CHAPTER-5A
AN IMPROVED PROCESS FOR THE PREPARATION OF ZAFIRLUKAST - AN ANTI ASTHMA DRUG
AN IMPROVED PROCESS FOR THE PREPARATION OF ZAFIRLUKAST: AN ANTI ASTHMA DRUG

5. 1.1 INTRODUCTION

Asthma is a disease that causes swelling and narrowing the airways of the lungs. Airways are air carriers to and from lungs. Swollen and narrower airways affect the air flow to and from the lungs and this lead to tightness of chest, wheezing, shortness of breath and cough. These symptoms are often occurs in early morning and in night. Asthma is caused by genetic and environmental factors, it was not curable completely but this can be controlled with good medical care.

Leukotriene antagonists also known as leukast are the medicaments that are used to reduce leukotrienes, which are produced by several types of cells and causes inflammation in asthma and bronchitis. Leukotriene antagonists that are available in market are Montelukast, Zafirlukast and Pranlukast. Zafirlukast is the first leukast compound approved for management of Asthma. US FDA approved zafirlukast in the form of 10 mg and 20 mg tablet with the brand name of Accolate®.1 Subsequently this was approved and launched by innovator in few other countries.

Importance of Leukotriene antagonists for treating asthma are motivated us to develop an improved and cost effective process for the preparation of Zafirlukast.
5. 1.1.1 PRODUCT PROFILE

1. Generic name : Zafirlukast
2. Chemical structure :

![Chemical Structure Image]

4. Molecular formula : C\(_{31}\)H\(_{33}\)N\(_3\)O\(_6\)S
5. Molecular weight : 575.69
6. CAS No : 107753-78-6
7. Therapeutic category : Anti asthmatic

5. 1.1.2 PHYSICAL CHARACTERISTICS

1. Description : Off white to pale yellow powder
2. Solubility : Tetrahydrofuran (Rx-list)
3. Melting point : 137 – 140°C

5. 1.1.3 MARKET INFORMATION

1. Applicant : AstraZeneca
2. Patentee : ICI
3. Brand name : ACCOLATE
5. 1.2 LITERATURE REVIEW

There are many synthetic routes for the preparation of Zafirlukast 4 is well documented in literature. Some of the key approaches are discussed here under. Scientists from ICI Americas Inc\(^2\) have reported process for the synthesis of 4, which starts with esterification of 3-methoxy-4-methyl benzoic acid 53 using methanol in presence of acetyl chloride (Scheme 5.1).

Scheme 5.1: Synthesis of zafirlukast 4 (product patent route)
Allylic bromination of methyl ester \textbf{54} using bromine in presence of \(\text{CCl}_4\) resulted bromo compound \textbf{55}, which was reacted with 5-nitro indole \textbf{124} using silver oxide as catalyst to obtain condensed compound \textbf{125}. \(N\)-methylation of \textbf{125} utilizing methyl iodide in presence of NaH afforded \(N\)-methyl indole derivative \textbf{57}. Thus obtained \textbf{57} was subjected to reduction using palladium carbon (Pd/C) in methanol followed by reacted with cyclopentyl chloroformate to obtain compound \textbf{59}. Hydrolysis of \textbf{59} using LiOH.H\textsubscript{2}O subsequently reaction with \(o\)-toluene sulfonamide (OTSA) in presence of 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (DMAPEC) and DMAP furnished zafirlukast \textbf{4}. Matassa \textit{et al}\textsuperscript{3} also reported similar procedure for the synthesis of Zafirlukast \textbf{4}.

Gutman \textit{et al}\textsuperscript{4} reported process for synthesis of zafirlukast \textbf{4} commenced with hydrolysis of \textbf{125} as depicted in Scheme 5.2. Basic hydrolysis of \textbf{125} using NaOH provided \textbf{126} in the form of sodium salt, which was converted into acid \textbf{127} by treating \textbf{126} in aqueous HCl. Simultaneous \(N\)-methylation and methyl esterification of acid \textbf{127} using dimethyl sulfate followed by reduction of nitro compound \textbf{57} in presence of 10\% Pd/C provided amine \textbf{58}. The resulted \textbf{58} was reacted with cyclopentyl chloroformate to obtain cyclopentyl carbamate \textbf{59}, which was subjected to hydrolysis under basic conditions (NaOH) to obtain acid compound in the form of its sodium salt \textbf{128}. Thus obtained \textbf{128}
was isolated and further treated with HCl to get acid 60. Reaction of 60 with OTSA in presence of DMAPEC and DMAP furnished Zafirlukast 4.

