CHAPTER - I
CHAPTER I

INTRODUCTION

A REVIEW ON 2H-1,4-BENZOAXIN-3(4H)-ONES – THEIR IMPORTANCE, SYNTHESIS AND REACTIVITY

Benzoxazinones are well known in literature as potential medicinal agents apart from their varied biological properties and belong to a nitrogen and oxygen heterocyclic family.

The important medicinal properties associated with benzoxazinones are reported in literature as cardiotonics\(^1\), antihelminetics\(^2\), antibacterials\(^3\), antifungals\(^4\), anti-inflammatory\(^5\) and bronchodilating agents\(^6\).

A good number of benzoxazinone derivatives are also reported in literature as agrochemicals\(^7\), herbicides\(^8\), algicides\(^9\) and insecticidal agents\(^9\).

STRUCTURAL FEATURES

The benzoxazinone ring system is obtained theoretically by fusion of morpholinone ring through its 5,6-bond to a benzenoid ring system.

![Structural Diagram](image)

The nitrogen as well as oxygen, which are present in the benzoxazinone ring system, are sp\(^3\) in character and the nitrogen is acidic in nature.

The numbering of the benzoxazinone system is as given below. The numbering starts from oxygen and there after the numbering follows in an anti-clockwise direction.

![Numbers Diagram](image)
In the benzoxazinone system the >C=O group is present at C-3 position. Therefore, it is designated as 2H - 2,3-dihydro-1,4-benzoxazin-3(4H)-one (I).

The hydrogen present on nitrogen is acidic in nature (sp\(^3\) in character) as it exists in its iminol form.

![Chemical Structure of Benzoxazinones](image)

**IMPORTANCE OF 2H-1,4-BENZOXAZIN-3(4H)-ONES IN HETEROCYCLIC CHEMISTRY:**

As stated earlier a few 2H-1,4-benzoxazin-3(4H)-ones are reported in literature as fine pharmaceuticals and have got wide application in medicinal chemistry. Atrasentan (II)\(^{10}\) is used as an *antiemetic* agent where as Bisoxatin acetate (III)\(^{11}\) is reported to be a *Laxative*.

![Chemical Structures of Pharmaceutical Compounds](image)

Quite a good number of benzoxazinones are reported in literature as fine pharmaceuticals, pesticides and as their synthetic intermediates. The biological and pharmacological activity of few benzoxazinones is given below in a tabular form.
# BIOLOGICAL & PHARMACOLOGICALLY ACTIVE BENZOXAZINONES

