Synthesis and biological screening of 1-N-[4'-[4",4"'-difluoro diphenyl]-methyl]-piperazine-1'-yl]-4-arylidene-2-penyl-5-oxo-imidazolines

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1-N-[4"'-4",4"'-Difluorodiphenyl]-methyl]-piperazine-1'-yl]-4-arylidene-2-phenyl-5-oxo-imidazolines 3a-j have been synthesized by the condensation of 1-amino-4-[(4', 4''-difluorodiphenyl)-methyl]-piperazine with different oxazolones. The products have been assayed for their antimicrobial screening against Gram +ve and Gram –ve bacteria, and fungi. Some of the products show moderate activity compared with known standard drugs viz. ampicillin, chloramphenicol, norfloxacin and greseofulvin at the same concentration 50 µg/mL, which is represented in Table I. All the synthesized compounds 3a-j showed moderate to good and remarkable activities with known standard drugs at the same concentration, which is represented in Table II.

Experimental Section

All the melting points were measured in open glass capillary method and are uncorrected. I.R. absorption spectra (in cm\(^{-1}\)) were recorded on a Shimadzu IR-435 spectrophotometer using KBr pellet method and \(^1\)H NMR spectra on Hitachi R-1200 (300 MHz) spectrometer using TMS as an internal standard (chemical shifts in \(\delta\), ppm) and mass spectra on a Jeol 300 eV instrument. The compounds were routinely checked by TLC using silica gel G.

1-Nitroso-4-[4',4''-difluorodiphenyl]-methyl]-piperazine, 1

1-[4',4''-Difluorodiphenyl]-methyl]-piperazine (8.6 g, 0.03 mol) in 50 mL of ice cold water containing 24 mL of diluted HCl was nitrosated with 2.1 g NaNO\(_2\) in 10 mL water. The reaction mixture was made alkaline by the addition of NaOH solution and an oily layer was formed. The oily product was separated and crystallized from 5 mL ethyl acetate and 70 mL n-hexane. The resultant solid was purified by recrystallisation from a mixture of 2-propanol and hexane to give 1-nitroso-4-[4',4''-difluorodiphenyl]-methyl]-piperazine. m.p.153-55°C. Yield 80.56%. Anal. C\(_{17}\)H\(_{12}\)N\(_{3}\)F\(_2\)O requires: C, 64.34; H, 5.40; N, 13.24. Found: C, 64.30; H, 5.37; N, 13.20%.

1-Amino-4-[4',4''-difluorodiphenyl]-methyl]-piperazine, 2

1-Nitros4-[4',4''-difluorodiphenyl]-piperazine (10 g, 0.03 mol) in 140 mL of anhyd. ether and 5 mL

Note
Scheme I

1. Treatment of compound 1 with NaNO₂ + HCl at 0-5 °C.
2. Reduction of compound 1 with LiAlH₄.
3. Reaction of compound 2 with pyridine to form compound 3a-j.

R = Aryl
NOTES

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of benzene was added drop-wise to a suspension of 1.9 g of lithium aluminium hydride in 140 mL of ether. The reaction mixture was stirred for 1 hr at RT and then refluxed and stirred for 2 hr. The reaction mixture was cooled in an ice bath and excess lithium aluminium hydride was decomposed by the addition of ethyl acetate. The reaction mixture was hydrolyzed by drop-wise addition of 2 mL of water and 2 mL of 20% NaOH solution. The inorganic salts were filtered and washed with ether. The filtrate was dried over anhyd. sodium sulphate. The solvent was evaporated and the residue was dissolved in benzene. The solvent was evaporated once again to give 1-amino-4-[(4′,4″-difluorodiphenyl)-methyl]-piperazine. m.p. 126-29°C. Yield 57.72%. Anal. C_{17}H_{32}F_{2}N_{3} requires: C, 67.31; H, 6.31; N, 13.85. Found: C, 67.27; H, 6.29; N, 13.83%. IR (KBr): 2910 (C-H str, asym), 2837 (C-H str, sym), 1454 (C-H def), 3033 (aromatic, C-H str), 1197 (C-H str, i.p def), 759 (C-H str, 0.0 p.), 1361 (C-N str.), 3274 (C-NH str.), 1606 (C-NH ben.), 3330 cm^{-1} (N-H str.); ^{1}H NMR (DMSO-d_{6}): δ 2.19-2.23 (4H, d d, N-CH_{2}), 2.66-2.71 (4H, d d, N-CH_{2}), 6.93-7.21 (8H, m, Ar-H), 5.19 (1H, s, C-H), 2.57 (2H, s, N-NH); MS: m/z 53, 76,95, 127, 177, 205, 219, 230, 257, 269, 282, 303.

