SYNTHESIS, SPECTRAL AND BIOLOGICAL STUDIES OF SOME S-TRIAZINE DERIVATIVES OF 1-(1-(4METHXYPHENYL)ETHYL) CYCLOHEXANOL

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ABSTRACT

With the help of some new synthetic protocols a series of s-triazine derivatives with aliphatic and aromatic urea along with 1-(1-(4-methoxyphenyl)ethyl)cyclohexanol is prepared. All the synthesized compounds of this series were characterized by spectral analysis using IR, and 1H NMR spectroscopy. Biological activities were evaluated for the selected synthesized derivatives. Some of the compounds were found good active against different gram positive, gram negative or fungal stains.

KEYWORDS: aromatic urea, s-triazine, antimicrobial activity, cyanuric chloride, antifungal.

INTRODUCTION

S-triazine derivatives are of great interest among the researchers in medicinal chemistry. It is due to their vital role in many biological processes and synthetic drugs. The replacement of all three chlorine atoms in the molecule of cyanuric chloride by basic groups is greatly facilitated by the ring nitrogen atoms of the symmetrically built s-triazine moiety. These derivatives of s-triazine are reported as antimalarials[1], anticancer agents[2], antiprotozoals[3], antimicrobials[4], antitumour[5], anti-inflammatory[6], antibacterial[7], antiviral[8] and many more. Due to these diversified activities in the present work we have synthesized a series of s-triazine derivatives and the compounds were evaluated for their biological activities.
MATERIAL AND METHODS
All the chemicals and reagents used in the work were of analytical grade and used without further purification. All the melting points were determined on SUNBIM apparatus by open glass capillary method and were uncorrected. The reactions were monitored by thin layer chromatography (TLC) using silica gel-G coated standard aluminum plates and spots were visualized under UV radiation. IR spectra were recorded on Bruker ALPHA FTIR spectrophotometer in KBr pellets. The H-NMR spectra were recorded on Bruker Avance II spectrometer in d-DMSO. Chemical shifts relative to TMS used as internal standard were obtained in d unit.

EXPERIMENTAL
As cyanuric chloride contains three chloro groups which can replaced by three different amine groups at three different temperatures viz. 0-5°C, room Temperature and at 45-50°C. The synthesis work was carried out in three steps.

Scheme: Synthesis of s-triazine derivatives of 1-(1-(4-methoxyphenyl)ethyl) cyclohexanol.
Step-I: Preparation of 4,6-dichloro-N(substituted phenyl)-1,3,5-triazin-2-amine

In the ice bath at 0-5°C mixture of toluene and cyanuric chloride was stirred and then allowed to react with different amines with adjusting pH by bicarbonate solution. Getting reaction completion indication from TLC, reaction mass was added in crushed ice. This mixture is further stirred for half an hour and separated solids (a to e) were filtered and re-crystallized in absolute ethanol.

Step-II: Preparation of aromatic floroamine derivatives of 4,6-dichloro-N(substituted phenyl)-1,3,5-triazin-2-amine

In the second step products (a to e) were treated with aromatic flouro-amines(equimolecular) at room temperature in acetone for 17-20 hours with constant stirring. After completing the TLC check reaction was stopped for each compound and reaction mass was poured in to the ice cold water the solid product (a1 to a10) were filtered washed and purified.

Step-III: Preparation of aromatic floroamine derivatives of 4,6-dichloro-N(substituted phenyl)-1,3,5-triazin-2-amine with 1-(2-amino-1-(4-methoxyphenyl)ethyl)cyclohexanol.

Products of step-II (a1 to a10) were taken in 80 ml acetone in an RBF and added 1-(2-amino-1-(4-methoxyphenyl) ethyl)cyclohexanol the mass was refluxed at 50 to 60 °C with constant stirring on heating mental. The pH was kept neutral by using diluted bicarbonate solution. After TLC check the reaction mass was poured in chilled distilled water. Again the pH of the solution was made 7. After constant stirring about half an hour the solid products were obtained. All the compounds (B1 to B10) were filtered, washed and re-crystallized in pure ethanol. physical properties of compounds prepared in this work are given in the table-1.

Table 1: Physical properties of compounds.

