Synthesis and antimicrobial activity of [2"-ARYL(QUINOXALINE)-3-YL]-(METHYLENE PHENYL AMINO)-6-[BIS-(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE

P. J. Kathiriya, H. D. Purohit, D. M. Purohit*
Shree M. & N. Virani Science College, Kalawad Road, Rajkot-5 Gujarat, India

*E-mail address: purohitdm@yahoo.com

Keywords: Quinoxalines; S-Triazine

ABSTRACT

The compounds 5d, 5e, 5g, 5i showed moderate antimicrobial activity then other synthesized compounds, compared with known standard drugs.

1. INTRODUCTION

Quinoxalines derivative possess broad spectrum of pharmacological activities which are reflected by their use as CNS depressant\(^1\), Antitubercular\(^2\), Antiulcer\(^3\), Analgesic\(^4\), Anxiolytic\(^5\), Antihypertensive\(^6\), Antitumor\(^7\) etc. In view of getting potent therapeutic agents to synthesized titles compounds.

2-\{4"-'(4"'-aryl)-3"'-cyano-2"'-methoxy-pyridine-6"'-yl]-phenyl amino\}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine have been synthesized by the condensation of 2-\{4"–\[(3"–aryl) – 2"–propene–1"–one phenyl amino\}–6– [Bis(2"–chloroethyl) amino– 4–methoxy–1,3,5 triazine with bromine in glacial acetic acid and o-phenylenediamine.

2-\{4"–\[(3"–aryl)–2"–propene–1"–one phenyl amino\}–6–[(Bis(2"–chloro ethyl)amino)]–4–methoxy–1,3,5–triazine (4a – 4k) have been synthesized by the reaction of 2–(4"–acetyl phenyl amino)–6–[Bis (2"–chloro ethyl)amino]–4–methoxy–1,3,5–triazine (3) with aromatic aldehyde in the present of aq. NaOH solution.

2–(4"–acetyl phenyl amino)–6–[Bis(2"–chloro ethyl)amino]–4–methoxy–1,3,5–triazine (3) have been synthesized by the condensation of 2–(4"–acetyl phenyl amino)–6–chloro–4– methoxy–1,3,5–triazine (2) with 2,2"–dichlorodiethyl amine hydrochloride in the presence of aq. NaOH and dioxane at 110 °C temp.

2–(4"–Acetyl phenyl amino)–6–chloro–4–methoxy–1,3,5–triazine (2) have been synthesized by the reaction of 2–(4"–acetyl phenyl amino)–4,6–dichloro–1,3,5–triazine (1) with sodium methoxide in methanol at room temp.

2–(4"–Acetyl phenyl amino)–4,6–dichloro–1,3,5–triazine (1) have been synthesized by the condensation of 2,4,6–trichloro–S–triazine with 4–amino acetophenone in aq. NaOH and acetone at 0 °C temp.

2. MATERIALS AND METHODS

2.1 Antimicrobial activity

Quinoxalines (5a-5k) were evaluated in vitro for antimicrobial activity against \textit{B. Mega}, \textit{B. Subtillis}, \textit{E. Coli}, \textit{P. Fluoresences} and for antifungal activity against \textit{A. awamori} using DMF as solvent at 50 µg concentration by cup-plate method\(^8\). After 24 hrs. of incubation at 37 0°C temp., the zone or inhibition were measured in mm. The activity was compared with the known antibiotics viz.
Amicillin chloramphenicol, Norfloxacain, Greseofulvin at same concentration which is represented in Table-I and comparable anti microbial activity represented in Table no. II.

3. METHOD SECTION

All the melting points were taken in open glass capillaries and are uncorrected. IR absorption spectra were recorded on a Shimadzu-FT-IR 8400 spectro-photometer using KBr pellet and $^1$H NMR spectra on a Bruker DPX-200 spectrometer (300 MHz) using DMSO as solvent and TMS as internal standard. Purity of the compounds were routinely checked by TLC using silica gel G.