Claire and co-workers have reported an alternate synthesis for preparation of 4, which starts with hydrolysis of ester 57 as described in Scheme 5.3. Hydrolysis of 57 in presence of hydrochloric acid provided acid 129, which was converted into acid chloride 130 by treating with thionyl chloride followed by reacted with o-toluene sulfonamide in presence of DMAP to obtain amide 131. Thus obtained amide 131 was
subjected to reduction using Pd/C followed by reacted with cyclopentyl chloroformate to obtain Zafirlukast 4.

Scheme 5.3: Synthesis of zafirlukast 4

Keesari et al\textsuperscript{6} have reported synthesis of 4 from benzoic acid derivative 133 and N-methyl nitro indole 56 as described in Scheme 5.4. Reaction of 133 with 56 in presence of ZnBr\textsubscript{2} offered nitro acid 129, which was hydrogenated using Raney nickel to obtain amine 134. The resulted amine 134 was treated with OTSA in presence DCC as coupling agent followed by reaction with cyclopentyl chloroformate in presence of NMM furnished zafirlukast 4.
Scheme 5.4: Synthesis of zafirlukast

The reported synthetic routes for preparation of zafirlukast have certain disadvantages, (i) possibility for formation of N-alkylated by-products are high when unprotected indole compound was used for the condensation reaction (synthetic routes 5.1, 5.2 and 5.3), (ii) selectivity of alkylation at C-3 position depends on the substituents on indole nitrogen atom. Usage of unsubstituted indole for condensation reaction leads to formation of C-2 alkylated by product rather than alkylation at C-3 position, (iii) formation of amide linkage via acid chloride is not suitable for commercial level since acid chloride intermediate is non solid, unstable and moister sensitive intermediates (scheme 5.3), (iv) preparation of sulfonamide 135 via DCC mediated coupling reaction
leads to formation of dimer compounds because unprotected primary amine \textbf{134} underwent intermolecular coupling with acid group and (v) removal of dicyclohexyl urea (obtained as by product in DCC mediated coupling reactions) from the sulfonamide compounds needed purification, which makes process expensive.

Apart from these drawbacks, the reported synthetic processes for preparation of zafirlukast \textbf{4} involves usage of commercially unsafe reagents, such as sodium hydride, acetyl chloride, \textbf{Br}_2, \textbf{CH}_3\textbf{I} and hydrazine hydrate, expensive reagents palladium carbon, 1-[3-(dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride (DMAPEC) and usage of column chromatography techniques purifications of crude compounds.

\section*{5. 1.3 PRESENT WORK}

\subsection*{5. 1.3.1 OBJECTIVE}

The drawbacks associated with the reported processes motivated us to develop an efficient, cost-effective and large-scale process for the synthesis of zafirlukast. As per retro-synthetic path way, synthesis of zafirlukast involves majorly four reactions (Figure 5.1).

(i) Sulfonamide linkage.

(ii) Carbamate linkage.

(iii) C-C bond formation.

(iv) \textit{N}-Methylation.
All the raw materials resulted from retero-synthetic pathway are commercially available.

5.1.3.2 RESULT AND DISCUSSION

In this context, an improved synthetic approach (scheme 2.5) for preparation of 4 has been designed, which commenced with the esterification of commercially available benzoic acid 53. The major drawback associated with the esterification reaction is longer reaction time (about 36 hours). At our end after screening the key reaction parameters, reaction time was significantly reduced to 3 hours from 36 hours by replacing the earlier reported acetyl chloride\(^2\) with thiony chloride. This modification is allowed us to isolate ester 54 with about 98% yield and more than 99 % of purity. Further, workup and isolation process was simplified by quenching the reaction mixture with water.
Modification of solvent system (chloroform with cyclohexane) in subsequent allylic bromination reaction is avoided the tedious workup process. Targeted bromo compound 55 was isolated with about 85% yield and more than 99% purity by adopted simple crystallization at lower temperature (about 4 °C). In addition to the above modifications both esterfication reaction and allylic bromination reactions were performed in one pot.

