Synthesis and antimicrobial activity of 2-{4'-(6''-ARYL)2''-HYDROXY-3'',4''-DIHYDRO-PYRIMIDINE-4''-YL]-PHENYL AMINO}-6-[BIS (2''''-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE

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Keywords: Hydroxy pyrimidines; S-Triazine; Antibacterial screening; Antifungal screening

ABSTRACT

The titled compounds (5a-5k) have been synthesized by the condensation of 2-4-{3"-aryl)-2"-Propene-1"-one]-Phenyl amino]-6-[bis-2''''-chboroethyl] amino]-4-methoxy-1,3,5-triazine with urea in presence of conc. HCl (0.3ml) The biological activities of these compounds have been examined against various Gram +ve, Gram –ve bacteria and fungi. The structure of the products was confirmed by IR, 1H NMR, Mass spectra and elemental analysis.

1. INTRODUCTION

Pyrimidine nucleus possess broad spectrum of pharmacological activities which are reflected by their use as analgesic, anticonvulsant, antimicrobial, antipyretics, antiinflammatory, antitumor, antineoplastic, antimalarial, antithyroid, antihelmintic, Anti-HIV, antiviral, antagonists etc. With a view to getting of synthesis pyrimidine derivatives.

2. ANTIMICROBIAL ACTIVITY

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

3. MATERIAL AND METHODS

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

Synthesis of 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-amino acetophenone (1.35 gm, 0.01 M) in aceton (25 ml) and aq. NaOH solution till solution basic. The reaction mixture was stirring 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 : 82%, m.p. 112 °C. (Found : C, 46.61, H, 2.79, N, 19.75, C12H12N4OCl2 required C, 46.64, H, 2.82, N, 19.79%). IR : (cm⁻¹) : 2952 (C–H str., asym.), 2870 (C–H Str., Sym), 1420 (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.) 1H NMR : (δ ppm) :
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, 221, 240, 259, 283. TLC : Hexane : Acetone (6:3), Rᵣ = 0.56

Synthesis of 2–(4′–Acetyl phenyl amino)–6–chboro–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 79%. IR : 3199 (C=O sym), 2923 (C–H sym), 2852 (C–H asym), 1433 (C=C sym), 1319 (C=C asym), 1111 (C–H i.p. def.), 761 (C–H str. aromatic), 1102 (C–N str.), 1618 (–NH Str.), 1244 (C–O–C Str.), 761 (C–Cl str), 1702 (C=O str). ¹H NMR : (δ ppm) : 7.03 (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, 221, 240, 259, 283. TLC : Hexane : Acetone (6:3), Rᵣ = 0.56

Synthesis of 2–(4′–Acetyl phenyl amino)–6–[bis (2′–chloroethyl) amino]–4–methoxy–1,3,5–triazine. (3):
A mixture of 2–(4′–acetyl phenyl amino)–6–chloro–4–methoxy–1,3,5–triazine (2.78 gm, 0.01 M), 2,2′–di chloro diethyl amine hydrochloride (1.43 gm, 0.01 M); dioxane (25 ml) andaq. 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. IR : 3199 (C=O sym), 2923 (C–H sym), 2852 (C–H asym), 1433 (C=C sym), 1319 (C=C asym), 1111 (C–H i.p. def.), 761 (C–H str. aromatic), 1102 (C–N str.), 3342 (N–H Str.) 1242 (C–O–C Str.), 761 (C–Cl str), 1702 (C=O str). ¹H NMR : (δ ppm) : 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, 384. TLC : Hexane : Methanol (4:6), Rᵣ = 0.73

Synthesis 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. (4e):
A mixture of 2–(4′–acetyl phenyl amino)–6–[bis(2′′–chloro ethyl amino]–4–methoxy–1,3,5–triazine (3.84 gm, 0.01 M), 4–methoxy benzaldehyde (1.36 gm, 0.01 M), sodium methoxide (0.56 gm, 0.01 M)). 178 °C. ¹H NMR : (δ ppm) : 3.62 (s, 3H, Ar–COCH₃); 3.91 (d, 3H, Ar–NCH₃); 4.98 (s, 1H, Ar–H), 15.94%.) IR : (cm⁻¹) : 2923 (C–H str), 1188 (C=O str.), 1511 (C=C str.) 1121 (C–N str.), 3342 (N–H Str.) 1242 (C–O–C Str.), 761 (C–Cl str), 1702 (C=O str). ¹H NMR : (δ ppm) : 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, 384. TLC : Hexane : Methanol (4:6), Rᵣ = 0.69

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

Synthesis of 2–[4′–[6′–(4′′′–Methoxy phenyl)–2′–hydroxy–3′′,4′′–dihydro-pyrimidine-4′′-yl]-phenylamino]–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, 0.01 M) and urea (0.60 g, 0.01 M)
was refluxed at 90° C. for 12 hrs. in presence of conc. HCl (0.3 ml) in methanol the reaction mixture was poured into crushed ice, filtered and dried the product was isolated, crystallised from dioxane. Yield : 78%, m.p. 110° C. (Found : C : 55.11; H : 4.95; N : 17.99; C_{25}H_{27}O_{3}N_{7}Cl_{2} required C : 55.14; H : 4.96; N : 18.01%). IR : (cm\(^{-1}\)) : 2925 (C–H str. asym), 2876 (C–H str. sym.) 1460 (C–H def. asym), 1355 (C–H def. sym.), 3081 (C–H str. aromatic) 1180 (C–H i. p. def.), 806 (C–H o.o.p. def.), 1473 (C=C str), 1141 (C–N str.), 1589 (C=N str.), 3407 (N–H str.) 1247 (C–O–C str. asym.), 1068 (C–O–C str. sym.), 767 (C–Cl str.), 3350 (N–H str.), 1116 (C–N str.), 1616 (C=N str.). \(^1\)H NMR (δ ppm) : 3.50 – 3.69 (s, 6H, Ar–OCH\(_3\)), 7.49-7.90 (d.d., 4H, Ar-H), 7.92-9.27 (d.d. 4H, Ar–H), 4.62-4.65 (t, 4H, -CH\(_2\)-Cl), 2.32-2.92 (t, 4H, -NCH\(_2\)), 9.69 (s, 2H, Ar–NH), 9.78 (s, 2H, Ar-NH\(_2\)). Mass : (m/z) 143, 141, 151, 157, 188, 247, 279, 337, 347, 388, 424, 452, 543. TLC : Hexane : Acetone (3:7), \(R_f = 0.74\)

