Chapter-3

Synthesis of (4-Benzyl oxy)-1H-Indole Derivatives,
Synthesis of Irbesartan and Pioglitazone hydrochloride
by newer route.
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Synthesis of (4-Benzylxoy)-1H-Indole Derivatives,
Synthesis of Irbesartan and Pioglitazone hydrochloride
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The chapter-3 deals with the synthesis of various (4-Benzylxoy)-1H-Indole derivatives like Schiff base, 2-Azetidinones, 4-Thiazolidinones, 5-Arylidine derivatives, 1,3,5-Oxadiazines and Tetrazole derivatives and remaining part comprise of synthesis of Irbesartan and Pioglitazone hydrochloride by newer route.

The presence of azo methine [>C=N-] group is of great importance by considering the fact that it can be transformed into various heterocyclic ring compounds. The availability of the presence and significant biological properties of the members known so far prompted the authors to extend moieties like 2-azetidinones, 4-thiazolidinones, 5-Arylidines, 1,3,5-oxadiazine and Tetrazole derivatives.

In this context, whole chapter is divided into three sections.

Section – A comprises the synthesis of various (4-Benzylxoy)-1H-Indole derivatives like Schiff base, 2-Azetidinones, 4-Thiazolidinones, 5-Arylidine derivatives, 1,3,5-Oxadiazines and Tetrazole derivatives.

Section – B comprises the synthesis of Irbesartan by newer route

Section – C comprises the synthesis of Pioglitazone hydrochloride by newer route.
Section-A

Synthesis of Various (4-Benzylxy)-1H-Indole Derivatives

3.1 Synthesis of Schiff base of (4-Benzylxy)-1H-Indole

Theoretical consideration:

Organic chemists are frequently facing the problem of characterizing and ultimately elucidating the structure of organic compounds. The worker in the field of natural product has the prospects of isolating such compounds from their sources in a pure state and then determining their structure. On the other hand the synthetic organic chemist encounters new or unexpected compounds in the course of investigations.

All reactions were carried out under prescribed laboratory conditions. All the reactions requiring anhydrous conditions were conducted in flame dried apparatus.

The solvents and reagents used in the synthetic work were of laboratory reagent grade and were purified by distillation and crystallization techniques wherever necessary and their melting points were checked with the available literature.

Melting points of newly synthesized compounds were determined by open capillary method. The final product was purified by recrystallization.

The reaction, the reagents and the conditions of the reaction system are given in the following scheme 3.1 and 3.2 as follows,
3.1.1 Synthesis of (4-Benzylloxy)-1H-Indole BOIH (3)

(4-Benzylloxy)-1H-Indole (1) (0.01 mole) and chloro ethyl acetate (0.01 mole) in acetone (5 ml) were taken in round bottom flask [100 ml]. Then charge K$_2$CO$_3$ (0.005 mole) and mixture were refluxed for 5-8 hrs. The solution was filtered through hyflow bed and filtrate ml was distilled out to get crude solid product. This is in turn purified by dissolving in methanol and pure product fall out by adding water. This in turn filtered and washed with water and dried for 12 hrs at 50-55\(^0\) C.

The newly compound (2) (0.01 mole) dissolved in absolute ethanol. Hydrazine hydrate (99%, 0.02M) and few drops of concentrated sulphuric acid were added. The reaction mixture was refluxed for 6 hours. The resulting solid obtained was filtered, dried and crystallized from ethanol [96, 97].

![Scheme 3.1]

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$\text{NH}_2\text{NH}_2\text{H}_2\text{O}$

BOIH

Scheme 3.1
3.1.2 Synthesis of N-methyl acid hydrazide derivatives of (4-Benzylxy)-1H-Indole (4a-f).

The Schiff bases of (4-Benzylxy)-1H-Indole (4a-f) were prepared by method reported [98-102].

Benzaldehyde derivative (Given in Table: 3.1) (0.01mole), N-methyl acid hydrazide derivatives of (4-Benzylxy)-1H-Indole BOIH (3) (0.01mole) and ethanol (20 ml) were taken in a RBF [100ml], few drop of concentrated sulfuric acid was added. The mixture was heated until a clear solution was obtained. The clear solution was kept overnight when respective Schiff base fall out which was filtered, washed by petroleum ether and air dried. The resultant Schiff bases are designated as (4a-f) and their details are shown as follows.
Table 3.1  List of Raw materials used for Schiff bases
Formation of BOIH