To enhance the selectivity at indole C-3 position and to reduce the formation of N-alkylated by products, N-Methyl indole 56 was chosen for condensation reaction at indole C-3 position. N-Methyl indole 56 was synthesized with about 99.0 % yield and more than 99.5 % purity by reacting 5-nitroindole 124 with dimethyl sulfate (DMS) in presence of NaOH and DMF, where as similar reaction was performed earlier using expensive catalysts and reagents such as DABCO, CH$_3$I and (CH$_3$)$_2$CO$_3$ at elevated temperature (90 °C).$^7$

Expensive reagents like Ag$_2$CO$_3$, ZnBr$_2$ and Ag$_2$O are previously used$^{2-6}$ for the reaction of N-methyl indole 56 and bromo compound 55. In order to improve the process efficiency and to reduce the manufacturing cost, commercially available and less expensive reagents such as Cu$_2$O, CuCl, ZnO, AlCl$_3$ and Al$_2$O$_3$ are examined along with the reported reagents for synthesis of 57.

**Table 5.1:** Alkylation of compound 56 using different reagents
Experimental results are indicated that lower amount of dialkylated (C-2 and C-3) compound 136 (figure 5.4) and better yield and purity was observed in Cu$_2$O (Table 5.1, entry 7) when compared with other reagents.

\[ \text{136} \]

**Figure 5.2:** Chemical structures of 136

The resulted crude compound 57 was subjected to purification for removal of the related substances. Various purification techniques and different solvents were screened for the purification of 57, but did not
succeed. Hence it was decided to proceed to subsequent stage rather than the purification of crude compound \(57\). In subsequent step, previously reported expensive and pyrophoric reducing reagents like Raney nickel and Pd/C for reduction of \(57\) was replaced with plant-friendly and low toxic reducing agent sodium dithionite.

\[
\text{Scheme 5.5: Improved synthesis of zafirlukast}
\]

The resulted amine \(58\) was subjected to purification for elimination of related compounds. After screening the various
purification techniques, purity of the 58 was significantly improved (more than 99.5%) by converting crude compound 58 as its HCl salt. Having developed advantageous process for synthesis of 58, our focus was moved towards subsequent reactions. Reaction of amine 58 with cyclopentyl chloroformate using N-Methyl morpholine as base in toluene medium afforded carbamate 59 with 98 % yield and about 99.7 % purity. Thereafter, 59 was converted into 60 using lithium hydroxide monohydrate as base in mixture of methanol and water with 98% yield and more than 99% of purity. These processes are advantageous over the processes reported in literature with respect to yield, cycle time and purity.

Good number of references available in literature for the condensation of acid 60 with o-toluene sulfonamide and these processes involves the usage dicyclo carbodiimide (DCC) as coupling agent. Usage of DCC as coupling reagent for formation of amide linkage facilitates formation of dicyclohexylurea (DCU) as by-product. As per the ICH guidelines limit of DCU in final drug compound is less than or equivalent to 0.1%. To meet the regulatory requirement, DCU present in crude zafirlukast 4 need to be removed by employing purification. Multiple purifications lead to loss of yield and this makes process expensive. In view of this, DCC is replaced with non toxic and commercially available coupling reagent propylphosphonic anhydride also known as T3P®. By-products obtained during the T3P mediated
amide formation are water soluble and these can be removed with simple water washings. By implement all the process improvements, zafirlukast was obtained with more than 99.5% purity and all other known and unknown impurities are less than 0.1%.

An improved synthetic method depicted in Scheme 5.5 for the preparation of Zafirlukast 4 has certain advantages over the earlier reported processes that are mentioned below.

(i) Time cycle for esterification reaction was reduced from 36 hours to 3 hours.

(ii) Tedious work-up processes were avoided.

(iii) Formation of N-alkylated by products was controlled by using N-methyl indole 56 as starting material for alkylation reaction.

(iv) Formation of dialkylated compound 136 during alkylation reaction is significantly reduced to below 4.0%.

(v) Expensive and pyrophoric reducing reagents like Raney nickel and Pd/C are replaced with plant-friendly and low toxic reducing agent like sodium dithionite.

