Synthesis and characterization of new series of imidazolidin-2,4-dione derivatives and its antimicrobial activity

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ABSTRACT

The synthesis of compound (2) was achieved using cyclization method of compound (1) with ethyl chloro acetate and fused sodium acetate. Compound (2) was underwent mannich reaction to give compound (3a-3f). The Chemical structures were elucidated by IR, ¹H NMR, and elemental analysis. The compounds (2) and (3a-3f) have been screened for in vitro antimicrobial action against various strains of bacterial and fungi.

Key words: Imidazolidin-2, 4-dione, mannich base, antimicrobial activity.

INTRODUCTION

Imidazolidin-2,4-dione derivatives are significant biological and pharmacological properties of anti-inflammatory¹, antimicrobial activity² (antifungal, antibacterial), anticonvulsant³. Number of literature methods are indicated that various synthetic methods used to prepared imidazolidin-2,4-dione and their biological screening⁴-⁶. Resent literature methods are indicated that aromatic benzene present in third position of imidazolidin2, 4-dione ring and it was involved mannich base reactions⁷. Basically mannich base were found to potential of biological activities such as antibacterial⁸, antifungal⁹.

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Major role of this study, a new series of mannich base derivatives (3a-3f) was prepared from imidazolidin-2,4-dione with 4-substituted benzaldehyde and semicarbazone the synthesized compounds (2) and (3a-3f) were compared the level of antimicrobial action.

MATERIAL AND METHODS

Meting points were recorded in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr on a FT –IR shimadzu 8201pc (4000-400 cm⁻¹) and ¹H NMR on a Bruker DRX-300 MHz. Elemental analyses (C, H, N, and S) were undertaken using an Elementer analyzer model vario EL III. The purity of the compounds was checked by thin layer chromatography (TLC) with silica gel plates.

Synthesis of 2-(pyridin-2-ylmethylidene) hydrazinecarboxamide (1)

A mixture of pyridine-2-aldehyde (0.1mol), semicarbazide (0.1mol) in ethanol (10mol), and the reaction mixture was heated and reflux for 4 hr on water-bath. The reaction mixture was cooled, and poured in to crushed ice, the solid was filtered, and recrystallised from suitable alcohol.

IR( KBr, cm⁻¹ ): 3374(NH), 3285(NH₂), 3021(aromatic CH stretching), 1723(C=O), 1623 (C=N); ¹H NMR-(DMSO-d6,δ(ppm)): 10.55
(s,1H, NH), 10.11(s,1H, CH= N), 8.59-7.23 (m,4H, pyridyl), 6.20(s,2H, NH),

Synthesis of 3-([pyridin-2-yilmethylene]amino) imidazolidine-2,4-dione (2)

A mixture of pyridine-2-carbaldehyde semicarbazone (0.01mol) and ethyl chloroacetate (0.01mol) and fused sodium acetate (0.03 mol) in ethanol, the reaction mixture was heated under reflux for 4 hr on water-bath. The reaction mixture was cooled, and poured in to crushed ice, the solid was filtered, and recrystallised from ethanol.

IR (KBr, cm−1): 3342.11(NH), 3234 (aromatic C-H stretching), 1695.82(C=O, in imidazolidine ring), 1631.42(C=N cm−¹); ¹HNMR-(DMSO-d6, δ (ppm)): 8.67 – 7.67 (d, 4H, pyridyl), 7.42 (s, 1H, CH=N), 6.01(s,1H, NH in imidazolidin ring), 3.84 (s, 2H, CH₂N in imidazolidin ring);

Elemental analysis
Calculated for C₉H₈N₄O₂: C, 52.94; H, 3.95; N, 27.44. Found: C, 52.87; H, 3.91; N, 27.40 %.

