Abstract

The thesis entitled **"Synthesis and Characterization of COX-2 Inhibitors and Carbazole Derivatives"** is divided into five chapters.

CHAPTER-1

This chapter deals with the introduction and pharmacological importance of COX-2 inhibitors (isoxazoles and pyrazoles), carbazole derivatives and importance of impurity profile study of active pharmaceutical ingredients.

CHAPTER-2

In this chapter, a novel approach for the synthesis of valdecoxib **1** is described. The synthesis involved [3+2] cycloaddition between an alternative dipolarophile **3** and the known nitrile oxide (generated *in situ* from **4**) as 1,3-dipole to produce the pyrrolidinylisoxazoline **5**, which was then converted into valdecoxib after aromatization and sulfamidation (scheme 1).

***Scheme 1*:** Novel approach for the synthesis of valdecoxib

In the synthesis of valdecoxib, five related substances were identified by a simple high performance liquid chromatographic (HPLC) method. Based on the LC–MS data and synthetic pathway, structures for related substances were proposed as shown in figure 1. These related substances were synthesized and confirmed by ^{1}H NMR, ^{13}C NMR, mass and IR spectral data. The root cause for the formation of related substances was also explained.

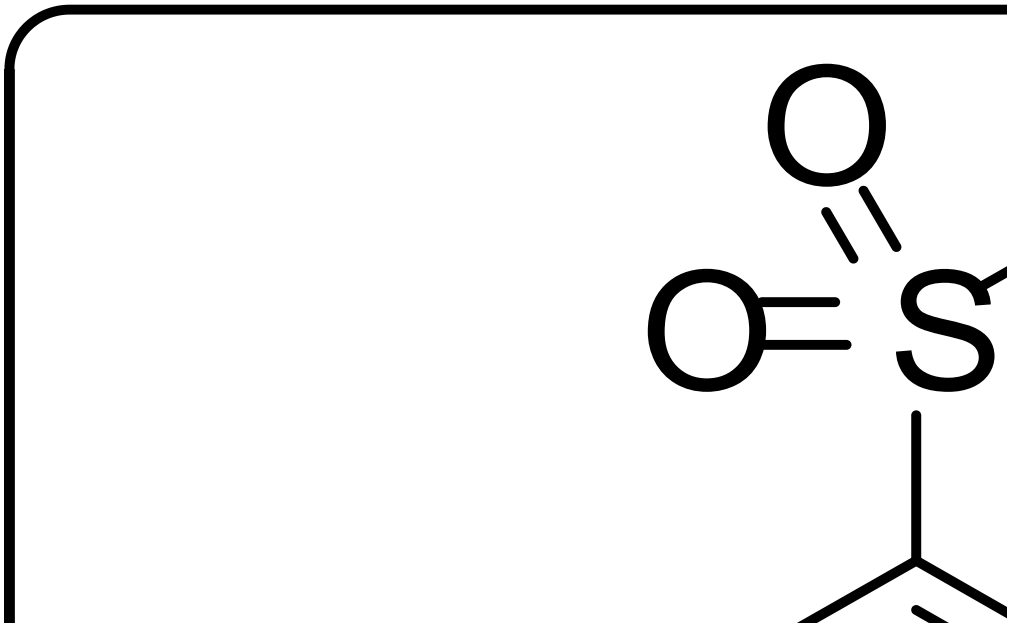


***Figure 1*:** Chemical structures for the related substances of valdecoxib

CHAPTER-3

This chapter deals with a cost effective and regulatory quality complying process for celecoxib **15**. Condensation of 4,4,4-trifluoro-1-(4-methylphenyl)butane-1,3-dione (**13**) and 4-sulphonamidophenyl hydrazine hydrochloride (**14**) in a mixture of ethyl acetate and water under reflux conditions followed by recrystallisation from toluene furnished celecoxib in 84 % overall yield with more than 99.97 % purity (scheme 2).

***Scheme 2*:** Synthesis of celecoxib

Six impurities were observed in the HPLC analysis of crude celecoxib. Out of these six impurities three were identified as known impurities (figure 2) by performing the co-injection analysis.

***Figure 2*:** Structures of known impurities **16**, **17** and **18**

The unknown impurities (figure 3) were synthesized and characterized with ^{1}H NMR, ^{13}C NMR, mass and IR.

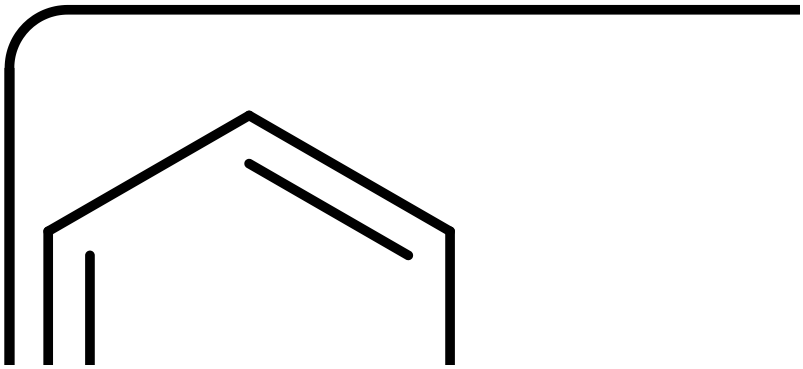


***Figure 3*:** Structures of impurities **19**, **20** and **21**

CHAPTER-4

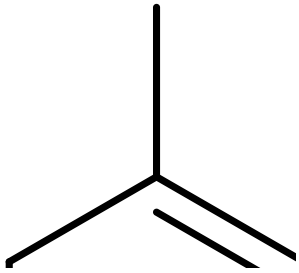
Synthesis and characterization of new carbazole based β-amino alcohols and their corresponding oxazolidine and oxazolidinone derivatives have been described in this chapter.

Synthesis of β-amino alcohols **23a–l** commenced from oxirane **22** by reacting with different amines. Synthesis of oxazolidines **24a–u** was achieved by reacting β-amino alcohols **23a–l** with different aldehydes. Oxazolidinones **25a–l** were prepared by cyclizing the corresponding β-amino alcohols **23a–l** with ethyl chloroformate (scheme 3). The oxazolidines **24a–u** and oxazolidinones **25a–l** were confirmed by ^{1}H NMR, ^{13}C NMR, mass, and IR spectral data.

Compound **a**

23, **24**, **25**

& **26**



***Scheme 3*:** Synthesis of β-amino alcohol, oxazolidine and oxazolidinone derivatives

CHAPTER-5

Abstract

In continuation to the synthesis of oxazolidine and oxazolidinone derivatives, synthesis and characterization of new carbazole based morpholine, its mono and dicarbonyl derivatives from β-amino alcohols is presented in this chapter.

Morpholine derivatives **28a–l** were synthesized efficiently from β-amino alcohols **23a–l** and 1-bromo-2-chloroethane. In the similar way morpholinones **29a–l** and morpholinediones **30a–l** were prepared by reacting the β-amino alcohols **23a–l** with chloroacetyl chloride and ethyl chlorooxoacetate, respectively (scheme 4). Based on mass, IR, ^{1}H NMR and ^{13}C NMR spectral data morpholine, morpholinones and morpholinediones were characterized.

***Scheme 4*:** Synthesis of morpholine, morpholinone and morpholinedione derivatives