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Synthesis and Antibacterial Activity of Some Novel 4-Benzyl-piperazinyl-*s*-triazine Derivatives

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Considerable interest has been attracted in *s*-triazine scaffold and its derivatives because of their large variety of pharmacological activities. In this project, a series of 4-benzyl-piperazinyl-*s*-triazine derivatives **5a** to **5j** were synthesized by three steps substitution reaction of cyanuric chloride with various nucleophilic compounds in presence of a base. Molecular structures of the synthesized compounds were elucidated by FTIR, ^{1}H NMR, ^{13}C NMR, MS spectral data and elemental analyses. The *in vivo* antibacterial activity was evaluated by broth dilution method against representative four Gram-positive and four Gram-negative bacterial strains. Many compounds have displayed comparable better antibacterial activity against *Bacillus subtilis, Staphylococcus aureus, Staphylococcus epidermis* and *Pseudomonas aeruginosa* with reference to streptomycin.

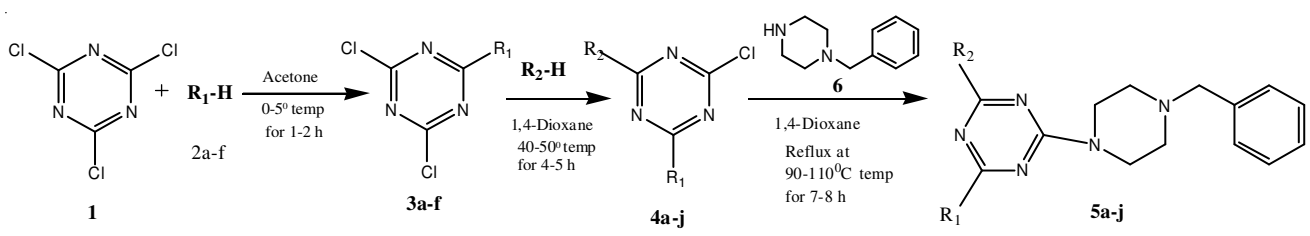
Key Words: Antibacterial, *s*-Triazine, MIC, Zone of inhibition, Cyanuric chloride.

INTRODUCTION

The pathogens rapidly develop the resistance to most of the known antibiotics and create a serious health problem[1-3]. Coupled with mounting bacterial resistance, an aging population and a dearth of novel therapeutics, there is an important unmet clinical need to develop new antibiotics[4,5]. In view of the above, the design and synthesis of effective and potent antimicrobials is an area of immense significance for medicinal chemistry[1-12]. A considerable part of research carried out in the development of new drugs is devoted to the study of heterocyclic compound. There are vast numbers of pharmacologically active nitrogen containing heterocyclic compound. Among them *s*-triazine scaffold is of immense importance. Substituted *s*-triazine derivatives have become attractive targets for medicinal chemistry due to its potent biological activity such as antiprotozoal[13], anticancer[14-16], estrogen receptor modulators[17], antimalarial[18-21], cyclin-dependent kinase inhibitors[22], antiviral[23], vascular inflammatory disease[24], CNS depressant[25], antitubercular[26], antifungal[27] and also possess potent antibacterial activity[28-32]. Many of the piperazine ring containing compounds exhibited the antibacterial activities[33,34]. Herein, we report the synthesis and antibacterial activity of a variety of 4-benzyl-piperaziyl-*s*-triazine derivatives.