2-[(2,4-dioxo-3-[([pyridin-2-ylmethylene]amino)imidazolidin-1-yl)(phenyl)methyl] hydrazinecarboxamide (3a)

To prepare the solution of Compound (2) (0.1mol), 4-substituted benzaldehyde (0.01 mol) and thiosemicarbazone (0.01 mol) in 25 ml of absolute ethanol, the reaction mixture was heated under reflux for 5hr. The reaction mixture was cooled and poured in to ice-cold water. The solid was filtrate and recrystallised from absolute ethanol. Using the above procedure was followed for all the remaining compounds (3b-3f).

IR (KBr, cm−1): 3301(NH), 3285(NH₂), 3021(aromatic C-H stretching), 1723(C=O), 1623(C=N), 1493(C=S), 1092(N=CH= N), ¹HNMR-(DMSO-d6, δ (ppm)): 11.96 ( s,1H,-OH), 10.41 (s,1H,-CH=N- ), 9.47 (s, 2H, NH₂), 7.42-7.12 (m, 4H, pyridyl), 6.61(s,1H, -CH-), 4.20 ( s, 2H, H₂C-N ), 2.38 (s, 1H, NH-CS);

Elemental analysis
Calculated for C₁₇H₁₇N₇O₃S: C,51.07;H, 4.25;N,24.53; S, 8.01; Found: C, 51.12; H, 4.29; N, 24.59; S, 8.09 %.

Synthesis of 2-[(4-chlorophenyl)(2,4-dioxo-3-[[pyridin-2-ylmethylene]amino]imidazolidin-1-yl) methyl] hydrazinecarboxamide (3b)

IR (KBr, cm−1): 3485(NH₂), 3021(aromatic C-H stretching), 1728.71(C=O), 1638(C=N), 1450(OH), 1098(N=CH-N); ¹HNMR-(DMSO-d6, δ (ppm)): 11.96 ( s,1H,-OH), 10.41 (s,1H,-CH=N- ), 9.47 (s, 2H, NH₂), 7.42-7.12 (m, 4H, pyridyl), 6.61(s,1H, -CH-), 4.20 ( s, 2H, H₂C-N ), 2.38 (s, 1H, NH-CS);

Elemental analysis
Calculated for C₁₇H₁₆ClN₇O₂S: C,48.81;H, 3.82; N, 23.45; S, 7.65; Found: C, 48.88; H, 3.85; N, 23.40; S, 7.61 %.

Synthesis of 2-[(2,4-dioxo-3-[[pyridin-2-ylmethylene]amino]imidazolidin-1-yl)(4-hydroxyphenyl)methyl] hydrazinecarboxamide (3c)

IR (KBr,cm−1): 3328 (NH), 3281(NH₂), 3011(aromatic C-H stretching), 1737 (C=O), 1628(C=N), 1472(C=S), 1450(OH), 1098(N=CH-N); ¹HNMR-(DMSO-d6, δ (ppm)): 10.32(s,1H, -CH=N-), 9.64 (s, 2H, NH₂), 7.75-7.41 (m, 4H, pyridyl), 7.47 (s, 2H, NH₂), 6.72 (s,1H, -CH-), 4.28 ( s, 2H, H₂C-N ), 2.35( s, 1H, NH-CS );

Elemental analysis
Calculated for C₁₇H₁₇N₇O₃S: C,51.07;H, 4.25;N,24.53; S, 8.01; Found: C, 51.12; H, 4.29; N, 24.59; S, 8.09 %.

Synthesis of 2-[(2,4-dioxo-3-[[pyridin-2-ylmethylene]amino]imidazolidin-1-yl)(4-methoxyphenyl)methyl] hydrazinecarboxamide (3d)

IR (KBr, cm−1): 3328 (NH), 3285(NH₂), 3021(aromatic C-H stretching), 1723(C=O), 1623(C=N), 1493(C=S), 1092(N=CH-N); ¹HNMR-(DMSO-d6, δ (ppm)): 11.96 ( s,1H,-OH), 10.41 (s,1H,-CH=N- ), 9.47 (s, 2H, NH₂), 7.75-7.41 (m, 4H, pyridyl), 7.47 (s, 2H, NH₂), 6.72 (s,1H, -CH-), 4.28 ( s, 2H, H₂C-N ), 4.12( s, 3H, CH₃), 2.35 ( s, 1H, NH-CS );

