Synthesis, characterisation and antimicrobial activity of some novel 3-[3-(3-(4-flourophenyl)-1-isopropyl indole-2-yl) allyl)piperazin-1-yl] 1, 2-benzisothiazole and derivatives

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INTRODUCTION

Heterocycles and medicines are both inter related because human are totally dependant on drugs derived from heterocyclic ring. Heterocycles and their derivatives have attracted the attention of chemist mainly because of broad spectrum biological and pharmacological activities. Heterocyclic ring system containing nitrogen and sulphur exhibit potent chemotherapeutic activities. Among a wide variety of heterocycles that have explored for developing pharmaceutically important molecules, indoles and derivatives possesses antimicrobial¹¹, antifungal¹², antibacterial¹³, antidepressant¹⁴, anticancer, antihypertension and anti-inflammatory activity¹⁵ have been reported in literature. Above references indicate versatile nature of indole derivatives from biological activity point of view. Compound bearing 3-(piperazin-1-yl) 1,2-benzisothiazole moiety 5a-h with enhanced biological activity. All the synthesized products are evaluated for their antibacterial activity against Staphylococcus aureus, Bacillus pumilis, Escherichia coli and Proteus vulgaris and antifungal activity against Aspergillus niger, Aspergillus flavus, Penicillium Chrysogenum and Fusarium moniliforme. Characterisation of all the compounds has been done by IR, ¹H NMR, MS and elemental analysis.

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ABSTRACT

Series of new heterocyclic compounds viz. 3-[3-(4-flourophenyl)-1-isopropyl indole-2-yl) allyl)piperazin-1-yl] 1, 2-benzisothiazole (5a-h) have been synthesized by the interaction of substituted 3-[3-(4-flourophenyl)-1-isopropyl indole-2-yl] acrylaldehyde (4a-h) with 3-(piperazin-1-yl) 1,2-benzisothiazole to obtained a biodynamic heterocyclic moiety (5a-h) with enhanced biological activity. All the synthesized products are evaluated for their antibacterial activity against Staphylococcus aureus, Bacillus pumilis, Escherichia coli and Proteus vulgaris and antifungal activity against Aspergillus niger, Aspergillus flavus, Penicillium Chrysogenum and Fusarium moniliforme. Characterisation of all the compounds has been done by IR, ¹H NMR, MS and elemental analysis.

KEYWORDS

1,2-Benzisothiazole derivatives; Indoles; Antimicrobial activity.

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in pharmacological and biological field, and in continuation of our work on biological active heterocycles\cite{14}. In the present work it was considered worthwhile to synthesize certain new chemical entities incorporating two active pharmacophores, namely 3-(piperazin-1-yl) 1,2-benzisothiazole and substituted 3-[3-(4-flourophenyl)-1-isopropyl indole-2-yl] acrylaldehyde (4a-h) in a single molecular framework and to get them evaluated for their antibacterial and antifungal activity.

**RESULT AND DISCUSSION**

In the present work, the N-isopropyl aniline (1a-h) was prepared by the action of substituted aniline with acetone using NaBH$_4$CN. The compounds 1a-h were reacted with 4-fluorophenacyl chloride in presence of DMF to obtained 2-(N-isopropyl-N-phenylamino)-1-(4-flourophenyl) ethanone (2a-h). The compounds (2a-h) further cyclised by using ZnCl$_2$ and IPA as solvent to obtained 3-(4-flourophenyl)-1-isopropyl indole (3a-h). Further the compounds (3a-h) treated with acrolein using POCl$_3$ and CH$_3$CN to offered 3-[3-(4-flourophenyl)-1-isopropyl indole-2-yl] acrylaldehyde (4a-h). The compounds (4a-h) on condensation with 3-(piperazin-1-yl) 1,2-benzisothiazole to yielded 3-[3-(3-(4-flourophenyl)-1-isopropyl indole-2-yl) allyl] piperazin-1-yl] 1,2-benzisothiazole (5a-h) (SCHEME 1). The structure of the synthesized compounds (TABLE 1) were confirmed by IR, $^1$H NMR, MS and elemental analysis. Further, the compounds were tested for antibacterial and antifungal activity.