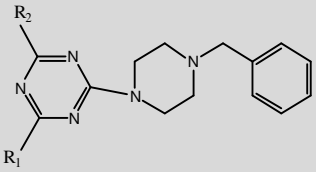
EXPERIMENTAL

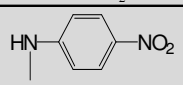
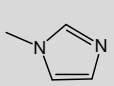
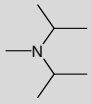
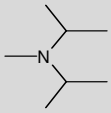
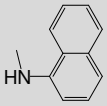
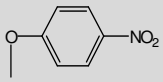
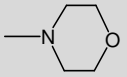
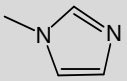
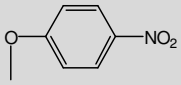
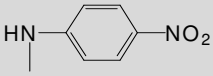
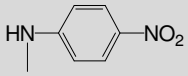
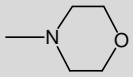
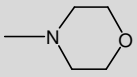
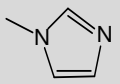
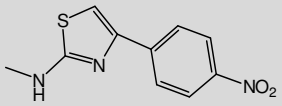
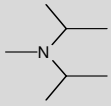
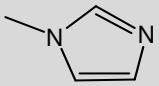
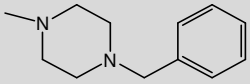
Synthetic methods adopted for making compounds **5a** to **5j** are illustrated in **Scheme-I**. Synthesis of *s*-triazine derivatives were performed by means of nucleophilic displacement[35] of three chlorine atoms of cyanuric chloride (1) by thee nucleophiles by three steps in which one common nucleophile was benzyl piperazine and other two nucleophiles were different. According to this, compounds **3a-f** was obtained by treating equimolecular various nucleophile (**2a-f**) with cyanuric chloride (1). The compounds **4a-f** was synthesized by treating equimolecular **3a-f** with various other nucleophiles, R_2-H (Table-1) and finally compounds **5a-f** were obtained by treating equimolecular **4a-f** with 1-benzyl-piperazine.



Scheme-I

TABLE-1



Compound	R_1	R_2	m.f.[a]	m.p. (ºC)	Yield (%)
5a			$C_{24}H_{30}N_8O_2$	217-220	76.86
5b			$C_{23}H_{32}N_8$	254-257	54.86
5c			$C_{30}H_{37}N_7$	140-142	78.86
5d			$C_{24}H_{27}N_7O_4$	310-312	69.86
5e			$C_{23}H_{22}N_8O_3$	252-254	57.86
5f			$C_{26}H_{25}N_9O_4$	240-243	64.86
5g			$C_{22}H_{31}N_7O_2$	264-266	67.86
5h			$C_{26}H_{24}N_{10}O_2S$	212-214	76.86
5i			$C_{24}H_{39}N_7$	184-186	78.96
5j			$C_{28}H_{33}N_9$	265-267	48.74

[a]Elemental analyses for C, H and N were within ±0.4% of the theoretical values

Synthetic procedure: All the compounds (**5a** to **5i**) were synthesized using synthetic grade chemicals and further purification also carried out for some chemicals and solvents.

Synthesis of monosubstituted 2,4-dichloro-*s*-triazine (3a-f)[35,36]: Cyanuric chloride (0.01 M) was dissolved in acetone (25 mL) and different nucleophilic compounds **2a-f** (R1-H) as show in Table-1 (0.01 M) was added to it at 0-5 ºC temperature and stirred for 1-2 h, in presence 10 % sodium carbonate solution. Ice water was poured into reaction mixture. The solid was separated out, washed with distilled water and recrystallized.

Synthesis of disubstituted 2-chloro-*s*-triazine (4a-j): A mixture of **3a-f** (0.01 M) and different nucleophilic compounds (R_2-H) as show in Table-1 (0.01 M) were dissolved in 1,4-dioxane (50 mL) and stirred at 40-50 ºC temperature for 4-5 h, in presence 10 % sodium carbonate solution. Ice water was poured into reaction mixture. The solid separated out, washed with distilled water and recrystallized

Synthesis of 4,6-*bis*-(substituted)-2-(4-benzyl-piperazin-1-yl)-*s*-triazine derivatives (5a-f): A mixture of **4a-j** (0.01 M) and 1-benzyl piperazine (0.01 M) were dissolved in 1,4-dioxane (50 mL) and the reaction mixture was refluxed at 90-110 ºC for 7-8 h, in presence 10 % sodium carbonate solution. Ice water was poured into reaction mixture. The solid separated out, washed with distilled water and recrystallized. The final product was finally purified by column chromatography.

All the synthesized compounds (Table-1) were characterized by spectroscopic data as ^{1}H NMR, ^{13}C NMR, FT-IR, mass and elemental analysis.

