Synthesis, characterization and biological evaluation of N-aryl amino-4-acetamido-2-ethoxy benzamides

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KEYWORDS
4-Acetamido-2-ethoxy benzoyl hydrazine; Different aromatic acid chloride; Pyridine; N-aryl amino-4-acetamido-2-ethoxy benzamides; Antimicrobial activity.

INTRODUCTION

The arylacetamide derivatives exhibit broad spectrum of therapeutic activity. The several biological activity associated with arylacetamide have been described as antiulcer[1], antiallergy[2], antimicrobial[3], tranquilizer[4], analgesic[5], anticonvulsant[6], cardiofonic[7], flerbiccidal[8], etc.

Dumot and Delerck[9] have studied the hypnotic and sedative effect of urides, carbamides, acetamides and sulphones. Iodo-acetamide and N-ethyl maleamide inhibit a number of viruses including the pleuropneumonia and entro group[10].


In view of therapeutic activities of arylacetamide derivatives and p-amino salicylic acid moiety, it was contemplated to synthesise some new arylacetamide derivatives, in search of agents possessing higher biological activity with least side effect.

In presence work we have first prepared 4-acetamido-2-ethoxy benzoyl hydrazine and condensed with different aromatic acid chloride which obtains due to the reaction different aromatic acid with Thionyl chloride. To produce higher functionalized N-aryl amino-4-acetamido-2-ethoxy benzamide derivative in good yields for biological interest.

RESULTS AND DISCUSSION

The starting material 4-acetamido-2-ethoxy benzoyl hydrazine (2) was prepared by reacting me-
Scheme 1: Synthesis of some new N-arylamino-4-acetamido-2-ethoxybenzamides

TABLE 1: Synthesis of some new N-arylamino-4-acetamido-2-ethoxybenzamides

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Temp in °C</th>
<th>Time in hrs.</th>
<th>Yield</th>
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<tr>
<td>2</td>
<td>OCOCH₃</td>
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<td>3i</td>
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<tr>
<td>10</td>
<td>OCH₃</td>
<td>3j</td>
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<td>CH=CH⁻</td>
<td>3l</td>
<td>80</td>
<td>17</td>
<td>76</td>
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thyl-4-acetamido-2-ethoxy phenyl benzoate (1) with hydrazine hydrate at ambient temperature. The yield of compounds is good (65 to 80%). The different aromatic acid chlorides are reactive with 4-acetamido-2-ethoxy benzoyl hydrazine (2). The different aromatic acid chloride was prepared by re-
ported procedure\cite{15,16} by reaction of different aromatic acid with Thionyl chloride. The different aromatic acid chloride was not isolated but direct condensed with 4-acetamido-2-ethoxy benzoyl hydrazine (2) in the presence of pyridine at 70-80º C. Benzene is used as solvent and content was stirred for several hours at 70-80º C. Then cool at room temperature. After work up afforded new N-arylamino-4-acetamido-2-ethoxy benzamides (3) (a-l) in good moderate yields. The IR spectrum of 3a exhibited an absorption band at 1654 cm\(^{-1}\) due to the \(\text{C}=\text{O}\) stretching for \(-\text{CONHNH-}\) and \(\text{C}=\text{O}\) of \(-\text{NHCOCH}_3\) at 1647 cm\(^{-1}\), \(\text{C}=\text{O}\) str. (amide) at 1685 cm\(^{-1}\), C-N str. vibration at 1115 cm\(^{-1}\), N-H stretching at 3271 cm\(^{-1}\) and N-H deformation at 1590 cm\(^{-1}\).

In the \(^1\text{H}\) NMR spectrum of 3a, singlet at \(\delta\) 2.33 for three protons of \(-\text{NHCOCH}_3\), singlet at 8.60 for NH-NH consist two protons. Triplet for three protons at 1.5 and quartet for two protons at 4.28 indicate the presence of \(-\text{OCH}_2\text{CH}_3\) group, multiplet at 6.83-8.36 consist six protons indicate aromatic character.

The structure of (3a) was farther confirmed by Mass spectral analysis. It exhibited a molecular ion peak at M/Z 341 corresponding to its molecular weight.