4-(4′-Methoxybenzylidene)-2-phenyl-5-oxazolone

A mixture of (benzoylamino)-acetic acid, (hippuic acid) (5.19 g, 0.029 mol), acetic anhydride (3.26 g, 0.032 mol), sodium acetate (2.62 g, 0.032 mol) and 4-methoxy benzaldehyde (4.35 g, 0.032 mol) was heated on a water bath for 4 hr. Resulting mass was poured into ice cold water, filtered and purified by

### Table I — The physical characterization data and antimicrobial activity of compounds 3a-j. [Zone of inhibition in mm]

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>Mol. formula</th>
<th>m.p. °C</th>
<th>Yield (%)</th>
<th>% N</th>
<th>Antibacterial activity, zone of inhibition in mm</th>
<th>Anti fungal activity zone of inhibition in mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>C_{6}H_{5}</td>
<td>C_{33}H_{32}N_{2}F_{2}</td>
<td>134</td>
<td>65.00</td>
<td>10.48</td>
<td>22, 16, 14</td>
<td>18, 19</td>
</tr>
<tr>
<td>3b</td>
<td>3-OH-C_{6}H_{4}</td>
<td>C_{33}H_{32}O_{2}N_{2}F_{2}</td>
<td>114</td>
<td>67.54</td>
<td>10.18</td>
<td>15, 21, 20</td>
<td>16, 22</td>
</tr>
<tr>
<td>3c</td>
<td>4-OH-C_{6}H_{4}</td>
<td>C_{33}H_{32}O_{2}N_{2}F_{2}</td>
<td>104</td>
<td>72.32</td>
<td>10.18</td>
<td>19, 15, 14</td>
<td>22, 19</td>
</tr>
<tr>
<td>3d</td>
<td>2-OCH_{3}-C_{6}H_{4}</td>
<td>C_{33}H_{32}O_{2}N_{2}F_{2}</td>
<td>137</td>
<td>75.51</td>
<td>9.92</td>
<td>9.90, 21, 21, 21</td>
<td>14, 21</td>
</tr>
<tr>
<td>3e</td>
<td>4-OCH_{3}-C_{6}H_{4}</td>
<td>C_{33}H_{32}O_{2}N_{2}F_{2}</td>
<td>142</td>
<td>65.85</td>
<td>9.92</td>
<td>9.90, 17, 14, 15</td>
<td>16, 16</td>
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<tr>
<td>3f</td>
<td>2-Cl-C_{6}H_{4}</td>
<td>C_{33}H_{32}O_{2}N_{2}F_{2}</td>
<td>162</td>
<td>69.24</td>
<td>9.85</td>
<td>9.83, 24, 20, 22</td>
<td>20, 20</td>
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<td>3g</td>
<td>4-F-C_{6}H_{4}</td>
<td>C_{33}H_{32}O_{2}N_{2}F_{2}</td>
<td>113</td>
<td>63.25</td>
<td>10.14</td>
<td>10.12, 18, 19, 15</td>
<td>17, 14</td>
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<tr>
<td>3h</td>
<td>3-NO_{2}-C_{6}H_{4}</td>
<td>C_{33}H_{32}O_{2}N_{2}F_{2}</td>
<td>154</td>
<td>59.63</td>
<td>12.08</td>
<td>12.05, 16, 23, 19</td>
<td>19, 19</td>
</tr>
<tr>
<td>3i</td>
<td>3-NO_{2}-C_{6}H_{4}</td>
<td>C_{33}H_{32}O_{2}N_{2}F_{2}</td>
<td>140</td>
<td>57.87</td>
<td>12.08</td>
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<td>22, 17</td>
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<tr>
<td>3j</td>
<td>C_{6}H_{3}O</td>
<td>C_{33}H_{32}O_{2}N_{2}F_{2}</td>
<td>127</td>
<td>69.70</td>
<td>10.68</td>
<td>10.65, 22, 21, 19</td>
<td>18, 23</td>
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</table>