Melting point of the synthesized compounds was determined on Veego melting point apparatus. IR spectra were obtained on Perkin Elmer, spectrum RX-I, infrared spectrometer. ^{1}H NMR spectra were recorded on Bruker Avance II (300.40 MHz) spectrometer and ^{13}C NMR on Bruker Avance II (100 MHz) spectrometer in DMSO-d_6 and $CDCl_3$. The mass

spectra were recorded on TOF mass spectrophotometer. Elemental analysis was performed using a Perkin Elmer CHN-OS analyzer.

6-(4-Benzylpiperazin-1-yl)-N^2,N^2-diethyl-N^4-(4-nitrophenyl)-1,3,5-triazine-2,4-diamine(5a): Brownish yellow; IR (KBr, ν_{max}, cm^{-1}): 3349 (N-H$_{stretch}$, >NH), 3092 (C-H$_{stretch}$, Ar), 2971 (C-H$_{stretch}$), 2362 (C-N$_{stretch}$, *s*-triazine), 1621 (N-H$_{bend}$), 1601, 1500 (C-C$_{stretch}$, Ar), 1550, 1431 (N-O$_{stretch}$, -NO$_2$), 1374 (C-H$_{bend}$), 1318, 1250 (C-N$_{stretch}$, Ar), 1178 (C-N$_{stretch}$), 849 (C-H$_{bend}$, Ar); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.788 (s, 2H, *J* = 1.00, Ar-H), 6.790 (s, 2H, *J* = 1.26, Ar-H), 7.323, 7.283, 7.070 (t, 5H, *J* = 10.69, Ar-H), 4.654 (s, 1H, *J* = 6.00, -NH), 3.652 (s, 2H, *J* = 1.51, -CH$_2$-), 3.171 (s, 4H, *J* = 1.51, -CH$_2$-), 3.106 (s, 4H, *J* = 12.06, -CH$_2$-), 2.594 (s, 4H, *J* = 3.04, -CH$_2$-), 1.097 (s, 6H, *J* = 9.08, -CH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.4, 179.2, 159.4 (C of *s*-triazine), 138.4, 135.6 (Ar-C), 128.9, 128.5, 127.3, 121.9 (Ar-C), 60.1 (-CH$_2$), 52.2, 50.0 (-CH$_2$-), 44.7 (-CH$_2$-), 13.0 (-CH$_3$); MS m/e): 462.15 [M$^+$].

4-(4-Benzylpiperazin-1-yl)-6-(1*H*-imidazol-1-yl)-*N,N*-diisopropyl-1,3,5-triazine-2-amine(5b): Brownish gray; IR (KBr, ν_{max}, cm^{-1}): 3099 (C-H$_{stretch}$, Ar), 2917 (C-H$_{stretch}$), 2345, 2367 (C-N$_{stretch}$, *s*-triazine), 1551, 1453 (C-C$_{stretch}$, Ar), 1304, 1229 (C-N$_{stretch}$), 1105 (C-N$_{stretch}$), 1383 (C-H$_{bend}$), 809 (C-H$_{bend}$, Ar); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.825, 7.747, 7.561 (t, 3H, *J* = 0.55, Ar-H), 7.335, 7.317, 7.256 (t, 5H, *J* = 0.55, Ar-H), 3.799 (s, 2H, *J* = 14.83, -CH$_2$-), 3.548, 3.446 (d, 4H, *J* = 15.92, -CH$_2$-), 2.447 (s, 2H, *J* = 1.0, >CH-), 1.315, 1.293, 1.165, 1.154 (m, 12H, *J* = 32.54, -CH$_3$); ^{13}C NMR (100 MHz, DMSO-*d*6): δ 181.0, 172.9 (C of *s*-triazine), 135.6 (C-Ar), 134.5,128.9, 128.5, 127.8, 127.3, 114.7 (-CH- of Ar), 60.1 (-CH$_2$-), 52.2, 50.0 (-CH$_2$-), 46.9 (-CH-), 21.5 (-CH$_3$); MS (*m/e*): 420.56 [M$^+$].

