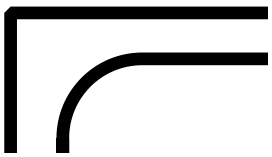


SUMMARY

The thesis entitled **"Synthesis and Characterization of COX-2 Inhibitors and Carbazole Derivatives"** had been divided into five chapters. The entire thesis work is summarized briefly as below.

CHAPTER-1: Introduction to isoxazole, pyrazole and carbazole derivatives and importance of impurity profile study in drug substances

This chapter presents the introduction to COX-2 inhibitors (isoxazoles, pyrazoles), carbazole derivatives and their therapeutic activity in different areas followed by a brief review on importance of impurity profile study in active pharmaceutical ingredients.

CHAPTER-2: Application of [3+2] cycloaddition in the synthesis of valdecoxib, synthesis and characterization of its related substances

Selective COX-2 inhibitory activity of valdecoxib had promoted us to design an efficient and novel approach for the synthesis of valdecoxib. [3+2] cycloaddition utilizing alkyne/enolate as a dipolarophile and benzonitrile oxide as a 1, 3-dipole for the preparation of valdecoxib is known in the literature. Our novel synthesis involved the [3+2] cycloaddition utilizing an alternative dipolarophile, enamine **3** and the known nitrile oxide as 1, 3-dipole. The enamine **3** underwent [3+2] cycloaddition reaction with the nitrile oxide (generated *in situ* from **4**) to produce the pyrrolidinylisoxazoline **5**. This was aromatized in presence of

aqueous HCl followed by subjecting to chlorosulfonation and amidation to afford valdecoxib **1** (scheme 1).

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

Formation of new impurities can not be ruled out, as synthesis of valdecoxib **1** involved the new synthetic route. As predicted, five related substances were found in the drug substance by a simple high performance liquid chromatographic (HPLC) method. Hence to identify and characterize these impurities, a systematic study was under taken.

In this regard LC–MS analysis was performed on valdecoxib sample and found the molecular weights of impurities as 393, 314, 314, 315 and 611. Based on the chemistry involved in the synthesis and LC–MS data, the following structures were predicted (figure 1). These impurities were

synthesized and confirmed based on ^{1}H NMR, ^{13}C NMR, mass and IR spectral data.

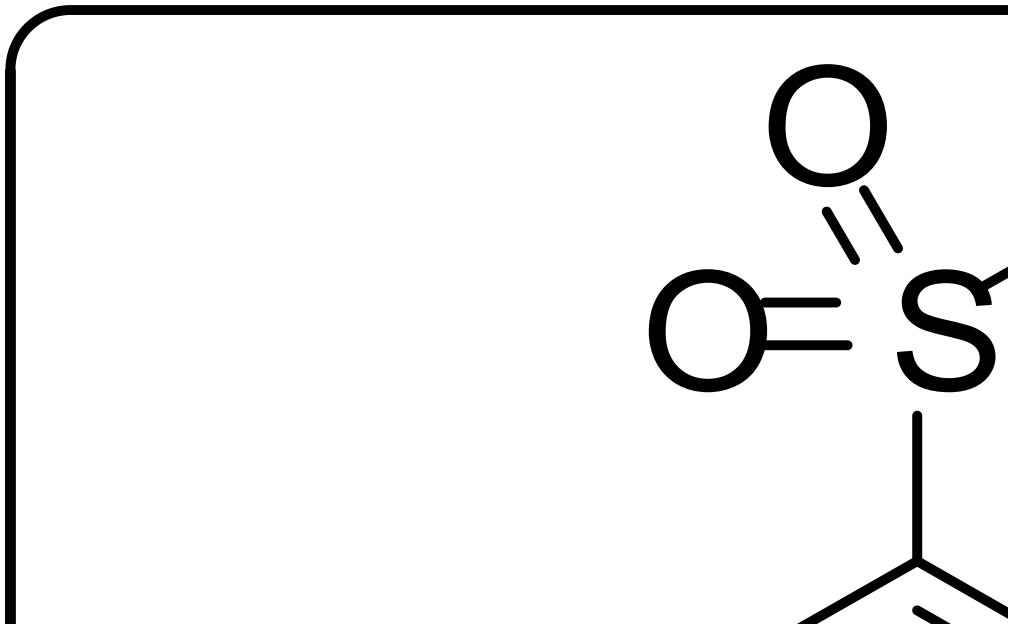


***Figure 1*:** Structures for the related substances of valdecoxib

Root cause for the formation of related substances **8**, **9**, **10**, **11** and **12** and their synthetic procedure was also described in this chapter.