(vi) Purifications for removal of DCU (obtained as by-product in DCC mediated coupling reactions) in crude Zafirlukast 4 is avoided using commercially available less toxic coupling reagent T₃P® instead of DCC.

(vii) Usage of toxic reagents like bromine and acetyl chloride is avoided.
5. 1. 4 CONCLUSION

In conclusion, an efficient, robust and large scale manufacturing process for zafirlukast 4 was developed. The product obtained by this process fulfills all the regulatory needs.

5. 1. 5 EXPERIMENTAL SECTION

5. 1. 5.1 Process description

5. 1.5.1.1 Methyl 4-bromomethyl-3-methoxybenzoate (55)

\[
\begin{align*}
\text{Br} & \quad \text{OCH}_3 \\
\quad & \quad \text{OCH}_3
\end{align*}
\]

Thionyl chloride (50 mL, 0.689 mol) was slowly added to the stirring solution of acid 53 (100 g, 0.602 mol) & methanol (150 mL). Reaction mass was heated to 60 °C and stirred at same temperature for 3 hours, quenched with precooled water at below 15 °C. Separated solid was filtered, washed with 10 % aqueous Na\textsubscript{2}CO\textsubscript{3} solution (200 mL) to afford 108 g of ester compound 54. To the stirring solution of ester 54 in cyclohexane (600 mL), DBDMH (80 g, 0.28 mol) and AIBN (0.6 g, 3.6 mmol) were charged and the resultant reaction mixture was heated to 80 °C and stirred for 4 hours. AIBN (0.1 g, 0.601 mmol) and DBDMH (20 g, 0.072 mol) charged into reaction mixture at ambient temperature then heated to 80 °C and stirred for 2 hours. Reaction mass was quenched with water (400 mL) at 55 °C and stirred for 45–60 min. Organic phase
and aqueous phase was separated at about 55 °C, organic phase was
cooled to 10 °C and stirred at same temperature for 1 hour. The
separated solid was collected by filtration, washed with cyclohexane (50
mL) and dried under reduced pressure 50 °C for 4 hours to give 84 %
(130 g) of title compound 55 with 99.1 % purity.

**IR (KBr, cm⁻¹):** 2951 (Ali, CH), 1717 (ester, C=O), 1276 (Ether, C-O-C).

**¹H NMR (200 MHz, CDCl₃):** δ 7.60 (d, 1H, Ar-H), 7.54 (s, 1H, Ar-H),
7.39 (d, 1H, Ar-H), 4.55 (s, 2H, CH₂), 3.95 (s, 3H, CH₃), 3.92 (s, 3H,
CH₃).

**MS (m/z):** 283.2 (M⁺ + Na).

5. 1.5.1. 2 1-Methyl-5-nitro-1H-indole (56)

Dimethyl sulfate (91 g, 0.722 mol) was slowly added to the
suspension of NaOH (52 g, 1.3 mol), DMF (400 mL) and indole
compound 124 (100 g, 0.617 mol) and stirred at 28 °C for 4 hours.
Water (1.0 L) was added to the reaction mass and stirred for 1 hour. The
separated solid was filtered, washed with water (500 mL) and dried
under reduced pressure at 55 °C for 4 hours to afford 99 % of title
compound 56 with 99.6 % purity.

**IR (KBr, cm⁻¹):** 1579 & 1397 (NO₂, asym. and sym.).
**1H NMR (200 MHz, CDCl₃):** δ 8.56 (d, 1H, Ar-H), 8.10 (dd, 1H, Ar-H), 7.32 (d, 1H, Ar-H), 7.20 (d, 1H, Ar-H), 6.66 (dd, 1H, Ar-H), 3.85 (s, 3H, CH₃).

**MS (m/z):** 177.0 (M⁺ + H).

5. 1.5.1. 3 Methyl 3-methoxy-4-(1-methyl-5-nitro-1H-indol-3-yl methyl) benzoate (57)

A suspension of bromo derivative 55 (95.5 g, 0.368 mol), N-methyl indole compound 56 (50 g, 0.284 mol), Cu₂O (12.2 g, 0.853 mol) and 1,4-dioxane (350 mL) was heated to 95 °C and stirred at same temperature for 27 hours. Thus obtained reaction mass was filtered through celite bed and washed with 1, 4-dioxane (100 mL). Solvent from the filtrate was evaporated, methanol (450 mL) and ethyl acetate (50 mL) was added. The resultant reaction mixture was heated to 65 °C and stirred for 1 hour, then cooled to ambient temperature and stirred for 4 hours. The separated solid was collected by filtration and dried at 55 °C to give 85 % of title compound 57 with 85 % purity.