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Structure of the Compound</th>
<th>Biological Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>Anti-inflammatory¹²</td>
</tr>
<tr>
<td></td>
<td>R=R¹= H, CH₃</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R=H; R¹= CH₃</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R= C₂H₅; R¹= H</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>Antifungal, Antimicrobial¹²</td>
</tr>
<tr>
<td></td>
<td>R= H, CH₃, C₂H₅, CH₂Ph</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>CNS depressant¹³</td>
</tr>
<tr>
<td></td>
<td>(CH₂)₃N(CH₃)₂</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Structure 4" /></td>
<td>Antibacterial⁴</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Structure 5" /></td>
<td>Antibacterial³</td>
</tr>
<tr>
<td></td>
<td>R¹=R²= H</td>
<td></td>
</tr>
<tr>
<td>S.No.</td>
<td>Structure of the Compound</td>
<td>Biological Activity</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>6</td>
<td><img src="image1.png" alt="Structure 6" /></td>
<td>Hypoglycemic&lt;sup&gt;15&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>R=H, R&lt;sub&gt;1&lt;/sub&gt;=R&lt;sub&gt;2&lt;/sub&gt;=CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R=R&lt;sub&gt;1&lt;/sub&gt;=H, R&lt;sub&gt;2&lt;/sub&gt;=CH&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>7</td>
<td><img src="image2.png" alt="Structure 7" /></td>
<td>Anti-Inflammatory&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>R=H, R&lt;sub&gt;1&lt;/sub&gt;=CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="image3.png" alt="Structure 8" /></td>
<td>Diuretic&lt;sup&gt;16&lt;/sup&gt;</td>
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<td>9</td>
<td><img src="image4.png" alt="Structure 9" /></td>
<td>Antihookworm&lt;sup&gt;2a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=H, R&lt;sup&gt;2&lt;/sup&gt;=CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
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<tr>
<td></td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=NHCO&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;, R&lt;sup&gt;2&lt;/sup&gt;=H</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td><img src="image5.png" alt="Structure 10" /></td>
<td>Antifungal&lt;sup&gt;4&lt;/sup&gt;</td>
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<td></td>
<td>R=R&lt;sub&gt;1&lt;/sub&gt;=CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R=H, R=CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R&lt;sup&gt;1&lt;/sup&gt;=H, R=C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td></td>
</tr>
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<td>S.No.</td>
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<td>Biological Activity</td>
</tr>
<tr>
<td>-------</td>
<td>---------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>11</td>
<td><img src="image1" alt="Structure 1" /> R=R'=R2=H, CH₃, R=CH₃, R'=R₂=H</td>
<td>Cardiotonic agent¹⁸</td>
</tr>
<tr>
<td>12</td>
<td><img src="image2" alt="Structure 2" /> R=Cl, Br</td>
<td>α₂-Adreno receptor¹⁷</td>
</tr>
<tr>
<td>13</td>
<td><img src="image3" alt="Structure 3" /> R=Cl, Br</td>
<td>Anti-inflammatory¹⁸</td>
</tr>
<tr>
<td>14</td>
<td><img src="image4" alt="Structure 4" /> R=Cl, Br</td>
<td>Hypoglycemic and antiobesity¹⁹</td>
</tr>
<tr>
<td>15</td>
<td><img src="image5" alt="Structure 5" /> R=H, ClH₃, R'=H, Br, Cl, Me, NO₂, R²=H, Me; R³=H, Br, Me</td>
<td>Insecticidal activity⁹</td>
</tr>
<tr>
<td>S.No.</td>
<td>Structure of the Compound</td>
<td>Biological Activity</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>16</td>
<td><img src="image1" alt="Structure" /></td>
<td><em>Herbicides and Algicides</em>&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>17</td>
<td><img src="image2" alt="Structure" /></td>
<td><em>Antifungal</em>&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td>18</td>
<td><img src="image3" alt="Structure" /></td>
<td><em>Antioxidants</em>&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>19</td>
<td><img src="image4" alt="Structure" /></td>
<td><em>Potassium channel modulators</em>&lt;sup&gt;22&lt;/sup&gt;</td>
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<tr>
<td>20</td>
<td><img src="image5" alt="Structure" /></td>
<td><em>CNS depressants</em>&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>21</td>
<td><img src="image6" alt="Structure" /></td>
<td><em>Anti-inflammatory</em>&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
SYNTHESIS: SOME OF THE APPROACHES TOWARDS THE SYNTHESIS OF BENZOXAZINONE DERIVATIVES:

Good numbers of synthetic methods are reported in literature for the synthesis of benzoxazinone derivatives and a few of the methodologies are given below:

i) Condensation of \( o \)-aminophenols with \( \alpha \)-haloacyl halides.

ii) By intramolecular cyclization.

iii) Ring expansion of isatins (five membered system) to benzoxazinones.

iv) Condensation of \( o \)-aminophenols with epoxy carboxylic acid derivatives.

i) Condensation of \( o \)-aminophenols with \( \alpha \)-haloacyl halides:

a) One of the classical approaches for the synthesis\(^{25}\) of 2H-1,4-benzoxazin-3(4H)-one is condensation of \( o \)-aminophenol(IV) with \( \alpha \)-chloroacetyl chloride in MIBK in presence of aqueous sodium bicarbonate in a single step.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} & \quad \text{OH} & \quad \text{H}_2\text{N} & \quad \text{NaHCO}_3/\text{MIBK} & \quad \Delta \\
\text{O} & \quad \text{C} & \quad \text{O} & \quad \text{N} & \quad \text{I} & \quad \text{H} \\
\text{Cl} & \quad \text{Cl} & \quad \text{IV} & & & \quad \text{I}
\end{align*}
\]