**Antimicrobial activity**

The compounds (5a-h) were screened for their antimicrobial activity \textit{in vitro} at doses 50 $\mu$g in 0.1 ml of DMF against a variety of bacterial strains such as \textit{Staphylococcus aureus}, \textit{Bacillus pumilis}, \textit{Escherichia coli} and \textit{Proteus vulgaris}, fungi such as \textit{Aspergillus niger}, \textit{Aspergillus flavus}, \textit{Penicillium chrysogenum}, \textit{Fusurium moneliforme}. The antimicrobial activity was compared with standard drugs ciprofloxacin and nystatin and DMF was used as culture medium and the method employed was cup-plate method\cite{15,16}. The zone of inhibition was measured in mm, the results are given in TABLES 2 and 3.

The investigation of antibacterial screening revealed that compounds (5b,c,d,h) were highly active and showed a very good zone of inhibition of all the four
TABLE 1: Physical constant and spectral data of compounds (5a-h)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>mp (b.p.) °C</th>
<th>Yield %</th>
<th>IRcm⁻¹</th>
<th>¹H NMR δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>(5a)</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>132-134</td>
<td>85</td>
<td>1.63-1.61(d, 6H, 2CH₃), 3.28-3.25(t, 4H, piperazine ring), 3.66-3.64 (t, 4H, piperazine ring), 3.15-3.11 (d, 2H, methylene)4.83-4.81 (m, 1H, methine), 5.89-5.80 (m, 1H, ethylene)6.59-6.55 (d, 1H, ethylene), 7.29-7.09(m, 4H, benzene)7.39-7.35 (m, 2H, indole), 7.45-7.41(t, 1H, benzene), 7.58-7.54 (t, 1H, benzene)7.72-7.68(m, 2H, indole)8.12-8.06 (dd, 2H , benzene).</td>
<td></td>
</tr>
<tr>
<td>(5b)</td>
<td>Br</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>110-113</td>
<td>75</td>
<td>1.72(d, 6H, 2CH₃), 3.26-3.22(t, 4H, piperazine ring), 3.64-3.62(t, 4H, piperazine ring), 3.30-3.26(d, 2H, methylene)4.90-4.83(m, 1H, methine), 6.02-5.91(m, 1H, ethylene)6.62 -6.59(d, 1H, ethylene), 7.25-7.00(m, 4H, benzene)7.45-7.30(m, 2H, indole), 7.55-7.49(m, 2H, benzene)7.68 (s, 1H, indole), 8.00-7.89(dd, 2H , benzene).</td>
<td></td>
</tr>
<tr>
<td>(5c)</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>188</td>
<td>80</td>
<td>1.68(d, 6H, 2CH₃), 3.27-3.21(t, 4H, piperazine ring), 3.66-3.63(t, 4H, piperazine ring), 3.25-3.21(d, 2H, methylene)4.89-4.86(m, 1H, methine), 5.92-5.84(m, 1H, ethylene)6.40-6.36(d, 1H, ethylene), 7.31-7.16(m, 4H, benzene)7.40-7.36(m, 2H, indole), 7.60-7.48(m, 2H, benzene)7.65(s, 1H, indole), 8.10-7.91(dd, 2H , benzene).</td>
<td></td>
</tr>
<tr>
<td>(5d)</td>
<td>F</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>129-131</td>
<td>95</td>
<td>1.69(d, 6H, 2CH₃), 3.39-3.26(t, 4H, piperazine ring), 3.69-3.63(t, 4H, piperazine ring), 3.00-2.93(d, 2H, methylene)4.96-4.82(m, 1H, methine), 5.92-5.84(m, 1H, ethylene)6.40-6.36(d, 1H, ethylene), 7.31-7.16(m, 4H, benzene)7.40-7.36(m, 2H, indole), 7.60-7.48(m, 2H, benzene)7.65(s, 1H, indole), 8.10-7.91(dd, 2H , benzene).</td>
<td></td>
</tr>
<tr>
<td>(5e)</td>
<td>C₂H₅</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>145</td>
<td>83</td>
<td>1.20(t, 3H, CH₃), 1.76(d, 6H, 2CH₃), 2.60(q, 2H, CH₂), 3.26-3.20(bs, 4H, piperazine ring)3.65-3.61(bs,4H,piperazine ring)3.00-2.93(d, 2H, methylene)4.85-4.81(septed, 1H, methine)5.85-5.80(m, 1H, ethylene)6.51-6.47(d, 1H, ethylene)7.29-7.12(m, 4H, benzene)7.44-7.38(m, 2H, indole),7.49-7.47 (t, 1H, benzene), 7.54-7.53(t, 1H, benzene), 7.11(s, 1H, indole), 8.02-7.96(dd, 2H, benzene)</td>
<td></td>
</tr>
<tr>
<td>(5f)</td>
<td>C₂H₅</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>160</td>
<td>80</td>
<td>1.22(t, 3H, CH₃), 1.70(d, 6H, 2CH₃), 2.62(q, 2H, CH₂), 3.21-3.14(bs, 4H, piperazine ring)3.69-3.60 (bs,4H,piperazine ring)3.34-2.29(d, 2H,methylene)4.89-4.82(septed, 1H, methine)5.88-5.82(m, 1H, ethylene)6.55-6.51(d, 1H, ethylene)7.30-7.11(m, 4H, benzene)7.40-7.36(m, 2H, indole), 7.46-7.41(t, 1H, benzene), 7.55-7.53(t, 1H, benzene)7.00(s, 1H, indole), 8.00-7.91(dd, 2H, benzene)</td>
<td></td>
</tr>
<tr>
<td>(5g)</td>
<td>NO₂</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>135</td>
<td>90</td>
<td>1.68-1.66(d, 6H, 2CH₃), 3.39-3.35(t, 4H, piperazine ring),3.65 -3.60 (t, 4H, piperazine ring), 3.26-3.20 (d,2H, methylene)4.90-4.86 (m, 1H, methine), 5.93-5.86 (m, 1H, ethylene)6.62- 6.59 (d, 1H, ethylene), 7.31-7.10 (m, 4H, benzene)7.42-7.38 (m, 2H, indole), 7.47-7.44 (t, 1H, benzene)7.59-7.52 (t, 1H, benzene)7.70-7.65(s, 1H, indole)8.11-8.05 (dd, 2H , benzene).</td>
<td></td>
</tr>
<tr>
<td>(5h)</td>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>151</td>
<td>84</td>
<td>1.70(d, 6H, 2CH₃), 3.20-3.16(t, 4H, piperazine ring), 3.60-3.56(t, 4H, piperazine ring), 3.30-3.26(d, 2H, methylene)4.99-4.85(m, 1H, methine)6.10-5.95(m, 1H, ethylene)6.90-6.81(d, 1H, ethylene)7.30-7.06(m, 4H, benzene)7.38-7.31(m, 2H, indole), 7.53-7.49(m, 2H, benzene)7.72(s, 1H, indole), 8.10-8.02(dd, 2H, benzene).</td>
<td></td>
</tr>
</tbody>
</table>