**IR (KBr, cm⁻¹):** 2949 (Ali, CH), 1709 (ester, C=O), 1579 & 1324 (asym. and sym., NO₂), 1291 (ether, C-O-C).
\(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 6.9-8.6 (m, 1H, Ar-H), 3.98 (s, 3H, CH\(_3\)), 3.94 (s, 3H, CH\(_3\)) and 3.80 (s, 2H, CH\(_2\)).

**MS** (\(m/z\)): 377 (M\(^+\) + Na).

5. 1.5.1.4 Methyl 4-((5-amino-1-methyl-1\textit{H}-indole-3-yl-methyl)-3-methoxybenzoate (58)

\[
\text{To the stirring suspension of compound 57 (100 g, 0.282 mol),}
\]
dichloromethane (500 mL), triethylamine (78.7 mL, 0.565 mol) and sodium dithionite (98.3 g, 0.565 mol) was added slowly water (100 mL) at 28 °C and stirred for 4 hours. Thus obtained reaction mass was acidified with 50% aqueous hydrochloride solution (100 mL) at 27 °C and stirred for 45 minutes. The separated compound was filtered and washed with water (50 mL). Wet compound, water (500 mL) and dichloromethane (500 mL) was stirred at 28 °C for 4 hours. The obtained solid was filtered, water (500 mL) was added to the resulted wet compound and pH of the reaction mixture was adjusted to 7-8 with 10% Na\(_2\)CO\(_3\) solution. The precipitated solid was filtered to give 44 % of title compound 58 with 99.5 % HPLC purity.
**IR (KBr, cm\(^{-1}\))**: 3442 & 3360 (Amine, NH\(_2\)), 2937 (Ali, CH), 1703 (ester, C=O), 1297 (ether, C-O-C).

**\(^1\)H NMR (200 MHz, CDCl\(_3\))**: δ 6.7–7.50 (m, 7H, Ar-H) 4.07 (s, 2H, CH\(_2\)), 3.93 (s, 3H, CH\(_3\)), 3.90 (s, 3H, CH\(_3\)), 3.66 (s, 3H, CH\(_3\)).

**MS (m/z)**: 325 (M\(^+\) + H).

### 5. 1.5.1.5 4-(5-Cyclopentyloxycarbonylamino-1-methyl-1H-indol-3-yl methyl)-3-methoxybenzoic acid methyl ester (59)

![Chemical Structure](image.png)

To a stirring solution of amine 58 (70 g, 0.216 mol), toluene (350 mL) and N-methyl morpholine (27 g, 0.267 mol) was slowly added cyclopentyl chloroformate (50 g, 0.337 mol) at ambient temperature and stirred at same temperature for 1 hour. Solvent from the resulted reaction mixture was evaporated completely, methanol (350 mL) was charged to the obtained crude and stirred for 30 minutes. Separated solid was filtered, washed with methanol (70 mL) and dried at 55 °C for 3 hours to afford 98 % of title compound with more than 99.6 % purity.

**IR (KBr, cm\(^{-1}\))**: 3247 (amine, NH), 1719 (ester, C=O), 1692 (carbamate, C=O), 1232 (ether, C-O-C).
$^1$H NMR (400 MHz, DMSO–$d_6$): $\delta$ 9.18 (bs, 1H, NH), 7.0-7.60 (s, 7H, Ar-H) 5.0−5.1 (m, 1H, CH), 4.0 (s, 2H, CH$_2$), 3.9 (s, 3H, CH$_3$), 3.8 (s, 3H, CH$_3$), 3.7 (s, 3H, CH$_3$), 1.6−1.9 (m, 8H, CH$_2$).

MS (m/z): 437.4 ($M^+ + H$).

