INTRODUCTION

Quinolines possess various biological properties including antibacterial, anti-asthmatic and anti-inflammatory.\(^1\)\(^-\)\(^3\) Several drugs based on the quinoline structure have improved the therapy of protozoal diseases, especially malaria.\(^4\) 3-arylquinolines are extracted from natural sources.\(^5\)\(^-\)\(^6\) Vanillin derivatives inhibit glucose production in hepatic cells. Among them, 4-hydroxy-3-methoxyacetophenone and 5-nitrosalicylaldehyde showed strong inhibitory without exhibiting cytotoxic effects. In the case of benzaldehyde, 4-hydroxy-3-methoxy or 2,5-disubstituted derivatives may have important roles in the inhibitory activities of these compounds against glucose production.\(^7\)

On the other hand, the synthesis of indoles and substituted indoles with therapeutic and biological activities has been of considerable interest to chemists.\(^8\) Among of them, bis(indolyl)methanes and bis(indolyl)ethanes are important derivatives of indole. bis(indolyl)methanes (BIMs) display diverse biological activities.\(^9\)

Various methods have been developed for the synthesis of BIMs.\(^10\) The reaction of aldehydes and indoles in the presence of protic11,12 or Lewis acids13-23 is one of the straightforward approaches for the synthesis of bis(indolyl)methanes. In spite of potential utility of aforementioned routes for the synthesis of bis(indolyl)methane derivatives some of these methods suffer from severe drawbacks such as long reaction times,13-15 unsatisfactory yields,16 use of toxic solvents15,17 and catalysts,18 use of expensive reagents and catalysts13,15 and harsh reaction conditions. Because of these drawbacks, use of ionic liquids as reaction medium has been improved.24-26 The advantages of this method are low temperature, easy recovery of catalysts and facile product separation by distillation. However, with regard to high cost of most of the conventional room temperature ionic liquids and toxicity of some of them, development of a new procedure for the synthesis of these bioactive compounds would be highly desirable.
Recently, we have been involved in the study of the catalytic activity of ruthenium towards organic reactions such as condensation of indoles and aldehydes,27 oxidation of aromatic and heteroaromatic compounds,28 double-conjugate 1,4-addition to enones,29 nucleophilic addition to epoxides,30 oxidative trimerization of indoles31 and cross aldol reactions.32 As a matter of fact, many organic transformations which involve ruthenium species as catalyst are known and well-documented.33-35

In this contribution, we report the synthesis of new bis(indolyl)methane derivatives with quinoline, vanillin and other backbones as potential biologically active compounds (Scheme 1, 2).

RESULTS AND DISCUSSION

In a typical experiment, a mixture of an aldehyde and indole (2 mmol indole per 1 mmol aldehyde functionality) was treated in the presence of RuCl₃.nH₂O (1.2 mol%) in an environment friendly solvent (EtOH or MeOH) at room temperature for the appropriate time, which was monitored by TLC. The results are summarized in Table 1.
Table 1: RuII catalyzed condensation of indoles and aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>![Product 1]</td>
<td>30</td>
<td>75&lt;sup&gt;a&lt;/sup&gt;</td>
<td>304-308</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2a</td>
<td>![Product 2]</td>
<td>20</td>
<td>85&lt;sup&gt;a&lt;/sup&gt;</td>
<td>318-320</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2a</td>
<td>![Product 3]</td>
<td>20</td>
<td>92&lt;sup&gt;a&lt;/sup&gt;</td>
<td>284-286</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>2b</td>
<td>![Product 4]</td>
<td>20</td>
<td>75&lt;sup&gt;a&lt;/sup&gt;</td>
<td>240-243</td>
</tr>
<tr>
<td>5</td>
<td>1c</td>
<td>2b</td>
<td>![Product 5]</td>
<td>15</td>
<td>85&lt;sup&gt;a&lt;/sup&gt;</td>
<td>292-294</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>2c</td>
<td>![Product 6]</td>
<td>30</td>
<td>85&lt;sup&gt;a&lt;/sup&gt;</td>
<td>220-225</td>
</tr>
<tr>
<td>7</td>
<td>1c</td>
<td>2d</td>
<td>![Product 7]</td>
<td>10</td>
<td>80&lt;sup&gt;c&lt;/sup&gt;</td>
<td>262-264</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>2e</td>
<td>![Product 8]</td>
<td>15</td>
<td>75&lt;sup&gt;c&lt;/sup&gt;</td>
<td>128-130</td>
</tr>
<tr>
<td>9</td>
<td>1c</td>
<td>2e</td>
<td>![Product 9]</td>
<td>5</td>
<td>80&lt;sup&gt;c&lt;/sup&gt;</td>
<td>176-180</td>
</tr>
<tr>
<td>10</td>
<td>1b</td>
<td>2f</td>
<td>![Product 10]</td>
<td>20</td>
<td>80&lt;sup&gt;c&lt;/sup&gt;</td>
<td>198-200</td>
</tr>
<tr>
<td>11</td>
<td>1c</td>
<td>2f</td>
<td>![Product 11]</td>
<td>15</td>
<td>86&lt;sup&gt;c&lt;/sup&gt;</td>
<td>265-270</td>
</tr>
</tbody>
</table>