<table>
<thead>
<tr>
<th>List of Raw Materials</th>
<th>Structure</th>
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<td>2-Bromo benzaldehyde</td>
<td><img src="image" alt="2-Bromo benzaldehyde Structure" /></td>
</tr>
<tr>
<td>4-Chloro benzaldehyde</td>
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<tr>
<td>4-Nitro benzaldehyde</td>
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<tr>
<td>4-Hydroxy benzaldehyde</td>
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</tr>
<tr>
<td>4-Methoxy benzaldehyde</td>
<td><img src="image" alt="4-Methoxy benzaldehyde Structure" /></td>
</tr>
</tbody>
</table>

The formation of Schiff bases is presented in scheme 3.2.
Where,

\[ \text{Ar} = \text{phenyl}, \text{phenyl-Br}, \text{phenyl-Cl}, \text{phenyl-NO}_2, \text{phenyl-OH}, \text{phenyl-OMe} \]

\[ \text{(4a-h)} \]

\[ \text{Scheme 3.2} \]
3.2 Synthesis of 2-Azetidinone derivatives of (4-Benzylloxy)-1H-Indole (5a-f)

Schiff base of Benzyl oxy indole hydrazone (BOIH) (4a-f) cyclo condense with chloro acetyl chloride in presence of 1, 4-dioxane solvent and Tri ethyl amine as a base to yield corresponding 2-Azetidinone derivatives (5a-f) [103-107].

The formation of 2-Azetidinone derivatives is presented in scheme 3.3.

Where,

\[
\text{Ar} = \text{Ph}, \quad \text{Ph-Br}, \quad \text{Ph-Cl}, \quad \text{Ph-NO}_2
\]
\[
\text{Ph-OH}, \quad \text{Ph-OMe}
\]

Scheme 3.3
3.2.1 Synthesis of 1-[N-acetamido-4-benzyloxy-1H-Indole]-3-chloro-4-aryl azetidin-2-ones (5a-f)

A mixture of N-methyl (4-Benzyloxy)-1H-Indole acid (substituted benzylidene)-hydrazide (4a-f) (0.01 mole) and tri ethyl amine (TEA) (0.03mole) was dissolved in 1,4-dioxane (50 ml) cooled and stirred. To this well stirred cooled solution chloro acetyl chloride (0.012 mole) was added drop wise. The reaction mixture was stirred for 14 hrs at room temperature. Excess of solvent was removed by distillation. The residue was poured over crushed ice and then air dried. The product thus obtained was purified by column chromatography over silica gel using 20% ethyl acetate: 80% n-hexane as eluent. Recrystalization from ether/n-hexane gave white powdered 1-[N-acetamido-4-benzyloxy-1H-Indole]-3-chloro-4-aryl azetidin-2-ones (5a-f), which were obtained in 45-65% yield.
3.3 **Synthesis of 4-Thiazolidinone derivatives of (4-Benzyloxy)-1H-Indole (6a-f).**

Schiff base of Benzyl oxy indole hydrazide (BOIH) (4a-f) cyclo condense with mercapto acetic acid in presence of Di methyl formamide (DMF) solvent and anhydrous zinc chloride as a catalyst to yield corresponding 4-thiazolidinone derivatives (6a-f) [108-113].

The formation of 4-Thiazolidinone derivatives is presented in scheme 3.4.

![Scheme 3.4](image-url)

Where,

\[
\text{Ar} = \text{Ph}, \quad \text{Ph-Br}, \quad \text{Ph-Cl}, \quad \text{Ph-NO}_2, \quad \text{Ph-OH}, \quad \text{Ph-OME}
\]
3.3.1 Synthesis of 3-[N-acetamido-4-benzyloxy-1H-Indole]-2-aryl-1,3-thiazolidin-4-ones (6a-f)

A mixture of N-methyl (4-Benzylloxy)-1H-Indole acid (substituted benzylidine)-hydrazide (4a-f) (0.01 mole) in Dimethyl formamide (50 ml) and Thioglycolic acid (0.87ml, 0.0125 mole) with a pinch of anhydrous zinc chloride was refluxed for about 8-9 hours. The Excess solvent was removed under vacuum and residue was poured into ice cold water and then neutralized with sodium bicarbonate solution. Solid separated was filtered and dried. The product thus obtained was purified by column chromatography over silica gel using n-hexane: ethyl acetate (7:3 V/V) mixture as eluent. The eluate was concentrated and the product crystallized from alcohol (Yield = 50-60%).
3.4 Synthesis of 5-arylidine-4-thiazolidinone derivatives of (4-Benzylxy)-1H-Indole (7a-f).