b) Similarly, the condensation\(^{26}\) of \( o \)-aminophenol derivative(IV) with \( \alpha \)-chloroacetyl chloride in chloroform in the presence of sodium bicarbonate using a phase transfer catalyst also yielded the corresponding benzoxazinone derivative (I) at room temperature in good yield.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} & \quad \text{OH} & \quad \text{H}_2\text{N} & \quad \text{NaHCO}_3/\text{TEBAC/CHCl}_3 & \quad \Delta \\
\text{O} & \quad \text{C} & \quad \text{O} & \quad \text{N} & \quad \text{R} & \quad \text{H} \\
\text{Cl} & \quad \text{Cl} & \quad \text{IV} & & & \quad \text{I}
\end{align*}
\]
c) In another method\textsuperscript{37}, \(\alpha\)-aminophenol derivative(IV) on condensation with ethyl \(\alpha\)-bromo acetate (V carboxylic acid ester derivative) in the presence of potassium fluoride and dimethylformamide yielded the respective benzoxazinone derivative (VI).

\[
\begin{align*}
\text{(V)} & \quad \text{(IV)} & \quad \text{(VI)} \\
R^1 & \quad \text{KF/DMF} & \quad R^1 \quad \text{O} \quad \text{N} \\
\text{Br} \quad \text{OC}_{2}H_{5} & \quad \text{H}_{2}N \quad \text{H}_{2}N \quad \text{H}_{2}N
\end{align*}
\]

ii) By intramolecular cyclisation:

a) In another interesting approach, the intramolecular cyclisation\textsuperscript{24} of 2-amino alkoxy aminoalkyl ester derivative(VII) gave the respective benzoxazinone derivative(I) and is given below.

\[
\begin{align*}
\text{(VII)} & \quad \text{Cyclisation} & \quad \text{(I)} \\
R^{1}R^{2}N & \quad \text{AcOH} & \quad \text{O} \quad \text{N}
\end{align*}
\]

b) Reaction of 2-methoxy-N-methylaniline (VIII) with chloroacetyl chloride in benzene and pyridine at RT followed by cyclisation using aluminium chloride at 150-160\(^{\circ}\)C gives the respective benzoxazinone derivative\textsuperscript{29} (IX).
c) Condensation of 2-nitrophenol(X) with chloroacetic acid followed by reduction with palladium/carbon and cyclisation of the resulting derivative gives exclusively 2H-1,4-benzoxazin-3(4H)-one \(^{(1)}\).

\[
\begin{array}{c}
\text{Cl} - \text{CH}_{3} - \text{C} - \text{O} - \text{CH} = \text{N} - \text{CH}_{3} \\
\text{O} - \text{N} - \text{CH}_{3} \\
\end{array}
\]

\(\text{(IX)}\)

d) Similarly, condensation of \(o\)-nitrophenol(X) with diethyl \(\alpha\)-bromomalonate followed by reduction with palladium/carbon as in earlier experiment gave 2H-2,3-dihydro-1,4-benzoxazin-3(4H)-one \(^{(1)}\) in good yield.

\[
\begin{array}{c}
\text{Cl} + \text{HO} - \text{C} - \text{O} - \text{HO} - \text{N}_{2} \\
\text{O} - \text{N} - \text{CH}_{3} \\
\end{array}
\]

\(\text{(X)}\)

\(\text{(I)}\)
e) Base catalysed cyclisation of o-bromo alkoxy amide derivatives(XI) gave the respective benzoxazinone(XII).

\[
\begin{align*}
\text{(XI)} & \quad \text{base-catalysed} \\
\text{Cyclisation} & \quad \text{(XII)} \\
\end{align*}
\]

f) In situ cyclisation of N-alkyl derivative-2-bromo-o-hydroxyalkanoylanilide derivatives (XIII) in aq. sodium hydroxide also yielded respective benzoxazinone(XIV) derivatives.\(^{32}\)

\[
\begin{align*}
\text{(XIII)} & \\
\end{align*}
\]

g) Interestingly the electro-chemical reduction\(^{33}\) (at 900 millivolts) of o-nitrophenoxycetic acid derivatives(XV) gave the 2-substituted-3-benzoxazinone derivative(XIV) in good yield.

