Discussion and Conclusion
Chapter 5

Discussion and Conclusion

5.1 Discussion

Non steroidal anti-inflammatory drugs are used for the relief of pain and inflammation. They produce their effects through inhibition of cyclooxygenase (COX), a key enzyme responsible for the synthesis of PGs and TXA2\textsuperscript{154}. Pain and inflammation research in animals over last two decades has led to new and improved methods for controlling pain and inflammation.

In the present study the antiinflammatory, analgesic and antipyretic activities were assessed through such types of experimental pain, inflammation and pyrexia models in which animals were exposed to the minimum intensity of stimuli to carry out the experiments\textsuperscript{155}. All the thiazolidin-4-one derivatives viz., 4-nitro-2-phenoxypyphenyl 4-thiazolidinone, sulphonyl 4-thiazolidinone, ethoxyphenyl 4-thiazolidinone, coumarinyl 4-thiazolidinone, hydroxyphenyl 4-thiazolidinone exhibited significant (p<0.01) anti-inflammatory activity in both acute and subacute models of inflammation. Our results support the earlier studies of other 4-
thiazolidinone derivatives having anti-inflammatory activity, irrespective of various substitutions to 4-thiazolidinone moiety. However, the efficacy of the different derivatives was variable depending upon the various substitutions like 4-nitro phenoxyphenyl and coumarinyl moieties. The R, R1, R2, substitutions on the thiazolidinyl moiety in all 4-thiazolidinone compounds also modified the anti-inflammatory activity. In particular, derivatives of sulphonyl 4-thiazolidinone, ethoxyphenyl 4-thiazolidinone, coumarinyl 4-thiazolidinone showed significant and maximum anti-inflammatory activity as compared to 5-spiro substituted derivatives of 4-thiazolidinone. The hydroxyphenyl 4-thiazolidinone derivatives showed significant but minimum inhibition of edema.

In the present study, anti-inflammatory activity of all 4-thiazolidinone derivatives can be directly correlated with their COX-2 enzyme inhibitory activity, indicating their mechanism of action. All 4-thiazolidinone derivatives also showed peripheral analgesic and antipyretic activity very much similar to their anti-inflammatory activity. In sub acute toxicity study, compound ethoxyphenyl 4-thiazolidinone derivative (C3) was found to produce more toxicity on stomach, liver and kidney than other compounds tested. The toxicity observed may be correlated with its significant inhibition of COX-1 and COX-2 activity. The inhibition of COX-2 enzyme by diverse structures of 4-thiazolidinones appears to be due flexible nature of the COX-2 enzyme structure as indicated also by the earlier studies.
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From the results of biological screening the possible structure activity relations that could be inferred are given below:

- In the case of 4-nitro 2-phenoxyphenyl 4-thiazolidinone derivatives synthesized from nimesulide, all the compounds retained the activity of nimesulide however the intensity of activity was variable due to substitutions in thiazolyl and benzoyl group.

- Compounds with substitution of methyl, methoxy, hydroxyl and flouro groups at R, R1, R2 showed maximum activity compared to other substituted compounds viz, \( \text{A}_4 \), \( \text{A}_5 \) and \( \text{A}_8 \). Again flouro substituted 4-thiazolidinone \( \text{A}_8 \) showed maximum activity.

- The 5-spiro 4-thiazolidinones\( (\text{A}_9-\text{A}_{11}) \) with chloro, bromo and flouro substitution at either R, R1, R2 resulted in reduced activity. Suggesting that presence of spiro group at 5 position is interfering with the stereospecific binding of the compounds with the COX-2 enzyme which is evident by the negligible COX-2 enzyme inhibitory activity of spiro derivatives. However 5-spirothiazolidinones showed significant analgesic and antipyretic activity as these effects are mediated by other mechanisms alongwith minimum COX-2 inhibitory activity.

- In case of sulphonyl 4-thiazolidinone synthesised from sulphanilamide, all the compounds retained the activity similar to nimesulide as many potent COX-2 inhibitors have sulphonamide group \[\text{I}]. The results revealed that the substitution of various groups on benzoyl moiety did not modify the activity significantly suggesting that sulphonamide group is essential for activity.
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- The 5-spiro 4-thiazolidinones (B9-B11) with chloro, bromo and flouro substitution at either R, R1, R2 resulted in reduced activity, suggesting that the presence of spiro group at 5 position is interfering with the stereospecific binding of the compounds with the COX-2 enzyme which is evident by the negligible COX-2 enzyme inhibitory activity of spiro derivatives. However 5-spirothiazolidinones have significant analgesic and antipyretic activity as these effects may be mediated by other mechanisms alongwith minimum COX-2 inhibitory activity.

- Thiazolidinones with paraethoxymethyl group substitution(C1-C4) showed significant and good anti-inflammatory, analgesic and antipyretic activity. The inhibition of carrageenan edema by these compounds were maximum at 1st hour. Even in antipyretic activity, compounds C2, C3 and C4 showed maximum activity within 30 minutes. The substitutions at R, R1, R2 positions did not modify the activity of these compounds. The paraethoxyl or coumarinyl group substitution instead of sulphonamide group may have modified the mechanism of action, since paraethoxyl (C1-C4) and coumarinyl (C5-C7) substituted derivatives produced maximum activity during the 1st hour as the edema formation by carrageenan is due to release of histamine, serotonin and bradykinin during 0-2 hours along with their inhibition of PGs (2-4 hours).

- The thiazolidinones with coumarinyl substitution produced compounds with high anti-inflammatory, analgesic, antipyretic, COX-2 inhibitory activity comparable to nimesulide.

- Compound C3 is the only compound amongst thiazolidinones which has shown inhibition of both COX-1 and COX-2 activity and has shown in-
creased activity in 1\textsuperscript{st} hour even at 50mg/kg.

- Thiazolidin4-one with p-hydroxyphenyl substitution (D\textsubscript{1}-D\textsubscript{4}) showed significant but very less anti-inflammatory, analgesic and antipyretic, COX-1 and COX-2 enzyme inhibitory activity. Probably due to hydroxyphenyl group substitution which may increase the polar nature of the compounds and interfere with lipid solubility and availability at site of action as compared to other compounds.

### 5.2 Conclusion

Our study indicates that various 4-thiazolidinone derivatives can be further explored as anti-inflammatory agents with better efficacy and reduced toxicity. Compounds A\textsubscript{8}(4-nitrophenyl4-thiazolidinone), B\textsubscript{8}(sulphonyl 4-thiazolidinone) and C\textsubscript{7}(coumarinyl 4-thiazolidinone) derivatives can be further selectively evaluated amongst other compounds. Also our study reaffirms that COX-2 enzyme structure appears to be flexible in nature as reported by many other studies.
Table 5.1: Structure of identified lead moieties

<table>
<thead>
<tr>
<th>Compound Code</th>
<th>Structure</th>
<th>Chemical name</th>
</tr>
</thead>
<tbody>
<tr>
<td>A8</td>
<td><img src="image1" alt="Structure A8" /></td>
<td>2-(4-fluorophenyl)-2-methyl-3-(4-nitro-2-phenoxyphenyl)thiazolidin-4-one</td>
</tr>
<tr>
<td>B8</td>
<td><img src="image2" alt="Structure B8" /></td>
<td>4-[2-(4-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]benzenesulfonamide</td>
</tr>
<tr>
<td>C7</td>
<td><img src="image3" alt="Structure C7" /></td>
<td>2-(4-methyl-2-oxochroman-7-yloxy)-N-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)acetamide</td>
</tr>
</tbody>
</table>