6-(4-Benzylpiperazin-1-yl)-N^2,N^2-diisopropyl-N^4-(naphthalen-1-yl)-1,3,5-triazine-2,4-diamine(5c): Gray; IR (KBr, ν_{max}, cm^{-1}): 3353 (N-H$_{stretch}$, >NH), 3081 (C-H$_{stretch}$, Ar), 2917 (C-H$_{stretch}$), 2367, 2324 (C-N$_{stretch}$), 1565, 1500, 1452 (C-C$_{stretch}$, Ar), 1312, 1287 (C-N$_{stretch}$), 1012 (C-N$_{stretch}$), 1387 (C-H$_{bend}$); 887.40 (C-H$_{bend}$, Ar); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.469, 7.336, 7.247 (m, 5H, *J* = 3.64, Ar-H), 8.062, 8.039, 7.842, 7.621, 7.595, 6.940 (m, 7H, Ar-H), 4.357 (s, 1H, *J* = 1.50, NH), 3.822, 3.696 (d, 4H, *J* = 5.79, -CH$_2$-), 3.535 (s, 2H, *J* = 0.03,-CH$_2$-), 2.883 (s, 1H, *J* = 0.34, >CH-), 1.255 (s, 12H, *J* = 11.57, -CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$): δ 182.4, 179.2, 159.4 (C of *s*-triazine), 142.0, 135.6, 134.3, 124.7 (C-Ar), 128.9, 128.6, 128.5, 127.3, 126.6, 126.0, 125.0, 121.0,119.0, 109.4 (-CH- Ar), 60.1 (-CH$_2$-), 52.2, 50.0 (-CH$_2$-), 46.9 (>CH-), 21.5 (-CH$_3$); MS (*m/e*): 495.38 [M$^+$].

2-(4-Benzylpiperazin-1-yl)-4-morpholino-6-(4-nitrophenoxy)-1,3,5-triazine(5d): Yellowish white, IR (KBr, ν_{max}, cm^{-1}): 3088 (C-H$_{stretch}$, Ar), 2936 (C-H$_{stretch}$), 2367, 2361 (C-N$_{stretch}$, *s*-triazine), 1547, 1453 (C-C$_{stretch}$, Ar), 1304, 1229 (C-N$_{stretch}$), 1123 (C-N$_{stretch}$), 1383 (C-H$_{bend}$), 807 (C-H$_{bend}$, Ar); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.788 (s, 2H, *J* = 1.00, Ar-H), 6.790 (s, 2H, *J* = 1.26, Ar-H) 7.323, 7.283, 7.070 (t, 5H, *J* = 10.69, Ar-H), 3652 (s, 2H, *J* = 12.06, -CH$_2$-), 3.171, 3.106 (d, 4H, *J* = 12.06), 3.654 (s, 2H, *J* = 1.51), δ 2.594 (s, 2H, *J* = 3.04); ^{13}C NMR (100 MHz, DMSO-d_6): δ δ183.7, 178.6, 177.9 (C of *s*-triazine), 161.3, 144.3, 135.6 (C-Ar), 128.9, 128.5, 127.3,122.2, 122.1 (C-Ar), 60.1 (-CH$_2$-), 52.2, 50.0 (-CH$_2$-), 66.4, 46.3 (-CH$_2$-), 44.7 (-CH$_2$-), 13.0 (-CH$_3$); MS (*m/e*): 477.23 [M$^+$].

2-(4-Benzylpiperazin-1-yl)-4-(1*H*-imidazol-1-yl)-6-(4-nitro-phenoxy)-1,3,5-triazine(5e): Brownish Yellow; IR (KBr, ν_{max}, cm^{-1}): 3090 (C-H$_{stretch}$, Ar), 2981 (C-H$_{stretch}$), 2354, 2362 (C-N$_{stretch}$), 1557, 1454 (C-C$_{stretch}$, Ar); 1304, 1229 (C-N$_{stretch}$), 1105 (C-N$_{stretch}$), 1383 (C-H$_{ben}$), 807 (C-H$_{bend}$, Ar); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.057,7.496, 7.251(t, 3H, Ar-H), 7.677, 7.158 (d, 2H, Ar-H), 7.370, 7.344, 7.318 (t, 5H,Ar-H) 3.799 (s, 2H, *J* = 14.80, -CH$_2$-), 3.548 (s, 2H, *J* = 15.92, -CH$_2$-), 2.447 (s, 2H, *J* = 1.0, -CH$_2$-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.3, 180.4, 174.8 (C of *s*-triazine), 161.3, 135.6 (C-Ar), 134.5, 128.9, 128.5, 127.8,127.3, 122.2, 122.1, 114.7 (-CH-), 60.1 (-CH$_2$-), 52.2, 50.0 (-CH$_2$-); MS (*m/e*): 458.47 [M$^+$].

