Cyclooxygenases (COXs) are key enzymes in the synthesis of prostaglandin H$_2$ which is a precursor for the biosynthesis of prostaglandins, thromboxanes, and prostacyclins. COX enzymes exist in two isoforms: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). The COX-1 enzyme is constitutively expressed and is critical for protection of gastric mucosa, platelet aggregation, and renal blood flow whereas the COX-2 enzyme is inducible and expressed during inflammation, pain, and oncogenesis. The association of COX-2 with induced inflammation has led to the hypothesis that selective inhibition of COX-2 over COX-1 might provide good anti-inflammatory agents with reduced side effects than classical NSAIDs. Therefore, selective COX-2 inhibitors (coxibs) with better safety profile have been marketed as a new generation NSAIDs. But careful prospective examination of coxibs has revealed unexpected cardiovascular adverse effect. Therefore, development of novel compounds having anti-inflammatory and analgesic activities with an improved safety profile is still a necessity. In addition, inflammation is known not only as a symptom of great deal of common diseases but also as an early phase of some life-threatening diseases such as cancer, heart vascular diseases and Alzheimer’s dementia. Thus the discovery of novel anti-inflammatory agents has been attracting a lot of interests.

Taking into consideration, the present work entitled “Design, Synthesis and biological activity of few heterocycles as anti-inflammatory agents.” describes the synthesis of diaryl pyrazole heteroazoles, diaryl payrazoline heteroazoles, Monoaryl pyrazole heteroazoles and diaryl imidazole heteroazoles as anti-inflammatory agents.
CHAPTER 1: Introduction to inflammation and targets involved in inflammation

CHAPTER 2: Synthesis of 1,5-diaryl-pyrazoline-3-heteroazoles

Section A:
This section deals with Synthesis of 1,5-diaryl-4,5-dihydro-1H-pyrazol-3-yl-5-substituted-[1,3,4]-oxadiazoles. It includes 3 series and 25 NCE’s (New chemical entities)

\[ \text{X} = \text{H}, \text{SO}_2\text{NH}_2 \]
\[ \text{R} = \text{H}, \text{OH}, \text{NH}_2, \text{SH}, \text{CH}_3, \text{CF}_3, \text{COOH}, \text{COOEt}, \text{CH}_2\text{COOH}, \text{CH}_3\text{COOEt}, \]

Section B:
This section deals with synthesis of 1,5-diaryl-4,5-dihydro-1H-pyrazol-3-yl-5-substituted-[1,2,4] oxadiazoles and tetrazoles. It includes 2 series and 12 NCE,s.

\[ \text{X} = \text{H}, \text{SO}_2\text{NH}_2 \]
\[ \text{Y} = \text{H}, \text{CH}_3 \]
\[ \text{R} = \text{H}, \text{OH}, \text{NH}_2, \text{SH}, \text{CH}_3, \text{CF}_3, \text{COOH}, \text{COOEt}, \text{CH}_2\text{COOH}, \text{CH}_3\text{COOEt}, \]

Section C:
This section deals with the biological evaluation of diaryl pyrazoline compounds for anti-inflammatory activity using Rat Paw Edema method for 30 NCE’s and COX-2 inhibition assay of selected 4 NCE’s. The selected 4 NCE’s were evaluated for analgesic activity using acetic acid induced writhing method.
CHAPTER 3: Synthesis of 1,5-diaryl-pyrazole-3-heteroazoles

Section A:
This section deals with Synthesis of 1,5-diaryl-pyrazol-3-yl-5-substituted-[1,3,4]oxadiazoles. It includes 2 series and 14 NCE’s

\[
\begin{array}{c}
\text{X} = \text{H, SO}_2\text{NH}_2 \\
\text{R} = \text{H, OH, NH}_2, \text{SH, CH}_3, \text{CF}_3, \text{COOH, COOEt}
\end{array}
\]

Section B:
This section deals with Synthesis of 1,5-diaryl-pyrazol-3-yl-5-substituted-[1,2,4]-oxadiazoles and tetrazoles. It includes 1 series and 8 NCE’s

\[
\begin{array}{c}
\text{X} = \text{H, SO}_2\text{NH}_2 \\
\text{Y} = \text{H, CH}_3 \\
\text{R} = \text{H, OH, NH}_2, \text{SH, CH}_3, \text{CF}_3, \text{COOEt, CH}_2\text{COOEt}
\end{array}
\]

Section C:
This section deals with the biological evaluation of diaryl pyrazole compounds for anti-inflammatory activity using Rat Paw Edema method for 18 NCE’s and COX-2 inhibition assay of 4 selected NCE’s. The 4 NCE’s were evaluated for analgesic activity using acetic acid induced writhing method.
CHAPTER 4: Synthesis of monoaryl-pyrazole-4-heteroazoles

Section A:
This section deals with Synthesis of 1-(4-trifluoromethyl-phenyl)-pyrazol-4-yl-5-substituted-[1,3,4]-oxadiazoles. It includes 1 series and 10 NCE’s

\[
\begin{align*}
\text{N}^N\text{N}-\text{O} - \text{R} \\
\text{CF}_3
\end{align*}
\]

\[ R = \text{H, OH, NH}_2, \text{SH, CH}_3, \text{CF}_3, \text{COOH, COOEt} \]

Section B:
This section deals with Synthesis of 1-(4-trifluoromethyl-phenyl)-pyrazol-4-yl-5-substituted- [1,2,4]-oxadiazoles and tetrazoles. It includes 1 series and 8 NCE’s

\[
\begin{align*}
\text{N}^N\text{O} - \text{R} \\
\text{CF}_3
\end{align*}
\]

\[
\begin{align*}
\text{N}^N\text{N}-\text{N}^N\text{N}-\text{Y} \\
\text{CF}_3
\end{align*}
\]

\[ Y = \text{H, CH}_3 \\
R = \text{CH}_3, \text{CF}_3, \text{COOEt, CH}_2\text{COOEt} \]

Section C:
This section deals with the biological evaluation of Monoaryl pyrazole compounds for anti-inflammatory activity using Rat Paw Edema method for 15 NCE’s and COX-2 inhibition assay of 11 selected NCE’s. The 2 NCE’s were evaluated for analgesic activity using acetic acid induced writhing method.
CHAPTER 5: Synthesis of substituted imidazoles as anti-inflammatory agents.

Section A:

This section describes synthesis of 4-[1-(4-Fluoro-phenyl)-4-(5-Substituted-[1,3,4]-heterodiazol-2-yl)-IH-imidazol-2-yl]-pyridine as P38 MAP kinase inhibitors. It includes 2 series and 16 NCE,s. COX-2 inhibition assay of 4 selected NCE’s evaluated.

Section B: Development of new synthetic methodologies for Benzimidazole, Imidazopyridine, Benzoheteroazolone and 2-Aminobenzothiazole.

1. Lithium bromide catalyzed solvent free method for synthesis of 2-substituted benzimidazoles and imidazopyridines was developed.
2. Lithium bromide catalyzed unique reaction of alkyl cyanoformate with 1-amino 2-heteroaryl substrates and its application towards synthesis of benzoheteroazolones and 2-aminobenzothiazoles was studied.

\[ \text{NH}_2 \quad \text{LiBr} \quad 110-115^\circ C \quad 1hr \quad \text{K}_2\text{CO}_3/\text{EtOH} \]

\[ X = \text{NH}_2, \text{OH}, \text{SH}; \ Y = \text{NCOOEt}, \text{O}, \text{S}; \ Z = \text{NH}, \text{O}, \text{S}; \ R = \text{O}, \text{NH} \]

**CHAPTER 6: Conclusion**