4-Thiazolidinone derivatives of Benzyl oxy indole hydrazide (BOIH) (6a-f) condense with 4-bromo benzaldehyde in presence of ethanol solvent and sodium methoxide as a base to yield corresponding 5-arylidine-4-thiazolidinone derivatives (7a-f) [114-118].

The formation of 5-arylidine-4-Thiazolidinone derivatives is presented in scheme 3.5.

\[ \text{4-THIAZOLIDINONE DERIVATIVES OF BOIH (6a-h)} \]
\[ \text{4-BROMO BENZALDEHYDE} \]
\[ \text{5-ARYLIDINE DERIVATIVES OF 6a-h (7a-h)} \]

Where,

\[ \text{Ar} = \text{aryl, phenyl-Br, phenyl-Cl, phenyl-NO}_2, \text{phenyl-OH, phenyl-OMe} \]

Scheme 3.5
3.4.1 Synthesis of N-[2-aryl-4-(4-bromo phenyl arylidene)-5-oxothiazolidin-3-yl]-(1H-4-benzyloxy-1H-indole)-acetic acid hydrazide (7a-f)

A mixture of 4-thiazolidinone derivatives (6a-f) (0.01 moles) and 4-bromo benzaldehyde (0.01 moles) in ethanol (35 ml) in presence of sodium ethoxide were refluxed on a water bath for about 5 hrs and cooled. The solid separated was collected by filtration, dried and recrystallized from ethanol.
3.5 Synthesis of Tetrazole derivatives of (4-Benzylxyloxy)-1H-Indole (9a-f).

Various Schiff bases of (4-Benzylxyloxy)-1H-Indole (4a-f) reacted with phosphorous pentachloride to yield corresponding imidoyl chloride derivatives (8a-f) which in turns heterocyclised with sodium azide yield corresponding tetrazole derivatives (9a-f). The synthetic route is shown in Scheme-3.6. Experimental procedure for the synthesis of this series compounds have been adopted according to reported methods [119].
Schiff bases of BOIH

\[
\begin{align*}
\text{PCl}_3 & \\
\end{align*}
\]

Chlorinated Schiff bases of BOIH

\[
\begin{align*}
\text{NaN}_3 & \\
\end{align*}
\]

Tetrazole derivatives of BOIH

Where,

\[
\begin{align*}
\text{Ar} = & \quad \text{aryl}, \quad \text{aryl-Br}, \quad \text{aryl-Cl}, \quad \text{aryl-NO}_2 \\
& \quad \text{aryl-OH}, \quad \text{aryl-OMe} \\
\end{align*}
\]

Scheme 3.6
3.5.1 Synthesis of 5-substituted phenyl – 1 - [(1H-4-benzyloxy-1H-indole)-acetic acid hydrazide]-1H-Tetrazole (9a-f)

A mixture of Schiff bases (4a-f) (0.01 mole) and Phosphorous pentachloride [PCl₅] (0.01 mole) was heated at 100 °C for 1 hour. When the evolution of fumes of HCl ceased, excess of PCl₅ was removed under reduced pressure and the residual imidoyl chloride (8a-f) was treated with an ice-cold solution of sodium azide (0.02 mole) in water (75 ml), sodium acetate (0.01 mole) and acetone (100 ml) with stirring. Stirring was continued for overnight, there after acetone was removed under reduced pressure. The remaining aqueous portion was extracted with chloroform and dried to give white crystals of product (9a-f) which is obtained in 50-70% yield.
3.6 Synthesis of 1, 3, 5-Oxadiazine derivatives of (4-Benzylxy)-1H-Indole (10a-f).

Various Schiff bases of (4a-f) on heterocyclization reaction with benzoyl isothiocyanate yield corresponding 1,3,5-oxadiazine derivatives (10a-f). The synthetic route is shown in Scheme-3.7. Experimental procedure for the synthesis of this series compounds have been adopted according to reported method [120].