organisms employed. Compounds (5d) showed 19mm, 15mm, 18mm, 17mm zone of inhibition for S.aureus, B.pumilis, E.coli and P.vulgaris respectively. Compounds (5b) showed 19mm and 18mm zone of inhibi-
TABLE 2: Antibacterial screening results of the compounds (5a-h)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>S.aureus (Inhibition zone in mm)</th>
<th>B.pumilis</th>
<th>E.coli</th>
<th>P.vulgaris</th>
</tr>
</thead>
<tbody>
<tr>
<td>(5a)</td>
<td>07</td>
<td>06</td>
<td>09</td>
<td>11</td>
</tr>
<tr>
<td>(5b)</td>
<td>14</td>
<td>18</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>(5c)</td>
<td>17</td>
<td>13</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>(5d)</td>
<td>19</td>
<td>15</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>(5e)</td>
<td>14</td>
<td>11</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>(5f)</td>
<td>15</td>
<td>12</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>(5g)</td>
<td>10</td>
<td>10</td>
<td>09</td>
<td>08</td>
</tr>
<tr>
<td>(5h)</td>
<td>12</td>
<td>13</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>24</td>
<td>18</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>

DMSO -ve -ve -ve -ve

-table no antibacterial activity

TABLE 3: Antifungal screening results of the compounds (5a-h)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>A.niger</th>
<th>A.flavus</th>
<th>P.chrysogenum</th>
<th>F.moneliforme</th>
</tr>
</thead>
<tbody>
<tr>
<td>(5a)</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
<td>+ve</td>
</tr>
<tr>
<td>(5b)</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
<td>(5c)</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
</tr>
<tr>
<td>(5d)</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
</tr>
<tr>
<td>(5e)</td>
<td>+ve</td>
<td>+ve</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
<td>(5f)</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
</tr>
<tr>
<td>(5g)</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>-ve</td>
</tr>
<tr>
<td>(5h)</td>
<td>-ve</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
</tr>
<tr>
<td>Nystatin</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
<td>-ve</td>
</tr>
<tr>
<td>Control</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
<td>+ve</td>
</tr>
</tbody>
</table>