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

\[
\begin{align*}
\text{(1)} & \quad \text{NaOCH}_3 \\
\text{(2)} & \quad \text{RT, Methanol} \\
\text{(3)} & \quad \text{RT, Methanol} \\
\text{(4a - 4k)} & \quad \text{H}_2\text{N-}\text{NH}_2 \\
\text{(5a - 5k)} & \quad R = \text{Aryl}
\end{align*}
\]
4. RESULTS AND DISCUSSION

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

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>Mol. Formula</th>
<th>M.P. °C</th>
<th>Yield (%)</th>
<th>Calc. (Found)</th>
<th>B. Mega</th>
<th>B. Subtilis</th>
<th>E. Coli</th>
<th>P. Fluorescens</th>
<th>A. awamori</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>C5H7</td>
<td>C13H22Cl2N2O2</td>
<td>180</td>
<td>81</td>
<td>19.06 (19.03)</td>
<td>20</td>
<td>12</td>
<td>18</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>5b</td>
<td>2-OH C5H7</td>
<td>C13H21ClN2O2</td>
<td>228</td>
<td>79</td>
<td>18.48 (18.41)</td>
<td>23</td>
<td>14</td>
<td>17</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>5c</td>
<td>3-OH C5H7</td>
<td>C13H21ClN2O2</td>
<td>262</td>
<td>83</td>
<td>18.48 (18.43)</td>
<td>21</td>
<td>18</td>
<td>19</td>
<td>23</td>
<td>19</td>
</tr>
<tr>
<td>5d</td>
<td>4-OH C5H7</td>
<td>C13H21ClN2O2</td>
<td>280</td>
<td>85</td>
<td>18.48 (18.47)</td>
<td>24</td>
<td>19</td>
<td>22</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>5e</td>
<td>4-OCH3 C5H7</td>
<td>C13H24ClN2O2</td>
<td>110</td>
<td>78</td>
<td>18.01 (17.99)</td>
<td>19</td>
<td>18</td>
<td>16</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>5f</td>
<td>4-Br, 5-OCH3 C5H7</td>
<td>C13H24ClN2O2</td>
<td>192</td>
<td>76</td>
<td>17.49 (17.43)</td>
<td>17</td>
<td>16</td>
<td>15</td>
<td>18</td>
<td>17</td>
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<tr>
<td>5g</td>
<td>4-Br C5H7</td>
<td>C13H22BrClN2O2</td>
<td>224</td>
<td>79</td>
<td>16.53 (16.51)</td>
<td>22</td>
<td>15</td>
<td>17</td>
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<td>19</td>
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<tr>
<td>5h</td>
<td>3-NO C5H7</td>
<td>C13H20ClN2O3</td>
<td>265</td>
<td>81</td>
<td>20.03 (20.01)</td>
<td>18</td>
<td>17</td>
<td>20</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>5i</td>
<td>4-NO C5H7</td>
<td>C13H20ClN2O3</td>
<td>249</td>
<td>84</td>
<td>20.03 (20.02)</td>
<td>23</td>
<td>19</td>
<td>16</td>
<td>24</td>
<td>20</td>
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<tr>
<td>5j</td>
<td>4-N,N-CH2Cl C5H7</td>
<td>C13H22ClN2O2</td>
<td>213</td>
<td>79</td>
<td>20.10 (20.08)</td>
<td>19</td>
<td>20</td>
<td>17</td>
<td>16</td>
<td>16</td>
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<tr>
<td>5k</td>
<td>C6H9O (Furfuryl)</td>
<td>C13H22ClN2O2</td>
<td>211</td>
<td>83</td>
<td>19.44 (19.41)</td>
<td>17</td>
<td>16</td>
<td>14</td>
<td>21</td>
<td>18</td>
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</table>

* Zone of inhibition in mm.

Table II
Antimicrobial activity compared with known standard drugs.

<table>
<thead>
<tr>
<th>Compd</th>
<th>B. Mega</th>
<th>B. Subtilis</th>
<th>E. Coli</th>
<th>P. Fluorescens</th>
<th>A. awamori</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a-5k</td>
<td>5b, 5d, 5i</td>
<td>5d, 5i, 5j</td>
<td>5c, 5d, 5h</td>
<td>5c, 5d, 5i</td>
<td>5b, 5d, 5h</td>
</tr>
<tr>
<td>1</td>
<td>Ampicillin (50 µg)</td>
<td>23</td>
<td>19</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Chloramphenicol (50 µg)</td>
<td>24</td>
<td>19</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Norfloxacin (50 µg)</td>
<td>23</td>
<td>20</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Griseofulvin (50 µg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

5. CONCLUSION

The titled compounds (5a – 5k) have been synthesized and evaluated in vitro their antimicrobial screening. The compounds 5b, 5c, 5d, 5i, 5h, showed moderately comparable antibacterial and antifungal activity then other synthesized compounds which are compare with known standard drugs e.g. Ampicillin, Chloramphenicol, Norfloxacin, Griseofulvin at same concentration (50 µg/ml)

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