Note: All products were characterized by 1H NMR and IR data. (a) Isolated yields. (b) Ethanol as solvent. (c) Methanol as solvent.
in high yields under mild reaction conditions. This shows high tolerance of ruthenium catalyst toward a variety of functional groups.

Except one case (entry 8, purified by preparative TLC (petroleum ether-ethyl acetate, 10:3)), all products were insoluble in the reaction media, so simple filtration of the reaction mixture and rinsing with the cold reaction solvent gave spectroscopically pure products. In addition, it was observed that the rate of reaction is accelerated if an electron donating group is present on the nucleophile (indoles 1b, 1c). A proposed mechanism for this transformation based on azafulvenium salt species has been reported previously.36

The reaction of indoles with ethereal dialdehydes bearing methoxy and alkoxy groups, also, gave corresponding products in high yields (Table 1, entries 7-11). These products may have biological activities related to anti-diabetic effects of vanillin derivatives.7

**EXPERIMENTAL**

General. All products were characterized by spectroscopic data (IR, 1H NMR). IR spectra were recorded on a shimadzu FTIR-8400S spectrometer. 1H NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer using CDCl3 or (CD3)2SO as solvent and tetramethylsilane was used as internal standard (0.00 ppm). Melting points were measured with a BUCHI Melting Point B-540 apparatus and are uncorrected.

Materials. Synthetic aldehydes were synthesized according to the reported procedure37-41. Fluorene-2-carbaldehyde, Indoles and solvents were used as obtained from Merck without further purification.

Ruthenium-catalyzed double addition of indoles to aldehydes. A mixture of indole (2 mmol), aldehyde (1 mmol) and RuCl3.nH2O (1.2mol%, 0.012 mmol) was stirred at room temperature for the appropriate time (see Table 1). After completion of the reaction as was monitored by TLC, the precipitated product was filtrated and rinsed with cold reaction solvent. In the case of entry 8 in Table 1, purification of the reaction mixture by preparative TLC (petroleum ether-ethyl acetate, 10:3) provided the pure product.

2- Chloro-3-[3,3'-bis(indolyl)-methyl]-quinoline, Solid; mp: 304-308 °C (3aa)  
IR (KBr): v (cm−1), 740, 795, 1025, 1045, 1138, 1330, 1450, 1485, 1585, 2920, 3160, 3410 (NH); 1H NMR ( (CD3)2SO): δ= 3.60 (s, 1H, Ar-CH), 6.83 (d, J = 2.03 Hz, 2H), 6.89 (t, J = 7.60 Hz, 2H), 7.07 (t, J = 7.60 Hz, 2H), 7.29 (d, J = 7.94 Hz, 2H), 7.39 (d, J = 8.12 Hz, 2H), 7.55 (t, J = 7.79 Hz, 1H), 7.75 (dt, J = 8.29, 1.05 Hz, 1H), 7.87(d, J = 8.05 Hz, 1H), 7.96 (d, J = 8.45 Hz, 1H), 8.10 (s, 1H), 10.95 (s, 2H, NH) ppm.

2- Chloro-3-[3,3'-bis(1-methyl indolyl)-methyl]-quinoline, Solid; mp: 318-320 °C (3ba)  
IR (KBr): v (cm−1), 735, 765, 1030, 1130, 1157, 1195, 1370, 1470, 1585, 2920, 3050; 1H NMR (CDCl3): δ= 3.60 (s, 6H, CH3), 6.27 (s, 2H, Ar-CH), 6.60 (t, J = 7.50 Hz, 2H), 7.09 (t, J = 7.63 Hz, 2H), 7.22 (d, J = 8.24 Hz, 2H), 7.27 (d, J = 7.96 Hz, 2H), 7.36(t, J = 7.96 Hz, 1H), 7.53 (d, J = 7.92 Hz, 1H), 7.56 (dt, J = 8.20, 1.16 Hz, 1H), 7.83 (s, 1H), 7.89 (d, J = 8.47 Hz, 1H) ppm.