+ve Growth no antifungal activity, -ve No growth antifungal activity observed

-ve no antibacterial activity

The investigation of antifungal activity data revealed that compounds (5a-d,f,h) shows inhibitory effect against A. niger, compounds (5a,c,d,f,h) shows inhibitory action against A. flavus, compounds (5d,e,g) shows inhibitory activity against P.chrysogenum similar compounds (5b,c,e,f,h) are active against F.moneliforme.

### EXPERIMENTAL

Melting points (m.p.) were determined in open capillary tube and are uncorrected. IR spectra were recorded using a Perkin-Elmer 1600FT spectrometer at a ca. 5-15% solution in DMSO-d$_6$ or CDCl$_3$ (TMS as internal standard), GCMS was recorded on Perkin-Elmer clarus 500 mass spectrometer. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapors or by irradiation with ultraviolet lights (254nm). Physical constants and spectral characterization data of all the compounds reported in this paper are summarized in TABLE 1.

**General procedure for the preparation of Isopropyl aniline (1a)**

A mixture of aniline (0.161mmol) and acetone (0.161mmol) was taken into three necked round bottom flask in that NaBH$_4$CN (0.322mmol) in 25ml of methanol was added under continuous stirring. When the starting material disappeared almost completely (after 1hr, checked by TLC), the reaction mixture was quenched with 10% HCl and neutralized with the base and the reaction product was extracted with ethyl acetate (25ml). The ethyl acetate extract was washed with brine and dried over Na$_2$SO$_4$ and concentrated under vaccume to obtained pure product.

Other compounds (1b-h) was prepared the similar way using various anilines. Characterization data are presented in TABLE 1.

**Compound (1a)**

Yield 93%, m.p. low melting, (Anal. Calcd for C$_9$H$_{13}$N: C, 79.95; H, 9.69; N, 10.36. Found, C, 79.93; H, 9.68; N, 10.35%), $^1$H NMR: 1.22-1.28(d, 6H, 2CH$_3$), 3.52-3.64(m, 1H, -CH), 6.23-7.52(m, 5H, Ar-H).

**General procedure for the preparation of 2-(N-isopropyl-N-phenylamino)-1-(4-flourophenyl) ethanone (2a)**

4-fluorophenacyl chloride (0.088mmol) was dissolved in 100ml of DMF in which isopropyl aniline (1a) (0.148mmol) was added with continuous stirring. Reaction mixture was reflux for 6hrs. at 105°C. After cooling to room temp., the reaction mixture was treated with water to obtained crude product. The solid obtained was filtered, washed with water and crystallized from isopropanol.

Other compounds (2b-h) was prepared the similar way using (1b-h) and 4-fluorophenacyl chloride. Characterization data are presented in TABLE 1.

**Compound (2a)**

Yield 35%, m.p.80-82°C, (Anal. Calcd for C$_{17}$H$_{18}$FNO: C, 75.25; H, 6.69; N, 5.16. Found, C,
75.23; H, 6.68; N, 5.15%), \(^1H\) NMR: 1.17-1.23(d, 6H, 2CH\(_3\)), 3.56-3.59(septet, 1H, -CH), 4.65(s, 2H, N-CH\(_2\)), 6.70-7.22(m, 4H, Ar-H), 7.31-7.50(m, 4H, Ar-H of Fluoro benzene).

**General procedure for the preparation of 3-(4-flourophenyl)-1-isopropyl indole (3a)**

To a solution of (2a) (0.044mmol) in isopropanol (100ml) was added ZnCl\(_2\) (0.335mmol) and it was refluxed for 5hrs. After cooling to 10\(^0\)C, the reaction mixture was treated with dil. HCl followed by 200ml of DCM. The DCM layer was separated and washed with brine. The organic phase were dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to obtained (3a).

Other compounds (3b-h) was prepared the similar way using (2b-h). Characterization data are presented in TABLE 1.