6-(4-Benzylpiperazin-1-yl)-N^4, N^4-*bis*-(4-nitrophenyl)-1,3,5-triazine-2,4-diamine (5f): Yellow; IR (KBr, ν_{max}, cm^{-1}): 3374 (N-H$_{stretch}$, >NH), 3082 (C-H$_{stretch}$, Ar); 2964 (C-H$_{stretch}$), 2367 (C-N$_{stretch}$), 1601, 1500, 1450 (C-C$_{stretch}$, Ar), 1550, 1431 (N-O$_{stretch}$, -NO$_2$), 1324 (C-H$_{bend}$), 1318, 1250 (C-N$_{stretch}$, Ar); 1214 (C-N$_{stretch}$), 848 (C-H$_{bend}$, Ar); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.138, 8.055, 8.027 (t, 5H, *J* = 7.23, Ar-H), 8.215 (s, 2H, *J* = 7.23, Ar-H), 7.411 (s, 2H, *J* = 1.50, Ar-H), 4.223 (s, 1H, *J* = 2.15, NH), 3.326 (s, 2H, *J* = 28.04), 2.677, 2.639 (d, 4H, *J* = 1.36, -CH$_2$-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.4, 161.0 (C of *s*-triazine), 149.2, 138.4, 135.6 (C-Ar), 128.9, 128.5, 127.3, 121.9, 117.2 (-CH-), 60. 1(-CH$_2$-) 52.2, 50.0 (-CH$_2$-); MS (*m/e*): 527.21 [M$^+$].

2-(4-Benzylpiperazin-1-yl)-4,6-dimorpholino-1,3,5-triazine(5g): White ; IR (KBr, ν_{max}, cm^{-1}): 3098 (C-H$_{stretch}$, Ar), 2989 (C-H$_{stretch}$), 2367, 2352 (C-N$_{stretch}$), 1557, 1454 (C-C$_{stretch}$, Ar), 1305, 1256 (C-N$_{stretch}$) 1105 (C-N$_{stretch}$), 1362 (C-H$_{bend}$), 874 (C-H$_{bend}$, Ar); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.330, 7.316, 7.256 (t, 5H, Ar-H), 3.781, 3.728, 3.710, 3.704, 3.531 (m, 10H, *J* = 46.03, -CH$_2$-); ^{13}C NMR (100 MHz, CDCl$_3$): δ 182.4, 177.6 (C of *s*-triazine); δ 135.6 (C-Ar), 128.9, 128.5, 127.3 (-CH-), 60.1 (-CH$_2$-) 52.2, 50.0 (-CH$_2$-), 66.4, 46.3 (-CH$_2$-); MS (*m/e*): 425.24 [M$^+$].