### Table II — Comparable activity of synthesised compounds with known standard drugs

<table>
<thead>
<tr>
<th>Compd 3a-j</th>
<th>B. subtilis 3a, 3d, 3f, 3i, 3j</th>
<th>B. cerus 3b, 3d, 3f, 3h, 3j</th>
<th>E. coli 3b, 3d, 3f, 3i, 3j</th>
<th>E. aerogen 3a, 3c, 3f, 3h, 3i, 3j</th>
<th>A. niger 3b, 3d, 3h, 3j</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard  Drugs</td>
<td>B. subtilis</td>
<td>B. cerus</td>
<td>E. coli</td>
<td>E. aerogen</td>
<td>A. niger</td>
</tr>
<tr>
<td>Ampicillin (50 µg/mL)</td>
<td>23</td>
<td>22</td>
<td>21</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>Chloramphenicol (50 µg/mL)</td>
<td>22</td>
<td>23</td>
<td>21</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Norfloxacin (50 µg/mL)</td>
<td>24</td>
<td>21</td>
<td>23</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>Griseofulvin (50 µg/mL)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>23</td>
</tr>
</tbody>
</table>
recrystallisation from acetone and water. Yield 86%, m.p. 155°C.

Similarly, other oxazolones have been prepared by Erlenmeyer oxazolone method\textsuperscript{15}.

1-N\{4′-(4′,4″-difluorodiphenyl)methyl\}piperazine-1′-yl\}-4-(4″‴-methoxybenzylidene)-2-phenyl-5-oxo-imidazoline, 3e

A mixture of 1-amino-4-[4′,4″-difluorodiphenyl]-methyl]-piperazine (3.03 g, 0.01 mol) and 4-(4″‴-methoxybenzylidene)-2-phenyl-5-oxazolone (2.79 g, 0.01 mol) in dry pyridine (20 mL) was refluxed for 12 hr in an oil bath. The resulting mass was poured into crushed ice and neutralized with dil. HCl, filtered and the product was purified by recrystallization from 1,4-dioxan. Yield 65.85%. m.p. 142°C. Anal. C\textsubscript{34}H\textsubscript{30}O\textsubscript{2}N\textsubscript{4}F\textsubscript{2} requires: C, 72.32; H, 5.36; N, 9.92. Found: C, 72.30; H, 5.34; N, 9.90%. IR (KBr): 2937 (C-H str.asym.), 2875 (C-H str. sym.), 1443 (C-H def.asym.), 1374 (C-H def. sym.), 3090 (C-H str. aromatic), 1523 (C=C str. aromatic), 1197 (C-H i.p.def.), 785 (C-F str.), 1323 (C-N str. piperazine), 1274 (C-O-C str.), 1172 (C-N str.), 1575 (C=N str.), 168 cm\textsuperscript{-1} (C=O str.); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): \delta 2.43-2.44 (8H,d, N-CH\textsubscript{2}), 3.75 (3H, s, Ar-OCH\textsubscript{3}), 5.10 (1H, s, C-H), 7.28-7.30 (2H, d, Ar-H), 7.42-7.49 (4H, dd, Ar-H), 7.61-7.64 (2H, d, Ar-H), 7.71-7.74 (4H, d, Ar-H), 7.81-7.84 (3H, d, Ar-H), 7.95-8.10 (3H, d, Ar-H, C-H); MS: m/z 78, 84, 97, 108, 160, 180, 194, 202, 220, 256, 275, 288, 303, 330, 350, 362, 400, 458, 488, 567.

Similarly, other compounds 3a-j were prepared and their physical data are recorded in Table I.

**Conclusion**

1-N-{4′-\{4″‴-Difluorodiphenyl\}-methyl\}-piperazine-1′-yl\}-4-arylidene-2-phenyl-5-oxo-imidazolines 3a-j have been synthesized and some of the compounds 3a, 3d, 3f, 3h, 3i and 3j showed good to remarkable antibacterial and antifungal activity when compared to known standard drugs e.g. ampicillin, chloramphenicol, norfloxacin and greseofulvin at the same concentration 50 mg/mL, which is represented in Table II.

**Acknowledgements**

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**References**