2- Chloro-3-[3,3'-bis(2-methyl indolyl)-methyl]-quinoline, Solid; mp: 284-286 °C (3ca)  
IR (KBr): v (cm−1), 735, 765, 1010, 1130, 1300, 1330, 1460, 1590, 2910, 3050, 3290 (NH); 1H NMR (CDCl3): δ= 2.03 (s, 6H, CH3), 6.16 (s, 1H, Ar-CH), 6.68 (t, J = 7.48 Hz, 2H), 6.78 (d, J = 7.95 Hz, 2H), 6.92 (t, J = 7.43 Hz, 2H), 7.26 (d, J = 8.03 Hz, 2H), 7.57 (t, J = 7.45 Hz, 1H), 7.78(t, J = 7.68 Hz, 1H), 7.86 (d, J = 8.12 Hz, 1H), 7.96 (d, J = 8.44 Hz, 1H), 8.01 (s, 1H), 10.89 (s, 2H, NH) ppm.

2-[3,3'-bis(1-methyl indolyl)-methyl]-fluorene, Solid; mp: 204-243 °C (3bb)  
IR (KBr): v (cm−1), 740, 1010, 1130, 1150, 1220, 1325, 1370, 1425, 1470, 1610, 2900, 3050; 1H NMR (CDCl3): δ= 3.74 (s, 6H, CH3), 3.88 (s, 2H, CH3), 6.01 (s, 1H, Ar-CH), 6.60 (s, 2H, CH3), 7.04 (dt, J = 7.78, 0.58 Hz, 2H), 7.25 (dt, J = 7.95, 0.71 Hz, 2H), 7.30 (dt, J = 7.35, 0.84 Hz, 1H), 7.34 (d, J = 8.21 Hz, 2H), 7.39 (t, J = 7.39 Hz, 1H), 7.42 (d, J = 7.81 Hz, 1H), 7.46 (d, J = 7.93 Hz, 2H), 7.54-7.56 (m, 2H), 7.74 (d, J = 7.83 Hz, 1H), 7.79 (d, J = 7.55 Hz, 1H) ppm.

2-[3,3'-bis(2-methyl indolyl)-methyl]-fluorene, Solid; mp: 292-294 °C (3cb)  
IR (KBr): v (cm−1), 735, 760, 1010, 1220,

1295, 1425, 1460, 2900, 3050, 3400 (NH); 1H NMR (CD$_3$)$_2$SO: $\delta$ = 2.09 (s, 6H, CH$_3$), 3.82 (s, 2H, CH$_2$), 6.01 (s, 1H, Ar-CH), 6.67 (t, J = 7.44 Hz, 2H), 6.86-6.90 (m, 4H), 7.21-7.24 (m, 3H), 7.28 (t, J = 7.29 Hz, 1H), 7.36 (t, J = 7.39 Hz, 1H), 7.40 (s, 1H), 7.53 (d, J = 7.41 Hz, 1H), 7.76 (d, J = 7.88 Hz, 1H), 7.83 (d, J = 7.52 Hz, 1H), 10.75 (s, 2H, NH) ppm.

6,6'-bis-{4-[3,3'-bis(2-methyl indolyl)-methyl]-2-methoxy phenol}, Solid; mp: 220-225 °C (4cc)

IR (KBr): $\nu$ (cm$^{-1}$), 741, 1046, 1128, 1221, 1240, 1290, 1344, 1458, 1587, 1591, 3051, 3262-3485 (br, OH), 3384 (NH); 1H NMR (CD$_3$)$_2$SO: $\delta$ = 1.97 (s, 12H, CH$_3$), 3.60 (s, 6H, OCH$_3$), 5.78 (s, 2H, Ar-CH), 6.47 (d, J = 1.58 Hz, 2H), 6.65 (t, J = 7.53 Hz, 6H), 6.73-6.77 (m, 6H), 6.88 (t, J = 7.42 Hz, 4H), 6.93 (d, J = 7.98 Hz, 4H), 7.19 (d, J = 8.02 Hz, 4H), 8.12 (s, 2H, OH), 10.59 (s, 4H, NH) ppm.

1,4-bis-{2-[3,3'-bis(2-methyl indolyl)-methyl]phenoxy}-butane, Solid; mp: 262-264 °C (4cd)

IR (KBr): $\nu$ (cm$^{-1}$), 740, 1020, 1105, 1240, 1300, 1460, 1485, 1595, 2920, 3050, 3400 (NH); 1H NMR (CD$_3$)$_2$SO: $\delta$ = 1.02 (m, 4H, CH$_2$), 1.99 (s, 12H, CH$_3$), 3.20 (m, 4H, OCH$_2$), 5.99 (s, 2H, Ar-CH), 6.64 (t, J = 7.53 Hz, 6H), 6.73-6.77 (m, 6H), 6.88 (t, J = 7.51 Hz, 4H), 6.98 (dd, J = 7.49, 1.15 Hz, 2H), 7.16 (dt, J = 7.81 Hz, 2H), 7.20 (d, J = 8.01 Hz, 4H), 10.62 (s, 4H, NH) ppm.