Similarly, IR, NMR, Mass spectroscopy and elemental analysis, characterized all the compounds.

**EVALUATION OF ANTIMICROBIAL ACTIVITE**

The newly synthesized N-aryl sulphonamido-4-acetamido-2-ethoxy benzamides compounds (4a-p) have been screened for antimicrobial activity against staphylococcus aureus, Escherichia coli, B. mega, P. vulgaris using amoxicillin, ampicillin, ciprofloxacin erythromycin as standard and antifungal activity against aspergillus niger using griseofulvin as standard by the cup-plate method\cite{24,25}. The results are cited in TABLE-2.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Antimicrobial activity zone of inhibition in mm</th>
<th>Antifungal activity zone of inhibition in mm</th>
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<tr>
<td></td>
<td>P.Valganis</td>
<td>E.Coli</td>
</tr>
<tr>
<td>3a</td>
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</tr>
<tr>
<td>3b</td>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>3k</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>3l</td>
<td>12</td>
<td>16</td>
</tr>
</tbody>
</table>

TABLE 2: Antimicrobial activity of the compounds (3a-l)

**EXPERIMENTAL**

General procedures, melting points were estimated in open capillaries and may be uncorrected. IR spectra were recorded on KBr discs, using RTIR-8400 spectrometer. \(^1\text{H}\) NMR spectra were taken on
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a BRUKER AVANCE IT 400 spectrometer in CDCl$_3$/DMSO. Chemical shift and are given in ppm relative to TMS. Mass spectra were determined using direct inlet probe on a SCMS-QP2010 mass spectrometer (shimadzu). Elemental analyses were performed on a Carlo Erba EA1108 elemental analyzer at SAIF, CDRI Lucknow. Reactions were monitored on Merk alumina thin layer chromatography (TLC, UV 254nm) plates. Visualization was accomplished either on UV chamber or in iodine paper.

General procedure for the synthesis of N-aryl amino-4-acetamido-2-ethoxy benzamides

A mixture of methyl-4-acetamido-2-ethoxy benzoylhydrazine (1) and hydrazine hydrate (2.0 ml, 0.04M) in methanol was refluxed for 7 hrs. The solution was then poured on to crushed ice, filtered and the resulting solid was crystallized from ethanol to afford 4-acetamido-2-ethoxy benzoylhydrazine (2).

A mixture of aromatic acid (0.01 M) and Thionyl chloride (10 ml) was refluxed for 6 hrs. Excess of Thionyl chloride was removed by distillation under vacuum and the resulting aromatic acid chloride was not isolated but directly reacts with 4-acetamido-2-ethoxy benzoylhydrazine (1) at 70-80º C for 10-24hrs in the presence of benzene as solvent. TLC monitored reaction. The solvent was removed in vacum and resulting reaction mixture was poured on to crushed ice and ice water. The separated product was filtered and crystallized from ethanol to give pure compounds (3a-l). The reaction temp. time and yields are depicted in TABLE-1.

**N-Benzoylamino-4-acetamido-2-ethoxy benzamide (3a)**

White solid, M. P. 172º C, IR (KBr) $\nu_{\text{max}}$ = 3300 cm$^{-1}$ (N-H str), 1660 cm$^{-1}$ (>C=O str. of –NHCOCH$_3$), 1650 cm$^{-1}$ (>C=O str. of –CONHNH), 1685 cm$^{-1}$ (>C=O str. of –NHCOR), 1700 cm$^{-1}$ (>C=O str. of –OCOCH$_3$), 3040 cm$^{-1}$ (C-H str. of aromatic), 2930, 1580, 1260, 1140, 1030, 690, 720, 830 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm = 1.2 (T, 3H, -OCH$_2$CH$_3$), 2.5 (S, 3H, -NHCOCH$_3$), 4.4 (Q, 2H, -OCH$_2$CH$_3$), 6.9-9.2 (M, 7H, Ar-H). MS (EI): 341 M/Z. Anal. Calculated for C$_{18}$H$_{19}$N$_3$O$_4$; C, 63.34; H, 5.57; N, 12.32; Found: C, 63.90; H, 5.50; N, 12.80%.