5. 1.5.1.6 [4-(5-Cyclopentyloxycarbonylmethyl-1-methyl-1H-indol-3-ylmethyl)-3-methoxybenzoic acid (60)]

Mixture of carbamate compound 59 (50 g, 0.115 mol), methanol (300 mL), LiOH.H$_2$O (7.5 g, 0.178 mol) and water (75 mL) was heated to 65 °C and the stirred at same temperature for 2 hours. The resulted reaction mass pH was adjusted to 1.0-2.0 with diluted hydrochloric acid at 28 °C and stirred for 2 hours. Separated solid was filtered, washed with water (100 mL) and dried under reduced pressure at 75 °C to provide 98 % of title compound 60 with more than 99 % of purity.

IR (KBr, cm$^{-1}$): 3288 (amine, NH), 2957 (hydroxyl, OH), 1696 (acid, C=O), 1646 (carbamate, C=O), 1264 (ether, C-O-C).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.63 (s, 1H), 7.1−7.6 (m, 7H, Ar-H), 6.8 (s, 1H, CH), 5.1−5.2 (m, 1H, CH), 4.1 (s, 2H, CH$_2$), 3.9 (s, 3H, CH$_3$), 3.7 (s, 3H, CH$_3$), 1.6−1.9 (m, 8H, CH$_2$).
MS (m/z): 423.3 (M⁺ + H).

5.1.5.1.7 \{3-[2-Methoxy-4-(toluene-2-sulfonylaminocarbonyl) benzyl]-1-methyl-1H-indol-5-yl\} acetic acid cyclopentyl ester (4)

Propylphosphonic anhydride in dichloromethane solution (170 mL, 0.355 mol) was slowly added to the stirring suspension of compound 60 (50 g, 0.118 mol), diisopropyl ethylamine (41.3 mL, 0.236 mol), o-toluene sulfonamide (24.2 g, 0.141 mol) and dichloromethane (400 mL) at 28 °C and stirred at same temperature for 4 hours. The resultant reaction mixture was quenched with water (500 mL), organic phase and aqueous phase was separated. Solvent from organic phase was evaporated; acetonitrile (200 mL) was added to the crude compound and stirred at 27 °C for 45 minutes. Separated solid was filtered, washed with methanol (50 mL) and dried under reduced pressure at 75 °C to afford 85 % of crude 4. Suspension of crude zafirlukast (20 g), silica gel (40 g) and DCM (300 mL) were stirred at ambient temperature for 1 hour and filtered the reaction mixture. Filtrate solvent was evaporated, acetonitrile (240 mL) charged into crude compound and stirred at 80 °C for 45 minutes. The resultant reaction mass was cooled
to 28 °C and stirred at same temperature for 45 minutes. Separated solid was filtered, washed with acetonitrile (60 mL) and dried under reduced pressure at 75 °C to afford pure zafirlukast with more than 99.5% purity.

**IR (KBr, cm⁻¹):** 3371 (amine, NH), 2960 (Ali, CH), 1690 (amide, C=O), 1340 & 1162 (asym. and sym, SO₂).

**¹H NMR (400 MHz, CDCl₃):** δ 9.35 (br, 1H), 7.0-8.2 (m, 11H, Ar-H), 6.7 (s, 1H), 6.5 (s, 1H), 5.1-5.2 (m, 1H), 4.00 (s, 2H, CH₂), 3.8 (s, 3H, CH₃), 3.68 (s, 3H, CH₃), 2.7 (s, 3H, CH₃), 1.5-1.9 (m, 8H, CH₂).

**¹³C NMR (100 MHz, CDCl₃):** δC 20.0, 23.4, 23.4, 24.8, 32.3, 32.5, 55.2, 77.5, 109.1, 109.4, 109.7, 111.7, 115.2, 119.8, 126.0, 127.7, 128.0, 129.4, 129.7, 131.1, 132.1, 133.5, 134.0, 136.0, 136.7, 137.4, 154.3, 157.1, 164.8.

**MS (m/z):** 576 (M⁺ + H).
5.7 REFERENCES


SUMMARY & CONCLUSIONS

CHAPTER-1

We have described importance of: (i) novel anti-diabetic agent pioglitazone hydrochloride 1 (ii) anti-anginal drug Ranolazine 2, (iii) anti-thrombotic drug clopidogrel bisulfate 3 (iv) anti-asthma drug zafirlukast 4 and PDE5 inhibitor tadalafil 5. We further discussed significance of impurity profile (Related substances) in the process development.