4-(4-Benzylpiperazin-1-yl)-6-(1*H*-imidazol-1-yl)-*N*-[4-(4-nitro phenyl) thiazol-2-yl]-1,3,5-triazine-2-amine (5h): Brown; IR (KBr, ν_{amx}, cm^{-1}): 3399 (N-H$_{stretch}$, >NH); 3096 (C-H$_{stretch}$, Ar); 2917 (C-H$_{stretch}$), 2345 (C-N$_{stretch}$), 1654 (N-H$_{bend}$), 1601, 1500, 1450 (C-C$_{stretch}$, Ar), 1557, 1421 (N-O$_{stretch}$, -NO$_2$), 1323 (C-H$_{bend}$), 1189, 1207 (C-N$_{stretch}$), 1214.78 (C-N$_{stretch}$), 842 (C-H$_{bend}$, Ar); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.416, 7.411 (d, 4H, *J* = 7.32, Ar-H), 8.243, 8.215, 8.138 (t, 5H, *J* = 7.32, Ar-H), 8.388, 8.055, 8.027 (t, 3H, *J* = 7.32, Ar-H), 7.223 (s, 1H, *J* = 2.15, thiazolyl), 4.026 (s, 1H, *J* = 1.86, NH), 2.677, 2.639 (d, 4H, *J* = 1.36), 2.501 (s, 2H, *J* = 31.26, -CH$_2$-); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.0, 176.1, 161.2 (C of *s*-triazine), 160.5, 148.4 (thiazolyl-C) 148.2, 139.2, 135.6 (C-Ar), 134.5, 128.9, 128.5, 128.4, 127.3, 127.8, 121.6, 114.7 (-CH-), 100.0 (-CH-), 60.1 (C of -CH$_2$-), 52.2, 50.0 (-CH$_2$-); MS (*m/e*): 540.21 [M$^+$].

6-(4-Benzylpiperazin-1-yl)-N^2,N^2-diethyl-N^4,N^4-diisopropyl-1,3,5-triazine-2,4-diamine(5i): Yellowish white, IR (KBr, ν_{max}, cm^{-1}): 3089 (C-H$_{stretch}$, Ar), 2929 (C-H$_{stretch}$), 2351, 2347 (C-N$_{stretch}$), 1550, 1451 (C-C$_{stretch}$, Ar), 1354, 1229

($C\text{-}N_{stretch}$), 1142 ($C\text{-}N_{stretch}$), 1379 ($C\text{-}H_{bend}$), 804 ($C\text{-}H_{bend}$, Ar); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.335, 7.317, 7.256 (t, 5H, *J* = 0.55, Ar-H), 3.799 (s, 2H, *J* = 14.83, $-CH_2-$), 3.548, 3.248 (d, 4H, *J* = 2.52, $-CH_2-$), 3.018 (s, 2H, *J* = 4.72, >CH-), 1.165, 1.154 (d, 18H, *J* = 32.54, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.4, 179.2, 176.0 (C of *s*-triazine); δ135.6 (C-Ar), 128.9, 128.5, 127.3 (-CH-), 60.1 ($-CH_2-$), 52.2, 50.0 ($-CH_2-$), 46.9 (>CH-), 44.7 ($-CH_2-$), 21.5 ($-CH_3$), 13.0 ($-CH_3$); MS (*m/e*): 425.37 [M^+].

2, 4-*Bis*-(4-benzylpiperazin-1-yl)-6-(1*H*-imidazol-1-yl)-1,3,5-triazine (5j): Brownish yellow, IR (KBr, ν_{max}, cm^{-1}): 3084 ($C\text{-}H_{stretch}$, Ar), 2983 ($C\text{-}H_{stretch}$), 2365, 2358 ($C\text{-}N_{stretch}$), 1607, 1557, 1518 ($C\text{-}C_{stretch}$, Ar), 1304, 1229 ($C\text{-}N_{stretch}$), 105.73 ($C\text{-}N_{stretch}$), 1383 ($C\text{-}H_{bend}$), 806 ($C\text{-}H_{bend}$, Ar); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7323, 7.283, 7.070 (t, 10H, *J* = 10.69, Ar-H); δ 6.790, 6.531, 6.145 (t, 3H, *J* = 9.08, Ar-H), 3.652 (s, 2H, *J* = 6.0, $-CH_2-$), 3.652, 3.57, 3.356, 3.356 (t, 6H, *J* = 26.0, $-CH_2-$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.0, 172.9 (C of *s*-triazine), 135.6 (C-Ar), 134.5, 128.9, 128.5, 127.8, 127.3, 114.7 (-CH-), 60.1 ($-CH_2-$), 52.2, 50.0 ($-CH_2-$); MS (*m/e*): 495.29 [M^+].

