Thesis at a glance

Much research has been carried out in discovery and research of novel selective estrogen receptor modulators. Non-steroidal compounds were designed as inhibitors based on triphenylethylene structure resembling with tamoxifen for targeting estrogen receptor alpha (ERα). A computer-aided strategy was used to screen the molecular database. Initially compounds of the different structure with known biological relevance were collected and then, designed a library of molecules resembling with 4-hydroxytamoxifen. After energy minimization of lead molecules, they were subjected to docking process with estrogen receptor. Molecular dynamics study was also used to obtain the globally minimized state of ligand and receptor.

The present work highly potent, ER-selective, oxindole and methyl jasmonate based compounds are designed and synthesised. Biological evaluation of this conjugate is underway to expand our knowledge in optimizing the pharmacophore with improved potential.

On the other part, intrinsically fluorescent small molecules are preferably and widely employed as they can enter live cells easily and offer screening through visual detection. Therefore, different types of small molecular fluorescent probes have been designed and synthesised. They are further employed to successfully imaging of cancer cells. Simultaneously, they have been used to detect intracellular analytes in cancer cells.

In chapter 1, we have presented a general and concise background on the mechanistic aspects on the role of estrogen and estrogen receptors in cancer pathology. We have briefly discussed about the design principle and methods used for molecular modelling studies. We have started our journey derived from synthetic diphenolethyne viz. the designed oxindole based diphenolethyne by incorporating an oxindole unit into the bisphenolic or bis-arylidene moiety and finally mimicking some molecules resembling tamoxifen/4-OHT. Furthermore, we have succeeded in designing some molecules without any basic dimethylamino alkyl side chain and in due course, we found that this molecule also retains excellent ER selectivity.
In chapter 2, we have reported a new family of bis-arylideneoxindole and methyl jasmonate derivatives, that show highly selective estrogen receptor (ER)-mediated anticancer activity at low-micromolar concentrations in ER-positive (ER+) breast cancer cells. In order to know the biological pathways of these molecules, they are also labeled with some fluorescent molecules. Biological evaluation is underway to expand our knowledge in optimizing the pharmacophore with improved potential.

In chapter 3, some unique FRET based fluorescent probes have been developed for selective cancer cell imaging. In this present work we have designed some of the FRET molecules based on environmentally sensitive fluorophores. These molecules give rise emission in presence and absence of analytes. We have used FRET technique to measure the concentrations of some important metal ions which are relatively less known in different cancer cells.
In chapter 4, some fluorescent probes have been designed and developed for selective detection of analytes in cancer cells. Luminescence bioimaging offers an exclusive advance in visualizing morphological details of tissues with subcellular resolution. It is a powerful tool for monitoring and investigating of micro species in living cells. We have presented the general design principles of luminescent chemosensors for bioimaging and summarized recent advances in the detection of metal cations and amino acids in vitro and in vivo, developed by us. On the basis of the advantages and disadvantages of the present luminescent chemosensors used for bioimaging, several future directions in this field should be followed to develop better luminescent chemosensors and to exploit their further application.