ABSTRACT

Thesis entitled “SYNTHESIS AND CHARACTERIZATION OF SOME ACTIVE PHARMACEUTICAL INDOLE DERIVATIVES AND THEIR ANALOGS” has been presented as five chapters.

Chapter-1 deals with the general introduction and biological importance of indole derivatives and fused indole derivatives. Also presents, a brief introduction to process development, importance of impurity profile (Related substances) and polymorphic studies in the process development. Chapter-2 comprises process development of zafirlukast, an anti-asthma drug, preparation of stable amorphous and new acetonitrile solvate polymorph. Chapter-3 deals with a complete impurity profile of zafirlukast including identification, synthesis, characterization and root cause of their formation. Chapter-4 explains the synthesis and characterization of new zafirlukast related analogs. Chapter-5 presents an alternative synthesis of tadalafil from D-tryptophan and sarcosine ethyl ester. Described the impurity profile of two commercial viable schemes with the identification, synthesis, characterization and root cause of their formation.

Chapter-1: Introduction to process development of APIs and a brief review on indole and fused indole derivatives

In this chapter introduction and biological importance of indole derivatives and fused indole derivatives were described. Also, a brief
introduction to the process development, importance of impurity profile and polymorphic studies in the process development was presented.

**Chapter-2: An improved process for the preparation of Zafirlukast-an anti asthma drug**

Zafirlukast (1) is a selective and competitive oral leukotriene receptor antagonist (LTRA) marketed under the brand name accolate.

![Figure 1: Zafirlukast 1](image)

Figure 1: Zafirlukast 1

Explains the improved synthesis for zafirlukast from 3-methoxy-4-methyl benzoicacid 2 (scheme 1). Esterification of acid 2 in the presence of thionyl chloride in methanol produced ester 3, which was subjected to benzylic bromination under DBDMH and AIBN in cyclohexane to provide bromo derivative 4.

*N*-Methylation of 5-nitroindole 5 using dimethylsulfate (DMS) as a methylating agent in the presence of sodium hydroxide in dimethyl formamide (DMF) medium under very mild reaction conditions, furnished compound 6 in 99.0 % yield and more than 99.5 % purity by HPLC.
Scheme 1: Improved synthesis of zafirlukast 1

C-Alkylation of indole derivative 6 with bromo compound 4 was achieved by using cuprous oxide in 1,4-dioxane to afford nitro compound 7.
Compound 7 was converted to amine 8 in the presence of Raney nickel, further it was converted to carbamate 9 by using cyclopentyl chloroformate (CPC) and N-methylmorpholine (NMM). Alkaline hydrolysis of ester 9 with lithium hydroxide provided acid 10, which was subjected to amidation with OTSA (ortho-toluene sulfonamide) by utilizing simple amide coupling reagents DCC/DMAP in dichloromethane (DCM) to furnish zafirlukast 1. Pure zafirlukast was isolated in acetonitrile medium, after treating the solution of zafirlukast in dichloromethane with silica gel.

Amorphous polymorph was prepared by solvent evaporation technique from solution of zafirlukast in dichloromethane. The obtained zafirlukast amorphous was meeting all the regulatory requirements. Spectral data of final compound was found to be in complete agreement with the reported data.

**Chapter-3: Identification, Synthesis and Characterization of Related Substances of Zafirlukast**

In the previous chapter an improved process is described. Our continued interest in the development of active pharmaceutical indole derivatives let us to undertake the impurity profile study of zafirlukast. In this chapter complete impurity profile study of zafirlukast including, identification, synthesis, characterization and route cause of their formation is described. The following impurities (figure 2) were identified during the process development of zafirlukast.
Figure 2: Structures of zafirlukast impurities

All the impurities were prepared and characterized by spectral data and confirmed by co-injection with zafirlukast samples.
**Chapter-4: Synthesis and Characterization of Zafirlukast analogs**

Indole derivatives have attracted enormous interest due to their diverse biological activities. However, since the isolation of indole alkaloids, these derivatives have been explored for their potential application as antibiotics, anti-inflammatory, anti-hypertensive and antitumor agents.

Herein, we describe the design and synthesis of four new series of zafirlukast analogs (figure 3). First series of analogs were prepared by modifying the substitution on indole amine group and amide group.

Second series of analogs were prepared from main core of des N-methyl zafirlukast by modification of sulfonamide substitution. Acid moiety is common for third (DCU) and fourth (dimer) series of analogs. Dimer and DCU analogs were prepared from suitably protected acid with different amines and DCC respectively.
All the synthesized zafirlukast analogs were characterized by mass, IR and NMR spectral data.

**Figure 3:** Structures of zafirlukast analogs, 19a-y, 20a-e, 21a-c & 22a-c
Chapter-5: An alternative synthesis of tadalafil – PDE-5 inhibitor, identification, synthesis and characterization of its related substances

Tadalafil 23 (figure 4) is used for the treatment of erectile dysfunction. Some other drugs are also available in this area are sildenafil and verdanafil.

![Tadalafil 23](image)

Figure 4: Tadalafil 23

An alternative synthesis of tadalafil is disclosed along with impurity profile study of two different commercially viable routes are presented in this chapter.

An alternative synthesis of tadalafil commenced from D-tryptophan 24. Pictet–Spengler coupling reaction of 24 with piperonal 25 was achieved under acidic conditions to yield chiral pure 27. Coupling of compound 27 with sarcosine ethyl ester hydrochloride under DCC and HOBT conditions provided tadalafil 23 (scheme 2).
Scheme 2: Alternative synthesis of tadalafil 23

To study the impurity profile of alternative synthesis of tadalafil (prepared from scheme 2) were analyzed by HPLC and LC–MS and tentative structures were proposed (figure 5) the based on the mass data for the impurities.

Figure 5: Potential related substances in tadalafil from scheme 2
In the second scheme, Daugan and co-workers reported the Pictet-Spengler coupling of D-tryptophan methyl ester hydrochloride 28 with 25 followed by cyclization in the presence of trifluoroacetic acid (TFA) in isopropylalcohol (IPA) produced chiral pure 29. N-Acylation of 29 with chloroacetylchloride resulted in amide 30, which upon treatment with methyl amine yielded tadalafil 23 (scheme 3).

Scheme 3: Synthesis of tadalafil 23 using chloroacetylchloride

To study the impurity profile of tadalafil in product patent route (prepared from scheme 3) were analyzed by HPLC and LC–MS. The following tentative structures were proposed (figure 6) the based on the mass data for the impurities.
Apart from process impurities described above, metabolite 36 (figure 7) also synthesized and characterized.

All the impurities were synthesized by using well known reactions and characterized by $^1$H NMR, $^{13}$C NMR, mass and IR spectral data.
Summary and conclusions

In summary, highly efficient cost effective, eco-friendly, improved and scalable process for anti asthma drug zafirlukast and amorphous, new acetonitrile solvate polymorphs has been developed. An alternative synthesis of a PDE-5 inhibitor tadalafil also described. Complete impurity profile study of both the drugs was established and all the identified impurities were synthesized and characterized by spectral analysis. Additionally, four new series of zafirlukast analogs were also synthesized and characterized.