Elemental analysis
Calculated for C₁₈H₁₉N₇O₃S: C,52.24; H, 4.59; N, 23.70; S, 7.73; Found: C, 52.27; H, 4.55; N, 23.65; S, 7.77 %.
2-[(2,4-dioxo-3-[pyridin-2-ylmethylene]amino)imidazolidin-1-yl)-(4-nitrophenyl)methyl]hydrazinecarboxamide (3e)

IR (KBr, cm⁻¹): 3334 (NH₂), 3021 (aromatic C-H stretching), 2974 (NH), 1732 (C=O), 1623 (C=N), 1530 (NO₂), 1490 (C=S), 1080 (N-CH-NO₂); ¹HNMR-(DMSO-d₆,d(ppm)): 10.47 (s, 1H, -CH=N-), 9.61 (s, 2H, NH₂), 7.57-7.30 (m, 4H, pyridyl), 7.42 (s, 2H, NH₂), 6.62 (s, 1H, -CH-), 4.20 (s, 2H, H₂C-N), 2.31 (s, 1H, NH-CS);

Elemental analysis
Calculated for C₁₇H₁₆N₈O₄S: C, 47.61; H, 3.73; N, 26.14; S, 9.46;
Found: C, 47.66; H, 3.77; N, 26.18; S, 9.41 %.

Synthesis of 2-[(2,4-dioxo-3-([pyridin-2-ylmethylene]amino)imidazolidin-1-yl)-(4-dimethylamino)methyl]hydrazinecarboxamide (3f)

IR (KBr, cm⁻¹): 3341(NH₂), 3214(NH), 3021(aromatic C-H stretching), 1721(C=O), 1627 (C=N), 1457 (C=S), 1093 (N-CH=NO₂); ¹HNMR-(DMSO-d₆,d(ppm)): 9.98 (s, 1H, -CH=N-), 9.47 (s, 2H, NH₂), 7.61-7.47 (m, 4H, pyridyl), 4.32 (s, 2H, H₂C-N), 2.41 (s, 1H, NH-CS), 1.82 (s, 6H, -N(CH₃)₂);

Elemental analysis
Calculated for C₁₉H₂₂N₈O₂S: C, 53.45; H, 5.15; N, 26.19; S, 7.47 %.

Antimicrobial activity

In vitro anti bacterial activity

Compounds (2), (3a-3f) were evaluated for their in vitro antibacterial activity against Escherichia coil, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, by agar dilution method. The compounds and standard were tested at a concentration of 100 µg/ml in DMSO. The zone of inhibition were measured incubated at 37°C for 24h. The compounds were chosen as a standard of antibacterial activity.

In vitro anti fungal activity

The compounds were evaluated for their in vitro antifungal activity of Aspergillus niger, Candida albicans, Cryptococcus neoformans, A.fumigatus using an agar dilution method. Each compound and standard were tested at a concentration of 100µg/ml in DMSO. The zone of inhibition were measured incubated at 37°C for 24h. Clotrimazole was used as a standard.

Table 1: Characterization data of compounds (2), (3a-3f)

<table>
<thead>
<tr>
<th>Comp. no</th>
<th>R</th>
<th>mp(°C)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>152</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>163</td>
<td>60</td>
</tr>
<tr>
<td>3a</td>
<td>H</td>
<td>172</td>
<td>51</td>
</tr>
<tr>
<td>3b</td>
<td>Cl</td>
<td>190</td>
<td>55</td>
</tr>
<tr>
<td>3c</td>
<td>OH</td>
<td>201</td>
<td>50</td>
</tr>
<tr>
<td>3d</td>
<td>NO₂</td>
<td>195</td>
<td>55</td>
</tr>
<tr>
<td>3e</td>
<td>OCH₃</td>
<td>200</td>
<td>58</td>
</tr>
<tr>
<td>3f</td>
<td>N(CH₃)₂</td>
<td>210</td>
<td>60</td>
</tr>
</tbody>
</table>
imidazolidin ring appeared at $\delta$ 3.84, while CH=N protons appeared at $\delta$ 7.42 and respectively.