Antibacterial activity: The *in vitro* antibacterial screening of all the compounds was evaluated against selected (Table-1) four Gram-positive organisms *viz*. *Bacillus subtilis* (NCIM 2063), *Bacillus cerus* (NCIM 2156), *Staphylococcus aureus* (NCIM 2079), *Staphylococcus epidermis* (NCIM 2493) and four representative Gram-negative organisms *viz*. *Escherichia coli* (NCIM 2065), *Klebseilla pneumonia* (NCIM 2706), *Proteus mirabilis* (NCIM 2241), *Pseudomonas aeruginosa* (NCIM 2036) along with streptomycin as standard by broth dilution method recommended by European committee for antibacterial susceptibility testing (EUCAST) standards[37]. The zones of inhibition of all the synthesized compounds (Table-2) were determined preliminary for antibacterial screening by disk-diffusion method (Kirby-Bauer method) recommended by clinical and laboratory standards[38].

RESULTS AND DISCUSSION

We observed that all the ten compounds for antibacterial activity. Beside these six compounds (**5a, 5c, 5e, 5g, 5i** and **5j**) showed satisfied antibacterial activity and other four compounds (**5b, 5d, 5f** and **5h**) did not display little antibacterial activity.

The zone of inhibition of synthesized compounds (six compounds) against representative micro-organisms showed a significant activity with degree of variation and these are given in Table-2.

The MIC values of substituted 4-benzyl piperazinyl-*s*-triazine derivatives found to be in the range between 2-32 μg mL^{-1} and these are given in Table-3.

It was found that the 4-benzyl piperazinyl-*s*-triazine derivatives showed significant antibacterial activity in comparison to streptomycin. The **5a** and **5c** against *S. aureus*; **5a** against *B. subtilis* and **5c** against *S. epidermis* showed same MIC value as standard streptomycin. Most of the synthesized compounds showed antibacterial activity against *P. aeruginosa*, except **5j** showed activity only against *P. mirabilis*. The compound **5i** showed broad spectrum activity; **5a** and **5c** have better activity against Gram-positive organisms than Gram-negative; **5e** and **5j** have activity against only Gram-negative organisms. Among the organisms *B. subtilis*, *B. cerus*, *S. aureus*, *S. epidermis*, *P. aeruginosa*, *P. mirabilis* are more susceptible and *E. coli* and *K. pneumonia* are less susceptible to synthesized compounds. Among all the synthesized

TABLE-2
ZONE OF INHIBITION OF SYNTHESIZED COMPOUNDS

Compound	Zone of inhibition (mm)[a,b]							
	Gram-positive organisms				Gram-negative organisms			
	B. subtilis	*B. cerus*	*S. aureus*	*S. epidermis*	*E. coli*	*K. pneumonia*	*P. aeruginosa*	*P. mirabilis*
5a	9.67 ± 0.471	7.0 ± 0.816	11.67 ± 0.471	6.67 ± 0.471	-	-	4.67 ± 0.471	-c
5c	6.67 ± 0.471	-	9.0 ± 0.816	9.67 ± 0.471	-	-	4.0 ± 0.816	-
5e	-	-	-	-	3.0 ± 0.471	-	4.67 ± 0.471	-
5g	-	7.67 ± 0.471	-	-	3.67 ± 0.816	-	10.67 ± 0.471	-
5i	5.67 ± 0.471	9.0 ± 0.816	10.67 ± 0.471	5.67 ± 0.471	-	6.0 ± 0.816	8.67 ± 0.471	7.67 ± 0.471
5j	-	-	-	-	-	-	-	7.0 ± 0.816
Streptomycin	9.67 ± 0.471	11.0 ± 0.816	10.67 ± 0.471	9.67 ± 0.471	10.0 ± 0.816	9.67 ± 0.471	11.67 ± 0.471	10.67 ± 0.471

[a]DMSO as negative control; [b]Data are mean of three replications; [c]No inhibition was observed