<u>CHAPTER-3:</u> An improved and scalable process for celecoxib, synthesis and characterization of its related compounds

In view of importance of selective COX-2 inhibitors, another selective COX-2 inhibitor, celecoxib **15** was taken up to develop an improved, scalable and cost effective process. Many processes were reported in the literature for the preparation of celecoxib, but possess some disadvantages. To overcome these disadvantages and to have a robust

process, a systematic study was carried out. Finally celecoxib was obtained in an overall yield of 84 % and more than 99.97 % purity from the condensation of **13** and **14** in a mixture of ethyl acetate and water under reflux conditions followed by recrystallisation from toluene (scheme 2).

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

Impurities **16**, **17**, **18**, **19**, **20,** and **21** were found in the crude celecoxib. Of these six impurities, three impurities were confirmed as known impurities (figure 2) by performing co-injection with known samples in HPLC analysis.

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

In order to identify the molecular weights of unknown impurities, LC–MS analysis was performed. Surprisingly, same mass number, 303 was observed for all unknown impurities. A detailed study was carried out about the process involved for the synthesis of celecoxib and starting materials **13** and **14**. Based on the synthetic pathway and LC–MS data, the tentative structures were assigned for unknown impurities (figure 3).

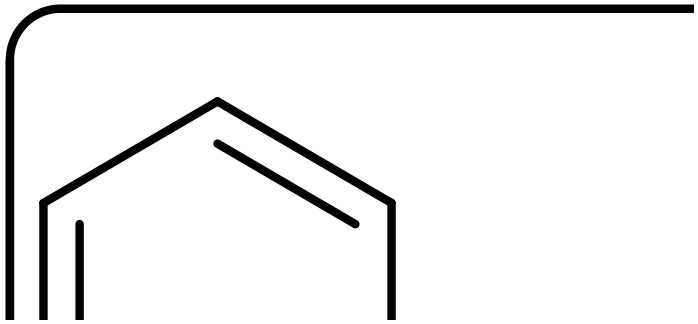


***Figure 3*:** Structures of impurities **19**, **20** and **21**

To confirm the above structures, the predicted impurities were synthesized and characterized with ^{1}H NMR, ^{13}C NMR, mass and IR spectral data. The probable root cause for the formation and process for the preparation of all impurities were furnished in this chapter.

<u>CHAPTER-4:</u> Synthesis of carbazole derived β-amino alcohols and their application in the synthesis of carbazole based oxazolidines and oxazolidinones

Carbazole derivatives having different therapeutic activities attracted us towards the synthesis of new derivatives. β-Amino alcohol derivatives, carazolol and carvedilol were basis for planning to design the new

carbazole based β-amino alcohols and corresponding oxazolidines and oxazolidinones. In view of this, a strategy for the preparation and characterization of carbazole based β-amino alcohols, oxazolidines and oxazolidinones was under taken.

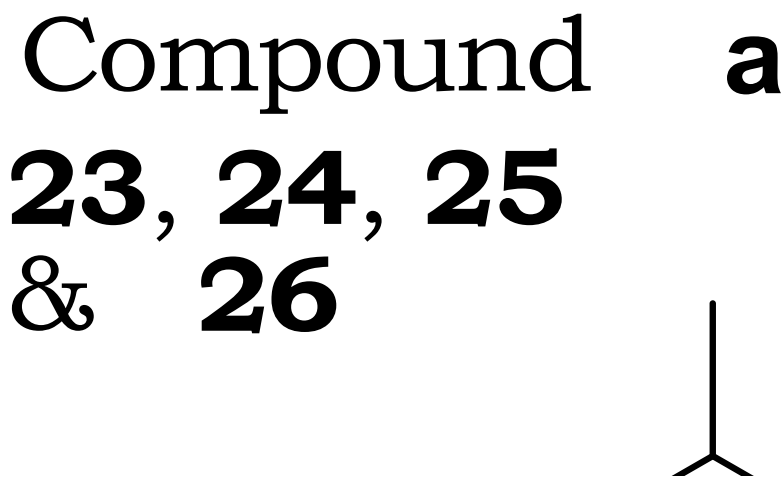
Oxirane **22** was identified as the starting material for the preparation of carbazole based β-amino alcohols **23a–l**. Reaction of oxirane **22** with different amines provided a variety of β-amino alcohol derivatives **23a–l** (scheme 3).