**N-(O-Acetoxy benzoylamino)-4-acetamido-2-ethoxy benzamide (3b)**

White solid, M. P. 172º C, IR (KBr) $\nu_{\text{max}}$ = 3300 cm$^{-1}$ (N-H str), 1660 cm$^{-1}$ (>C=O str. of –NHCOCH$_3$), 1650 cm$^{-1}$ (>C=O str. of –CONHNH), 1685 cm$^{-1}$ (>C=O str. of –NHCOR), 1700 cm$^{-1}$ (>C=O str. of –OCOCH$_3$), 3040 cm$^{-1}$ (C-H str. of aromatic), 2930, 1580, 1260, 1140, 1030, 690, 720, 830 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm = 1.2 (T, 3H, -OCH$_2$CH$_3$), 2.5 (S, 3H, -NHCOCH$_3$), 4.4 (Q, 2H, -OCH$_2$CH$_3$), 6.9-9.2 (M, 7H, Ar-H). MS (EI): 399 M/Z. Anal. Calculated for C$_{20}$H$_{21}$N$_3$O$_6$; C, 60.15; H, 5.26; N, 10.53; Found: C, 60.50; H, 5.20; N, 10.60%.

**N-(Methylene benzoylamino)-4-acetamido-2-ethoxy benzamide (3c)**

White solid, M. P. 85º C, IR (KBr) $\nu_{\text{max}}$ = 3280 cm$^{-1}$ (N-H str), 1650 cm$^{-1}$ (>C=O str. of –NHCOCH$_3$), 1640 cm$^{-1}$ (>C=O str. of –CONHNH), 1680 cm$^{-1}$ (>C=O str. of –COCH$_3$), 3030 cm$^{-1}$ (C-H str. of aromatic), 2940, 2870, 1575, 1260, 1140, 1030, 690, 720, 830 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm = 1.2 (T, 3H, -OCH$_2$CH$_3$), 2.5 (S, 3H, -NHCOCH$_3$), 4.4 (Q, 2H, -OCH$_2$CH$_3$), 3.9 (S, 2H, -CH$_2$), 6.8-9.2 (M, 8H, Ar-H). MS (EI): 355 M/Z. Anal. Calculated for C$_{19}$H$_{21}$N$_3$O$_4$; C, 64.22; H, 5.92; N, 11.83; Found: C, 64.00; H, 6.04; N, 12.10%.

**N-(O-Chloro benzoylamino)-4-acetamido-2-ethoxy benzamide (3d)**

White solid, M. P. 172º C, IR (KBr) $\nu_{\text{max}}$ = 3280 cm$^{-1}$ (N-H str), 1650 cm$^{-1}$ (>C=O str. of –NHCOCH$_3$), 1640 cm$^{-1}$ (>C=O str. of –CONHNH), 1680 cm$^{-1}$ (>C=O str. of –COCH$_3$), 3030 cm$^{-1}$ (C-H str. of aromatic), 2940, 2870, 1575, 1260, 1140, 1030, 690, 720, 830 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm = 1.2 (T, 3H, -OCH$_2$CH$_3$), 2.5 (S, 3H, -NHCOCH$_3$), 4.4 (Q, 2H, -OCH$_2$CH$_3$), 3.9 (S, 2H, -CH$_2$), 6.8-9.2 (M, 8H, Ar-H). MS (EI): 375 M/Z. Anal. Calculated for C$_{18}$H$_{18}$N$_3$O$_4$Cl; C, 57.6; H, 4.8; N, 11.2; Found: C, 57.75; H, 4.3; N, 11.3%.