1,4-bis-{2-[3,3'-bis(1-methyl indolyl)-methyl]phenoxy}-butane, Solid; mp: 128-130 °C (4be)

IR (KBr): v (cm$^{-1}$), 743, 763, 1054, 1271, 1329, 1371, 1475, 1585, 2933, 3053; 1H NMR (CD$_3$)$_2$SO: $\delta$ = 1.65 (m, 4H, CH$_3$), 3.65 (s, 12H, CH$_3$), 3.71 (m, 4H, OCH$_3$), 3.82 (s, 6H, OCH$_3$), 6.32 (s, 2H, Ar-CH), 6.54 (s, 4H), 6.79 (d, J = 8.00 Hz, 2H), 6.84 (d, J = 8.00 Hz, 2H), 6.92-6.95 (m, 6H), 7.16 (t, J = 7.55 Hz, 4H), 7.26 (d, J = 8.08 Hz, 4H), 7.40 (d, J = 7.85 Hz, 4H) ppm.

1,4-bis-{2-[3,3'-bis(2-methyl indolyl)-methyl]phenoxy}-butane, Solid; mp: 176-180 °C (4ce)

IR (KBr): v (cm$^{-1}$), 746, 951, 1063, 1277, 1304, 1464, 1582, 2949, 3055, 3394 (NH); 1H NMR (CD$_3$)$_2$SO: $\delta$ = 1.29 (m, 4H, CH$_3$), 2.00 (s, 12H, CH$_3$), 3.48 (m, 4H, OCH$_3$), 3.74 (s, 6H, OCH$_3$), 6.08 (s, 2H, Ar-CH), 6.65 (t, J = 7.49 Hz, 4H), 6.72 (dd, J = 6.53, 2.29 Hz, 2H), 6.78 (d, J = 7.96 Hz, 4H), 6.84-6.90 (m, 8H), 7.18 (d, J = 7.98 Hz, 4H), 10.64 (s, 4H, NH) ppm.

1,4-bis-{4-[3,3'-bis(1-methyl indolyl)-methyl]-2-methoxy-phenoxy}-butane, Solid; mp: 198-200 °C (4bf)

IR (KBr): v (cm$^{-1}$), 741, 1036, 1134, 1223, 1267, 1326, 1458, 1503, 2932, 3051; 1H NMR (CD$_3$)$_2$SO: $\delta$ = 1.83 (m, 4H, CH$_3$), 3.64 (s, 6H, OCH$_3$), 3.69 (s, 12H, CH$_3$), 3.96 (m, 4H, OCH$_3$), 5.76 (s, 2H, Ar-CH), 6.80-6.84 (m, 8H), 6.90 (t, J = 7.45 Hz, 4H), 7.00 (d, J = 1.68 Hz, 2H), 7.10 (t, J = 7.59 Hz, 4H), 7.31 (d, J = 7.92 Hz, 4H), 7.36 (d, J = 8.23 Hz, 4H) ppm.

1,4-bis-{4-[3,3'-bis(2-methyl indolyl)-methyl]-2-methoxy-phenoxy}-butane, Solid; mp: 265-270 °C (4cf)

IR (KBr): v (cm$^{-1}$), 746, 1032, 1132, 1225, 1246, 1267, 1460, 1510, 1600, 2928, 3050, 3395 (NH); 1H NMR (CD$_3$)$_2$SO: $\delta$ = 1.85 (m, 4H, CH$_3$), 2.06 (s, 12H, CH$_3$), 3.54 (s, 6H, OCH$_3$), 3.98 (m, 4H, OCH$_3$), 5.86 (s, 2H, Ar-CH), 6.62 (dd, J = 8.29, 1.30 Hz, 2H), 6.68 (t, J = 7.42 Hz, 4H), 6.82 (d, J = 8.36 Hz, 2H), 6.85-6.89 (m, 10H), 7.20 (d, J = 8.01 Hz, 4H), 10.69 (s, 4H, NH) ppm.

CONCLUSION

In summary, we have reported a series of new BIM derivatives using a simple and eco-compatible protocol. The remarkable features of this method are easy purification procedure, low catalyst loading, high yields of products, short reaction times and mild reaction conditions.

ACKNOWLEDGEMENTS

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REFERENCES