4. EXPERIMENTAL AND SPECTRAL SECTION

(A) 2–(4’–Acetyl phenyl amino)–4,6–dichloro–1,3,5–triazine (1):

A mixture of 2,4,6–trichloro–S–triazine (1.845 gm, 0.01 m), 4-amoeno acetophenone (1.35 gm, 0.01 m) in acetone (25 ml) and aq. NaOH solution till solution basic. The reaction mixture was stirred at 0 °C temp. for 5 hrs. The content was poured into crushed ice, filtered and washed with water. The isolated product was crystallized from dioxane. yield : 86%, MP. 178 °C. (Found : C, 46.61 , H, 2.79, N, 19.10). IR : 3291 (C=O str.) 1618 (N Str.) 1620 (N str.) 1242 (C Str.), 1702 (C=O str.) NMR : 3.10 (s, 3H, Ar O), 3.22 (s, 3H, Ar OCH3), 3.62 (s, 3H, Ar OCH3), 7.03 (D.D. 4H Ar Hb, Hc), 9.95 (s, 1H, N–H) Mass : (m/z) 77, 103, 139, 145, 172, 198, 221, 240, 259.

(B) 2–(4’–Acetyl phenyl amino)–6–chloro–4–methoxy–1,3,5–triazine (2):

A mixture of 2–(4’–acetyl phenyl amino)–4,6–dichloro–1,3,5–triazine (2.83 gm, 0.01 m); sodium methoxide (0.56 gm, 0.01 m) in methanol. The reaction mixture was stirring at room temp. for 7 hrs. The content was poured into crushed ice, filtered and wash with water. The isolated product was crystallized from dioxane. yield : 86%, M. P. 178°C. (Found C, 51.65 H, 3.91, N, 20.09, C12H17N2O2Cl required C, 51.70, H, 3.94, N, 20.10%) IR : 2950 (C–H str. asym), 2871 (C–H def.), 3056 (C–H str. aromatic), 1509 (C=C str.), 1118 (C–N str.), 1620 (N–H bend), 768 (C–Cl Str.), 1700 (C=O str.) NMR : 3.10–3.20 (s, 3H, Ar–COCH3); 6.50–6.63 (m, 4H, Ar–H), 9.95 (s, 1H, N–H) Mass : (m/z) 77, 103, 139, 145, 172, 198, 221, 240, 259.

(C) 2–(4’–Acetyl phenyl amino)–6–[Bis (2”–chloroethyyl) amino]–4–methoxy–1,3,5 triazine. (3):

A mixture of 2–(4’–acetyl phenyl amino)–6–chloro–4–metholy–1,3,5–triazine (2.78 gm, 0.01 m), 2,2’–di chloro diethyl amine hydrochloride (1.43 gm, 0.01m); dioxane (25 ml) and aq. NaOH. The reaction mixture was reflux at 110 °C temp. for 6 hrs. The content was cooled and poured into crushed ice, Filtered and washed with water. The isolated product was crystallized from dioxane. yield 79%, M. P. 249 °C. (Found : C, 49.88, H, 4.91, N, 18.19, C16H16N4O2Cl2 required C, 50.00, H, 4.94, N, 18.22%) IR : 2921 (C–H str. asym), 2850 (C–H str. sym.), 1431 (C–H def.), 3062 (C–H str. aromatic), 1166 (C–H i.p. def.), 842 (C–H, o.p. def.), 1511 (C=C Str.) 1121 (C–N str.), 3342 (N–H Str.) 1242 (C–O–C Str.), 1702 (C=O str.) NMR : 3.10–3.22 (s, 3H, Ar–COCH3), 3.62–3.86 (s, 3H, –OCH3), 7.01–7.03 (D.D. 4H, (Ar–H)), 4.79–4.80 (t, 4H, –CH2–Cl), 9.95 (s, 1H, –NH), Mass : (m/z) 77, 103, 145, 172, 210, 228, 265, 282, 302, 326, 355, 370.
A mixture or 2-4'-acetyl phenyl amino-6-[Bis(2''-chloro ethyl) amino]-4-methoxy-1,3,5-triazine (4e):