Having synthesized the required β-amino alcohol derivatives **23a–l**, focus shifted to cyclization of amine and hydroxyl functionalities with different one carbon source in order to synthesize the oxazolidine and oxazolidinone derivatives.

The oxazolidines **24a–u** were synthesized by reacting **23a–l** with different aldehydes in methanol at 25–35 °C (scheme 3).

Synthesis of oxazolidinones **25a–l** was achieved in two different ways (scheme 3), wherein ethyl chloroformate was the source for carbonyl function. Method-A provided **25a–l** in two step sequence. In the first step **23a–l** were reacted with ethyl chloroformate in the presence of K_2CO_3 in dichloromethane at 40 °C to furnish **26a–l**. In subsequent step, **26a–l** were cyclised in presence of K_2CO_3 in DMF at 130–140 °C to yield oxazolidinones **25a–l**.

In method-B, **25a–l** were obtained in a one-pot sequence, wherein, the compound **23a–l** was reacted with ethyl chloroformate in presence of K_2CO_3 in DMF at 130–140°C.



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

The oxazolidines **24a–u** and oxazolidinones **25a–l** were characterized

based on ^{1}H NMR, ^{13}C NMR, mass and IR spectral data.

CHAPTER-5: Synthesis and characterization of carbazole derived morpholines, morpholinones and morpholinediones

In continuation of our interest for the synthesis of new carbazole derivatives, preparation of a new class of carbazole based six membered heterocyclic compounds was planned. Literature survey revealed that carbazole based morpholines, morpholinones and morpholinediones were not known. In this regard, a strategy was designed to utilize the β-amino alcohols **23a–l** for the cyclization with suitable two carbon sources to furnish morpholines, morpholinones and morpholinediones derivatives.

The reaction between amino alcohols **23a–l** and 1-bromo-2-chloroethane in presence of potassium carbonate in DMF at 90–100 °C provided morpholines **28a–l** (scheme 4).

Morpholinone derivatives **29a–l** were furnished from **23a–l** and chloroacetyl chloride in two different ways (scheme 4).

In method-A morpholinone derivatives **29a–l** were obtained in two-step process. This included the reaction of **23a–l** and chloroacetyl chloride in presence of NaOH in dichloromethane at 0–5 °C followed by cyclisation of **27a–l** in presence of K_2CO_3 in DMF at 130–140 °C.

Where as method-B provided **29a–l** in one-pot manner (without isolation of the intermediate **27a–l**) by reacting **23a–l** with chloroacetyl chloride in presence of potassium carbonate in DMF at 130–140 °C.

Morpholinediones **30a–l** were synthesized by reacting **23a–l** with ethyl chlorooxoacetate in presence of sodium hydroxide in DCM at 0–5 °C.

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

Morpholines **28a–l**, mopholinones **29a–l** and morpholinediones **30a–l** were fully characterized by ^{1}H NMR, ^{13}C NMR, mass and IR spectral data.

CONCLUSION

In conclusion, this thesis work has contributed to the existing knowledge of heterocyclic chemistry in the following aspects.

1. A novel synthetic approach was developed for the synthesis of isoxazole derivative, valdecoxib. This approach involved a [3+2] cycloaddition between an alternative dipolarophile, enamine and 1, 3-dipole, benzonitrile oxide.
2. An improved, scalable, eco-friendly and cost effective process for pyrazole derivative, celecoxib was developed in excellent yield and quality.
3. Synthesis and characterization of new carbazole based β-amino alcohols and corresponding oxazolidines and oxazolidinones was accomplished.
4. Novel carbazole based morpholine, morpholinone and mopholinedione derivatives were synthesized and characterized.