**Compound (3a)**

Yield 60%, m.p.94-95\(^0\)C, (Anal. Calcd for C\(_{17}\)H\(_{16}\)FNO: C, 80.60; H, 6.37; N, 5.53. Found, C, 80.61; H, 6.36; N, 5.54%), \(^1H\) NMR: 1.50(d, 6H, 2CH\(_3\)), 4.70(septet, 1H, -CH), 7.51(s, 1H, Ar-H of indole), 7.46-7.52(m, 2H, Ar-H of indole), 7.35-7.42(m, 2H, Ar-H of indole), 7.01-7.15(m, 4H, Ar-H of Flouro benzene)

**General procedure for the preparation of 3-[3-(4-flourophenyl)-1-isopropyl indole-2-yl] acrylaldehyde (4a)**

A mixture of POCl\(_3\) (0.0403mmol) and acetonitrile (15ml) was cooled to -10\(^0\)C, to this acrolein (0.0308 mmol) in 10ml of acetonitrile was added slowly. Then the reaction mixture was brought to room temp and (3a) (0.0237mmol) in 10ml of acetonitrile was added with continuous stirring. The reaction mixture was cooled to 10\(^0\)C and sodium borohydride (0.078mmol) was added in lots, after complete addition reaction mixture was brought to room temp and stirred for 5hrs., then the reaction mixture was quenched with 10% HCl and neutralized with base. It was extracted with ethyl acetate, the extracted layer was washed with brine and dried over Na\(_2\)SO\(_4\) and concentrated under vaccum to obtain the titled product (5a).

Other compounds (5b-h) was prepared the similar way using (5b-h) and 3-(piperazin-1-yl) 1,2-benzisothiazole. Characterization data are presented in TABLE 1.

**Compound (4a)**

Yield 93%, m.p.122-124\(^0\)C, (Anal. Calcd for C\(_{20}\)H\(_{18}\)FNO: C, 78.15; H, 5.90; N, 4.56. Found, C, 78.13; H, 5.98; N, 4.55%), \(^1H\) NMR: 1.60(d, 6H, 2CH\(_3\)), 5.03(septet, 1H, -CH), 6.01-6.10(dd(dd, 1H, ethylene attached to aldehyde), 7.68-7.70(d, 1H, ethylene attached to benzene indole), 9.40-9.48(d, 1H, aldehydic proton), 7.49-7.56(m, 2H, Ar-H of indole), 7.40-7.44(m, 2H, Ar-H of indole), 7.00-7.20(m, 4H, Ar-H of Flouro benzene)

**General procedure for the preparation of 3-[3-(3-(4-flourophenyl)-1-isopropyl indole-2-yl) allyl] piperazin-1-yl] 1, 2-benzisothiazole (5a)**

To a solution of (4a) (0.019mmol) in methanol (100ml) was taken in round bottom flask in this 3-(piperazin-1-yl) 1,2-benzisothiazole (0.0195mmol) was added with continuous stirring. The reaction mixture was cooled to 10\(^0\)C and sodium borohydride (0.078mmol) was added in lots, after complete addition reaction mixture was brought to room temp and stirred for 5hrs., then the reaction mixture was quenched with 10% HCl and neutralized with base. It was extracted with ethyl acetate, the extracted layer was washed with brine and dried over Na\(_2\)SO\(_4\) and concentrated under vaccum to obtain the titled product (5a).

Other compounds (5b-h) was prepared the similar way using (5b-h) and 3-(piperazin-1-yl) 1,2-benzisothiazole. Characterization data are presented in TABLE 1.

**Compound (5a)**

Yield 80%, m.p.132-134\(^0\)C, (Anal. Calcd for C\(_{31}\)H\(_{31}\)FNO\(_4\)S: C, 72.91; H, 6.12; N, 10.97. Found, C, 72.80; H, 5.95; N, 9.58%). \(^1H\) NMR: 1.63-1.61(d, 6H, 2CH\(_3\)), 3.28-3.25(t, 4H, piperazine ring), 3.66-3.64(d, 4H, piperazine ring), 3.15-3.11(d, 2H, methylene), 4.83-4.81(m, 1H, methine), 5.89-5.80(m, 1H, ethylene), 6.59-6.55(d, 1H, ethylene), 7.29-7.09(m, 4H, benzene), 7.39-7.35(m, 2H, indole), 7.45-7.41(t, 1H, benzene), 7.58-7.54(t, 1H, benzene), 7.72-7.68(m, 2H, indole), 8.12-8.06(dd,2H, benzene).
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