A mixture or 2-(4'-acetyl phenyl amino)–6-[Bis(2''-chloro ethyl) amino]-4-methoxy–1,3,5-triazine (3.8 gm, 0.01 M) took in methanol (25 ml). A few drops of conc. H$_2$SO$_4$ & bromine in glacial acetic acid was added. The reaction mixture was heated at 90° C. for 1 hr. in water bath. The reaction mixture poured into crushed ice, filtered, dried and crystallised from dioxane. Yield: 69%, M. P. 239° C. (Found C : 61.00; H : 4.89; N : 13.94%) IR : 2923 (C–H asym), 1450 (C–O str.), 1118 (C–H str.), 3315 (N–H str.) 3097 (C=C str.), 1245 (C–Cl str.), 1436 (C–H str. asym), 1371 (C–H str. sym) 3097 (C–H str. aromatic) 1276 (C–H i.p. def.), 821 (C–H, o.o.p. def.), 1677 (C=O str.), 1118 (C–N str.), 3311 (N–H str.) 3045 (C=C str.), 1245 (C–O–C Str.), 768 (C–Cl str.) NMR : 3.62–3.86 (s, 6H, Ar–OCH$_3$), 7.01–7.03 (D. D. 4H, Ar–Hb), 8.08–8.72 (D. D. 4H, Ar–Hc), 4.79–4.80 (t, 4H, CH$_2$–Cl), 2.50–2.51 (t, 4H, -NCH$_2$), 9.95 (s, 1H, –NHf), 4.80–4.83 (s, 2H, CH=CHg) Mass : (m/z) 112, 130, 212, 262, 271, 280, 285, 325, 335, 371, 428, 461, 502.

Similarly other chalcones (4a – 4k) where prepared and their physical data and antimicrobial activities data published in other journal.

(E) $[2''(4''''-Methoxy phenyl)-(quinoxaline)-3-yl]-(methylene phenyl amino)-6-[Bis(2''-chloro ethyl amino)-4-methoxy-1,3,5-triazine (5e):

A mixture of 2-4'[3''-(4''''-methoxy Phenyl) – 2'' – Propene – 1''-one] Phenyl amino}–6-[Bis (2''-chloro ethyl) amino]-4-methoxy – 1,3,5 – triazine (5.02 gm, 0.01M and o-phenylene diamine (1.08 gm, 0.01 M) taken in methanol (25 ml). A few drops of conc. H$_2$SO$_4$ & bromine in glacial acetic acid was added. The reaction mixture was heated at 90° C. for 1 hr. in water bath. The reaction mixture poured into crushed ice, filtered, dried and crystallised from dioxane. Yield : 69%, M. P. 239° C. (Found C : 61.00; H : 4.89; N : 16.58; C$_{30}$H$_{29}$O$_2$N$_2$Cl$_2$ required C : 61.01; H : 4.91; N : 16.60%) IR : 2900 (C–H str. asym), 2881 (C–H str. sym.) 1450 (C–H def. asym), 1369 (C–H def. sym.), 1450 (-CH$_2$ Str.), 3058 (C–H str. aromatic) 1265 (C–H i.p. def.), 800 (C–H o.o.p. def.), 1487 (C=C str), 1070 (C–N str.), 1598 (C=N str.), 3315 (N–H str.), 1558 (N–H ben.), 1265 (C–O–C str. asym.), 1070 (C–O–C str. sym.), 800 (C–Cl str.), 1608 (C=N str.), 1089 (C–N str.) NMR : 3.60-4.00 (s, 6H, Ar–OCH$_3$), 7.94-7.98 (DD, 4H, Ar-H$_b$), 8.07-8.40 (D.D. 4H, Ar–Hc), 4.10-4.14 (t, 4H, -CH$_2$–Cl), 2.77 (t, 4H, -NCH$_2$), 10.23 (s, 1H, Ar–NH), 7.34 (s, 2H, Ar-H), 7.28-8.07 (m, 4H, Ar-H). Mass : (m/z) 137, 144, 167, 179, 188, 255, 271, 340, 358, 384, 432, 462, 590.