**N-(m-chloro benzoylamino)-4-acetamido-2-ethoxy benzamide (3e)**
Off white solid, M. P. 130º C, IR (KBr) ν<sub>max</sub> = 3370 cm<sup>-1</sup> (N-H str), 1630 cm<sup>-1</sup> (>C=O str. of –NHCOCH<sub>3</sub>), 1650 cm<sup>-1</sup> (>C=O str. of –CONHNH<sub>2</sub>), 1675 cm<sup>-1</sup> (>C=O str. of –COR), 3030 cm<sup>-1</sup> (C-H str. of aromatic), 2970, 2840, 1550, 1230, 1150, 1030, 750, 810, 840 cm<sup>-1</sup>. ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>ppm</sub> = 1.6 (T, 3H, -OCH<sub>2</sub>CH<sub>3</sub>), 2.4 (S, 3H, -NHCOCH<sub>3</sub>), 4.4 (Q, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 6.9-9.3 (M, 7H, Ar-H). MS (EI): 375 M/Z. Anal. Calculated for C<sub>18</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub>; C, 63.50; H, 5.38; N, 12.10%.

N-(O-Methoxy benzoylamino)-4-acetamido-2-ethoxy benzamide (3i)

White solid, M. P. 150º C, IR (KBr) ν<sub>max</sub> =3250 cm<sup>-1</sup> (N-H str), 1650 cm<sup>-1</sup> (>C=O str. of –NHCOCH<sub>3</sub>), 1635 cm<sup>-1</sup> (>C=O str. of –CONHNH<sub>2</sub>), 1670 cm<sup>-1</sup> (>C=O str. of –NHCOR), 3030, 1565, 1225, 1150, 1020, 830 cm<sup>-1</sup>. ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>ppm</sub> = 1.6 (T, 3H, -OCH<sub>2</sub>CH<sub>3</sub>), 2.4 (S, 3H, -NHCOCH<sub>3</sub>), 4.5 (Q, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 4.0 (S, 3H, -OCH<sub>3</sub>), 6.8-9.2 (M, 7H, Ar-H). MS (EI): 371 M/Z. Anal. Calculated for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>; C, 61.40; H, 5.60; N, 33.98%.

N-(m-Methyl benzoylamino)-4-acetamido-2-ethoxy benzamide (3k)

White solid, M. P. 125º C, IR (KBr) ν<sub>max</sub> =1665 cm<sup>-1</sup> (>C=O str. of –NHCOCH<sub>3</sub>), 1650 cm<sup>-1</sup> (>C=O str. of –CONHNH<sub>2</sub>), 1685 cm<sup>-1</sup> (>C=O str. of –NHCOR), 3030 cm<sup>-1</sup> (C-H str. of aromatic), 2930, 2850, 1570, 1255, 1150, 1030, 810,840 cm<sup>-1</sup>. ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>ppm</sub> = 1.7 (T, 3H, -OCH<sub>2</sub>CH<sub>3</sub>), 2.3 (S, 3H, -NHCOCH<sub>3</sub>), 4.4 (Q, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 6.1 (S, 1H, -OH), 6.9-9.2 (M, 7H, Ar-H). MS (EI): 355 M/Z. Anal. Calculated for C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>; C, 65.40; H, 5.7; N, 34.33%.

N-(a-Ethylene benzoylamino)-4-acetamido-2-ethoxy benzamide (3l)

Pale yellow solid, M. P. 115º C, IR (KBr) ν<sub>max</sub> =1655 cm<sup>-1</sup> (>C=O str. of –NHCOCH<sub>3</sub>), 1640 cm<sup>-1</sup> (>C=O str. of –CONHNH<sub>2</sub>), 1665 cm<sup>-1</sup> (>C=O str. of –NHCOR), 3285 cm<sup>-1</sup> (N-H str), 3030, 3100, 1570, 1250, 1145, 1040, 690, 720, 840 cm<sup>-1</sup>. ¹H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>ppm</sub> = 1.8 (T, 3H, -OCH<sub>2</sub>CH<sub>3</sub>), 2.5 (S, 3H, -NHCOCH<sub>3</sub>), 4.4 (Q, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 6.7-9.3 (M, 10H, Ar-H + CH=CH). MS (EI): 367 M/Z. Anal. Calculated for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>; C, 65.40; H, 5.7; N, 34.33%.

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CONCLUSION

In conclusion, in this article we have been reported some novel highly functionalized N-aryl amino-4-acetamido-2-ethoxy benzamide in good yield and evaluated for antimicrobial activity. Some of the newly synthesized compounds exhibited good to excellent activity against both gram positive and gram negative bacteria and fungi.

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REFERENCES