	22	19	R	19	R
5i	18	21	21	18	R	20
5j	19	20	22	17	23	R
Penicillin[a]	≥22	≥22	≥29	≥29	----	----
Cefotaxime[a]	≥20	≥20	≥20	≥20	----	----
Fluconazole[a]	----	----	----	----	≥22	≥19
Nystatin[a]	----	----	----	----	≥15	≥17

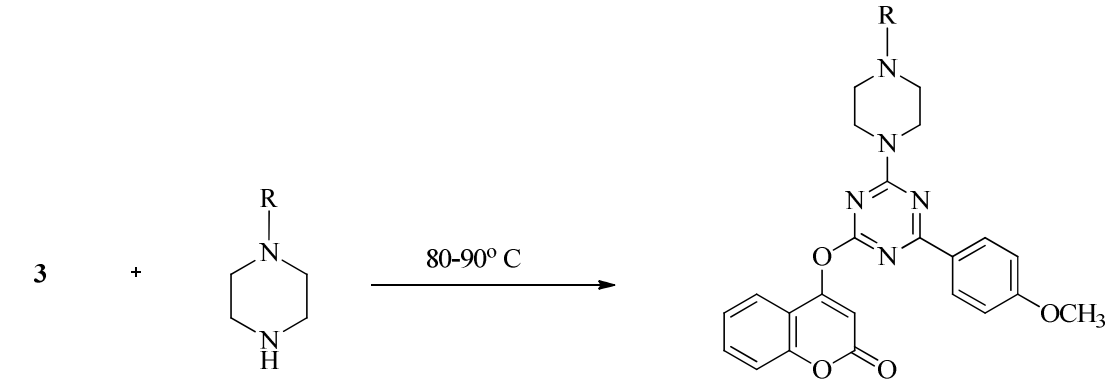
R=Resistant, [a]Standard



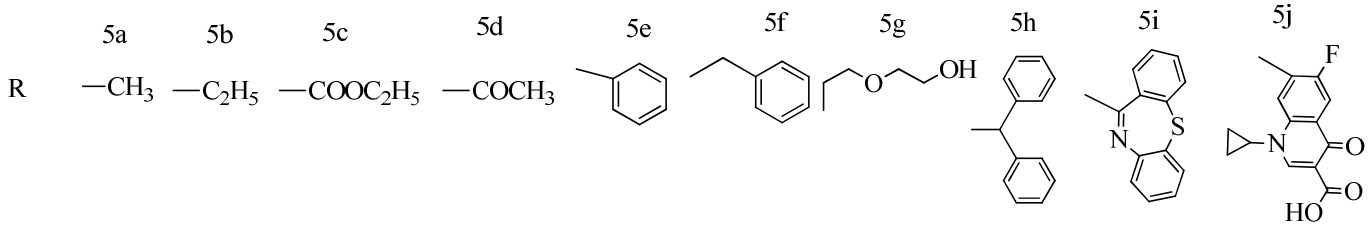
2,4,6-Trichloro-1,3,5-triazine Anisole **1**



4-hydroxy-2*H*-chromen-2-one **2** **3**



4a-j **5a-j**



Reagents and conditions: (i) anisole, anhydrous $AlCl_3$, 0-5°C; (ii) 4-hydroxy coumarin, DMF,10% $NaHCO_3$, 35-40°C; (iii) N-substituted piperazine derivatives, DMF, 10% $NaHCO_3$, 80-90°C.

Scheme
Synthesis of final compounds 5a-j

Antimicrobial Activity: The antimicrobial activity assay have been determined by using the Kirby-Bauer disc diffusion method[21] by measuring the inhibition zones in mm as recommended by the National Committee for Clinical laboratory Standards (NCCLS)[22]. All the synthesized compounds were screened for their antimicrobial activity against a variety of bacterial strains such as two gram-negative bacteria (*E.coli* and *K. pneumonia*), two gram-positive bacteria (*S. aureus* and *B. subtilis*) and also two fungal species (*C. albicans* and *S. cerevisiae*). Known drugs like Penicillin, Cefotaxime, Fluconazole and Nystatin were used as standard drugs. Solutions of these tested compounds and reference drugs were dissolved in dimethyl sulfoxide (DMSO). The antimicrobial assay in the Kirby-Bauer method have been carried out by preparing plates with Muller Hinton agar medium for rapidly growing aerobic organisms. The medium in the plates was sterile and have a depth of about 4 mm. Pure cultures were used as inoculums. Then, 3-4 similar colonies have been selected and transfred those into about 5 ml tryptone soya broth, incubated at 35 ^{o}C for 2-8 hours till light to moderate turbidity developed. Then, sterile cotton swab was dipped into the standardize inoculum and rotated the soaked swab firmly against the upper inside wall of the tube above the fluid level to remove excess inoculum. Then, streaked the entire agar surface of the plate with the swab three times and allowed the inoculums to dry for 5-15 minutes with lid in place, within 30 minutes after applying the discs using aseptic technique incubated the plates 35-37 ^{o}C overnight and after that measured the zones showing complete inhibition and recorded the diameters of the zones to the nearest millimeter.

Conclusion

The present work is focused on the synthesis of N-substituted piperazine annulated s-triazine derivatives which were screened for their antimicrobial activity against different strains. s-Triazine nucleus is emerged to be an active constituent in many standard drugs, and is known to increase the pharmacological activity of the molecules. Due to the biological potential of 4-hydroxy coumarin moiety, it is worthy to note that it is expected to increase the net biological activity. All the compounds were found to exhibit moderate activity against mentioned organism. Hence, it is concluded that, trisubstituted s-triazine bearing coumarin and piperazine nucleus are proved to be beneficial in augmenting antimicrobial probe. Thus, there is enough scope to explore s-triazine substituted analogous. Overall it is noticed that most of the compounds appeared promising activity as compared to standard drugs for all representative panel of bacterial and fungal strains and which leads a powerful incentive for further research in this area.

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