Where,

\[ \text{Ar} = \begin{array}{c} \text{Ph} \\ \text{Br} \\ \text{Cl} \\ \text{NO}_2 \\ \text{OH} \\ \text{OMe} \end{array} \]
3.6.1 Synthesis of 3-[(1H-4-benzyloxy-1H-indole)-acetic acid hydrazide]-2-substituted aryl-6-phenyl-1,3,5-oxadiazine-4-thione (10a-f)

A mixture of Schiff bases of BOIH (4a–f) (0.01 mole), benzoyl isothiocyanate (0.01 mole), and tri ethyl amine (three-four drops) in 1,4-dioxane (20 ml) was refluxed for 2 hours. The separated solid that formed upon dilution with water (20 ml) was filtered, dried, and recrystallized from xylene to give yellow crystals of product (10a-f) which were obtained in 50-70% yield.
**Section-B**

*Synthesis of Irbesartan by newer improved route*

Irbesartan is classified as an angiotensin II receptor type 1 antagonist invented by jointly by Sanofi-synthelabo and Bristol-Myers squibb. Angiotensin II receptor type 1 antagonists are widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy [121]. Irbesartan is an orally active lipophilic drug and possesses rapid oral absorption. It causes reduction in blood pressure and is used in treatment of hypertension. Irbesartan delays progression of diabetic nephropathy and is indicated for the reduction of renal disease progression in patients with type 2 diabetes. It is jointly marketed by Sanofi-Aventis and Bristol-Myers Squibb under the trade name Aptovel®, Karvea® and Avapro® [122,123]. Irbesartan is also available in a combination formulation with a low dose thiazide diuretic, invariably hydrochlorothiazide, to achieve an additive antihypertensive effect.

This section presents the development of efficient commercial process for the preparation of highly pure Active pharmaceutical ingredients (API) like Irbesartan. Irbesartan could be an attractive target for the generic industries.

During the last few years, considerable attention has been devoted to various synthesis route of Irbesartan. But, existing route having some disadvantage, say Long route of synthesis, Use of very costly and number of reagents, having moderate yield and quality, having complicated workup procedure, time staking procedure and number of impurities generated [124].

Here, in this section new route of Irbesartan is reported which having only two steps route of synthesis, use of very cheap raw material and reagents, having excellent yield and quality and lastly having very simple reaction and workup procedure.

Hence, the present communication comprises the study of new route for scalable process of Irbesartan presented in scheme 3.8.
3.7 Preparation of Irbesartan

3.7.1 Preparation of Irbesartan Crude

Charge 25 g 4’-(bromo methyl)biphenyl-2-carbonitrile, 21.2 g 2-Butyl-1,3-diazaspiro[4,4]-non-1-en-4-one hydrochloride and 6 g TBAB in 75 ml toluene into this add sodium hydroxide solution [Prepared by dissolving 10 g NaOH in 40 ml water] and stir resulting slurry for 20 hours. Check TLC of reaction mass and then add 100 ml water, stirred and do layer separation. Take toluene layer distilled out toluene under vaccum till thick mass observed. Charge 125 ml Xylene, 12.5 g sodium azide,
26.5 g triethylamine hydrochloride and stirred. Heat reaction mass to 120-125°C and maintain for 24 hours. Check TLC of reaction mass and then cool to 25-30°C. Charge 25 ml water and cool to 10-15°C. To this add sodium nitrite solution [by dissolving 13 g NaNO₂ in 130 ml water] then adjust pH 2.0 to 3.0 using dilute sulfuric acid [prepared by dissolving 16.5 ml H₂SO₄ with 325 ml water]. Raise temperature to 25-30°C, filter and dry at 50-55°C for 8 – 10 hours in Hot air oven to give Irbesartan crude (37.5 g)

3.7.2 Preparation of Irbesartan Pure

Charge 35 g Irbesartan crude + 280 ml Water and stirred, adjust pH 6.5 to 7.5 using liquor ammonia and stir. Further adjust pH 4.2 to 4.8 using dilute sulfuric acid and stir. Filter the slurry. Charge 140 ml special denature spirit (5-10% moisture containing ethanol) and heat to make clear solution and cool to 25-30°C, stir and filter. Charge 140 ml special denature spirit (5-10% moisture containing ethanol) into wet cake and heat to reflux and cool to 35-40°C and filter. Dry wet cake under vacuum for 12 hours at 50-55°C to get 22.5 gm Irbesartan pure.