\[
\begin{align*}
\text{(XV)} & \quad \text{(XIV)} \\
\end{align*}
\]

h) In another interesting method\(^{34}\), the o-nitrophenol derivatives(XVI) followed by reductive cyclisation led to the respective benzoxazinone(I) derivatives in good yields.
iii) Ring expansion of isatins (five membered system) to benzoxazinones:

The synthesis of benzoxazinones can also be achieved by ring expansion\textsuperscript{15} of five membered isatin (XVII) ring systems. The reaction of isatin with m-CPBA followed by reduction of the lactone carbonyl gives benzoxazinone (Ib).

\[
\begin{align*}
\text{O} & \quad \text{m-CPBA} \\
\text{O} & \quad \text{KBIH}_4 \\
\end{align*}
\]

(iv) Condensation of o-aminophenols with epoxy carboxylic acids:

Reaction of o-aminophenols derivatives (IV) with trans-dichloroethylcarboxylates in the presence of DCC or after activating with t-BuOCOC\textsubscript{2} gave the corresponding carboxamido intermediate (XVIII) which on cyclisation using DBU in ethanol yielded the corresponding benzoxazinone derivative\textsuperscript{34} (XIX).
GENERAL REACTIONS OF BENZOXAZINONES:

1) Nuclear substitution:

Chlorosulfonation\textsuperscript{37}: Benzoxazinones (I) undergo a facile substitution reaction with chlorosulfonic acid, to yield respective 6-substituted derivative (XX) in good yield.

\[ \text{Acetylation: Electrophilic reagents like acetic anhydride, acetyl chloride, chloroacetyl chloride and succinic anhydride react easily with benzoxazinones (I) in the presence of Lewis acids leading to the respective 6-substituted derivatives (XXI, XXII, XXIII).} \]

\[ \text{Interestingly, in all the above cases, no N-substitution products were formed.} \]

Chlorination\textsuperscript{40}: The iminol form of benzoxazinone (I) undergoes a facile substitution reaction with phosphorous oxychloride in dichloroethane to yield 3-chlorobenzoxazine (XXIV).
Nitration \[^{11}\]: The facile nitration of 6-chlorobenzoxazinone (XXV) with nitric acid in the presence of a mixture of acetic acid and acetic anhydride yielded the 6-chloro-7-nitrobenzoxazinone (XXVI).

2) Condensation with aromatic aldehydes \[^{13}\]: An interesting reaction of benzoxazinones (I) is condensation with aromatic aldehydes in the presence of acetic anhydride and triethylamine with the active methylene group of lactam gave the corresponding C\(_2\) arylidene derivatives (XXVII).

3) Alkylation of benzoxazinones \[^{30}\]:

   a) It is interesting to note that the reaction of benzoxazinones (I) with alkylating agents like dimethyl sulphate in the presence of strong bases like sodium hydroxide yielded the respective N-alkylated derivative (XXVIII) indicating that the lactam is stable towards strong bases.
b) In a similar reaction with propargyl bromide in acetone and potassium carbonate (under anhydrous conditions) benzoxazinone (I) yielded the respective N-propynyl benzoxazinone derivative (XXIX).

c) It is interesting to note that benzoxazinone (I) also undergoes acylation with Boc₂O (at RT in THF) to give the respective Boc derivative (XXX) in good yield.

4) Thionation of benzoxazinones: Phosphorous pentasulfide reacts with benzoxazinone (I) rapidly in the presence of xylene and yields the corresponding 3-thione derivative (XXXI) in excellent yield.
SPECTRAL PROPERTIES OF BENZOXAZINONE RING SYSTEM:

i) Ultraviolet absorption spectra:

The ultraviolet spectrum of four benzoxazinones were measured in 95% ethanol. The \( \lambda_{\text{max}} \) (log e) was observed at 254–256 nm (3.66–3.90) as a stronger absorption and at 281.5–283.0 (3.42–3.78) as a weaker absorption indicating the aromatic absorption and absorption due to a lactam carbonyl group. The UV absorption data is given below in tabular form:

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the compound</th>
<th>UV (max) m( \mu ) (log e) in 95% ethanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2H - 1,4-Benzoxazin-3(4H)-one</td>
<td>256.4 (3.66) 282.5 (3.42)</td>
</tr>
<tr>
<td>2</td>
<td>2-Methyl-2H-1,4-benzoxazin-3(4H)-one</td>
<td>254.6 (3.86) 282.0 (3.74)</td>
</tr>
<tr>
<td>3</td>
<td>4-Methyl-2H-1,4-benzoxazin-3(4H)-one</td>
<td>256.4 (3.79) 283.0 (3.63)</td>
</tr>
<tr>
<td>4</td>
<td>2,4-Dimethyl-2H-1,4-benzoxazin-3(4H)-one</td>
<td>254.5 (3.90) 281.5 (3.78)</td>
</tr>
</tbody>
</table>

ii) Infrared absorption spectra:

The infrared absorption of few benzoxazinones is reported in literature, both in solid (KBr) and solution state (chloroform). The strong absorption around 1680 – 1700 cm\(^{-1}\), another absorption around 3140 – 3160 cm\(^{-1}\) are indicative of lactam carbonyl and amide NH group respectively. These absorptions indicate that the predominant tautomer exists in keto form in solid state.

iii) NMR Spectra:

The NMR spectra of number of benzoxazinones are reported in literature. The \(^1\)H-NMR spectrum of simple 2H-1,4-benzoxazin-3(4H)-one has been recorded in DMSO – d\(_6\). The two (C\(_2\)) methylene protons were observed as singlet at \( \delta \) 4.52 (s, 2H, -OCH\(_2\)) relatively in a down field. The aromatic protons (C\(_{5,6}\)) appeared in the aromatic region as a multiplet at \( \delta \) 6.80 – 6.95 (m, 4H, aryl). The lactam proton was observed in the far down field region as a singlet at \( \delta \) 10.60 (s, 1H, -NH).
iv) Mass spectra:

In the mass spectrum of the 2H-1,4-benzoxazin-3(4H)-ones, the molecular ion was fairly stable and was found to be the base peak in the spectra. Fragment at m/e 120 (73%) was observed due to the loss of (-H & CO) groups. Similarly two more fragments were observed at m/e 93 (3%) and 79 (5%) due to the loss of benzyle and NCOCH$_2$ respectively from the molecular ion.
ACTION OF NSAIDS TOWARDS COX-1 AND COX-2 ENZYMES

Nonsteroidal anti-inflammatory drugs (or NSAIDS) are the chemical entities that are used as pain relievers and being treated in arthritis apart from inflammation and lowering the fever.

In 1853, Gerhardt for the first time prepared acetyl salicylic acid and was not marketed because of its improper physiological activity studies. In 1895 a German chemist, Felix Hoffman rediscovered this drug and named it as Aspirin (i.e., Acetyl salicylic acid). It is the first Nonsteroidal anti-inflammatory drug (or NSAID) and also used as an analgesic agent. Incidentally it was also found that this drug is effective for rheumatoid arthritis. The mechanism of NSAIDS is fully conversant as on today after the detailed study made by John Vane. He found that NSAID Aspirin is effective as analgesic and anti-inflammatory drug. It was also found that it suppresses inflammation primarily by inhibiting the PGHS or COX enzyme.

Inflammation

Inflammation is manifestation of the body's response to tissue damage and infection. The basic symptoms of inflammation are redness, swelling, heat pain and deranged function. A response of redness, swelling, pain and feeling of heat in certain areas, that is meant to protect tissues, is affected by injury or disease. The net result is loss of function in those areas. The immuno response for this is complex stereotypical reaction involving a number of cellular, molecular changes and the result observed is inflammation.

Some of the common traditional NSAIDS that are available in the market other than Aspirin are Ibuprofen, Naproxen and Nabumetone.

The important side effects that are associated with the NSAIDS are nausea or an upset in stomach and interference with kidney function.
The mechanism of action of NSAIDs is primarily, inhibition of prostaglandin biosynthesis by an enzyme called cyclooxygenase (COX) or prostaglandin H synthase (PGHS).

