| Fig.<br>No. | Figure Captions  | Page<br>No. |
|-------------|--|-------------|
| 1.1         | Chemical classification of NSAID's   | 6           |
| 1.2         | Chemical structures of NSAID's   | 7           |
| 1.3         | The conversion of arachidonic acid to prostaglandins   | 9           |
| 1.4         | Schematic representation of the COX-2 active site  | 11          |
| 1.5         | The structure of azapropazone  | 12          |
| 3.1         | The design strategy for the proposed compounds under Series 1 and Series 2 using molecular hybridization approach  | 35          |
| 4.1         | Possible mechanism of reaction for the synthesis of compounds  | 39          |
|             | S14a- S14o   |             |
| 4.2         | Possible mechanism of reaction for the synthesis of compounds<br>S21a– S21e  | 42          |
| 4.3         | Possible mechanism of reaction for the synthesis of compounds S22a-S22e  | 43          |
| 4.4         | Possible mechanism of reaction for the synthesis of compounds $S_23a-S_23e$  | 43          |
| 4.5         | Possible mechanism of reaction for the synthesis of compounds <b>S24a- S24e</b>  | 44          |
| 5.1         | Photomicrographs (10x magnification) of <b>[A]</b> Control; <b>[B]</b><br>Indomethacin; <b>[C]</b> Compound <b>S14d</b> and <b>[D]</b> Compound <b>S14e</b><br>treated groups in rat stomach tissues | 75          |
| 5.2         | Photomicrographs (10x magnification) of <b>[A]</b> Control; <b>[B]</b><br>Indomethacin; <b>[C]</b> Compound <b>S14d</b> and <b>[D]</b> Compound <b>S14e</b><br>treated groups in rat liver tissues   | 75          |
| 5.3         | Photomicrographs (10x magnification) of <b>[A]</b> Control; <b>[B]</b><br>Indomethacin; <b>[C]</b> Compound <b>S14d</b> and <b>[D]</b> Compound <b>S14e</b><br>treated groups in rat kidney tissues  | 76          |
| 5.4         | Lineweaver–Burk plot of <i>in vitro</i> COX–2 inhibition by potential derivatives of Series 1  | 80          |
| 5.5         | 3D view of the docking study of the minimum energy structure of the complex of <b>S14d</b> docked in COX–2 (PDB: 1CX2), viewed using the Glide XP visualiser of the Schrödinger Maestro 9.3 module   | 81          |
| 5.6         | 3D view of the docking study of the minimum energy structure of the complex of $S_14e$ docked in COX-2 (PDB: 1CX2), viewed using the Glide XP visualiser of the Schrödinger Maestro 9.3 module       | 81          |
| 5.7         | Protein–ligand RMSD. RMSD evaluation of a protein (left Y–axis); the ligand RMSD (right Y–axis) indicating the stability of ligand $S_14d$ with respect to the protein and its binding pocket        | 83          |
| 5.8         | The detailed atomic interactions of ligand $S_14d$ with the key  | 83          |

|      | amino acid residues at the active site of COX-2   |     |
|------|---|-----|
| 5.9  | Stacked bar charts of protein interactions with ligand $S_14d$ as monitored throughout the MD simulation  | 83  |
| 5.10 | Photomicrographs (10x magnification) of <b>[A]</b> Control group; <b>[B]</b> :<br>Indomethacin; <b>[C]</b> : Celecoxib; <b>[D]</b> : Compound <b>S</b> <sub>2</sub> <b>2d [E]</b> :<br>Compound <b>S</b> <sub>2</sub> <b>2e [F]</b> : Compound <b>S</b> <sub>2</sub> <b>3c</b> treated groups in rat<br>stomach tissues | 103 |
| 5.11 | Photomicrographs (10x magnification) of <b>[A]</b> Control; <b>[B]</b><br>Indomethacin; <b>[C]</b> Celecoxib <b>[D]</b> Compound <b>S22d [E]</b> : Compound<br><b>S22e [F]</b> : Compound <b>S23c</b> treated groups in rat liver tissues   | 104 |
| 5.12 | Photomicrographs (10x magnification) of <b>[A]</b> Control; <b>[B]</b><br>Indomethacin; <b>[C]</b> Celecoxib <b>[D]</b> Compound <b>S</b> <sub>2</sub> <b>2d [E]</b> : Compound<br><b>S</b> <sub>2</sub> <b>2e [F]</b> : Compound <b>S</b> <sub>2</sub> <b>3c</b> treated groups in rat kidney tissues                  | 104 |
| 5.13 | Lineweaver–Burk plot of <i>in vitro</i> COX-2 inhibition by compounds S <sub>2</sub> 2c-S <sub>2</sub> 2e and S <sub>2</sub> 3c-S <sub>2</sub> 3e   | 109 |
| 5.14 | Overlay of docked pose of celecoxib (green) with its crystallographic conformation  | 113 |
| 5.15 | 3D view of the docking study of the minimum energy structure of the complex of $S_22e$ docked in COX-2 (PDB: 3LN1)  | 114 |
| 5.16 | 3D view of the docking study of the minimum energy structure of the complex of $S_22d$ docked in COX-2 (PDB: 3LN1)  | 114 |
| 5.17 | 3D view of the docking study of the minimum energy structure of the complex of <b>S</b> <sub>2</sub> <b>2c</b> docked in COX-2 (PDB: 3LN1)  | 114 |
| 5.18 | Minimum energy conformer for compounds <b>S<sub>2</sub>4a- S<sub>2</sub>4e</b>  | 115 |
| 5.19 | Protein–ligand RMSD. RMSD evaluation of a protein (left Y–axis);<br>the ligand RMSD (right Y–axis) indicating the stability of ligand<br>$S_22e$ with respect to the protein and its binding pocket   | 117 |
| 5.20 | The detailed atomic interactions of ligand $S_22e$ with the key amino acid residues at the COX-2 active site  | 117 |
| 5.21 | Stacked bar charts of protein interactions with ligand $S_2 2e$ as monitored throughout the MD simulation   | 117 |