Similarly other (5a – 5k) have been synthesized and their physical data represented in Table no. I.
REACTION SCHEME:

\[
\begin{align*}
(1) \quad & R = \text{Aryl} \\
(2) \quad & 0^\circ C, \text{Acetone} \\
(3) \quad & \text{NaOCH}_3, \text{RT, Methanol} \\
(4) \quad & 110^\circ C, \text{1,4-Dioxane} \\
(5) \quad & \text{RT, Methanol} \\
\end{align*}
\]

\[
\text{Br}_2, \text{gl. CH}_3\text{COOH}
\]

\[
R = \text{Aryl}
\]
5. RESULTS AND DISCUSSION:

The physical data and antimicrobial activity of compounds (5a - 5k)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mol Formula</th>
<th>M.P (°C)</th>
<th>Yield (%)</th>
<th>N (%)</th>
<th>Calc. (found)</th>
<th>Anal. Activity</th>
<th>A. ensement</th>
<th>E. coli</th>
<th>S. faecalis</th>
<th>S. aureus</th>
<th>P. fluorescens</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>C₈H₇C₆N₅O₄</td>
<td>199</td>
<td>80</td>
<td>17.49</td>
<td>17.01</td>
<td>12</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>5b</td>
<td>C₉H₈C₆N₅O₃</td>
<td>204</td>
<td>76</td>
<td>17.01</td>
<td>17.01</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>5c</td>
<td>C₁₀H₈C₆N₅O₃</td>
<td>204</td>
<td>76</td>
<td>17.01</td>
<td>17.01</td>
<td>12</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>5d</td>
<td>C₁₀H₉C₆N₅O₃</td>
<td>204</td>
<td>76</td>
<td>17.01</td>
<td>17.01</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>5e</td>
<td>C₁₀H₁₀C₆N₅O₃</td>
<td>204</td>
<td>76</td>
<td>17.01</td>
<td>17.01</td>
<td>12</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>5f</td>
<td>C₁₁H₁₀C₆N₅O₃</td>
<td>204</td>
<td>76</td>
<td>17.01</td>
<td>17.01</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>5g</td>
<td>C₁₁H₁₁C₆N₅O₃</td>
<td>204</td>
<td>76</td>
<td>17.01</td>
<td>17.01</td>
<td>12</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>5h</td>
<td>C₁₁H₁₂C₆N₅O₃</td>
<td>204</td>
<td>76</td>
<td>17.01</td>
<td>17.01</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>5i</td>
<td>C₁₂H₁₃C₆N₅O₃</td>
<td>204</td>
<td>76</td>
<td>17.01</td>
<td>17.01</td>
<td>12</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>5j</td>
<td>C₁₂H₁₄C₆N₅O₃</td>
<td>204</td>
<td>76</td>
<td>17.01</td>
<td>17.01</td>
<td>16</td>
<td>17</td>
<td>17</td>
<td>18</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>5k</td>
<td>C₁₃H₁₅C₆N₅O₃</td>
<td>204</td>
<td>76</td>
<td>17.01</td>
<td>17.01</td>
<td>12</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
</tr>
</tbody>
</table>

* Zone of inhibition in mm.
Table-II
Comparable antimicrobial activity.

<table>
<thead>
<tr>
<th>Compd</th>
<th>B. Megi</th>
<th>B. Stabillis</th>
<th>E. Coli</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5a, 5d, 5i</td>
<td>5a, 5d, 5i</td>
<td>5a, 5d, 5i</td>
</tr>
<tr>
<td>1 Ampiicillin (50 μg)</td>
<td>23</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>2 Chloramphenicol (50 μg)</td>
<td>24</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>3 Norfloxacin (50 μg)</td>
<td>24</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>4 Goseoflox (50 μg)</td>
<td>-</td>
<td>-</td>
<td>23</td>
</tr>
</tbody>
</table>
6. CONCLUSION

The compounds 5d, 5e, 5g, 5i showed moderate antimicrobial activity then other synthesized compounds, compare with known standard drugs.

ACKNOWLEDGEMENT
The authors are thankful to the management and Principal of Shree M. & N. Virani Science College, Rajkot for providing research facilities.

References


(Received 03 April 2015; accepted 17 April 2015)