<table>
<thead>
<tr>
<th>Compound</th>
<th>MF (MW)</th>
<th>M.P.</th>
<th>Yield (%)</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C% Cal., (found) H% Cal., (found) N% Cal., (found)</td>
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<tr>
<td>B1</td>
<td>C_{26}H_{33}F_{6}N_{6}O_{2} 480.58</td>
<td>138</td>
<td>61</td>
<td>64.98, (64.99) 6.92, (6.91) 17.49, (17.50)</td>
</tr>
<tr>
<td>B2</td>
<td>C_{30}H_{31}F_{6}N_{6}O_{2} 528.62</td>
<td>125</td>
<td>56</td>
<td>68.16, (68.16) 6.29, (6.31) 15.90, (15.90)</td>
</tr>
<tr>
<td>B3</td>
<td>C_{30}H_{32}ClF_{6}N_{6}O_{2} 562.23</td>
<td>167</td>
<td>47</td>
<td>63.99, (63.98) 5.73, (5.74) 14.93, (14.92)</td>
</tr>
<tr>
<td>B4</td>
<td>C_{30}H_{33}F_{6}N_{6}O_{2} 563.07</td>
<td>154</td>
<td>55</td>
<td>63.99, (63.97) 5.73, (5.75) 14.93, (14.94)</td>
</tr>
<tr>
<td>B5</td>
<td>C_{30}H_{32}F_{7}N_{6}O_{4} 573.62</td>
<td>98</td>
<td>41</td>
<td>62.82, (62.81) 5.62, (5.63) 17.09, (17.08)</td>
</tr>
<tr>
<td>B6</td>
<td>C_{26}H_{32}F_{2}N_{6}O_{2}</td>
<td>106</td>
<td>65</td>
<td>62.64, (62.65) 6.47, (6.46) 16.86, (16.86)</td>
</tr>
</tbody>
</table>
RESULTS AND DISCUSSIONS

The results of characterization of the synthesized compounds are as follows.

1-(2-((4-(ethylamino)-6-((2-fluorophenyl)amino)-1,3,5-triazin-2-yl)amino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (B1): IR(KBr) cm⁻¹: 3463(O-H str), 3351 (N-H str) 2969(C-H aromatic), 1410 (C-C), 1130(C-O-C methoxy), 1020(C-F). ¹H NMR (DMSO-d₆, δ) ppm: 1.14(t, 3H), 1.49-1.68(m, 10H), 3.08(t, 1H), 3.46(m, 2H), 3.48(d, 2H) 3.65(s, 1H), 3.83(s, 3H), 6.78-7.79 (m, 8H) 9.67(t, 1H), 13.58(s, 2H).

1-(2-((4-(2-fluorophenyl)amino)-6-(phenylamino)-1,3,5-triazin-2-yl)amino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (B2): IR(KBr) cm⁻¹ : 3484(O-H str), 3356 (N-H str) 2963(C-H aromatic), 1423 (C-C), 1143(C-O-C methoxy), 1032(C-F). ¹H NMR (DMSO-d₆, δ) ppm: 1.29-1.39(m, 10H), 3.08(t, 1H), 3.47(d, 2H) 3.67(s, 1H), 3.88(s, 3H), 6.61-7.63(m, 13H) 9.98(t, 1H), 14.18(s, 2H).

1-(2-((4-(4-chlorophenyl)amino)-6-((2-fluorophenyl)amino)-1,3,5-triazin-2-yl)amino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (B3): 3455(O-H str), 3361 (N-H str) 2923(C-H aromatic), 1442 (C-C), 1142(C-O-C methoxy), 1027(C-F), 693(C-Cl). ¹H NMR (DMSO-d₆, δ) ppm: 1.21(t, 2H), 2.21-2.50(m, 10H), 3.28(t, 1H), 3.81(s, 3H), 4.23(s, 1H), 6.98-8.32(m, 12H) 9.63(t, 1H), 11.37(s, 2H).

1-(2-((4-(2-chlorophenyl)amino)-6-((2-fluorophenyl)amino)-1,3,5-triazin-2-yl)amino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (B4): 3469(O-H str), 3366(N-H str) 2930(C-H aromatic), 1449 (C-C), 1153(C-O-C methoxy), 1029(C-F), 701(C-Cl). ¹H NMR (DMSO-d₆, δ) ppm: 1.22(t, 2H), 2.25-2.53(m, 10H), 3.29(t, 1H), 3.78(s, 3H), 4.41(s, 1H), 6.61-8.20(m, 12H) 9.71(t, 1H), 13.81(s, 2H).
1-(2-((4-((2-fluorophenyl)amino)-6-((2-nitrophenyl) amino)-1,3,5-triazin-2-yl)amino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (B5): 3510(O-H str), 3385(N-H str) 2927C-H aromatic), 1451 (C-C), 1140(C-O-C methoxy), 1034(C-F). $^1$H NMR (DMSO-d$_6$, δ) ppm: 1.13(t, 2H), 2.09-2.33(m, 10H), 3.09(t, 1H), 3.88(s, 3H), 4.12(s, 1H), 6.56-8.05(m, 12H) 10.02(t, 1H), 14.11(s, 2H).