TABLE-3
MINIMUM INHIBITORY CONCENTRATION (MIC) OF SYNTHESIZED COMPOUNDS

Compound	MIC (μg mL^{-1})[a]							
	Gram-positive organisms				Gram-negative organisms			
	B. subtilis	*B. cerus*	*S. aureus*	*S. epidermis*	*E. coli*	*K. pneumonia*	*P. aeruginosa*	*P. mirabilis*
5a	8	8	2	16	-	-	16	-[b]
5c	16	-	2	4	-	-	16	-
5e	-	-	-	-	32	-	16	-
5g	-	8	-	-	32	-	4	-
5i	16	8	2	16	-	16	8	4
5j	-	-	-	-	-	-	-	4
Streptomycin	8	4	2	4	4	4	4	2

[a]DMSO as negative control; [b]No antibacterial activity

compounds **5a, 5c** and **5i** have better antibacterial activity than others. A comparative MIC bar plot of synthesized compounds with reference streptomycin is given in Fig. 1.

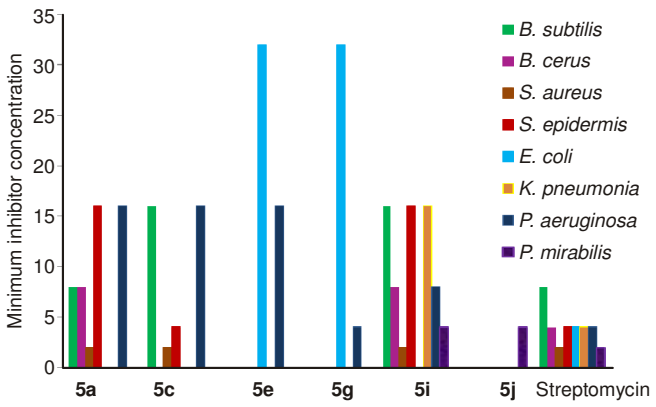


Fig. 1. A comparative MIC bar plot of synthesized compounds with streptomycin

Antibacterial susceptibility testing results reflects that aliphatic amino (diethyl amino, isopropyl amino) substituted 4-benzyl-piperazinyl-1,3,5-triazine (**5a, 5c** and **5i**) show better and broad spectrum activity; aromatic amino (naphthalen-1-yl group in **5c**) and aromatic amino with electronegative group (4-nitrophenyl amino in group **5a**) also shows better activity. But *bis*-(4-nitro-phenyl amino) substituted 1,3,5-triazine (**5f**) have no activity, hence attachment of more electronegative group decreases or destroy the activity.

The interesting point is that the amino substituted *s*-triazine show antibacterial activity but other substitution like phenoxy substitution (**5d** and **5e**) shows no or little activity. Other heterocyclic substitution like imidazolyl (**5b, 5h** and **5j**) and morpholino group (**5d, 5g**) are not improved or slightly improved the activity. Although 4-(4-nitrophenyl)-thiazol-2-amino substituted-1,3,5-triazine[32] and 4-benzyl piperazinyl substituted-1,3,5-triazine show better antibacterial activity but 4-(4-nitrophenyl)-thiazol-2-amino with 4-benzyl piperazinyl substituted-1,3,5-triazine (**5h**) derivatives have no antibacterial activity and *bis*-(4-benzylpiperazinyl) substituted 1,3,5-triazine (**5j**) have little antibacterial activity.

Conclusion

We have presented a new economical synthesis of a series of 4-benzyl-piperazinyl-*s*-triazine. The operational simplicity, good yield in significantly very short reaction times, can impose this procedure as a useful and attractive alternative to the currently available antibacterial. With an objective to investigate a compound for bacterial resistance we have found that most of compounds exhibited moderate to significant *in vitro* antibacterial activity. Aliphatic amino (diethyl amino, isopropyl amino) substituted 4-benzyl-piperazinyl-1,3,5-triazine (**5a, 5c** and **5i**) show better and broad spectrum activity, aromatic amino (naphthalenyl group in **5c**) and aromatic amino with electronegative group (4-nitrophenyl amino in group **5a**) also shows better activity. Hence, it is concluded that the nitro substituted phenyl amine, aliphatic amine substituted 4-benzyl-piperazinyl-*s*-triazine derivatives are potential key approach to design newer antibacterial agents.

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