IR spectrum of the compound (3a-3f) showed absorption bands at 1737 - 1720 cm$^{-1}$ and 1424 - 1493 cm$^{-1}$ corresponding to the C=O and C=S groups respectively. The N-C-N stretching frequency at 1098 - 1021 cm$^{-1}$ clearly indicates the formation of manich base reaction. $^1$HNMR spectral data of the compound (3a-3f) showed the absence of CH$_2$N protons appeared at $\delta$ 4.17 - 4.32 regions, while N-CH-N proton appeared at $\delta$ 6.61 - 6.72 ppm respectively it is clearly indicates that manich base derivatives.

**Anti microbial screening**

Compounds (2), (3a-3f) were screened for antibacterial activity against *S. aureus, Enterococcus faecalis, Pseudomonas aeruginosa, and Klebsiella pneumonia*. The comparison of the compounds (2) and (3a-3f), compounds (3a-3f) has highly active than the compound 2. The compound (3b) containing 4-Cl-phenyl group has highly active against *Enterococcus faecalis* compared with nitrofurantoin.

Compounds (2),(3a-3f) were exhibit antifungal activity against *A. niger, C.albicans, A.fumigatus, Cryptococcus neoformans*. The comparison of the compounds (2), (3a-3f) was found to exhibit compounds (3a-3f) has highly active against all fungal organisms. The compound (3e) containing 4-NO$_2$-phenyl group has highly active against *A.fumigatus* compared with clotrimazole.

Scheme 1: Synthesis of manich base imidazolidin-2, 4-dione derivatives
Table 2: Antibacterial activity of compounds (2), (3a-3f) Zone of inhibition (mm)

<table>
<thead>
<tr>
<th>Compounds</th>
<th><em>S. aureus</em></th>
<th><em>E. faecalis</em></th>
<th><em>P. aeruginosa</em></th>
<th><em>K. pneumoniae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>7</td>
<td>-</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>3a</td>
<td>12</td>
<td>-</td>
<td>16</td>
<td>-</td>
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<tr>
<td>3b</td>
<td>13</td>
<td>22</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>3c</td>
<td>18</td>
<td>8</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>3d</td>
<td>16</td>
<td>-</td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td>3e</td>
<td>9</td>
<td>-</td>
<td>17</td>
<td>-</td>
</tr>
<tr>
<td>3f</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>15</td>
<td>17</td>
<td>23</td>
<td>20</td>
</tr>
</tbody>
</table>

Indicates above bacteria's were resistant to the compound concentration (100µg/ml).
Nitrofurantoin is used as the standard.

Table 3: Antifungal activity of compounds (2),(3a-3f) Zone of inhibition (mm)

<table>
<thead>
<tr>
<th>Compounds</th>
<th><em>A. niger</em></th>
<th><em>C. albicans</em></th>
<th><em>A. fumigatus</em></th>
<th><em>Cr. neoformans</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>-</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3a</td>
<td>12</td>
<td>13</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>3b</td>
<td>6</td>
<td>18</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>3c</td>
<td>13</td>
<td>14</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>3d</td>
<td>6</td>
<td>18</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>3e</td>
<td>5</td>
<td>-</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>3f</td>
<td>8</td>
<td>10</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>25</td>
<td>15</td>
<td>15</td>
<td>22</td>
</tr>
</tbody>
</table>

Indicates above fungal were resistant to the compound concentration (100µg/ml).
Clotrimazole is used as the standard.

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REFERENCES