CHAPTER-2

An efficient, new and robust synthetic method (two alternative routes) for the preparation of pioglitazone 1 is developed and these are more compatible on commercial scale. Our new synthetic methods to 1 are schematically described in Scheme 1 and scheme 2.

Scheme-1:
Possible potential impurities generated during the synthesis of pioglitazone 1 and its key intermediate 11 are identified, synthesized and controlled in pioglitazone 1. Structures of these impurities are depicted in Figure 1.
CHAPTER-3

An efficient, commercially viable and greener process for the synthesis of ranolazine 2 has been disclosed in this chapter. Additionally, comprehensive study on impurity profile of crude ranolazine and its key intermediates including identification, synthesis and characterization is presented in this chapter.

Synthesis of ranolazine 2 started from the commercially available starting materials 2, 6-dimethyl aniline 20 and 2-methoxy phenol 25 as described in Scheme 3.

Scheme-3:

Based on the molecular weight obtained from LC-MS data, reaction conditions and reagents/reactants used for reactions, impurities generated during synthesis of 2 and its key intermediates (Figure 2) were identified and characterized with spectral data. All these
impurities were controlled to below 0.05% level in final ranolazine 2 and root causes for the formation of these impurities were discussed.

**Figure 2:**

![Chemical structures](image)

**CHAPTER-4**

Whilst there are many synthetic routes to clopidogrel bisulfate 3, we focused on two which have potential for industrial manufacturing with some limitations that are addressed in this chapter. Our efficient and large scale processes to 3 are described in Scheme 4 and Scheme 5.
Additionally, two unknown impurities generated during the synthesis of **3** were identified, synthesized and characterized by spectral data. Further, synthetic process for the preparation of the three USP listed impurities along with the two new impurities (Figure 3) is presented in this chapter.
CHAPTER-5

This chapter divided into two parts. In the first part (part-A) an improved process for the synthesis for zafirlukast 4 is described. In the second part (part B) an alternative synthetic approach for the preparation of PDE5 inhibitor tadalafil 5 is presented.

**Part A:**

An improved process for the synthesis of zafirlukast 4 is developed. This process is commenced with the commercially available key raw material 3-methoxy-4-methyl benzoic acid 53 and N-methyl 5-nitro indole 56 as described in Scheme 6. Usage of expensive and pyrophoric reducing reagents like Raney nickel and Pd/C are replaced with plant-friendly and low toxic reducing agent like sodium dithionite. Purifications for removal of DCU (obtained as by-product in DCC mediated coupling reactions) in crude Zafirlukast 4 is avoided using commercially available less toxic coupling reagent T₃P® instead of DCC.
Part B:

An alternative synthesis of tadalafil 5 starts with the coupling of commercially available amino acid, D-tryptophan 61 and piperonal 62. Coupling of D-tryptophan 61 with piperonal 62 under Pictet–Spengler reaction conditions furnished \( \beta \)-carboline derivative 63 with the diastereomeric mixture ratio 70(cis):30(trans), which was treated with aqueous hydrochloric acid to get optically pure \( \beta \)-carboline derivative 64.
Diimidation of 64 with sarcosine ethyl ester hydrochloride under DCC and HOBr conditions provided tadalafil 5 (scheme 7).

Scheme-7:


2. An efficient synthesis of 1-(2-methoxyphenoxy)-2, 3-epoxypropane: Key intermediate of β-blockers.


*Synthetic communications*, 2008, 38, 4265-4271

4. An efficient and large scale synthesis of Clopidogrel: Antiplatelet drug
5. An efficient and greener synthesis of Zafirlukast: Anti Asthma drug.


*Manuscript is ready for communication*

6. An efficient and high-yielding synthesis of Ranolazine: Antianginal drug


*Presented in National seminar on recent advances in heterocyclic chemistry (NSRACH 2011) organized by department of chemistry, JNTUH college of engineering during November 4th and 5th, 2011.*

7. An efficient and large scale synthesis of Clopidogrel: Antiplatelet drug


*Presented in National seminar on recent research trends in chemical sciences (RRTCS 2011) held on 23rd December, 2011 at Sri Venkateswara University, Tirupati.*