1-(2-((4-((3,4-difluorophenyl)amino)-6-(ethylamino)-1,3,5-triazin-2-yl)amino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (B6): 3445(O-H str), 3363 (N-H str) 2958(C-H aromatic), 1435 (C-C), 1134(C-O-C methoxy), 1017(C-F). $^1$H NMR (DMSO-d$_6$, δ) ppm: 1.16(t, 3H), 1.43-1.63(m, 10H), 3.07(t, 1H), 3.41(m, 2H), 3.45(d, 2H) 3.70(s, 1H), 3.88(s, 3H), 6.55-7.39 (m, 7H) 9.77(t, 1H), 12.98 (s, 2H).

1-(2-((4-((3,4-difluorophenyl)amino)-6-(phenylamino)-1,3,5-triazin-2-yl)amino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (B7): 3464(O-H str), 3348 (N-H str) 2957(C-H aromatic), 1438 (C-C), 1167(C-O-C methoxy), 1041(C-F). $^1$H NMR (DMSO-d$_6$, δ) ppm: 1.43-1.68(m, 10H), 3.11(t, 1H), 3.47-3.50(d, 2H) 3.68(s, 1H), 3.71(s, 3H), 6.54-7.61(m, 12H) 9.77(t, 1H), 13.76 (s, 2H).

1-(2-((4-((4-chlorophenyl)amino)-6-((3,4-difluorophenyl)amino)-1,3,5-triazin-2-yl)amino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (B8): 3474(O-H str), 3358(N-H str) 2944(C-H aromatic), 1452 (C-C), 1139(C-O-C methoxy), 1013(C-F), 695(C-Cl). $^1$H NMR (DMSO-d$_6$, δ) ppm: 1.23(t, 2H), 2.19-2.35(m, 10H), 3.21(t, 1H), 3.83(s, 3H), 4.13(s, 1H), 6.55-7.79(m, 11H) 9.88(t, 1H), 12.96 (s, 2H).

1-(2-((4-((2-chlorophenyl)amino)-6-((3,4-difluorophenyl)amino)-1,3,5-triazin-2-yl)amino) -1-(4-methoxyphenyl)ethyl)cyclohexanol (B9): 3478(O-H str), 3386(N-H str) 2947(C-H aromatic), 1438 (C-C), 1123(C-O-C methoxy), 1015(C-F), 699(C-Cl). $^1$H NMR (DMSO-d$_6$, δ) ppm: 1.21(t, 2H), 2.15-2.44(m, 10H), 3.33(t, 1H), 3.62(s, 3H), 4.22(s, 1H), 6.68-8.11(m, 11H) 9.55(t, 1H), 12.92(s, 2H).

1-(2-((4-((3,4-difluorophenyl)amino)-6-((2-nitrophenyl)amino)-1,3,5-triazin-2-yl)amino)-1-(4-methoxyphenyl)ethyl)cyclohexanol (B10): 3525(O-H str), 3377(N-H str) 2954(C-H aromatic), 1434 (C-C), 1121(C-O-C methoxy), 1066(C-F). $^1$H NMR (DMSO-d$_6$, δ) ppm: 1.28(t, 2H), 2.39-2.53(m, 10H), 3.18(t, 1H), 3.69(s, 3H), 4.31(s, 1H), 6.56-7.89(m, 11H) 9.91(t, 1H), 13.31(s, 2H).
BIOLOGICAL ACTIVITIES

Selected synthesized compounds were evaluated for their antimicrobial potential against two selected gram +ve bacterial organism (E. coli & P. aeruginosa), two selected gram –ve bacterial organisms (S. aureus & S. pyogenus) as well as three selected fungal organisms (C. albicans, A. niger & A. clavatus) by Broth dilution method. The minimal inhibition concentrations (MIC) of synthesized molecules and the reference standard drugs are given in the Table-2. The effects of the synthesized molecules were compared with the reference drugs like Ampicillin, Chloramphenicol, & Ciprofloxacin for antibacterial tests and Nystatin & Greseofulvin for anti fungal activity tests.

Table 2: Antibacterial activities for the selected compounds.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Minimal Inhibition Concentration (μg/mL)</th>
<th>E. coli</th>
<th>P. aeruginosa</th>
<th>S. aureus</th>
<th>S. pyogenus</th>
<th>C. albicans</th>
<th>A. niger</th>
<th>A. clavatus</th>
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<tbody>
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<td>250</td>
<td>100</td>
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<td>Chloramphenicol</td>
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<td>Ciprofloxacin</td>
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<tr>
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<td>Greseofulvin</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>500</td>
<td>100</td>
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</table>

CONCLUSION

The series of the selected compounds was synthesized with good to moderate yields. From the biological data it was come to know that compound B7 contains potential activity against 

P. aeruginosa. and E. coli while all other compounds are moderate to less active against selected species. In the case of fungicidal effects compound B10 found moderate active against C. albicans. All other compounds are less active or inactive against selected fungal species.

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REFERENCES


