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ABSTRACT OF THE THESIS

The thesis entitled “Synthesis and characterization of Novel Anti-Lipidemic Agents; Studies in the synthesis of Montelukast, Olanzapine and Diltiazem” is divided into five chapters.

This program supports research aimed at the design and development of novel anti-lipidemic agents and studies in the synthetic approaches for the known APIs i.e., Montelukast, Olanzapine and Diltiazem that are suitable for industrial application. Therefore, the present thesis work is oriented towards both academic research and industrial research.

CHAPTER-1:

Chapter-1 deals with the introduction and pharmacological importance of: (i) novel anti-lipidemic agents; (ii) anti-asthmatic drug Montelukast sodium (with worldwide sales of ~ 6496.2 million US dollars and a worldwide consumption of 27,441.5 kgs by June 2011); (iii) anti-psychotic drug Olanzapine (with worldwide sales of ~ 6545.9 million US dollars and a worldwide consumption of 10,774.3 kgs by June 2011); and (iv) anti-hypertensive drug Diltiazem hydrochloride (with worldwide sales of ~ 1186.8 million US dollars and a worldwide consumption of 408,931.9 kgs by June 2011) (Source for worldwide sales & consumption: Newport Premium database by Thomson Reuters).
CHAPTER-2:

Chapter-2 deals with synthesis and characterizaion of novel anti-lipidemic agents.

In view of the importance of hydrophilicity of statins, it is hypothesized that introduction of more hydrophilic scaffolds into the statin compounds by linking the pharmacophore ‘dihydroxy heptanoic acid moiety’ with more hydrophilic scaffolds result in compounds, which may act as better anti-lipidemic agents especially as HMG-CoA reductase inhibitors. Such introduction of hydrophilic scaffolds may improve the level of hepato selectivity and expected to reduce the risk of adverse effects such as diarrhoea, abdominal pain, constipation, flatulence etc.

The starting point for the synthesis of novel anti-lipidemic agents of the present work is tert-butyl 2-((4S,6S)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (1), which is a key intermediate of the statin drug Atorvastatin, which contains the derivatized ‘dihydroxy heptanoic acid moiety’. To this, relatively polar scaffolds are embedded when compared to most of the existing statins in order to act as more hydrophilic groups towards the objective of the present work (Scheme-2.1).
Scheme-2.1:

(R = Isobutyryl, Acetyl, Benzoyl, Benzyl and 4-methyl benzyl)

(i) IPA, reflux; (ii) TEA, 70°C; (iii) CDI, 4-DMAP, THF, room temperature; (iv) Aq. MeNH₂, MeOH, reflux; (v) acyl anhydride or alkyl halide, pyridine, room temperature; (vi) aq. HCl, acetonitrile, room temperature; (vii) aq. NaOH, acetonitrile, room temperature, 45°C.
CHAPTER-3:

This chapter deals with novel synthetic approaches for the manufacture of Montelukast sodium (25).

This chapter deals with a first novel synthetic route (scheme-3.5) via a novel ester intermediate for the preparation of Montelukast (29) and its salts. This work was published as Reguri et al.\textsuperscript{51} and Chandra et al.\textsuperscript{[ii]}

Scheme-3.5:

The present work further provides a second novel synthetic approach (Scheme-3.6) via a novel nitrile intermediate for the preparation of
Montelukast (29) and its salts. This work was published as Sundaram et al.\textsuperscript{53} and Chandra et al.\textsuperscript{[iii].}

**Scheme-3.6:**

(46) was prepared from (61) by hydrolysis with methanolic NaOH.

**Scheme-3.11:**
The chapter also deals with identification, preparation and characterization of related substances or impurities of Montelukast sodium and its intermediates in the present work.

The chapter further deals with study on polymorphism in Montelukast and its salts. Different processes for preparation of crystalline form of Montelukast acid, amorphous form of Montelukast sodium, crystalline form of (44) were studied and the resulting polymorphs were characterized by X-ray powder diffraction patterns.

**CHAPTER-4:**

The objective of this chapter is to develop an improved, scalable, cost effective and impurity controlling process for the manufacture of Olanzapine (69) that was exclusively developed with the intention to use the resulting Olanzapine API for early entry into some of the European countries (e.g., Spain) and Canada as these countries did not have valid patent protection for Olanzapine as product. In these countries, only process claims were present/valid in the respective basic patents.

Two novel synthetic approaches and an improved process for the preparation of Olanzapine (69) were presented in this work and they are schematically represented here under.
The chapter also deals with identification, preparation and characterization of related substances or impurities of Olanzapine (69) obtained in the present work.
CHAPTER-5:

This chapter deals with simplified, improved, scalable and cost effective processes for the manufacture of Diltiazem hydrochloride in view of the draw backs of the reported synthetic procedures. Therefore, the present work has an objective to develop an improved process for the preparation of Diltiazem hydrochloride (88) by modifying the conditions of the reported synthetic procedures; by replacing expensive reagents and solvents with simple and cost effective reagents, which are available commercially and are inexpensive on commercial scale; and by simplifying the steps to produce cost competitive Diltiazem hydrochloride (88) when compared to reported synthetic procedures.

First part of the work in this chapter deals with cost reduction in the process for manufacture of the key intermediate called cis-lactam (89) and the second part deals with cost reduction in the process for the manufacture of Diltiazem hydrochloride (88).

The syntthetic approaches studied as part of the present work are represented in the following schemes for Diltiazem hydrochloride (88) and its key intermediate cis-lactam (89).
Scheme-5.7:

Scheme-5.8:
Scheme-5.9:

Scheme-5.11:

The chapter also deals with identification, preparation and characterization of related substances or known impurities of Diltiazem hydrochloride.