Synthesis and molecular docking studies of certain chalcones of benzimidazole

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ABSTRACT

Molecular docking is routinely used for understanding drug-receptor interaction in modern drug design. In the present work involved the synthesis of three different chalcones of benzimidazole by three steps. Initially by using o-phenylene diamine and lactic acid as the starting materials for the synthesis of 2-(a-hydroxyethyl) benzimidazole and this undergone oxidation reaction in solid phase method with potassium permanganate and solid neutral alumina to form 2-Acetyl benzimidazole. Final step involves the synthesis of chalcones of benzimidazole by 3 different aromatic aldehydes. Then the 3 synthesized compounds were docked against HMG CoA reductase involved in cholesterol biosynthesis using Argus Lab software. The protein file of HMG CoA reductase [PDB ID: 1DQ8] was taken from the protein data bank. All the derivatives have shown best ligand binding energy between –10.28 kcal/mol to -9.70kcal/mol from 1-3 hydrogen bonds. Out of the 3 derivatives S1 show good ligand binding energy as -9.70kcal/mol with 3 hydrogen bonds.

Key words: Chalcones, Benzimidazole, HMG CoA reductase, Argus Lab

INTRODUCTION

Benzimidazole is a bicyclic heterocyclic system consisting of two nitrogen atoms and fused phenyl ring1. Benzimidazole derivatives play a vital role in biological fields such as anti-inflammatory, anticancer, anticonvulsant2, antiviral, antioxidant3, antimicrobial4 and antitubercular5 activities.

Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial, anti-inflammatory, analgesic, ant platelet, ant ulcerative, ant malarial, anticancer, antiviral, antileishmanial antioxidant, ant tubercular, ant hyperglycemic, immunomodulatory, inhibition of chemical mediators release, inhibition of leukotriene B4, inhibition of tyrosinase and inhibition of aldose reductase activities6. Claissen-Schmidt condensation with aryl aldehyde to produce corresponding chalcones. The presence of reactive, b-unsaturated keto group in chalcone is found to be responsible for their biological activity6. A classical synthesis of these compounds involves the condensation of acetophenones and aldehydes to give chalcones. The combination of solvents and long reaction time, costly chemicals / catalyst makes this method environmentally hazardous. This provided the stimulus to synthesize some new chalcones using grindstone technique7. In grindstone technique, reaction occurs through generation of local heat by grinding of crystals of substrate and reagent by mortar and pestle. Reactions are initiated by grinding, with the small amount of energy through friction. In some cases, a mixture and reagents turns to a glassy material. Such reaction are simple to handle, reduce pollution, comparatively cheaper to operate and may be regarded as more economical and ecologically favorable procedure in chemistry8. Solid-state reaction occurs more efficiently and more selectively than does the solution reaction, since molecules in the crystal are arranged tightly and regularly.

Cholesterol is an essential element of cell membranes, where it provides structural support and may even serve as a protective antioxidant. It is essential for conducting nervous impulses, especially at the level of the synapse9. Hypercholesterolemia produced either by cholesterol feeding or by cholesterol-free, purified diets (“endogenous” hypercholesterolemia) results in the accumulation of cholesterol in adipose tissue10. Cholesterol biosynthesis is a tightly regulated pathway that employs multiple feedback mechanisms to maintain homeostasis. The first committed step in sterol synthesis, the NADPH-dependent reduction of HMG-CoA to mevalonate, is catalyzed by HMG-CoA Reductase (HMGR, 3-Hydroxy-3-methylglutaryl coenzyme A reductase) at the endoplasmic reticulum (ER) membrane11.

In the present work involves the synthesis of 2-(a-hydroxyethyl) benzimidazole by the reaction of o-phenylenediamine and lactic acid and which on oxidation with potassium permanganate and aluminium oxide gives 2-acetylbenzimidazole. This product had undergone grindstone technique with different aromatic aldehydes and sodium hydroxide to form chalcones of benzimidazole.

MATERIALS AND METHODS:

The melting points were recorded on techinoco apparatus and are uncorrected.

General procedure for the synthesis of Chalcones of Benzimidazole12, 13:

Step I: Synthesis of 2-(a-hydroxyethyl) benzimidazole: A mixture of 27 gm (0.25mole) of o-phenylene diamine, 25.5 ml (30.6 gm, 0.34 mole) of Lactic acid was refluxed for 2 ½ hours. Reaction mixture was cooled, and made alkaline by the gradual addition of 10% sodium hydroxide solution. The residue was collected. The crude product obtained was dissolved in 400ml of boiling water. To this 2 gm of decolorizing carbon was added and digested for 15 minutes. The digested solution was filtered rapidly at the pump through a pre heated Buchner funnel, the filtrate was cooled to about 100°C. The product obtained was filtered and washed with 25 ml of cold water and dried at 100°C. The purity of the compound is confirmed by getting a single spot in TLC.

Step II: Synthesis of 2 – acetyl Benzimidazole:
The alumina supported permanganate was prepared by mixing solid KMnO4 (2 gm, 12.65 mmoles) and solid neutral alumina (2.5 gm) in a mortar and ground with a pestle until a fine homogenous purple powder was obtained. Later, Step I compound (5mmoles) was added to the above mixture and ground with a pestle for some more time at room temperature. Examination of the mixtures by TLC showed complete disappearance of starting material which requires approximately 5 – 10 minutes. Then acetone (20 ml) was added to the reaction mixture and after vigorous stirring the mixture was filtered and the acetone filtrate was evaporated to obtain a crude residue. The latter was taken up in chloroform (15 ml) and washed with water (30 ml) to remove any inorganic matter and dried over anhydrous sodium
sulphate. The crude product obtained was recrystallised from hot water to get the pure needle like crystals. A single spot on the TLC plate confirmed the purity.