It is reported that two isoforms of COX are in existence and are known as COX-1 and COX-2. The first one is COX-1 and can be expressed constitutively. The second one is COX-2 and cannot be expressed constitutively, however it is inducible to inflammation stimuli.\(^52\)

Some of the important drugs that are used for inhibiting COX-1 are Indomethacin\(^53\) and Aspirin etc. A few important latest discoveries for COX-2 inhibition are Celecoxib, Rofecoxib and Valdecoxib\(^54-56\).

**Present Work**

It is evident from the above literature review that benoxazinones are found to be biologically important molecules. Keeping in view of this, the synthesis of various substituted benoxazinone derivatives and evaluation of some of the synthesized compounds for their biological activity towards COX-1 & COX-2 enzyme inhibition is discussed in this thesis.

First chapter deals with the introductory aspects of 2H-1,4-benoxazin-3(4H)-one derivatives - their importance, nomenclature, synthetic approaches and general reactions. This chapter basically consists a review on the importance of 2H-1,4-benoxazin-3(4H)-one derivatives in medicinal chemistry apart from various synthetic approaches towards their synthesis based on the literature survey. It also deals briefly the role of NSAIDS and a few aspects of COX-1 and COX-2 enzymes.

Second chapter describes the biological activity associated with substituted furan-2(5H)-ones in brief and various synthetic approaches based on literature survey. Keeping in view of this, various benoxazinones containing the substituted furanone & thiazolobenzimidazole moieties were prepared by the condensing the 6-(2-chloroacetyl)-2H-
1,4-benzoxazin-3(4H)-one with substituted phenylacetic acids and substituted 2-mercaptobenzimidazoles followed by cyclisation.

Third chapter describes the biological properties associated with indoles and different methods to build the substituted indole-3-acetic acids based on the literature. The synthesis of [2-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-carbonyl)-1H-indol-3-yl]acetic acid by condensing the 6-(2-chloroacetyl)-2H-1,4-benzoxazin-3(4H)-one with 3-[2-(toluene-4-sulfonylamino)-phenyl]acrylic acid methyl ester and its derivatives are described.

Fourth chapter initially deals with the brief review on the biological activity, synthesis of aminothiazoles and substituted thiazolobenzimidazoles. 2H-1,4-benzoxazin-3-(4H)-one is reacted with phenyl acetyl chloride to give corresponding acetylated compound, which on further reaction with bromine in acetic acid gave respective α-bromo derivative. This on reaction with substituted phenylthiourea gave the corresponding substituted 2-aminothiazole derivative. Reaction of α-bromo derivative with substituted benzimidazole-2-thiols followed by cyclisation of the resulting compound yielded substituted 2-phenyl thiazolobenzimidazole derivatives.

Fifth chapter deals with the biological activity and few synthetic methods of pyrazolo & isoxazolobenzoxazinones and thiazolothiadiazinobenzoxazinones. Reaction of 6-Phenylacetyl-4H-benzo[1,4]oxazine-3-one with N,N-dimethylformamide dimethylacetal (DMF-DMA) yielded N,N-dimethylamino methylene derivative, which on further condensation with substituted hydrazines gave pyrazolobenzoxazinone derivatives. Similarly, reaction of N,N-dimethylamino methylene derivative with hydroxylamine hydrochloride yielded substituted isoxazolobenzoxazinone derivatives. Treatment of substituted 6-chloroacetyl benzoxazinones with 5-substituted 4-amino-4H-[1,2,4]triazole-3-thiol gave triazolothiadiazinobenzoxazinones.
Sixth chapter describes the method followed for screening of the prepared compounds towards COX-2 enzyme inhibitory activity. Some of the selected compounds are tested for COX-1 & COX-2 inhibition studies by using Copeland method, using Indomethacin (an age old drug of NSAID) as an internal standard for COX-1 and Celecoxib (selective COX-2 inhibitor – A drug) for COX-2, the results of which, are given in this chapter.
References


12. Reddy Sastry C V., Srinivasa Rao K., Krishnan V S H., Rastogi K., Jain M L.,