Comparative data of various route of Irbesartan

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<th>Source</th>
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<th>HPLC %Purity</th>
<th>Number of steps</th>
<th>EP Impurity - A</th>
<th>Remarks</th>
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<td>98-99%</td>
<td>03</td>
<td>0.10</td>
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</tr>
<tr>
<td>Adopted ROS</td>
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<td>99.0 – 99.5%</td>
<td>02</td>
<td>0.04</td>
<td>Cheaper raw materials</td>
</tr>
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</table>
**Section-C**

*Synthesis of Pioglitazone hydrochloride by newer improved route*

Pioglitazone hydrochloride, (RS)-5-(4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl)thiazolidine-2,4-dione hydrochloride) is an oral ant diabetic agent used in the treatment of type 2 diabetes mellitus also known as non insulin dependent diabetes mellitus (NIDDM) or adult onset diabetes innovated by Takeda Pharma. Pioglitazone decrease insulin resistance in the periphery and liver, resulting in increased insulin dependent glucose disposal and decreased hepatic glucose output. Currently, it is marketed under the trade name Actos® [125]. It is a white or almost white crystalline, odourless powder, practically tasteless, insoluble in water and alcohols, but soluble in 0.1 N NaOH; it is freely soluble in dimethylformamide. It exhibits slow gastrointestinal absorption rate and inter individual variation of its bioavailability [126].

This section covers the development of efficient commercial process for the preparation of highly pure Active pharmaceutical ingredients (API) like Pioglitazone hydrochloride. Pioglitazone hydrochloride could be an attractive target for the generic industries.

During the last few years, considerable attention has been devoted to various synthesis route of Pioglitazone hydrochloride. But, existing route having some disadvantage, say Long route of synthesis, Use of very costly and number of reagents, having moderate yield and quality, having complicated workup procedure, time staking procedure and number of impurities generated [127].

Here, in this section new route of Pioglitazone hydrochloride reported which having only two steps route of synthesis, use of very cheap raw material and reagents, having excellent yield and quality and lastly having very simple reaction and workup procedure.
Hence, the present communication comprises the study of new route for scalable process of Pioglitazone hydrochloride presented in scheme 3.9.

Scheme-3.9 Novel and new route for synthesis of Pioglitazone hydrochloride
3.8 Preparation of Pioglitazone hydrochloride

3.8.1 Preparation of Pioglitazone Stage-1

Charge 5 gm NaOH and 30 ml water and stirred then charge 100 ml Methylene dichloride, 15 gm 5-ethyl-2-pyridine ethanol, 6 gm Tetra butyl ammonium bromide and 23 gm p-toluene sulfonyl chloride and mixture were stirred for 2 hours at 25-30°C. To the reaction mixture add 12 gm 4-hydroxy benzaldehyde, 100 ml water and 8 gm sodium hydroxide and stirred reaction mixture at 40-50°C for 12 hours. Do layer separation. Dry Organic layer over Na₂SO₄ and distilled out Methylene dichloride to give 29 gm of 4-[2-(5-ethyl-2-pyridinyl)ethoxy]benzaldehyde as oil.

3.8.2 Preparation of Pioglitazone Stage-2

Charge 27 gm oil of 4-[2-(5-ethyl-2-pyridyl)ethoxy]benzaldehyde, 33 gm 2,4-thiazolidinone, 300 ml methanol and 14 ml concentrated aqueous ammonia, heat resulting mixture to reflux for 5 hours. The product crystal were separated was filtered and recrystallized from 1,2-dichloro ethane gives 21.6 gm 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzylidine}-2,4-thiazolidinone.

3.8.3 Preparation of Pioglitazone Base

Charge 10gm 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzylidine} -2,4-thiazolidinone and 100 ml methanol and stirred. Charge 5 gm NaOH solution in 5 ml water into reaction mass and stirred. Charge 10 gm NaBH₄ (sodium borohydride) into reaction mass and cool to 15-17°C. Maintain reaction mass for 5-6 hours at 15-17°C. filter slurry to remove solid material and concentrate filtrate mother liquor under vacuum to get crude product, which is recrystallized from methanol to give 6.6 gm pure crystal of 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinone.
3.8.4 Preparation of Pioglitazone Hydrochloride

Charge Pioglitazone base 10 gm and 30 ml acetone and stirred. Cool reaction mixture to 5-10°C. Adjust pH of reaction mass to 2 to 3 by purging HCl gas. (HCl gas produce by adding sulfuric acid in sodium chloride), stir reaction mass for 60 minutes at 5-10°C. Filter resulting slurry and wash wet cake with 5 ml acetone. Dry under vacuum at 40-45°C for 5 hours Dry weight = 10 gm.

Comparative data of various route of Pioglitazone Hydrochloride

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<tr>
<th>Source</th>
<th>Overall yield %</th>
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<th>Remarks</th>
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<td>98-99%</td>
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<td>0.12</td>
<td>Use of number of raw materials</td>
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<tr>
<td>Adopted ROS</td>
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<td>04</td>
<td>0.06</td>
<td>Using cheaper and easily available raw materials</td>
</tr>
</tbody>
</table>