**Step III: Synthesis of Chalcones:**

NaOH pellets (0.02mmole) and compound from step (2) (0.01mmoles) were ground in a mortar to a fine powder at room temperature. To this 0.01mmoles of aromatic aldehyde is added and the mixture was ground by pestle at room temperature for a few more minutes till the condensation was complete as shown by TLC. The obtained solid mixture was diluted with cold water, neutralized by dil HCl. The crude compound was recrystallised from a suitable organic solvent (acetic acid) to get the pure product. A single spot on the TLC plate confirmed the purity.

\[
\begin{align*}
\text{NaOH} & + \text{CH}_3\text{COOH} \\
\rightarrow & \text{2-(a-hydroxyl ethyl) benzimidazole} \\
\text{Kmno}_4 / \text{Al}_2\text{O}_3(n) & \rightarrow \text{2-Acetyl benzimidazole}
\end{align*}
\]

**RESULTS AND DISCUSSION:**

In the present work, totally three compounds were synthesized in single scheme. Step I involves the formation of 2-(a-hydroxyl ethyl) benzimidazole from o-phenylenediamine and lactic acid. Step 1 product undergo oxidation reaction in solid phase method with potassium permanganate and solid neutral alumina to form 2-Acetyl benzimidazole. Then the next step involves the formation of highly reactive intermediate of different substituted chalcones with aromatic aldehydes in solid phase method. Molecular docking study was carried out for the synthesized 3 different chalcones of benzimidazole (S$_1$, S$_2$, S$_3$) fig1 for HMG CoA Reductase protein. The potential active site amino acids of HMG CoA Reductase were predicted using CASTp. Among the 80 active sites predicted, pocket 1 found to be the best active site which contains 45 amino acids. The Fig.3 shows the active site of the target protein. The target protein and inhibitors were geometrically optimized. All the 3 synthesised chalcones of benzimidazole inhibitors were docked against active site of the target protein using Argus lab which gives an insight into the binding modes for the various inhibitors. Out of 3 inhibitors analyzed (i.e. S$_1$, S$_2$, S$_3$) S$_3$ has showed binding energy of -9.70 Kcal/mol with 3 hydrogen bond against the target protein. The binding energy and hydrogen bonds of all the inhibitors was shown in Table: 2.

![Fig: 1 Scheme for the synthesis of Chalcones of Benzimidazole](image1)

![Fig: 2 Structure of HMG CoA Reductase protein](image2)

**Table: 1 Physical data of the synthesized chalcones of benzimidazole**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Molecular Weight</th>
<th>M.pt(°C)</th>
<th>% yield</th>
<th>R$^+$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S$_1$</td>
<td>H</td>
<td>C$_7$H$_7$N$_2$O</td>
<td>248</td>
<td>205</td>
<td>74</td>
</tr>
<tr>
<td>S$_2$</td>
<td>4-Cl</td>
<td>C$_7$H$_5$N$_2$O</td>
<td>282</td>
<td>213</td>
<td>65</td>
</tr>
<tr>
<td>S$_3$</td>
<td>3-NO$_2$</td>
<td>C$_7$H$_6$N$_3$O$_3$</td>
<td>293</td>
<td>215</td>
<td>77</td>
</tr>
</tbody>
</table>

*Solvent used for TLC= Acetone: Chloroform (5:5)

**Molecular docking studies:**

The Structure of the Protein HMG CoA Reductase with the PDB ID: 1DQ8 was retrieved from the Protein Data Bank. It is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. After obtaining the structure from Protein Data Bank, the possible binding sites of the Protein were searched using Computed Atlas of Surface Topography of Proteins (CASTp). The inhibitor (synthesized chalcones of benzimidazole) and target protein was geometrically optimized and docked using the docking engine Argus Dock. (http://www.arguslab.com/). Argus Lab consists of a user interface that supports OpenGL graphics display of molecule structures and runs quantum mechanical calculations using the Argus compute server.

**Table: 2 Summary of binding energy of all synthesized chalcones of benzimidazole against the target HMG CoA Reductase protein (PDB ID: 1DQ8)**

<table>
<thead>
<tr>
<th>S.No</th>
<th>Name of the drugs</th>
<th>No of conformation</th>
<th>Binding Energy</th>
<th>Hydrogen bonds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S$_1$</td>
<td>140</td>
<td>-10.28</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>S$_2$</td>
<td>140</td>
<td>-10.33</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>S$_3$</td>
<td>140</td>
<td>-9.70</td>
<td>3</td>
</tr>
</tbody>
</table>

*Fig: 1 Scheme for the synthesis of Chalcones of Benzimidazole*
CONCLUSION:
Overall, three different chalcones of benzimidazoles were synthesized from o-phenylenediamine and lactic acid as starting materials, where as 2-(α-hydroxy ethyl) benzimidazole and 2-Acetyl benzimidazole as intermediates. Then the synthesized compounds were checked for their anticholesterol effect by molecular docking studies against HMG CoA Reductase which is the main enzyme involved in the biosynthesis of cholesterol. The synthesized 3 chalcone derivatives of benzimidazole (S1-S3) were docked with HMG CoA Reductase protein by using Argus Lab to find out the best hits. The best drug was selected, depending upon the binding energy and hydrogen bonds formed. Out of the 3 derivatives S3 shows highest affinity towards HMG CoA Reductase protein compared with that of the other 2 compounds. Thus S3 may act as a better and efficient drug to treat hypercholesterolemia than the other two synthesized chalcones of benzimidazole.

REFERENCES:

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